MCHBS2021 Virtual Workshop

Mathematical Modelling and Control for Healthcare and Biomedical Systems

28-30 September 2021

BOOK OF ABSTRACTS

Editors: A. Borri, G. Bretti, F. Castiglione, R. Natalini, P. Palumbo, S. Panunzi, G. Pontrelli

ISBN: 978-88-8080-138-2 (printed version), ISBN: 978-88-8080-148-1 (on-line version)

Contents

Preface

MCHBS2021 is a multidisciplinary international workshop that focuses on modelling for biomedical technologies and healthcare and provides a unique meeting place for scientists in the field to present their latest research. The workshop is a formal activity of the European Consortium of Mathematics in Industry (ECMI) Special Interest Group on Implantable Devices & Drug Delivery Systems.

This event will build on the highly successful previous editions of MEDDS (Modelling & Experiments in Drug Delivery Systems), which took place in Coimbra (2016) and Glasgow (2018, sponsored by ECMI), as well as on symposia at ECMI2016 (Applied Mathematics in Stent Development), ECMI2018 (Mathematical Modelling in Biomedical applications), SIMAI2018 (Advances in Mathematical Modeling in Biology and Medicine), ECMTB2018 (Recent trends in the modeling and control of the glucose-insulin system), with an added emphasis on industrial and clinical problems and on COVID-19 issues.

Mathematical models and computer simulations are playing an increasingly important role in medicine, since they represent a useful tool to complement theoretical and experimental work. Moreover, models pave the way for investigating control problems consisting of personalized approaches for patient treatment.
Smart healthcare and medical devices have become common in clinical everyday use. Popular examples include insulin pumps, inhalers and ventilators for breathing conditions, as well as implants, microcapsules and nanoparticles for drug delivery.
Many of these technologies are controlled drug delivery systems, combining a platform or a carrier with a drug to be delivered efficiently to a target tissue or organ, while maintaining the dose within a therapeutic window.
While many have achieved successful results clinically, there remain a number of scientific and technological challenges and an opportunity for further fine-tuning and optimization. Addressing these challenges requires multi-disciplinary approaches and competences ranging from clinical expertise and academic research to the industrial sector.

Due to the COVID-19 pandemic, MCHBS2021 is held as a virtual event, with public talks live-streamed by the registered participants.

SCIENTIFIC COMMITTEE

G. Pontrelli, R. Natalini, G. Bretti, F. Castiglione (chairs) (CNR-IAC)
S. Panunzi, A. Borri (chairs) (CNR-IASI)
P. Palumbo (chair) (Univ. Milano-Bicocca / CNR-IASI)
A. De Gaetano (CNR-IRIB)
E. Barchiesi (CNRS Brest, France)
D. Gui, S. Magalini (Catholic University of the Sacred Heart, Italy)
S. McGinty (Univ. Glasgow, UK)
A. Barakat (Ecole Polytechnique, Palaiseau, France)
L. Preziosi (Politecnico of Torino)
M. Sammartino (Univ. Palermo)
M. Meere (National Univ. Ireland)
L. Formaggia (Politecnico of Milan)
S. Schnell (University of Michigan, USA)
L. Teresi (Univ. Roma Tre)

ORGANIZING COMMITTEE

IAC-CNR:
G. Pontrelli,
G. Bretti,
R. Natalini,
F. Castiglione.

IASI-CNR:
S. Panunzi,
A. Borri,
P. Palumbo (IASI-CNR/UNIMIB).

Partners and Sponsors

The organizers are grateful for the support of CNR, MIUR, ECMI, ESMTB, SIMAI, COPMAT, Università Cattolica Sacro Cuore, Università degli Studi di Milano Bicocca.

The workshop is partly supported by the National Research Project Grant "Mathematics of active materials: from mechanobiology to smart devices" (PRIN 2017, prot. 2017KL4EF3).

Schedule at a glance

	Tuesday - 28 September		Wednesday - 29 September		Thursday - 30 September	
9.00	*Opening*		*Keynote (Grassi M.)*		*Keynote (Manca D.)*	
9.10	*Welcome (Campana E.)*					
9.20	*Keynote (Kovacs L.)*					
9.40			**Session 6**	*Masiello D.*	**Session 11**	*Lu Y.*
10.00	**Session 1**	*Ciarletta P.*		*D'Orsi L.*		*Giorgio I.*
10.20		*Lucci G.*		*Jia J.*		*Cerasuolo M.*
10.40		*Chiari G.*	*Virtual Coffe break*		*Virtual Coffe break*	
11.00	*Virtual Coffe break*		**Session 7**	*Fensterseifer A.*	**Session 12**	*Bellino L.*
11.20	**Session 2**	*Zunino P.*		*McQueen A.*		*Calandrini S.*
11.40		*Braun E.C.*		*Sung B.*		*Madubueze C.E.*
12.00		*Roselli N.*	**Session 8**	*Rochowski P.*	**Session 13**	*Florio G.*
12.20	**Session 3**	*Morilla I.*		*Coclite A.*		*Galuzzi B.G.*
12.40		*Fiandaca G.*		*Conte F.*		*Di Stefano S.*
13.00	*Lunch*		*Lunch*		*Lunch*	
13.30		*Poster (4 parallel rooms)*		*Poster (4 parallel rooms)*		*Poster (4 parallel rooms)*
14.00						
14.30	**Session 4**	*Jain A.*	**Session 9**	*Iacono F.*	**Session 14**	*Vauchelet N.*
14.50		*Sequeira A.*		*Di Felice F.*		*Erdal M.K.*
15.10		*Manzoni E.*		*Di Loreto I.*		*Azizi T.*
15.30		*Bretti G.*	*Virtual Coffe break*			*Lo Presti E.*
15.50	*Virtual Coffe break*		**Session 10**	*Cotta R.*	*Closing*	
16.10	**Session 5**	*El Khalifi M.*		*Daei M.*		
16.30		*Sibilio P.*		*Pompa M.*		
16.50		*Iacoviello D.*				

Program

28 September

- 9:00-9.10 – Opening
- 9.10-9.20 – Welcome address by E. Campana (CNR)
- 9.20-10.00 *Keynote*: L. Kovacs (Obuda University, Budapest, Hungary), Taming cancer: control engineering based tumor therapy.

Session 1

- 10.00-10.20 P. Ciarletta (Polyt. Milano, Italy), Mathematical models and tools for personalized medicine.
- 10.20-10.40 G. Lucci (Polyt. Torino, Italy), A mechanical and computational model for glioblastoma multiforme growth and proliferation including patient-specific data.
- 10.40-11.00 G. Chiari (Polyt. Torino, Italy) A mathematical study of the influence of hypoxia on phenotypic heterogeneity in cancer and its impact on radiotherapy effectiveness.

  11.00- 11-20 *Virtual coffee break*

Session 2

- 11.20-11.40 P. Zunino (Polyt. Milan, Italy) , A multiscale computational model for microvascular oxygen transfer applied to radiotherapy.
- 11.40-12.00 E.C. Braun (Univ. Roma Tre, Italy), Mathematical modelling and model calibration of organ-on-chips.
- 12.00-12.20 N. Roselli (IAC-CNR, Italy), Short-range dynamics in immunocompetent cancer-on-chip experiment: a hybrid PDE-ODE model.

Session 3

- 12.20-12.40 I. Morilla (Univ. Sorbonne, Paris, France), Personalised risk predictor for acute cellular rejection in lung transplantation.
- 12.40-13.00 G. Fiandaca (Polyt. Torino, Italy), Tumour phenotypic heterogeneity: the impact of mixing evolutionary trade-offs with a dynamic surrounding micro-environment.

13.00-14.00 *Lunch break*

Poster session I (4 parallel rooms)

- 13.30 – 14.30
  - A. Procopio et al. (Univ. Magna Graecia, Italy) , Nonlinear Mixed-Effects Modeling approach for the STEMI patients classification.
  - M. E. Antunes et. al. (S. Paolo State Univ., Brazil), Computational simulations of a mathematical model applied to RAI treatment for metastatic papillary thyroid cancer.
  - M. Nascimben et al. (Engisoft, Eng. Padua, Italy), Molecular fingerprint-based spiking neural network QSAR for bioconcentration prediction.
  - C. Mahapatra (Univ. California, USA), Computational modeling of action potential generation in Gallbladder smooth muscle Cell.

Session 4

- 14.30-14.50 A. Jain (Univ. Texas, USA) , Theoretical analysis of multi-layer convection-diffusion-reaction transport for understanding and improving drug delivery.
- 14.50-15.10 A. Sequeira (Ist. Sup. Tecnico, Lisbon, Portugal), Recent advances in the description of blood near-wall transport in aneurysms.
- 15.10-15.30 E. Manzoni (Univ. Padova, Italy), Modernization of a cardiovascular hydrodynamic testing system through the automation of its peripheral resistance device.
- 15.30-15.50 G. Bretti (IAC-CNR, Italy), Parameter estimation for cardiovascular flow modeling of fetal circulation.

15.50-16.10 *Virtual coffee break*

Session 5

- 16.10-16.30 M. El Khalifi, (Ibn Tofail Univ. Morocco), The dynamics of a Covid-19 epidemic model.
- 16.30-16.50 P. Sibilio et al. (Univ. Sapienza, Roma, Italy) , Network-based scenario analysis of in silico drug repurposing: the case of COVID-19.
- 16.50-17.10 D. Iacoviello (Sapienza Univ. Roma, Italy), Covid-19 emergency: state dependent optimal control strategy.

29 September

- 9:00-9.40 *Keynote*: M. Grassi (Univ. Trieste, Italy), Drug delivery and mathematical modeling: an historical perspective.

Session 6

- 9.40-10.00 D. Masiello (Univ. Edinburgh, UK), Mechanistic model of dissolution for irregularly shaped drug particles.
- 10.00-10.20 L. D'Orsi (IASI- CNR, Italy), Modeling of ventilator-patient interaction.
- 10.20-10.40 J. Jia (Univ. Edinburgh, UK), Simulation study of mechanical ventilation control system based on electrical impedance tomography.

10.40- 11.00 *Virtual coffee break*

Session 7

- 11.00-11.20 A. Fensterseifer Schmidt (Univ. Glasgow, UK), In silico modelling of endovascular drug delivery.
- 11.20-11.40 A. McQueen (Univ. Glasgow, UK), Preliminary approaches to understand how anti-proliferative drugs modulate in-stent restenosis.
- 11.40-12.00 B. Sung (UST, Korea), Analytical model for predicting the temperature-responsive behaviours of implantable and biodegradable microgels.

Session 8

- 12.00-12.20 P. Rochowski (Univ. Gdansk, Poland), Mass diffusion through composite systems – an electric circuit-based model.
- 12.20-12.40 A. Coclite (Polyt. Bari, Italy) A dynamic-immersed boundary approach for computing transport and adhesion of micro-sized carriers in narrow capillaries.
- 12.40-13.00 F. Conte (IASI-CNR, Italy) Recognition of gene signatures in breast cancer subtypes.

13.00-14.00 *Lunch break*

Poster session II (4 parallel rooms)

- 13.30 – 14.30
  - V. Fazio et. al. (Univ. Trento, Italy), A multiscale model to unveil the role of humidity and temperature in the mechanical response of protein materials.
  - G. Fiscon (IASI CNR, Roma, Italy) SAveRUNNER: a network-based algorithm for drug repurposing and its application to COVID-19.
  - Sonu et al. (Indian Inst. Technology, India), Cost-effective optimal control intervention strategies implemented on a COVID-19 model under the influence of awareness: a case study on India.
  - J. Matos et al. (San Paulo State University, Brazil), Mathematical model of metastasis involving immunotherapy with CAR T cells.

Session 9

- 14.30-14.50 F. Iacono (Univ. Pavia, Italy), Patient-tailored LSTM model for hypoglycemia prevention: an in-silico case study.
- 14.50-15.10 F. Di Felice (Univ. L'Aquila, Italy), Deep reinforcement learning methods for closed-loop glucose control.
- 15.10-15.30 I. Di Loreto (Univ. L'Aquila, Italy), Decentralized glucose control through contracts theory.

15.30-15.50 *Virtual coffee break*

Session 10

- 15.50-16.10 R. Cotta (Fed. Univ Rio Janeiro, Brazil), Diffusion-Reaction drug release model in non-homogeneous micro-capsules via integral transform.
- 16.10-16.30 M. Daei Daei (Ecole Polyt, Paleiseau, France), Computational modelling of stentriever thrombectomy.
- 16.30-16.50 M. Pompa (Univ. Catt. Sacro Cuore, Rome, Italy), A new mathematical model of the human thyroid.

30 September

- 9:00-9.40 *Keynote*: D. Manca (Polyt. Milan, Italy), Physiologically based pharmacokinetic modeling for individualized medicine with control applications.

Session 11

- 9.40-10.00 Y. Lu (Univ. Technology Warsaw, Poland), Influence of the frequency of periodic mechanical loads on the bone tissue regeneration process.
- 10.00-10.20 I. Giorgio (Univ. L'Aquila, Italy), A diffusive model to describe the biological stimulus in bone remodeling.
- 10.20-10.40 M. Cerasuolo (Univ. Portsmouth, UK), On the use of a hybrid approach to explore drug interaction in the treatment of prostate cancer.

10.40- 11.00 *Virtual coffee break*

Session 12

- 11.00-11.20 L. Bellino (Polyt. Bari, Italy), A micromechanical-based model for axonal damage.
- 11.20-11.40 S. Calandrini (Univ. Perugia, Italy), Model calibration with Italian data to study the impact of SARS-CoV-2 lineages and the vaccination plan on transmissibility.
- 11.40-12.00 C.E. Madubueze (Fed. Univ. Agric., Makurdi, Nigeria), The role of public health education and environmental control on the transmission dynamics of schistosomiasis.

Session 13

- 12.00-12.20 G. Florio (Polyt. Bari, Italy) A new coarse-grained approach for the mechanical behaviour of biomacromolecules.
- 12.20-12.40 B.G. Galuzzi (Univ. Milan Bicocca, Italy) Differential reaction expression analysis for single-cell metabolic network.
- 12.40-13.00 S. Di Stefano (Polyt. Bari, Italy), Continuum modelling for cell-matrix interactions.

13.00-14.00 *Lunch break*

Poster session III (4 parallel rooms)

- 13.30 – 14.30
  - B. Nath (ISC- CNR, Italy), Computational modeling of drug release from a compound droplet in the presence of Poiseuille flow.
  - M. P. Borthakur (ISC- CNR, Italy), Drug release from an emulsified droplet subjected to external shear.
  - Y. Hernandez Rodriguez (Warsaw Univ. Techn., Poland), A new mathematical model for bone's remodelling with dynamic features that predicts bone's behavior.
  - N. Branecka (Warsaw Univ. Techn., Poland), Modeling the reaction of a living cell to mechanical stress in a flowing liquid.

Session 14

- 14.30-14.50 N. Vauchelet (Univ. Sorbonne, Paris, France), Mathematical modeling of a replacement technique to control mosquito-borne diseases.
- 14.50-15.10 M.K. Erdal (Univ. California, USA), Optimal experiment design for learning pharmacokinetic dynamics.
- 15.10-15.30 T. Azizi (Kansas State Univ, USA), Modelling gold nanoparticle biodistribution.
- 15.30-15.50 E. Lo Presti (IRIB- CNR, Italy), From uptake of Zoledronate acid to Isopentenyl Pyrophosphate accumulation: a practice simple mathematical model.

  15.50 Closing

KEYNOTE SPEAKERS

Drug delivery and mathematical modeling: an historical perspective

Mario Grassi[1], Michela Abrami[2], Lucia Grassi[1], Rossella Farra[2], Barbara Dapas[3], Rosario Di Vittorio[1], Gesmi Milcovich[3], Gabriele Grassi[4]

[1] Dept. of Engin. and Archit., Trieste University, Italy, [2] Dept. of Medical Sciences, Trieste University (Cattinara), Italy, [3], School of Chemical Sciences, Dublin City University, Ireland, [4] Dept. of Life Sciences, Trieste University (Cattinara), Italy

It is probably not well known that 4000 years BC Sumerians were able to prepare many medicaments and that the same were used to do Assyrians, Babylonians and Egyptians 3000 years BC. Interestingly, the idea that illness is a sort of divine punishment and healing is the consequent purification, was born in that time and this view heavily affected the western world up to the modern age. If Hippocrates and Galenus, the two most famous witnesses of the Greek and Roman medicinal world, started detaching from this viewpoint, the scientific darkness permeating Europe after the end of the Roman Empire reaffirmed this way of conceiving illness. Only in the 9th -13th centuries, thanks to the golden age of the Arab Science, something changed and, undoubtedly, represented the basis for the big cultural and scientific revolution represented by Renaissance. Interestingly, in the first half of the 16th century, Paracelsus, with a very modern vision, conceived human body as a chemical laboratory. However, it is only at the end of the 19th century that, under a rigorous experimental Galilean approach, the real origins of many diseases were discovered. Consequently, this can be considered as the beginning of the modern pharmaceutics whose task is to optimize and improve the clinical effects of drugs. Since then, drug delivery has developed and after the 2nd world war it entered in its modern age with the realization of the first controlled release system (1952). Notably, the first example of mathematical modelling trying to simulate drug release from a delivery system appeared 9 years later (1961) and the clear affirmation of mathematical modelling in the biopharmaceutical field took place in the last twenty years of the 20th century thanks to valuable researchers such as Peppas and Langer. The third millennium opens with new important challenges for delivery systems designing and mathematical modelling such as the overcoming of biological barriers. This means stopping focusing only on the mathematical modelling of drug release but also considering adsorption, distribution and elimination processes that rule drug fate in vivo. The theoretical bridge joining these two aspects of mathematical modelling could be the ancient, but evergreen, mass balance stating that the administered dose does not disappears but it spreads among tissues before complete elimination/metabolization. In so doing, the idea of Paracelsus about human body has been definitely accepted.

