MATHEMATICAL MODELLING IN BIOMEDICINE

ABSTRACTS OF INTERNATIONAL CONFERENCE

Moscow, Russia, September 30 – October 4, 2019

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МАТЕМАТИЧЕСКОЕ МОДЕЛИРОВАНИЕ В БИОМЕДИЦИНЕ

ТЕЗИСЫ МЕЖДУНАРОДНОЙ КОНФЕРЕНЦИИ

Москва, Россия, 30 сентября – 4 октября 2019 г.

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C8 **Математическое моделирование в биомедицине = Mathematical modelling in biomedicine** : сборник тезисов. Москва, Россия, 30 сентября – 4 октября 2019 г. – Москва : РУДН, 2019. – 103 с.

На конференции представлено современное состояние математического моделирования в биологии с особым акцентом на сердечно-сосудистых заболеваниях, моделировании рака и математической иммунологии. Также обсуждаются методы моделирования и математического анализа соответствующих моделей. Участие медицинских исследователей подчёркивает междисциплинарный характер конференции.

The conference presents the state of the art in mathematical modelling in biology with a particular emphasis on cardio-vascular diseases, cancer modelling and mathematical immunology. Methods of modelling and mathematical analysis of the corresponding models are also discussed. Participation of medical researchers reinforces the interdisciplinarity of the conference.

Brownian dynamics simulation of cytochrome c di usion and binding with cytochrome c1 in mitochondrial crista

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Cytochrome c shuttles electrons from respiratory complex III (from subunit of cytochrome c1) complex IV, deposited in membranes of mitochondria. In work [1] Leigh syndrome { mitochondr disease, a ecting mitochondrial energy production { was considered. It was found that crista lum (where cytochrome c di used) width was signi cantly increased from 120 A (in healthy control) to 164 A.

We simulated brownian dynamics di usion of oxidized cytochrome c (cytC) and formation tanzient complex with water soluble part of reduced cytochrome c1 (cytC1) by the ProKSim so ware. We used structures of cytC1 with PDB ID 1BGY and cytC with PDB ID 3O1Y. We estimate values of the model parameters to get the same dependence of the association second-orde constant on the ionic strength as in experiment [2].

We also used the model with estimated values of parameters for the solution to study kin characteristics of cytC and cytC1 complex formation in crista lumen. The model scene wa parallelepiped with soft boundary conditions. Distance between 2 surfaces, simulated crista m branes, varied. CytC1 molecules were xed at their initial positions near the cristae membra CytC molecules di used under the action of the random Brownian force and electrostatic force a formed tranzient complex with cytC1. We estimated the half life time of process from simulated netic curves of complexes formaftion. We get increasing in 2.1 times of half life time with increas crista lumen width from 120 to 160A.

The research is carried out using the equipment of the shared research facilities of HPC c puting resources at Lomonosov Moscow State University

The work was supported by the Russian Foundation for Basic Research (projects no. 19 00999).

R e f e r e n c e s

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Mathematical modelling of hematopoiesis

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In this talk, we present several cell population mathematical models for hematopoiesis that played an important role in the understanding of qualitative dynamics of blood cell production, i.e. the time evolution properties for the cell populations – equilibrium, extinction, oscillation or unlimited growth. Forty years ago, one of the first mathematical models of hematopoiesis was proposed in which a stem cell population is divided into a proliferating and a quiescent fraction (M.C. Mackey, 1978). Four parameters describe the cell cycle: the rateof entry into proliferation, the duration of the proliferative phase and the rate of loss (apoptosis) for the proliferative phase and for the quiescent phase (differentiation). It was shown that an increase in therate of apoptosis was sufficient to explain the observed oscillations in reticulocyte numbers in haemolytic anaemia. Spatial models of the bone marrow are being developed to help understanding the role of cell movement and competition for space. These spatial models can be reaction-diffusion equations. Compartment models address specific questions related to hematotoxicity of various drugs, in the sense that they do not aim at explaining the origin or the dynamics of the diseases but at quantitatively predicting therapeutic outcomes of these drugs. We chose to present some examples of applications of mathematical models in hematopoiesis: periodic physiological hematopoiesis; chronic and acutemyeloid leukaemia; spatial competition within the bone marrow; and feedback regulation and self-renewal in the erythroid lineage after stress. These examples have been chosen amongst many others because they appear to be significant illustrations of the different models of hematopoiesis.

Simulation of microtubule shaft dynamics on long timescales

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Eukaryotic cells have a dynamic network of constantly reorganizing cytoskeletal microtubules, essential for performing a number of functions, ranging from directed cargo transport to mitosis. Microtubules are polymers of tubulin arranged in cylindrical structures with an outer diameter of 25 nm. Each tubulin dimer consists of α/β-tubulin monomers stacked longitudinally with the same orientation, conferring an internal polarity to the whole microtubule. The β-tubulin subunit faces the plus-end and tends to grow rapidly while depolymerizes slowly, in contrast to minus-end, known to be less dynamic. Plenty of numerical models were proposed to explain and recapitulate observed unstable behavior of microtubules, a cycling between growing and shrinking periods, but none of them, to our knowledge, attempted to model a difference between polar ends dynamics since minus-end is usually stabilized in vivo, whereas plus-end can freely explore cellular space and interact with other proteins of interest. However, a class of microtubule-associated proteins (MAPs) includes so-called severing enzymes, known to destabilize the non-covalent bonds of tubulin dimers by forming holes in the lattice causing filaments to expose both αand β-tubulin monomers, thereby creating two different kinetic behaviors at opposite sides of the hole.

The development of a microtubule two-end dynamics model was based on the existing Monte-Carlo simulation approach [1], where matrix cells represent states of microtubule subunits with a given probability of chemical reactions depending on kinetic rate constants. Here we have expanded this model to include latest structural data on tubulin switching between bent and straight conformations. Recent results of molecular dynamic simulations, as well as Brownian dynamics simulations on tubulin conformational transitions were used to extract information about stiffnesses of longitudinal contacts, i.e. the probability of conformational transitions at each type of contacts. We show that parameterized stochastic model of the microtubule lattice dynamics successfully describes concentration dependence of de/polymerization velocities at both ends and can be applied to model severing enzymes, responsible for neurodegenerative diseases. This model helps to reveal severing enzymes mechanism of action and makes new predictions on their regulation pathways.

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Dynamics of an HIV mathematical model with CTL and antibody immunities

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The aim of this work is to study a mathematical model describing the human immunodeficiency virus (HIV) along with the presence of CTL and antibody immune responses. The mathematical model consists of a system of equations reflecting the dynamics of the essential components such as the uninfected CD4+ T cells, the infected ones, the free HIV viruses and the immunity. In this work, we are interested mainly to the adaptive immune response which will be represented by two kinds of responses, the first one is named cytotoxic T-lymphocyte (CTL) response which is responsible to attack and kill the infected cells; while the second one stands for the humoral immune response, which is the antibodies that are produced by the B cells and are programmed to attack and neutralize the viruses. In order to check the impact of this adaptive immunity, different numerical simulations are performed in order to show whether the disease will die out or remain persistent depending on the key parameters of the problem. It was shown that the adaptive immune response can minimize viral replication and maximize the healthy CD4+ T cells.

Numerical solution of time-dependent Maxwell's equations for modeling light scattering in human eye's structures

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We propose an explicit iterative leap-frog discontinuous Galerkin method for time-domain Maxwell's equations in anisotropic materials and we focus on deriving stability and convergent estimates of fully discrete schemes. We consider anisotropic permittivity tensors, which arise naturally in our application of interest. An important aspect in computational electromagnetic problems, which will be discussed, is the implementation of the boundary conditions. We illustrate the theoretical results with numerical examples. We also present the results of numerical computations in the context of modeling scattered electromagnetic wave's propagation through human eye's structures.

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Integrative modeling of nucleosomes and their complexes

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Eukaryotic chromatin contains DNA in a highly compacted state. The main building blocks of chromatin conferring essential degree of DNA compactization are nucleosomes. Nucleosomes comprise an octamer of histone proteins (H3, H4, H2A, H2B) which wraps around 150 base pairs of DNA around it. Apart from DNA compactization, nucleosomes are highly involved in chromatin functioning by providing epigenetic markup to the genome and participating dynamically in all DNA processing and maintenance pathways. The dynamic nature of nucleosomes [1] combined with its variability through histone post-translational modifications and incorporation of histone variants [2] provides delicate mechanisms for gene expression regulation and genome maintenance. These mechanisms are of much interest and are the focus of many studies in molecular biology today. However, our ability to understand the molecular details of processes happening at the nucleosome level in chromatin are rather scarce. Nucleosomes are around 10 nm in size, key complexes of nucleosomes with chromatin proteins are within the 100 nm range. It is rather difficult to study nucleosomes or their complexes using conventional structural biology methods, such as, X-ray crystallography, NMR or electron microscopy, even if macromolecules are prepared in a compact stable state, which in turn is not often achievable due to the dynamic nature of interactions. Hence, using molecular modeling techniques which integrate different (often indirect) experimental datasets is an important way to rationalize the behavior of nucleosomes and their complexes at the molecular level. In this report we will dwell on our efforts to use molecular modeling techniques combined with the analysis of various experimental data sources to elucidate the structures and dynamical properties of nucleosomes and their complexes. We will outline how various approaches can be used to tackle the problem at different levels and size scales.

Despite the elucidation of the canonical nucleosome structure using X-ray crystallography around two decades ago, nucleosome structures only with a few carefully prepared DNA sequences have been solved in this way. These sequences are usually selected and trimmed to position tightly around the nucleosome core. So, a larger problem remains, how to reveal the exact nucleosome structure or the ensemble of nucleosome structures reconstituted on an arbitrary DNA sequence. If a DNA sequence larger than 150 bp is provided, the histone octamer is free to choose an unknown position on the DNA sequence which will be more energetically favorable. To address this problem one can resort to the detailed analysis of the hydroxyl-radical footprinting (HRF) experiments and molecular modeling of the expected footprinting cleavage patters. In HRF experiments DNA in a

Mathematical problems of blood coagulation

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The blood coagulation system is one of the most important systems in humans that protects our body from fatal blood loss. This system provides rapid closure of vascular damage, forming a thrombus in the area of damage. The system operates in a complex network of vessels in severe hydrodynamic conditions. The basic principle of the system is the formation in the area of damage of a solid clot from components circulating in the blood. This is a complex self-organizing process that includes transfer processes, biochemical reactions, and a lot of positive and negative feedbacks. Understanding the patterns of the formation of a blood clot is impossible without a theoretical study and modeling of the different stages of this process. The lecture will be dedicated to the review of mathematical problems arising in the course of blood coagulation studies. Some of the most interesting results that these studies bring will be highlighted. These results sometimes open up new medical horizons, bringing ideas for new diagnostic and therapeutic approaches. In addition, they often not only expand our understanding of blood coagulation mechanisms, but also introduce new types of dynamic systems and processes of self-organization.

Using Quantitative Systems Pharmacology modeling to predict response and resistance of immune checkpoint inhibitors (ICI) in murine syngeneic tumors

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Objectives: Experimental mouse syngeneic models are commonly used to explore mechanisms of action for immunotherapies, as well as for identification of potential immune biomarkers correlating with tumor response or resistance. Syngeneic models also differ from one another in their susceptibility to immunotherapy treatment and baseline immune conditions. The objectives of this work: (1) to develop a quantitative systems pharmacology (QSP) model, which describes the dynamics of tumor growth during immune checkpoint inhibition (ICI, anti PD-1, anti CTLA-4 or their combination) across various syngeneic models; (2) to link parameters of the model with baseline immune biomarkers; and (3) to validate the model via the prediction of independent experimental data.

Methods: The mechanistic population QSP model is based on our previous work [Mosely, S. et al., 2017]. It was used to incorporate data from six syngeneic tumors (4T1, LLC, CT-26, MC-38, B16, RENCA) into one quantitative framework, by capturing corresponding differences in tumor microenvironment (TME) baseline conditions as well as immune cell tumor cell interactions [Kosinsky Y. et al, 2018] under anti PD-L1 and CTLA-4 mAb therapies in these six syngeneic tumors. Variability in individual tumor size dynamics was taken into account using a mixed-effects feature in the model at the level of tumor-infiltrating T cell influx.

Results: The model adequately described individual- and cohort-level tumor size dynamics patterns for all treatment regimens across all six syngeneic tumors. Anti PD-L1 therapy was incorporated into the model via a direct increase in an immune activation rate (IAR) function within the TME, thereby confirming the validity of our previous results [Kosinsky Y. et al, 2018]. Also, the QSP model adequately described observed differences in treatment responses, depending on the start of treatment time (i.e., tumor age).

In the frame work of external cross validation the developed QSP model accurately predicted the absence of treatment response in Pan-02, based solely on TME baseline conditions and pre-wired

immune cell tumor cell kinetic interactions in the model. Using the model we hypothesised that the main immunosuppressive factor in Pan-02 could be traced to the high density of immunosuppressive myeloid cells in the TME, which can explain intrinsic resistance of this syngeneic model to ICIs [Kaneda M. et al, 2016]; (2) In A20 tumors, on the contrary, the QSP model predicted a 40% to 80% of animals with complete tumour rejection during ICI treatment, which was in excellent agreement with published data. Using the model further we inferred that response to anti CTLA-4 therapy was associated with relatively high T_{reg} numbers at baseline in A20 TME [Pachter A. et al, 2017].

Conclusions: The mechanistic QSP model demonstrated its suitability for predicting tumor size dynamics in response to various ICI treatments in several syngeneic models. In particular, it was shown that one of the key factors influencing the treatment efficacy (or resistance) under PD-L1, CTLA-4, or combination ICI in syngeneic models, is the relative abundance of regulatory T cells and immunosuppressive myeloid cells.

Mechanism of Ndc80 protein and microtubule interaction based on the force spectroscopy data

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The study of cell division and the mechanics of chromosome movement in mitosis is important, because cancerous cell transformations lead to impaired control of cell division. The basis of mitosis is the formation of the mitotic spindle, which ensures the correct segregation of sister chromosomes. In this process chromosomes are associated with microtubules using a range of protein complexes located in a specific region of the chromosome - kinetochore. Ndc80 complex is the most important among these proteins. To understand the nature of the forces that ensure the movement of chromosomes and the dynamics of mitotic spindle, it is extremely important to investigate the dynamics of Ndc80 interaction with a microtubule under the forces. The most informative and modern method to do it is the newly developed method of ultrafast force-clamp spectroscopy of single molecules. In this method, the microtubule is attached between two beads that are captured by laser traps. Molecule of interest attached under the microtubule to the immobilized pedestal. A constant force is applied to the beads, and the microtubule moves over molecule. Interactions of the molecule with the microtubule are observed by changes in beads velocity. Recent work in our laboratory revealed asymmetrical gliding of human Ndc80 subjected to external force depending on the direction of motion. Two hypotheses are proposed for a possible explanation of the observed asymmetry. One suggests that the potential well of the interaction between Ndc80 and the microtubule has a highly asymmetric shape. The second implies the presence of an additional binding site in the Ndc80 molecule capable to bind the microtubule only under the action of a force directed toward the plus end of the microtubule. We developed a mathematical model which allows to check what experimental conclusions can lead each of the hypotheses. Calculations showed that the model with an additional binding site predicts a weak dependence of the microtubule velocity relative to the molecule till forces directed to the plus end of the microtubule. In the model with an asymmetric well this effect is much less significant. We are planning to conduct experiments that will check these predictions and allow us to choose the right molecular mechanism of the process.

