INSTITUTE OF FUNDAMENTAL TECHNOLOGICAL RESEARCH
POLISH ACADEMY OF SCIENCES

PHD DISSERTATION

Mathematical analysis of a new model of bone pattern formation

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Warsaw, Poland
2019

Abstract

In this work we study a mathematical model proposed in reference [16] to describe processes of pattern formation in morphogenesis. In fact, the model is dedicated to bone formation phenomena in vertebrate embryos. The first equation of the considered system does not fall into any of the three basic classes of partial differential equations. To be more precise, this equation is parabolic in time and space and hyperbolic with respect to time and a pair of auxiliary independent variables describing the state of the cells. This fact does not allow us to use, at least straightforwardly, the usual methods of analysis assigned either to strictly parabolic or strictly hyperbolic problems and, according to our knowledge based on literature search and private communications, there are no theorems guaranteeing the existence of such equations even the homogeneous case. Similar difficulties occur when we attempt to carry out the numerical simulations of the model.

Our study of the problems connected with the analysed system is divided into two parts. In first part, see Part II, we consider a scalar equation retaining the basic difficulties of the system. We do not take into account the non-local terms (which are the source of aggregation phenomena), but concentrate on the existence of solutions to linear equations, homogeneous as well as inhomogenous ones. We manage to construct the solutions by means of appropriately defined solution kernels, both in the spatially unbounded as well as bounded case. We prove that the constructed solutions are unique in appropriate spaces of functions. We can also show the validity of the expressions defining solutions to homogeneous equations, when the initial data are given in the product form and the problem can be solved starightforwardly. In second part, see Part III, we deal with the whole system of three equations describing the analysed system, however we use another approach to prove the existence of its solutions. The approach consists in assigning to this system a modified version of the Rothe numerical scheme with time interval discretized into intervals of the lenght Δt. By deriving a series of a priori estimates, we are able to prove that the proposed numerical scheme produces, in the limit $\Delta t \to 0$, a solution to the system, in which, similarly to Part II we replace the non-local term by local functions.

Acknowledgments

I would like to express my gratitude to my supervisor Bogdan Kaźmierczak, for his deliberate discussions, continuous support, care, protection and indulgence that I received from him during my PhD study and research. His patience, motivation and exceptionally refined intuition has always been a great source of inspiration to me.

I also would like to thank all the Professors, my colleagues and the staffs of my Institute. A special thanks to Slawomir Bialecki for his constant help. I also thanks to Dr. Marek Kochańczyk for his help.

My research was partially sponsored by the grants 2016/21/B/ST1/03071. I would like to thank the principal investigator of the grant Bogdan Kaźmierczak, for the financial help.

Contents

Part I

Introduction

1 Background and motivation

Morphogenesis is one of the most interesting phenomenon in biology. It is extremely intriguing to explain, how from an initially homogeneous set of identical cells, spatial patterns composed of differentiated cells, leading to the formation of tissues organs and finally whole organisms can be created.

One of the important example of morphogenetic processes is the vertebrate limb formation. The formation of the skeletal pattern in vertebrate limbs received particular attention by the researchers. To be more precise, the mechanism of cellular and molecular interactions during the growth of the avian forelimb, for example, spatio-temporal differentiation of cartilage, such that the number of bone primordial changes in time from one (humerus), to two (radius and ulna) and to three (digits) get significant attention. Here we should keep in mind that the mechanism of chondrogenesis may differ from species to species, but its main features are common to all the vertebrates. In the experimental context the bone formation process is most often described for mice or chickens. At the initial stages of embryo development, limb mesenchymal cells started to condense to so called precartilage. After then the precartilage mesenchymal cells organize themselves into spot- or rod-like condensations of nearly uniform size [8, 7, 22], which are then turn into definite cartilage, followed by bone. These phenomena, together with appropriate geometry of the limb bud have been the subjects of many biological as well as mathematical models (see e.g. the reviews [33] , [27], [28]). In Appendix B (after the **References**), we attach a review by P. Chatterjee, T. Glimm & B. Kazmierczak [5], submitted to the journal of Mathematical Biosciences, which, among others, relates the considered model to other models of pattern formation, especially to the one presented in [2]. (However, let us emphasize that [5] is not a part of this dissertation and has been appended only for completeness.) The nature of the bone pattern formation, especially in its initial stages is still being not fully recognized and there are different candidates for proteins responsible for the onset of this process. In an experimental paper [3], Bhat et al. suggested that two members of a class of glycan-binding proteins CG(chicken galectin)-1A and CG-8 play a crucial role in cell condensation in the developing chicken limb. During the experiment, it was observed by Bhat et al. that, in vitro, CG-1A promotes supernumerary condensation formation and in vivo, it induces digit formation, while CG-8 inhibits both of these processes. Also, CG-1A induces the expression of the receptor, which binds both of CG-1A and CG-8 (the shared receptor).

In [16], Glimm et al., proposed a mathematical model describing the interactions of CG-1A and CG-8, based on the above mentioned experiment. It was verified in [16], that the proposed model reproduces well the experimental findings.

Mathematical formulation of the considered model

The model describes the spatio-temporal evolution of the following quantities:

1. $c_1^u = c_1^u(t, \mathbf{x})$ - concentration of freely diffusible CG-1A (that is, CG-1A not bound to receptors on cell membranes),

2. $c_8^u = c_8^u(t, \mathbf{x})$ - concentration of freely diffusible CG-8 (that is, CG-8 not bound to receptors on cell membranes)

3. $R = R(t, \mathbf{x}, c_1, c_8^8, c_8^1, \ell_1, \ell_8)$ - cell density.

Let us note that the cell density R depends on several variables representing various chemical concentrations **besides** to time and space, that is to say: c_1 - concentration of CG-1A proteins bound to shared receptors on cell membranes, c_8^8 - concentration of CG-8 proteins bound to CG-8 receptors on cell membranes, c_8^1 - concentration of CG-8 proteins bound to shared receptors on cell membranes, ℓ_1 - concentration of shared receptors (not bound to galectins) on cell membranes and ℓ_8 - concentration of CG-8 receptors (not bound to galectins) on cell membranes.

In [16] the following system of equations is proposed for $t \in (0, T)$, x from some bounded domain $\Omega \subset \mathbb{R}^{n_\Omega}$, $n_\Omega \geq 1$, $(c_1, c_8^8, c_8^1, \ell_1, \ell_8) \in (0, \infty)^5$:

$$\frac{\partial R}{\partial t} = \underbrace{D_R \nabla^2 R}_{\text{cell diffusion}} - \underbrace{\nabla \cdot (R\,\mathbf{K}(R))}_{\text{cell-cell adhesion}}$$

$$\underbrace{-\frac{\partial}{\partial c_1}(\alpha R) - \frac{\partial}{\partial c_8^8}(\beta_8 R) - \frac{\partial}{\partial c_8^1}(\beta_1 R)}_{\text{binding/unbinding of galectins to receptors}} - \underbrace{\frac{\partial}{\partial \ell_1}\left[(\lambda - \alpha - \beta_1)R\right] - \frac{\partial}{\partial \ell_8}\left[(\delta - \beta_8)R\right]}_{\text{change in receptors}} \quad (1.1)$$

$$\frac{\partial c_1^u}{\partial t} = \underbrace{D_1 \nabla^2 c_1^u}_{\text{diffusion}} \underbrace{+\overline{\nu}\int c_8^8 R\, dP}_{\substack{\text{pos. feedback of CG-8}\\ \text{on prod. of CG-1A}}} \underbrace{-\int \alpha R\, dP}_{\substack{\text{binding of CG-1A}\\ \text{to its receptor}}} \underbrace{-\overline{\pi}_1 c_1^u}_{\text{degradation}} \quad (1.2)$$

$$\frac{\partial c_8^u}{\partial t} = \underbrace{D_8 \nabla^2 c_8^u}_{\text{diffusion}} \underbrace{+\overline{\mu}\, c_1 R\, dP}_{\substack{\text{pos. feedback of CG-1A}\\ \text{on prod. of CG-8}}} \underbrace{-\int \beta_1 R\, dP - \int \beta_8 R\, dP}_{\substack{\text{binding of CG-8}\\ \text{to receptors}}} \underbrace{-\overline{\pi}_8 c_8^u}_{\text{degradation}} \quad (1.3)$$

subject to the following initial and boundary conditions:

$$R(0, \mathbf{x}, c_1, c_8^8, c_8^1, \ell_1, \ell_8) = R_0(\mathbf{x}, c_1, c_8^8, c_8^1, \ell_1, \ell_8) \quad (1.4)$$

$$\frac{\partial R}{\partial \mathbf{n}} = 0 \text{ for } \mathbf{x} \in \partial\Omega,\ R\big|_{c_1=0} = R\big|_{c_8^8=0} = R\big|_{c_8^1=0} = R\big|_{\ell_1=0} = R\big|_{\ell_8=0} = 0 \quad (1.5)$$

$$\frac{\partial c_1^u}{\partial \mathbf{n}} = \frac{\partial c_8^u}{\partial \mathbf{n}} = 0 \text{ for } \mathbf{x} \in \partial\Omega, \quad (1.6)$$

where $\mathbf{n} = \mathbf{n}(\mathbf{x})$ denotes the unit outward vector to the boundary $\partial\Omega$ and

$$\frac{\partial}{\partial \mathbf{n}} := \mathbf{n} \cdot \nabla_x\ .$$

Remark Let us emphasize that in Eqs. (1.1)-(1.6), the quantities c_1, c_8^8, c_8^1, ℓ_1, ℓ_8 are treated as independent variables **similarly to time** t **and space** $\mathbf{x}$. □

The cell-cell adhesion term is assumed to have the form:

$$\mathbf{K} = \Psi\Big(\nu; dist(\mathbf{x}, \partial\Omega)\Big)\overline{\alpha}_K\, c_1 \int\int_{D_{\rho_0}(\mathbf{x})} \tilde{c}_1\, \sigma(R(t, \mathbf{x}+\mathbf{r}, \tilde{c}_1, \tilde{c}_8^8, \tilde{c}_8^1, \tilde{\ell}_1, \tilde{\ell}_8))\, d\tilde{P}\, \frac{\mathbf{r}}{|\mathbf{r}|}\, d\mathbf{r} \quad (1.7)$$

Here $\overline{\alpha}_K$ is a constant which represents the strength of the adhesion, whereas for some $\nu > 0$ sufficiently small, $\Psi(\nu; \cdot)$ is a smooth, monotone cut-off function such that $\Psi(\nu; y) \equiv 1$ for $y \geq 2\nu$ and $\Psi(\nu; y) \equiv 0$ for $y \leq \nu$. For example, we can take

$$\Psi(\nu; y) := \begin{cases} 0 & y \in (0, \nu] \\ \dfrac{\Psi_*(y-\nu)}{\Psi_*(y-\nu) + \Psi_*(2\nu - y)} & y \in (\nu, 2\nu) \\ 1 & y \geq 2\nu\,, \end{cases} \quad (1.8)$$

where

$$\Psi_*(s) = \begin{cases} e^{-\frac{1}{s}}, & s > 0 \\ 0, & s \leq 0\,. \end{cases}$$

The function $\sigma(R)$ describes the dependence of the adhesion forces on the cell density.

We concentrate here only on showing the structure of the proposed equations. The precise expressions of the terms entering the above system can be found in [16].

Model modifications

As we noted above, the independent variables of system (1.1)-(1.2)-(1.3) are $t, \mathbf{x}, c_1, c_8^8, c_8^1, \ell_1$ and ℓ_8. In [16], using time scale separation, a simpler set of equations based on the assumption of fast receptor binding and unbinding has been proposed.

Let T_1 denote the total concentration of CG-1A receptors (whether unbound or bound to CG-1A or CG-8), i.e.

$$T_1 = c_1 + c_8^1 + \ell_1. \tag{1.9}$$

Similarly, the total concentration of CG-8 receptor can be defined as:

$$T_8 = c_8^8 + \ell_8. \tag{1.10}$$

Under the assumption that the process of 'galectin binding' is very fast, we obtain (after non-dimensionalization procedure) the following system of equations presented in [16]:

$$\frac{\partial R}{\partial t} = d_R \nabla^2 R - \nabla \cdot (R\,\mathbf{K}(R)) - \frac{\partial}{\partial T_1}\left(\widetilde{\gamma}(c_1^u, c_8^u, T_1)\, R\right) - \frac{\partial}{\partial T_8}\left(\widetilde{\delta}(c_8^u, T_8)\, R\right) \tag{1.11}$$

$$\frac{\partial c_1^u}{\partial t} = \nabla^2 c_1^u + \widetilde{\nu}\int_0^\infty\int_0^\infty c_8^8\, R\, dT_1\, dT_8 - c_1^u \tag{1.12}$$

$$\frac{\partial c_8^u}{\partial t} = \nabla^2 c_8^u + \widetilde{\mu}\int_0^\infty\int_0^\infty c_1\, R\, dT_1\, dT_8 - \widetilde{\pi}_8\, c_8^u \tag{1.13}$$

with

$$c_8^8 = c_8^8(t, \mathbf{x}, T_8) = \frac{c_8^u T_8}{1 + c_8^u}, \quad c_1 = c_1(t, \mathbf{x}, T_1) = \frac{c_1^u T_1}{1 + f c_8^u + c_1^u} \tag{1.14}$$

$$\widetilde{\gamma}(c_1^u, c_8^u, T_1) = \left(\frac{2c_1^u}{\frac{c_1^u T_1}{c_1^u + f c_8^u + 1} + \widetilde{c}_1} - \widetilde{\gamma}_2\right)\frac{T_1}{c_1^u + f c_8^u + 1}, \quad \widetilde{\delta}(c_8^u, T_8) = 1 - \widetilde{\delta}_2 \frac{T_8}{1 + c_8^u} \tag{1.15}$$

$$\mathbf{K}(t, \mathbf{x}, T_1, R(t;\cdot)) =$$

$$\Psi\Big(\delta; dist(\mathbf{x}, \partial\Omega)\Big)\widetilde{\alpha}_K\, c_1(t, \mathbf{x}, T_1)\int_0^\infty\int_0^\infty\int_{D_{r_0}(\mathbf{x})} c_1(t, \mathbf{s}, \tilde{T}_1)\widetilde{\sigma}(R(t, \mathbf{s}, \tilde{T}_1, \tilde{T}_8))\,\frac{\mathbf{s}}{|\mathbf{s}|}\, ds\, d\tilde{T}_1\, d\tilde{T}_8 \tag{1.16}$$

Here one can either use a linear $\widetilde{\sigma}(R) = R$ or logistic form for $\widetilde{\sigma}$ in the expression for the adhesion flux

$$\tilde{\sigma}(R) = \eta_\sigma \max\left(1 - \frac{1}{\widetilde{R}_m}\int_0^\infty\int_0^\infty R\, dT_1\, dT_8, 0\right), \tag{1.17}$$

where η_σ and $\widetilde{R}_m$ are positive constants. According to (1.5), the following boundary conditions hold:

$$\frac{\partial R}{\partial \mathbf{n}} = 0 \text{ for } \mathbf{x} \in \partial\Omega,\; R\big|_{T_1=0} = R\big|_{T_8=0} = 0. \tag{1.18}$$

System (1.11)-(1.13) was analysed numerically in [16]. It was shown that the system is possible to generate periodic structures.

In system (1.11)-(1.13), the quantity R denotes the concentration of cells at time t and at a given point in $\Omega \times \mathbb{R}^2_{T_1 T_8}$. Hence the spatial concentration of cells at a given point $\mathbf{x} \in \Omega$ should be calculated as an integral over the whole $\mathbb{R}^2_{T_1 T_8}$, in fact over its non-negative quadrant P_{18} of this space. That is to say:

$$R^x(t, \mathbf{x}) = \int_{P_{18}} R(t, \mathbf{x}, T_1, T_8)\, dT_1 dT_8. \tag{1.19}$$

2 Specificity of the system and the objective of the dissertation

As T_1 and T_8 are independent variables, then even for given functions c_1^u and c_8^u, Eq.(1.11) is not parabolic. Due to the form in which T_1 and T_8 enter this equation, we can say that it is of mixed parabolic-hyperbolic type. According to *our* best knowledge, as well as to the opinions of the leading specialists in partial differential equations expressed in private communications, there is no general theory of such equations. Thus we cannot 'a priori' guarantee the existence and uniqueness of solutions even locally in time. The situation is complicated by the presence of the non-local adhesion term. It should be noticed that the simplified system given by Eqs (1.11)-(1.13) inherit qualitatively the same difficulties as the full system (1.1)-(1.3).

The presence of the hyperbolic terms in Eq.(1.11) can be formally justified by means of the continuity equation

$$\frac{\partial \rho}{\partial t} + \nabla_x \cdot (\rho v) = 0$$

applied to the flow in the space (T_1, T_8). Let us start from the continuity equation in the space T_1. Identifying density ρ with R and T_1 with the spatial variable x_1, and v with $\dfrac{\partial T_1}{\partial t}$, we can write the continuity equation in the form:

$$\frac{\partial R}{\partial t} + \frac{\partial\left(R\frac{\partial T_1}{\partial t}\right)}{\partial T_1} = 0.$$

As the speed of the flow in the space T_1, $\dfrac{\partial T_1}{\partial t}$ can be interpreted as the rate of production of T_1. Likewise, in the space (T_1, T_8) we can write the continuity equation in the form:

$$\frac{\partial R}{\partial t} + \nabla_{T_1,T_8} \cdot \left(R\left(\frac{\partial T_1}{\partial t}, \frac{\partial T_8}{\partial t}\right)\right) = 0,$$

where the components of the vector $\left(\dfrac{\partial T_1}{\partial t}, \dfrac{\partial T_8}{\partial t}\right)$ can be interpreted as the rates of production of T_1 and T_8 quantities. The validity of these arguments can be seen by noticing the correspondence of the terms $\dfrac{\partial}{\partial T_1}\left(\widetilde{\gamma}(c_1^u, c_8^u, T_1)\, R\right)$ and $\dfrac{\partial}{\partial T_8}\left(\widetilde{\delta}(c_8^u, T_8)\, R\right)$ in the Eq.(1.11) with the terms in the second line of Eq.(1.1). In Eq.(1.11), these rates are denoted as $\widetilde{\gamma}$ and $\widetilde{\delta}$ and depend additionally on the quantities c_1^u and c_8^u. In a sense, the presence of the hyperbolic like terms is similar as in equations describing population dynamics models.

The objective of this dissertation is to prove at least local in time existence theorems for system (1.11)-(1.13). To be more precise, in our study we will concentrate on further simplified forms of system (1.11)-(1.13). The main simplification consists in the fact that the integral term will be either ignored (as in Part II) or replaced by a local terms depending on R and its gradient ∇R. This approach can be justified by the fact that the existence problem of Eq.(1.11) without the hyperbolic like terms were considered in the papers [9], [10]. Moreover, having the local existence theorems for the equation without the non-local integral terms $\nabla \cdot (R\,\mathbf{K}(R))$, we can study the existence of system (1.11)-(1.13) in its full generality.

The analysis of system (1.11)-(1.13) is divided into two parts, which are distinguished according to the approaches used. In Part II we confine ourselves to a scalar equation, representing the considered system with the non-local integral term replaced by a given function of (t, x, T_1, T_8). Beside to this, to obtain an initial insight, in sections 3-9, we introduce additional simplification consisting in modelling the investigated biological object representing the limb bud by the whole space. (Of note, this kind of approach has been used in the papers [9], [10].) For technical reasons, we also restrict ourselves to the functions $\widetilde{\gamma}$ and $\widetilde{\delta}$ depending *mainly* only on T_1 and T_8 respectively and independent of t. (In sections 4 and 12, we allow the function Γ and B to depend also on t.) The advantage of introducing these simplifying conditions are mainly manifested in the fact that we are able to obtain solutions in explicit form, which can be relatively easy to analyse. In section 11, using section 10, we formulate the existence results in bounded regions. In section 4, we discuss the uniqueness of solutions Eq.(3.1) and its inhomogeneous counterpart. In section 12, we establish natural generalizations of the obtained results to the case of any number of T-variables.

The strong simplifying conditions imposed on equations of system (1.11)-(1.13) are essentially relaxed in the Rothe method approach applied in Part III. In fact, in Part III we analyse system (15.2)-(15.4), which differs from (1.11)-(1.13) only by replacement of the non-local (integral) term by a given function of R and the components of ∇R. For such a system of differential equations, it is possible to prove the existence of solutions to system (15.2)-(15.4) by showing the convergence of the solutions to the systems with discretized time as the time step $\Delta t \to 0$. The precise description of the methods applied in Part III is given in section 15.2 and we will not repeat it here.

Part II

Linearized scalar equation representing system (1.11)–(1.13). The Green's function approach

3 The case of $\tilde{\gamma}$ and $\tilde{\delta}$ independent of x and t

As we mentioned above, due to the presence in Eq.(1.11) of the convective terms with respect to T_1 and T_8, we cannot *a priori* guarantee the existence and uniqueness of solutions to system (1.11)-(1.13) even for small times. To get some preliminary insight, we will consider in this section linear scalar equations, which can be regarded as linearised forms of Eq.(1.11). We start from the simplest equation retaining the parabolic-hyperbolic features of Eq.(1.11), i.e. for Γ and B being linear functions of T_1 and T_8 respectively, but then consider more general cases. In subsection 5 we consider weak asymptotics of solutions to homogeneous equations of the form (3.1) with respect to a scaling parameter λ describing the magnitude of the functions Γ and B (see subsection 5.1, in particular Lemma 5.5), as well as similar weak asymptotics of solutions to non-homogeneous equations of the form (3.55) (see subsection 5.2). Lemma 5.5 can be considered as a partial justification of the reduced system proposed formally in [16] as a radical approximation of system (1.11)-(1.13). These results are rewritten in section 6, where weak formulation of Eq.(3.1) has been considered.

It seems that the **main result** of Part II is the construction of the solution to Eq.(3.1) and its inhomogeneous version (3.55). This solution corresponds to a convolution of the two semigroups. As we mentioned above, to establish this fact, we examined a couple of cases, starting from the simplest possible case and then increasing the generality of the functions Γ and B, but we allowed ourselves to retain these cases in the dissertation. The **second important result** concerns the possibility of arriving at the solution to Eq.(3.55) from a parabolic equation obtained by adding small diffusional terms with respect to T_1 and T_8. To be more precise, in section 9 we state that adding diffusional terms $\varepsilon^2(R_{,T_1T_1} + R_{,T_8T_8})$ does not change the properties of the solutions, which tend in the space of smooth functions to the solutions for $\varepsilon = 0$.

If $\tilde{\gamma}$ and $\tilde{\delta}$ do not depend on c_1^u and c_8^u, i.e. when $\tilde{\gamma}(c_1^u, c_8^u, T_1) = \Gamma(T_1)$, $\tilde{\delta}(c_8^u, T_8) = B(T_8)$ and $K(R) = 0$, then the first equation of system (1.11)-(1.13) becomes separated. Let us suppose additionally, for convenience, that $\Omega \equiv \mathbb{R}^3$. In this case, Eq.(1.11) takes the form

$$\frac{\partial R}{\partial t} = d_R \nabla^2 R - \frac{\partial}{\partial T_1}\left(\Gamma(T_1)\, R\right) - \frac{\partial}{\partial T_8}\left(B(T_8)\, R\right) \qquad (t, \mathbf{x}, (T_1, T_8)) \in (0, T] \times \mathbb{R}^3 \times \mathbb{R}^2_+, \tag{3.1}$$

together with the boundary conditions

$$R(t, \mathbf{x}, T_1, T_8) = 0 \qquad \text{for } \{(t, x, T_1, T_8) : T_1 = 0 \vee T_8 = 0\}.$$

Above and below we use the following denotations of the positive (non-negative) subsets of the real axis and the plane:

$$\mathbb{R}_+ := \{r \in \mathbb{R} :\, r > 0\}, \qquad \overline{\mathbb{R}_+} := \{r \in \mathbb{R} :\, r \geq 0\},$$

and

$$\mathbb{R}^2_+ := \{(r_1, r_8) \in \mathbb{R}^2 :\, r_1 \geq 0,\, r_8 \geq 0\}, \qquad \overline{\mathbb{R}^2_+} := \{(r_1, r_8) \in \mathbb{R}^2 :\, r_1 \geq 0,\, r_8 \geq 0\}. \tag{3.2}$$

Before proceeding, let us formulate an obvious conservation law.

Lemma 3.1. *Let the initial data* $R_0(x, T_1, T_8)$ *satisfy the equality*

$$\int_{\mathbb{R}^3}\int_{\mathbb{R}^2_+} R_0(x, T_1, T_8)dT_1dT_8\, dx = M_0.$$

Suppose that a solution $R : [0, T] \times \mathbb{R}^3 \times \mathbb{R}^2_+$ *to Eq.(3.1) satisfies the conditions* $R(t, x, T_1, T_8) \equiv 0$ *for* $T_1 = 0$ *or* $T_8 = 0$ *and that* $\nabla_x R = o(\|\mathbf{x}\|^{-2})$ *as* $\|\mathbf{x}\| \to \infty$ *and* $R = o((|T_1|+|T_8|)^{-1})$ *as* $|T_1|+|T_8| \to \infty$. *Then for all* $t \in [0, T]$

$$\int_{\mathbb{R}^3}\int_{\mathbb{R}^2_+} R(t, x, T_1, T_8)dT_1dT_8\, dx = M_0.$$

Proof Let us note that The proof follows by considering the improper integrals over the set $\mathbb{R}^3\times\mathbb{R}^2 \ni (x, T_1, T_8)$ of the both sides of Eq.(3.1) using Fubini's and Gauss-Ostrogradskii theorems. In fact, the integration of the left hand side gives

$$\frac{\partial}{\partial t}\int_{\mathbb{R}^3}\int_{\mathbb{R}^2_+} R(t, x, T_1, T_8)dT_1dT_8\, dx,$$

whereas the values of the integrals of the right hand sides over the sets $B^3(0, r) \times \left(B^2(0, r) \cap R^2_+\right)$, where $B^k(0, r)$ denotes a k=dimensional open ball with centre at 0 and the radius r, tend to 0 as $r \to \infty$. □

Similarly to Eq.(1.11), Eq.(3.1) is of mixed type. It is parabolic in the direction of spatial variables $\mathbf{x} = (x_1, x_2, x_3)$ and hyperbolic in the direction (T_1, T_8). To begin with, let us analyse the possible characteristic curves of Eq.(3.1). Our discussion will be based upon [32, chapter 2]. The principal part of the operator

$$P(t, x_1, x_2, x_3, T_1, T_8; D) := -\frac{\partial R}{\partial t} + d_R\nabla^2 R - \frac{\partial}{\partial T_1}\left(\Gamma(T_1)\, R\right) - \frac{\partial}{\partial T_8}\left(B(T_8)\, R\right)$$

(acting on R) is equal to

$$d_R\,\nabla^2 = d_R\left(\left(\frac{\partial}{\partial x_1}\right)^2 + \left(\frac{\partial}{\partial x_2}\right)^2 + \left(\frac{\partial}{\partial x_3}\right)^2\right).$$

Let, at a given point $(t, x_1, x_2, x_3, T_1, T_8) \in [0, T] \times \mathbb{R}^3 \times \mathbb{R}^2$,

$$\sigma(t, x_1, x_2, x_3, T_1, T_8) = (\sigma_t, \sigma_{x_1}, \sigma_{x_2}, \sigma_{x_3}, \sigma_{T_1}, \sigma_{T_8})(t, x_1, x_2, x_3, T_1, T_8), \qquad \sigma^2 = 1,$$

denote a unit vector orthogonal to a characteristic surface of Eq.(3.1), i.e. a vector tangent locally to a characteristic curve. The characteristic equation for the operator P reads

$$d_R\,(\sigma^2_{x_1} + \sigma^2_{x_2} + \sigma^2_{x_3}) = 0,$$

which implies that $\sigma_{x_k} = 0$, $k = 1, 2, 3$. Thus along each of the characteristic curves the tangent vector has the form $(\sigma_t, 0, 0, 0, \sigma_{T_1}, \sigma_{T_8})$). This implies that $\mathbf{x} = const$, hence by Eq.(3.1) we conclude that, **on each of the characteristic curves**, the equation

$$\frac{\partial R}{\partial t} = -\frac{\partial}{\partial T_1}\left(\Gamma(T_1)\, R\right) - \frac{\partial}{\partial T_8}\left(B(T_8)\, R\right) \tag{3.3}$$

is satisfied. It follows that the characteristic curve assigned to a point $(\mathbf{x}, T_{10}, T_{80}) \in \mathbb{R}^3\times\mathbb{R}^2$ is given by the mapping:

$$[0, T] \ni t \mapsto (t, \mathbf{x}, T_1(T_{10}, t), T_8(T_{80}, t)), \tag{3.4}$$

where the functions $(T_1(T_{10}, t), T_8(T_{80}, t))$ are solutions to the initial ode problem:

$$\frac{dT_1}{dt}(t) = \Gamma(T_1), \quad \frac{dT_8}{dt}(t) = B(T_8), \quad T_1(0) = T_{10},\ T_8(0) = T_{80}. \tag{3.5}$$

As the functions $\Gamma(\cdot)$ and $B(\cdot)$ are independent of $\mathbf{x}$, then the time courses of the functions $T_1(t)$ and $T_8(t)$ are also independent of $\mathbf{x}$.

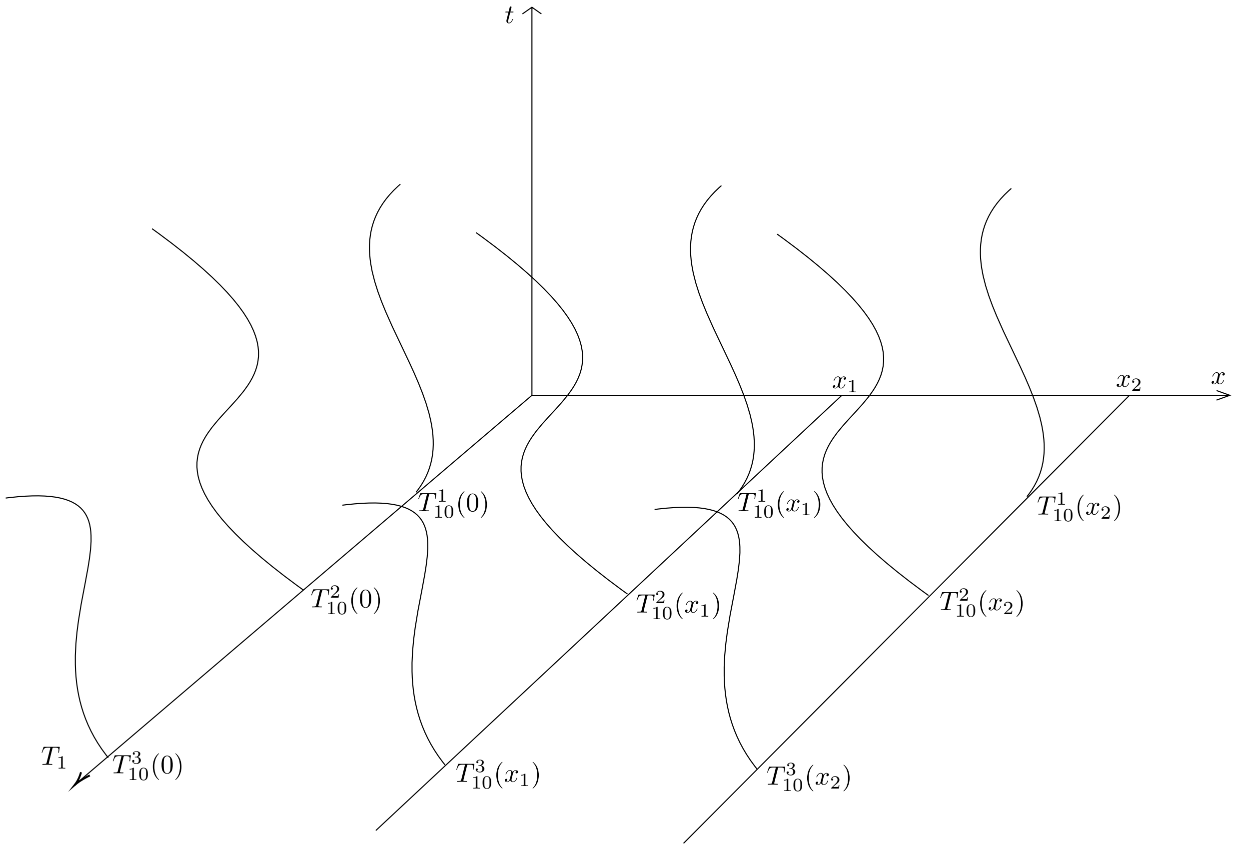

Figure 1: The schematic display of characteristic curves determined by system (3.5). To be able to illustrate properly the features of the problem, we confine ourselves to the case $x \in \mathbb{R}^1$ and consider only T_1-variable instead of (T_1, T_8). Each curve lies in the plane $x = const.$ In the picture, there are three groups of curves lying in the planes $x = 0$, $x = x_1$ and $x = x_2$. In the case shown, the characteristic curves depend only on the initial value for $t = 0$ and do not depend on x, i.e. the function Γ depends only on T_1 and not on x. In general, the characteristic curves depend also on the point $\mathbf{x}$ as in Fig. 2.

Remark From what we said above, it follows that we can expect two different ways of information transfer connected with the initial data. Thus, in the $\mathbf{x}$-space, the initial distribution is spread by diffusion, whereas in the space (T_1, T_8) it can be transduced along the projection of the characteristic curves onto the (T_1, T_8)-space. Motivated by this reasoning, we will construct a solution to an initial value problem corresponding to Eq.(3.1). This solution is composed of the heat kernel in $\mathbb{R}^3$ and the curves defined in (3.4). It is given by equality (3.52) in Lemma 3.8 or equality (3.27) in the case of linear Γ and B. □

Remark Although, from the biological point of view, T_1 and T_8 can attain only non-negative values, so in principle Γ and B are defined only on the non-negative half-lines, for technical reasons, we will treat the functions Γ and B as defined on the whole real line. This extension can be done, if these functions are sufficiently smooth. *For simplicity the extended functions, will be denoted in the same way.* □

Assumption 3.2. *Assume that $\Gamma(T_1)$ and $B(T_8)$ are of C^{k+1} class, $k \geq 2$, and that for all (T_{10}, T_{80}) system (3.5) has a unique C^{k+1} solution $(T_1(\cdot), T_8(\cdot))$ satisfying the initial conditions $T_1(0) = T_{10}$, $T_8(0) = T_{80}$, defined for all $t \geq 0$. Suppose that there exists a positive number ρ_{18}, such that*

$$\Gamma(T_1) \geq 0 \quad \textit{for } |T_1| \leq \rho_{18}$$

$$B(T_8) \geq 0 \quad \textit{for } |T_8| \leq \rho_{18}.$$

Remark Below, for simplicity, the symbol $\mathbf{x}$ will be reduced to x. □

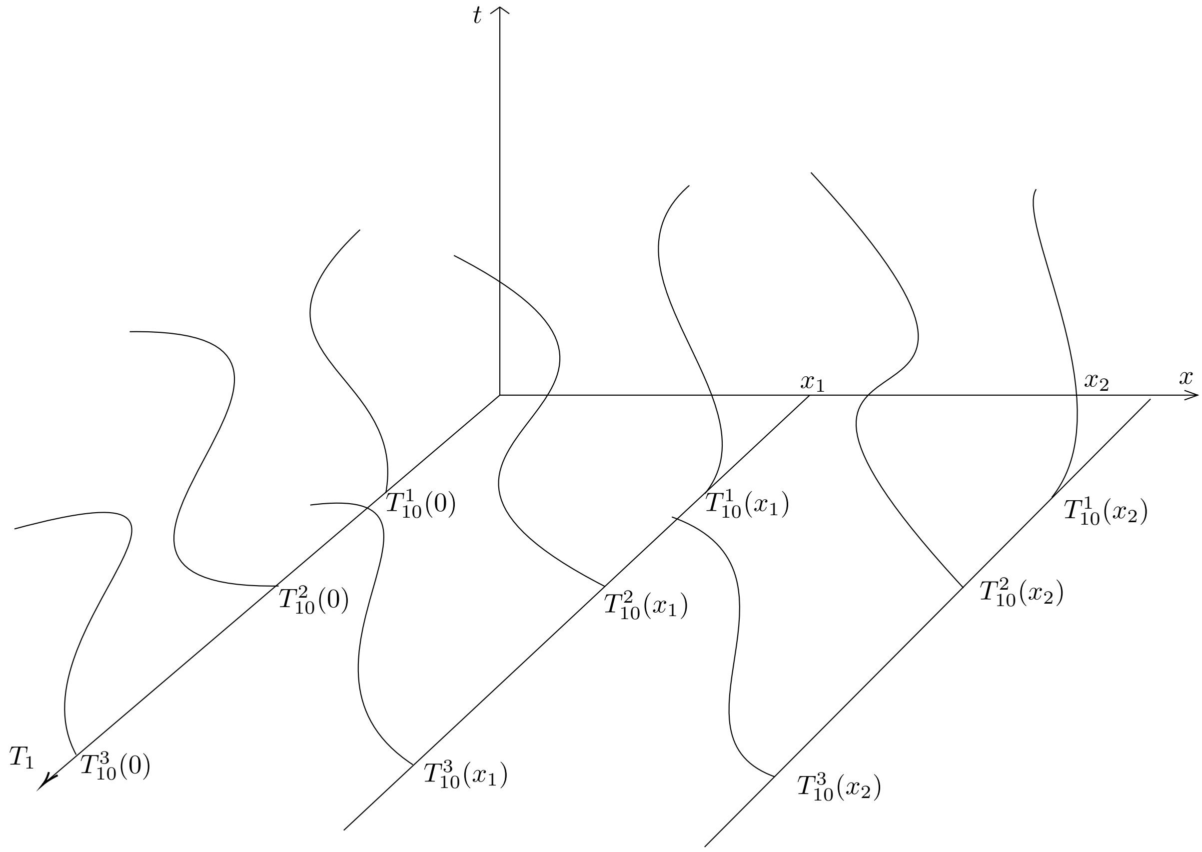

Figure 2: The schematic display of characteristic curves determined by system (3.5). Each curve lies in the plane $x = const$. In the picture, there are three groups of curves lying in the planes $x = 0$, $x = x_1$ and $x = x_2$. In contrast to Fig. 1, the characteristic curves depend also on x. In this case, the function Γ depends not only on T_1 but also on x.

Assumption 3.3. *Assume that for all $x \in \overline{\Omega}$, $R_0(x, T_1, T_8) \not\equiv 0$ only for (T_1, T_8) from some open precompact set in $\mathbb{R}^2_+$.*

The idea applied in this approach is to construct the solution to the boundary initial value problem corresponding to Eq.(3.1) by means of the Green's function of the parabolic part of this equation and the reversed in time solutions to system (3.5).

We have:

$$\frac{dT_1}{dt} = \Gamma(T_1), \quad T_1(0) = T_{10}. \tag{3.6}$$

hence

$$\int_{T_{10}}^{T_1} (\Gamma(s))^{-1} ds = t. \tag{3.7}$$

Thus for $Int(y) := \displaystyle\int_{(\cdot)}^{y} (\Gamma(s))^{-1} ds$, we obtain

$$Int(T_1) - Int(T_{10}) = t.$$

According to Assumption 3.2, given T_{10} we can uniquely determine the value of $T_1(T_{10}, t)$, for any $t \geq 0$. On the other hand, fixing T_1 and $t \geq 0$, we can ask about the initial condition T_{10} such that the value of solution to the initial problem (3.6) at time t is equal to T_1. This initial condition will be denoted below by $T_{10}(T_1, t)$.

It follows by differentiation of (3.7) with respect to t, treating T_1 as given, that $T_{10}(T_1, t)$ is a solution to the initial value problem:

$$\frac{\partial T_{10}}{\partial t} \cdot (\Gamma(T_{10}))^{-1} = -1, \quad T_{10}(T_1, 0) = T_1$$

so

$$\frac{\partial T_{10}}{\partial t} = -\Gamma(T_{10}), \quad T_{10}(T_1, 0) = T_1. \tag{3.8}$$

whereas, for fixed $t \geq 0$, by differentiation of (3.7) with respect to T_1 we obtain:

$$\frac{\partial T_{10}}{\partial T_1} = \frac{\Gamma(T_1)^{-1}}{\Gamma(T_{10})^{-1}} = \frac{\Gamma(T_{10})}{\Gamma(T_1)}, \tag{3.9}$$

which should be written in a detailed form as

$$\frac{\partial T_{10}}{\partial T_1}(t) = \frac{\Gamma(T_1)^{-1}}{\Gamma(T_{10}(T_1,t))^{-1}} = \frac{\Gamma(T_{10}(T_1,t))}{\Gamma(T_1)}. \tag{3.10}$$

In the similar way, we can prove that

$$\frac{\partial T_{80}}{\partial t} = -B(T_{80}), \quad T_{80}(T_8, 0) = T_8. \tag{3.11}$$

and

$$\frac{\partial T_{80}}{\partial T_8}(t) = \frac{B(T_1)^{-1}}{B(T_{80}(T_8,t))^{-1}} = \frac{B(T_{80}(T_8,t))}{B(T_8)}. \tag{3.12}$$

Remark For completeness we derived relation (3.9) explicitly, but it is a special case of [18, Corollary 3.1, Chapter V], according to which

$$\frac{\partial T_1}{\partial T_{10}}(t) = \exp\Big(\int_0^t \frac{\partial \Gamma(T_1(T_{10},s))}{\partial T_1} ds\Big) = \exp\Big(\int_0^t \frac{\partial \Gamma(T_1(T_{10},s))}{\partial T_1}\Big[\Gamma(T_1(T_{10},s)\Big]^{-1} dT_1\Big)$$

hence at $T_1 = T_1(T_{10}, t)$

$$\frac{\partial T_{10}}{\partial T_1}(t) = \exp\Big(-\int_0^t \frac{\partial \Gamma(T_1(T_{10},s))}{\partial T_1} ds\Big) = \exp\Big(-\int_0^t \frac{\partial \Gamma(T_1(T_{10},s))}{\partial T_1}\Big[\Gamma(T_1(T_{10},s)\Big]^{-1} dT_1\Big).$$

On the other hand, using [18, Corollary 3.1, Chapter V] to Eq.(3.9), we obtain obvious equivalent expressions:

$$\frac{\partial T_{10}}{\partial T_1}(t) = \exp\Big(-\int_0^t \frac{\partial \Gamma(T_{10}(T_1,\sigma))}{\partial T_{10}} d\sigma\Big) = \exp\Big(-\int_0^t \frac{\partial \Gamma(T_{10}(T_1,\sigma))}{\partial T_{10}}\Big[-\Gamma(T_{10}(T_1,\sigma))\Big]^{-1} dT_{10}\Big)$$

and at $T_{10} = T_{10}(T_1, t)$

$$\frac{\partial T_1}{\partial T_{10}}(t) = \exp\Big(\int_0^t \frac{\partial \Gamma(T_{10}(T_1,\sigma))}{\partial T_{10}} d\sigma\Big) = \exp\Big(\int_0^t \frac{\partial \Gamma(T_{10}(T_1,\sigma))}{\partial T_{10}}\Big[-\Gamma(T_{10}(T_1,\sigma))\Big]^{-1} dT_{10}\Big).$$

These identities hold also for the function Γ depending on T_1 and t. To obtain (3.9) (in the case of Γ independent explicitly on t), we use the change of variables $ds = dT\,(\Gamma(T(T_{10}, s)))^{-1}$, by which

$$\int_0^t \frac{\partial \Gamma(T_1(T_{10},s))}{\partial T_1} ds = \int_{T_{10}}^{T_1} \frac{\partial\, log(\Gamma(T))}{\partial T} dT.$$

□

Similar remarks concerns the relation (3.12).

Having the family of curves determined by system (3.6), we can define a candidate for a solution to Eq.(3.1):

$$R(t, x, T_1) = \int_{\mathbb{R}^3} G_\Gamma(t, x; 0, \xi) R_0(\xi, T_{10}(T_1, t)) d\xi \tag{3.13}$$

where $R_0(\cdot,\cdot,\cdot)$ is the initial concentration of the cells,

$$G_\Gamma = \exp\Big(- \int_0^t \frac{\partial \Gamma}{\partial T_1}\Big(T_1(T_{10},\tau)\Big)\, d\tau\Big) \cdot G_0(t,x;0,\xi), \tag{3.14}$$

or, equivalently:

$$G_\Gamma = \exp\Big(\int_0^t \frac{\partial \Gamma}{\partial T_{10}}\Big(T_{10}(T_1,\tau)\Big)\, d\tau\Big) \cdot G_0(t,x;0,\xi),$$

and

$$G_0(t,x;\tau,\xi) = \frac{1}{(4\pi d_R(t-\tau))^{3/2}}\, e^{-\dfrac{|x-\xi|^2}{4d_R(t-\tau)}} \tag{3.15}$$

is the Green's function for the heat equation in $\mathbb{R}^3$.

$$\frac{\partial R}{\partial t} = d_R \nabla^2 R \tag{3.16}$$

In particular, for $t \geq \tau \geq 0$, it satisfies the equation

$$\frac{\partial G}{\partial t} - d_R \nabla^2 G = \delta(t-\tau)\delta(x-\xi). \tag{3.17}$$

Below, we will often use use the following properties of the fundamental solution for the heat equations in $\mathbb{R}^n$.

Lemma 3.4. *Let $n \geq 1$, $\tau \geq 0$ and*

$$G_0^n(t,x;\tau,\xi) = \frac{1}{(4\pi d_H(t-\tau))^{n/2}}\, e^{-\dfrac{|x-\xi|^2}{4D_H(t-\tau)}}. \tag{3.18}$$

Then the following statements hold:

1. *For any $t > \tau$, $x \in \mathbb{R}^n$:*

$$\int_{\mathbb{R}^n} G_0^n(t,x;\tau,\xi)d\xi = 1$$

2. *If $g(\cdot) \in C^0(\mathbb{R}^n) \cap L^\infty(\mathbb{R}^n)$, then, for all $x \in \mathbb{R}^n$:*

$$\lim_{t\to\tau} \int_{\mathbb{R}^n} G_0^n(t,x;\tau,\xi)g(\xi)d\xi = g(x).$$

3. *If $g(\cdot) \in C^0(\mathbb{R}^n) \cap L^\infty(\mathbb{R}^n)$, then, for all $t > \tau$, the integral*

$$\int_{\mathbb{R}^n} G_0^n(t,x;\tau,\xi)g(\xi)d\xi$$

is a $C^{1,2}$ solution to the homogeneous heat equation

$$\frac{\partial H}{\partial t} = d_H \nabla^2 H$$

with the initial condition $H(\tau,x) = g(x)$.

4. *If $f \in C^{\alpha/2,\alpha}_{t,x}([0,T]\times\mathbb{R}^n) \cap L^\infty_x(\mathbb{R}^n)$, uniformly with respect to $t \in [0,T]$, then the function*

$$H(t,x) = \int_\tau^t \Big(\int_{\mathbb{R}^n} G_0^n(t,x;\sigma,\xi) f(\sigma,\xi)d\xi\Big) d\sigma.$$

is a $C^{1,2}$ solution to the inhomogeneous heat equation

$$\frac{\partial H}{\partial t} = d_H \nabla^2 H + f$$

with the initial condition $H(\tau, x) = 0$.

Proof Points 2 and 3 are stated in Theorem 1 of Section 2.3.1 in [13], whereas point 1 in the preceding lemma. Point 4 is stated in Theorem 2 of Section 2.3.1 in [13]. □

In the simplest possible case, let us assume that

$$\Gamma(T_1) = sT_1 + s_0. \tag{3.19}$$

Then

$$T_1(T_{10}, t) = (T_{10} + \frac{s_0}{s})e^{st} - \frac{s_0}{s}, \quad T_{10}(T_1, t) = (T_1 + \frac{s_0}{s})e^{-st} - \frac{s_0}{s} \tag{3.20}$$

and it is seen that the ratio

$$\frac{\Gamma(T_{10}(T_1, t))}{\Gamma(T_1)} = e^{-st}, \tag{3.21}$$

thus *does not depend on* T_1.

According to the assumed linearity of the function $\Gamma(\cdot)$, the equation

$$\frac{dT_1}{dt} = \Gamma(T_1),$$

has a stable positive singular point $(-\frac{s_0}{s})$, if and only if $s < 0$ and $s_0 > 0$, whereas it has an unstable positive singular point if and only if $s > 0$ and $s_0 < 0$. □

As Γ does not depend on x (and t), then

$$\exp\Big(- \int_0^t \frac{\partial \Gamma}{\partial T_1}\Big(T_1(T_{10}, \tau)\Big)\, d\tau\Big) = \exp(-st)$$

so

$$G_\Gamma = \exp(-st) \cdot G_0(t, x; 0, \xi),$$

Thus, in this case, (3.13) takes the form:

$$R(t, x, T_1) = \int_{\mathbb{R}^3} \exp(-st) \cdot G_0(t, x; 0, \xi) R_0(\xi, T_{10}(T_1, t)) d\xi\,. \tag{3.22}$$

To show that this function satisfies Eq.(3.1), let us note that

$$R \cdot \frac{\partial \Gamma}{\partial T_1}(T_1) = R \cdot s$$

and by (3.9)

$$\frac{\partial R}{\partial T_1} \cdot \Gamma(T_1) = \Big(\int_{\mathbb{R}^3} G_\Gamma(t, x; 0, \xi) R_{0,T_{10}}(\xi, T_{10}(T_1, t)) d\xi\Big) \cdot \frac{\partial T_{10}}{\partial T_1}(T_1, t) \cdot \Gamma(T_1) =$$
$$\Big(\int_{\mathbb{R}^3} G_\Gamma(t, x; 0, \xi) R_{0,T_{10}}(\xi, T_{10}(T_1, t)) d\xi\Big) \cdot \frac{\Gamma(T_{10}(T_1, t))}{\Gamma(T_1)} \cdot \Gamma(T_1) =$$
$$\frac{\partial}{\partial T_{10}} \Big(\int_{\mathbb{R}^3} G_\Gamma(t, x; 0, \xi) R_0(\xi, T_{10}(T_1, t)) d\xi\Big) \cdot \Gamma(T_{10}(T_1, t)).$$

In view of the last equality, calculating the time derivative of the function R defined by (3.22), we obtain

$$\frac{\partial R}{\partial t} = d_R\nabla^2 R - sR + \frac{dT_{10}}{dt}\frac{\partial}{\partial T_{10}}\int_{\mathbb{R}^2} G_\Gamma(t,x;0,\xi)R_0(\xi,T_{10}(T_1,t))d\xi =$$
$$d_R\nabla^2 R - sR - \Gamma(T_{10}(T_1,t))\frac{\partial T_1}{\partial T_{10}}\frac{\partial}{\partial T_1}\int_{\mathbb{R}^2} G_\Gamma(t,x;0,\xi)R_0(\xi,T_{10}(T_1,t))d\xi =$$
$$d_R\nabla^2 R - R\frac{\partial\Gamma(T_1)}{\partial T_1} - \Gamma(T_1)\frac{\partial R}{\partial T_1}.$$

We have thus shown that the function given by (3.22) satisfies Eq.(3.1).

This construction can be generalized to the case of nonzero linear function B. Let us take:

$$B = rT_8 + r_0. \tag{3.23}$$

Then

$$T_8 = (T_{80} + \frac{r_0}{r})e^{rt} - \frac{r_0}{r}, \quad T_{80} = (T_8 + \frac{r_0}{r})e^{-rt} - \frac{r_0}{r}, \tag{3.24}$$

$$\frac{dT_{80}}{dt} = -B(T_{80}), \tag{3.25}$$

and

$$\frac{\partial B}{\partial T_8} = r,$$

so *does not depend on* T_8. Also, the ratio

$$\frac{B(T_{80}(T_8,t))}{B(T_8)} = e^{-rt}, \tag{3.26}$$

thus does not depend on T_8. In this way, repeating the arguments concerning the function Γ, we obtain

$$R(t,x,T_1,T_8) = \int_{\mathbb{R}^3} G_{\Gamma B}(t,x;0,\xi)R_0(\xi,T_{10}(T_1,t),T_{80}(T_8,t))d\xi\,. \tag{3.27}$$

with

$$G_{\Gamma B} = \exp(-(s+r)t)\cdot G_0(t,x;0,\xi). \tag{3.28}$$

The function $G_{\Gamma B}$ is a solution of the equation

$$\frac{\partial G}{\partial t} - d_R\nabla^2 G + (s+r)G = \delta(t)\delta(x-\xi). \tag{3.29}$$

Let us note that in the considered linear case, $G_{\Gamma B}$ depends neither on T_1 nor on T_8. For R defined by (3.27), we have, by means of (3.8) and (3.11)

$$\frac{\partial R}{\partial t} = d_R\nabla^2 R - \Big(\Gamma'(T_1) + B'(T_8)\Big)R - \frac{\partial R}{\partial T_1}\cdot\Gamma(T_1(t)) - \frac{\partial R}{\partial T_8}\cdot B(T_8(t)),$$

where

$$\Gamma'(T_1) := \frac{\partial\Gamma(y)}{\partial y}\Big|_{y=T_1} = s, \quad B'(T_8) := \frac{\partial B(y)}{\partial y}\Big|_{y=T_8} = r.$$

As

$$\frac{\partial R}{\partial T_1}\cdot\Gamma(T_1) = \frac{\partial}{\partial T_{10}}\left(\int_{\mathbb{R}^3} G_{\Gamma B}(t,x;0,\xi)R_0(\xi,T_{10}(T_1,t),T_{80}(T_8,t))d\xi\right)\cdot\frac{\Gamma(T_{10}(T_1,t))}{\Gamma(T_1)}\Gamma(T_1).$$

and

$$\frac{\partial R}{\partial T_8}\cdot B(T_8) = \frac{\partial}{\partial T_{80}}\left(\int_{\mathbb{R}^3} G_{\Gamma B}(t,x;0,\xi)R_0(\xi,T_{10}(T_1,t),T_{80}(T_8,t))d\xi\right)\cdot B(T_8)\frac{B(T_{80}(T_8,t))}{B(T_8)}$$

we conclude that R defined by (3.27) satisfies Eq.(3.1).

Before proceeding to nonlinear Γ and B, let us consider a non-homogeneous case. By considering the function $\exp\left((s+r)t\right)u(t,x)$ and using point 4 of Lemma 3.4 with $\tau=0$, we conclude that the solution to the initial value problem

$$\frac{\partial u}{\partial t} = d_R \nabla^2 u - su - ru + f(t,x), \quad u(0,x)=0, \tag{3.30}$$

has the form

$$u(t,x) = \int_0^t \Big(\int_{\mathbb{R}^3} G_{\Gamma B}(t,x;\tau,\xi) f(\tau,\xi) d\xi \Big) d\tau. \tag{3.31}$$

Note that u given by (3.31) does not depend on T_1, T_8 hence $\frac{\partial u}{\partial T_1} \equiv 0$, $\frac{\partial u}{\partial T_8} \equiv 0$. It follows that

$$\frac{\partial R}{\partial T_1}\Gamma(T_1) + \frac{\partial R}{\partial T_8}B(T_8) = \frac{\partial (R+u)}{\partial T_1}\Gamma(T_1) + \frac{\partial (R+u)}{\partial T_8}B(T_8).$$

In consequence, $R+u$, where R is given by (3.27) and u by (3.31) satisfies the equation

$$\frac{\partial Y}{\partial t} = d_R \nabla^2 Y - \frac{\partial}{\partial T_1}\left(\Gamma(T_1)\,Y\right) - \frac{\partial}{\partial T_8}\left(B(T_8)\,Y\right) + f(t,x) \tag{3.32}$$

with the initial condition $Y(0,x,T_1,T_8) = R_0(0,x,T_1,T_8)$.

Remark Note that fixing T_{10} we have

$$\exp\Big(- \int_0^t \frac{\partial \Gamma}{\partial T_1}\Big(T_1(T_{10},\tau)\Big)\, d\tau \Big) = \frac{\Gamma(T_{10}(T_1,t))}{\Gamma(T_1)}. \tag{3.33}$$

This identity can be proved by the change of integration variables $\tau \mapsto T_1(T_{10},\tau)$ with $dT_1 = \Gamma(T_1)d\tau$, namely

$$\begin{gathered}\int_0^t \frac{\partial \Gamma}{\partial T_1}\Big(T_1(T_{10},\tau)\Big)\, d\tau = \int_{T_{10}}^{T_1(T_{10},t)} \frac{\partial \Gamma}{\partial T_1}\Big(T_1\Big)\Gamma(T_1)^{-1}\, dT_1 = \\ \int_{T_{10}}^{T_1(T_{10},t)} \frac{\partial}{\partial T_1} log\Big(\Gamma(T_1)\Big)\, dT_1 = log\Big(\frac{\Gamma(T_1(T_{10},t))}{\Gamma(T_1(T_{10},0))}\Big) = log\Big(\frac{\Gamma(T_1)}{\Gamma(T_{10}(T_1,t))}\Big)\end{gathered} \tag{3.34}$$

which gives (3.33). Likewise, for fixed T_1, by changing of integration variables $\tau \mapsto T_{10}(T_1,\tau)$ we have

$$\begin{gathered}\int_0^t \frac{\partial \Gamma}{\partial T_{10}}\Big(T_{10}(T_1,\tau)\Big)d\tau = -\int_{T_1}^{T_{10}(T_1,t)} \frac{\partial}{\partial T_{10}}\Gamma(T_{10})\Big(\frac{dT_{10}}{d\tau}\Big)^{-1} dT_{10} = \\ -\int_{T_1}^{T_{10}(T_1,t)} (\Gamma(T_{10}))^{-1}\frac{\partial}{\partial T_{10}}\Gamma(T_{10})\; dT_{10} = -\int_{T_1}^{T_{10}(T_1,t)} \frac{\partial}{\partial T_{10}}\log(\Gamma(T_{10}))\, dT_{10} = \\ -\log\Big(\frac{\Gamma(T_{10}(T_1,t))}{\Gamma(T_1)}\Big) = \log\Big(\frac{\Gamma(T_1)}{\Gamma(T_{10}(T_1,t))}\Big)\end{gathered}$$

hence

$$\exp\Big(- \int_0^t \frac{\partial \Gamma}{\partial T_{10}}\Big(T_{10}(T_1,\tau)\Big)\, d\tau \Big) = \frac{\Gamma(T_{10}(T_1,t))}{\Gamma(T_1)}. \tag{3.35}$$

By using the second equality in (3.20), we check that for $\Gamma(T_1) = sT_1 + s_0$,

$$\frac{\Gamma(T_{10}(T_1,t))}{\Gamma(T_1)} = \exp(-st) \tag{3.36}$$

in agreement with (3.21). Similarly,

$$\exp\Big(- \int_0^t \frac{\partial B}{\partial T_8}\Big(T_8(T_{80},\tau)\Big)\, d\tau \Big) = \frac{B(T_{80}(T_8,t))}{B(T_8)} = \exp\Big(\int_0^t \frac{\partial B}{\partial T_{80}}\Big(T_{80}(T_8,\tau)\Big)\, d\tau \Big). \tag{3.37}$$

Equalities (3.33),(3.35) and (3.37) will be confirmed by the form of the right hand side of (3.52) in Lemma 3.8. □

Let us consider the general form of Γ and B. To this end, let us first set:

$$S = \Gamma B R. \tag{3.38}$$

Then Eq.(3.1) changes to

$$\frac{\partial S}{\partial t} = d_R \nabla^2 S - \Gamma(T_1)\frac{\partial S}{\partial T_1} - B(T_8)\frac{\partial S}{\partial T_8}. \tag{3.39}$$

It seen that the (t, T_1, T_8)-projections of characteristics of the hyperbolic part of Eq.(3.39) are still determined by Eqs (3.5). Hence, as it can be easily checked, the solution to the initial value problem for Eq. (3.39) is given by the formula

$$S(t, x, T_1, T_8) = \int_{\mathbb{R}^3} G_0(t, x; 0, \xi) S_0(\xi, T_{10}(T_1, t), T_{80}(T_8, t)) d\xi \,. \tag{3.40}$$

Instead of proving it explicitly, we will prove in Lemma 3.8 that the function R corresponding to the solution given by (3.52) via the transformation (3.38) satisfies Eq.(3.1). To do this, we need the following auxiliary results.

Lemma 3.5. *Let Assumption 3.2 be satisfied. Suppose that the function* $\Gamma(\cdot) : \mathbb{R} \to \mathbb{R}$ *is* $(k+1)$*-times continuously differentiable. Let* $k_1 \geq 0$ *and* $k_2 \geq 0$*. Then for all* $T_1 \geq 0$ *and for all* $t > 0$*, the function*

$$\mathcal{K}_1(T_1; t) := \frac{\Gamma(T_{10}(T_1, t))}{\Gamma(T_1)} \tag{3.41}$$

is continuously differentiable k_1 *and* k_2 *times with respect to* t *and* T_1 *respectively, iff* $k_1 + s(k_2)(k_2 + 1) \leq k + 1$*, where* $s(k_2) = 1$*, if* $k_2 \geq 1$ *and* $s(0) = 0$*.*

Proof By (3.9) we have

$$\frac{\Gamma(T_{10}(T_1, t))}{\Gamma(T_1)} = \frac{\partial T_{10}}{\partial T_1} \tag{3.42}$$

and

$$\frac{d}{d\tau}\Big(\frac{\partial T_{10}}{\partial T_1}\Big) = \frac{\partial}{\partial T_1}\Big(\frac{dT_{10}}{d\tau}\Big) = -\frac{\partial}{\partial T_1}\Gamma(T_{10}(T_1, \tau)) = -\Big(\frac{\partial}{\partial T_{10}}\Gamma(T_{10}(T_1, \tau))\Big)\Big(\frac{\partial T_{10}}{\partial T_1}\Big) \tag{3.43}$$

Thus in accordance with Remark after (3.9)

$$L_0(T_1, t) := \frac{\partial T_{10}}{\partial T_1}(t) = \exp(-\int_0^t \frac{\partial \Gamma(T_{10}(T_1, \tau))}{\partial T_{10}} d\tau) \tag{3.44}$$

because for $t = 0$ and $\Gamma(T_1) \neq 0$, we have

$$\frac{\partial T_{10}}{\partial T_1}(0) = \Gamma(T_{10}(T_1, 0))\Gamma(T_1)^{-1}\Big|_{T_{10}=T_1} = 1. \tag{3.45}$$

Next, if T_{1*} is such that $\Gamma(T_{1*}) = 0$, then in the representation (3.44), the limit $T_1 \to T_{1*}$ exists for all $t \geq 0$ and has the form

$$\exp\Big(-\int_0^t \frac{\partial \Gamma(T_1)}{\partial T_1} d\tau\Big)\Big|_{T_1 = T_{1*}}$$

which in the case of $\Gamma(T_1) = sT_1 + s_0$ is equal to $\exp(-st)$ in accordance with (3.21). (Let us note that applying de l'Hospital rule to find the limit as $T_1 \to T_{1*}$ of $L_0(T_1, t)$ gives no answer, because we obtain the relation $L_0(T_{1*}, t) = 1 \cdot L_0(T_{1*}, t)$.) Thus, by means of $L_0(T_1, t)$, the function (3.41) can be well determined for all T_1 in the considered region.

Now, we can show the differentiability of the ratio $\dfrac{\Gamma(T_{10}(T_1, t))}{\Gamma(T_1)}$ for finite $t \geq 0$. We have, according to (3.44),

$$L_1(T_1,t) := \frac{\partial}{\partial T_1}\mathcal{K}_1(T_1;t) = \frac{\partial}{\partial T_1}L_0(T_1,t) = \frac{\partial}{\partial T_1}\frac{\Gamma(T_{10}(T_1,t))}{\Gamma(T_1)} = \frac{\partial}{\partial T_1}\exp(-\int_0^t \frac{\partial\Gamma(T_{10}(T_1,s))}{\partial T_{10}}ds) =$$
$$\frac{\partial}{\partial T_1}\Big(-\int_0^t \frac{\partial\Gamma(T_{10}(T_1,s))}{\partial T_{10}}ds\Big)\exp(-\int_0^t \frac{\partial\Gamma(T_{10}(T_1,s))}{\partial T_{10}}ds) =$$
$$\Big(-\int_0^t \frac{\partial^2\Gamma(T_{10}(T_1,s))}{\partial T_{10}^2}L_0(T_1,s)ds\Big)\exp(-\int_0^t \frac{\partial\Gamma(T_{10}(T_1,s))}{\partial T_{10}}ds), \tag{3.46}$$

Likewise:

$$L_2(T_1,t) := \frac{\partial^2}{\partial T_1^2}\mathcal{K}_1(T_1;t) =$$
$$\frac{\partial}{\partial T_1}L_1(T_1,t) = \frac{\partial}{\partial T_1}\Big[\Big(-\int_0^t \frac{\partial^2\Gamma(T_{10}(T_1,s))}{\partial T_{10}^2}L_0(T_1,s)ds\Big)\exp(-\int_0^t \frac{\partial\Gamma(T_{10}(T_1,s))}{\partial T_{10}}ds)\Big] =$$
$$\Big(-\int_0^t \frac{\partial^3\Gamma(T_{10}(T_1,s))}{\partial T_{10}^3}L_0(T_1,s)ds\Big)\exp(-\int_0^t \frac{\partial\Gamma(T_{10}(T_1,s))}{\partial T_{10}}ds) + \tag{3.47}$$
$$\Big(-\int_0^t \frac{\partial^2\Gamma(T_{10}(T_1,s))}{\partial T_{10}^2}L_1(T_1,s)ds\Big)\exp(-\int_0^t \frac{\partial\Gamma(T_{10}(T_1,s))}{\partial T_{10}}ds) +$$
$$\Big(-\int_0^t \frac{\partial^2\Gamma(T_{10}(T_1,s))}{\partial T_{10}^2}L_0(T_1,s)ds\Big)L_1(T_1,t).$$

It follows that $L_1(T_1,0) = 0$, $L_2(T_1,0) = 0$ and $L_1(T_1,t)$ together with $L_2(T_1,t) = 0$ is bounded as long as $T_{10}(T_1,t)$ is bounded. In general, it is seen that if Γ is $(k+1)$ times continuously differentiable, then

$$L_k(T_1,t) := \frac{\partial^k}{\partial T_1^k}\mathcal{K}_1(T_1;t)$$

can be expressed by the derivatives of Γ up till the $(k+1)$-order, and $L_k(T_1,t)$ is bounded as long as $T_{10}(T_1,t)$ is bounded. Now, by (3.43) and (3.44), one can see that

$$\frac{\partial\mathcal{K}_1}{\partial t}(T_1;t) = -\Big(\frac{\partial}{\partial T_{10}}\Gamma(T_{10}(T_1,t))\Big)L_0(T_1,t),$$

$$\frac{\partial^2\mathcal{K}_1}{\partial t\partial T_1}(T_1;t) = \frac{\partial}{\partial t}L_1(T_1,t) =$$
$$L_0(T_1,t)\Big[-L_0(T_1,t)\frac{\partial^2\Gamma(T_{10}(T_1,t))}{\partial T_{10}^2} + \frac{\partial\Gamma(T_{10}(T_1,t))}{\partial T_{10}}\int_0^t \frac{\partial^2\Gamma(T_{10}(T_1,s))}{\partial T_{10}^2}L_0(T_1,s)ds\Big]$$

and

$$\frac{\partial^2\mathcal{K}_1}{\partial t^2}(T_1;t) = -\frac{\partial}{\partial t}\Big(L_0(T_1,t)\frac{\partial}{\partial T_{10}}\Gamma(T_{10}(T_1,t))\Big) =$$
$$L_0(T_1,t)\Big[\Big(\frac{\partial}{\partial T_{10}}\Gamma(T_{10}(T_1,t))\Big)^2 + \frac{\partial^2\Gamma(T_{10}(T_1,t))}{\partial T_{10}^2}\Gamma(T_{10}(T_1,t))\Big].$$

By induction, we can show that the derivatives of the form

$$\frac{\partial^k\mathcal{K}_1}{\partial t^{k_1}\partial T_1^{k_2}}(T_1;t)$$

exist and are bounded, **iff** the function $\Gamma(\cdot)$ is $k_1 + s(k_2)(k_2+1)$-times differentiable, where $s(k_2) = 1$, if $k_2 \geq 1$ and $s(0) = 0$. □

In the same way we can prove:

Lemma 3.6. *Let Assumption 3.2 be satisfied. Suppose that the function $B(\cdot) : \mathbb{R} \to \mathbb{R}$ is $(k+1)$-times continuously differentiable. Let $k_1 \geq 0$ and $k_2 \geq 0$. Then for all $T_8 \geq 0$ and for all $t > 0$, the function*

$$\mathcal{K}_8(T_8; t) := \frac{B(T_{80}(T_8, t))}{B(T_8)} \tag{3.48}$$

is continuously differentiable k_1 and k_2 times with respect to t and T_8 respectively, iff $k_1 + s(k_2)(k_2 + 1) \leq k + 1$, where $s(k_2) = 1$, if $k_2 \geq 1$ and $s(0) = 0$.

Finally, the following auxiliary lemma holds.

Lemma 3.7. *For any function $\widetilde{F}(T_1, T_{10}(T_1, t-\tau)) = F(T_{10}(T_1, t-\tau))/\Gamma(T_1)$ we have for all $\tau \in [0, t]$:*

$$\frac{\partial}{\partial t}\widetilde{F}(T_1, T_{10}(T_1, t-\tau)) = -\frac{\partial}{\partial T_1}\Big(\Gamma(T_1)\tilde{F}(T_{10}(T_1, t-\tau)) = -\frac{\partial}{\partial T_1}F(T_{10}(T_1, t-\tau)) \tag{3.49}$$

and, likewise, for any function $\widetilde{H}(T_8, T_{80}(T_8, t-\tau)) = H(T_{80}(T_8, t-\tau))/B(T_8)$,

$$\frac{\partial}{\partial t}\frac{\widetilde{H}(T_{80}(T_8, t-\tau))}{B(T_8)} = -\frac{\partial}{\partial T_8}\Big(B(T_8)\tilde{H}(T_{80}(T_8, t-\tau))\Big) = -\frac{\partial}{\partial T_8}H(T_{80}(T_8, t-\tau)) \tag{3.50}$$

Proof Let us show the first of these equalities. We have

$$\begin{aligned}
&\frac{\partial}{\partial t}\frac{F(T_{10}(T_1, t-\tau))}{\Gamma(T_1)} = \frac{1}{\Gamma(T_1)}\frac{\partial}{\partial t}F(T_{10}(T_1, t-\tau)) = \frac{1}{\Gamma(T_1)}\Big[\frac{\partial}{\partial T_{10}}F(T_{10}(T_1, t-\tau))\Big] \cdot \frac{\partial T_{10}(T_1, t-\tau)}{\partial t} = \\
&\frac{1}{\Gamma(T_1)}\Big[\frac{\partial}{\partial T_1}F(T_{10}(T_1, t-\tau))\Big] \cdot \frac{\partial T_1}{\partial T_{10}} \cdot \frac{\partial T_{10}(T_1, t-\tau)}{\partial t} = \\
&-\frac{1}{\Gamma(T_1)} \cdot \frac{\Gamma(T_1)}{\Gamma(T_{10}(T_1, t-\tau))} \cdot \Gamma(T_{10}(T_1, t-\tau))\Big[\frac{\partial}{\partial T_1}F(T_{10}(T_1, t-\tau))\Big] = -\frac{\partial}{\partial T_1}F(T_{10}(T_1, t-\tau))
\end{aligned} \tag{3.51}$$

Thus (3.49) is proved. Similarly we prove the validity of (3.50). □

Lemma 3.8. *The function*

$$R(t, x, T_1, T_8) = \int_{\mathbb{R}^3} G_0(t, x; 0, \xi)\mathcal{K}(T_1, T_8; t)R_0(\xi, T_{10}(T_1, t), T_{80}(T_8, t))d\xi\,, \tag{3.52}$$

where

$$\mathcal{K}(T_1, T_8; t) := \frac{\Gamma(T_{10}(T_1, t))}{\Gamma(T_1)}\frac{B(T_{80}(T_8, t))}{B(T_8)}, \tag{3.53}$$

is a solution to equation

$$\frac{\partial R}{\partial t} = d_R\nabla^2 R - \frac{\partial}{\partial T_1}\left(\Gamma(T_1)\, R\right) - \frac{\partial}{\partial T_8}\left(B(T_8)\, R\right) \tag{3.54}$$

with the initial condition

$$R(0, x, T_1, T_8) = R_0(x, T_1, T_8).$$

If $R_0 \in C^{\alpha,2,2}_{x,T_1,T_8}$, $\alpha \in (0,1)$, whereas Γ and B are of C^3 class of their arguments in $\mathbb{R}^2_+$, then R given by (3.52) is of $C^2(R^2)$ class with respect to (T_1, T_8) and $C^{1+\alpha/2, 2+\alpha}_{t,x}([0,T] \times \mathbb{R}^3)$.