Keywords: Drug delivery, drug absorption, mathematical modelling, historical perspective.

Taming Cancer: Control engineering based tumor therapy

Levente Kovacs[1,2]

[1] Physiological Controls Research Center, Obuda University, Hungary, [2] ELKH SZTAKI, Budapest, Hungary

Cancer is one of the leading causes of death worldwide [1]. Optimization of cancer treatment is a complex task composed of several subtasks, but with a common breakthrough goal: taming cancer, i.e., living with the tumor or totally eliminating the tumor. The core component of this digitalized therapy optimization is a mathematical model that describes the fundamental evolution of tumor growth and by which the effect of therapy can be influenced using control algorithms [2,3]. However, creating such a model poses several challenges. The first one is identifying the most important physiological phenomena that need to be modeled [4,5,6]; the second challenge is the identification of the model parameters based on measurements that are generally limited and hardly suitable for identification, but represent the key aspect in the personalized treatment idea [4,7]. The Physiological Controls Research Center at Obuda University has developed the concept of taming cancer during our running ERC StG project [4-13], creating a mathematical model of tumor growth to be used in further personalized cancer treatment approaches. Our model has been validated using mice experiments and contributed to test and validate our first therapy optimization algorithms [12]. We have extensive collaboration with medical doctors and strong collaboration with cancer researchers who carry out the experiments that are redesigned to be suitable for the identification of our mathematical models, i.e., to demonstrate the viability of the personalized approach. The mathematical model of tumor growth can be used for therapy optimization. Based on the newest research findings in pharmacokinetic and pharmacodynamic optimization, model predictive control, and robust control approaches have been used in order to demonstrate the personalized concept and optimize drug injection and costs, while decreasing side effects. In silico tests proved that our algorithms are suitable for optimizing therapies demonstrated on animal experiments dealing with inter- and intrapatient variability, positivity, and impulsive nature of the control input.

Keywords: physiological control, tumor modelling, control engineering.

Physiologically based pharmacokinetic modeling for individualized medicine with control applications

Davide Manca[1]

[1] PSE-Lab at CMIC Department –Politecnico di Milano – Italy

Once a drug is administered to an individual via different means of dispensation (e.g., intravenous, intramuscular, per os, transdermal, sublingual), ADME processes (i.e. assorption, distribution, metabolism, excretion) summarize the disposition of the active principle within the organism. Pharmacokinetics (PK) encapsulates the ADME processes and describes quantitatively the drug concentration dynamics into the different organs and tissues. PK models may be either basic, with few compartments that schematize and condense the whole structure of the human body, or ground on the anatomy and physiology of the patient and implement a larger number of specialized compartments that nevertheless combine the organs and tissues according to some suitable lumping criteria. The latter approach adds the PB prefix (physiologically based) to the PK suffix. PBPK opens the modeling of mammals' pharmacokinetics to the special features of animals and human species and allows accounting for the individual characteristics of patients such as weight, height, gender, race, age, and liver and renal efficiencies just to cite the most important. The availability of an individualized model of the patient paves the way to optimal individualized treatments over long-time horizons (e.g., anticancer and chronic therapies) or optimal control of surgical operations over short-time horizons (e.g., administration of anesthetic and analgesic drugs in general anesthesia). A further brick to make the whole engine consistent and effective consists of pharmacodynamics. This is a further model that quantifies the effect produced by the administered drug on the patient once it distributes in their body according to the (PB)PK predictions. The PBPK-PD association constitutes the model-based engine that may be used to optimize several problems of individualized medicine. Namely, the presentation summarizes the PK, PBPK, and PD modeling evolution and describes the modeling approach to PBPK and targeted PD for anesthesia. It covers how to design, program, and deploy a flexible simulator capable of covering different drugs and administration routes. It then focuses on a few case-studies and shows how an in-silico approach allows solving the optimal administration of drugs to specific patients and dynamically support the anesthesiologist in administering both anesthetic and analgesic principles while optimizing the induction, maintenance, and resuscitation trajectories in general anesthesia. Finally, the model-based approach to PBPK-PD may cover the advanced in-silico training of specializing medical doctors/nurses and virtually handle specific categories of patients such as obese individuals, the elderly, children, and pregnant women.

Keywords: PBPK modeling, model-based control, individualized medicine, in-silico medicine, medical training.

POSTER SESSIONS

(Alphabetic order)

Computational simulations of a mathematical model applied to RAI treatment for metastatic papillary thyroid cancer

Maria E. Antunes[1], Izabel C.R. Silva[2], Paulo F.A. Mancera[3], Jairo G. Silva[4]

[1] Graduate Program in Biometrics, São Paulo State Univ. (Unesp), Inst. of Biosci., Botucatu, SP, Brazil; [2] Faculty of Ceilandia, Univ. of Brasília, Brasília, DF, Brazil; [3] São Paulo State Univ. (Unesp), Inst. of Biosci. Botucatu, SP, Brazil; [4] Fed. Inst. of Mato Grosso (IFMT), Barra do Garças, MT, Brazil

In 2021, 44.280 new cases of thyroid cancer and 2.200 deaths are expected in the USA, showing that this disease is a public health issue. The most common subtype of the Differentiated Thyroid Cancer (DTC) is the PTC (Papillary Thyroid Cancer), which represents almost 80% of the cases. Tumoral biomarkers are macromolecules capable of providing information about the presence of cancer and, specifically for PTC, important biomarkers are the thyroglobulin (Tg) and the interleukin-6 (IL-6). In this work we numericaly simulate the mathematical model presented in Jairo G. Silva's Ph.D. thesis aiming to evaluate the response of metastatic PTC to different periodic treatment protocols, considering more than one application 131I (RAI). The model consists of a system of ordinary differential equations, which has as variables the activity of RAI used, the number of tumor cells, the serum concentrations of IL-6 and thyroglobulin and was solved using the 4th order Runge-Kutta method. Within the simulated scenarios we consider different values for the RAI efficiency ratio. Besides that, periodic treatment protocols with the same dose were used (4 GBq, 5 GBq or 7.4 GBq) and also with decreasing amount of doses, with a higher dose first (11 GBq), followed by smaller ones. Some results showed that the number of cancer cells do not decrease, which can be associated with a resistance to RAI and can cause a biologically deficiency in the production of NIS (sodium iodide). Besides that, RAI treatments with alternating doses, where initially a higher dose is applied followed by a lower one showed a scenario of successful treatment response, indicating tumor elimination.

Keywords: thyroid cancer; interleukin; radiodine; mathematical model.

Drug release from an emulsified droplet subjected to external shear

Manash Pratim Borthakur[1]

[1] Inst. of Complex Systems, National Research Council Italy, Rome -00185, Italy

In the present study, we examine the transport of a drug from a compound droplet into a surrounding medium under the combined action of diffusion and shear flow. The focus is to understand how the shear induced by the flow alters the transfer of the drug loaded in a circular droplet and encapsulated in a thin shell of another immiscible fluid, into the ambient carrier fluid. In contrast to the previous studies, which do not consider the effect of the background flow and/or interfacial tension, the present work couples these intricate features and examine the transient evolution of the drug concentration in the domain. As illustrated in Fig 1., the computational domain is considered to be an ideal Couette flow setup in order to avoid additional complexities arising out of droplet translation. The interplay of inertial, viscous and interfacial forces on the drug release process are explored in detail.

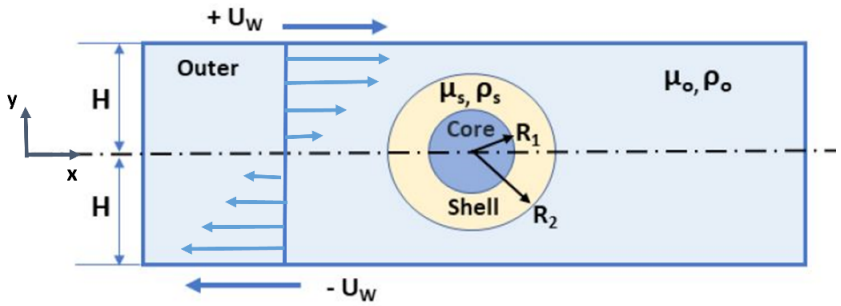


Figure 1: The schematic representation of a compound droplet having a drug loaded in the core region and subjected to external shear.

Keywords: computational fluid dynamics, compound droplet, drug release, interfacial flow.

Modeling the reaction of a living cell to mechanical stress in a flowing liquid

Natalia Branecka[1]

[1] Faculty of Production Engineering, Warsaw University of Technology, Warsaw, Poland

Studies on single living cells are very important in predicting their behavior in living tissue in response to naturally occurring mechanical stimuli. By recreating the types of stress that a given type of cells experiences in the natural microenvironment and by examining their reactions, it is possible to model the behavior of both cells and entire tissues in the body. Particular attention should be paid to the cells of the bone tissue, which is subject to the constant influence of mechanical stresses that change over time and is constantly adapting, affecting the functioning of the whole organism. By studying how cells respond to mechanical stress, one can predict what conditions will cause them to die and which conditions will increase their metabolic activity. This knowledge is extremely important in prosthetics and in the treatment of bone diseases. The subject of the work is the development of a mathematical description and associated two-dimensional finite element model in which a cell is subjected to hydrodynamic loads. An important aspect of modeling a dynamical interaction between cells and fluid is finding an adequate physical description of the cell evolution in response to mechanical stress. Several such models are compared in the work. The interaction between the fluid flowing in the microchannel and the cell structure causes its deformation, the correct interpretation of which allows to determine the reaction between the substrate and the cell, and to predict how its cytoskeleton will remodel and affect cell activities. The stimulation of the flow makes it possible to determine which conditions are optimal for the cells and which cause their damage. By verification the model with the experiment, it is also possible to perform identification of the mechanical properties of the cell based on its deformation.

Keywords: finite element model; bone tissue; mechanical stress.

A multiscale model to unveil the role of humidity and temperature in the mechanical response of protein materials

Vincenzo Fazio[1], Domenico De Tommasi [2], Nicola Maria Pugno[1,3], Giuseppe Puglisi[2]

[1] Dept. of Civil, Environmental and Mechanical Engineering, Univ. of Trento, Trento, Italy, [2] Dept. of Civil Environmental Land Building Engineering and Chemistry, Polytechnic Univ. Bari, Italy, [3] School of Engineering and Materials Science, Queen Mary University of London, London, UK.

Environmental conditions such as humidity and temperature can significantly affect the behavior of macromolecular structured proteins. Water and temperature effects are different depending on the protein microstructure: crystal-like structures (e.g. strong alpha-helices and beta-sheets and weak beta turns), hydrophobic and hydrophilic domains. The role of such domains is crucial in several fundamental directions such as protein folding and unfolding domains, secondary and tertiary structures formation [1]. Here, we refer on the important role that environmental conditions can have in strongly modifying the protein material mechanical response. To focus on a specific material, by following [2], we consider the interesting case of spider silks, extensively considered per se, but also in many bioinspired materials. Specifically, we propose to study such protein materials starting from a detailed description at the macromolecular scale. We thus considered the material as a composite system, with different material phases with hard crystalline domains and soft amorphous fractions. Based on the different presence of crystal domains and of their stability, in humid environments, water molecules decrease the percentage of crosslinks in the softer region inducing a variation of natural configuration of the macromolecules leading sometimes to striking experimental effects such as supercontraction. As we show we obtain a surprisingly effective macroscopic model predicting quantitatively different experimentally observed phenomena (temperature and humidity softening, variation of limit stretches, supercontraction, etc.). Since the material parameters of the obtained macroscopic system, with damage, permanent stretch and dissipation, explicitly depend from microscale parameters, we believe that the proposed model not only can be important to study humidity and temperature effects in other protein materials with similar structures, but also in the perspective of giving the predictive tools in the choice of the composing proteins and their percentage of new bioinspired materials.

Keywords: protein material, spider silk, multiscale model.

References

[1] G. Puglisi, D. De Tommasi, V. Fazio, N. M. Pugno, "Spider silks mechanics: predicting humidity and temperature effects", submitted (2021).

[2] G. Florio, N. M. Pugno, M. J. Buehler, G. Puglisi, "A coarse-grained mechanical model for folding and unfolding of tropoelastin with possible mutations", submitted (2021).

A new mathematical model for bone's remodelling with dynamic features that predicts bone's behavior

Yunuhén Hernández Rodríguez[1]

[1] Warsaw University of Technology

The dental practice has been facing the problem of how to expand prostheses life-span from a long time ago. Many approaches have been tried but it seems clear that the thesis "one implant fits all" is no longer valid. Better ways are needed to fit an implant to a specific patient that has certain bone characteristics and individual overall needs. To meet that peculiarity, better ways of implant designing and prediction of their functionality are needed, as well as, a better understanding of trabecular bone failure at which the implant is fixed. We aim to study a new model that correctly predicts the functionality of bone remodelling in several cases, that could be used to study bone interaction with a dental implant with or without the presence of bone substitute material. The new model could be used, as well, as a guide to predict the lifespan of a certain implant with some mechanical characteristics into patience with specific bone mechanical characteristics, for example, diseases.

Keywords: bone remodelling.

Computational modeling of action potential generation in gallbladder smooth muscle cell

Chitaranjan Mahapatra[1]

[1] Cardiovascular Research Institute, University of California San Francisco, USA

The gallbladder smooth muscle cell (GSM) contributes to cholesterol gallstone disease by modulating its' contractility activity. The electrical properties such as the membrane depolarization and spontaneously evoked action potentials in GSM cells initiate and modulate these contractions. Therefore, a complete understanding of the action potential biophysics will be an efficient tool in identifying novel pharmacological targets for the cholesterol gallstone disease. The action potential is evoked by the activation of various ion channels across the GSM cell membrane. This study aims in establishing a computational model of the single GSM cell to simulate the action potential after incorporating all-important ion channels. The internal kinetics of all active ion channels are described by the ordinary differential equations. The steady state value of activation and inactivation parameters are built with respect to the classical Hodgkin and Huxley formalism. All ion channels are incorporated and the action potential is simulated by injecting both current and neurotransmitter stimulus. All simulations are performed using the NEURON software platform. This computational model generates experimental action potential and the underlying ionic currents in the GSM cell successfully. It is found that the inhibitor of L-type calcium channel has reduced the inward current significantly and blocked the action potential generation. The calcium dependent potassium ion channel is a major contributor of the total outward current and modulates the resting membrane potential and repolarization phase of the action potential. However, the voltage gated potassium channel also modulates the action potential repolarization phase in the absence of the calcium dependent potassium ion channel. Therefore, the application of L-type Calcium channel antagonist or the potassium ion channel agonist will be helpful in controlling the spontaneous activities in the GSM tissue. In summary, this mathematical model contributes an elemental tool to shed light on the genesis of cholesterol gallstone disease.

Keywords: gallbladder smooth muscle, action Potential, mathematical model.

Mathematical model of metastasis involving immunotherapy with CAR T Cells

Janielly Matos[1], Diego S. Rodrigues[2], Paulo F. A. Mancera[3]

[1] Graduate Program in Biometrics, Institute of Biosciences, São Paulo State University (UNESP), Brazil, [2] State University of Campinas (UNICAMP) School of Technology, Brazil, [3] Institute of Biosciences, São Paulo State University (UNESP), Brazil

The essence of cancer is characterized by the disordered growth of cells having the ability to invade tissues and injured adjacent organs. Classified as a world health problem, cancer lies among the four leading death causes worldwide, being metastasis responsible for over 90% of all cancer-related deaths. In order to eradicate the disease, several therapies are under development, being the immunotherapy on prominence for not causing severe damages to the normal cells, reinforcing the patient's immune system so it could better fight the cancer cells. Using Ordinary Differential Equations, we considered a mathematical model of metastasis involving immunotherapy with CAR T cells. In the model, metastasis is modeled as a migratory phenomenon, where two populations of cancer cells coexist and develop in two different locations. Through numerical simulations, we studied the tumor dynamics in different scenarios, where these were obtained by varying the initial condition of the tumor cells and in the amount of CAR T cells used. Because it is a personalized therapy, there is still no universal protocol, however, through mathematical modelling, we can evaluate different strategies that aim at an optimal amount of cells to be used depending on the tumor mass.

Keywords: CAR T-cell therapy, immunotherapy, mathematical modelling, metastasis, ordinary differential equations.