Mathematical modeling of bacterial resistance to antibiotics

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Bacterial resistance to antibiotics, which is defined as the ability of bacteria to resist the effects of antibiotics designed to eliminate or control them, is one of the most actually relevant problems. While there are some new antibiotics in development, none of them are expected to be effective against the most dangerous forms of antibiotic-resistant bacteria. In fact, the World Health Organization has named antibiotic resistance as one of the three most important public health threats of the 21st century.

In this work we study the problem using an ODE model, in which we separate bacteria in different kinds of resistance assuming that drug resistance is acquired through mutations and plasmid transmission, we consider a medical treatment with antibiotics of bactericide and bacteriostatic actions. We identify the prevalence and stability conditions for the equilibria points, and then we study the scenario of bifurcations. Here we show our first results of my Ph.D.s project.

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Modeling electrotonic interaction between mechanically active cardiomyocyte and cardiac fibroblasts

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In mammalian heart tissue, fibroblasts are one of the main types of cardiac cells along with cardiomyocytes, but mechanisms of their interaction with the cardiomyocyte and contribution of this interaction to the cardiomyocyte electromechanical activity have not been fully studied [1]. Earlier, several mathematical models have been developed to describe and analyze this interaction, including the MC07 (MacCannell2007) model [2], where the effect of the number of fibroblasts electrically connected with the cardiomyocyte on the electrical function of the latter was studied. However, cardiomyocyte mechanics was not considered in that work. In our work we fill the lack and analyze the fibroblast effect on the electromechanical coupling in the cardiomyocyte. We have earlier developed the TP+M model [3], which combines TP (Ten Tusscher-Panfilov) model with the module of the cardiomyocyte mechanical activity from the Ekaterinburg-Oxford electromechanical model [4]. Now we substituted the original TP model for the TP+M one within the MC07 to assess the effects of the electrotonic interaction of the fibroblasts with the cardiomyocyte on its electromechanical activity. Our simulations displayed additional effect of the fibroblasts-cardiomyocyte electrical interaction on the electrical function of the cardiomyocyte, as compared to the MC07 model (in particular on a decrease in the cardiomyocyte Action Potential Duration (APD)). Moreover, electrotonic interaction with fibroblasts decreased not only APD, but also mechanical activity of the cardiomyocyte, and both decreases became more prominent with the number of the connected fibroblasts. The work was carried out within the framework of the IIF UrB RAS themes No AAAA-A18-118020590031-8, AAAA-A18-118020590134-6 and was supported by the RFBR grants (18-29-13008, 18-01-00059, 18-015-00368) and by RF Government Act #211 of March 16, 2013 (agreement 02.A03.21.0006).

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Coarse-grained computer simulations of primary hemostasis

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Primary platelet adhesion is probably the most responsible stage of arterial and microvascular thrombogenesis. If the hemodynamic flows are quite intensive and near-wall shear stresses are relatively high, the clotting of blood plasma is inhibited, until the platelets are reliably attached to the injury. Numerous mechanisensitive mechanisms and signaling cascades are involved in this process [1]. One of the most important is based on the interaction between platelet membrane receptors with a plasma-bourne protein von Willebrand factor (VWF) [2]. The latter is normally peresent in the form of long concatamers (or multimers) that are sensitive to local hydrodynamics and thus act as a trigger for platelet adhesion [3].

Here we present a 3D coarse-grained computer model of platelet initial adhesion via binding to VWF multimers in a flowing blood. The model explicitly accounts for conformational changes of VWF and the hydrodynamics-induced activation of adhesivity of these protein concatamers to GPIb receptor of blood platelets. We use a combination of the fluctuating Lattice Boltzmann method with the Lagrangian particle dynamics with fluid-to-particle coupling by a viscous Stokes-like force. The model has been tuned and validated against the experimental data and is capable of simulating red blood cells, platelets, VWF multimers and microvesicles in both Poiseuille and Couette flows [4,5]. The simulations suggest that the contour length is an important parameter that controls the functionality of VWF multimers during initial stages of thrombosis.

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A model of chronic inflammation in atherosclerosis

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Atherosclerosis is a chronic progressive disease leading to the formation of atherosclerotic plaques in the walls of arteries, narrowing its lumen (see, for example, [1]). In this work, we present a mathematical model of atherosclerosis development based on a reaction-diffusion system for the concentrations of cells and cytokines of innate immunity. This system describes a chronic inflammatory response in the intima of an artery vessel wall. We begin the analysis of the model with the corresponding kinetic system of fifteen ordinary differential equations. First, the stationary points and their stability for reduced kinetic systems of two, four and seven ODEs are investigated. The relationship of the obtained results is analyzed, and their biological interpretation is given.

The reduced system of two equations

$$\frac{dM}{dt} = \lambda_1 \frac{C + L_{ox}}{k_1 + C + L_{ox}} - d_1 M,$$

$$\frac{dC}{dt} = \lambda_2 \frac{C}{k_2 + C} M - d_2 C$$

is similar to the model considered in [2]. Here M is the density of macrophages, C is concentration of pro-inflammatory agents. The analysis of the model shows that the development of atherosclerosis depends on the concentration L_{ox} of low-density lipoproteins (bad cholesterol). If this concentration is low, then atherosclerosis does not develop. For some intermediate values it can be initiated by some additional factors such as inflammation or injury. Finally, for large concentrations of L_{ox} the disease will necessarily develop. Atherosclerotic plaque spreads in the intima as a reaction-diffusion wave.

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Mathematical modeling: bridging the gap between concept and realization in synthetic biology

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Mathematical modeling plays an important and often indispensable role in synthetic biology because it serves as a crucial link between the concept and realization of a biological circuit. We review mathematical modeling concepts and methodologies as relevant to synthetic biology, including assumptions that underlie a model, types of modeling frameworks (deterministic and stochastic), and the importance of parameter estimation and optimization in modeling. Additionally we expound mathematical techniques used to analyze a model such as sensitivity analysis and bifurcation analysis, which enable the identification of the conditions that cause a synthetic circuit to behave in a desired manner. We also discuss the role of modeling in phenotype analysis such as metabolic and transcription network analysis and point out some available modeling standards and software. Following this, we present three case studies – a metabolic oscillator, a synthetic counter, and a bottom-up gene regulatory network – which have incorporated mathematical modeling as a central component of synthetic circuit design.

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Mathematical modelling in immunology

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The immune system defends its host organism against foreign pathogens and tumor development. Modern experimental techniques for global screening and visualization of immune processes in tissues and organs with the resolution spanning multiple spatial- and temporal scales resulted in the accumulation of Big data on the structural organization and regulatory networks underlying the functioning of the immune system [1-3]. To comprehend the immune system dynamics and gain understanding required for a predictive control of the immune processes, an efficient methodology of formulating high-resolution multi-scale and hybrid mathematical models of hierarchically organized, spatially structured and nonlinearly regulated physical, biochemical and physiological processes has to be developed [4]. We review key aspects of the formulation and numerical implementation of the mathematical models describing the network structure and multi-scale dynamics of the immune responses. Mathematically, the models are built by using various types and classes of equations including ODEs, delay-differential equations, stochastic differential equations, reaction-diffusion equations, cellular Potts models and Markov Chain-based models, continuous or discrete in time and embedded into spatial structures of the lymphatic system. Particular focus is given to the computational geometric modelling of the lymphatics system elements. The mathematical models are developed for applications in studies of infectious diseases in humans and experimental animals. The practical potential of the models is demonstrated by predicting the therapeutic effect of anti-PD-L1 blockade on the viral load and CD4 T cell gain for HIV patients of different disease progression phenotypes.

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Multiscale modelling of platet-fibrin thrombus growth in the flow

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Blood coagulation is a multiscale mechanism that is triggered following the injury of endothelial tissues. In this process, local hemodynamics regulate the type and the organization of the formed thrombus. To investigate this question, we develop a novel multiscale model of thrombus formation in flow. The model uses partial differential equations to describe blood flow and the concentration of clotting factors in the plasma. Platelets are described as discrete spheres that migrate with the flow. They can attach, aggregate, detach, become active, and express procoagulant proteins on their surface. The intracellular regulation of each platelet is simulated using an ordinary differential equation. The immersed boundary method (IBM) is used to capture the flow-platelets interaction, and the fibrin net is treated as a porous medium. After the validation of the model, we use it to describe the formation of white and red thrombi under arterial and venous flows respectively. Then, we describe the main properties of each type and we identify the normal and pathological regimes of arterial and venous thrombus formation.

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Evolutionary adaptation of replicator systems and its application to the problem of treatment cells and bacterial disease

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In this study we examine evolutionary adaptation for fitness landscape and mutation matrix under environment changing in open quasispecies replicator systems. The typical example of that situation takes place when one type of cancer cells or bacteria disease is subjected to regular annihilation. We suppose that one of the principium of evolution based on Fishers theorem on natural selection. Other hypothesis is contained in assumption that the specific time of evolutionary adaptation is slower that the time which described the dynamics of the system up to steady state. Various examples of evolutionary adaptation both fitness landscape and mutation matrix are considered.

Optimal protocol for the mathematical model of the DC and anti-PD-L1 injections effects on a tumor

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The immune system is able to overcome various diseases mainly without additional stimulants. But the immune system fails to overcome cancer for a number of reasons. One of these reasons is that there are programmed death-1 (PD-1) receptors on active T-cells, which bind to the programmed death-ligand 1 (PD-L1), which inhibits the activity of T-cells. An anti-PD-L1(that is injected into the abdominal cavity) treatment allows you to block the path between the receptor PD-1 and its ligand PD-L1. Injections into the blood and tumor of dendritic cells(DC) activate T-cells to create an immune response. The present work is devoted to analyzing a mathematical model that captures the dynamics of the adaptive response to cancer vaccines, finding optimal doses of DC and anti-PD-L1 by using numerical methods and formulation of the optimal control problem.

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Geometry and physics of transport in complex microvascular networks

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Across mammalian species, solute transport takes place in complex microvascular networks. However, despite recent advances in three-dimensional (3D) imaging, there has been poor understanding of geometric and physical factors that determine solute exchange and link the structure and function. Here, we use an example of the human placenta, a vital fetal life-support system, where the primary functional exchange units, terminal villi, contain disordered networks of fetal capillaries and are surrounded externally by maternal blood. We show how the irregular internal structure of a terminal villus determines its exchange capacity for a wide range of solutes. Integrating 3D image-based geometric and transport features into new non-dimensional parameters, we characterise the structure-function relationship of terminal villi via a simple and robust algebraic approximation, revealing transitions between flow- and diffusion-limited transport at vessel and network levels. The developed theory accommodates for nonlinear blood rheology and tissue metabolism and offers an efficient method for multi-scale modelling. Our results show how physical estimates of transport, based on scaling arguments and carefully defined geometric statistics, provide a useful tool for understanding solute exchange in placental and other complex microvascular systems.

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A dynamics on Michealis-Menten kinetics based tumor-immune interactions

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The tumor-immune dynamics is a perennial subject that draws attention from researchers of different background due to the unpredictable growth of tumor [1]. In this respect, mathematical modeling potential insights might benefit us to better understanding. In this talk, we study the dynamics of a 3D tumor-immune interactions system. Local dynamics of the system at biologically feasible equilibrium and the existence of Hopf bifurcation have been studied. Further, chaotic nature have also been investigated by measuring the asymptotic growth of the corresponding time trajectory with parameters of the system [2]. We also performed numerical simulations, which reveals the rich dynamics of the studied system. It is observed that the model shows the periodic oscillations as well as chaotic behavior, which are often indicators of long-term tumor relapse.

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On mechanically driven biological stimulus for bone remodeling as a diffusive phenomenon

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In the past years, many attempts have been made in order to model the process of bone remodeling. This process is complex, as it is governed by not yet completely understood biomechanical coupled phenomena. It is well known that bone tissue is able to self-adapt to different environmental demands of both mechanical and biological origin. The mechanical aspects are related to the functional purpose of the bone tissue, i.e., to provide support to the body and protection for the vitally important organs in response to the external loads. The many biological aspects include the process of oxygen and nutrients supply. To describe the biomechanical process of functional adaptation of bone tissue, the approach commonly adopted is to consider it as a feedback control regulated by the bone cells, namely osteoblasts and osteoclasts. They are responsible for bone synthesis and resorption, respectively, while osteocytes are in charge of sensing the mechanical status of the tissue. Within this framework, in [1] a model based on a system of integro-differential equations was introduced aiming to predict the evolution of the process of remodeling in surgically reconstructed bones. The main idea in the aforementioned model was to introduce a scalar field, describing the biological stimulus regulating the interaction among all kinds of bone cells at a macro-scale. This biological field was assumed to depend locally on certain deformation measures of the (reconstructed) bone tissue. However, biological knowledge suggests that this stimulus, after having been produced, diffuses in bone tissue, so controlling in a complex way its remodeling. This means that the cells which are target of the stimulus may not be located in the same place occupied by the cells producing it. In this paper, we propose a model which intends to explain the diffusive nature of the biological stimulus to encompass the time-dependent and space-time displaced effects involved in bone reconstruction process. Preliminary numerical simulations performed in typical cases are presented. These numerical case studies suggest that the diffusive model of stimulus is promising: we plan to continue these kinds of studies in further investigations.

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Minimizing variance and error itselfin the problem of recovering the n-th derivative

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The problem of reconstruction of the derivative belongs to the general problem of reconstruction operators and is closely related to the Stechkin problem of the best approximation of an unbounded linear operator by linear bounded operators [1]-[5]. The solution of this problem is a topical issue for the organization of modern experimental observations and processing of numerical information obtained in the course of such experiments.

This work was initiated by studies [6]-[8] carried out at the Laboratory of Physical Biochemistry of the Hematological Research Center of the Russian Academy of Medical Sciences: according to the measurement of the luminescence intensity A of the enzyme activating blood clotting introduced into the blood, it is necessary to restore the concentration of thrombin F (coagulation factor). In the simplest mathematical model, the function A is a solution to the diffusion equation, the right side of which is F. The biomedical aspect of the problem requires the representation in a unified metric of guaranteed accuracy of restoration of the function F from the approximate values of function A.

