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Priti Kumar Roy · Xianbing Cao · Xue-Zhi Li · Pratulananda Das · Satya Deo *Editors*

Mathematical Analysis and Applications in Modeling

ICMAAM 2018, Kolkata, India, January 9–12

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Preface

International Conference on "Mathematical Analysis and Applications in Modeling" was held on January 9–12, 2018 at the Department of Mathematics, Jadavpur University, Kolkata, India. The talks, both invited and contributory, during the conference period covered various branches of Pure and Applied Mathematics. The present volume of this book series, entitled *Mathematical Analysis and Applications in Modeling*, is based on the selected invited and contributory talks during the abovementioned international conference. The conference was inaugurated by Pro-Vice-Chancellor of Jadavpur University. World-renowned scientist Dr. Gaston N'Guerekata, currently holding the chair of Associate Dean for Undergraduate Studies and University Distinguished Professor of School of Computer, Mathematical and Natural Sciences at the Morgan State University, Baltimore, USA, chaired the inaugural session. Dr. Igor Schreiber, the renowned Professor at the Department of Chemical Engineering (UCHI) of the University of Chemistry and Technology, Prague, Czech Republic, was the honorable guest who delivered the keynote address. There were 15 plenary lectures, 17 invited lectures, and 168 eight contributory lectures given by the participants. There were more than 300 participants from different parts of India and abroad. NBHM, ISI Kolkata and DST-PURSE provided us financial support to organize this conference without any hurdle.

Both the invited and contributory talks touch various areas of pure and applied mathematics and illustrate the latest advances in the field of mathematics, medical sciences, oil exploration from environmentally friendly, renewable resources and production, dynamical systems, biological sciences, algebra, analysis, etc.

This book contains 37 chapters from different mathematical fields. These chapters include reaction network theory, periodic evolution equations, optimization models, topology, compositional square root functions, atherosclerotic plaque formation, effects of unequal diffusion coefficients, cellular neural network model, coordinate search method, two-echelon supply chain, quasi-isometric invariants, statistical outlook, gravitational waves, Banach spaces, large-scale production of biodiesel, bifurcation control, and many other branches of mathematics. Thus this

book is useful to gain knowledge about the streams of mathematics covered by the chapters.

We expect this book will draw an immense impact on theoretical and application fields of Mathematics and hence on the whole world of Science. Our endeavor is to enlighten each and every unknown or less known branch of Mathematics, which was the one-point goal of our international conference.

It is not easy to sum up all the topics based on different fields of Mathematics and its application in 37 chapters. But we and our team tried our level best to cover all the branches to make the unknown known. We can call our initiative successful if this book will help the students in their research and contribute to societal benefits.

We thank the Almighty, our friends, scholars, well-wishers, and our family for their cordial support and assistance in finishing this job and publishing this book series for a better knowledge of different fields of Mathematics. With all our willpower, energy, constructive mind, and time, we have tried to be the editor of such a scientifically useful book series of various research articles with supreme concern. If there is any inaccuracy or drawbacks in this book, we are ready to take all the responsibilities and we wish to receive fruitful suggestions for improvement of our future work as editors.

Kolkata, India — Prof. Dr. Priti Kumar Roy
Beijing, China — Prof. Dr. Xianbing Cao
Xinxiang, China — Prof. Dr. Xue-Zhi Li
Kolkata, India — Prof. Dr. Pratulananda Das
Allahabad, India — Prof. Dr. Satya Deo

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We would like to thank Shamim Ahamad, Editor for Mathematics & Statistics, Springer IN to write a book on the subject Springer Proceedings in Mathematics & Statistics, with book title *Mathematical Analysis and Applications in Modeling, ICMAAM 2018, Kolkata, India, and January 9–12*. We would like to thank our Ph.D. and post-doctoral research students of Jadavpur University, Kolkata, working under the guidance of Prof. Priti Kumar Roy, for giving us the motivation and incessant effort to write a book on the above subject. Without their active help and support, it is quite an impossible task for us to complete the book.

In recent years, the Department of Mathematics, Jadavpur University, in collaboration with renowned nationally and internationally acclaimed mathematicians, has published a significant number of research works in diverse topics of mathematics. Such collaborations and awards have given birth to an innovative exchange of ideas in the past decade, which have amounted to successful conferences. ICMAAM 2018 was hopefully, thus, a forerunner to more significant contributions that came into the light of publishing this book. We are grateful to all of the contributing authors for their wholehearted cooperation, constant perseverance, and excellent support during this painful time without whom we could not have finished this book.

We extend our heartfelt salute to the contributors to the volume for their articles and christening us the honor to do this work. We would like to make our gratitude to those who reviewed materials for the book and provided valuable comments.

We are also grateful to all of our previous and ongoing research scholars namely: Dr. Amar Nath Chatterjee, Dr. Jayanta Mondal, Dr. Nikhilesh Sil, Dr. Biplab Sinha Mahapatra, Dr. Abhirup Datta, Dr. Fahad al Basir, Dr. Mithun Kumar Ghosh, Dr. Dibyendu Biswas, Dr. Shubhankar Saha, Mr. Amit Kumar Roy and Mr. Salil Ghosh and post-doctoral researcher Dr. Arnab Banerjee, and all colleagues for their tremendous effort and their incessant encouragement and motivation. Without their hard-strained efforts and impulsive collaboration, it is impossible for us as editor to edit this book.

We are pleased to acknowledge the financial support by the Government of India, National Board of Higher Mathematics.

Finally, we would like to thank the production team of Springer IN for their proofreads and valuable corrections made during the production process.