References

[1] Levine, B. L.; Miskin, J.; Wonnacott, K.; Keir, C. Global manufacturing of CAR T cell therapy. Molecular Therapy-Methods & Clinical Development, v.4, p.92-101, 2017.

[2] León-Triana, O. et al. Dual-target CAR-Ts with on-and off-tumour activity may override immune suppression in solid cancers: A mathematical proof of concept. Cancers, v. 13, n. 4, p. 703, 2021.

[3] Pinho, S. T. R., Freedman, H. I., Nani, F. (2002). A chemotherapy model for the treatment of cancer with metastasis. Mathematical and Computer Modelling, v. 36, n. 7-8, p. 773-803

[4] Rodrigues, B. D. J. Modelagem matemática da imunoterapia com células CAR T, 2019. Dissertaçao (Mestrado) - Laboratório Nacional de Computação Científica.

Molecular fingerprint-based spiking neural network QSAR for bioconcentration prediction

Mauro Nascimben[1, 3], Silvia Spriano[2], Manolo Venturin[1], Lia Rimondini[3]

[1] Enginsoft SpA, Padua, Italy, [2] Department of Applied Science and Technology, Polytechnic University of Turin, Turin, Italy, [3] Department of Health Sciences, University of Eastern Piedmont, Novara, Italy

Different aspects of molecules' 2D structure can be represented by molecular fingerprints (MF), which encode chemical structural properties in binary bit strings. Besides, bit sequences are the natural input of spiking neural networks (SNN), the 3rd generation of neural networks, a biologically inspired machine learning method that models neuron activity as a cell rather than an input summator.In the present analysis, we will develop an SNN-based quantitative structure-activity relationship (QSAR) model to determine the mechanisms of bioconcentration. In previous works, MFs have already been used inside the machine learning domain to predict toxicity [1], ligand biological activity [2], or ionic liquid properties [3]. To the best of our knowledge, our analysis is the first attempt to analyze MFs with SNNs. The investigation will focus on three distinct sections:

1. Evaluate which fingerprint type better suits SNNs (Morgan, atom-pair, MACCS, etc.) as an input signal.

2. Study which SNN architecture maximizes target outcome in terms of neurons, synapse models, and learning rule.

3. Test integration of additional static functional attributes by converting them in bitstrings for data fusion with structural MFs or acting on the SNN classifying layer. In the presence of small datasets, additional data inclusion could lead to more accurate predictions.

The expected advantages of exploiting SNNs instead of ANN are the computational speed, reduced number of layers, and a low number of trials needed to initialize weights.

Keywords: molecular fingerprints, spiking neural network, quantitative structure-activity relationship, bioconcentration prediction.

References

[1] Wu, Y., & Wang, G. (2018). Machine learning based toxicity prediction: from chemical structural description to transcriptome analysis. Intern. J. of mol. sci., 19(8), 2358.

[2] Myint, K. Z., Wang, L., Tong, Q., & Xie, X. Q. (2012). Molecular fingerprint-based artificial neural networks QSAR for ligand biological activity predictions. Mol. pharma., 9(10), 2912-2923.

[3] Ding, Y., Chen, M., Guo, C., Zhang, P., & Wang, J. (2021). Molecular fingerprint-based machine learning assisted QSAR model development for prediction of ionic liquid properties. J. of Mol. Liq., 326, 115212.

Computational modeling of drug release from a compound droplet in the presence of Poiseuille flow

Binita Nath[1]

[1] Institute of Complex Systems, National Research Council Italy, Rome - 00185, Italy

In the present work, we investigate the dynamics of drug release from a compound droplet into a surrounding medium under the combined action of diffusion and droplet translation. A compound droplet is considered as a model carrier of the drug material, which is encapsulated inside the core region of the droplet. A pressure driven flow inside a channel induces the translation of the droplet. The study uncovers the mechanism of drug release under the combined action of diffusion as well as the fluid flow induced by the droplet actuation. The critical interaction of the hydrodynamic parameters ultimately decides the rate and mechanism of drug release from the droplet into the surrounding medium. The insights from our study can provide design guidelines for improving the performance of drug delivery platforms using droplet based technologies. The schematic of the computational domain is shown in Fig.2. The radius of core and shell are taken as R_i and R_o, respectively. The drug is loaded in the inner core and its properties are considered to be the same as the outer suspending fluid.

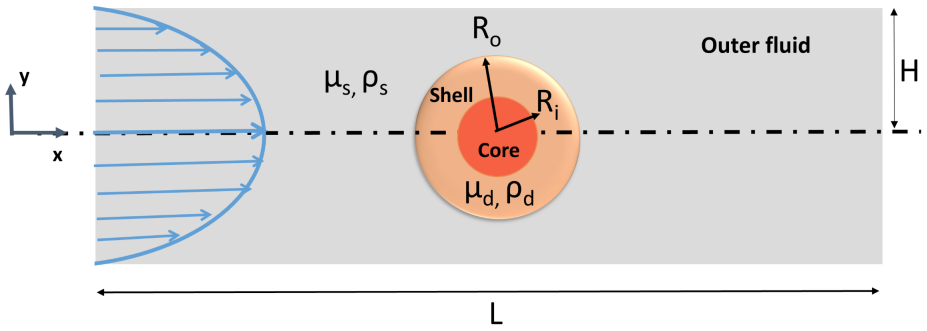


Figure 2: The schematic representation of a compound droplet having a drug loaded in the core region and subjected to Poiseuille flow.

Keywords: drug release, compound droplet, pressure driven flow.

Nonlinear mixed-effects modeling approach for the STEMI patients classification

Anna Procopio[1], Salvatore De Rosa[2], Carlo Cosentino[1,3]

[1] Dept. of Experimental and Clinical Medicine, University Magna Graecia of Catanzaro, 88100 Catanzaro, Italy, [2] Dept. of Medical and Surgical Sciences, University Magna Graecia of Catanzaro, 88100 Catanzaro, Italy, [3] Dept. of Electrical Engineering and Information Technology, Università degli Studi di Napoli Federico II, 80125 Napoli, Italy

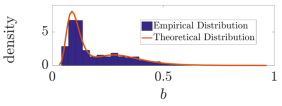
Nonlinear mixed-effects models describe the response of a dynamical system by means of a nonlinear function of the predictor and parameters vector, expressed as the combination of fixed and random effects. The present work investigates the application of mixed-effects models to a specific clinical dataset of patients subjected to Acute Myocardial Infarction (AMI) of the ST-segment elevation (STEMI) type. In particular, we studied the effects of the different available covariates on the time-course of the plasma concentration of the cardiac biomarker cardiac troponin T (cTnT). The proposed model-based approach aims at extracting useful information for the classification and correct treatment of AMI patients.
Among the tested models, we selected the one that takes into account the effects of dyslipidemia, Fig. 3 (a). The fixed and random effects for the selected model are reported in Fig. 3 (b). A deeper analysis of this model showed a statistically significant effect of dyslipidemia on model parameter as shown in Fig. 3 (c). Future works conducted on a larger dataset are needed to have more thorough and reliable classifications of this heterogeneous class of patients.

Model	1 Cov	2 Cov	3 Cov	LL	BIC	st. error
1				-1613.80	-1576.76	0.655
2	dyslipidemia			-1617.07	-1569.93	0.427
3	aortic insufficiency			-1638.79	-1595.02	0.553
4	prev. AMI			-1627.24	-1586.83	0.255
5	dyslipidemia	aortic insufficiency		-1655.09	-1604.58	1.575
6	dyslipidemia	prev. AMI		-1654.32	-1607.18	0.492
7	aortic insufficiency	prev. AMI		-1643.52	-1596.38	0.412
8	aortic insufficiency	prev. AMI	dyslipidemia	-1645.95	-1595.89	0.531

a) Effects of the covariates on the mathematical model. For each model, we have reported the log-likelihood and the bayesian information criterion (BIC) indices.

Fixed Effects			
Parameter	Value	S.E.	R.S.E(%)
a_{pop}	0.0361	0.00675	18.7
b_{pop}	0.0986	0.0144	14.6
$\beta_{Dyslip.}$	1.16	0.241	20.9
T_{pop}	193	17.9	9.26
$C_{\omega_{pop}}$	15.1	4.3	28.4
$C_{\sigma_{pop}}$	23.5	7.34	31.2
Random Effects (std)			
Parameter	Value	S.E.	R.S.E(%)
ω_a	0.682	0.165	24.2
ω_b	0.329	0.109	33.2
ω_{T_d}	0.221	0.0611	27.7
$\omega_{C_{\omega}}$	1.4	0.188	13.5
$\omega_{C_{\sigma}}$	1.47	0.204	13.8

b) Fixed and random effects estimated for each parameter. S.E. and R.S.E(%) are reported for both effects.



c) Empirical and theoretical distribution of the estimated values for parameter b. This distribution shows a visible bimodal trend, indicating the existence of two distinct classes of STEMI patients in the provided dataset.

Figure 3: Summary of the main results: the table in a) reports the results obtained by testing several models. In Table b), we report the fixed and random estimated effect for the selected model (red box in Table a). The histogram in c) shows the bimodal distribution of the estimated values of in dyslipidemic and non-dyslipidemic patients.

Keywords: nonlinear mixed effects model; STEMI classification; dyslipidemia.

Network-based scenario analysis of in silico drug repurposing: the case of COVID-19

Pasquale Sibilio[1,2], Simone Bini[1], Giulia Fiscon[2,3], Marialuisa Sponziello[1], Federica Conte[2], Valeria Pecce[1], Cosimo Durante[1], Paola Paci[2,4], Rosa Falcone [5], Lorenzo Farina[4], Antonella Verrietti[1]

[1] Dept. of Translational and Precision Medicine, Sapienza Univ. of Rome, Rome, Italy, [2] Inst. for Systems Analysis and Computer Science "Antonio Ruberti", CNR, Rome, Italy, [3] Fondaz. per la Medicina Personalizzata, Via Goffredo Mameli, 3/1 Genova, Italy, [4] Dept. of Computer, Control and Management Engineering, Sapienza Univ. of Rome, Rome, Italy, [5] Phase 1 Unit-Clinical Trial Center Gemelli Univ. Hosp., Agostino Gemelli square, 8 00168 Rome

SARS-CoV-2 pandemic is a worldwide public health emergency and, despite the beginning of a vaccination campaign, the finding of new drugs to appropriately treat COVID-19 patients remains a priority. Drug repurposing represents an effective drug discovery strategy from existing drugs faster and cheaper than de novo drug discovery. Being a single study not sufficient to cover the multiform clinical frame of the disease, here we explored the different scenarios provided by three different network-based approaches to identify possible repurposable drugs for Covid-19. We analyzed transcriptomic data from whole blood cells of COVID-19 patients and other 21 related conditions, compared to those of healthy subjects and we found, in addition to conventional drugs (e.g. anticoagulants, antihistaminics, anti-TNFα antibodies, corticosteroids, etc.), also "unconventional" candidate compounds, such as neurotropic drugs and SCN5A inhibitors. However, clinical judgment and validation through clinical trials are always mandatory before using the identified drugs in a clinical setting.

Keywords: COVID-19; drug repurposing; corticosteroid; heparin; inflammatory bowel disease; septic shock.

Cost-effective optimal control intervention strategies implemented on a COVID-19 model under the influence of awareness: a case study on India

Sonu Sonu[1], Prashant K. Srivastava[1]

[1] Department of Mathematics, Indian Institute of Technology Patna, India

As of May 2021, there were approximately 177 million cases of the COVID-19, with over 3.7 million deaths worldwide. Although social awareness has played an important role in slowing the transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), several strategies have also been proposed to reduce the spread of the SARS-CoV-2 virus. In this paper, we conduct a cost-effective optimal control analysis of interventions implemented on a COVID-19 model under the influence of social awareness. We consider a deterministic compartmental model for disease transmission in India incorporating social awareness. First, we demonstrate all the basic dynamical properties including local and global stability analysis of equilibrium points. We then introduce home quarantine and treatment as time-dependent controls to the model and establish the existence and uniqueness of optimal controls using the Filippov–Cesari existence theorem. Pontryagin's minimum principle (PMP) describes the optimality condition and gives the necessary condition for minimization of the corresponding Hamiltonian, the objective functional is formulated to minimize both the infection and the costs of interventions implemented. The optimal control model is solved using forward-backward sweep method (FBSM) that combines the forward application of a fourth-order Runge-Kutta (RK4) method for solving the original system with the backward application of a RK4 method for solving the adjoint system. The results are then simulated using MATLAB. The comparative cost-effective analysis shows that implementing a single strategy at a time is the cheapest but it is not recommended because the application of both the control strategies along with the social awareness is the most optimal and sustainable way to flatten the COVID-19 curves in a short period of time.

Keywords: SARS-CoV-2, COVID-19, cost-effective optimal control, Pontryagin's minimum principle, forward-backward sweep method (FBSM).

ORAL SESSIONS

(Alphabetic order)

The Role of Public Health Education and Environmental Control on the Transmission Dynamics of Schistosomiasis

Agatha Abokwara[1], Chiwnedu E. Madubueze[1], Reuben I. Gweryina[1]

[1] Dept. of Mathematics, Statistics and Computer Science, Federal University of Agriculture, Makurdi, Nigeria

Schistosomiasis is one of the neglected tropical disease affecting communities in flood prone environment or where fishing activities take place. This has been a draw back to the health and economic life of the citizens in these areas. This study is to evaluate the impact of public health education and snail control activities on the spread of schistosomiasis. The model is developed with attention given to the snail and human populations which are the hosts of the miracidia and cercariae respectively. The existence and stability of disease free-equilibrium and endemic states are established. The disease-free equilibrium state is showed to be locally and globally asymptotically stable whenever the basic reproduction number is less than unity. The stability of endemic equilibrium state of the model is also analysed using centre manifold theory and Lyapunov function for its local and global stability when basic reproduction number is more than unity. The numerical simulations of the model are carried to evaluate the impact of these control strategies, public health education and snail control on schistosomiasis transmission. It was observed that public health education and snail control activities play an important role in mitigating the spread of the disease.

Keywords: public health education, snail control, bifurcation analysis, reproduction number, schistosomiasis.

Model calibration with Italian data to study the impact of SARS-CoV-2 lineages and the vaccination plan on transmissibility

Chiara Antonini[1], Sara Calandrini[1,2], Fortunato Bianconi[3]

[1] ICT4life, Perugia, Italy, [2] Department of Engineering, University of Perugia, Perugia, Italy, [3] COVID-19 Epidemiological Unit, Regional Government of Umbria, Italy

The novel variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have caused in Italy a third epidemic wave of COVID-19 peaking in March 2021 [1]. At the end of 2020, different vaccines were approved in order to prevent hospitalizations. However, due to the unstoppable evolution of COVID-19, non-pharmaceutical interventions (NPIs) are still necessary. This work aims to study this scenario adopting an epidemiological model focusing on Italy and especially Umbria, the first region affected by variants in February. The main objective is prediction of the possible future evolution of COVID-19 pandemic, evaluating the impact of new variants and the role of natural and vaccine immunity response. We extend the Susceptible-Exposed-Infectious-Removed model with lock-down measures (SEIR-L) used in our study in [2] with inclusion of new lineages and vaccination execution (SEIRL-V). We estimate model parameters using the Bayesian method Conditional Robust Calibration [3] against the Italian and Umbria data, simulating multiple scenarios to forecast the dynamics of COVID-19 from 2021 onwards, varying the vaccination rate and the relaxation of NPIs. The results confirm the increase of reproduction number R0 and of transmission parameters due to the diffusion of variants. The study highlights the efficacy of a multi-strategy approach to control the COVID-19 diffusion based on the efficacy of vaccines, social distancing and isolation of detected cases. Finally, under the hypothesis of waning immunity, the predictions show that a periodic vaccination with a medium rate controls the epidemic.

Keywords: COVID-19, vaccination, SARS-CoV-2 variants, SEIR model, Bayesian parameter estimation.

References:

[1] Prevalence of VOCs (Variant Of Concern) of the SARS-CoV-2 virus in Italy: lineage B.1.1.7, P.1 and B.1.351, and other variants (Variant Of Interest, VOI) including lineage P.2 and lineage B.1.525 (survey of 20/4/2021). https://www.iss.it/documents/20126/0/Relazione+tecnica+indagine+rapida+varianti+SARS-COV-2.pdf/f425e647-efdb-3f8c-2f86-87379d56ce8d?t=1620232350272, 2021.

[2] Antonini, C.; Calandrini, S.; Stracci, F.; Dario, C.; Bianconi, F. (2020). Mathematical Modeling and Robustness Analysis to Unravel COVID-19 Transmission Dynamics: The Italy Case. Biology, 9 (11), 392.

[3] Bianconi, F., Tomassoni, L., Antonini, C., & Valigi, P. (2020). A new Bayesian methodology for nonlinear model calibration in Computational Systems Biology. In: Frontiers in Systems Biology .

