Lomonosov Moscow State University

BIOKYBERNETIKA 2019

4th Russian-German Conference

MultiScale BioMathematics – Coherent Modeling of Human Body System

with

EURASIAN HEALTH & MEDICINE 2019

2nd International Conference

Molecular Health - From Cell to Population

and

GeneSEES IMPACT 2019

3rd Transcontinental Conference

Coherent Control of Health Impacts From Person's Life-Sphere Surroundings in Populations Across EurAsia

jointly make

EURASIA'S YOUNG SCIENCE TALENTED & AMBITIOUS

THE BIG BRAIN of 2019

Conference for Collaboration in EurAsia

Конференция по сотрудничеству в Евразии 2019г

2019 年亚欧地区合作会议

पूर्व-पाश्चात्य जीवविज्ञानम् -2019

Organizers

acad RAS Boris N. Chetverushkin (MSU)

Jochen Mau (Heinrich Heine University Düsseldorf)

Sergey I. Mukhin (Moscow State University)

Sergey V. Bogomolov (Moscow State University)

Special Organizer for Russian-German Cooperation in Health

foreign memb RAS prof. dr. med. dr. h.c. mult. Helmut Hahn

Koch Mechnikov Forum - an Initiative of Petersburg Dialogue

30 September - 04 October 2019

Moscow, Russia

Lomonosov Moscow State University

BIG BRAIN 2019

The 2019 Conference for Collaboration in EurAsia

Конференция по сотрудничеству в Евразии 2019г

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Contents

Committees

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foreign memb RAS prof. Helmut Hahn (KMF Berlin)

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Vorwort Предисловие 发刊词 Foreword

After 2018-triple of conferences in Shenzhen (China), Moscow (Russia) and Krefeld/Düsseldorf (Germany), BIOKYBERNETIKA 2019, with its embedded topics of EURASIAN HEALTH & MEDICINE 2019 in the vein of past Shenzhen Conference and of GeneSEES IMPACT 2019 in the vein of past Krefeld Conference, it aims to unite the different aspects now in a single place. A few words on the specifics of each format may be helpful:

EURASIAN HEALTH & MEDICINE aims to advance research into aspects of human health and medicine that are specific for Eurasian populations, and to foster a "EurAsian scientific cooperative" devoted to health-intent research in transcontinentally standardized formats and profile-shaping high-end studies with regional populations across EurAsia.

MOLECULAR HEALTH - FROM CELL TO POPULATION has its focus on molecular characterization of effects from exposures as human genome-proteome environment interaction, briefly HuGePEI, and a corresponding profiling of subpopulations who may benefit most or incur extra risks from prevention or from therapeutic intervention in pre-clinical, clinical or post-clinical care.

BIOKYBERNETIKA is dedicated to MultiScale BioMathematics; it aims to advance coherent modelling of human body from a mathematical systems and an automation-engineering viewpoint. This involves dynamics of effectuation across several functional levels with highly interwoven control structures. Kybernetik кибернетика 控制论 is way of thinking that separates functional concept from physical realization, in systems analysis. In clinical medicine, it seeks causes of 'puzzling' syndromes and complex diseases of unknown cause in disorders of the multi-scale controls that maintain the dynamic equilibria in human body physiology system.

GeneSEES IMPACT aims to advance a comprehensive understanding of health and diseases under GeneSEES (Genetic disposition, Systemic conditions, Environmental exposures, Economic options, and Social embedding) impact on human body system’s cellular material, physio-functional controls, and on person’s autonomous steering of his or her operations.

HYGIOKYBERNETIK aims at integrative views of said factors in a combination across all dimensions, and at concepts for coherent control of their impact on a person’s body system. It will replace GeneSEES IMPACT which has a more book-keeping definition, as visible in current epidemiological research.

While within-body research can often be started in sizable numbers of healthy subjects or selective patients, the outside-world impact research needs a broad spectrum of variation for which the Eurasian landmass offers unique opportunities:

First, Eurasian landmass catches a huge spectrum of variation in climates, cultures, ethnicities, which makes an optimal opportunity for cutting-edge research.

Second, the mission is to establish the variation of exposures, diseases, and response to medical interventions in prevention and clinical care across the EurAsian populations.

Third, cooperative research across the Eurasian landmass means more comprehensive understanding, deeper insight, and higher visibility with lasting impact.

To exploit this resource for gaining inside into how the outside factors modify or change in-body dynamics, EurAsia's Young Science Talented & Ambitious is called to combine into a EURASIA'S BIG BRAIN. This year's conference is then dedicated to their future in the sciences.

Sergey Bogomolov	Jochen Mau	Sergey Mukhin
Moskau	Krefeld / Düsseldorf	Moskau

Conference Layout

Monday, 30 September 2019

11 am **SATELLITE MEETING 2**

Venue: DWIH Германская служба академических обменов (DAAD),
Московское отделение, Ленинский проспект 95А, 119313 г. Москва

Tuesday, 01 October 2019

10 am **OPENING SESSION**

10:00 am — 10:30 am **Welcome Speeches**

10:30 am — 10:45 am **Group Photo**

10:45 am — 12:15 am **INTRODUCTION TO EURASIAN COLLABORATION**

12:15 am — 01:15 pm **Lunch Break**

01:15 pm — 06:00 pm **SCIENTIFIC CONFERENCE SESSIONS**

Wednesday, 02 October 2019

10:00 am — 12:15 am **SCIENTIFIC CONFERENCE SESSIONS**

12:15 am — 01:15 pm **Lunch Break**

01:15 pm --- 06:00 pm **SCIENTIFIC CONFERENCE SESSIONS**

Thursday, 03 October 2019

10:00 am — 12:15 am **SCIENTIFIC CONFERENCE SESSIONS**

12:15 am — 01:15 pm **Lunch Break**

01:15 pm — 05:00 pm **SCIENTIFIC CONFERENCE SESSIONS**

5:10 pm **CLOSING SESSION**

Friday, 04 October 2019 **CULTURAL PROGRAM**

TBA Visit of MSU Main Building

SATELLITE MEETING 1:

"Initiative for Higher International Visibility of

Clinical Research in the Russian Federation"
Organizer: Jochen Mau

FOCUS: NEUROLOGY

Predictors of acute cerebral embolic lesions during carotid artery stenting

Tanashyan M.M.[1], Medvedev R.B.[1], Gemdzhian E.G.[2], Skrylev S.I.[1], Krotenkova M.V.[1]

Предикторы острых церебральных эмболических повреждений при стентировании сонных артерий

Танашян М.М.[1], Медведев Р.Б.[1], Гемджян Э.Г.[2], Скрылев С.И.[1], Кротенкова М.В.[1]

TANASHYAN Marine M. , MD PhD , Professor, Deputy Director for Research,
Head 1-st Neurological Department, Research Center of Neurology, Moscow, Russia
ТАНАШЯН Маринэ Мовсесовна , д.м.н., профессор – заместитель директора по научной работе.
Руководитель 1-го неврологического отделения ФГБНУ НЦН, Москва, Россия.

MEDVEDEV Roman B. , MD PhD , Researcher
1-st Neurological Department, Research Center of Neurology, Moscow, Russia
МЕДВЕДЕВ Роман Борисович, к.м.н. – научный сотрудник 1-го неврологического отделения ФГБНУ НЦН, Москва, Россия

GEMDZHIAN Eduard G. , Senior Researcher
Biostatistics Laboratory, National Research Center for Hematology, Moscow, Russia
ГЕМДЖЯН Эдуард Георгиевич, старший научный сотрудник лаборатории биостатистики ФГБУ «Национальный медицинский исследовательский центр гематологии» Минздрава России, Москва, Россия

SKRYLEV Sergei I. , MD PhD , Head
Head of the Department of Vascular and Endovascular Surgery, Research Center of Neurology, Moscow, Russia
СКРЫЛЕВ Сергей Иванович , д.м.н.
руководитель отделения сосудистой и эндоваскулярной хирургии ФГБНУ НЦН, Москва, Россия

KROTENKOVA Marina V. , MD PhD , Head,
Head of the Radiology Department, Research Center of Neurology, Moscow, Russia
КРОТЕНКОВА Марина Викторовна , д.м.н.
руководитель отделения лучевой диагностики ФГБНУ НЦН, Москва, Россия

THE SATELLITE MEETING 1 IS INTEGRATED INTO THE SCIENTIFIC SESSIONS

SATELLITE MEETING 2:

"Opportunities from the New Russian-German
Roadmap on Cooperation
in Education, Science, Research and Innovation of 12/2018"
Organizer: Helmut Hahn

Participants:
forgn memb RAS prof Helmut HAHN , KMF, Berlin
prof Jochen MAU, iqmeth Krefeld
prof. PAVLOV V.N., rector BashGMU, Ufa, (conf. Pending)
LAPSHIN V.N., PhD, director Programs &Strategies, VEB, Moscow ;
N.N.

with
Dr. A. HOESCHEN, Leiter der DAAD-Außenstelle Moskau /
Руководитель Московского отделения, Германская служба академических обменов (DAAD), Московское отделение,
acting as the local host.

Проф Хельмут Хан в флруме Петербурский диалог , VI «Петербургский диалог» «Европейская ответственность Германии и России» , Дрезден, 9–11 октября 2006 года «Deutschland und Rußland in Europäischer Verantwortung», Dresden, 9-11 Oktober 2006

Koch Mechnikov Forum - German-Russian Non-Government Organization: A Model for Civil-Society Interaction in Politically Dynamic Times

Helmut Hahn
Koch-Mechnikov Forum, Berlin, Germany

The Russian-German Roadmap on Cooperation in Education, Science, Research, and Innovation of December 10, 2018,[1] has opened new perspectives for German-Russian scientific and professional cooperation. Of particular interest is the long-range scope of this roadmap, which is planned for the coming 10 years ahead, and in this way making planning of future cooperative projects much easier.

KMF was founded at the 6th Petersburg Dialogue (2006) in Dresden as an initiative of the Petersburg Dialogue and was officially mandated by the President of the Russian Federation, Vladimir Putin, and the Chancellor of the Federal Republic of Germany, Angela Merkel. It unites health care professionals and other health workers as well as representatives from the medical products industry who share an interest in working with Russia.

Koch-Mechnikov Forum (KMF) brings together physicians and other people active in the medical sciences to discuss health problems independently of the vagaries of daily politics. Thus, members of KMF are best suited to act as ambassadors of goodwill and of peacemaking between nations and, right in keeping with the motto of the 18th Petersburg Dialogue (Bonn, 2019), “Cooperation as Leitmotiv for a peaceful Europe”.[2,3] In fact, German-Russian cooperation in health sciences is continuing at high pace, and Koch-Mechnikov Forum acts as a mediator of exchange of medical competence, information, ideas, and mutual stimulation.