Proof The part of the time derivative of $u(t, x, T_1, T_8)$ taken with respect to t inside G_0 is equal to:

$$\Big(\frac{\partial R}{\partial t}\Big)^0 = \int_{\mathbb{R}^3} G_{0,t}(t, x; 0, \xi)\mathcal{K}(T_1, T_8; t)R_0(\xi, T_{10}(T_1, t), T_{80}(T_8, t))d\xi = d_R\nabla^2 R(t, x, T_1, T_8).$$

Now, let us consider the t-differentiation of the function

$$\mathcal{S} = \mathcal{K}(T_1, T_8; t) R_0(\xi, T_{10}(T_1, t), T_{80}(T_8, t)) =$$

$$\frac{1}{\Gamma(T_1) B(T_8)} \Big[\Gamma(T_{10}(T_1, t)) B(T_{80}(T_8, t)) R_0(\xi, T_{10}(T_1, t), T_{80}(T_8, t)) \Big].$$

We have:

$$\frac{\partial \mathcal{S}}{\partial t} = \frac{B(T_{80}(T_8, t))}{B(T_8)} \Big\{ \frac{\partial}{\partial t} \Big[\frac{\Gamma(T_{10}(T_1, t))}{\Gamma(T_1)} R_0(\xi, T_{10}(T_1, t), Y) \Big] \Big\} \Big|_{Y = T_{80}(T_8, t))} +$$
$$\frac{\Gamma(T_{10}(T_1, t))}{\Gamma(T_1)} \Big\{ \frac{\partial}{\partial t} \Big[\frac{B(T_{80}(T_8, t))}{B(T_8)} R_0(\xi, Y, T_{80}(T_8, t))) \Big] \Big\} \Big|_{Y = T_{10}(T_1, t)}$$

Thus, due to Lemma 3.7

$$\frac{\partial \mathcal{S}}{\partial t} = -\frac{B(T_{80}(T_8, t))}{B(T_8)} \Big\{ \frac{\partial}{\partial T_1} \Big[\Gamma(T_{10}(T_1, t)) R_0(\xi, T_{10}(T_1, t), Y) \Big] \Big\} \Big|_{Y = T_{80}(T_8, t))} -$$
$$\frac{\Gamma(T_{10}(T_1, t))}{\Gamma(T_1)} \Big\{ \frac{\partial}{\partial T_8} \Big[B(T_{80}(T_8, t)) R_0(\xi, Y, T_{80}(T_8, t))) \Big] \Big\} \Big|_{Y = T_{10}(T_1, t)} =$$
$$-\frac{\partial}{\partial T_1} \Big[\frac{B(T_{80}(T_8, t))}{B(T_8)} \Gamma(T_{10}(T_1, t)) R_0(\xi, T_{10}(T_1, t), Y) \Big] -$$
$$\frac{\partial}{\partial T_8} \Big[\frac{\Gamma(T_{10}(T_1, t))}{\Gamma(T_1)} B(T_{80}(T_8, t)) R_0(\xi, Y, T_{80}(T_8, t))) \Big] = -\frac{\partial}{\partial T_1} (\Gamma(T_1) \mathcal{S}) - \frac{\partial}{\partial T_8} (B(T_8) \mathcal{S})$$

It follows that

$$\int_{\mathbb{R}^3} G_0(t, x; 0, \xi) \frac{\partial \mathcal{S}}{\partial t} d\xi = \int_{\mathbb{R}^3} G_0(t, x; 0, \xi) \Big\{ -\frac{\partial}{\partial T_1} (\Gamma(T_1) \mathcal{S}) - \frac{\partial}{\partial T_8} (B(T_8) \mathcal{S}) \Big\} d\xi =$$
$$-\frac{\partial}{\partial T_1} \Big\{ (\Gamma(T_1) \int_{\mathbb{R}^3} G_0(t, x; 0, \xi) \mathcal{S}) d\xi \Big\} - \frac{\partial}{\partial T_8} \Big\{ (B(T_8) \int_{\mathbb{R}^3} G_0(t, x; 0, \xi) \mathcal{S}) d\xi \Big\}$$

which proves that the function defined by (3.52) satisfies the homogeneous version of Eq.(3.1). The smoothness properties follow from Lemma 3.5, Lemma 3.6 and the properties of the fundamental solution G_0 (see points 3,4 of Lemma 3.4). □

Now, we will find an expression for the solution to the inhomogeneous equation

$$\frac{\partial R}{\partial t} = d_R \nabla^2 R - \frac{\partial}{\partial T_1} \left(\Gamma(T_1) \, R \right) - \frac{\partial}{\partial T_8} \left(B(T_8) \, R \right) + f(t, x, T_1, T_8). \tag{3.55}$$

Lemma 3.9. *The function*

$$u(t, x, T_1, T_8) = \int_0^t \Big(\int_{\mathbb{R}^3} \mathcal{K}(T_1, T_8; t-\tau) G_0(t, x; \tau, \xi) f(\tau, \xi, T_{10}(T_1, t-\tau), T_{80}(T_8, t-\tau)) d\xi \Big) d\tau \tag{3.56}$$

where

$$\mathcal{K}(T_1, T_8; t) := \frac{\Gamma(T_{10}(T_1, t))}{\Gamma(T_1)} \frac{B(T_{80}(T_8, t))}{B(T_8)} \tag{3.57}$$

is a solution to Eq.(3.55) with zero initial condition at $t = 0$. If $f \in C^{\alpha/2, \alpha, 2, 2}_{t, x, T_1, T_8}$, $\alpha \in (0, 1)$, whereas Γ and B are of C^3 class of their arguments (in $\overline{\mathbb{R}^2_+}$), then u given by (3.56) is of $C^2(\overline{\mathbb{R}^2_+})$ class with respect to (T_1, T_8) and $C^{1+\alpha/2, 2+\alpha}_{t, x}([0, T] \times \mathbb{R}^3)$.

Proof The part of the time derivative of $u(t, x, T_1, T_8)$ taken with respect to t inside G_0 and in the upper limit of the integral is, by means of s 2 and 3 Lemma 3.4, equal to:

$$\Big(\frac{\partial u}{\partial t}\Big)^0 = \int_0^t \Big(\int_{\mathbb{R}^3} \mathcal{K}(T_1,T_8;t-\tau)G_{0,t}(t,x;\tau,\xi)f(\tau,\xi,T_{10}(T_1,t-\tau),T_{80}(T_8,t-\tau))d\xi\Big)d\tau +$$

$$\lim_{\tau\to t}\int_{\mathbb{R}^3} \mathcal{K}(T_1,T_8;t-\tau)G_0(t,x;\tau,\xi)f(\tau,\xi,T_{10}(T_1,t-\tau),T_{80}(T_8,t-\tau))d\xi$$

$$= d_R\nabla^2 u(t,x,T_1,T_8) + f(t,x,T_1,T_8)$$

because $T_{10}(T_1,t-\tau)|_{\tau=t} = T_1$ and $T_{80}(T_8,t-\tau)|_{\tau=t} = T_8$. Thus $f(\tau,\xi,T_{10}(T_1,t-\tau),T_{80}(T_8,t-\tau))|_{\tau=t} = f(\tau,\xi,T_1,T_8)$ and $\mathcal{K}(T_1,T_8;t-\tau)|_{\tau=t} = 1$.

Now, let us consider the derivative

$$\Big(\mathcal{K}(T_1,T_8;t-\tau)f(\tau,\xi,T_{10}(T_1,t-\tau),T_{80}(T_8,t-\tau))\Big)_{,t}$$

The differentiated expression can be written as $(\Gamma(T_1)B(T_8))^{-1}\Psi(\tau,\xi,T_{10}(T_1,t-\tau),T_{80}(T_8,t-\tau))$. We have:

$$\frac{d}{dt}\Big((\Gamma(T_1)B(T_8))^{-1}\Psi(\tau,\xi,Y_1(t-\tau),Y_8(t-\tau))\Big) =$$

$$\frac{B(Y_8)}{B(T_8)}\Big|_{Y_8=T_{80}(T_8,t-\tau)}\ \frac{d}{dt}\Big(\frac{1}{\Gamma(T_1)}\cdot\Gamma(T_{10}(T_1,t-\tau))f(\tau,\xi,T_{10}(T_1,t-\tau),Y_8)\Big)\Big|_{Y_8=T_{80}(T_8,t-\tau)}+$$

$$\frac{\Gamma(Y_1)}{\Gamma(T_1)}\Big|_{Y_1=T_{10}(T_1,t-\tau)}\ \frac{d}{dt}\Big(\frac{1}{B(T_8)}\cdot B(T_{80}(T_8,t-\tau))f(\tau,\xi,Y_1,T_{80}(T_8,t-\tau))\Big)\Big|_{Y_1=T_{10}(T_1,t-\tau)}.$$

Using Lemma 3.7 with

$$F(T_{10}(T_1,t-\tau)) = \Gamma(T_{10}(T_1,t-\tau))f(\tau,\xi,T_{10}(T_1,t-\tau),Y_8)$$

with Y_8 fixed and

$$H(T_{80}(T_8,t-\tau))) = B(T_{80}(T_8,t-\tau))f(\tau,\xi,Y_1,T_{80}(T_8,t-\tau))$$

with Y_1 fixed, one notes, as in the proof of Lemma 3.8, that:

$$\int_0^t\int_{\mathbb{R}^3} G_0(t,x;\tau,\xi)\Big(\mathcal{K}(T_1,T_8;t-\tau)f(\tau,\xi,T_{10}(T_1,t-\tau),T_{80}(T_8,t-\tau))\Big)_{,t}\, d\xi d\tau = -$$

$$\int_0^t\int_{\mathbb{R}^3}\Big[\frac{B(T_{80}(T_8,t-\tau))}{B(T_8)}\frac{\partial}{\partial T_1}F(T_{10}(T_1,t-\tau)) + \frac{\Gamma(T_{10}(T_1,t-\tau))}{\Gamma(T_1)}\frac{\partial}{\partial T_8}H(T_{80}(T_8,t-\tau))\Big]G_0(t,x;\tau,\xi)d\xi d\tau$$

$$= -\frac{\partial}{\partial T_1}\Big(\Gamma(T_1)\int_0^t\int_{\mathbb{R}^3} G_0(t,x;\tau,\xi)\mathcal{K}(T_1,T_8;t-\tau)f(\tau,\xi,T_{10}(T_1,t-\tau),T_{80}(T_8,t-\tau))d\xi\, d\tau\Big)$$

$$-\frac{\partial}{\partial T_8}\Big(B(T_8)\int_0^t\int_{\mathbb{R}^3} G_0(t,x;\tau,\xi)\mathcal{K}(T_1,T_8;t-\tau)f(\tau,\xi,T_{10}(T_1,t-\tau),T_{80}(T_8,t-\tau))d\xi\, d\tau\Big) =$$

$$-\frac{\partial}{\partial T_1}(\Gamma(T_1)u) - \frac{\partial}{\partial T_8}(B(T_8)u).$$

The smoothness properties follow from Lemma 3.4 (points 3 and 4) together with Lemma 3.5 and Lemma 3.6. The lemma is proved. □

Remark An important note should be made concerning the construction of the solution. As can be seen from the proof of Lemma 3.8 and Lemma 3.9, it is crucial that in the expression for the solution there is a term $(\Gamma(T_1)B(T_8))^{-1}$. Otherwise, the last expression in the sequence of equalities (3.51) would have a form $[-\Gamma(T_1)\frac{\partial}{\partial T_1}F(T_{10}(T_1,t-\tau))]$, so Eq.(3.1), so could not be written as a derivative with respect to T_1. The same concerns the derivative with respect to T_8. In consequence, Eq.(3.55) could not be fulfilled. □

The last remark touches the problem of uniqueness of solutions.

4 Uniqueness of solutions

In this section, we will present two theorems concerning the uniqueness of solutions to different generalizations equations of Eq.(3.55) **under the assumption that they exist**. In these generalizations, we will assume that the functions Γ and B may additionally depend on t and x. Assuming the dependence on t is justified by the fact that in section 8.4 we show that in the case of the product initial data, the existence of solutions to the homogeneous equation (3.1) is implied by the existence to the assigned hyperbolic equation. At the end of section 8.4, we also give an example of solution to Eq.(3.1) in the case of the general initial data.

In the first uniqueness lemma we will consider the equation:

$$\frac{\partial R}{\partial t} = d_R \nabla^2 R - \frac{\partial}{\partial T_1}\left(\Gamma(T_1, t)\, R\right) - \frac{\partial}{\partial T_8}\left(B(T_8, t)\, R\right) + f(t, x, T_1, T_8). \tag{4.1}$$

Similarly to the case of Γ and B not depending explicitly on t, the characteristic curves assigned to the hyperbolic part of Eq.(4.1) are given by the system of odes for $t \in [0, T]$:

$$\frac{dT_1}{dt}(t) = \Gamma(T_1, t), \quad \frac{dT_8}{dt}(t) = B(T_8, t), \quad T_1(0) = T_{10},\; T_8(0) = T_{80}. \tag{4.2}$$

Let

$$\mathcal{W}_1 = \{u : [0, T] \times \mathbb{R}^3 \times \overline{\mathbb{R}^2_+} \mapsto \mathbb{R}\} = C^1\Big([0, T], L^2(\mathbb{R}^3)\Big) \cap BC\Big([0, T], W^{2,2}_x(\mathbb{R}^3) \cap C^{1,1}_{T_1,T_8}(\mathbb{R}^2_+)\Big).$$

The following uniqueness result holds.

Lemma 4.1. *Suppose that the functions Γ and B are of C^2 class of their arguments and that for $t \in [0, T]$ the characteristic curves given by solutions to system (4.2) fill out the whole $\overline{\mathbb{R}^2_+}$ and that for $t \in [0, T]$ the set $\overline{\mathbb{R}^2_+}$ is positively invariant with respect to system (4.2). Then, solutions to Eq.(4.1) are unique in the space $\mathcal{W}_1$ (defined above) such that their derivatives with respect to x behaving like $o(|x|^{-2})$ as $|x| \to \infty$.*

Proof Suppose that the thesis of the lemma is not true. Let D denote the difference between any of two solutions to Eq.(3.55). We thus have:

$$\frac{\partial D}{\partial t} = d_R \nabla^2 D - \frac{\partial}{\partial T_1}\left(\Gamma(T_1, t)\, D\right) - \frac{\partial}{\partial T_8}\left(B(T_8, t)\, D\right) \tag{4.3}$$

and $D(0, x, T_1, T_8) \equiv 0$. Multiplying Eq.(4.3) by D, we obtain

$$\begin{aligned}\frac{1}{2}\frac{\partial}{\partial t} D^2 = d_R \nabla \cdot \Big(D\, \nabla D\Big) - \frac{1}{2} d_R (\nabla D)^2 - \frac{\partial}{\partial T_1}\left(\Gamma(T_1, t)\, D^2\right) + \frac{1}{2}\Gamma(T_1, t)\frac{\partial}{\partial T_1} D^2 - \frac{\partial}{\partial T_8}\left(B(T_8, t)\, D^2\right) \\ + \frac{1}{2} B(T_8, t)\frac{\partial}{\partial T_8} D^2\end{aligned} \tag{4.4}$$

what can be written as

$$\begin{aligned}&\frac{\partial}{\partial t} D^2 = d_R \nabla \cdot \Big(\nabla D^2\Big) - d_R (\nabla D)^2 \\ &-2\frac{\partial}{\partial T_1}\left(\Gamma(T_1, t)\right) D^2 - \Gamma(T_1, t)\frac{\partial}{\partial T_1} D^2 - 2\frac{\partial}{\partial T_8}\left(B(T_8, t)\right) D^2 - B(T_8, t)\frac{\partial}{\partial T_8} D^2.\end{aligned} \tag{4.5}$$

Integrating, for each (t, T_1, T_8) with respect to x over the whole $\mathbb{R}^3$ (by integrating over the finite radius balls and passing to the limit), using the Gauss-Ostrogradskii theorem and denoting $Q = \int_{\mathbb{R}^3} D^2 dx$, we obtain

$$\frac{\partial}{\partial t} Q = -2\frac{\partial}{\partial T_1}(\Gamma(T_1, t))\ Q - \Gamma(T_1, t)\frac{\partial}{\partial T_1}\ Q - 2\frac{\partial}{\partial T_8}(B(T_8, t))\ Q - B(T_8, t)\frac{\partial}{\partial T_8}\ Q - \mathcal{G}(D)(t, T_1, T_8), \tag{4.6}$$

where $Q(0, T_1, T_8) \equiv 0$ and $\mathcal{G}(D)$ is a functional, which attains positive values for all $D \not\equiv 0$. Suppose that $D \not\equiv 0$. Then $\mathcal{G}(D)$ can be considered as a **given** function of $(t, T_1, T_8) \in C^0$ such that it is strictly positive. Let us consider an auxiliary equation

$$\frac{\partial}{\partial t}\underline{Q} = 2\frac{\partial}{\partial T_1}(\Gamma(T_1, t))\ \underline{Q} - \Gamma(T_1, t)\frac{\partial}{\partial T_1}\ \underline{Q} - 2\frac{\partial}{\partial T_8}(B(T_8, t))\ \underline{Q} - B(T_8, t)\frac{\partial}{\partial T_8}\ \underline{Q} \tag{4.7}$$

Using the uniqueness result for hyperbolic equations, we conclude that this equation can be satisfied only for $\underline{Q} = 0$. Now, if $Q \not\equiv 0$, then $\frac{\partial Q}{\partial t} > 0$ for some $t > 0$, which leads to a contradiction. To show this, let us note that, according to equalities (21) in [13, 3.2.2], the characteristic curves for Eqs (4.7) and (4.6) are the same, so can be parametrized in the same way. Let us consider an arbitrary characteristic curve starting for $t = 0$ at a point $(T_{10}, T_{80}) \in \overline{\mathbb{R}^2_+}$ (parametrized with time): $t \mapsto (t, T_1(T_{10}, t), T_8(T_8(T_{80}))$. Thus, using the second equation of (21) [13, 3.2.2], we obtain for $t \in (0, T)$:

$$\frac{d}{dt}\underline{Q}(t, T_1(t), T_8(t)) = -2\frac{\partial}{\partial T_1}(\Gamma(T_1(t), t))\,\underline{Q}(t, T_1(t), T_8(t)) - 2\frac{\partial}{\partial T_8}(B(T_8(t), t))\,\underline{Q}(t, T_1(t), T_8(t))$$

and

$$\frac{d}{dt}Q(t, T_1(t), T_8(t)) =$$
$$-2\frac{\partial}{\partial T_1}(\Gamma(T_1(t), t))\,Q(T_1(t), T_8(t), t) - 2\frac{\partial}{\partial T_8}(B(T_8(t), t))\,Q(t, T_1(t), T_8(t)) - \mathcal{G}(D)(t, T_1(t), T_8(t)).$$

Both of these equations are supplemented by the initial condition at $t = 0$ equal to 0, i.e. $\underline{Q}(0, T_{10}, T_{80}) = 0$ and $Q(0, T_{10}, T_{80}) = 0$. Let us define:

$$w(t) := 2\frac{\partial}{\partial T_1}(\Gamma(T_1(t))) + 2\frac{\partial}{\partial T_8}(B(T_8(t)))$$

$$\underline{Q}_* := \underline{Q} \cdot \exp(\int_0^t w(s)ds), \quad Q_* := Q \cdot \exp(\int_0^t w(s)ds).$$

In this way, the equations for $\underline{Q}$ and Q along the characteristics can be transformed to:

$$\frac{d}{dt}\underline{Q}_*(t, T_1(t), T_8(t)) = 0$$

and

$$\frac{d}{dt}Q_*(t, T_1(t), T_8(t)) = -\mathcal{G}(t, T_1(t), T_8(t)) \cdot \exp(\int_0^t w(s)ds).$$

It follows that $\underline{Q}_*(t, T_1(t), T_8(t)) = 0$ hence $\underline{Q}(t, T_1(t), T_8(t)) = 0$ for all $t \in [0, T]$. Finally, if $\mathcal{G}(t, T_1(t), T_8(t)) \not\equiv 0$, then $\frac{dQ_*}{dt} \le 0$ for $t \in (0, T]$. Thus, as $Q_* \ge 0$, we must have $Q_* \equiv 0$, so $\mathcal{G} \equiv 0$, in contradiction to our assumption. □

In Lemma 4.1 we assumed the integrability of solutions with respect to x, however, for each $x \in \mathbb{R}^3$, we could assume only their boundedness with respect to (T_1, T_8). In contrast, in the next lemma we will only assume integrability with respect to (T_1, T_8). Moreover, in this approach, we are able to consider the dependence of the functions Γ and B on x. Besides, to obtain uniqueness, we do not have to assume anything about the behaviour of the characteristic curves.

Thus, in the next lemma we will consider the equation

$$\frac{\partial R}{\partial t} = d_R \nabla^2 R - \frac{\partial}{\partial T_1}\left(\Gamma(T_1, t; x)\, R\right) - \frac{\partial}{\partial T_8}\left(B(T_8, t; x)\, R\right) + f(t, x, T_1, T_8). \tag{4.8}$$

Let

$$\mathcal{W}_2 = \{u : [0,T] \times \mathbb{R}^3 \times \overline{\mathbb{R}^2_+} \mapsto \mathbb{R}\}$$

be the space of functions satisfying the following conditions:

1. u is uniformly bounded with respect to $(t, x, (T_1, T_8))$
2. $u \in L^2(\mathbb{R}^2_+) \cap W^{1,2}_{,T_1}(\mathbb{R}^2_+) \cap W^{1,2}_{,T_8}(\mathbb{R}^2_+)$, $u = o(|(T_1, T_8)|^{-2})$ as $|(T_1, T_8)| \to \infty$.
3. the first and second derivatives of u with respect to the components of x belong to the space $L^2(\mathbb{R}^2_+)$, i.e. are integrable with respect to (T_1, T_8).

Lemma 4.2. *Suppose that the functions Γ and B are of C^2 class with respect to t, T_1 and T_8 and of C^1 class with respect to x. Then, solutions to Eq.(3.55) are unique in the space $\mathcal{W}_2$.*

Proof The proof will resemble the proof of Lemma 4.1, however this time we will carry out the integration with respect to $T_1 T_8$ instead of x. As in the previous case, the difference of solutions D satisfies the equation:

$$\begin{aligned}\frac{1}{2}\frac{\partial}{\partial t} D^2 &= \frac{1}{2} d_R \nabla \cdot \left(\nabla D^2\right) - \frac{1}{2} d_R (\nabla D)^2 \\ &- \frac{\partial}{\partial T_1}\left(\Gamma(T_1, t; x)\, D^2\right) + \frac{1}{2}\Gamma(T_1, t; x)\frac{\partial}{\partial T_1} D^2 - \frac{\partial}{\partial T_8}\left(B(T_8, t; x)\, D^2\right) + \frac{1}{2} B(T_8, t; x)\frac{\partial}{\partial T_8} D^2.\end{aligned} \tag{4.9}$$

Let us note that

$$-\frac{\partial}{\partial T_1}\left(\Gamma\, D^2\right) + \frac{1}{2}\Gamma \frac{\partial}{\partial T_1} D^2 = -\frac{\partial}{\partial T_1}\left(\Gamma\, D^2\right) + \frac{1}{2}\frac{\partial}{\partial T_1}(\Gamma D^2) - \frac{1}{2} D^2 \frac{\partial}{\partial T_1}\Gamma = -\frac{1}{2}\frac{\partial}{\partial T_1}(\Gamma D^2) - \frac{1}{2} D^2 \frac{\partial}{\partial T_1}\Gamma.$$

Thus, omitting for brevity the arguments of the functions Γ and B, we obtain

$$\frac{\partial}{\partial t} D^2 = d_R \nabla \cdot \left(\nabla D^2\right) - d_R (\nabla D)^2 - \frac{\partial}{\partial T_1}\left(\Gamma\, D^2\right) - D^2 \frac{\partial}{\partial T_1}\Gamma - \frac{\partial}{\partial T_8}\left(B(T_8)\, D^2\right) - D^2 \frac{\partial}{\partial T_8} B \tag{4.10}$$

Now, let

$$P(t, x) := \max_{T_1, T_8 \in \overline{\mathbb{R}^2_+}} \Big\{ -\frac{\partial}{\partial T_1}\Gamma(T_1, t; x) - \frac{\partial}{\partial T_8} B(T_8, t; x)\Big\}.$$

It is seen that $P(t, x)$ is a bounded function of $(t, x) \in [0, T] \times \mathbb{R}^3$. Then

$$\frac{\partial}{\partial t} D^2 \leq d_R \nabla \cdot \left(\nabla D^2\right) - d_R (\nabla D)^2 - \frac{\partial}{\partial T_1}\left(\Gamma(T_1)\, D^2\right) - \frac{\partial}{\partial T_8}\left(B(T_8)\, D^2\right) + P(t, x) D^2. \tag{4.11}$$

Next, integrating the both sides with respect to T_1 and T_8, over the sets $B^2(0, \rho_{18}) \bigcup \overline{\mathbb{R}^2_+}$ using the assumptions of the lemma and auxiliary Lemma 9.3, we obtain, by passing to the limit $\rho_{18} \to \infty$,

$$\frac{\partial}{\partial t} Q \leq d_R \nabla^2 Q + PQ - \mathcal{G}(D)(t, x), \tag{4.12}$$

where $\mathcal{G}(D)(t, x) = d_R \int_{\mathbb{R}^2_+} (\nabla D)^2 dT_1 dT_8$ can be treated as a given function, which is non-negative and not equivalent to 0 only, if $D \equiv 0$. Due to the boundedness of the function Q at x-infinity and the boundedness of the function P, we note that the conditions of [30, Theorem 10, Section 6] (Phragmen-Lindelöf principle) are satisfied. It follows that, as $Q(0,x) \equiv 0$, then $Q(t,x) \leq 0$ for $t \in [0,T]$. As $Q \geq 0$ by definition, it follows that $Q \equiv 0$ and $D \equiv 0$. The lemma is proved. □

For the convenience of the reader, we present the Phragmen-Lindelöf principle in the form of [30, Theorem 10, Section 6].

Lemma 4.3. *(***Phragmen-Lindelöf principle***) Let Ω be an unbounded domain in n-dimensional space and let E be the domain $(0,T) \times \Omega$. Suppose that u satisfies $(L+h)[u] \geq 0$ in E with L a uniformly parabolic operator of the form*

$$L \equiv \sum_{i,j=1}^{n} a_{ij}(t,x) \frac{\partial^2}{\partial x_i \partial x_j} + \sum_{i=1}^{n} b_i(t,x) \frac{\partial}{\partial x_i} - \frac{\partial}{\partial t}$$

with bounded coefficients and with $h(t,x)$ bounded from above in E. Assume that u satisfies the growth condition

$$\liminf_{r \longrightarrow \infty} e^{-cr^2} \left[\max_{\substack{x_1^2+x_2^2+\cdots+x_n^2=r^2 \\ 0 \leq t \leq T}} u(t,x) \right] \leq 0$$

for some positive constant c. If $u \leq 0$ for $t=0$ and $u \leq 0$ on $(0,T) \times \partial\Omega$, then $u \leq 0$ in E.

5 Asymptotics of the solution given by Lemmas 3.8 and 3.9

Let us consider the asymptotics of the functions given by Lemmas 3.8 and 3.9. The asymptotics will be understood either with respect to $t >> 1$ or with respect to a parameter scaling the strength of convective (hyperbolic) terms. This parameter will be denoted below by λ.

In this section we will assume the uniqueness of solutions to the system $(\Gamma(T_1), B(T_8)) = (0,0)$ or at least that there is a unique solution to this system in the support of R (with respect to (T_1, T_8))) for all $t \in [0,T]$ and all $x \in \mathbb{R}^3$ (see Assumption 5.3).

Let us consider the volume of the support of the function $R(t,x,T_1,T_8)$ with respect to (T_1,T_8) as a function of time. (Let us emphasize that we consider the case of Γ and B independent of x.) In view of the right hand side of (3.52), we have thus to consider the 2-d volume of the form:

$$\int_{\mathbb{R}^2} \chi_t(T_1, T_8; \xi) dT_1 dT_8,$$

where $\chi_t(T_1,T_8;\xi) = 1$, **iff** $(T_{10}(T_1,t), T_{80}(T_1,t)) \in supp\, R_0(\xi,\cdot,\cdot)$. Fixing t and changing the variables in the above integral:

$$T_1 \to T_{10}(T_1,t) = T_{10}, \quad T_8 \to T_{80}(T_8,t) = T_{80},$$

we obtain

$$\begin{aligned} dT_1 &= dT_{10} \frac{dT_1}{dT_{10}} = dT_{10} \frac{\Gamma(T_1)}{\Gamma(T_{10})}, \\ dT_8 &= dT_{80} \frac{dT_8}{dT_{80}} = dT_{80} \frac{B(T_8)}{B(T_{80})} \end{aligned} \tag{5.1}$$

and, due to Assumptions 3.2 and 3.3,

$$\begin{aligned} \int_{\mathbb{R}^2} \chi_t(T_1,T_8;\xi) dT_1 dT_8 &= \int_{\mathbb{R}^2} \chi_0(T_{10},T_{80};\xi) \det(J(T_1,T_8;t)) dT_{10} dT_{80} \\ &= \int_{\mathbb{R}^2_+} \chi_0(T_{10},T_{80};\xi) \det(J(T_1,T_8;t)) dT_{10} dT_{80} \\ &= \textstyle\int_{\mathbb{R}^2_+} \chi_0(T_{10},T_{80};\xi) \frac{\Gamma(T_1(T_{10},t))}{\Gamma(T_{10})} \frac{B(T_8(T_{80},t))}{B(T_{80})} dT_{10} dT_{80} \end{aligned} \tag{5.2}$$

where $J(T_1, T_8; t)$ is the Jacobian matrix of the mapping $(T_{10}, T_{80}) \mapsto (T_1(T_{10}, t), T_8(T_{80}, t))$, i.e.

$$J(T_1, T_8; t) = \begin{pmatrix} \dfrac{\partial T_1(T_{10}, t)}{\partial T_{10}} & 0 \\ 0 & \dfrac{\partial T_8(T_{80}, t)}{\partial T_{80}} \end{pmatrix} = \begin{pmatrix} \dfrac{\Gamma(T_1(T_{10}, t))}{\Gamma(T_{10})} & 0 \\ 0 & \dfrac{B(T_8(T_{80}, t))}{B(T_{80})} \end{pmatrix}. \tag{5.3}$$

If Γ and B are linear and given by (3.19) and (3.23), then, similarly to (3.36), we can show straightforwardly that $\det(J(t)) = \exp(st)\exp(rt)$. It follows that in this case

$$\int_{\mathbb{R}^2} \chi_t(T_1, T_8; \xi) dT_1 dT_8 = \exp((s + r)t) \int_{\mathbb{R}^2_+} \chi_0(T_{10}, T_{80}; \xi) dT_{10} dT_{80}$$

hence for $s, r < 0$ the support of the function R with respect to T_1 and T_8 decreases in volume as $\exp(-(|s| + |r|)t)$ and, in fact, tends to a stable singular point $(-s_0/s, -r_0/r)$.

To consider more general form of the functions Γ and B, let us suppose the following.

Assumption 5.1. *Suppose that for all $\xi \in \mathbb{R}^3$, for all (T_{10}, T_{80}) from some open neighbourhood of $\operatorname{supp} R_0(\xi, \cdot, \cdot)$ in (T_{10}, T_{80}) space, the solutions $(T_1(T_{10}, t), T_8(T_{80}, t)$ to system (3.5) tend, as $t \to \infty$, to a unique attracting stationary point (A_1, A_8) such that $\Gamma(A_1) = 0$, $B(A_8) = 0$.*

Lemma 5.2. *Suppose that Assumption 3.2 and 5.1 are fulfilled. Then, for each $x \in \overline{\Omega}$, the support of $R(t.x, T_1, T_8)$ tends to a point (A_1, A_8) as $t \to \infty$.*

Proof The proof follows from the form of the right hand side of (5.2). Thus for fixed $(A_1, A_8) \neq (T_{10}, T_{80}) \in \operatorname{supp} R_0(x, T_{10}, T_{80})$, $(T_{10}, T_{80}) \neq (A_1, A_8)$,

$$\det(J(T_1(T_{10}, t), T_8(T_{80}, t); t)) = \frac{\Gamma(T_1(T_{10}, t)}{\Gamma(T_{10})} \frac{B(T_8(T_{80}, t)}{B(T_{80})} \to 0$$

as $t \to \infty$. □

Remark In Lemma 5.5, instead of the limit $t \to \infty$, similar behaviour is derived with respect to the asymptotics $\lambda|s|, \lambda|r| \to \infty$. □

5.1 Asymptotic weak limit of the terms $\frac{\partial}{\partial T_1}\Gamma(T_1)R$ and $\frac{\partial}{\partial T_8}B(T_8)R$ with R given by Lemma 3.8

By means of (5.2), we can analyse also the asymptotic weak limit of the terms $\frac{\partial}{\partial T_1}\Gamma(T_1)R$ and $\frac{\partial}{\partial T_8}B(T_8)R$ with R given by the right hand side (3.52).

Suppose that $R_0(x, T_1, T_8)$, for each $x \in \Omega$, has a compact support S^x inside the positive quadrant of the space (T_1, T_8). Suppose also that

$$0 \leq \sup_{(T_1, T_8) \in S^x} R_0(x, T_1, T_8) \leq \rho^x < \bar{\rho}. \tag{5.4}$$

Let us multiply the right hand side of (3.52) by a smooth function $\phi(T_1, T_8)$ of compact support inside the non-negative quadrant $\overline{\mathbb{R}^2_+} = \{T_1 \geq 0, T_8 \geq 0\}$. Integrating by parts with respect to T_1 and using (1.18), we obtain:

$$\int_{\mathbb{R}^2_+} \frac{\partial}{\partial T_1}\Big(\Gamma(T_1)R\Big)\, \phi \, dT_1 dT_8 = \int_{\mathbb{R}^2_+} \Gamma(T_1)R \frac{\partial}{\partial T_1}\phi \, dT_1 dT_8.$$

Using (3.52), we obtain the estimate

$$\Big| \int_{\mathbb{R}^2_+} \Gamma(T_1) R \frac{\partial}{\partial T_1} \phi \, dT_1 dT_8 \Big| \le \phi_1 \int_{\mathbb{R}^3} G_0(t,x;0,\xi) \, \rho^{\xi} \left[\int_{\mathbb{R}^2_+} \Big| \Gamma(T_1) \, \mathcal{K}(T_1,T_8;t) \Big| \, \chi_t^{\xi}(T_1,T_8) \, dT_1 dT_8 \right] d\xi,$$

where $\phi_1 := \sup_{T_1,T_8} \Big| \dfrac{\partial \phi}{\partial T_1} \Big|$, $\mathcal{K}(T_1,T_8;t)$ is given by (11.2) and $\chi_t^x(T_1,T_8) = 1$, iff $(T_{10}(T_1,t), T_{80}(T_8,t)) \in S^x$.

Assumption 5.3. *Suppose that there exists a compact set S_M in the space (T_1,T_8) such that $S^x \Subset S_M$ for all $x \in \mathbb{R}^3$, $\int_{S_M} dT_1 dT_8 = V_M$. Suppose that inside S_M there exists a unique singular point $A = (A_1, A_8)$ of system (3.5) which is attractive. Let*

$$\sup_{(T_1,T_8) \in S_M} \Big| T_1 - A_1 \Big| \le d_1, \qquad \sup_{(T_1,T_8) \in S_M} \Big| T_8 - A_8 \Big| \le d_8,$$

To proceed, we will consider times $t >> 1$ or assume that away of the singular points the absolute value of Γ and B are relatively large. Thus, let us rescale the functions Γ and B by writing

$$\Gamma(T_1) = \lambda \tilde{\Gamma}(T_1), \quad B(T_8) = \lambda \tilde{B}(T_8), \tag{5.5}$$

where $\lambda \in (0,\infty)$ will be a parameter at our disposal.

Assumption 5.4. *Suppose that $\|\tilde{\Gamma}(\cdot)\|_{C^1(\mathbb{R})} = b_1$ and $\|\tilde{B}(\cdot)\|_{C^1(\mathbb{R})} = b_8$, where b_1 and b_8 are independent of λ. Assume that inside the set S_M we have, for $s < 0$, $r < 0$,*

$$\widetilde{\Gamma}(T_1) \le s(T_1 - A_1), \;\; \textit{for } T_1 - A_1 > 0, \quad \widetilde{\Gamma}(T_1) \ge s(T_1 - A_1), \;\; \textit{for } T_1 - A_1 < 0,$$
$$\widetilde{B}(T_8) \le r(T_8 - A_8), \;\; \textit{for } T_8 - A_8 > 0, \quad \widetilde{B}(T_8) \ge r(T_8 - A_8), \;\; \textit{for } T_8 - A_8 < 0.$$

Assumption 5.4 implies that solutions to system (3.5) satisfy the inequalities:

$$|T_1(T_{10},t) - A_1| \le |T_{10} - A_1| \exp(\lambda s t), \quad |T_8(T_{80},t) - A_8| \le |T_{80} - A_8| \exp(\lambda r t). \tag{5.6}$$

The same assumption implies that

$$|\Gamma(T_1(T_{10},t)| \le \lambda |s| |T_{10} - A_1| \exp(\lambda s t), \quad \text{and} \;\; B(T_8(T_{80},t) \le \lambda |r| |T_{80} - A_8| \exp(\lambda r t). \tag{5.7}$$

Note that, according to (5.3),

$$\det J(T_1,T_8;t) = (\mathcal{K}(T_1,T_8;t))^{-1}. \tag{5.8}$$

We thus have

$$\begin{aligned}
&\Big| \int_{\mathbb{R}^2_+} \Gamma(T_1) \, \mathcal{K}(T_1,T_8;t) \, \chi_t^{\xi}(T_1,T_8) \, dT_1 dT_8 \Big| = \\
&\Big| \int_{\mathbb{R}^2_+} \Gamma(T_1(T_{10},t)) \det J(T_1(T_{10},t), T_8(T_{80},t);t) \, \mathcal{K}(T_1(T_{10},t), T_8(T_{80},t);t)) \chi_0^{\xi}(T_{10},T_{80}) \, dT_{10} dT_{80} \Big| = \\
&\Big| \int_{\mathbb{R}^2_+} \Gamma(T_1(T_{10},t)) \chi_0^{\xi}(T_{10},T_{80}) \, dT_{10} dT_{80} \Big| = \\
&\Big| \int_{\mathbb{R}^2_+} \lambda |s| |T_{10} - A_1| \exp(\lambda s t) \, \chi_0^{\xi}(T_{10},T_{80}) \, dT_{10} dT_{80} \Big| \le \lambda |s| \exp(\lambda s t) d_1 V_M,
\end{aligned} \tag{5.9}$$

hence taking into account the integrability of the fundamental solution G_0, we conclude that

$$\Big| \int_{\mathbb{R}^2_+} \Gamma(T_1) R \frac{\partial}{\partial T_1} \phi \, dT_1 dT_8 \Big| \le \bar{\rho} \phi_1 \lambda |s| \exp(\lambda s t) d_1 V_M \to 0 \tag{5.10}$$

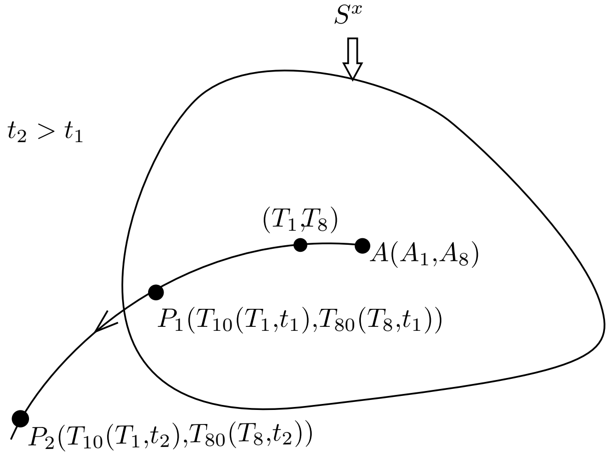

Figure 3: Backward trajectory starting from (T_1,T_8). For t_2 sufficiently large the point (T_1,T_8) escapes from the initial support.

as $\lambda s \to -\infty$ for any finite $t > 0$. Likewise,

$$\Big|\int_{\mathbb{R}^2_+} B(T_8)R\,\frac{\partial}{\partial T_8}\phi\, dT_1 dT_8\Big| \le \bar{\rho}\phi_1\lambda|r|\exp(\lambda r t)d_8 V_M \to 0 \tag{5.11}$$

as $\lambda r \to -\infty$ for any finite $t > 0$. In view of the fact that the function ϕ was arbitrary, it follows that the terms

$$\frac{\partial}{\partial T_1}\Big(\Gamma(T_1)R\Big) \quad \text{and} \quad \frac{\partial}{\partial T_8}\Big(B(T_8)R\Big)$$

vanish **weakly** asymptotically as λ tends to infinity. Similarly, for fixed λ, s and r, the relations (5.10) and (5.11) hold as $t \to \infty$. The last case is shown in Fig.5.1.

Now, let us note that, according to (3.52) and (5.8), we obtain as in (5.9):

$$\int_{\mathbb{R}^2_+} R(t,x,T_1,T_8)dT_1dT_8 = \int_{\mathbb{R}^3} G_0(t,x;0,\xi)\Big[\int_{\mathbb{R}^2_+} R_0(\xi,T_{10},T_{80})dT_{10}dT_{80}\Big]d\xi =:$$
$$\int_{\mathbb{R}^3} G_0(t,x;0,\xi)\Big[\rho_0(\xi)\Big]d\xi.$$

Due to the properties of the function G_0, we infer that, for each $t > 0$ and $x \in \mathbb{R}^3$, we have for nonzero initial data

$$\lim_{\lambda|r|,\lambda|s|\to\infty}\int_{\mathbb{R}^2_+} R(t,x,T_1,T_8)dT_1dT_8 = \mathcal{R}(t,x) > 0.$$

As for each $(t,x) \in (0,T)\times\mathbb{R}^3$, the volume of the support of $R(t,x,T_1,T_8)$ with respect to (T_1,T_8) tends to 0 (and is concentrated around the point (A_1,A_8)) the following lemma has been shown.

Lemma 5.5. *Suppose that Assumptions 3.2, 3.3, 5.3 and 5.4 are satisfied. Then, for all* $(t,x) \in (0,T]\times\overline{\Omega}$, *as* $\lambda|s| \to \infty$ *and* $\lambda|r| \to \infty$,

$$R(t,x,T_1,T_8) \to \mathcal{R}(t,x)\cdot\delta(T_1 - A_1)\delta(T_8 - A_8).$$

5.2 Asymptotic weak limit of the terms $\frac{\partial}{\partial T_1}\Gamma(T_1)R$ and $\frac{\partial}{\partial T_8}B(T_8)R$ with R given by Lemma 3.9

Assumption 5.6. *Suppose that for each* $(t,x) \in [0,T]\times\mathbb{R}^3$ *the support* S^f_{tx} *of the function* $f(t,x,\cdot,\cdot)$ *is a compact set. Let* $S_f = \bigcup_{(x,t)\in[0,T]\times\mathbb{R}^3} S^f_{tx}$. *Suppose that* $\overline{S_f} \subset S^M_f$, *where* S^M_f *is compact and its* 2*-dimensional measure satisfies*

$$|\overline{S_f^M}| < W_M.$$

and that

$$\sup_{t\in[0,T],x\in\mathbb{R}^3,(T_1,T_8)\in\overline{\mathbb{R}^2_+}} |f(t,x,T_1,T_8)| < \mathcal{F} \tag{5.12}$$

for some constants W_M *and* $\mathcal{F}$*.*

Let us note that by changing the integration variable from τ to $\eta = t-\tau$, the right hand side of (3.56) can be written as

$$u(t,x,T_1,T_8) = \int_0^t \Big(\int_{\mathbb{R}^3} \mathcal{K}(T_1,T_8;\eta)G_0(t,x;t-\eta,\xi)f(t-\eta,\xi,T_{10}(T_1,\eta),T_{80}(T_8,\eta))d\xi\Big)d\eta$$

Proceeding as in the case of the right hand side of (3.52), i.e. multiplying the expression $\dfrac{\partial(B(T_8)u)}{\partial T_8}$, by a function $\phi_1(T_1,T_8)$ of compact support in $\overline{\mathbb{R}^2_+}$, integrating by parts using Assumption 5.6, we obtain:

$$\left|\int_{\mathbb{R}^2_+} \Gamma(T_1)u\,\frac{\partial}{\partial T_1}\phi\,dT_1dT_8\right|$$
$$\leq \mathcal{F}\phi_1 \int_{\mathbb{R}^3}\left\{\int_0^t G_0(t,x;t-\eta,\xi)\left[\int_{\mathbb{R}^2_+} |\Gamma(T_1)\,\mathcal{K}(T_1,T_8;\eta)|\,\chi^f_\eta(T_1,T_8)\,dT_1dT_8\right]d\eta\right\}d\xi,$$

where $\phi_1 =: \sup_{T_1,T_8}\dfrac{\partial\phi}{\partial T_1}$, and

$$\chi^f_t(T_1,T_8) = \begin{cases} 1 & \text{if } (T_{10}(T_1,t),T_{80}(T_8,t)) \in S^f \\ 0 & \text{if } (T_{10}(T_1,t),T_{80}(T_8,t)) \notin S^f \end{cases}$$

Now, we can proceed as in the proof of Lemma 3.8. First, according to (5.7) with t replaced by η, we have

$$\int_{\mathbb{R}^2_+} |\Gamma(T_1)\,\mathcal{K}(T_1,T_8;\eta)|\,\chi^f_t(T_1,T_8)\,dT_1dT_8 = \int_{\mathbb{R}^2_+} |\Gamma(T_1(T_{10},\eta))|\chi^f_0(T_{10},T_{80})\,dT_{10}dT_{80} \leq$$
$$\int_{\mathbb{R}^2_+} \lambda|s||T_{10}-A_1|\exp(\lambda s\eta)\,\chi^f_0(T_{10},T_{80})\,dT_{10}dT_{80}\Big| \leq \lambda|s|\exp(\lambda s\eta)d_1W_M < \lambda|s|\exp(\lambda s\eta)d_1V_M.$$

It follows that for $\Delta\eta = (\sqrt{\lambda})^{-1} << 1$ we have, in view of the properties of the function G_0 (see Lemma 3.4, point 2),

$$\int\Big\{\int_{\mathbb{R}^3}\Big[\int_0^t\Big(\Gamma(T_1)\mathcal{K}(T_1,T_8;\eta)G_0(t,x;t-\eta,\xi)f(t-\eta,\xi,T_{10}(T_1,\eta),T_{80}(T_8,\eta))\Big)d\eta\Big]d\xi\Big\}dT_1dT_8 =$$
$$\int\Big\{\int_{\mathbb{R}^3}\Big[\int_{\Delta\eta}^t\Big(\Gamma(T_1)\mathcal{K}(T_1,T_8;\eta)G_0(t,x;t-\eta,\xi)f(t-\eta,\xi,T_{10}(T_1,\eta),T_{80}(T_8,\eta))\Big)d\eta\Big]d\xi\Big\}dT_1dT_8+$$
$$\int_0^{\Delta\eta}\Big[\int_{\mathbb{R}^3}\Big(\int\Big\{\Gamma(T_{10}(T_1,\eta))G_0(t,x;t-\eta,\xi)f(t-\eta,\xi,T_{10}(T_1,\eta),T_{80}(T_8,\eta))\Big\}dT_1dT_8\Big)d\xi\Big]d\eta =$$
$$O((exp(-\lambda|s|t) - exp(-\Delta\eta\lambda|s|)) +$$

$$\int_0^{\Delta\eta}\Big[\int_{\mathbb{R}^3}\Big(\int\Big\{\Gamma(T_{10}(T_1,\eta))G_0(t,x;t-\eta,\xi)f(t-\eta,\xi,T_{10}(T_1,\eta),T_{80}(T_8,\eta))\Big\}dT_1dT_8\Big)d\xi\Big]d\eta \underset{n\to\infty}{\longrightarrow}$$
$$O(exp(-\Delta\eta\lambda|s|)) + W(n),$$

where

$$W(n) = \Big| \lim_{n\to\infty} \int_{\mathbb{R}^3} \Big[\int_{\Delta\eta/n}^{\Delta\eta} \Big(\int \Big\{ \Gamma(T_{10}(T_1,\eta)) G_0(t,x;t-\eta,\xi) f(t-\eta,\xi,T_{10}(T_1,\eta),T_{80}(T_8,\eta)) \Big\} dT_1 dT_8 \Big) d\eta \Big] d\xi \Big|$$

According to the mean value theorem, the integral inside [ ] can be estimated as

$$\lim_{n\to\infty} G_0(t,x;t-\eta_*,\xi) f(t-\eta_*,\xi,T_{10}(T_1,\eta_*),T_{80}(T_8,\eta_*)) \int_{\Delta\eta/n}^{\Delta\eta} \Big((\Gamma(T_1(T_{10},\eta))\chi_0^f(T_{10},T_{80})\, dT_{10} dT_{80} \Big) d\eta,$$

where $\eta_* \in (\Delta\eta/n, \Delta\eta)$. Using (5.7) we infer that, independently of how small is $\Delta\eta$, we have for $n \to \infty$

$$\int_{\Delta\eta/n}^{\Delta\eta} \Big((\Gamma(T_1(T_{10},\eta))\chi_0^f(T_{10},T_{80})\, dT_{10} dT_{80} \Big) d\eta \le S^f \cdot C_{T_1} \cdot \int_{\Delta\eta/n}^{\Delta\eta} \lambda |s| \exp(\lambda s t) d\eta \le S^f \cdot C_{T_1},$$

where

$$C_{T_1} = \sup_{T_{10}\in S^M} |T_{10} - A_1|.$$

Using the fact that for any continuous function $\psi(\xi)$, $\int_{\mathbb{R}^3} G_0(t,x;t-\eta_*,\xi)\psi(\xi)d\xi \to \psi(x)$ pointwise as $\eta_* \to 0$, we have

$$\Big| \lim_{\eta_*\to 0} \int_{\mathbb{R}^3} G_0(t,x;t-\eta_*,\xi) f(t-\eta_*,\xi,T_{10}(T_1,\eta_*),T_{80}(T_8,\eta_*)) d\xi \Big| \to f(t,x,T_{10}(T_1,0),T_{80}(T_8,0))$$
$$= f(t,x,T_1,T_8).$$

In particular, due to (5.12),

$$lim_{n\to\infty} W(n) \le \mathcal{F} \cdot C_{T_1}.$$

Similar estimates can be obtained for the weak limit of the expression

$$\frac{\partial}{\partial T_8}(B(T_8)u).$$

We can thus conclude the validity of the following lemma.

Lemma 5.7. *Suppose that Assumptions 3.2, 3.3, 5.3, 5.4 and 5.6 are satisfied. Then, asymptotically as $\lambda \to \infty$, the weak limit of the expression*

$$[\frac{\partial}{\partial T_1}(\Gamma(T_1)u(t,x,T_1,T_8))] + [\frac{\partial}{\partial T_8}(B(T_8)u(t,x,T_1,T_8))]$$

at time $t > 0$, with u determined by (3.56), does depend only on the value of the function f at time t and does not depend on the values of this function at smaller times $\tau \in [0,t)$.

6 Weak formulation of Eq.(3.1)

As above, we consider the case $\Omega = \mathbb{R}^3$. In the previous section, we proved that in some sense, the solution $R(t,x,T_1,T_8)$ of (3.1) may converge to a generalized function $\mathcal{R}(t,x)\cdot\delta(T_1-A_1)\delta(T_8-A_8)$. In fact, we may consider the weak version of Eq. (3.1) by looking for solutions in the space of distributions $\mathcal{D}'((0,\infty)\times\Omega\times\mathbb{R}^2_+)$.

Lemma 6.1. *Suppose $\mathcal{R}(t,x)$ is a classical solution of the equation $R_t = d_R\nabla^2 R$. Suppose that the functions $\Gamma(T_1)$ and $B(T_8)$ have isolated zeros A_1 and A_8. Then $R(t,x,T_1,T_8) = \mathcal{R}(t,x)\cdot\delta(T_1 - A_1)\delta(T_8 - A_8)$ is a solution to (3.1) in the space $C^{1,2}_{t,x}([0,T)\times\Omega) \cap \times\mathcal{D}'(\mathbb{R}^2_+)$.*

Proof Let us write Eq.(3.1) in the form

$$\frac{\partial R}{\partial t} - d_R \nabla^2 R = -\frac{\partial}{\partial T_1}\left(\Gamma(T_1)\, R\right) - \frac{\partial}{\partial T_8}\left(B(T_8)\, R\right).$$

Multiplying the both sides of this equation by a test function $\psi(T_1,T_8) \in \mathcal{D}(\mathbb{R}^2_+)$, taking $R(t,x,T_1,T_8) = \mathcal{R}(t,x)\cdot\delta(T_1 - A_1)\delta(T_8 - A_8)$ and integrating over $\mathbb{R}^2_+$, we conclude that the left hand side becomes equal to 0, whereas the right hand side, in view of (1.18) is equal to:

$$\begin{aligned}
&\langle -\frac{\partial}{\partial T_1}\left(\Gamma(T_1)\, R\right) - \frac{\partial}{\partial T_8}\left(B(T_8)\, R\right), \psi\rangle = \\
&\mathcal{R}(t,x)\cdot\Big(\int_{\mathbb{R}^2_+}\Gamma(T_1)\,\delta(T_1 - A_1)\delta(T_8 - A_8)\cdot\psi_{T_1}(T_1,T_8)dT_1dT_8 + \\
&\qquad \int_{\mathbb{R}^2_+} B(T_8)\,\delta(T_1 - A_1)\delta(T_8 - A_8)\cdot\psi_{T_8}(T_1,T_8)dT_1dT_8\Big) = 0.
\end{aligned} \tag{6.1}$$

This proves the lemma. □

Lemma 6.2. *Suppose that Assumptions (5.3) and (5.4) hold. Let $R(t,x,T_1,T_8)$ be a nonegative solution of (3.1) for initial data $R_0(t,x,T_1,T_8)$ as given in (5.4) and Assumption 5.3. Let*

$$\mathcal{R}(t,x) = \int_{\mathbb{R}^2_+} R(t,x,T_1,T_8)dT_1dT_8.$$

Suppose also that for all $t \in [0,T]$ the 'total mass' integral is finite, i.e.

$$\int_{\mathbb{R}^3}\mathcal{R}(t,x)dx = M_t < \infty.$$

Then

$$R(t,x,T_1,T_8) - \mathcal{R}(t,x)\delta(T_1 - A_1)\,\delta(T_8 - A_8) \to 0$$

in the weak sense in $\mathcal{D}'(\mathbb{R}^n \times \mathbb{R}^2_+)$ as $t \to \infty$ (for fixed λ) or $\lambda \to \infty$ (for fixed $t > 0$).

Proof For a test function $\psi(x,T_1,T_8) \in \mathcal{D}(\mathbb{R}^n \times \mathbb{R}^2_+)$ of compact support, we have by means of (3.52), (11.2) and (5.3):

$$\begin{aligned}
&D_\delta = \langle R(t,x,T_1,T_8) - \mathcal{R}(t,x)\delta(T_1 - A_1)\,\delta(T_8 - A_8), \psi\rangle \\
&= \int_{\mathbb{R}^3}\int_{\mathbb{R}^2_+} R(t,x,T_1,T_8)\left(\psi(x,T_1,T_8) - \psi(x,A_1,A_8)\right)dT_1\,dT_8\,dx = \\
&\int_{\mathbb{R}^3}\int_{\mathbb{R}^2_+}\Big[\int_{\mathbb{R}^3} G_0(t,x;0,\xi)R_0(\xi,T_{10}(T_1,t),T_{80}(T_8,t))d\xi\Big]\times \\
&\qquad \Big(\psi(x,T_1,T_8) - \psi(x,A_1,A_8)\Big)\mathcal{K}(T_1,T_8;t)\,dT_1\,dT_8\,dx\,.
\end{aligned} \tag{6.2}$$

Now, using Assumption 5.3 we have

$$\begin{aligned}
&|D_\delta| = \Big|\int_{\mathbb{R}^n}\int_{S_M}\Big[\int_{\mathbb{R}^3} G_0(t,x;0,\xi)R_0(\xi,T_{10},T_{80})d\xi\Big]\times \\
&\Big(\psi(x,T_1(T_{10},t),T_8(T_{80},t)) - \psi(x,A_1,A_8)\Big)\mathcal{K}(T_1,T_8;t)\cdot\det(J(T_1,T_8;t)\,dT_{10}\,dT_{80}\,dx\Big| \le \\
&\sup_{(T_{10},T_{80})\in S_M, x\in\mathbb{R}^3}\Big|\psi(x,T_1(T_{10},t),T_8(T_{80},t)) - \psi(x,A_1,A_8)\Big|\times \\
&\qquad \int_{\mathbb{R}^3}\int_{S_M}\Big[\int_{\mathbb{R}^3} G_0(t,x;0,\xi)R_0(\xi,T_{10},T_{80})d\xi\Big]\,dT_{10}\,dT_{80}\,dx.
\end{aligned} \tag{6.3}$$

Note that by Assumption 5.4 we have

$$|\psi(x,T_1(T_{10},t),T_8(T_{80},t)) - \psi(x,A_1,A_8))| \\ \le \|\nabla\psi\|_\infty(|T_{10}-A_1|\exp(\lambda st) + |T_{80}-A_8|\exp(\lambda rt)).$$

In addition, one computes, by means of (3.52), (5.1) and (5.8),

$$\int_{\mathbb{R}^3}\int_{S_M}\Big[\int_{\mathbb{R}^3} G_0(t,x;0,\xi)R_0(\xi,T_{10},T_{80})d\xi\Big]\,dT_{10}\,dT_{80}\,dx =$$
$$\int_{\mathbb{R}^3}\int_{S_M}\Big[\int_{\mathbb{R}^3} G_0(t,x;0,\xi)R_0(\xi,T_{10}(T_1,t),T_{80}(T_8,t))\Big(\det(J(T_1,T_8;t)\Big)^{-1}d\xi\Big]\,dT_1\,dT_8\,dx =$$
$$\int_{\mathbb{R}^3}\int_{S_M}\Big[\int_{\mathbb{R}^3} G_0(t,x;0,\xi)R_0(\xi,T_{10}(T_1,t),T_{80}(T_8,t))\,\mathcal{K}(T_1,T_8;t)d\xi\Big]\,dT_1\,dT_8\,dx =$$
$$\int_{\mathbb{R}^3}\mathcal{R}(t,x)dx = M_t < \infty.$$

Thus putting everything together, we obtain

$$|\langle R(t,x,T_1,T_8) - \mathcal{R}(t,x)\delta(T_1-A_1)\,\delta(T_8-A_8),\psi\rangle| \le \|\nabla\psi\|_\infty\, M_t \times \\ (\sup_{(T_{10},T_{80})\in S_M}|T_{10}-A_1|e^{\lambda st} + \sup_{(T_{10},T_{80})\in S_M}|T_{80}-A_8|e^{\lambda rt}). \tag{6.4}$$

This expression clearly converges to zero as $t\to\infty$ (for fixed λ) or $\lambda\to\infty$ (for fixed t). □

Remark In the above proof we did not take into account that ψ has a compact support with respect to x. If this fact is taken into account, the lemma could be proved without the assumption of compactness of R_0 with respect to ξ, because the integral $\int_{\mathbb{R}^3}\int_{S_M}\Big[\int_{\mathbb{R}^3} G_0(t,x;0,\xi)R_0(\xi,T_{10},T_{80})d\xi\Big]dT_1dT_8dx$ can be replaced by the integral $\int_{S_\psi^x}\int_{S_M}\Big[\int_{\mathbb{R}^3} G_0(t,x;0,\xi)R_0(\xi,T_{10},T_{80})d\xi\Big]dT_1dT_8dx$, where S_ψ^x denotes the support of ψ with respect to x. This integral is finite. □

7 Integral equality satisfied by the function given by (3.52)

In this section we establish a conservation equality satisfied by the function determined by the right hand side of Eq.(3.52), similarly to Lemma 3.1. Next, we demonstrate that the integral of this function with respect to T_1 and T_8 is equal to a product of a constant and the solution $\mathcal{R}:[0,T]\times\mathbb{R}^3\mapsto\mathbb{R}$ to the heat equation $\mathcal{R}_t = d_R\nabla^2\mathcal{R}$. We thus show that the function defined by (3.52) satisfies a necessary condition of being a solution to Eq.(3.1). This property is shown in Lemma 7.2.

Lemma 7.1. *Suppose that the functions Γ, B and R_0 are of C^2 class of their arguments. Suppose that the support of R_0 is compact, both with respect to $(T_1,T_8)\in\overline{\mathbb{R}_+^2}$ and $x\in\mathbb{R}^3$. Then the right hand side of equality (3.52) satisfies the conservation law*

$$\int_{\mathbb{R}^3}\int_{\mathbb{R}_+^2}\Big[\int_{\mathbb{R}^3} G_0(t,x;0,\xi)R_0(\xi,T_{10}(T_1,t),T_{80}(T_8,t))\,\mathcal{K}(T_1,T_8;t)d\xi\Big]\,dT_1\,dT_8\,dx = M_0$$

where M_0 is a constant independent of $t\in[0,T]$.

Proof It suffices to show that the assumptions of Lemma 3.1 are fulfilled. The proof follows from the properties of the fundamental solution $G_0(t,x;0,\xi)$. Let $S_\xi^* = \bigcup_{T_1,T_8} Supp_\xi(T_1,T_8)$, where $Supp_\xi(T_1,T_8)$ denotes the support of R_0 with respect to ξ for $(T_1,T_8)\in\overline{\mathbb{R}_+^2}$. Note that differentiation with respect to the components of x can be replaced by differentiation with respect to corresponding components of ξ, hence

$$\nabla_x \Big[\int_{\mathbb{R}^3} G_0(t,x;0,\xi) R_0(\xi, T_{10}(T_1,t), T_{80}(T_8,t))\, \mathcal{K}(T_1,T_8;t) d\xi \Big] =$$

$$- \int_{S_\xi^*} \nabla_\xi G_0(t,x;0,\xi) R_0(\xi, T_{10}(T_1,t), T_{80}(T_8,t))\, \mathcal{K}(T_1,T_8;t) d\xi$$

$$- \int_{S_\xi^*} G_0(t,x;0,\xi) \nabla_\xi R_0(\xi, T_{10}(T_1,t), T_{80}(T_8,t))\, \mathcal{K}(T_1,T_8;t) d\xi.$$

Thus if R_0 is of C^1 class with respect to ξ, then, in view of (3.15) with $\tau = 0$, $\|\nabla_x R(t,x,T_1,T_8)\|$, vanishes as fast as $\exp(-d_x^2/(4d_R t))$, where d_x denotes the distance of x from the set S_ξ^*. In view of Lemma 3.1, the lemma is proved. □

Lemma 7.2. *Suppose that $R(t,x,T_1,T_8)$ satisfies Eq.(3.1). Suppose that for all $t \in [0,T]$ the support of $R(t,x,T_1,T_8)$ is compact with respect to (T_1,T_8), i.e. $R(t,x,T_1,T_8) \equiv 0$ if $|T_1| + |T_8|$ is sufficiently large (independently of $t \in [0,T]$ and $x \in \mathbb{R}^3$). Then the function*

$$\mathcal{R}(t,x) = \int_{\mathbb{R}^2_+} R(t,x,T_1,T_8) dT_1 dT_8$$

satisfies the diffusion equation

$$\frac{\partial \mathcal{R}}{\partial t} = d_R \nabla^2 \mathcal{R}.$$

Proof The proof follows by considering the improper integral over $\mathbb{R}^2_+$ of the both sides of Eq.(3.1) as a limit of integrals over the sets $B(0,r) \cap \mathbb{R}^2_+$. Proceeding as in the proof of Lemma 3.1), that is to say, writing the sum of the last two terms of Eq.(3.1) as $[-\nabla \cdot (\Gamma(T_1)R, B(T_8)R)]$. and using the the Gauss-Ostrogradskii theorem, we conclude that the integral of this sum vanishes. □

From Lemma 7.2, we conclude that if the function defined by the right hand side of Eq.(3.52) is in fact a solution to Eq.(3.1), then it should satisfy the identity

$$\int_{\mathbb{R}^2_+} \Big[\int_{\mathbb{R}^3} G_0(t,x;0,\xi) R_0(\xi, T_{10}(T_1,t), T_{80}(T_8,t))\, \mathcal{K}(T_1,T_8;t) d\xi \Big] dT_1 dT_8 = C \cdot \int_{\mathbb{R}^3} G_0(t,x;0,\xi) \mathcal{R}_0(\xi) d\xi$$

for some function $\mathcal{R}_0$ independent of t and (T_1,T_8). To show this, let us note that due to (5.8) we have

$$\int_{\mathbb{R}^2_+} R_0(\xi, T_{10}(T_1,t), T_{80}(T_8,t))\, \mathcal{K}(T_1,T_8;t) dT_1 dT_8 = \int_{\mathbb{R}^2_+} R_0(\xi, T_{10}, T_{80})\, dT_{10} dT_{80} := \mathcal{R}_0(\xi).$$

8 The case of the product initial data

In this section, we will consider the specific case of the initial data, which can be expressed as a product of the functions depending on x and (T_1,T_8). In this case, in principle, we can give explicit expressions for solutions also in for Eq.(3.1) with the functions Γ and B depending explicitly on t. This section can serve as a test for the validity of Lemma 3.8.

We will thus consider the equation:

$$\frac{\partial R}{\partial t} = d_R \nabla^2 R - \frac{\partial}{\partial T_1} (\Gamma(T_1,t)\, R) - \frac{\partial}{\partial T_8} (B(T_8,t)\, R). \tag{8.1}$$

Let us seek the function R satisfying Eq.(3.1) in the form of the product

$$R(t,x,T_1,T_8) := R_p(t,x) \cdot R_h(t,T_1,T_8)$$

where the function R_p satisfies the associated heat equation, i.e.

$$\frac{\partial R_p}{\partial t} = d_R \nabla^2 R_p \tag{8.2}$$

and R_h satisfies the hyperbolic equation (3.3), i.e.

$$\frac{\partial R_h}{\partial t} = -\frac{\partial}{\partial T_1}(\Gamma(T_1, t) R_h) - \frac{\partial}{\partial T_8}(B(T_8, t) R_h) \tag{8.3}$$

As, by assumption, R_p does not depend on T_1 and T_8 and R_h does not depend on x, then by calculating the partial derivative, we obtain:

$$\frac{\partial (R_p R_h)}{\partial t} = R_h \nabla_x^2 (R_p) - R_p \cdot \Big(\frac{\partial}{\partial T_1}(\Gamma R_h) + \frac{\partial}{\partial T_8}(B R_h) \Big) =$$

$$\nabla_x^2 (R_p R_h) - \Big(\frac{\partial}{\partial T_1}(\Gamma R_p R_h) + \frac{\partial}{\partial T_8}(B R_p R_h) \Big) = 0.$$

Thus, if the initial data for R have a product form, namely

$$R_0(0, x, T_1, T_8) = R_{p0}(x) \cdot R_{h0}(T_1, T_8) \tag{8.4}$$

then $R_p \cdot R_h$ satisfies Eq.(1.11). We have thus shown the following lemma.

Lemma 8.1. *Suppose that the initial data satisfy condition (8.4) and that the functions Γ and B do not depend on t and x. Then there exists a solution to Eq.(8.1) having the form $R(t, x, T_1, T_8) = R_p(t, x) \cdot R_h(t, T_1, T_8)$, where R_p satisfies Eq.(8.2) and R_h satisfies Eq.(8.3).*

In the simple example, let us consider the case of linear Γ and B functions, which seems to be the simplest example expressing the characteristic features of the analysed equation. First, let us solve the hyperbolic counterpart of Eq.(3.1), i.e. Eq.(3.3). To begin with, note that in the linear case defined by (3.19) and (3.23), Eq.(3.3) takes the form

$$\frac{\partial R_h}{\partial t} = -(s + r) R_h - \Gamma(T_1) \frac{\partial}{\partial T_1} R_h - B(T_8) \frac{\partial}{\partial T_8} R_h \tag{8.5}$$

hence by defining

$$\hat{R}_h := \exp((s + r)t) \cdot R_h. \tag{8.6}$$

we obtain

$$\frac{\partial \hat{R}_h}{\partial t} = -\Gamma(T_1) \frac{\partial}{\partial T_1} \hat{R}_h - B(T_8) \frac{\partial}{\partial T_8} \hat{R}_h \tag{8.7}$$

To simplify the example as much as possible, let us suppose that

$$s = r, \quad s_0 = r_0. \tag{8.8}$$

According to equalities (17) in [13, 3.2.2], the function $\hat{R}_h$ is invariant along the trajectories of the associated flow, i.e.

$$\frac{d\hat{R}_h}{dt} = 0$$

from where it follows that

$$\hat{R}(t, T_1(T_{10}, t), T_8(T_{80}, t)) = \hat{R}_0(T_{10}, T_{80})$$

hence

$$\hat{R}_h(t, T_1, T_8) = \hat{R}_{h0}(T_{10}(T_1, t), T_{80}(T_1, t)),$$

where the functions $T_{10}(T_1, t)$ and $T_{80}(T_1, t)$ are determined by (3.8) and (3.11). Now, inverting (8.6), we obtain:

$$R_h(t,T_1,T_8) = \exp(-(s+r)t)\hat{R}_h(t,T_1,T_8) = \exp(-(s+r)t)\hat{R}_{h0}(T_{10}(T_1,t),T_{80}(T_1,t)) =$$

$$\exp(-(s+r)t)R_{h0}(T_{10}(T_1,t),T_{80}(T_1,t)).$$

Suppose now that the condition (8.4) is satisfied. Then, according to Lemma 8.1, the solution has the form

$$R_p(t,x)\cdot\exp(-(s+r)t)R_{h0}(T_{10}(T_1,t),T_{80}(T_1,t)). \tag{8.9}$$

Let us compare this expression with the equality (3.27), i.e.

$$R(t,x,T_1) = \int_{\mathbb{R}^3}\exp(-(s+r)t)\cdot G_0(t,x;0,\xi)R_0(\xi,T_{10}(T_1,t),T_{80}(T_8,t))d\xi =$$

$$\Big(\int_{\mathbb{R}^3} G_0(t,x;0,\xi)R_{p0}(\xi)d\xi\Big)\cdot\exp(-(s+r)t)R_{h0}(T_{10}(T_1,t),T_{80}(T_8,t)) = R_p(t,x)\cdot R_h(t,T_1,T_8),$$

where we used point 4 of Lemma 3.4. Thus, in the considered case Lemma 8.1 and formula (3.27) give the same results.

Suppose that the support of the initial distribution is equal to the circle $C_{S0} = \overline{B^2((-s_0/s,-r_0/r),p_0)}$. Thus, let us assume that, for $p_0 < -s_0/s$, $\hat{R}_{h0}(T_1,T_8) = cos^4\Big((\pi\sqrt{(T_1+s_0/s)^2+(T_8+r_0/r)^2}\,(2p_0)^{-1}\Big)$ for $(T_1,T_8)\in C_{S0}$ and identically equal to 0 otherwise. For simplicity, let us suppose that $r=s$ and $r_0=s_0$. The projections of the characteristic curves of Eq.(8.7) on the (T_1,T_8) space, determined by system (3.5), are straight half-lines originating from the point $(T_1,T_8) = (-\frac{s_0}{s},-\frac{s_0}{s})$. According to (3.20), (3.26), we have

$$(T_{10}(T_1,t)+s_0/s) = (T_1+s_0/s)\exp(-st), \quad \text{and} \quad (T_{80}(T_8,t)+s_0/s) = (T_8+s/s_0)\exp(-st). \tag{8.10}$$

In the course of time, the support of the the function $R_h(t,T_1,T_8)$ (corresponding to the support of the function $R_{h0}(T_{10}(T_1,t),T_{80}(T_8,t))$) changes to a closure of the ball $B^2((-s_0/s,-r_0/r),p(t)) =: C_{St}$, where $p(t) = p_0\cdot\exp(st)$. It follows that the area of the support behaves as $\pi p_0^2\exp(2st)$. On the other hand, using (8.10) and the fact that $2\pi\int_0^1 cos^4(\pi/2\ s)sds = \frac{-16+3\pi^2}{8\pi} \cong 0.54$, we obtain

$$\int_{\mathbb{R}^2_+} R_h(t,T_1,T_8)dT_1dT_8 = \exp(-(s+r)t)\cdot\int_{C_{S_t}} R_{h0}(T_1,T_8)dT_1dT_8 =$$

$$\exp(-(s+r)t)\int_{C_{St}} cos^4\Big((\pi\sqrt{(T_{10}(T_1,t)+s_0/s)^2+(T_{80}(T_8,t)+r_0/r)^2}\,(2p(0))^{-1}\Big)dT_1dT_8 =$$

$$\exp(-(s+r)t)\int_{C_{S0}} cos^4\Big((\pi\sqrt{(T_{10}+s_0/s)^2+(T_{80}+r_0/r)^2}\,(2p_0)^{-1}\Big)\frac{dT_1}{dT_{10}}(t)\frac{dT_8}{dT_{80}}(t)dT_{10}dT_{80} =$$

$$\exp(-(s+r)t)\exp((s+r)t)\int_{C_{S0}} cos^4\Big((\pi\sqrt{(T_{10}+s_0/s)^2+(T_{80}+r_0/r)^2}\,(2p_0)^{-1}\Big)dT_{10}dT_{80} =$$

$$2\pi\int_0^{p_0} cos^4\Big(\pi h(2p_0)^{-1}\Big)hdh = p_0^2\Big(2\pi\int_0^1 cos^4(\pi/2s)sds\Big) \cong 0.54p_0^2.$$

Summing up, the support of the function R_h becomes exponentially in time concentrated around the point $(-s_0/s,-r_0/r)$ and its area is equal to $\exp((s+r)t)\pi p_0^2$. On the other hand, the integral $\int_{\mathbb{R}^2_+} R_h(t,T_1,T_8)dT_1dT_8$ is constant and equal approximately to $0.54p_0^2$. It follows that, in the considered case

$$R_h(t,T_1,T_8) \underset{t\to\infty}{\longrightarrow} 0.54p_0^2\delta(-s_0/s,-r_0/r).$$

This is in agreement with the fact that, according to (8.10)

$$R_h(t,T_1,T_8) = \exp(-2st)cos^4\Big((\pi\sqrt{(T_1+s_0/s)^2\exp(-2st)+(T_8+s_0/s)^2\exp(-2st)}\,(2p(0))^{-1}\Big) \tag{8.11}$$

if $\sqrt{(T_1+s_0/s)^2\exp(-2st)+(T_8+s_0/s)^2\exp(-2st)} \le p(0)$ and 0 otherwise. Thus the maximal value of R_h grows as fast as $\exp(-2st)$. The cross sections of the graphs of the function R_h as given by the right hand side of (8.11) for $s=-2$, $s_0>2$ and $p(0)=1$ for three times $t=0$, $t=0.5$ and $t=1$ are shown in Fig.4. By cross sections we mean here cross sections with planes perpendicular to the (T_1,T_8)-plane passing through the point $(-s_0/s,-r_0/r)$.