Modelling gold nanoparticle biodistribution

Tahmineh Azizi[1]

[1] Department of mathematics, Kansas State University, Manhattan, KS, USA

Nowadays, nanoparticles have a growing use in industry specially medicine. There are some studies about applications of NPs in therapeutic areas, however, the number of these studies is not a lot. Increasing the importance of studies about tumors and concentration of drugs and NPs in tumors or other tissues has enhanced the role of in vitro models to simulate absorption process of drugs and NPs. Pharmacokinetic and physiological models are useful means to demonstrate the relationships between different drug administrations, and drug exposure or concentration. A mathematical model for drug or NP distributions is a structural model, consisting of compartments such as adipose, tissues, brain, gut, heart, kidney, liver, lung, muscle, spleen, skin, and bone and gastrointestinal tract including mouth, esophagus, and abdomen which are connected by the cardiovascular system. In mathematical perspective, they describe biological systems by converting into mathematical and theoretical equations and parameters and then using computer code to solve the model system computationally. To check the accuracy of any mathematical model, we need to use different methods and because of existence of uncertainty in experimental data, it can be often complicated. Uncertainty and sensitivity analysis are useful techniques which help us to identify these uncertainties in data and then control them. Pharmacokinetic models are mathematical models which provide insights into the interaction of chemicals with biological processes. During recent decades, these models have become central of attention in industry that caused to do a lot of efforts to make them more accurate. Current work studies the process of drug and nanoparticle (NPs) distribution throughout the body which consists of a system of ordinary differential equations. We use a tri-compartmental model to study the perfusion of NPs in tissues and a six-compartmental model to study drug distribution in different body organs. We have performed global sensitivity analysis by LHS Monte Carlo method using PRCC. We identify the key parameters that contribute most significantly to the absorption and distribution of drugs and NPs in different organs in body.

Keywords: Global sensitivity analysis, Latin Hypercube Sampling (LHS), Partial Rank Correlation Coefficient (PRCC), physiological systems, drug and NPs Distribution.

A micromechanical-based model for axonal damage

Luca Bellino[1], Giuseppe Florio[2], Giuseppe Puglisi[2]

[1] Polytechnic University of Bari, DMMM, Bari, Italy, [2] Polytechnic University of Bari, DICATECh, Bari, Italy

Human brain exhibits an incredible level of complexity and the study of the behaviour of neurons is fundamental for the comprehension of neurodegenerative diseases as the Parkinson and the Alzheimer. Besides the electrochemical effects, clinical evidence shows that also mechanical forces, impacts and traumatic accidents play a crucial role at the microscale and may cause severe damages at the brain level, such as in the case of the pathologies classified as Traumatic Brain Injury (TBI) [1]. In particular, the mechanism of damage is generated at the length scale of the axons, the long part of the neuron cell, responsible for the transmission and production of neurochemical signals. From a mechanical point of view, the axon is made of bundles of microtubules (MTs), almost rigid hollow rods, held together by the so-called tau-proteins. It is clinically recognised that in patients suffering from neurodegenerative diseases the white matter presents scattered lesions and the axonal failure can happen abruptly or with a progressive, time dependent degradation [2]. In particular, it is possible to identify three different damage regimes depending on both the strength and velocity of application of the involved forces. If both the strain and the strain rate are small, the microtubules can slide along the axons and the tau-proteins are able to detach and reattach to other successive vacant sites with an almost reversible damage. When the load is increased it may happen that the proteins are not anymore able to reattach, and some connections cannot be recovered. If both the strain and the strain rate assume large values, the microtubules can break, possibly causing important and irreversible dysfunctions and damages [3]. In order to study the above described physical problem, the thermomechanical properties and the rate effects, we propose a microscale-based model mimicking the behaviour of the system composed by two microtubules linked by tau-proteins under shear loading conditions. Following [4], we consider the tau proteins as breakable links and the MTs as elastic units and obtain the force-displacement relations. We find that, depending on the constitutive parameters and on the assigned velocity, the mechanical response of the system may vary drastically showing a fragile to ductile transition in the fracture behaviour.

Keywords: traumatic brain injury, axonal damage, tau proteins, microtubules, rate effects.

References:

[1] M. D. Tang-Schomer et al, The FASEB Journal 24, 1401 (2010).
[2] K. J. Rosenberg et al, PNAS 105, 7445 (2008).
[3] H. van den Bedem and E. Kuhl, Biophysical journal 109, 2215 (2015).
[4] G. Puglisi and L. Truskinovsky, PRE, 87, 032714 (2013).

Mathematical modelling and model calibration of Organ-on-chips

Elishan Christian Braun [1,2], Gabriella Bretti[2], Roberto Natalini[2]

[1] Dept. of Mathematics, Univ. of Roma Tre, Rome, Italy, [2] Istituto per le Applicazioni del Calcolo "Mauro Picone", CNR-IAC, Rome, Italy

Organs-on-Chips (OOC) are microfluidic chip environments, that have attracted large interest in recent years because of their potential to provide insight into organ functioning and disease pathophysiology. Inspired by recent laboratory experiments that investigate the cross-talk between immune and cancer cells, a mathematical model is derived which is based on coupled reaction-diffusion-transport equations with different chemotactic functions to model a variety of possible cell mechanics and takes into account the possibility of drug administration for drug testing effects.

Our aim is the development of a simulation tool, capable of re-producing immune cell migration and interaction with cancer on the OOC. Moreover, using available experimental data to calibrate the model parameters and infer the intrinsic underlying chemotactic behaviour, see Fig. 4 for a reconstruction of immune cell population in the left and right compartments of the microfluidic chip during the experiment.

The work is divided into two problem categories: The proper derivation of the mathematical model on the OCC and the efficient parameter estimation of the mathematical model with the available experiment data. For this reason we introduce mass-preserving and positivity-preserving conditions, to balance the incoming and outgoing fluxes passing through the interfaces between 2D and 1D domains of the Organ-on-Chip. For the calibration problem aganist real data, mostly available in microscopic data as cell positions several techniques such as regularization and multigrids applications are used to improve the results.

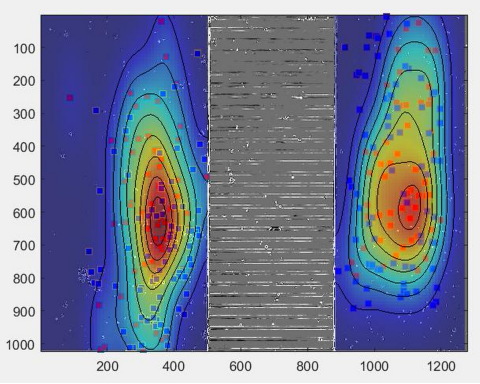


Figure 4: Reconstruction of immune cell density in the microfluidic chip compartments.

Keywords: Organ-on-Chip, chemotaxis, parameter estimation.

Short-range dynamics in immunocompetent Cancer-on-Chip Experiment: a hybrid PDE-ODE model

Gabriella Bretti[1], Adele De Ninno[2], Daniele Peri[1], Roberto Natalini[1], Nicole Roselli[3]

[1] Ist. per le Applic. del Calc. "M.Picone", Rome, 00185, Italy, [2] Ist. di Fot. e Nanotecn., Rome, 00156 Italy, [3] Dept. SBAI, Sapienza Univ. of Rome, 00185 Italy

The Organs-on-Chip approach (OOC) represents a novel instrument to investigate how different populations of cells migrate, interact and respond to signals emanated from the micro-environment. Thus, confining cells on a well-defined domain allows experimentalists to have a major control on them and to obtain experimental results closer to in vitro reality. In the late years OOC was employed to analyze how immune cells (ICs) migrate in presence of tumor cells (TCs), which were treated with chemotherapeutic agents and therefore experiencing the process of immunogenic cell death. Although the use of chips can help to unravel most of the hidden facets of cell behaviors, some mechanisms still remain unknown, i.e. the concentration of chemical gradients in the environment. To provide a mathematical formulation of the problem, we consider a hybrid model given by the coupling between a partial differential equation equipped with Robin inhomogeneous boundary conditions, which describes changes in the concentration of the chemoattractant and an ordinary differential equation to describe the motion for each ICs. Then, we propose an original strategy for the calibration of model parameters, consisting in comparing the average velocity fields obtained by synthetic data with the velocity fields produced by the model solutions. To accomplish this, we interpolate the velocities of the cells at each time producing a velocity field surface, see Fig. 5 and then constructing the objective function. Our calibration algorithm showed to be robust and accurate on synthetic data, thus representing a first step to deal with real data.

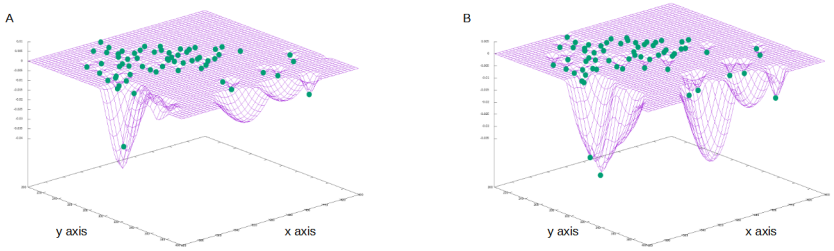


Figure 5: Interpolated surfaces: A) Velocities in the x-direction, B) Velocities in the y-direction. Green points indicate the values in the corresponding positions.

Keywords: differential equations, mathematical biology, cell migration, microfluidic chip.

Parameter estimation for cardiovascular flow modeling of fetal circulation

Gabriella Bretti[1], Roberto Natalini[1], Annalisa Pascarella[1], Giancarlo Pennati[2], Daniele Peri[1], Giuseppe Pontrelli[1]

[1] Istituto per le Applicazioni del Calcolo "Mauro Picone", CNR-IAC, Rome, Italy,
[2] Dept. Bioeng. Politecnico of Milan, Milan, Italy

The present paper represents a first methodological work for the construction of a robust and accurate algorithm for the solution of an inverse problem given by the identification of the parameters of a lumped mathematical model of fetal circulation introduced by G. Pennati et al. (1997).

The underlying estimation techniques here applied are two global search methods, respectively a Parameter Space Investigation (PSI) and the Ensemble Kalman Filter (EnKF), with a refinement performed with a local search method, i.e. Levenberg-Marquardt method (LM). The results here presented show the soundness of our methodology and opens the possibility to apply these techniques for the parameter identification of waveforms obtained from Doppler clinical measurements in the next future.

Our final goal is to build a non-invasive simulation tool for the description of the circulation of fetuses in the context of a patient-specific model in order to help clinicians in early diagnosis of pathologies like cardiac distress or growth retardation.

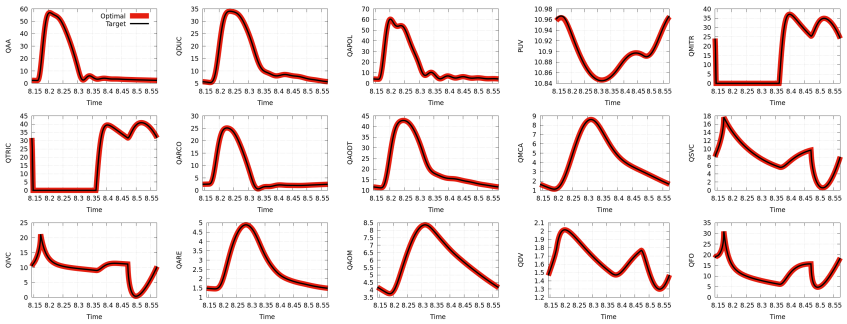


Figure 6: Plot of fetal blood flow and pressure profiles obtained with lumped mathematical model VS the target profiles.

Keywords: lumped mathematical model, fetal circulation, parameter estimation algorithm.

On the use of a hybrid approach to explore drug interaction in the treatment of prostate cancer

Marianna Cerasuolo[1], Leo Turner[1], Andrew Burbanks[1]

[1] University of Portsmouth, School of Mathematics and Physics, Portsmouth, UK

A hybrid system of ODEs and PDEs has been implemented to assess the role of cells and chemicals diffusion on the dynamics of prostate cancer in a multistage murine model TRAMP (transgenic adenocarcinoma of the mouse prostate) under different therapeutic strategies. The model describes the interdependence of cancer cells on tumour microenvironment as well as the onset of resistance following treatment with a second generation drug (androgen receptor antagonist) called enzalutamide.

The proposed mathematical model, whose development strongly relied on experimental data and their statistical analysis, represents a theoretical framework to bridge the in vitro and in vivo experiments used to assess the effect of single- or combined-drug therapies on TRAMP mice and TRAMP-derived cells. The model revealed that combination therapies can delay the onset of resistance to enzalutamide, and in the suitable scenario with alternating drug therapies, can eliminate the disease. The model also showed that some of the drug combinations can cause the formation of smaller-size tumour clusters, which could give rise to metastasis.

Keywords: hybrid ODE-PDE model, prostate cancer.

A mathematical study of the influence of hypoxia on phenotypic heterogeneity in cancer and its impact on radiotherapy effectiveness

Giulia Chiari[1]

[1] DISMA, Dept. of math. sci. Giuseppe Luigi Lagrange, Politecnico di Torino, Italy

In the study of cancer evolution and radiotherapy treatments, scientific evidence shows that a key dynamics lies in the tumor-abiotic-factors interaction. In particular, oxygen concentration plays a central role in the determination of the phenotypic heterogeneity of the cancer cell population, both from a qualitative and geometric point of view. Hypoxia acts as an environmental stressor promoting the selection of aggressive phenotypes and affecting therapeutic efficacy in a twofold way. On the one hand, selected cells are characterized by high resistance to hostile environments, resulting in the ability to survive in those areas in which the radiotherapy treatment is less effective because of the lack of oxygen (oxygen is responsible for the enhancement of the detrimental effect of ionizing radiation). On the other hand, selected cells present a low proliferative rate, thus being less exposed to radiotherapy action, which acts damaging the DNA of cells involved in the replication process. In this talk, we present a continuous mathematical model to study the influence of hypoxia on the evolutionary dynamics of cancer cells. The model is settled in the mathematical framework of phenotype-structured population dynamics and it is formulated in terms of systems of coupled non-linear integro-differential equations. We consider a three-dimensional domain in which two dimensions are dedicated to the spatial representation while the other one features the phenotypic state related to the expression of the hypoxia-resistance gene. Numerical simulations are performed using Galerkin finite element methods, implemented in Python with FEniCS tool, with the aim to test different vessel dispositions, allowing to represent various biological situations (without the constraint of radial symmetry), such as cancer mass developing in well-oxygenated or highly inhomogeneous tissues and tumor cords growing around single vessels. Then, the effects of radiotherapy treatment are included in the model and numerical simulations are driven to analyze the influence of the heterogeneity in oxygen concentration and phenotypic distribution of cancer cells on the treatment effectiveness. Various therapeutical protocols, differentiated per doses and timing, are considered. The computational outcomes show that the mutual interactions between the tumor mass and the oxygen distribution can result in a geometric characterization of tumor niches differentiated by phenotypic characteristics that determine a heterogeneous response to radiotherapy. The analysis of the study results provides suggestions about possible therapeutic strategies to optimize the radiotherapy protocol in light of the phenotypic and geometric inhomogeneities of the tumor.

Keywords: cancer modeling, structured population, hypoxia, radiotherapy.

Mathematical models and tools for personalized medicine

Pasquale Ciarletta[1]

[1] MOX Laboratory, Dip.to di Matematica Politecnico di Milano, Italy

In the first part, I will present the result of research project in collaboration with Ospedale Neurologico Besta and Instituto IFOM in Milan funded by Associazione Italiana per la Ricerca sul Cancro. In this work, we have proposed a predictive mathematical model and we have built simulation tools to describe the growth the most aggressive brain tumour, glioblastoma multiforme (GBM), using patient-specific data, together with its response to therapy, to assist medical doctor in optimizing individual therapeutic strategies. The model has been calibrated and validated against the data collected by a clinical study performed at the Istituto Neurologico Besta on a cohort of 32 patients diagnosed with GBM that have been screened by the most advanced bio-imaging techniques during diagnosis, biopsy, surgery, adjuvant therapy and post-therapy follow-up. The computational tools use clinical data deriving from patient specific advanced Magnetic Resonance and Diffusion Tensor Imaging into to a mathematical model which is able to consider and exploit both chemical and mechanical phenomena driving GBM evolution. This multidisciplinary approach has proved to aid clinicians in the customization of therapeutic strategies in the new field of precision medicine and, in particular, of personalized neuro-oncology.

In the second part, I will present a mathematical model, based on pre-clinical observations performed at Ospedale San Raffaele in Milan, of tumor evolution in presence of adoptive cellular therapy, a type of immunotherapy that enhances the immune system natural response by means of genetic manipulations of autologous T cells. The diffuse-interface model is described by a Cahn-Hilliard type equation coupled with a reaction-diffusion equation for the local nutrient concentration, accounting for the interaction between engineered T cells and tumor cells through a Michaelis-Menten kinetics. The trafficking of engineered T cells into the tumor micro-environment is modeled through a reaction–diffusion–advection equation, while the spatio-temporal variation of the chemical signal is described by a reaction-diffusion equation. The model is solved numerically using the finite-element method, on a computational domain generated from the pre-clinical imaging data of mouse prostatic adenocarcinoma, and calibrated with data already available in literature. Finally, we performed numerical simulations in order to assess the efficacy of the therapy in combination with different modulations of the tumor microenvironment. The numerical results show how the local availability of engineered T cells modifies the tumor evolution, resulting in a slowed tumor growth or complete regression in four weeks after the treatment, in accordance with the experimental outcomes reported in literature.