Prof. Dr. Priti Kumar Roy
Prof. Dr. Xianbing Cao
Prof. Dr. Xue-Zhi Li
Prof. Dr. Pratulananda Das
Prof. Dr. Satya Deo

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About the Editors

Priti Kumar Roy is Professor in the Department of Mathematics, Jadavpur University, Kolkata, India. Earlier, he served at several government colleges in different parts of West Bengal, India. He is an eminent member of several national and international societies like Biomathematical Society of India, International Association of Engineers, European Society of Clinical Microbiology and Infectious Diseases and European Society for Mathematical and Theoretical Biology. Professor Roy has received the Best Paper Award at the World Congress on Engineering 2010 in London. He was awarded the "Siksha Ratan" Award in 2012. He is also recipient of Royal Society of Edinburg and Poland Academy of Science Fellowship through INSA. He has published a significant number of research papers on control therapeutic approaches and host–pathogen interactions on infectious as well as noninfectious diseases to enlighten new insights on the subjects. With over 120 peer-reviewed research papers, more than 50 invited talks (abroad), 30 invited talks (India) in different international and national institutes, Professor Roy is a dedicated researcher in mathematical modeling and has expertise in numerical and analytical solutions to complex problems on real-life system dynamics. He has published two books on "Mathematical Models for Therapeutic Approaches to Control HIV Disease Transmission" (Springer in 2015) and "Mathematical Models for Therapeutic Approaches to Control Psoriasis" (Springer in 2019). He also edited two books on "Insight and Control of Infectious Disease in Global Scenario (by Intech Publishers)" and "A collection of Writings Objective Articulation from Socio-Academic Spectrum". His research interests are also devoted to epidemiological issues on the chronic infectious disease such as HIV, Cutaneous Leishmaniasis and Leprosy, Biodiesel Production, Enzyme Kinetics, Methanol Toxicity, etc.

Professor Roy also works on the neglected tropical disease like Psoriasis and has formulated robust mathematical models on the dynamics of such disease.

Xianbing Cao is Professor and Director, Beijing Technology and Business University, China. Earlier he served as Dean, School of Science, BTBU. He received his Ph.D. in Stochastic Control Theory from the Chinese Academy of Sciences, in 2002. He is an eminent researcher in the field of Biostatistics. Internationally as a reputed Statistician as well as Mathematician, several research

papers he has published in internationally reputed journals. He is the author or co-author of two books in the areas of stochastic and adaptive control systems and probability theory. His research interests include stochastic control systems, system identification, and financial time series analysis.

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Satya Deo is Senior Scientist at The National Academy of Sciences, India, and Honorary Professor at Harish-Chandra Research Institute, Allahabad, India. He was awarded the Distinguished Service Award by the Mathematical Association of India for outstanding contributions to the cause of teaching and research in 2006 and the Indian Science Congress Gold Medal by the then Prime Minister of India, in 2010. He has guided 17 Ph.D. students and published over 70 papers in reputed international journals and proceedings. His area of specialization includes algebraic and differential topology, topological and differentiable group actions, homology–cohomology theories, cohomological dimension theory, Burnside rings, Hopfian and co-Hopfian rings, spline modules, and topological combinatorics.

Optimal Strategies of the Psoriasis Treatment by Suppressing the Interaction Between T-Lymphocytes and Dendritic Cells

Ellina V. Grigorieva and Evgenii N. Khailov

Abstract This report contains the results devoted to the study of a mathematical model of psoriasis, proposed by P. K. Roy. This model is formulated as a Cauchy problem for the system of three nonlinear differential equations that describe the relationships between the concentrations of T-lymphocytes, keratinocytes and dendritic cells, the interactions of which cause the occurrence of psoriasis. Moreover, in this model we include a bounded scalar control responsible for a dose of a medication that suppresses the interaction of T-lymphocytes and dendritic cells. On the given time interval, for the control mathematical model, a problem of minimizing the concentration of keratinocytes at the end of time interval is considered. To analyze this problem, the Pontryagin maximum principle is applied. The adjoint system and the maximum condition for the optimal control are written. Using the corresponding system of differential equations, the switching function describing the behavior of the optimal control is studied. Such a system of equations allows us to determine the type of the optimal control: whether this control is only of a bang-bang type, or, in addition to the portions of a bang-bang type, it also contains a singular arc. When a singular arc occurs, the report discusses its order, the fulfillment of the necessary optimality condition for it, and its concatenation with portions of a bang-bang type. The obtained analytical results are illustrated by numerical calculations. The corresponding conclusions are made.

Keywords Psoriasis · Nonlinear system · Optimal control · Pontryagin maximum principle · Switching function · Singular arc

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1 Introduction

Psoriasis is an autoimmune disease with symptoms of chronic inflammation of the skin [6, 8]. In psoriasis, skin cells grow very rapidly, which leads to the appearance of red, dry and flake rashes. The main organ which is damaged is the skin, although other organs and systems of a person, in particular nails and joints, can be affected besides this. Psoriasis starts from the processes taking place in the epidermis. In the deep layer of the epidermis, immature skin cells called keratinocytes are formed. They produce keratin, a hard protein that is a building material for hair, nails and skin. Normally, keratinocytes grow and move from the lower layer to the surface of the skin almost imperceptibly. This process takes about a month. In people with psoriasis, keratinocytes proliferate very rapidly and move from the deep layer to the surface in about four days. The skin cannot get rid of these cells quickly enough, so that in a short time their amount increases dramatically, which leads to the formation of densified, dry patches on the skin or plaques. The lower layer of the dermis with blood, lymphatic vessels and nerves becomes inflamed and swollen.

Skin is an important immune organ. Specific skin cells, such as keratinocytes, promote the maturation of T-lymphocytes, which are the main element of the immune system of the skin. T-lymphocytes make up 90% of all lymphocytes of the skin and are located mainly in the upper and middle layers of the skin. The main function of dendritic cells is the presentation of antigens to T-lymphocytes. This means that they absorb antigens from the environment. Then they "process" them to the form that T-lymphocytes are able to recognize and develop an immune response. They also perform important immune-regulatory functions. Dendritic cells and activated T-lymphocytes play an important role in the development of psoriasis. The interactions between these two groups of cells trigger mechanisms leading ultimately to the development of the inflammatory process and the formation of psoriatic skin lesions.

Adequate treatment of psoriasis is challenging and drugs, leading to a complete cure, do not yet exist. Significant progress has been made, both in understanding the mechanisms of the disease and in finding new ways of treatment, and in standardizing the assessment of the severity of the disease. Mathematical models are effectively used to predict the behavior of skin cells, both in normal and in pathological states.