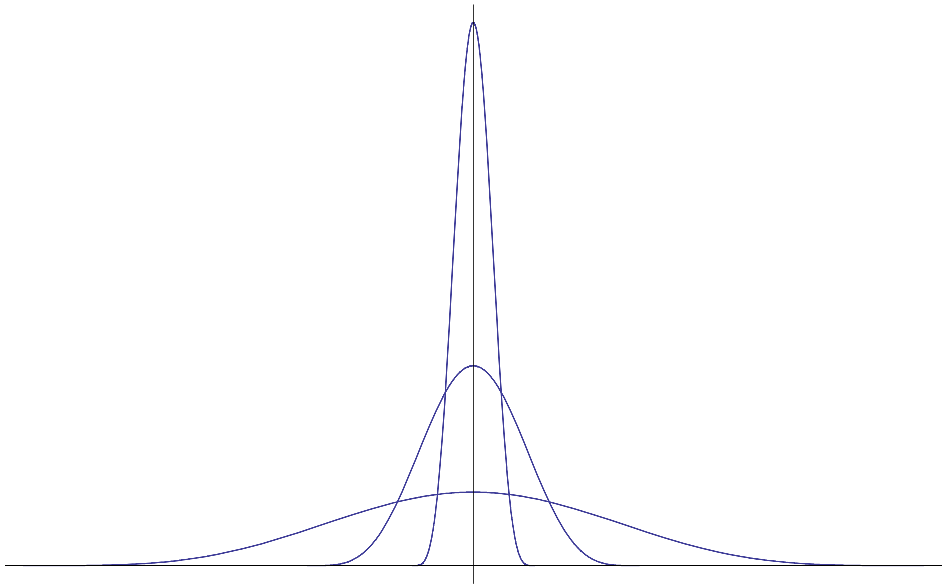

Figure 4: *Cross sections of the graphs of R_h defined by (8.11) with $s=-2$, $s_0=3$, $p(0)=1$ for $t=0$ (the flattest curve), $t=0.5$ and $t=1$ (the steepest curve).*

.

Now, the two remarks should be made.

Remark It should be emphasized that the factorization property concerns only solutions to the homogeneous equation. □

Remark It should be noted that for Γ and B independent of t, the result of Lemma 8.1 can be recovered via the analysis of equality (3.52). Thus, it follows from the assumption (8.4) that

$$R(t,x,T_1,T_8) = \Big(\int_{\mathbb{R}^3} G_0(t,x;0,\xi)R_{p0}(x)d\xi\Big)\cdot\mathcal{K}(T_1,T_8;t)R_{h0}(T_{10}(T_1,t),T_{80}(T_8,t)) \tag{8.12}$$

Let us note, as before, that we can write

$$\frac{\partial R_h}{\partial t} = -\Big(\frac{\partial\Gamma(T_1)}{\partial T_1}+\frac{\partial B(T_8)}{\partial T_8}\Big)R_h - \Gamma(T_1(s))\,\frac{\partial}{\partial T_1}\,R_h - B(T_8)\frac{\partial}{\partial T_8}\,R_h. \tag{8.13}$$

Let us consider the above equation on the characteristic curves $[0,T]\ni t\mapsto(t,T_1(t),T_8(t))$. Using the second equation of (21) [13, 3.2.2], we obtain for $t\in(0,T]$:

$$\frac{dR_h}{dt} = -\Big(\frac{\partial\Gamma(T_1(t))}{\partial T_1}+\frac{\partial B(T_8(t))}{\partial T_8}\Big)R_h. \tag{8.14}$$

Considering the characteristic curve starting for $t=0$ from (T_{10},T_{80}) and defining

$$\hat{R}_h := \exp\Big(\int_0^t\frac{\partial\Gamma(T_1(s))}{\partial T_1}ds\Big)\cdot\exp\Big(\int_0^t\frac{\partial B(T_8(t))}{\partial T_8(s)}ds\Big)\cdot R_h, \tag{8.15}$$

we obtain the equation

$$\frac{d\hat{R}_h}{dt} = 0 \tag{8.16}$$

with the initial condition $\hat{R}_h(0) = R_{h0}(T_{10}, T_{80})$. We thus obtain:

$$R_h(t, T_1(t), T_8(t)) = \exp\Big(-\int_0^t \frac{\partial\Gamma(T_1(s))}{\partial T_1} ds\Big) \cdot \exp\Big(-\int_0^t \frac{\partial B(T_8(t))}{\partial T_8(s)} ds\Big) \cdot R_{h0}(T_{10}, T_{80}).$$

Using Remark after (3.32), we have

$$\exp\Big(-\int_0^t \frac{\partial\Gamma}{\partial T_1}\Big(T_1(T_{10}, \tau)\Big)\, d\tau\Big) = \frac{\Gamma(T_{10}(T_1, t))}{\Gamma(T_1)},$$

and

$$\exp\Big(-\int_0^t \frac{\partial B}{\partial T_8}\Big(T_8(T_{80}, \tau)\Big)\, d\tau\Big) = \frac{B(T_{80}(T_1, t))}{B(T_8)}.$$

It follows that

$$R_h = \mathcal{K}(T_1, T_8, t) \cdot R_{h0}(T_{10}(T_1, t), T_{80}(T_8, t))$$

in agreement with (8.12). $\square$

Now, referring to the second sentence of this section, we will give a very simple example of a solution to the hyperbolic counterpart of Eq.(3.1). Now, starting from (8.13), we can generalize this analysis to the case of Γ and B depending on t. In this case we have

$$\frac{\partial R_h}{\partial t} = -\Big(\frac{\partial\Gamma(T_1, t)}{\partial T_1} + \frac{\partial B(T_8, t)}{\partial T_8}\Big) R_h - \Gamma(T_1(s), t)\, \frac{\partial}{\partial T_1}\, R_h - B(T_8, t)\frac{\partial}{\partial T_8}\, R_h. \tag{8.17}$$

Not to lose conciseness, we tacitly assume that Assumption 3.2 is satisfied for all $t \in [0, T]$.

Let us consider the above equation on the characteristic curves $[0, T] \ni t \mapsto (t, T_1(t), T_8(t))$. This time they are given by the equations:

$$\begin{aligned} \frac{dT_1}{dt} &= \Gamma(T_1, t), \quad T_1(0) = T_{10}, \\ \frac{dT_8}{dt} &= B(T_8, t), \quad T_{80}(0) = T_{80}. \end{aligned} \tag{8.18}$$

Using the second equation of (21) [13, 3.2.2], we obtain for $t \in (0, T]$:

$$\frac{dR_h}{dt} = -\Big(\frac{\partial\Gamma(T_1(t), t)}{\partial T_1} + \frac{\partial B(T_8(t), t)}{\partial T_8}\Big) R_h. \tag{8.19}$$

Considering the characteristic starting for $t = 0$ from (T_{10}, T_{80}) and defining

$$\hat{R}_h := \exp\Big(\int_0^t \frac{\partial\Gamma(T_1(T_{10}, s), s)}{\partial T_1} ds\Big) \cdot \exp\Big(\int_0^t \frac{\partial B(T_8(T_{80}, s), s)}{\partial T_8} ds\Big) \cdot R_h \tag{8.20}$$

we obtain the equation

$$\frac{d\hat{R}_h}{dt} = 0 \tag{8.21}$$

with the initial condition $\hat{R}_h(0) = R_{h0}(T_{10}, T_{80})$. Consequently

$$R_h(t, T_1(t), T_8(t)) = \exp\Big(-\int_0^t \frac{\partial\Gamma(T_1(s), s)}{\partial T_1} ds\Big) \cdot \exp\Big(-\int_0^t \frac{\partial B(T_8(t), s)}{\partial T_8(s)} ds\Big) \cdot R_{h0}(T_{10}, T_{80}).$$

Below, we will consider the simple but relatively general case:

$$\Gamma(T_1,t)=p_1(t)\Gamma_*(T_1) \quad \text{and} \quad B(T_8,t)=p_8(t)B_*(T_8) \tag{8.22}$$

with $p_1(t)>0$, $p_8(t)>0$ for all $t\in[0,T]$.

Under this assumption, we have, by means of (8.18) and (8.22),

$$\begin{aligned}
&\exp\Big(-\int_0^t \frac{\partial\Gamma(T_1(s),s)}{\partial T_1}ds\Big)=\exp\Big(-\int_0^t \frac{\partial\Gamma_*(T_1(s))}{\partial T_1}p_1(s)ds\Big)=\\
&\exp\Big(-\int_0^t \frac{\partial\Gamma_*(T_1(s))}{\partial T_1}dT_1\Big)=\frac{\Gamma_*(T_{10}(T_1,t))}{\Gamma_*(T_1)}=\frac{\partial T_{10}}{\partial T_1}(t)\\
&\Big(\ =\frac{\Gamma_*(T_{10}(T_1,t))p_1(t)}{\Gamma_*(T_1)p_1(t)}=\frac{\Gamma(T_{10}(T_1,t),t)}{\Gamma(T_1,t)}\ \Big),
\end{aligned} \tag{8.23}$$

where we took into account that $T_1(0)=T_{10}$. Likewise,

$$\begin{aligned}
&\exp\Big(-\int_0^t \frac{\partial B(T_8(s),s)}{\partial T_8}ds\Big)=\exp\Big(-\int_0^t \frac{\partial B_*(T_8(s))}{\partial T_8}p_8(s)ds\Big)=\\
&\exp\Big(-\int_0^t \frac{\partial B_*(T_8(s))}{\partial T_8}dT_1\Big)=\frac{B_*(T_{80}(T_8,t))}{B_*(T_8)}=\frac{\partial T_{80}}{\partial T_8}(t)\\
&\Big(\ =\frac{B_*(T_{80}(T_8,t))p_1(t)}{B_*(T_8)p_8(t)}=\frac{B(T_{80}(T_8,t),t)}{B(T_8,t)}\ \Big),
\end{aligned} \tag{8.24}$$

To show that the function

$$R(t,x,T_1,T_8)=\int_{\mathbb{R}^3} G_0(t,x;0,\xi)\cdot\frac{\Gamma_*(T_{10}(T_1,t))}{\Gamma_*(T_1)}\frac{B_*(T_{80}(T_8,t))}{B_*(T_8)}R_0(\xi,T_{10}(T_1,t),T_{80}(T_8,t))\,d\xi, \tag{8.25}$$

we can use the modification of the proof of Lemma 3.7. The modification consists in taking into account the fact that in the considered case, according to (8.23),(8.24), we have:

$$\frac{1}{\Gamma_*(T_1)}\cdot\frac{dT_1}{dT_{10}}\cdot\frac{\partial T_{10}(T_1,t)}{\partial t}=-p_1(t)$$

and

$$\frac{1}{B_*(T_8)}\cdot\frac{\partial T_8}{\partial T_{80}}\cdot\frac{dT_{80}(T_8,t)}{dt}=-p_8(t).$$

9 Extension to the equation with added diffusion terms

Let us consider the equation with additional diffusional terms with respect to T_1 and T_8:

$$\frac{\partial R}{\partial t}=d_R\nabla^2R+\varepsilon^2\Big(\frac{\partial^2R}{\partial T_1^2}+\frac{\partial^2R}{\partial T_8^2}\Big)-\frac{\partial}{\partial T_1}\left(\Gamma(T_1)\,R\right)-\frac{\partial}{\partial T_8}\left(B(T_8)\,R\right)+f(t,x,T_1,T_8) \tag{9.1}$$

where $\varepsilon\ge 0$.

The following lemmas generalize Lemma 3.8 and 3.9 to the case of Eq.(9.1).

Lemma 9.1. *The function*

$$\begin{aligned}
&R(t,x,T_1,T_8;\varepsilon)=\\
&\int_{\mathbb{R}^2_+}\int_{\mathbb{R}^3} G_0(t,x;0,\xi)Q_{1\varepsilon}(t,T_1;0,\mathcal{T}_1)Q_{8\varepsilon}(t,T_8;0,\mathcal{T}_8)\mathcal{K}(\mathcal{T}_1,\mathcal{T}_8;t)R_0(\xi,T_{10}(\mathcal{T}_1,t),T_{80}(\mathcal{T}_8,t))d\xi d\mathcal{T}_1 d\mathcal{T}_8,
\end{aligned} \tag{9.2}$$

where $\mathcal{K}(T_1, T_8; t)$ is defined by (11.2) is a solution to Eq. (9.1) with $f \equiv 0$ with the initial condition

$$R(0, x, T_1, T_8) = R_0(x, T_1, T_8)$$

and with the boundary conditions

$$R(t, x, T_1 = 0, T_8) = 0, \quad R(t, x, T_1, T_8) = 0$$

Here G_0 is given by (3.15), whereas G_1 and G_8 are Green's functions of the heat equation for the half lines $T_1 \geq 0$ and $T_8 \geq 0$, i.e. solutions to the equations

$$\frac{\partial G_{k\varepsilon}}{\partial t} - \varepsilon^2 \frac{\partial^2 G}{\partial^2 T_k} G_{k\varepsilon} = \delta(t)\delta(T_k - \mathcal{T}_k)$$

with $T_k \geq \mathcal{T}_k$ and $k = 1, 8$.

The proof follows by simple extension of the arguments used in the proof of Lemma 3.8.

Remark The explicit form of the functions $Q_{k\varepsilon}$ can be found, e.g. in [29, Section 7.1]

$$\begin{aligned} Q_{k\varepsilon}(t, T_k; \tau, \mathcal{T}_k) = (4\pi\varepsilon^2(t-\tau))^{-1/2} exp\Big(-\frac{|T_k - \mathcal{T}_k|^2}{4\varepsilon^2(t-\tau)}\Big) - (4\pi\varepsilon^2(t-\tau))^{-1/2} exp\Big(-\frac{|T_k + \mathcal{T}_k|^2}{4\varepsilon^2(t-\tau)}\Big) := \\ Q^-_{k\varepsilon} - Q^+_{k\varepsilon}. \end{aligned} \tag{9.3}$$

□

In the similar way the extension of Lemma 3.9 can be shown.

Lemma 9.2. *The function*

$$\begin{aligned} &u(t, x, T_1, T_8; \varepsilon) = \\ &\int_0^t \int_{\mathbb{R}^2_+} \int_{\mathbb{R}^3} G_0(t, x; \tau, \xi) \times \\ &Q_{1\varepsilon}(t, T_1; \tau, \mathcal{T}_1) Q_{8\varepsilon}(t, T_8; \tau, \mathcal{T}_8) \mathcal{K}(\mathcal{T}_1, \mathcal{T}_8; t-\tau) f(\tau, \xi, T_{10}(\mathcal{T}_1, t-\tau), T_{80}(\mathcal{T}_8, t-\tau)) d\xi d\mathcal{T}_1 d\mathcal{T}_8 \, d\tau \end{aligned} \tag{9.4}$$

is a solution to Eq.(9.1) with zero initial condition.

Now, let us note that

$$\begin{aligned} \lim_{\varepsilon\to 0} \int_{\mathbb{R}^2_+} Q_{1\varepsilon}(t, T_1; 0, \mathcal{T}_1) Q_{8\varepsilon}(t, T_8; 0, \mathcal{T}_8) \mathcal{K}(\mathcal{T}_1, \mathcal{T}_8; t) R_0(\xi, T_{10}(\mathcal{T}_1, t), T_{80}(\mathcal{T}_8, t)) d\mathcal{T}_1 d\mathcal{T}_8 = \\ \mathcal{K}(T_1, T_8; t) R_0(\xi, T_{10}(T_1, t; \xi), T_{80}(T_8, t)). \end{aligned} \tag{9.5}$$

Remark It is worthwhile to emphasize that we do not pass to the limit $\tau \to t$ at the left hand side of (9.5). Instead, while considering the convergence of solution to its initial data, is replaced by the equivalent limit $\varepsilon \to 0$. This passage guarantees that the product $\varepsilon^2(t-\tau) \to 0$. □

From (9.5), it is seen that for every $(T_1, T_8) \in \overline{\mathbb{R}^2_+}$

$$\begin{aligned} &\lim_{\varepsilon\to 0} R(t, x, T_1, T_8; \varepsilon) = \\ &\int_{\mathbb{R}^3} G_0(t, x; 0, \xi) \mathcal{K}(T_1, T_8; t) R_0(\xi, T_{10}(\mathcal{T}_1, t), T_{80}(\mathcal{T}_8, t)) d\xi = R(t, x, T_1, T_8). \end{aligned} \tag{9.6}$$

Likewise, using the fact that for every function $\mathcal{J}(t, \tau, \xi, \mathcal{T}_1, \mathcal{T}_8)$ of C^1 class with respect to its arguments, we have

$$\lim_{\varepsilon\to 0}\int_{\mathbb{R}^2_+} Q_{1\varepsilon}(t,T_1;\tau,\mathcal{T}_1)Q_{8\varepsilon}(t,T_8;\tau,\mathcal{T}_8)\mathcal{J}(t,\tau,\xi,\mathcal{T}_1,\mathcal{T}_8)d\mathcal{T}_1 d\mathcal{T}_8 \to \mathcal{J}(t,\tau,\xi,T_1,T_8), \tag{9.7}$$

it is seen that for every $(T_1,T_8)\in\mathbb{R}^2_+$

$$\lim_{\varepsilon\to 0} u(t,x,T_1,T_8;\varepsilon) = u(t,x,T_1,T_8). \tag{9.8}$$

In (9.6) and (9.8) denote the functions provided by Lemma (3.8) and (3.9) respectively.

Now, we will consider the behaviour of the derivatives of the functions R and u. First, let us present a convenient auxiliary result, which can be derived from the Gauss-Ostrogradskii theorem, but is more general. For convenience of the reader, its proof will be presented below.

Lemma 9.3. *Let $\mathcal{G}$ be a bounded region in $\mathbb{R}^m$, $m\geq 1$, whose boundary $S_\mathcal{G}$ is a closed, piecewise smooth surface which is positively oriented by a unit normal vector $\mathbf{n}$ directed outward from $\mathcal{G}$. If $f=f(y)$ is a scalar function with continuous partial derivatives at all points of $\overline{\mathcal{G}}$ (determined by appropriate limits as $y\to S_\mathcal{G}$). Then*

$$\int_{S_\mathcal{G}} \mathbf{n}(s)f(s)ds = \int_\mathcal{G} \nabla f(y)dy.$$

In particular, if n_j denotes the j-th component of the normal vector $\mathbf{n}$, then

$$\int_{S_\mathcal{G}} n_j(s)f(s)ds = \int_\mathcal{G} \frac{\partial}{\partial y_j}f(y)dy.$$

Proof Let $\mathbf{e}_j$, $j=1,\dots,m$, denote the unit versors of the Cartesian system in $\mathbb{R}^m$. We have:

$$\nabla f(y) = \sum_{j=1}^n \mathbf{e}_j\,\nabla\cdot(f(y)\mathbf{e}_j),$$

where ∇f denotes the gradient of a scalar function f and $\nabla\cdot\mathbf{g}$ denotes the divergence of a vector function $\mathbf{g}$. In this way, be means of the Gauss theorem,

$$\int_\mathcal{G}\nabla f(y)dy = \sum_{j=1}^n \mathbf{e}_j\int_\mathcal{G}\nabla\cdot(f(y)\mathbf{e}_j)dy =$$

$$\textstyle\sum_{j=1}^n \mathbf{e}_j\displaystyle\int_{S_\mathcal{G}}(f(y)\mathbf{e}_j)\cdot\mathbf{n}\;ds = \int_{S_\mathcal{G}} f(s)\sum_{j=1}^n \mathbf{e}_j[\mathbf{e}_j\cdot\mathbf{n}]\;ds = \int_{S_\mathcal{G}}\mathbf{n}f(s)ds.$$

The lemma has been proved. □

Note, that using (9.3) we can write, for $k=1,8$,

$$\frac{\partial Q_{k\varepsilon}}{\partial T_k} = -\frac{\partial Q^-_{k\varepsilon}}{\partial\mathcal{T}_k} - \frac{\partial Q^+_{k\varepsilon}}{\partial\mathcal{T}_k}$$

hence

$$\begin{aligned}&\frac{\partial}{\partial T_k}R(t,x,T_1,T_8;\varepsilon) = \\ &-\int_{\mathbb{R}^3} G_0(t,x;0,\xi)\int_{\mathbb{R}^2_+}\frac{\partial}{\partial\mathcal{T}_k}\Big(Q^-_{k\varepsilon}(t,T_k;0,\mathcal{T}_k)+Q^+_{k\varepsilon}(t,T_k;0,\mathcal{T}_k)\Big)Q_{k_*\varepsilon}(t,T_{k*};0,\mathcal{T}_{k*})\times \\ &\mathcal{K}(\mathcal{T}_1,\mathcal{T}_8;t)R_0(\xi,T_{10}(\mathcal{T}_1,t),T_{80}(\mathcal{T}_8,t))d\mathcal{T}_1 d\mathcal{T}_8\,d\xi\end{aligned} \tag{9.9}$$

where k_* is an index complementary to k, i.e.

$$k_* = \begin{cases} 8 & \text{if } k = 1, \\ 1 & \text{if } k = 8. \end{cases}$$

It follows that

$$\frac{\partial}{\partial T_k} R(t, x, T_1, T_8; \varepsilon) =$$
$$- \int_{\mathbb{R}^3} G_0(t, x; 0, \xi) \int_{\mathbb{R}^2_+} \frac{\partial}{\partial \mathcal{T}_k} \Big(\left[Q^-_{k\varepsilon}(t, T_k; 0, \mathcal{T}_k) + Q^+_{k\varepsilon}(t, T_k; 0, \mathcal{T}_k) \right] Q_{k_*\varepsilon}(t, T_{k*}; 0, \mathcal{T}_{k*}) \times$$
$$\mathcal{K}(\mathcal{T}_1, \mathcal{T}_8; t) R_0(\xi, T_{10}(\mathcal{T}_1, t), T_{80}(\mathcal{T}_8, t)) \Big) d\mathcal{T}_1 d\mathcal{T}_8 \, d\xi + \tag{9.10}$$
$$\int_{\mathbb{R}^3} G_0(t, x; 0, \xi) \times \int_{\mathbb{R}^2_+} \left[Q^-_{k\varepsilon}(t, T_k; 0, \mathcal{T}_k) + Q^+_{k\varepsilon}(t, T_k; 0, \mathcal{T}_k) \right] Q_{k_*\varepsilon}(t, T_{k*}; 0, \mathcal{T}_{k*}) \times$$
$$\frac{\partial}{\partial \mathcal{T}_k} \Big(\mathcal{K}(\mathcal{T}_1, \mathcal{T}_8; t) R_0(\xi, T_{10}(\mathcal{T}, t), T_{80}(\mathcal{T}_8, t)) \Big) d\mathcal{T}_1 d\mathcal{T}_8 d\xi$$

Above, the formal integrals over $\mathbb{R}^2_+$, can be understood as as the limit of the integrals

$$\int_{\mathbb{R}^2_+} (\cdot) d\mathcal{T}_1 d\mathcal{T}_8 = \lim_{r \to \infty} \int_{\mathcal{I}_C(r)} (\cdot) d\mathcal{T}_1 d\mathcal{T}_8,$$

over the region $\mathcal{I}_C$ comprised within the contours C composed of the lines $\{\mathcal{T}_1 = 0, \{0 \leq \mathcal{T}_8 \leq r\}$, $\{\mathcal{T}_8 = 0, \{0 \leq \mathcal{T}_1 \leq r\}$, and the quarter-circle $\{\mathcal{T}_1 \leq 0, \mathcal{T}_8 \geq 0, \mathcal{T}_1^2 + \mathcal{T}_8^2 = r^2\}$. Let us note that due to the fact that the initial support R_0 of the function R with respect to (T_1, T_8) is compact independently of $\xi \in \overline{\Omega}$ thus, for given $t > 0$, there exists $r(t) > 1$ sufficiently large such that $R_0(\xi, T_{10}(\mathcal{T}_1, t), T_{10}(\mathcal{T}_1, t)) \equiv 0$ if $\mathcal{T}_1^2 + \mathcal{T}_8^2 \geq r(t)$. It follows that for fixed $t > 0$ and $\xi \in \mathbb{R}^3$:

$$\left[Q^-_{k\varepsilon}(t, T_k; 0, \mathcal{T}_k) + Q^+_{k\varepsilon}(t, T_k; 0, \mathcal{T}_k) \right] Q_{k_*\varepsilon}(t, T_{k*}; 0, \mathcal{T}_{k*}) \mathcal{K}(\mathcal{T}_1, \mathcal{T}_8; t) R_0(\xi, T_{10}(\mathcal{T}_1, t), T_{80}(\mathcal{T}_8, t)) \equiv 0$$

together with its derivatives for $\mathcal{T}_1^2 + \mathcal{T}_8^2 \geq r(t)$. Next, the function $R_0(\xi, T_{10}(\mathcal{T}_1, t), T_{80}(\mathcal{T}_8, t))$ vanish for $\mathcal{T}_1 = 0$ or $\mathcal{T}_8 = 0$, the last expression is equal to zero also on the axes $T_1 = 0$ and $T_8 = 0$. Thus, using the second identity in Lemma 9.3 with $m = 2$ and $n_j = n_k$, we obtain

$$\int_{\mathbb{R}^2_+} \frac{\partial}{\partial \mathcal{T}_k}$$
$$\Big(\left[Q^-_{k\varepsilon}(t, T_k; 0, \mathcal{T}_k) + Q^+_{k\varepsilon}(t, T_k; 0, \mathcal{T}_k) \right] Q_{k_*\varepsilon}(t, T_{k*}; 0, \mathcal{T}_{k*}) \mathcal{K}(\mathcal{T}_1, \mathcal{T}_8; t) R_0(\xi, T_{10}(\mathcal{T}_1, t), T_{80}(\mathcal{T}_8, t)) \Big) d\mathcal{T}_1 d\mathcal{T}_8$$
$$= \lim_{r \to \infty} \int_{\mathcal{I}_C(r)} \frac{\partial}{\partial \mathcal{T}_k}$$
$$\Big(\left[Q^-_{k\varepsilon}(t, T_k; 0, \mathcal{T}_k) + Q^+_{k\varepsilon}(t, T_k; 0, \mathcal{T}_k) \right] Q_{k_*\varepsilon}(t, T_{k*}; 0, \mathcal{T}_{k*}) \mathcal{K}(\mathcal{T}_1, \mathcal{T}_8; t) R_0(\xi, T_{10}(\mathcal{T}_1, t), T_{80}(\mathcal{T}_8, t)) \Big) d\mathcal{T}_1 d\mathcal{T}_8$$
$$= \int_{C(r)} \left[Q^-_{k\varepsilon}(t, T_k; 0, \mathcal{T}_k) + Q^+_{k\varepsilon}(t, T_k; 0, \mathcal{T}_k) \right]$$
$$\times Q_{k_*\varepsilon}(t, T_{k*}; 0, \mathcal{T}_{k*}) \mathcal{K}(\mathcal{T}_1, \mathcal{T}_8; t) R_0(\xi, T_{10}(\mathcal{T}_1, t), T_{80}(\mathcal{T}_8, t)) n_k ds(r),$$

where $ds(r)$ is the infinitesimal arc length over the circle $C(0, r)$. It follows from (9.10) that

$$\frac{\partial}{\partial T_k} R(t, x, T_1, T_8; \varepsilon) = \int_{\mathbb{R}^3} G_0(t, x; 0, \xi) \int_{\mathbb{R}^2_+} \left[Q^-_{k\varepsilon}(t, T_1; 0, \mathcal{T}_1) + Q^+_{k\varepsilon}(t, T_1; 0, \mathcal{T}_1) \right] Q_{k_*\varepsilon}(t, T_8; 0, \mathcal{T}_8) \times$$
$$\frac{\partial}{\partial \mathcal{T}_k} \Big(\mathcal{K}(\mathcal{T}_1, \mathcal{T}_8; t) R_0(\xi, T_{10}(\mathcal{T}_1, t), T_{80}(\mathcal{T}_8, t)) \Big) d\mathcal{T}_1 d\mathcal{T}_8 \, d\xi \tag{9.11}$$

Likewise, we can show that

$$\frac{\partial}{\partial T_k}u(t,x,T_1,T_8;\varepsilon) = \int_0^t \int_{\mathbb{R}^3}\int_{\mathbb{R}^2_+} G_0(t,x;\tau,\xi)\ \left[Q^-_{k\varepsilon}(t,T_k;0,\mathcal{T}_k) + Q^+_{k\varepsilon}(t,T_k;0,\mathcal{T}_k)\right] Q_{k_*\varepsilon}(t,T_{k*};0,\mathcal{T}_{k*})$$

$$\times\frac{\partial}{\partial T_k}\Big(\mathcal{K}(\mathcal{T}_1,\mathcal{T}_8;t-\tau)f(\tau,\xi,T_{10}(\mathcal{T}_1,t-\tau),T_{80}(\mathcal{T}_8,t-\tau))d\mathcal{T}_1 d\mathcal{T}_8\Big)\ d\xi\ d\tau$$

Finally, using the identities (9.6) and (9.8) one can prove that

$$\lim_{\varepsilon\to 0}\frac{\partial}{\partial T_k}R(t,x,T_1,T_8;\varepsilon) = \frac{\partial}{\partial T_k}R(t,x,T_1,T_8) \tag{9.12}$$

and

$$\lim_{\varepsilon\to 0}\frac{\partial}{\partial T_k}u(t,x,T_1,T_8;\varepsilon) = \frac{\partial}{\partial T_k}u(t,x,T_1,T_8). \tag{9.13}$$

This follows from the form of the functions $Q_{1\varepsilon}$, $Q_{8\varepsilon}$ given by (9.3), the Remark after (9.5), point 2 of Lemma 3.4 resulting in the following simple lemma.

Lemma 9.4. *Suppose that the support of the function $g(T_1,T_8)\in C^0(\mathbb{R}^2)$ is compact and contained in $\mathbb{R}^2_+$. Then*

$$\lim_{\varepsilon\to 0}\int_{\mathbb{R}_+}\int_{\mathbb{R}_+}\times$$
$$\Big(G^-_{1\varepsilon}(t,T_1;0,\mathcal{T}_1)\pm G^+_{1\varepsilon}(t,T_1;0,\mathcal{T}_1)\Big)\Big(G^-_{8\varepsilon}(t,T_1;0,\mathcal{T}_1)\pm G^+_{8\varepsilon}(t,T_1;0,\mathcal{T}_1)\Big)g(\mathcal{T}_1,\mathcal{T}_8)d\mathcal{T}_1 d\mathcal{T}_8 =$$
$$= g(T_1,T_8).$$

Proof Due to the compactness of the support of the function g we can write

$$\lim_{\varepsilon\to 0}\int_{\mathbb{R}_+}\int_{\mathbb{R}_+}\times$$
$$\Big(G^-_{1\varepsilon}(t,T_1;0,\mathcal{T}_1)\pm G^+_{1\varepsilon}(t,T_1;0,\mathcal{T}_1)\Big)\Big(G^-_{8\varepsilon}(t,T_1;0,\mathcal{T}_1)\pm G^+_{8\varepsilon}(t,T_1;0,\mathcal{T}_1)\Big)g(\mathcal{T}_1,\mathcal{T}_8)d\mathcal{T}_1 d\mathcal{T}_8 =$$
$$\lim_{\varepsilon\to 0}\int_{\mathbb{R}_+}\Big(G^-_{8\varepsilon}(t,T_1;0,\mathcal{T}_1)\pm G^+_{8\varepsilon}(t,T_1;0,\mathcal{T}_1)\Big)\times$$
$$\Big[\lim_{\varepsilon\to 0}\int_{\mathbb{R}_+}\Big(G^-_{1\varepsilon}(t,T_1;0,\mathcal{T}_1)\pm G^+_{1\varepsilon}(t,T_1;0,\mathcal{T}_1)\Big)g(\mathcal{T}_1,\mathcal{T}_8)d\mathcal{T}_1\Big]d\mathcal{T}_8$$

As $g(T_1,\mathcal{T}_8)\equiv 0$ for $T_1\leq 0$ and all $\mathcal{T}_8\in\mathbb{R}$, we have $H(-T_1)g(T_1,\mathcal{T}_8) = H(T_1)g(-T_1,\mathcal{T}_8)\equiv 0$ hence by point 2 of Lemma 3.4

$$\lim_{t\to 0}\int_{\mathbb{R}_+}\Big(G^-_{1\varepsilon}(t,T_1;0,\mathcal{T}_1)\pm G^+_{1\varepsilon}(t,T_1;0,\mathcal{T}_1)\Big)g(\mathcal{T}_1,\mathcal{T}_8)d\mathcal{T}_1 =$$
$$\lim_{t\to 0}\int_{\mathbb{R}}\Big(G^-_{1\varepsilon}(t,T_1;0,\mathcal{T}_1)\pm G^+_{1\varepsilon}(t,T_1;0,\mathcal{T}_1)\Big)H(\mathcal{T}_1)g(\mathcal{T}_1,\mathcal{T}_8)d\mathcal{T}_1 =$$
$$H(T_1)g(T_1,\mathcal{T}_8)\pm H(T_1)g(-T_1,K_8) = g(T_1,\mathcal{T}_8).$$

Similarly, as $g(T_1,\mathcal{T}_8)\equiv 0$ for $\mathcal{T}_8\leq 0$ and all $T_1\in\mathbb{R}$, we have $H(-\mathcal{T}_8)g(T_1,\mathcal{T}_8) = H(\mathcal{T}_8)g(T_1,-\mathcal{T}_8)\equiv 0$ hence

$$\lim_{t\to 0}\int_{\mathbb{R}_+}\Big(G^-_{8\varepsilon}(t,T_8;0,\mathcal{T}_8)\pm G^+_{8\varepsilon}(t,T_8;0,\mathcal{T}_8)\Big)g(T_1,\mathcal{T}_8)d\mathcal{T}_8 =$$
$$\lim_{t\to 0}\int_{\mathbb{R}}\Big(G^-_{8\varepsilon}(t,T_8;0,\mathcal{T}_8)\pm G^+_{8\varepsilon}(t,T_8;0,\mathcal{T}_8)\Big)H(\mathcal{T}_8)g(T_1,\mathcal{T}_8)d\mathcal{T}_8 =$$
$$H(T_8)g(T_1,T8)\pm H(T_8)g(T_1,-T_8)=g(T_1,T_8).$$

The lemma is proved. □

The same analysis can be carried out in case of the second derivatives with respect to T_k, $k=1,8$. Then repeating twice the analysis presented above we obtain:

$$\frac{\partial^2}{\partial T_1\partial T_8}R(t,x,T_1,T_8;\varepsilon)=$$
$$\int_{\mathbb{R}^3}G_0(t,x;0,\xi)\int_{\mathbb{R}^2_+}\left[Q^-_{1\varepsilon}(t,T_1;0,\mathcal{T}_1)+Q^+_{1\varepsilon}(t,T_1;0,\mathcal{T}_1)\right]\left[Q^-_{8\varepsilon}(t,T_1;0,\mathcal{T}_1)+Q^+_{8\varepsilon}(t,T_1;0,\mathcal{T}_1)\right]\times$$
$$\frac{\partial^2}{\partial\mathcal{T}_1\partial\mathcal{T}_8}\Big(\mathcal{K}(\mathcal{T}_1,\mathcal{T}_8;t)R_0(\xi,T_{10}(\mathcal{T}_1,t),T_{80}(\mathcal{T}_8,t))\Big)d\mathcal{T}_1d\mathcal{T}_8\,d\xi. \tag{9.14}$$

Next, due to the fact that, for $k=1,8$,

$$\frac{\partial^2 Q_{k\varepsilon}}{\partial T_k^2}=\frac{\partial^2 Q_{k\varepsilon}}{\partial \mathcal{T}_k^2},$$

we obtain

$$\begin{aligned}&\frac{\partial^2}{\partial T_k^2}R(t,x,T_1,T_8;\varepsilon)=\int_{\mathbb{R}^3}G_0(t,x;0,\xi)\int_{\mathbb{R}^2_+}Q_{1\varepsilon}(t,T_1;0,\mathcal{T}_1)\cdot Q_{8\varepsilon}(t,T_1;0,\mathcal{T}_1)\times\\&\frac{\partial^2}{\partial\mathcal{T}_1\partial\mathcal{T}_8}\Big(\mathcal{K}(\mathcal{T}_1,\mathcal{T}_8;t)R_0(\xi,T_{10}(\mathcal{T}_1,t),T_{80}(\mathcal{T}_8,t))\Big)d\mathcal{T}_1d\mathcal{T}_8\,d\xi.\end{aligned} \tag{9.15}$$

Likewise

$$\frac{\partial^2}{\partial T_1\partial T_8}u(t,x,T_1,T_8;\varepsilon)=$$
$$\int_{\mathbb{R}^3}G_0(t,x;0,\xi)\int_{\mathbb{R}^2_+}\left[Q^-_{1\varepsilon}(t,T_1;0,\mathcal{T}_1)+Q^+_{1\varepsilon}(t,T_1;0,\mathcal{T}_1)\right]\left[Q^-_{8\varepsilon}(t,T_1;0,\mathcal{T}_1)+Q^+_{8\varepsilon}(t,T_1;0,\mathcal{T}_1)\right]\times$$
$$\frac{\partial^2}{\partial\mathcal{T}_1\partial\mathcal{T}_8}\Big(\mathcal{K}(\mathcal{T}_1,\mathcal{T}_8;t-\tau)f(\tau,\xi,T_{10}(\mathcal{T}_1,t-\tau),T_{80}(\mathcal{T}_8,t-\tau))d\mathcal{T}_1d\mathcal{T}_8\Big)d\mathcal{T}_1d\mathcal{T}_8\,d\xi. \tag{9.16}$$

and

$$\begin{aligned}&\frac{\partial^2}{\partial T_k^2}u(t,x,T_1,T_8;\varepsilon)=\int_{\mathbb{R}^3}G_0(t,x;0,\xi)\int_{\mathbb{R}^2_+}Q_{1\varepsilon}(t,T_1;0,\mathcal{T}_1)\cdot Q_{8\varepsilon}(t,T_1;0,\mathcal{T}_1)\times\\&\frac{\partial^2}{\partial\mathcal{T}_k^2}\Big(\mathcal{K}(\mathcal{T}_1,\mathcal{T}_8;t-\tau)f(\tau,\xi,T_{10}(\mathcal{T}_1,t-\tau),T_{80}(\mathcal{T}_8,t-\tau))d\mathcal{T}_1d\mathcal{T}_8\Big)d\mathcal{T}_1d\mathcal{T}_8\,d\xi.\end{aligned} \tag{9.17}$$

Similarly to (9.12) and (9.13) we have, for $k,l=1,8$,

$$\lim_{\varepsilon\to 0}\frac{\partial^2}{\partial T_k\partial T_l}R(t,x,T_1,T_8;\varepsilon)=\frac{\partial^2}{\partial T_k\partial T_l}R(t,x,T_1,T_8) \tag{9.18}$$

and

$$\lim_{\varepsilon\to 0} \frac{\partial^2}{\partial T_k \partial T_l} u(t,x,T_1,T_8;\varepsilon) = \frac{\partial^2}{\partial T_k \partial T_l} u(t,x,T_1,T_8). \tag{9.19}$$

Consequently, the following lemma holds.

Lemma 9.5. *Let $R(t,x,T_1,T_8;\varepsilon)$ and $u(t,x,T_1,T_8;\varepsilon)$ denote the functions defined in (9.2) and (9.4), whereas $R(t,x,T_1,T_8)$ and $R(t,x,T_1,T_8)$ the corresponding functions defined by 3.8 and 3.9. Then, for every $t \in [0,T)$,*

$$R(t,x,T_1,T_8;\varepsilon) \to R(t,x,T_1,T_8) \quad \text{and} \quad u(t,x,T_1,T_8;\varepsilon) \to u(t,x,T_1,T_8)$$

as $\varepsilon \to 0$, in the $C^2(\overline{\Omega} \times \overline{\mathrm{IR}^2_+})$ norm.

Remark It follows straightforwardly from Eq.(9.1) that also the time derivatives of the functions $R(t,x,T_1,T_8;\varepsilon)$ and $u(t,x,T_1,T_8;\varepsilon)$ tend the time derivatives of $R(t,x,T_1,T_8)$ and $u(t,x,T_1,T_8)$ as $\varepsilon \to 0$ for each $(x,T_1,T_8) \in \overline{\Omega} \times \overline{\mathrm{IR}^2_+}$. □

10 Remarks on the existence of the Green's function for the Neumann problems in bounded regions

The explicit form of the Green's function with homogeneous boundary conditions of Robin type has been found for many specific bounded regions, like an interval, a sphere [26], or a rectangle [14]. However, in many standard books in the theory of parabolic differential equations, the existence of Green's function for Neumann problems is not stated. (In [15] such an existence is only mentioned as a result of [15, Problem 5, chapter 5]. Instead, in [15] or [29] (which in the context of Green's function approach is based on the results in [15]) another form of integral representation of the solution to the Neumann (second type) initial boundary value problem is presented (see (3.5) in [15, section 3, chapter 5]).

Let $\Omega \subset \mathrm{IR}^m$ be a bounded domain with the boundary of class $C^{2+\upsilon}$, $\upsilon \in (0,1)$. For $\tau \geq 0$, $T > \tau$, let us consider the linear parabolic equation:

$$\begin{aligned} &Au = f(t,x) && \text{in } (\tau,T)\times\Omega,\\ &u(\tau,x) = \psi(x) && \text{on } \overline{\Omega},\\ &\frac{\partial u(t,x)}{\partial \nu(t,x)} = 0 && \text{on } (\tau,T)\times\partial\Omega, \end{aligned} \tag{10.1}$$

where ψ and f given,

$$A := L - \frac{\partial u}{\partial t}, \tag{10.2}$$

and

$$L := \sum_{i,j=1}^{m} a_{ij}(t,x) \frac{\partial^2}{\partial x_i \partial x_j} + \sum_{j=1}^{m} b_j(t,x) \frac{\partial}{\partial x_j} + c(t,x) \tag{10.3}$$

is a second order uniformly elliptic operator with sufficiently smooth coefficients depending on (t,x). $\nu(t,x)$ denotes the vector with components $\nu_i(t,x) = \sum a_{ij}(t,x) n_j(x)$, where $n(x) = (n_1(x),\ldots,n_m(x))$ is the unit outward vector normal to $\partial\Omega$ at x. Thus

$$\frac{\partial u(t,x)}{\partial \nu(t,x)} = \nu(t,x)\cdot\nabla u(t,x) = \sum a_{ij}(t,x) n_j(x) \frac{\partial u}{\partial x_j}(t,x). \tag{10.4}$$

In fact, the left hand side of (10.4) denotes the diffusional flux through the boundary at point $x \in \partial\Omega$. Let $\Gamma(t,x;\tau,\xi)$ denotes the fundamental solution to the first equation of system (10.1). We thus assume that Γ satisfies the equation $Au = 0$ as a function of (t,x) in $\Omega\times(0,T)$ for all $(\tau,\xi) \in \Omega\times(0,T)\cap\{\tau < t\}$ and that for any $\psi \in C^0(\overline{\Omega})$ and any $x \in \Omega$, we have

$$\lim_{t\searrow\tau} \int_\Omega \Gamma(t,x;\tau,\xi)\psi(\xi)d\xi = \psi(x). \tag{10.5}$$

In particular, if L is equal to $d_R\Delta$, then Γ is given by the right hand side of (3.15), i.e.

$$\Gamma(t,x;\tau,\xi) = \frac{1}{(4\pi d_R(t-\tau))^{3/2}} e^{-\frac{|x-\xi|^2}{4d_R(t-\tau)}}.$$

Basing on the representation of solution to system (10.1), given by (3.5) in [15, section 3, chapter 5], it is proved in [6] the existence of the Green's function for problem (10.1). Moreover, in a sense, the Green's function is defined explicitly. Thus, let

$$M_1(t,x;\tau,\xi) = -2\frac{\partial\Gamma(t,x;\tau,\xi)}{\partial\nu(t,x)}$$

and

$$M_{\rho+1}(t,x;\tau,\xi) = \int_\tau^t \int_{\partial\Omega} M_1(t,x;\sigma,\eta)M_\rho(\sigma,\eta;\tau,\xi)d\eta d\sigma.$$

Having shown the convergence of the series

$$\sum_{\rho=1}^{s_\rho} M_\rho(t,x;\tau,\xi)$$

as $s_\rho \to \infty$, it is proved in [6, Section 3] that the Green's function for (10.1) can be constructed, in a way, explicitly. Thus, if

$$\mathcal{N}(t,x;\tau,\xi) = -2\frac{\partial}{\partial\nu(t,x)}\Gamma(t,x;\tau,\xi) - 2\sum_{\rho=1}^{\infty}\int_\tau^t\int_{\partial\Omega} M_\rho(t,x;\sigma,\eta)\frac{\partial}{\partial\nu(\sigma,\eta)}\Gamma(\sigma,\eta;\tau,\xi)d\eta d\sigma, \tag{10.6}$$

then the following lemma holds.

Lemma 10.1. *The Green's function for problem (10.1) is equal to*

$$G(t,x;\tau,\xi) = \int_\tau^t \int_{\partial\Omega} \Gamma(t,x;\sigma,\eta)\mathcal{N}(\sigma,\eta;\tau,\xi)d\eta d\sigma + \Gamma(t,x;\tau,\xi). \tag{10.7}$$

This function satisfies the identity

$$G(t,x;\tau,\xi) = \int_\Omega G(t,x;\sigma,\eta)G(\sigma,\eta;\tau,\xi)d\eta \quad \tau < \sigma < t$$

and if $c(t,x) = 0$, *then*

$$\int_\Omega G(t,x;\tau,\xi)d\xi = 1.$$

The solution to problem (10.1) can be represented in the form:

$$u(t,x) = \int_\Omega G(t,x;\tau,\xi)\psi(\xi)d\xi + \int_\tau^t \left(\int_\Omega G(t,x;\xi,s)f(x,s)d\xi\right) ds.$$

Remark It follows from Lemma 10.1 and (10.5) that the Green's function for the bounded region Ω (with sufficiently smooth boundary) satisfies the properties corresponding to points 1,2,3,4 of Lemma 3.4. □

Remark Suppose that for all $\xi \in \Omega$, $t > \tau$, the fundamental solution $\Gamma(t,x;\tau,\xi)$ of the equation $Au = 0$ (which is, in general, different than the heat kernel given by (3.18)) satisfies the boundary conditions

$$\frac{\partial\Gamma(t,x;\tau,\xi)}{\partial\nu(t,x)} = 0 \qquad\qquad \text{on } (0,T)\times\partial\Omega.$$

Then, according to (10.6) and (10.7), $G(t,x;\tau,\xi) = \Gamma(t,x;\tau,\xi)$. □

Remark Let us note that, in the case $a_{ij} = \delta_{ij}d_R$, then, due to definition (10.4)), the condition $\dfrac{\partial u(t,x)}{\partial\nu(t,x)} = 0$ implies the homogeneous Neumann boundary condition

$$\frac{\partial\, u}{\partial n} = 0 \quad \text{for } n = n(x),\, x\in\partial\Omega.$$

□

11 The case of bounded regions

In view of section 10, we can generalize our previous results to bounded regions. To be more precise, the following statement holds.

Theorem 11.1. *Let $\Omega\subset\mathbb{R}^j$, $1\le j\le 3$ be a bounded domain with sufficiently smooth boundary. Then Lemma 3.8, Lemma 3.9, uniqueness results in section 4, and the convergence statements in section 9 remain valid.*

Proof The proof of this statement is due to the fact that all the expressions exploited in above can be used modulo the formal change of $G_0\mapsto G$, where G is the Green's function for the problem (10.1) for $L = d_R\nabla^2$. To prove it suffices to apply the previous analysis to the integrals over finite space regions Ω. □

In particular, the unique solution to the initial value problem for the homogeneous and inhomogeneous equation corresponding to (3.1) is given in the following lemma.

Theorem 11.2. *Let $m = 1,2,3$. Let Ω be a bounded region with the boundary $\partial\Omega$ in $C^{2+\upsilon}$ class. Let G denotes the Green's function for the problem (10.1) with $L = d_R\nabla^2$. Suppose that Assumption 3.3 holds for all $x\in\overline{\Omega}$, and that for all $(T_1,T_8)\in\overline{\mathbb{R}^2_+}$, the function $R_0:\overline{\Omega}\times\overline{\mathbb{R}^2_+}$, satisfies*

$$\frac{\partial}{\partial n(x)}R_0(x,T_1,T_8) = 0 \quad \textit{for } x\in\partial\Omega.$$

Then, the function

$$R(t,x,T_1,T_8) = \int_\Omega G(t,x;0,\xi)\mathcal{K}(T_1,T_8;t)R_0(\xi,T_{10}(T_1,t),T_{80}(T_8,t))d\xi\,, \tag{11.1}$$

where

$$\mathcal{K}(T_1,T_8;t) := \frac{\Gamma(T_{10}(T_1,t)}{\Gamma(T_1)}\frac{B(T_{80}(T_8,t)}{B(T_8)}, \tag{11.2}$$

is a solution to the equation

$$\frac{\partial R}{\partial t} = d_R\nabla^2 R - \frac{\partial}{\partial T_1}\left(\Gamma(T_1;x)\,R\right) - \frac{\partial}{\partial T_8}\left(B(T_8;x)\,R\right) \tag{11.3}$$

with the initial condition

$$R(0,x,T_1,T_8) = R_0(x,T_1,T_8)$$

and the homogeneous Neumann boundary conditions

$$\frac{\partial}{\partial n(x)}R(t,x,T_1,T_8) = 0 \quad \textit{for } x\in\partial\Omega.$$

Next, the function

$$u(t,x,T_1,T_8) = \int_0^t \Big(\int_\Omega \mathcal{K}(T_1,T_8;t-\tau)G(t,x;\tau,\xi)f(\tau,\xi,T_{10}(T_1,t-\tau),T_{80}(T_8,t-\tau))d\xi\Big)d\tau \tag{11.4}$$

is the solution to the non-homogeneous equation

$$\frac{\partial R}{\partial t} = d_R \nabla^2 R - \frac{\partial}{\partial T_1}\left(\Gamma(T_1)\, R\right) - \frac{\partial}{\partial T_8}\left(B(T_8)\, R\right) + f(t, x, T_1, T_8). \tag{11.5}$$

with zero initial conditions and the homogeneous Neumann boundary conditions. If $R_0 \in C^{\upsilon,2,2}_{x,T_1,T_8}$ *and* $f \in C^{\upsilon/2,\upsilon,2,2}_{t,x,T_1,T_8}$, *whereas* Γ *and* B *are of* C^3 *class of their arguments (in the corresponding domains), then the functions given by the right hand sides of (11.1) and (11.4) are bounded in the norm of the space* $C^{1+\upsilon/2,2+\upsilon,2}_{t,x,(T_1,T_8)}([0,T] \times \overline{\Omega} \times \overline{\mathbb{R}^2_+})$. *These solutions are unique in the space of functions* $\mathcal{W}_{2B}$ *which is defined similarly to the space* $\mathcal{W}_2$ *before Lemma 4.2 by replacing* $\mathbb{R}^3$ *with* $\overline{\Omega}$.

12 Final remarks

12.1 Generalization to bigger dimensions

The obtained results can be extended to equations for the spatial sets $\Omega \subseteq \mathbb{R}^n$ with arbitrary $n < \infty$ and arbitrary number s of T variables, that is to say to equations of the form:

$$\frac{\partial R}{\partial t} = d_R \nabla^2 R - \sum_{\kappa=1}^{s} \frac{\partial}{\partial T_\kappa}\left(\Gamma(T_\kappa)\, R\right) + f(t, x, T_1, \ldots, T_s). \tag{12.1}$$

Assumption 12.1. *Assume that* $\Gamma_1(T_1), \ldots, \Gamma_s(T_s)$ *are of* C^{k+1} *class,* $k \geq 2$, *and that for all* $(T_{10}, \ldots, T_{s0})$ *the system*

$$\frac{dT_1}{dt}(t) = \Gamma_1(T_1), \ldots, \frac{dT_s}{dt}(t) = \Gamma_s(T_s), \quad T_1(0) = T_{10}, \ldots, T_s(0) = T_{s0}. \tag{12.2}$$

has a unique C^{k+1} *solution* $(T_1(\cdot), T_8(\cdot))$ *satisfying the initial conditions* $T_1(0) = T_{10}$, …, $T_s(0) = T_{s0}$, *defined for all* $t \geq 0$. *Suppose that there exists a positive number* ρ_{1-s}, *such that*

$$\Gamma_1(T_1) \geq 0 \quad \textit{for } |T_1| \leq \rho_{1-s},$$

$$\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots$$

$$\Gamma_s(T_s) \geq 0 \quad \textit{for } |T_s| \leq \rho_{1-s}.$$

Assumption 12.2. *Assume that for all* $x \in \overline{\Omega}$, $R_0(x, T_1, \ldots, T_s) \not\equiv 0$ *only for* $(T_1, \ldots, T_s)$ *from some open precompact set in* $\mathbb{R}^2_+$.

Let $\Omega = \mathbb{R}^n$ or let Ω be a bounded open subset of $\mathbb{R}^n$ with the boundary $\partial\Omega$ belonging to $C^{2+\upsilon}$ class, $\upsilon \in (0,1)$. Then the unique solution to the homogeneous version of Eq.(12.1) (with $f \equiv 0$), satisfying the homogeneous Neumann boundary conditions if Ω is bounded, can be expressed in the form

$$R(t, x, T_1, \ldots, T_s) = \int_\Omega G(t, x; 0, \xi) \mathcal{K}(T_1, \ldots, T_s; t) R_0(\xi, T_{10}(T_1, t), \ldots, T_{s0}(T_s, t)) d\xi\,.$$

Here G is either equal to G_0^n specified in Lemma 3.4 (if $\Omega = \mathbb{R}^n$), or G is equal to the Green's function for the homogeneous Neumann boundary value problem discussed in section 10, whereas

$$\mathcal{K}(T_1, \ldots, T_s; t) := \prod_{k=1}^{s} \frac{\Gamma_k(T_{k0}(T_k, t))}{\Gamma(T_k)}.$$

Next, the unique solution to the inhomogeneous problem with zero initial condition is equal to

$$u(t, x, T_1, \ldots, T_s) = \int_0^t \Big(\int_\Omega \mathcal{K}(T_1, \ldots, T_s; t-\tau) G(t, x; \tau, \xi) f(\tau, \xi, T_{10}(T_1, t-\tau), \ldots, T_{s0}(T_s, t-\tau)) d\xi \Big) d\tau.$$

If R_0 and f are of C^2 class and Γ_k, $k = 1, \ldots, s$ are of C^3 class of their arguments (in the corresponding domains), then the functions R and u are bounded in the norm of the space $C^{1+\upsilon/2, 2+\upsilon, 2}_{t,x,(T_1,\ldots,T_s)}([0,T] \times \overline{\Omega} \times \overline{\mathbb{R}^s_+})$. These solutions are unique in the space of functions $\mathcal{W}_{2B}$ which is defined similarly to the space $\mathcal{W}_2$ before Lemma 4.2 by replacing $\mathbb{R}^3$ with $\overline{\Omega}$.

12.2 Convolution notation

Let us note that the obtained expressions can be written in a bit more abstract form. Namely, if P denote the solution operator we have for the hyperbolic equation acting on the initial data function R_0, i.e. $P(R_0)(t, x, T_1, T_8)$ is a solution at time t. Then (3.52) can be written

$$R(t, x, T_1, T_8) = \int_\Omega G(t, x; 0, \xi) P(R_0)(t, \xi, T_1, T_8) d\xi =: G(t, x; 0, \xi) \circledast P(R_0)(t, \xi, T_1, T_8). \qquad (12.3)$$

The last expression can be interpreted as a kind of convolution of the solution to the hyperbolic equation Eq.(3.3) with the Green's function G for the diffusion equation. Moreover, if G depends only on $x - \xi$, as it is for $\Omega = \mathbb{R}^n$ (see Lemma 3.4), then this expression is a usual convolution with respect to ξ, i.e.

$$R(t, x, T_1, T_8) = G(t, x; 0, \xi) \star_\xi P(R_0)(t, \xi, T_1, T_8). \qquad (12.4)$$

Let us note that the above formula can be generalized to initial data at time $t = \tau > 0$. In this case, R_0 should be treated as a function of τ also, i.e.

$$R_0(\tau) = R_0(\tau, x, T_1, T_8).$$

Then the above equalities should be written as

$$R(t, x, T_1, T_8) = \int_\Omega G(t, x; \tau, \xi) P(R_0(\tau))(t, \xi, T_1, T_8) d\xi, \qquad (12.5)$$

and

$$R(t, x, T_1, T_8) = G(t, x; \tau, \xi) \circledast P(R_0(\tau))(t, \xi, T_1, T_8), \qquad (12.6)$$

where τ is fixed. In this notation

$$P(R_0(\tau))(t, \xi, T_1, T_8) = \mathcal{K}(T_1, T_8; t - \tau) \cdot R_0(\tau, \xi, T_{10}(T_1, t - \tau), T_{80}(T_8, t - \tau)).$$

Recall that $T_{10}(T_1, t-\tau)$ denotes the value of T_1 on the characteristic curve at time τ and $T_{80}(T_8, t-\tau)$ denotes the value of T_8 on the characteristic at time τ.

Let us note, that (12.3) and (12.4) are also valid, if $\Gamma = \Gamma(T_1, t)$ and $B = B(T_8, t)$, if P denotes the solution operator for Eq.(3.3). This follows from the first part of the proof of Lemma 3.52 and the fact that if $P(R_0)(t, \xi, T_1, T_8)$ satisfies Eq.(3.1), with $\Gamma = \Gamma(T_1, t)$ and $B = B(T_8, t)$, then

$$\Big(P(R_0)(t, \xi, T_1, T_8)\Big)_{,t} = -\frac{\partial}{\partial T_1}\Big(\Gamma(T_1, t) P(R_0)\Big) - \frac{\partial}{\partial T_8}\Big(B(T_8, t) P(R_0)\Big).$$

Now, as $G(t, x; 0, \xi)$ does not depend on T_1 and T_8, we conclude that

$$\begin{aligned}
R(t, x, T_1, T_8) &= \int_\Omega \Big(G(t, x; 0, \xi) P(R_0)(t, \xi, T_1, T_8)\Big)_{,t} d\xi = \\
&-\frac{\partial}{\partial T_1}\Big(\Gamma(T_1, t) \int_\Omega G(t, x; 0, \xi) P(R_0)(t, \xi, T_1, T_8) d\xi\Big) \\
&-\frac{\partial}{\partial T_8}\Big(B(T_8, t) \int_\Omega G(t, x; 0, \xi) P(R_0)(t, \xi, T_1, T_8) d\xi\Big) = \\
&-\frac{\partial}{\partial T_1}\Big(\Gamma(T_1, t) R(t, x, T_1, T_8)\Big) - \frac{\partial}{\partial T_8}\Big(B(T_8, t) R(t, x, T_1, T_8)\Big).
\end{aligned}$$

This fact is in agreement with the results of section 8.4. An example of a solution to Eq.(3.1) in the case of Γ and B depending also explicitly on t is given at the end of section 8.4.

Now, in the case of Γ and B not depending explicitly on t, as it follows from (3.56), the solution to the inhomogeneous equation (3.55) can be written as

$$R(t, x, T_1, T_8) = \int_\Omega \int_0^t G(t, x; \tau, \xi) P(f(\tau))(\tau, \xi, T_1, T_8) d\tau d\xi, \tag{12.7}$$

what can be displayed in the convolution form:

$$R(t, x, T_1, T_8) = G(t, x; \tau, \xi) \star P(f(\tau))(\tau, \xi, T_1, T_8).$$

It seems that in the case of Γ and B depending explicitly on t, equality corresponding to (12.7) do not hold. Similarly, in the case of Γ and B depending explicitly on x, we have not been able to derive the corresponding expressions for the solution even in the homogeneous case.

To obtain stronger results in the analysis of (1.1)-(1.3), in the remaining sections, we will propose a discrete time method, which can at least partially overcome these difficulties and study the existence of solutions to system (1.11)-(1.13).

Part III

Existence theorems via the Rothe method

13 Modified discrete Rothe method

The formulation of the discrete Rothe method for system (1.11)-(1.13) has been proposed in paper [19]. It was shown in [19] that, after some essential modifications taking into account the existence of characteristic curves for the hyperbolic counterpart in the first equation, the Rothe method can be used effectively to study the existence of solutions and well-disposed of the initial boundary value problem.

As it was noticed in the previous section, system (1.11)-(1.13) can neither be studied by means of classical methods dedicated exclusively to systems of parabolic equations, nor by the methods dedicated exclusively to hyperbolic ones. The method proposed in [19] consists in a combined discretization of the variables t, T_1, T_8. In this setting, an implicit difference scheme exploits essentially in the form of the characteristic curves. The resulting sequence of elliptic PDE's is well posed and inherit, in a way, the basic properties of the original system (1.11)-(1.13).

Let $h = (\Delta t, \Delta T_1, \Delta T_8)$, $t^i = i\Delta t$, $T_1^j = j\Delta T_1$, $T_8^k = k\Delta T_8$ and

$$Z_h = \left\{ (t^i, T_1^j, T_8^k) : \; i,j,k = 0,1,\ldots \right\}, \quad Z'_h = \left\{ (T_1^j, T_8^k) : \; j,k = 0,1,\ldots \right\}.$$

Let $R^{i,j,k}(x) = R(t^i, x, T_1^j, T_8^k)$. Given any function $v : Z'_h \to R$, an interpolation operator I_h acting on v, can be defined informally by:

$$I_h v(T_1, T_8) = \text{ piecewise linear interpolation}$$

for $T_1 \in [T_1^{j-1}, T_1^j]$, $T_8 \in [T_8^{k-1}, T_8^k]$, $j,k = 1,2,\ldots$ In particular, we write below $I_h R^{i-1}(x; T_1, T_8)$ for the interpolation $I_h v$ where $v^{j,k} := R^{i-1,j,k}(x)$.

Thus the following numerical scheme for solving system (1.11)-(1.13) was proposed in [19]:

$$\begin{aligned} \frac{R^{i,j,k} - I_h R^{i-1}(x; \tau_1^{j,k}(x), \tau_8^{j,k}(x))}{\Delta t} &= d_R \nabla^2 R^{i,j,k} - \nabla \cdot (R^{i,j,k}\, \mathbf{K}^{i-1}(R^{i-1})) \\ -R^{i,j,k} \Bigg[\frac{\partial}{\partial T_1} \Big(\widetilde{\gamma}(c_1^{u;i-1}, c_8^{u;i-1}, I_h T_1^j) \Big) &+ \frac{\partial}{\partial T_8} \Big(\widetilde{\delta}(c_8^{u;i-1}, I_h T_8^k) \Big) \Bigg] \end{aligned} \tag{13.1}$$

$$\frac{c_1^{u;i} - c_1^{u;i-1}}{\Delta t} = \nabla^2 c_1^{u;i} + \widetilde{\nu} \int_0^\infty \int_0^\infty I_h c_8^{8;i-1}\, I_h R^{i-1}\, dT_1\, dT_8 - c_1^{u;i} \tag{13.2}$$

$$\frac{c_8^{u;i} - c_8^{u;i-1}}{\Delta t} = \nabla^2 c_8^{u;i} + \widetilde{\mu} \int_0^\infty \int_0^\infty I_h c_1^{i-1,j}\, I_h R^{i-1}\, dT_1\, dT_8 - \widetilde{\pi}_8\, c_8^{u;i}. \tag{13.3}$$

where, for each $x \in \Omega$, $\tau_1^{j,k}, \tau_8^{j,k}$ are computed from the equations:

$$\frac{T_1^j - \tau_1^{j,k}(x)}{\Delta t} = \widetilde{\gamma}(c_1^{u;i-1}(x), c_8^{u;i-1}(x), T_1^j), \tag{13.4}$$

$$\frac{T_8^k - \tau_8^{j,k}(x)}{\Delta t} = \widetilde{\delta}(c_8^{u;i-1}(x), T_8^k). \tag{13.5}$$

Since $\dfrac{dT_1}{dt} \approx \dfrac{\Delta T_1}{\Delta t}$, $\dfrac{dT_8}{dt} \approx \dfrac{\Delta T_8}{\Delta t}$ the above equations are finite difference approximations of the equations determining the characteristics of the hyperbolic part of Eq.(1.11)

$$\frac{\partial R}{\partial t} = -\frac{\partial}{\partial T_1} \left(\tilde{\gamma}(c_1^u, c_8^u, T_1)\, R \right) - \frac{\partial}{\partial T_8} \left(\tilde{\delta}(c_8^u, T_8)\, R \right)$$

that is, by the equations:

$$\frac{dT_1}{dt} = \tilde{\gamma}(c_1^u, c_8^u, T_1) \tag{13.6}$$

$$\frac{dT_8}{dt} = \tilde{\delta}(c_8^u, T_8). \tag{13.7}$$

□

In section 15 we propose a different numerical scheme, where $x \in \overline{\Omega}$, T_1 and T_2 are treated as a continuous variable. This change is dictated by the fact that we will concentrate mainly on the existence of solutions, putting aside the qualitative results of numerical simulations.

14 Preliminary lemmas and properties

In this section we establish some of the properties of the coefficient functions in system (1.11)-(1.13), and find some a priori estimates of its solutions.

14.1 Preliminary lemmas

Below, we will make use of the following formulation of the maximum principle for elliptic equations.

Lemma 14.1. *Let $\Omega \in \mathbb{R}^{m_\Omega}$, $m_\Omega \geq 1$, be a bounded domain with $\partial\Omega$ of $C^{2+\alpha}$ class, $\alpha \in (0,1)$. Let a_{ij}, $i,j \in \{1,\dots,m_\Omega\}$ and b_j, $j \in \{1,\dots,m_\Omega\}$ be of $C^{1+\alpha}(\overline{\Omega})$ class. Let*

$$Lw = \sum_{i,j=1}^{m_\Omega} a_{ij}(x)\frac{\partial^2 w}{\partial x_i \partial x_j} + \sum_{j=1}^{m_\Omega} b_j(x)\frac{\partial w}{\partial x_j}$$

be a uniformly elliptic operator. Suppose that w satisfies the equation

$$Lw - c(x)w + f(x) = 0 \quad \text{in } \Omega, \tag{14.1}$$

$$\frac{\partial w}{\partial \mathbf{n}}(x) \quad \textit{for } x \in \partial\Omega, \tag{14.2}$$

where $c(x) > 0$ for $x \in \overline{\Omega}$ and f are non-negative in Ω. Then $w \geq 0$ in Ω and $w > 0$ in Ω unless $w \equiv 0$. In particular $w > 0$ in Ω, if $f \not\equiv 0$. Suppose that w attains a non-negative maximum at $x = x_0 \in \Omega$. Then

$$w(x_0) \leq \frac{f(x_0)}{c(x_0)}. \tag{14.3}$$

In general, for all $x \in \overline{\Omega}$,

$$0 \leq w(x) \leq \sup_{x\in\Omega}\left[\frac{f(x)}{c(x)}\right]. \tag{14.4}$$

□

Proof The proof follows from the fact that, thanks to boundary condition (14.2), the constant functions $\underline{w} \equiv 0$ and $\overline{w} \equiv \sup_{x\in\Omega}\left[\frac{f(x)}{c(x)}\right]$ are respectively sub and supersolution of Eq.(14.1) (see, e.g. [29, section 3.2]). The positivity of $w(\cdot)$ in $\overline{\Omega}$ follows from [29, Lemma 4.2, section 1.4]. Also, (14.3) follows from the proof of inequality (1.5) in [24, chapter III]. □

Below, we will also use the following generalization of Lemma 14.1 not assuming the non-negativity of the function f.

Lemma 14.2. *Let the assumptions of Lemma 14.1 be satisfied except for the assumption that $f(\cdot) \geq 0$. Then*

$$\inf_{y\in\Omega}\left[\frac{f(y)}{c(y)}\right] \le w(x) \le \sup_{y\in\Omega}\left[\frac{f(y)}{c(y)}\right]. \tag{14.5}$$

14.1.1 The uniqueness of solutions

Lemma 14.3. *Positive solutions to problem (14.1)-(14.2) are unique.*

Proof Let $r \in C^1(\Omega)$ and $r(x) > 0$ for $x \in \Omega$. Consider the eigenvalue problem:

$$(L - c(x) + \lambda r(x))\phi = 0 \tag{14.6}$$

for ϕ satisfying homogeneous boundary conditions. By means of Theorem 1.2 of chapter 3 in [29] and the assumption $c(x) > 0$ for $x \in \overline{\Omega}$, the principal eigenvalue λ^*, i.e. the eigenvalue $\lambda(r)$ satisfying Eq.(14.6) with the smallest real part, is real and positive $\lambda^* > 0$. Moreover, the corresponding eigenfunction ϕ^* is positive in Ω. Finally, using Theorem 3.2 of chapter 3 in [29], and noting that the upper solution and lower solutions can be taken in the form $K^* > 0$ and $(-K^*) < 0$ respectively satisfying

$$K^* \ge \sup_{x\in\Omega}\left[\frac{f(x)}{c(x)}\right].$$

we conclude that solutions to problem (14.1)-(14.2) are unique. □

Remark Lemma 14.3 can be also proved straightforwardly by means of the maximum principle applied to the homogeneous equation $Lw = 0$. (Any extremum cannot be attained at the boundary, unless w is constant, which for $c(x) \ge 0$, must be equal to zero. On the other hand and internal extremum must be also equal to zero.) □

Below, we will extensively use the following differentiability property for linear elliptic second order equations. This theorem is provided by general Schauder estimates in [1]. (See Theorem 7.3 for $\mathfrak{U} = \mathfrak{D}$.)

Lemma 14.4. *Suppose that Ω is bounded open subset of $\mathbb{R}^{m_\Omega}$, $m_\Omega \ge 1$, $l \ge 2$ and that $\partial\Omega \in C^{l+\beta}$ for some $\beta \in (0,1)$. Suppose that the coefficients of the elliptic operator*

$$\mathcal{L} = \sum_{i,j=1}^{m_\Omega} a_{ij}(x)\frac{\partial^2}{\partial x_i \partial x_j} + \sum_{j=1}^{m_\Omega} b_j(x)\frac{\partial}{\partial x_j} - c(x)$$

have their $C^{(l-2)+\beta}$ norms bounded. Suppose that U satisfies the system

$$\mathcal{L}U = F(x) \quad \text{in } \Omega \tag{14.7}$$

$$n(x)\cdot\nabla U = \Phi(x) \quad \text{on } \partial\Omega. \tag{14.8}$$

Then U satisfies the estimate

$$\|U\|_{C^{l+\beta}(\Omega)} \le C_l\left(\|F\|_{C^{l-2+\beta}(\Omega)} + \|\Phi\|_{C^{l-1+\beta}(\partial\Omega)} + \|U\|_{C^0(\Omega)}\right).$$

The term $\|U\|_{C^0(\Omega)}$ can be omitted if the homogeneous problem has no nontrivial solutions.

Remark Similar estimate in the case of Dirichlet boundary conditions is given by inequality (1.11) of Section 1 of ch. 3 in [24]. □

An L_p version of the above property is given by the following lemma.