Keywords: personalized medicine, glioblastoma, immunotherapy, mathematical modelling, patient-specific.

A dynamic-immersed boundary approach for computing transport and adhesion of micro-sized carriers in narrow capillaries

Alessandro Coclite[1]

[1]Dip.to di Ingegneria Elettrica e dell'Informazione (DEI), Politecnico di Bari, Bari, Italy

In vascular targeted therapies, blood-borne carriers should realize sustained drug release from the luminal side towards the diseased tissue. In this context, such carriers are required to firmly adhere to the vessel walls for a sufficient period of time while resisting force perturbations induced by the blood flow and circulating cells. Here, a hybrid computational model, combining a Lattice Boltzmann (LBM) and Immersed Boundary Methods (IBM), is proposed for predicting the dynamics of rigid and deformable adhesive micro-carriers navigating a capillary with physiological hematocrit. Red cells and particles are modeled as a collection of mass-spring elements responding to a bending resistance, an elastic potential and total enclosed volume conservation constraint. Furthermore, particle surfaces are uniformly decorated with adhesive molecules (ligands) interacting with receptors disposed on the walls. Particle adhesion is modeled as a short-range ligand-receptor interaction and in term of formation and destruction probability functions that discriminate whether a chemical bond can be formed or destroyed. If a bond is established an attractive elastic force is activated. In this work, the interaction between blood cells and particles is characterized in two different situations. Firstly, particle transport and adhesion are characterized in terms of their ability to reach the capillary peripheries (margination rate) and firmly adhere the vasculature. This analysis is carried out systematically by varying particles' and cells' releasing positions and stiffness in a 10 μm capillary with physiological hematocrit. Then, the strength of adhesion of already adhering particles in narrow capillaries traversed by blood cells is measured as a function of cell and particle shape and stiffness. These data demonstrate that stiffness weakly influence the margination rate while significantly affect the ability of such constructs to efficiently interact with the endothelium by forming stable chemical bonds.

Keywords: dynamic forcing, moving least squares, fluid-structure interaction, drug delivery, particle margination, deforming particle, particle adhesion.

Recognition of gene signatures in breast cancer subtypes

Federica Conte[1], Pasquale Sibilio[1,2], Giulia Fiscon[1], Anna Maria Grimaldi[3], Katia Pane[3], Peppino Mirabelli[3], Simona Baselice[3], Rosa Giannatiempo[4], Francesco Messina[4], Monica Franzese[3], Marco Salvatore[3], Mariarosaria Incoronato[3], Paola Paci[1, 5]

[1] Inst. for Systems Analysis and Computer Science "Antonio Ruberti", IASI-CNR, 00185 Rome, Italy, [2] Dept. of Translational and Precision Medicine, Sapienza Univ. of Rome, 00185 Rome, Italy, [3] IRCCS SDN, Via Emanuele Gianturco 113, 80143 Naples, Italy, [4] Ospedale Evangelico Betania, Via Argine 604, 80147 Naples, Italy, [5] Dept. of Computer, Control and Management Engineering, Sapienza Univ. of Rome, 00185 Rome, Italy

Breast cancer (BC) is a heterogeneous and complex disease as witnessed by the existence of different subtypes and clinical characteristics. Despite the remarkable increase in the depth of understanding of BC, this disease is still a major public health problem worldwide and poses significant open challenges. Here, searching for molecular signatures underlying different subtypes of BC, we applied one of the most promising network-medicine-based algorithms, named SWItch Miner (SWIM), on The Cancer Genome Atlas (TCGA)-Breast Invasive Carcinoma (BRCA) dataset. Specifically, SWIM methodology builds upon the structural properties of gene co-expression networks to mine key genes (called switch genes) likely associated with disease state transitions. The transcriptomic profiles of TCGA-BRCA patients were stratified into different BC subtypes according to the well-established immunohistochemistry and PAM50 genetic classifications, to identify both switch genes shared among different subtypes and those specific for each subtype. Firstly, we focused our attention on shared switch genes to unveil a common disease module univocally altered in all BC subtypes, and thus to suggest a new vision to face the disease heterogeneity. We identified 266 and 372 switch genes from immunohistochemistry and PAM50 classifications, respectively. By intersecting the switch genes of the two classifications, we selected a common signature of 28 genes that were BC subtype-independent and classification subtype-independent. Data were validated both in vitro (10 BC cell lines) and ex vivo (66 BC tissues) experiments. Results showed that four switch genes (AURKA, CDC45, ESPL1, and RAD54L) were over-expressed in all BC subtypes. Moreover, the inhibition of one of them (AURKA) similarly affected all subtypes. Next, for probing the clinical utility of switch genes deregulated in a subtype-specific manner, we focused on the switch genes specific for the most aggressive subtype (basal-like) and screened 11 of them which were significantly associated with patient survival. Correlation analyses were performed. Overall, our findings could provide advancements in the ongoing effort to identify prognostic biomarkers and potential therapeutic targets for basal-like subtype, so to improve the clinical management of this disease.

Keywords: breast cancer subtypes, TCGA, SWIM, switch genes, data integration.

Computational modelling of stentriever thrombectomy

Mahdi Daei Daei[1], Abdul I. Barakat[1]

[1] Hydrodynamics Laboratory, Ecole Polytechnique, France

Strokes are among the most debilitating pathologies worldwide. The development of a stroke involves the blockage of a cerebral blood vessel by a thrombus (a blood clot). Since 2014, a new strategy for stroke treatment, stentriever thrombectomy, has been approved for the treatment of stroke. Stentriever thrombectomy involves the physical removal of the clot from the cerebral vessel using a stent-like device. A principal concern with stentrievers is the possibility of clot rupture (embolism) which can lead to secondary strokes. The goal of this project is to develop a computational framework that provides a map of the risk of clot rupture for different clot types and vessel geometries. A computational model of the blood clot, the stentriever (with its deployment system), and the complex cerebral vascular geometry was reconstructed and input into ABAQUS. The computational results provide the stresses in both the stentriever and the blood clot at various points during the retrieval process. A "damage model" links the stresses within the clot to the likelihood of clot rupture. The forces required for successful retrieval of different types of thrombi are also computed. Different clot types are simulated: a cerebral thrombus may be "white", i.e. a thrombus that is rich in fibrin, poor in red blood cells, and highly elastic or "red", i.e. a thrombus that is rich in red blood cells and is typically mechanically fragile. Additionally, different friction coefficients between the clot and the arterial wall are studied. The next goal is to diagnose the risky locations in the brain vascular system in terms of clot rupture and to rebuild those risky geometries in the computational framework. Different clot types are being placed inside the risky locations and retrieval forces are compared. The final goal would be integrating all of the information into a graphical user interface that serves as an aid to physicians in their assessment of the risk of embolism, retrieval speed, and retrieval force at each vascular location.

Keywords: finite element, thrombi, embolism, stentriever, stroke.

Deep reinforcement learning methods for closed-loop glucose control

Francesco Di Felice[1], Alessandro Borri[2], Maria Domenica Di Benedetto[1]

[1] Dept. of Information Engineering, Computer Science, and Mathematics, Center of Excellence for Research DEWS, Univ. of L'Aquila, [2] Inst. for Systems Analysis and Computer Science "Antonio Ruberti", IASI-CNR, 00185 Rome, Italy

Multilayer neural networks (NNs) are applied to replicate the glucose-insulin dynamics in the Artificial Pancreas thus allowing the development of personalized therapies for the automatic treatment of diabetes. By exploiting their predictive capacity, the application of neural networks in the artificial pancreas was considered for the approximation of the glucose-insulin system, starting from data generated by simulations of the so-called βIG model, keeping fixed the values of the parameters constituting the model. Therefore, a neural network was designed which, taking as input the values of G (glucose) and I (insulin) at the generic time instant t, would return an adequate forecast of future states. The training was carried out on a set of data collected through the iterated simulative replication of the βIG model. The network thus designed, however, is not able to adapt the behavior when changes occur in the parameters of the model (such as the value of the meal). The neural network was then modified also taking into account the glucose-insulin values (starting from a generic time t) in past sampling instants. During the network test phase, it was possible to validate the behavior of the neural network, verifying its ability to predict the trajectories of the model even when the value of the meal varies in a predetermined range of values, thus showing an improvement in the parametric sensitivity compared to the value of the glycemic meal. The research activity was then focused on the problem of insulin control in patients with Diabetes Mellitus. Agents equipped with Reinforcement learning decision-making algorithms were designed, thus exploiting the control methodology based on the observation-action dynamics, since the glucose-insulin system is characterized by a strongly complex and non-linear dynamics. The control algorithm was built by combining neural networks and reinforcement learning, in the so-called field of deep reinforcement learning, in order to adequately approximate the key functions present in the Reinforcement Learning algorithms. The problem of glucose regulation in diabetic patients was solved through the application of the Deep Deterministic Policy Gradient (DDPG) and Soft Actor-Critic (SAC) algorithms, evaluating the performance of the two agents with a deterministic and stochastic policy. In both cases the environment used for the interactions of the agents is represented by the βIG model, which however remains completely unknown to the agents in the training phase, thus adopting a model-free control methodology. Preliminary results obtained in the testing phase showed that DDPG and SAC agents can optimally control glucose dynamics, making the proposed approach promising for future studies.

Keywords: diabetes, multilayer neural networks, AI algorithms.

COVID-19 emergency: state dependent optimal control strategy

Paolo Di Giamberardino[1], Daniela Iacoviello[1]

[1] Department of computer, control and management engineering Antonio Ruberti, Sapienza University of Rome

The world has been tackling the COVID-19 pandemic since January 2020; this emergency is having an impact on all the aspects of human life, evidencing a lack of coordination among Countries. Up to December 2020 the most effective control action was the social distancing applied with different modalities, depending on the incidence of the pandemic, whereas since January 2021 the vaccination campaign is immunizing the world population. Since the very beginning of the pandemic, the challenge of all the Governments has been to balance the severity of the containment measures with the needs of the population, a tough balance requiring the definition of a solution weighting each demand wisely. The suitable framework appears to be the mathematical epidemic modeling and the optimal control. This paper focuses on the vaccination influence based on the information available on the immunization level and duration. It is proposed a new mathematical model in which two connected sub-populations are considered: one regards the non-vaccinated individuals and the other the vaccinated ones; each sub-population is described by a SEIR model, including the possible loss of immunity after some months from healing or vaccination. The motivation of this choice relies in the evidence that, with the available vaccines, a vaccinated subject could be infected and, despite the evolution of the disease should not be fatal, this can represent anyway a social cost. In this scenario, the optimal control strategy proposed allows to introduce the most suitable combination and scheduling of the vaccination campaign and containment measures by using state dependent switching cost index, that behaves like the different control phases adopted by the governments. This corresponds to the realistic scenario in which the containment measures (that could be different whether the subject is vaccinated or not, with one or two doses) are relaxed or increased depending on the number of infected patients, but also considering the vaccination campaign characteristics (number of doses administered daily, kind of vaccine). The problem appears interesting in view of possible time limited effect of the immunization; this implies a vaccination campaign not limited to one cycle about one year long but applied continuously up to the condition in which this virus is not a danger anymore. It is mandatory including limitations in resources, also from operative point of view. The specific choice of the cost index, and of the weights of its terms, corresponds to political choices, aiming at balancing contrasting requirements.

Keywords: epidemic modelling, optimal control, switching control.

Decentralized glucose control through contracts theory

Ilaria Di Loreto[1], Alessandro Borri[2], Maria Domenica Di Benedetto[3]

[1,3] Dept. of Inf. Engin., Computer Science, and Mathematics, Center of Excellence for Research DEWS, Univ. of L'Aquila, Italy, [2] CNR-IASI Biomathematics Laboratory, National Research Council of Italy, Rome, Italy

Biological systems are often complex systems, composed of different modules interacting with each other. Analysis and control of such systems can be very challenging. Glucose regulation is a topic of major importance in diabetes treatment, in the context of the Artificial Pancreas (AP), i.e. the set of control strategies, sensors and actuators aiming at automatizing the process of glucose control in diabetic patients. Diabetes is characterized by a dysfunction in insulin production/efficacy, therefore exogenous insulin needs to be administered to control glycemia, which must lay in a narrow safe interval [1]. Adopting a compositional approach, by solving the problem of glucose regulation in a decentralized way, through contracts theory, is the first step to tackle the complexity of the task. Contracts theory allows to assess the correct behaviour of a composed system, by checking the satisfaction of "local" tasks by each component, through the definition of sets of assumptions on the external inputs and sets of guarantees on the state and outputs [2]. As our first attempt we consider a reduced model with two equations: the glucose dynamics and the insulin one. We define a contract for the glucose and insulin subsystem, where assumptions and guarantees are piecewise-constant intervals, not known a priori [3]. At each sampling instant, the guarantees for the insulin subsystem are computed, by imposing the glucose dynamics to stay in the safe set. The goal is to steer the insulin subsystem into an insulin safe set, through the control input, guaranteeing the safety for the glucose subsystem as well.

Keywords: biological systems, control application, formal verification.

References

IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045, Diabetes Research and Clinical Practice, vol. 138, 2018, pp. 271-281. [2] A. Saoud, A. Girard, and L. Fribourg, "Assume-guarantee contracts for discrete and continuous-time systems", preprint submitted to Automatica, 2019. [3] I. D. Loreto, A. Borri and M. D. Di Benedetto, "An assume-guarantee approach to sampled-data quantized glucose control", 59th IEEE Conference on Decision and Control (CDC), pp. 3401–3406, 2020.

Continuum modelling for cell-matrix interactions

Salvatore Di Stefano[1], Giuseppe Florio[1], Giuseppe Puglisi[1]

[1] Dipartimento di Ingegneria Civile, Ambientale, del Territorio, Edile e di Chimica, Politecnico di Bari - Italy

Important biological functions of living cells, such as locomotion, proliferation and orientation, require a stable mechanical attachment with the extra-cellular matrix to be sustained [1]. A crucial example in this field is given by focal adhesions (see, for instance, [1, 2] and references therein). In this contribution, we propose a mathematical model to characterise important mechanical features of focal adhesions and of the interactions exchanged between cells and the extra-cellular environment. Following the approach introduced in [1, 2], we propose a new model addressing the mechanical properties of focal adhesions in which we include the fundamental decohesion effects. Macroscopic decohesion results as a homogenized effect of micro-scale processes (see, for instance, [3, 4]) leading to the rupture of molecular bonds between the integrin receptors and ligands of the extra-cellular matrix. In this scenario, a region of the adhesion plaque results to be detached from the extra-cellular matrix. Specifically, we propose a one-dimensional scheme comprising two interacting phases subjected to decohesion. In particular, following [4] we consider a Griffith type variational approach and search for the minima of the total (elastic plus decohesion) energy, formulated as a "free interface problem". In fact, whereas in some cases of interest the presence of defects and asymmetries may help to know the most probable nucleation and evolution of the decohesive process, in more general situations this is not possible. Our model let us deduce the macroscopic quantities (decohesion force, dissipated energy, elongation thresholds) and the decohesion front evolution, based on the constitutive properties of the adhering layers and cohesion energy.

Keywords: cell-matrix interactions, decohesion, free interface problem, variational approach.

References

[1] Cao X. et al. Biophys. J. 109.9, 1807-1817 (2015).
[2] Cao X. et al. Proc. Nat. Acad. Sci. USA. 114(23), E4549-E4555 (2017).
[3] Florio G. et al., Phys. Rev. Res. 2 (3), 033227 (2021).
[4] Puglisi G. et al., Phys. Rev. E 87 (3), 032714 (2013).

Modeling of ventilator-patient interaction

Laura D'Orsi[1], Alessandro Borri[1], Andrea De Gaetano[1,2]

[1] Inst. for Systems Analysis and Computer Science "A. Ruberti", IASI-CNR, BioMatLab, UCSC Largo A. Gemelli 8, 00168 Rome, Italy, [2] Inst. for Biomedical Research and Innovation, IRIB-CNR, Via Ugo La Malfa, 153, 90146 Palermo, Italy

The Mechanical Pulmonary Ventilator (MPV) is the most commonly used life-saving medical device in hospitals and in particular in the Intensive Care Units. The MPV is not only reserved to patients with respiratory diseases like asthma or Chronic Obstructive Pulmonary Disease (COPD), but is also indicated for improving the chances of survival of severely ill patients, with respiratory insufficiency or in the post-operative phase. A mathematical description of the complex mechanisms involved during pulmonary ventilation, in fact, can support the Anesthesiologists and Resuscitators choices in the mechanical ventilator parameters setting, like frequency, applied airway pressures and inspiratory time fraction. In this scenario, our goal is to provide a global mathematical model that takes into account the different physiological and mechanical respiratory aspects, with the aim of providing to the Anesthesiologists and Resuscitators the adequate ventilation parameters set to avoid Acute Respiratory Distress Syndrome (ARDS). Differential-algebraic equations (DAE) describe mechanical aspects of breathing and physiological mechanism as vascular perfusion of the lung and oxygen transport in blood up to the tissues. The artificial ventilation aspect is introduced and the patient-ventilator complex is taken into account by modeling the pressure wave provided by the mechanical lung ventilator as an external input, with wave shape predetermined but with maximum value and insufflation time estimated with the model. A Respiratory Trauma Index (RTI) is defined, with the aim of describing the trauma induced on the patient by ventilator, taking into account the value of arterial saturation that needs to be achieved to maintain a physiological condition (around 95%). Minimizing the RTI it is possible to provide the optimal parameters to be set on the mechanical ventilator which allow to provide adequate air flow to the patient without causing barotrauma in all physiological or pathological situations.