2 Optimal Control Problem

On a given time interval $[0, T]$ we consider the nonlinear control system of differential equations:

$$\begin{cases} l'(t) = \sigma - \delta v(t) l(t) m(t) - \gamma_1 l(t) k(t) - \mu l(t), \\ k'(t) = (\beta + \delta) v(t) l(t) m(t) + \gamma_2 l(t) k(t) - \lambda k(t), \\ m'(t) = \rho - \beta v(t) l(t) m(t) - \nu m(t), \\ l(0) = l_0,\ k(0) = k_0,\ m(0) = m_0;\ l_0, k_0, m_0 > 0. \end{cases} \tag{1}$$

It describes the interactions of various types of cells in a human body with drug therapy of psoriasis [3, 10, 11]. In system (1), $l(t)$, $k(t)$, and $m(t)$ are the concentrations of T-lymphocytes, keratinocytes and dendritic cells; l_0, k_0, m_0 are their initial conditions, respectively. The values σ, ρ, μ, λ, ν, γ_1, γ_2, δ, β are the given positive parameters of this system, which have the following meaning. The values σ and ρ are the appropriate inflow rates of T-lymphocytes and dendritic cells, μ and ν are the removal rates of these cells, respectively; λ is the decay rate of keratinocytes. In addition, the rate of activation of keratinocytes due to T-lymphocytes is indicated by γ_1 and the rate of keratinocytes growth is denoted by γ_2. The value δ is the activation rate of T-lymphocytes by dendritic cells, β is conversely the activation rate of dendritic cells due to T-lymphocytes. The interactions between T-lymphocytes and dendritic cells help to form keratinocytes through some cell biological procedures and thus the concentrations of both T-lymphocytes and dendritic cells are reduced by the terms δvlm and βvlm, respectively. On the other hand, under mixing homogeneity, the combined interaction of T-lymphocytes and dendritic cells contributes to the growth of concentration of epidermal keratinocytes by the term $(\beta + \delta)vlm$. Model (1) was kindly provided for analysis by Professor P. K. Roy (Centre for Mathematical Biology and Ecology, Department of Mathematics, Jadavpur University, Kolkata, India).

In system (1), $v(t)$ is a control function that satisfies the constraints:

$$0 < v_{\min} \leq v(t) \leq 1. \tag{2}$$

We note that the control $v(t)$ is an auxiliary. It is introduced into system (1) to simplify analytical analysis. The corresponding physical control $\widetilde{v}(t)$ in the same system is related to the control $v(t)$ by the formula $\widetilde{v}(t) = 1 - v(t)$. Therefore, where the auxiliary control $v(t)$ has a maximum value of 1, the appropriate physical control $\widetilde{v}(t)$ takes a minimum value of 0, and vice versa. The physical control $\widetilde{v}(t)$ is responsible for the dose of drug, which suppresses the interaction of T-lymphocytes and dendritic cells. Despite its importance, in the following arguments we focus on the analysis of auxiliary control $v(t)$. The set of admissible controls $\Omega(T)$ consists of all possible Lebesgue measurable functions $v(t)$ that satisfy constraints (2) for almost all $t \in [0, T]$.

Now, let us define the following positive constants:

$$\eta = \min\{\mu; \lambda; \nu\}, \quad K = \rho\left(1 + \beta^{-1}\delta\right)\gamma_1 + \sigma\gamma_2,$$
$$M = \gamma_2 l_0 + \gamma_1 k_0 + \left(1 + \beta^{-1}\delta\right)\gamma_1 m_0 + \eta^{-1}K,$$

and introduce the set:

$$\Theta = \left\{(l, m, k) : l > 0,\ m > 0,\ k > 0,\ \gamma_2 l + \gamma_1 k + \gamma_1\left(1 + \beta^{-1}\delta\right)m < M\right\}.$$

Then, the boundedness, positivity, and extendability of solution of this system is established by the following lemma.

Lemma 1 *Let the inclusion* $(l_0, m_0, k_0) \in \Theta$ *be valid. For an arbitrary admissible control* $v(t)$*, the corresponding absolutely continuous solution* $(l(t), k(t), m(t))$ *to system (1) are defined on the entire interval* $[0, T]$ *and satisfy the inclusion:*

$$(l(t), m(t), k(t)) \in \Theta, \quad t \in (0, T]. \tag{3}$$

The proof of Lemma 1 is fairly straightforward and we omit it. Proofs of such statements are given, for examples, in [2, 4, 10].

For system (1) on the set of admissible controls $\Omega(T)$, we consider the problem of minimizing the functional

$$J(v) = k(T), \tag{4}$$

which means the concentration of keratinocytes at the final moment T of the psoriasis treatment. Justification for using such a functional for system (1) was previously discussed in [5].

In the minimization problem (1), (4) the restrictions (3) provide the existence of the optimal control $v_*(t)$ and the corresponding optimal solution $(l_*(t), k_*(t), m_*(t))$ (see [7]).

Finally, based on the results from [3, 11], we assume that the inequalities:

$$\gamma_1 \neq \gamma_2, \qquad (\beta + \delta)\gamma_1 > \delta\gamma_2, \qquad \lambda > \mu, \qquad \lambda > \nu$$

are valid.

3 Pontryagin Maximum Principle

In order to analyze the optimal control $v_*(t)$ and the corresponding optimal solution $(l_*(t), k_*(t), m_*(t))$, we apply the Pontryagin maximum principle [9]. Firstly, we write down the Hamiltonian

$$\begin{aligned} H(l, k, m, v, \psi_1, \psi_2, \psi_3) = {} & (\sigma - \delta v l m - \gamma_1 l k - \mu l)\psi_1 \\ & + ((\beta + \delta) v l m + \gamma_2 l k - \lambda k)\psi_2 + (\rho - \beta v l m - \nu m)\psi_3, \end{aligned}$$

where ψ_1, ψ_2, ψ_3 are adjoint variables.