Lemma 14.5. *(Theorem 15.2 in [1]) Suppose that $l \ge 2$ and that $\partial\Omega \in C^{l+\beta}$ for some $\beta \in (0,1)$. Suppose that the coefficients of the elliptic operator $\mathcal{L}$ have their L^{l-2} norms bounded. Then, for any $p > 1$:*

$$\|U\|_{W_p^l} \le C_l\left(\|F\|_{W_p^{l-2}} + \|\Phi\|_{W^{l-1-(1/p)}(\partial\Omega)} + \|U\|_{C^0(\Omega)}\right),$$

where the constant C_l does not depend on the functions F, Φ and u_0. The term with $\|U\|_{C^0}$ can be omitted, if the corresponding homogeneous problem (with $F \equiv 0$) has no nontrivial solutions.

Similar property concerning linear parabolic equation is given by corresponding Schauder estimates.

Lemma 14.6. *(See, [23, Section IV, Theorem 5.3]) Let Ω is bounded open subset of $\mathbb{R}^{m_\Omega}$ and*

$$\mathcal{L} = \sum_{i,j=1}^{m_\Omega} a_{ij}(t,x) \frac{\partial^2}{\partial x_i \partial x_j} + \sum_{j=1}^{m_\Omega} b_j(t,x) \frac{\partial}{\partial x_j} - c(t,x).$$

Let $T > 0$, $m_\Omega > 0$ be a non-integer number, $\partial\Omega \in C^{m_\Omega+2}$, and the coefficients of the operator $\mathcal{L}$ belong to the class $C^{m_\Omega/2, m_\Omega}(\Omega)$. Then, for any $f \in C^{m_\Omega/2, m_\Omega}(\Omega)$, and $\phi = U(o,x)$ and $\Phi \in C^{m_\Omega+1}(\partial\Omega)$, which satisfy compatibility conditions of order $\left[\frac{m_\Omega+1}{2}\right]$, the problem

$$\frac{\partial u}{\partial t} = \mathcal{L}u + f(t,x) \quad in\ (0,T) \times \Omega$$

$$u(0,x) = \phi(x) \quad in\ \Omega$$

$$n(x) \cdot \nabla u = \Phi(x) \quad on\ \partial\Omega$$

has a unique solution from $C^{1+m_\Omega/2, 2+m_\Omega}(\Omega)$ satisfying the estimate

$$\|u\|_{C^{1+m_\Omega/2,2+m_\Omega}} \leq c \left(\|f\|_{C^{m_\Omega/2,m_\Omega}((0,T)\times\Omega)} + \|\phi\|_{C^{m_\Omega+2}(\Omega)} + \|\Phi\|_{C^{m_\Omega+1}(\partial\Omega)} \right),$$

where, for given $T > 0$, the constant c can be taken as independent of $t \in (0,T)$.

Remark In the case of homogeneous Neumann boundary conditions, that is to say, for $\Phi \equiv 0$, the compatibility conditions mentioned in Lemma 14.6, and defined explicitly before Theorem 5.1 in Section IV.5 of [23], are satisfied. □

15 Discrete-continuous numerical scheme for the simplified system

As we mentioned above, we propose a modified version of the numerical scheme (13.1)-(13.3). In this section, to get a preliminary insight into the properties of the considered system, we will put aside the proposed numerical method, discrete in the variables t, T_1 and T_8, and replace it by the iterative system (15.5)-(15.7). Instead of considering the complicated convective term, we will mimick it by adding appropriate terms proportional to R and the components of ∇R. We will assume that these terms are equal identically to zero close to the boundary of Ω (see Assumption 15.2). For simplicity, we will also change the notation and denote $\widetilde{\gamma}$ and $\widetilde{\delta}$ by γ and δ. Thus, below:

$$\begin{aligned} \gamma(c_1^u, c_8^u, T_1) &:= \left(\frac{2c_1^u}{\frac{c_1^u T_1}{c_1^u + f c_8^u + 1} + \widetilde{\widetilde{c}}_1} - \widetilde{\gamma}_2 \right) \frac{T_1}{c_1^u + f c_8^u + 1} = \widetilde{\gamma}(c_1^u, c_8^u, T_1), \\ \delta(c_8^u, T_8) &:= 1 - \delta_2 \frac{T_8}{1 + c_8^u} = \widetilde{\delta}(c_8^u, T_8). \end{aligned} \tag{15.1}$$

For simplicity, we have also denoted $\delta_2 := \widetilde{\delta}_2$ in the definition of the function δ.

In this part, we will deal with the further simplified system, which differs from (1.11)-(1.13) only by replacement of the non-local (integral) term by a given function of R and the components of ∇R. We will thus consider the system:

$$\frac{\partial R}{\partial t} = d_R \nabla^2 R - \frac{\partial}{\partial T_1}\left(\gamma(c_1^u, c_8^u, T_1)\, R\right) - \frac{\partial}{\partial T_8}\left(\delta(c_8^u, T_8)\, R\right) - \Big(R \cdot F_1(t, x, T_1, T_8) - F_0(t, x) \cdot \nabla R\Big) \tag{15.2}$$

$$\frac{\partial c_1^u}{\partial t} = \nabla^2 c_1^u + \widetilde{\nu} \int_0^\infty \int_0^\infty c_8^8\, R\, dT_1\, dT_8 - c_1^u \tag{15.3}$$

$$\frac{\partial c_8^u}{\partial t} = \nabla^2 c_8^u + \widetilde{\mu} \int_0^\infty \int_0^\infty c_1\, R\, dT_1\, dT_8 - \widetilde{\pi}_8\, c_8^u. \tag{15.4}$$

To study the above system, we will use the following recurrence scheme:

$$d_R \nabla^2 R^i - \Big\{ R^i \left[\frac{\partial}{\partial T_1}\Big(\gamma(c_{1*}^{u;i-1}, c_{8*}^{u;i-1}, T_1)\Big) + \frac{\partial}{\partial T_8}\Big(\delta(c_{8*}^{u;i-1}, T_8)\Big) + F_1((i-1)\Delta t, x, T_1, T_8) + \frac{1}{\Delta t} \right]$$
$$- \frac{R^{i-1}(x; \tau_1^{i-1}, \tau_8^{i-1})}{\Delta t} - F_0((i-1)\Delta t, x) \cdot \nabla R^i \Big\} \;=\; 0 \tag{15.5}$$

$$\frac{\partial c_1^{u;i}}{\partial t} = \nabla^2 c_1^{u;i} + \widetilde{\nu} \int_0^\infty \int_0^\infty c_{8*}^{8;i-1}\, R^{i-1}\, dT_1\, dT_8 - c_1^{u;i} \quad \text{for } t \in ((i-1)\Delta t, i\Delta t] \tag{15.6}$$

$$\frac{\partial c_8^{u;i}}{\partial t} = \nabla^2 c_8^{u;i} + \widetilde{\mu} \int_0^\infty \int_0^\infty c_{1*}^{i-1}\, R^{i-1}\, dT_1\, dT_8 - c_8^{u;i} \pi_8 \quad \text{for } t \in ((i-1)\Delta t, i\Delta t] \tag{15.7}$$

As in the previous scheme, for each $x \in \overline{\Omega}$, $\tau_1^{i-1}, \tau_8^{i-1}$ are computed from the equations:

$$\frac{T_1 - \tau_1^{i-1}}{\Delta t} = \gamma(c_{1*}^{u;i-1}(x), c_{8*}^{u;i-1}(x), T_1), \tag{15.8}$$

$$\frac{T_8 - \tau_8^{i-1}}{\Delta t} = \delta(c_{8*}^{u;i-1}(x), T_8). \tag{15.9}$$

For all the considered $i \geq 0$, we assume that the functions R^i, $c_1^{u;i}$ and $c_8^{u;i}$ satisfy, according to a (1.5) and (1.6), the homogeneous Neumann boundary conditions.

In Eq.(15.5), $c_{1*}^{u;0}(x) = c_{10}^u(x)$, $c_{8*}^u(x) = c_{80}^u(x)$, whereas for $i \in \{1, \ldots, n+1\}$ we denoted:

$$c_{1*}^{u;i-1}(x) := c_{1*}^u((i-1)\Delta t, x), \quad c_{8*}^{u;i-1}(x) := c_{8*}^u((i-1)\Delta t, x). \tag{15.10}$$

In Eqs (15.6)-(15.9), for $i \in \{1, 2, \ldots, n+1\}$ we denoted:

$$c_{1*}^{i-1}(x, T_1, T_8) := \frac{c_{1*}^{u;i-1}(x) T_1}{1 + f c_{8*}^{u;i-1}(x) + c_{1*}^{u;i-1}(x)}, \quad c_{8*}^{8;i-1}(x, T_1, T_8) := \frac{c_{8*}^{u;i-1}(x) T_8}{1 + c_{8*}^{u;i-1}(x)}. \tag{15.11}$$

Eqs.(15.6),(15.7) are solved sequentially on each of the interval $[(i-1)\Delta t, i\Delta t)$ by assuming the initial conditions at $t = (i-1)\Delta t$:

$$c_1^{u;i}((i-1)\Delta t, x) = c_1^{u;i-1}((i-1)\Delta t, x) = c_{1,*}^u(x), \quad c_8^{u;i}((i-1)\Delta t, x) = c_8^{u;i-1}((i-1)\Delta t, x) = c_{8,*}^u(x). \tag{15.12}$$

15.1 Main assumptions

Below, we will suppose that the following conditions are satisfied.

Assumption 15.1. *Ω is a bounded domain (open and connected) in $\mathbb{R}^3$, with the boundary $\partial\Omega$ of $C^{3+\beta}$ class with $\beta \in (0, 1)$.*

Remark In general, the analysis which is carried out below hold also for $\Omega \subset \mathbb{R}^{m_\Omega}$, with $m_\Omega \geq 1$. □

Assumption 15.2. *The function $F_1 : [0,T] \times \overline{\Omega} \times \mathbb{R}^2 \mapsto \mathbb{R}$ is of C^1 class with respect to t and all of its derivatives up to the order of 4 with respect to the components of x and (T_1, T_8) are continuous and bounded. Let $\|F_1\|$ denote the sum of the suprema of $|F_1|$, $|F_{1,t}|$ and all the derivatives with respect to the components of x and (T_1, T_8) up to order 4. Let*

$$f_1 := \|F_1\|.$$

The function $F_0 = (F_{01}, F_{02}, F_{03}) : [0,T] \times \overline{\Omega} \mapsto \mathbb{R}^3$ is of $C^{t,x}_{1,4}([0,T])$ class. Let

$$f_0 := \|F_0\|_{C^{t,x}_{1,4}([0,T]\times\overline{\Omega})}.$$

There exists a number $\delta > 0$ such that $F_1(t, x, T_1, T_8) \equiv 0$, $F_0(t, x) \equiv 0$ for all $(t, T_1, T_8) \in [0,T] \times \mathbb{R}^2$, if only $dist(x, \partial\Omega) < \delta$.

Note that the last assumption is in accordance with the cutting off properties of the function Ψ in definition (1.7). Additionally, we assumed that the function F_0 does not depend on T_1, T_8. This assumption significantly simplifies the problem of obtaining 'a priori' estimates.

In our analysis, we will fix finite $T > 0$ and consider the above scheme for $t \in [0,T]$, and $i \in \{1, n\}$, with n sufficiently large, and Δt satisfying the condition

$$T = n\Delta t. \tag{15.13}$$

It means that n depends on Δt, $n = n(\Delta t) = \dfrac{T}{\Delta t}$.

Remark The right hand side of Eqs (15.6)-(15.7) depend on the function R^{i-1} which, in general, is discontinuous as a function of the index $i-1$. However, on each of the open set $((i-1)\,\Delta t, i\Delta t)$ one can treat these equations as a system of two parabolic equations depending in a non-local way on the function $R^{i-1}(x)$, which is smooth with respect to $x \in \Omega$. □

Remark Due to the uniqueness of solutions to the considered parabolic initial boundary value problems, we can treat Eqs (15.6)-(15.7) as defined on the whole of the time interval $[0,T]$. In this approach, let us define:

$$c_1^u(t,x) := \sum_{i=1}^{n} \chi_i c_1^{u;i}(t,x), \quad c_8^u(t,x) := \sum_{i=1}^{n} \chi_i c_8^{u;i}(t,x) \tag{15.14}$$

where χ_i denotes the characteristic function of the interval $[(i-1)\Delta t, i\Delta t)$. □

From the definition (15.8)-(15.9) we can extract a simple fact, which will be the basis of our estimates below.

Lemma 15.3. *Suppose that the functions $c_{1*}^{u;i-1}(\cdot)$ and $c_{8*}^{u;i-1}(\cdot)$ are of $C^1(\overline{\Omega})$ class. Then, for $k \in \{1,2,3\}$, $i = \{2, \ldots, n+1\}$ and all $\Delta t > 0$, we have for each fixed T_1 and T_8:*

$$\frac{\partial \tau_1^{i-1}}{\partial x_k} = -\frac{\partial (T_1 - \tau_1^{i-1})}{\partial x_k} = -\frac{\partial \gamma(c_{1*}^{u;i-1}(x), c_{8*}^{u;i-1}(x), T_1)}{\partial x_k} \cdot \Delta t,$$

$$\frac{\partial \tau_8^{i-1}}{\partial x_k} = -\frac{\partial (T_8 - \partial\tau_8^{i-1})}{\partial x_k} = -\frac{\partial \delta(c_{8*}^{u;i-1}(x), T_8)}{\partial x_k} \cdot \Delta t.$$

These derivatives are thus of the order $O(\Delta t)$ as $\Delta t \to 0$ and of class $C^0(\overline{\Omega})$.

Likewise, if the functions $c_{1*}^{u;i-1}(\cdot)$ and $c_{8*}^{u;i-1}(\cdot)$ are of $C^p(\overline{\Omega})$ class, then the p-th order derivatives of τ_m^{i-1} with respect to the components of x are of class $C^0(\overline{\Omega})$ and are products of Δt and functions independent of Δt.

Our analysis are based on the assumption of smoothness of the initial data as well as of the compactness of the initial data with respect to the variables T_1 and T_8. In reference to system (15.5)-(15.7), this assumption can be expressed in the following form.

As in section 3 (see (3.2)), let us define

$$\overline{\mathbb{R}^2_+} := \{(r_1, r_8) \in \mathbb{R}^2 : r_1 \geq 0,\, r_8 \geq 0\}.$$

Assumption 15.4. *Suppose that:*

1. $R^0 \in C^4(\overline{\Omega} \times \overline{\mathbb{R}^2_+})$ *is compactly supported, with the support contained in* $\overline{\Omega} \times [0, T^0_{1*}] \times [0, T^0_{8*}]$ *and that*

R_0 *satisfies conditions (1.18)*

2. $c_1^{u;0}, c_8^{u;0} \in C^4(\overline{\Omega})$

3. $R^0(x, T_1, T_8) \geq 0$, $c_1^{u;0}(x), c_8^{u;0}(x) \geq 0$, *for all* $(x, T_1, T_8) \in \partial\Omega \times \overline{\mathbb{R}^2_+}$.

Remark The smoothness demands of the initial data R^0, $c_1^{u;0}$, $c_8^{u;0}$ are implied by the method of obtaining a priori estimates used below, which are established by consecutive differentiation. □

15.2 Description of the method of proving the existence of solutions to a variation of system (1.11)-(1.13)

The solutions to system (15.5)-(15.7), (15.8)-(15.9) will be used to obtain solutions to system (1.11)-(1.13) with the term $\nabla \cdot (R\,\mathbf{K}(R))$ replaced by the term $(R \cdot F_1(t, x, T_1, T_8) - F_0(t, x) \cdot \nabla R)$. By this replacement we fix our attention on the problems connected with the lack of diffusion terms of the variables T_1 and T_8, and put aside the difficulties connected with the term $\nabla \cdot (R\,\mathbf{K}(R))$. These issues have been undertaken and, at least partially solved, for a scalar equation corresponding to Eq.(1.11) in the papers [9], [10], where *in contrast* the hyperbolic like terms $\frac{\partial}{\partial T_1}(\gamma\, R)$ and $\frac{\partial}{\partial T_8}(\delta\, R)$ are not present. Below, by studying the properties of the numerical scheme (15.5)-(15.7), (15.8)-(15.9), we will be interested in establishing the existence classical solutions to system (15.2)-(15.4).

The method of proving the existence of solutions to system (15.2)-(15.4) is based on deriving a series of a priori estimates for solutions to system (15.5)-(15.7), (15.8)-(15.9), i.e. the functions R^i, $c_1^{u;i}$, $c_8^{u;i}$ in the spaces of differentiable functions. According to this, we estimate the derivatives of the functions R^i both with respect to the components of the space variable x as well as with respect to T_1 and T_8. These estimates stay bounded for all i and keep their validity for $\Delta t \to 0$.

In the preliminary step we modify the function γ in the region $T < 0$. The objective of such a modification is to guarantee that the support of the functions R^i does not contain points (x, T_1, T_8) with negative values of T_1.

Thus in section 15.5 we establish a priori bounds of the absolute values of the functions R^i. These bounds can be found due the appropriate structure of the function δ and the modified function γ, implying agreeable properties of their derivatives (examined and listed in Lemma 15.7). An additional assumption necessary to establish the bounds for R^i is the non-negativity of the functions $c_1^{u;i}$, $c_8^{u;i}$. However, this feature is inherited at every step of the iterative sequence, so is implied by the initial data. In the same section, using the properties of the functions γ and δ, we find the bounds for the increase of the support of the functions R^i with respect to (T_1, T_8) (see Lemma 15.9). In the next step, we examine differential properties of the functions c_1^u and c_8^u defined in (15.45) as functions of $t \in [0, T]$ and $x \in \overline{\Omega}$. Interestingly enough, these functions are of $C_{t,x}^{(1+\beta)/2, 1+\beta}$ class, i.e. they are Hölder continuous in t with exponent $(1+\beta)/2$, $\beta \in (0, 1)$, and have continuous in t first derivatives with respect to x (see Lemma 15.11). Having the uniform (with respect to i) boundedness of the functions $c_1^{u;i}$, $c_8^{u;i}$ in $C^1(\Omega)$ norm, which can be obtained only on the condition that $\|R^i\|_{C^0}$ is uniformly bounded, we can establish the uniform boundedness of the derivatives of the functions R^i. In section 15.8 we find the estimates for the first derivatives of R^i with respect to T_l, $l = 1, 8$, in section 15.11 the second order derivatives $R^i_{T_l T_m}$, whereas in section 15.12 for the third order derivatives $R^i_{T_l T_m T_p}$. In sections 15.9 and 15.10, we obtain the estimate for the first order derivatives of R^i with respect to the components of x. In section 15.14 we find a priori estimates for the mixed second order derivatives of the form $R^i_{x_k T_m}$. The bounds of the first derivatives $R^i_{x_k}$ and $R^i_{T_l}$ allow us to prove Lemma 15.12. By means of these estimates, in section 15.15, we are able to analyse the difference between the functions corresponding to subsequent values of i. To be more precise, we analyse the functions $Z^i = R^i - R^{i-1}$ and the functions $H^i_j = R^i_{T_j} - R^{i-1}_{T_j}$. This result empowers us to demonstrate, in section 15.16, the uniform with respect to i boundedness of $C_x^{1+\beta}$ norms of the functions R^i. Using the last conclusion, we show in section 15.17 the higher order differentiability of the functions $c_1^{u;i}$ and $c_8^{u;i}$, in particular the fact that the differences between the corresponding derivatives of these functions with respect to the components of x on adjacent intervals, i.e. $[(i-1)\Delta t, i\Delta t]$ and $[i\Delta t, (i+1)\Delta t]$ are of the order of $O(\Delta t)$. This finding is crucial to obtaining in section 15.18, estimates of first order derivatives of Z^i with respect to x_k, together with the differences of the mixed second derivatives $R^i_{x_k T_j} - R^{i-1}_{x_k T_j}$, and bounds for the $C_x^{2+\beta}$ norm of R^i in section 15.19. In the same section we use the refined version of the Gagliardo-Nirenberg inequality from [4] and obtain additionally some Hölder estimates for the derivatives of the functions Z^i. Finally in section 16, using the functions R^i, c_1^u and c_8^u, we construct an approximate solution to system (15.2)-(15.4) and consider its convergence to a classical solution as $\Delta t \to 0$.

The method of the existence proof can thus be displayed schematically in a graphical form as below.

1 Subsection 15.3. Modification of the function γ aimed to guarantee that $R(t, x, T_1, T_8) \equiv 0$ in the region $\{(T_1, T_8) : T_1 < 0 \vee T_8 < 0\}$ (proved in lemma 15.5).

2 Subsection 15.4. A priori bounds of the functions γ and δ and their derivatives established in Lemma 15.6 and Lemma 15.7.

3 Subsection 15.5. Estimates for the upper bound of the function R^i for sufficiently small $\Delta t > 0$.
(Based on **2**.)

4 Subsection 15.5. Estimates of the support of R^i with respect to (T_1, T_8).
(Based on **2** and **3**.)

5 Subsection 15.7. Estimates for the upper bounds of the $C_{t,x}^{(1+\beta)/2,1+\beta}$ norms of the functions

$$c_1^u(t,x) := \sum_{i=1}^{n} \chi_i c_1^{u;i}(t,x), \text{ and } c_8^u(t,x) := \sum_{i=1}^{n} \chi_i c_8^{u;i}(t,x)$$

(Lemma 15.11). (Based on **3** and **4**.)

6 Subsection 15.8. A priori estimates of the first derivatives of the function $R^i(x, T_1, T_8)$ with respect to T_m, $m = 1, 8$.

7 Subsection 15.9. Interior estimates of the first derivatives of the function $R^i(x, T_1, T_8)$ with respect to x_r, $r = 1, 2, 3$.

8 Subsection 15.10. Estimates of the first derivatives of the function $R^i(x, T_1, T_8)$ with respect to x_r, $r = 1, 2, 3$, at the boundary of Ω. (Based on **6**.)

9 Subsections 15.11 and 15.12. Estimates of the second and third order derivatives of functions $R^i(x, T_1, T_8)$ with respect to T_1 and T_8. (Based on **6**.)

10 Subsection 15.13. Estimates of the mixed second order derivatives of function $R^i(x, T_1, T_8)$ with respect to x_r and T_m for $r = 1, 2, 3$ and $m \in \{1, 8\}$. (Based on **6**, **7** and **8**.)

11 Subsection 15.14. Estimates for the mixed third order derivatives of $R^i_{x_r T_l T_m}(x, T_1, T_8)$.

12 Subsection 15.15. Estimates of the differences Z_i between the functions R^i corresponding to subsequent values of i.

13 Subsection 15.16. Estimates of $C^{1+\beta}_x$ norms of the functions R^i:

$$\|R^i\|_{C^{1+\beta}(\Omega)} \leq C_{1\beta}.$$

(Based on **12**.)

14 Subsection 15.17. Estimates of higher order derivatives of the functions $c_1^{u;i}$ and $c_8^{u;i}$ on the subintervals $[(i-1)\Delta t, i\Delta t]$. (Based on **13**.)

15 Subsection 15.18. Estimates of the first derivatives of the functions Z^i with respect to x_k.

16 Subsection 15.19. Estimates of $C^{2+\beta}_x$ norms of the functions R^i:

$$\|R^i\|_{C^{2+\beta}(\Omega)} \leq C_{2\beta}.$$

These estimates enable us to use the refined version of Gagliardo-Nirenberg inequality to obtain Hölder estimates for the derivatives of the functions Z^i. (Based on **15**.)

17 Subsection 15.20. Estimates of the differences $Z^i - Z^{i-1}$ via a version of the Gagliardo–Nirenberg interpolation inequality. (Based on **12** and **15**.)

18 Section 16. Convergence of the approximate solutions to solutions to system (15.2)-(15.4).

15.3 Modification of the function γ

To begin with, let us note that, from the biological point of view, the probability of finding cells characterized by negative values of T_1 and T_8 should be identically equal to zero, i.e. $R(t, x, T_1, T_8) = 0$ for $(t, x) \in [0, T] \times \overline{\Omega}$, if only $T_1 < 0$ or $T_8 < 0$. In general, the support of R with respect to T_1 and T_8 can change during the evolution, and after some time comprise points with negative values of T_1 or T_8, even if such points are outside the support of R for $t = 0$.

According to the form of the function δ, for $\Delta t \geq 0$ and all $c_{8*}^{u;i-1}$ such that $\overline{c}^u_{8*} \leq c_{8*}^{u;i-1}(x) \geq 0$ for $x \in \Omega$, we have, for each $i \in \{2, \dots, n\}$,

$$\tau_8^{i-1}(c_{8*}^{u;i-1}(x), T_8) < T_8 - \Delta t + \Delta t \frac{T_8\ \delta_2}{1 + \overline{c}^u_{8*}} = T_8\Big(1 + \Delta t \frac{\delta_2}{1 + \overline{c}^u_{8*}}\Big) - \Delta t$$

hence

$$\tau_8^{i-1}(x, T_8) < 0$$

if $T_8 \leq 0$ independently of $\Delta t \geq 0$. As it will be shown in the proof of Lemma 15.5, this inequality implies that $R^{i-1}(x, T_1, T_8) \equiv 0$ for all $T_8 < 0$, if only $R^0(x, T_1, T_8)$ satisfies the same condition.

However, to guarantee that our numerical scheme implies the similar property with respect to the variable T_1, we will consider system (15.5)-(15.7) with appropriately modified function γ.

Let

$$\gamma_* = \gamma \cdot \Psi_\gamma(T_1),$$

where

$$\Psi_\gamma(T_1) := \begin{cases} 0 & T_1 \in (-\infty, -1/2\tilde{\tilde{c}}_1] \\ \dfrac{\Psi_*(T_1 + 1/2\tilde{\tilde{c}}_1)}{\Psi_*(T_1 + 1/2\tilde{\tilde{c}}_1) + \Psi_*(-1/4\tilde{\tilde{c}}_1 - T_1)} & T_1 \in (-1/2\tilde{\tilde{c}}_1, -1/4\tilde{\tilde{c}}_1) \\ 1 & T_1 \geq -1/4\tilde{\tilde{c}}_1\,, \end{cases} \tag{15.15}$$

and $\Psi_*(s)$ is given after (1.8). As a result, the function γ_* is smooth everywhere in the region $\{(c_1^u, c_8^u, T_1) : c_1^u \geq 0, c_8^u \geq 0, T_1 \in \mathbb{R}\}$. Next, we will show that for such a modified function $\gamma = \gamma_*$, we can find a global estimate of the maximal values of the functions $c_1^u(t,x)$ and $c_8^u(t,x)$ for $(t,x) \in [0,T] \times \overline{\Omega}$. This will imply that the function γ_* is bounded for all $(t,x,T_1) \in [0,T] \times \overline{\Omega} \times \mathbb{R}$. Consequently, in this set

$$\tau_1^{i-1}(x,T_1) = T_1 - \gamma_*(x,T_1)\Delta t, \tag{15.16}$$

where by $\gamma_*(x,T_1)$ we denoted $\gamma_*(c_{1*}^{u;i-1}(x), c_{8*}^{u;i-1}(x), T_1)$. Due to the form of γ_*, $\gamma_*(x, T_1 = 0) = 0$

$$\tau_1^{i-1}(x,T_1) - T_1 = -\gamma_{*,T_{1*}} T_1\, \Delta t,$$

where $T_{1*} \in (0,T_1)$, hence for $T_1 > 0$. Now, due to the estimates provided by Lemma 15.7 (see (15.22) below the derivative of γ_* with respect to T_1 is uniformly bounded, i.e. $|-\gamma_{*,T_1}| < C_{1\gamma}$, thus for $\Delta t < \dfrac{1}{2C_{1\gamma}}$ we have for $T_1 \geq 0$:

$$\tau_1^{i-1}(x,T_1) > T_1 - \frac{1}{2}T_1 = \frac{1}{2}T_1 \geq 0. \tag{15.17}$$

Likewise, for $T_1 < 0$, we have for $\Delta t < \dfrac{1}{2C_{1\gamma}}$ by means of (15.16):

$$\tau_1^{i-1}(x,T_1) < T_1 + \frac{1}{2}|T_1| = \frac{1}{2}T_1 < 0. \tag{15.18}$$

It follows that for $\Delta t > 0$ sufficiently small the regions $T_1 > 0$ and $T_1 < 0$ do not mix under the action of system (15.8)-(15.9). In view of the above, the following lemma holds.

Lemma 15.5. *Suppose that for all $i \in \{0,1,\ldots,n\}$ and all $(t,x) \in [0,T] \times \overline{\Omega}$ the functions $c_1^{u;i}(t,x)$ and $c_8^{u;i}(t,x)$ are non-negative and uniformly bounded in their absolute value by a (finite) constant. Suppose that $R^0(x,T_1,T_8) = 0$ in the region $\{T_1 < 0\} \cup \{T_8 < 0\}$. Then, for $\Delta t \geq 0$ sufficiently small,*

$$R^i(x,T_1,T_8) = 0 \quad \textit{for all } i \in \{1,\ldots,n\} \textit{ in the region } \{T_1 < 0\} \cup \{T_8 < 0\}. \tag{15.19}$$

Proof The proof follows by induction. Thus, suppose that, for $i \in \{1,\ldots,n-1\}$, $R^{i-1}(x,T_1,T_8) \equiv 0$ in the set $\{T_1 < 0\} \cup \{T_8 < 0\}$, hence by what noted above, in particular, by (15.18), $R^{i-1}(x, \tau_1^{i-1}(x,T_1), \tau_1^{i-1}(x,T_8)) = 0$ Then, by means of estimate (14.4) in Lemma 14.1 and the subsection 14.1.1, $R^i(x,T_1,T_8) \equiv 0$ in the region $\{T_1 < 0\} \cup \{T_8 < 0\}$. □

Lemma 15.5 implies a strategy to guarantee that $R(t,x,T_1,T_8) \equiv 0$ in the region $\{(T_1,T_8) : T_1 < 0 \vee T_8 < 0\}$. Then, due to the fact that the modification of γ takes place in the region $\{T_1 < 0\}$, we will be able to conclude that we have obtained a solution for the system with non-modified function γ.

15.4 Properties of the function δ and the modified function γ_*

As it is seen from Eq. (1.11), crucial for the analysis of the considered system are the properties of the functions γ_* and δ.

Lemma 15.6. *The values of the functions γ and δ are bounded from above and below for any compact subset of the set $\{(T_1, T_8, c_1^u, c_8^u) : (T_1, T_8) \geq 0,\ (c_1^u, c_8^u) \geq 0\}$. Given the values of c_1^u and c_8^u*

$$\delta(c_8^u, T_8) < 0 \quad \text{for} \quad \delta_2 T_8 > (1 + c_8^u).$$

Similarly,

$$\gamma_*(c_1^u, c_8^u, T_1) < 0 \quad \text{for } T_1 > \max\left\{0, \frac{(2c_1^u - \widetilde{\overline{c}}_1\gamma_2)(c_1^u + f c_8^u + 1)}{c_1^u \gamma_2}\right\}.$$

Finally, for all $(T_1, T_8, c_1^u, c_8^u) \in \{(T_1, T_8, c_1^u, c_8^u) : (T_1, T_8) \geq 0,\ (c_1^u, c_8^u) \geq 0\}$, we have:

$$\gamma_*(c_1^u, c_8^u, T_1) \leq 2 \quad \text{and} \quad \delta(c_8^u, T_8) \leq 1. \tag{15.20}$$

Next, the following lemma holds.

Lemma 15.7. *For $c_8^u \geq 0$*

$$\frac{\partial}{\partial T_8}\delta(c_8^u, T_8) = -\delta_2 \frac{1}{1 + c_8^u} < 0. \tag{15.21}$$

The partial derivative

$$\frac{\partial}{\partial T_1}\gamma_*(c_1^u, c_8^u, T_1)$$

is bounded from above and below uniformly with respect to $(T_1, T_8) \in \mathbb{R}^2$ and $(c_1^u, c_8^u) \geq (0, 0)$, i.e. there exist finite positive constants A_- and A_+ such that

$$-A_- \leq \frac{\partial}{\partial T_1}\gamma_*(c_1^u, c_8^u, T_1) \leq A_+ \tag{15.22}$$

and

$$-A_- \leq \frac{\partial^2}{\partial T_1^2}\gamma_*(c_1^u, c_8^u, T_1) \leq A_+. \tag{15.23}$$

Also,

$$\begin{aligned} -\delta_2\, T_8 &\leq \frac{\partial^2}{\partial c_8^u}\delta(c_8^u, T_8) < 0, \\ -\delta_2 &\leq \frac{\partial^2}{\partial c_8^u \partial T_8}\delta(c_8^u, T_8) < 0, \end{aligned} \tag{15.24}$$

and there exists a non-negative constant $\mathcal{M}$, depending on $\widetilde{\overline{c}}_1$, f, and γ_2, such that

$$-\mathcal{M}T_1 \leq \frac{\partial}{\partial c_1^u}\gamma_*(c_1^u, c_8^u, T_1),\ \frac{\partial}{\partial c_8^u}\gamma_*(c_1^u, c_8^u, T_1) \leq \mathcal{M}T_1 \tag{15.25}$$

$$-\mathcal{M} \leq \frac{\partial^2}{\partial c_1^u \partial T_1}\gamma_*(c_1^u, c_8^u, T_1),\ \frac{\partial^2}{\partial c_8^u \partial T_1}\gamma_*(c_1^u, c_8^u, T_1) \leq \mathcal{M} \tag{15.26}$$

together with

$$\begin{aligned} -\mathcal{M} &\leq \frac{\partial^3}{\partial c_k^u \partial c_m^u \partial T_1}\gamma_*(c_1^u, c_8^u, T_1) \leq \mathcal{M}, \quad k, m = 1, 8, \\ -\mathcal{M}T_1 &\leq \frac{\partial^2}{\partial c_k^u \partial c_m^u}\gamma_*(c_1^u, c_8^u, T_1) \leq \mathcal{M}T_1, \quad k, m = 1, 8, \end{aligned} \tag{15.27}$$

and

$$-2 \leq \frac{\partial^3}{\partial c_8^u \partial c_8^u \partial T_8}\delta(c_8^u, T_8) < 0. \tag{15.28}$$

for all non-negative T_1, T_8, c_1^u and c_8^u.

Proof The proof follows from straightforward differentiation. For example, we have:

$$\frac{\partial}{\partial T_1}\gamma_*(c_1^u, u_3, T_1) = \frac{2c_1^u\widetilde{\widetilde{c}}_1(c_1^u + fc_8^u + 1)}{(\widetilde{\widetilde{c}}_1(c_1^u + fc_8^u + 1) + c_1^u T_1)^2} - \gamma_2\frac{1}{c_1^u + fc_8^u + 1}$$

from where follow the first two claims of the lemma. The remaining statements are proven in the similar way. □

15.5 Estimate of the upper bound of the functions R^i

Let us start from deriving an estimate of the norm $\|R^i\|_{L^\infty}$, $i = 1, \ldots, n$, where

$$\|R^i\|_{L^\infty} = \sup_{x\in\overline{\Omega}, T_1\in\mathbb{R}, T_8\in\mathbb{R}} |R^i(x, T_1, T_8)|.$$

These estimates will be obtained by means of Lemma 14.1, hence the *sine qua non* property of system (15.5)-(15.7) allowing for their establishing is the boundedness of the expression

$$\left[\frac{\partial}{\partial T_1}\left(\gamma(c_{1*}^{u;i-1}, c_{8*}^{u;i-1}, T_1)\right) + \frac{\partial}{\partial T_8}\left(\delta(c_{8*}^{u;i-1}, T_8)\right) + F_1((i-1)\Delta t, x, T_1, T_8)\right]$$

for all $(t, x) \in [0, T] \times \overline{\Omega}$ and all non-negative values of $c_{1*}^{u;i-1}, c_{8*}^{u;i-1}, T_1, T_8$.

Remark Below, for simplicity, we will denote the function γ_* by γ. □

Lemma 15.8. *For all sufficiently small $\Delta t > 0$ and all $i \in \{1, \ldots, n\}$*

$$\|R^i\|_{L^\infty} \le \|R^0\|_{L^\infty}\frac{1}{\left((1 - A\frac{T}{n})^n\right)^{\frac{i}{n}}} < \frac{3}{2}\|R^0\|_{L^\infty}\exp(Ai\Delta t), \tag{15.29}$$

where

$$A := -A_- - \delta_2 - f_{1-} \tag{15.30}$$

with A_- and δ_2 defined in Lemma 15.7 and

$$f_{1-} := \inf_{t\in[0,T], x\in\overline{\Omega}, T_1\in\mathbb{R}, T_8\in\mathbb{R}} F_1(t, x, T_1, T_8).$$

Proof By means of Lemma 15.7 and the fact that the parameter Δt can be taken sufficiently small, we can derive, using Lemma 14.1, the following recurrence inequalities:

$$\|R^i\|_{L^\infty} \le \frac{\|R^{i-1}\|_{L^\infty}/\Delta t}{1/\Delta t - A}$$

hence

$$\|R^i\|_{L^\infty} \le \frac{\|R^{i-1}\|_{L^\infty}}{1 - A\Delta t}\ .$$

By composing the above inequalities for $i \le n$, we obtain

$$\|R^i\|_{L^\infty} \le \frac{\|R^0\|_{L^\infty}}{(1 - A\Delta t)^i}\ .$$

Thus for $i = n$ and with n sufficiently large

$$\|R^n\|_{L^\infty} \le \frac{\|R^0\|_{L^\infty}}{(1 - A\Delta t)^n} = \frac{\|R^0\|_{L^\infty}}{(1 - A\dfrac{T}{n})^n} < \frac{3}{2}\|R^0\|_{L^\infty}\exp(An\Delta t). \tag{15.31}$$

It follows that for $\Delta t > 0$ sufficiently small:

$$\|R^i\|_{L^\infty} \le \|R^0\|_{L^\infty}\frac{1}{\left((1 - A\frac{T}{n})^n\right)^{\frac{i}{n}}} < \frac{3}{2}\|R^0\|_{L^\infty}\exp(Ai\Delta t). \tag{15.32}$$

□

Remark Let $\mathcal{N}_A := AT$ and let, for $\mathbb{N} \ni n > \lceil \mathcal{N}_a \rceil$, $\mathbb{R} \ni \kappa_n := n/\mathcal{N}_A$, where $\lceil \mathcal{N}_A \rceil$ denotes the least integer that is greater than or equal to $\mathcal{N}_A$. Then

$$\frac{1}{(1-\frac{AT}{n})^n} = \left[\frac{1}{\left(1-\frac{1}{\kappa_n}\right)^{\kappa_n}} \right]^{\mathcal{N}_A}.$$

It follows that to analyse the left hand side of this relation it suffices to consider the sequence inside the square bracket at the right hand side. We have

$$\log\left(\frac{1}{(1-\frac{1}{y})^y}\right) = \log\left(\frac{y^y}{(y-1)^y}\right) = y\log\left(1+\frac{1}{y-1}\right).$$

As the Taylor expansion of $\log(1+z)$ around $z=0$ is an alternating series with the first element equal to z, then, according to the Leibniz theorem for alternating series, its sum is smaller than z. It follows that the last expression is smaller than $\dfrac{y}{y-1}$. It follows that for every $\mathcal{W} > 1$ there exists y so large that

$$\frac{y}{y-1} \le \log(\mathcal{W} + \exp(1)) = \log(\mathcal{W}) + 1.$$

This holds for $y \ge 1 + 1/log(\mathcal{W})$. Consequently, for $\kappa_n \ge 1 + 1/log(\mathcal{W})$

$$\frac{1}{\left(1-\dfrac{1}{\kappa_n}\right)^{\kappa_n}} \le \mathcal{W}\exp(1),$$

and

$$\left[\frac{1}{\left(1-\dfrac{1}{\kappa_n}\right)^{\kappa_n}}\right]^{\mathcal{N}_A} \le \mathcal{W}^{\mathcal{N}_A}\exp(\mathcal{N}_A).$$

Suppose that

$$\mathcal{W}^{\mathcal{N}_A} \le m_A. \tag{15.33}$$

(In our choice $m_A = 3/2$.) Then $\mathcal{W} \le (m_A)^{\frac{1}{\mathcal{N}_A}}$ and $log(\mathcal{W}) \le log(m_A)/\mathcal{N}_A$, hence

$$\kappa_n \ge 1 + \frac{\mathcal{N}_A}{log(m_A)},$$

so

$$n = \left\lceil \mathcal{N}_A \cdot \kappa_n \right\rceil \ge \mathcal{N}_A \cdot \left(1 + \frac{\mathcal{N}_A}{log(m_A)}\right).$$

Note, that we can also write

$$\mathcal{W}^{\mathcal{N}_A}\exp(\mathcal{N}_A) = \exp\left(\mathcal{N}_A(1 + log(\mathcal{W}))\right) \le \exp\left(\mathcal{N}_A + log(m_A)\right).$$

□

Lemma 15.8 will be the basis of our subsequent estimates.

15.6 Bounds for the evolution of the support of the function R^i

To proceed, let us consider the increase the support of the function R^i with respect to T_1 and T_8 in subsequent iterations. Let us denote

$$Supp_i(T_1, T_8) := \cup_{x\in\overline{\Omega}} Supp_x R^i, \tag{15.34}$$

where

$$Supp_x R^i := \{(T_1, T_8); (x, T_1, T_8) \in Supp R^i\}$$

and $Supp R^i$ is the support of the function R^i in the space $\overline{\Omega} \times \mathbb{R}^2$. The following lemma holds.

Lemma 15.9. *Suppose that, given $i \geq 1$, for all $x \in \overline{\Omega}$ we have $R^{i-1}(x, T_1, T_8) = 0$ for $T_1 > T_1^{i-1}$ and $T_8 > T_8^{i-1}$. Then $R^i(x, T_1, T_8) \equiv 0$ for $0 > T_1 > T_1^i = T_1^{i-1} + 2\Delta t$ and $0 > T_8 > T_8^i = T_8^{i-1} + \Delta t$.*

Proof By means of Lemma 15.7, for $\Delta t > 0$ sufficiently small, the expression inside the square bracket multiplying R^i in Eq.(15.5) is positive in $\overline{\Omega}$, so by Lemma 14.1, we conclude that $R^i(x, T_1, T_8) \equiv 0$, if

$$R^{i-1}(x, \tau^{i-1}(x, T_1), \tau_8^{i-1}(x, T_8)) = 0$$

for all $x \in \overline{\Omega}$. By (15.20), we have

$$\tau_1^{i-1}(x, T_1) = T_1 - \gamma(x, T_1)\Delta t > T_1 - 2\Delta t$$

so

$$\tau_1^{i-1}(x, T_1) > T_1^{i-1} \quad \text{for } T_1 > T_1^{i-1} + 2\Delta t.$$

Likewise,

$$\tau_8^{i-1}(x, T_8) > T_8^{i-1} \quad \text{for } T_8 > T_8^{i-1} + \Delta t.$$

The lemma is proved. □

15.7 Estimates of the a priori bounds of the functions $c_1^{u;i}$ and $c_8^{u;i}$

For each $x \in \overline{\Omega}$, we thus have, according to (1.14) and Lemma 15.9

$$\begin{aligned}\int_0^\infty \int_0^\infty c_{8*}^{8;i-1} R^{i-1}\, dT_1\, dT_8 &\leq \|R^{i-1}\| \iint_{Supp_{i-1}} T_8 \, dT_1\, dT_8 \leq \\ &\leq \|R^{i-1}\|\, (T_{1*0}^0 + 2(i-1)\Delta t) \cdot (T_{8*}^0 + (i-1)\Delta t)^2/2 =: \\ &\frac{\|R^0\|}{(1 - A\Delta t)^{i-1}}\, W_1(T_{1*}^0, T_{8*}^0, (i-1)\Delta t) =: K_1^{i-1}\end{aligned} \tag{15.35}$$

and

$$\begin{aligned}\int_0^\infty \int_0^\infty c_{1*}^{i-1} R^{i-1}\, dT_1\, dT_8 &\leq \|R^{i-1}\| \iint_{Supp_{i-1}} T_1 \, dT_1\, dT_8 \leq \\ &\leq \|R^{i-1}\|(T_{1*}^0 + 2(i-1)\Delta t)^2/2 \cdot (T_{8*}^0 + (i-1)\Delta t) =: \\ &\frac{\|R^0\|}{(1 - A\Delta t)^{i-1}}\, W_8(T_{1*}^0, T_{8*}^0, (i-1)\Delta t) =: K_8^{i-1}\end{aligned} \tag{15.36}$$

where $\|\cdot\| = \|\cdot\|_{L^\infty}$. In (15.35) and (15.36), in accordance with the definition (15.34)

$$T_{1*}^0 := \sup_{Supp_0(T_1,T_8)} T_1, \quad T_{8*}^0 := \sup_{Supp_0(T_1,T_8)} T_8. \tag{15.37}$$

Using the inequalities (15.35) and (15.36), we will find a bound for absolute values of the functions $c_1^{u;i}$ and $c_8^{u;i}$ on the interval $[(i-1)\Delta t, i\Delta t]$ for all $i \in \{1, \ldots, n\}$. These estimates take into account Lemma 15.5 and the inequalities preceding this lemma, where we assumed the non-negativity of the functions $c_1^{u;i}$ and $c_8^{u;i}$. The non-negativity property is inherited by the functions with index $i \geq 1$ from the functions with index $i-1$ via the relation $Supp_{i-1}(T_1, T_8) \subset \overline{\mathbb{R}_+^2}$ (see (15.34)) implied by

Lemma 15.5. In view of this, let us note that, given non-negative $c_1^{u;i-1}$ and $c_8^{u;i-1}$, the equations for $c_1^{u;i}$ and $c_8^{u;i}$ can be written as

$$\frac{dc_1^{u;i}}{dt} = \nabla^2 c_1^{u;i} + \widetilde{\nu}\,\mathcal{C}_1^i(x) - c_1^{u;i} \tag{15.38}$$

with the function $\mathcal{C}_1^i(x) \geq 0$ given. The function $c_1^{u;i}$ should be determined for $(t,x) \in [(i-1)\Delta t, i\Delta t] \times \overline{\Omega}$, satisfies homogeneous Neumann boundary conditions and initial condition $c_1^{u;i}((i-1)\Delta t, x) = c_1^{u;i-1}((i-1)\Delta t, x) \geq 0$. Thus, according to (15.35) and the theory of sub- and supersolutions, the function $c_1^{u;i} \equiv 0$ is a subsolution, whereas a supersolution to Eq. (15.38) on the interval $[(i-1)\Delta t, i\Delta t]$ can be chosen as the solution to the ordinary differential equation of the form

$$\frac{dc_1^{u;i}}{dt} = \widetilde{\nu} K_1^{i-1} - c_1^{u;i} \tag{15.39}$$

where K_1^{i-1} is defined in (15.35). Let us note that the solution to the equation

$$\frac{d}{dt}c = -\omega_1 c + \omega_2 K, \quad c(t_0) = c_0 > 0.$$

equals

$$c(t) = \frac{\omega_2}{\omega_1}\left(1 - e^{-\omega_1(t-t_0)}\right) K + e^{-\omega_1(t-t_0)} c_0.$$

It follows that for $\omega_1 > 0$, $\omega_2 > 0$, $c_0 > 0$ and $t \in [t_0, t_0 + \Delta t)$ we have

$$c(t) \leq \frac{\omega_2}{\omega_1}\left(1 - e^{-\omega_1 \Delta t}\right) K + e^{-\omega_1(t-t_0)} c_0 < \omega_2 \Delta t K + e^{-\omega_1(t-t_0)} c(t_0)$$

and

$$c(t_0 + \Delta t) < \omega_2 \Delta t K + e^{-\omega_1 \Delta t} c(t_0).$$

It thus follows that, for $i = 1, \ldots, n+1$,

$$\|c_1^{u;i}\| < e^{-\Delta t}\|c_1^{u;i-1}\| + \Delta t\ \widetilde{\nu} W_1(T_{1*}^0, T_{8*}^0, (i-1)\Delta t)\frac{\|R^0\|}{(1 - A\Delta t)^{i-1}} \tag{15.40}$$

By putting consecutively the estimate for $\|c_1^{u;j-1}\|$ into the estimate for $\|c_1^{u;j}\|$, starting from $j = 1$ up till $j = i$, we obtain

$$\begin{aligned}
\|c_1^{u;i}\| &< e^{-i\Delta t}\|c_1^{u;0}\| + \sum_{j=1}^{i} \widetilde{\nu}\Delta t\ W_1(T_{1*}^0, T_{8*}^0, (j-1)\Delta t)\frac{\|R^0\|}{(1 - A\Delta t)^{j-1}} \leq \\
& e^{-i\Delta t}\|c_1^{u;0}\| + \ \widetilde{\nu} W_1(T_{1*}^0, T_{8*}^0, (i-1)\Delta t)\frac{\|R^0\|}{(1 - A\Delta t)^{i-1}}\sum_{j=1}^{i}\Delta t \leq \\
& e^{-i\Delta t}\|c_1^{u;0}\| + i\Delta t\ \widetilde{\nu} W_1(T_{1*}^0, T_{8*}^0, i\Delta t)\frac{\|R^0\|}{(1 - A\Delta t)^{i-1}}\ .
\end{aligned}$$

Let us note that for all $\Delta t > 0$ sufficiently small (so, due to (15.13), for all n sufficiently large), we have

$$\frac{1}{(1 - A\Delta t)^{n+1}} < \frac{3}{2} e^{AT}$$

hence, by means of arguments leading to (15.32), we arrive at the inequality

$$\|c_1^{u;i}\| < e^{-i\Delta t}\|c_1^{u;0}\| + \frac{3}{2}\, i\Delta t\ \widetilde{\nu} W_1(T_{1*}^0, T_{8*}^0, i\Delta t)\|R^0\| e^{A\, i\Delta t}, \tag{15.41}$$

where $W_1(T_{1*}^0, T_{8*}^0, i\Delta t)$ is defined in (15.35). Likewise, we have

$$\|c_8^{u;i}\| < e^{-\pi_8 i\Delta t}\|c_1^{u;0}\| + \frac{3}{2}\, i\Delta t\ \frac{\widetilde{\mu}}{\pi_8} W_8(T_{1*}^0, T_{8*}^0, i\Delta t)\|R^0\| e^{A\, i\Delta t} \tag{15.42}$$

Using the estimates (15.32),(15.41) and (15.42), we can proceed to further characterize the properties of the functions R^i, $c_1^{u;i}$ and $c_8^{u;i}$. In particular, we can estimate the L^∞ norm of their first derivatives.

Lemma 15.10. *Suppose that for $(t,x) \in (0,T] \times \Omega$, and $a > 0$, u satisfy the equation*

$$\frac{\partial u}{\partial t} = \Delta u - au + f(t,x)$$

$$\frac{\partial u}{\partial \mathbf{n}}(t,x) = 0 \quad \textit{for } x \in \partial\Omega, \quad u(0,x) = \phi(x)$$

and that the compatibility conditions are satisfied, i.e. $\dfrac{\partial \phi}{\partial \mathbf{n}} = 0$ *on* $\partial\Omega$*. Then, for all* $\beta \in (0,1)$*, the following estimate holds:*

$$\|u\|_{C_{t,x}^{(1+\beta)/2,1+\beta}((0,T)\times\Omega)} \le C_p \left[\|f\|_{L^\infty((0,T)\times\Omega)} + \|\phi\|_{C_x^{1+\beta}(\Omega)} \right] \tag{15.43}$$

with the constant C_p depending on β, T and the parameters characterizing Ω.

Proof The estimate (15.48) is a particular version of Theorem 6.49 of section VI in [25]. (Note that $f \in L^\infty(\Omega \times (0,T))$ belongs also to the Morrey space $M_{1,1+m+\beta}$.) □

Remark Let us comment on the membership of the function $f \in L^\infty(\Omega \times (0,T))$ in the Morrey space $M_{1,1+m+\beta}$. According to the definition given before Theorem 7.37 in [25], the Morrey space $M^{p,q}$, $p \in (1,\infty)$, $q \le 2$, can be defined as the subset of the space L^p with the finite norm of the form

$$\|u\|_{p,q} = \sup_{Q(r), r < diam\Omega_T} \left(r^{-q} \int_{Q(r)} \int |u|^p dX \right),$$

where $\Omega_T = [0,T] \times \Omega$ and

$$\|X\| := \max(|x|, |t|^{1/2})$$

with

$$|x| := \left(\sqrt{\sum_{j=1}^m x_j^2} \right).$$

Next (see, sec. I.3 in [25])

$$Q(X_0, r) = \{|x - x_0| < r, |t - t_0| < r^2; t < t_0\}.$$

It follows that as $r \to 0$, then $\int_{Q(r)} dX = O(r^{m+2})$. As $f \in L^\infty(\Omega_T)$, then, for all $\beta \in (0,1)$, $\|f\|_{1,1+m+\beta} < \infty$. □

In applying Lemma 15.10 to Eqs (15.6) and (15.7), let us note that ϕ can be identified with $c_1^{u;0}$ and $c_8^{u;0}$, whereas $f : (0,T] \times \Omega$ can be identified with the functions:

$$\begin{aligned} &\tilde{\nu} \textstyle\sum_{i=1}^{n+1} \chi_i \int_0^\infty \int_0^\infty c_{8*}^{8;i-1} \, R^{i-1} \, dT_1 \, dT_8 = \tilde{\nu} \sum_{i=1}^{n+1} \chi_i \int_0^\infty \int_0^\infty c_8^{8;i-1}((i-1)\Delta t, x) \, R^{i-1} \, dT_1 \, dT_8 \\ &\tilde{\mu} \textstyle\sum_{i=1}^{n+1} \chi_i \int_0^\infty \int_0^\infty c_{1*}^{i-1} \, R^{i-1} \, dT_1 \, dT_8 = \tilde{\mu} \sum_{i=1}^{n+1} \chi_i \int_0^\infty \int_0^\infty c_1^{i-1}((i-1)\Delta t, x) \, R^{i-1} \, dT_1 \, dT_8 \end{aligned} \tag{15.44}$$

where χ_i is the characteristic function of the interval $[(i-1)\Delta t, i\Delta t]$. As the integrands in the above integrals are continuous with respect to x on each of the intervals $[(i-1)\Delta t, i\Delta t]$, then these integrals are of $L^\infty([0,T] \times \overline{\Omega})$ class. Let us denote:

$$c_1^u(t,x) := \sum_{i=1}^n \chi_i c_1^{u;i}(t,x), \quad c_8^u(t,x) := \sum_{i=1}^n \chi_i c_8^{u;i}(t,x) \tag{15.45}$$

where χ_i is the characteristic function of the interval $[(i-1)\Delta t, i\Delta t]$.

Lemma 15.11. *Let $n \geq 3$ be fixed. Suppose that for each $i \in \{0, 1, \ldots, n\}$ and each $x \in \overline{\Omega}$, the $C^0(\overline{\Omega})$ norms of the functions R^i are bounded from above uniformly with respect to i. Then, for each $\beta \in (0,1)$, c_1^u and c_8^u are of class $C_{t,x}^{(1+\beta)/2,1+\beta}((0,T) \times \Omega)$. To be more precise, there exist constants $C_1(\beta,\Omega)$, $C_8(\beta,\Omega)$, K_1 and K_8, depending on T, such that*

$$\|c_1^u\|_{C_{t,x}^{(1+\beta)/2,1+\beta}((0,T)\times\Omega)} \leq C_1(\beta,\Omega)\left[K_1 + \|c_1^{u;0}\|_{C_x^{1+\beta}(\Omega)}\right] \tag{15.46}$$

and

$$\|c_8^u\|_{C_{t,x}^{(1+\beta)/2,1+\beta}((0,T)\times\Omega)} \leq C_8(\beta,\Omega)\left[K_8 + \|c_8^{u;0}\|_{C_x^{1+\beta}(\Omega)}\right]. \tag{15.47}$$

Proof The lemma follows from Lemma 15.10, together with (15.41) and (15.41). The constants K_1 and K_8 can be chosen as independent on n. □

Lemma 15.12. *Let $n \geq 3$ be fixed. Suppose that for each $i \in \{0, 1, \ldots, n\}$ the $C^1(\Omega)$ norms of the functions R^i are bounded from above uniformly with respect to i. Then, for each $\beta \in (0,1)$, c_1^u and c_8^u are of class $C_{t,x}^{1+\beta/2,2+\beta}(((i-1)\Delta t, i\Delta t) \times \Omega)$. To be more precise, there exist constants $C_1(\beta,\Omega)$, $C_8(\beta,\Omega)$, K_1 and K_8, depending on T, such that*

$$\|c_1^u\|_{C_{t,x}^{1+\beta/2,2+\beta}(((i-1)\Delta t,i\Delta t)\times\Omega)} \leq C_{1\Delta}(\beta,\Omega)\left[K_1 + \|c_1^u((i-1)\Delta t,\cdot)\|_{C_x^{2+\beta}(\Omega)}\right] \tag{15.48}$$

and

$$\|c_8^u\|_{C_{t,x}^{1+\beta/2,2+\beta}(((i-1)\Delta t,i\Delta t)\times\Omega)} \leq C_{8\Delta}(\beta,\Omega)\left[K_8 + \|c_8^u((i-1)\Delta t,\cdot)\|_{C_x^{2+\beta}(\Omega)}\right]. \tag{15.49}$$

In particular, there exists a constant P independent of i such that as $\Delta t \to 0$

$$\|c_1^u(i\Delta t,\cdot) - c_1((i-1)\Delta t,\cdot)\|_{C^0(\Omega)} \leq P\Delta t, \quad \|c_8^u(i\Delta t,\cdot) - c_8((i-1)\Delta t,\cdot)\|_{C^0(\Omega)} \leq P\Delta t. \tag{15.50}$$

and for all $t \in [(i-1)\Delta t, i\Delta t]$:

$$\|c_1^u(t,\cdot)-c_1((i-1)\Delta t,\cdot)\|_{C^0(\Omega)} \leq P\left(t-(i-1)\Delta t\right), \quad \|c_8^u(t,\cdot)-c_8((i-1)\Delta t,\cdot)\|_{C^0(\Omega)} \leq P\left(t-(i-1)\Delta t\right). \tag{15.51}$$

Proof The lemma follows from Lemma 15.10, according to which c_1^u and c_8^u (defined in (15.45)) are of $C_{t,x}^{(1+\beta)/2,1+\beta}((0,T)\times\Omega)$ class. Starting from the initial data equal to $c_1^{u,0}$ and $c_8^{u,0}$ (and assuming that they are of $C_x^{2+\beta}(\Omega)$ class) we obtain a $C_{t,x}^{1+\beta/2,2+\beta}$ solution on the set $([0,\Delta t)\times\Omega)$. Treating $c_1^{u;1}(t=\Delta t,x)$ and $c_8^{u;1}(t=\Delta t,x)$ as the initial data on the interval we obtain a solution of $C_{t,x}^{1+\beta/2,2+\beta}$ class on the set $([1\cdot\Delta t, 2\cdot\Delta t)\times\Omega)$. Proceeding consecutively in this way, we obtain a $C_{t,x}^{1+\beta/2,2+\beta}$ solution on the set $([(i-1)\cdot\Delta t, i\cdot\Delta t)\times\Omega)$ for all $i \in \{1,\ldots,n\}$, hence using the Schauder esimates, we obtain inequalities (15.48) and (15.49). As the constants K_1 and K_8 can be chosen as independent on n and i, then, due to the fact that the time derivative of the solutions is bounded (and Holder continuous), there exists a constant P such that for $\Delta t > 0$ sufficiently small, inequality (15.50) holds. □

Remark The following counterpart of inequalities (15.48) and (15.49) follow straightforwardly from Lemma 15.10:

$$\|c_1^u\|_{C_{t,x}^{(1+\beta)/2,1+\beta}(((i-1)\Delta t,i\Delta t)\times\Omega)} \leq C_{1\Delta}(\beta,\Omega)\left[K_{1\Delta i} + \|c_1^u((i-1)\Delta t,\cdot)\|_{C_x^{1+\beta}(\Omega)}\right] \tag{15.52}$$

and

$$\|c_8^u\|_{C_{t,x}^{(1+\beta)/2,1+\beta}(((i-1)\Delta t,i\Delta t)\times\Omega)} \leq C_{8\Delta}(\beta,\Omega)\left[K_{8\Delta i} + \|c_8^u((i-1)\Delta t,\cdot)\|_{C_x^{1+\beta}(\Omega)}\right]. \tag{15.53}$$

□

15.8 Estimates of first order derivatives of R^i with respect to T_m

In this section, we will examine the differentiability properties of solutions to system (15.5)-(15.7) (together with (15.8)-(15.9)) with respect to the variables T_1 and T_8. Differentiating Eq.(15.5) with respect to T_1 we obtain for any pair (T_1, T_8):

$$\begin{aligned}0 = d_R\nabla^2 B_1^i - B_1^i\Big[\frac{\partial}{\partial T_1}\Big(\gamma(c_{1*}^{u;i-1}, c_{8*}^{u;i-1}, T_1)\Big) + \frac{\partial}{\partial T_8}\Big(\delta(c_{8*}^{u;i-1}, T_8)\Big) + F_1((i-1)\Delta t, x, T_1, T_8) + \frac{1}{\Delta t}\Big] \\ -R^i\Big[\frac{\partial^2}{\partial T_1^2}\Big(\gamma(c_{1*}^{u;i-1}, c_{8*}^{u;i-1}, T_1)\Big) + \frac{\partial}{\partial T_1}F_1((i-1)\Delta t, x, T_1, T_8)\Big] \\ +F_0((i-1)\Delta t, x)\cdot\nabla B_1^i + \frac{B_1^{i-1}(x;\tau_1^{i-1}, \tau_8^{i-1})}{\Delta t},\end{aligned} \tag{15.54}$$

where

$$B_1^i(x, T_1, T_8) := \frac{\partial R^i}{\partial T_1}(x, T_1, T_8).$$

Recall that, according to (15.8) and (15.9),

$$\tau_1^{i-1} = T_1 - \Delta t\cdot\Big(\gamma(c_{1*}^{u;i-1}(x), c_{8*}^{u;i-1}(x), T_1)\Big), \tag{15.55}$$

$$\tau_8^{i-1} = T_8 - \Delta t\cdot\delta(c_{8*}^{u;i-1}(x), T_8). \tag{15.56}$$

It follows that

$$\begin{aligned}\frac{\partial\tau_1^{i-1}}{\partial T_1} &= 1 - \Delta t\,\frac{\partial\gamma(c_{1*}^{u;i-1}(x), c_{8*}^{u;i-1}(x), T_1)}{\partial T_1}, \\ \frac{\partial\tau_8^{i-1}}{\partial T_8} &= 1 - \Delta t\,\frac{\partial\delta(c_{1*}^{u;i-1}(x), c_{8*}^{u;i-1}(x), T_8)}{\partial T_8},\end{aligned} \tag{15.57}$$

hence

$$\begin{aligned}B_1^{i-1}(x;\tau_1^{i-1}, \tau_8^{i-1}) := \frac{\partial R^{i-1}}{\partial\tau_1^{i-1}}(x, \tau_1^{i-1}, \tau_8^{i-1})\cdot\frac{\partial\tau_1^{i-1}}{\partial T_1} = \\ \frac{\partial R^{i-1}}{\partial\tau_1^{i-1}}(x, \tau_1^{i-1}, \tau_8^{i-1})\cdot\left(1 - \Delta t\,\frac{\partial\gamma(c_{1*}^{u;i-1}(x), c_{8*}^{u;i-1}(x), T_1)}{\partial T_1}\right)\end{aligned} \tag{15.58}$$

and

$$\begin{aligned}B_8^{i-1}(x;\tau_1^{i-1}, \tau_8^{i-1}) := \frac{\partial R^{i-1}}{\partial\tau_8^{i-1}}(x, \tau_1^{i-1}, \tau_8^{i-1})\cdot\frac{\partial\tau_8^{i-1}}{\partial T_8} = \\ \frac{\partial R^{i-1}}{\partial\tau_8^{i-1}}(x, \tau_1^{i-1}, \tau_8^{i-1})\cdot\left(1 - \Delta t\,\frac{\partial\delta(c_{1*}^{u;i-1}(x), c_{8*}^{u;i-1}(x), T_8)}{\partial T_8}\right).\end{aligned} \tag{15.59}$$

Now, let us fix (T_1, T_8) and, for given $x \in \overline{\Omega}$, $(\tau_1^{i-1}, \tau_8^{i-1})$ as well. In this way, we can treat $B_1^i(\cdot, T_1, T_8)$ and $B_1^{i-1}(\cdot;\tau_1^{i-1}(\cdot, T_1), \tau_8^{i-1}(\cdot, T_8))$ as functions of x only. If extremum of the absolute value of $B_1^i(x, T_1, T_8)$ is attained at $y \in \Omega$, then

$$\nabla B_1^i(y, T_1, T_8) = 0,$$

and, due to the maximum principle, (15.58) and Lemma 15.7:

$$
\begin{aligned}
&|B_1^i(y,T_1,T_8)| \le \Big(R^i(y,T_1,T_8)\Big|\frac{\partial^2}{\partial T_1^2}\gamma(c_{1*}^{u;i-1}(y), c_{8*}^{u;i-1}(y), T_1)+\\
&\frac{\partial}{\partial T_1}F_1((i-1)\Delta t, y, T_1, T_8)\Big| + \Big|\frac{B_1^{i-1}(y;\tau_1^{i-1},\tau_8^{i-1})}{\Delta t}\Big|\Big) \left(-A+\frac{1}{\Delta t}\right)^{-1} \le\\
&\Big(R^i(y,T_1,T_8)(A_M+f_1) + \Big|\frac{B_1^{i-1}(y;\tau_1^{i-1},\tau_8^{i-1})}{\Delta t}\Big|\Big) \left(-A+\frac{1}{\Delta t}\right)^{-1} =\\
&\Big(R^i(y,T_1,T_8)(A_M+f_1)\Delta t + |B_{\tau_1}^{i-1}(y;\tau_1^{i-1},\tau_8^{i-1})|(1+A\Delta t)\Big)\,(1-A\Delta t)^{-1},
\end{aligned}
\tag{15.60}
$$

where

$$
A_M := \max\{A_-, A_+\} \tag{15.61}
$$

with A_-, A_+ defined in inequality (15.23) of Lemma 15.7, and A defined by (15.30).

Now, let us suppose that the global extremum of the absolute value of $B_1^i(x,T_1,T_8)$ is attained at $y \in \partial\Omega$. Suppose that this extremum is a positive maximum. Then, from the fact that $\partial R^i(x,T_1,T_8)/\partial n(x) = 0$, we conclude that

$$
\frac{\partial B_1^i(x,T_1,T_8)}{\partial n(x)} = 0 \quad \text{for } x \in \partial\Omega, \tag{15.62}
$$

hence

$$
\frac{\partial^2 B_1^i(y,T_1,T_8)}{\partial n(y)^2} \le 0
$$

as otherwise $B_1^i(x,T_1,T_8)$ would not have attained a maximum at $x = y \in \partial\Omega$. Next, the Laplacian of $B_1^i(x,T_1,T_8)$ for $x \in \partial\Omega$ is equal to the sum of the second derivatives with respect to $n(x)$ and the second derivatives with respect to the directions lying in the plane tangent to $\partial\Omega$ at x. This is seen from the form of the Laplace operator with respect to variables locally connected with $\partial\Omega$ supplied by the Appendix A. Due to the fact that B_1^i has a maximum at $x = y$, each of these derivatives is non-positive. It follows that $\nabla^2 B_1^i(y,T_1,T_8) \le 0$, hence the estimate of the form (15.60) holds. It should be noted that, according to Assumption 15.2, in this case the terms proportional to F_0 and F_1 do not take part in the estimates, because they are identically equal to zero at $\partial\Omega$. The same arguments can be applied in the case, when the extremum is a non-positive minimum.

As we showed above, thanks to the assumption concerning the compactness of the initial data, for each $i \in \{1,\dots,n\}$ the points (T_1,T_8) for which $R^i(x,T_1,T_8) \not\equiv 0$ are contained in a compact set $\mathcal{S}^i$. For all $i \in \{1,\dots,n\}$, $y = y(T_1,T_8)$, so we can take a supremum over $(T_1,T_8) \in \mathcal{S}^i$. In this way, we obtain the estimate for

$$
\mathcal{B}_1^i := \sup_{(T_1,T_8)\in\mathcal{S}^i} |B_1^i(y(T_1,T_8),T_1,T_8)|.
$$

$\mathcal{B}_1^0$ is given by the initial conditions. Next, let us note that, if

$$
L := (1-A\Delta t)^{-1} \tag{15.63}
$$

then

$$
(1+A\Delta t) < L, \tag{15.64}
$$

hence, for $i \ge 1$ we have,

$$
\mathcal{B}_1^i \le \left(\|R^i\| A_f(\Delta t) + \mathcal{B}_1^{i-1} L\right) L, \tag{15.65}
$$

where

$$
A_f = A_M + f_1. \tag{15.66}
$$

In arriving to (15.88) we used the fact that

$$\sup_{x\in\Omega,\tau_1,\tau_8} |B_{\tau_1}^{i-1}(x,\tau_1,\tau_8)| \le \sup_{x\in\Omega,T_1,T_8} |B_1^{i-1}(x,T_1,T_8)| \tag{15.67}$$

We have

$$\mathcal{B}_1^1 \le \left(\|R^1\| A_f(\Delta t) + \mathcal{B}_1^0 L\right) L,$$

$$\mathcal{B}_1^2 \le \left(\|R^2\| A_f(\Delta t) + \mathcal{B}_1^1 L\right) L \le \left(\|R^2\| A_f(\Delta t) + (\|R^1\| A_f(\Delta t) + \mathcal{B}_1^0 L) LL\right) L$$

so inductively, for $i \in \{3, \ldots, n(\Delta t)\}$,

$$\mathcal{B}_1^i \le \mathcal{B}_1^0 L^{2i} + A_f(\Delta t) \sum_{j=1}^{i} \|R^j\| L^{2(i-j)+1}.$$

Using (15.31) and (15.63), we obtain

$$\mathcal{B}_1^i \le L^{2i}\left(\mathcal{B}_1^0 + A_f(\Delta t)\textstyle\sum_{j=1}^i \|R^j\| L^{-2j+1}\right) \le L^{2i}\left(\mathcal{B}_1^0 + A_f(\Delta t)\|R^0\|\textstyle\sum_{j=1}^i L^{-j+1}\right) \le$$

$$L^{2i}\left(\mathcal{B}_1^0 + A_f(\Delta t)\|R^0\|\textstyle\sum_{j=1}^i L^{-j+1}\right) \le L^{2i}\left(\mathcal{B}_1^0 + A_f(\Delta t) i \|R^0\|\right).$$

so consequently, as $i\Delta t = \dfrac{i}{n}T$, we have by means of Remark after (15.32), for $\Delta t > 0$ sufficiently small:

$$\mathcal{B}_1^i \le \frac{3}{2} A_f\, i\Delta t \|R^0\|_{L^\infty} \exp(2A\frac{i}{n}T) + \frac{3}{2}\mathcal{B}_1^0 \exp(2A\frac{i}{n}T). \tag{15.68}$$

Denoting $t := i\Delta t$, we can write:

$$\mathcal{B}_1^i \le \frac{3}{2} A_f t \|R^0\|_{L^\infty} \exp(2At) + \frac{3}{2}\mathcal{B}_1^0 \exp(2At) \tag{15.69}$$

Likewise, we have the estimate

$$\mathcal{B}_8^i \le \frac{3}{2} A_f\, i\Delta t \|R^0\|_{L^\infty} \exp(2A\frac{i}{n}T) + \frac{3}{2}\mathcal{B}_8^0 \exp(2A\frac{i}{n}T). \tag{15.70}$$

which, after inserting $t := i\Delta t$, can be written as:

$$\mathcal{B}_8^i \le \frac{3}{2} A_f t \|R^0\|_{L^\infty} \exp(2At) + \frac{3}{2}\mathcal{B}_8^0 \exp(2At), \tag{15.71}$$

where

$$\mathcal{B}_8^i := \sup_{(T_1,T_8)\in\mathcal{S}^i} |B_8^i(y(T_1,T_8),T_1,T_8)|.$$

with

$$B_8^i(x,T_1,T_8) := \frac{\partial R^i}{\partial T_8}(x,T_1,T_8).$$

15.9 Estimates of the first order derivatives of R^i with respect to the components of x inside Ω

We will start from the estimates of the absolute values of the first derivatives of the functions R^i with respect to the components of x attained inside Ω.

