Folia Mathematica
Vol. 19, No. 1, pp. 30–49
Acta Universitatis Lodziensis


# MATHEMATICAL MODELS AND COMPUTATIONS IN BIOSCIENCES AND MECHANICS

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## 1. Preface

The Department of Mathematical Analysis and Control Theory from the point of scientific research deal with several domains of mathematical analysis and computer sciences. The members of the Department are engaged in small groups and working in variety of scientific activities. In what follow we describe several of them which are related more or less to the title of the note. We do not give exact results they are or will be published in other journals. Our aim is only to give a reader an insight what kind of problems we study in our Department i.e. it is an introduction to research we do and to which we invite all being interested in to enjoy with us in research.

## 2. Model of Lane - Emden - Fowler type

We begin with the model of Lane - Emden - Fowler type

$$\begin{cases} \triangle u(x) + f(x, u(x)) + g(||x||)x \cdot \nabla u(x) = 0, & \text{for } x \in \Omega_R, \\ \lim\limits_{||x|| \to \infty} u(x) = 0, \end{cases} \tag{1}$$

where $n > 2$, $R > 1$, for $x, y \in \mathbb{R}^n$, $||x|| := \sqrt{\sum\limits_{i=1}^{n} x_i^2}$, and $x \cdot y := \sum\limits_{i=1}^{n} x_i y_i$, $\Omega_R = \{x \in \mathbb{R}^n, ||x|| > R\}$, or its more general form

$$\triangle u(x) + f(x, u(x)) - (u(x))^{-\alpha} ||\nabla u(x)||^{\beta} + g(||x||)x \cdot \nabla u(x) = 0, \tag{2}$$

with $0 < 2\alpha \leq \beta \leq 2$, $f(x, \cdot)$ can be sub- or suberlinear and smoothness is assumed only locally. These models are used to describe some stars structures, in non-Newtonian fluid mechanics and glaciology, in molecular biology and genetic population. The investigations of (1) considered on $\mathbb{R}^n \backslash B(0, r)$, $B(0, r)$ a ball in $\mathbb{R}^n$, concern existence of nondecreasing sequences of positive and bounded classical solutions (see [40]). To prove those results the

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method of subsolutions and supersolutions, basing on the results of Noussair and Swanson, is applied. As a next step the (2) with singular term is study in the same domain. The first results obtained (see [41] ) pertain existence of at least one positive solution to (2). The natural question arise: are the mentioned assumptions on $f(x,\cdot)$ sufficient to get existence of minimal positive solution to (2) i.e. having property that $x \mapsto ||x||^{n-2}u(x)$ is uper bounded and below in $\mathbb{R}^n \backslash B(0,r)$.

## 3. Shape and location of the source

Let us consider an optimum design problem with the aim to determine the best location of hollows $\gamma$ in a given bounded subdomain $\omega$ surrounded by the exterior subdomain $\Omega$ in $\mathbb{R}^2$ with smooth boundaries $\partial\omega$, $\Gamma = \partial\Omega\backslash\partial\omega$. In the interior subdomain $\omega$ the physical phenomenon are described by the linear PDE and in the exterior domain the processes are governed by nonlinear PDE subject to some external function. The design problem can be considered as a two level optimization problem. At the first level an optimal control within a set of admissible controls is determined for a given location of the source. At the second level an optimal location of the source in terms of its characteristic function is selected in such a way that the resulting value of the cost functional is the best possible within the set of admissible locations. Thus we study the following problem of optimizing the shape and location of the source $\gamma$ in $\omega \subset \Omega$:

$$\text{minimize } J(\gamma) = \frac{1}{2}\int_{\Omega}(u(x) - z_d(x))^2 dx \tag{3}$$

subject to

$$-\Delta u(x) = F(x, u(x)), \qquad x \in D\backslash\gamma, \tag{4}$$

$$u(x) = 0, \quad x \in \Gamma, \tag{5}$$

$$u(x) = \varphi(x),\ \partial_n u(x) = \partial_n \varphi(x),\ x \in \partial\omega \tag{6}$$

$$\partial_n u(x) = 0 \ \text{ on } \ \partial\gamma, \tag{7}$$

where $\omega \subsetneq \Omega$ is an open set, such that $\epsilon_2 \geq vol\ \omega \geq \epsilon_1 > 0$. The numbers $\delta$, $\epsilon_1$, $\epsilon_2$ are given; $z_d : \Omega \mapsto \mathbb{R}$ is given target functions, $\varphi : \omega \mapsto \mathbb{R}$, a fixed function, $u : \Omega\backslash\gamma \mapsto \mathbb{R}$ is the state,

$$F(x, u(x)) = \begin{cases} -u^3(x) + f(x), & x \in \Omega \\ 0, & x \in \omega\backslash\gamma. \end{cases}$$

where $f : \Omega \mapsto \mathbb{R}$.Our aim is to apply the particular variational method, widely used in the new approach to optimal control theory, i.e. the dual dynamic programming technique. In this way, we need neither relaxation nor homogenization of the problem under investigation. We develop a new computational technic basing on dual dynamic method to characterize the best approximate location of the source explicitly, which is useful for possible applications (see [30]),i.e. in the above problem we are inerested not only in shape of $\gamma$ but also a location of $\gamma$ in $\omega$.