Secondly, we calculate the required partial derivatives:

$$\begin{aligned} H'_l(l, k, m, v, \psi_1, \psi_2, \psi_3) = {} & v m(-\delta\psi_1 + (\beta + \delta)\psi_2 - \beta\psi_3) \\ & + k(\gamma_2\psi_2 - \gamma_1\psi_1) - \mu\psi_1, \\ H'_k(l, k, m, v, \psi_1, \psi_2, \psi_3) = {} & l(\gamma_2\psi_2 - \gamma_1\psi_1) - \lambda\psi_2, \\ H'_m(l, k, m, v, \psi_1, \psi_2, \psi_3) = {} & v l(-\delta\psi_1 + (\beta + \delta)\psi_2 - \beta\psi_3) - \nu\psi_3, \\ H'_v(l, k, m, v, \psi_1, \psi_2, \psi_3) = {} & l m(-\delta\psi_1 + (\beta + \delta)\psi_2 - \beta\psi_3). \end{aligned}$$

Then, in accordance with the Pontryagin maximum principle, for the optimal control $v_*(t)$ and the optimal solution $(l_*(t), k_*(t), m_*(t))$ there exists a vector-function $\psi_*(t) = (\psi_1^*(t), \psi_2^*(t), \psi_3^*(t))$ such that:

- $\psi_*(t)$ is a nontrivial solution of the adjoint system:

$$\begin{cases} \psi_1^{*\prime}(t) = -v_*(t)m_*(t)(-\delta\psi_1^*(t) + (\beta+\delta)\psi_2^*(t) - \beta\psi_3^*(t)) \\ \qquad\qquad -k_*(t)(\gamma_2\psi_2^*(t) - \gamma_1\psi_1^*(t)) + \mu\psi_1^*(t), \\ \psi_2^{*\prime}(t) = -l_*(t)(\gamma_2\psi_2^*(t) - \gamma_1\psi_1^*(t)) + \lambda\psi_2^*(t), \\ \psi_3^{*\prime}(t) = -v_*(t)l_*(t)(-\delta\psi_1^*(t) + (\beta+\delta)\psi_2^*(t) - \beta\psi_3^*(t)) + \nu\psi_3^*(t), \\ \psi_1^*(T) = 0,\ \psi_2^*(T) = -1,\ \psi_3^*(T) = 0; \end{cases} \tag{5}$$

- the control $v_*(t)$ maximizes the Hamiltonian

$$H(l_*(t), k_*(t), m_*(t), v, \psi_1^*(t), \psi_2^*(t), \psi_3^*(t))$$

with respect to the variable $v \in [v_{\min}, 1]$ for almost all $t \in [0, T]$, and therefore it satisfies the relationship:

$$v_*(t) = \begin{cases} 1 & , \text{if} \quad L(t) > 0, \\ \text{any } v \in [v_{\min}, 1] & , \text{if} \quad L(t) = 0, \\ v_{\min} & , \text{if} \quad L(t) < 0 \end{cases} \tag{6}$$

in which, by Lemma 1, the function

$$L(t) = -\delta\psi_1^*(t) + (\beta+\delta)\psi_2^*(t) - \beta\psi_3^*(t) \tag{7}$$

is the switching function describing the behavior of the control $v_*(t)$ according to formula (6).

4 Properties of the Switching Function

An analysis of the function $L(t)$ leads to the validity of the following lemma.

Lemma 2 *There is such a value $t_0 \in [0, T)$ that on the interval $(t_0, T]$ the switching function $L(t)$ is negative.*

Proof The functions $\psi_1^*(t)$, $\psi_2^*(t)$, $\psi_3^*(t)$, as the components of the absolutely continuous solution $\psi_*(t)$ to system (5), are absolutely continuous as well. Hence, by formula (7), the switching function $L(t)$ is also absolutely continuous, and therefore a continuous function. Due to formula (7) and the initial conditions of system (5), it takes the negative value at $t = T$:

$$L(T) = -(\beta+\delta) < 0.$$

Then, the stability of the sign of the continuous function $L(t)$ yields the required fact. This completes the proof.

Corollary 1 *From Lemma 2 and formula (6), it follows the relationship:*

$$v_*(t) = v_{\min}, \quad t \in (t_0, T].$$

Now, we introduce positive constants:

$$\alpha = \gamma_2^{-1}((\beta+\delta)\gamma_1 - \delta\gamma_2), \quad \varepsilon = \alpha(\lambda-\nu) + \delta(\lambda-\mu),$$

and then also the following functions:

$$\begin{aligned}
g_{11}(t) &= v_*(t)(\delta m_*(t) + \beta l_*(t)) + \nu,\\
g_{21}(t) &= v_*(t)m_*(t)(\gamma_1(\delta k_*(t) - (\beta+\delta)l_*(t)) + \delta(\mu-\nu)),\\
g_{22}(t) &= (\lambda-\mu)\varepsilon^{-1}\gamma_1(\delta k_*(t) - (\beta+\delta)l_*(t))\\
&\quad +\varepsilon^{-1}(\alpha(\lambda-\nu)\lambda + \delta(\lambda-\mu)(\lambda-\nu+\mu)),\\
g_{31}(t) &= \gamma_1 v_*(t)m_*(t), \quad g_{32}(t) = (\lambda-\mu)\gamma_1\varepsilon^{-1},\\
g_{33}(t) &= (\gamma_1 k_*(t) - \gamma_2 l_*(t)) - (\lambda-\mu)\varepsilon^{-1}\gamma_1(\delta k_*(t) - (\beta+\delta)l_*(t))\\
&\quad +\varepsilon^{-1}(\alpha(\lambda-\nu)\mu + \delta(\lambda-\mu)\nu).
\end{aligned}$$

In addition, let us define the auxiliary functions:

$$\begin{aligned}
Q(t) &= \gamma_2\psi_2^*(t) - \gamma_1\psi_1^*(t),\\
G(t) &= (\delta k_*(t) - (\beta+\delta)l_*(t) + \gamma_2^{-1}(\beta+\delta)(\lambda-\nu))Q(t) + \varepsilon\psi_1^*(t),
\end{aligned}$$

and introduce the following function of two variables:

$$\begin{aligned}
\Phi(l,k) = &-\alpha\delta\gamma_1(\lambda-\nu)k^2 - \alpha(\beta+\delta)\gamma_2(\mu-\nu)l^2 - 2\delta(\beta+\delta)\gamma_1(\lambda-\mu)lk\\
&-(\beta+\delta)(\alpha(\lambda-\nu)\nu + \delta(\lambda-\mu)(2(\mu-\nu)+\nu))l\\
&+\delta(\alpha(\lambda-\nu)(2(\lambda-\mu)+\nu) + \delta(\lambda-\mu)(2(\lambda-\nu)+\nu))k\\
&+(\beta+\delta)(\sigma\varepsilon + \gamma_2^{-1}\delta(\lambda-\mu)(\lambda-\nu)(\mu-\nu)).
\end{aligned}$$