Remark To avoid confusion, the derivative of $R^{i-1}(x;\tau_1^{i-1}(x,T_1),\tau_8^{i-1}(x,T_8))$ with respect to τ_k^{i-1}, $k=1,8$, will be denoted below by $B^{i-1}_{\tau_k}(x;\tau_1^{i-1}(x,T_1),\tau_8^{i-1}(x,T_8))$, where, for simplicity, we have omitted the index $i-1$. □

Differentiating Eq.(15.5) with respect to x_r, $r=1,2,3$, we obtain the equation:

$$
\begin{aligned}
&0 = d_R\nabla^2 Q_r^i - Q_r^i\left[\frac{\partial}{\partial T_1}\Big(\gamma(c_{1*}^{u;i-1},c_{8*}^{u;i-1},T_1)\Big)+\frac{\partial}{\partial T_8}\Big(\delta(c_{8*}^{u;i-1},T_8)\Big)+F_1^{i-1}+\frac{1}{\Delta t}\right]-\\
&R^i\Big[\frac{\partial^2}{\partial c_{1*}^{u;i-1}\partial T_1}\Big(\gamma(c_{1*}^{u;i-1},c_{8*}^{u;i-1},T_1)\Big)c_{1*,x_r}^{u;i-1}+\frac{\partial^2}{\partial c_{8*}^{u;i-1}\partial T_1}\Big(\gamma(c_{1*}^{u;i-1},c_{8*}^{u;i-1},T_1)\Big)c_{8*,x_r}^{u;i-1}+\\
&\frac{\partial^2}{\partial c_{8*}^{u;i-1}\partial T_8}\Big(\delta(c_{8*}^{u;i-1},T_8)\Big)c_{8*,x_r}^{u;i-1}+\frac{\partial F_1^{i-1}}{\partial x_r}\Big]+\frac{Q^{i-1}(x;\tau_1^{i-1},\tau_8^{i-1})}{\Delta t}+\\
&\frac{B^{i-1}_{\tau_1}(x;\tau_1^{i-1}(x,T_1),\tau_8^{i-1}(x,T_8))}{\Delta t}\cdot\frac{\partial\tau_1^{i-1}}{\partial x_r}+\frac{B^{i-1}_{\tau_8}(x;\tau_1^{i-1}(x,T_1),\tau_8^{i-1}(x,T_8))}{\Delta t}\cdot\frac{\partial\tau_8^{i-1}}{\partial x_r}+\\
&F_0^{i-1}\cdot\nabla\left(\frac{\partial R^i}{\partial x_r}\right)+\frac{\partial F_0^{i-1}}{\partial x_r}\cdot\nabla R^i,
\end{aligned}
\tag{15.72}
$$

where, for $i\in\{1,\ldots,n\}$,

$$Q_r^i(x,T_1,T_8):=\frac{\partial R^i}{\partial x_r}(x,T_1,T_8)$$

and, for simplicity we denoted

$$F_0^{i-1}:=F_0((i-1)\Delta t,x),\quad F_1^{i-1}:=F_1((i-1)\Delta t,x,T_1,T_8).$$

According to (15.8) we have:

$$
\begin{aligned}
&\frac{1}{\Delta t}\cdot\frac{\partial\tau_1^{i-1}}{\partial x_l}=-\frac{\partial\gamma(c_{1*}^{u;i-1}(x),c_{8*}^{u;i-1}(x),T_1)}{\partial x_l}=\\
&-\frac{\partial\gamma(c_{1*}^{u;i-1},c_{8*}^{u;i-1},T_1)}{\partial c_{1*}^{u;i-1}}\cdot\frac{\partial c_{1*}^{u;i-1}}{\partial x_l}-\frac{\partial\gamma(c_{1*}^{u;i-1},c_{8*}^{u;i-1},T_1)}{\partial c_{8*}^{u;i-1}}\cdot\frac{\partial c_{1*}^{u;i-1}}{\partial x_l}
\end{aligned}
\tag{15.73}
$$

and, according to (15.9) :

$$\frac{1}{\Delta t}\cdot\frac{\partial\tau_8^{i-1}}{\partial x_l}=-\frac{\partial\delta(c_{8*}^{u;i-1}(x),T_8)}{\partial x_l}=-\frac{\partial\widetilde{\delta}(c_{8*}^{u;i-1},T_8)}{\partial c_{1*}^{u;i-1}}\cdot\frac{\partial c_{8*}^{u;i-1}}{\partial x_l}\tag{15.74}$$

hence (15.72) can be written as

$$
\begin{aligned}
&0 = d_R\nabla^2 Q_r^i - Q_r^i\left[\frac{\partial}{\partial T_1}\Big(\gamma(c_{1*}^{u;i-1},c_{8*}^{u;i-1},T_1)\Big)+\frac{\partial}{\partial T_8}\Big(\delta(c_{8*}^{u;i-1},T_8)\Big)+F_1^{i-1}+\frac{1}{\Delta t}\right]\\
&\qquad+\frac{Q_r^{i-1}(x;\tau_1^{i-1},\tau_8^{i-1})}{\Delta t}+\Big\{-R^i\Big[\frac{\partial^2}{\partial c_{1*}^{u;i-1}\partial T_1}\Big(\gamma(c_{1*}^{u;i-1},c_{8*}^{u;i-1},T_1)\Big)c_{1*,x_r}^{u;i-1}\\
&+\frac{\partial^2}{\partial c_{8*}^{u;i-1}\partial T_1}\Big(\gamma(c_{1*}^{u;i-1},c_{8*}^{u;i-1},T_1)\Big)c_{8*,x_r}^{u;i-1}+\frac{\partial^2}{\partial c_{8*}^{u;i-1}\partial T_8}\Big(\delta(c_{8*}^{u;i-1},T_8)\Big)c_{8*,x_r}^{u;i-1}+\frac{\partial F_1^{i-1}}{\partial x_r}\Big]\\
&-B^{i-1}_{\tau_1}(x;\tau_1^{i-1}(x,T_1),\tau_8^{i-1}(x,T_8))\cdot\frac{\partial\gamma(c_{1*}^{u;i-1}(x),c_{8*}^{u;i-1}(x),T_1)}{\partial x_r}-\\
&B^{i-1}_{\tau_8}(x;\tau_1^{i-1}(x,T_1),\tau_8^{i-1}(x,T_8))\cdot\frac{\partial\delta(c_{8*}^{u;i-1}(x),T_8)}{\partial x_r}\Big\}+F_0^{i-1}\cdot\nabla\left(\frac{\partial R^i}{\partial x_r}\right)+\frac{\partial F_0^{i-1}}{\partial x_r}\cdot\nabla R^i\,.
\end{aligned}
\tag{15.75}
$$

Now, using (15.26) and Lemma 15.11, we conclude that

$$\Big|\frac{\partial^2}{\partial c_{1*}^{u;i-1}\partial T_1}\left(\gamma(c_{1*}^{u;i-1},c_{8*}^{u;i-1},T_1)\right)c_{1*,x_r}^{u;i-1}+\frac{\partial^2}{\partial c_{8*}^{u;i-1}\partial T_1}\left(\gamma(c_{1*}^{u;i-1},c_{8*}^{u;i-1},T_1)\right)c_{8*,x_r}^{u;i-1}\Big|\leq$$
$$\mathcal{M}\left(C_1(\beta,\Omega)\|c_1^{u;0}\|_{C_x^{1+\beta}(\Omega)}+C_8(\beta,\Omega)\|c_8^{u;0}\|_{C_x^{1+\beta}(\Omega)}\right).$$

Recall that the constants $C_8(\beta,\Omega)$, and $C_8(\beta,\Omega)$ are independent of i, as, in fact, the x-derivatives of the functions defined by (15.45) are Hölder continuous in t for $t\in[0,T]$.

Next, using (15.25) and Lemma 15.11, we conclude that:

$$\Big|\frac{\partial\gamma(c_{1*}^{u;i-1}(x),c_{8*}^{u;i-1}(x),T_1)}{\partial x_r}\Big|\leq T_{1i}\,\mathcal{M}\left(C_1(\beta,\Omega)\|c_1^{u;0}\|_{C_x^{1+\beta}(\Omega)}+C_8(\beta,\Omega)\|c_8^{u;0}\|_{C_x^{1+\beta}(\Omega)}\right),\qquad(15.76)$$

where T_{1i} is estimated from above in Lemma 15.9 as $T_{1*}^0+2i\Delta t$.

The corresponding inequalities for the function δ take the form:

$$\Big|\frac{\partial^2}{\partial c_{8*}^{u;i-1}\partial T_8}\left(\delta(c_{8*}^{u;i-1},T_8)\right)c_{8*,x_r}^{u;i-1}\Big|\leq\delta_2\,C_8(\beta,\Omega)\|c_8^{u;0}\|_{C_x^{1+\beta}(\Omega)}$$

(see (15.24)) and

$$\Big|\frac{\partial\delta(c_{8*}^{u;i-1}(x),T_8)}{\partial x_r}\Big|\leq T_{8i}\delta_2C_8(\beta,\Omega)\|c_8^{u;0}\|_{C_x^{1+\beta}(\Omega)},\qquad(15.77)$$

where T_{8i} is estimated from above in Lemma 15.9 as $T_{8*}^0+i\Delta t$. Let

$$G_1:=\mathcal{M}\Big(C_1(\beta,\Omega)\|c_1^{u;0}\|_{C_x^{1+\beta}(\Omega)}+C_8(\beta,\Omega)\|c_8^{u;0}\|_{C_x^{1+\beta}(\Omega)}\Big)\Big|_{\beta=0},\quad G_8:=\Big(\delta_2\,C_8(\beta,\Omega)\|c_8^{u;0}\|_{C_x^{1+\beta}(\Omega)}\Big)\Big|_{\beta=0}.\qquad(15.78)$$

Let

$$\sup_{r=1,2,3}|Q_r^i|=|Q_\rho^i|$$

and

$$Q^i:=\Big|Q_\rho^i\Big|.$$

for some $\rho\in\{1,2,3\}$. Obviously Q^i (as well as Q_r^i) are functions of T_1 and T_8.

Now, the absolute value of the term $F_0^{i-1}\cdot\nabla\left(\frac{\partial R^i}{\partial x_\rho}\right)+\frac{\partial F_0^{i-1}}{\partial x_\rho}\cdot\nabla R^i$ at a point of the global extremum, where $\nabla\frac{\partial R^i}{\partial x_\rho}=\nabla Q^i=0$ can be estimated as

$$\Big|\frac{\partial F_0^{i-1}}{\partial x_\rho}\cdot\nabla R^i\Big|\leq 3f_0Q^i.\qquad(15.79)$$

In this way we can find an L^∞ estimate for the expression in the curly bracket in (15.75) (including the term $\partial F_1^{i-1}/\partial x_r$ with its absolute value estimated from above by f_1) as:

$$\Big\|\Big\{\cdot\Big\}\Big\|_{L^\infty}\leq\|R^i\|_{L^\infty}\cdot(G_1+G_8+f_1)+\mathcal{B}_1^i\cdot G_1\cdot(T_{1*}^0+2n\Delta t)+\mathcal{B}_8^i\cdot G_8\cdot(T_{8*}^0+n\Delta t),\qquad(15.80)$$

where G_1 and G_8 are defined in (15.78). Using inequalities (15.68), (15.70) we can write

$$\Big\|\Big\{\cdot\Big\}\Big\|_{L^\infty}\leq S_Q\exp(2A\frac{i}{n}T),$$

where, for $n=T/\Delta t$,

$$S_Q := \frac{3}{2}\|R^0\|_{L^\infty} \cdot (G_1 + G_8 + f_1) + b_1\, G_1 \cdot (T^0_{1*} + 2T) + b_8\, G_8 \cdot (T_{8*} + T)$$

with

$$b_1 = \frac{3}{2} A_f\, T \|R^0\|_{L^\infty} + \frac{3}{2}\mathcal{B}^0_1$$

and

$$b_8 = \frac{3}{2} A_f\, T \|R^0\|_{L^\infty} + \frac{3}{2}\mathcal{B}^0_8.$$

Lemma 15.13. *Let $T > 0$, $s \in \mathbb{N}$ and $\mathbb{N} \ni n \gg 1$ be fixed. Let $\Delta t = Tn^{-1}$ and $L := (1 - A\Delta t)^{-1}$, $A > 0$. Then, for all n sufficiently large, we have:*

$$\sigma_n = \Delta t\left(1 + L^s + L^{2s} + \ldots + L^{ns}\right) < \frac{3}{2}\frac{1}{sA}\exp(Ans\Delta t).$$

Next, for any $i \le n$,

$$\sigma_i := \Delta t\left(1 + L^s + L^{2s} + \ldots + L^{ns}\right) \le \frac{3}{2}\frac{1}{A}(\exp(Ans\Delta t))^{i/n} = \frac{3}{2}\frac{1}{sA}\exp(Ais\Delta t).$$

Proof By (15.64), we have $L^s > (1 + A\Delta t)^s > 1 + sA\Delta t$, hence

$$\sigma_n = \Delta t\left(1 + L^s + L^{2s} + \ldots, L^{ns}\right) = \Delta t\frac{L^{(n+1)s} - 1}{L^s - 1} < \Delta t\frac{L^{(n+1)s}}{L^s - 1} < \frac{L^{(n+1)s}}{sA}.$$

Next, for n sufficiently large, we have

$$L^{(n+1)s} = \left(\frac{1}{1 - A\dfrac{T}{n}}\right)^{ns}\left(\frac{1}{1 - A\dfrac{T}{n}}\right)^{s} = \left(\frac{1}{1 - sA\dfrac{T}{ns}}\right)^{ns}\left(\frac{1}{1 - A\dfrac{T}{n}}\right)^{s} < \frac{3}{2}\exp(AsT)$$

thus, for $\Delta t \to 0$,

$$\sigma_n < \frac{3}{2}\frac{1}{A}\exp(Asn\Delta t).$$

In general, for $i \le n$, we have

$$\sigma_i < \frac{3}{2}\frac{1}{sA}\exp(A\frac{i}{n}sT) = \frac{3}{2}\frac{1}{sA}\exp(Ais\Delta t).$$

The lemma is proved. □

Now, recall that by Lemma 15.7 the first two terms in the bracket multiplying Q^i_r in (15.75) are uniformly bounded from below for all non-negative values of their arguments by the constant $(-A)$.

In consequence, for fixed $t \in [0, T]$ and n satisfying (15.13), it follows from (15.75) by means of Lemma 14.1, that, for $i = 1, \ldots, n$, the estimate from above of

$$\mathcal{Q}^i := \sup_{T_1, T_8} Q^i = \sup_{x \in \Omega, T_1, T_8, r=1,2,3}\left|\frac{\partial R^i}{\partial x_r}(x, T_1, T_8)\right|, \tag{15.81}$$

in relation to the value of $\mathcal{Q}^{i-1}$, can be written as

$$\mathcal{Q}^i \le \frac{\mathcal{Q}^{i-1} + S_Q\Delta t\, \exp(2A\dfrac{i}{n}T)}{1 - (A + 3f_0)\Delta t} < \frac{\mathcal{Q}^{i-1} + S_Q\Delta t\, \exp(2AT)}{(1 - A_1)}$$

where A is defined in (15.30),

$$A_1 = (A + 3f_0) \tag{15.82}$$

and $\mathcal{Q}^{i-1}$ corresponds to $Q^{i-1}(x; \tau_1^{i-1}, \tau_8^{i-1})$. Denoting, similarly as in (15.63), $L := (1 - A_1\Delta t)^{-1}$, we thus have

$$\mathcal{Q}^1 \leq \Big(\mathcal{Q}^0 + S_Q \Delta t \exp(2AT)\Big) L,$$

$$\mathcal{Q}^2 \leq \left(\mathcal{Q}^1 + S_Q \Delta t \exp(2AT)\right) L = \left(\left(\mathcal{Q}^0 + S_Q \Delta t \exp(2AT)\right) L + S_Q \Delta t \exp(2AT)\right) L =$$

$$\mathcal{Q}^0 L^2 + S_Q \Delta t \exp(2AT) \left(L^2 + L^1\right)$$

and by induction, for any $i \leq n$,

$$\mathcal{Q}^i \leq \mathcal{Q}^0 L^i + S_Q \Delta t \exp(2AT) \left(L^i + \ldots + L^2 + L^1\right).$$

Using Lemma 15.13 and proceeding as in the proof of (15.68) and (15.69), we can show that for n sufficiently large (and $\Delta t > 0$ satisfying equality (15.13)), for all $i \in \{1, \ldots, n\}$, we have:

$$\mathcal{Q}^i \leq \frac{3}{2} \frac{1}{A_1} S_Q \exp(2AT + A_1 \frac{i}{n} T) + \frac{3}{2} \mathcal{Q}^0 \exp(A_1 \frac{i}{n} T). \tag{15.83}$$

Thus the C_x^1 norm of the function R^i can be estimated by the C_x^1 norm of the initial conditions $\mathcal{Q}^0$, where $\mathcal{Q}^0$ is defined in (15.81).

15.10 Estimates of the first order derivatives of R^i with respect to the components of x at $\partial\Omega$

Let us consider the case when an extremum of the absolute value of the spatial derivative is attained on the boundary $\partial\Omega$. Suppose that in the initial system of coordinates,

$$M_1 := \max_j \sup_{x \in \bar{\Omega}} \left\{ \left| \frac{\partial R^i}{\partial x_j}(x) \right| \right\} = \left| \frac{\partial R^i}{\partial x_r}(x_0) \right|$$

for some $r \in \{1, 2, 3\}$ and $x_0 \in \partial\Omega$. Without losing generality, we can assume that this extremum of the absolute value corresponds to a positive maximum of $R^i_{,x_r}$.

If $\hat{x}_r \parallel n(x_0)$, then $\dfrac{\partial R^i}{\partial x_r} = 0$. So, suppose that $\hat{x}_r \not\parallel n(x_0)$. Let $N(x_0) := \hat{x}_r$. We can decompose

$$N(x_0) = \frac{1}{\sqrt{3}} \left(n(x_0) + s_1(x_0) + s_2(x_0)\right),$$

where $n(x_0)$ is a unit vector outward-normal to the boundary $\partial\Omega$ at $x = x_0$ and unit vectors $s_1(x_0)$, $s(x_0)$ belong to a space tangent to $\partial\Omega$ at $x = x_0$. By appropriate rotations of the system of coordinates, we can achieve that $n(x_0) = \hat{x}_3$ and $s_l(x_0) = \hat{x}_l$ for $l = 1, 2$. In the (possibly) new system of coordinates, we have

$$N(x_0) \cdot (\nabla R^i)(x_0) = \frac{1}{\sqrt{3}} \left(n(x_0) + s_1(x_0) + s_2(x_0)\right) \cdot (\nabla R^i)(x_0) =$$

$$\frac{1}{\sqrt{3}} \left(\hat{x}_3 + \hat{x}_1 + \hat{x}_2\right) \left(\hat{x}_3 \frac{\partial R^i}{\partial x_3} + \hat{x}_1 \frac{\partial R^i}{\partial x_1} + \hat{x}_2 \frac{\partial R^i}{\partial x_2} \right) = \frac{1}{\sqrt{3}} \left(\frac{\partial R^i}{\partial x_1} + \frac{\partial R^i}{\partial x_2} \right).$$

It follows that (after appropriate rotation of coordinate system around the axis parallel to $\hat{x}_3$) it suffices to consider the derivative $\dfrac{\partial R^i}{\partial x_l}$ with $\hat{x}_l \perp n(x_0)$ and $l = 1, 2$. Then

$$\frac{\partial}{\partial x_3} \left(\frac{\partial R^i}{\partial x_l} \right) = \frac{\partial}{\partial x_l} \left(\frac{\partial R^i}{\partial x_3} \right) = 0.$$

where from we obtain

$$\frac{\partial}{\partial x_3} \left(\frac{\partial R^i}{\partial x_l} \right) = 0. \tag{15.84}$$

As we assumed that $R^i_{,x_l} > 0$ at $x = x_0$, then

$$\frac{\partial^2 R^i_{,x_l}}{\partial x_3^2} \leq 0$$

at $x = x_0$. Next, as it was assumed that $R^i_{,x_l}$ has a positive maximum as $x = x_0$, then $\dfrac{\partial R^i_{,x_l}}{\partial x_1} = \dfrac{\partial R^i_{,x_l}}{\partial x_2} = 0$ and the second order derivatives of $R^i_{,x_l}$ with respect to x_1 and x_2 are non-positive. Using (15.84) and the lemma from Appendix A (with S identified with $\partial\Omega$ in the vicinity of x_0), we infer that at $x = x_0$ we have $\Delta R^i_{,x_l} \leq 0$ and to estimate the value of $\dfrac{\partial R^i}{\partial x_r}(x_0)$, we can use the maximum principle as if $x_0 \in \Omega$. The same reasoning holds if the extremum is a non-positive minimum, i.e. $\dfrac{\partial R^i}{\partial x_r}(x_0) \leq 0$.

15.11 Second order derivatives of R^i with respect to T_l and T_m

We will show how to estimate the second derivative $\partial^2 R^i/\partial T_1^2$. The other second order derivatives with respect to T_1 and T_8 variables can be estimated in the similar way. Differentiating the both sides of the equation (15.54) with respect to T_1, we obtain

$$\begin{aligned}
0 = {} & d_R \nabla^2 B^i_{11} - B^i_{11}\left[\frac{\partial}{\partial T_1}\Big(\gamma(c^{u;i-1}_{1*}, c^{u;i-1}_{8*}, T_1)\Big) + \frac{\partial}{\partial T_8}\Big(\delta(c^{u;i-1}_{8*}, T_8)\Big) + F_1((i-1)\Delta t, x, T_1, T_8) + \frac{1}{\Delta t}\right] \\
& -2B^i_1\left[\frac{\partial^2}{\partial T_1^2}\Big(\gamma(c^{u;i-1}_{1*}, c^{u;i-1}_{8*}, T_1)\Big) + \frac{\partial F_1}{\partial T_1}((i-1)\Delta t, x, T_1, T_8)\right] \\
& -R^i\Big[\frac{\partial^3}{\partial T_1^3}\Big(\gamma(c^{u;i-1}_{1*}, c^{u;i-1}_{8*}, T_1)\Big) + \frac{\partial^2 F_1}{\partial T_1^2}((i-1)\Delta t, x, T_1, T_8)\Big] \\
& + \frac{B^{i-1}_{11}(x; \tau^i_1, \tau^i_8)}{\Delta t} + F_0((i-1)\Delta t, x) \cdot \nabla B^i_{11},
\end{aligned} \tag{15.85}$$

where

$$B^i_1(x, T_1, T_8) := \frac{\partial R^i}{\partial T_1}(x, T_1, T_8) \quad \text{and} \quad B^i_{11}(x, T_1, T_8) := \frac{\partial^2 R^i}{\partial T_1^2}(x, T_1, T_8).$$

The term $B^{i-1}_{11}(x, \tau^{i-1}_1, \tau^{i-1}_8)$ is defined as:

$$\begin{aligned}
& B^{i-1}_{11}(x, \tau^{i-1}_1, \tau^{i-1}_8) = B^{i-1}_{11}(x, \tau^{i-1}_1(x, T_1), \tau^{i-1}_8(x, T_8)) = \\
& \frac{d^2 R^{i-1}}{dT_1^2}(x, \tau^{i-1}_1, \tau^{i-1}_8) = \frac{d}{dT_1}\left(\frac{\partial R^{i-1}}{\partial \tau_1}(x, \tau^{i-1}_1, \tau^{i-1}_8) \cdot \left(1 - \Delta t\, \frac{\partial \gamma(c^{u;i-1}_{1*}(x), c^{u;i-1}_{8*}(x), T_1)}{\partial T_1}\right)\right) = \\
& \frac{\partial^2 R^{i-1}}{\partial \tau_1^2}(x, \tau^{i-1}_1, \tau^{i-1}_8) \cdot \left(1 - \Delta t\, \frac{\partial \gamma(c^{u;i-1}_{1*}(x), c^{u;i-1}_{8*}(x), T_1)}{\partial T_1}\right)^2 - \\
& \Delta t\ \frac{\partial R^{i-1}}{\partial \tau_1}(x, \tau^{i-1}_1, \tau^{i-1}_8) \cdot\ \frac{\partial^2 \gamma(c^{u;i-1}_{1*}(x), c^{u;i-1}_{8*}(x), T_1)}{\partial T_1^2} = \\
& B^{i-1}_{\tau_1\tau_1}(x, \tau^{i-1}_1, \tau^{i-1}_8) \cdot \left(1 - \Delta t\, \frac{\partial \gamma(c^{u;i-1}_{1*}(x), c^{u;i-1}_{8*}(x), T_1)}{\partial T_1}\right)^2 - \\
& \Delta t\ B^{i-1}_{\tau_1}(x, \tau^{i-1}_1, \tau^{i-1}_8) \cdot\ \frac{\partial^2 \gamma(c^{u;i-1}_{1*}(x), c^{u;i-1}_{8*}(x), T_1)}{\partial T_1^2}.
\end{aligned} \tag{15.86}$$

Assuming that

$$\mathcal{B}^i_{11} := \sup_{x\in\Omega,T_1,T_8} |B^i_{11}(x,T_1,T_8)|$$

is attained for $y \in \Omega$ and some (T_1, T_8), we conclude that

$$\nabla B^i_{11}(y,T_1,T_8) = 0.$$

Thus taking into account (15.67), the inequality

$$\sup_{x\in\Omega,\tau_1,\tau_8} |B^{i-1}_{\tau_1\tau_1}(x,\tau_1,\tau_8)| \le \sup_{x\in\Omega,T_1,T_8} |B^{i-1}_{11}(x,T_1,T_8)|, \tag{15.87}$$

using the maximum principle and proceeding as in arriving at (15.60), we obtain the relation

$$\begin{aligned} &\mathcal{B}^i_{11} \le \left(\|R^i\|A_{31} + 2\mathcal{B}^i_1(A_- + f_1) + \mathcal{B}^{i-1}_1 A_M + \frac{\mathcal{B}^{i-1}_{11}(1+\Delta t A)^2}{\Delta t}\right)\left(-A + \frac{1}{\Delta t}\right)^{-1} = \\ &\left(\|R^i\|A_{31}\Delta t + 2\mathcal{B}^i_1(A_- + f_1)\Delta t + \mathcal{B}^{i-1}_1 A_M\Delta t + \mathcal{B}^{i-1}_{11}(1+A\Delta t)^2\right)(1-A\Delta t)^{-1} \le \\ &\left(\Big[\|R^i\|A_{31} + 2\mathcal{B}^i_1 A_f + \mathcal{B}^{i-1}_1 A_M\Big]\Delta t + \mathcal{B}^{i-1}_{11}L^2\right) L \end{aligned} \tag{15.88}$$

where A is defined in (15.30), L is defined by (15.63), A_M in (15.61), A_f defined in (15.66), whereas

$$A_{31} = \sup\left|\frac{\partial^3}{\partial T_1^3}\left(\gamma(c^{u;i-1}_{1*}, c^{u;i-1}_{8*}, T_1)\right)\right| + f_1. \tag{15.89}$$

According to (15.68), we can write

$$\begin{aligned} &\|R^i\|A_{31} + 2\mathcal{B}^i_1 A_f + \mathcal{B}^{i-1}_1 A_M \le \frac{3}{2}\|R^0\|\cdot(A_{31} + 2A_f A_f i\Delta t)\exp(2A\frac{i}{n}T) + 3A_f\mathcal{B}^0_1\exp(2A\frac{i}{n}T) + \\ &\frac{3}{2}\|R^0\|\,A_f A_M(i-1)\Delta t\exp(2A\frac{i-1}{n}T) + \frac{3}{2}A_M\mathcal{B}^0_1\exp(2A\frac{i-1}{n}T) \le \\ &\exp(2AT)\Big\{(\frac{3}{2}A_{31} + 3A_f^2 T)\|R^0\| + 3A\mathcal{B}^0_1 + \frac{3}{2}\|R^0\|A_f A_M T + \frac{3}{2}A_M\mathcal{B}^0_1\Big\} =: S_{11}(T). \end{aligned} \tag{15.90}$$

We have $\mathcal{B}^1_{11} \le \left(S_{11}(T)\Delta t + \mathcal{B}^0_{11}L^2\right)L$, $\mathcal{B}^2_{11} \le \left(S_{11}(T)\Delta t + S_{11}L^3\Delta t + \mathcal{B}^0_{11}L^5\right)L$ and in general, for $i \le n$,

$$\mathcal{B}^i_{11} = \left(S_{11}(T)\Delta t\sum_{l=0}^{i-1} L^{3l} + \mathcal{B}^0_{11}L^{3i-1}\right)L$$

Thus using Lemma 15.13, we obtain, for $\Delta t > 0$ sufficiently small, i.e. for L sufficiently close to 1

$$\mathcal{B}^i_{11} \le \frac{3}{2}\frac{1}{3A}S_{11}(T)\exp(3iA\Delta t) + \frac{3}{2}\mathcal{B}^0_{11}\exp(3iA\Delta t). \tag{15.91}$$

The estimate for $\mathcal{B}^i_{88}$ has a simpler form due to the fact that $\partial^2\delta/\partial T_8^2 \equiv 0$. This implies that the last term in the expression for B^{i-1}_{88} (corresponding to (15.86)), hence the term corresponding to $\mathcal{B}^{i-1}_1 A_M$ in (15.88), equals zero. Next, A_{31} in (15.88) reduces to f_1. Similarly to $\mathcal{B}^i_{11}$, we have

$$\mathcal{B}^i_{88} \le \frac{3}{2}\frac{1}{3A}S_{88}(T)\exp(3iA\Delta t) + \frac{3}{2}\mathcal{B}^0_{88}\exp(3iA\Delta t), \tag{15.92}$$

but this time, according to (15.90),

$$S_{88}(T) = \frac{3}{2}\,\|R^0\|f_1\,\exp(2AT) + 2\mathcal{B}^n_8 A_f,$$

where $\mathcal{B}^n_8$ is obtained from (15.70) by taking $i = n$.

Similar estimates can be found for $\mathcal{B}^i_{18}$. In this case the second line of (15.85) takes the form

$$B_8^i\left[\frac{\partial^2}{\partial T_1^2}\left(\gamma(c_{1*}^{u;i-1},c_{8*}^{u;i-1},T_1)\right)+\frac{\partial F_1}{\partial T_1}((i-1)\Delta t,x,T_1,T_8)\right]+B_1^i\left[\frac{\partial F_1}{\partial T_8}((i-1)\Delta t,x,T_1,T_8)\right],$$

whereas the third one takes the form

$$R^i\Big[\frac{\partial^2 F_1}{\partial T_1 T_8}((i-1)\Delta t,x,T_1,T_8)\Big]$$

We thus have

$$\mathcal{B}_{18}^i\le\frac{3}{2}\frac{1}{3A}S_{18}(T)\exp(3iA\Delta t)+\frac{3}{2}\mathcal{B}_{18}^0\exp(3iA\Delta t),\tag{15.93}$$

with

$$S_{18}(T)=\frac{3}{2}\,\|R^0\|f_1\,\exp(2AT)+(\mathcal{B}_8^n+\mathcal{B}_1^n)\,A_f,$$

where $\mathcal{B}_1^n$ and $\mathcal{B}_8^n$ are obtained from (15.68) and (15.70) by taking $i=n$.

15.12 Third order derivatives of R^i with respect to T_l, T_m and T_p

Using the same approach we are able to give estimates for third order derivatives of the functions with respect to T_l, T_m and T_p, $l,m.p\in\{1,8\}$, which are independent of i. Similarly to (15.91), (15.92) and (15.93), these estimates have the following structure:

$$\mathcal{B}_{lmp}^i\le\mathcal{S}_{lmp}\exp(k_{3;1}iA\Delta t)+\mathcal{B}_{lmp}^0\exp(k_{3;2}iA\Delta t),\tag{15.94}$$

where $k_{3;1}$ and $k_{3;2}$ are finite natural numbers and S_{lmp} depends on T and the norms of the coefficient functions of system (15.5)-(15.7).

15.13 Mixed second order derivatives of R^i with respect to x_k and T_m

Now, we will estimate the absolute values of the mixed derivatives

$$Q_{k,m}^i:=\frac{\partial^2 R^i}{\partial x_k\partial T_m}=\frac{d^2R^i}{dx_k dT_m},\quad k=1,2,3,\ m=1,8.$$

Let $g_1:=\gamma$, $g_8:=\delta$. Then

$$\begin{aligned}&\frac{d}{dx_k}\Big[\frac{\partial R^{i-1}}{\partial T_m}(x,\tau_1^{i-1},\tau_8^{i-1})\Big]=\frac{d}{dT_m}\Big[\frac{dR^{i-1}}{dx_k}(x,\tau_1^{i-1},\tau_8^{i-1})\Big]=\\&\frac{d}{dT_m}\Big[\frac{\partial R^{i-1}}{\partial x_k}(x,\tau_1^{i-1},\tau_8^{i-1})+B_{\tau_1}^{i-1}(x,\tau_1^{i-1},\tau_8^{i-1})\frac{\partial\tau_1^{i-1}}{\partial x_k}+B_{\tau_8}^{i-1}(x,\tau_1^{i-1},\tau_8^{i-1})\frac{\partial\tau_8^{i-1}}{\partial x_k}\Big]=\\&\frac{d}{dT_m}\Big[B_{\tau_1}^{i-1}(x,\tau_1^{i-1},\tau_8^{i-1})\frac{\partial\tau_1^{i-1}}{\partial x_k}+B_{\tau_8}^{i-1}(x,\tau_1^{i-1},\tau_8^{i-1})\frac{\partial\tau_8^{i-1}}{\partial x_k}\Big]+\\&Q_{k,\tau_m}^{i-1}(x,\tau_1^{i-1},\tau_8^{i-1})\cdot\left(1-\Delta t\,\frac{\partial g_m(c_1^{u;i-1}(x),c_8^{u;i-1}(x),T_m)}{\partial T_m}\right).\end{aligned}\tag{15.95}$$

Differentiating Eq.(15.75) with respect to T_m, we obtain the equation:

$$
\begin{aligned}
&0 = d_R \nabla^2 Q^i_{k,m} - Q^i_{k,m} \left[\frac{\partial}{\partial T_1} \left(\gamma(c^{u;i-1}_{1*}, c^{u;i-1}_{8*}, T_1) \right) + \frac{\partial}{\partial T_8} \left(\delta(c^{u;i-1}_{8*}, T_8) \right) \right. \\
&\left. + F_1((i-1)\Delta t, T_1, T_8) + \frac{1}{\Delta t} \right] - Q^i_k \left[\frac{\partial^2 \gamma}{\partial^2 T_1} \delta_{1m} + \frac{\partial F^i_1}{\partial T_m}((i-1)\Delta t, x, T_1, T_8) \right] \\
&+ \frac{Q^{i-1}_{k,\tau_m}(x; \tau^{i-1}_1, \tau^{i-1}_8)}{\Delta t} \left(1 - \Delta t \, \frac{\partial g_m(c^{u;i-1}_{1*}(x), c^{u;i-1}_{8*}(x), T_m)}{\partial T_m} \right) \\
&+ \Big\{ - B^i_m \Big[\frac{\partial^2}{\partial c^u_{1*} \partial T_1} \left(\gamma(c^{u;i-1}_{1*}, c^{u;i-1}_{8*}, T_1) \right) c^{u;i-1}_{1*,x_k} + \frac{\partial^2}{\partial c^u_{8*} \partial T_1} \left(\gamma(c^{u;i-1}_{1*}, c^{u;i-1}_{8*}, T_1) \right) c^{u;i-1}_{8*,x_k} + \\
&\frac{\partial^2}{\partial c^u_{8*} \partial T_8} \left(\delta(c^{u;i-1}_{8*}, T_8) \right) c^{u;i-1}_{8*,x_k} + \frac{\partial F^{i-1}_1}{\partial x_k}((i-1)\Delta t, x, T_1, T_8) \Big] - \\
&R^i \Big[\frac{\partial^3}{\partial c^u_{1*} \partial^2 T_m} \left(g_m(c^{u;i-1}_{1*}, c^{u;i-1}_{8*}, T_m) \right) c^{u;i-1}_{1*,x_k} + \frac{\partial^3}{\partial c^u_{8*} \partial^2 T_m} \left(g_m(c^{u;i-1}_{1*}, c^{u;i-1}_{8*}, T_m) \right) c^{u;i-1}_{8*,x_k} + \\
&\frac{\partial^2 F^{i-1}_1}{\partial x_k \partial T_m}((i-1)\Delta t, x, T_1, T_8) \Big] + \\
&B^{i-1}_{\tau_1 \tau_m}(x; \tau^{i-1}_1(x, T_1), \tau^{i-1}_8(x, T_8)) \, \frac{1}{\Delta t} \cdot \frac{\partial \tau^{i-1}_1}{\partial x_k} \cdot \frac{\partial \tau_m}{\partial T_m} + \\
&B^{i-1}_{\tau_8 \tau_m}(x; \tau^{i-1}_1(x, T_1), \tau^{i-1}_8(x, T_8)) \, \frac{1}{\Delta t} \cdot \frac{\partial \tau^{i-1}_8}{\partial x_k} \cdot \frac{\partial \tau_m}{\partial T_m} + \\
&B^{i-1}_{\tau_1}(x; \tau^{i-1}_1(x, T_1), \tau^{i-1}_8(x, T_8)) \, \frac{1}{\Delta t} \cdot \frac{\partial}{\partial T_m} \left(\frac{\partial \tau^{i-1}_1}{\partial x_k} \right) \delta_{1m} + \\
&B^{i-1}_{\tau_8}(x; \tau^{i-1}_1(x, T_1), \tau^{i-1}_8(x, T_8)) \, \frac{1}{\Delta t} \cdot \frac{\partial}{\partial T_m} \left(\frac{\partial \tau^{i-1}_8}{\partial x_k} \right) \delta_{8m} \ \Big\} + \\
&F^{i-1}_0(x) \cdot \nabla Q_{k,m(x,T_1,T_8)} + \frac{\partial F^{i-1}_0}{\partial x_k} \cdot \nabla B_m(x, T_1, T_8).
\end{aligned} \tag{15.96}
$$

Recall that $\partial \tau_m / \partial T_m$ has the form determined by (15.57), whereas $\partial \tau_l / \partial x_k$ is determined in (15.73) and (15.74). It follows from (15.73) and (15.74) that

$$
\begin{aligned}
&\frac{1}{\Delta t} \cdot \frac{\partial}{\partial T_m} \left(\frac{\partial \tau^{i-1}_j}{\partial x_l} \right) = - \frac{\partial}{\partial T_m} \left(\frac{\partial g_j(c^{u;i-1}_{1*}(x), c^{u;i-1}_{8*}(x), T_j)}{\partial x_l} \right) \delta_{jm} = \\
&- \frac{\partial^2 g_m(c^{u;i-1}_{1*}, c^{u;i-1}_{8*}, T_m)}{\partial c^{u;i-1}_{1*} \partial T_m} \cdot \frac{\partial c^{u;i-1}_{1*}}{\partial x_l} - \frac{\partial^2 g_m(c^{u;i-1}_{1*}, c^{u;i-1}_{8*}, T_1)}{\partial c^{u;i-1}_{8*}} \cdot \frac{\partial c^{u;i-1}_{1*}}{\partial x_l}
\end{aligned} \tag{15.97}
$$

hence, by Lemma 15.7, (15.76) and (15.77), the L^∞-norm of the function coefficients multiplying $B^{i-1}_{\tau_1 \tau_m}$, $B^{i-1}_{\tau_8 \tau_m}$, $B^{i-1}_{\tau_1}$ and $B^{i-1}_{\tau_8}$ in (15.96) are bounded by a finite number $C^B_{xT_*}$ depending on (T_1, T_8) (and other parameters of the system). Likewise, the coefficient function multiplying R^i is bounded in its L^∞-norm by a finite number $C^R_{xT_*}$. Recall also that the sum of the absolute values of the coefficients multiplying B^i_m can be estimated from above by a finite number (Lemma 15.11).

Let us estimate the maximal absolute value of the derivatives $Q^i_{k,m}$ **inside** Ω, for fixed $(T_1, T_8) \in \overline{\mathbb{R}}^2_+$. Suppose that the maximum of $|Q^i_{k,m}(\cdot, T_1, T_8)|$ is realized at some point

$$x^i_{k,m} = x^i_{k,m}(T_1, T_8) \in \Omega$$

thus

$$\nabla Q^i_{k,m}(x^i_{k,m}, T_1, T_8) = 0.$$

Let

$$\sup_{k=1,2,3;\, m=1,8; T_1,T_8} |Q^i_{k,m}(x_{km}, T_1, T_8)| = |Q^i_{\bar{k},\bar{m}}(x_{\bar{k}\bar{m}}, \bar{T}_1, \bar{T}_8)| =: |Q^i_{\bar{k},\bar{m}}(\bar{x}, \bar{T}_1, \bar{T}_8)| =: \mathcal{Q}^i_{*,*} \qquad (15.98)$$

Obviously, $(\nabla_x Q^i_{\bar{k},\bar{m}})(\bar{x}, \bar{T}_1, \bar{T}_8) = 0$ and, according to the definition of $Q^i_{\bar{k},\bar{m}}(\bar{x}, \bar{T}_1, \bar{T}_8)$, we have

$$\left| \frac{\partial F^i_0}{\partial x_k} \cdot \nabla B_{\bar{m}}(\bar{x}, \bar{T}_1, \bar{T}_8) \right| \leq 3 f_0 |Q^i_{\bar{k},\bar{m}}(\bar{x}, \bar{T}_1, \bar{T}_8)|. \qquad (15.99)$$

Next, proceeding like in sections 15.9 and 15.11, and using the estimates derived there, we can show that the following recurrence inequality holds:

$$Q^i_{*,*} \leq \Big(E_{*,*} \exp[5AT] \Delta t + Q^{i-1}_{*,*} L \Big) L,$$

where $E_{*,*}$ depends on the initial data R_0, T and the coefficient functions of system (15.5)-(15.7). This leads to the inequality

$$\mathcal{Q}^i_{*,*} \leq \frac{3}{2} E_{*,*} \exp[5AT] \exp(2Ai\Delta t) + \frac{3}{2} \mathcal{Q}^0_{*,*} \exp(2Ai\Delta t). \qquad (15.100)$$

Remark Let us note that we calculated the maximal value of $|Q^i_{k,m}|$ tacitly assuming that it is attained inside Ω. In fact, the same procedure can be applied in the case when $|Q^i_{k,m}|$ attains it‘s maximal value at the boundary $\partial\Omega$. This follows from subsection 15.10 and the fact that the boundary properties of $Q^i_{k,m}$ are the same as the properties of Q^i_k. □

Remark The necessity of taking the supremum over the index k (and m) as in (15.98) follows from the presence of the term $F_0 \cdot \nabla R^i$ and is dictated by the possibility of the assessment (15.99). Without this term, we could keep the indices k and m fixed. □

15.14 Mixed third order derivatives R^i with respect to x_k, T_m and T_l

Similarly, we can estimate the absolute value third order derivatives of the form:

$$Q^i_{k,m,l} := \frac{\partial^3 R^i}{\partial x_k \partial T_m \partial T_l} = \frac{d^3 R^i}{d x_k d T_m d T_l}, \quad k = 1,2,3,\ m = 1,8.$$

These estimates have the form corresponding to (15.101). Thus, in view of the second Remark after (15.101), we have:

$$\mathcal{Q}^i_{*,**} \leq \frac{3}{2} E_{*,**} \exp(k_{12;1} Ai\Delta t) + \frac{3}{2} \mathcal{Q}^0_{*,**} \exp(k_{12;2} Ai\Delta t), \qquad (15.101)$$

where for the first asterisk we can take $1, 2, 3$, whereas for the second and third asterisk we can take 1 or 8. The constants $k_{1,2;1}$, $k_{1,2;2}$ are finite natural numbers. $E_{*,**}$ depend on T and the norms of the coefficient functions of system (15.5)-(15.7).

15.15 Basic lemma concerning the difference between functions corresponding to subsequent values of i

For further analysis, we will suppose that a simplifying technical assumption.

Assumption 15.14. *The function F_0 does not depend on t.*

In this subsection, using the results of the previous subsections, we will estimate the difference

$$Z^i(x, T_1, T_8) := R^i(x, T_1, T_8) - R^{i-1}(x, T_1, T_8).$$

For $i \geq 2$, Z^i satisfies the equation:

$$d_R \nabla^2 Z^i + F_0(x) \cdot \nabla Z^i - \frac{Z^i(x;T_1,T_8)}{\Delta t} + \frac{Z^{i-1}(x,T_1,T_8)}{\Delta t} - \frac{Z_*^{i-1}(x,T_1,T_8)}{\Delta t} -$$

$$\left\{ Z^i \left[\frac{\partial}{\partial T_1} \left(\gamma(c_{1*}^{u;i-1}, c_{8*}^{u;i-1}, T_1) \right) + \frac{\partial}{\partial T_8} \left(\delta(c_{8*}^{u;i-1}, T_8) \right) + F_1((i-1)\Delta t, x, T_1, T_8) \right] \right\} + R^{i-1} \Delta V^i = 0 \tag{15.102}$$

where

$$Z_*^{i-1} := (R_*^{i-1} - R^{i-1}) - (R_*^{i-2} - R^{i-2}), \tag{15.103}$$

because

$$R^i - R_*^{i-1} - (R^{i-1} - R_*^{i-2}) = (R^i - R^{i-1}) - (R^{i-1} - R^{i-2}) + (R^{i-1} - R_*^{i-1}) - (R^{i-2} - R_*^{i-2}).$$

Above, for fixed (T_1, T_8) we denoted for brevity

$$R_*^k := R^k(x, \tau_1(x,T_1), \tau_8(x,T_8)) \tag{15.104}$$

with $\tau_1(x,T_1), \tau_8(x,T_8)$ determined by (15.8)-(15.9), i.e.

$$\tau_1^{i-1} = T_1 - \gamma(c_{1*}^{u;i-1}(x), c_{8*}^{u;i-1}(x), T_1) \cdot \Delta t =: T_1 - \gamma^{i-1}(x,T_1) \cdot \Delta t, \tag{15.105}$$

$$\tau_8^{i-1} = T_8 - \delta(c_{8*}^{u;i-1}(x), T_8) \cdot \Delta t =: T_8 - \delta^{i-1}(x,T_8) \cdot \Delta t \tag{15.106}$$

and

$$\begin{aligned} \Delta V^i = &\left[\frac{\partial}{\partial T_1} \left(\gamma(c_{1*}^{u;i-1}, c_{8*}^{u;i-1}, T_1) \right) + \frac{\partial}{\partial T_8} \left(\delta(c_{8*}^{u;i-1}, T_8) \right) + F_1((i-1)\Delta t, x, T_1, T_8) \right] - \\ &\left[\frac{\partial}{\partial T_1} \left(\gamma(c_{1*}^{u;i-2}, c_{8*}^{u;i-2}, T_1) \right) + \frac{\partial}{\partial T_8} \left(\delta(c_{8*}^{u;i-2}, T_8) \right) + F_1((i-2)\Delta t, x, T_1, T_8) \right]. \end{aligned} \tag{15.107}$$

In view of the inequality (15.50),

$$\Delta V^i \leq B_v \Delta t \quad \text{as} \quad \Delta t \to 0$$

for all $i \geq \{2, \ldots, n\}$ and some $B_v \geq 0$.

Remark Above, we used the following lemma specifying the one term Taylor expansion for many variables scalar function.

Lemma 15.15. *Suppose that $f \in C^{\mathcal{K}+1}$ class. Then*

$$f(\mathbf{y}) = f(\mathbf{y}_0) + \sum_{1 \leq |\alpha| \leq \mathcal{K}} \frac{1}{\alpha!} (D^\alpha f)(\mathbf{y}_0)(\mathbf{y}-\mathbf{y}_0)^\alpha + \sum_{|\alpha| = \mathcal{K}+1} \frac{\mathcal{K}+1}{\alpha!} (\mathbf{y}-\mathbf{y}_0)^\alpha \int_0^1 (1-s)^{\mathcal{K}} (D^\alpha f)(\mathbf{y}_0 + s(\mathbf{y}-\mathbf{y}_0))\, ds.$$

□

Taking into account the boundedness of the first and second second derivatives of the functions R^i, $i \in \{1, \ldots, n\}$ with respect to T_1 and T_8 provided by sections 15.8, 15.11, we can write:

$$R^{i-1} - R_*^{i-1} = R^{i-1}(x, T_1, T_8) - R^{i-1}(x, \tau_1(x, T_1), \tau_8(x, T_8)) =$$

$$R^{i-1}(x, T_1, T_8) - R^{i-1}(x, T_1, T_8) - B_1^{i-1}(x, T_1, T_8) \cdot \gamma^{i-1}(x, T_1)\Delta t - B_8^{i-1}(x, T_1, T_8) \cdot \delta^{i-1}(x, T_8)\Delta t -$$

$$\sum_{k,l=1,8} \frac{2}{2!}(\tau_k^{i-1} - T_k) \cdot (\tau_l^{i-1} - T_l) \int_0^1 (1-s) B_{\tau_k \tau_l}^{i-1}\Big(x, T_1 + s(\tau_1^{i-1} - T_1), T_8 + s(\tau_8^{i-1} - T_8)\Big)\, ds =$$

$$-B_1^{i-1}(x, T_1, T_8) \cdot \gamma^{i-1}(x, T_1)\Delta t - B_8^{i-1}(x, T_1, T_8) \cdot \delta^{i-1}(x, T_8)\Delta t -$$

$$\sum_{k,l=1,8} (\tau_k^{i-1} - T_k) \cdot (\tau_l^{i-1} - T_l) \int_0^1 (1-s) B_{\tau_k \tau_l}^{i-1}\Big(x, T_1 + s(\tau_1^{i-1} - T_1), T_8 + s(\tau_8^{i-1} - T_8)\Big)\, ds. \tag{15.108}$$

Remark In accordance with Remark before (15.72), to avoid ambiguity, we will assume the following convention of denoting the total derivatives of the quantities $R^i(x, \tau_1^i(x, T_1), \tau_8(x, T_8))$ with respect to T_1 and T_8. Thus, these derivatives will be denoted by

$$\frac{dR^i(x, \tau_1^i(x, T_1), \tau_8(x, T_8))}{dT_1} = B_{\tau_1}^i(x, \tau_1^i(x, T_1), \tau_8(x, T_8)) \cdot \frac{d\tau_1}{dT_1} =: B_1^i(x, \tau_1^i(x, T_1), \tau_8(x, T_8)),$$
$$\frac{dR^i(x, \tau_1^i(x, T_1), \tau_8(x, T_8))}{dT_8} = B_{\tau_8}^i(x, \tau_1^i(x, T_1), \tau_8(x, T_8)) \cdot \frac{d\tau_8}{dT_1} =: B_8^i(x, \tau_1^i(x, T_1), \tau_8(x, T_8)).$$

□

Next

$$B_1^{i-1}(x, T_1, T_8) \cdot \gamma^{i-1}(x, T_1)\Delta t - B_1^{i-2}(x, T_1, T_8) \cdot \gamma^{i-2}(x, T_1)\Delta t =$$

$$\Big(B_1^{i-1}(x, T_1, T_8) - B_1^{i-2}(x, T_1, T_8)\Big) \cdot \gamma^{i-1}(x, T_1)\Delta t + B_1^{i-2}(x, T_1, T_8)\Big(\gamma^{i-1}(x, T_1) - \gamma^{i-2}(x, T_1)\Big)\Delta t :=$$

$$H_1^{i-1}(x, T_1, T_8) \cdot \gamma^{i-1}(x, T_1)\Delta t + B_1^{i-2}(x, T_1, T_8)\Big(\gamma^{i-1}(x, T_1) - \gamma^{i-2}(x, T_1)\Big)\Delta t.$$

Likewise:

$$B_8^{i-1}(x, T_1, T_8) \cdot \delta^{i-1}(x, T_1)\Delta t - B_8^{i-2}(x, T_1, T_8) \cdot \delta^{i-2}(x, T_1)\Delta t =$$

$$\Big(B_8^{i-1}(x, T_1, T_8) - B_8^{i-2}(x, T_1, T_8)\Big) \cdot \delta^{i-1}(x, T_1)\Delta t + B_1^{i-2}(x, T_1, T_8)\Big(\delta^{i-1}(x, T_1) - \delta^{i-2}(x, T_1)\Big)\Delta t :=$$

$$H_8^{i-1}(x, T_1, T_8) \cdot \delta^{i-1}(x, T_1)\Delta t + B_8^{i-2}(x, T_1, T_8)\Big(\delta^{i-1}(x, T_1) - \delta^{i-2}(x, T_1)\Big)\Delta t.$$

As $(\tau_k^{i-1} - T_k) = O(\Delta t)$, it follows that there exists a positive constant r_1 independent of i such that

$$|(R_*^{i-1} - R^{i-1}) - (R_*^{i-2} - R^{i-2})| \leq \Big(|H_1^{i-1}|\overline{\gamma} + |H_8^{i-1}|\overline{\delta}\Big)\Delta t + r_1(\Delta t)^2 \tag{15.109}$$

and positive constants r_2, r_3 (independent of i) such that

$$|Z^i| \leq (|Z^{i-1}| + r_2(\Delta t)^2 + r_3|H|^{i-1}\Delta t)L, \tag{15.110}$$

The last inequality is obtained via the consecutive use of the maximum principle and the denotation

$$|H|^i := \sup\{|H_1^i|, |H_8^i|\}, \tag{15.111}$$

As R^0 is given by the initial data, then

$$
\begin{aligned}
&d_R\nabla^2 Z^1 - \frac{Z^1(x;T_1,T_8)}{\Delta t} + F_0(x)\cdot\nabla Z^1 + \\
&\Big\{R^1\left[\frac{\partial}{\partial T_1}\Big(\gamma(c_{1*}^{u;0},c_{8*}^{u;0},T_1)\Big) + \frac{\partial}{\partial T_8}\Big(\delta(c_{8*}^{u;0},T_8)\Big) + F_1(0\cdot\Delta t,x,T_1,T_8)\right] + \\
&\left(\Delta_{xx}R^0 + \frac{[R^0(x,\tau_1^0(x,T_1),\tau_8^0(x,T_8)) - R^0(x,T_1,T_8)]}{\Delta t}\right) + F_0(x)\cdot\nabla R^0\Big\} \;=\; 0.
\end{aligned}
\tag{15.112}
$$

It is seen that the terms in the curly brackets $\{\cdot\}$ are of $O(1)$ terms as $\Delta t \to 0$. It follows that there exists a constant $G_{0Z}^1 \geq 0$ such that for all $i \in \{2,\ldots,n\}$

$$
|Z_1(x)| < \Delta t\, G_{0Z}^1, \quad \text{for } x \in \overline{\Omega}. \tag{15.113}
$$

To proceed, let us analyse the difference $H_1^i = B_1^i - B_1^{i-1}$ for $i = \{1,\ldots,n\}$. This will be done by means of the equation obtained by subtracting from Eq.(15.54) for B_1^i the corresponding equation for the function B_1^{i-1}. For $i \geq 2$, we obtain:

$$
\begin{aligned}
&d_R\nabla^2 H_1^i + F_0(x)\cdot\nabla H_1^i = \\
&H_1^i\left[\frac{\partial}{\partial T_1}\Big(\gamma(c_{1*}^{u;i-1},c_{8*}^{u;i-1},T_1)\Big) + \frac{\partial}{\partial T_8}\Big(\delta(c_{8*}^{u;i-1},T_8)\Big) + F_1((i-1)\Delta t,x,T_1,T_8) + \frac{1}{\Delta t}\right] + \\
&B_1^{i-1}[\Delta V_i] + Z^i\Big[\frac{\partial^2}{\partial T_1^2}\Big(\gamma(c_{1*}^{u;i-1},c_{8*}^{u;i-1},T_1)\Big) + \frac{\partial}{\partial T_1}F_1((i-1)\Delta t,x,T_1,T_8)\Big] + \\
&R^{i-1}\Big[\frac{\partial^2}{\partial T_1^2}\gamma(c_{1*}^{u;i-1},c_{8*}^{u;i-1},T_1) - (\frac{\partial^2}{\partial T_1^2}\gamma(c_{1*}^{u;i-2},c_{8*}^{u;i-2},T_1)) + \\
&\frac{\partial}{\partial T_1}F_1((i-1)\Delta t,x,T_1,T_8) - \frac{\partial}{\partial T_1}F_1((i-2)\Delta t,x,T_1,T_8)\Big] - \\
&\frac{B_1^{i-1}(x;\tau_1^{i-1}(x,T_1),\tau_8^{i-1}(x,T_8)) - B_1^{i-2}(x;\tau_1^{i-2}(x,T_1),\tau_8^{i-2}(x,T_8))}{\Delta t}.
\end{aligned}
\tag{15.114}
$$

Denoting

$$
\gamma_{T_1}^i := \frac{\partial\gamma(c_1^{u;i},c_8^{u,8},T_1)}{\partial T_1},\ \delta_{T_8}^i := \frac{\partial\delta(c_8^{u,8},T_1)}{\partial T_8}, \quad B_{\tau_1}^{i-1} := \frac{\partial R^{i-1}}{\partial\tau_1},\ B_{\tau_1}^{i-2} := \frac{\partial R^{i-2}}{\partial\tau_1},
$$

we have:

$$
\begin{aligned}
&\Big|B_1^{i-1}(x;\tau_1^{i-1}(x,T_1),\tau_8^{i-1}(x,T_8)) - B_1^{i-2}(x;\tau_1^{i-2}(x,T_1),\tau_8^{i-2}(x,T_8))\Big| = \\
&\Big|B_{\tau_1}^{i-1}(x;\tau_1^{i-1}(x,T_1),\tau_8^{i-1}(x,T_8))(1-\gamma_{,T_1}^{i-1}\Delta t) - B_{\tau_1}^{i-2}(x;\tau_1^{i-2}(x,T_1),\tau_8^{i-2}(x,T_8))(1-\gamma_{,T_1}^{i-2}\Delta t)\Big| = \\
&\Big|\,\big[B_{\tau_1}^{i-1}(x;\tau_1^{i-1}(x,T_1),\tau_8^{i-1}(x,T_8)) - B_{\tau_1}^{i-2}(x;\tau_1^{i-2}(x,T_1),\tau_8^{i-2}(x,T_8))\big]\cdot(1-\gamma_{,T_1}^{i-1}\Delta t) - \\
&B_{\tau_1}^{i-2}(x;\tau_1^{i-2}(x,T_1),\tau_8^{i-2}(x,T_8))\cdot\Big[\gamma_{,T_1}^{i-1}\Delta t - \gamma_{,T_1}^{i-2}\Delta t\Big]\,\Big|
\end{aligned}
\tag{15.115}
$$

Let us note that

$$
|\gamma_{,T_1}^{i-1}(x,T_1)\Delta t - \gamma_{,T_1}^{i-2}(x,T_1)\Delta t| = |\Big(\gamma_{,T_1}^{i-1}(x,T_1) - \gamma_{,T_1}^{i-2}(x,T_1)\Big)|\Delta t < G_{11}(\Delta t)^2.
$$

Next, we have, according to Lemma 15.15, with $\mathcal{K} = 0$,

$$B^{i-1}_{\tau_1}(x;\tau^{i-1}_1(x,T_1),\tau^{i-1}_8(x,T_8)) - B^{i-2}_{\tau_1}(x;\tau^{i-2}_1(x,T_1),\tau^{i-2}_8(x,T_8)) =$$

$$B^{i-1}_{\tau_1}(x;\tau^{i-1}_1(x,T_1),\tau^{i-1}_8(x,T_8))$$

$$-B^{i-2}_{\tau_1}\Big[x;\tau^{i-1}_1(x,T_1) - \{\tau^{i-1}_1(x,T_1) - \tau^{i-2}_1(x,T_1)\}, \tau^{i-1}_8(x,T_8) - \big\{\tau^{i-1}_8(x,T_8) - \tau^{i-2}_8(x,T_8)\big\}\Big] =$$

$$B^{i-1}_{\tau_1}(x;\tau^{i-1}_1(x,T_1),\tau^{i-1}_8(x,T_8)) - B^{i-2}_{\tau_1}(x;\tau^{i-1}_1(x,T_1),\tau^{i-1}_8(x,T_8)) -$$

$$\Big[(\tau^{i-1}_1(x,T_1) - \tau^{i-2}_1(x,T_1))\int_0^1 (B^{i-1}_{\tau_1\tau_1}(x,\tau^{i-1}_1 + s(\tau^{i-2}_1 - \tau^{i-1}_1), \tau^{i-1}_8 + s(\tau^{i-2}_8 - \tau^{i-1}_8))\,ds +$$

$$(\tau^{i-1}_8(x,T_8) - \tau^{i-2}_8(x,T_8))\int_0^1 (B^{i-2}_{\tau_1\tau_8}(x,\tau^{i-1}_1 + s(\tau^{i-2}_1 - \tau^{i-1}_1), \tau^{i-1}_8 + s(\tau^{i-2}_8 - \tau^{i-1}_8))\,ds\Big]. \tag{15.116}$$

Now, we have the identity:

$$d_R\nabla^2 B^0_1 + F_0(0\cdot\Delta t,x)\cdot\nabla B^0_1 - \frac{B^0_1(x;T_1,T_8)}{\Delta t} - \Big\{d_R\nabla^2 B^0_1 + F_0(0\cdot\Delta t,x)\cdot\nabla B^0_1 - \frac{B^0_1(x;T_1,T_8)}{\Delta t}\Big\} = 0.$$

By subtracting this identity from (15.54) for $i = 1$, and taking into account Assumption 15.14, we conclude that, for $i = 1$, (15.114) is substituted by the equation:

$$\begin{aligned}
&0 = d_R\nabla^2 H^1_1 + F_0(x)\cdot\nabla H^1_1 - H^1_1\frac{1}{\Delta t} - \\
&B^1_1\Big[\frac{\partial}{\partial T_1}\Big(\gamma(c^{u;i-1}_{1*}, c^{u;i-1}_{8*}, T_1)\Big) + \frac{\partial}{\partial T_8}\Big(\delta(c^{u;i-1}_{8*}, T_8)\Big) + F_1(0\cdot\Delta t, x, T_1, T_8)\Big] - \\
&R^1\Big[\frac{\partial^2}{\partial T_1^2}\Big(\gamma(c^{u;i-1}_{1*}, c^{u;i-1}_{8*}, T_1) + \frac{\partial}{\partial T_1}F_1(0\cdot\Delta t, x, T_1, T_8)\Big)\Big] + \\
&F_0(0\cdot\Delta t,x)\cdot\nabla B^0_1 + d_R\nabla^2 B^0_1 + \frac{B^0_1(x;\tau^0_1(x,T_1),\tau^0_8(x,T_8)) - B^0_1(x;T_1,T_8)}{\Delta t}.
\end{aligned} \tag{15.117}$$

Taking into account that

$$\Big|\frac{B^0_1(x;\tau^0_1(x,T_1),\tau^0_8(x,T_8)) - B^0_1(x;T_1,T_8)}{\Delta t}\Big| =$$

$$\left|\frac{B^0_{\tau_1}(x;\tau^0_1(x,T_1),\tau^0_8(x,T_8))\dfrac{\partial\tau^0_1}{\partial T_1} - B^0_1(x;T_1,T_8)}{\Delta t}\right|$$

assuming the sufficient smoothness of the initial data and using the maximum principle we obtain the inequality

$$\Big|H^1_1\Big| < h^1_1\Delta t. \tag{15.118}$$

Likewise, we can obtain the estimate

$$\Big|H^1_8\Big| < h^1_8\Delta t. \tag{15.119}$$

Using these estimates, we can consider the equation for Z^2, given by (15.102) with $i = 2$. Let us note that, due to (15.118) and (15.119), Z^1_* given by (15.103) can be estimated as

$$|Z_*^1| = |(R^1 - R_*^1) - (R^0 - R_*^0)| \leq$$

$$|B_{\tau_1}^1 \tau_1(c_1^{u;0}(x), c_8^{u;0}(x), T_1) \cdot \Delta t - B_{\tau_1}^0 \tau_1(c_1^{u;0}(x), c_8^{u;0}(x), T_1)| + 2\mathcal{B}_{11}(\Delta t)^2 +$$

$$|B_{\tau_8}^1 \tau_8(c_8^{u;0}(x), T_8) \cdot \Delta t - B_{\tau_8}^0 \tau_8(c_8^{u;0}(x), T_8)| + 2\mathcal{B}_8(\Delta t)^2 \leq$$

$$\Big(|h_1^1 \gamma(c_1^{u;0}(x), c_8^{u;0}(x), T_1)| + 2\mathcal{B}_{11}\Big) (\Delta t)^2 + \Big(|h_8^1 \gamma(c_1^{u;0}(x), c_8^{u;0}(x), T_1)| + 2\mathcal{B}_{18}\Big) (\Delta t)^2,$$

hence

$$|Z_*^1| \leq \left(h_1^1 \overline{\gamma} + h_8^1 \overline{\delta}\right) (\Delta t)^2 + (2\mathcal{B}_{11} + 2\mathcal{B}_{88})(\Delta t)^2, \tag{15.120}$$

where

$$\overline{\gamma} = \sup |\gamma|, \quad \overline{\delta} = \sup |\delta|. \tag{15.121}$$

It thus follows from (15.102) and (15.120) by means of the maximum principle that

$$|Z^2| \leq (|Z^1| + K_{1*}(\Delta t)^2)L,$$

for some constant K_{1*}, where $L = (1 - A\Delta t)^{-1}$.

The crucial fact for further analysis is contained in the following lemma.

Lemma 15.16. *Let $x \in \overline{\Omega}$ and (T_1, T_8) be fixed. Then*

$$-(\tau_1^{i-2}(x, T_1) - \tau_1^{i-1}(x, T_1)) = (\gamma(c_{1*}^{u;i-1}(x), c_{8*}^{u;i-1}(x), T_1) - \gamma(c_{1*}^{u;i-2}(x), c_{8*}^{u;i-2}(x), T_1)) \cdot \Delta t$$

and

$$-(\tau_8^{i-2}(x, T_8) - \tau_8^{i-1}(x, T_8)) = (\delta(c_{8*}^{u;i-1}(x), T_8) - \delta(c_{8*}^{u;i-2}(x), T_8)) \cdot \Delta t$$

hence

$$| - \left(\tau_1^{i-2}(x, T_1) - \tau_1^{i-1}(x, T_1)\right) | \leq G_{21}(\Delta t)^2,$$

where G_{21} is independent of i, and

$$| - \left(\tau_8^{i-2}(x, T_8) - \tau_8^{i-1}(x, T_8)\right) | \leq G_{28}(\Delta t)^2,$$

where G_{28} is independent of i.

Moreover, for $p = 1, 8$,

$$\Big| \frac{\partial \gamma}{\partial c_{p*}^{u;i-1}} (c_{1*}^{u;i-1}(x), c_{8*}^{u;i-1}(x), T_1) - \frac{\partial \gamma}{\partial c_{p*}^{u;i-2}} (c_{1*}^{u;i-2}(x), c_{8*}^{u;i-2}(x), T_1) \Big| \leq G_{c\gamma p} \Delta t. \tag{15.122}$$

and

$$\Big| \frac{\partial \delta}{\partial c_{8*}^{u;i-1}} (c_{8*}^{u;i-1}(x), T_1) - \frac{\partial \gamma}{\partial c_{8*}^{u;i-2}} (c_{8*}^{u;i-2}(x), T_1) \Big| \leq G_{c\delta} \Delta t \tag{15.123}$$

Proof By (15.8) and (15.9), we obtain straightforwardly the first pair of inequalities. The second pair of estimates follow from inequality (15.25) in Lemma 15.7, the form of the function δ and the estimates (15.50). To prove estimate (15.122) we use Lemma 15.15 and write the expression inside the mid signs $| \cdot |$ at the left hand side of (15.122) in the form

$$\frac{\partial\gamma}{\partial c^u_{p*}}(c^{u;i-1}_{1*}(x), c^{u;i-1}_{8*}(x), T_1) - \frac{\partial\gamma}{\partial c^u_{p*}}(c^{u;i-2}_{1*}(x), c^{u;i-2}_{8*}(x), T_1) =$$
$$\frac{\partial\gamma}{\partial c^u_{p*}}\Big(c^{u;i-2}_{1*}(x) + [c^{u;i-1}_{1*}(x) - c^{u;i-2}_{1*}(x)], c^{u;i-2}_{8*}(x) + [c^{u;i-1}_{8*}(x) - c^{u;i-2}_{8*}(x)], T_1\Big) -$$
$$\frac{\partial\gamma}{\partial c^u_{p*}}(c^{u;i-2}_{1*}(x), c^{u;i-2}_{8*}(x), T_1) =$$
$$\textstyle\sum_{r=1,8}[c^{u;i-1}_{r*}(x) - c^{u;i-2}_{r*}(x)]\cdot$$
$$\int_0^1 \frac{\partial^2\gamma}{\partial c^u_{p*}\partial c^u_{r*}}\Big(c^{u;i-2}_{1*}(x) + s[c^{u;i-1}_{1*}(x) - c^{u;i-2}_{1*}(x)], c^{u;i-2}_{8*}(x) + s[c^{u;i-1}_{8*}(x) - c^{u;i-2}_{8*}(x)], T_1\Big)ds.$$

Now, using inequalities (15.50) in Lemma 15.12 and the second inequality (15.27) in Lemma 15.7, we obtain (15.122). In the same way we can obtain (15.123). □

Consequently, by (15.116), we conclude that

$$\Big|B^{i-1}_{T_1}(x;\tau^{i-1}_1(x,T_1),\tau^{i-1}_8(x,T_8)) - B^{i-2}_{T_1}(x;\tau^{i-2}_1(x,T_1),\tau^{i-2}_8(x,T_8))\Big| \le$$
$$\Big|\left[B^{i-1}_{\tau_1}(x;\tau^{i-1}_1(x,T_1),\tau^{i-1}_8(x,T_8)) - B^{i-2}_{\tau_1}(x;\tau^{i-1}_1(x,T_1),\tau^{i-1}_8(x,T_8))\right]\cdot(1-\gamma^{i-1}_{,T_1}\Delta t)\Big| +$$
$$\Big(\mathcal{B}_{11}G_{21} + \mathcal{B}_{11}G_{28}\Big)(\Delta t)^2 \le |H^{i-1}_1|(1 + A_M\Delta t) + \Big(\mathcal{B}_{11}G_{21} + \mathcal{B}_{18}G_{28}\Big)(\Delta t)^2,$$

where

$$A_M := \max\{A_-, A_+\} \tag{15.124}$$

with A_-, A_+ defined in inequality (15.23) of Lemma 15.7, and A defined by (15.30).

It thus follows by means of the maximum principle that

$$|H^i_1| \le (|H^{i-1}_1|(1 + A_M\Delta t) + W_{H_1}(\Delta t)^2 + \Delta t\,|Z^i|)L, \tag{15.125}$$

where $W_{H_1} = \mathcal{B}_{11}G_{21} + \mathcal{B}_{18}G_{28}$. In the same way, for some constant W_{H_8},

$$|H^i_8| \le (|H^{i-1}_8|(1 + \delta_2\Delta t) + W_{H_8}\Delta t + \Delta t\,|Z^i|)L. \tag{15.126}$$

By defining, as before,

$$|H|^i := \sup\{|H^i_1|, |H^i_8|\},$$

we obtain

$$|H|^i \le (|H^{i-1}|(1 + A_{18}\Delta t) + W_H(\Delta t)^2 + \Delta t\,|Z^i|)L, \tag{15.127}$$

where $W_H = \sup\{W_{H_1}, W_{H_8}\}$ and $A_{18} = \sup\{A_M, \delta_2\}$.

By combining (15.110) and (15.172) we obtain the system:

$$\begin{aligned} |Z^i| &\le (|Z^{i-1}| + r_2(\Delta t)^2 + r_3|H|^{i-1}\Delta t)L. \\ |H|^i &\le (|H^{i-1}|(1 + A_{18}\Delta t) + W_H(\Delta t)^2 + \Delta t\,|Z^i|)L. \end{aligned} \tag{15.128}$$

We will find an upper bound for $|Z|^i$ and $|H|^i$ provided by solutions to the following system of equations:

$$|Z^i| = (|Z^{i-1}| + a_*(\Delta t)^2 + a|H|^{i-1}\Delta t)L.$$
$$|H|^i = (|H^{i-1}|(1 + b\Delta t) + a_*(\Delta t)^2 + \Delta t\,|Z^i|)L, \tag{15.129}$$

where

$$a_* := \max\{W_H, r_2\}, \quad b := A_{18}.$$

In fact, we will consider the system for the differences:

$$\psi(i) := |Z^i| - |Z^{i-1}|, \quad \phi(i) := |H|^i - |H|^{i-1},$$

$i \in \{2, \ldots, n\}$, which reads

$$\psi(i) = (\psi(i-1) + a\phi(i-1)d)L$$
$$\phi(i) = (\phi(i-1)(1 + bd) + \psi(i)d)L,$$

where

$$d := \Delta t.$$

Using the first equation in the second one, we can write the system in the standard form of recursive sequences:

$$\psi(i) = (\psi(i-1) + a\phi(i-1)d)L$$
$$\phi(i) = (\psi(i-1)dL + \phi(i-1)(1 + bd + ad^2L))L. \tag{15.130}$$

Note that, due to (15.113), (15.118), (15.119) and (15.129), we have:

$$\psi(2) = O(\Delta t^2), \quad \phi(2) = O(\Delta t^2).$$

If $X(i) := (\psi(i), \phi(i))^T$, then system (15.130) can be written as

$$X(i) = \mathcal{A}X(i-1), \tag{15.131}$$

with

$$\mathcal{A} = \begin{pmatrix} L & adL \\ dL^2 & (1 + bd + ad^2L)L \end{pmatrix}. \tag{15.132}$$

For $d > 0$ sufficiently small, the eigenvalues λ_1 and λ_2 of the matrix $\mathcal{A}$ are both positive and are equal to

$$\lambda_1 = \frac{1}{2}\left(cL - L\sqrt{c^2 + 4ad^2L} + 2L\right), \quad \lambda_2 = \frac{1}{2}\left(cL + L\sqrt{c^2 + 4ad^2L} + 2L\right), \tag{15.133}$$

where

$$c = bd + ad^2L.$$

The solutions to (15.131) are given by the powers of the matrix $\mathcal{A}$. To find $\mathcal{A}^n$, we will use the following result from [11].