References

[1] https://m.minobrnauki.gov.ru/common/upload/library/2018/12/Rossijsko-Germanskaya_dorozhnaya_karta.pdf
[2] 18–20 июля в Бонне состоялся XVIII Форум «Петербургский диалог» Тема Форума: «Сотрудничество как лейтмотив для мирной Европы: вклады гражданских обществ России и Германии» (http://petersburger-dialog.ru/ezhegodnye-forumy/2019.html) / 18. Petersburger Dialog vom 18.-20. Juli 2019 in Bonn/Königswinter
[3] «Свою эффиктивность подтвердили действующие патагены петербургского диалога (…), форум Кох Мечников по медицине, …. (Ihre Effektivität haben aktive Gestalter des Petersburger Dialogs nachgewiesen, (…) das Koch Metschnikow-Forum in der Medizin,…)» Citation from https://www.youtube.com/watch?v=K4L9fWVk8W8 (1:45)

Foreign Minister of the Federal Republic of Germany

Heiko Maas

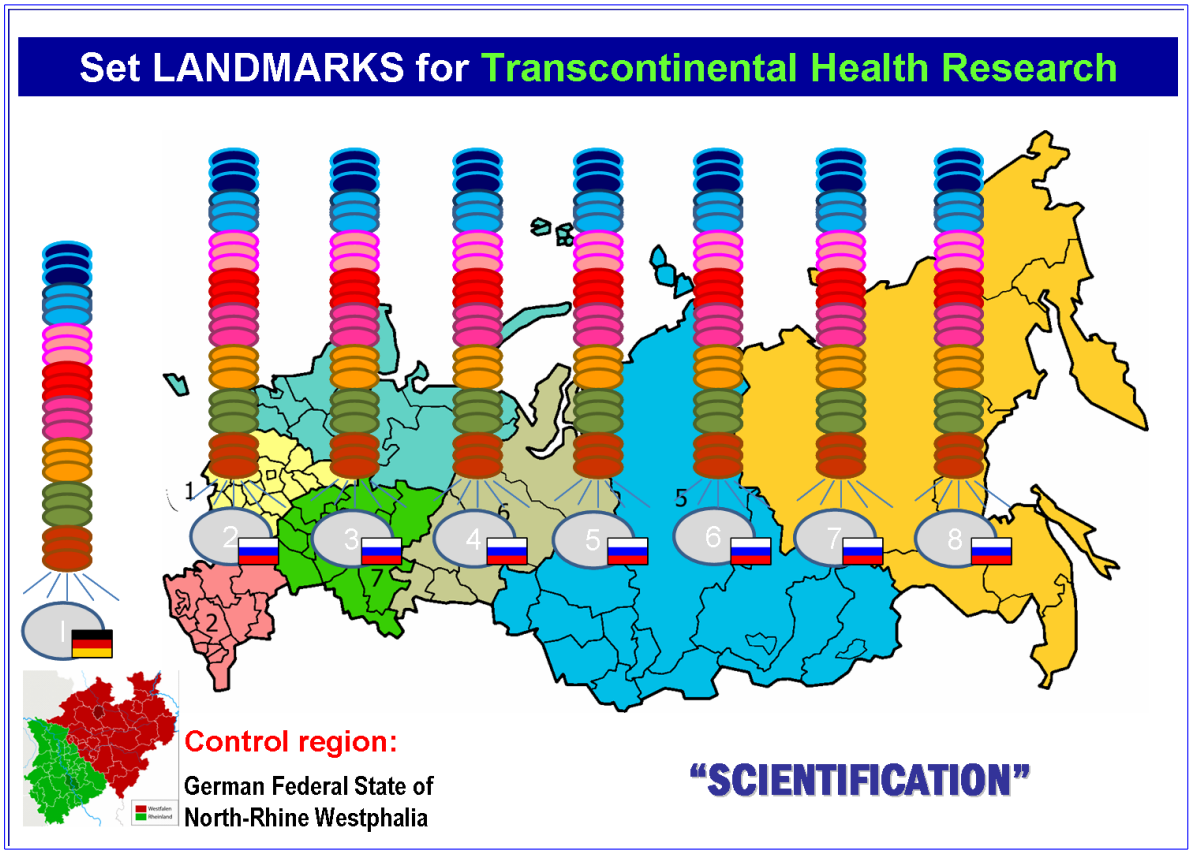
https://www.youtube.com/watch?v=L7cb8H6cSKk

Foreign Minister of the Russian Federation

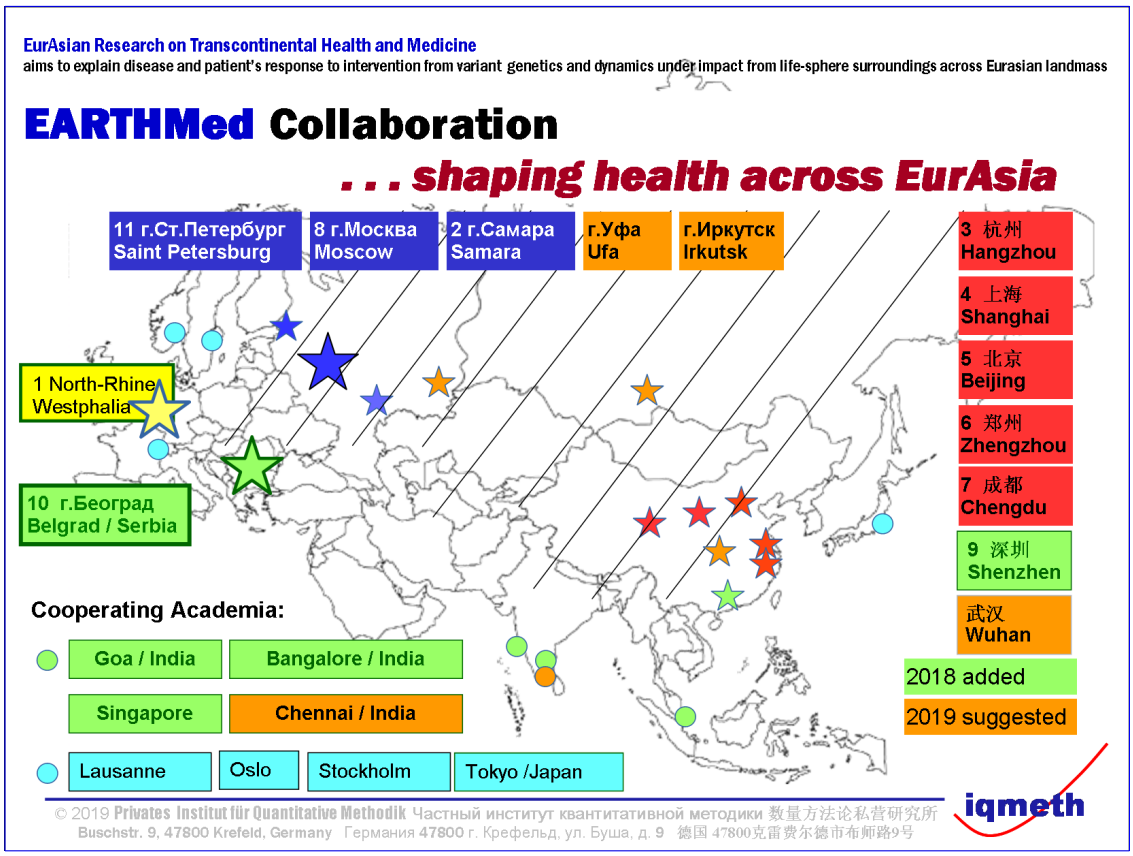
Sergey Lavrov

https://www.youtube.com/watch?v=K4L9fWVk8W8

«Proof-of-Concept» across the Russian Federation



and later application across EURASIA



for «return of investment»

BIG BRAIN 2019 Conference for Collaboration in EurAsia
30 September - 04 October 2019, Moscow, Russia
LOMONOSOV MOSCOW STATE UNIVERSITY BIOKYBERNETIKA

Collaborative Research in Health and Academic Medicine Across Eurasia: Mandate, Investment and Returns

Jochen Mau
iqmeth Institut für Quantitative Methodik – Private Academic Consultancy for Research and Development, Krefeld, Germany

Shared economy in fair trade seems to be widely believed to avoid problems, to resolve issues and even to almost 'guarantee' prosperity and welfare for all — and everywhere, when looking at all the summits on and around economic development and global trade. But 'global economy' seems to add to disparity, to induce as well unhappiness and dissent that may grow into struggles and more, when looking at daily newsline streams of reports about unrest, clashes and political disasters: *Scientification* is mandated.

When all roads have been built, all railway tracts been laid, all houses been constructed – in other words, given satisfactory levels of life-goods supply, food and shelter, according to prevalent societal settings, a **person's health** and a **person's subjective perception of** his or her **"life worthiness"** may then come into focus, and a person's optimistic views on future may gain relevance for his or her integration into a harmonious society. *Local scientification* is needed.

At society level, this translates into investments for health care at high level and into investments for higher education. For the former, it will mean **equivalent prevention, equivalent medical care, and equivalent long-term nursing** for all according to local settings, while for the latter, it will mean an **education of young talent aimed at highest achievement in the sciences**, including career opportunities of last in top-level research that will keep them in their home country.

For **Transcontinental Collaboration in Health and Academic Medicine TCHAM**, one will then have to invest in joint research and educational programs, common understandings of methodologies, and sustained structures for management.

Four Initiatives will hence shape the infrastructure:

A. **Strategic Partnership in EurAsian Research** for **amplification and potentiation** in a EurAsian network of research on transcontinental issues in health and medicine, ***SPEAR*** ,
B. **Doctors for EurAsian Research** to **promote young talent** with qualifications for collaboration in the EurAsian research network, ***DEAR*** ,
C. **Harmonized EurAsian Research Methodology** to create **common understanding** and **coherent application** of concepts within the EurAsian research network, ***HEARMe*** ,
D. **Sustained EurAsian Management** to develop **lasting structures and competences** for transnational management in EurAsian collaboration, ***SEAM***.

Research Programs shall aim to explain disease and patient's response to intervention from variant genetics and functional bio-dynamics under impact from his or her life-sphere surroundings, across the EurAsian landmass.

Three Challenges will require transdisciplinary research for two or more generations:
molecular health Human Genome Proteome Environment Interactions HugePEI for cellular health,
biokybernetik body system's functional dynamics and their in-body controls,
hygiokybernetik impact of person's life-sphere factors and their coherent control from outside,
- towards an optimizing **algorithmic medicine** built from mathematical systems theory and control.

Returns of investment arise, when best health secures productive power in industry and economy and best education secures power of innovation and development, since jointly they are necessary for a nation's prosperity and welfare. Noteworthily, returns to society arise from outstanding achievements in highly contested fields of the sciences by which one visibly occupies a key field in scientific research, then takes a leading role in international competition and keeps it for a long time. The huge spectrum of variation in populations, cultures, topography and climates, makes EurAsian landmass a unique research field, and the expanding middle-classes in its rising economies an interesting "market" for health research and health industry.

Использование многослойных мемристорных элементов в самообучающихся спайковых нейронных сетях

Наталья Андреева, Дмитрий Чигирев, Антон Бобков, Марина Герасимова
Кафедра микро- и наноэлектроники, СПбГЭТУ "ЛЭТИ", Санкт-Петербург, Россия

В работе рассматривается подход к моделированию нейронных сетей на аппаратном уровне, в основе которого лежит использование металлооксидных гетероструктур с эффектами многоуровневого переключения сопротивления и памятью. Такие структуры могут выполнять роль искусственных синапсов в нейронных сетях, обеспечивая модуляцию синаптической передачи в широком диапазоне величин. В сочетании с простейшей моделью спайкового нейрона "интегрировать-и-сработать" с утечками, предлагаемый подход позволяет организовать импульсную нейронную сеть прямого распространения с механизмом синаптической пластичности, зависимой от времени активации [1]. Результаты компьютерного моделирования свидетельствуют о способности спайковых нейронный сетей с имплементированными электронными многоуровневыми синапсами к самообучению и обработке асинхронных потоков входных данных.

Для имитации механизма синаптической передачи в искусственных нейронных сетях, были изготовлены тонкопленочные двухслойные металлоксидные структуры, представленные последовательностью слоев оксидов титана и алюминия (толщинами 30 нм и 5 нм, соответственно) [2]. Синтезированные методом атомно-слоевого осаждения двухслойные структуры уверенно демонстрируют многоуровневое переключение сопротивления в диапазоне семи порядков по величине. Нужный уровень запоминаемого сопротивления задается путем приложения напряжения между электродами гетероструктуры. Относительно заданного уровня сопротивления, наблюдается биполярное резистивное переключение, при котором отношение величины сопротивления в высоокомном состоянии к низкоомному (R_{OFF}/R_{ON}) составляет один-два порядка. Появление многоуровневых резистивных состояний в TiO_2/Al_2O_3 двухслойных структурах обусловлено обратимой модификацией физических свойств слоя оксида алюминия, за счет дрейфа кислородных вакансий из второго слоя структуры - оксида титана, играющего роль резервуара кислородных вакансий.

Результаты компьютерного моделирования импульсной нейронной сети на базе электрических схем с распределенными параметрами и мемристивных структур с многоуровневым переключением показали, что изменение синаптической пластичности в диапазоне трех порядков по величине позволяет обрабатывать асинхронные потоки данных с сенсоров, использующихся в протезах сетчатки, а также определять направление движения. Предполагается, что увеличение диапазона синаптической пластичности до семи порядков по величине обеспечит возможность унификации нейронной сети для решения разного рода задач (распознавание звуковых паттернов, формы трансмембранных потенциалов) и самоонастройки ее основных параметров.

