Accordo di cooperazione scientifica CNR/RA

Final report

"Analysis and Optimization of mathematical models ranging from bio-medicine to engineering"

Project period: 2020-2022

Team of the project:

Italian part:

Elisabetta Rocca (director of project of the Italian part), full professor at the University of Pavia and Research Associate at the IMATI of CNR in Pavia, Dipartimento di Matematica, Universita' di Pavia, Via Ferrata 5, 27100 Pavia, Italy. E-mail: elisabetta.rocca@unipv.it

Pierluigi Colli, full professor at the University of Pavia and Research Associate at the IMATI of CNR in Pavia, Dipartimento di Matematica, Universita' di Pavia, Via Ferrata 5, 27100 Pavia, Italy. E-mail: pierluigi.colli@unipv.it

Alberto Gandolfi, Research Associate at the Istituto di Analisi dei Sistemi ed informatica "A. Ruberti" - CNR, Via dei Taurini, 19, 00185 Roma. E-mail: alberto.gandolfi@iasi.cnr.it

Mimmo Iannelli, Research Associate at the IMATI of CNR in Pavia. E-mail: iannelli.mimmo@gmail.com

Romanian part:

Gabriela Marinoschi (director of project of the Romanian part), senior researcher I, "Gheorghe Mihoc-Caius Iacob" Institute of Mathematical Statistics and Applied Mathematics of the Romanian Academy, Calea 13 Septembrie 13, Bucuresti, Romania. E-mail: gabriela.marinoschi@acad.ro

Viorel Barbu - senior researcher I, Octav Mayer Institute of Mathematics of the Romanian Academy, Bdul. Carol I, 8 Iasi, Romania. E-mail: vb41@uaic.ro

Ionut Munteanu, researcher, Octav Mayer Institute of Mathematics of the Romanian Academy, Bdul. Carol I, 8 Iasi, Romania. E-mail: ionut.munteanu@uaic.ro

I. Description of the program

The main goal was to establish mathematical results which allow to get further insights into more refined models of some important phenomena. These models consist essentially of evolutionary PDEs and arise from Bio-Medicine, Engineering and Materials Science. We can mention in this framework: tumor growth models, 3D printing processes and electrically driven potentials in membranes.

The project relied on the idea of joining different real-world applications coming from Biology, Medicine, and Engineering under the common feature of diffuse interface problems where interfaces are seen as regions of positive small thickness, and the transition between two adjoining "species" or "phases" occurs in a continuous way. A suitable order parameter, generally called *phase-field*, is introduced (e.g., the concentration of one phase) whose sharp variation is concentrated within a thin mixing region. The paradigmatic equations which rule the evolution of the phase-field variable are the so-called Cahn-Hilliard or Allen-Cahn equations. Their basic versions are the conserved or non-conserved gradient flows of a non-convex (possibly nonlocal) nonlinear free energy functional. However, the partial differential equations can have additional terms which account for chemical reactions and/or they can be coupled with other equations (e.g. the Navier-Stokes system, the Darcy's law, reaction-diffusion equations, elasticity equations).

Many interesting mathematical questions arised in this framework regarding for example the notion of weak solutions for the highly nonlinear related PDEs, their weak-strong uniqueness, their long-time behavior, and the study of the associated optimal control, optimization, and inverse problems.

The goal was to analyze models which are as close as possible to the physical reality.

In this respect, we intended to perform also numerical simulations with the aim of validating the analytical results and comparing them with the outcome of real-world experiments. The cooperation between the two units, already witnessed by their joint publications, was the fundamental starting point in view of the project success.

The expertise of the Italian unit on the phase-field modeling and analysis have been complemented by the one of the Romanian unit on the resolution of optimal control, inverse and numerical problems.