Lemma 15.17. *(see [11, Theorem 1]) Let U be a $k \times k$ nonsingular matrix with eigenvalues $\lambda_1, \ldots, \lambda_k$ and let $M(0) = I$, $M(j) = \Pi_{i=1}^{j}(U - \lambda_i I)$, $j \geq 1$. Suppose that $u_j(m)$ satisfy the (recursive) system*

$$u_1(m+1) = \lambda_1 u_1(m), \quad u_1(0) = 1$$
$$u_{j+1}(m+1) = \lambda_{j+1}u_{j+1}(m) + u_j(m), \quad u_{j+1}(0) = 0, \;\; j = 1, \ldots, k-1.$$

Then, for $m \geq k$

$$U^m = \sum_{j=0}^{k-1} u_{j+1}(m) M(j). \tag{15.134}$$

In our case

$$M_1 = (\mathcal{A} - \lambda_1 I) = \begin{pmatrix} \frac{1}{2}\left(\sqrt{c^2+4ad^2L} - c\right) L & adL \\ dL^2 & \frac{1}{2}\left(c + \sqrt{c^2+4ad^2L}\right) L. \end{pmatrix} \tag{15.135}$$

Now, let us note that we have

$$u_1(m) = \lambda_1^m.$$

Next, as $u_2(0) = 0$, we have

$$u_2(1) = \lambda_2 u_2(0) + u_1(0) = 1,$$

$$u_2(2) = \lambda_2 u_2(1) + u_1(1) = \lambda_2 + \lambda_1$$

$$u_2(3) = \lambda_2(\lambda_2 + \lambda_1) + \lambda_1^2 = \lambda_2^2 + \lambda_2\lambda_1 + \lambda_1^2$$

and, in general, for $m \geq 2$,

$$u_2(m) = \sum_{s=0}^{m-1} \lambda_1^s \lambda_2^{m-1-s} = \frac{\lambda_2^m - \lambda_1^m}{\lambda_2 - \lambda_1}$$

As, $\lambda_2 > \lambda_1$, then it follows from (15.134) that

$$\mathcal{A}^m = \lambda_1^m\, I + \left(\textstyle\sum_{s=0}^{m-1} \lambda_1^s \lambda_2^{m-1-s}\right)(\mathcal{A} - \lambda_1 I) < \lambda_1^m\, I + \lambda_2^{m-1}\Big(m \cdot (\mathcal{A} - \lambda_1 I)\Big) \tag{15.136}$$

where the last inequality should be understood entry-wise. By means of the identity $\sqrt{y_1 + y_2} < \sqrt{y_1} + \sqrt{y_2}$, we conclude that

$$\frac{1}{2}\left(c - \sqrt{c^2+4ad^2L}\right) L \geq -\sqrt{a_L} dL,$$

$$\frac{1}{2}\left(c + \sqrt{c^2+4ad^2L}\right) L \leq cL + \sqrt{a_L} dL = (b + \sqrt{a_L}) L\, d + ad^2 L,$$

where $\sqrt{a_L} = \sqrt{a}\sqrt{L}$, hence, according to (15.133),

$$\begin{aligned} &L\left(1 - \sqrt{a_L} d\right) < \lambda_1 < L \\ &0 < \lambda_2 < \left(1 + d(b + \sqrt{a_L}) + ad^2\right) L. \end{aligned} \tag{15.137}$$

Recall that $L = (1 - A\Delta t)^{-1}$. Let $d = \Delta t$ be so small that $L < 2$. Then, by means of the definition of $\sqrt{a_L}$, we have

$$S = (b + \sqrt{a_L}) + ad < b + \sqrt{2}\sqrt{a} + ad.$$

If necessary, let us decrease d to the values so small that $(1 + Sd) < (1 - Sd)^{-1} < 2$. (This can be done without losing generality, because we are interested in the limit $d = \Delta t \to 0$.) It follows that ,

$$\lambda_2 = \left(1 + \frac{1}{2}\left(c + \sqrt{c^2 + 4ad^2}\right)\right) L < (1 + Sd)\, L < L(1 - dS)^{-1}.$$

Thus

$$\lim_{n\to\infty} \lambda_2^{n-1} \leq \lim_{n\to\infty} \lambda_2^{n-1} < \lim_{n\to\infty} L^n (1 - dS)^{-n}.$$

By means of Remark after (15.32), we can estimate the last limit as $\exp(AT)\exp(ST)$. Moreover, we can also find n so large that $\lambda_2^n < 9/4\exp(AT)\exp(ST)$ for $d = T/n$. Next, according to (15.135)

$$\frac{1}{d}\cdot(\mathcal{A}-\lambda_1 I) = \begin{pmatrix} \frac{1}{2}\left(\sqrt{\tilde{c}^2+4aL}-\tilde{c}\right)L & aL \\ & \\ L^2 & \frac{1}{2}\left(\tilde{c}+\sqrt{\tilde{c}^2+4aL}\right)L. \end{pmatrix} \tag{15.138}$$

where $\tilde{c} = c/d = b + adL$. The entries of the last matrix stays of the order of $O(1)$ as $d \to 0$. It is thus seen that $(\mathcal{A}-\lambda_1 I)d^{-1} = (\mathcal{A}-\lambda_1 I)nT^{-1} = O(1)$ as $n \to \infty$. Likewise, as for d arbitrarily small $\lambda_1 < L$, then

$$\lim_{n\to\infty}\lambda_1^n < \lim_{n\to\infty} L^n < \exp(AT).$$

Due to Remark after (15.32) for all $n = T/d$ sufficiently large we have $\lambda_1^n < \dfrac{3}{2}\exp(AT)$. By means of (15.136), the matrix $\mathcal{A}^n$ stays uniformly bounded as $n \to \infty$ and $d = T/n \to 0$. Moreover, as the matrix $\mathcal{A}$ (given by (15.132)) satisfies the inequality $\mathcal{A} > I$ (in the sense of entries), then for $m_1 < m_2$

$$\mathcal{A}^{m_2} > \mathcal{A}^{m_1}.$$

In fact, $\psi(i)$ and $\phi(i)$ are well defined for $i \geq 2$. However, for technical reasons, we can assume additionally that $\psi(1) = O(\Delta t^2) = O(n^{-2})$ and $\phi(1) = O(\Delta t^2) = O(n^{-2})$. Hence for any $2 \leq i \leq n$,

$$(\psi(i),\phi(i))^T \leq (\psi(1),\phi(1))^T + \mathcal{A}^{i-1}(\psi(1),\phi(1))^T \leq (\psi(1),\phi(1))^T + (O(\Delta t^2), O(\Delta t^2))^T. \tag{15.139}$$

Consequently,

$$(\sum_{m=1}^{n}\psi(m), \sum_{m=1}^{n}\phi(m)) \leq n(O(\Delta t)^2), O(\Delta t)^2)) \leq (O(\Delta t), O(\Delta t)).$$

Equivalently we can consider system (15.129), which after replacing $|Z^i|$ by z_i, $|H|^i$ by h_i and inserting $|Z^i|$ into the equations for $|H|^i$ we obtain for $i \in \{2,\ldots,n\}$

$$\begin{aligned} z_i &= (z_{i-1} + a_*(\Delta t)^2 + ah_{i-1}\Delta t)L. \\ h_i &= (h_{i-1}(1+b\Delta t + a(\Delta t)^2 L) + a_*(\Delta t)^2 + \Delta t\, z_{i-1}L + a_*(\Delta t)^3 L)L. \end{aligned} \tag{15.140}$$

This recursive system of equations can be written in the following matrix form

$$Y(i) = \mathcal{A}Y(i-1) + G, \tag{15.141}$$

where

$$Y(i) = \begin{pmatrix} z_i \\ \\ h_i \end{pmatrix}$$

$$G = \begin{pmatrix} a_* d^2 \\ \\ a_* d^2 + a_* d^3 L \end{pmatrix} \tag{15.142}$$

and $\mathcal{A}$ is given as above by (15.132). Now, by means of the Corollary 3.18 in [12], we have for $m \geq 2$:

$$Y(m) = \mathcal{A}^m Y(1) + (\sum_{r=1}^{m-1}\mathcal{A}^{m-r-1})G.$$

By the previous estimates

$$\mathcal{A}^m < \mathcal{A}^n, \quad \text{for } n > m > 1$$

in the sense of inequalities between the entries. We can thus estimate

$$\sum_{r=1}^{n-1} \mathcal{A}^{n-r-1} < n\mathcal{A}^n,$$

hence

$$\begin{aligned} &Y(n) = \mathcal{A}^n Y(1) + (\textstyle\sum_{r=1}^{n-1} \mathcal{A}^{m-r-1})G < \mathcal{A}^n Y(1) + n\mathcal{A}^n G = \\ &O(1) \cdot Y(1) + O(1) \cdot (n\, O(1/n^2)) = O(1) \cdot O(1/n) + O(1) \cdot O(1/n) = O(d). \end{aligned} \tag{15.143}$$

Thus we are in a position to formulate the main result of this section:

Lemma 15.18. *For all $i \in \{1, \ldots, n\}$, the following estimates hold:*

$$\|Z^i\|_{C^0(\overline{\Omega}\times\overline{\mathbb{R}^2_+})} < G_{0Z}\,\Delta t,\ \|H_1^i\|_{C^0(\overline{\Omega}\times\overline{\mathbb{R}^2_+})} < G_{0H1}\,\Delta t \text{ and } \|H_8^i\|_{C^0(\overline{\Omega}\times\overline{\mathbb{R}^2_+})} < G_{0H8}\,\Delta t, \tag{15.144}$$

where the constants G_{0Z}, G_{0H1}, G_{0H8} are independent of i.

15.16 Estimates of $C_x^{1+\beta}$ norms of the functions R^i

By means of the results of the previous section, we will now give estimates of $C_x^{1+\beta}$ norms of R^i. This will be done by rewriting Eq. (15.5) in the form not containing the terms proportional to $(\Delta t)^{-1}$, namely as

$$\begin{aligned} &d_R \nabla^2 R^i + F_0(x) \cdot \nabla R^i - \\ &\Big\{R^i \left[\frac{\partial}{\partial T_1}\Big(\gamma(c_{1*}^{u;i-1}, c_{8*}^{u;i-1}, T_1)\Big) + \frac{\partial}{\partial T_8}\Big(\delta(c_{8*}^{u;i-1}, T_8)\Big) + F_1((i-1)\Delta t, x, T_1, T_8)\right] + W^i\Big\} = 0, \end{aligned} \tag{15.145}$$

where, by (15.108),

$$\begin{aligned} &W^i := \frac{1}{\Delta t}\left(R^i(x, T_1, T_8) - R^{i-1}(x; \tau_1^{i-1}, \tau_8^{i-1})\right) = \\ &\frac{1}{\Delta t}\left([R^i(x, T_1, T_8) - R^{i-1}(x, T_1, T_8)] + [R^{i-1}(x, T_1, T_8) - R^{i-1}(x; \tau_1^{i-1}, \tau_8^{i-1})]\right) = \\ &\frac{1}{\Delta t}\left(Z^i(x, T_1, T_8) + [R^{i-1}(x, T_1, T_8) - R^{i-1}(x; \tau_1^{i-1}, \tau_8^{i-1})]\right) = \\ &\frac{Z^i}{\Delta t} + \frac{1}{\Delta t}\Big(- B_1^{i-1}(x, T_1, T_8) \cdot \gamma^{i-1}(x, T_1)\Delta t - B_8^{i-1}(x, T_1, T_8) \cdot \delta^{i-1}(x, T_8)\Delta t - \\ &\textstyle\sum_{k,l=1,8}(\tau_k^{i-1} - T_k) \cdot (\tau_l^{i-1} - T_l) \displaystyle\int_0^1 (1-s) B_{\tau_k\tau_l}^{i-1}\Big(x, T_1 + s(\tau_1^{i-1} - T_1), T_8 + s(\tau_8^{i-1} - T_8)\Big)\, ds\Big). \end{aligned}$$

By Lemma 15.18, $Z^i/\Delta t < G_{0Z}$, hence by the results of sections 15.5 and 15.7, we conclude that the expression in the curly brackets is of the order of $O(1)$. It follows from Lemma 14.5, by taking $l = 2$ and the integration power p sufficiently large that

$$\|R^i\|_{W_p^2} \leq C_{2p}$$

where the constants C_{2p} are uniformly bounded for all p. By using the Sobolev imbedding theorem, we conclude that for all $\beta \in (0, 1)$ there exists a constant $C_{1\beta}$ independent of $i \in \{1, \ldots, n\}$ such that

$$\|R^i\|_{C^{1+\beta}(\Omega)} \leq C_{R1\beta}. \tag{15.146}$$

15.17 Estimates of the higher order norms of the functions $c_k^{u;i}$

Using the estimate (15.146), we will find the bound for higher order derivatives of the functions $c_k^{u;i}$.

Lemma 15.19. *Let $n \geq 3$ be fixed. Suppose that for each $i \in \{0, 1, \ldots, n\}$ and $\beta \in (0, 1)$, the $C^{1+\beta}(\Omega)$ norms of the functions R^i are bounded from above uniformly with respect to i. Then, c_1^u and c_8^u are of class $C_{t,x}^{(3+\beta)/2, 3+\beta}(((i-1)\Delta t, i\Delta t) \times \Omega)$. To be more precise, there exist constants $C_1(\beta, \Omega)$, $C_8(\beta, \Omega)$, K_1 and K_8, depending on T, such that*

$$\|c_1^u\|_{C_{t,x}^{(3+\beta)/2,2+\beta}(((i-1)\Delta t, i\Delta t)\times\Omega)} \leq C_{1\Delta}(\beta, \Omega) \left[K_1 + \|c_1^u((i-1)\Delta t, \cdot)\|_{C_x^{2+\beta}(\Omega)}\right] \tag{15.147}$$

and

$$\|c_8^u\|_{C_{t,x}^{(3+\beta)/2,3+\beta}(((i-1)\Delta t, i\Delta t)\times\Omega)} \leq C_{8\Delta}(\beta, \Omega) \left[K_8 + \|c_8^u((i-1)\Delta t, \cdot)\|_{C_x^{2+\beta}(\Omega)}\right]. \tag{15.148}$$

In particular, there exists constants P and P_1 independent of i such that as $\Delta t \to 0$

$$\|c_1^u(i\Delta t, \cdot) - c_1((i-1)\Delta t, \cdot)\|_{C^0(\Omega)} \leq P\Delta t, \quad \|c_8^u(i\Delta t, \cdot) - c_8((i-1)\Delta t, \cdot)\|_{C^0(\Omega)} \leq P\Delta t, \tag{15.149}$$

$$\|c_1^u(i\Delta t, \cdot) - c_1((i-1)\Delta t, \cdot)\|_{C^1(\Omega)} \leq P_1\Delta t, \quad \|c_8^u(i\Delta t, \cdot) - c_8((i-1)\Delta t, \cdot)\|_{C^1(\Omega)} \leq P_1\Delta t \tag{15.150}$$

and for $t \in [(i-1)\Delta t, i\Delta t]$

$$\|c_1^u(t, \cdot) - c_1((i-1)\Delta t, \cdot)\|_{C^0(\Omega)} \leq P(t-(i-1)\Delta t), \quad \|c_8^u(t, \cdot) - c_8((i-1)\Delta t, \cdot)\|_{C^0(\Omega)} \leq P(t-(i-1)\Delta t) \tag{15.151}$$

together with

$$\|c_1^u(t, \cdot) - c_1((i-1)\Delta t, \cdot)\|_{C^1(\Omega)} \leq P_1(t-(i-1)\Delta t), \quad \|c_8^u(t, \cdot) - c_8((i-1)\Delta t, \cdot)\|_{C^1(\Omega)} \leq P_1(t-(i-1)\Delta t) \tag{15.152}$$

Proof The proof of the lemma follows from Lemma 14.6. Starting from the initial data $c_1^{u,0}$, $c_8^{u,0}$ belonging to $C_x^{3+\beta}(\Omega)$ class and using the fact that $R^0 \in C^{1+\beta}$ class, we obtain a $C_{t,x}^{(3+\beta)/2,3+\beta}$ solution on the set $([0, \Delta t) \times \Omega)$. Treating $c_1^{u;1}(1 \cdot \Delta t, x)$ and $c_8^{u;1}(\Delta t, x)$ as the initial data we obtain a solution of $C_{t,x}^{(3+\beta)/2,3+\beta}$ class on the set $((1 \cdot \Delta t, 2 \cdot \Delta t] \times \Omega)$. Proceeding consecutively in this way, we obtain a $C_{t,x}^{(3+\beta)/2,3+\beta}$ solution on the set $(((i-1) \cdot \Delta t, i \cdot \Delta t] \times \Omega)$ for all $i \in \{1, \ldots, n\}$, hence using the Schauder estimates, we obtain inequalities (15.147) and (15.148). As the constants K_1 and K_8 can be chosen as independent of n and i, then in view of Leray-Schauder estimates, in particular due to the fact that the time derivative of the solutions is Holder continuous, there exists a constant P such that for $\Delta t > 0$ sufficiently small, inequality (15.149) holds. Next, noting that that, according to the definition of norms in this space, the subnorm

$$\Big\| \frac{\partial}{\partial t} \left(\frac{\partial^{|\alpha|}}{(\partial x)^\alpha} \right) \Big\|_{C^0(\Omega)}$$

with $|\alpha| \leq 1$ is finite (see [23], Theorem IV.5.3 and Section I.1), we arrive at inequalities (15.150). □

15.18 Estimates of first order derivatives of Z^i with respect to x_k

To proceed, we will analyse the equation for spatial derivatives $Z^i_{,x_k}$, $k \in \{1, 2, 3\}$. By fixing k, we will for simplicity denote

$$' := \frac{\partial}{\partial x_k}, \quad Z^i_{,x_k} := Z'^i.$$

Remark In the proof below, for each $i \in \{2, \ldots, n\}$, we will be interested in the quantity

$$\max_{k\in\{1,\ldots,dim(\Omega)\},(T_1,T_8)\in\overline{\mathbb{R}^2_+}} \Big(\sup_{x\in\Omega} \frac{\partial Z^i}{\partial x_k}\Big) = Z'^i.$$

However, for the sake of concise notation, we will the notation Z'^i, independently of i. □

By differentiating Eq.(15.102) and using Assumption 15.14 we obtain the equation:

$$\begin{aligned}
&d_R\nabla^2 Z'^i + (F_0(x)\cdot\nabla)Z'^i + (F_0'(x)\cdot\nabla)Z^i - \\
&\frac{Z'^i(x;T_1,T_8)}{\Delta t} + \frac{Z'^{i-1}(x,T_1,T_8)}{\Delta t} + \frac{Z'^{i-1}_*(x,T_1,T_8)}{\Delta t} - \\
&\Big\{Z'^i\Big[\frac{\partial}{\partial T_1}\Big(\gamma(c^{u;i-1}_{1*},c^{u;i-1}_{8*},T_1)\Big) + \frac{\partial}{\partial T_8}\Big(\delta(c^{u;i-1}_{8*},T_8)\Big) + F_1((i-1)\Delta t,x,T_1,T_8)\Big] + \\
&Z^i\Big[\Big(\frac{\partial}{\partial T_1}\Big(\gamma(c^{u;i-1}_{1*},c^{u;i-1}_{8*},T_1)\Big) + \frac{\partial}{\partial T_8}\Big(\delta(c^{u;i-1}_{8*},T_8)\Big) + F_1((i-1)\Delta t,x,T_1,T_8)\Big]'\Big\} - \\
&(R^{i-1}\Delta V^i)' \ = 0
\end{aligned} \tag{15.153}$$

where

$$Z'^{i-1}_* := (R^{i-1}_* - R^{i-1})' - (R^{i-2}_* - R^{i-2})' \tag{15.154}$$

with R^{i-1}_* defined in (15.104) and ΔV is given by (15.107).

To begin with, let us note that according to (15.107) and (15.150) the term $(R^{i-1}\Delta V^i)'$ is of the order of $O(\Delta t)$. We are going to construct a recurrent sequence for $Z'^i - Z'^{i-1}$ and prove that these differences are of the order of $O(\Delta t)^2$. First, adapting the analysis of the term Z^i_* in Eq.(15.102), let us consider the term Z'^{i-1}_* . For $i \geq 2$, we have:

$$\begin{aligned}
&R'^{i-1} - R'^{i-1}_* = R'^{i-1}(x,T_1,T_8) - R'^{i-1}(x,\tau^{i-1}_1(x,T_1),\tau^{i-1}_8(x,T_8)) = \\
&R'^{i-1}(x,T_1,T_8) - R'^{i-1}(x,T_1,T_8) - \\
&B'^{i-1}_1(x,T_1,T_8)\cdot\gamma^{i-1}(x,T_1)\Delta t - B'^{i-1}_8(x,T_1,T_8)\cdot\delta^{i-1}(x,T_8)\Delta t - \\
&B^{i-1}_1(x,T_1,T_8)\cdot(\gamma^{i-1}(x,T_1))'\Delta t - B^{i-1}_8(x,T_1,T_8)\cdot(\delta^{i-1}(x,T_8))'\Delta t - \\
&\Big[(\tau^{i-1}_1 - T_1)^2\textstyle\int_0^1(1-s)(B^{i-1}_{\tau_1\tau_1}(x,T_1+s(\tau^{i-1}_1-T_1),T_8+s(\tau^{i-1}_8-T_8))\,ds + \\
&(\tau^{i-1}_8 - T_8)^2\textstyle\int_0^1(1-s)(B^{i-1}_{\tau_8\tau_8}(x,T_1+s(\tau^{i-1}_1-T_1),T_8+s(\tau^{i-1}_8-T_8))\,ds + \\
&2(\tau^{i-1}_1 - T_1)(\tau^{i-1}_8 - T_8)\textstyle\int_0^1(1-s)(B^{i-1}_{\tau_1\tau_8}(x,T_1+s(\tau^{i-1}_1-T_1),T_8+s(\tau^{i-1}_8-T_8))\,ds\Big]'.
\end{aligned} \tag{15.155}$$

Next, by means of section 15.13 and Lemma 15.16

$$\begin{aligned}
&B'^{i-1}_1(x,T_1,T_8)\cdot\gamma^{i-1}(x,T_1)\Delta t - B'^{i-2}_1(x,T_1,T_8)\cdot\gamma^{i-2}(x,T_1)\Delta t = \\
&\Big(B'^{i-1}_1(x,T_1,T_8) - B'^{i-2}_1(x,T_1,T_8)\Big)\cdot\gamma^{i-1}(x,T_1)\Delta t + B'^{i-2}_1(x,T_1,T_8)\Big(\gamma^{i-1}(x,T_1) - \gamma^{i-2}(x,T_1)\Big)\Delta t := \\
&H'^{i-1}_1(x,T_1,T_8)\cdot\gamma^{i-1}(x,T_1)\Delta t + B'^{i-2}_1(x,T_1,T_8)\Big(\gamma^{i-1}(x,T_1) - \gamma^{i-2}(x,T_1)\Big)\Delta t = \\
&H'^{i-1}_1(x,T_1,T_8)\cdot\gamma^{i-1}(x,T_1)\Delta t + \mathcal{Q}^{i-2}_{*,*}O(\Delta t)\Delta t
\end{aligned} \tag{15.156}$$

and

$$
\begin{aligned}
&B_1^{i-1}(x,T_1,T_8)\cdot(\gamma^{i-1}(x,T_1))'\Delta t - B_1^{i-2}(x,T_1,T_8)\cdot(\gamma^{i-2}(x,T_1))'\Delta t = \\
&\Big(B_1^{i-1}(x,T_1,T_8) - B_1^{i-2}(x,T_1,T_8)\Big)\cdot(\gamma^{i-1}(x,T_1))'\Delta t + B_1^{i-2}(x,T_1,T_8) \\
&\cdot\Big((\gamma^{i-1}(x,T_1))' - (\gamma^{i-2}(x,T_1))'\Big)\Delta t \\
&= H_1^{i-1}(x,T_1,T_8)\cdot\gamma^{i-1}(x,T_1)\Delta t + B_1^{i-2}(x,T_1,T_8)\cdot\Big((\gamma^{i-1}(x,T_1))' - (\gamma^{i-2}(x,T_1))'\Big)\Delta t
\end{aligned}
\tag{15.157}
$$

where, for $' = \dfrac{\partial}{\partial x_k}$,

$$
\begin{aligned}
&(\gamma^{i-1}(x,T_1))' - (\gamma^{i-2}(x,T_1))' = \textstyle\sum_{p=1,8}\Big\{\dfrac{\partial\gamma}{\partial c_{p*}^{u;i-1}}\cdot\dfrac{\partial c_{p*}^{u;i-1}}{\partial x_k} - \dfrac{\partial\gamma}{\partial c_{p*}^{u;i-2}}\cdot\dfrac{\partial c_{p*}^{u;i-2}}{\partial x_k}\Big\} = \\
&\textstyle\sum_{p=1,8}\Big\{\Big[\dfrac{\partial\gamma}{\partial c_{p*}^{u;i-1}} - \dfrac{\partial\gamma}{\partial c_{p*}^{u;i-2}}\Big]\cdot\dfrac{\partial c_{p*}^{u;i-1}}{\partial x_k} + \dfrac{\partial\gamma}{\partial c_{p*}^{u;i-2}}\cdot\Big[\dfrac{\partial c_{p*}^{u;i-1}}{\partial x_k} - \dfrac{\partial c_{p*}^{u;i-2}}{\partial x_k}\Big]\Big\}.
\end{aligned}
\tag{15.158}
$$

Likewise, by means of section 15.13 and Lemma 15.16

$$
\begin{aligned}
&B_8'^{i-1}(x,T_1,T_8)\cdot\delta^{i-1}(x,T_1)\Delta t - B_8'^{i-2}(x,T_1,T_8)\cdot\delta^{i-2}(x,T_1)\Delta t = \\
&\Big(B_8'^{i-1}(x,T_1,T_8) - B_8'^{i-2}(x,T_1,T_8)\Big)\cdot\delta^{i-1}(x,T_1)\Delta t + B_1'^{i-2}(x,T_1,T_8)\Big(\delta^{i-1}(x,T_1) - \delta^{i-2}(x,T_1)\Big)\Delta t \\
&:= H_8'^{i-1}(x,T_1,T_8)\cdot\delta^{i-1}(x,T_1)\Delta t + B_8'^{i-2}(x,T_1,T_8)\Big(\delta^{i-1}(x,T_1) - \delta^{i-2}(x,T_1)\Big)\Delta t \\
&= H_8'^{i-1}(x,T_1,T_8)\cdot\delta^{i-1}(x,T_1)\Delta t + \mathcal{Q}_{*,*}^{i-2}O(\Delta t)\Delta t
\end{aligned}
\tag{15.159}
$$

and

$$
\begin{aligned}
&B_8^{i-1}(x,T_1,T_8)\cdot(\delta^{i-1}(x,T_8))'\Delta t - B_8^{i-2}(x,T_1,T_8)\cdot(\delta^{i-2}(x,T_8))'\Delta t = \\
&\Big(B_8^{i-1}(x,T_1,T_8) - B_8^{i-2}(x,T_1,T_8)\Big)\cdot(\delta^{i-1}(x,T_8))'\Delta t + B_8^{i-2}(x,T_1,T_8) \\
&\qquad\cdot\Big((\delta^{i-1}(x,T_8))' - (\delta^{i-2}(x,T_8))'\Big)\Delta t \\
&= H_8^{i-1}(x,T_1,T_8)\cdot\delta^{i-1}(x,T_8)\Delta t + B_8^{i-2}(x,T_1,T_8)\cdot\Big((\delta^{i-1}(x,T_1))' - (\delta^{i-2}(x,T_1))'\Big)\Delta t
\end{aligned}
\tag{15.160}
$$

The first term of the right hand side of (15.157), due to Lemma 15.18, can be estimated by a constant (independent of i) times $(\Delta t)^2$. By the results of section 15.8, $|B_1^{i-2}(x,T_1,T_8)|$ is bounded uniformly with i. Next, by (15.122) in Lemma 15.16, the first square bracket at the right hand side of (15.158) is of the order of $O(\Delta t)$. Similarly, due to estimate (15.150) in Lemma 15.19, the second square bracket in (15.158) is of the order of $O(\Delta t)$. Similar conclusions can be drawn with respect to the expression given by the right hand side of (15.160). Finally, as $(\tau_1^{i-1} - T_1) = \gamma\Delta t$ and $(\tau_8^{i-1} - T_8) = \delta\Delta t$, in view of Lemma 15.12 (differentiability of the functions γ and δ) and section 15.14 (differentiability with respect to x_k of $B_{\tau_k\tau_l}$), we conclude that there exists a constant r_1 independent of i, such that for all $x \in \overline{\Omega}$ and $(T_1,T_8) \in \overline{\mathbb{R}_+^2}$,

$$
|(R_*'^{i-1} - R'^{i-1}) - (R_*'^{i-2} - R'^{i-2})| = \Big(|H_1'^{i-1}|\overline{\gamma} + |H_8'^{i-1}|\overline{\delta}\Big)\Delta t + r_1(\Delta t)^2.
$$

Suppose that

$$\|\nabla Z^i\| = \Big|\frac{\partial Z^i}{\partial x_k}(x_*)\Big| := Z'^i(x_*).$$

Then, by applying to Eq. (15.153) the maximum principle at the point x_*, we can estimate for Δt sufficiently small

$$|Z'^i(x_*)| \le \Big\{|Z'^{i-1}(x_*)|\frac{1}{\Delta t} + \Big(|H_1'^{i-1}|\overline{\gamma}\Delta t + |H_8'^{i-1}|\overline{\delta}\Delta t + r_1(\Delta t)^2\Big)\frac{1}{\Delta t} + r_4\Delta t\Big\}\Big(\frac{1}{\Delta t} - A - 3f_0\Big)^{-1}.$$

Denoting, similarly to (15.161),

$$|H'|^i := \sup\{|H_1'^i|, |H_8'^i|\}, \tag{15.161}$$

we arrive at the inequality corresponding to (15.110):

$$|Z'^i| \le (|Z'^{i-1}| + \tilde{r}_2(\Delta t)^2 + \tilde{r}_3|H'|^{i-1}\Delta t)L, \tag{15.162}$$

where

$$L = (1 - A_1\Delta t), \quad A_1 = A + 3f_0. \tag{15.163}$$

(Cf. (15.82).) Let us note that by differentiating Eq. (15.112) with respect to x_k, we can prove that

$$\|\nabla Z_1(\cdot)\|_{C^0(\Omega)} < \Delta t\, G_Z^1, \tag{15.164}$$

for some constant G_Z^1.

In the similar way, we can derive the equation for the components of ∇H_1^i for $i \in \{2, \dots, n\}$. Let, similarly as before:

$$' := \frac{\partial}{\partial x_k}, \quad H^i_{1,x_k} := H_1'^i, \quad H^i_{8,x_k} := H_8'^i,$$

where the index k is in general a function of i. The equation for H'^i has the form:

$$\begin{aligned}
&0 = d_R\nabla^2 H_1'^i + (F_0(x)\cdot\nabla)H_1'^i + (F_0'(x)\cdot\nabla)H_1^i - \\
&H_1'^i\left[\frac{\partial}{\partial T_1}\Big(\gamma(c_{1*}^{u;i-1}, c_{8*}^{u;i-1}, T_1)\Big) + \frac{\partial}{\partial T_8}\Big(\delta(c_{8*}^{u;i-1}, T_8)\Big) + F_1((i-1)\Delta t, x, T_1, T_8) + \frac{1}{\Delta t}\right] - \\
&B_1'^{i-1}[\Delta V_i] - B_1^{i-1}[\Delta V_i]' - Z'^i\Big[\frac{\partial^2}{\partial T_1^2}\Big(\gamma(c_{1*}^{u;i-1}, c_{8*}^{u;i-1}, T_1)\Big) + \frac{\partial}{\partial T_1}F_1((i-1)\Delta t, x, T_1, T_8)\Big] - \\
&Z^i\Big[\frac{\partial^2}{\partial T_1^2}\Big(\gamma(c_{1*}^{u;i-1}, c_{8*}^{u;i-1}, T_1)\Big) + \frac{\partial}{\partial T_1}F_1((i-1)\Delta t, x, T_1, T_8)\Big]' - \\
&\Big(R^{i-1}\Big[\frac{\partial^2}{\partial T_1^2}\gamma(c_{1*}^{u;i-1}, c_{8*}^{u;i-1}, T_1) - (\frac{\partial^2}{\partial T_1^2}\gamma(c_{1*}^{u;i-2}, c_{8*}^{u;i-2}, T_1)) + \\
&\frac{\partial}{\partial T_1}F_1((i-1)\Delta t, x, T_1, T_8) - \frac{\partial}{\partial T_1}F_1((i-2)\Delta t, x, T_1, T_8)\Big]\Big)' + \\
&\frac{\big(B_1^{i-1}(x; \tau_1^{i-1}(x, T_1), \tau_8^{i-1}(x, T_8)) - B_1^{i-2}(x; \tau_1^{i-2}(x, T_1), \tau_8^{i-2}(x, T_8))\big)'}{\Delta t}.
\end{aligned} \tag{15.165}$$

This equation can be obtained formally by differentiating (with respect to x_k) Eq.(15.114).

In accordance with (15.105) and (15.106), let us denote:

$$\gamma_{T_1}^i := \frac{\partial\gamma(c_{1*}^{u;i}, c_{8*}^{u,i}, T_1)}{\partial T_1}, \quad \delta_{T_8}^i := \frac{\partial\delta(c_{8*}^{u,i}, T_1)}{\partial T_8}.$$

We have:

$$\Big(B_1^{i-1}(x;\tau_1^{i-1}(x,T_1),\tau_8^{i-1}(x,T_8)) - B_1^{i-2}(x;\tau_1^{i-2}(x,T_1),\tau_8^{i-2}(x,T_8))\Big)' =$$

$$\Big(B_{\tau_1}^{i-1}(x;\tau_1^{i-1}(x,T_1),\tau_8^{i-1}(x,T_8))(1-\gamma_{T_1}^{i-1}\Delta t) - B_{\tau_1}^{i-2}(x;\tau_1^{i-2}(x,T_1),\tau_8^{i-2}(x,T_8))(1-\gamma_{T_1}^{i-2}\Delta t)\Big)' =$$

$$\Big(\,[B_{\tau_1}^{i-1}(x;\tau_1^{i-1}(x,T_1),\tau_8^{i-1}(x,T_8)) - B_{\tau_1}^{i-2}(x;\tau_1^{i-2}(x,T_1),\tau_8^{i-2}(x,T_8))]\cdot(1-\gamma_{T_1}^{i-1}\Delta t) -$$

$$B_{\tau_1}^{i-2}(x;\tau_1^{i-2}(x,T_1),\tau_8^{i-2}(x,T_8))\cdot\big[\gamma_{T_1}^{i-1}\Delta t - \gamma_{T_1}^{i-2}\Delta t\big]\,\Big)' \tag{15.166}$$

Let us note that, according to Lemma 15.19,

$$\Big(\gamma_{T_1}^{i-1}(x,T_1)\Delta t - \gamma_{T_1}^{i-2}(x,T_1)\Delta t\Big)' = (\gamma_{T_1}'^{i-1}(x,T_1) - \gamma_{T_1}'^{i-2})\Delta t < G_{11g}(\Delta t)^2.$$

Next, by (15.16),

$$\Big(B_{\tau_1}^{i-1}(x;\tau_1^{i-1}(x,T_1),\tau_8^{i-1}(x,T_8)) - B_{\tau_1}^{i-2}(x;\tau_1^{i-2}(x,T_1),\tau_8^{i-2}(x,T_8))\Big)' =$$

$$\Big(B_{\tau_1}^{i-1}(x;\tau_1^{i-1}(x,T_1),\tau_8^{i-1}(x,T_8)) -$$

$$B_{\tau_1}^{i-2}\Big[x;\tau_1^{i-1}(x,T_1) - \{\tau_1^{i-1}(x,T_1)-\tau_1^{i-2}(x,T_1)\},\tau_8^{i-1}(x,T_8) - \big\{\tau_8^{i-1}(x,T_8)-\tau_8^{i-2}(x,T_8)\big\}\,\Big]\Big)' =$$

$$\Big(B_{\tau_1}^{i-1}(x;\tau_1^{i-1}(x,T_1),\tau_8^{i-1}(x,T_8)) - B_{\tau_1}^{i-2}(x;\tau_1^{i-1}(x,T_1),\tau_8^{i-1}(x,T_8)) -$$

$$\Big[(\tau_1^{i-1}(x,T_1)-\tau_1^{i-2}(x,T_1))\int_0^1(B_{\tau_1\tau_1}^{i-2}(x,\tau_1^{i-1}+s(\tau_1^{i-2}-\tau_1^{i-1}),\tau_8+s(\tau_8^{i-1}-\tau_8^{i-2}))\,ds +$$

$$(\tau_8^{i-1}(x,T_8)-\tau_8^{i-2}(x,T_8))\int_0^1(B_{\tau_1\tau_8}^{i-2}(x,\tau_1^{i-1}+s(\tau_1^{i-2}-\tau_1^{i-1}),\tau_8^{i-1}+s(\tau_8^{i-2}-\tau_8^{i-1})\,ds\Big]\Big)'. \tag{15.167}$$

If $' = \dfrac{\partial}{\partial x_k}$, we have

$$\Big(B_{\tau_1}^{i-1}(x;\tau_1^{i-1}(x,T_1),\tau_8^{i-1}(x,T_8)) - B_{\tau_1}^{i-2}(x;\tau_1^{i-1}(x,T_1),\tau_8^{i-1}(x,T_8))\Big)' = H_1'^i(x,\tau_1^{i-1}(x,T_1),\tau_8^{i-1}(x,T_8))$$

$$+\Big(B_{\tau_1\tau_1}^{i-1}(x;\tau_1^{i-1}(x,T_1),\tau_8^{i-1}(x,T_8)) - B_{\tau_1\tau_1}^{i-2}(x;\tau_1^{i-1}(x,T_1),\tau_8^{i-1}(x,T_8))\Big)\cdot\frac{\partial\tau_1^{i-1}(x,T_1)}{\partial x_k}$$

$$+\Big(B_{\tau_1\tau_8}^{i-1}(x;\tau_1^{i-1}(x,T_1),\tau_8^{i-1}(x,T_8)) - B_{\tau_1\tau_8}^{i-2}(x;\tau_1^{i-1}(x,T_1),\tau_8^{i-1}(x,T_8))\Big)\cdot\frac{\partial\tau_8^{i-1}(x,T_1)}{\partial x_k} \tag{15.168}$$

Remark Recall that $\dfrac{\partial\tau_1^{i-1}(x,T_1)}{\partial x_k}$ and $\dfrac{\partial\tau_8^{i-1}(x,T_1)}{\partial x_k}$ are of the order of (Δt) as $\Delta t\to 0$ (see Lemma 15.3). It follows that the second and the third term in the above expression is of the order of $O((\Delta t)^2)$, if only the coefficients multiplying $\dfrac{\partial\tau_1^{i-1}(x,T_1)}{\partial x_k}$ and $\dfrac{\partial\tau_8^{i-1}(x,T_1)}{\partial x_k}$ are of the order of Δt. □

Next,

$\Big[(\tau_1^{i-1}(x,T_1)-\tau_1^{i-2}(x,T_1))\cdot$

$\int_0^1 (B^{i-2}_{\tau_1\tau_1}(x,\tau_1^{i-1}(x,T_1)+s(\tau_1^{i-2}(x,T_1)-\tau_1(x,T_1)),\tau_8(x,T_8)+s(\tau_8^{i-1}(x,T_8)-\tau_8^{i-2}(x,T_8)))\,ds\Big]'=$

$(\tau_1^{i-1}(x,T_1)-\tau_1^{i-2}(x,T_1))'\cdot$

$\int_0^1 (B^{i-2}_{\tau_1\tau_1}(x,\tau_1^{i-1}(x,T_1)+s(\tau_1^{i-2}(x,T_1)-\tau_1(x,T_1)),\tau_8(x,T_8)+s(\tau_8^{i-1}(x,T_8)-\tau_8^{i-2}(x,T_8)))\,ds+$

$(\tau_1^{i-1}(x,T_1)-\tau_1^{i-2}(x,T_1))\cdot$

$\int_0^1 \Big(B^{i-2}_{\tau_1\tau_1}(x,\tau_1^{i-1}(x,T_1)+s(\tau_1^{i-2}(x,T_1)-\tau_1(x,T_1)),\tau_8(x,T_8)+s(\tau_8^{i-1}(x,T_8)-\tau_8^{i-2}(x,T_8)))\Big)'\,ds$

Let us note that, in view of Lemma 15.16 and Lemma 15.19,

$$(\tau_1^{i-1}(x,T_1)-\tau_1^{i-2}(x,T_1)=O((\Delta t)^2), \quad \text{and} \quad (\tau_1^{i-1}(x,T_1)-\tau_1^{i-2}(x,T_1))'=O((\Delta t)^2)$$

as $\Delta t\to 0$. On the other hand the quantity

$$\Big(B^{i-2}_{\tau_1\tau_1}(x,\tau_1^{i-1}(x,T_1)+s(\tau_1^{i-2}(x,T_1)-\tau_1(x,T_1)),\tau_8(x,T_8)+s(\tau_8^{i-1}(x,T_8)-\tau_8^{i-2}(x,T_8)))\Big)'$$

is finite, if only the third order derivatives $B^k_{\tau_1\tau_1 x}(x,\tau_1,\tau_8)$, $B^k_{\tau_1\tau_1\tau_1}(x,\tau_1,\tau_8)$, $B^k_{\tau_1\tau_1\tau_8}(x,\tau_1,\tau_8)$ are bounded for all the possible x, τ_1 and τ_8 of interest. Likewise,

$$\Big(B^{i-2}_{18}(x,\tau_1^{i-1}+s(\tau_1^{i-2}-\tau_1^{i-1}),\tau_8^{i-1}+s(\tau_8^{i-2}-\tau_8^{i-1})\Big)'$$

is finite, if only the third order derivatives $B^k_{\tau_1\tau_1 x}(x,\tau_1,\tau_8)$, $B^k_{\tau_1\tau_8\tau_1}(x,\tau_1,\tau_8)$, $B^k_{\tau_1\tau_8\tau_8}(x,\tau_1,\tau_8)$ are bounded for all the possible x, T_1 and T_8 of interest.

In view of Remark after (15.168), we have to estimate the differences

$$H^i_{km}:=B^i_{km}(x,T_1,T_8)-B^{i-1}_{km}(x,T_1,T_8), \quad k,m\in\{1,8\}.$$

Let us consider the difference H^i_{11}. The remaining differences (H^i_{18} and H^i_{88}) can be considered similarly. The equation for H^i_{11} is obtained by subtracting the equation (15.85) for B^{i-1}_{11} from the equation for B^i_{11}. We have

$$
\begin{aligned}
&0 = d_R \nabla^2 H^i_{11} + F_0((i-1)\Delta t, x) \cdot \nabla H^i_{11} - \\
&H^i_{11}\left[\frac{\partial}{\partial T_1}\Big(\gamma(c^{u;i-1}_{1*}, c^{u;i-1}_{8*}, T_1)\Big) + \frac{\partial}{\partial T_8}\Big(\delta(c^{u;i-1}_{8*}, T_8)\Big) + F_1((i-1)\Delta t, x, T_1, T_8) + \frac{1}{\Delta t}\right] - \\
&B^{i-1}_{11}\Big\{\left[\frac{\partial}{\partial T_1}\Big(\gamma(c^{u;i-1}_{1*}, c^{u;i-1}_{8*}, T_1)\Big) + \frac{\partial}{\partial T_8}\Big(\delta(c^{u;i-1}_{8*}, T_8)\Big) + F_1((i-1)\Delta t, x, T_1, T_8)\right] - \\
&\qquad \left[\frac{\partial}{\partial T_1}\Big(\gamma(c^{u;i-2}_{1*}, c^{u;i-2}_{8*}, T_1)\Big) + \frac{\partial}{\partial T_8}\Big(\delta(c^{u;i-2}_{8*}, T_8)\Big) + F_1((i-2)\Delta t, x, T_1, T_8)\right]\Big\}_1 - \\
&2B^i_1\Big\{\left[\frac{\partial^2}{\partial T_1^2}\Big(\gamma(c^{u;i-1}_{1*}, c^{u;i-1}_{8*}, T_1)\Big) + \frac{\partial F_1}{\partial T_1}((i-1)\Delta t, x, T_1, T_8)\right] - \\
&\qquad \left[\frac{\partial^2}{\partial T_1^2}\Big(\gamma(c^{u;i-2}_{1*}, c^{u;i-2}_{8*}, T_1)\Big) + \frac{\partial F_1}{\partial T_1}((i-2)\Delta t, x, T_1, T_8)\right]\Big\}_2 - \\
&R^i\Big\{\Big[\frac{\partial^3}{\partial T_1^3}\Big(\gamma(c^{u;i-1}_{1*}, c^{u;i-1}_{8*}, T_1)\Big) + \frac{\partial^2 F_1}{\partial T_1^2}((i-1)\Delta t, x, T_1, T_8)\Big] - \\
&\qquad \Big[\frac{\partial^3}{\partial T_1^3}\Big(\gamma(c^{u;i-2}_{1*}, c^{u;i-2}_{8*}, T_1)\Big) + \frac{\partial^2 F_1}{\partial T_1^2}((i-2)\Delta t, x, T_1, T_8)\Big]\Big\}_3 - \\
&\quad Z^i\Big[\frac{\partial^3}{\partial T_1^3}\Big(\gamma(c^{u;i-1}_{1*}, c^{u;i-1}_{8*}, T_1)\Big) + \frac{\partial^2 F_1}{\partial T_1^2}((i-1)\Delta t, x, T_1, T_8)\Big] + \\
&\frac{1}{\Delta t}\Big[B^{i-1}_{T_1T_1}(x; \tau^{i-1}_1(x, T_1), \tau^{i-1}_8(x, T_8)) - B^{i-2}_{T_1T_1}(x; \tau^{i-2}_1(x, T_1), \tau^{i-2}_8(x, T_8))\Big]_4.
\end{aligned}
\tag{15.169}
$$

Recall that according to (15.86):

$$
\begin{aligned}
&B^{i-1}_{11}(x, \tau^{i-1}_1, \tau^{i-1}_8) = B^{i-1}_{11}(x, \tau^{i-1}_1(x, T_1), \tau^{i-1}_8(x, T_8)) = \\
&B^{i-1}_{\tau_1\tau_1}(x, \tau^{i-1}_1, \tau^{i-1}_8) \cdot \left(1 - \Delta t\,\frac{\partial \gamma(c^{u;i-1}_{1*}(x), c^{u;i-1}_{8*}(x), T_1)}{\partial T_1}\right)^2 - \\
&\Delta t\; B^{i-1}_{\tau_1}(x, \tau^{i-1}_1, \tau^{i-1}_8) \cdot \frac{\partial^2 \gamma(c^{u;i-1}_{1*}(x), c^{u;i-1}_{8*}(x), T_1)}{\partial T_1^2}.
\end{aligned}
\tag{15.170}
$$

Let us note that the expressions in the curly brackets $\{\cdot\}_1$, $\{\cdot\}_2$ and $\{\cdot\}_3$ in (15.169) are of the order $O(1)\Delta t$. Using (15.170) in the square bracket $[\cdot]_4$, we have

$$
\begin{aligned}
&[\cdot]_4 = \Big(B^{i-1}_{\tau_1\tau_1}(x, \tau^{i-1}_1, \tau^{i-1}_8) - B^{i-2}_{\tau_1\tau_1}(x, \tau^{i-2}_1, \tau^{i-2}_8)\Big) \cdot \left(1 - \Delta t\,\frac{\partial \gamma(c^{u;i-1}_{1*}(x), c^{u;i-1}_{8*}(x), T_1)}{\partial T_1}\right)^2 - \\
&B^{i-2}_{\tau_1\tau_1}(x, \tau^{i-2}_1, \tau^{i-2}_8) \cdot \Big(2 - \Delta t\,\frac{\partial \gamma(c^{u;i-1}_{1*}(x), c^{u;i-1}_{8*}(x), T_1)}{\partial T_1} - \Delta t\,\frac{\partial \gamma(c^{u;i-2}_{1*}(x), c^{u;i-2}_{8*}(x), T_1)}{\partial T_1}\Big) \cdot \\
&\Delta t\,\Big(\frac{\partial \gamma(c^{u;i-1}_{1*}(x), c^{u;i-1}_{8*}(x), T_1)}{\partial T_1} - \frac{\partial \gamma(c^{u;i-2}_{1*}(x), c^{u;i-2}_{8*}(x), T_1)}{\partial T_1}\Big) - \\
&\Delta t\,\Big(B^{i-1}_{\tau_1}(x, \tau^{i-1}_1, \tau^{i-1}_8) - B^{i-2}_{\tau_1}(x, \tau^{i-2}_1, \tau^{i-2}_8)\Big) \cdot \frac{\partial^2 \gamma(c^{u;i-1}_{1*}(x), c^{u;i-1}_{8*}(x), T_1)}{\partial T_1^2} - \\
&\Delta t\, B^{i-2}_{\tau_1}(x, \tau^{i-2}_1, \tau^{i-2}_8) \cdot \Big(\frac{\partial^2 \gamma(c^{u;i-2}_{1*}(x), c^{u;i-2}_{8*}(x), T_1)}{\partial T_1^2} - \frac{\partial^2 \gamma(c^{u;i-2}_{1*}(x), c^{u;i-2}_{8*}(x), T_1)}{\partial T_1^2}\Big)
\end{aligned}
\tag{15.171}
$$

The second, the third and the fourth term in (15.171) are of the order of $(\Delta t)^2$ (as $\Delta t \to 0$). Next, taking advantage of the fact that, according to section 15.12, the third order derivatives $B^i_{\tau_1\tau_1\tau_1}(x, \tau_1, \tau_8)$ and $B^i_{\tau_1\tau_1\tau_8}(x, \tau_1, \tau_8)$ are bounded independently of $x \in \overline{\Omega}$ and all $(T_1, T_8) \geq 0$, we obtain:

$B^{i-1}_{\tau_1\tau_1}(x,\tau_1^{i-1},\tau_8^{i-1}) - B^{i-2}_{\tau_1\tau_1}(x,\tau_1^{i-2},\tau_8^{i-2}) =$

$\Big(B^{i-1}_{\tau_1\tau_1}(x,\tau_1^{i-1},\tau_8^{i-1}) - B^{i-2}_{\tau_1\tau_1}(x,\tau_1^{i-1},\tau_8^{i-1})\Big) + \Big(B^{i-2}_{\tau_1\tau_1}(x,\tau_1^{i-1},\tau_8^{i-1}) - B^{i-2}_{\tau_1\tau_1}(x,\tau_1^{i-2},\tau_8^{i-2})\Big) =$

$\Big(B^{i-1}_{\tau_1\tau_1}(x,\tau_1^{i-1},\tau_8^{i-1}) - B^{i-2}_{\tau_1\tau_1}(x,\tau_1^{i-1},\tau_8^{i-1})\Big) +$

$\Big[(\tau_1^{i-1}(x,T_1) - \tau_1^{i-2}(x,T_1)) \int_0^1 (B^{i-1}_{11}(x, T_1 + s(\tau_1^{i-1}(x,T_1) - T_1), T_8 + s(\tau_8^{i-1}(x,T_8) - T_8))\, ds +$

$(\tau_8^{i-1}(x,T_8) - \tau_8^{i-2}(x,T_8)) \int_0^1 (B^{i-1}_{88}(x, T_1 + s(\tau_1^{i-1}(x,T_1) - T_1), T_8 + s(\tau_8^{i-1}(x,T_8) - T_8))\, ds\Big]$

Using (15.171), we obtain by means of the maximum principle that for some constant A_{*11}

$$|H^i_{11}| \leq |H^{i-1}_{11}|(1 - A\Delta t)^{-1} + A_{*11}(\Delta t)^2.$$

This recursive relation can be written formally as:

$$Y(i) = \mathcal{A}Y(i-1) + G,$$

where

$$Y(i) = |H^i_{11}|, \quad G = A_{*11}(\Delta t)^2\,,$$

$\mathcal{A}$ is given by (15.132) with $L = (1 - A\Delta t)^{-1}$ and A is defined in (15.30).

Let us note that by taking $i = 1$ in (15.169) and assuming sufficiently smooth initial conditions R^0, c_1^u and c_8^u it is seen that $|H^1_{11}| = O(\Delta t)$. Similarly by considering the equations corresponding to (15.169) for H^1_{18} and H^1_{88}, we conclude that $|H^1_{18}| = O(\Delta t)$ and $|H^1_{88}| = O(\Delta t)$.

Now, by means of the Corollary 3.18 in [12], we have for $m \geq 2$:

$$Y(m) = \mathcal{A}^m Y(1) + (\sum_{r=1}^{m-1} \mathcal{A}^{m-r-1})G.$$

By the previous estimates

$$\mathcal{A}^s < \mathcal{A}^{m-1}, \quad \text{for } m-1 > s \geq 1$$

in the sense of inequalities between the entries. Taking into account that $n = T(\Delta t)^{-1}$, we can thus estimate

$$G\sum_{r=1}^{m-1} \mathcal{A}^{m-r-1} < G\,(m-1)\mathcal{A}^{m-1} < G\,n\,\mathcal{A}^{m-1} = A_{*11}T\Delta t\,\mathcal{A}^{m-1} < A_{*11}T\Delta t\,\mathcal{A}^m,$$

hence for $\Delta t > 0$ sufficiently small and all $i \in \{1,\ldots,n\}$, using Remark after Lemma 15.8,

$$|H^i_{11}| \leq Y(i) \leq 3/2\exp(Ai\Delta t)H^1_{11} + 3/2\,\Delta t\,A_{*11}T\,\exp(Ai\Delta t) \underset{\Delta t\to 0}{\longrightarrow} 3/2\exp(Ai\Delta t)H^1_{11}.$$

In the same way we can show that

$$|H^i_{88}| \leq 3/2\exp(Ai\Delta t)H^1_{88} \underset{\Delta t\to 0}{\longrightarrow} 3/2\exp(Ai\Delta t)H^1_{88}$$

and

$$|H^n_{18}| \leq 3/2\exp(Ai\Delta t)H^1_{18} \underset{\Delta t\to 0}{\longrightarrow} 3/2\exp(Ai\Delta t)H^1_{18}.$$

Assuming that the derivatives B^j_{111} and B^j_{118} are bounded and continuous (independently of $j \in \{1,\ldots,n\}$, we conclude that

$$\left[B_{11}^{i-1}(x;\tau_1^{i-1},\tau_8^{i-1}) - B_{11}^{i-2}(x;\tau_1^{i-2},\tau_8^{i-2})\right] = \left(B_{11}^{i-1}(x;\tau_1^{i-1},\tau_8^{i-1}) - B_{11}^{i-2}(x;\tau_1^{i-1},\tau_8^{i-1})\right) +$$

$$\left[(\tau_1^{i-1}(x,T_1) - \tau_1^{i-2}(x,T_1)) \int_0^1 (B_{111}^{i-1}(x,T_1 + s(\tau_1^{i-1}(x,T_1) - T_1), T_8 + s(\tau_8^{i-1}(x,T_8) - T_8))\, ds + \right.$$

$$\left.(\tau_8^{i-1}(x,T_8) - \tau_8^{i-2}(x,T_8)) \int_0^1 (B_{118}^{i-1}(x,T_1 + s(\tau_1^{i-1}(x,T_1) - T_1), T_8 + s(\tau_8^{i-1}(x,T_8) - T_8))\, ds\right].$$

Taking into account the above estimates, and carrying out a similar analysis for the equation for $H_8'^i$, we can deduce the inequalities:

$$|H'|^i \leq (|H'|^{i-1}(1 + A_{g18}\Delta t) + W_{gH}(\Delta t)^2 + \Delta t\,|Z'^i|)L, \tag{15.172}$$

for some constants A_{g18} and W_{gH} independent of i.

Next, by differentiating Eq.(15.118) and using similar arguments, we conclude that:

$$\left|H_1'^1\right| < h_{g1}^1 \Delta t \quad \text{and} \quad \left|H_8'^1\right| < h_{g8}^1 \Delta t \tag{15.173}$$

hence

$$\max\left\{\left|H_1'^1\right|, \left|H_8'^1\right|\right\} \leq \max\{h_{g1}^1, h_{g8}^1\}\Delta t := \mathcal{H}^1 \Delta t.$$

Now, proceeding, like in section 15.15, either using the scheme of the form (15.131) or the scheme (15.141), we obtain estimates corresponding to the estimates (15.144). Let us use the scheme corresponding to (15.141).

Putting (15.162) into (15.172), we obtain a pair of inequalities:

$$\begin{aligned} |H'|^i &\leq (|H'|^{i-1}(1 + A_{g18}\Delta t + \tilde{r}_3(\Delta t)^2 L) + W_{gH}(\Delta t)^2 + \Delta t\,|Z'^{i-1}|L + \tilde{r}_2(\Delta t)^3 L)L, \\ |Z'^i| &\leq (|Z'^{i-1}| + \tilde{r}_2(\Delta t)^2 + \tilde{r}_3|H'|^{i-1}\Delta t)L. \end{aligned} \tag{15.174}$$

Replacing $|Z^i|$ by $\mathcal{Z}_i$, $|H|^i$ by $\mathcal{H}_i$, we obtain, for $i \in \{2, \ldots, n\}$, as in the case of system (15.140),

$$\begin{aligned} \mathcal{Z}_i &= (\mathcal{Z}_{i-1} + a_* d^2 + a\mathcal{H}_{i-1} d)L. \\ \mathcal{H}_i &= (\mathcal{H}_{i-1}(1 + bd + ad^2 L) + a_*(\Delta t)^2 + d\,\mathcal{Z}_{i-1}L + a_* d^3 L)L, \end{aligned} \tag{15.175}$$

where we denoted $d = \Delta t$, with the obvious identification of the constants a_*, a, b, which are in general different than the corresponding constants for system (15.140), but have been denoted similarly for simplicity. As above, L is given by (15.163). This recursive system of equations can be written in the following matrix form

$$\mathcal{Y}(i) = \mathcal{A}\mathcal{Y}(i-1) + G, \tag{15.176}$$

where

$$\mathcal{Y}(i) = \begin{pmatrix} \mathcal{Z}_i \\ \mathcal{H}_i \end{pmatrix}$$

and

$$\mathcal{Y}(1) \leq \begin{pmatrix} G_Z^1 \\ \mathcal{H}^1 \end{pmatrix} \Delta t.$$

The matrix $\mathcal{A}$ has formally the form given by (15.132), whereas G the form given by (15.142). Repeating the analysis of system (15.140), we can show the validity of the lemma below.

Lemma 15.20. *The following estimates hold:*

$$\|\nabla Z^i\| < G_Z\,\Delta t,\ \ \|\nabla H_1^i\| < G_{H1}\,\Delta t \text{ and } \|\nabla H_8^i\| < G_{H8}\,\Delta t \tag{15.177}$$

for some constants G_Z, G_{H1} and G_{H8} independent of i.

15.19 Estimates of $C_x^{2+\beta}$ norms of the functions R^i

By means of the above results, we can now derive an 'a priori' $C^{2+\beta}$ estimate of the functions R^i. As in section 15.16, this will be done by rewriting the equation (15.5) in the form

$$d_R\nabla^2 R^i + F_0((i-1)\Delta t, x)\cdot\nabla R^i -$$
$$\left\{R^i\left[\frac{\partial}{\partial T_1}\left(\gamma(c_{1*}^{u;i-1}, c_{8*}^{u;i-1}, T_1)\right) + \frac{\partial}{\partial T_8}\left(\delta(c_{8*}^{u;i-1}, T_8)\right) + F_1((i-1)\Delta t, x, T_1, T_8)\right] + W^i\right\} = 0. \tag{15.178}$$

with

$$W^i := \frac{1}{\Delta t}\left(R^i(x,T_1,T_8) - R^{i-1}(x;\tau_1^{i-1},\tau_8^{i-1})\right) =$$
$$\frac{1}{\Delta t}\left([R^i(x,T_1,T_8) - R^{i-1}(x,T_1,T_8)] + [R^{i-1}(x,T_1,T_8) - R^{i-1}(x;\tau_1^{i-1},\tau_8^{i-1})]\right) =$$
$$\frac{1}{\Delta t}\left(Z^i(x,T_1,T_8) + [R^{i-1}(x,T_1,T_8) - R^{i-1}(x;\tau_1^{i-1},\tau_8^{i-1})]\right) =$$
$$\frac{Z^i}{\Delta t} + \frac{1}{\Delta t}\Big(- B_1^{i-1}(x,T_1,T_8)\cdot\gamma^{i-1}(x,T_1)\Delta t - B_8^{i-1}(x,T_1,T_8)\cdot\delta^{i-1}(x,T_8)\Delta t -$$
$$\textstyle\sum_{k,l=1,8}(1-\theta)B_{kl}^{i-1}(x,\tau_1^{i-1}\theta(x,T_1),\tau_8^{i-1}\theta(x,T_1))(\tau_k^{i-1}-T_k)\cdot(\tau_l^{i-1}-T_l)\Big)$$

(see (15.108)). By (15.177), $\|\nabla Z^i\|/\Delta t < G_Z$, $\|\nabla H_1^i\|/\Delta t < G_{H1}$ and $\|\nabla H_8^i\|/\Delta t < G_{H8}$ (uniformly with respect to i), thus combining it with the results of sections 15.8 and 15.11, we conclude that the expression in the curly brackets has its $C^{1,0}$ norm of the order of $O(1)$. It follows from Lemma 14.5, by taking $l = 3$ and the integration power p sufficiently large that

$$\|R^i\|_{W_p^3} \le C_{3p}$$

where the constants C_{3p} are uniformly bounded for all p. By using the Sobolev imbedding theorem, we conclude that for all $\beta \in (0,1)$ there exists a constant $C_{2\beta}$ independent of $i \in \{1,\dots,n\}$ such that

$$\|R^i\|_{C^{2+\beta}(\Omega)} \le C_{R2\beta}. \tag{15.179}$$

Having these relations we can use the refined version of the Gagliardo-Nirenberg inequality (see [4]) to obtain higher order estimate for functions Z^i. Let us recall the result proved in [4].

Lemma 15.21. *Assume that the real numbers $s_1, s_2, s \ge 0$, $\theta \in (0,1)$ and $1 \le p_1, p_2, p \le \infty$ satisfy the relations $s = \theta s_1 + (1-\theta)s_2$, $\dfrac{1}{p} = \dfrac{\theta}{p_1} + \dfrac{1-\theta}{p_2}$. Suppose that the following condition* **does not hold***:*

$$\mathcal{P}:\ s_2 \ge 1 \text{ is an integer, } p_2 = 1 \text{ and } s_2 - s_1 \le 1 - \frac{1}{p_1}.$$

Then, for every $\theta \in (0,1)$, there exists a constant C, depending on $s_1, s_2, p_1, p_2, \theta$ and Ω such that

$$\|f\|_{W^{s,p}(\Omega)} \le C\|f\|^{\theta}_{W^{s_1,p_1}(\Omega)}\|f\|^{1-\theta}_{W^{s_2,p_2}(\Omega)}, \quad \forall f \in W^{s_1,p_1}(\Omega)\cap W^{s_2,p_2}(\Omega).$$

Remark The refinement of the above result with respect to the classical formulation of the Gagliardo-Nirenberg inequality consists in the fact that the numbers s_1, s_2 and s may not be integers. □

Let us apply Lemma 15.21 for $f = Z'^i$. Thus, using (15.177) and Eq.(15.178), we conclude that there exists a constant $C_{2'}$ such that, for any $p_3 \in [1, \infty)$,

$$\|Z'^i\|_{W^{2,p_3}} < C_{2'}.$$

(As before, for simplicity, for fixed $k \in \{1, 2, 3\}$, $' := \dfrac{\partial}{\partial x_k}$.)

Thus, we take $s_2 = 2$, $s_1 = 0$, $p_1 = \infty$ and $p_2 = p_3$. Then $s_2 - s_1 \not\leq 1 - \dfrac{1}{p_1} = 1$, hence condition $\mathcal{P}$ does not hold. Taking $\theta \in (0, 1/2)$, we have $s_2 = 2(1-\theta) > 1$, $p > p_3$ and

$$\|f\|_{W^{2(1-\theta),p}(\Omega)} \leq C\|f\|^{\theta}_{L^\infty(\Omega)}\|f\|^{1-\theta}_{W^{2,p_3}(\Omega)}.$$

As p_3 is at our disposal, then we can find the smallest p_3 such that that $(2(1-\theta) - \dim(\Omega)/p)/2 = 1/2 - \theta$. For example taking $\theta = 2/7$ and $p_3 > 7dim(\Omega)$, we obtain $2(1-\theta) - dim(\Omega)/p > 9/7$, hence we conclude that

$$\|Z'^i\|_{C^{9/7}} < C(\Delta t)^{2/7}, \tag{15.180}$$

which results in the estimate

$$\|Z^i\|_{C^{2+2/7}} < C(\Delta t)^{2/7}. \tag{15.181}$$

Similar reasoning can be applied to the functions $H_1'^i$ and $H_8'^i$. For $m = 1, 8$, we can thus obtain the inequalities of the form:

$$\|H_m'^i\|_{C^{9/7}} < C(\Delta t)^{2/7},$$

and consequently

$$\|H^i_m\|_{C^{2+2/7}} < C(\Delta t)^{2/7}. \tag{15.182}$$

15.20 Estimate of differences $Z^i - Z^{i-1}$

Note that Eq.(15.102) can be written as

$$\begin{aligned}
&d_R\nabla^2\left(Z^i(x, T_1, T_8) - Z^{i-1}(x, T_1, T_8)\right) - \frac{Z^i(x; T_1, T_8) - Z^{i-1}(x, T_1, T_8)}{\Delta t} - \\
&\frac{Z_*^{i-1}(x, T_1, T_8)}{\Delta t} - \left\{Z^i\left[\frac{\partial}{\partial T_1}\left(\gamma(c^{u;i-1}_{1*}, c^{u;i-1}_{8*}, T_1)\right) + \frac{\partial}{\partial T_8}\left(\delta(c^{u;i-1}_{8*}, T_8)\right) + F_1((i-1)\Delta t, x, T_1, T_8)\right]\right\} \\
&+R^{i-1}\Delta V^i + d_R\nabla^2 Z^{i-1}(x, T_1, T_8) + F_0((i-1)\Delta t, x)\cdot\nabla Z^{i-1} = 0
\end{aligned} \tag{15.183}$$

Now, using (15.177) and (15.181), we can use the maximum principle to conclude that

$$\frac{\|Z^i - Z^{i-1}\|_{C^0(\Omega)}}{\Delta t} = \left\|\frac{Z^i}{\Delta t} - \frac{Z^{i-1}}{\Delta t}\right\|_{C^0(\Omega)} \leq C_{diff}(\Delta t)^{2/7}. \tag{15.184}$$

Similarly, differentiating Eq.(15.183) with respect to T_m, $m = 1, 8$, (or rewriting Eq.(15.114) and using (15.177) and (15.182) we obtain by applying the maximum principle the inequalities:

$$\frac{\|H^i_m - H^{i-1}_m\|_{C^0(\Omega)}}{\Delta t} = \left\|\frac{H^i_m}{\Delta t} - \frac{H^{i-1}_m}{\Delta t}\right\|_{C^0(\Omega)} \leq C_{diff}(\Delta t)^{2/7}. \tag{15.185}$$

16 Convergence of the sequences as $\Delta t \to 0$

Let us write Eq.(15.5) in the form:

$$d_R \nabla^2 R^i + F_0(x)\cdot\nabla R^i - \frac{Z^i}{\Delta t} -$$
$$\Big\{ R^i \Big[\frac{\partial}{\partial T_1}\Big(\gamma(c_{1*}^{u;i-1}, c_{8*}^{u;i-1}, T_1)\Big) + \frac{\partial}{\partial T_8}\Big(\delta(c_{8*}^{u;i-1}, T_8)\Big) + F_1((i-1)\Delta t, x, T_1, T_8)\Big] - \widetilde{W}^i \Big\} \;=\; 0, \tag{16.1}$$

where, according to Lemma 15.15,

$$\widetilde{W}^i := \frac{1}{\Delta t}\,[R^{i-1}(x,T_1,T_8) - R^{i-1}(x;\tau_1^{i-1},\tau_8^{i-1})] =$$
$$\frac{1}{\Delta t}\Big(- B_{\tau_1}^{i-1}(x,T_1,T_8)\cdot\gamma^{i-1}(x,T_1)\Delta t - B_{\tau_8}^{i-1}(x,T_1,T_8)\cdot\delta^{i-1}(x,T_8)\Delta t -$$
$$\textstyle\sum_{k,l=1,8}(\tau_k^{i-1} - T_k)\cdot(\tau_l^{i-1} - T_l)\int_0^1 B_{\tau_k\tau_l}^{i-1}\left(x, T_1 + s(\tau_1^{i-1}(x,T_1) - T_1), T_8 + s(\tau_8^{i-1}(x,T_8) - T_8)\right)(1-s)ds\Big)$$
$$= -B_1^{i-1}(x,T_1,T_8)\cdot\gamma^{i-1}(x,T_1)\Delta t - B_8^{i-1}(x,T_1,T_8)\cdot\delta^{i-1}(x,T_8) + O(\Delta t).$$

For given $n \geq 1$, $\Delta t = Tn^{-1} > 0$ and the set of points $\{t_{i_t} := i_t\Delta t\}_{i_t=1}^{i_t=n}$, let us define the function

$$\mathcal{R}^n(t,x,T_1,T_8) := R^{i_t-1}(x,T_1,T_8) +$$
$$(\Delta t)^{-1}(t - t_{i_t-1})\Big(R^{i_t}(x,T_1,T_8) - R^{i_t-1}(x,T_1,T_8)\Big) \quad \text{for } t_{i_t-1} \leq t < t_{i_t}. \tag{16.2}$$

Below, we will analyse in sequence, the result of action of different operators of the left hand side of Eq.(15.5) on the function $\mathcal{R}^n$. For $t_{i_t-1} \leq t \leq t_{i_t}$, we thus have:

$$\Delta\mathcal{R}^n(t,x,T_1,T_8) = \Delta R^{i_t-1}(x,T_1,T_8) + (t - t_{i_t-1})\Big(\Delta R^{i_t}(x,T_1,T_8) - \Delta R^{i_t-1}(x,T_1,T_8)\Big)\cdot(\Delta t)^{-1}, \tag{16.3}$$

and, according to (15.181),

$$\|\Delta R^{i_t}(\cdot,T_1,T_8) - \Delta R^{i_t-1}(\cdot,T_1,T_8)\|_{C_x^{2/7}} \leq C_\Delta(\Delta t)^{2/7}, \tag{16.4}$$

uniformly in (T_1,T_8). Then, by definition (16.2), for $t \in [t_{i-1}, t_i]$,

$$\frac{\partial\mathcal{R}^n}{\partial t} = (\Delta t)^{-1}\Big(R^{i_t}(x,T_1,T_8) - R^{i_t-1}(x,T_1,T_8)\Big).$$

This function is constant on each interval $t \in [t_{i-1}, t_i]$ and, according to (15.181), the difference between these values is of the order of $O(\Delta t)$. Next, for $t \in [t_{i-1}, t_i]$

$$
\begin{aligned}
&\frac{\partial}{\partial T_1}\left(\gamma(c_1^u(t,x),c_8^u(t,x),T_1)\,\mathcal{R}^n\right)+\frac{\partial}{\partial T_8}\left(\delta(c_8^u(t,x),T_8)\,\mathcal{R}^n\right)=\\
&\mathcal{R}^n\cdot\frac{\partial}{\partial T_1}\gamma(c_1^u(t,x),c_8^u(t,x),T_1)+\mathcal{R}^n\cdot\frac{\partial}{\partial T_8}\delta(c_8^u(t,x),T_8)+\\
&+\gamma(c_1^u(t,x),c_8^u(t,x),T_1)\cdot\frac{\partial}{\partial T_1}\mathcal{R}^n(t,x,T_1,T_8)+\delta(c_8^u(t,x),T_8)\cdot\frac{\partial}{\partial T_8}\mathcal{R}^n(t,x,T_1,T_8)=\\
&\Big[\mathcal{R}^n\cdot\frac{\partial}{\partial T_1}\Big(\gamma(c_1^u(t,x),c_8^u(t,x),T_1)-\gamma(c_{1*}^{u;i-1}(x),c_{8*}^{u;i-1}(x),T_1)\Big)\\
&+\mathcal{R}^n\cdot\frac{\partial}{\partial T_8}\Big(\delta(c_8^u(t,x),T_8)-\delta(c_{8*}^{u;i-1}(x),T_8)\Big)+\\
&\frac{\partial}{\partial T_1}\mathcal{R}^n(t,x,T_1,T_8)\Big(\gamma(c_1^u(t,x),c_8^u(t,x),T_1)-\gamma(c_{1*}^{u;i-1}(x),c_{8*}^{u;i-1}(x),T_1)\Big)+\\
&\frac{\partial}{\partial T_8}\mathcal{R}^n(t,x,T_1,T_8)\Big(\delta(c_8^u(t,x),T_8)-\delta(c_{8*}^{u;i-1}(x),T_8)\Big)\Big]+\\
&\Big\{\mathcal{R}^n\cdot\frac{\partial}{\partial T_1}\gamma(c_{1*}^{u;i-1}(x),c_{8*}^{u;i-1}(x),T_1)+\mathcal{R}^n\cdot\frac{\partial}{\partial T_8}\delta(c_{8*}^{u;i-1}(x),T_8)\Big\}_1+\\
&\Big\{\gamma(c_{1*}^{u;i-1}(x),c_{8*}^{u;i-1}(x),T_1)\cdot\frac{\partial}{\partial T_1}\mathcal{R}^n(t,x,T_1,T_8)+\delta(c_{8*}^{u;i-1}(x),T_8)\cdot\frac{\partial}{\partial T_8}\mathcal{R}^n(t,x,T_1,T_8)\Big\}_2
\end{aligned}
\tag{16.5}
$$

where $c_1^u(t,x)$ and $c_8^u(t,x)$ are defined by (15.45). Due to Lemma 15.19 (inequalities (15.151)), (15.152), together with the boundedness of the function $\mathcal{R}^n$ (implied by the boundedness of R^m, $m\in\{1,\dots,n\}$) and the boundedness of the functions B_1^m, B_8^m, it is seen that the expression in the square bracket $[\cdot]$ above is of the order of $\Delta t\,O(1)$ as $\Delta t\to 0$.