## 4. NAVIER-STOKES EQUATION, SHAPE OPTIMIZATION

Distortions mean unwanted changes in the size and the shape of the object. During the thermal treatment of steel, the undesired alterations in the size and shape of the workpiece occur. They are the side effects at some stage in the manufacturing chain. Those distortions are caused by the thermal and structural stresses. Phase changes cause modifications in the volume and dimensions. The dimensions of the workpieces under the thermal treatment are differ from their output dimensions. The reason why the thermal treatment may lead to the alterations in a form of geometry is occurrence of the solid-solid phase transition during such treatment. These changes are caused by variations in the microstructure of the material, which is composed of components having different physical and chemical properties. It cause internal stresses along phase boundaries and macroscopic changes in geometry. It has been shown that deformations lead to serious economic losses, for example in the automotive industry. Recently, a new strategy has been developed, which allows us to eliminate deformations already during heat treatment without having the final step in many manufacturing chains. Distortion compensation means finding the desired phase mixture, so that the resulting internal stress and the associated changes in geometry compensate the distortion and thus lead to obtain the object of the desired size and shape. Mathematicaly the above problem can be modeled as follow. Let $\Omega \subset R^2$, $\Omega_1 \subseteq \Omega$, $\Omega_1$ be the domains with Lipschitz boundary, $\Gamma_D$ is a part of the boundary $\partial\Omega$, $\Gamma = \partial\Omega \backslash \bar{\Gamma}_D$, $\bar{\Gamma}_D \cup \Gamma = \partial\Omega$. The state of the crystal structure $u : \bar{\Omega} \to R^2$ with given control $\varphi$ is a weak solution of the Navier-Stokes equation (8)-(10)

$$-div\ \sigma = 0 \text{ in } \Omega, \tag{8}$$

$$u = 0 \text{ on } \Gamma_D, \tag{9}$$

$$\sigma\nu = 0 \text{ on } \partial\Omega \setminus \bar{\Gamma}_D, \tag{10}$$

where

$$\sigma = K\xi(u(x)). \tag{11}$$

$K$ is a stiffness matrix and $\xi$ is the relative linear deformation. To reflect the impact of the phase modeling we introduce the stiffness matrix depending on $\varphi$ and modify the equation (11) of the component $\tilde{\xi}$ representing the internal strain, which will also minimize changes in shape influenced by $\xi$. According to Hooke's law for small deformation we obtain

$$\sigma = K(\varphi(x))(\xi(u(x)) - \tilde{\xi}(\varphi(x), x)), \tag{12}$$

$$\tilde{\xi}(\varphi(x), x) = \left[\beta_1(x) + \frac{1}{2}(\varphi(x) + 1)(\beta_2(x) - \beta_1(x))\right] I, \tag{13}$$

$$K(\varphi(x)) = K_1 + \frac{1}{2}(\varphi(x) + 1)(K_2 - K_1), \tag{14}$$

$\sigma$ is the stress tensor, $I$ is a unit matrix, $\beta_1, \beta_2$ are given functions and

$$\xi(u(x)) = \frac{1}{2}(\nabla u(x) + (\nabla u(x))^T). \tag{15}$$

Let us define the functional, used to obtain a distribution of phases, as follows

$$J(\varphi, u) = J_1(\varphi) + J_2(u)$$

with

$$J_1(\varphi) = \int_\Omega \left(\frac{\gamma\eta}{2}||\nabla\varphi(x)||^2 + \frac{\gamma}{\eta}\psi(\varphi(x))\right) dx, \tag{16}$$

$$J_2(u) = \int_{\Omega_1} L_1(u(x))dx + \int_\Gamma L_2(u(x))dx, \tag{17}$$

The aim of our work is to develop a new method of computation to achieve the approximate optimal solution for optimal shape design problem inf $J(\varphi, u)$, such as system control phases. To this effect we construct the dual dynamic programming approach for approximate minimum. The main difficulties to overcome are the controls on the boundary as well nonlinearity of differential operator $\sigma$. This method allows us to design and describe the structure and components of products made from steel in order to achieve their approximate optimal structure. That problem is investigated in PhD thesis [34].

## 5. A class of epidemic problems with control on the boundary

The epidemic problem man-environment is stated in [7] as optimal control problem. The functional consists of three members and the state equations are governed by two PDE: parabolic linear equation and nonlinear first order equation with feedback operator on the boundary, i.e. the optimal control problem is to minimize

(18)

$$J(u_1, u_2, w) = \int_0^T \int_\Omega F(u_2(t, x)dxdt + \int_0^T \int_{\partial\Omega} h(w(t, x))dxdt + \int_\Omega l(u_2(T, x))dx$$

over all $(u_1, u_2, w)$ subject to state system

$$\frac{\partial u_1}{\partial t} - \Delta u_1 + a_{11}u_1 = 0, \text{in } Q = (0,T) \times \Omega, \tag{19}$$

$$\frac{\partial u_2}{\partial t} + a_{22}u_2 - g(u_1) = 0, \text{in } Q, \tag{20}$$

$$u_1(0,x) = u_1^0(x),\ u_2\ (0,x) = u_2^0(x) \text{ for } x \in \Omega, \tag{21}$$

(22)
$$\frac{\partial u_1}{\partial \nu} + \alpha u_1 = K * u_2 = \int_\Omega K(t,x,\sigma)u_2(t,x)dx,\ (t,\sigma) \in \sum_1 = (0,T) \times \Gamma_1\ ,$$

$$\frac{\partial u_1}{\partial \nu} = 0 \text{ in } \sum_2 = (0,T) \times \Gamma_2\ . \tag{23}$$

where $\Omega$ is a bounded and open subset of $R^2$ with a sufficiently smooth boundary $\Gamma = \Gamma_1 \cup \Gamma_2$, $a_{11}, a_{22}$ and $\alpha$ are positive constants, and

$$K(t,x,\sigma,w) = \sum_{i=1}^{N} w_i(t,\sigma)K_i(x,\sigma) \text{ for } t \in [0,T], x \in \Omega,\ \sigma \in \Gamma_1, \tag{24}$$