Список литературы

[1] Bichler O, Querlioz D, Thorpe SJ, Bourgoin JP, Gamrat C. Extraction of temporally correlated features from dynamic sensors with spike-timing-dependent plasticity. *Neural Networks* **32**:339-348, 2012.
[2] Andreeva N, Ivanov A, Petrov A. Multilevel resistive switching in TiO_2/Al_2O_3 bilayers at low temperature. *AIP Advances* **8**:025208, 2018.

Multilayer Memristive Devices for Spiking Neural Networks With Unsupervised Learning

Natalia Andreeva, Dmitriy Chigirev, Anton Bobkov, Marina Gerasimova
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We report a prospective approach to neural network modeling based on implementation of metal-oxide heterostructures with non-volatile memory behavior and multilevel resistive switching. These structures could be used as artificial synapses in neural networks, providing a modulation of synaptic strength in the range of seven orders of magnitude. Together with leaky integrated-and-fire neurons it allows to organize a feed-forward spiking neural network with embedded spike-timing-dependent plasticity mechanism at the hardware level [1]. The results of simulation demonstrate an ability of reconstructed networks based on electronic multilevel synapses to unsupervised learning and processing of asynchronous stream of spikes.

For mimicking a synaptic behavior we synthesized thin film bilayer metal oxide structures (based on a sequence of titanium and aluminum oxides active layers, with thicknesses of 30 nm and 5 nm, correspondingly) using atomic layer deposition [2]. In these structures, a large change in resistance (in the range of seven orders of magnitude) is achieved. Relative to the electrically tuned resistance state of the entire structure, bipolar resistive switching occurs with R_{OFF}/R_{ON} ratio in the range of 1 - 2 orders of magnitude. The appearance of multilevel resistance states in TiO_2/Al_2O_3 bilayer structures is associated with the reversible modification of the Al_2O_3 layer properties due to oxygen vacancies drifting in under a bias voltage. In this case, the TiO_2 layer acts as a reservoir of oxygen vacancies.

The computer modeling of the spiking neural network based on electrical circuits with distributed parameters and implemented multilevel memristive devices reveals that variation of the synaptic strength in the range of three orders of magnitude ensures the possibility of tracking the asynchronous data stream from dynamic vision sensors (used in retinal implants) and recognition of the movement direction. While increasing the range of synaptic strength variation up to seven orders of magnitude allows to unify the network for multiple tasks (audio data recognition, transmembrane spike sorting) and provides an option for the network parameter self-tuning.

References

[1] Bichler O, Querlioz D, Thorpe SJ, Bourgoin JP, Gamrat C. Extraction of temporally correlated features from dynamic sensors with spike-timing-dependent plasticity. *Neural Networks* **32**:339-348, 2012.
[2] Andreeva N, Ivanov A, Petrov A. Multilevel resistive switching in TiO_2/Al_2O_3 bilayers at low temperature. *AIP Advances* **8**:025208, 2018.

Анализа стабилности модела реакционих система

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Анализа Стехиометријских Мрежа (АСМ, или CHA енг.) је развијена за одређивање стабилности реакционих система. [1-3] Под реакционим системима подразумевамо сложене мреже састављене из више корака, „реакција“, у којима се дешавају трансформације између реакционих врста. У свакој реакцији реактанти се трансформишу у продукте. Трансформације између реакционих врста резултирају у променама њихових концентрација. Штавише, захваљујући принципу о дејству маса, брзина сваке реакције је пропорционална концентрацијама реактаната. Тако у систему могу настати повратне спреге у којима концентрација реактанта утиче на брзину сопствене промене. Пошто свака реакциона врста може учествовати у више реакција, било као реактант или као продукт, њихов сплет се јавља у форми мреже повратних спрега. Даље, реакциони системи су специфични међу динамичким системима по томе што су трансформације међу реакционим врстама увек одређене стехиометријским односима. То значи да се у сваком појединачном реакционом кораку, концентрације учесника у реакцији увек мењају у фиксираним односима – стехиометријским коефицијентима. Зато су стехиометријске мреже посебно погодне за моделирање реакционих система.

Проширена варијанта Аутокаталатора са три променљиве [4] ће овде бити коришћена да се илуструје ефикасност АСМ. Овај модел садржи каскаду од три реакције које трансформишу масу система линеарно и два нелинеарна каталитичка корака. Линеарни део модела је упоредив са линеарним моделима епидемије са прелазима између резервоара подложних зарази, заражених, заразних, оболелих и опорављених. Сваки прелаз у овом ланцу одговара једној реакцији у реакционом моделу са флуксом/брзином која се добија множењем константе брзине са масом/концентрацијом доступном за прелаз/реакцију. Међутим, у Аутокаталатору са три променљиве постоје и реакциони кораци у којима се дешавају интеракције међу конституентима. Прецизније, брзина једне од реакција, познате под називом *аутокатализа*, пропорционална је концентрацији производа. Тако је омогућена појава читавог спектра егзотичних феномена, укључујући једноставне периодичне осцилације и хаос. [5] Све ове изванредне могућности су условљене стабилношћу устаљених стања система од три обичне диференцијалне једначине које карактеришу динамику промена концентрација интермедијера у реакционој мрежи.

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Stability Analysis of the Model of Reaction Systems

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Stoichiometric Network Analysis (SNA) has been developed to evaluate the stability of reaction systems. [1-3] Reaction systems are considered to be complex networks consisting of multiple steps, the "reactions", in which transformations between reactive species occur. In each reaction, reactants are transformed to products. Transformations between reactive species results in changes of their concentrations. Moreover, due to the mass-action principle, the rate of each reaction is proportional to the reactant concentrations. Hence, feedback loops may emerge where reactant concentrations influence rate of its own change in the system. Since each reactive species may be part of multiple reactions, either as a reactant or product, their joint interconnection appears as a network of feedback loops. Furthermore, reaction systems are specific among dynamic systems in a way that transformations between reactive species are always governed by the stoichiometry. It means that in each individual reaction step concentrations are always changed in fixed ratios – stoichiometric coefficients. Therefore, stoichiometric networks are particularly convenient for modeling reaction systems.

Three-Variable Autocatalator model [4] will be used here to demonstrate efficiency of SNA. It is based on a cascade of three reactions that transform mass at linear rates and two nonlinear catalytic steps. The linear part of the model would be comparable to a linear epidemic model of transitions from a pool of susceptible to stages of infected, infectious, diseased, and recovered. Each transition in this chain corresponds to one reaction in reaction model, with flux/rate obtained by multiplication of rate-constant with mass/concentration available for transition/reaction. However, in Three-Variable Autocatalator model there are also reaction steps where reactions between different constituents occur. More precisely, there is one reaction step with rate proportional to the concentration of product, which is known as the *autocatalysis*. As a consequence a spectrum of exotic phenomena, including simple periodic oscillations, mixed-mode periodic oscillations and chaos can be obtained. [5] All of these exciting possibilities depend on the stability of the steady state solution of a set of three interwoven differential equations that characterize the dynamics of changes of concentrations in the intermediary species of the reaction network.

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Differentiation of Valence Emotional States in Localized EEG Signals using Motif Patterns

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Emotions are the fundamental intellectual capacity of human that is characterized by perception, attention, and behavior. It plays a vital role in decision making, cognitive, and social interactions. Emotion-related mental disorders are one of the major causes of death worldwide [1]. Moreover, emotional abnormalities are associated with depression, stress, and indecisive irritability. Analysis of emotions finds various application ranging from gaming to clinical studies [2].Emotions are described using two-dimensional arousal and valence scales. Arousal represents the emotion while valence scale defined the pleasantness of the emotion perceived by the human [3]. Physiological signal based emotional state analysis can provide relevant information for better diagnostics. Electroencephalography (EEG) are widely used signal due to its noninvasiveness. Further, source localized EEG signal analysis reduces complexity and provides a better clinical relevance [4].

In recent years, several signal processing methods have been proposed for the emotion recognition. However, highly source localized EEG based pattern analysis is not well established for assessment of the emotional states. In this work, source localized EEG signals in the frontal region of the brain are analyzed to characterize the positive and negative valance states of emotion. For this, the EEG signals from publically available online DEAP database are considered. The EEG electrodes namely, Fp1, Fp2, AF3, and AF4 are selected and the signals are converted to triadic motif sequences. Further, the probability of occurrence of each motif patterns are computed and used for analysis [5]. Two features namely, permutation entropy and motif occurrence index are extracted to study the valence emotional states.

The results show that the proposed approach is able to differentiate positive and negative valence states of emotions. The mean and median value of permutation entropy is found to be greater in positive valence for Fp2 and AF4 electrodes. The proposed motif occurrence index feature shows higher mean and median for negative valence class. All the features are found to be distinct and statistically significant for both the electrodes ($p \leq 0.05$). Further, the motif pattern-based verification of source localized EEG signals can discriminate the valence states of emotions. Thus, it appears that the proposed approach could be useful in the analysis of emotions in EEG signals for different clinical conditions.

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Точность и эффективность разных способов оценки активности механизма передачи возбудителей инфекционных заболеваний

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На протяжении всего времени существования человечества инфекционные заболевания оставались основной причиной смерти. С начала XX века ситуация изменилась – как заболеваемость большинством инфекционных заболеваний, так и вероятность смерти вследствие заболевания стала значительно снижаться, и на первые места в структуре причин, вызывающих смерть, вышли болезни сердечно-сосудистой системы и онкологические заболевания. Среди причин, вызывающие снижение заболеваемости и смертности от инфекционных заболеваний: появление вакцин для предупреждения заболеваний и антибиотиков для их лечения.

Однако в последние десятилетия появились и негативные тенденции. Увеличилась прослойка неиммунных, в том числе и из-за негативного отношения части населения к вакцинации. Стремительно увеличивается устойчивость микробов к антибиотикам. В связи с этим актуальным остается задача слежения за активностью механизма передачи возбудителей инфекционных болезней человека.

Для количественной оценки активности механизма используется такой показатель, как контактное число (basic ratio index), или R_0. Оно равно среднему количеству инфицированных, которые заражаются от одного инфицированного. Оценивать данную величину можно по: (1) Уровню средней многолетней заболеваемости, (2) Соотношению заносных и контактных случаев, (3) Доли восприимчивой части населения, (4) Скорости роста заболеваемости после заноса нового возбудителя в популяцию, (5) Соотношению заболеваемости в разных возрастных группах, или (6) Длине периода в циклических колебаниях многолетней заболеваемости.

При кажущейся простоте связи большинства данных показателей с R_0 имеются «подводные камни». На указанные соотношения существенно влияют гетерогенность популяции (наличие групп риска) и возрастная структура населения. Если использовать чрезмерно упрощенные модели, то будут получены оценки R_0, чрезвычайно сильно отличающиеся от истинных. Если же пытаться использовать максимально обобщенные модели эпидемического процесса, то для их валидизации нужны количественные значения распределения по индивидуальной восприимчивости и заразности, что нереально при современном уровне эпидемиологии.

В работе исследован ряд разных способов оценки величины контактного числа, изучены причины, приводящие к погрешностям, и величины смещения оценок, и получены области применимости данных методов.

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Accuracy and effectiveness of different methods for assessing the activity of the transmission mechanism of infectious disease pathogens

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Infectious diseases have been remaining the main cause of death throughout the entire existence of mankind. The situation has changed since the beginning of the XX century: both infectious diseases and following death rates have dramatically decreased and now cardiovascular and oncological diseases are ranking number one among death causes. Amongst causes that reduce morbidity and mortality from infectious diseases there are: creation of vaccines to prevent diseases and antibiotics to treat them.

The situation, however, is not entirely positive. There has been an increase in the number of nonimmune recipients, in particular, due to the present negative attitude towards vaccination among the population. Antibiotic resistance in microbes is rapidly increasing. That is why the problem of monitoring the activity of the transmission mechanism of contagious-disease pathogens remains relevant.

The contact number indicator (basic ratio index), or R0, is used for the quantitative evaluation of the activity of the mechanism. It is equal to the average number of infected people who got a virus from one infected person. This value can be measured by (1) the level of average long-term morbidity rate, (2) the ratio of adventitious and communicable means of transmission, (3) the proportion of the receptive population, (4) morbidity rates growth after the introduction of a new pathogen into the population, (5) the ratio of morbidity levels in different age groups, or (6) the length of the period in the cyclic fluctuations of long-term morbidity.