Of interest is also the restoration of the derivative in terms of minimizing the variance of the error.

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Immunotherapy: a paradigm-changing evolution in cancer therapy

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Immunotherapy of cancer consists in mobilizing the patients immune system to destroy cancer cells. The importance of the immune system has long been suspected by the increase of cancer observed in immunosuppressed patients. Several approaches have been used to boost the immune system, including cytokines which activate immune cells and antibodies which recognize tumor cells causing destruction by immune cells. More recently two novel types of immunotherapies of cancer have profoundly modified the therapeutic landscape: immune checkpoint inhibitors and CAR-T cells. Immune checkpoints (IC) are naturally occurring systems which avoid an excessive activation of the immune system, which could lead to auto-immune disease. Cancer cells have been shown in some instances to pervert IC in order to avoid immune detection and destruction. Immune checkpoint inhibitors (ICI) are monoclonal antibodies which block immune checkpoint utilization by cancer cells, thereby allowing an appropriate immune response to cancer cells and their subsequent destruction. Although active in only a minority of cancer patients, ICI have induced durable remissions in otherwise incurable situations such as advanced melanoma, lung cancer, bladder cancer and Hodgkins disease. There are currently several ICI which are approved for therapy and several hundred trials are ongoing to evaluate the role of ICI as single agents and in combination with other cancer therapies. However ICI also induce a significant number of autoimmune processes and their toxicity may be significant in some patient. The second more recent breakthrough is Chimeric Antigen Receptor T cells (CAR-T) which are genetically engineered patient T lymphocytes. These cells are modified ex vivo then reinfused in the patient as a single infusion. They then expand in the patient and specifically recognize and destroy tumor cells. Currently CAR-T cells are limited to certain hematological malignancies such as leukemias and lymphomas but several studies are ongoing in solid tumor indications. Side effects of CAR-T cells may also be significant, inclusing the Cytokine Release Syndrome (CRS) and neurological complications. Overall these antigen-indifferent (ICI) and antigen-specific (CAR-T cells) strategies have brought highly active yet also potentially toxic therapies to the anticancer pharmacopeia. Additional studies are required to better determine which patients will benefit most from these novel therapies.

Modeling of hand-arm vibration syndrome occurrence

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The problem of hand-arm vibration syndrome (HAVS) is relevant in all industrialized countries, in the Russian Federation its share is over 30% of all newly identified cases of occupational diseases [1]. At the same time, there are very few works concerning mathematical modeling of HAVS occurrence [2]. The model based on the method of normalizing intensive indicators (NIP) made it possible not only to calculate the risk of HAVS in persons in contact with local vibration (LV), but also to evaluate the complex effect of adverse factors, and to predict the likelihood of HAVS at the collective and individual level for the organization of preventive measures. In calculation of the risk of HAVS according to the NIP, a range of possible risk values was determined by a set of influencing factors (work experience in contact with the LV, age).The maximum risk was determined for workers over 40 years old, with a total experience of local vibration exceeding 10 years, of which 8 years or more in the Far North.

Analysis of regression models, where the experience dose of vibration (EDV) was the influencing factor, and indicators of neurohumoral and immune systems were the resulting variables, showed that dose-effective dependence is subject to both HAVS-specific indicators of the cardiovascular system (pain, vibration, tactile sensitivity) and nonspecific indicators of neurohumoral and immune systems, which proves the presence of disadaptative processes. Analysis of the behavior of the regression functions in response to the increase in EDV revealed differences of responses in healthy workers exposed to LV and of patients with HAVS associated with the presence of a significant misalignment hypothalamo-pituitary-adrenal system. The estimation of regression dependences allows to reveal those changes in an organism which are not always revealed at the analysis of group averaged indicators.

The contribution of EDV to the occurrence of HAVS was determined by comparing the values of unconditional and conditional entropy, the difference between which gave an assessment of the level of dependence of HAVS occurrence on the influencing factor. Development of variants of information-entropy model and their verification were carried out with the participation of doctor of technical Sciences V. I. Zorkaltsev. Model calculations showed that with the growth of EDV, pathological parameters of the main activity of the brain and thyroid system contributed the most to the formation of HAVS (82.6%). Information-entropy model makes it possible to analyze the parameters of the functional systems of the body that respond to the impact of LV, which will further rationalize the diagnostic process.

Studies on these models have shown the possibility of their successful use in occupational medicine, while it was found that the connection of specific clinical and functional indicators specific for this pathology in the formation of an individual model of occurrence of HAVS will increase their adequacy, accuracy and sensitivity.

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Prediction of the structure property correlation for chelated zinc compounds and some Cannabis-derived cannabinoids

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The method of quantitative structure-activity relationships (QSAR) is widely used for the searching of new biologically active molecules. A retrospective look at the existing drugs with the use of QSAR method can reveal the hidden relationship between the properties and structure of the compounds and can be useful for the development of new molecules. In this research we have investigated the relationship between the Balaban index, which reflects the structure of compounds, and biopharmaceutical characteristics of the substances recommended by WHO for the treatment of tuberculosis. A large number of experimental data on the antitubercular (anti-TB) activity of zinc served as the basis for the study of its chelated compounds and evaluation of their properties as promising antitubercular drugs. The most common Cannabis-derived cannabinoids have also been reviewed.

The purpose of the study was to predict the biological activity of different compounds using the Balaban index. To identify the "Balaban index lipophilicity" correlation anti-TB drugs of such pharmacological groups as the derivatives of isonicotinic acid (Isoniazid, Pyrazinamide, Cycloserine, Para-aminosalicylic acid) and fluoroquinolones (Ofloxacin, Moxifloxacin, Gatifloxacin) were taken. The topological graphs of the compounds were constructed using "ChemicPen" software product. To calculate the Balaban index J the saved files were exported to the "Chemical descript" software. The values of lipophilicity (logP) for selected compounds were found in databases Pubchem, Toxnet (National Institutes of Health, USA) and Drugbank (Canadian Institutes of Health Research, Canada). Further, the "Balaban index property of the substance" dependence was graphically represented using the "Origin" software (OriginLab, USA). Selected anti-TB drugs, as well as a number of biogenic amino acids (glycine, valine, phenylalanine, alanine, methionine, leucine), were used to build chelated complexes with zinc. The values of Balaban index for these compounds were calculated manually, the lipophilicity was predicted with the online service https://www.molinspiration.com/ (Molinspiration Cheminformatics, Slovakia).

For the fluoroquinolones, an inverse relationship, characterized by a decrease of lipophilicity with an increase of the Balaban index ($r = -0.75$), was found. After the introduction of the zinc cation into the fluoroquinolones molecules, both the lipophilicity and the Balaban Index decreased, the reverse relationship is preserved ($r = -0.72$), the zinc-moxifloxacin complex has the highest lipophilicity. In the group of derivatives of isonicotinic acid with an increase in the Balaban index, lipophilicity increases ($r = 0.80$), though after the introduction of zinc, an inverse relationship is

observed ($r = -0.82$), the pyrazinamide complex has the greatest lipophilicity value. In the case of zinc-amino acid compounds ($r = -0.93$), the highest lipophilicity (at pH= 7) is observed for the zinc-phenylalanine complex, which can be considered as a competitor to the zinc-glycinate complex.

For the cannabinoids, the topological graphs were constructed and the Balaban index was calculated. The values of logP, TPSA (Topological Polar Surface Area) and pKa were found. To predict the biological activity, the "Balaban index property" dependences were also graphically represented.

The results indicate a correlation between the molecular descriptor (Balaban index) and the biopharmaceutical characteristics of selected drugs. The modification of pharmacokinetic parameters of anti-TB compounds after the introduction of the zinc cation into their structure was shown, so this potentially allows us to consider the obtained chelated compounds as an alternative to already known anti-TB drugs.

The electron-transport protein-protein complex formation of plastocyanin and cytochrome *f* of higher plants, green alga and cyanobacteria

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The interaction of proteins is an inalienable stage of most processes in the cell. Mobile proteins interact with their redox partners, transferring electrons in electron transport chains. These interactions give rise to many events occurring in a living cell at various spatial and time scales: from the redistribution of electron density on atoms in a molecule (times of the order of femtoseconds and the distance of an angstrom), the movement of atoms in a molecule (picoseconds and nanometers), to the diffusion of proteins in cell (microseconds and micrometers). The combined approach of Brownian and molecular dynamics and hierarchical cluster analysis was used to investigate the mechanisms of plastocyanin and cytochrome *f* complex formation in higher plants (*Spinacia oleracea* and *Brassica rapa*), green microalgae *Chlamydomonas reinhardtii*, and two types of cyanobacteria (*Phormidium laminosum* and *Nostoc* sp.). In higher plants and green algae, electrostatic interactions hold the plastocyanin molecule near the heme of cytochrome *f*. We have shown that, despite the structural similarity of the studied electron-transport proteins in different photosynthetic organisms, the complexity of the molecular mechanisms of complex formation increases in the following sequence: vegetative cells and cyanobacterial akineta – cyanobacterial heterocyst – green algae – flowering plants [1].

The research is carried out using the equipment of the shared research facilities of HPC computing resources at Lomonosov Moscow State University. This work was supported by RFBR grants No. 17-04-00676, 18-07-01219 and 19-04-00999.

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Some mathematical models of HIV infection treatment strategies

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About twenty years ago (1996-1997), the era of highly active antiretroviral therapy (HAART) began in the history of HIV infection. The introduction of treatment based on the use of a combination of antiviral drugs, has led to a significant improvement in the quality of life of patients and has caused a clear decrease in AIDS-related diseases and mortality.

In the paper short overview of some mathematical models is presented. The models can be used for: development of personalized therapy that takes into account individual characteristics of a patient; development of complex combinatorial treatment schemes, studies of the joint action of drugs; assessing the toxicity of applied drugs for the patient; development and research of new treatment strategies.

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Multiscale Modelling of Mosquito-Borne Infections

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Mosquitoes cause more infectious diseases than any other vector. Mosquito-borne diseases include malaria, dengue, West Nile virus, chikungunya, yellow fever, filariasis, tularemia, dirofilariasis, Japanese encephalitis, Saint Louis encephalitis, Western equine encephalitis, Eastern equine encephalitis, Venezuelan equine encephalitis, Ross River fever, Barmah Forest fever, La Crosse encephalitis, and Zika fever, as well as newly detected Keystone virus and Rift Valley fever. In this presentation, I will discuss a new method for development of multiscale models of mosquito-borne diseases at host-level. The multiscale modelling method for mosquito-borne diseases in this presentation is an extension of our previous works on multiscale models of infectious diseases systems [1,2] which established a basic science and accompanying theory of how pathogen population dynamics at within-host scale scales up to between-host scale and in turn how it scales down from between-host scale to within-host scale. A specific example, malaria, will be discussed to show the utility of method.

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Multiscale model of HIV transmission in lymphoid tissues

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Human Immunodeficiency Virus (HIV) infection represents a complex set of processes regulated at multiple scales: by intracellular HIV replication and antiviral signaling, by spatial dynamics of immune cells' locomotion and of extracellular distributions of virions and signaling molecules in lymphoid tissues (LT), and at systemic level mediated by blood and lymph circulation. Thus the development of multiscale models which integrate descriptions of processes at the mentioned levels is needed for proper analysis of HIV infection [1].

The core module of the multiscale model is the model of T cell motility. It is important to reproduce the actual patterns of T cell locomotion in LT because cells act as moving sources in right-hand side of reaction-diffusion equations describing the extracellular fields of virions and molecules. Such model, which is based on second Newton's law equation, was developed and calibrated in [2]. The model was used to determine the numbers of HIV-specific cytotoxic T cells needed to locate infected cells before they start to secrete virions.

HIV infection propagates in LT using two mechanisms: cell-to-cell transmission and infection by extracellular virions secreted by infected cells. Both mechanisms are accounted in the multiscale model as stochastic processes, with their rates depending on local numbers of free virions and infected cells. For each infected cell, intracellular HIV replication and antiviral interferon response is modelled using a hybrid algorithm following [3], which couples discrete stochastic and continuous deterministic descriptions. The model is used to study the local dynamics of HIV transmission in LT at various immunophysiological conditions.

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Analysis of a multiple strain virus infection with within host mutations

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We consider a population level model of a multiple strain infection disease propagation taking into account the within-host mutations as well as a number of variations of the considered baseline model. Our research is primarily motivated by the practical need of modeling HIV infection while taking into account the inherent variability of the virus [1,2].

We analyze the structural properties of the model and present a number of results aimed at facilitating parameter identification and validation of the model. In particular, we characterize and analyze the behavior of the basic reproduction number R_0 under different assumptions about the model structure: differentially effective controls, variable contagiousness and the action of prophylaxis.

Furthermore, we show that the endemic equilibrium state depends in a non-trivial way on the structure matrix, describing the probabilities of within-host mutations. We conclude by presenting a sensitivity analysis along the lines described in [3] and making a number of suggestions aimed at improving the intervention strategies design for combating the disease.

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Molecular dynamics modeling of tubulin protofilaments

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Tubulins are essential, and they are some of the most abundant proteins in eukaryotic cells. In living cells and in vitro, tubulin heterodimers bound to guanosine triphosphate (GTP) self-assemble into microtubules, which represent hollow cylindrical structures, usually made of 13 parallel strands, or protofilaments. After incorporation into the microtubule lattice at the ends of protofilaments, GTP molecules experience hydrolysis, so the majority of tubulins in microtubule lattice, except for a few terminal layers, transform to guanosine diphosphate (GDP) form. It is not currently understood why, but GDP-tubulin lattice turns out to be less stable than GTP-tubulin lattice. Therefore, when a critical number or density of GTP-tubulins is lost from the microtubule tip, remaining GDP-tubulin lattice depolymerizes by losing tubulin oligomers from the disassembling end. Recent cryo electron microscopy reconstructions of microtubules in the GDP-state and GTP-like state (in presence of a slowly hydrolyzing GTP analog, GMPCPP), have provided the first inhibitor-free structures of tubulins and confirmed an older underappreciated finding that tubulin dimers experience a small but highly reproducible longitudinal compaction upon GTP hydrolysis. The mechanistic role of this inter-dimer compaction and its relevance to microtubule dynamics has remained elusive. Here we have carried out several microseconds of all-atom explicit solvent molecular dynamics simulations of tubulin oligomers to investigate effects of nucleotide phosphorylation state on tubulin mechanics. We found that initially straight tubulin tetramers relax to very similar non-radially curved conformations independent of the nucleotide. Strikingly, GTP hydrolysis dramatically affected the flexibility of the inter-dimer interface without a strong impact on the shape or flexibility of tubulin dimers. Inter-dimer interfaces in presence of GTP were significantly more flexible compared to intra-dimer interfaces. We argue that such a difference in flexibility could be a key for distinct stability of opposite microtubule ends. Overall, our data support a model, in which extended interface between GTP-tubulin dimers is softer, compared to that between compacted GDP-tubulin dimers. Hence, GTP-tubulin protofilaments are less energetically costly to straighten and incorporate into microtubule lattice, at least partially accounting for the mechanism of microtubule dynamic instability. This work was carried out using the equipment of the shared research facilities of the high-performance computational resources at Lomonosov Moscow State University, supported by the grant from the Russian Science Foundation, project No. 17-74-20152.