$K_i \in L^\infty(\Omega \times \Gamma_1)$, $w_i \in L^\infty((0,T) \times \Gamma_1)$ for $i = 1, ..., N$. We set $w(t,\sigma) = (w_1(t,\sigma), ..., w_N(t,\sigma))$, it is a control function, control on the boundary. In [2] for that problem existence and necessary optimality conditions, as well two gradient type algorithms are derived. In [7] analytical results are given in support of the well posedness of the problem.The essential point in the convergence of gradient algorithm (using the necessary optimality conditions - Pontryagin maximum principle) is that it starts from arbitrary control function and stop when the difference between two computed controls in next two steps is smaller than given $\varepsilon$. However, we do not know whether the calculated sequence of controls converges to optimal control or the values of the cost functional for those controls converge to optimal value. Moreover, we do not know when to stop the proces in order to get near optimal value i.e. whether for calculated controls the cost of the functional is near optimal value (we do not know it a priori). We need sufficient optimal conditions to grasp such an information. In the literature there is not any optimal control theory of sufficient optimality conditions which can be applied to the above control problem. The main reason is that we deal with the state equations having controls on the boundary. In the next section we develop new dual dynamic programming theory to derive verification theorem - sufficient optimality conditions for problem (18)-(22).

However the main advantage of our study is that we also develop sufficient conditions for $\varepsilon$-optimality i.e. we formulate conditions which allow us to assert that for calculated control (e.g. numerically) we know how far we are from optimal value. Just this approximate theory is fundamental for our numerical algorithm (for details see [35]).

## 6. Shape optimisation for a class of epidemic problems

The epidemic problem with local control applied to a subregion of the whole habitat we are interested in is described and analyzed in [3]. However in that paper mainly stabilization problem had been considered. Our aim is to formulate an optimal control problem with respect to some functional depending on sanitation parameters $\gamma_1$, $\gamma_2$ applied to a suitable subregion $\omega$ of the whole habitat $\Omega$, i.e. our controls are $\gamma_1$, $\gamma_2$ and a subregion $\omega$. Thus we are looking not only for an optimal control $\gamma = (\gamma_1, \gamma_2)$ but also for a shape of $\omega$ which may consist of a finite number of mutually disjoint subdomains.

Problem (P): minimize

$$J(u_1, u_2, \gamma, \omega) = \int_0^T \int_\Omega \beta(\gamma_1(x) u_1(t,x)) \chi_\omega(x) dx dt$$

$$+ \int_0^T \int_\Omega \lambda(\gamma_2(x) u_2(t,x)) \chi_\omega(x) dx dt + \int_\Omega l(u_2(T,x)) dx \tag{25}$$

over all $(\gamma, \omega)$ and $u_1, u_2$ subject to the state system

$$\frac{\partial u_1}{\partial t}(t,x) - d_1 \Delta u_1(t,x) + a_{11} u_1(t,x)$$

$$= \int_\Omega k(x,x') u_2(x',t) dx' - \gamma_1(x) \chi_\omega(x) u_1(t,x) \text{ in } Q = (0,T) \times \Omega, \tag{26}$$

$$\frac{\partial u_2}{\partial t}(t,x) + a_{22} u_2(t,x) + g(u_1(t,x)) = -\gamma_2(x) \chi_\omega(x) u_2 \ (t,x) \in Q, \tag{27}$$

$$u_1(0,x) = u_1^0(x), \ u_2(0,x) = u_2^0(x) \text{ for } x \in \Omega, \tag{28}$$

$$\frac{\partial u_1}{\partial \nu}(t,x) + \alpha u_1(t,x) = 0, \ (t,\sigma) \in \Sigma = (0,T) \times \partial\Omega. \tag{29}$$

The idea underlying the choice of the chosen cost functional is the following:

$$\int_0^T \int_\Omega \beta(\gamma_1(x) u_1(t,x)) \chi_\omega(x) dx dt$$

represents the cost of the programme of sanitation of the environment in the subregion $\omega$;

$$\int_0^T \int_\Omega \lambda(\gamma_2(x)u_2(t,x))\chi_\omega(x)dxdt$$

represents the cost of treatment of the infected population in the subregion $\omega$;

$$\int_\Omega l(u_2(T,x))dx$$

represents the negative psychological and economic effects due to the duration of the epidemic in the entire habitat $\Omega$. $\beta, \lambda, l$ are suitably chosen continuous functions. We assume

(30)

$$u_1(t,x), u_2(t,x) \geq 0,\ (t,x) \in\ Q; \gamma_1, \gamma_2 \in L^\infty(\Omega), \gamma_1(x), \gamma_2(x) \geq \delta > 0, x \in \Omega,$$

where $\Omega$ is a bounded and open subset of $\boldsymbol{R}^N$ with a sufficiently smooth boundary $\Gamma = \partial\Omega$; $d, a_{11}, a_{22}$ and $\alpha$ are positive constants and $k \in L^\infty(\Omega \times \Omega)$, $k(x,x') \geq 0$ a.e. in $\Omega \times \Omega$ such that

$$\int_\Omega k(x,x')dx > 0, \quad \text{a.e. } x' \in \Omega. \tag{31}$$

$u_1^0, u_2^0 \in L^\infty(\Omega)$, $u_1^0(x)\ u_2^0(x) \geq 0$ a.e. in $\Omega$. Moreover we assume that $\omega \subsetneq \Omega$ is an open set such that $vol\ \Omega \geq vol\ \omega \geq \epsilon > 0$ where $\epsilon, \delta$ are given numbers; $\chi_\omega$ is the characteristic function of $\omega$. We set $\gamma = (\gamma_1\ \ \gamma_2)$ as control function in $\omega$, while $(u_1, u_2) : Q \to \boldsymbol{R}^2$ denotes the state. We assume $g : \boldsymbol{R} \times \boldsymbol{R} \to [0,\infty)$ to be Lipschitz continuous and increasing with respect to the second variable in $[0,\infty)$; $g(y,s) = 0$ for $y \in \boldsymbol{R}$ and $s \in (-\infty, 0]$, $g(\cdot, s)$ measurable for $s \in \boldsymbol{R}$ . Let us observe that by [5], [6] we have the existence, uniqueness and nonnegativity of solutions to (26) - (29).