Then, using the equations of systems (1) and (5), we obtain the system of differential equations for the functions $L(t)$, $G(t)$ and $Q(t)$:

$$\begin{cases}
L'(t) = g_{11}(t)L(t) + G(t), \quad t \in [0,T],\\
G'(t) = g_{21}(t)L(t) + g_{22}(t)G(t)\\
\qquad + \left(2\delta(\beta+\delta)v_*(t)l_*(t)m_*(t) - \varepsilon^{-1}\Phi(l_*(t),k_*(t))\right)Q(t),\\
Q'(t) = g_{31}(t)L(t) + g_{32}(t)G(t) + g_{33}(t)Q(t),\\
L(T) = -(\beta+\delta), \quad Q(T) = -\gamma_2,\\
G(T) = -\left(\gamma_2(\delta k_*(T) - (\beta+\delta)l_*(T)) + (\beta+\delta)(\lambda-\nu)\right).
\end{cases} \tag{8}$$

Now, let us analyze formula (6). We have the following conclusions.

- If for some value $t_{(+)} \in [0, T]$ the switching function $L(t)$ is positive, then it is also positive in some neighborhood of this value. Then the corresponding optimal control $v_*(t)$ takes the value 1 in this neighborhood.
- Similarly, if for some value $t_{(-)} \in [0, T]$ the switching function $L(t)$ is negative, then it is also negative in some neighborhood of this value. Then the corresponding optimal control $v_*(t)$ takes the value $v_{\min}$ in this neighborhood.
- Since the function $L(t)$ is absolutely continuous, it can vanish either at separate points or on certain intervals. In the first case, the optimal control $v_*(t)$ is bang-bang, it takes only values $v_{\min}$ and 1. In this case, the value $t_0 \in (0, T)$, at which $L(t_0) = 0$ and such that passing this point the function $L(t)$ changes its sign, is a switching of this control. Then, naturally, the question of estimating the number of zeros of the switching function $L(t)$ arises. Such a question relates to the estimate of the number of switchings of the control $v_*(t)$, and here system (8) plays a significant role. In the second case, at such intervals the optimal control $v_*(t)$ has singular arcs [12, 13]. This phenomenon requires additional studies also using this system.

Now, let us study the existence of a singular arc of the optimal control $v_*(t)$, which means that the switching function $L(t)$ can vanish identically on some interval $\Delta \subset [0, T]$. We use the first two equations of system (8) to find on this interval the first two derivatives of the function $L(t)$:

$$L'(t)\Big|_{L(t)=0} = 0, \qquad L''(t)\Big|_{L(t)=0,\ L'(t)=0} = 0.$$

As a result, the equality can be obtained:

$$\left(2\delta(\beta+\delta)v_*(t)l_*(t)m_*(t) - \varepsilon^{-1}\Phi(l_*(t), k_*(t))\right) Q(t) = 0, \quad t \in \Delta. \tag{9}$$

From the analysis of formula (9) the following conclusions are made.

- The second derivative of the function $L(t)$ contains the control $v_*(t)$. This means that the order q of the singular arc is equal to one.
- On the interval Δ the optimal control $v_*(t)$ is singular and is given by the formula:

$$v^*_{\text{sing}}(t) = \frac{\Phi(l^*_{\text{sing}}(t), k^*_{\text{sing}}(t))}{2\varepsilon\delta(\beta+\delta)l^*_{\text{sing}}(t)m^*_{\text{sing}}(t)}\,. \tag{10}$$

From this formula it follows that such a control has the form of feedback, that is, it depends only on the functions $l^*_{\text{sing}}(t)$, $k^*_{\text{sing}}(t)$, $m^*_{\text{sing}}(t)$, which are the corresponding components of the optimal solution $(l_*(t), k_*(t), m_*(t))$ on this interval. We assume that such a control is admissible, that is, the inclusion $v^*_{\text{sing}}(t) \in [v_{\min}, 1]$ is valid everywhere on the interval Δ.

- The necessary optimality condition of a singular arc (the Kelly condition [12, 13]) has the form:

$$2\delta(\beta+\delta)l^*_{\text{sing}}(t)m^*_{\text{sing}}(t)Q(t) \geq 0, \quad t \in \Delta. \tag{11}$$

The non-triviality of the vector-function $\psi_*(t) = (\psi_1^*(t), \psi_2^*(t), \psi_3^*(t))$ implies the validity of the following lemma.

Lemma 3 *On the interval Δ the function $Q(t)$ is sign-definite, that is, it only takes either positive or negative values.*

Corollary 2 *From Lemma 3 and inequality (11) it follows that the Kelly condition either holds in the strengthened form:*

$$2\delta(\beta+\delta)l^*_{\text{sing}}(t)m^*_{\text{sing}}(t)Q(t) > 0, \quad t \in \Delta,$$

or is not satisfied at all, that is:

$$2\delta(\beta+\delta)l^*_{\text{sing}}(t)m^*_{\text{sing}}(t)Q(t) < 0, \quad t \in \Delta.$$

Finally, when the inclusion $v^*_{\text{sing}}(t) \in (v_{\min}, 1)$ is true for all $t \in \Delta$, Lemma 2, Corollary 2 and formula (10) provide the concatenation of the singular arc with the other bang-bang portions of the control $v_*(t)$.