Mathematical modelling and simulation for improved diagnosis and therapy of sepsis

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Sepsis is defined as a life-threatening multiple organ dysfunction caused by an inadequate host response to an infection, a disease that can lead to an irreversible collapse of the entire organ system. Every 5 seconds a person dies of sepsis. The global death toll in sepsis is estimated between six and nine million per year. This disease has become a serious threat and is currently one of the biggest medical challenges.

According to experts, many of these deaths are avoidable, if it is possible to detect the disease earlier, to better understand the possible causes and processes of sepsis, and to develop methods of prevention and therapy. To overcome the challenges of sepsis as a disease of the whole system leading to a multiple organ dysfunction, quantitative concepts and methods are in demand. In a joint project Scientific Computing for the Improved Diagnosis and Therapy of Sepsis (SCIDATOS) with scientists from Intensive Care at the University Hospital Mannheim and IWR we pursue the following goals:

- mathematical modelling and simulation of the essential biophysical, biochemical and physiological processes, ranging from the cellular level to the system of the organs,
- determination and analysis of the required experimental and clinical data,
- development and implementation of tools for efficient diagnosis and treatment strategies.

Inflammation, the reaction of the immune system to an attack (in case of sepsis by infections) and arising dysfunctions are in the focus of the investigation. The pro-inflammatory and anti-inflammatory processes and the influences on the local and global situation of the organism have to be analyzed, taking into account that substances may change the pro- and anti-role during the process.

In this lecture we give a survey about the results we obtained so far on the initiation phase of inflammation, considering processes in arteries, in particular the change of permeabilities of the endothelial layer and the structures of the vessel walls, influencing e.g. the flow and transport through the vessel system and the tissues. Regardless of their importance for the necessary basic understanding of the dynamics of sepsis, new purely analytical and numerical questions arise for mathematics, which so far rarely were studied in fluid-structure interaction.

Due to the collateral damage, caused in the defense, stopping inflammation is a necessary phase of the disease treatment. Analyzing immune suppression is a highly important topic. We concentrated at first on the mathematical modelling of biochemical and biophysical processes connected

with hypoxia, the lack of oxygen, that has immediately consequences to the energy supply in the system, leading to a chain of changes in the cells, their microenvironments, in tissues and subsystems, finally on the network of the organs. We also present a summary on the results we obtained modelling and simulating respiration processes and the supply of the system with ATP, the main energy resource.

SCIDATOS is funded by Klaus Tschira Foundation. The report is based in particular on joint research with I. Yang (Mathematics, Heidelberg), M. Gahn (Mathematics, Heidelberg), M. Neuss-Radu (Mathematics, Erlangen), J. Knoch (Integrated Life Sciences, Erlangen), Th. Richter (Numerical Mathematics, Magdeburg), T. Silva-Fortes (Mathematics, Praia (Cape Verde) /Lisbon), A. Sequeira (Numerical Mathematics, Lisbon), G. Bocharov (Mathematical Immunology, Moscow), M. Thiel (Intensive Care, Heidelberg).

Development of interface for the QM/MM calculations

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Combined quantum mechanics / molecular mechanics (QM/MM) methods are utilized to describe the chemically active part of the molecular system with the quantum chemical methods taking into account the influence of the external environment on its properties [1].

Recently, an interface for QM/MM calculations has been developed within the framework of the molecular dynamic package NAMD 2.12 [2]. We introduce a shell for the joint application of the NAMD 2.12 and the quantum mechanical package Firefly 8.2.0 [3].

The model composed of a 4,5-dimethyl-2-(2-hydroxyphenyl) imidazole chromophore in a water solution was used as a test system. The simulations were carried out within the QM/MM MD method using NPT ensemble, periodic boundary conditions and CGenFF [4] and TIP3P [5] force field parameters. The QM subsystem was composed of an organic chromophore and a dynamic set of water molecules within 5 Å of the chromophore; it was treated at DFT/B3LYP/6-31G** [6,7] level. The rest of water molecules were in the MM subsystem.

The research is carried out using the equipment of the shared research facilities of HPC computing resources at Lomonosov Moscow State University with the financial support of the Russian Foundation for Basic Research (project 18-03-00605).

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Polarization of concave domains by traveling wave pinning

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Pattern formation is one of the most fundamental phenomenon in physics and biology. In the paper we propose a new mechanism of generation of stable stationary non-constant solutions to reaction-diffusion systems. This mechanism consists in traveling fronts pinning on concave portions of the boundary of 3-dimensional domains. Such a scheme of domain polarization arises even for scalar bistable reaction-diffusion equations, and, depending on geometry, a number of stationary fronts may be formed leading to complex spatial patterns. The main advantage of the pinning mechanism, with respect to the Turing bifurcation, is that it allows for maintaining gradients in the specific regions of the domain. By linking the instant domain shape with the spatial pattern, the mechanism can be responsible for cellular polarization and differentiation.

Model of ligand-receptor adhesion for microparticles and ellipsoidal cells

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Platelets play a key role in arterial and microvascular hemostasis. To study the functions of platelets, various models are built that allow the selection of the most significant parameters regulating the formation of blood clots, occlusion of blood vessels [1,2]. This study examines ellipsoid cells which interact with the substrate surface through the formation of ligand-receptor bonds. The movement of a platelet at a constant speed, directed perpendicular to the surface, and under the action of a constant force, also directed perpendicularly to the surface, is considered. These two regimes can be realised in experiments [3]. The effect of platelet shape is investigated. In the case of the constant force setup, the threshold disjointing force was calculated for different values of the parameters. We determine two possible states: the separation of a platelet from the wall and its retention at the surface. This study was supported by Russian Foundation for Basic Research (grants 19-02-00480-a, 19-31-70002-mol-a-mos).

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Automated fast ECG modeling approach

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Mathematical modeling is an increasingly popular method for studying the function of the heart. Numerous computational models of electrical function have been developed over the years to understand better function of the heart in normal and pathology with the ultimate goal of assisting personalized diagnostics and treatment. The main problem of the models is a large number of input parameters and high computational cost, which complicates the use of such models in practice. The aim of this work is to develop algorithms and methods for using mathematical models together with machine learning methods for automatization of mathematical modeling of the electrical function of the heart and increase the availability of mathematical modeling.

To solve this problem, we developed a software where all stages were fully automated. The data processing pipeline has following stages:

1. Fully automated segmentation of CT and MRI images and the construction of personalized geometries of the heart, lungs, torso.

2. Construction of a finite element model of a torso containing lungs and heart with assigned field of myocardial fibers.

3. Solving the eikonal equation in the heart, finding local activation times at nodes of heart geometry.

4. Setting the action potential value at points of the heart depending on the activation time to obtain the dynamics of the propagation of an electric wave in the heart.

5. Finding extracellular potential of the heart, calculation of 12 lead ECG.

Using this approach, one can significantly save time for searching for personalized parameters in a mathematical model. We conducted a preliminary study of the sensitivity of the model to changes in the parameters of local and global conductivity, the location of the infarct on the ECG signal. In addition, the developed approach does not require a large amount of resources for solving problems.

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Population Modeling Approach to Study Age-Related Effects on the Excitation-Contraction Coupling in Human Cardiomyocytes

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Aging is the dominant risk factor for cardiovascular diseases. Very few experimental data is available on the age-related changes in the the human cardiomyocytes. Mathematical models can be used as a valuable tool for predicting adverse consequences of the age-related changes in the myocardial function.

Methods. In this study, we used our combined electromechanical model (TNNP+M) of the human cardiomyocyte and a population modeling approach to investigate the variability in the response of cardiomyocytes to age-related changes in the parameters of the molecular and cellular mechanisms of excitation-contraction coupling (ECC). To generate a model population, we used a set of 9 parameters (the conductivities of 6 ion channels, the maximal velocity of the NKX and NCaX exchangers, and SERCA pump). We randomly generated 20,000 parameter sets using the Latin hypercube sampling with each parameter ranged from 0 to 200% of a referent value (200 cycles at a pacing rate of 1 Hz for each model sample). Then, based on experimental data, we excluded model samples with biomarkers falling outside the physiological ranges and used the normal population consisted of 1028 samples of virtual cardiomyocytes. To estimate variability in the response to age-related parameter modulation in the model population, we have evaluated electrophysiological response to age-related changes in 4 model parameters reported in literature: a reduction in the density of the potassium transient outward current (g_to), maximal velocity of SERCA (Vmax), and an increase in the density of NaCa current (K_NaCa) and CaL current (g_CaL).

Results. First, we assessed sensitivity of action potential biomarkers (e.g. action potential duration (APD)) to individual parameter variation (by 20, 50, 70%) in every model of the control population. Each parameter modulation we tested caused an increase in APD in every model, while sensitivities to the changes in g_CaL and Vmax were much higher than effects of g_to and K_NaCa changes. Then we randomly generated 60 age-related sets of the 4 parameters using normal distributions for parameter deviation from reference value with 25% mean and 10% SD and applied each set of the aging parameters to every model in the control population (so we analyzed 60 aged sub-populations each consisted of 1028 models). We calculated a fraction of model samples with repolarisation anomalies (EAD, DAD) in the aged model sub-population as an arrhythmogenic score of the aging. A linear dependence of the arrhythmogenic score on the deviation of the parameter vector from the reference values showed a high determination coefficient (0.986) with the most significant impact of the age-related change in the CaL current. The population based approach allowed us to characterize a sub-population of control models with high risk (more than 50%) of age-related repolarization abnormalities. Specific features of the ionic mechanisms in the sub-population were shown to be up-regulated g_CaL, g_K1, g_Na, g_Kr and down-regulated Vmax and K_NaCa as compared to the whole control population.

Conclusions. Age-related changes in the cellular ionic currents may lead to an arrhythmogenic increase in APD and the emergence of EAD in human cardiomyocytes. The population based analysis allowed us to classify age-related effects by different ECC mechanisms. An increase in the CaL current and a decrease in the SERCA flow were shown to be the significant factors of age-related cellular remodeling increasing risk of arrhythmogenic abnormalities in elderly.

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Interactions between cationic antiseptics and model bacterial plasma membrane by coarse-grained molecular dynamics

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Antiseptics are antimicrobial compounds used in a clinical setting. Positively charged cationic antiseptics bind strongly to the cell walls and membranes of bacteria because of their opposite negative charge. The plasma cell membrane of a bacterial cell is supposed to be the main target of antiseptic action [1].

We created molecular dynamics coarse-grained models of four cationic antiseptics: miramistin, chlorhexidine, octenidine, picloxydine and carried out molecular dynamics simulations during one microsecond for each model. It was found that at the concentrations used in medical preparations (0.05-0.15%), chlorhexidine and picloxydine exist in water solution in monomeric form, while miramistin and octenidine form micelle-like aggregates at concentrations three times higher.

The model plasma membrane consisted of 180 POPE and 60 POPG molecules. To study the molecular mechanism of action of antiseptics at different concentrations, we designed molecular models of membrane with antiseptic molecules, with antiseptic to lipid ratio of 1/24, 1/8 and 1/4. The systems with 1/24, 1/8 antiseptic/lipid ratio were simulated for 3 microseconds, the system with 1/4 antiseptic/lipid ratio was simulated for 30 microseconds. The area per lipid, the density profiles, order parameters, and bilayer thickness were calculated for all systems. It was shown that cationic antiseptic molecules effectively penetrate into the bacterial plasma membrane, and their positively charged beads are located in the region of phosphate residues, while the terminal beads of the antiseptics molecules are located in the area of lipid fatty acids. It was demonstrated that octenidine has the most pronounced disintegrating effect on the bacterial plasma membrane by the significant change in the area of lipid and bilayer thickness.

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Computation of steady states of virus infection models

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Many virus infections, such as infections caused by hepatitis and immunodeficiency viruses, are among the most dangerous infections for humans. Mathematical models with time delays are widely used to analyze the mechanisms of the virus infections dynamics [1,2]. These models are usually calibrated according to acute forms of the virus infections dynamics. At the same time, they can also be used to study chronic forms that are more difficult to treat. However, this potential of the models has not yet been practically realized, which, in particular, is due to the fact that finding all possible steady states of a given model that correspond to chronic forms turned out to be a nontrivial problem, and until recently, algorithms for solving of it were not known.

This report is devoted to the technology of guaranteed computation of all steady states of a given virus infection model with fixed values of the model parameters and analysis of their stability proposed in [3,4]. As example, we consider the model of the disease dynamics caused by lymphocytic choriomeningitis virus and the Marchuk-Petrov model of antiviral immune response. These models have the following structural elements: the logistic description of virus growth, Lotka-Volterra type of virus-immune system interaction with a bell-shaped functional response, confined exponential equation for immune cell homeostasis, and time delay of immune reaction. The proposed technology is particularly designed for virus infection models with such properties; it features guaranteed computation of all steady states in the considered region of parameters and applies an algebraic approach for the analysis of their stability. When studying stability, the leading eigenvalues of the corresponding nonlinear eigenproblem are not traced along the model parameters but are computed for each new parameter value by solving the complete eigenvalue problem for a rational approximation of the original nonlinear matrix pencil and refining the computed approximate leading eigenvalues by a local method. This ensures that the eigenvalue with the maximum real part is always correctly computed.

It should be noted that currently there are numerical software packages DDEBIFTOOL [5, 6], knut (formerly PDDE-CONT) [7] and TRACE-DDE [8], which implement various methods for steady states computation and their stability analysis for time delay systems of more general forms than models of virus infections (e.g., systems with state-dependent delays). The first package is designed for bifurcation analysis of time delay systems. It allows one to obtain the continuation of steady states along parameters starting from specified initial steady state solution. However, the problem of guaranteed computation of all steady states is not considered. The eigenproblems are

solved by the subspace iteration based on solving the initial value problems for the corresponding linearized equations. The second package is designed for analysis of periodic solutions. Steady states are treated as constant periodic solutions. The third package is not designed for searching or tracing of steady states. It allows one to find the stability regions of a given steady state by two variable parameters. To solve the eigenvalue problems, an approximation of the infinitesimal generator for the linearized equations by the collocation method on the Chebyshev grid is used.