In [2] for a different epidemic problem - no control being a set, existence and necessary optimality conditions, as well two gradient type algorithm are derived. Essential point in the convergence of gradient algorithm (using the necessary optimality conditions - Pontryagin maximum principle) is that it starts from arbitrary control function and stop when the difference between two computed controls in next two steps is smaller than given $\varepsilon$. However we do not know whether the calculated sequence of controls converges to optimal control or the values of the cost functional for those controls and corresponding states converges to optimal value. To the knowledge of the authors, in literature there is no optimal control theory providing sufficient conditions which can be applied to the above control problem. The main reason is that we deal with the state equations with controls being sets.

Problems with the characteristic function of a subset $\omega$ being unknown appear in many papers. In [7] the optimum design for two-dimensional wave equation is studied and an optimal location of the support of the control for one-dimensional wave equation is determined, in [22] the optimal geometry for controls in stabilization problem is considered. In all mentioned papers different approaches to the design problems have been investigated, and some numerical results are presented. A problem similar to (P), but with all integrals taken over $\omega$ and without control $v$, is discussed from the point of view of the existence of an optimal shape in the book [7] and from the geometrical point. The existence of an optimum design is essential if we have not at hand any sufficient optimality conditions. From the beginning of the last century, under strong influence of Hilbert, the existence issue became one of the fundamental questions in many branches of mathematics, especially in calculus of variations as well as in its branch, the optimal control theory. Of course, following the existence proof, the next step is the derivation of necessary optimality conditions and evaluation of the minimum argument. However, it should be pointed out that for many variational problems the existence of a solution accompanied by some necessary optimality conditions are not sufficient to find the argument of minimum in practice. On the other hand, having in hand a stronger result, i.e., the sufficient optimality conditions for a minimum in a specific problem, replaces the requirement for the existence. In the calculus of variations it was pointed out already by Weierstrass that the most important from a practical point of view for the solution procedure are the so-called sufficient optimality conditions for a *relative* minimum, i.e. the optimality conditions relative to some possibly smaller set of arguments of functional which is determined by additional (practical) conditions. Some steps in this direction were done in [39] where the functional is quadratic and the state equation is linear and elliptic with Dirichlet boundary condition. Now we develop new dual dynamic programming theory to derive verification theorem - sufficient optimality conditions for problem (25)-(29). However the main advantage of that approach is that we also develop sufficient conditions for $\varepsilon$-optimality i.e. we formulate conditions which allow us to assert that for calculated control (e.g. numerically) we know how far we are from optimal value. Just this approximate theory is fundamental for our numerical algorithm (for details see [1]).

## 7. Optimal control of inhibiting tumor growth by GM-CSF, sufficient $\varepsilon-$optimality

In recent time was done experiments which measured the effect of inhibiting tumor growth by GM-CSF treatment in mice with HIF-1$\alpha$-defcient or

HIF-2$\alpha$-defcient macrophages (see e.g. [16], [17], [18]). In the paper [15] these experiments were presented by a mathematical model based on a system of partial differential equations. More exactly in [15] was developed a mathematical model of a tumor that includes the interactions among tumor cells (live or dead), macrophages, endothelial cells, and the cytokines, such as M-CSF, GM-CSF, VEGF, sVEGFR-1, MCP-1/CCL2, and oxygen. It was also included the effects of HIF-1 and HIF-2 in GM-CSF-treated or untreated tumor growth. The boundary of the tumor moves with velocity $\vec{v}$ in the direction of the normal. The model is used to predict the growth of the tumor volume under partial blocking of HIF-1 or stabilization of HIF-2, with injection of GM-CSF. Such results can be used to evaluate the benefit of therapeutic intervention targeting HIF-1 inhibition. The model focus on major cells such as live/dead tumor cells, macrophages and endothelial cells (EC) and the cytokines include M-CSF, MCP-1/CCL2, GM-CSF, VEGF, sVEGFR-1, as well as oxygen molecules. This is a two-phase free boundary model: the tumor is modeled as a growing continuum $\Omega(t)$ with boundary $\partial\Omega(t)$, both of which evolve in time. The tumor region $\Omega(t)$ is contained in a fixed domain $D \subset \boldsymbol{R}^3$ and the region $D \setminus \Omega(t)$ represents the healthy tissue. Both live and dead tumor cells are assumed to be in $\Omega(t)$ while macrophages and EC are assumed to be in both tumor and healthy tissue; cytokines and oxygen molecules can diffuse throughout the whole domain $D$. A macroscopic velocity field $\boldsymbol{v}$ in $\Omega(t)$ is not zero, while $\boldsymbol{v} = 0$ in $D \setminus \Omega(t)$. The tumor size is determined by the volume of $\Omega(t)$. The system of ten equations - live tumor cells density is written as:

$$\frac{\partial c}{\partial t} + \bigtriangledown \cdot (c\boldsymbol{v}) = \lambda_1(w)c(1 - \frac{c}{c^*}) - \lambda_2(w)c - \mu_c c, \tag{32}$$

where c* is the carrying capacity of the cells, proliferation and necrosis directly depend on oxygen level thus it is given by piecewise linear approximations

$$\lambda_1(w) = \left\{ \begin{array}{ll} 0 & \text{if } w < w_h, \\ \lambda_1(w - w_h)/(w_0 - w_h) & \text{if } w_h \le w \le w_0, \\ \lambda_1 & \text{if } w > w_0, \end{array} \right\},$$