Keywords: healthcare and medical systems, mechanical ventilation, mathematical modeling in physiology, optimal mechanical ventilator parameters.

References:

[1] L. D'Orsi, M. Mameli, A. Borri, A. De Gaetano, Assisted ventilation control based on phase and frequency estimation of respiratory drift, Proceedings of the 2019 IEEE International Conference on Systems, Man, and Cybernetics (SMC 2019), Bari, Italy, pp. 889-895, 2019.

[2] L. D'Orsi, A. Borri, A. De Gaetano, Modelling the ventilator-patient interaction: a pressure-cycled control strategy, Proceedings of the 56th IEEE Conference on Decision and Control (CDC 2017), Melbourne, Australia, pp. 5032-5037, 2017.

The dynamics of a Covid-19 epidemic model

Mohamed El Khalifi[1], Brahim Boukanjime[2], Tomás Caraballo[2], Mohamed El Fatini[2]

[1] Laboratory of PDEs, Algebra and Spectral Geometry, Faculty of Sciences, BP 133, Ibn Tofail University, Kénitra, Morocco, [2] Dpto. Ecuaciones Diferenciales y Análisis Numérico, Facultad de Matemáticas, Universidad de Sevilla, Tarfia, s/n, 41012, Sevilla, Spain

We analyze a stochastic coronavirus Covid-19 epidemic model which is perturbed by both white noise and telegraph noise incorporating general incidence rate. Firstly, we investigate the existence and uniqueness of a global positive solution. Then, we establish the stochastic threshold for the extinction and the persistence of the disease. The data from Indian states, are used to confirm the results established along this paper.

Keywords: stochastic epidemic model, general incidence, white noise, telegraph noise.

Optimal experiment design for learning pharmacokinetic dynamics

Murat K. Erdal[1], Kevin W. Plaxco[2], Julian Gerson[3], Tod E. Kippin[3], João P. Hespanha[1]

[1] Department of electrical and computer engineering, University of California, Santa Barbara, USA, [2] Department of chemistry and biochemistry, University of California, Santa Barbara, USA, [3] Department of psychological and brain sciences, University of California, Santa Barbara, USA.

Determining the pharmacokinetics (PK) of individual subjects is an important but challenging step in the development of personalized medical treatments. One of the biggest obstacles in producing reliable data-driven, individualized PK models had been the lack of high temporal resolution measurement data. Recently, however, the development of electrochemical aptamer-based (EAB) sensors has enabled the in-vivo measurements of drug levels with seconds-resolution. Motivated by this, we study experimental design approaches that aim to find the drug injection input profiles that maximize the precision with which we can identify the system parameters given the noisy measurements. When designing an injection profile to learn the PK dynamics, we encounter two main problems. The first problem is the lack of system information. This is a common problem in experiment design that is typically addressed by using prior information about the system. However, for drugs with large subject-to-subject variability, reliable prior information is generally not available. For such cases, we propose to use an initial bolus injection to obtain a prior distribution for the model parameter-values. We then use this prior to design an input profile for the remainder of the experiment to minimize the uncertainty of the system identification process. The second problem we face is computing the solution to the experimental design problem itself. It has been shown that finding the best possible input profile under magnitude constraints, such as maximum and minimum injection rates, is NP-hard even for linear systems. There have been several relaxations suggested to overcome this problem. However, we show that it is possible to use modern nonlinear solvers to obtain viable candidates for PK experiment design. To test these ideas, we employed simulations based on parameters identified from actual experiments. The results of these simulations indicate that these methods produce drug infusion profiles that produce far narrower confidence intervals around the estimated system parameters than would be achieved by more naive infusion profiles, such as bolus injections or continuous infusions.

Keywords: experiment design, system identification, pharmacokinetics.

In silico modelling of endovascular drug delivery

André Fensterseifer Schmidt[1], Javier Escuer[2], Sean McGinty[1]

[1] Division of Biomedical Engineering, University of Glasgow, UK, [2] Aragón Institute for Engineering Research (I3A), University of Zaragoza, Spain.

The current treatment of ischaemic artery disease is based on a minimally invasive surgery followed by localised drug delivery — either from a balloon or through the implantation of a scaffolding device (stent). In each case, understanding the role of pharmacokinetics is crucial to design a safe and effective therapy, thus improving treatment outcome. To this end, in silico tools excel as a platform of mechanistic investigation and hypothesis testing. This narrative presents two models of endovascular drug delivery devices: a drug-eluting stent (DES) and a drug-coated balloon (DCB). Modelling is performed in COMSOL Multiphysics, including aspects of (I) luminal fluid flow, (II) transmural fluid flow, and (III) transport and retention of drug. The governing equations and boundary conditions of these processes are introduced, together with computation-related subjects such as meshing and solver settings. The fluid velocity and pressure fields, drug release profiles, drug content, and receptor saturation levels are presented for a number of different scenarios. Comparisons are made with a particular focus on safety and efficacy indicators.

Keywords: in silico modelling, drug-eluting stents, drug-coated balloons.

Tumour phenotypic heterogeneity: the impact of mixing evolutionary trade-offs with a dynamic surrounding micro-environment

Giada Fiandaca[1]

[1] Dept. of Mathematical Sciences, Politecnico di Torino, Italy

Recent advances in the studies of population evolutionary phenomena show that heterogeneity in a population can emerge when individuals are under selective pressure to perform several tasks, but cannot be optimal at all tasks owing to trade-offs between them. The dichotomy observed between the motility ability and the proliferating potential in tumour cells is a clear example of this relationship: clinical evidence shows indeed that cells with high migratory capacities are characterized by low proliferation rates and vice-versa. Motility of cancer cells is a key element in cancer development since it is at the basis of the metastatic spread i.e. to cancer aggressiveness. In this talk, a mathematical model is presented to investigate how tumour aggressiveness can be influenced by the presence of heterogeneous cells in terms of this trade-off, by the surrounding micro-environment and by the interaction between them. The focus is on the description of the adaptive dynamics of the phenotype of cancer cells in various scenarios that lead to the emergence of different local ecological niches. The physical modelled situation is a one-dimensional cross section of a growing tumour spheroid. The model is formulated in terms of systems of coupled nonlinear partial differential equations in the mathematical framework of population dynamics and of phenotype-structured population. In particular the presence of viable and necrotic cell fractions is taken into account and the metabolic active part of the disease is described by a one-dimensional spatially explicit phenotype-structured equation according to a continuous trait that identifies cell variants with distinct degrees of motility and proliferation potential. The haptotatic and pressure stimuli, the oxygen kinetics and local consumption of extracellular matrix (ECM) elements are the main ingredients that guide the growth process. Numerical simulation are performed to show how the model is able to reproduce the classical layers structure in spheroids constituted by a necrotic core, an internal rim of highly proliferative cells and an external one of the more motile ones and how this structure could change in terms of both morphology and composition under biophysical and environmental variations. Finally, an interpretation in a therapeutic perspective of the obtained results will be proposed to eventually suggest some biomedical strategies to reduce tumor aggressiveness highlighting the potential of the model results in targeting more aggressive cell phenotypes as well as in restricting the invasive part of the tumour.

Keywords: tumour growth, tumour phenotypic heterogeneity, evolutionary trade-offs.

SAveRUNNER: a network-based algorithm for drug repurposing and its application to COVID-19

Giulia Fiscon[1,2], Federica Conte[1], Lorenzo Farina[3], Paola Paci[1,3]

[1] Inst. for Systems Analysis and Computer Science "Antonio Ruberti", CNR, Rome, Italy, [2] Fondaz. per la Medicina Personalizzata, Via Goffredo Mameli, 3/1 Genova, Italy, [3] Dept. of Computer, Control and Manag. Engin., Sapienza Univ. of Rome, Italy

Currently, no proven effective drugs for the novel coronavirus disease COVID-19 exist and despite widespread vaccination campaigns, we are far short from herd immunity. The number of people who are still vulnerable to the virus is too high to hamper new outbreaks, leading to a compelling need of finding new therapeutic options devoted to combat SARS-CoV-2 infection. Drug repurposing represents an effective drug discovery strategy from existing drugs that could shorten the time and reduce the cost compared to de novo drug discovery. We developed a new network-based algorithm for drug repurposing called SAveRUNNER (Searching off-lAbel dRUg aNd NEtwoRk), with the aim to offer a promising framework to efficiently detect putative novel indications for currently marketed drugs against diseases of interest. SAveRUNNER predicts drug-disease associations by quantifying the interplay between the drug targets and the disease-associated proteins in the human interactome through the computation of a novel network-based similarity measure, which prioritizes associations between drugs and diseases located in the same network neighborhoods. SAveRUNNER was successfully applied to predict off-label drugs to be repositioned against the new human coronavirus (2019-nCoV/SARS-CoV-2), and it achieved high accuracy in the identification of well-known drug indications, thus revealing itself as a powerful tool to rapidly detect potential novel medical indications for various drugs that are worthy of further investigation. SAveRUNNER has been developed in R and its source code is freely available at https://github.com/sportingCode/SAveRUNNER.git, along with a comprehensive user guide.

Keywords: network medicine, drug repurposing, COVID-19/SARS-CoV-2.

A new coarse-grained approach for the mechanical behaviour of biomacromolecules

Giuseppe Florio[1,2], Nicola M. Pugno[3,4], Markus J. Buehler[5,6,7], Giuseppe Puglisi[1]

[1] Dip. di Ing. Civ., Amb., Territ., Edile e Chim., Polit. di Bari, [2] INFN, Sezione di Bari, I-70126 Bari, Italy, [3] Lab. of Bio-inspired, Bionic, Nano, Meta Mater. & Mech., Univ. of Trento - Italy, [4] School of Eng. and Mater. Sci., Queen Mary Univ. of London, UK, [5] Lab. for Atom. and Molec. Mech., Massach. Inst. of Tech., Cambridge, MA, USA, [6] Center for Mater. Sci. and Engin., Massach. Inst. of Tech., Cambridge, MA, USA, [7] Center for Comp. Engin., Massach. Inst. of Tech., Cambridge, MA, USA

The possibility of predicting the mechanical behavior of protein molecules is crucial in different fields such as biological processes, biomedical applications and new materials design. We propose a new approach [1], based on a careful coarse graining deduction, for the study of mechanical features and conformational transition of macromolecules. In particular, our model can be applied in order to describe phenomena that extend to larger scale effects (protein bundles, protein-protein interactions, cyclic loading). We neglect details at the single amino acid scale and focus on the overall macromolecule configurational and mechanical behavior. After the coarse graining step, obtained by grouping several amino acids in fictitious particles, we introduce Morse type NN (nearest neighbor) and NNN (non-nearest neighbor) interactions, phenomenologically chosen to reproduce the folding/unfolding experimental behavior. Specifically, nearest neighbor energy terms are introduced to reproduce the interaction among the fictitious particles, rescaled according with the number of composing amino acids. Next, non-nearest neighbor energy terms inter and intra functional blocks are phenomenologically added, describing the presence of hydrophobic/hydrophilic domains. This model is paradigmatic for a significant number of problems in the field of protein mechanics of interest both in biology and medical fields. To demonstrate the effectiveness of the approach, we focus on the folding and unfolding behavior of tropoelastin and its mutations. As we show, the dynamics of the resulting system reproduces important properties of the folding-unfolding mechanical response, including the monotonic and cyclic force-elongation behavior representing a physiologically important information for elastin and mutation effects.

Keywords: coarse-grained modeling, protein folding, force-elongation diagram, mutations.

References

[1] G. Florio, N. M. Pugno, M. J. Buehler, G. Puglisi, "A coarse-grained mechanical model for folding and unfolding of tropoelastin with possible mutations", submitted (2021).

Differential reaction expression analysis for single-cell metabolic network

Bruno Galuzzi[1], Chiara Damiani[1,2]

[1] Dept. of Biotechnology and Biosciences, University of Milan-Bicocca, Italy, [2] SYSBE-IT/SYSBIO Centre of Systems Biology, University of Milano-Bicocca, Milan, Italy

Understanding human metabolism is a crucial factor to study several human diseases, such as cancer. Most of current mathematic models to simulate cell metabolism are based on the integration of omics data (e.g., transcriptional data) into a genome-scale metabolic network (GEM). A metabolic network lists the majority of biochemical reactions occurring in a cell, describing their physiological and biochemical properties. This list is converted into a mathematical model through the stoichiometric matrix, where the rows represent the metabolites, and the columns represent the reactions. The classical way to integrate transcription data into a GEM model is through the Gene-Protein-Reaction rules (GRPs), where genes that concur to catalyze a reaction are encoded through logical formulas. Conjunctive propositions (AND) are employed when distinct genes encode different subunits of the same enzyme. Disjunctive propositions (OR) describe the situation in which distinct genes encode isoforms of the same enzyme. Starting from the single-cell RNA-seq (scRNAseq) count matrix and a list of GPRs, it is possible to quantify the abundance of transcript available for each reaction in a specific cell, using the Reaction Activity Scores (RASs) [1]. In a nutshell, such a method solves each GPR using the sum and min functions to evaluate the OR and AND operators, respectively and builds a RAS matrix in which each row represents a reaction, and each column represents a cell. The entries in each column are the RAS scores of each cell. In this talk, we examine the possibility of using cluster analysis on the RAS matrix to identify possible clusters of cells based on the expression level of metabolic reactions. Starting from a generic metabolic network, we compute the RAS matrix for several single-cell RNA-seq datasets taken from the literature in which prior information about the cells is present (e.g., cancer vs normal). Then, we perform cluster analysis to identify a list of reactions better discriminating the metabolic differences between groups of cells.

Keywords: metabolic networks, cluster analysis.

References

[1] Graudenzi, A., Maspero, D., Di Filippo, M., Gnugnoli, M., Isella, C., Mauri, G., Antoniotti, M., Damiani, C. (2018). Integration of transcriptomic data and metabolic networks in cancer samples reveals highly significant prognostic power. Journal of biomedical informatics, 87, 37-49.

A diffusive model to describe the biological stimulus in bone remodeling

Ivan Giorgio[1]

[1] Dip.to di Ingegneria Civile, Edile-Architettura e Ambientale (DICEAA), Univ. of L'Aquila, 67100 L'Aquila, Italy

The mechanically driven biological stimulus in bone tissues regulates and controls the action of special cells called osteoblasts and osteoclasts. Some different models have been proposed to describe the important and not yet completely understood phenomena related to this feed-back process. Recently in [1] an integro-differential system of equations has been studied to describe the remodelling process in reconstructed bones where the biological stimulus in a given instant t depends on the deformation state of the tissue at the same instant. Instead, biological knowledge suggests that the biological stimulus, once produced, is 'diffused' in bone tissue to reach the target cells. A model for describing biological stimulus diffusion in remodelling tissues in which 'diffusive' time dependent phenomena are taken into account is proposed (see [2]). Some preliminary numerical simulations are presented which suggest that this model is promising and deserves further investigations.

Keywords: bone remodeling, biomechanics, generalized materials.

References [1] Lekszycki T. and Dell'Isola F. (2012) A mixture model with evolving mass densities for describing synthesis and resorption phenomena in bones reconstructed with bio-resorbable materials. Z Angew Math Mech 92(6):426–444.

[2] Giorgio, I., Dell'Isola, F., Andreaus, U., Alzahrani, F., Hayat, T., Lekszycki, T. (2019) On mechanically driven biological stimulus for bone remodeling as a diffusive phenomenon, Biomechanics and Modeling in Mechanobiology, 18(6): 1617–1663.