The topic proposed in this project had both a theoretical and practical importance, since the theoretical results were adapted and applied to concrete problems put by other sciences and will face towards a research line of current international interest. The models developed on the basis of these researches gave the possibility of a better understanding of some peculiarities of the concerned physical and biological processes. We obtained more efficient procedures for solving differential equations and the associated control and inverse problems. The results were accompanied by numerical simulations intended to put into evidence the features of the solutions of the modeled processes and to respond to certain questions put by the other sciences. In this way, we aimed to use us researches as a tool in assisting the specific practice, as for example in medicine.

Thus, our research followed the objectives:

- Modelling: development of new models and improvement of old ones
- Proof of the existence, uniqueness and qualitative properties of the solutions
- Optimal control and optimization of the trajectories of the solutions as a response to certain practical demands
- Approaches of some inverse problems which consist in the determination of the process parameters or the determination of cavities in material design problems, based on the available observations
- Numerical simulations and interpretations.

The impact of the project in the main domain of research, which is mathematics, was ensured by the publication of the common original results in high impact journals.

1. **Optimization with constraints.**

   The main part of the project was concerned with the development, analysis and application of new, innovative mathematical techniques for the solution of constrained optimization. Such optimization problems arise in a large variety of important applications in the form of, e.g., parameter identification problems, optimal design problems, or optimal control problems. The solution of PDE constrained optimization problems has a strong impact on more traditional applications e.g. in engineering (for example in 3D printing processes) and chemical processing, in materials and life sciences including environmental protection, pharmacology, and medicine. The appropriate mathematical treatment of PDE constrained optimization problems requires the integrated use of advanced methodologies from the theory of optimization and optimal control in a functional analytic setting, the theory of PDEs as well as the development and implementation of powerful algorithmic tools from numerical mathematics and scientific computing. Experience has clearly shown that the design of efficient and reliable numerical methods requires a fundamental understanding of the relation between optimization in function spaces and numerical discretization techniques that can only be achieved by a close cooperation between researchers from the above mentioned fields. The phase-field approach can be used in this case as an alternative and effective method for the resolution of different topology optimization problems arising for example in Engineering (like the ones stemming from additive-manufacturing technology).

2. **Optimization with applications in medicine.**

This essential part of our project approached models of tumor growth described on the one-hand by systems of nonlinear reaction-diffusion equations with nonlinear, possible singular potentials and on the other hand, by hyperbolic systems of nonlinear nonlocal equations. In the first case, we shall focus on diffuse tumor growth models coupling viscous or degenerate Cahn-Hilliard type equations for the phase variable, describing the microstructure order variation with reaction-diffusion equations for the nutrient. Alternatively, the equation for the phase parameter can be replaced by the Allen-Cahn type equation. Using some additional terms in these equations we model the interaction between the growth/reduction of tumors, function of the play between the nutrient variation, the rate of the tumor cell production and the cell apoptosis. After analyzing the model, an optimization of this process is dealt with, having the objective of reducing the tumor by simultaneously acting on the nutrient concentration and a particular therapy. Numerical simulations will complete this study, in particular in the case of Allen-Cahn type which result particularly useful in case of prostate tumor models.

A different kind of models takes into account a more detailed way of formation of the cells. This is a model with age-structure and here the principal role is played by the particularities of cell proliferation or formation, expressed as conditions at zero age, which gives the number of various cell type newborns. The equations contain nonlocal terms accounting for very specialized coupling processes between the different type of cells: proliferant, differentiated, apoptotic. The model is particularized for epidermis growth and so also the formation of corneous cells is considered. Optimization here can refer to the optimal therapy scenario which allow the growth of differentiated cells and reduction of the proliferation in the upper layers of the skin, which can involve a serious pathology.

II. Objectives of research

From the mathematical viewpoint, we aimed to develop methods for the study of nonlinear PDE, which can be parabolic or hyperbolic, even nonlocal or describing phenomena with free boundaries and in particular:

1. Modelling and model analysis
2. Particular situations of controllability of these systems
3. Feedback stabilization
4. Optimization and inverse problems in Engineering and Bio-Medicine
5. Numerical computations on the basis of simulation scenarios giving importance to the various parameters of the models and interactions between the solution components.