$$\lambda_2(w) = \left\{ \begin{array}{ll} \lambda_2 & \text{if } w < w_n, \\ \lambda_2(w_h - w)/(w_h - w_n) & \text{if } w_n \le w \le w_h, \\ 0 & \text{if } w > w_h, \end{array} \right\},$$

where $w_0$ is the normal oxygen level, while $[0, w_n]$ , $(w_n, w_h]$ and $(w_h, w_o]$ are oxygen levels in necrosis, extreme hypoxia and hypoxia. The equation of dead tumor cells is given by

$$\frac{\partial b}{\partial t} + \bigtriangledown \cdot (b\boldsymbol{v}) = \lambda_2(w)c + \mu_c c - \mu_b \frac{w}{w_0} mb. \tag{33}$$

Two first terms (cells death due to necrosis and apoptosis) of the right side are obtained from previous equation. The last term means clearing cells by macrophages. The equation

$$\frac{\partial m}{\partial t} + \bigtriangledown \cdot (m\boldsymbol{v}) = - \bigtriangledown \cdot (k_p m \bigtriangledown p) - \bigtriangledown \cdot (k_g m \bigtriangledown g), \tag{34}$$

describes macrophage density, chemotactic coefficients $k_p$ and $k_g$ are assumed to be constant. The evolution equation for density of EC is

$$\frac{\partial e}{\partial t} + \bigtriangledown \cdot (e\boldsymbol{v}) = - \bigtriangledown \cdot (k_h e \bigtriangledown h), \tag{35}$$

chemotactic coefficients $k_h$ is assumed to be constant as well. In the above equations diffusion was ignored due to its not significant value. The equation of M-CSF density is

$$\frac{\partial q}{\partial t} + \bigtriangledown \cdot (q\boldsymbol{v}) = \bigtriangledown \cdot (D_q \bigtriangledown q) + \lambda_3 c - \mu_q q, \tag{36}$$

where constant $\lambda_3$ is secretion rate of M-CSF by tumor cells and decay rate $\mu_q$ is also constant. The MCP-1/CCL2 is secreted by macrophages in a response to binding M-CSF by receptors:

$$\frac{\partial p}{\partial t} + \bigtriangledown \cdot (p\boldsymbol{v}) = \bigtriangledown \cdot (D_p \bigtriangledown p) + \lambda_4(w) \frac{q}{q + q_0} m - \mu_p p, \tag{37}$$

decay rate $\mu_p$ is also constant, the second term of the right side of the equation depends on oxygen level being piecewise linear function $\lambda_4$

$$\lambda_4(w) = \left\{ \begin{array}{ll} 0 & \text{if } w < w_n, \\ 0.4\lambda_4 & \text{if } w_n \le w \le w_h, \\ \lambda_4 & \text{if } w > w_h. \end{array} \right\}$$

The VEGF density is described with constant decay rate $\mu_h$ by

$$\frac{\partial h}{\partial t} + \bigtriangledown \cdot (h\boldsymbol{v}) = \bigtriangledown \cdot (D_h \bigtriangledown h) + \lambda_5(w)c + \theta_1 \lambda_6(w) \frac{q}{q + q_0} m - \overline{\mu}_s sh - \mu_h h, \tag{38}$$

where $\lambda_5(w) = \lambda_5 \phi(w)$ and

$$\Phi(w) = \left\{ \begin{array}{ll} 0 & \text{if } w < w_n, \\ (w - w_n)/(w^* - w_n) & \text{if } w_n \le w < w^*, \\ 1 - 0.7(w - w^*)/(w_0 - w^*) & \text{if } w^* < w \le w_0, \\ 0.3 & \text{if } w > w_0, \end{array} \right\}$$

where $w^* \in (w_h, w_0)$ refers to the threshold at which the hypoxic effect is maximal. The equation for sVEGFR-1 density

$$\frac{\partial s}{\partial t} + \bigtriangledown \cdot (s\boldsymbol{v}) = \bigtriangledown \cdot (D_s \bigtriangledown s) + \theta_2 \lambda_7 \frac{g + \overline{v} g_0}{g + g_0} m - \overline{\mu}_h hs - \mu_s s, \tag{39}$$

where coefficient $\theta_2$ has value equals 1 for normal mice whereas it is much smaller than 1 for mice with HIF-2$\alpha$ deficient macrophages. In normal situation macrophages secret relatively small amount of this cytokine, that is why small factor $\overline{v}$ was added. Coefficient $g_0$ is saturation and the last term is constant decay rate $\mu_s$. All elements influencing oxygen level are described in

$$\frac{\partial w}{\partial t} + \bigtriangledown \cdot (w\boldsymbol{v}) = \bigtriangledown \cdot (D_w \bigtriangledown w) + \lambda_8 e - \lambda_9 mw - \lambda_{10} cw. \tag{40}$$

Oxygen is delivered by diffusion (first term of the right side) and by endothelial cells (second term of the right side), it is also consumed by macrophages (third term of the right side) and live tumor cells (fourth term of the right side) and at the same time. The last equation

$$\frac{\partial g}{\partial t} + \bigtriangledown \cdot (g\boldsymbol{v}) = \bigtriangledown \cdot (D_g \bigtriangledown g) + u(t) - \mu_g g, \tag{41}$$

describes GM-CSF density. Mainly it depends on injection (control) $u(t)$, being periodic function. In [15] the above model for simplicity is considered to be a spherical model i.e. $D$ is a closed, fixed spherical domain with radius $r = L$ and $\Omega(t)$ is a spheroid with time-dependent radius $r = R(t)$. The endothelial cells, macrophages, cytokines and oxygen move in the domain $[0, L]$. We do not make these restrictions and as it is seen in numerical calculations the tumor, in general, is not a spheroid. However if we do not confine ourselves to the spheroidal tumor then we have lack equations for three more velocity. In [15] we have only one velocity - radial velocity. We derive these three additional equations for three more velocities from the algebraic equation $c + b + m + e = \theta_3 c^*$ and equations (32)-(35) i.e. we get:
(42)

$$\Delta\theta_3 c^* v_1 - \Delta P r_{r_1}(\lambda_1(w)c(1 - \frac{c}{c^*})) + \Delta(k_p m \frac{\partial p}{\partial r_1}) + \Delta(k_g m \frac{\partial g}{\partial r_1}) + \Delta(k_h e \frac{\partial h}{\partial r_1}) = 0,$$