We do not exclude that on the basis of the methods cited above, it is possible to develop another technology that also automatically (without handwork) computes all stationary states of viral infection models with delay, as functions of model parameters, and investigate their stability, but today the only technology that solves the above problem is the technology which we propose in this report.

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Optimal disturbances of steady states of viral infection models

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Nowadays systems of delay differential equations are widely used to describe the dynamics of viral infections and the antiviral immune response [1,2]. Usually, there are several possible variants of the dynamics of viral diseases, including those with large and small viral loads. The first case corresponds to a chronic disease with a low level of immune response, and the second corresponds to the state of a recovered organism with immune memory, which is maintained by low-intensity antigenic stimulation. These alternatives of the disease development are reflected in the bistability [3] of the corresponding model, that is, in the existence of at least two stable steady states with the same parameter values. For bistable systems, the calculation of multicomponent actions that cause maximum response and transfer the system from a state with a high viral load into a state with a low viral load is relevant.

This talk is devoted to an original approach to the calculation of multicomponent actions that cause the maximum response of a given bistable system and transfer it from a state with a high viral load to a state with a low viral load. It is proposed to calculate these actions based on optimal disturbances.

The concept of optimal disturbances is widely used in aerodynamics to describe the mechanism of the subcritical laminar-turbulent transition. For dynamic delay systems the concept of optimal disturbances were first determined and used in [4,5,6]. In these works a fairly simple algorithm for optimal disturbances calculation was proposed and justified. It is based on the reduction of the original problem to the computation of matrix products. This algorithm is effective for low-dimensional delay systems that do not require too fine grid for integration over time (as compared to delays). In [7] algorithms for efficient optimal disturbances computation for high-dimensional delay systems that require a sufficiently fine grid for integration over time were proposed and justified. These algorithms are modifications of algorithms for optimal disturbances calculation for systems without delays proposed in [8].

The talk briefly describes and compares the mentioned algorithms for optimal disturbances calculation for delay systems. The model of dynamics of the lymphocytic choriomeningitis viral infection and the Marchuk-Petrov model of the antiviral immune response are considered as examples. Both these models have the property of bistability with certain parameter values.

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Variation of heart rate intervals (R-R) as stochastic process. Analysis of mechanisms for sinus arrhythmia

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Observed variations of R-R are treated as a influence of regulation factors on cells of atrium node, thus sinus arrhythmia, SA. The target of a regulation is the number of functioning ion-channels during different phase of R-R interval. However, direct observation of time series of R-R and their Fourier transform make plausible hypothesis: time series of R-R is a stochastic process.

Aim: (a) To investigate stochastic approach to the data of ECG, (b) To propose one number as a characteristic of SA, (c) To develop criteria for an appearance of breathing or/and myogenic influence on SA.

Method. Math model for R-R variations becomes stochastic if Ca-channels change (or preserve) their state for unit of time with some probability. Depolarization time being significant factor for R-R interval, is proportional to the number of closed Ca-channels.

Results. Treatment of 10 min segments of R-R series (= 4000) reveals that 60% of treated segments are in agreement with simple stochastic description. There are three causes not to be simple: (1) No stability in time series segment 7%; (2) Appearing significant breathing influence 20%; (3) Appearing significant frequencies around 0.08Hz 15%.

Conclusion: (a) R-R variation can be explained by stochastic origin of signals due to the variation of number of open ion-channels; (b) Simple stochastic explanation works in 60% of all cases, it compromised by influence of breathing (20%), Meier waves (15%) and no stable recording (7%).

Microcirculations influence on oxygen delivery

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Introduction. There are two factors that influence oxygen delivery to a tissue: (1) A distribution of red blood cells (RBC) between systemic and micro circulation characterized by cell factor $Fc = Htb/Ht1$. Thus Fc is a factor for delivery O2 by a variation of Hta; (2) Blood flow (Q) throughout a tissue depends on a fraction of open microvessels, fo. The same time there is a migration of openness throughout a tissue, thus the rate of exchange of open-close for microvessels, R, is the factor for O2 delivery. Aim of the paper is to back given statements and to present methods to measure Fc and R.

Method 1. In experiments with blood withdraw a perivascular probe (Transonic Sys Inc., Ithaca, NY) was placed on tube, filled with 0.9 NaCl solution. Changes of blood density was recorded after injection of 0.9% NaCl, and also after blood lost. Analysis of the changes in the blood density at these manipulations allows us to estimate Fc.

Method 2. Calculation of R. Using LDF-flowmeter (LAKK-M, Lasma, Moscow) we received LDF-gramms. It is established that LDF reading is proportional blood flow under probe. Thus, variations of flow, according to Krogh, are proportional to the number of open microvessels. We accept the stochastic scheme of variation of number of open microvessel and using that scheme we can obtain the rate of exchange of open-close for microvessels (rate of vasomotion) form LDF curve.

Results. The propagation speed of erythrocytes in the microvascular blood flow compared to this in the blood plasma specifies Fc. If the speed is high then the majority of erythrocytes are in the systemic circulation, and Fc is low. At high Fc erythrocytes are mostly in the microvascular blood flow. Low R means that the same microvessels are perfused. High R means even perfusion of tissue. Experiments reveal that Fc could be from 0.65 to 1.0, and R varies from 0.02 to 2.0 which lead to up to 3 times increasing of O2 delivery.

Two factors: Cell factor and rate of vasomotion, that characterized microcirculation, and methods of their calculation were presented.

Optimization of radiotherapy fractionalization for improvement of efficiency of combined anti-tumor therapy by means of mathematical modeling

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Despite the significant successes of molecular medicine, the search for drugs that can completely cure cancer has not yet yielded significant results. In this regard, the strategy of transferring cancer from the acute phase to the chronic one, with an increase in the duration and quality of life of patients, is of vast importance in oncology. The promising aspect of this strategy is the search for combinations of existing types of therapy with high integrated antitumor efficacy as the result of their successful combination. Many recent preclinical and clinical studies have focused on combining one of the standard treatment methods, radiotherapy (RT), with the relatively new one, anti-angiogenic therapy (AAT), aimed at inhibition of angiogenesis, i.e., the formation of new blood vessels that feed the tumor.

Interest in this combination is mainly due to the fact that AAT often causes a temporary increase in the concentration of oxygen in the tumor (i.e., alleviation of intratumor hypoxia), which increases the efficiency of subsequent irradiation of the tumor, since oxygen is a key radiosensitizer [1]. The key reason for this effect is considered to be the normalization of the structure of tumor microvessels caused by AAT, which leads to an increase in tumor perfusion and, consequently, to an increase in the oxygen inflow to it [2]. However, due to the temporary nature of this phenomenon, its manifestation does not guarantee that the addition of AAT will improve the overall effectiveness of the fractionated RT. Moreover, the final result and the primary goal of AAT is to deprive the tumor of nutrients, which means exacerbation of hypoxia in the long term. In this regard, it is not surprising that preclinical and clinical studies demonstrate ambiguous results regarding the effectiveness of such combined treatment [3,4]. Moreover, in the currently available studies, exclusively classical fractionation options for radiotherapy are considered, in which the daily dose of radiation is kept constant throughout the course.

We present a spatially-distributed mathematical model of tumor growth under combined RT and AAT. The key properties of this model are the account of characteristics of capillaries formed in result of tumor angiogenesis, and simultaneous consideration of two main nutrients, oxygen and glucose. We introduce an optimization algorithm, developed to search for the most effective RT fractionation scheme for a given set of tumor parameters and for a given total radiation dose. We propose qualitative recommendations for modification of RT fractionation schemes, based, in particular, on the optimal use of the effect of alleviation of intratumor hypoxia, which in clinical practice can increase the effectiveness of combined RT and AAT.

The study has been prepared with the support of the RUDN University Program 5-100.

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Method of virtual information modeling of living system

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The report is the evolved original method of biological information system (BIS) that allows describing a human organism with any degree of accuracy that is available at the moment. The virtual information n-dimentional system of organism is being developed. Virtual information modeling of biological objects, which is based on the original multidimensional numerical model of the organism, is a grouping of information points in a confined space of the object under study. Each dot of the geometric model consists of the set of the numerical indexes, each of these points carries a set of logical and numerical information characterizing a specific anatomical area. These numerical indexes reflect the definite anatomic and physiologic areas. There are mutual relations between points that affect their properties. The basis for creating a model is presented by two-dimensional layered electronic images of the object in the form of bitmaps. These images are translated into a spreadsheet, which becomes a model the basis of an electronic database accessed by computer programs solving problems of modeling the structure and simulation in the computer version of the functions of the body or its individual parts. The result of modeling, according to the above principles, is a point multidimensional information-simulation model. Thus scientific significance of BIS is connected with the development of a universal approach to creating a unified virtual information model (VIM) for prospective research of radiology medicine and biology. The application of virtual information modeling in medicine computer diagnostic and clinical radiology practice gives encouraging results. The study presents the principles of creating electrodynamic model of the heart, modeling the spread of electrical excitation in the body. It is shown that the concept of VIM being applied to the creation of computer training simulators of the heart can be successfully used in clinical arrhythmology. Viewed from the perspective of mathematical morphology theory, the technology of virtual information modeling of physiological and pathological processes in human body was developed on the basis of pattern recognition. A virtual information model of a bio-medical object is a system created as a result of a computer modeling, reflecting the form, internal structure and basic functions of objects of living nature.

Comparison of the conformational mobility of GTP- and GDP-bound tubulin using the molecular dynamics method

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The α- and β-tubulin molecules form heterodimers, which build up microtubules - the main component of the cytoskeleton of eukaryotes. In addition to maintaining cell shape, microtubules perform many other functions, such as forming a system of pathways for intracellular transport and moving chromosomes during cell division. The possibility of such multifunctionality provides a phenomenon known as dynamic instability: instead of being in a state of dynamic equilibrium with a solution, the ends of the microtubules spontaneously switch between two stages – slow growth and rapid shortening. It is known that hydrolysis of GTP, attached to β-tubulin, to GDP is related to transitions between growth and shortening phases.

There is an assumption that GTP hydrolysis changes the tubulin conformation, which affects the overall bend of the tubulin protofilament. To test this hypothesis and answer the question of what conformational changes hydrolysis entails, we constructed full-atom models of free tetramers of GTP- and GDF-bound tubulin in solution in direct conformation, according to experimental data on the structure of protofilaments in the microtubule wall. From the molecular-dynamic calculations, we obtained data on conformational mobility of these structures. To analyze the contribution of conformational changes to the bending of the tetramer, Euler angles were calculated characterizing the change in the mutual arrangement of tubulin molecules on the interfaces in the tetramer. Differences in the magnitude of flexural deformations on the intra- and interdimensional interfaces were identified, and differences in the behavior of GTP-and GDF-bound tubulin were found, which were not previously recorded in studies of the structure of tubulin in the presence of a statmin protein in experiment.

The research is carried out using the equipment of the shared research facilities of HPC computing resources at Lomonosov Moscow State University. This work was supported by a grant from the Russian National Science Foundation 17-74-20152.

Sudden Infant Death Syndrome: a multifactorial disease

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Sudden Infant Death Syndrome (SIDS) is defined as the sudden and unexpected death of a child under 1 year of age that cannot be explained after a thorough case investigation. SIDS is a subcategory of SUID (Sudden Unexpected Infant Death). In France, SIDS represents 6% of all causes of death in this age group and is considered as an exclusion diagnosis, once all the explainable causes have been eliminated such as cardiac and pulmonary malformations, metabolic abnormalities, cardiac arrhythmia, viral and inflammatory processes for example. Most of the cases occur before 6 months of age. The incidence of SIDS was observed to increase 4-fold between the seventies and the nineties, as prone sleeping positions were used more and more often by parents, mostly for fear of aspiration during a gastro-esophageal reflux episode. In reaction to this important increase in the rate of SIDS preventive campaigns were initiated in the early nineties and the incidence of SIDS has now come down to approximately 1/5,000 live births. Intense epidemiological studies have identified a number of factors predisposing to SIDS, including prone sleeping position, sleeping alone in a room, parental smoking, inappropriate bedding conditions, being born preterm and male sex. Besides the latter, with a sex ratio of 1.3, most of the identified factors are preventable. The underlying hypothesis of the cause of SIDS is that a relatively immature baby placed in asphyxiating conditions will not react appropriately and will ultimately die of asphyxia. Several mechanisms are believed to contribute to this syndrome, including alterations in the autonomous neurological system, which regulates in particular the heart rhythm, the respiratory function and the arousal system, with a focus on neurotransmitter such as serotonin and orexin. Overall SIDS is considered to be a multifactorial disease, well integrated in a triple risk model, linked to several environmental parameters which can be modified to reduce the risk of occurrence.

Theoretical investigation of non-equilibrium bio-heat transfer during thermal therapy

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This study theoretically investigates the non-equilibrium heat transfer within living biological tissues during different thermal therapy applications. Numerical solution of the present problem has been done by Chebyshev wavelet Galerkin method. The use of Chebyshev wavelet is found to be accurate, simple and fast. Larger differences in the temperature prediction at the treatment position have been observed using different equilibrium and non-equilibrium based bioheat models. It is observed that the porosity and the convective heat transfer are the factors that contribute most to the non-equilibrium heat transfer within living biological tissues. The whole analysis is presented in dimensionless form.

Investigation of solid tumor progression with account of proliferation-migration dichotomy via Darwinian mathematical model

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One of the key characteristics of malignant cells is the high frequency of mutations in their genome. It leads to an increase in the aggressiveness of cancer tumors over time and causes the emergence of tumor resistance to chemotherapeutic drugs [1]. Nevertheless, in the vast majority of works on mathematical modeling of oncological diseases, malignant tumors are considered as monoclonal populations of cells, each of which has the same characteristics. This approach does not allow to model tumor progression, which seriously limits its potential. This drawback has led to the emergence of more complex models in which the tumor cell population is structured according to the phenotypic parameter that determines the properties of individual cells [2,3].

We propose a new continuous spatially distributed model of solid tumor progression, which explicitly takes into account mutations/epimutations of tumor cells that occur during their division. The model takes into account two reasons for the movement of tumor cells in space: their own motility and convective flows, which arise due to the proliferation of cells in a dense incompressible tissue. We present a study on the progression of a model solid tumor with phenotypic changes that have a reciprocal effect on the cell proliferation rate and cell motility. The biological rationale for the problem is that cell proliferation and motility depend on two parallel metabolic pathways, each of which actively uses glucose: pentose phosphate pathway generates the necessary elements for the synthesis of amino acids, nucleotides and fatty acids; while glycolysis is the main route for the production of energy for the motion of the malignant cells. Experimental evidence suggest that the inhibition of one of the enzymes associated with one of these processes slows down the corresponding process and accelerates the other [4].