Patient-tailored LSTM model for hypoglycemia prevention: an in-silico case study

Francesca Iacono[1], Lalo Magni[2], Chiara Toffanin[1]

[1] Dept. of Electrical, Computer and Biomedical Engineering, University of Pavia, Italy, [2] Dept. of Civil and Architecture Engineering, University of Pavia, Italy

Type 1 diabetes is a pathology characterized by high Blood Glucose (BG) due to a lack of insulin production. It requires exogenous insulin administrations that, if excessive, lead to hypoglycemia (BG<70 mg/dl). Alarm Systems (ASs) are implemented in Continuous Glucose Monitoring (CGM) devices and artificial pancreas to avoid Hypoglycemia Events (HEs). One method to generate these alarms is based on glucose predictions: foreseeing glucose trend to raise alarms allows patients to react to avoid HEs. These systems are based on models which goodness determinates the AS performance. In the last years, promising results have been achieved by systems that exploit neural networks. A Long Short-Term Memory network (LSTM) is here exploited to design an AS for a representative case-study. The LSTM is trained on in-silico data of an adult patient of the UVA/Padova Simulator [1] using 16 days for training and 4 days for validation, to predict BGs given the injected insulin and carb intake. For the training phase only measures obtained by CGM and affected by noise are available. The data are rescaled using mean normalization, the output is filtered to reduce the effect of the noise and the hyperparameters are optimized using Keras-tuner. The AS considers the LSTM predictions at time k^* over a prediction window of 40 mins. If the predicted BGs remain behind 70 mg/dl for at least 10 mins, an alarm is raised. The same settings used in [2] are applied here with a different model. The AS performance is evaluated on a 28-days dataset and compared to the algorithm used in [2], where a tailored-model of a real patient was considered for the same amount of time. Sensitivity, that represents the ability to detect a HE, and precision, the ability to avoid false alarms are considered. The proposed LSTM approach obtained sensitivity = 93.18%, precision = 100% compared to sensitivity = 94.44%, precision = 77.27% of [2]. Sensitivity is worsened by 1.35% gaining 29.42% in precision and avoiding false alarms. Only 3 not severe HEs on 44 are undetected. The proposed AS based on LSTM showed promising results. Future developments include an exhaustive in-silico test of the AS on all patients and its application on free-living data, then the AS can be included in a MPC controller to prevent HEs.

Keywords: LSTM, diabetes, alarm system, hypoglycemia prevention.

References

[1] Visentin R., et al. "The UVA/Padova type 1 diabetes simulator goes from single meal to single day." J. of diabetes science and technology 12.2 (2018): 273-281,

[2] Toffanin C., et al. "Glucose-insulin model identified in free-living conditions for hypoglycaemia prevention." J. of Process Control 64 (2018): 27-36.

Theoretical analysis of multi-layer convection-diffusion-reaction (CDR) transport for understanding and improving drug delivery

Ankur Jain[1]

[1] Dept. of Mechanical & Aerospace Engineering, University of Texas at Arlington

Theoretical modeling of multilayer transport problems is of much interest for a number of bioengineering problems such as drug elution from stents, drug delivery from multi-alyer capsules and drug absorption in arterial walls. Such problems are also of much theoretical interest due to the occurrence of imaginary eigenvalues in the solution. This presentation will discuss recent work on theoretical analysis of a one-dimensional Cartesian multilayer heat transfer problem with diffusion, advection and linear, concentration-dependent reaction (absorption) occurring in each layer. A general eigenfunction-based series solution of the problem is derived. Orthogonality of eigenfunctions is proved, and an explicit expression for the eigenequation is derived. The special case of a two-layer body is discussed. Key non-dimensional parameters governing the problem are identified. It is shown that, under specific conditions, this problem admits two types of imaginary eigenvalues, one of which is related to divergence of the solution at large times. The impact of various problem parameters related to diffusion, advection and heat generation on the appearance of imaginary eigenvalues is discussed. Specifically, due to the directional nature of fluid flow, advection in each layer of a two-layer body has opposing impact on the occurrence of imaginary eigenvalues. It is shown that a balance between generation/absorption, diffusion and advection determines whether an imaginary eigenvalue is encountered, and consequently, whether divergence of the solution may occur. A formal proof is also presented to show that even if imaginary eigenvalues may be present, the solution of the problem itself remains real under all circumstances, as expected. Results presented here expand the theoretical understanding of multilayer heat transfer, and may also contribute towards improved design and optimization of drug delivery techniques.

Keywords: convection, diffusion, reaction, multilayer, drug delivery.

From uptake of zoledronate acid to isopentenyl pyrophosphate accumulation: a practice simple mathematical model

Elena Lo Presti[1], Andrea De Gaetano[1,2]

[1] National Research Council (CNR)—Institute for Biomedical Research and Innovation (IRIB), 90146 Palermo, Italy, [2] CNR-IASI BioMatLab (Italian National Research Council - Inst. of Analysis, Systems and Computer Science), 00185 Rome, Italy

The mevalonate pathway is an attractive target for many areas of research, such as autoimmune disorders, atherosclerosis, and Alzheimer's disease, and cancer. Indeed, manipulation of this pathway results in the alteration of malignant cell growth with a promising therapeutic potential. There are several pharmacological options to block the mevalonate pathway in cancer cells such as statins and Zoledronate acid (ZA) (an N-bisphosphonate (N-BP)). The latter inhibits Farnesyl pyrophosphate (FPP) synthase enzyme-inducing the cell cycle arrest, apoptosis, inhibition of protein prenylation, and cholesterol reduction and leads to the accumulation of isopentenyl pyrophosphate (IPP). Considering the immunomodulatory function of ZA, extensive evidences from preclinical researches shown that ZA exerts its anticancer actions in different ways for example through the immunomodulation of $V\gamma 9V\delta 2$ T lymphocytes, cytotoxic $CD3^+$ T cells with anti-cancer features, that recognize IPP. The temporal relationship between ZA-treatment and its effects has received great attention but, until now, it misses a model that describes the pharmacodynamic of ZA and the relative accumulating of IPP into the tumour cells. In general, pharmacokinetics and pharmacodynamics of zoledronic acid have been studied by clinical exams in patients with bone metastases from a variety of primary cancers, and the relationships between the dose and safety were analysed to support the clinical dosing schedule of ZA in patients. Thus, the general aim of this study is to give a simple mathematical model that describes the dynamic of the ZA's uptake into tumor cells (in vitro culture system) and to predict the IPP accumulation in any experiment to better transfer this knowledge to clinical practice. In future, this study could have an interesting application in immunotherapies based on the expansion of activated $V\gamma 9V\delta 2$ lymphocytes. We propose a mathematical model that, for the first time, permits to predict the efficiency of this treatment by looking at the cellular model in vitro and, thus improving the emerging $\gamma\delta$ T cells based-immunotherapies.

Keywords: zoledronate acid, pharmacodynamic, immunotherapy, $\gamma\delta$ T cells, tumor immunology.

Influence of the frequency of periodic mechanical loads on the bone tissue regeneration process

Yanfei Lu[1], Tomasz Lekszycki[1]

[1] Institute of Mechanics and Printing, Warsaw University of Technology, Warsaw, Poland

The fact that bone tissue adapts to mechanical stress has long been known and well documented. It is also known that loads varying in time have a much greater effect than static loads. A number of experimental studies have also been carried out, which show that some vibration frequencies activate bone cells more than others. However, the processes excited by periodic loads occurring on a micro scale, and in particular the interactions between the flowing liquid, living cells and the deformable matrix and the related intercellular signalling, are very complex and still insufficiently described. In this work, a simplified mathematical model of the effects mentioned here was proposed, which enables the analysis of bone remodelling and regeneration processes under the influence of periodic loads. This theoretical model was used in numerical simulations to perform a parametric analysis and investigate the effect of mechanical stress frequencies on cell activity during adaptation and regeneration of bone tissue. Such a tool may facilitate in future the planning of orthopaedic surgery treatments and medical procedures used in rehabilitation.

Keywords: bone remodelling, periodic loading, mathematical model.

A mechanical and computational model for Glioblastoma Multiforme growth and proliferation including patient-specific data

Giulio Lucci[1], Chiara Giverso[1], Luigi Preziosi[1], Abramo Agosti[2] and Pasquale Ciarletta[3]

[1] Dept. of Math. Sci. "G.L. Lagrange", Politecnico di Torino, Turin (Italy), [2] Dept. of Math., University of Pavia (Italy), [3] MOX-Politecnico di Milano (Italy)

Glioblastoma Multiforme (GBM) is one of the most aggressive and malignant types of brain tumour. Besides the typical hallmarks of cancer, such as uncontrolled cellular proliferation and genomic instability, GBM also exhibits dramatic invasive potential, propensity for necrosis and resistance to common therapies: even with a complete treatment including neurosurgery, chemotherapy and radiotherapy, the median survival time is about 10-16 months. Moreover, GBM tends to show three-dimensional and irregular growth patterns. Hence, there is a critical need to understand and replicate the biological complexity of the brain, in order to predict tumour evolution and arrange therapeutic strategies accordingly. In the last decades several models with different frameworks that describe brain cancer growth have been proposed. Nevertheless, the vast majority of these models does not consider realistic mechanical and constitutive properties of brain tissue, as well as the role of stress and deformations exerted by the growing tumour. Instead, the presence of a growing mass inside the brain may be critical and dangerous for the patient: it is then important to evaluate the mechanical impact of Glioblastoma on the surrounding healthy tissue. To improve the description of GBM growth, we propose a multiphase mathematical and computational model, based on Continuum Mechanics, which includes two main novelties: the first one is brain hyperelasticity, in order to study the effects of structural changes, deformations and stresses on brain tissue due to the presence of a growing tumour. In particular, we resort to the theory of mixtures and employ the multiplicative decomposition of the deformation gradient to include the contribution of growth inelastic strains. Secondly, following [1], we use a sample of patient-specific imaging data that allow us to perform simulations on a realistic geometry; at the same time, thanks to these medical data, we are able to explicitly introduce brain tissue anisotropy due to the presence of nerve fibers, by reconstructing spatially dependent diffusion and permeability tensors.
In summary, after a brief biomedical introduction, the main aspects of our mechanical model and the results of some finite element simulations, performed on the reconstructed brain mesh using the Python-based software FEniCS, will be shown.

Keywords: glioblastoma multiforme; cancer growth; mixture theory; personalized medicine; hyperelasticity.

References

[1] M.C. Colombo, C. Giverso, E. Faggiano, C. Boffano, F. Acerbi, P. Ciarletta. Towards the personalized treatment of glioblastoma: integrating patient-specific clinical data in a continuous mechanical model, PLoS One 10(7):e0132887 (2015)

Modernization of a cardiovascular hydrodynamic testing system through the automation of its peripheral resistance device

Eleonora Manzoni[1], Mirco Rampazzo[1], Luigi Di Micco[2], Francesca M. Susin[2]

[1] Dept. of Inf. Engin., University of Padua, Italy, [2] Dept. of Civ. Environ. and Archit. Engin., University of Padua, Italy

Cardiovascular hydrodynamic systems, such as pulse duplicators, reproduce the human systemic circulation and they play a pivotal role as in vitro assessment tools for testing heart medical devices such as aortic valves and stents [1]. Hence, specific ISO standards govern their safety assessment, prescribing in vitro experiments aimed at replicating the target operating conditions in humans [2]. In this scenario, the modernization of existing mock circulatory loops, in terms of both hardware and software components, offers new possibilities to dominate their intrinsic complexity, through the rapid exploration of new suitable solutions. This research involves the modernization of an existing non-commercial pulse duplicator in use at the Healing Research Laboratory at the University of Padua, Italy [3]. The cardiovascular hydrodynamic system is characterized by high customizability, modularity, and it allows simulating a wide range of physiological and pathologic conditions. The focus of this research is the automation of a crucial system component that is the peripheral resistance device, aggregating the system effects of resistance to flow providing a suitable pressure drop. To this aim, a new motorized peripheral resistance valve, equipped with a stepper DC motor, a H-bridge, and Arduino Uno board, replaces the current manual device. Specifically, the problem of valve automatic setting adjustment is tackled in a data-driven way by means of an Extremum Seeking Control algorithm exhibiting interesting plug and play characteristics. The proposed approach can handle the intrinsic system complexity to fix the incomplete knowledge of certain system characteristics while guaranteeing good performance in a wide range of system configurations and operating conditions. The effectiveness of the automated peripheral resistance device has been verified through experimental tests and the automation of other fundamental system components will be considered in the future.

Keywords: cardiovascular engineering; data-driven control systems.

References

[1] Dewi, D.E.O et al, 2018. Cardiovascular Engineering: Tech. Adv., Rev., and Applic. Springer Nature.

[2] Burriesci et al., 2016. In vitro hemodynamic testing of amplatzer plugs for paravalvular leak occlusion after transcatheter aortic valve implantation. Intern. J. of Card. 203, 1093–1099.

[3] Di Micco et al. 2016. Influence of the experimental workbench on the assessment of hydrodynamic performance of heart valve prostheses. In: Proceedings of the XXXV National Conference on Hydraulics and Hydraulic Works.

Mechanistic model of dissolution for irregularly shaped drug particles

Davide Masiello[1], Giuseppe Pontrelli[2], Mario Grassi[3]

[1] School of Engineering University of Edinburgh, UK, [2] IAC-CNR, Roma, Italy, [3] Dept. of Engineering and Architecture, Trieste University, Italy

The quantitative prediction of the dissolution kinetics of drugs is critically important for the understanding of their pharmaceutical behavior. This process, which proceeds according to the four energetic steps of wetting, fusion, solvation and diffusion, has been extensively studied only for the relatively simple case of regularly shaped particles such as spheres, cylinders and parallelepipeds [1]. In this work, we develop a model able to simulate the more realistic case of the dissolution of particles of any arbitrary initial shape. In addition to this, our model accounts for all the critical aspects affecting the process kinetics, such as particles size, mass transfer resistance, particle motion, drug recrystallization and liquid/solid volume ratio. Our simulations show the relevant role of curvature, wettability, hydrodynamic film thickness and particles-fluid relative velocity in determining the dissolution kinetics. Experimental studies of particles loaded with theophylline are used to to assign appropriate value to the thermodynamic and transport coefficients of the model.

Keywords: Drug dissolution, recrystallization, mathematical modelling, simulation.

References

[1] M. Abrami et al., ADMET & DMPK 8(3) (2020) 297-313.

Preliminary approaches to understand how anti-proliferative drugs modulate in-stent restenosis

Alistair McQueen[1], Javier Escuer[2], Ankush Aggarwal[3], Simon Kennedy[4], Chris McCormick[5], Keith Oldroyd[4], Sean McGinty[1,3]

[1] Division of Biomedical Engineering, University of Glasgow, UK, [2] Aragón Institute for Engineering Research (I3A), University of Zaragoza, Spain, [3] Glasgow Computational Engineering Centre, University of Glasgow, UK, [4] Inst. of Cardiovascular and Medical Sciences, Univ. of Glasgow, UK, [5] Dept. of Biomedical Engineering, University of Strathclyde, UK

Drug-eluting stents (DES) have revolutionized the treatment of coronary artery disease. Devices are deployed into diseased vessels, restoring natural blood flow whilst simultaneously releasing anti-proliferative drugs into the arterial wall to combat restenotic tissue growth. First generation devices incorporated paclitaxel or sirolimus on durable polymer coatings, where notable improvements on in-stent restenosis were exhibited compared to bare metal stents. However, further technological innovations (e.g. thinner struts) were required to improve stent performance, reducing the likelihood of late adverse events. Nonetheless, delayed arterial healing has been a recurring problem with DES linked to the hypersensitive reaction by a permanent coating. Recently, a meta-analysis [1] presented conflicting evidence with various DES, emphasizing the possible significance of drug and release kinetics on re-endothelization.

Computational modelling has proven instrumental in improving stent performance, where efforts are subdivided into three distinct categories: (i) structural mechanics and fluid dynamics, (ii) drug release and transport, and (iii) arterial healing. However, a disconnect between these research areas often exists. Particularly of significance is (ii) and (iii) where smooth muscle cell (SMC) proliferation is the driving force behind restenosis, inhibited through anti-proliferative drugs. Models of drug release and transport are becoming increasingly complex but fail to incorporate the effect of the drug on cell proliferation.

Recently, we questioned [2] whether we truly understand how drug modulates the arterial healing response. Various models of increasing complexity were simulated to try to capture the in vitro response of cells exposed to different drugs at various doses for different exposure times. In accordance with previous efforts in the literature, simpler models of binding kinetics were better able to capture experimental data of drug-induced inhibition of cell proliferation. Our most recent work eludes to the possible significance of SMC age and spatiotemporal distribution of drug on the effectiveness of antiproliferative drugs.

Keywords: drug-eluting stents, smooth muscle cells, proliferation.

References

[1] Taglieri, et al. JACC: Cardiovasc. Intervent., 13 (24) 2868–2878, 2020.

[2] McQueen A, et al. Int J Pharm. 601:120575, 2021 [1] M. Abrami et al., ADMET & DMPK 8(3) (2020) 297-313.

Personalised risk predictor for acute cellular rejection in lung transplantation

Ian Morilla[1], Alexy Tran Dinh[2,3]

[1] Dept. of mathematics, LAGA, University Sorbonne Paris Nord, France, [2] INSERM UMR 1148, University of Paris, France, [3] Dept. of Anesthesiology and Critical Care Medicine, Bichat-Claude Bernard University Hospital, APHP, Paris, France

Lung transplant (LT) is a life-saving therapy that may be offered to selected patients with end-stage pulmonary disease. Acute cell rejection (ACR) is common complication that have nearly the 30% of lung transplant recipients within the first year of follow-up. The development of surrogate markers that could help identify recipients at risk of developing ACR would be a major diagnostic aid to the clinician. CD31, the receptor most represented on the endothelial surface, is cleaved and released into the plasma upon endothelial activation and is therefore a powerful biomarker of endothelial dysfunction.