Despite the apparent simplicity of the connection between most of these indicators with R0, there are some underlying potential problems. These ratios are greatly influenced by the population heterogeneity (the presence of risk groups) and the age structure of the population. If you use oversimplified models, the obtained R0 values will extremely differ from the real ones. If we try to use the most generalized models of the epidemic process, then their validation requires quantitative values of the distribution of individual sensitivity and contagion, which is impossible taking into account the current level of epidemiology.

The study offers research on various ways to evaluate the contact number, includes both the causes leading to errors and magnitude of the bias, the applicability of these methods has been estimated as well.

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Биолошки осцилатори у репродуктивној биологији

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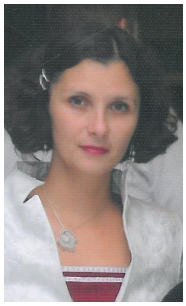

Наручито занимљиви и од посебног значаја за репродуктивну биологију и медицину су хормонски осцилаторни процеси [1] чија активност има за последицу осцилаторне феномене на нивоу ћелија, ткива, органа и органских система од значаја за репродуктивно здравље јединке. Хормонске осцилације циркадијалне, лунарне, ануалне ће се одразити на осцилаторне процесе оогенезе и сперматогенезе, на састав и квалитет унутарћелијског садржаја репродуктивних ћелија али и састава ћелијских мембрана и омотача. Сви ови осцилаторни системи морају бити међусобно синхронизовани не само унутар једног организма већ и између јединки оба пола небили дошло до успешне оплодње. Аутор сматра, да се поред ових осцилаторних феномена који су већ познати у литератури, сам процес ћелијске оплодње може сматрати осцилаторним процесом [2].

Green и Purves R.D. су још 1984. [3] изнели хипотезу о пенетрацији сперматозооида кроз јајну ћелију са биомеханичког аспекта, помињући осцилације релаксације као могући механизам пенетрације. Према теорији [2] у току процеса *in vitro* оплодње осцилаторно кретање многобројних сперматозооида и њихов периодични утицај на површину јајне ћелије промениће основно осцилаторно стање саме јајне ћелије. Претпоставка је да се процес пенетрације једног сперматозооида дешава у тренутку када јајна ћелија постигне резонантно стање на фреквентном опсегу који одговара фрекфенцији/јама осциловања бар једног сперматозооида. Концепт оплдње као осцилторног процеса објашњен је помоћу биомеханичког осцилаторног модела зоне пелуциде. Помоћу квазистатичког апроксимативног модела зоне пелуцида у виду шупље сфере [4] анализиран је деформациони рад зоне пелуциде настао као последица симетричног дејства сперматозооида на њену површину а у зависности од дебљине зоне пеуциде и спољњег притиска који изазивају сперматозооиди. Недостатци квазистатичког модела ће такође бити разматрани.

Кључне речи: репродуктивна биологија, сложени осцилатори, синхронизација, оплодња
Захвалница: Део овог истраживања је потпомогнут од стране Минстарства просвете, науке и технолошког развоја Републике Србије преко Математичког института Српске Академије Наука и Уметности (МИ САНУ), Београд, и пројекта Бр. ОИ174001: „Динамика хибридних система сложених структура. Механка материјала.“

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Biological Oscillators in Reproductive Biology

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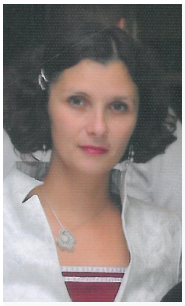

Specifically interesting and of special importance for reproductive biology and medicine are hormonal oscillatory processes [1] whose activity results in an oscillatory phenomenon at the level of cells, tissues, organs and systems of organs of importance for the reproductive health of the individual. The hormonal oscillations and their circadian, lunar, annual rythm will affect the oscillatory processes of oogenesis and spermatogenesis; the composition and quality of intracellular contents of reproductive cells, as well as the composition of cell membranes and envelopes. All these oscillatory systems must be synchronized not only within one organism, but also between both genders for successful fertilization to occur. In addition to these oscillatory phenomena already known in literature, the author proposes that the process of cellular fertilization itself can be considered an oscillatory process [2].

Green and Purves R.D. were introduced in 1984. [3] a hypothesis on the penetration of spermatozoa through the egg cell from the biomechanical aspect, referring to oscillations of relaxation as a possible penetration mechanism. According to theory [2], during the in vitro fertilization process, the oscillatory movement of numerous spermatozoa and their periodic influence on the surface of the oocyte will change the basic oscillatory state of the oocyte itself. The assumption is that the penetration process of one spermatozoa is occurring at a time when the oocyte reaches a resonant state at a frequency corresponding to the frequency oscillation of at least one spermatozoa. The concept of fertilization as an oscillatory process is explained by the biomechanical oscillatory model of the *zona pelucida*. Using the quasistatic approximative model of the *zona pelucida* in the form of a hollow sphere [4], the deformation of the zona pelucida was analyzed as a result of the impact of symmetric spermatozoa distribution on its surface, depending on the thickness of the *zona pelucida* and the external pressure caused by spermatozoa. The limitations of the quasistatic model of the *zona pelucida* will also be considered.

Key words: reproductive biology, complex oscillators, synchronization, fertilization

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Biomedical Imaging: The Information Processing Perspective

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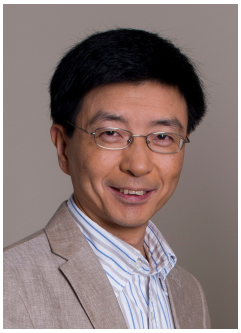

Imaging technologies are one of the driving forces for the rapid developments in life sciences [1]. From an information processing perspective, it is the field of biomedical image analysis / understanding that bridges the huge gap between the ever increasing amount of complex data and the relevant comprehensive information by automatic extraction and quantification algorithms. In particular, it is hardly possible for humans to manually screen and quantify large-scale datasets. Biomedical image analysis [2,3,4] offers a rich spectrum of theories and algorithmic methods to face the multifaceted issues and challenges from imaging-based research and development in life sciences. The recent stormy development in machine learning and deep learning [5,6,7,8] marks the next qualitative leap in extraction and quantification quality, with numerous applications to various subfields of life sciences (e.g. brain image analysis [9], breast cancer diagnosis [10]).

This talk begins with a brief summary of the research topics of biomedical image analysis and their relevance to life science research. The focus will then be on some of our work in this area, ranging from imaging techniques [11,12] to automatic image analysis including image segmentation [13,14] and motion analysis [15,16]. Finally, an attempt will be made to address current and future challenges associated with biomedical imaging such as application transfer in deep learning [17], handling large volumetric data, and multiscale imaging.

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Хигучијева фрактална димензија и обрада неурофизиолошких сигнала

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Последњих година расте интересовање за употребу нелинеарних мера у анализи физиолошких сигнала као што су електроенцефалограм (ЕЕГ), електрокардиограм (ЕКГ), електромиограм (ЕМГ), “current clamp” сигнали итд. [1-5]. Ови сигнали су производ више различитих и међуделујућих временских скала, а одражавају интегративно понашање сложених нелинеарних динамичких подсистема као што су нервни или кардиоваскуларни систем. Хигучијева Фрактална Димензија (ХФД), као нелинеарна мера, корисна је за описивање динамике ових комплексних подсистема у здрављу и болести [2]. Употреба ХФД у биомедицини еволуирала је од анализе различитих података о физиолошким и клиничким временским серијама па до најновије примене у аутоматској детекцији и мониторингу различитих патолошких стања [2].

Циљ овог излагања је да представи методолошке и епистемолошке аспекте нашег недавног истраживања о употреби ХФД у неурофизиологији с нагласком на анализи “бурстинг” облика нервне активности. У том смислу, расправљаћемо о практичном оквиру у којем је могуће истаћи предности и ограничења примене ХФД у ћелијској, али и системској неурофизиологији.

У пракси се показало да је ХФД ефикасна у праћењу активности филогенетски, анатомски и функционално различитих неурона и неуронских група у различитим експерименталним условима [1-6]. Наш главни фокус био је на примени ХФД у анализи “бурстинг” активности Бр неурона пужа пре и после излагања константном магнетном пољу (КМП), индукције 2,7 mT и 10 mT, са или без примене лека оуабаина (инхибитор Na+/K+ пумпе) [3, 6]. Ове студије су дале додатни увид у модулаторни ефекат КМП умерене индукције на активност једног неурона. Штавише, ово истраживање је такође показало да се поред класичних метода за анализу “бурстинг” активности, ХФД може успешно користити и за раздвајање акционих потенцијала (АП) од интер-спајк интервала (ИСИ) и интер-бурст интервала (ИБИ) [6].

Међутим, као што је то случај са сваком мером комплексности, и ХФД има своје недостатке јер није најпрецизнија мера у свим експерименталним условима [1]. Из ових разлога, комбинована употреба ХФД са другим нелинеарним и линеарним методама на аутоматизован или не-аутоматизован начин обезбеђује економичну и поуздану квантитативну процену неуронске активности у здрављу и болести [1, 2, 5]. Изгледи за даљу примену ХФД у основним истраживањима и клиници су, према томе, више него светли.

***Захвалница*:** Овај рад је подржан од стране Министарства просвете, науке и технолошког развоја Републике Србије, пројекат ОИ173027.

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Higuchi Fractal Dimension and Neurophysiological Signals Processing

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In recent years there has been a growing interest in the use of non-linear measures for the analysis of the physiological signals such as electroencephalogram (EEG), electrocardiogram (ECG), electromyogram (EMG), “current clamp” recordings, etc. [1-5]. These signals arise from several different and interacting temporal scales, and they reflect the integrative behavior of complex nonlinear dynamical subsystems such as nervous or cardiovascular system. Higuchi Fractal Dimension (HFD), as a non-linear measure, is helpful to describe dynamics of these complex subsystems in health and disease [2]. The use of HFD has evolved from the analysis of different types of physiological and clinical time-series data to the latest application in the automatic detection and monitoring of various pathological conditions [2]

This presentation will give a methodological and epistemological overview of our recent research on the use of HFD in neurophysiology with the particular emphasis on neuronal “bursting” activity. In this respect, we will discuss the practical framework in which it is possible to highlight the advantages and limitations of the application of HFD in both cellular and systems neurophysiology.

So far, HFD proves to be useful in monitoring the activity of phylogenetically, anatomically, and functionally distinct neurons and neuronal ensembles in different experimental conditions [1-6]. Our primary focus was on the use of HFD in monitoring bursting activity of the snail Br neuron before and after exposure to 2.7 mT and 10 mT static magnetic fields (SMFs), with and without ouabain (Na^+/K^+ pump inhibitor) administration [3,6]. These studies provided additional insight into the modulation of single-neuron activity by moderate-intensity SMFs. Moreover, this research also showed that besides “classical” methods for the analysis of bursting activity, HFD could be used to distinguish action potentials (AP), interspike intervals (ISI) and interburst intervals (IBI) [6].

However, as the case with the most complexity measures, HFD has its shortcomings because it is not the most accurate measure in all experimental conditions [2]. For these reasons, the combined use of HFD with other nonlinear and linear methods in automated or non-automated manner provides the cost-effective and reliable quantitative estimate of neuronal dynamics in health and disease [1, 2, 5]. The prospects for further research and clinical applications of HFD are, therefore, more than promising.

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Корреляция Стрелера-Милдвана объясняет происхождение старения

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Показано, что в адекватных условиях даже состарившиеся части тела могут восстанавливать структуру и функцию [1]. Есть данные, что возможны условия жизни, способствующие значительному замедлению старения человека за счет более адекватного и стабильного функционирования систем управления организмом [2, 3].

