MINISYMPOSIUM

MATHEMATICAL MODELING IN PHYSIOLOGY: ONE MAIN ROAD TOWARDS PERSONALIZED MEDICINE

Organizer
Andrea de Gaetano
ADG, CNR Consiglio Nazionale delle Ricerche, IASI Istituto di Analisi dei Sistemi e Informatica "A. Ruberti"
Rome, Italy
andrea.degaetano@biomatematica.it

Co-organizer
Jerry Batzel
Institute of Physiology,
Medical University of Graz,
Stiftingtal 8, Graz, Austria
jerry.batzel@medunigraz.at

Minisymposium Keywords: Personlized Medicine, Cardio-Respiratory System, Parameter Estimation, Experimental Design

Over the past several years heightened attention has been directed to personalized medical treatment for improving therapeutic effectiveness, decreasing costs and side effects, and for addressing atypical clinical situations. Mathematical modeling of patient pathophysiology represents one of the main tools whereby medical treatment can be optimized to address specific patient needs and in addition such modeling has the potential to improve the interpretation of data collected during treatment and medical diagnosis. Such applications confront a number of challenges including limited data related to complex physiological mechanisms and interpretation of data for immediate decision making. In this minisymposium mathematical modeling of cardiovascular and respiratory physiology will provide the context to address the clinical relevance of developed computational solutions as well as the shortcomings currently confronted, the goals yet to be reached, and the most promising avenues for continuing research in mathematical modeling for patient specific medical treatment.

The first speaker will provide an overview of key issues related to developing and applying mathematical models for patient specific medical treatment including theoretical issues as well as applications for concrete examples as for instance EPO-administration for dialysis patients and determining key parameters for a global cardiovascular model.

The second speaker will address methods and challenges related to data interpretation and decision making in critical care and intensive care medicine. The abundance of clinical data presents an opportunity to systematically fuse and analyze the available data streams, through appropriately chosen mathematical models, and to provide clinicians with insights that may not be readily extracted from visual review of the available data streams.

The third speaker will examine the use of the mechanical ventilator in the Intensive Care Units. Mathematical models of lung mechanical ventilation have been employed in the last few years, in order to support the Anesthesiologists and Resuscitators choices in the mechanical ventilator parameters setting, like frequency, applied airway pressures and inspiratory time fraction.

The fourth speaker will explore the usefulness of a mathematical model of cardio-circulatory mechanisms and its fitness with regard to experimental data, while elucidating ongoing experimentation of induced hemorrhagic shock in pigs. In particular, an *in silico* implementation of the model analyzing the experimental data from an induced-hemorrhage protocol was examined. The simple model of the swine cardiovascular system and its responses to the hemorrhagic challenge were examined in terms of predefined variables and parameters as monitored throughout the experimental protocol.

Wednesday, 25th, 10:30 **Room: C8.2.13**

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CHALLENGES FOR MATHEMATICAL MODELLING IN VIEW OF PERSONALIZED MEDICINE

Franz Kappel

franz.kappel@uni-graz.at

Institute of Mathematics and Scientific Computing, University of Graz, Heinrichstrasse 36, A 8010 Graz, Austria

Keywords: Model based therapy, Parameter subset selection, Generalized sensitivities, EPO-administration for dialysis patients.

Tailoring of medical treatment to the individual characteristics of a patient (definition of “Personalized Medicine” by the US President’s Council of Advisors on Science and Technology, [1]) among many other requirements puts new challenges for mathematical modeling of the dynamics of subsystem of the human body. In the presentation we shall first shortly discuss some of the definitions of personalized medicine or precision medicine available in the literature. Then we present as examples for challenges to mathematical modeling investigations concerned with parameter subset selection [2] and generalized sensitivity functions [3]. Finally we illustrate some of the results for concrete examples as for instance model based EPO-administration for dialysis patients [4], parameter identification in case of a global model for the cardiovascular system and the minimal model for the intravenous glucose tolerance test [3].

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MODEL-BASED ESTIMATION FOR NONINVASIVE INTRACRANIAL PRESSURE MONITORING

Thomas Heldt

Thomas@mit.edu

Institute for Medical Engineering & Science, Massachusetts Institute of Technology,
77 Massachusetts Avenue, Cambridge, MA 02139, USA

Keyword: Intensive care modeling.

Large volumes of heterogeneous data are now routinely collected and archived from patients in a variety of clinical environments, to support real-time decision-making, monitoring of disease progression, and titration of therapy. This rapid expansion of available physiological data has resulted in a data-rich – but often knowledge-poor – environment. Yet the abundance of clinical data also presents an opportunity to systematically fuse and analyze the available data streams, through appropriately chosen mathematical models, and to provide clinicians with insights that may not be readily extracted from visual review of the available data streams.