(43)

$$\Delta\theta_3 c^* v_2 - \Delta P r_{r_2}(\mu_b \frac{w}{w_0} mb) + \Delta(k_p m \frac{\partial p}{\partial r_2}) + \Delta(k_g m \frac{\partial g}{\partial r_2}) + \Delta(k_h e \frac{\partial h}{\partial r_2}) = 0,$$

(44) $$\Delta\theta_3 c^* v_3 + \Delta(k_p m \frac{\partial p}{\partial r_3}) + \Delta(k_g m \frac{\partial g}{\partial r_3}) + \Delta(k_h e \frac{\partial h}{\partial r_3}) = 0.$$

The optimal control problem takes the form:

(45) $$\text{minimize } J(x,u) = \frac{1}{I}\int_0^T u(t)dt + \int_{\Omega(T)} c(r,T)dr$$

subject to the above thirteen equations (32)-(44). We develop dual dynamic programming theory to derive verification theorem - sufficient $\varepsilon$-optimality conditions for approximate solutions of problem the above. The aim of the verification theorem is to give some conditions which allow to verify when the $(u_\varepsilon, x_\varepsilon)$ is approximate ($\varepsilon$-optimal) pair for $J$. We develop approximate approach to dual dynamic programming theory and verification theorem. That approximate approach to the above problem allows us to present numerical algorithm which can also be some hints how to apply drugs to minimize tumor (for details see [25], PhD thesis [24]).

## 8. $\varepsilon$-optimality conditions for existence of athero- sclerosis

The disease-atherosclerosis, is the leading cause of death over the world. It originates from a plaque which builds up in the arteries and may eventually trigger a heart attack or a stroke. There are a several mathematical models that describe the growth of a plaque in the artery. All these models recognize the critical role of the "bad" cholesterols, LDL, and the "good" cholesterol, HDL, in determining whether a plaque, once formed, will grow or shrink. The most recent and most comprehensive model (see [4], [33]) includes smooth muscle cells, $\boldsymbol{T}$ cells and various cytokines satisfies a system of 17 PDEs. In [4] is determined by rigorous mathematical analysis, whether small steady state plaques exist and whether they are stable. In turn in [19] is investigated significant simplification of the model from [4] and finally the system of four equations is considered. In this paper basing on the model from [4] we build an optimal control problem allowing to find solution how to control LDL and HDL to shrink the plaque. We construct sufficient optimality conditions allowing to assert that the control satisfying some conditions is realy optimal. Next on this basis we develop approximate optimaity conditions and provide sufficient $\epsilon$-optimality conditions for approximate minimum. That in turn allows us to formulate and to describe numerical algorithm for calculation an approximate control and approximate value. In the last section we give effective example of applying numerical algorithm. We shall follow the same geometry as in simplified model form [19] i.e. the artery is assumed to be a long circular cylinder, its diameter, $2B$, will be taken to be 2 $cm$, and all variables are functions of $(t,s)$ only. The plaque is given by $R(t) < s < 1$, where $s$ is measured in unit of $cm$, and $t$ is measured in unit of $days$, we assume $t \in [0,\mathcal{T}]$. The optimal control problem reads:

$$\text{minimize} \int_0^{\mathcal{T}} (2u_1 + 2u_2 + 2u_3 + u_4 + u_5 + u_6)dt + (1 - R(\mathcal{T})) \tag{46}$$

subject to

$$\frac{\partial H}{\partial t} - D\Delta H = -u_1 k_H r H - \frac{\varphi_H(u_1,u_2)k_{AF}}{1+m}\frac{HF}{K_F+F}, \tag{47}$$

$$\begin{aligned} \frac{\partial L_{OX}}{\partial t} - D\Delta L_{OX} = \ & -u_2 k_{L_{OX}} r L_{OX} \\ & -\varphi_{L_{OX}}(u_1,u_2) \left(\lambda_{L_{OX}M_1}\frac{L_{OX}}{K_{L_{OX}}+L_{OX}}M_1 \right. \\ & \left. -\lambda_{L_{OX}M_2}\frac{L_{OX}}{K_{L_{OX}}+L_{OX}}M_2\right), \end{aligned} \tag{48}$$

$$\begin{aligned} \frac{\partial M_1}{\partial t} + \nabla\cdot(\boldsymbol{u}M_1) & \\ -D\Delta M_1 \ = \ & -\nabla(M_1\chi_C\nabla P) + \lambda_{M_1I_\gamma}M_1\frac{I_\gamma}{I_\gamma+K_{I_\gamma}} \\ & -\lambda_{L_{OX}M_1}\frac{L_{OX}}{K_{L_{OX}}+L_{OX}}M_1 - d_{M_1}M_1, \end{aligned} \tag{49}$$

$$\begin{aligned} \frac{\partial M_2}{\partial t} + \nabla\cdot(\boldsymbol{u}M_2) & \\ -D\Delta M_2 \ = \ & \frac{\varphi_H(u_1,u_2)k_{AF}}{1+m}\frac{HF}{K_F+F}, \end{aligned} \tag{50}$$