Предложена простая модель появления старения в неадекватных условиях даже у потенциально нестареющих особей. Модель основана на дополнении дифференциального уравнения Гомперца [4] для приращения смертности M, связанного с приращением возраста t, вторым членом, связанным с изменением внешних условий (“давления среды”), в которых существует популяция. И p - наивероятнейшее значение этого флуктуирующего давления окружающей среды в относительных единицах. Затем было обосновано предположение, что кинетический параметр Гомперца a (скорость старения) линейно падает с ростом p, т.к. эффективность процессов самоподдержания зависит не только от особенностей организма, но и от условий, в которых он существует. Решение этого модифицированного дифференциального уравнения в случае квазистабильного p (среднее $p \approx \text{const}$) совпадает с классическим законом Гомперца (экспоненциальный рост смертности) [4]. 135 лет спустя было показано, что набор различных экспоненциальных зависимостей характеризуется отрицательной корреляцией между их параметрами в полулогарифмическом масштабе [5], т.е. между $\ln M_o$ и a, что характерно для потенциально нестареющих организмов [2, 3].

Биологические соображения позволяют понять, как адекватные значения p побуждают организм функционировать так, чтобы его тело полностью обновлялось, оставаясь нестареющим. Но для выживаемости этот диапазон p не является оптимальным, т.к. в такой окружающей среде высока смертность от внешних причин. Для снижения этой смертности особь ищет менее агрессивную среду. Таким образом, она идет на компромисс, жертвуя оптимальным функционированием (полным обновлением) в пользу менее агрессивной среды. В результате самообновление организма становится неполным, приводя к старению и возрастному увеличению смертности. Но этот рост смертности с возрастом компенсируется более значительным снижением смертности от внешних причин. Оптимальный баланс, поддерживаемый эволюционными силами, оптимизирует среднюю приспособленность популяции организмов. Принимая это во внимание, можно предположить, что в компромиссной ситуации параметр a экспоненциальной части закона Гомперца (который отражает вклад скорости старения) должен снижаться по мере увеличения давления окружающей среды. В то же самое время предэкспоненциальный множитель закона Гомперца (стартовая сила смертности M_o) должен расти с увеличением давления окружающей среды. Таким образом, между этими двумя параметрами существует отчетливая взаимосвязь. И она неоднократно наблюдалась как у людей, начиная с 1960 года [5], так и в дальнейшем у приматов, крыс и мух, Основываясь на этой закономерности и на свойствах потенциально нестареющих стволовых клеток можно понять, как возникает старение при неадекватном влиянии внешней среды на организмы.

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The Strehler-Mildvan Correlation Explains the Origin of Aging

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The newest findings indicate that in adequate conditions even aged parts of the body can restore their structure and function [1]. In addition, the analysis shows that living conditions are possible that contribute to a significant slowdown in human aging rate due to more adequate and stable functioning of the body's control systems [2, 3].

A simple model was proposed to explain the inevitability of aging in some inadequate environment, even with the perfect design of a potentially ageless body. The model based on the extension of Gompertz differential equation [4] for an age-dependent increment in mortality rate $\boldsymbol{M}$ connected with an increment of age $\boldsymbol{t}$ via introducing to initial equation an additional term related with the alterations in total external conditions ("environmental pressure") in which the population exists. And $\boldsymbol{p}$ is the most probable value of this fluctuating environmental pressure in relative units. Then the proved assumption was made that Gompertz kinetic parameter $\boldsymbol{a}$ (rate of aging) approximately linearly depends on $\boldsymbol{p}$. Because the effectiveness of self-maintenance processes may depend not only on the peculiarities of a body but also on the conditions in which it exists. The solution of this modified differential equation in case of quasi-stable $\boldsymbol{p}$ (an average $\boldsymbol{p}\approx$const) is the same as the classic Gompertz Law (exponential growth of mortality rate) [4]. 135 years later, it was shown empirically [5] that the set of different exponential dependences was characterized by a negative correlation between their parameters on a semi-log scale (between $\ln\boldsymbol{M_o}$ and $\boldsymbol{a}$), which is characteristic of a potentially non-aging organisms [2, 3].

Biological consideration allows for the conclusion that a reasonable amount of $\boldsymbol{p}$ plays a stimulating role for body functioning and within this range a body can completely renew itself, thus remaining ageless. However, this range of $\boldsymbol{p}$ is not optimal for survival because the environment induces a heavy death toll among such populations and the mortality is high for environmental reasons. To reduce this mortality the body will favors a less aggressive ambience. It thus compromises by sacrificing optimal functioning (complete renewal) for the benefits of the less aggressive environment. As a result, the body's self-renewal becomes incomplete, and senescence generates an age-related increase in mortality rate. This age-related mortality increase is compensated for by a more significant decline in mortality due to external causes. The optimal balance is kept by evolutionary forces, which optimize the average fitness of a population of organisms. Taking this into account, one can assume that in the compromised situation the Gompertzian exponential parameter (which reflects the contribution of the rate of aging) must decline as environmental pressure increases. At the same time, the age-independent part of Gompertz mortality rate (another Gompertzian parameter) must increase when the environmental pressure increases. Thus there is distinctly reciprocal relationship between these two parameters, which has been repeatedly observed for human beings, primates, rats and flies since 1960 [5]. So we suggest that natural aging may be caused by an inadequate environment-to-body interaction.

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Сегментация гистологических изображений с помощью модели обучаемого контура

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В последнее время, разработка гибридных методов стала перспективным направлением в обработке и анализе изображений. Эти методы представляют собой комбинацию нейронных сетей и классических математических методов обработки изображений. Сочетание хорошей обобщающей способности нейронных сетей и гибкости классических моделей позволяет существенно помочь в решении большого числа задач обработки изображений, что особенно актуально для анализа медицинских изображений. В данной работе рассматривается задача сегментации слизистых желёз на гистологических изображениях.

Алгоритмы семантической сегментации желёз на гистологических изображениях [1] в некоторых случаях позволяют разделить смежные железы, однако, в общем случае, результирующая сегментация не является идеальной. Принципиальным улучшением в этом случае является переход от задачи семантической сегментации к задаче объектной сегментации для детектирования отдельных желёз на изображении. Существует ряд нейросетевых алгоритмов, использующихся для объектной сегментации, например Mask R-CNN [2] и Deep Watershed [3]. Однако, они не могут быть напрямую использованы в решаемой задаче. Кроме того, ни одна из этих архитектур не использует информацию о форме сегментируемых объектов, что может быть крайне полезным при выделении гистологических структур (границы желёз в большинстве случаев гладкие и часто приближены к эллипсам).

Для работы с подобной информацией мы предлагаем использовать модификацию модели обучаемого активного контура [4] и гибридный метод сегментации желёз на гистологических изображениях, основанный на этой модели. Главной отличительной чертой модели обучаемого активного контура является то, что параметры вариационной модели активного контура предсказываются в каждом пикселе изображения с помощью свёрточной нейронной сети со структурным предсказанием.

Также, в рамках рассматриваемого гибридного метода реализован специальный алгоритм постобработки, который позволяет разрешить проблему коллизии контуров и корректно сегментировать смежные железы на изображении. Предложенный метод был протестирован на наборе данных PATH-DT-MSU [5, 6] и продемонстрировал хорошие результаты. Среднее значение меры IoU на тестовой выборке составило 0.81.

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Histological Image Segmentation With a Trainable Active Contour Model

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Currently, the development of hybrid methods becomes a perspective direction in image processing and analysis. These methods represent a combination of neural networks and classical mathematical approaches of image processing. This combination of good generalization ability of neural networks and the flexibility of classical mathematical models allow to significantly help in solving a number of problems of image processing and especially of medical image analysis. In this work a problem of mucous glands segmentation in histological images is considered.

Algorithms that perform semantic segmentation of glands in histological images [1] allow in some cases to divide adjacent glands, however, in general, the performed segmentation is not perfect. The principal improvement is the transition from the task of semantic segmentation to the task of instance segmentation for detecting individual glands in the image. There are several CNN-based algorithms that are used for instance segmentation, such as Mask R-CNN [2] and Deep Watershed [3]. However, they can't be used directly for the current problem. In addition, none of these architectures uses information about the shape of segmented objects, which could be extremely useful in the case of histological structures (the boundaries of the glands are mostly smooth and in a large number of cases are close to ellipses).

To work with this kind of information we consider a modification of trainable active contour model [4] and a hybrid method of glands segmentation in histological images, that is based on this model. The main distinguishing feature of trainable active contour model is that variational parameters of active contour are predicted for each pixel in the image and can be learned by a convolutional neural network with training in terms of structured prediction.

Also, within this hybrid method a special postprocessing algorithm is implemented, which allows to resolve contours' collisions and correctly segment adjacent glands in the image. The proposed method was tested on PATH-DT-MSU dataset [5, 6] and demonstrated good results. The average value of IoU for all test images is 0.81

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Программные и позиционные управляемые стратегии для анти-раковой терапии

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В этом докладе управляемая модель соревнования Лотки-Вольтерры используется для описания взаимодействия здоровых и раковых клеток. Для этой управляемой модели рассматривается задача минимизации терминального функционала, которая представляет собой взвешенную разность концентраций раковых и здоровых клеток в конечный момент периода лечения. Три типа лечения рассматриваются. Используя принцип максимума Понтрягина, для каждого типа лечения устанавливаются свойства оптимальных управлений, которые подтверждаются соответствующими численными расчетами. Также, для данной управляемой модели доклад представляет результаты аналитических и численных исследований задачи терминального управления для двух вариантов ограничений на управления. Полученные результаты продолжают исследования, представленные в [1].

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Program and Positional Control Strategies for Anti-Cancer Therapy

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In this report, the controlled Lotka-Volterra competition model is used to describe the interaction between concentrations of healthy and cancer cells. For this controlled model, the minimization problem of the terminal functional is considered, which is a weighted difference of the concentrations of cancerous and healthy cells at the final moment of the treatment period. Three types of treatment are considered. Using the Pontryagin maximum principle, for each type of treatment, the properties of the optimal controls are established, which are confirmed by the corresponding numerical calculations. Also, for the given controlled model the report presents the results of the analytical and numerical studies of the terminal control problem for two variants of the control constraints. The obtained results continue studies presented in [1].

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Application of Neural Networks for Analysis of Results of Hemodynamic Modeling

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Моделовање неуроендокриног хипоталамо-хипофизно-адреналног (ХХА) система

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Хипоталамо-хипофизно-адренална (ХХА) оса је комплексни биолошки систем који је природно у осцилаторном динамичком стању. Тако, хормони ХХА осе, као што су кортизол, алдостерон, адренокортикотропин, и други, испољавају комплексно осцилаторно понашање са два карактеристична периода: унутардневне (ултрадијалне) осцилације са периодом између 20 и 120 минута, суперпониране на дневне (циркадијалне) осцилације са периодом од око 24 h. Таква динамичка стања се могу реализовати само у нелинеарним системима под неравнотежним условима. [1] Међутим, ултрадијалне осцилације су проузроковане директним интеракцијама између реакционих врста укључених у ХХА осу, односно унутрашњим самоорганизујућим феноменима, док циркадијалне осцилације потичу из анатомске локације која је изван ХХА осе и под јаким су утицајем дневног ритма као спољне периодичне променљиве.

У излагању ће бити разматрано математичко моделирање динамике ХХА осе и њених пертурбација (стрес). Да би се симулирале ултрадијалне осцилације, временска еволуција концентрације основних хормона ХХА осе је моделирана коришћењем стехиометријских релација између реакционих врста као и закона дејства масе. [2-4] Дневни ритам је симулиран помоћу изабране периодичне функције која је суперпонирана на ултрадијалне осцилације. [2, 5] Такође ће бити показано да се основни модел ХХА осе [2, 3] може лако проширити за различите сврхе, на пример, када је потребно да се узму у обзир додатне реакције и додатне врсте, као што су унутрашњи и спољни холестерол [3, 6], или етанол [7], који у овом моделу игра улогу типичне спољне врсте. [8] Поред тога, подвучене су предности стехиометријског приступа за моделирање сложених нелинеарних биохемијских система и њиховог одговора на спољне и унутрашње поремећаје или побуде.