5 Numerical Results

Further, only numerical investigation of optimal control $v_*(t)$ is possible. For the corresponding numerical calculations, the following values of the parameters and initial conditions of system (1) were used [3, 11], as well as the control constraints (2):

$$\begin{array}{llll} \sigma = 15.0 & \rho = 3.6 & \beta = 0.4 & \delta = 0.005 \\ \mu = 0.01 & \nu = 0.02 & \gamma_1 = 0.8 & \gamma_2 = 0.05 \\ l_0 = 100.0 & k_0 = 40.0 & m_0 = 50.0 & \\ v_{\min} = 0.3 & T = 100.0 & & \end{array}$$

The numerical calculations were carried out using the software "BOCOP 2.0.5" (see [1]), and are shown in Figs. 1 and 2.

In Fig. 3 the surface $\Phi(l, k)$ is presented. It can be seen that positive values of the function $\Phi(l, k)$ in formula (10) in the region of variation of the variables l and k provide the admissibility of singular control $v^*_{\text{sing}}(t)$.

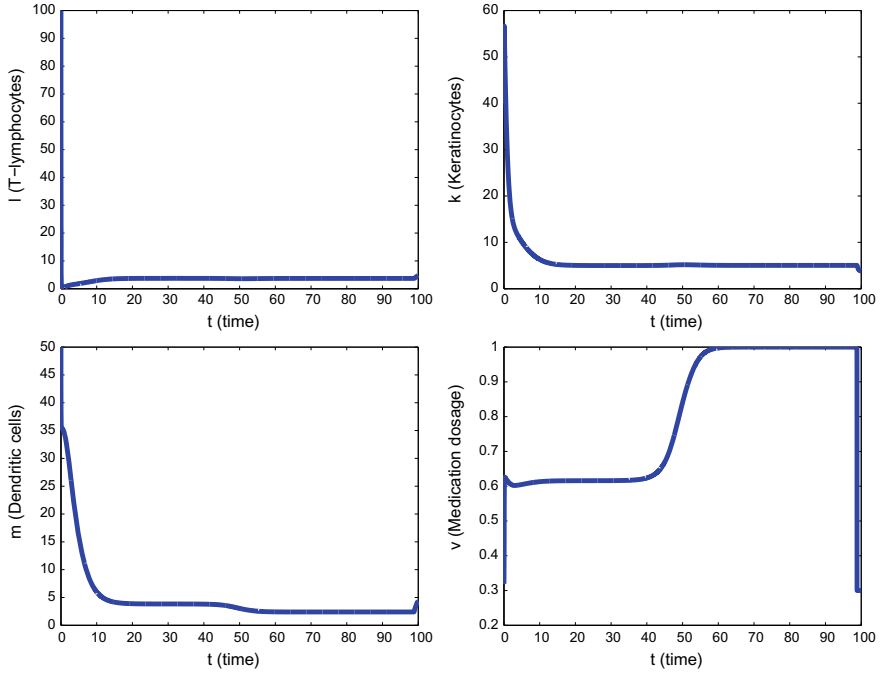

Fig. 1 Graphs of optimal solutions and optimal control for $\lambda = 0.9$: upper row: $l_*(t)$, $k_*(t)$; lower row: $m_*(t)$, $u_*(t)$

6 Conclusions

Physical optimal control $\widetilde{v}_*(t)$ according to Figs. 1 and 2 describes the situation when, first there is the period of the psoriasis treatment with greatest intensity. Next, it is followed by the period of the treatment with a smooth decrease in the dose of the used medication from the greatest intensity to the lower intensity. Then, there is a period of the psoriasis treatment with lower intensity, and finally the switching occurs to the period of the treatment with greatest intensity. Also, we emphasize that in all performed numerical calculations, the optimal concentration of keratinocytes $k_*(t)$ decreases to the end T to the level that is the minimal for the entire period $[0, T]$ of the psoriasis treatment (see Figs. 1 and 2).

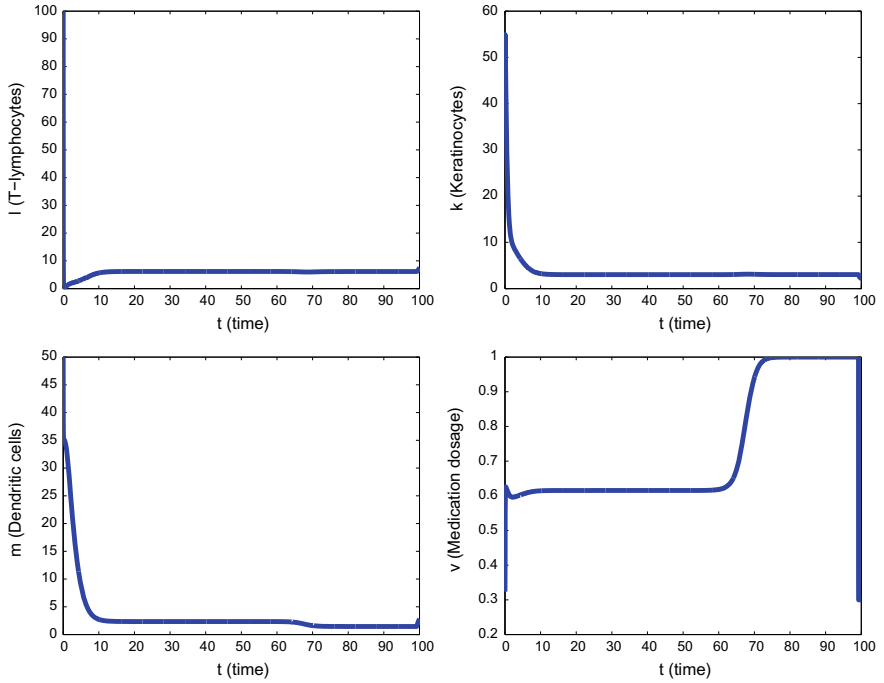

Fig. 2 Graphs of optimal solutions and optimal control for $\lambda = 1.5$: upper row: $l_*(t)$, $k_*(t)$; lower row: $m_*(t)$, $u_*(t)$

