BOOK OF ABSTRACTS

MATHEMATICS MEET PHARMACY

WORKSHOP

Hradec Kralove, Czech Republic

23-24 September 2019

Workshop organizing committee

Main organizers

Assoc. Prof. Jurjen Duintjer Tebbens (chair)
Faculty of Pharmacy in Hradec Kralové, Charles University, Hradec Kralove, Czech Republic

PD Dr. Elfriede Friedmann
Institute of Applied Mathematics, University Heidelberg, Germany

Assoc. Prof. Zuzanna Szymańska
Interdisciplinary Centre for Mathematical and Computational Modelling, University in Warsaw, Poland

Prof. Petr Pávek
Faculty of Pharmacy in Hradec Kralové, Charles University, Hradec Kralove, Czech Republic

Local Organizing Committee of the Department of Biophysics and Physical Chemistry

Dr. Martin Drastík

Mgr. Julia Marushka

Mgr. Andreas Matthios

Lenka Peterková

Program

Monday, 23 September, 2019, Lecture hall C

8:30–9:30	Registration
9:30–9:35	Organizers: Opening words
9:35–10:15	**Pavek, P.**; Duintjer Tebbens, J. (Charles University, Czech Republic) *Mathematics in pharmacology and beyond*
10:15–11:00	**Meldgaard Lund, T.** (University of Copenhagen, Denmark) *An introduction to population PKPD modelling*
11:00–11:30	Coffee break
11:30–13:00	**Contributed talks**
11:30–12:00	Ratschan, S. (Czech Academy of Sciences, Czech Republic) *Formal verification and its potential application in pharmacy*
12:00–12:30	Michalickova, D. (Charles University, Czech Republic) *Pharmacokinetics of phenobarbital in neonates on extracorporeal membrane oxygenation*
12:30–13:00	Zitko, J. (Charles University, Czech Republic) *Computer-aided drug design in medicinal chemistry*
13:00–15:00	Lunch: Tereziansky dvur
15:00–16:30	**Contributed talks**
15:00–15:30	Kindermann, S. (Johannes Kepler University Linz, Austria) *Parameter identification for a mathematical model of xenobiotic metabolizing enzyme induction*
15:30–16:00	Papacek, S. (University of South Bohemia in Ceske Budejovice, Czech Republic) *Modeling of drug-induced enzyme production in pharmacotherapy (with special attention to the dose-dependent behavior, periodic dosing and slow-fast decomposition)*
16:00-16:30	Lanzendörfer, M. (Charles University, Czech Republic) *Extending a pharmacodynamic model: towards compartments with spatial resolution*
16:30–17:00	Coffee break
17:00–18:00	**Contributed talks**
17:00–17:30	Kopecz, S. (University of Kassel, Germany) *Modified Patankar-Runge-Kutta schemes for the solution of positive production-destruction systems*
17:30–18:00	Svihlova, H. (Charles University, Czech Republic) *Computational fluid dynamics in cerebral aneurysms: our experience*
19:15	Workshop dinner: Pivovarske domy

Program

Tuesday, 24 September, 2019, Lecture hall C

9:00–9:45	**Ferreira, J. A.** (Coimbra University, Portugal) *A cardiologist meets a mathematician: the effect of atherosclerotic plaques on the pharmacokinetics of a drug released from a DES*
9:45–10:30	Silva, P. (Coimbra Institute of Engineering, Portugal) *Ophthalmologists meet mathematicians*
10:30–11:00	Coffee break
11:00–12:00	**Contributed talks**
11:00–11:30	Olkhovskiy, V. (Heidelberg University, Germany) *Modeling and simulation of the aqueous humor flow in the anterior chamber*
11:30–12:00	Stein, J. (Heidelberg University, Germany) *Modeling of drug distribution in the human vitreous*
12:00–14:00	Lunch: Terezіansky dvur
14:00–15:00	**Contributed talks**
14:00–14:30	Dörsam, S. (Heidelberg University, Germany) *Finite element simulation of drug distribution in the human vitreous*
14:30–15:00	Drobny, A. (Heidelberg University, Germany) *Numerical solution of viscoelastic fluid-structure-diffusion systems with applications in ophthalmology*