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Modelling the Neuroendocrine Hypothalamic-Pituitary-Adrenal (HPA) System

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The hypothalamic-pituitary-adrenal (HPA) axis is a complex biological system that is naturally in an oscillatory dynamic state. Thus, HPA axis hormones, such as cortisol, aldosterone, adrenocorticotropin (ACTH) *etc.*, exhibit complex oscillatory behavior with two characteristic periods: ultradian oscillations, with a period between 20-120 min, superimposed on circadian oscillations, with a period of about 24 h. Such dynamic states can only be realized in a nonlinear system under nonequilibrium conditions [1] However, ultradian oscillations are caused by direct interactions between reaction species involved in the HPA axis, that is by internal self-organizing phenomena, whereas circadian oscillations originate from an anatomical location that is outside of the HPA axis and are strongly influenced by the daily rhythm as an external periodic variation.

Mathematical modelling of HPA axis dynamics and perturbations of HPA axis dynamics known as stress, will be discussed. To simulate ultradian oscillations, the time evolution of essential HPA axis hormone concentrations is modelled using stoichiometric relations between reaction species and the law of mass action. [2-4] The daily rhythm is emulated by a selected periodic function that is superimposed on the ultradian oscillations. [2, 5] It will also be shown that the basic model of the HPA axis [2, 3] can be easily expanded for different purposes, for example, to account for additional reactions and additional species, such as internal and external cholesterol [3, 6], or ethanol [7], which in this model plays the role of a typical external species. [8] Besides, the advantages of the stoichiometric approach for modelling complex nonlinear biochemical systems and their response to external and internal perturbations or stimuli is underlined.

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Лейкозы – Новые уроки анализа данных Российского регистра ХМЛ.

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Урок 1. Вера в то, что «не просто ответ, но ранний ответ на терапию» является предиктором благоприятных отдаленных результатов, до сих пор распространена среди специалистов по лечению хронического миелоидного лейкоза (ХМЛ). Однако последние исследования в этой области показали, что время до ответа не является адекватной суррогатной конечной точкой, заменителем общей выживаемости. Мы проверили это положение на данных Российского ХМЛ регистра и модельных данных. Регистр ХМЛ включает более 10 тыс. записей о пациентах, собранных начиная с 2009 года. В настоящий анализ включено 8326 пациентов в хронической фазе ХМЛ, которым начато лечение ингибиторами тирозинкиназы (ИТК). 91% больных лечились Иматинибом, 9% - другими ИТК. Средний возраст 47.3 лет, 4607 женщин/ 3705 мужчин. Датой достижения полного цитогенетического ответа (ПЦО) считалась дата первого теста с 0% of Ph'+ клеток или дата молекулярного теста с уровнем BCR/ABL≤0.1%. Общая выживаемость оценивалась начиная с определенной даты - ланд-марк (ЛМ) стартовой временной точки. Анализ данных и симуляционное моделирование проводилось в среде пакета SAS. Распределения времен до ответа и до летального исхода моделировалось смесью экспоненциальных распределений, параметры распределения оценивались по реальным данным.

Вывод из урока 1: Популяция больных ХМЛ в первом приближении - это смесь двух суб-популяций: когда-нибудь отвечающих на терапию и не отвечающих никогда. Результаты традиционного ЛМ анализа неверно трактуются как свидетельство того, что время до ответа влияет на общую выживаемость. Более специализированный анализ показывает, что эта кажущаяся зависимость выживаемости от времени до ответа – это эффект бинарной гетерогенности популяции больных, меняющейся взвеси суб-популяций в разных ЛМ точках. Это продемонстрировано, как на реальных данных, так и в модельном эксперименте.

Урок 2: Важно учитывать социальные и демографические персональные данные в анализе и интерпретации результатов любых популяционных исследований в онкологии. Но складывается впечатление, что роль социального статуса недооценивается как фактора, влияющего на выживаемость больных ХМЛ. Целью исследования было оценить прогностическое значение таких параметров, как семейное положение и уровень образования в сравнении с известными факторами риска для данного заболевания. Анализ проводился на тех же данных, упомянутых в перовой части (урок 1).

Вывод из урока 2: Социальные и демографические персональные данные должны включаться в любое исследование популяции хронических онкологических больных. Семейное положение и уровень образования очевидно ассоциированы с приверженностью к терапии и тем самым очевидно влияют на долговременные ее результаты. Высшее образование – благоприятный фактор, семейное положение разведен/вдовец – неблагоприятный фактор прогноза долговременных результатов терапии и выживаемости больных ХМЛ.

Chronic Myeloid Leukemia - New Lessons from the Russian Registry

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Lesson 1. The belief that "not only the response, but also the early response to therapy" predicts the best long-term clinical outcome is common in chronic myeloid leukemia (CML). The latest data do not confirm that time to response is relevant for overall survival. The aim of this study was to check it on the data of the Russian CML Registy and on simulation model. Russian CML Registry include more than 10 thousand patients(pts) data. In the analysis 8,326 CML pts in chronic phase(CP) with first-line TKI therapy were included: 91% of pts were treated by Imatinib and 9% by other TKIs. Mean age was 47.3 years, 4,607 were female and 3,705 male. Date of Complete Cytogenetic Response (CCyR) was assessed as the date of first test with 0% of Ph'+ cells or date of molecular test with BCR/ABL≤0.1% IS. OS was estimated starting land-mark (LM) time point, event was death for any reason, date of last contact was used for survivors beyond follow-up (censored survival time). Survival analysis and simulation was performed with SAS Statistical Analysis System. Distributions of time to response and of time to death were modeled as mixture of exponentials with parameters fitted to real data.

Conclusions of Lesson 1: The population of CML pts is a mixture of "any time" responders and "never"-responders. Traditional LM analysis output is wrongly treated as evidence that survival depends of the time to respond. More specific analysis does not confirm that. This was demonstrated on big population data and explained by simulation model.

Lesson 2: Social and demographic personal data are important to be included in analysis and interpretation of results of any population studies in oncology. But it looks like social status is underestimated as cofounder for survival of patients with chronic myeloid leukemia (CML). The aim of this study was to check the prognostic value of social parameters like marital status and education level in comparison with standard risk factors. Russian CML Registry include more than 10 thousand patients(pts) data. In the analysis 8,326 CML pts in chronic phase (CP) with first line TKI therapy were included: 91% of pts were treated by Imatinib and 9% by other TKIs. Mean age was 47.3 years, 4607 f / 3705 m. Median of follow-up was 7 years. Overall survival (OS) was estimated starting the diagnosis date, event was death from any reason, date of last contact was censored for alive pts.

Conclusions of Lesson 2: The social and demographic personal data should be included in any analysis of CML population data. Marital Status and Education are obviously associated with adherence behavior of CML patients and must influent on longitude therapy output. The highly education level is favorable factor, widowed/divorced marital status is unfavorable factor for OS prognosis.

Modeling of Global Evolution of World Community

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A distributed mathematical model of global evolution of humanity is considered. The world community is seen as a united complex self-developing and self-organizing system. One of the main parameters characterizing the evolution of this system is the total world population N. It is known that the humanity has shown stable hyperbolic low of population growth throughout its history; this was confirmed in 1960 by von H. Foerster's group. It supposed that such unusual growth in blow-up regime for biological populations is caused by the positive feedback between the population size N and the level of technological development, which is precisely the main driving force of social-economical evolution. Besides, humanity, increasing in numbers by hyperbolic law, spread to populate the planet, uniting into various socio-economic integrations. In this sense, the evolution of human society is reflected in the evolution of spatial structures - cities, states, empires, geopolitical and economic societies, *et cetera*.

S.P. Kurdyumov was the first who advanced the idea of modeling the evolution of human society by the nonlinear heat equation with a source. He has proposed to investigate global dynamics of world community during the whole history throughout the prism of the developing of spatial-temporal structures. The investigation shows that the evolution of human civilization can be described in terms of blow-up regime [1]. However, stable hyperbolic low of population growth is only the basic trend of evolution; more detailed examination reveals that the last one includes a number of socio-economic and socio-cultural cycles. According to one of the accepted classifications, there are 11 historical cycles [2]. Each of them corresponds to certain epoch; one epoch is replaced by the other by the way of innovation, when qualitatively new socio-economic technologies or cultural patterns shift the World-System to a new higher level of development.

In the base of Kurdyumov's model we have developed new model of human evolution [3]. The model utilizes a quasilinear heat equation for the population density. Positive feedback between population size and levels of technological and cultural development was taken into account through averaged cooperative interactions in the model: it is represented by the nonlinear coefficient of diffusion and the nonlinear volume source. The model parameters have been chosen so that 1) total population size (that is, the total integral of population density) follows stable hyperbolic growth, consistent with the demographic data; 2) the dynamic evolution of the system has cyclic character and duration of stages corresponds to 11 real historical epochs.

The model describes some global properties of human evolution, such as: the blow-up regime of population size growth, compression of spatiotemporal scales over time, increase in the instability of development, the alternation of different stages of development at every turn of evolutionary spiral. The objective laws of spatial-temporal structures evolution can prompt the possible directions of future development of our civilization and realize the necessary alterations we need make with our society.

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Mathematical Modeling of Qualitative Dynamic of Interactions Between Two Actors

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A rather general mathematical model describing the interaction between two actors is considered. The actors may be various social subjects, ranging from individuals and social groups to states and nations.: social or political groups, economic agents, individuals, states, nations, etc. The model is based on a system of two nonlinear ordinary differential equations. It is sufficiently simple (not more complex that the well-known predator–prey system or the two-species competition model). The model is an extension of the Murray–Gottman model originally proposed to investigate marital interaction. The phase variables describing the actor states may be positive or negative, unlike biological models where the size of the interacting populations is always positive. Positive states are associated with feelings of satisfaction, friendship, or cooperation, whereas negative states signal dissatisfaction, unfriendliness, or enmity. Moving over the scale of states from negative to positive values, we obtain various degrees of bad or good relations between the partners. In this model, collaboration is represented as positive feedback between the actors, i.e., a positive state of one actor boosts the positive state of the other actor, whereas a negative state of one actor amplifies the other actor's negative state. Competition is modeled as negative feedback, when a positive state of one actor amplifies the negative state of the other actor, whereas a negative state of one actor amplifies the positive state of the other (in other words, what is worse for one is better for the other)/

The system dynamics for excitable, self-sufficient, and some other types of actors who, in the absence of a partner, do not strive to a neutral state, as in the Murray–Gottman model was studied. New functions are investigated describing the mutual influence of the partners. In particular, the influence function depends not only on the states of the partners, but also on their own states. New types of dynamic behavior are discovered. In particular, the model in some cases displays oscillatory dynamics, which has not been observed in earlier models.

The model has a rich set of phase portraits describing the interaction dynamics between two actors and can be applied to model various socio-economic interrelationships between two partners.

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Акустофлюидные функциональные элементы в реализации миниатюрных биомедицинских устройств

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Научную и практическую важность миниатюрных гибридных устройств для быстрого клинического анализа (лаборатория-на-чипе) трудно переоценить. Однако при разработке таких устройств возникает ряд проблем, связанных с особенностями миниатюризации каналов для жидкостей и их интеграции в сложные многофункциональные гибридные устройства, в том числе: 1) разработка физико-технических основ для создания миниатюрных сенсорных/ актюаторных элементов (САЭ); 2) интеграция элементов и транспортных, погрузочных, сенсорных и т. д. систем и 3) дизайн биологически чистого, эргономичного и интеллектуального устройства.

В этом исследовании были рассмотрены конструкция и технология САЭ, основанных на принципе поверхностной акустической волны (ПАВ), интегрированных в гибридные аналитические микроустройства. Применяемые принципы акустофлюидики привели к таким преимуществам, как: простота производства, высокая биосовместимость, универсальность, компактная и недорогая конструкция, быстрое и эффективное приведение в действие жидкостей, бесконтактное и неинвазивное манипулирование клетками и совместимость с другими встроенными лабораторными компонентами.

Акустофлюидный актюатор представляет собой гибридное устройство, выполненное на основе пьезоэлектрической подложки с нанесенными плоскими встречно-цифровыми преобразователями (ВШП), интегрированными в микрофлюидную систему. Основой функционирования такого элемента являются ПАВ явления в пьезоэлектрических кристаллах. ВШП выполнены в виде двухфазных электродных решеток, нанесенных на пьезоэлектрическую подложку. Современные технологии позволяют достичь высокой точности позиционирования (менее 10 мкм) формирования ВШП, что обеспечивает высокую точность формирования сигнала, а также возможность интеграции в сложные гибридные аналитические системы, в том числе одноразовые.