$$\begin{aligned} \frac{\partial F}{\partial t} + \nabla\cdot(\boldsymbol{u}F) & \\ -D\Delta F \ = \ & \lambda_{L_{OX}M_1}\frac{L_{OX}}{K_{L_{OX}}+L_{OX}}M_1 \\ & -\frac{\varphi_H(u_1,u_2)k_{AF}}{1+m}\frac{HF}{K_F+F} - d_F F, \end{aligned} \tag{51}$$

$$\frac{\partial L}{\partial t} - D\Delta L = -u_3 k_L r L, \tag{52}$$

$$\frac{\partial r}{\partial t} - D\Delta r = r_0 - u_4 r(k_L L + k_H H), \tag{53}$$

$$\frac{\partial P}{\partial t} - D\Delta P = \lambda_{PE} \frac{L_{OX}}{K_{L_{OX}} + L_{OX}} M_1 - d_P P, \tag{54}$$

$$\frac{\partial I_\gamma}{\partial t} - D\Delta I_\gamma = \lambda_{I_\gamma T} T - d_{I_\gamma} I_\gamma, \tag{55}$$

$$\begin{aligned} \frac{\partial I_{12}}{\partial t} - D\Delta I_{12} &= \lambda_{I_{12} M_1} M_1 \frac{M_1}{K_{M_1} + M_1} (1 + \frac{I_\gamma}{K_{I_{12}} H + I_\gamma}) \\ &\quad + \lambda_{I_{12} F} \frac{F}{K_F + F} - d_{I_{12}} I_{12}, \end{aligned} \tag{56}$$

$$\frac{\partial G}{\partial t} - D\Delta G = \lambda_{GM_1} M_1 + \lambda_{GF} F + \lambda_{GS} S - d_{I_\gamma} I_\gamma, \tag{57}$$

$$\frac{\partial Q}{\partial t} - D\Delta Q = \lambda_{QS} S + \lambda_{QM_1} M_1 - d_{Q_r Q} Q_r Q - d_Q Q, \tag{58}$$

$$\frac{\partial Q_r}{\partial t} - D\Delta Q_r = \lambda_{Q_r S} S + \lambda_{Q_r M_1} M_1 - d_{Q_r Q} Q_r Q - d_{Q_r} Q_r, \tag{59}$$

$$\frac{\partial T}{\partial t} + \nabla \cdot (\boldsymbol{u} T) - D\Delta T = \lambda_{T I_{12}} \frac{M_1}{K_{M_1} + M_1} I_{12} - d_T T, \tag{60}$$

$$\frac{\partial S}{\partial t} + \nabla \cdot (\boldsymbol{u} S) - D\Delta S = -\nabla \cdot (S \chi_C \nabla P) - \nabla \cdot (S \chi_C \nabla G) - \nabla \cdot (S \chi_C \nabla \rho), \tag{61}$$

$$-\Delta \sigma + D\Delta \rho = \phi + \psi + u_5, \tag{62}$$

$$\frac{\partial \rho}{\partial t} - D\rho\Delta\rho = -(\phi + \psi)\rho + \nabla\sigma \cdot \nabla\rho + \psi, \tag{63}$$

where $\phi$, $\psi$ and boundary conditions are as in the former section except the control on the boundary $s = R(t)$ for $H, L_{OX}, L, F$:

$$\frac{\partial H}{\partial n} + \alpha\alpha_H(H - H_0) = u_1, \tag{64}$$

$$\frac{\partial L_{OX}}{\partial n} = u_2, \tag{65}$$

$$\frac{\partial F}{\partial n} = u_6, \tag{66}$$

$$\frac{\partial L}{\partial n} + \alpha\alpha_L(L - L_0) = u_3, \tag{67}$$

and $R(t)$ satisfies the equation (velocity $V_n = -\frac{\partial\sigma}{\partial n}$)

$$\frac{dR(t)}{dt} = V_n(R(t), t), \quad t \in [0, \mathcal{T}]. \tag{68}$$

For datails on results for that problems see [36], [38]

## 9. Analysis of blowup time for diffusion equations with control by new dynamic programming approach

The phenomenon of blowup time in the theory of reaction diffusion equations is of great interest as from theoretical as well practical point of view. The model problem is semilinear parabolic equation to which we add a control $u$ in a source function:

$$x_t - \Delta x = f(t, z, x, u) \quad \text{in } \mathbb{R}^+ \times D, \tag{69}$$