Via numerical calculations of the model, we demonstrate, that the most important characteristic that gives a cell population an evolutionary advantage is the rate of its intergrowth into the surrounding normal tissue, which depends on both the proliferation rate and its own cellular motility. We show that the increase in tumor intergrowth speed is not always associated with increase in motility of tumor cells. Depending on the parameters of the functions, that describe phenotypic alterations, tumor cellular composition may evolve towards: 1) maximization of cell proliferation rate, 2) maximization of cell motility, 3) non-extremum values of cell proliferation rate and motility. Scenarios are found, where after initial tendency for maximization of cell proliferation rate, the direction of tumor progression sharply switches to maximization of cell motility, which is accompanied by decrease in total speed of tumor growth.

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Mathematical modeling and stability analysis of left ventricular remodeling post-myocardial infarction

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In this work, new mathematical models of the left ventricular remodeling after myocardial infarction (MI) are studied. First we consider a model that consists of a system of nonlinear ordinary differential equations. It represents the interactions among heart cells and the immune system post-MI without any medical interventions. Next, we consider a system that models the regeneration process of cardiomyocytes different at possible medical interventions. Moreover, qualitative analysis of the models and numerical simulations are presented.

Reaction-diffussion model of virus mutation

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This paper is devoted to the study of persistence and evolution of virus strain taking into account virus reproduction, mutation, and genotype dependent mortality, either natural or determined by an antiviral treatment. The model describes the virus density distribution $u(x;t)$ as a function of genotype x considered as a continuous variable and of time t. It consists of a reaction-diffusion equation with an integral term characterizing virus competition for host cells. The analysis of the model shows that virus strain persists if the range of admissible genotypes where virus reproduction rate exceeds its mortality is sufficiently large. If admissible interval of genotypes is narrow or if the virus mutation rate determined by the diffusion coefficient is sufficiently large, then the virus population goes to extinction.

Analyzing spatial distribution of individuals predisposed to arterial hypertension in Saint Petersburg using synthetic populations

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Arterial hypertension (AHT) is one of the most common cardiovascular diseases that can lead to serious complications. To prevent mortality of individuals from the consequences of hypertension in Russian cities, it is necessary to estimate the number of city dwellers exposed to hypertension, as well as their spatial distribution. Such information will help optimize the delivery of patients to medical institutions and their treatment [1].

This paper presents an algorithm for modeling the spatial distribution of individuals predisposed to arterial hypertension, based on the approach of synthetic populations [2], [3]. On the basis of the synthetic population of St. Petersburg, an assessment was made of the distribution of individuals prone to hypertension, followed by the analysis of their spatial location. The status of a patient with AHT was determined on the basis of a statistical model of the incidence of AHT based on the age and sex characteristics of individuals using Monte Carlo methods. The results of the study will be used to assess the input flows of patients to medical institutions and optimize their workflow.

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Modeling the dynamics of population immunity to influenza in Russian cities

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The dynamics of population immunity to influenza largely determines the course of seasonal influenza epidemics [1] and affects the effectiveness of the implementation of control measures to curb the disease incidence. Currently, there is a limited number of studies devoted to the analysis of the immunity dynamics in Russian cities [2], and the existing works mainly rely on aggregated data on the proportion of immune individuals.

The purpose of this work is the analysis and statistical modeling of the dynamics of immunity in 12 cities of the Russian Federation in 2009-2018, taking into account the difference of age groups and virus strains - A (H1N1) pdm09, A (H3N2) and B. With the help of regression analysis, the dependence of the dynamics of immunity on the starting moment of the strain circulation was evaluated, the accuracy of the retrospective prediction of the proportion of immune individuals in the population was estimated using the proposed regression models. The immunity levels were compared for different cities of the Russian Federation, and the algorithm for recovering incomplete data on the proportion of immune ones is demonstrated.

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Stochastic compartmental model of HIV-1 infection

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We constructed a stochastic model of the dynamics of HIV-1 infection describing the interaction of target cells and viral particles in the lymphatic nodes and their movement between the lymphatic nodes. The lymphatic system is represented as a graph, vertices of which are the lymphatic nodes, and edges are the lymphatic vessels. The novelty of the model consists in the description of populations of cells and viral particles in terms of a multidimensional birth and death process with the random point-distributions. The random point-distributions describe the transition times of cells and virus particles between lymphatic nodes and the times of their transition between developmental stages. The duration of transitions of viral particles and cells between the lymphatic nodes are not random and based on the rate of lymph flow. The durations of the developmental stages of infected target cells are assume to be constant. The graph theory for the formalization and compact representation of the model is used. An algorithm for modeling the dynamics of the studied populations is constructed basing on the Monte-Carlo method. The results of computational experiments for a system consisting of several lymphatic nodes are presented.

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Molecular dynamics study of the interaction between kinetochore complex NDC80 and microtubule

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During cell division, it is necessary to distribute the duplicated genetic material between the daughter cells with high accuracy. The main participants of this process are tubulin microtubules and kinetochores, the large protein complexes that attach chromosomes to the ends of microtubules. A key role in this attachment is played by the NDC80 complex, which consists of four proteins: Hec1, Nuf2, Spc24, and Spc25. Published studies have shown that blocking the functions of this kinetochore complex leads to the mitosis disruption. Thus, inhibiting NDC80 functions seems to be a promising therapeutic strategy for stopping the division of tumor cells. Creating such an inhibitor requires a detailed understanding of the molecular aspects of NDC80 and microtubule interaction, which has not yet been achieved. In the crystal structure of the microtubule and NDC80 complex, Hec1 subunit appears to be bound to the microtubule. But mutations in the Nuf2 are also known to weaken the interaction, suggesting that Nuf2 also contributes to the tubulin binding.

To shed light on this problem, we analyzed the interaction between NDC80 and microtubule using molecular dynamics. We have constructed a full-atomic molecular dynamics model of a microtubule fragment and NDC80 complex with explicit solvent. Not only the globular domains of the NDC80 and tubulin proteins, but also their important mobile unstructured chains were taken into account. The results of our simulations showed that the interaction occurs between globular and mobile parts of proteins. During the simulation direct contact of Nuf2 was formed with both the C-terminal tubulin tail and the tubulin globules, which provides an explanation for the influence of point mutations that are distant from the microtubule-binding interface. Our calculations also make it possible to evaluate contacts between NDC80 and tubulins for the pharmacophore search for the inhibitor. We hope that this work will allow us to better understand the molecular mechanisms of interaction between kinetochores and microtubules and will help to find an effective NDC80 inhibitor to fight the proliferation of cancer cells. Work was carried out using the equipment of the shared research facilities of the high-performance computational resources at Lomonosov Moscow State University, supported by the grant from the Russian Science Foundation, project # 17-74-20152.

Modelling collective cell migration in biology and medicine

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Collective cell migration is a common phenomenon in biology, occurring in normal development, repair (for example, wound healing) and disease (for example, cancer). This talk will consider two applications – one in developmental biology, and one in wound healing/cancer. In early development, neural crest cells have to travel long distances to reach their destination, and this process is still not fully understood. In this talk I will show how, using a very simple hybrid agent-based model, we have analysed cranial neural crest migration and, in a close collaboration with experimentalists, have discovered new biological insights on the mechanisms that lead to the observed behaviour. In wound healing and tumour development, the formation of new blood vessels (angiogenesis) is an important process. A common simple model for this is the so-called snail-trail model, which is a partial differential equation model for cell density. We will show that a systematic derivation of the model actually leads to a new model, and we will compare it with the standard model.

Pulses and waves for reaction-diffusion systems in blood coagulation

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The main function of blood coagulation is to terminate bleeding caused by the vessel damage by covering the injury site with a fibrin clot. The fibrin polymerization involves many proteins that activate each others in complex enzymatic loops. Clot formation can be modeled with traveling wave solutions of reaction-diffusion systems that describe the reactions of the coagulation cascade. In this lecture we present various existence results of pulses for these reaction-diffusion systems. The motivation is to have an insight on the threshold condition for solid clot formation to occur.

These results are published in the following papers in collaboration with T. Galochkina, N. Ratto and V. Volpert.

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Data Science application to Environmental and Biological Systems Effects on Health: Multiscale-Multilevel Modelling Approach

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The organisms and their interaction with the environment form the world we live in. It is therefore imperative to understand how, as humans, we adapt to environmental changes that affect our existence in the short and long term. Today there are huge challenges faced by human kind as a result of growing populations and change of lifestyles resulting in greater energy needs and in turn negatively impacting on climate. The environmental, social and cultural changes taking place give us an opportunity to delve into issues on how adaptation occurs. Our determination to survive gives the impetus to fight to mitigate detrimental effects due to environmental changes. Human kind is therefore forced to study biological and climatic systems in order to ensure sustainability. This is partially achieved through scientific investigations of processes involving chemistry and physics of the atmosphere, biological systems, ecology, and many other phenomena. These investigations have mainly gained traction due to computing capacity that has been growing parallel to other researches. Based on these facts, the need for bringing together various theories to address national challenges related to biological and environmental impacts on energy production and use becomes critical. The objective of my presentation is to project a focused study of the Southern African biosphere for purposes of ensuring sustainability. In that regard the development of multiscale and multilevel systems models becomes crucial. These will result in multiscale and multilevel experimentally generated data to be used for the development of models for reliable prediction of the outcomes of the interactions between biological and environmental systems that affect humans negatively causing, for example, health problems. This goal can be achieved by using integrative systems approach in our investigations. Thus, the study of the diseases transmission and management dynamics is considered as an example of the application of multiscale and multilevel systems modelling approach in the attempt to preserve life.

Modeling of the transport function of lymphatic vessels

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Modeling of the lymph flow in the human lymphatic system is an actual task, because of its importance in providing normal functioning of the human organism. There are many diseases related to disorders of the lymph flow, and new investigations show an important role of lymph flow in the diseases, which commonly have been not considered as connected to lymphatic system disorders, for example, plastic bronchitis.

The main goal of our work is to create a model of lymph flow in the human lymphatic system. For modeling lymph flow through the whole human lymphatic system, we use the quasi-one-dimensional approach. Lymph vessels have specific structure and functioning, so new models of lymph flow in quasi-one-dimensional approximation should be proposed. Such models are proposed and investigated in current work.

Lymphatic vessels have valves in the lumen which prevent backward flow. Also, they can produce active spontaneous contractions. Usually, it is considered that the interaction of valves and contractions is one of the causes of lymph movement, and is an analog of the "muscle pump". We propose a mathematical model of this process and study the efficiency of such "pump" for the single vessel and the whole anatomically adequate graph of the human lymphatic system.

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On age-related ionic remodeling and repolarization abnormalities in population of cardiomyocyte models

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Atrial fibrillation (AF) is one of the common diseases in the human population, especially for the senior age group. Repolarisation abnormalities in cardiomyocytes, such as early afterdepolarization (EAD) and late afterdepolarization (DAD), were shown to induce ectopic activity in atria with the following development of the AF. Reported changes in the transmembrane currents in human and canine atrial cardiomyocytes with aging ([1,2]) were suggested to contribute to increasing pro-arrhythmical activity in the myocardium.

In this study, we used ionic models of atrial cardiomyocytes to study possible effects of ionic current variations in wide ranges on the action potential (AP) bio-markers: amplitude and duration of AP at different phases. The goal of the study was to assess if the atrial cellular models predict an increase in the repolarization abnormalities of the ionic currents under the age-related changes.

We used three mathematical models of human atrial cardiomyocytes (Courtemanche98, Nygren98, Maleckar08) and one model of canine atrial cardiomyocytes (Ramirez00). We randomly varied a number of ionic current parameters in a wide range from 0 to 200% of the reference value in each model. This way, we produced four model populations and classified different sub-groups in every population: a normal group where action potential bio-markers fall within the reported ranges of measured values; an EAD and DAD groups where repolarization abnormalities are generated; and a "pathology group" consisted of the rest of the models where AP signals do not match to any of the above criteria.

We found a significant part of the APs showing EAD and DAD in every population. The distribution of model parameters fraught with the EAD or DAD were different between the models. Neither of the models we tested showed a significant increase in EAD, DAD vulnerability in the parameter sub-space corresponding to the age-related changes in the ionic currents. At the same time, we founded a significant overlap between the age-related parameter sub-spaces and the parameter area with AP duration greater than the average normal value.

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The dynamics and effects of heavy alcohol consumption on the transmission of gonorrhea with optimal control

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Alcoholism has become a global threat and has a serious health consequence in the society. In this paper, a deterministic alcohol model is formulated and analyzed, and the basic properties are established. The reproduction number R0 of system is determined. The steady states are examined, and local stability is found to be both locally and globally stable. The endemic state exhibits three equilibria solutions. Furthermore, time dependent control is incorporated into the system in order to establish the best strategy in controlling the alcohol consumption and gonorrhea dynamics, using Pontryagins Maximum Principle. The numerical results depict that the best strategy to controlling gonorrhea is the application of the three controls at the same time.

Mathematical modeling on the control of HIV/AIDS with campaign on vaccination and therapy

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HIV/AIDS in a global pandemic ravaging nation with negative adverse effect create high level of mortality rate and increase the number of ophaus worldwide. The controls of this pandemic disease like any other disease become a global fight. We use Mathematical epidemic model with effective public health campaign on the need for vaccination and effective therapeutic doze due to vaccine failure to put a measure on its spread. Compartment models (S, V, E, I, I_2) were developed; we concluded a qualitative analysis on the models performing the local and global stability analysis. The basic reproduction number was found using the next generation matrix method (R_0), we discovered that $R_0 < 1$, indicating that with effective public health campaign on the need for vaccination and therapeutic doze, the HIV/AID burden will be drastically reduced, which will reduce the viral load and consequently reduce the transmission.

Formation of Lipodiscs Stabilyzed by Amphyphilic Copolymers: Molecular Dynamics Simulations

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Amphiphilic copolymers consisting of alternating units of maleic acid and styrene (SMA) have caused an important methodological breakthrough in experimental studies of membrane proteins. SMA copolymers are capable of directly solubilizing membrane proteins from artificial and natural membranes forming disc-shaped particles (SMALP). These nanosized particles consist of a lipid or protein-lipid central region surrounded by a polymer belt and have a diameter of 10 to 30 nm, depending on the preparation protocol. Within a specific protocol, the resulting SMALP nanoparticles have the same size, which makes them a convenient tool for various experimental applications, including Cryo-EM and EPR spectroscopy. Although numerous experimental studies indicate the great potential of using SMALP for protein solubilization and characterization, the mechanism of their formation and a detailed picture of their organization at the atomic level are not completely clear. In particular, the reasons for the narrow size distribution of SMALPs, the nativity of lipids in them, and the influence of various factors (for example, the specific monomer composition of the SMA polymer) on the solubilization efficiency remain undetermined.