In this talk we will give examples of how one might be able to leverage this opportunity. In particular, I will focus my presentation on our model-based approach to noninvasive, patient-specific and calibration-free estimation of intracranial pressure (ICP). ICP is the hydrostatic pressure of the cerebrospinal fluid and can be critically elevated in a number of neurological conditions, such as hydrocephalus, hemorrhagic stroke, brain tumor, or traumatic brain injury, which makes control of ICP an important task in neurocritical care. Currently, ICP can only be monitored invasively by drilling a hole into the skull and placing a catheter or sensor into the cerebrospinal fluid or brain tissue. This invasiveness limits the measurement to as small subset of those patients who could benefit from knowledge of ICP. To close this gap, we have developed and validated a model-based approach to estimate ICP from waveform recordings of the arterial blood pressure and cerebral blood flow velocity. Here, we will present the approach and highlight some of the difficulties we had to overcome in validating the method in patients in neurocritical care.

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MODELING OF VENTILATOR-PATIENT INTERACTION

Andrea de Gaetano
andrea.degaetano@biomatematica.it
CNR-IASI, BioMatLab
Joint work with Alessandro Borri (CNR-IASI, BioMatLab), Laura d'Orsi (CNR-IASI, BioMatLab)

Keywords: Healthcare and medical systems, Mechanical ventilation, Modeling, Optimal mechanical ventilator parameters.

The use of the mechanical ventilator in the Intensive Care Units is widely diffused, because is not only reserved to patients with respiratory diseases like asthma or Chronic Obstructive Pulmonary Disease (COPD), [6, 10, 7], but is also indicated for improving the chances of survival of severely ill patients, with respiratory insufficiency or in the post-operative phase. Mathematical models of lung mechanical ventilation have been employed in the last few years, in order to support the Anesthesiologists and Resuscitators choices in the mechanical ventilator parameters setting, like frequency, applied airway pressures and inspiratory time fraction [8]. Since the early 1990s, several authors focused their attention on various aspect to the mechanisms of pulmonary ventilation, describing different aspect of respiratory physiology or patient-ventilation interaction. In this so varied scenario our goal is to provide a global mathematical model that takes into account the different physiological and mechanical respiratory aspects, with the aim to provide to the Anesthesiologists and Resuscitators the adequate ventilation parameters set to avoid Acute Respiratory Distress Syndrome (ARDS). Frequently, in fact, in order to supply sufficient ventilatory volume, ICU doctors increase the pressure delivered by the ventilator, which, however, induces pressure-derived trauma in some of ICU patients and actually worsens the ARDS picture, with prolonged dependency on mechanical ventilation, prolongation of ICU stay and increased incidence of ICU deaths [12, 9, 5, 11, 13]. In this work, differential and algebraic equations 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, whit wave shape predetermined but with maximum value estimated by the model. Moreover is defined an index (the Respiratory Trauma Index) that describes the trauma induced on the patient by ventilator and that takes into account the value of arterial saturation that needs to be achieved to maintain a physiological condition (around 95%). Furthermore lung stratification is considered with different values of Compliance for each layer. In this way it is possible to consider different physiological parameters for each layers and it is possible to consider various scenarios that characterize patients or different pathologies. Minimizing the RTI it is possible to provide the optimal parameters to be set on the mechanical ventilator that allows to provide adequate air flow to the patient without causing barotrauma in all physiological or pathological situations. The considered approach looks promising, since a preliminary in-silico validation of the resulting patient-ventilator system shows that the target value of the arterial saturation is readily tracked in all considered scenarios with limited control effort.

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A SIMPLE CARDIOVASCULAR MODEL FOR THE STUDY OF HAEMORRHAGIC SHOCK

Luciano Curcio

luciano.curcio@biomatematica.it

CNR IBIM BioMatLab, Via Ugo La Malfa 153, 90146 Palermo, Italy

Joint work with Fabio Cibella (CNR IBIM BioMatLab, Via Ugo La Malfa 153, 90146 Palermo, Italy), Jiraphat Yokrattanasak (Department of Mathematics, KingMongkut's Institute of Technology Ladkrabang Bangkok, 10520, Thailand) and Andrea De Gaetano (CNR-IASI BioMatLab, UCSC Largo A. Gemelli 8, 00168 Rome, Italy)

Keywords: Cardio-Respiratory System, Parameter Estimation.