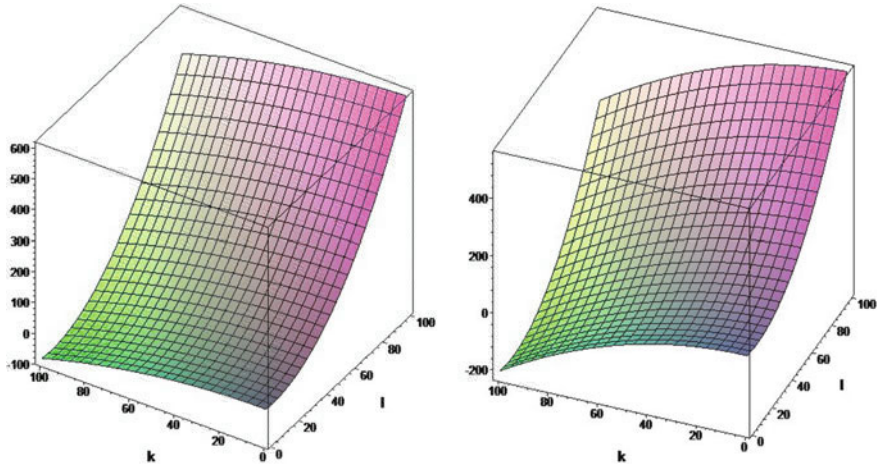

Fig. 3 Surface $\Phi(l, k)$ for $\lambda = 0.9$ and $\lambda = 1.5$

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The Use of Reaction Network Theory for Finding Network Motifs in Oscillatory Mechanisms and Kinetic Parameter Estimation

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Abstract Stoichiometric network analysis (SNA) is a method of studying stability of steady states of reaction systems obeying mass action kinetics. Reaction rates are expressed as a linear combination of elementary subnetworks with nonnegative coefficients (convex parameters) as opposed to standard formulation using rate coefficients and input parameters (kinetic parameters). We present examples of core reaction subnetworks that provide for oscillatory instability. Frequently there is an autocatalytic cycle in the core subnetwork, but in biochemical reactions such cycle is often replaced by a pathway called competitive autocatalysis. Rate coefficients in complex networks are often only partly known. We present a method of estimating the unknown rate coefficients, in which known/measured kinetic parameters and steady state concentrations are used to determine convex parameters, which in turn allows for determination of unknown rate coefficients by solving a set of constraint equations.

Keywords Stoichiometric networks · Oscillating (bio) chemical reactions · Dynamical instabilities · Parameter estimation

1 Introduction

Reaction networks corresponding to biochemical processes occurring in living organisms, such as genome-scale metabolic networks [13] are typically large. To understand various operating modes embedded within such systems, the networks at steady states are decomposed into elementary subnetworks (elementary fluxes, extreme currents) by taking advantage of a pseudolinear form of the corresponding model equations. In terms of linear algebra, these modes are represented by vectors including a collection of reaction rates at steady state. The elementary fluxes describe

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simplest chemical processes/functions that are available in the network with only a limited number of reaction rates turned on. Subsequently, they can be linearly combined using arbitrarily chosen non-negative coupling coefficients, producing the full network with contributions from all reactions. Such decomposition relies on stoichiometry only and does not require specification of reaction kinetics. However, leaving out kinetics precludes determination of stability of the steady state and one must assume it to be stable. In many systems, dynamical instabilities are essential for performing appropriate function, such as periodic oscillations or bistable switches. In those cases, the framework for analysis is provided by stoichiometric network analysis [3], which assumes that power law kinetics are provided and examines stability of the network's steady states.

The elementary subnetworks, or small subnetworks that are formed by combining suitable elementary subnetworks, can be tested for potential instability. Such a test does not require knowledge of rate coefficients and steady state concentrations of participating species. When an unstable subnetwork is coupled with other subnetworks, its (potential) instability will dominate the entire network provided that the coupling of the unstable subnetwork is strong enough.

This estimate of stability allows for identification of a core subnetwork that gives rise to an oscillatory instability and thereby provides a natural explanation for observing chemical oscillations [3–6, 16, 18]. Moreover, the oscillatory core subnetworks may be arranged into groups sharing certain topological features, which allows for a categorization of chemical oscillators [5, 16], each category being represented by a prototype network or a motif. At the same time, species within each prototype can be classified based on the role they play in generating the oscillations.

As mentioned above, such a classification is still based on analysis that does not involve knowledge of rate coefficients and steady state concentrations. When describing a specific experimental system, some of these parameters are known while others are not. Below we outline a procedure, that uses the notion of potential instability as introduced by the SNA and attempts to estimate the set of unknown rate coefficients and/or steady state cocentrations. To that goal, we utilize the idea that the coupling coefficients of the elementary subnetworks and steady state concentrations (convex parameters) must be consistent with known rate coefficients and inflow/initial constraints (kinetic parameters).

In our previous work [11, 15] we initiated the outlined approach and applied it to an oscillatory enzyme reaction and the classical inorganic Belousov-Zhabotinsky reaction. In this work we extend the list of subnetworks having a distinct motif and provide a mathematical framework for employing these motifs as reference subnetworks in models with extensive and complex mechanisms.

2 Theoretical Part

All spatially homogeneous isothermal chemical oscillators are based on stoichiometry and kinetics and fall within the formal mathematical description given below.

Let us assume a system involving m reactions and a total number of species n^{tot},

$$\nu^L_{1j} A_1 + \cdots + \nu^L_{n^{tot}\,j} A_{n^{tot}} \rightarrow \nu^R_{1j} A_1 + \cdots + \nu^R_{n^{tot}\,j} A_{n^{tot}}\,,\ j = 1, \ldots, m, \tag{1}$$

where A_i are the reacting species and ν^L_{ij}, ν^R_{ij} are left and right stoichiometric coefficients. Any reversible reaction is treated as a pair of forward and backward steps. In a spatially homogeneous system, such as a flow-through reactor, dynamics of $n \leq n^{tot}$ species that are not inert products or in a pool condition are governed by a set of coupled mass balance equations which have the following pseudolinear form:

$$\frac{\mathrm{d}\mathbf{x}}{\mathrm{d}t} = \mathbf{N}\,\mathbf{v}(\mathbf{x})\,, \tag{2}$$

where $\mathbf{x} = (x_1, \ldots, x_n)$ is the vector of concentrations of the interacting dynamical species, $\mathbf{N} = \{\Delta\nu_{ij}\} = \{\nu^R_{ij} - \nu^L_{ij}\}$ is the $(n \times m)$ stoichiometric matrix and $\mathbf{v} = (v_1, \ldots, v_m)$ is the non-negative vector of reaction rates (fluxes) (All vectors are assumed being column vectors). The reaction rates are assumed to follow mass action kinetics,