We have developed a coarse-grained molecular model of SMA polymers within the framework of the MARTINI force field. The resulting model made it possible to study the behavior of SMA copolymers with different composition/charge/concentration in an aqueous solution, as well as their interaction with lipid membranes. First, we found that SMA copolymers tend to aggregate in solution into clusters of a certain size, which is probably the reason for the homogeneity of SMALP size. Secondly, molecular dynamics modeling showed that periodic SMA copolymers with styrene/maleic acid ratios of 2:1 ($[SSM]_n$) and 3:1 ($[SSSM]_n$) interact differently with lipid bilayers. While clusters of 2:1 SMA copolymers induced the formation of transmembrane pores, clusters of 3:1 SMA copolymers extracted bilayer fragments from the membrane, forming SMALP-like structures. A similar process was observed when modeling 3:1 SMA copolymers with different lengths and a statistical distribution of styrene and maleic acid units. Analysis of molecular dynamics trajectories and comparison with experimental data allowed us to conclude that the formation of SMALP requires copolymer molecules, which consist of blocks of more than two consecutive styrene monomers [1].

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Junction of 3D-1D models of a vessel with elastic wall

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An axisymmetric cylindrical vessel with an elastic thin laminated wall with a viscous flow inside is considered. The problem depends on two small parameters: the ratio of the radius to the characteristic length and the thickness of the wall and the radius. The stiffness of the wall materials is as well considered as a parameter (large or small). An asymptotic expansion of the solution of the coupled system of Stokes equation and elasticity equations is constructed. It is used then for the modeling of junction condition between 3D and 1D models.

Non-linear waves and cardiac arrhythmias

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Sudden cardiac death as a result of cardiac arrhythmias is the leading cause of death in the industrialized countries. Although cardiac arrhythmias has been studied well over a century, their underlying mechanisms remain largely unknown. One of the main problems is that cardiac arrhythmias occur at the level of the whole organ only, while in most of the cases only single cell experiments can be performed. Due to these limitations alternative approaches, such as multiscale computer modelling of the heart, are currently of great interest.

In my talk I will explain the mechanisms of cardiac arrhythmias from the point of view of basic scientist and present the main ideas behind the multi-scale computer modelling of the heart. Then, I will report on the research directions of my group, specifically on development of virtual human heart model and its application to studies the mechanisms of sudden cardiac death. I will also report on how modelling can be used in combination with new experimental technologies in the field, such as cardiac cell cultures and optogenetics and discuss their possible application for treatment of cardiac arrhythmias.

Modeling of HIV-1 infection dynamics based on the compartment model

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We consider a mathematical model of the dynamics of HIV-1 infection in the human body. The model is built on the basis of a system of nonlinear delay differential equations, assuming the distribution of model variables over several compartments. An analytical and numerical study of the behavior of the model solutions is carried out. The modes of dynamics of model variables interpreted as possible eradication of HIV-1 infection are obtained. The results of the study are supplemented by the results of modeling the dynamics of HIV-1 infection on the basis of a stochastic model with integer variables.

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Numerical modeling of elastic waves in human body

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The study of elastic waves behavior in soft tissues is necessary for the research in different areas of medicine – diagnostic ultrasound, high-intensity focused ultrasound, sport traumas, etc. The modeling of wave effects at the moment [1] is mostly based on acoustic or viscoacoustic material model. It allows to reproduce the basic behavior of soft tissues under an ultrasound pulse, which is enough to use numerical modeling for adjustment and development of ultrasound transducers. The modeling of ultrasound and impact effects in presence of bones [2] requires to improve the material model and consider shear waves that can be generated on the contact between acoustic and elastic media.

In this study, three numerical methods are considered. The comparison of all three methods concerning elastic waves modeling problem is given.

The first one is the grid-characteristic method [2]. It considers the characteristic properties of the equations system for an elastic body and allows to apply complex border and contact conditions. The second method is the discontinuous Galerkin method [3]. It is a stable and reliable method that allows to use complex calculation grids based on real biological data without numerical oscillations. The third method is the wavefront construction ray tracing method [4]. This modification of the classic ray tracing method allows to model wavefronts with a guaranteed spatial resolution in any point of the calculation area. This method can significantly speed up the calculation process, but requires to solve border and contact problems separately, which is a complicated problem in case of elastic media.

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Structural and sensitivity analysis of the model of tuberculosis

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Till nowadays, the analysis of the dynamics of tuberculosis (TB) transmission and propagation remains an active research topic. Due to their particular structure, dynamical models of tuberculosis exhibit a number of interesting phenomena such as, e.g. backward bifurcations and multi-stability, [1]. We consider a sufficiently simple, yet realistic model of TB propagation and control proposed by A. A. Romanyukha and co-authors (see, e.g., [2,3]) and analyze its structural properties. In particular, for the uncontrolled model we study the role of the endogenous activation/superinfection transmission parameter α and its influence on the appearance of backward bifurcation.

We further compute the controlled basic reproduction number $R_0(u_B; u_D)$ for the extended model including the action of two types of controls and analyze the sensitivity of $R_0(u_B; u_D)$ with respect to both controls following the approach introduced in [4]. It is shown that the computed sensitivity coefficients admit a clear epidemiological interpretation and can be used in assessing the efficacy of the respective types of intervention.

We conclude the presentation with a brief outlook for the further study.

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A reduced model of blood coagulation cascade

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Blood coagulation is a complex process involving many biochemical factors and reaction between them in order to stop bleeding and to protect damaged vessel. If the concentrations of blood factors are homogeneous in space, then their evolution in time can be modeled by ODE systems. It should be noted that reaction rate constants are subject-specific and their values may not be precisely known. In spite of numerous models existing in literature, both detailed and simplified, their application to describe clinical data encounters certain difficulties because of the complexity of the process, limitations of the models, and uncertainty of the parameters. In this talk we present a reduced model of blood coagulation, involving only three equations for the concentrations of thrombin, prothrombin, and activated factor X. This model is obtained as an approximation of more detailed model used in literature. The model is applied for the characterization of normal and hemophilia subjects on the basis of thrombin generation curves.

Qualitative and quantitative features of delay differential equations in biosciences

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Delay differential equations (DDEs) have received considerable attention and been shown to model many real life problems, traditionally formulated by systems of ordinary differential equations (ODEs), more naturally and more accurately. Such class of DDEs is widely used for analysis and predictions of systems with memory such as population dynamics, epidemiology, immunology, physiology, neural networks and other biological and physical systems. In most of biological and engineering systems, time-lags or time-delays exist intrinsically. Therefore, modelling of such systems by differential equations with memory, represented by time-delays (time-lags) has more advantages than models without memory. The presence of memory in the differential equations improves the stability of the solutions and enrich the dynamics of the model. The aim of this talk is to provide a wide range of DDEs with integer and fractional-order derivatives, and show that they have a richer mathematical framework (compared with differential equations without memory) for the analysis of biological systems.

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Data driven modelling the CD4+T-cells activation

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The human immune system is a complex structure consisting of many elements. Despite the fact that the basic principles of its functioning at the moment are becoming clear, there are still many questions, the answers to which are yet to be clarified. One of these questions is whether the network of fibroblastic reticular cells (FRC) affects an event that triggers an adaptive immune response when viruses are infected by an organism activation of T-lymphocytes by antigen-presenting cells (APC), and if so, to what extent. Observations of medical practitioners state: yes, there is influence, and it is significant. However, there are publications whose conclusions deny the significance of this connection[1]. For verification, we have constructed a model that is close to the available experimental data and takes into account important aspects of the functioning of the studied components of the immune system. We took into account the characteristics of T-cell motility, the effects of chemotaxis and interaction with FRC, and also used a model of a network of fibroblastic reticular cells based on existing data[2]. The simulation results demonstrated the expected result, showing the link between the structural integrity of the FRC network and the time it takes the T-cell to search for the antigen-presenting cell. The data obtained correlate with the processes observed in people infected by HIV infection, and also allow us to estimate the limits of system stability with the gradual destruction of the FRC structure.

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Using Bayesian model-based meta-analysis for studying safety of PD-1 and CTLA-4 inhibitors monotherapies and their combination

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Background: Immune checkpoint inhibitors (ICIs) are efficient against various cancers. They can lead to immune-mediated adverse events (imAEs), especially in combinations. The objective of this study was to apply Bayesian model-based meta-analysis to quantitatively study dependence of immune-mediated adverse events on dose of PD-1 and CTLA-4 inhibitors

Methods: We searched the PubMed and TrialTrove databases, ASCO and ESMO abstracts to identify published relevant ICI safety data. To quantitatively compare safety dose dependence in monotherapy and combination studies, we converted the dosing regiments into drug exposures derived from corresponding pharmacokinetic models and then normalized the exposures by the drug potency in order to compare different drugs to the same target. Then Bayesian meta-analysis was done for Grades 3/4 treatment related AEs (trAEs) and imAEs of five organ classes: gastrointestinal (GI), skin, pulmonary, hepatic, and endocrine. Bayesian meta-analysis and meta-regression were implemented using STAN with the RStan and BRMS software packages.

Results: A total of 102 articles were identified, covering 21,305 patients in 153 dosing cohorts treated with ICI monotherapy or combination therapy. No statistically significant relationship between AE rates and PD-1 inhibitor monotherapy dose was observed. Statistically significant dose dependence was observed for total grade 3/4 trAEs (AE rates for lower and higher doses subgroups – 22% and 34% (BMA) vs. 23% and 37% (MA)) and hepatic imAEs (AE rates – 0.5% and 7% (BMA) vs. 1% and 7% (MA)) for CTLA-4 inhibitor monotherapy, and for total grade 3/4 trAEs (34% and 53% vs. 35% and 53%), and for organ groups imAE: gastrointestinal (7% and 18% vs. 6.5% and 7%), hepatic (8% and 15% vs. 8.5% and 18%) and skin (3.5% and 5% vs. 4% and 6%) for CTLA-4 + PD-1 inhibitor combination therapy. AE rates for CTLA-4 + PD-1 inhibitor combination regimens were supra-additive versus the respective monotherapies. AE rates were higher in the first line setting versus previously treated patients, and in studies combining ICI with chemotherapy versus monotherapy. Influence of baseline patients characteristics was studied on dose dependence. The results of the Bayesian meta-analysis agree with the model-based meta-analysis obtained using random effects model performed in the metaphor R package.

Conclusions: Significant AE dose/exposure dependence for CTLA-4 inhibitor monotherapy, CTLA-4 inhibitor + PD-1 inhibitor combination therapy, and ICI + chemotherapy combination therapy was observed for multiple AE types. Patients receiving first-line ICI therapy had higher AE rates versus patients receiving second line or later ICI therapy. There was no influence of patients PD-L1 status on the observed relationships between AE rates and ICI dose/exposure. The results of this study agree with our previous results of standard meta-analysis. This novel model-based meta-analysis methodology provides a quantitative framework for positioning ICI doses and dosing regimens with respect to specific AE rates.

Joint modeling for different longitudinal measurements and risk of death in non-small cell lung cancer

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In non-small cell lung cancer (NSCLC) tumor size is a well-known biomarker for assessment of treatment efficiency and survival. However, accounting for the kinetics of other markers can improve the prediction of the outcome of interest. Joint modeling is a common tool for characterization between longitudinal and time-to-event data. The present work is aimed to investigate the influence of different longitudinal biomarkers on overall survival in patients with NSCLC and compare the results between two different studies.

Data from the comparator arms of two phase 3 clinical trials in second-line metastatic NSCLC were obtained from Project Data Sphere, comprising 512 patients treated with erlotinib (NCT00364351), 596 patients treated with docetaxel from ZODIAC trial (NCT00312377). Four univariate joint models were assessed with different longitudinal biomarkers: sum of longest diameters of the target lesion (SLD), lactase dehydrogenase, neutrophil count and neutrophil-to-lymphocyte ratio (NLR). Joint model parameter estimation was made in JM package in R.

We found the significant association between all investigated biomarkers and overall survival. Additionally, the link between SLD and NLR with the risk of death turned out to be similar for both studies that allow to efficiently describe the survival in the NSCLC studies with different drugs using similar association parameters between longitudinal biomarkers and survival. In summary, we showed that joint models can be used to evaluate the relationship between survival and tumor size as well as other longitudinal biomarkers for patients with NSCLC. The results can be used for the development of more complex multivariate joint models to improve prediction precision for NSCLC clinical studies.

Numerical analysis of the effects of the left ventricle geometry on heart performance in health and disease

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Multiscale numerical simulation of the heart is a fast developing field of science. The models used in the simulations combine the descriptions of processes at different levels: electromechanics of cardiac muscle at the cellular level, properties of myocardium at the tissue level and the approximations of the heart or its chambers at the organ level. The heart model is commonly incorporated into a lumped parameter model of the cardiovascular system. The majority of the models consider very accurate descriptions of ionic currents and were applied to simulate various dysfunction of the propagation of electrical waves through the walls of the heart. However, very few numerical investigations of the influence of myocardium dysfunctions and/or the geometry of the heart chambers on the heart performance were performed, presumably because of the quite simple approximations of the mechanics of cardiac muscle usually used in the multiscale models of the heart.

Here we present an application of our new model of circulation, which includes a multiscale model of the left ventricle of the heart. The ventricle is approximated by a body of rotation. Both passive and active stresses in ventricular myocardium are considered. The last one is specified by our kinetic model of the contraction and activation of cardiac muscle. Blood circulation was described by our new lumped parameter model that treated the atria and right ventricle as viscoelastic reservoirs. The whole model was approbated by the simulations of a normal heart-beat, some arrhythmias, and valve dysfunctions [1].

A number of numerical experiments were performed to examine a normal and pathological functioning of the left ventricle of various shapes. The performance of the heart at different shape indexes of the left ventricle was examined numerically. We have also simulated some cases of pre-surgical and post-surgical treatment of local apical myocardium infarction. Ejection fractions and longitudinal strains for the ventricles of different shape were estimated and compared to published data. The results of 2D modelling demonstrate how the influence of changes in muscle properties and heart geometry on the heart performance can be investigated by our new model, which could be expanded for 3D simulations.