$$x(t, z) = 0 \qquad \text{on } \mathbb{R}^+ \times \partial D, \tag{70}$$

$$x(0, z) = v_0(z), \tag{71}$$

This type of problems arise in a great variety of situations where, as well as diffusive transport of heat or mass, there is some source term representing, for example, heat generation or population growth. The usual interpretation of this equation is that $x$ represents the temperature of a substance in $D \subset \mathbb{R}^N$ subject to chemical reaction and $f$ represent a heat source under control $u$ due to an exothermic reaction. The diffusion and the boundary condition have the tendency to decrease the solution, as in problem ( 69)-( 71) reaction together with control, diffusion and the cooling at the boundary act together simultaneously, it is natural to ask which one prevails. The solution ceases to exist if $\lim_{t\to T^-} \sup_{z\in D} |x(t,z)| = \infty$ for some $T > 0$ i.e. a solution exists only on the interval $[0, T)$. Blow-up phenomena for reaction-diffusion problems in bounded domains have been studied by many authors (see e.g. [8], [28], [22], [21] and the references therein). We analyse the problem of controlling a system which may blow up in finite time. We want to minimize the blowup time as it is a case e.g. with fuel efficiency in a car engine . The first who studied optimal control of blowup were Baron and Liu [9] in 1996. In [9] was mentioned that the authors were motivated by distributed system i.e. by system like ( 69)-( 71), however as they considered such a control problem is "substantially more difficult than the case of ordinary differential equations". In that paper the authors studied optimal control of blowup for autonomous ordinary differential equations (ODE). The theory of necessary conditions for an optimal control for the blowup problem is developed and the Pontryagin maximum principle is derived on the basis of the Hamilton-Jacobi equation. In the subsequent paper of those authors [10] they studied the problem of controlled diffusions for stochastic Ito equations. In last ten years several authors continue the research of [9] for ordinary differential equations see e.g. [29], [31], [32]. In all those papers the functionals are blowup time and in most of them autonomous systems are investigated only. In [32] a special type of non-autonomous system is considered. The main goals of those papers are existence of optimal control for blowup as well necessary optimality conditions. Sufficient optimality conditions for controlled blowup time are not investigated up to now in any papers. As it is noted in [9] when we tread the blowup problem for ( 69)-( 71) we have to face the difficulties with obtaining the regularity of the blowup time with respect to the initial data. Since the initial data is now in a function space we need to determine the Frechet or Gateaux differentiability of the blowup time and the regularity of the associated value function. Differentiability of the blowup time is not known even for the uncontrolled case with the semilinear parabolic model problem. The aim of our study is to construct a new dynamic programming approach to optimal control of blowup for ( 69)-( 71) and to prove verification theorem (sufficient optimality conditions) in terms of these new dynamic programming notions. In this approach we do not need any regularities of value function. We extend our primal space $(t, z, x)$ to a space $(t, z, x, y)$ in which we define new dynamic programming equation. This approach is in the spirit of machine learning described first by Vapnik [45]. The solution of that equation allows us to define new trajectories $y(t, z)$ in the space $(t, z, y)$ and relation between primal trajectories $x(t, z)$ and new one $y(t, z)$. Next we define new set of admissible pairs $(x, u)$ at which we look for minimum of blowup time. This means we look for relative minimum in the sense of Weierstrass. In practice to calculate any blowup time we use numerical methods and thus we obtain only approximate solution. Therefore we need a verification theorem which allow us to check whether calculated blowup time is really near optimal. To this effect we construct and prove theory of approximate solution to new dynamic programming equation in the form of verification theorem. That means we prove that each solution to that inequality is approximate ( $\varepsilon$-optimal) blowup time. Fot detaila see [37]

## 10. Geometric properties of the Fuglede modulus and the module of a foliation

Fuglede $p$–modulus, where $p > 1$, (associated with the Lebesgue measures of leaves of foliations on Riemannian manifolds) can be defined for any system of measures, but for our purposes we use this notion in a particular case. Let $\mathcal{F}$ be a foliation on a Riemannian manifold $(M, g)$. By a $p$–modulus of $\mathcal{F}$ we mean the number

$$\operatorname{mod}_p(\mathcal{F}) = \inf_f \int_M f^p \operatorname{vol}_M,$$

where infimum is taken with respect to all Borel non–negative functions $f$ such that $\int_L f \operatorname{vol}_L > 1$ for all leaves $L \in \mathcal{F}$ (called admissible). If such function does not exist we put $\operatorname{mod}_p(\mathcal{F}) = \infty$. An admissible function $f_0$ realizing the infimum is called extremal.

It appears that $p$–modulus or, more precisely, extremal function, if exists, carries geometric properties of $\mathcal{F}$ and its orthogonal complement $\mathcal{F}^{\perp}$. For example, if $\mathcal{F}$ has closed leaves and $f_0$ is $C^2$–smooth then the mean curvature of $\mathcal{F}^{\perp}$ equals $H_{\mathcal{F}^{\perp}} = (p-1)\nabla^{\top}(\ln f_0)$ [14]. Considering the $p$–modulus functional we derive the conditions for critical points [11] and stability (in the codimension one case) [13] written in terms of mean curvature vectors and geometric quantities involving Ricci curvature, derivatives of extremal function and derivatives of normal unit vector. The key observation that led to all these results is the integral formula, which in a sense relates the integral over the leaves with the integral over the manifold [14]. Moreover, we have studied the condition $\operatorname{mod}_p(\mathcal{F})\operatorname{mod}_q(\mathcal{F}^{\perp}) = 1$, where $p$ and $q$ are conjugate coefficients, showing that this condition holds for conjugate submersions [12].

The module of a foliation is a generalization of the capacity of a condenser. For a given exponent $p \geq 1$, $p$-module is defined as the infimum of $L^p$-norms of the family of the admissible functions, i.e. functions satisfying certain conditions. That notion has evolved from the module of a family of plane curves to the module of a family of k-dimensional submanifolds of an arbitrary Riemannian manifold. In particular, we can consider the module of a foliation. The inspiration for those study were the papers [12] and [42], in which sufficient conditions for the product of modules being 1 are formulated : in the case of a pair of orthogonal foliations and a pair of condensers, respectively. It is considered a diffeomorphism $G : M \to N$, acting between two Riemannian manifolds, and one examines the relation between the structure of the Jacobian of $G$ and the conservation of the module of a foliation, or the conservation of the product of modules of a finite number of mutually orthogonal foliations, by that diffeomorphism. From this relation one derives sufficient conditions for the product of modules of a finite system of foliations being 1. Moreover, generalizing the notion of the module of a family of $k$-forms, one can consider the module of a family of $k$-chains, defined on a Riemannian manifold. Owing to that, it is possible to compute the module of a singular homology class. The formula for the module of each element of a $k$-dimensional homology group on the flat torus are derived. It is also worth to mention that a considerable part of PhD thesis ([26]) is devoted to the module of a geodesic foliation on the flat torus .

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