By (16.2), the first term in the curly bracket $\{\cdot\}_1$ equals:

$$
\Big(R^{i_t-1}(x,T_1,T_8)+(\Delta t)^{-1}(t-t_{i_t-1})\left(R^{i_t}(x,T_1,T_8)-R^{i_t-1}(x,T_1,T_8)\right)\Big)\cdot\frac{\partial}{\partial T_1}\gamma(c_{1*}^{u;i-1}(x),c_{8*}^{u;i-1}(x),T_1)
$$

$$
=R^{i_t-1}(x,T_1,T_8)\cdot\frac{\partial}{\partial T_1}\gamma(c_{1*}^{u;i-1}(x),c_{8*}^{u;i-1}(x),T_1)+O(1)\Delta t,
$$

where the last estimate is obtained via the boundedness of of the derivative of γ (see Lemma 15.7) and inequalities (15.144). Likewise,

$$
\mathcal{R}^n\cdot\frac{\partial}{\partial T_8}\delta(c_{8*}^{u;i-1}(x),T_8)=R^{i_t-1}(x,T_1,T_8)\cdot\frac{\partial}{\partial T_1}\delta(c_{8*}^{u;i-1}(x),T_1)+O(1)\Delta t,
$$

Similarly, the expression in the bracket $\{\cdot\}_2$ equals

$$
\begin{aligned}
&\frac{1}{\Delta t}\cdot\Big(\Delta t\cdot\gamma(c_1^u(t,x),c_8^u(t,x),T_1)\cdot\frac{\partial}{\partial T_1}\mathcal{R}^n(t,x,T_1,T_8)+\Delta t\cdot\delta(c_8^u(t,x),T_8)\cdot\frac{\partial}{\partial T_8}\mathcal{R}^n(t,x,T_1,T_8)\Big)=\\
&\frac{1}{\Delta t}\cdot\Big(\Delta t\cdot\Big(\gamma(c_1^u(t,x),c_8^u(t,x),T_1)-\gamma(c_{1*}^{u;i-1},c_{8*}^{u;i-1},T_1)\Big)\cdot\frac{\partial}{\partial T_1}\mathcal{R}^n(t,x,T_1,T_8)+\\
&\Delta t\cdot\Big(\delta(c_8^u(t,x),T_8)-\delta(c_{8*}^{u;i-1},T_8)\Big)\cdot\frac{\partial}{\partial T_8}\mathcal{R}^n(t,x,T_1,T_8)\Big)+\\
&\frac{1}{\Delta t}\cdot\Big(\Delta t\cdot\gamma(c_{1*}^{u;i-1},c_{8*}^{u;i-1},T_1)\cdot\frac{\partial}{\partial T_1}\mathcal{R}^n(t,x,T_1,T_8)+\Delta t\cdot\delta(c_{8*}^{u;i-1},T_8)\cdot\frac{\partial}{\partial T_8}\mathcal{R}^n(t,x,T_1,T_8)\Big)=\\
&-\frac{1}{\Delta t}\cdot\Big(\mathcal{R}^n(t,x,T_1-\Delta t\cdot\gamma,T_8-\Delta t\cdot\delta)-\mathcal{R}^n(t,x,T_1,T_8)+(\Delta t)^2\,O(1)\Big),
\end{aligned}
$$

what follows from inequality (15.151) together with the boundedness of the derivatives of the function $\mathcal{R}^n$ with respect to T_1 and T_8 (implied by the boundedness of the functions B_1^m, B_8^m).

Now, using the definition (16.2), for $t\in[t_{i-1},t_i]$, denotations (15.105) and (15.106)), and the results of section 15.15 (see (15.144)), we have:

$$\begin{aligned}
&\frac{1}{\Delta t}\Big(\mathcal{R}^n(t,x,T_1-\Delta t\cdot\gamma,T_8-\Delta t\cdot\delta)-\mathcal{R}^n(t,x,T_1,T_8)\Big)=\\
&\frac{1}{\Delta t}\Big\{R^{i-1}(t,x,T_1-\Delta t\cdot\gamma^{i-1},T_8-\Delta t\cdot\delta^{i-1})-R^{i-1}(t,x,T_1,T_8)+\\
&(\Delta t)^{-1}(t-t_{i_t-1})\Big(\Big[R^i(t,x,T_1-\Delta t\cdot\gamma^i,T_8-\Delta t\cdot\delta^i)-R^i(t,x,T_1,T_8)\Big]-\\
&\qquad\Big[R^{i-1}(t,x,T_1-\Delta t\cdot\gamma^{i-1},T_8-\Delta t\cdot\delta^{i-1})-R^{i-1}(t,x,T_1,T_8)\Big]\Big)\Big\}
\end{aligned}\tag{16.6}$$

Now, according to (15.109), the absolute value of the expression

$$\Big[R^i(t,x,T_1-\Delta t\cdot\gamma^i,T_8-\Delta t\cdot\delta^i)-R^i(t,x,T_1,T_8)\Big]-\Big[R^{i-1}(t,x,T_1-\Delta t\cdot\gamma^{i-1},T_8-\Delta t\cdot\delta^{i-1})-R^{i-1}(t,x,T_1,T_8)\Big]$$

is bounded from above by $\Big(|H_1^{i-1}|\overline{\gamma}+|H_8^{i-1}|\overline{\delta}\Big)\Delta t+r_1(\Delta t)^2$ for some constant r_1 independent of i, hence by Lemma 15.18 is of the order of $O((\Delta t)^2)$. It follows that

$$\begin{aligned}
&\frac{1}{\Delta t}\Big(\mathcal{R}^n(t,x,T_1-\Delta t\cdot\gamma,T_8-\Delta t\cdot\delta)-\mathcal{R}^n(t,x,T_1,T_8)\Big)=\\
&\frac{1}{\Delta t}\Big\{R^{i-1}(t,x,T_1-\Delta t\cdot\gamma^{i-1},T_8-\Delta t\cdot\delta^{i-1})-R^{i-1}(t,x,T_1,T_8)\Big\}+O(\Delta t).
\end{aligned}$$

Finally, for $t\in[t_{i-1},t_i]$, we have:

$$\begin{aligned}
&F_0(x)\cdot\nabla\mathcal{R}^n(t,x,T_1,T_8)=\\
&F_0(x)\cdot\nabla R^{i_t}(x,T_1,T_8)+[(t-t_{i_t-1})\cdot(\Delta t)^{-1}-1]\,F_0(x)\cdot\Big(\nabla R^{i_t}(x,T_1,T_8)-\nabla R^{i_t-1}(x,T_1,T_8)\Big)=\\
&F_0(x)\cdot\nabla R^{i_t}(x,T_1,T_8)+\Big[(t-t_{i_t-1})\cdot(\Delta t)^{-1}-1\Big]\,F_0(x)\cdot\Big(\nabla Z^i(x,T_1,T_8)\Big).
\end{aligned}\tag{16.7}$$

By (15.177) the last term vanishes as fast as Δt for $\Delta t\to 0$. It thus follows that for $t\in[t_{i-1},t_i]$ we can write

$$\begin{aligned}
&d_R\nabla^2\mathcal{R}^n-\frac{\partial\mathcal{R}^n}{\partial t}-\frac{\partial}{\partial T_1}\left(\gamma(c_{1*}^{u;i-1},c_{8*}^{u;i-1},T_1)\,\mathcal{R}^n\right)-\frac{\partial}{\partial T_8}\left(\delta(c_{8*}^{u;i-1},T_8)\,\mathcal{R}^n\right)+\\
&F_0(x)\cdot\nabla\mathcal{R}^n-F_1((i-1)\Delta t,x,T_1,T_8)\,\mathcal{R}^n=\\
&d_R\nabla^2R^i-\Big\{R^i\left[\frac{\partial}{\partial T_1}\left(\gamma(c_{1*}^{u;i-1},c_{8*}^{u;i-1},T_1)\right)+\frac{\partial}{\partial T_8}\left(\delta(c_{8*}^{u;i-1},T_8)\right)+F_1((i-1)\Delta t,x,T_1,T_8)+\frac{1}{\Delta t}\right]\Big\}+\\
&\frac{R^{i-1}(x;\tau_1^{i-1},\tau_8^{i-1})}{\Delta t}+F_0(x)\cdot\nabla R^i+(\Delta t)^{2/7}O(1)=0+(\Delta t)^{2/7}O(1).
\end{aligned}$$

Let us consider the convergence properties of the sequence $\mathcal{R}^n$. We will use the Arzela-Ascoli lemma in the spaces $W_q^{2,1}(M_T)$, $M_T=\Omega\times(0,T)\times\mathcal{A}_{TT}$, where $\mathcal{A}_{TT}$ is any open simply connected set with a smooth boundary comprising the support of the functions R^i for all $i\in\{1,\ldots,n\}$ with the norm defined by

$$\|u\|_{q,Q_T}^{(2)}=\sum_{j=0}^{2}<<u>>_{q,Q_T}^{(j)}$$

where (cf. (1.3),(1.4) in I.1 of [23])

$$<< u >>^{(0)}_{q,Q_T} = \|u\|_{q,Q_T}, \quad << u >>^{(1)}_{q,Q_T} = \sum_{k=1,2,3} \Big\| \frac{\partial u}{\partial x_k} \Big\|_{q,Q_T} + \sum_{l=1,8} \Big\| \frac{\partial u}{\partial T_l} \Big\|_{q,Q_T},$$

$$<< u >>^{(2)}_{q,Q_T} = \sum_{k,s=1,2,3} \Big\| \frac{\partial^2 u}{\partial x_k \partial x_s} \Big\|_{q,Q_T} + \sum_{l,m=1,8} \Big\| \frac{\partial^2 u}{\partial T_l \partial T_m} \Big\|_{q,Q_T} + \Big\| \frac{\partial u}{\partial t} \Big\|_{q,Q_T},$$

and

$$\|f\|_{q,Q_T} = \Big(\int_0^T \Big(\int_{\Omega \times \mathcal{A}_{TT}} |f(t,x,T_1,T_8)|^q \, dx dT_1 dT_8 \Big) dt \Big)^{1/q}.$$

According to the estimates derived in the previous sections, for each $n \in \mathbb{N}$, the norm of the functions $\mathcal{R}^n$ have their $W^{2,1}_{q,Q_T}$ uniformly bounded for any arbitrarily large $q > 0$. As it follows from the Corollary after Theorem 9.1 of section IV.9 (which is based on Lemma 3.3 of chapter II) in [23], for all $n \in \mathbb{N}$, the functions $\mathcal{R}^n$ satisfy the norm inequality

$$\|\mathcal{R}^n\|^{(2-\Upsilon)} \leq C_\Omega \|\mathcal{R}^n\|^{(2)}_{q,Q_T}, \quad \Upsilon = \frac{dim(\Omega \times A_{TT}) + 2}{q},$$

for some constant C_Ω, where $\| \cdot \|^\chi$ denotes the Hölder norm $\| \cdot \|^{\chi/2,\chi}_{t,x}$. It follows that the functions $\mathcal{R}^n$ are uniformly bounded in the $C^{\tilde{\mu}(q)/2,\tilde{\mu}(q)}_{t,(x,T_1,T_8)}$ norm, with $\tilde{\mu}(q)$ satisfying the inequality

$$\tilde{\mu}(q) < 2 - \frac{dim(\Omega \times \mathcal{A}_{TT})}{q} = 2 - \frac{7}{q},$$

hence $\tilde{\mu}(q) > 1 + \beta$, for any $\beta \in (0,1)$ if q is sufficiently large. Now, by the Arzela-Ascoli lemma, from the sequence $\{\mathcal{R}^n\}_{n=1}^\infty$, we can choose a subsequence converging to a function $\mathcal{R} \in C^{\mu/2,\mu,1+\mu}_{t,x,(T_1,T_8)}([0,T] \times \overline{\Omega} \times \overline{\mathbb{R}^2_+})$ for any $\mu < \tilde{\mu}(q)$ (cf. section 15.12). Simultaneously, as $n \to \infty$, then the functions c^u_1 and c^u_8 tend along the appropriate subsequence (being, in general, a subsequence of the subsequence along which $\{\mathcal{R}^n\}_{n=1}^\infty$ converges), to some functions c^u_{1D} and c^u_{8D} belonging to the space $C^{(1+\beta)/2,1+\beta}_{t,x}([0,T] \times \overline{\Omega})$ for any $\beta \in (0,1)$. Now, for fixed (T_1,T_8) and for every $n < \infty$, we can multiply the equation satisfied by $\mathcal{R}^n$ by a smooth test function $\phi^*(t,x)$, integrate by parts and consider it as an equation for weak solutions $\mathcal{R}^n$ as a function of (t,x). By passing to the limit $\Delta t \to 0$, we conclude that $\mathcal{R}$ is a weak solution to the equation:

$$\frac{\partial \mathcal{R}}{\partial t} = d_R \nabla^2 \mathcal{R} + f(t,x,(T_1,T_8)) \tag{16.8}$$

where

$$f(t,x,(T_1,T_8)) = F_0(x) \cdot \nabla \mathcal{R} +$$

$$\Big(- \frac{\partial}{\partial T_1} \left(\gamma(c^u_{1D}(t,x), c^u_{8D}(t,x), T_1) \, \mathcal{R} \right) - \frac{\partial}{\partial T_8} \left(\delta(c^u_{8D}(t,x), T_8) \, \mathcal{R} \right) - F_1(t,x,T_1,T_8) \, \mathcal{R} \Big) \in C^{\mu/2,\mu}_{t,x}$$

with (T_1,T_8) treated as parameters. Let us note that given the function $f(t,x)$, Eq.(16.8), supplemented with the homogeneous Neumann boundary conditions and $C^{4,4}_{x,(T_1,T_8)}$ initial conditions (as it was supposed in Assumption 15.4) has a solution with finite $C^{1+\mu/2,2+\mu,2+\mu}_{t,x,(T_1,T_8)}$ norm. This solution is unique. For, suppose that it is not true, and that, for fixed (T_1,T_8), there exists another solution $\mathcal{P}$ to this equation (with the same boundary and initial conditions). By subtracting, multiplying by $\mathcal{D} = \mathcal{R} - \mathcal{P}$ and integrating by parts it is seen that $\mathcal{D}$ satisfies the equation

$$\frac{1}{2} \frac{\partial}{\partial t} \int_\Omega \mathcal{D}^2(t,x,T_1,T_8) dx = -d_R \int_\Omega |\nabla \mathcal{D}(t,x,T_1,T_8)|^2 dx.$$

As $\mathcal{D}(0,x,T_1,T_8) \equiv 0$, we conclude that $\mathcal{D}(t,x,T_1,T_8) \equiv 0$.

We are thus in a position to formulate the summarizing theorem of Part III.

Theorem 16.1. *The triple $(\mathcal{R}, c^u_{1D}, c^u_{8D})$ satisfies system (15.2)-(15.4). The function $\mathcal{R} \in C^{1+\mu/2,2+\mu}_{t,(x,T_1,T_8)}((0,T)\times \overline{\Omega} \times \overline{\mathbb{R}^2_+})$, whereas the functions c^u_{1D}, $c^u_{8D} \in C^{1+\mu/2,2+\mu}_{t,x}((0,T)\times\Omega)\cap C(([0,T]\times\overline{\Omega})$.*

Proof The fact that $\mathcal{R}, c^u_{1D}, c^u_{8D} \in C^{1+\mu/2,2+\mu}_{t,(x,T_1,T_8)}((0,T)\times\overline{\Omega}\times\overline{\mathbb{R}^2_+})$ has been shown above. We also showed that these functions satisfy Eq. (15.5). We will prove that they satisfy Eqs (15.6)-(15.7). Let us consider the second equation in system (15.5)-(15.7). For $t\in[(i-1)\Delta t, i\Delta t)$ it can be written in the form

$$\frac{\partial c_1^{u;i}}{\partial t} = \nabla^2 c_1^{u;i} + \widetilde{\nu}\int_0^\infty\int_0^\infty c_{8*}^{8;i-1}\,\mathcal{R}^n\,dT_1\,dT_8 - c_1^{u;i} - \widetilde{\nu}\int_0^\infty\int_0^\infty c_{8*}^{8;i-1}\,\delta_{Rni}\,dT_1\,dT_8 \tag{16.9}$$

where $\delta_{Rni} = (\Delta t)^{-1}(t-t_{i_t-1})\Big(R^{i_t}(x,T_1,T_8) - R^{i_t-1}(x,T_1,T_8)\Big)$. As, independently of t and $\Delta t = Tn^{-1}$, $(\Delta t)^{-1}(t-t_{i_t-1})\le 1$, then using Lemmata 15.18 and 15.20, we conclude that for each (T_1,T_8),

$$\lim_{n\to\infty}\|\delta_{Rni}(\cdot,\cdot,(T_1,T_8))\|_{C^{0,\mu}_{t,x}} = 0.$$

By using the functions defined by (15.45), for fixed n, the set of equations (16.9) can be written as the equation

$$\frac{\partial c_1^u}{\partial t} = \nabla^2 c_1^u + \widetilde{\nu}\int_0^\infty\int_0^\infty c_{8*}^8(c_u^8,T_8)\,\mathcal{R}^n\,dT_1\,dT_8 - c_1^{u;i} - \widetilde{\nu}\int_0^\infty\int_0^\infty c_{8*}^8(c_u^8,T_8)\,\delta_{Rni}\,dT_1\,dT_8. \tag{16.10}$$

In fact, we should consider c_1^u as a weak solution to Eq.(16.10). Let us note that $\int_0^\infty\int_0^\infty c_{8*}^8(c_u^8,T_8)\,\mathcal{R}^n\,dT_1\,dT_8$ is a continuous function of (t,x), whereas the function $\int_0^\infty\int_0^\infty c_{8*}^8(c_u^8,T_8)\,\delta_{Rni}\,dT_1\,dT_8$ is of L^∞ class. It follows from Theorem 15.11 that the functions c_1^u and c_8^u have finite $C^{(1+\beta)/2,1+\beta}_{t,x}$ norm for all $\beta\in(0,1)$. Thus by considering a subsequence of $\{n\}_1^\infty$, for which all the considered sequences of functions converge, we conclude that c^u_{1D}, c^u_{8D} are of the class $C^{(1+\tilde\beta)/2,1+\tilde\beta}_{t,x}$, with $\tilde\beta\in(0,1)$ and, in fact, are weak solutions to the equation on $(0,T)\times\Omega$

$$\frac{\partial c^u_{1D}}{\partial t} = \nabla^2 c^u_{1D} - c^u_{1D} + f(t,x),T_1,T_8), \tag{16.11}$$

where

$$f(t,x) = \widetilde{\nu}\int_0^\infty\int_0^\infty c^8_{8D}\,\mathcal{R}\,dT_1\,dT_8$$

and $c^8_{8D}(t,x,T_8) = c^u_{8D}\;T_8\,(1+c^u_{8D})^{-1}$. As $f(t,x)\in C^{(1+\beta)/2,1+\beta}_{t,x}$ then using, e.g. [23, Theorem 5.3, chapter IV], we conclude that there exists a solution to Eq. 16.11, with the homogeneous Neumann boundary conditions and initial conditions in $C^4(\overline{\Omega})$ class as supposed in Assumption 15.4, has a solution in $C^{1+\beta/2,2+\beta}_{t,x}([0,T]\times\overline{\Omega})$ class. As $f(t,x)$ is fixed, then the solution is unique, what can be shown as in the case of the equation for $\mathcal{R}$. The third equation in system (15.5)-(15.7) can be considered in the similar way. □

17 Conclusions

In the dissertation, we used two different approaches to study the initial boundary value problems connected with system (1.11)-(1.13). In Part II, we considered scalar linear equations with the form of their differential part similar to that of Eq. (1.11), and despite its mixed parabolic-hyperbolic structure, we managed to construct explicit solutions in the homogeneous and inhomogeneous cases. Besides to the construction of solutions, an important result of this part presented in Lemma 9.5 (see also Lemma 11.1), states that, in a sense, these solutions can be treated as a limit of solutions with added diffusional terms with respect to the auxiliary variables T_1 and T_8. This result seems to be particularly significant in designing the method of numerical analysis of the model. In Part III we applied a modification of the Rothe method and proved the existence of solution to a simplified version of system (1.11)-(1.13) in the limit of the size of the step interval $\Delta t \to 0$. To obtain a priori estimates, necessary for the proof of convergence of the family of solutions, we use the maximum principle for elliptic equations. In derivation of these estimates we extensively took advantage of the celebrated paper [1]. It seems that this method can be used to general classes of similar systems. Its applicability depends on appropriate behaviour of characteristics to the hyperbolic part of the equation of the mixed type. In particular, we assumed that the projections of the characteristics onto the (T_1, T_8)-plane enter its positive quarter in the course of time.

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A Appendix A – Laplace operator in $\mathbb{R}^m$ in local coordinates connected with an $(n-1)$ dimensional hypersurface

Consider a hypersurface $S = \{(x_1, x_2, \ldots, x_n) : x_1 - \omega(x_2, \ldots, x_n) = 0\}$ defined in the vicinity of the point $\mathbf{x}_0 \in S$. Assume that the hyperplane $x_1 = 0$ is tangent to the hypersuface S at the point $\mathbf{x}_0$. It follows that

$$\frac{\partial \omega}{\partial x_i}(\mathbf{x}_0) = 0, \quad i = 2, \ldots, n. \tag{A.1}$$

Let

$$\xi = x_1 - \omega(x_2, \ldots, x_n) \quad \eta_i = x_i \quad \text{for } i = 2, \ldots, n. \tag{A.2}$$

Let us derive the expression for the Laplace operator Δ in the variables $(\xi, \eta_1, \ldots, \eta_n)$ at the point $\mathbf{x} = \mathbf{x_0}$.

Lemma A.1. *Suppose that (A.1) and (A.2) hold. Then at $x = x_0$:*

$$\Delta_{\xi,\eta_1,\ldots,\eta_n} = \Big(\frac{\partial^2}{\partial \xi^2} + \sum_{i=2,\ldots,n}^{n} \frac{\partial^2}{\partial \eta_i^2}\Big) + \sum_{i=2,\ldots,n}^{n} \kappa_k(\mathbf{x}_0)\frac{\partial}{\partial \xi}$$

where $\kappa_k(\mathbf{x}_0) := -\dfrac{\partial^2 \omega}{\partial x_k^2}(\mathbf{x}_0)$, $\quad k = 2, \ldots, n$ are the principal curvatures of the surface S at $\mathbf{x} = \mathbf{x}_0$.

We have:

$$\frac{\partial}{\partial x_1} = \frac{\partial \xi}{\partial x_1}\frac{\partial}{\partial \xi} + \sum_{i=2}^{n} \frac{\partial \eta_i}{\partial x_1}\frac{\partial}{\partial \eta_i}.$$

and

$$\frac{\partial}{\partial x_k} = \frac{\partial \xi}{\partial x_k}\frac{\partial}{\partial \xi} + \sum_{i=2}^{n} \frac{\partial \eta_i}{\partial x_k}\frac{\partial}{\partial \eta_i}.$$

It follows that

$$\frac{\partial^2}{\partial x_1^2} = \frac{\partial \xi}{\partial x_1}\frac{\partial}{\partial \xi}\Big(\frac{\partial \xi}{\partial x_1}\frac{\partial}{\partial \xi} + \sum_{i=2}^{n} \frac{\partial \eta_i}{\partial x_1}\frac{\partial}{\partial \eta_i}\Big) + \sum_{i=2}^{n} \frac{\partial \eta_i}{\partial x_1}\frac{\partial}{\partial \eta_i}\Big(\frac{\partial \xi}{\partial x_1}\frac{\partial}{\partial \xi} + \sum_{j=2}^{n} \frac{\partial \eta_j}{\partial x_1}\frac{\partial}{\partial \eta_j}\Big)$$

and

$$\frac{\partial^2}{\partial x_k^2} = \frac{\partial \xi}{\partial x_k}\frac{\partial}{\partial \xi}\Big(\frac{\partial \xi}{\partial x_k}\frac{\partial}{\partial \xi} + \sum_{i=2}^{n} \frac{\partial \eta_i}{\partial x_k}\frac{\partial}{\partial \eta_i}\Big) + \sum_{i=2}^{n} \frac{\partial \eta_i}{\partial x_k}\frac{\partial}{\partial \eta_i}\Big(\frac{\partial \xi}{\partial x_k}\frac{\partial}{\partial \xi} + \sum_{j=2}^{n} \frac{\partial \eta_j}{\partial x_k}\frac{\partial}{\partial \eta_j}\Big)$$

Due to (A.2) we have in some vicinity of $\mathbf{x}_0$:

$$\frac{\partial \xi}{\partial x_1} = 1, \quad \frac{\partial \eta_i}{\partial x_1} = 0, \quad \frac{\partial \eta_i}{\partial x_k} = \delta_{ik}, \quad \text{for } i, k \in \{2, \ldots, n\},$$

and exactly at $\mathbf{x} = \mathbf{x}_0$, for $k = 2, \ldots, n$,

$$\frac{\partial \xi}{\partial x_k} = -\frac{\partial \omega}{\partial x_k} = 0.$$

We thus have at $\mathbf{x}_0$,

$$\frac{\partial^2}{\partial x_1^2} = \frac{\partial^2}{\partial \xi^2}$$

and, for $k = 2, \ldots, n$,

$$\frac{\partial^2}{\partial x_k^2} = \frac{\partial}{\partial \eta_k}\Big(\frac{\partial \xi}{\partial x_k}\frac{\partial}{\partial \xi}\Big) + \frac{\partial^2}{\partial^2 \eta_k} = -\frac{\partial}{\partial x_k}\Big(\frac{\partial \omega}{\partial x_k}\Big)\frac{\partial}{\partial \xi} + \frac{\partial^2}{\partial^2 \eta_k} = -\Big(\frac{\partial^2 \omega}{\partial x_k^2}\Big)\frac{\partial}{\partial \xi} + \frac{\partial^2}{\partial^2 \eta_k}.$$

Thus finally at $\mathbf{x} = \mathbf{x}_0$:

$$\Delta_{\xi,\eta_1,\ldots,\eta_n} \;=\; \Big(\frac{\partial^2}{\partial \xi^2} \;+ \sum_{i=2,\ldots,n}^{n} \frac{\partial^2}{\partial \eta_i^2}\Big) \;+\; \sum_{i=2,\ldots,n}^{n} \kappa_k(\mathbf{x}_0)\frac{\partial}{\partial \xi}$$

where

$$\kappa_k(\mathbf{x}_0) := -\frac{\partial^2 \omega}{\partial x_k^2}(\mathbf{x}_0), \quad k = 2, \ldots, n,$$

can be interpreted as the principal curvatures of the surface S at $\mathbf{x} = \mathbf{x}_0$.

Appendix B

This appendix contains the review of the mathematical models of chondrogenetic processes in vertebrates submitted to the journal of Mathematical Biosciences.

Mathematical modeling of chondrogenic pattern formation during limb development: Recent advances in continuous models

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Abstract

The phenomenon of chondrogenic pattern formation inside the vertebrate limb is one of the best studied examples of organogenesis. Many different models, mathematical as well as conceptual, have been proposed for it in the last fifty years or so. In this review, we give a brief overview of the fundamental biological background, then describe in detail several models which aim to describe qualitatively and quantitatively the corresponding biological phenomena. We concentrate on several new models that have been proposed in recent years, taking into account recent experimental progress. The major mathematical tools in these approaches are ordinary and partial differential equations. In particular, we analyze a subtle and interwoven relation between the positional information postulate and reaction-diffusion convection mechanisms. Moreover, we discuss models with non-local flux terms implied by cell-cell adhesion forces and a structured population model with diffusion. We also include a detailed list of potential morphogens which have been identified to play a role in the process of limb formation and its growth.

1 Introduction

Organogenesis is one of the most intriguing phenomena in biology. The question 'How does an initially homogeneous and indistinguishable set of cells give rise to subgroups of differentiated cells, tissues and whole organs?' is an extremely challenging and complicated modeling problem.

An important example of organogenesis is vertebrate limb development. Models explaining the mechanism of limb formation are based on the experimental study of limb bud outgrowth and shaping as well as on skeleton formation. Conceptually, limb bud outgrowth and its shaping is a different process from skeleton formation [180]. However, limb bud outgrowth and its shaping are dynamically interconnected with the process of skeleton formation [106]: limb bud outgrowth and its shaping influence the formation of skeleton. This can be observed experimentally and confirmed by relatively simple mathematical models based on reaction-diffusion equations, where the associated self-organizing process is influenced by the form of the boundary conditions, as well as the shape and size of the domain [15, 181, 182, 183]. Physical properties of the respective tissues [63] also influence the mathematical and computational modeling of limb outgrowth and its shaping. Basically limb bud mesenchymal mass (mesoblast) is a deformable viscoelastic material which is not miscible with the surrounding flank mesenchyme. These cells divide either isotropically or directionally change the shape and size of the mesoblast, stretch and alter the tissue mass. There is an epithelium sheet around the mesoblast and under an acellular basement membrane, which is a source of molecular signals that generate and modulate the cellular behaviours of the underlying mesenchyme [180].

In this paper, we give an overview of limb development phenomena in vertebrates and present several mathematical models that describe these processes. We concentrate on continuous models formulated as systems of partial differential equations representing various chemical concentrations as well as cell densities. In the last six years in particular, new classes of reaction-diffusion models [143, 128, 49, 11, 12, 177] have been proposed which are based on new experimental insights into the molecular basis of chondrogenesis and incorporate much more detailed interactions from gene regulatory networks than previous models. While self contained, our survey can also be seen as an update of previous surveys of mathematical models in chondrogenesis (see [188, 187, 48]). We also include a list of all gene products that have been found to be relevant for limb chondrogenesis and who may play important roles as morphogens.

2 Biology of limb bud growth and basic concepts of sketal pattern formation

The process of limb growth is almost the same in all tetrapods, but most of the experimental work has been done on chicken and mice embryos. For chicken, the complete developmental process from a fertilize egg to hatchling takes about three weeks. Limb buds begin to emerge from the embryonic body at the end of third day and elongate rapidly. On the fourth day the humerus begins to appear in the form of a chondrogenic condensation, that is, a tight aggregate of precartilage cells. The complete pattern of the limb skeleton is laid out in cartilage elements by the seventh day.

2.1 Limb bud outgrowth and shaping

The vertebrate limb is an outgrowth from the embryonic body wall, due to the influence of a diffusible morphogen, fibroplast growth factor 8 (FGF8), which is secreted from the ectoderm.

As outgrowth proceeds, a morphologically distinct ectodermal thickening, consisting of a partially stratified epithelium, forms at the distal tip, known as the apical ectodermal ridge (AER) (see Figure 1), which is the source of FGF8 [180]. The AER forms in three steps: induction of precursor cells, migration of precursor cells and compaction of the ridge.

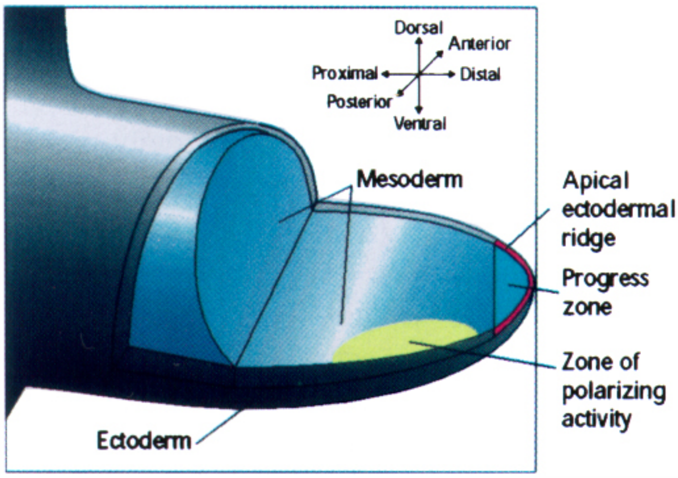

Figure 1: Schematic illustration of a limb bud. Positions of the AER (Apical Ectodermal Ridge), the ZPA (Zone of Polarising Activity) are shown along the limb axes in the developing limb. The image also shows a region which is identified as the "Progress Zone" in Wolpert's Progress Zone model. (Modified from [185], page no. 214)

In an embryo, during the early stages of limb formation, the limb bud is evolving along three axes: the axis from shoulder to hand is known as proximal-distal or PD axis, from thumb to little fingers is known as anterior-posterior or AP axis and the axis from back of hand to palm is called as dorsal-ventral or DV axis as shown in Figure 2.

Initially, the limb bud is composed of a set of mesodermal cells covered by a relatively thin layer of ectoderm. The limb bud arising from the chick 'body' wall is flat and almost elliptic in cross section with its major and minor axes parallel to AP and DV axes (see Figure 2) respectively [29]. At the Hamburger-Hamilton stage

21 [1] (HH 20), the dorsal parts of the chick limb start to round up, whereas the ventral side starts to flatten. During the limb outgrowth, the region from somite to wing tip, called PD length, expands very fast [29] and the posterior part of the limb grows faster than the anterior one [66].

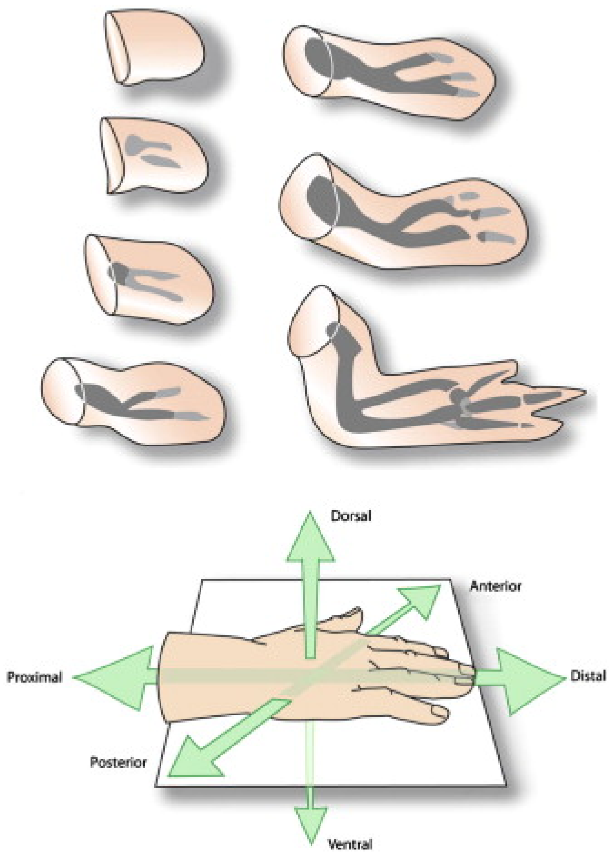

Figure 2: Outgrowth and shaping of vertebrate limb. Development of a chicken limb in three axes: Proximal-Distal (humerus in wing, femur in leg), Anterior-Posterior (radius and ulna in wing, tibia and fibula in leg) and Dorsal-Ventral (digits in wing and leg). (Modified from [180])

[1] In developmental biology, the Hamburger–Hamilton stages (HH) describe 46 chronological stages in chick development, starting from egg laying and ending with a hatched chick. These stages are described, e.g. in [56]. During development of chick limb, the segmentation of dorsal mesoderm into blocks, called somites, takes place [29].

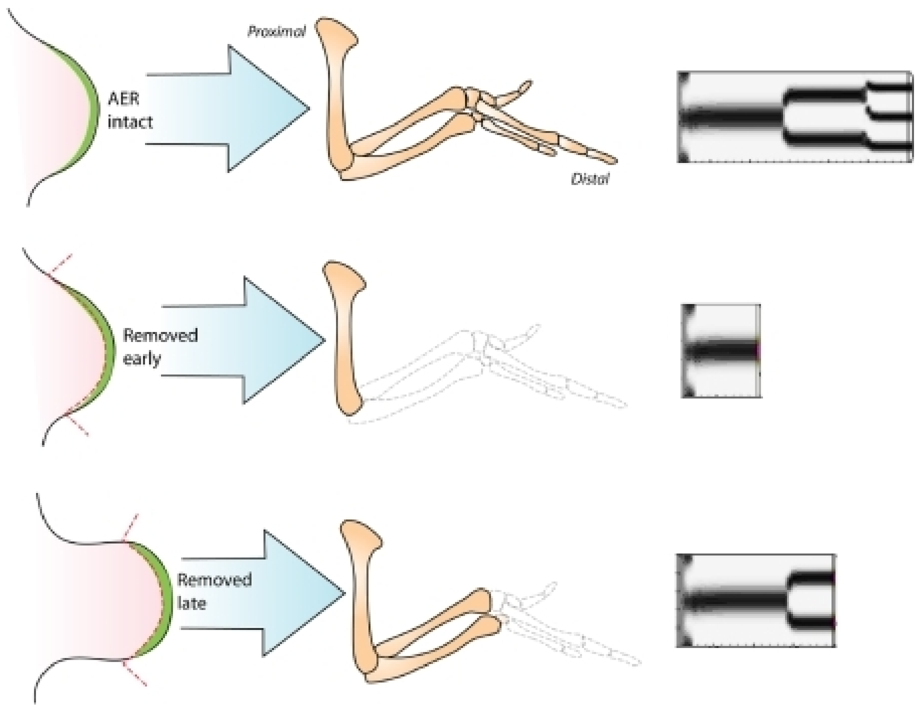

Figure 3: Role of the AER in vertebrate limb development: Top: Normal development of a wing with the AER. Middle: formation of wing if the AER removed early. Bottom: formation of wing if the AER removed later. (Modified from [180]).

The AER and underlying mesoderm play an important role in the outgrowth of the limb. If the AER is removed during the growth of the limb, the underlying mesoderm stops dividing and consequently limb outgrowth stops [47, 133, 138]. Also it is observed in tissue cultures that the mesoderm is induced to proliferate if the AER is combined with limb mesoderm. Actually, there is a two sided dependency between the AER and the underlying mesoderm: If mesoderm is removed from an early limb, the AER regresses. In contrast, if prospective limb mesoderm is amputated in flank ectoderm before the outgrowth of the limb bud, the still AER forms and the limb develops [61].

The first to carry out the experiments with AER removal was Saunders [137]. In his experiments, he partially used some much older ideas and methods, e.g. Lillie [76] and Peebles [124]. He was also motivated by certain observations made by Willier [170] and Hamburger [55]. In his paper [137], Saunders described the removal of the AER from the tip of the wing bud resulting in truncation of wing depending on the stage at which the AER was removed. He concluded from these results that the AER plays an essential role in growth of a wing and 'the orderly formation of the wing parts' [162].

The main idea of this experiment was revisited by Rowe and Fallon [132] (for wings and legs). It has been shown there that if the AER is removed in 18 or early 19 HH stage of development, this results in the absence of some of the digits of the evolving limb. Moreover, the bigger the piece cut off from the anterior part of the AER (between the somite levels 15 and 20), the more digits are absent in the final limb. (See Table 1 and Table 2 in [132]). Figure 3 shows the result of removal of AER in various stages of development.

In the experiment based paper [137], Saunders proposed the fate maps of early chick wing along the proximo-distal by injecting small clumps of carbon particles into the dorsal surface of bud as a marker.

Summerbell furthered the ideas of Sauders in [149, 150] by inserting impermeable barriers in chicken wings, at the Hamilton-Hamburger stages 16-18 and 20-22 [56] through the dorsal-ventral axis, perpendicular to the body wall of the limb bud at different anterior-posterior somite levels. Due to this, distal anterior and posterior tissues of limb bud were seperated [132]. Inserting the barriers at different somite levels resulted in the lack of digits situated at the anterior side of the barrier. To explain this fact, it was proposed in [150] “that pattern is specified by the concentration of a diffusible morphogen controlled by the zone of polarizing activity” and that the insertion of the barriers prevented this morphogen from reaching anterior mesoderm, which resulted in the faliure of anterior structure.

It has been also observed that taking the AER before Hamilton-Hamburger stage 29 and grafting it onto a younger limb (i.e. with a younger mesoderm) results in a proper limb development [133]. Likewise taking a young AER and grafting it onto an older mesoderm does not lead to any limb-elements duplications. This suggests that information of the proper sequence of limb development is programmed in the limb's mesoderm, not in the AER. In particular, the AER emits signals that do not change qualitatively in time (do not depend on its developmental stage). However, after Hamilton-Hamburger stage 29, the AER loses the capacity to induce a complete limb. According to these findings, the role of the AER seemed to be permissive rather than instructive, that is to say “keeping distal cells labile and able to change positional values by an unknown mechanism” [85] (see Figure 4).

For many years, the effects of limb morphogens (in particular FGFs) were regarded as mitogenic, i.e., they promote cell division at the distal tip to drive limb bud outgrowth. Recent works suggest that mesenchymal cells of the limb bud show a chemotactic migratory response to FGF gradients [75] towards the AER and oriented movement and growth [180, 14, 174]. Cell orientation depends on Wnt signaling, whereas its velocity depends on FGF signaling [51].

Some models (like the model, proposed in [16]), suggest that the flow of the limb mesenchyme is mechanically guided by the dorsal and ventral ectoderm, while some indicate that the dorsal ectoderm, excepting the underlying base membrane, is not necessary for normal limb shaping [86, 180].

Another important question concerning limb development is how the identity of limbs (hindlimb and forlimb) is determined. Forelimbs and hindlimbs emerge from the body wall of the embryo, initially composed of undifferentiated mesenchymal cells covered by a layer of ectoderm. The determination of limb identity depends on two transcription factors: Tbx5 and Tbx4 (T-box transcription factor) [46]. Both of these factors accelerate Fgf10 expression [1, 97, 110, 111] during limb bud initiation. In absence of Tbx5 in mice prohibits Fgf10 expression and forelimb skeletal formation [1], while Tbx4 knockout in mouse prevents hindlimb development, but a small hindlimb is formed due to the retention of low FGF10 levels [104]. Similarly to Tbx4, Pitx1 (a paired-like homeodomain 1, which is a protein and is encoded by the PITX1 gene) also influences in the formation of hindlimb [155]. In tetrapods, the identity of limb depends on the rostrocaudal positions of Tbx4, Tbx5 and Pitx1 expression, which are influenced by Hox family of genes. Mainly HoxA and HoxD clusters controls the limb development. The regulatory elements of these clusters are confined within two flanking topologically associating domains (TADs), which encompass the adjacent gene desert. During limb initiation the telomeric TAD controls the early waves of HoxA and HoxD gene expression in the lateral plate mesoderm. At a specific position, Hox genes are sequentially activated in a rostrocaudal pattern and this is crucial for the induction of limb growth. During this forelimb initiation process Tbx5 expression is induced under a rostral Hox expression pattern, leading to forelimb development. Similarly, it is hypothesized that Pitx1 and Tbx4 drive the hindlimb development due to caudal Hox expression pattern [125].

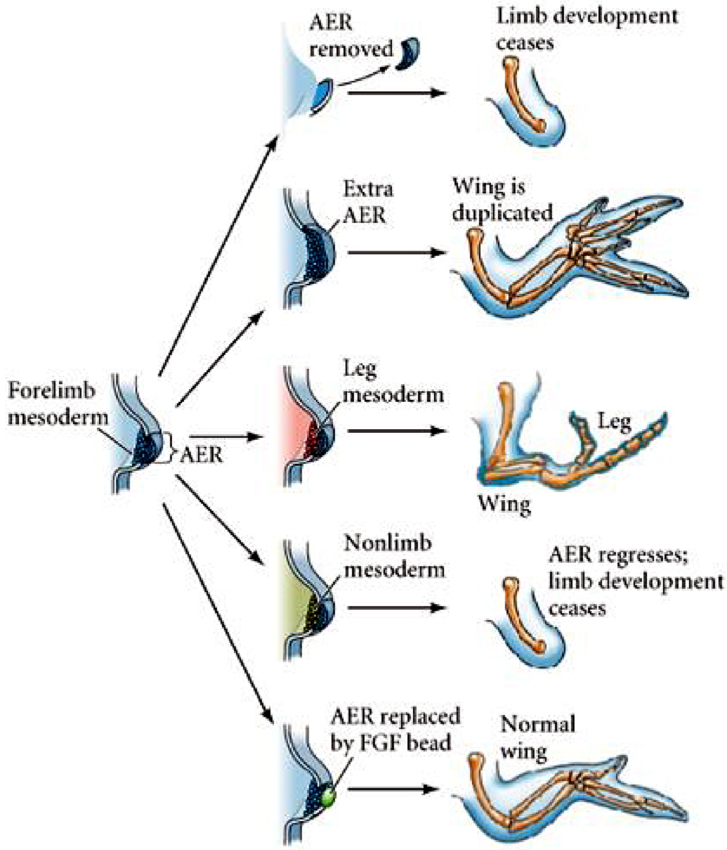

Figure 4: Role of the AER in limb development (Modified from [186])

2.2 Skeletal pattern formation on the growing limb

The skeleton is a complex organ which protects a number of internal organs and stores ions, particularly calcium [61]. The skeleton is formed by two different tissues, cartilage and bone, which support each other. Low metabolic rate, avascularity, capability for continued growth and high tensile strength coupled with resilience and elasticity are the distinctive properties of cartilage, whereas constant renovation to meet both mechanical and metabolic demands, vascularity, displaying rigidity and hardness are the properties of bone. Bones differ individually by size and shape, forming discrete arrays of elements.

During embryonic development, the skeleton and muscles grow from the paddle shaped limb bud mesoblast which is covered by epithelium, called ectoderm [126]. In most vertebrate, skeletons progress as a series of primordial cartilage in proximal-distal form [108]. In the case of the chicken, the humerus of the upper wing is established first, then radius-ulna in mid-wing, followed by the wrist bones and the digits lastly. Bones replace cartilage in most vertebrate.

Before cartilage forms, mesenchymal cells of the mesoblast form tight aggregates called precartilage mesenchymal condensations. These are the morphological basis of the skeleton [53, 54, 107]. This process is accompanied by the production and secretion of ECM glycoproteins, like fibronectin, which trap the cells at specific positions [41, 42]. The aggregation of cells becomes firm due to cell-cell adhesion which depends on cell-surface molecules such as NCAM [169](neural cell adhesion molecule), N-cadherin [114] or cadherin-11 [70, 80]. In the final step of chondrogenesis, precartilage cells differentiate into cartilage, a process associated with various gene products [115] and cartilage specific ECM [129].

2.2.1 Proximal-Distal Patterning

Several conceptual models have been proposed to understand the limb patterning along the proximal-distal axis.

2.2.1.1 Progress Zone model

The most influential model is without a debt the celebrated Progress Zone Model proposed by Lewis Wolpert in [171] (see also [148]). The Progress Zone (PZ) refers to a region of undifferentiated mesodermal cells approximately 300μm beneath the AER in the developing limb bud (see Figure 1). The PZ model postulates that cells obtain positional information via the amount of time spent within this region. Specifically, the cells 'measure' the time they spend in the Progress Zone. When the cells leave this region, their clock stops. As all cells are dividing within the Progress Zone, this is a continuous process. Thus the humerus is formed by the cells which are 'first' to leave the zone, whereas the digits are formed by the cells that are 'last' to leave this zone (see Fig.1 in [160]). These postulates have been supported by the experiments done by Saunders et. al. [133], and Summerbell et. al. [149, 150] (see Section 2.1). Removal of the AER stops the change of positional information value in the apical mesenchyme and progress halts in the zone at the tip. Then the cells lose their lability prematurely. Thus their proliferation rate is reduced and they start to differentiate according to the positional value they had just before the AER extirpation. As a result, the outcome limb is shorter and lacks distal elements [148]. Similarly, if the tip of a very young limb is removed and replaced by a tip of an older limb, the developing limb contains deletions, which is consistent with the idea of the Progress Zone Model [160].

Though the progress zone model was able to explain the results of the basic AER removal and limb X-irradiation experiments, it was called into question, mainly because of the non-specified mechanism in which cells in the progress zone obtain the positional information [32, 85].

2.2.1.2 Early Specification Model

An essentially different model was proposed by Dudley et. al. in [32] and was originally called the 'Early Specified Model', but later became known as 'Early Specification Model'. This model assumes that the limb pattern is specified at a very early stage of development and the limb segments already have distinct molecular features before the limb bud grows out [32, 160]. It is postulated that during llimb growth, the cells undergo a process of appropriate differentiation (corresponding to their early specification) and proliferation resulting in the expansion of the limb elements. The assumptions of the model were based on the experiments done by Dudley et. al. in [32], where they analyzed the effects of the AER extirpation on the formation of limb elements. By tracking the (labeled) limb bud cells, it was observed that the removal of the AER resulted in the death of underlying distal mesenchymal cells along with the truncation of distal elements. This suggests that distal cells do not take part in the chondrogenetic process after AER removal. The early specification assumptions are also consistent with experiments in which grafting of an early limb bud tip on a neutral site resulted only in digit-like elements, indicating that the mesenchymal cells were already specified at very early stage [32, 160]. These observations led Dudley and the collaborators to the conclusion that cell fates are pre-established within the early stage of limb bud growth.

2.2.1.3 Progress Zone model versus Early Specification model

Under some additional assumptions, both of these models have a potential to explain the process of limb formation. Soon after the work of Dudley et. al. [32] was published, Wolpert et. al. in [160] indicated that the results of the experiments presented in [32] leading to the early specification model, can be also interpreted within the progress zone model. Moreover, the Early Specification Model was criticized, because it would imply that each of the seven cartilaginous limb bud elements (humerus, radius and ulna, two carpal elements that are initially same size as the radius and ulna but fail to grow and a maximum of three digital elements) would correspond to approximately 4 layers of cells. The reasoning of Wolpert was the following: the early bud is

300μm long and the average mesenchymal cell diameter is assumed to be equal to 10 μm, so each cartilaginous elements will only be approximately 40μm, i.e. four cells.

Also, in [160] Wolpert suggested that the X-irradiation experiments on early limb buds presented in [173] provide some strong evidence for progress zone model. In these experiments, to reduce the rate of cells leaving the progress zone, mesenchymal cells of limb at stages 18/19 (Hamilton-Hamburger), stage 21 or the AER stage 24, were killed by X-irradiation. As a result, the progress zone needs to be repopulated before the cells can begin to leave again, so the time spent by some cells in the progress zone is increased. Increments of X-irradiation doses (the ectoderm is not influenced at these doses) resulted in the loss of proximal structures, whereas distal structures with the digits were relatively unaffected. Moreover, for still bigger doses of X-irradiation the structure of digits became abnormal. If the radiation was above 2500 rads, then no structures were observed at all. This seems consistent with the analysis based on the progress zone model because a very few cells could spend a short time in this region, resulting the deletion of proximal structure. Within the early specification model, this deletion was interpreted via the progressive determination of limb structures – the differentiation of cells into distal elements occurs later than into proximal ones [32].

On the other hand, in support of the early specification model, the results of fate mapping experiments described in [123, 136] may be cited. These experiments suggested that along the proximo-distal axis, cell lineage-restricted compartments might exist [164].

The process of limb development proposed by these two models is shown in Figure 5.

2.2.1.4 Mathematical Models, in particular Turing-type models

The above mentioned models of the formation of the skeletal pattern are conceptual models that synthesize biological, biochemical and physical ideas, but do not use any mathematical specifications of their concepts. In contrast, several mathematical models have been proposed. These models investigate how the interaction of gene expression, cell proliferation, cell movement and adhesion and differentiation can lead to the spontaneous emergence of chondrogenic patterns. Central to most of these models is the Turing mechanism for pattern formation in systems of reacting and diffusing chemicals (see [166]). In the first model of chondrogenic pattern formation based on the Turing mechanism, in [105], Newman and Frisch proposed an application of a single linear stationary reaction-diffusion equation for the concentration of a hypothetical morphogen (including the differentiation of mesenchymal cells into precartilage ones) to track the emergence of consecutive bones as a result of the limb bud growth, via the analysis of the eigenfunctions corresponding to the cross sections perpendicular to the proximal-distal axis. To this end, the limb is approximated by an appropriate cuboid. It is assumed that distribution of the (hypothetical) morphogen forms a prepattern which is then replicated by the distribution of the precartilage cells. This approach gave a very intuitive insights into the basic features of the precartilage pattern formation, though, of course, it is a drastic simplification of the corresponding process. In ensuing years, much work has been done on incorporating more realistic reaction kinetics, the effect of growth and realistic non-rectangular domains and explicitly modeling the response of cells via diffusive, chemotactic or cell-cell adhesion fluxes.

Given the very different natures of the conceptual biological models and the more concrete mathematical models, the two are often somewhat hard to compare and contrast. For instance, in the widest sense, Wolpert's positional information model postulates that a cell's spatial position determines its fate, but does a priori not stipulate the exact mechanism of how the cell senses its position, or how this information is translated into its behavior. Temporal or spatial gradients of morphogens are central to this mechanism, but there are many different ways in which they may be set up and maintained. In a sense, the Turing mechanism may be regarded as a possible mechanism for the establishment of morphogen gradients, although in a more narrow sense, the positional information concept is that the spatial morphogen gradients are set up by regions of specialized cells such as the Zone of Polarizing Activity (ZPA) in the limb; this sense is not compatible with the Turing mechanism, where patterns are set up in an autonomous, self-organizing way that does not require a group of specialized cells.

In section 3, we further discuss the relationship between Wolpert's positional information model and the Turing mechanism, then survey recent mathematical models in the ensuing section.

2.2.1.5 Other approaches

The classical experiments of AER removal, X-ray irradiation and other experiments regarding the limb formation and its development can be analyzed by the both of progress zone model and early specification model. But, recent experiments on morphogens (mainly on FGF4 and FGF8), concerning their effects on pattern formation of cartilage of the limb (see [74, 153]), can not be fully explained by any of these models. Therefore these two models are not sufficient [156].

The identification of molecular clock genes presented in e.g., [121, 122], would support the progress zone model. Unfortunately, these findings do not present a satisfactory evidence for a cell autonomous clock for the limb patterning [156]. Also, the formation of distinct proximodistal progenitor pools can not be explained by the early specification model.

Although neither of the above mentioned models is able to explain the process of proximodistal patterning fully, their general ideas seem to be interwoven in other approaches. Thus, for example, so called 'intercalation model' can be thought as a sort of modification of the progress zone model [82, 85]. By analyzing the effects of gradual increase of FGF-encoding genes knockout, it was hypothesized in [164] that the intermediate structures are specified at a later stage of development. To be more precise, the extreme proximal and distal parts of the limb are the first PD elements to be specified, e.g. by diffusion gradients of retinoic acid from the body and FGFs from the the AER. Later on, the strucures of intermediate positional values (radius and ulna) are intercalated. A new idea of this model is that it takes into account a possible influence of the embryo's body on the formation of the limb structures.

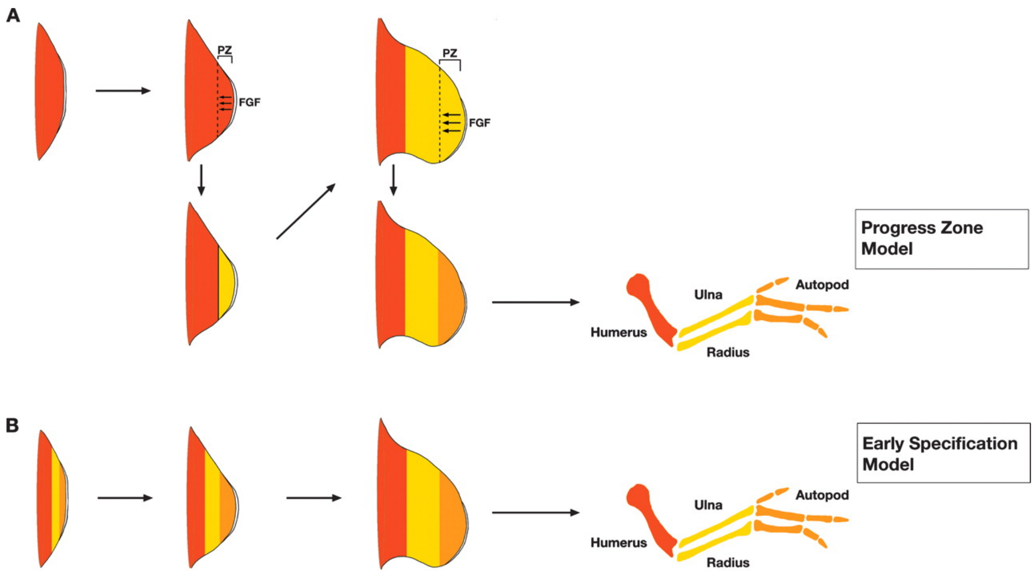

Figure 5: (A) The Progress Zone Model: in early stages of limb development, whole limb has proximal identity, specifically stylopod which is specified by red colour. As the limb grows, zeugopod appears slightly distally due to the influence of FGF, produced by the tip of limb, specified by yellow colour. Later, as the outgrowth proceeds, cells at the progress zone started to divide. The cells, which are not within the range of influence of FGF, maintain their specified fate. While the cells near to tip, are within the range of influence of FGF started to divide more distally. Therefore autopod appears, shown in orange colour. (B) The Early Specification Model: all the segments of proximal-distal axis in early limb bud are specified - stylopod is specified by red, zeugopod by yellow and orange corresponds to autopod (Modified from [156])).

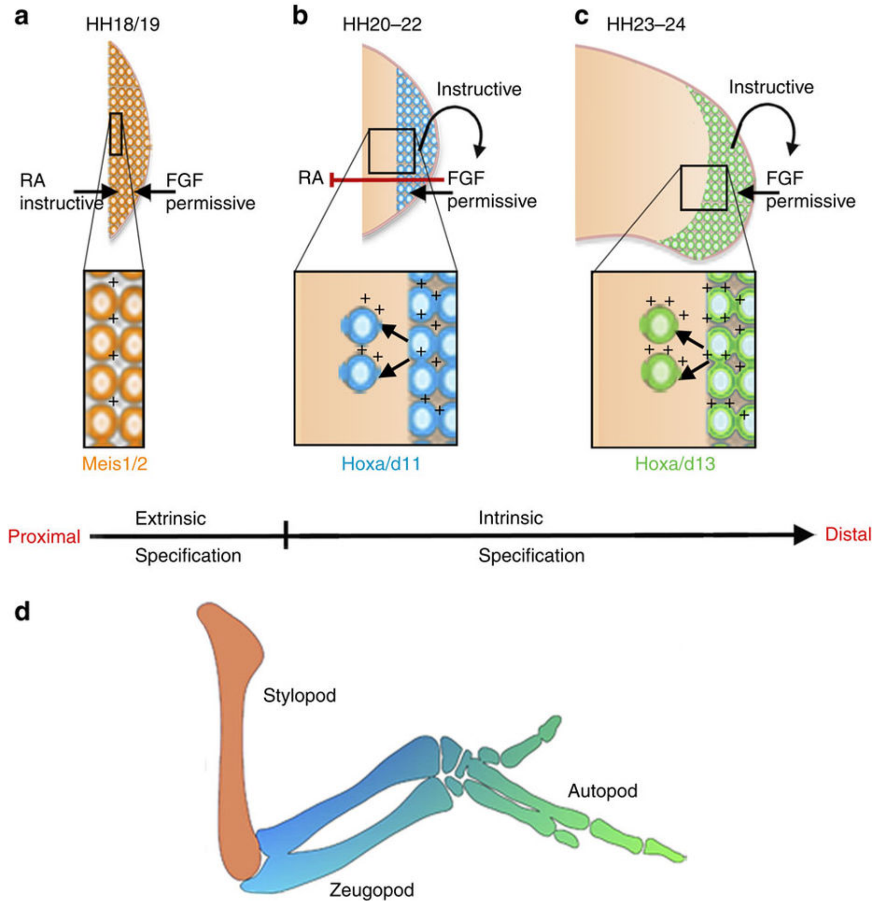

Figure 6: A graphical scheme of the model for proximo-distal patterning of chick wing proposed by Towers et. al in [134]. **a**. Specification of positional values for the stylopod (humerus, orange in **d**) by trunk secreted retinoic acid at early limb initiation stages (HH18 or HH19). **b**. Intrinsic time specification of positional values for the zeguopod (blue in **d**) at stages HH 20-22. **c**. Specification of positional values for the autopod (wrist/digits, green in **d**) at later stages, HH23-24. AER secreted FGFs, which are responsible for limb bud growth, supress the Meis1/2 expression to terminate the proximal process by inducing the retinoic acid degrading enzyme Cyp26b1 indicated by the red line in **b**. Deficiency of retinoic acid in the distal part of the limb bud, turns on intrinsic timing phase and the cells express 5'Hoxa/d genes and sustain the subsequent level of FGFs (secreted by AER). At subsequent stages, the cell adhesion properties and positional values of proximal specification intrinsically change over time (the + symbols indicate the greater adhesion properties of cells). This implies a spatial inhomogeneity of proximo-distal positional values due to the dispacement of cells from the distal mesenchyme (arrows in insets **a-c**) by an intrinsic programme of proliferation. (Modified from [134])

Towers et. al. in [134] proposed, what they called, 'a complete model of proximo-distal limb patterning', which is a conjugate modification of the progress zone model and positional information idea. At early limb initiation stages of chick wings (HH18/19), the positional value of the stylopod (humerus) is determined by trunk secreted retinoic acid (RA). At later HH stages, FGFs secreted by AER induce expression of Cyp26b1 [127], which is a retinoic acid-degrading enzyme. This process combined with limb bud growth generates a retinoic acid-free distal mesenchyme domain (see Fig. 6, b, c). It is suggested in [134] that this phenomenon 'triggers an intrinsic timer in distal mesenchyme cells and the switch from proximal (stylopod) to distal (zeugopod/autopod) specification'. At HH stages 20-22 (Fig.6 b), distal mesenchyme cells inducing this process, initially enter zeugopod specification phase characterized by Hoxa/d11 expression and then at HH stages 23-24, they undergo a phase of autopod specification, characterized by Hoxa/d13 expression (Fig.6 c).

Recently, Towers et. al. in [135] provide an experimental evidence that the final distinction in morphological forms dictated by differences in proximo-distal positional values is mediated by cell-cell adhesion which is position-specific [168]. Also, the cell-cell adhesion properties are influenced by 5' Hox transcription factors, mainly, by Hoxa13. It is suggested in [135] that the correct allocation of cells into the autopod (via specific positional values) is guaranted by Hoxa13 most probably by an appropriate control of cell-surface properties.

2.2.2 Anterior-Posterior Patterning

The mechanism behind Anterior-Posterior Patterning is very similar to the formation of PD axis. Classical experiments [151, 152, 159] show that a region at the posterior of the growing limb bud, organizes the AP patterning across the distal limb, known as the zone of polarizing activity (ZPA). The protein Sonic Hedgehog (Shh), produced from ZPA, influences the distinct fates of the limb cells along the anterior-posterior axis.

Therefore digit 1 (thumb or big toe) consists of cells with lowest concentrate of Shh in the distal limb, whereas the most posterior digits (little finger or small toe) arises from the region close to the ZPA. This suggests that the duration of exposure to high Shh, instead of short term duration of Shh concentration gradient at a single moment in time, defines AP digits [140, 163, 48]. Thus Shh is important in controlling digit number and patterning along the AP axis of vertebrate limb buds [164, 165]. In the experiment based paper [57], Harfe et al. suggested that the digit formation along AP axis not only depends on concentration of Shh, but also the duration of exposure to Shh is important in the specification of the differences between the digits.

In the previous section we have mentioned the role of RA in Proximal-Distal arrangement of the limb. It turns out that retinoic acid (RA) plays an important role in anterior-posterior patterning. It was found that RA present in the chick limb, shows a biggest gradient at posterior margin [157] and the existence of two phases of RA signaling is necessary for vertebrate limb development [94].

Moreover, according to experiments described in [83], if the amputated salamander limbs were soaked in retinoic acid (RA), a duplicated limb grows, e.g. two sets of radius and ulna grows. It was also observed that RA can produce the same duplication of digits by an additional the ZPA [159, 151].

We must however be aware that the impact of RA on the limb formation process is, in a way, combined with its interaction with Shh morphogen. Through the regulation of Meis gene expression, RA is involved in proximal limb formation and its effects on anterior posterior pattern are mediated via the transcriptional activation of Shh [164].

AP Patterning implied by growth

Growth/morphogen models of chick wing patterning emphasize that growth plays a vital role to specify the positional values of morphogen concentration in the early limb bud. This process, controlled by Shh signaling, was described, e.g. by [163, 164]. It was shown there that Shh controls the high-level expression of several genes, so that digits rise in the digit-forming region of the early wing bud, in polarizing region cells, digit 4 rises and in adjacent posterior cells, digit 2 and 3 rise [164]. Experiments described in [140] proved that the loss of posterior digits were caused by inhibition of Shh signaling by cyclopamine, but later it was revealed that this was due to combination of reduced AP growth and specification [163]. Towers et al. [163, 164] showed that the fate maps of cyclopamine-treated chick wings describes all prospective digit progenitors contributes to the anterior elements. Also, along the AP axis, overexpression of the cyclin-dependent kinase inhibitor, $p21^{cip1}$, as well as the application of $p21^{cip1}$ transcription inducer, known as deacetylase inhibitor trichostatin A (TSA), inhibits the growth. As a result, limb grows without anterior digits [163, 164]. These studies indicate that Shh normally promotes anterior-posterior expansion and specify the digit number and identity in chick limb.

Numerical simulation of growth of AP and PD axes are done by Dillon et. al.[28, 30], considering a simplified version with two diffusible morphogens produced at the AER and the ZPA regions respectively. This model allows to verify signaling pathways for morphogen signaling [61]. The equations of the mathematical model proposed in [28, 30] are described in the section 4.

Polarity of anterior-posterior axis in forelimb are determined by Hox genes, but for hind limb, no such evidence is found [161].

2.2.3 Dorsal-Ventral Patterning

In comparison to Proximal-Distal and Anterior-Posterior patterning, Dorso-Ventral patterning has received much less attention, although some experimental works have been done to elucidate its mechanism, see [21]. Experiments done by Chen et. al. in [19] suggest that Dorsal-Ventral axis is formed by cells derived from both mesoderm and ectoderm at different stages of development.

When some parts of limb bud mesoderm were detached and centrifugally compacted limb bud cells were reattached into the ectodermal hull of a three or four day chick wing bud, and then grafted to the flank of the host embryo, it was found that the skeleton and musculature of the distal elements have a Dorso-Ventral axis which conforms to that of the ectoderm [61]. Similarly, in case of leg buds of chick embryo, if the intact mesodermal cores were remerged with ectodermal hulls, the Dorso-Ventral axis of the ectoderm was reversed and the skeleton with musculature was also reversed along the Dorso-Ventral axis [61, 19]. It indicates that before the appearing of the AER, the ectoderm can specify the Dorso-Ventral axis and the mesoderm is able to impart Droso-Ventral positional information onto the ectoderm [19].

Other mesoderm and ectoderm recombination experiments revealed that, most probably, the ectoderm acquires Dorso-Ventral polarity from the underlying mesoderm prior to limb bud outgrowth at approximately Hamburger-Hamilton stage no 15 [19, 44].

3 Mathematical ideas behind the models of chondrogenic pattern formation

Chondrogenesis is one of a plethora of examples of pattern formation in embryogenesis, giving rise to a fundamental questions in developmental biology: What are the fundamental mechanisms by which biological patterns (structures and shapes) form [50]? In the following subsections, we concentrate on two well known ideas, Turing's reaction-diffusion (RD) mechanism and the Positional Information (PI) approach proposed by Lewis Wolpert.

3.1 Mechanism based on diffusion and interaction between appropriate groups of molecules

In description of embryological development, reaction-diffusion models are widely used to explain self-regulated pattern formation [72]. In 1952, in the celebrated paper *The Chemical Basis of Morphogenesis* [166] Alan Turing proposed reaction-diffusion (RD) model addressing the problem of biological patterns formation.

Turing revealed that a simple system of two equations for interacting morphogens can describe six types of spatial patterns, including traveling waves and oscillations as well as stable periodic patterns, such as stripes or spots, arising from a uniform field of cells [50]. The major achievement of these findings is the Turing pattern, which can be developed due to the diffusion driven instability, called Turing the instability.

This phenomenon can be mathematically stated in the following way: under some additional conditions, a homogeneous steady state of a dynamical system stable to small perturbations in the absence of diffusion, may become unstable to small spatially non-homogeneous perturbations if the diffusion is added in the system. This is surprising and unexpected as diffusion usually degrades spatial patterns and leads to uniformity in the long run (see, e.g. [50, 103]).

Turing's ideas about pattern formation continues to enjoy popularity among mathematical modelers and developmental biologists. This interest is mainly due to the fact that time evolution of proteins and chemicals can be well described by means of reaction-diffusion systems of equations. Such a description reflects two basic processes which determine their space-time distribution, i.e. undirected random motion (diffusion) and mutual interaction.

Several examples of biological patterning, such as animal coat patterns of zebra, leopard, mollusc shell pigmentation patterns, can be explained by using the Turing instability in the appropriate reaction-diffusion systems (see, for example, [90, 103]). However, it is not known whether the Turing mechanism is the only reason behind these phenomena [50, 119]. To be more precise, it is often difficult to assign concrete morphogens playing the role of activators or inhibitors in the abstract mathematical model describing the process of pattern formation, although, in several cases, morphogens corresponding to the applied reaction-diffusion systems have been identified with varying degrees of certainty (see e.g. [3, 36, 84, 95, 100, 128, 145]). In the most popular version of a two-morphogen system, the Turing mechanism also requires diffusion coefficients of activating and inhibiting morphogens to be of different sizes, often one or more orders of magnitude.

The notion of Turing instability is mainly used to explain the appearance of periodic biological patterns. However, reaction-diffusion description may be also applied to understand mechanisms of emergence of the non-periodic patterns (see, e.g. [101, 141, 144]).

3.2 Positional Information mechanism

Lewis Wolpert proposed the Positional Information (PI) model in the late 1960s. Wolpert was interested in how a complex pattern could be determined from simple asymmetries in the tissue and how the scale of this pattern could be coordinated over large tissue domains (rather than how a periodic pattern could arise from arbitrarily small spatial perturbation of the spatially homogeneous steady state, as investigated by Turing) [50]. Specifically he wanted to pattern formation could be directed depending on existant heterogeneities or polarities across the tissue. The key idea is that spatial morphogen gradients, i.e. changes in morphogens' concentrations over space, may result in different cellular behaviour, which in turn may lead to the formation of spatial patterns [171, 172, 50].

Compared to Turing's RD models, which suggest, for example, that stripes or spots of morphogens directly produce stripes or spots of cell types in the resulting tissue, Wolpert introduced an 'interpretation' step, according to which cells can interpret the local concentration of 'positional molecules' and choose their fate appropriate for that position [50]. This interpretation step implies an additional freedom that not only allows a smooth, monotonic molecular concentration gradient to give rise to any arbitrary pattern, periodic (like stripes or spots) and non-periodic (like the French Flag pattern 7), but also allows the exact same pair of orthogonal morphogens to induce cells to form different patterns depending on the cell type [50]. Positional Information model is well illustrated by the development of Drosophila segments [50]. In the Positional Information framework, the morphogen concentrations effectively work as positional coordinates. In the other words, the spatial distribution of PI molecules isomorphic to the developing or final limb skeletal patterns [180]. That is, they serve only as informational factors, rather than an isomorphic prepattern.

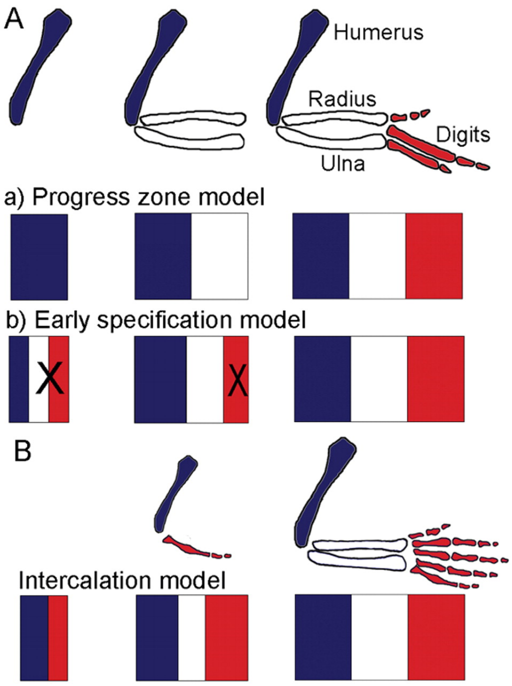

Figure 7: Schematic representation of limb development according to different proposed model with the help of french flag (Modified from [164]).