Invited Speakers

In alphabetical order

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EUROPEAN UNION
European Structural and Investing Funds
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Contributed Speakers

In alphabetical order

Contributed Speakers

In alphabetical order

AN INTRODUCTION TO POPULATION PKPD MODELLING

LUND, T.M[1]

[1]Department of Drug Design and Pharmacology, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark
e-mail: trine.lund@sund.ku.dk

Describing the plasma concentration-time profile (pharmacokinetics, PK) and understanding, the quantitative link to therapeutic response (pharmacodynamics, PD) of a drug is paramount for selection of the optimal dosing regimen to treat patients and minimize unwanted adverse events. PKPD modelling is the science of developing computer-based mathematical and statistical models that provide useful mechanistic understanding of the processes involved in drug exposure and corresponding therapeutic effect as a function of time.
Population PKPD modelling allows for analysis of both the population mean response in addition to description and explanation of inter-individual differences in therapeutic response and characterization of residual variability in studies[1].
As an example of application of population PKPD modelling a study on repeated-time-to-event (RTTE) modelling on opioid consumption data from 63 patients undergoing hip surgery will be presented[2,3].

References

1. Mould, D.R. & Upton, R.n.: Basic Concepts in Population Modeling, Simulation, and Model-Based Drug Development. CPT: Pharmacometrics & Systems Pharmacology, 2012 1(9), e6
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3. Juul, R.V., nyberg, j., lund, t.m. rasmussen, s., kreilgaard, m, christrup, l.l & simonsson, u.s.h.: A Pharmacokinetic-Pharmacodynamic Model of Morphine Exposure and Subsequent Morphine Consumption in Postoperative Pain. Pharmaceutical Research, 2016, 33, 1093–1103.

A CARDIOLOGIST MEETS A MATHEMATICIAN: THE EFFECT OF ATHEROSCLEROTIC PLAQUES ON THE PHARMACOKINETICS OF A DRUG RELEASED FROM A DES

FERREIRA, J. A.[1]

[1]Department of Mathematics, Faculty of Sciences and Technology, University of Coimbra, Portugal
e-mail: ferreira@mat.uc.pt

Atherosclerosis is the most common cardiovascular disease. It is characterized by the narrowing and hardening of arteries due to the lipid plaques' accumulation. The evolution of atherosclerosis plaques can be generally divided into four stages: endothelial injury, oxidation of low- density lipoproteins (LDL) in the reaction with free radicals produced by macrophages, endothelial cells, or smooth muscle cells; inflammatory process and calcification. Once a plaque is formed, a fibrous cap, consisting of elastin, collagen and smooth muscle cells, covers it. To prevent the rupture of the fibrous cap and to restore the lumen space, different treatments have been developed. In some of the proposed medical procedures (bloom angioplasty and bare metal stents), restenosis is a common problem. This occurs as a result of the endothelium injury. Drug eluting stents (DES) are the most widely used medical devices. Their aim is to prevent the proliferation of smooth muscle cells. DES are composed of a metallic structure with a polymeric coating of a drug to inhibit smooth muscle cells proliferation. Sirolimus and Paclitaxel are nowadays the most commonly used antiproliferative drugs. The main actors in the drug release from the DES and its absorption by the vessel wall are: the fluid uptake by the polymeric coating; the dissolution process; the drug transport through the polymer; the polymeric degradation; the drug transport in the vessel wall taking into account the effect of the plaques nature and their distribution.

In this talk, using mathematical modeling and numerical simulation, we intent to contribute to the understanding of the drug release from the DES, the effect of the plaques composition in the drug distribution and in the drug sorption by the vessel wall, as well as to identify zones with a higher risk of restenosis.

This work was supported by Centro de Matemtica da Universidade de Coimbra UID/MAT/00324/2013, funded by the Portuguese Government through FCT/MCTES and co-funded by the European Regional Development Fund through the Partnership Agreement PT2020.