III. Work plan

The work plan was followed:

Task	2020	2021	2022
Models for prostate tumor growth			
Model and analysis			
Optimization and numerical simulations			
Models for skin tumor growth			
Model and analysis			
Optimization			
Numerical simulations			

Results in published articles during the project

P. Colli, H. Gomez, G. Lorenzo, G. Marinoschi, A. Reali, E. Rocca, Optimal control for a prostate tumor growth model, Math. Models Methods Appl. Sci. 31, 1419-1468, 2021

P. Colli, G. Gilardi, G. Marinoschi, Solvability and sliding mode control for the viscous Cahn-Hilliard system with a possibly singular potential, Math. Control Relat. Fields 11 (4), 905-934, 2021

P. Colli, G. Gilardi, I. Munteanu, Stabilisation of a linearised Cahn-Hilliard system for phase separation by proportional boundary feedbacks. Internat. J. Control 94, 452–460, 2021

P. Colli, H. Gomez, G. Lorenzo, G. Marinoschi, A. Reali, E. Rocca, Mathematical Analysis and Simulation Study of a Phase-Field Model of Prostate Cancer Growth with Chemotherapy and Antiangiogenic Therapy Effects, Math. Models Methods Appl. Sci., 30 (7), 1253-1295, 2020

A. Gandolfi, M. Iannelli, G. Marinoschi, The basal layer of the epidermis: a mathematical model for cell production under a surface density constraint, SIAM J. Appl. Math. 80 (1), 543-571, 2020

References

[1] V. Barbu, P. Colli, G. Gilardi, G. Marinoschi, Feedback stabilization of the Cahn-Hilliard type system for phase separation, J. Differential Equations, 262, 2286-2334, 2017

[2] V. Barbu, P. Colli, G. Gilardi, G. Marinoschi, E. Rocca, Sliding mode control for a nonlinear phase-field system, SIAM J. Control Optim. 55, 3, 2108-2133, 2017

[3] V. Barbu, A. Favini, G. Marinoschi, Nonlinear parabolic flows with dynamic flux on the boundary, J. Differential Equations 258, 2160-2195, 2015

[4] P. Colli, G. Gilardi, G. Marinoschi, A boundary control problem for a possibly singular phase field system with dynamic boundary conditions, J. Math. Anal. Appl. 434, 432-463, 2016

[5] P. Colli, G. Gilardi, G. Marinoschi, E. Rocca, Optimal control for a phase field system with a possibly singular potential, Math. Control Relat. Fields 6, 95-112, 2016

[6] P. Colli, G. Marinoschi, E. Rocca, Sharp interface control in a Penrose-Fife model, ESAIM Control Optim. Calc. Var. 22, 473-499, 2016

[7] P. Colli, G. Gilardi, G. Marinoschi, E. Rocca, Optimal control for a conserved phase field system with a possibly singular potential, Evol. Equ. Control Theory, 7, 1, 95-116, 2018

[8] P. Colli, G. Gilardi, G. Marinoschi, E. Rocca, Distributed optimal control problems for phase field systems with singular potential, An. Stiint. Univ. "Ovidius" Constanta Ser. Mat. 26, 2, 71-85, 2018

[9] P. Colli, G. Gilardi, G. Marinoschi, E. Rocca, Sliding mode control for phase field system related to tumor growth, Appl. Math.Optim. 79, 647—670, 2019.

[10] A. Gandolfi, M. Iannelli, G. Marinoschi, The steady state of epidermis: mathematical modeling and numerical simulation, J. Math. Biology, doi:10.1007/s00285-016-1006-4

[11] I. Munteanu, Boundary stabilization of the phase field system by finite-dimensional feedback controllers, J. Math. Anal. Appl. 412, 964-975, 2014