A key difference between Turing's and Wolpert's ideas, which has certainly had an important impact on their reception, is their intuitive appeals. Turing's reaction-diffusion mechanism is not intuitive. Self-organizing, morphological patterns arising from 'nothing' (to be more precise from arbitrarily small spatial perturbations) are difficult to understand as diffusion usually induces stability. On the contrary, Wolpert's positional information approach is more intuitive and is easy to grasp. In Wolpert's theory, one can regard morphological patterns as a result of an interplay between the spatial concentrations of different morphogens secreted from the corresponding sources, which are usually separated and localized in different positions of the evolving organ. In the case of limb bud growth these sources can be e.g., the AER secreting FGFs, and the ZPA secreting SHH (see Figure1).

3.3 Turing's bifurcation and Wolpert's positional information mechanisms as congruous morphogenetic processes

Turing's RD and Wolpert's PI approaches have often been considered as two different ideas, contrary to each other. In principle however, these two ideas can work together, each of them providing its specific benefits to the system analysis: Turing's bifurcation method can explain the symmetry-breaking of the initially homogeneous set of cells, whereas Wolpert's positional information mechanism can explain the distinction of differently specialized sub-regions in a growing embryo following the created patterns of morphogens. For instance, the presence of a chemical gradient which influences the kinetics of a reaction-diffusion system may modify the resulting Turing patterns in specific ways, see e.g. [189, 190, 191].

On the other hand, the formal distinction between these approaches seems artificial. In general, these two mechanisms are often combined. To be more precise, it is usually very difficult to split apart the time scales of the morphogen evolution and the cell differentiation or proliferation as in [18], equivalent to assuming that pattern formation is mechanistically separated from cell movement. Such an approach is sometimes called the morphostatic approximation. In fact, the differentiated cells secret morphogens (at a rate dependent on concentrations of additional agents). On the other hand, morphogen concentration may influence (upregulate or downregulate) the cell proliferation or differentiation [2, 60, 49]. Moreover, very complicated morphological motifs can be generated via a prepattern-pattern sequence, in which a preceding pattern prepares the prerequisites for the subsequent pattern, a bit like in a very complex reaction chains in the regulatory pathways of molecular chemistry [93].

4 A short review of mathematical models related to limb development

The intriguing phenomena connected with vertebrate limb growth and bone pattern formation have attracted interest of many researches and resulted in a large number of mathematical as well as computational models aiming to explain the process of chondrogenesis. There is enduring interest in the development and refinement of such models due to ever increasing computational power and biological data provided by experiments.

To investigate the mechanisms of limb development and pattern formation, mathematical modeling is extremely useful. It can establish the necessity of concrete assumptions of interactions. The interplay between experiment and model is a process of reciprocal influence: Models are not only established from the experiments, but often lead to additional experiments verifying new hypotheses. Obviously, except for very simple models, it is not easy to derive quantitative conclusions, thus complicated numerical simulations, using advanced techniques and methods, should be appropriately designed.

The mathematical models of chondrogenesis can, in principle, be divided in two groups [180]:

(a) Models related to growth and shape of limb bud.

(b) Models related to formation of skeleton patterns via morphogen's interaction.

4.1 Models related to growth and shape of limb bud

Experiment based growth models that describe the process of vertebrate limb growth and bone pattern formation attracted scientists for a long time. Since late 1960's, several computational and mathematical models of the limb bud outgrowth have been developed.

One of the main questions here is what the basic mechanism of limb outgrowth is, and how it is generated in the early limb [48]. The pioneering work in modeling the growth of embryonic limb bud was done by Ede and Law in late 1960s [37, 48]. They proposed a simple model involving cell proliferation and motion, to know about the necessity of difference in rates of cell reproduction at the proximal and distal part of the limb during the limb growth. Ede and Law concluded from the simulations of the model that the cell proliferation rate at proximal and distal parts do not effect on early shaping of the limb [48]. Later, they found that the proliferation rate is crucial during the limb growth, when the limb bud attains its characteristic paddle shape. It was observed by them that in this period of growth, more distal cells are dividing more frequently than the proximal cells with a tendency of cells to move slightly distally. These important results along with the estimated differences in the rate of proliferation have been widely accepted and used in several simulations [28, 30, 62, 126].

• *Dillon and Othmer's model*
It seems that the first mathematical and computational model describing effectively the process of limb growth and experimentally observed gene expression patterns during its development was proposed by Dillon and Othmer in [28, 29, 180].

It was a mathematical model of cell fluid flow coupled with elastic boundaries representing the mechanical and biochemical properties of the ectoderm surrounding the limb mesoblast. The fluid motion is described by the Navier-Stokes equations

$$\begin{aligned} &\nabla \cdot \mathbf{u} = S(\mathbf{c}(\mathbf{x},t)), \\ &\rho\frac{\partial \mathbf{u}}{\partial t} + \rho(\mathbf{u}\cdot\nabla)\mathbf{u} = -\nabla p + \mu(\nabla^2\mathbf{u} + \frac{1}{3}\nabla S) + \rho\mathbf{F}. \end{aligned} \tag{1}$$

Here the term S can be interpreted as the local source strength of growth. It depends on the concentrations c_1 and c_2, where c_1 corresponds to the morphogen secreted from the AER and c_2 corresponds to the morphogen secreted from the ZPA (For convenience (c_1, c_2) is denoted by $\mathbf{c}$) as well as the location of the tissue within the limb bud, and the age of the limb. $\mathbf{x}$ is the position within the limb and t is the age of the limb, ρ is fluid density, p its pressure and μ fluid viscosity. The morphogens are convected at u the local velocity of the limb bud mesoderm. Limb bud ectoderm exert the force density $\mathbf{F}$ on the fluid surrounding it. Their model incorporates the effect of morphogens, like Shh, FGFs with sources at the AER and the ZPA. It is governed by a reaction-diffusion-advection system

$$\frac{\partial \mathbf{c}}{\partial t} + \nabla\cdot(\mathbf{u}\mathbf{c}) = D\nabla^2\mathbf{c} + R(\mathbf{c}), \tag{2}$$

where D is the diffusion matrix for the morphogens and the production rate is denoted as $R(\mathbf{c})$. In fact, the above model has been to the only successful attempt to consider constructively the relation between growth as a physical process, the effects of morphogens on the parameters of growth, and adjusting the numerical results to the experimental findings concerning the dynamics of limb bud expansion. Some of the physical and biological assumptions are reevaluated because of new information along with the extension by the same authors [30], yet the model is up till now the most relevant in the context of integration of the two main kind of processes influencing the limb growth.

The AER morphogen is only produced in the AER($\mathbf{\Omega_1}$) and the ZPA morphogen is in the ZPA ($\mathbf{\Omega_2}$). Thus $R = (R_1, R_2)$ has the form

$$R_k = \begin{cases} r_k(\mathbf{c}) - \kappa_k c_k & \mathbf{x} \in \mathbf{\Omega_k}, \\ \\ -\kappa_k c_k & \text{Otherwise} \end{cases}$$

where $r_k(\mathbf{c}) > 0$ except at $\mathbf{c} = \mathbf{0}$ and the corresponding Michaelis-Menten kinetics are as follows with rate constants V_k and K_k:

$$r_1(c) = V_1\frac{c_2}{K_1 + c_2}, \quad r_2(c) = V_2\frac{c_1}{K_2 + c_1}.$$

The source term S has the form:

$$S = s_1 c_1 + s_2$$

where s_1 and s_2 are constants. Hence the local growth rate linearly depends on the local concentration of c_1.

• *Model of Murea et. al.*

In [102, 180], Murea et al. presented a model of limb outgrowth as a free boundary problem governed by creeping motion of expanding mesoblast (due to nutrient supply) and ectodermal boundary with nonuniform surface tension. In contrary to Dillon et al. [28], the authors of [102] didn't assume that Proximal-Distal gradient is mitotic. Later Boehm et al. [14] approved this assumption. It was also claimed in [102] that in the case, when the rate of growth $S(x,t)$ is relatively big, then it should be taken into account as an additional source of cells' movement. Neglecting simultaneously the inertial term in the Navier Stokes equation, and assuming very high viscosity of mesenchymal cells, they finally arrive at the simplified equation of the form:

$$-\mu\Delta\mathbf{v} + \nabla p = \mathbf{f} + \frac{\mu}{3}\nabla S \tag{3}$$

together with the additional equation combining the the growth rate with the divergence of the speed:

$$\nabla \cdot \mathbf{v} = S$$

Here $p = P - p_{air}$ is tissue pressure and P is fluid pressure, p_{air} is the pressure of the surrounding air. μ and $\mathbf{v}$ are fluid viscosity and velocity, while $S(x,t)$ is the rate of growth. The gradient of p and the gradient of S determine the velocity of the limb bud outgrowth.

• *Model of Morishita et al.*
Morishita et al. in [99] proposed "growth based morphogenesis" model to describe the changes of organ morphology during limb development. This model proposes a discrete reaction diffusion equations defined in a network of nodes. This nodes are divided into M- and E- nodes (representing mesenchyme and epithelium cells). The equations have form:

$$c_i^M(t+dt) = c_i^M(t) + D\{\sum_j (c_j^M(t) - c_i^M(t)) + \sum_k (c_k^{AER} - c_i^M(t))\}dt - \gamma c_i^M(t)dt, \tag{4}$$

where c_i^M, c_k^{AER} are the AER-signal concentrations at the M-node i and E-node k respectively. D is diffusion constant and γ is degradation rate of the AER-signal at each M-node. Here the first summation indicates all M-nodes j linked with node i and the second one for all E-nodes k linked with node i. c_k^{AER} assumed to be constant. As it is seen from (32), the chemical flux at each node is proportional to the difference between focal node and its neighbors.

Although the some of conclusions following the numerical simulations in [99] have been questioned, this relatively simple computational discrete model proved useful in analyzing morphological processes controlled by the spatiotemporal pattern of volume sources.

• *Model of Boehm et al.*
The development of vertebrate limb bud has been studied for a long time in the context of the spatial distribution of cell fates. On the other hand, the question how the limb bud physically elongates, attracted much less attention. In [14], the authors proposed a similar fluid dynamics model like the models in [28, 99], to study numerically the elongation process, using finite element computational method in three dimensions incorporating quantitative data on shape changes and proliferation rates. They concluded that limb bud elongates due to the process concerning cell division, migration, and therefore cannot be explained by a mere proliferation gradient hypothesis.

This model, based on Navier-Stokes equations, showed the patterns of cell division considering the mesenchyme as a viscous incompressible fluid, whose volume increases with s (a distributed material source term, in fact, s represents the proportional volumetric growth per unit time):

$$\begin{aligned} &\frac{\partial \mathbf{v}}{\partial t} + \nabla p - \frac{1}{Re}\nabla \cdot [\nabla \mathbf{v}] = 0, \\ &\nabla \cdot \mathbf{v} = s, \end{aligned} \tag{5}$$

Here the term v represents velocity and the pressure is represented by the term p. Re is Reynolds number. Such a conclusion has been also confirmed by the results of the cellular automata-based limb bud shaping model in[126].

As follows from the above models, limb bud growth and shaping is a complicated process involving many interwoven phenomenona. In the experiment based paper [178], Zeng et al. investigated the limb formation mechanism in vitro and in vivo. They observed that precartilage formation in the limb is controlled by the differential adhesion of cells: less adhesive cells construct one large humerus in the proximal region whereas more adhesive cells generate many small sized digits in the distal area. This observation leads to the result of density dependent pattern formation in the limb due to cell adhesion along with chemotaxis.

The basic theoretical idea behind this approach is that the proper specification of localized volume source (e.g., cell proliferation) is able to guide organ morphogenesis, and that the specification is given by chemical gradients. As it is also suggested in [63], polarity of mesoderm and cartilage cells in the limb bud (governed mainly by noncanonical Wnt signalling) can play a significant role in directional movement and oriented division. Thus concluded that the directional activities like orientation of cell division and their motility drives the limb outgrowth [174, 180].

In principle, by choosing proper initial distribution of proliferation morphogens, we can obtain an appropriate shape and size of the growing limb bud (see Figure 8), however such an approach may leads to a theoretical contradictions which can be resolved only by introducing new 'driving factors'.

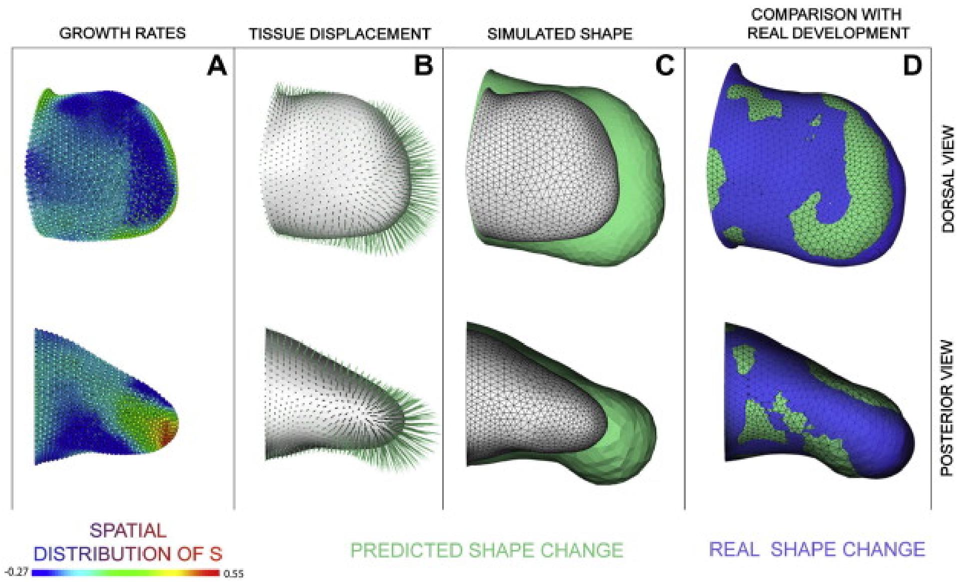

Figure 8: [180] Result of computational optimization of a finite element model for limb bud shaping. (A) red/yellow shows a discrete region of very high proliferation at the distal tip and blue as shrinking areas dorsal and ventrally. (B) generate a shape (green in (C) and (D)), which is similar to real shape (blue in (D)). As it is noted in [180], the final growth pattern conflict with experimental values only for a distribution of proliferation rates. (Modified from [180])

4.2 Models related to formation of skeleton patterns via morphogen interaction

Formally, we can distinguish two groups of models describing the dynamics of morphogens leading to skeletal pattern formation [180]: the 'isomorphic' and 'non-isomorphic' ones. In isomorphic models it is assumed that there is an isomorphic shape preserving mapping between the spatial distribution of morphogens and the skeletal elements. This isomorphism can be realized by means of different phenomena, e.g. by enhancing the differentiation of mesenchymal cells into cartilage cells (which then differentiate into chondrocytes), attracting (chemotactic) processes and others. In the non-isomorphic case, there is no a straightforward spatial correspondence between the chemical prepattern and the final localization of bones. In this case the morphogen dynamics is a part of a broader process, and can impact the pattern formation mainly implicitly, e.g. by influencing the shape of the growing limb, upregulating proliferation, differentiation or apoptosis, and initiating regulatory pathways. In both cases, the existence of appropriate mechanisms should be assumed. On the other hand, the necessity of their verification is an additional motivation for profound experimental studies.

- *Meinhardt's boundary model*

In [89, 91], several points about the limb bud development, such as, positioning of the limbs along the body axes and the reconstruction of limb structure in urodele amphibians were discussed. In contrast to the "gradient hypothesis" of PI model [158], in [89, 91] the "boundary model" to study other developmental issues, like the formation of new structures, including gradient sources at the interface of two or more distinct tissues or populations of cells, has been proposed. In the gradient like models, each cell's positional identity is determined by the local values of chemical concentrations or exposure-duration of their gradients, whereas in the former (the boundary model), the gradients are set up by a direct confrontation of independently induced cell populations. These gradients are completely unrelated to the determinants of the original tissues and can lead to further modifications and spatially nonuniform development of one or both of the interacting cell types. The Meinhardt boundary model proposed in [89, 91] has proved many features of developmental systems in spite of lack of experimental data to specify the locations of skeleton elements [93, 180]. The gradient system studied by Meinhardt in [91] is presumed to establish the positional identity along the AP axis of limb bud, in this way unifying, in a sense, the generation of PD positional information with AP positional information, although this seems to contradict the original PI model, which asserts that there is an internal cellular clock that caused the cells in a non-differentiating distal environment [148]. Addressing these issues, Meinhardt [91] suggested a "bootstrap" model, where proximal differentiating cells emanate signal to the AER to keep the levels of morphogen elevated above the values able to specify the distal most positional identities of the limb.

In fact, to simulate the process of skeleton formation, we should take into account both the morphogens' interaction as well as the process of limb bud growth, because these two phenomena, are going on simultaneously. However, even if we confine ourselves to a fixed shape and size of the limb bud, thus assuming that the growth is slow compared to the speed of pattern formation induced by the morphogens' interaction, we can verify the possibility of skeleton development with the chosen set of morphogens. The general form of PDEs of reaction-diffusion type exploiting so called auto-activation with lateral inhibition (LALI) mechanism to model the spatiotemporal dynamics of generic morphogens can be written as:

$$\frac{\partial C}{\partial t} = D\nabla^2 C + R(C), \tag{6}$$

where C is a vector $(c_1, c_2, \cdots, c_n)$ representing the concentrations of morphogens produced by the cells of developing organ with rate $R(C)$ and D is diagonal matrix of diffusion coefficients (see, e.g. [92, 93]). This type of Turing-like systems were studied in many works (see, e.g. [9, 27, 26]). Not only they analyze the spatiotemporal dynamics of non-isomorphic morphogen patterns, but also the underlying modeling framework for morphogen patterns isomorphic to the limb skeleton were discussed. It is worthwhile to note that there is no general consent on the set of morphogens playing a leading role in the process of skeleton formation. In fact, different models put an accent on different set of morphogens. On one hand this freedom may be a result of a great complexity of the chondrogenetic phenomena, on the other hand, it may be a consequence of insufficient amount of experimental data.

•*Model of Dillon et al.*
In one of the most promising approach, having a relatively well documented experimental justification, the primary role in the chondrogenetic pattern onset is assigned to Shh protein and its complexes (cf. table 1). This approach has been studied in a series of papers initiated by [27]. Later on, the results of [27] concerning the growth and morphogen patterning of the limb were extended with new findings of Shh signaling pathways. Namely, the relation between Shh receptor Patched (Ptc) and the associated membrane signal transduction factor Smo was discussed by Dillon et al. in [28, 30].

They supplemented reaction-diffusion system by incorporating the new terms related to the influence of Shh receptor and mediator proteins, coupled (in addition to terms for FGF in 2-D) with the Navier-Stokes equations. In this way, using the model one can simulate the effects of ectopic sources of Shh and compares the results with the experiments. The model analyzes the interaction between Shh, Shh transmembrane receptor Patched (Ptc) and Smoothened (Smo) (see [25, 174]), a transmembrane protein mediating Shh signaling through phosphorylation of the Gli family of transcription factor. For example, the interaction between Shh and Ptc can be described, neglecting the other terms, as in [180]:

$$\frac{\partial}{\partial t}[\text{Shh}] = [\text{diffusion of Shh}] - [\text{association of Shh and Ptc}]$$
$$+ [\text{disassociation of Shh-Ptc complex}] - [\text{degradation of Shh}] + [\text{Shh production}],$$

$$\frac{\partial}{\partial t}[\text{Ptc}] = -[\text{association of Shh and Ptc}] + [\text{disassociation of Shh-Ptc complex}]$$
$$- [\text{association of Smo and Ptc}] + [\text{disassociation and degradation of Smo-Ptc complex}]$$
$$+ [\text{Ptc productions by itself and by Smo}] - [\text{degradation of Ptc}],$$

$$\frac{\partial}{\partial t}[(\text{Shh-Ptc complex})] = [\text{association of Shh and Ptc}]$$
$$- [\text{disassociation and degradation of Shh-Ptc complex}].$$

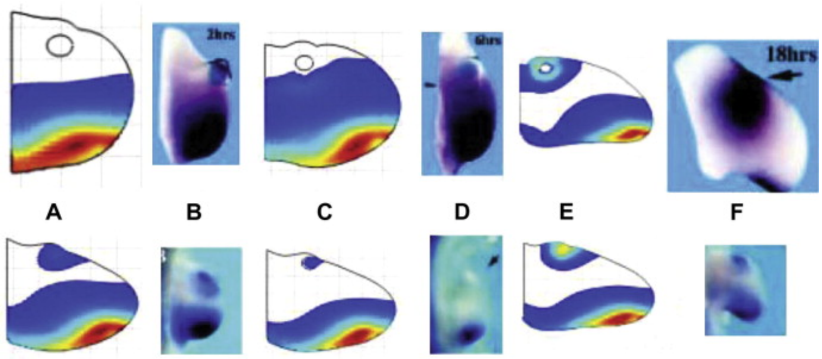

Figure 9: The computational and experimental results of Patched (Ptc) responses to Sonic hedgehog (Shh) bead implants (upper panels) and the ZPA tissue implants (lower panels). (Upper) The rescaled figures of numerical simulations of Ptc concentration 2, 6, and 18 h after bead implants (A, C, and E, respectively), whereas in lower, Ptc concentration 12, 16, and 20 h after tissue implant (A, C, and E, respectively). Experimental results are from Drossopoulou et al. [31] for ptc transcript expression 2, 6, and 16 h post-bead implants and for the ZPA grafts, 4, 8, and 16 h post-implant (B, D, and F, respectively). (From Dillon et al. [30]).

It is also supposed in the model that Smo has two forms: active (associated with free Ptc) and inactive (interacting with Shh-Ptc) and that different forms of Shh have the same diffusion constants. (The last assumption was brought into question in [40].) The main idea of this work was to compare the effects of implantation of ectopic sources of Shh (Shh beads) and ectopic the ZPA tissue. The excellent agreement between the numerical simulations within the model and experimental findings, seem to prove both the relative validity of the model assumptions as well as the fact that the ZPA is a source of Shh morphogen. The last conclusion seems to be the main and outstanding result of [30]. The comparison between the model and the experimental results is shown in Fig. 9.

•*Model of Hirashima et al.*
The interactions between the AER and the ZPA is an intriguing question, the answer to which plays crucial role in the study of skeleton pattern formation. Several experiments were done to enlighten these interactions (see, e.g. [7, 10]). Hirashima et al. in [62] proposed a model in this direction. Namely, they addressed the question

of interaction between FGF expression at the AER and Shh expression at the ZPA, especially the positive effect of FGF on the production of Shh by mesenchymal cells. This model was implemented on a simplified one dimensional domain $\{x : 0 < x < \infty\}$ with the AER at the left boundary and the ZPA at a chosen distance from the AER. It took into account the following processes :

a) Diffusion of FGFs from the AER.
b) Shh expression in the mesenchymal cells.
c) Diffusion of SHH from the mesenchymal cells.
d) Fgfs expression in the AER cells.

The system of equations in $\Omega := (0, \infty) \times (0, \infty) \ni (x, t)$ describing the above phenomena was proposed as:

$$\frac{\partial F}{\partial t} = D_F \frac{\partial^2 F}{\partial x^2} - \gamma_F F, \quad \text{for } x > 0, \tag{7}$$

$$\frac{\partial R}{\partial t} = \alpha_R \frac{F^{h_2}}{F^{h_2} + K_2^{h_2}} - \gamma_R R, \tag{8}$$

$$\frac{\partial S_{in}}{\partial t} = \alpha_S \frac{F^{h_1}}{F^{h_1} + K_1^{h_1}} \frac{K_3^{h_3}}{R^{h_3} + K_3^{h_3}} - (\gamma_{S,in} + \beta_S) S_{in}, \tag{9}$$

$$\frac{\partial}{\partial t} S = D_S \frac{\partial^2}{\partial x^2} S - \gamma_S S + \beta_S S_{in} \quad \text{for } x > 0, \tag{10}$$

$$\frac{d}{dt} F_{in}^{(0)}(t) = \alpha_F \frac{S(0,t)^{h_4}}{S(0,t)^{h_4} + K_4^{h_4}} - (\gamma_{F,in} + \beta_F) F_{in}^{(0)}(t). \tag{11}$$

It was supplemented by the following boundary conditions at $x = 0$ and at $x = \infty$:

$$-D_F \frac{\partial}{\partial x} F(0,t) = \beta_F F_{in}^{(0)}(t), \tag{12}$$

$$F(\infty, t) = 0, \tag{13}$$

$$\frac{\partial}{\partial x} S(0,t) = 0, \tag{14}$$

$$S(\infty, t) = 0. \tag{15}$$

Equation (16) describes diffusion of FGFs (mainly FGF4) from the AER with the diffusion constant D_F, together with its degradation with the rate γ_F. The production of FGFs in the AER and its influx into the mesenchyme is described by the boundary condition (12). Here $F(x,t)$ is the extracellular FGF concentration and $F_{in}^{(0)}(t)$ is the Fgf gene expression level in the AER cells. Equation (13) indicates that the FGF concentration approaches 0 very far from the AER.

Equations (8) and (9) describe the dynamics of Shh expression in the mesenchymal cells. According to equation (8), the concentration of repressor R increases with the extracellular FGF concentration F. Equation (9) describes the level of Shh expression in mesenchymal cells, denoted as S_{in}. The parameters of production and degradation of repressor are α_R and γ_R respectively, while α_S and $\gamma_{S,in}$ are the corresponding parameters of SHH. β_S is the rate of transport of SHH to the outside of cells. K_1, K_2, and K_3 are dissociation constants and h_1, h_2, and h_3 are Hill coefficients. The extracellular SHH concentration is denoted as S.

Equation (10) describes the spatio-temporal dynamics of SHH outside the mesenchymal cells. The first two terms of the right-hand side of equation (10) represent SHH diffusion and degradation, respectively with the diffusion coeffient D_S and its degradation with rate γ_S. SHH is activly transport from inside to the outside of mesenchyme cells as it is mentioned in equation (8). S satisfies the no-flux boundary conditions at $x = 0$ and at $x = \infty$ as is indicated by equations (14)-(15).

Assuming that the activation of Fgf expression by SHH-signal occurs only in the AER cells ($x = 0$), but not in mesenchymal cells ($x > 0$), equation (11), describes the dynamics of Fgf expression level, denoted as

$F_{in}^{(0)}(t)$, in the AER cells. This expression is stimulated by the extracellular SHH concentration at $x = 0$ via the appropriate Michaeles-Menten kinetics, with FGF production rate α_F. As mentioned above, γ_F is degradation rate and β_F is the active transport rate of FGF to the extracellular space.

The main objective of [62] was the study of the role of coupled dynamics of positive feedback and feed-forward interactions between Fgf expression at the AER and Shh expression at the ZPA. As it was mentioned above the AER is assumed to be localized at $x = 0$, whereas the position of the ZPA is identified with the point, where the maximum of Shh expression level in $\hat{S}_{in}$ occurs. It has been concluded in [62] that appropriately defined interaction between the AER and the ZPA enhances the robustness of the distance between the AER and the ZPA. By robustness we mean here that this distance is weakly sensitive to the changes of the parameters of the model. Interestingly, the repression of the acitivity of the ZPA by the repressor R (modeled in the first term at the right hand side of equation (9)) plays a crucial role. The robustness of the distance between the AER and the ZPA is very important in the limb development, because both the AER and the ZPA act as sources of positional information.

• *Model of Armstrong et al.*

In [4], Armstrong et al. designed a nonlinear partial differential equation aimed to described the phenomenon of cell-cell adhesion. This model was later analyzed by Dyson et al. in [34] and [35]. This non-local term represents the phenomena of cell-cell adhesion and cell-extracellular matrix adhesion. These processes are crucial in many biological contexts leading to different kinds of pattern formation.

To observe the formation of aggregations of cells or cell clusters for an initially distributed cell population with the strong cell-cell adhesion, Armstrong et al. considered first a population of one species cell together with uniform adhesive properties.

In one spatial dimension the model reads [35]:

$$\frac{\partial u(x,t)}{\partial t} = \frac{\partial u^2(x,t)}{\partial x^2} - \frac{\partial}{\partial x}\left(uK(u)\right) \tag{16}$$

where

$$K(u) = \frac{\phi}{R}\int_{-R}^{R} \alpha g(u(x+x_0))\,\omega(x_0)\,dx_0. \tag{17}$$

Here $u(x,t)$ denotes the cell density. The cell-cell adhesion is represented by the term $K(u)$, while the corresponding forces and their effects on the local cell density are described by the term $g(u(x+x_0))$. The strength of cell-cell adhesive force is represented by α and $\omega(x_0)$ characterizes the direction and magnitude of the force (changing with x_0). ϕ is a constant of proportionality related to viscosity and R is sensing radius of the cells. Figure 10 illustrates the schematic representation of the cell movement.

Equation (16) is considered for $x \in (-\infty, \infty)$, with initial condition $u(x,0) = u_0(x)$.

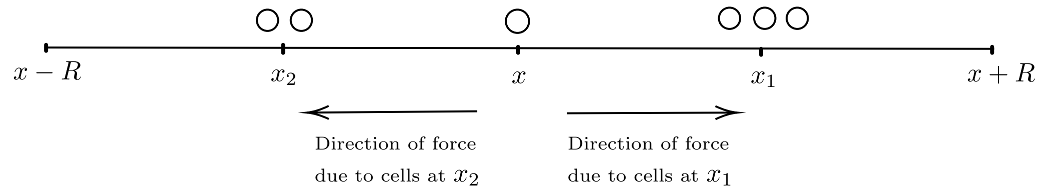

Figure 10: Schematic representation of cell movement due to the attractive force [4].

In [4], the term $g(u(x+x_0))$ is considered either linear i.e., $g(u(x+x_0)) = u(x+x_0)$ or of logistic type:

$$g(u(x+x_0)) = \begin{cases} u(x+x_0)(1-u(x+x_0)/M) & if \quad u(x+x_0) < M \\ 0, & otherwise \end{cases}$$

where M represents the crowding capacity of the population.

The form of $\omega(x_0)$ reflects the adhesive nature of cell-cell interaction and its form should depend on its specific form (depending on the cells). For linear functions $g(u(x+x_0))$, it has been proposed in [4], $\omega(x_0)$ as a simple step function

$$\omega(x_0) = \begin{cases} -1 & -R < x_0 < 0 \\ 1, & 0 < x_0 < R \end{cases}$$

It should be, however, kept in mind that many more realistic forms of $\omega(x_0)$ can be considered in the model.

In the same paper [4], a system describing two populations of different types of cells. The proposed model has the form:

$$\begin{aligned} u_t &= u_{xx} - (uK_u(u,v))_x \\ v_t &= v_{xx} - (vK_v(u,v))_x \end{aligned} \tag{18}$$

where

$$K_u(u,v) = \underbrace{S_u \int_{-1}^{1} g_{uu}(u(x+x_0), v(x+x_0))\omega_{uu}(x_0)dx_0}_{u-v\ adhesion} + \underbrace{C \int_{-1}^{1} g_{uv}(u(x+x_0), v(x+x_0))\omega_{uv}(x_0)dx_0}_{u-v\ adhesion} \tag{19}$$

and

$$K_v(u,v) = \underbrace{S_v \int_{-1}^{1} g_{vv}(u(x+x_0), v(x+x_0))\omega_{vv}(x_0)dx_0}_{v-u\ adhesion} + \underbrace{C \int_{-1}^{1} g_{vu}(u(x+x_0), v(x+x_0))\omega_{vu}(x_0)dx_0}_{v-u\ adhesion}. \tag{20}$$

Here $u(x,t)$ and $v(x,t)$ denote the populations' cell densities. The terms $K_u(u,v)$ and $K_v(u,v)$ represent the adhesion of cells. In K_u, the first term denotes the self-population adhesion of first type of cells and the other term indicates the cross-population adhesion. Similarly, in K_v, the first term represents the self-population adhesion of second type of cells and the other term indicates the cross-population adhesion. The self-adhesive strength of population u and v are represented by the terms S_u and S_v, while the cross-adhesive strength between the populations is represented by C.

In the same paper [4], the models describing the one population and two interacting populations in one spatial dimension, were extended to two spatial dimensions, i.e. for $x \in \mathbb{R}^2$.

The one population model in this case takes the form

$$u_t = \nabla^2 u - \nabla \cdot (uK(u)) \tag{21}$$

where

$$K(u) = \alpha \int_0^1 \int_0^{2\pi} g(u(\underline{x} + r\,\underline{\eta}))\,\Omega(r)\,\underline{\eta}\,r\,d\theta\,dr. \tag{22}$$

Here $\underline{x} \in \mathbb{R}^2$ denotes the position of the cell. $\underline{x} + r\,\underline{\eta}$ denotes the position of other cells within the sensing disc of radius R scaled to $R = 1$. $\underline{\eta} = \underline{\eta}(r,\theta)$ is the unit outward normal to the circle $C(\underline{x}, r)$. The term $\underline{\eta}\,\Omega(r)$ replaces the functions $\omega(x_0)$ present in spatially one dimensional model (16)-(17).

Similarly, two interacting populations' model, defined in (18), was extended to two spatial dimensions as follows,

$$\begin{aligned} u_t &= \nabla^2 u - \nabla \cdot (uK_u(u,v)) \\ v_t &= \nabla^2 v - \nabla \cdot (vK_v(u,v)) \end{aligned} \tag{23}$$

where

$$K_u(u,v) = \int_0^1 \int_0^{2\pi} r\,\underline{\eta} \left[S_u\, g_{uu}(u(\underline{x}+r\,\underline{\eta}), v(\underline{x}+r\,\underline{\eta}))\,\Omega_{vv}(r) + C\, g_{uv}(u(\underline{x}+r\,\underline{\eta}), v(\underline{x}+r\,\underline{\eta}))\,\Omega_{uv}(r) \right] d\theta\,dr \tag{24}$$

and

$$K_v(u,v) = \int_0^1 \int_0^{2\pi} r\,\underline{\eta}\,\Big[S_v\, g_{vv}(u(\underline{x}+r\,\underline{\eta}), v(\underline{x}+r\,\underline{\eta}))\,\Omega_{uu}(r) + C\, g_{vu}(u(\underline{x}+r\,\underline{\eta}), v(\underline{x}+r\,\underline{\eta}))\,\Omega_{uv}(r)\Big]\, d\theta\, dr. \quad (25)$$

Here $u(\underline{x},t)$ denotes the cell density of first type cells and $v(\underline{x},t)$ denotes the cell density of second type cells at position $\underline{x}$ and time t. The terms K_u, K_v define the non-local adhesion described before. The dependence of the strength of adhesive binding on the radial distance is represented by the functions Ω_{uu}, Ω_{vv} and Ω_{uv}.

In the one population and spatially one dimensional model it is relatively easy to obtain an intuition about the influence of the non-local adhesion terms on solutions. In this case, one can approximate the integrals by local differential terms obtained formally by the expansion of the cell density within the integral [4]. So, substitution of the expansion of $u(x,t)$

$$u(x+x_0,t) = u(x,t) + x_0 u_x(x_0,t) + \frac{x_0^2}{2} u_{xx}(x_0,t) + \cdots$$

into the integral $K(u)$ changes equation (16) for $g(u) = u$ to

$$u_t = u_{xx} - A\alpha[uu_x]_x - B\alpha[uu_{xxx}]_x + \Phi(x_0^5) \quad (26)$$

where $A = \int_{-1}^1 x_0\omega(x_0)dx_0$ and $B = \frac{1}{6}\int_{-1}^1 x_0^3\omega(x_0)dx_0$ are both positive. Let us note that, as $\omega(x_0)$ is odd, then $\int_{-1}^1 x_0^k\omega(x_0)dx_0 = 0$ for all even integer k.

The second order term in equation (26) depends on the first spatial derivative u_x as in the models of chemotaxis [3][68].

It implies the cell movement up the gradients (towards higher concentration) of cell density, therefore cell aggregating may be potentially observed in solutions to equation (16)-(17). On the other hand, the fourth order term has a dampening effect, therefore the non-local term may help in cell aggregations without creating singularities and blows up phenomena. In a similar way, the PDE approximation can be done for two interacting populations.

Higher dimensional case:
Although the model was constructed initially in one and two dimensions by Armstrong et al. in [4], still higher dimensional studies are extremely important in the context of cancer modelling.

Therefore the above model was extended in N-dimensions by Dyson et al. in [35], as follows:

$$\frac{\partial u(x,t)}{\partial t} = \underbrace{D\Delta u(x,t)}_{\text{random motility}} \underbrace{-\nabla\cdot\left(u(x,t)\int_{B_\rho} g(u(x+\xi,t))\,\xi\,\omega(\xi)\,d\xi\right)}_{\text{cell adhesion}} + \underbrace{f(u(x,t))}_{\text{cell loss and gain}} \quad (27)$$

for $x \in \mathbb{R}^N$, $t > 0$ and B_ρ denoting the N-dimensional ball centred at 0 and of radius ρ with initial condition $u(x,0) = u_0(x),\ x \in \mathbb{R}^N$.

It is assumed that $f(0) = 0$ (for biological reason). Also, it is assumed that there is a number $P_1 > 0$ such that $f(u) > 0$ for $u \in (0, P_1)$, and $f(u) < 0$ for $u > P_1$. These assumptions suggest that there is cell gain at lower densities while in higher densities, due to the effects of crowding, cell loss occurs more rapidly in compared to the generation of new cells via division.

• *Model of Glimm et al.*
Recently in [49], Glimm et al. proposed a new model related to bone formation based upon the results of an experimental paper [13] (see also [79]). The mathematical formulation of this model incorporates a non-local flux term describing cell-cell adhesion forces (coinciding with the approach of Armstrong et al. in [4]), and has

a form of a structured population model with diffusion. In this context, the model proposed by Glimm et al. in [49] differs from models discussed in previous sections, and it has far reaching consequences for its mathematical analysis. This is due to the presence of hyperbolic terms inside the reaction-diffusion equations. (In Eq.(32) these are the terms $\dfrac{\partial}{\partial T_1}(\tilde{\gamma}(c_1^u, c_8^u, T_1)R)$ and $\dfrac{\partial}{\partial T_8}(\tilde{\delta}(c_8^u, T_8)R)$.)

In [13, 79], a crucial role of 'new' morphogens regulating the cells' aggregation and bone formation during avian limb growth has been reported. These 'new' regulating proteins are chicken galectins: CG-1A and CG-8. CG-1A and CG-8 and their respective counterreceptors are produced by all mesenchymal cells. The model proposed in [49] not only explains the interactions between CG-1A and CG-8 to form spatial patterns of condensations during cell aggregation and bone formation but also provides the crucial insights of the pattern formation from a physical prospect that the limb skeletal patterning is a morphodynamic process and thus depends on mesenchymal cell motility.

The biological foundations of the model formulated in [49] are as follows:

1. Mesenchymal cells move randomly with constant diffusion rate until they are trapped on the adhesive surface of condensations of mesenchymal cells.
2. CG-1A induces CG-8 gene expression and vice versa, CG-8 induces CG-1A gene expression.
3. CG-1A not only upregulates cell-cell adhesion but also promotes the formation of condensations, whereas CG-8 inhibits cell-cell adhesion suggests that the two galectins have a common counterreceptor. It is found that if CG-1A is added to cell cultures, the number of condensed cells (and their density) increase but addition of CG-8 inhibits the condensations [49].

These assumptions are schematically shown in Figure 12.

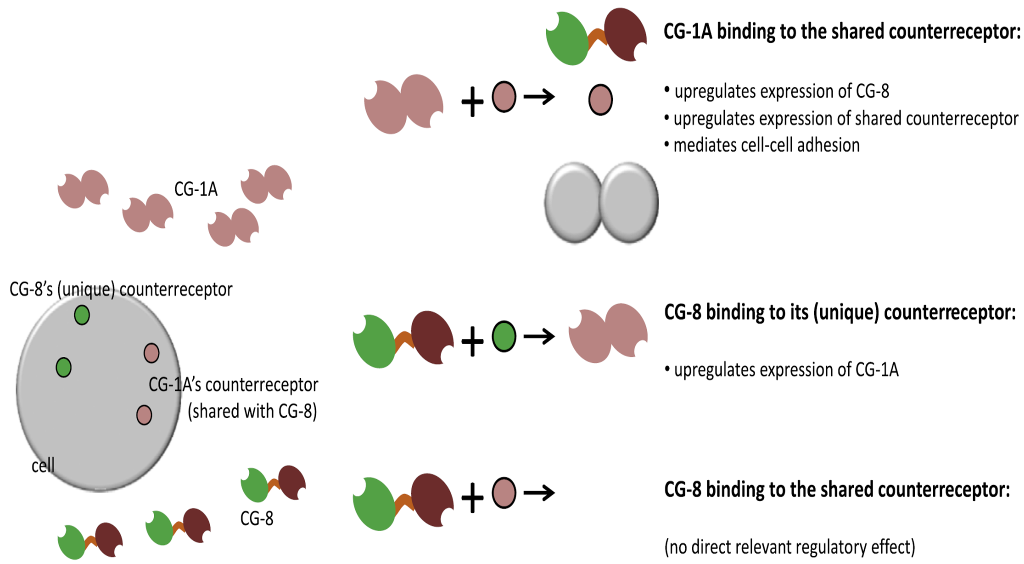

Figure 11: Schematic illustration of the key players and their basic roles in the galectins model proposed in [49]. (Modified from [49])

Glimm's model consists of a system of partial integro-differential equations, of the form:

$$\frac{\partial R}{\partial t} = \underbrace{D_R \nabla^2 R}_{\text{cell diffusion}} - \underbrace{\nabla \cdot (R\mathbf{K}(R))}_{\text{cell-cell adhesion}} \underbrace{-\frac{\partial}{\partial c_1}(\alpha R) - \frac{\partial}{\partial c_8^8}(\beta_8 R) - \frac{\partial}{\partial c_8^1}(\beta_1 R)}_{\text{binding/unbinding of galectins to counterreceptors}}$$
$$\underbrace{-\frac{\partial}{\partial l_1}[(\gamma - \alpha - \beta_1)R] - \frac{\partial}{\partial l_8}[(\delta - \beta_8)R]}_{\text{change in counterreceptors}} \tag{28}$$

$$\frac{\partial c_1^u}{\partial t} = \underbrace{D_1 \nabla^2 c_1^u}_{\text{diffusion}} \underbrace{+\bar{\nu} \int c_8^8 R dP}_{\text{positive feedback of CG-8 on prod. of CG-1A}} \underbrace{+ \int \alpha R dP}_{\text{binding CG-1A to its counterreceptor}} \underbrace{-\bar{\pi}_1 c_1^u}_{\text{degradation}} \tag{29}$$

$$\frac{\partial c_8^u}{\partial t} = \underbrace{D_8 \nabla^2 c_8^u}_{\text{diffusion}} \underbrace{+\bar{\mu} \int c_1 R dP}_{\text{positive feedback of CG-1A on prod. of CG-8}} \underbrace{+ \int \beta_1 R dP}_{\text{binding CG-8 to counterreceptor}} \underbrace{-\bar{\pi}_8 c_8^u}_{\text{degradation}} \tag{30}$$

A term with a bar over it e.g. $\bar{\mu}$ denoted as a constant. As we mentioned above, the cell-cell adhesion term $\nabla \cdot (R\mathbf{K}(R))$ is formulated basing on the approach of [4] (see the previous subsection, especially (17)) and is defined as

$$\mathbf{K}(R(t, \mathbf{x}, c_1, c_8^8, c_8^1, l_1, l_8)) = \bar{\alpha}_K c_1 \int\int_{D_{\rho_0}} \int \tilde{c}_1 \sigma(R(t, \mathbf{x}+\mathbf{r}, \tilde{c}_1, \tilde{c}_8^8, \tilde{c}_8^1, \tilde{l}_1, \tilde{l}_8)) d\tilde{P} \frac{\mathbf{r}}{|\mathbf{r}|} d^n r, \tag{31}$$

here $\bar{\alpha}_K$ is a constant which represents the strength of the adhesion and $\sigma(R)$ has either linear or logistic form. Here $c_1^u = c_1^u(t, \mathbf{x})$ is concentration of freely diffusible CG-1A and $c_8^u = c_8^u(t, \mathbf{x})$ is concentration of freely diffusible CG-8, whereas $R = R(t, \mathbf{x}, c_8^8, c_1^8, l_1, l_8)$ denotes morphogenetic cell density. The effective adhesion force on a cell at location $\mathbf{x}$ depends on the product of the concentration of bound CG-1A on the cell and the concentration of bound CG-1A at locations $\mathbf{x} + \mathbf{r}$, where the distance vector $\mathbf{r}$ varies over the n-dimensional ($n = 1; 2; 3$) ball $D_{\rho_0}(\mathbf{x})$ centred at $\mathbf{x}$. The radius ρ_0 is the "sensing" radius, which is a measure of the characteristic distance for adhesion; cells at distance greater than ρ_0 do not contribute to the adhesion forces (see figure 10).

The term $\gamma - \alpha - \beta_1$ models the rate at which the membrane-bound concentration of the shared counterreceptors which are not bound to either galectin changes. The change is due to the expression of new counterreceptors by the cells and degradation (leading to the effective rate γ), the binding and unbinding of the counterreceptor to CG-1A (the rate α) and the binding and unbinding of the counterreceptor to CG-8 (the rate β_1). Similarly, the term $\delta - \beta_8$ denotes the rate at which the membrane-bound concentration of its own counterreceptors which are not bound to CG-8 galectin changes.

Assuming "fast galectin binding" to the countereceptors, the following simplified system was obtained in [49] from the full model using the two auxiliary variables :

the total concentration of CG-1As counterreceptors

$$T_1 = c_1 + c_8^1 + l_1$$

and total concentration of CG-8s counterreceptors

$$T_8 = c_8^8 + l_8.$$

$$\frac{\partial R}{\partial t} = d_R \nabla^2 R - \nabla \cdot (R\mathbf{K}(R)) - \frac{\partial}{\partial T_1}(\tilde{\gamma}(c_1^u, c_8^u, T_1)R) - \frac{\partial}{\partial T_8}(\tilde{\delta}(c_8^u, T_8)R), \tag{32}$$

$$\frac{\partial c_1^u}{\partial t} = \nabla^2 c_1^u + \tilde{\nu} \int_0^\infty \int_0^\infty c_8^8 R \, dT_1 dT_8 - c_1^u, \tag{33}$$

$$\frac{\partial c_8^u}{\partial t} = \nabla^2 c_8^u + \tilde{\mu} \int_0^\infty \int_0^\infty c_1 R \; dT_1 dT_8 - \tilde{\pi}_8 c_8^u, \tag{34}$$

with

$$c_8^8 = c_8^8(t, \mathbf{x}, T_8) = \frac{c_8^u T_8}{1 + c_8^u},$$

$$c_1 = c_1(t, \mathbf{x}, T_1) = \frac{c_1^u T_1}{1 + f c_8^u + c_1^u},$$

$$\tilde{\gamma}(c_1^u, c_8^u, T_1) = \left(\frac{2c_1^u}{c_1 + \tilde{\tilde{c}}_1} - \tilde{\gamma}_2 \right) \frac{c_1}{c_1^u},$$

$$\tilde{\delta}(c_8^u, T_8) = 1 - \tilde{\delta}_2 \frac{T_8}{1 + c_8^u},$$

$$\mathbf{K}[R, c_1^u, c_8^u](t, \mathbf{x}, T_1, T_8) = \Psi(\delta; \mathrm{dist}(\mathbf{x}, \partial\Omega))$$

$$\tilde{\alpha}_K c_1(t, \mathbf{x}, T_1) \int_0^\infty \int_0^\infty \int_{D_{r_0}(0)} c_1(t, \mathbf{s}, \tilde{T}_1) \tilde{\sigma}(R(t, \mathbf{s}, \tilde{T}_1, \tilde{T}_8)) \frac{\mathbf{s}}{|\mathbf{s}|} ds \; d\tilde{T}_1 d\tilde{T}_8$$

Here $\tilde{\alpha}_K$ is a constant which represents the strength of the adhesion for some $\delta > 0$ sufficiently small, $\Psi(\delta; \cdot)$ is a smooth cut-off function such that $\Psi(\delta; y) \equiv 1$ for $y \geq 2\delta$, $\Psi(\delta; y) \equiv 0$ for $y \leq \delta$.

Numerical simulations in [49], evidence that the system (32)-(33)-(34) can produce spatial patterns in the morphogenetic density $R(t; x; T_1; T_8)$ for a wide range of the model parameters. The cell-cell adhesion flux term plays a crucial role in this spatial pattern formation, as can be observed in Figure 12.

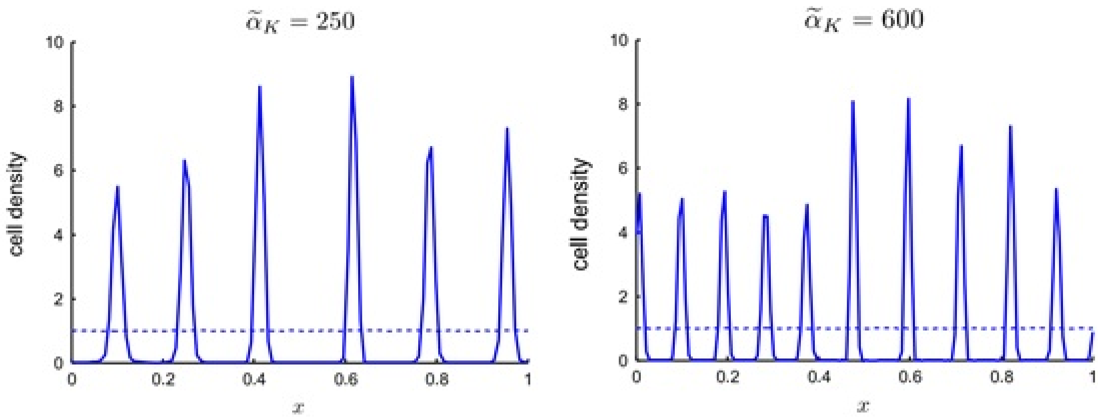

Figure 12: [49] Distribution of cell density $\int\int R(t; x; T_1; T_8) dT_1 dT_8$ at times $t = 0$ and $t = 1$ for different values of the cell-cell adhesion constant $\tilde{\alpha}_K$. Other values are $r_0 = 0.04$, $\tilde{\delta}_2 = 1$, $\tilde{\gamma}_2 = 1$, $\tilde{\tilde{c}}_1 = 1$, $f = 0.8$, $d_R = 0.04$, $\tilde{\pi}_8 = 1$, $\tilde{\nu} = 0.8$, $\tilde{\mu} = 2$. Initial distributions are represented by dashed lines and distributions at $t = 1$ are by solid lines. As $\tilde{\alpha}_K$ is increased, periodic patterns appear as a result of random spatial noise added to the initial distribution. Here periodic boundary conditions are used, so that the positions $x = 0$ and $x = 1$ denote the same physical point. (Modified from [49].)

• *Model of Iber-Badugu*
In [5], Iber et al. proposed a model for the mechanism of patterning of digits in mouse limb, based on BMP-receptor interaction. BMP signaling along with FGF gradient are important for digits formation [11, 12, 177]. It is fairly interesting that the influence of SHH on the digit pattern formation has not been taken into account in this model. This is based on the experiments described in [67, 147, 164], where it was found that the expression of SHH terminates much faster than the expression pattern of Sox9, which is responsible for digit pattern. Moreover in absence of Shh expression, digit pattern can also be observed [77]. Neglecting the effects of Shh along the anterior-posterior polarity, Iber and the coworkers focused on the interactions of BMP (denoted as B in the model), its receptor (denoted as R) and FGF (denoted as F) under which the digits emerge in the autopod. These interactions were well explained in figure 13. BMP and FGF diffuse relatively fast compared to plasma membrane based BMP receptors. In the model, the diffusion of the ligand bound receptors, residing mainly in cell, denoted as C in model, were ignored as they are internalised rapidly [69]. The rate of BMP receptor binding is proportional to R^2B, as BMPs are dimers, can bind two receptors. In the limb bud, BMP2 expression is reduced by the BMP2 signaling. Basing on this fact, the rate of BMP production is assumed in the form $P_B \dfrac{K_B}{K_B + [C]}$. In this way, the BMP and BMP-receptor dynamics is proposed as follows:

$$\begin{aligned} [\dot{B}] &= \underbrace{\bar{D}_B \bar{\Delta}[B]}_{\text{diffusion}} + \underbrace{P_B \frac{K_B}{K_B + [C]}}_{\text{production}} \underbrace{-d_B[B]}_{\text{degradation}} \underbrace{-k_{on}[R]^2[B] + k_{off}[C]}_{\text{complex formation}} \\ [\dot{C}] &= \underbrace{k_{on}[R]^2[B] - k_{off}[C]}_{\text{complex formation}} \underbrace{-d_C[C]}_{\text{degradation}} , \end{aligned} \tag{35}$$

where k_{on} and k_{off} are the binding and dissociation rate constants respectively. $\bar{D}_B$ is the diffusion coefficient for BMP molecules.

Production of receptor depends on the concentration of C as the signaling of BMP-bound receptors positively regulates receptor production.

$$[\dot{R}] = \underbrace{\bar{D}_R \bar{\Delta}[R]}_{\text{diffusion}} + \underbrace{p_R + p_C([C])}_{\text{production}} \underbrace{-d_R[R]}_{\text{degradation}} \underbrace{-2k_{on}[R]^2[B] + k_{off[C]}}_{\text{complex formation}}, \tag{36}$$

where p_R and p_C are constants.

The receptor ligand assumes its quasi steady-state almost instantaneously as the dynamics of receptors ligands complex are much faster than the dynamics of BMP, hence the concentration of bound receptors are proportional to R^2B, i.e.,

$$[C] \sim \frac{k_{on}}{k_{off} + d_C}[R]^2[B] = K_C[R]^2[B]; \;\; K_C = \frac{k_{on}}{k_{off} + d_C}$$

It was proved in [5] that the system 35–36 was sufficient to produce pattern and it can be reduced to classical Turing model Schnakenberg type if $p_C = 2d_C$ and $d_B = 0$.

Expression of BMP is induced by the FGF signaling, so the model was extended by the Badugu et al. in [5] by introducing the production rate P_B as a function of FGF concentration F,

$$P_B(F) = p_b + p_B^* \frac{[F]^n}{[F]^n + K_{BF}^n} \frac{K_B}{K_B + [C]},$$

where K_{BF} and n are the Hill constant and Hill coefficient repectively. It has been found that BMP-bound receptors signaling stimulate as well as inhibit FGF-dependent processes [33, 122]. Hence FGF activity is best described as

$$P_F([C]) = p_F \frac{[C]^n}{[C]^n + K_{F1}^n} \frac{K_{F2}^n}{[C]^n + K_{F2}^n},$$

where $K_{F1} \ll K_{F2}$ are the Hill constants for the activation and inhibition impacts of BMP signaling. So the dynamics of FGF is as follows,

$$[\dot{F}] = \underbrace{\bar{D}_F \Delta[F]}_{\text{diffusion}} + \underbrace{p_F \frac{[C]^n}{[C]^n + K_{F1}^n} \frac{K_{F2}^n}{[C]^n + K_{F2}^n}}_{\text{production}} - \underbrace{d_F[F]}_{\text{degradation}}, \tag{37}$$

where $\bar{D}_j$ $(j = B, R, F)$ are the diffusion coefficients with $\bar{D}_R \ll \bar{D}_B, \bar{D}_F$.

The shape of the domain was extracted from limb bud images at E12.5 and hence the system of equations were solved on a growing domain (see Figure. 13). Except at the flank, developing limb bud does not exchange with the surrounding, so zero-flux boundary conditions for B and R was incorparated with the system, while FGF production was implemented as a flux boundary condition,

$$\vec{n} \cdot \nabla F = \rho_F \frac{(R^2B)^n}{(R^2B)^n + \kappa_1^n} \frac{\kappa_2^n}{(R^2B)^n + \kappa_2^n},$$

where $\vec{n}$ is the unit normal vector.

An additional remark should be made here concerning a specific role of Sox9 gene which is not explicitly taken into account in this model. Sox9 serves an important role in digit pattern formation, but according to [5], only as a marker of endochondral differentiation. To be more precise, BMP-2 signalling stimulates the Sox9 expression and this enhances the Noggin expression, which has a negative impact on BMP signalling by changing BMP into an inactive complexes [5, 184]. However, this approach was questioned by Sharpe et al. in [128] due to the result that Sox9 is a part of Turing network rather than a marker of endochondral differentiation. Also, in [128], Sharpe et al. are doubtful about the assumption of the model proposed by Iber et al. in [5] that the diffusion of BMP receptors through tissue as it has no evidence.

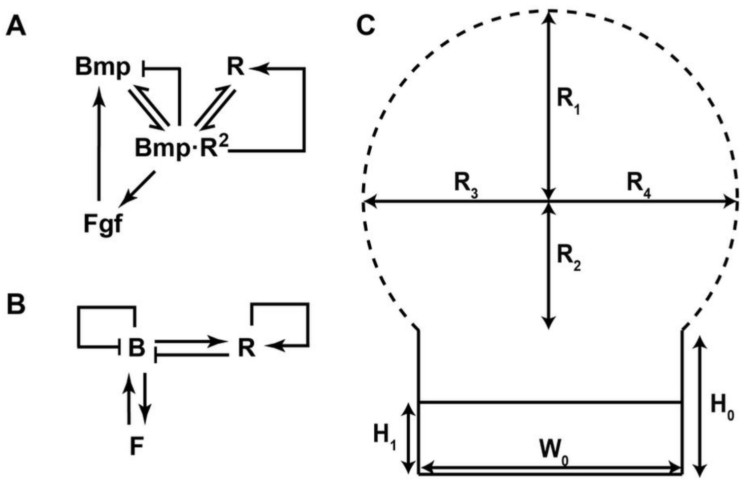

Figure 13: (A) It is considered in the model that the interactions of BMP, its receptor and FGF form a loop. In fact, BMP receptor complexs are formed due to the reversible binding of BMP and its receptor, which induce the production of receptors and enhances the FGF activity, while FGF induces BMP expression. (B) Therefore, BMP has a positive impact on receptor as well as on FGF, both via BMP-receptor complexs (excluded from the figure). It should be mentioned here that receptors act as auto-activatory when they are bounded by BMP, whereas BMP enhances self-decay by receptor binding, and hence they are auto-inhibitory, and a mutual enhancment is observed between BMP and FGF. (C) The domain of compuatation, based on the shape of a limb bud, at E11.5. The radial axes of the elliptic bud are denoted as R_i, $(i = 1, 2, 3, 4)$. Height and width of the stalk are represented by H_0 and W_0, respectively. In the stalk, the height of the domain is denoted by H_1. The expression of BMP is upgraded at the height of the domain in the stalk. (Modified from [5])

•*BSW Model (Raspopovic et al.)*
In Turing-type reaction-diffusion systems, the wavelength of the patterns produced typically shows a strong dependence on the parameters. So changes in the parameters will lead to changes in the wavelength. This observation is one of the principal objections to the applicability of the Turing mechanism to bone pattern formation in the vertebrate limb. After all, the number of elements is very stable and e.g. derivation from the number of digits (in the form of surplus digits (polydactyly) or missing or fused digits (syndactyly)) relatively rare.

Proponents of reaction-diffusion mechanisms have pointed out that the prevalence of congenital limb defects is high relative to other defects, and higher than e.g. either Down syndrome or cleft palate, with prevalence reported as 22.7 per 10,000 birth in a study in Thailand [65]; in a large study in Hungary, this number was reported as 1 in 1816, or about 5.5 per 10,000 births ([38] as cited in [48]). Still, these incidences are quite low on an absolute scale and do not put in question the basic argument of the robustness of the limb patterning network. A more convincing reply was presented in a remarkable study by Sheth et al. (2012) [143]. The authors generated a series of mouse mutants which lacked alleles for three genes that have beeen shown to be important in digit formation, namely the distal Hox genes *Hoxd11-13*, *Hoxa13*, and *Gli3*, the major mediator of Sonic Hedgehog sigmaling in limb development. Sheth et al present a total of 15 mutant types: 5 combination of different *Hox* gene deletions; namely *Hoxa13*$^{+/+}$; *Hoxd11-13*$^{+/+}$, *Hoxa13*$^{+/-}$; *Hoxd11-13*$^{+/-}$, *Hoxa13*$^{+/+}$; *Hoxd11-13*$^{-/-}$, and *Hoxa13*$^{-/-}$; *Hoxd11-13*$^{-/-}$. Each of these types was combined with eitehr the normal GLi3 dose, *Gli3*$^{+/+}$, or the heterozygous dose *Gli3*$^{+/\mathrm{XtJ}}$, or the null dose *Gli3*$^{\mathrm{XtJ/XtJ}}$. With progressive removal of *Hox* and Gli3, phenotypes show more and more digits, from the control number of 5 to 13 for the *Hoxd11-13*$^{+/-}$;

Hoxa13-/-;*Gli3*$^{\text{XtJ/XtJ}}$ mutant. Here the number of digits depends on the Hox dose, with finely graduated steps (see Figure 14).

Sheth et al. created in a simple linear reaction-diffusion model, in which the parameters of the reaction kinetics of a generic activator and a generic inhibitor were kept constant except the activator-dependent production rate of the inhibitor, which was assumed to be under the joint control of FGFs and Hox genes. The model showed that indeed, a reduction of Hox dose led to a decrease of the wavelength of the Turing pattern; this wavelength could be tuned through control of the Hox dose.

These experimental results were then incorporated into a much more detailed model by Raspopovic et al. (2014) [128], the so called BSW model. This model takes into account *Sox9*, the earliest skeletal marker in the mouse, bone morphogenetic proteins (BMPs) and WNT. It was found that all three show spatially periodic expression patterns. Sox9 was exactly out of phase with BMP and WNT, i.e. the peaks of concentration of Sox9 coincided with the concentration troughs of BMP and WNT, and vice versa. Two of the regulatory interactions between the three components are known: WNT signaling inhibits Sox9 and BMP upregulates Sox9. The other relationships in a Turing reaction-diffusion network were chosen in such a way that the linearized solutions show the same phase pattern as the experiments, with BMP and WNT being in-phase and Sox9 being exactly out-of-phase relative to them. In the linear reaction kinetics, a third order term was added to prevent blow up of concetrations. This yields the so-called BSW model:

$$\frac{\partial s}{\partial t} = \alpha_s + k_2 b - k_3 w - (s - s')^3$$

$$\frac{\partial b}{\partial t} = \alpha_b - k_4 s - k_5 b + d_b \nabla^2 b$$

$$\frac{\partial w}{\partial t} = \alpha_w - k_7 s - k_9 w + d_w \nabla^2 w$$

Here $s(x,t), b(x,t)$ and $w(x,t)$ are the concentrations of Sox9,BMP, and WNT, respectively. The parameters $\alpha_s, \alpha_w, \alpha_b, k_2, k_3, k_4, k_5, k_7, k_9$ are postive constants, and d_b, d_w are the diffusion coefficients of BMP and WNT, respectively. Note that Sox9 doesn't diffuse.

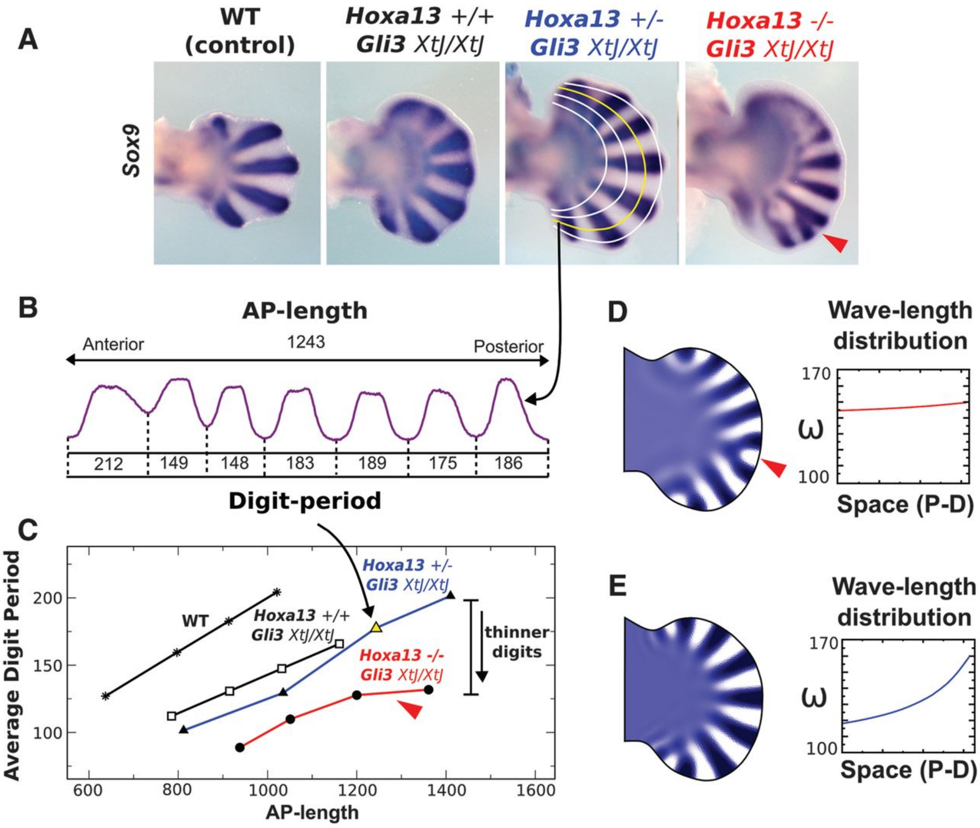

Figure 14: Digit formation is shown in forelimbs. (**A**) Expression of Sox9 in limbs (E12.5) of the $Hoxa13; Gli3$ allelic series. Use of AP profiles for the analysis of $Sox9$ is shown by white and yellow curved lines. A digit bifurcation is pointed by the red arrow and WT means wild type. (**B**) The curved lines indicate the staining intensity of $Sox9$ along the yellow profile of (**A**). Length of AP axis and the duration of each digit formation are measured and presented for $Hoxa13^{+/-}; Gli3^{XtJ/XtJ}$. (**C**) For each case of limb development, the average periods of digit formation versus AP lengths is shown: in case of WT (control) and $Gli3XtJ/XtJ$ (either the normal or heterozygous dose of $Hoxa13$), linear relation is noticed, while in the case of $Hoxa13^{-/-}; Gli3^{XtJ/XtJ}$ (red line), a flatter relation together with bifurcations (red arrowhead) is observed. Corresponding to the yellow line of (**A**) presented in (**B**) is shown by the curved arrow marks. Simulations of the reaction-diffusion model inside an E12.5, *Gli3* mutant limb shape are shown by (**D**) and (**E**). (**D**) Digit bifurcation (red arrow) similar to the $Hoxa13^{-/-} Gli3^{XtJ/XtJ}$ mutants is shown by the concentration of activator which is obtained in the simulation with a uniform modulation of wavelength ω (shown in the graph). (**E**) The result of simulation: a suitable PD gradient based modulated wavelength avoids bifurcations as the wavelength increases with growing AP length. (Modified from [143].)

5 Discussion and Outlook

Recent years have seen the proposal of several new mathematical models of pattern formation in the vertebrate limb, with the the Iber-Badugu model [5], the Glimm-Bhat-Newman galectin model [49] and the BSW model [128]. These models rely on a much more in-depth understanding of relevant gene regulatory networks than previous models. One of the limitations of current modeling approaches is the relative lack of data for species other than the mouse and the chicken. Thus it is presently not clear to which extent the proposed models transcend the specific details of the model organism to reflect generic mechanisms that apply to all tetrapods. For instance, Sox9 expression patterns are quite distinct for the mouse, the chicken and turtles, respectively [98], and Sox9-null limb mesenchyne still exhibits precartilage condensations [6]. In turn, galectin-1 null mice have been shown to have normally developed limb skeletons [45], so that questions about the generality of both the galectin model and the BSW model remain.

All mathematical models presented in this survey have taken into account only a small number of components, in contrast with the hundreds of molecules that have been shown to play a role in limb chondrogenesis. The process itself is characterized by a great robustness and redundancy of many components. Newman et al. argue in [109] that these models are not to be understood as necessarily competing explanations, but rather represent different modules of a multisystem complex which each are capable of generating patterns in a self-organizing way, but whose interplay yields the redundancy which is the source of the extraordinary robustness of the overall patterning process. For instance, they speculate that the BSW network evolved from a differentiation-inducing module that served as a 'readout' of an existing prepattern to a self-organizing patterning system in its own right.

Arguably, despite the progress in recent years with new mathematical models, the conceptual understanding of the mechanisms of chondrogenic pattern formation in the limb is lagging far behind experimental investigations, which have generated huge amounts of data through increasingly sophisticated visualization and experimentation techniques. Besides expanding the investigation of component mechanisms to more species than the mouse and the chicken, the analysis of how these different components may interact, reinforce each other and yield robustness is a crucial future task. Addressing these problems will certainly encompass sophisticated integrated computational multi-scale models carefully vetted against data. However, mathematical analysis of 'small' model will remain relevant, for instance in addressing the question of how two independent self-organizing systems acting in concert may enhance the robustness of the overall patterning process.

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List of morphogens connected with limb development			
Morphogen family	Sub-family	Role	References
FGFs (Fibroblast Growth Factors)	FGF-1 known as FGF acidic	Involved in embryonic development, cell growth, tissue repair etc. Modifies endothelial cell migration and proliferation. Controls blastema cell proliferation at the time of limb regeneration of the amphibians.	[179]
	FGF-2, known as FGF basic	Controls the patterning along Proximo-Distal and Anterior-Posterior axes. Over expression of FGF-2 up-regulates proliferation of mesenchymal cells, leads to a duplications along the Anterior-Posterior axis.	[39, 87, 131] [10, 51, 75, 112, 126]
	FGF-4, also known as FGF-K or K-FGF	Induces limb-bud initiation, growth and patterning. Promotes stem cell proliferation.	[17, 71, 113, 153]
	FGF-5	Enhances expansion of connective tissue fibroblasts. Suppresses skeletal muscle development in the limb.	[22]
	FGF-7, also known as KGF	Induces the formation of an AER in dorsal median ectoderm.	[176]
	FGF-8	Stimulates the activities of AER. Participates in the initiation of Shh expression in the mesoderm. Maintains mesoderm outgrowth and Shh expression in the established limb bud.	[17, 23, 74, 153]
	FGF-9, also known as HBGF-9 and GAF	Involved in formation of proximal skeletal element in the developing limb. Regulates early stages of chondrogenesis and promotes skeletal vascularization and osteogenesis.	[64, 153, 164]
	FGF-10	Regulates fgf10 gene expression in the lateral plate mesoderm and may be involved in the determination process of the limb territories. Acts as an endogenous initiator for limb formation. Involved in communication between limb mesenchyme and AER.	[88, 96, 117, 142]
	FGF-17	Acts similar to FGF-4 and FGF-9.	[74, 87, 93, 113]

	FGF-18	Plays a negative up-regulating role in skeletal development and bone homeostasis. Acts for specification of L-R asymmetry on limb development. Lack of FGF18 in mice results in expanded zones of proliferating and hypertrophic chondrocytes and increased chondrocyte proliferation, differentiation, and Indian hedgehog signaling.	[78, 118, 116]
	FGF-20	Acts similar to FGF-9.	[11, 52]
Hedgehog Family	Indian hedgehog (Ihh)	Involved in the growth of the endochondral skeleton, but is not directly involved in limb development.	[146, 167]
	Shh (Sonic hedgehog)	Regulates vertebrate organogenesis, especially the growth of digits of limbs. Shh is secreted from the ZPA.	[167] [153, 7, 20, 24, 40, 57, 130, 139, 140, 154]
Notch family	Notch-1	Regulates interactions between physically adjacent cells. Contributes in the regulation of mesenchymal apoptosis during digit formation. Involved in limb mesenchymal development, especially has an impact on autopod from the dorsal and/or ventral ectoderm.	[121]
	Notch-2		
	Notch-3		
	Notch-4		
TGFβ (transforming growth factor beta)		Regulates chondrocyte formation, proliferation and differentiation during limb development.	[43, 59, 73, 81]
RA (retinoic acid, a metabolite of vitamin A)		Stimulates the growth of the posterior end of the limb.	[127]
Wnt/beta-catenin		Acts during: 1. limb initiation, 2. limb patterning, 3. late limb morphogenesis, 4. myoblast differentiation in the limb, 5. long bone development.	[21, 58, 175]
TBox	TBX4	Induces the growth of hindlimb.	[125]
	TBX5	Accelerates the expression of FGF10 and growth of forelimb	[125]

Hox genes	HoxA & HoxB	Control the body plan along the craniocaudal axis of an embryo. At a specific position, Hox genes are sequentially activated in a rostrocaudal pattern and this is crucial for the induction of limb growth.	[125]
BMP(Bone morphogenetic protein)		Upregulates the FGF expression.	[5, 11, 12, 177]