MATHEMATICS IN PHARMACOLOGY AND BEYOND

PAVEK, P. [1], DUINTJER TEBBENS, J. [2]

1 Dep. of Pharmacology and Toxicology, Faculty of Pharmacy in Hradec Kralove, Hradec Kralove, Czech Republic
2Dep. of Biophysics and Physical Chemistry, Faculty of Pharmacy in Hradec Kralove, Hradec Kralove, Czech Republic
e-mail: pavek@faf.cuni.cz

The aim of the talk is to point out the need for and main advantages of mathematical models and other mathematical techniques in pharmacy, with particular emphasis on pharmacology. Pharmacodynamic and pharmacokinetic models are introduced with special attention for computational aspects and challenges. The central importance of parameter estimation, both for pharmacologic knowledge and for the computational process, is discussed. The talk also addresses the potential of extrapolating models for different stages in the drug development chain and the usage of models in pharmaceutical applications not directly related to pharmacology. Weaknesses and examples of misuse of models will be mentioned as well1. If time allows, some widely used statistical techniques will be shortly described.

References

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FINITE ELEMENT SIMULATION OF DRUG DISTRIBUTION IN THE HUMAN VITREOUS

DÖRSAM, S. [1], FRIEDMANN, E.[1]

[1] Mathematical modeling and simulations in ophthalmology,
Department of Applied Mathematics, Heidelberg University
e-mail: simon.doersam@iwr.uni-heidelberg.de

The injection of a drug into the vitreous body of a human eye for the treatment of retinal diseases is the most common form of medical intervention worldwide. In the worst case the treatment prevents that the patient loses his eyesight. The aim of an optimal therapy in the case of age related macular degeneration (AMD) is that the drug operates locally around the area of the macula as long as possible. We present numerical simulations of the drug distribution by using the software library deal.II and the Finite Element method. The mathematical model is a Darcy equation for the physiology of the aqueous humor flow coupled with a convection-diffusion equation for the drug in the inhomogeneous vitreous. The underlying geometry for the numerical grid is constructed with the help of parameter estimation methods, which fit measurement data from different patients. The discretization is realized by using the fractional step theta scheme in time, the Raviart-Thomas elements for the velocity, discontinuous zero-order elements for the pressure and Lagrange elements for the concentration.

Finally, we investigate the influence of the position of the injection on the drug distribution for different diseases. This is realized by introducing specific output functionals, which measure the mean or relative amount of the drug in the vitreous and in the area of action. For each disease, our simulations show how the injections should be located for a more efficient therapy.

This work was supported by the Klaus Tschira Stiftung gGmbH, Project No.00.265.2015

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NUMERICAL SOLUTION OF VISCOELASTIC FLUID-STRUCTURE-DIFFUSION SYSTEMS WITH APPLICATIONS IN OPHTHALMOLOGY

DROBNY, A. [1], FRIEDMANN, E.[1]

[1] Department of Applied Mathematics, Faculty of Mathematics and Informatics, Heidelberg University, Germany
e-mail: drobny@uni-heidelberg.de

The research of fluid-structure interaction problems is a continuously growing field, especially regarding applications in medicine and biology. We present the coupling of a potentially viscoelastic fluid with multiple hyperelastic structures incorporating chemical processes in the arbitrary Lagrangian Eulerian framework. This monolithic formulation allows a robust numerical solution with Newton's method. The discretization is based on the shifted Crank Nicholson scheme for temporal discretization and the Galerkin finite element method for spatial discretization. This fluid-structure interaction problem is applied to ophthalmology in order to improve the medical treatment of retinal diseases. The physiological processes include the elastic response of various structures like the sclera, lens and iris coupled to the fluid-like vitreous which is modeled by a viscoelastic Burgers type model for the healthy case and by the Newtonian Navier-Stokes equations for the pathological case. Since most medical treatments are based on the injection of medicine we furthermore investigate the drug distribution. In particular we study the vascular endothelial growth factor (VEGF) therapy which is modeled by two coupled convection-diffusion-reaction equations, in the whole eye for healthy and non-healthy pathologies.