Элемент образца был реализован на кристалле ниобата лития 128 ° YX $LiNbO_3$ с использованием методов осаждения металла и стандартной литографии. Диапазон рабочих частот составлял 10 - 17 МГц. Принцип смещения в таком исполнительном элементе основан на формировании волн контролируемого акустического давления. Для достижения эффекта смещения ВШП располагаются на одной стороне или на противоположных сторонах канала. Во втором случае они излучают встречные акустические волны, которые формируют интерференционную картину для формирования стоячей волны.

Топология и частотно-амплитудные режимы системы были оптимизированы с целью повышения точности манипулирования жидкими анализируемыми веществами. Устройство протестировано с использованием модельной системы, содержащей пекарские восточные клетки, красители и клетки крови. Селективность модельной системы позволила отделить клетки крови. Исходя из этого, потенциальная производительность системы при использовании в препаративных применениях, таких как разделение крови для инфузии, оценивается как 0,5 мл / мин. Устройство может быть использовано в мобильных экспресс-биомедицинских приложениях.

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Acoustofluidic Functional Elements in Implementing Miniature Biomedical Devices

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The scientific and practical importance of miniature hybrid devices for rapid clinical analysis (lab-on-a-chip) is difficult to overestimate. However, the development of such devices raises a number of problems associated with the specific features of miniaturization of channels for liquids and their integration into complex multifunctional hybrid devices, including: 1) the development of physical and technical foundations for the creation of miniature functional sensor/actuator elements (SAE); 2) integration of elements and transport, loading, sensory etc. systems and 3) design of biologically friendly, ergonomic and smart device.

In this study the design and technology of SAE based on surface acoustic wave (SAW) principle, integrated into hybrid analytical microdevices have been considered. The employed principles of acoustofluidics delivered such advantages as: simple manufacturing, high biocompatibility, versatility, compact and inexpensive design, quick and efficient actuation of liquids, non-contact and non-invasive manipulation of cells and compatibility with other laboratory built-in components.

The acoustofluidic actuator is a hybrid device made on the basis of a piezoelectric substrate with deposited planar interdigitated transducers (IDT), integrated into a microfluidic system. The basis of the functioning of such an element is the SAW phenomena in piezoelectric crystals. IDT are implemented as the two-phase electrode gratings deposited on a piezoelectric substrate. The modern technologies enable the high positioning accuracy (less than 10μm) of IDT formation to be achieved, which provides high accuracy of signal formation, as well as possibility of integration into complex hybrid analytical systems, including disposable once.

The sample element was implemented on the lithium niobate crystal 128 ° YX LiNbO3 by using metal deposition and standard lithography approaches. The working frequency range was 10–17MHz. The displacement principal in such an actuator element is based on formation of controlled acoustic pressure waves. To achieve displacement effect IDTs are positioned at one side, or at opposite sides of the channel. In the second case they emit counter propagating acoustic waves, which are forming the interference pattern to form the standing wave.

The topology and frequency/amplitude regimes of the system were optimized in order to increase the precision of manipulation of liquid analytes. The device is tested using a model system, containing baking east cells, dyes and blood cells. The selectivity of the model system enabled blood cells to be separated. On this basis the potential performance of the system when used in preparative applications, such as blood separation for infusion, is evaluated as 0.5 ml/min. The device could be used in mobile express biomedical applications.

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Autowave Model of Megapolises Development

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In the context of the historical dynamics of *homo sapiens*, structural spatial heterogeneity gradually developed in the anthroposphere due to the formation of cities and related adjacent territories (urban ecosystems, UES). These systems are characterized by high-rate population growth and the concentration of residential, industrial, commercial, and other facilities, as well as communications. The more complex the structure of the system, the greater the number of possible stable states in it. This property is called multistability. The study of UES development features allows for predicting the evolution of territories ensuring effective interaction and balanced development of all spheres of life. With cities being complex nonlinear systems, mathematical modelling proposing acceptable paths of their development is difficult.

Here, we offer a different approach based on the theory of active media. This theory is most widely used to describe biological systems, such as models of excitation processes in nerve cells, dynamics of blood coagulation, and pulse shape observed in the myocardium. From our point of view, the process of UES development can be considered as autowave self-organization in active media.

One of the most common and, at the same time, fairly simple models describing biological systems is the FitzHugh–Nagumo system. This is a system of two parabolic equations of activator–inhibitor type for autowave propagation in a homogeneous environment. To create a model describing such a complex and nonlinear object as UES, we made modifications to this system, changing it so that it could describe not only propagating fronts but also stationary solutions with large gradients at the boundaries of barriers (natural geobiocoenoses that prevent autowave motion). In addition, a cross-product component was added to the equation for the activator, enhancing the feedback between the activator and the inhibitor.

Using the example of Moscow expansion in the period from 1952 to 1968, a comparison was made of the model results with real data. The difference was less than 10%.

The model can be used to predict the development of megacities in various countries around the world. When used for this purpose, preliminary analysis should be conducted to determine the activators and inhibitors of megalopolis development and the characteristic scales.

By means of the model, a prediction of the development of Shanghai and the surrounding territory until 2030 was made. According to our forecast, the urban area of the territory will increase in the near future, as will the housing cost.

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孕妇外周血中胎儿游离 DNA 片段的研究

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出生缺陷给家庭和社会带来了沉重的负担。为降低出生缺陷的发生，应该尽早进行产前筛查。目前常用的方法有羊水细胞法、绒毛细胞法和胎儿脐带血法，但这些方法都是有创产前筛查，对胎儿和孕妇均有一定危险性。1997 年，卢煜明等在孕妇血浆中发现少量胎儿游离 DNA 片段（cffDNA），为无创产前检测提供了新途径。本研究主要是建立计算孕妇外周血中胎儿游离 DNA 片段（cffDNA）浓度和长度均值的新的数学模型。提出一种新的方法，该方法根据孕妇外周血中母亲和胎儿的 DNA 片段的长度分布不同利用 K-means 算法和 EM 算法开发新的算法。用该方法分析孕妇外周血测序数据，建立混合正态分布数学模型。描述样本的 DNA 片段长度分布，计算胎儿 DNA 片段浓度和片段长度均值以及计算胎儿 DNA 片段的长度方差值。数值实验表明我们提出的新方法分析孕妇外周血的 cffDNA 的浓度和长度均值是有效的、准确的。母亲外周血中胎儿 13,18 和 21 三倍体的无创诊断具有很重要的意义。我们根据孕妇外周血中游离 DNA 片段分别占每条染色体的比例不同，提出了新的计算三倍体的算法模型。并且探索了孕妇外周血中计算三倍体时胎儿片段的上下界，分别为 80bp 与 155bp。使用该范围结合我们的算法模型，灵敏度和特异性的准确性可以提高到 100%，用于检测三种最常见的常染色体非整倍体，即 13-三体，18-三体，21-三体。数值实验表明我们的方法是有效的，准确的。

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Prenatal Diagnosis of Fetal Trisomy From Maternal Plasma

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Molecular size determination of circulating free fetal DNA in maternal plasma is an important detection method for noninvasive prenatal testing (NIPT). The fetal DNA molecule is the primary factor determining the overall performance of NIPT and its clinical interpretation. 1. To propose new mathematical model of the cffDNA concentration and their length mean value in pregnant women's plasma. We propose a new method, which uses K-means algorithm and Expectation-Maximization (EM) algorithm to develop new method based on the length distribution of DNA fragments of mothers and fetuses in pregnant women's plasma.We mainly analyze the DNA fragments length distribution, cffDNA concentration and the length mean. Numerical experiments show that the calculation of the concentration and the length mean value in pregnant women's plasma are effective and accurate by using our new method which uses K-means algorithm and EM algorithm. 2. The proportion of cell-free fetal DNA molecules is expressed as the fetal DNA fraction in the plasma of pregnant women. We proposed an effective method to deduce fetal chromosomal aneuploidy based on the proportion of a certain range of DNA fragment lengths from maternal plasma. We gradually narrowed the range of the upper and lower boundary via a traversing algorithm. We explored the optimal range of the upper and lower boundary by using size-based DNA fragment length. Using this range, the accuracy of the sensitivity and specificity could be improved by up to 100% for detecting the three most common autosomal aneuploidies, namely trisomy 13, trisomy 18, trisomy 21 in the sample set. Numerical experiments demonstrate that our method is effective and efficient.

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A Mathematical Axiomatics of Functional Biodynamics, with Growing, Forced Learning, and Aging in Life Cycle*

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"Systems Neuroergonomics" [1] presented a holistic separation of human-body system into its cellular material and three functional groups: vital and physical productivity functions and "those higher operational functions that shape a person's behavior". It was then suggested, in a qualitative phenomenological way, that "resting phase performance" and "challenging exposures" bear important implications for concepts of neuroergonomics.

For a quantitative approach to the analysis of complex systems, further drill-down is necessary, from aggregated functional units to the functional aggregate's components, themselves again composed of even smaller functional units, such that behavior of the whole emerges from activity of functional components and coordination of their interaction, though not from a cellular tissue to the Whole, but from one functional level to the next. Multi-scale coherent dynamics of effectuation in a holistic functional structure were mathematically described in an axiomatic way (Mau, 2018), but their design was for autonomous pursuit of missions compliant with mainly anticipated functional challenges.

Here, the theory is carried forward to permit functional development in the sense of progressive adjustment of functional capacities in unforeseen scenarios. However, this implied "functional learning" is assumed to evolve much more slowly than the essential systems dynamics, and then needs a separate clock that measures time in weeks, for example.

For an even more comprehensive understanding, still another clock can be introduced for functional aging as a ubiquitous phenomenon human mind is particularly aware of, but which is also of concern in engineered systems; here, time will be measured in years or decades, for example. As functional aging will affect functional learning, the communality of the mathematical constructs specific for each, is helpful towards application of a simple principle, that includes the fast dynamics of vital functions as well: expressing dynamics in terms of intensity functions, a concept that relates current speed of transfers to residual amount of transfer, must not be dismissed as mathematical detail but appreciated for its key role in extending deterministic relations to their stochastification as well as the key to invoke very detailed and sophisticated statistical theory for estimation of dynamics from measurements, at every functional level; with this approach, entropy, the second law of axiomatic thermodynamics, re-appears and legitimizes a denomination as axiomatics of functional biodynamics.

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Предикторы острых церебральных эмболических повреждений при стентировании сонных артерий

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Выполнено проспективное исследование, целью которого явилось выявление предикторов острых эмболических повреждений (ОЭП) сосудов головного мозга при ангиопластике со стентированием внутренней сонной артерии (ВСА). В исследовании приняло участие 54 пациента, которым за период с мая 2015 г. по декабрь 2018 г. в отделении сосудистой и эндоваскулярной хирургии Научного центра неврологии была проведена каротидная ангиопластика со стентированием (КАС). Процедура стентирования ВСА может сопровождаться интраоперационными ОЭП. С целью обнаружения интраоперационных ОЭП сосудов головного мозга всем пациентам до и через 24 часа после вмешательства проводилась диффузионно-взвешенная магнитно-резонансная томография (ДВ-МРТ).

Для 36 пациентов использовались классические каротидные стенты (Xact и Acculink), для 18 – стенты Casper. Пациенты соответствующих групп были сопоставимы по 24 исследованным характеристикам, включая частоту интраоперационных церебральных ОЭП (18/36 при классических стентах и 10/18 при стенте Casper), что позволило объединить их в одну группу для увеличения мощности исследования. Все ОЭП, детектированные по ДВ-МРТ (до стентирования и через сутки после него) были клинически асимптомными (периоперационных инсультов не было).

Для обнаружения предикторов интраоперационных ОЭП сосудов головного мозга были проанализированы 22 характеристики пациентов, в результате чего были выявлены следующие признаки: (1) низкоинтенсивный (менее 20 дБ) ультразвуковой сигнал, отражённый от фрагментов атеросклеротической бляшки (при УЗИ-обследовании до стентирования) (p=0,001); признак ассоциирован с ОЭП сильно (чувствительность – 75%, специфичность – 92%); (2) симптомный стеноз (по анамнестическим данным) (p=0,02); признак ассоциирован с ОЭП значительно; (3) женский пол (p=0,06); признак ассоциирован с ОЭП умеренно; (4) ранее были (по анамнестическим данным) операции на коронарных и/или сонных артериях (p=0,09); признак ассоциирован с ОЭП слабо.