Faced with more limited traditional statistical models, we evaluated the contribution of artificial intelligence in the prediction of the risk of rejection after lung transplantation. To this end, we use early soluble CD31 plasma levels in combination with recipient hematosis as measured by PaO2/FiO2 whose ratio at 24 hours after LT correlates with mortality. In addition, PaO_2/PiO_2 <200 is also used in the analysis. This last measure stands for a particular threshold who provides an important qualitative information on patient's PaO_2/FiO_2 exchange during the post-operational.

Thus, we achieved to establish a novel multivariable characterisation of these three biomarkers as temporal series in LT follow-up. We leveraged this model as basal layers of a time distributed deep convolutional network to predict patient's outcomes after LT.

The convolutional neural network showed useful to reconstruct the underlying non-linear behaviour of CD31. This network consisted in three main features: linear spatial filtering to also estimate linear combinations of matrices from patient variables as transfer learning does, convolutive layers to acquire spectral features and separate routes depending on the time variables CD31 and PaO_2/FiO_2, and PaO_2/PiO_2 <200 respectively.

Finally, based on this model we establish an appropriate probabilistic context where to build a risk predictor of ACR with an associated percentage of accuracy to each individual.

Keywords: lung transplantation, time distributed multivariate network, patient's outcome.

Diffusion-reaction drug release model in non-homogeneous micro-capsules via integral transform

Carolina P. Naveira-Cotta[1], Giuseppe Pontrelli[2], Renato M. Cotta[1,3]

[1] Lab. of Nano- and Microfluidics and Microsystems, LabMEMS, Mech. Eng. Dept., POLI & COPPE, Fed. Univ. of Rio de Janeiro, UFRJ, Rio de Janeiro, Brazil, [2] General Directorate of Nucl. and Tech. Develop., DGDNTM, Brazilian Navy, Ministry of Defense, RJ, Brazil, [3] Ist. per le Applicazioni del Calcolo-CNR, Via dei Taurini 19 Rome 00185, Italy

A general mechanistic drug release model from a non-homogeneous sphere whose material properties change continuously along the radius is presented. The problem is described by a diffusion-reaction equation coupled with a boundary condition modelling a surface finite mass transfer resistance, which corresponds to the case of a coated capsule. We derive a closed-form analytical solution for the concentration in the sphere, based on an eigenfunction expansion, through the Generalized Integral Transform Technique (GITT). The Sturm-Liouville problem is solved through GITT, by choosing a simpler form for the auxiliary eigenvalue problem. Radial concentration profiles in the sphere and drug release curves are shown and the dependence and sensitivity of the solution on the parametric functions are analyzed.

Keywords: non-homogeneous capsule, drug release, integral transform, GITT

A new mathematical model of the human thyroid

Marcello Pompa[1], Simona Panunzi[2], Antonella Farsetti[3], Simona Nanni[4], Andrea De Gaetano[2]

[1] Univ. Cattolica del Sacro Cuore, [2] Inst. of System Analysis and Informatics (IASI) "A. Ruberti", [3] Inst. of Neurobiology and Molecular Medicine (IBCN), [4] Univ. Cattolica del Sacro Cuore, Institute of Medical Pathology

The thyroid is one of the largest endocrine glands in human [1]. It is organized in follicles, fillled with a secretory substance called colloid. The major constituent of collid is thyroglobulin (Tg), wich contains the thyroid hormones (thyroxine-T4 and triiodothyronine-T3) [1]. Thyroid hormone secretion is stimulated through a negative control feedback: thyroid-stimulating hormone (TSH) stimulates the T3 and T4 hormone production and high circulating levels of these two hormones inhibit in turn the thyrotropin-releasing hormone (TRH) and TSH production [1,2]. T3 and T4 production dependes also on the iodine intake: it is estimated that the necessary quantity of iodine per day is about 50 ug, assumed by means of food and water. The thyroperoxidase (TPO), which catalyzes the reaction between MIT and DIT for their transformation in T3 and T4, is another important player in the thyroid system. The present work deals with a new mathematical model of the thyroid and TSH control system by means of which the effect of hormone and iodine treatments can be also tested. The model is composed of 22 compartments which describe the dynamics of iodine, T3, T4, TSH, TRH and Tg in the blood and extra-cellular. NIS and TPO are also described and a gastrointestinal sub-model [3] is incorporated into the thyroid model to describe the administration of iodine and T4 dose during the day. The TSH oscillations occuring during the day are described in the present mathematical model by means of series impulses generated by a biological oscillator. The model has been tested on several independent clinical data sets presented in [4], where euthyroid volunteers underwent three doses (400, 450, 600 ug) of levothyroxine (L-T4).

Keywords: mathematical models; multicompartmental models.

References

[1] A.C. Guyton and J.E. Hall, Textbook of Medical Physiology (11th edition), Elsevier, 2006,

[2] M. Degon, S.R. Chipkin, C.V. Hollot, R.T. Zoeller and Y. Chait, A computational model of the human thyroid, Elsevier, Math. Biosci., 212:22-53, 2008,

[3] A. De Gaetano, S. Panunzi, A. Matone, A. Samson, J. Vrbikova, B. Bendlova, G. Pacini, Routine OGTT: A Robust Model Including Incretin Effect for Precise Identification of Insulin Sensitivity and Secretion in a Single Individual, PLOS ONE,8:1-16, 2013,

[4] M. Eisenberg, M. Samuels and J.J. DiStefano III, Extensions, Validation, and Clinical Applications of a Feedback Control System Simulator of the Hypothalamo-Pituitary-Thyroid Axis, Mary Ann Liebert, Inc., 18:1071-1085, 2008.

A multiscale computational model for microvascular oxygen transfer applied to radiotherapy

Luca Possenti[1,2], Alessandro Cicchetti[2], Riccardo Rosati[1], Maria L. Costantino[1], Tiziana Rancati[2], Paolo Zunino[3]

[1] Department of Chemistry, Materials and Chemical Engineering "Giulio Natta", Politecnico di Milano, [2] Prostate Cancer Program, Fondaz. IRCCS Ist. Naz. dei Tumori di Milano, [3] MOX, Dept. of Mathematics, Politecnico di Milano

The microcirculation serves vital oxygen and nutrient supply in tissues and controls functions in living systems. For this reason, microcirculation has been thoroughly studied in vitro and in vivo in the fundamental sciences. The purpose of this work is to develop a model for microcirculation and oxygen transfer that is particularly suited to describe the phenomena at the level of the tissue microenvironment (sub-millimeter scale), where heterogeneities of the distribution of oxygen in the tissue due to the possibly irregular layout of the micro-vessels. Such effects are particularly important in pathologies such as cancer. We present a multiscale oxygen transport model, able to solve the problem of fluid dynamics and haematocrit transport in the microcirculation, and we discuss the simulations of oxygen distribution in the capillary network and surrounding tissue. In this work, the oxygen transport model is based on non-linear constitutive equations, such as Michaelis-Menten formula for oxygen consumption and Hill equation for the equilibrium of oxygen between dissolved and haemoglobin-bound phases. We discuss the mathematical and computational platform's ability to describe realistic clinical scenarios relevant for cancer treatment, specifically, radiotherapy. Indeed, even though this treatment is based on the damage of the cell genetic material, preclinical and clinical studies have highlighted the so-called oxygen effect that impacts tumor sensitivity to ionizing radiation. More precisely, the multiscale flow and transport model is combined with a well-known radiobiological model, the Linear-Quadratic (LQ) model, to analyze the effect of the oxygen content on the surviving fraction of healthy and tumour cells irradiated by an ionizing source. The combination of the oxygen model and LQ models allowed us to estimate clinical quantities of interest, such as OER (Oxygen Enhancement Ratio) and TCP (Tumoral Control Probability).

Keywords: oxygen transfer, microcirculation, multiscale model, radiotherapy.

Mass diffusion through composite systems – an electric circuit-based model

Pawel Rochowski[1], Giuseppe Pontrelli[2]

[1] Inst. of Experimental Physics, Faculty of Mathematics, Physics and Informatics, University of Gdansk, Wita Stwosza 57, 80-308 Gdansk, Poland, [2] Ist. per le Applicazioni del Calcolo, CNR, Italy

Modelling mass diffusion plays an important role in various field of sciences, like soil physics, membrane science and pharmacology. In the latter case, a strong mismatch between advancements in fundamental research and expectations of the applied/industrial scientists can arise. The mismatch primary originates from the sophisticated models, methods and protocols delivered by theoreticians, which are, however, considered as a time-consuming and "blurry" for the straightforward system analysis. Eventually, the most popular mass release models for the pharmaceutical sciences usage are based on certain simplifications of the single diffusion model solutions or purely empirical formulas, like linear or exponential functions, power laws etc. Analogies between the charge and mass transport models, provided the Ohm's law and Fick's law, will be exploited to deliver direct correspondences between the elementary electric circuit components properties (resistance and capacity) and the release system characteristics (mass resistance, volume). These analogies will be exploited to model a mass release system, comprising of two main subsystems by means of electric circuit-models, involving set(s) of resistor/capacitor elements. For the simplest cases (involving one resistor/capacitor pair) it will be shown, that the normalized models include only one fitting parameter – the characteristic time - which depends on the intrinsic properties (characteristic lengths, diffusivity) of the releasing/absorbing system. The analysis will be extended to more demanding and physically-plausible systems, including multi-layer and porous materials, modelled by sets of resistor/capacitor elements. Again, the solutions will be presented by means of a single characteristic time, reflecting the basic composite system properties. The electric circuit-based model will be tested against experimental data for the system of pharmacological relevance (mimicking dermal absorption) and compared with predictions of the Fickian-based mass release model from a spherical capsule coated by a membrane.

Keywords: mass diffusion, electric circuits, characteristic time.

Analytical model for predicting the temperature-responsive behaviours of implantable and biodegradable microgels

Baeckkyoung Sung[1,2]

[1] KIST Europe Forschungsgesellschaft mbH, Germany, [2] Division of Energy & Environment Technology, University of Science Technology (UST), Korea

The artificial extracellular matrix (ECM) systems have recently been fuelled by the rapid advances in novel smart hydrogels for the applications to drug delivery and tissue regeneration [1]. In healthcare technologies, the ECM-resembling smart hydrogels become highly attractive when miniaturised in submillimetre to micrometre scales, due to their physiological compatibility and quick responsivity with respect to the external stimuli. Especially, such miniaturised hydrogels (termed as microgels) may hold an enhanced potential for therapeutic uses when they are designed to have biodegradability in the tissue-mimicking environments, which have been experimentally implemented by our group [2]: The microgels were fabricated based on the covalently crosslinked matrix of ECM-derived biopolymers (such as gelatine) in which thermoresponsive polymers of poly(N-isopropylacrylamide) [PNIPAM] were entrapped as a minor component. These microgels exhibited well-characterised degradation kinetics under in vivo-level enzyme concentrations, as well as on-demand drug release profiles driven by temperature-controlled deswelling at the body temperature range. For explaining such volume phase transition in terms of polymer thermodynamics, classical mean-field Flory-Huggins-Rehner theory [3] has long been used predominantly for pure PNIPAM microgels [4]. Nevertheless, this conventional modelling approach have significant limitations in the theoretical analysis of the temperature-dependent phase behaviours of our ECM-like hybrid microgels. In this presentation, we demonstrate a novel mathematical model on the thermally controlled volume phase behaviours of PNIPAM-doped gelatine/collagen microgels, by formulating the ternary mixing free energy of the polymer-solvent system and by generalising the elastic free energy term [5]. With this formalism, the decoupling of the Flory-Huggins interaction parameter between the PNIPAM and ECM biopolymer enables deriving a simple steady-state formula for the volume phase transition as a function of the structural and compositional parameters. Furthermore, we discuss the future development of this model for the magnetically actuated and degradable biodevices.

Keywords: hydrogel, mean field theory, Flory-Huggins equation.

References

[1] D. Seliktar, Science 336, 1124-1128 (2012)
[2] B. Sung, C. Kim, M-H. Kim, J. Colloid Interface Sci. 450, 26-33 (2015)
[3] P. J. Flory, Princ. of Polymer Chem. (Cornell Univ. Press, NY, 1953)
[4] M. Shibayama, T. Tanaka, Adv. Polym. Sci. 109, 1-62 (1993)
[5] B. Sung, Math. Meth. Appl. Sci. 43, 10637-10645 (2020)

Mathematical modeling of a replacement technique to control mosquito-borne diseases

Nicolas Vauchelet[1]

[1] LAGA UMR CNRS 7539, Université Sorbonne Paris Nord, France

In order to control epidemics of mosquito-borne diseases for which there is no vaccine, such as dengue fever, several strategies aim to act directly on the mosquito population. One technique is to introduce into the population an endosymbiotic bacterium, called Wolbachia. This bacterium is characterized by a maternal transmission and a cytoplasmic incompatibility which makes the mating of males infected by Wolbachia with uninfected females not possible. Interestingly, it blocks pathogen transmission to the human population. Then, releases of Wolbachia-infected mosquitoes are implemented in the field to replace the wild population of mosquitoes by a population unable to transmit diseases. Mathematical modelling is important for a safe and optimal use of this strategy. In this presentation, we will consider a system of reaction-diffusion equations modelling the replacement strategy. From this system, after reducing it to a simpler problem, we propose to study of the spatial spread of the bacteria into a population of mosquitoes. Then, we will present some mathematical and numerical results on the design and on the optimization of the releases protocol for this strategy. Our results rely on a careful study of the resulting reaction-diffusion equation. This is part of works in collaboration with Luis Almeida, Pierre-Alexandre Bliman, Michel Duprez, Grégoire Nadin, Yannick Privat, and Martin Strugarek.

Keywords: reaction-diffusion equation, traveling waves, control and optimization.

Mathematical modeling of a replacement technique to control mosquito-borne diseases

Iolanda Velho [1], Jorge Tiago[2], Alberto Gambaruto[3], Adélia Sequeira[2], Ricardo Pereira[4]

[1] CEMAT, Inst. Superior Técnico, Lisbon, Portugal, [2] CEMAT, Dept. of Mathematics, Inst. Sup. Técn., Lisbon, Portugal, [3] Dept. of Mechanical Engineering, Univ. of Bristol, Bristol, UK, [4] Coimbra Univ. Hospital, Coimbra, Portugal

Computational hemodynamics is now considered a valuable tool to describe the physiology of the cardiac system. Particularly, it has the potential to provide a better understanding of the connection between certain anomalies in physiological functions and arterial disease leading to aneurysms. Many authors built robust computational settings based on accurate computer-assisted registration, segmentation, and 3D geometry reconstruction from medical images of patient-specific cerebral aneurysms, and special techniques to derive appropriate boundary conditions. However, an accurate description of blood flow mechanics in the near-wall region, where mass transport to or from the blood and wall tissue remains to be achieved. One way to address such description consists of using a lower order approximation of the Lagrangian dynamics in the near-wall region, which allows for a meaningful characterization of both normal and parallel direction to the wall. We verify this computational approach in several aneurysms, including a follow-up case study, with a description of the near-wall flow structure. In some cases, we provide a comparison between computed flow indicators and the expression of several biomarkers known to be associated with vascular disease.

Keywords: computational hemodynamics, near-wall transport, aneurysms.

Simulation study of mechanical ventilation control system based on electrical impedance tomography

Zhixi Zhang [1], Hao Yu[1], Jiabin Jia[1]

[1] Agile Tomography Group, Inst. for Digital Communication, School of Engineering, The University of Edinburgh, UK

In recent years, more and more patients suffer from lung diseases, so the demand for mechanical ventilators is on the rise, in particular amid the Covid pandemic. The current mechanical ventilation equipment can only monitor whether the patient's breathing status is normal through the indicators, such as blood oxygen content, carbon dioxide content, and pressure, but cannot directly observe lung image showing real time ventilation. In fact, how a patient lies in bed, face up or on the side, could cause the lung to collapse or over-expand. As a highly advantageous new medical device, a mechanical ventilation system guided by electrical impedance tomography (EIT) could have a breakthrough for this problem. The basic principle of EIT imaging is that different tissues have different electrical impedance or conductivity. A small safe excitation current or voltage is injected into a pair of electrodes, and the corresponding voltage or current of the human body will be measured at the same time, then the image can be reconstructed. EIT is a non-invasive imaging method that has gradually been used in medical and industrial fields in recent years. This non-invasive imaging tool is low-cost and portable. It does not produce side effects on the human body. This new type of mechanical ventilation equipment based on EIT could provide more intelligent auxiliary treatment advice and become an important part of personalised medical equipment. EIT can monitor long-term respiratory process to guide the work of the ventilator with real time image information, which forms a closed-loop control system. In this work, by mathematically modelling the lungs, we simulated the lungs in different breathing states, including lungs with a certain spontaneous respiratory function, sudden or slow changes in breathing, and the breathing of newborns. During the modelling process, we tried our best to take into account the functional structure of the lungs, such as lung lobes, trachea and bronchi, and minimize the error as much as possible, to make the experimental data more reliable and closer to the real state. The simulation results demonstrate that the lungs in different breathing states can reach the target stable state under the intervene of the EIT mechanical ventilation equipment, and the assisted breathing function of the ventilator is realised successfully.

Keywords: mechanical ventilation, control system, EIT.

Author Index