The financial support for this project is provided by the Klaus Tschira Stiftung gGmbH, Project No.00.265.2015

PARAMETER IDENTIFIATION FOR A MATHEMATICAL MODEL OF XENOBIOTIC METABOLIZING ENCYME INDUCTION

KINDERMANN, S. [1], PAPACEK, S. [2], DUINTJER TEBBENS, J. [3]

[1] Industrial Math. Insittute, Johannes Kepler University Linz, Austria
[2] Inst. Complex Sys., Univ. South Bohem. C. Budejovice Nove Hrady, Czech Republic
[3]Dep. Biophy. and Phy. Chem, Facutly of Pharmacy in Hradec Kralove, Hradec Kralove, Czech Republic
e-mail: kindermann@indmath.uni-linz.ac.at

We discuss aspects and applications of tools from inverse problems for a parameter identification problem arising in the mathematical modelling of rifampicin-induced CYP3A4 enzyme production. Our work is based on a ODE-models by Luke et al., with enhancements by Duintjer Tebbens et al. As usual, these models involve coupling constants (rate parameters), which are unknown in practice and have to be deduced from data by parameter fitting. As an improvement compared to standard methods, we apply a non-parametric parameter identification, where the certain rate parameter are not treated as constant but may depend on time. This allows for a better data fit and enhances the explanatory power of the mode.

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2. Duintjer Tebbens, Matonoha,j. c., Matthios,c. a,, Papacek, s.: On parameter estimation in an in vitro compartmental model for drug-induced enzyme production in pharmacotherapy. J. A. M. 1 (2019), 1785.

MODIFIED PATANKAR-RUNGE-KUTTA SCHEMES FOR THE SOLUTION OF POSITIVE PRODUCTION-DESTRUCTION SYSTEMS

KOPECZ, S. [1], MEISTER, A.[1]

[1] Institute of Mathematics, University of Kassel, Germany
e-mail: kopecz@mathematik.uni-kassel.de

Modified Patankar-Runge-Kutta (MPRK) schemes are numerical methods for the solution of positive and mass conservative production-destruction systems. They adapt explicit Runge-Kutta schemes in a way to ensure positivity and mass conservation of the numerical approximation irrespective of the chosen time step size. They are able to integrate stiff ODEs and require only the solution of a linear system in each Runge-Kutta stage.
The talk will present recent theoretical results[1,2,3] on MPRK schemes and show examples that illustrate the applicability of these methods. In addition, we show how these methods can be generalized to solve an in vitro model describing the pharmacokinetics of rifampicin metabolism in a hepatocyte[4], which is stiff, positive but not mass conservative. The Rifampicin- and corresponding receptor (PXR)-concentration as well as the mRNA-level and the induced CYP3-enzyme converge towards an equilibrium point, whereas rifampicin is metabolized after approximately $6 \cdot 105$ minutes in accordance with the given initial dose and this is accompanied by producing mRNA and CYP3-enzyme.

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4. LUKE, N. S., DEVITO, M. J., SHAH, I., EL-MASRI, A. E.: Development of a Quantitative Model of Pregnane X Receptor (PXR) Mediated Xenobiotic Metabolizing Enzyme Induction. Bulletin of Mathematical Biology, v. 72, 2010, 1799–1819.

EXTENDING A PHARMACODYNAMIC MODEL: TOWARDS COMPARTMENTS WITH SPATIAL RESOLUTION

LANZENDÖRFER, M. [1], DUINTJER TEBBENS, J. [2], MATONOHA, C.[3]

[1] Faculty of Science, Charles University, Czech Republic
[2] Faculty of Pharmacy, Charles University, Czech Republic
[3] Institute of Computer Science, Czech Academy of Sciences, Czech Republic
e-mail: martin.lanzendorfer@natur.cuni.cz

Traditionally, the pharmacokinetic/pharmacodynamic (PK/PD) modelling methodology is based on compartmental models, that represent the processes of interest via defining a number of compartments representing organs, tissues, cells, cytoplasm or other units. The concentrations of all substances inside a compartment are by definition taken as homogeneous, determined directly by the amount of the substance present in the compartment, and by the compartment's actual size.

We will discuss the possibility of adding a spatial resolution to a compartment. That can be beneficial to address important issues like, among others, local exceeding of toxic drug levels, delay of transport or drug-drug interactions. We will briefly review the transition from a classical compartmental model, deriving a mixed system of partial differential equations coupled with ordinary differential equations.

We will present in particular an extension of a model by Luke et. al (2010), describing the action of the drug Rifampicin. The extension adds a spatial resolution for substances that are active in the cytoplasm and are involved in the negative feedback loop of the nuclear pregnane X receptor (PXR). Some issues related to the extension will be illustrated on the level of a more simplistic toy model.