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Model of volume change in the left heart ventricle

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The model for change in blood volume of the left heart ventricle presented is based on experimental data[1] and meets the criteria for mechanical heart activity. These are the equations that describe the dynamical changes in blood volume:

$V_V = V_1 + V_2 + V_3 + V_4$, where:

$V_1 = V_{ED} - \frac{V_{ED}-V_{ES}}{2} - 1.5396(V_{ED} - V_{ES}) \sin\left(\frac{\pi(t-r)}{\tau}\right) \cos^3\left(\frac{\pi(t-r)}{\tau}\right)$;

$V_2 = 0.27522(V_{ED} - V_{ES}) \cos^{20}\left(\pi\left(\frac{t-r}{\tau} - 0.47351148617\right)\right)$;

$V_3 = 0.2477(V_{ED} - V_{ES}) \cos^{20}\left(\pi\left(\frac{t-r}{\tau} - 0.621190811064\right)\right)$;

$V_4 = 0.3715(V_{ED} - V_{ES}) \cos^{30}\left(\pi\left(\frac{t-r}{\tau}\right)\right)$.

V_{ED} is the end diastolic volume, V_{ES} is the end systolic volume, τ is the length of the cardiac cycle, r is the phase shift coefficient and t is the variable which is time.

The mean relative error of the mathematical model has been calculated. It was about 0.211 cl, or 2.11 ml (or about 1.76%-4.22%, which means that the model could serve as a good approximation for describing the mechanical activity of the heart.)

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An *in vitro* mathematical model for Alzheimer's disease

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Alzheimer is a neurodegenerative disease leading to progressive neurons destruction. The disease is partly caused by accumulation of Aβ peptides having the ability to aggregate into oligomers and fibrils in the brain. Oligomers can interact with neurons through transmembrane receptors such as PrP^c .

These interactions lead to a misfolding of PrP^c , which results in the sending of cytotoxic signals to the neurons.

In this talk, we will presente an *in vitro* model describing the Aβ polymerization process with consideration to the PrP^c protein interaction. A mathematical analysis and some numerical illustrations will be adressed.

Velocity-Amplitude relationship in the Gray-Scott autowave model in isolated conditions

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Various chemical and biological systems involve autocatalytic steps and positive feedbacks which in spatial conditions can give them properties of active media, in particular autowave properties. The main autowave characteristics are velocity and amplitude. This report considers the autowave velocity-amplitude relation in the general mathematical model of active reactant formation from precursor with cubic kinetics followed by a linear inhibition/death step – the Gray-Scott model – in isolated conditions. The way to derive the explicit velocity-amplitude relation is proposed. This approach may be useful for investigation of more complex active media systems in biochemistry, combustion, and disease control. The work has been supported by the "RUDN University Program 5-100".

Molecular mechanics of regulation of muscle contraction: experiments, modelling and application to heart diseases

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Muscle contraction is powered by the interaction of contractile proteins, actin and myosin, organised in the thin and thick filaments, respectively. Myosin motors perform mechanical work using ATP hydrolysis. The contraction and relaxation of muscles are controlled by Ca^{2+} ions via regulatory proteins troponin (Tn) and tropomyosin (Tpm) associated with the thin filaments. Tpm is a coiled-coil dimer of parallel α-helices. Tpm molecules bind each other via overlap junctions and form a helical strand on the surface of an actin filament. Tn binds Tpm near the overlap junctions. In the absence of Ca^{2+} Tn binds actin and holds the Tpm strand in a position where it blocks myosin binding sites on actin and keeps muscle relaxed. Ca^{2+} binding to Tn releases it from actin. Tpm strand rotates with respect to the thin filament axis to an intermediate position and partially opens the myosin binding sites. Myosin binds actin and causes further rotation of the Tpm strand to the open position, that enables myosin binding to neighbour actin sites promoting muscle contraction.

Mechanistic model [1] suggests that the efficiency and cooperativity of Ca^{2+} regulation of muscle contraction depends on the bending stiffness of Tpm strand and its interaction with actin. A number of point mutations in the TPM1 gene that encodes cardiac Tpm cause inherited cardiomyopathies, dilated or hypertrophic [2]. To understand the relationship between Tpm structure and function and to reveal the molecular mechanisms underlying the cardiomyopathies we used recombinant Tpm constructs and several experimental techniques: differential scanning calorimetry, circular dichroism, co-sedimentation, light scattering, in vitro motility assay, and two-beam optical trap in combination with the molecular dynamics simulations [3-4]. The results of these studies support the idea that bending stiffness of Tpm strand is a major determinant of its regulatory function.

This work was supported by the RFBR grant No. 17-00-00066.

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Transformation of extracellular potential to transmembrane potential using deep neural networks

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Registration of the extracellular potential is an essential approach to study electrophysiological behavior of the whole heart or myocardial slabs. Usually, the extracellular potential is recorded from the myocardium in the biological experiment using a microelectrode array or in a clinical electrophysiological study of the heart using the unipolar catheter. Also, the extracellular potential can be reconstructed from body surface potentials in non-invasive cardiac mapping using inverse problem solver.

The extracellular action potential is a result of a transmembrane action potential that simultaneously appeared in a significant amount of cardiomyocytes. At first sight, the relationship between extracellular potential and transmembrane potential is well known. Bidomain model point outs that extracellular potential in a registration point is approximately equal to transmembrane potential multiplied with some negative coefficient if the myocardium slab is surrounded by non-conductive medium (air for example). However, the real extracellular potential is far from this definition because the registered signal is disturbed by the far-field effect, catheter motions, changes in conductance of the surrounding medium, and many other factors. Thus, current clinical and experimental observations confidently state only about positive linear correlations between extracellular action potential duration and transmembrane action potential duration.

In our study, we propose the deep artificial neural network that transforms registered extracellular potential with complex noise to normalized transmembrane potential in the myocardium region around the point of signal registration. The training dataset was generated by a finite element model of the myocardium electrical activity that uses the bidomain equation with bath and idealized geometry. Validation of the proposed method was performed with personalized models of human heart electrophysiological activity. Also, we propose the analytical theory that can prove the correctness of neural network transformation and may be used in the following improvements of the proposed approach.

We suppose that our approach can be directly applied for the analysis of unipolar catheter recordings and may be useful for a time-dependent regularization in non-invasive cardiac mapping.

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3D hemodynamics in time-dependent domains: are fluid-structureinteraction simulations inevitable?

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In the talk we present a new numerical scheme for fluid-structure interaction problems and verify it on several bechmarks. Also, we address three biomedical problems for flow in time-dependent domains which can be solved by simpler formulations than FSI. This is the joint work with M. Olshanskii, A. Lozovskiy, A. Danilov, T. Dobroserdova, V. Salamatova, A. Lyogkii.

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The study of the skin membrane permeability for chemical penetration enhancers and active molecules by molecular modeling approaches

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The skin is a protective barrier that prevents the entry of foreign substances into the body. At present, it has been proven that there are 2 main routes of penetration of various substances through intact skin: transfollicular and transepidermal. From both toxicological and therapeutic points of view, it is important to predict the way in which the drug penetrates the skin.

Various strategies are being developed to overcome the impermeability of stratum corneum (SC), the main barrier to transepidermal drug penetration. One of the most studied approaches is to increase the permeability of drugs through the skin with the use of special substances that accelerate the penetration of drugs through the skin: chemical penetration enhancers (CPE). The use of combinations of chemical enhancers is upon great interest due to a synergistic effect, which leads to a higher level of skin permeability to the active substance, what is especially important for the purposes of cosmetology, in wound healing, etc.

In the present study, we used *in silico* approaches to model the mechanisms of interaction of CPEs with a model membrane of SC. We used all-atom (CHARMM36) and coarse grained (MARTINI) models of the membranes and chemicals. As the result we characterized the parameters of the interaction of the two selected enhancers and the active substance with the model skin membrane.

The research is supported by the Russian Science Foundation under grant 19-71-00109.

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The effect of conformational changes in cytochrome C1 on the formation of cytochrome C and C1 complex

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Cytochrome c is a mobile electron carrier in the mitochondrial respiratory chain, which transports electrons from cytochrome bc1 complex to cytochrome c oxidase. Cytochrome c is a soluble protein located in the intermembrane space of mitochondria. Cytochrome c has heme c as functional group that is connected to the protein by two thioester bonds through cysteine residues.

Currently, the structure of the protein complex of cytochrome bc1 and cytochrome c from the mammals is not obtained by experimental methods. We built a model of the interaction of these protein macromolecules from *Bos taurus* using the methods of Brownian and molecular dynamics as well as one-parameter hierarchical cluster analysis. First, we obtained a set of encounter complexes with electrostatic attraction energy less than -8 kT using ProKSim [1] software for Brownian dynamics. Then this set was divided into two clusters and the further transformation of the central structures of the clusters into the final complexes was followed by explicit solvent all-atom molecular dynamics simulations using GROMACS software [2].

For simulations we used one cytochrome c structure (PDB ID: 6FF5) and two cytochrome c1 structures (PDB ID: 1NTM and 1BGY) which varied in the secondary structure of the loop region and α-helix (V168-G185), but had the same amino acid sequence. The structure of the interface site on the surface of cytochrome c1 strongly influenced the distribution of electrostatic potential. In the process of modeling of complex formation some significant differences were found in the ability to form a stable final complex for these two structures of cytochrome c1. The work was performed using the equipment of the Center for Collective Use of Super High Performance Computing Resources of the Moscow State University named after M.V. Lomonosov. This work was supported by the RFBR grant 18-07-01219.

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Brownian dynamics model of microtubule growing and shortening

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Microtubules are rigid cylindrical polymers and one of the key component of the cytoskeleton, responsible for many cellular processes, including search, capture and segregation of chromosomes in mitosis. They exhibit dynamic instability: phases of slow polymerization spontaneously alternate with the phases of fast depolymerization. Molecular mechanisms of this behavior of microtubules are not fully understood. In this work we theoretically explore mechanism of microtubule polymerisation using Brownian dynamics modeling. In contrast to previous models of tubulin self-assembly, we have recently demonstrated that microtubules grow by addition of curved GTP-tubulin to the tips of bent protofilaments at their tips (McIntosh et al., 2018). We directly consider this new structural information in our new model here. First, we calibrate the model parameters by matching experimentally observed speed of microtubule growth/shortening and the lengths of curled protofilaments at the microtubule tips. Second, we include into the model a coupling device analogous to circular kinetochore Dam1 complex in yeasts to model force production by shortening and growing microtubule tips. The model predicts that the microtubule not only can develop large pulling force during depolymerization, but can also sustain considerable assisting forces at the growing tip. Our results clarify the mechanisms of mechanical coupling between dynamics of the microtubule tips and chromosome motions in mitosis. The study was supported by the Ministry of Science and Higher Education of the Russian Federation (project -18-118012390250-0), and carried out using the equipment of the shared research facilities of the high-performance computational resources at Lomonosov Moscow State University.

Stem cell-enriched lipoaspirate in regenerative medicine

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Soft tissue defects can be treated with autologous fat grafts. Autologous fat is easily obtainable via liposuction with minimally invasive surgery. The procedure is normally quick, safe, and results in satisfactory outcomes. However, some concerns have to be addressed. Due to possible reabsorption rates of up to 70%, the outcome is somewhat unpredictable. This is most likely caused by a lack of vascularization in the fat graft environment.

Fat tissue contains Adipose-tissue derived mesenchymal stem cells (ADSCs). ADSCs can be isolated from harvested adipose tissue with a cell yield up to 500 times higher than from bone marrow. The minimal criteria to define MSCs, proposed by the Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy, are plastic adherence in standard culture conditions, the expression of CD105, CD73 and CD90 but deficiency of CD45 and HLA-DR surface molecules, and the potential to differentiate into the osteoblast, adipocyte and chondroblast lineages in vitro. Additionally, ADSCs have succesfully been differentiated into myocyte, neural, and endothelial lineages among others, making them interesting candidates for regenerative purposes. However, the growth factors and cytokines secreted by ASCs can induce neovascularization and promote cell survival and therefore are also an important factor in the regenerating potential of lipografts. One way to overcome the negative outcomes of autologous fat grafting is the combination of fat tissue with cells from the freshly isolated stromal vascular fraction. It has been shown that this cell assisted lipotransfer (CAL) has advantages regarding form stability and graft suirvival when compared to non-cell assisted lipotransfer, which can be explained by the pro-angiogenetic effects of ASCs. However, a stem cell enriching procedure that can be done in the operation theatre would be preferable in many situations.

We have tested different lipoaspirate processing procedures that reliably increase stem cell concentration in lipografts and are fast, safe, and easy to use. These cells show no substantial changes in their secretome expression profile and should be considered an option for regenerating lipotransfers. However, more experiments will be needed to optimize the process to get to the best combination of stem cell concentration enrichment, fast, safe, and easy handling, and mechanical properties of the graft tissue. Mathematical models could help in this process.

Front and pulse solutions for a system of reaction-diffusion equations with degenerate source terms

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Motivated by several biological models such as the SIS model from epidemiology and the Tuckwell-Miura model describing cortical spreading depression, we investigate the types of wave solutions that can exist for reaction-diffusion systems of two equations in which the reaction terms are degenerate in the sense that they are linearly dependent. In particular, we show that there are surprising differences between the types of waves that occur in a single reaction-diffusion equation and the types of waves that occur in a degenerate system of two equations. Importantly, and in contrast to previously published results, we demonstrate that non-stationary pulse solutions can exist for a degenerate system of two equations, but cannot exist for a single reaction-diffusion equation. We show that this has important consequences for the minimal model that can generate the types of waves observed in cortical spreading depression. On the other hand, stationary fronts can exist for both single reaction-diffusion equations and degenerate systems. However, for degenerate systems, such solutions cannot be accessed when perturbing a uniform rest state with a localised perturbation unless the diffusion coefficients of the two species are equal. We also give an explicit condition on the source term in a degenerate reaction-diffusion system that guarantees the existence of nonstationary and stationary pulse and front solutions. We use this approach to provide several examples of reaction terms that have analytical pulse and front solutions. We also show that the case in which one species cannot diffuse is singular in the sense that the degenerate reaction-diffusion system can admit infinite families of stationary piecewise constant solutions. We further show how such solutions can be accessed by perturbing a constant rest state with a localised continuous disturbance.

Mathematical model of kidney development

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Kidney development is initiated by the outgrowth of a ureteric bud of epithelial cells into a population of mesenchymal cells. Interactions between these two populations lead to the formation of the highly branched ureteric tree and the nephrons (basic structural and functional units of the kidney).

While it is now possible to collect data showing how the structure of kidneys evolves, the biophysical mechanisms responsible for these changes remain to be determined. We present a mathematical model of kidney morphogenesis, in which the development of the kidney is described by a fluid dynamics model. We show that branching of the ureteric tree can be regulated by instability of the growing tip surface: ureteric tree tip cells, that moved further from the smooth tip surface, are subject to higher levels of growth factors and, as a result, have higher rates of proliferation and chemotactic attraction to growth factors which leads to further expansion of the cells from the tip and development of a new branch. The tip branching is stabilised by bending resistance of the tip surface. The balance between stabilising and destabilising mechanisms defines the number of the appearing branches.

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