$$v_j = k_j \prod_{i=1}^{n} x_i^{\kappa_{ij}} = k_j \bar{v}_j\,, \tag{3}$$

where $\kappa_{ij} = \partial \ln v_j / \partial \ln x_i \geq 0$ is the reaction order of species i in reaction j and k_j is the corresponding rate coefficient, which may include fixed concentration(s) of pooled species and $\bar{v}_j$ is the reduced reaction rate. In vector notation we have $\mathbf{k} = (k_1, \ldots, k_m)$ and $\bar{\mathbf{v}}(x) = (\bar{v}_1, \ldots, \bar{v}_m)$. For elementary reactions, $\kappa_{ij} = \nu^L_{ij}$. However, in general case power law terms may also be used for quasi-elementary steps with $\kappa_{ij} \neq \nu^L_{ij}$. The kinetic matrix $\{\kappa_{ij}\}$ is denoted as $\mathbf{K}$. In flow systems, the inflows and outflows are included as pseudoreactions of zeroth and first order, respectively; the rate coefficient corresponding to an inflow term is $k_j = k_0 x_{i0}$ and that for an outflow is $k_j = k_0$, where k_0 is the flow rate and x_{i0} is the feed concentration of any inflowing species i.

At steady state Eq. (2) reduces to

$$\mathbf{N}\mathbf{v} = 0\,. \tag{4}$$

Since the reaction rates are non-negative, the set of all $\mathbf{v}_s$ satisfying the steady state condition is a non-negative subset of the null space of $\mathbf{N}$ represented by an $(m - d)$-dimensional convex polyhedral cone delimited by faces of dimension $1, \ldots, (m - d) - 1$, where d is the rank of $\mathbf{N}$. One-dimensional faces (or edges) represent a set of minimal, irreducible, connected subnetworks called elementary subnetworks or extreme currents or elementary fluxes. There are f edges of the cone satisfying $f \geq m - d$. The edges should be properly normalized, a convenient way is to let the components of the rate vector corresponding an edge sum up to 1. Endpoints of the normalized edges are apexes of a convex polytope of dimension $(m - d - 1)$. If $f = m - d$, the edges form a basis of the cone which is then called simplicial

and the corresponding polytope is a simplex. Extreme currents can be obtained by algorithms of linear programming [9] or other efficient algorithms [17].

Let $\mathbf{E}_k$ denote a normalized rate vector corresponding to an elementary subnetwork. The set of all such subnetworks can be put into a matrix

$$\mathbf{E} = [\mathbf{E}_1, \ldots, \mathbf{E}_f]\,. \tag{5}$$

Any feasible rate vector $\mathbf{v}_s$ satisfying the steady state condition can be conveniently expressed as a non-negative linear combination of the elementary subnetworks,

$$\mathbf{v}_s = \mathbf{E}\,\boldsymbol{\alpha}, \quad \boldsymbol{\alpha} = (\alpha_1, \ldots, \alpha_f)\,. \tag{6}$$

The rate vector $\mathbf{v}_s$ is determined by choosing linear combination vector $\boldsymbol{\alpha}$. Upon substituting for the rate vector from (3) and by choosing $\mathbf{x}_s$ the rate coefficients are

$$\mathbf{k} = (\mathbf{diag}\,\bar{\mathbf{v}}(\mathbf{x}_s))^{-1}(\mathbf{E}\,\boldsymbol{\alpha})\,. \tag{7}$$

Thus, for a given set of convex parameters $(\boldsymbol{\alpha}, \mathbf{x}_s)$, kinetic parameters are obtained via (7). However, unless the cone is a simplex, the convex parameters are redundant, which must be taken into account when constructing the network from its elementary subnetworks.

Using the convex parameters, the mass balances given by Eq. (2) are expressed as

$$\frac{\mathrm{d}\mathbf{x}}{\mathrm{d}t} = \mathbf{N}\,\mathbf{diag}\,(\mathbf{E}\,\boldsymbol{\alpha})\,(\mathbf{diag}\,\bar{\mathbf{v}}(\mathbf{x}_s))^{-1}\bar{\mathbf{v}}(\mathbf{x})\,. \tag{8}$$

Upon linearizing the r.h.s. at the steady state $\mathbf{x}_s$, the Jacobian matrix is obtained,

$$\mathbf{J} = \mathbf{N}\,\mathbf{diag}\,(\mathbf{E}\boldsymbol{\alpha})\,\mathbf{K}^T\,\mathbf{diag}\,\mathbf{h} = -\mathbf{V}\,\mathbf{diag}\,\mathbf{h}\,, \tag{9}$$

where $\mathbf{h} = (1/x_1^s, \ldots, 1/x_n^s)$ includes reciprocal values of the steady state concentrations and $\mathbf{K}^T = \{\kappa_{ji}\}$ is the transpose of kinetic matrix. Because of convenience suggested by the form of Eq. (9), the convex parameters are usually taken as $(\boldsymbol{\alpha}, \mathbf{h})$ rather than $(\boldsymbol{\alpha}, \mathbf{x}_s)$.

An instability of a steady state $\mathbf{x}_s$ can be determined by analyzing principal minors of the $(n \times n)$ matrix $\mathbf{V}$. If a principal minor of order ℓ involving a subset of indexes $i_1, \ldots, i_\ell$ of certain species is negative, then at least one eigenvalue of $\mathbf{J}$ is unstable, provided that the steady state concentrations of corresponding species $x_{i_1}^s, \ldots, x_{i_\ell}^s$ are sufficiently small [3]. It is sufficient to consider a leading negative minor with a minimal order ℓ since any higher order instability is derived from the minimal configuration. Edge is the simplest possible unstable subnetwork. Next in the hierarchy of unstable subnetworks is 2-face such that both edges constituting the 2-face are stable when analyzed separately. Such an instability is possible due to nonlinearity of kinetics. We call such a face primary unstable. Any primary unstable k-face,