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PHARMACOKINETICS OF PHENOBARBITAL IN NEONATES ON EXTRACORPOREAL MEMBRANE OXYGENATION

MICHALICKOVA D.[1], POKORNA P.[1,2,3], TIBBOEL D.[3], SLANAR O.[1], KNIBBE, C.A.J.[4,5], KREKELS E.H.J.[4]

[1] Institute of Pharmacology, First Faculty of Medicine, Charles University, Prague, Czech Republic;
[2] Department of Pediatrics, First Faculty of Medicine, Charles University, Prague, Czech Republic;
[3] Intensive Care and Department of Pediatric Surgery, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands;
[4] Division of Systems Biomedicine and Pharmacology, Leiden Academic Centre for Drug Research, Leiden University, Leiden, The Netherlands
[5] Department of Clinical Pharmacy, St. Antonius Hospital, Nieuwegein, The Netherlands
e-mail: danica.michalickova@lf1.cuni.cz

The use of extracorporeal membrane oxygenation (ECMO) is associated with changes in drug pharmacokinetics. This study characterizes the pharmacokinetics of phenobarbital and provides dosing recommendations in neonates on ECMO.

Therapeutic drug monitoring (TDM) data were available from 13 critically - ill neonates (birth bodyweight (bBW): 3.21 (2.65-3.72) kg; postnatal age (PNA) at start of treatment: 2 (0-7) days; gestational age: 38 (38-41) weeks) receiving veno-venous or veno-arterial ECMO, yielding 5, 31, and 19 phenobarbital concentrations before, during and after ECMO, respectively. Population pharmacokinetic analysis was performed using NONMEM 7.3.0. Maturation functions based on bBW and PNA for clearance (CL) and based on actual BW for distribution volume (Vd) were obtained from literature[1]. Additionally, kidney and liver function markers and flow and speed of ECMO were evaluated for their predictive properties regarding the PK of phenobarbital.

In a one-compartment model, CL and Vd for a typical neonate of median bBW (3.21 kg) at median PNA (2 days) off ECMO were 0.0096 L/h (RSE = 11%)) and 2.72 L (16%), respectively. During ECMO, CL was linearly increasing with time. Furthermore, phenobarbital CL initially decreased after decannulation compared to CL during ECMO, and subsequently increased driven by the maturation function. Changes in Vd during ECMO could not be identified, possibly due to sparse data collection shortly after the ECMO start. Simulations showed that optimal dosing includes a LD of 20 mg/kg and a MD of 4 mg/kg/day divided in 2 doses with an increase of 0.25 mg/kg every 12 h during ECMO treatment.

Continuously decreasing phenobarbital exposure during ECMO, resulting from the time-dependent increase in CL, increases the risk of therapeutic failure over time. Due to high remaining unexplained variability, frequent and repeated TDM over time is highly recommended.

This work was supported by the project CZ.02.2.69/0.0/0.0/16_027/0008495.

References

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MODELING AND SIMULATION OF THE AQUEOUS HUMOR FLOW IN THE ANTERIOR CHAMBER

OLKHOVSKIY, V. [1], FRIEDMANN, E.[1]

[1] Institute of Applied Mathematics, Mathematics and Computer Science, Heidelberg University, Germany
e-mail: vladislav.olkhovskiy@iwr.uni-heidelberg.de

One of the most common reasons for blindness is glaucoma. The primary risk factor for the development of the vision loss in glaucoma is an increased intraocular pressure (IOP) and lowering the IOP is currently the only therapeutic option with proven efficiency. To lower the IOP drug treatment and surgical interventions are common. To understand the behaviour of the aqueous humor flow and of the IOP in the anterior chamber of the human eye as well as the effectiveness of different treatment options, a mathematical model is developed. This model is given by Stokes and Darcy equations. With the help of the Darcy equation the mean pressure value is computed. This mean pressure value is incorporated into the Neumann boundary condition of the Stokes equation. The Stokes equation describes the aqueous humor flow in the anterior chamber and the Darcy equation describes the pressure in the trabecular meshwork which is a porous medium. The characteristical physical properties are given by the inflow rate of the aqueous humor at the ciliary body, the pressure of the episcleral veines and it is assumed that the cornea, the lens, the iris and the zornules are impermeable. Geometries for healthy, pathological and treated eyes are considered. Numerical simulations using the Finite Element method are performed in three dimensions. In the computation, mixed finite elements are used and the solutions of the equations are generated with deal.ii software[1]. Changing model parameters pharmacological effect on IOP is predicted. Furthermore, other strategies like trabeculectomy and stent insertion are illustrated.