Mathematical models and numerical simulations have been used to better understand the physiology of the cardiovascular system and certain pathological processes. Specifically, they have been relied on to estimate the parameters that allow us to represent the most relevant underlying mechanisms in identifiable mathematical terms.
After a comprehensive literature search of mathematical modeling techniques, we arrived at our approach to simulating the complex responses of the system to hemorrhage with the aim of first determining the hemodynamic effects of various bleeding rates in the absence of fluid infusion and, in prospective, also taking into account eventual pre- and post-hemorrhagic emergency therapies. Indeed, severe hemorrhage and/or hemorrhagic shock are major causes of permanent organ dysfunction and death in traumatic injuries. Prompt and sustained treatments have been shown to improve survival in trauma patients.
Ours is a simplified, ordinary differential equation model of the cardiovascular system geared to analyzing and simulating the quantitative and qualitative responses to acute alterations in blood volume and intravascular fluids. The rationale and design of the model was based on pursuing an acceptable trade-off between complexity-physiological fidelity and alignment with the empirical data.
The parameters of the model were identified based on hemodynamic measurements in experimental animal studies. In the more preliminary phases, the model had to undergo progressive fine-tuning. In particular our model was subjected to validation of model predictions through comparisons to empirical *in vivo* data derived from laboratory animals (i.e. swine). As of yet, albeit on a still limited but ongoing dataset, the model fit has proven valid: simulations conducted thus far have proven the model to perform correctly, also in qualitative terms, with regard to the targeted, clinically relevant, physiological responses.
From the perspective of the practice of medicine, the most desirable applications of mathematical modeling would likely address the potential for both "predicting" system behavior and controlling physiologic processes (optimization of therapy). Acknowledging the oft cited words of George Box, "All models are wrong, but some are useful" we propose to define the circumstances under which our model is demonstrably useful.

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PERSONALIZED MATHEMATICAL MODELING OF WHOLE BODY GLUCOSE METABOLISM FOR INSULIN THERAPY ADJUSTMENT

Irina Pashchenko

ira.pashchenko15@gmail.com

Faculty of Physics, M.V.Lomonosov Moscow State University, Moscow 119991, Russia

Joint work with A. Dreval, T. Sveshnikova, I. Barsukov (Moscow Regional Research and Clinical Institute ("MONIKI"). Moscow 129110, Russia), O. Medvedev, A. Sveshnikova, M. Panteleev (Faculty of Physics, M.V.Lomonosov Moscow State University, Moscow 119991, Russia)

Keywords: Mathematical modeling, Pharmacological modeling, Type 1 diabetes, Continuous glucose monitoring.

Type 1 diabetes mellitus (DM1) is a severe disorder caused by decreased insulin secretion. The only effective treatment is life-long the prescription of insulin injections. Every DM1 patient requires personalized insulin dosing that is usually determined by trial-and-error. Implantable continuous glucose monitoring (CGM) devices provide abundant information about metabolism, but there are currently no tools to help the doctors make decisions based on these data.

Here we aimed to use mechanism-driven mathematical model of whole body glucose metabolism to estimate metabolic parameters. The cause of type 1 diabetes mellitus (DM1) is a decrease, up to complete absence, of insulin secretion, and therefore the only effective treatment is the prescription of insulin drugs. At the same time, the necessary dose of short insulin prescribed before meals is calculated depending on the blood glucose level and the amount of carbohydrates in the upcoming meal.

The mathematical model was based on our previous study (Shepelyuk et al. Math Mod Nat Phenom 2016; 11: 91-101). It was comprised of six ordinary differential equations for glucose, insulin and other factors in blood. The "intercellular space" compartment was added for CGM analysis. The main model parameters were: efficiency of food, insulin-independent assimilation of glucose, clearance of contrinsular factors, insulin clearance.

CGM was used to obtain continuous glycemic curve (CGG) for seven DM1 patients over several days. Their parameters of glucose metabolism were adjusted on the basis of the data received during the first day and were used to predict the CGG during the second day. Fitting efficiency was evaluated using relative mean error RME (determined as squared root of the mean square of the difference between predicted and measured value divided by their averaged values)

The RMEs for patient description using non-adjusted model with parameters from the published papers was in the range of 30-75%. For the personalized models, the values were in range of 7-15. There was good correllation between the personal metabolic parameters obtained during the fittings performed on the first and second day. Prediction of glucose dynamics on the second day using the parameters from the first day yielded RMEs only slightly inferior to those obtained by direct fitting. Based on the metabolic parameter distribution, several clearly distinguishable groups of patients could be identified.

These results provide insight into the population glucose metabolic parameters and can form basis of automatic technology for early correction of insulin therapy in DM1 patients.

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