This work was supported by the Klaus Tschira Stiftung gGmbH, project 00.265.2015.

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MODELING OF DRUG-INDUCED ENZYME PRODUCTION IN PHARMACOTHERAPY (WITH SPECIAL ATTENTION TO THE DOSE-DEPENDENT BEHAVIOR, PERIODIC DOSING AND SLOW-FAST DECOMPOSITION)

PAPÁČEK, Š. [1], KINDERMANN, S. [2]

[1] Institute of Complex Systems, FFPW, University of South Bohemia, Czech Republic
[2] Industrial Mathematics Institute, Johannes Kepler University Linz, Austria
e-mail: spapacek@frov.jcu.cz

Our model, using an appropriate scaling of both the state variables and model parameters, represents a dimensionless formulation of the in vivo model published by Luke et al. (2010) 1. We pay a special attention to (i) the dose-dependent behavior, impossible to be explained by an introduction of a delay only as proposed in the original paper[1], (ii) periodic dosing, proportioning valuable data for further parameter identification, and (iii) slow-fast decomposition enabling an appropriate sensitivity analysis via the timescales separation and eventually an ODE system linearization and/or order reduction.

This work was supported by the OeAD (Austrian agency for international mobility and cooperation in education, science and research) within the programme "Aktion Oesterreich-Tschechien ".

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FORMAL VERIFICATION AND ITS POTENTIAL APPLICATION IN PHARMACY

RATSCHAN, S.[1]

[1] Institute of Computer Science, Czech Academy of Sciences
e-mail: stefan.ratschan@cs.cas.cz

Drug safety is an important concern in pharmacy. Formally and automatically proving safety of various types of systems is a central goal of the field of formal verification. Hence, the two fields have similar common interests.

However, formal verification has traditionally been interested in systems coming from computer science, for example, network communication protocols, or computer programs. Still, lately techniques have been developed that allow for the formal verification of physical systems, for example, cars or robots. Here, the physical systems are usually modeled using differential equations, and there is no fundamental reason, why those techniques should not be useful to models from pharmacy based on differential equations.

Hence, I feel that it is high time that the fields of formal verification and pharmacy talk to each other. In the talk, I will give an introduction to techniques from formal verification that I find must promising for application in pharmacy.

OPHTHALMOLOGISTS MEET MATHEMATICIANS

SILVA, P.M. [1,2], FERREIRA, J.A. [2], OLIVEIRA P. [2], SILVA, R.[3]

[1] IPC/ISEC - Department of Physics and Mathematics, ISEC, Coimbra, Portugal
[2] CMUC, University of Coimbra, Portugal
[3] Department of Ophthalmology – CHUC; Faculty of Medicine, University of Coimbra; Institute for Biomedical Imaging and Life Sciences (FMUC-IBILI); Association for Innovation and Biomedical Research on Light and Image (AIBILI). Coimbra. Portugal
e-mail: pascals@isec.pt

Different barriers against the entry of exogenous substances effectively protect human eyes. Consequently, the delivery of drugs to treat retina diseases is a challenging problem and nowadays several drug delivery routes are being investigated and used in clinical ophthalmology. Mathematical modeling is a powerful tool that can help pharmaceutical and medical researchers to design effective methodologies to break eye barriers to delivery drug accurately to the retina.

In this talk, our main goal is to discuss computationally two different routes to delivery drug to the retina: through the humor vitreous and through the sclera. Computational models that simulate the behavior of the drug, released from biodegradable polymeric platforms, in the different layers of the eye are studied. For the two delivery routes, the peak concentration and

the residence time in the retina are compared. The influence of the breakdown of the blood retinal barrier is simulated allowing a better understanding of the differences between the two routes. Numerical results are compared with available experimental data.

This work was supported by the Center for Mathematics of the University of Coimbra - UID/MAT/00324/2013, funded by Portuguese Government through FCT/MEC and co-funded by through the Partnership Agreement PT 2020.

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MODELING OF DRUG DISTRIBUTION IN THE HUMAN VITREOUS

STEIN J. [1], FRIEDMANN E. [1], PRŮŠA V. [2]

[1] Faculty of Mathematics and Computer Sciences, Heidelberg University, Germany
[2] Faculty of Mathematics and Physics, Charles University Prague, Czech Republic
e-mail: judith.stein@iwr.uni-heidelberg.de

The injection of a drug into the vitreous body for the treatment of retinal diseases is the most common medical intervention worldwide.
To analyze the effectiveness of a specific drug we develop a mathematical model for the drug distribution in the vitreous body of a human eye. The rheology of the individual vitreous body has a great impact on the drug distribution and the severity degree of the injury and changes with age and disease.
For a healthy vitreous with a dense collagen network we use porous media modeling and couple the convection diffusion equation of the drug with a steady permeating flow of the aqueous humor driven by a pressure drop. Additionally, the vitreous body in a healthy human eye behaves like a viscoelastic gel through the collagen fibers suspended in the network of hyaluronic acid and acts as a drug depot for the treatment of retinal diseases.
In a completely liquefied vitreous or a vitreous after vitrectomy the drug distribution occurs much faster than in a healthy viscoelastic one and the grade of injury is higher. In this case we couple the diffusion of the drug with the classical Navier-Stokes flow equations.

This work was supported by the Klaus Tschira Stiftung gGmbH, Project No. 00.265.2015.

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COMPUTATIONAL FLUID DYNAMICS IN CEREBRAL ANEURYSMS: OUR EXPERIENCE

ŠVIHLOVÁ, H. [1], HRON, J. [1], HEJČL, A. [2]

[1] Mathematical Institute, Faculty of Mathematics and Physics, Charles University, Czech Republic
[2] Department of Neurosurgery, J.E. Purkyne University, Masaryk Hospital, Usti nad Labem, Czech Republic
e-mail: helena.svihlova@mff.cuni.cz

The cerebral aneurysm is a local extension of a brain vessel with high prevalence in population (about 20%). The aneurysm rupture is the worst form of a stroke with high rate of mortality and severe morbidity (about 66%). On the other hand, treatment of unruptured aneurysms is an active and controversial topic since the aneurysm rupture is rare and the preventive surgery can also cause the damages.[1]
It is well known that hemodynamics has a significant role in an aneurysm development. Computational fluid dynamics (CFD) in cerebral aneurysms is currently a hot research topic because it can provide some of the hemodynamic parameters in a patient-specific manner. In fact, even the 'AHA/ASA Guidelines for Management of Aneurysmal Subarachnoid Hemorrhage' now recommends clinicians to 'consider hemodynamic characteristics of the aneurysm when discussing the risk of aneurysm rupture'.[2]
In our contribution, we will present assumptions and limitations of the models CFD uses as well as the potential benefits in a clinical practice in a near future.

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COMPUTER-AIDED DRUG DESIGN IN MEDICINAL CHEMISTRY

ZITKO, J.[1], JUHÁS, M.[1]

[1]Department of Pharmaceutical Chemistry and Drug Analysis, Faculty of Pharmacy in Hradec Králové, Charles University, Czech Republic
e-mail: jan.zitko@faf.cuni.cz

Computer-aided drug design (CADD) has become popular and widely acknowledged in both pharma industry and academic labs in the field of medicinal chemistry. Its usefulness for everyday research has risen greatly in the past few years due to great advances in computer technologies and accessibility of the software.

Plethora of software and web-based utilities may be used to predict important properties or behavior of molecules of interest while knowing very little about their real nature. The array of CADD application nowadays is enormous. One can start with simple de novo design of molecules for known (or even unknown), clinically relevant target on local low-end PC and finish with 'chemically accurate' simulations of the mechanism of action using quantum mechanical computations or molecular dynamics simulations on high-performance computing clusters, all available free of charge for academia.

In this presentation, we will present the most frequently used methods of CADD and give tips for freely available software and web-based utilities. We will briefly present the abilities and functions of MOE (Molecular Operating Environment, Chemical Computing Group, Canada), a complex software package for CADD. At the end we will open discussion how our team can help other researches both from the faculty and from outside with medchem and related research.

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