На основании полученных результатов предложена прогностическая шкала для оценки риска ОЭП сосудов головного мозга в процессе стентирования ВСА. Знание факторов, ассоциированных с интраоперационными ОЭП, позволит эндоваскулярному хирургу выделить пациентов с повышенным риском ОЭП.

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Predictors of Acute Cerebral Embolic Lesions During Carotid Artery Stenting

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The authors carried out a prospective study aimed at revealing predictors of acute embolic lesions of cerebral vessels during angioplasty with stenting of the internal carotid artery. The study enrolled a total of 54 patients who between May 2015 and December 2018 underwent carotid angioplasty with stenting performed at the Department of Vascular and Endovascular Surgery of the Research Centre of Neurology. The procedure of internal carotid artery stenting may be accompanied by intraoperative acute embolic lesions. In order to reveal intraoperative acute embolic lesions of cerebral vessels all patients before and 24 hours after the intervention were subjected to diffusion-weighted magnetic resonance imaging.

Thirty-six patients received classical carotid stents (Xact and Acculink) and 18 patients received Casper stents. The patients of both groups were comparable by 24 characteristics studied, including the incidence of intraoperative acute cerebral embolic lesions (18/36 for the classical stents and 10/18 for the Casper stent), which made it possible to unite them into one group in order to increase the power of the study. All acute embolic lesions detected by the diffusion-weighted magnetic resonance imaging (prior to stenting and 24 hours thereafter) were clinically asymptomatic, with no perioperative stroke observed.

In order to reveal predictors of intraoperative acute embolic lesions of cerebral vessels we analysed 22 characteristics of the patients, with the obtained findings demonstrating the following signs: a low-intensity (below 20 dB) ultrasonographic signal reflected from fragments of an atherosclerotic plaque during ultrasound examination prior to stenting ($p=0.001$) – a sign strongly associated with acute embolic lesions (sensitivity – 75%, specificity – 92%); symptomatic stenosis according to the anamnestic data ($p=0.02$) – a sign significantly associated with acute embolic lesions; female gender ($p=0.06$) – a sign moderately associated with acute embolic lesions; a history previously endured (according to the anamnestic data) operations on coronary and/or carotid arteries ($p=0.09$) – a sign weakly associated with acute embolic lesions.

Based on the obtained findings we proposed a prognostic scale to assess the risk of acute embolic lesions of cerebral vessels during internal carotid artery stenting. Knowing the factors associated with intraoperative acute embolic lesions will allow the endovascular surgeon to single out the patients at increased risk of acute embolic lesions.

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Выбор Минимальной Модели Непрерывной Гликемической Кривой

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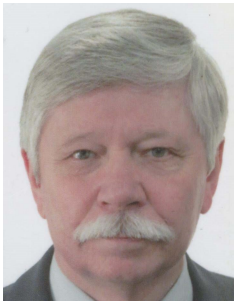

Для нужд медицины разработано много сложных моделей. Например, модели сердечно-сосудистых заболеваний [1], рака [2], уровня сахара в крови [3]. Целью построения сложных моделей является детальное описание физиологического процесса. В настоящее время много новых идей и подходов к анализу медицинских данных пришло из области машинного обучения [4, 5]. Одним из перспективных направлений применения машинного обучения в математическом моделировании является упрощение моделей. В этом случае целью математического моделирования является не детальное описание физиологического процесса, влияющего на состояние здоровья пациента, а создание модели, описывающей индивидуальные данные человека. Подобная «персонифицированная модель» оказывается проще и нуждается в меньшем числе данных для своей идентификации.

В докладе рассматривается чувствительность модели уровня сахара в крови по отношению к изменению её параметров. Для параметров, изменения которых мало влияют на выход модели, можно использовать оценки, полученные по данным наблюдения больших групп людей – популяционные оценки. Значения параметров, которые сильно влияют на результат, необходимо оценивать, используя индивидуальные данные. Такой подход позволяет конструировать персонифицированные модели пациентов для использования при лечении и, в частности, при разработке «умных» инсулиновых помп. В настоящем исследовании использовалась модель гликемической кривой, содержащая 12 параметров [6]. Рассматривалось изменение концентрации глюкозы в крови у здорового человека при приёме пищи. Гликемическая кривая характеризовалась двумя показателями: максимальным достигнутым уровнем сахара x_{max} и длительностью интервала спада кривой от максимального значения до уровня 100 единиц t_{relax}.

Чувствительность выхода модели - уровня сахара в крови, относительно изменения 12 коэффициентов модели исследовалась с помощью корреляционного анализа. Параметры модели 100 раз независимо возмущались случайным образом согласно нормальному распределению. Средние значения параметров равнялись параметрам модели здорового человека [6], дисперсии подбирались так, чтобы получалась правдоподобная гликемическая кривая. Вычислялись коэффициенты корреляции между показателями x_{max} и t_{relax} и возмущёнными коэффициентами. Как для x_{max}, так и для t_{relax} лишь 3 коэффициента модели из 12 имели коэффициенты корреляции значимо отличные от нуля: 1) постоянная времени снижения концентрации глюкозы из-за клиринга в инсулиннезависимые ткани, 2) коэффициент интенсивности влияния концентрации глюкагона на концентрацию глюкозы, 3) коэффициент интенсивности влияния пищи на концентрацию глюкозы.

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Selection of a Minimal Model for Individual Continuous Glucometer Curve

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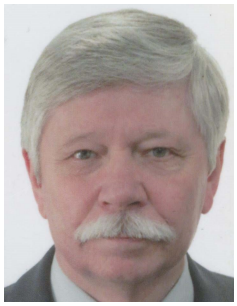

Many complex mathematical models are developed for medical practice. Examples are cardiovascular diseases [1], cancer [2], blood sugar regulation [3]. In complex models investigators tend to describe the modeling process in as many details as possible. At the same time many new ideas and approaches to data analysis came into medicine modeling from field of machine learning [4] and in [5]. The fruitful implementation of machine learning technique in mathematical modeling is model simplification. In this case the mathematical model is aimed not to describe in details a physiological process related with the patient's health conditions but to construct a model to describe individual data of the given patient. Such 'personalized model' possibly needs small number of observations for its identification.

In the report we consider the sensitivity of blood sugar level model when parameters of this model vary. For parameters whose changes cause small effect on the output, one can use estimates based on the data from a large group of patients — population estimates. The values of parameters that strongly influence the result should be estimated using individual patient observation data. If the number of such parameters is small, then the accuracy of the estimates will be sufficient even with a small number of observations. This allows to construct personalized patient models for further use in their treatment, in particular, for "smart" insulin pump personal tuning. A glycaemia model [6] with 12 parameters was used in the present study. The reaction of glucose concentration in the blood of a healthy person to the food supply was considered. As the criteria to characterize the glycaemia curve, we selected the maximum sugar level $x_{\max}$ and the length of relaxation period t_{relax} defined as the duration of the interval between the moments of reaching the maximum level of sugar and the intersection of level 100.

Correlation analysis was used to evaluate blood sugar level sensitivity to changes the model 12 parameters. The parameters were randomly disturbed according to normal distribution. Number of independent trails was 100. The mathematical expectations of the parameters were equal to the values of the parameters in the model of a healthy person [6]. Based on the correlation coefficients between model parameters and criteria $x_{1\max}$ and t_{relax} significant impact on the characteristics of the glycaemia curve show only three parameters: 1) the reciprocal of the time constant of the decrease in glucose concentration due to clearing into insulin-independent tissues; 2) the coefficient of the intensity of the influence of glucagon concentration on glucose concentration; 3) the coefficient of the intensity of the effect of food on glucose concentration.

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Modeling of the Transport Function of Lymphatic Vessels

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Nekonzervativnost Prirodnih Orbitalnih Sistemai Implikacije na Modeliranje Složenih Dinamičkih Sistema

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Sam način na koji savremena nauka prilazi analizi i modeliranju složenih sistema uveliko je uslovljena osnovama klasične, analitičke i racionalne mehanike, klasične termodinamike kao statističke mehanike, kao i suštinski verovatnostne metodologije kvantne mehanike, na dva načina: sa jedne strane, biohemijski i/ili fenomeni inherentni socijalnim pojavama kao što su nereverzibilnost, nastajanje i/ili samoorganizacija, višeskalnost, disipativnost (u smislu neuzetog u obzir dotoka energije), itd., smatraju se potpuno stranim ‘staroj nauci’ u domenima od atomsko-molekularnih do kosmoloških, a sa druge – u suštiskom koreišćenju unekoliko modifikovanih i proširenih postojecih metodologija, uključujuci tu i među-skalne/nivoske renormalizacije [1].

Sa napredovanjem bavljenja složenim sistemima i razvoja njima svojstvenim metodologija analize i modeliranja povećava se svesnost potrebe da se na delove sistema ne gleda kao da su univerzalni, a da je način na koji oni “rade zajedno” specifičan za svaki system, već pre da se sam način na koji delovi rade zajedno i međusobno reaguju posmatra i razmatra generalno, te da se tako dobijaju unificirani uvidi u sve vrste postojećih sistema – od fizike i metereologije, preko biohemije i zdravlja, do društvenih i duhovnih procesa.

Pošto svi sistemi mogu da se u krajnjoj meri svedu na atome i njima svojstvene ‘čestice’, a imajući u vidu da je fizika u tome domenu uveliko opredeljena već skoro četri veka starim radovima Keplera i Njutna, dovoljno temeljna analiza i kritičko razmtranje [2] odaje suštinske nedostatnosti, koje se mogu dovesti u vezu sa formulisanjem gravitacionog a kasnije i električnih i magnetnih polja kao takozvanih (precisznije, jedno-komponentnih) potencijalnih polja, to jest polja sile u kojima je rad po zatvorenoj putanji (t.j. po trajektoriji orbitalnog tela/cestice) jednak nuli. Štaviše, zbog suštinski neoscilatorne forme odgovarajućih nelineare diferencijalne jednačine kretanja, da bi se došlo o pragmatički zadovoljavajućih rešenja za trajektorije faktualno su postulirana takozvana dva Prva Integrala (održanja, t.j. vremenske nezavisnosti Energije i Momenta Količine Kretanja), na osnovu kojih se – uz neizostavne početne uslove – dobijaju rešenja koja ih zapravo ne zadovoljavaju !?

Uvodjenjem još jedne, izričito centrifugalne komponente centralne sile odnosno ubrzanja proporcionalnih sa 1/r^3 (pored centripetalnih, proporcionalnih sa 1/r^2), dobija se nelinearna diferencijalna jednačina čije rešenje odaje nerekurzivno t.j. ‘haotično’ ponašanje, uz inherentnu višeskalnost i bifurkativnost. Na osnovu pune potpore univerzalnosti takvog modeliranja od strane konzistentno razvijene i veoma ubedljive Eterodinamike V.A. Acjukovskog (referenca 7. u [2]) i W.M. Bauera [3], u predstojećoj prezentaciji biće sučeljeni i do izvesne mere razradjeni aspekti relevantni za složene sisteme, kao što su:

Nekonzervativnost prema Konzervtivnosti, Morfizam/Negentropzam prema Entropizmu; Asimetrija prema Simetriji; Multi-skalnost prema Multi-dimenzionalnosti, i Nepredvidljivi Determinizam prema Probabilisitčnosti i Stohastičnosti.

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Non-Conservativeness of Natural Orbital Systems and Implications to Modeling of Complex Systems Dynamics

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The very way the contemporary science approaches analysis and modeling of complex systems has largely been determined by the foundations of the classical, analytic and rational mechanics, classical thermodynamics along statistical mechanics, as well as the essentially probabilistic methodology of the quantum mechanics in twofold manner: for one thing, the biochemistry and/or the societal systems inherent phenomena as irreversibility, emergence and/or self-organization, multi-layerdness, dissipativity (in terms of unaccounted for energy inflow), etc., having been considered as fully alien to the 'old science' domains ranging from atomistic-molecular to cosmology, and for the other – in essentially re-using i.e. somewhat modifying and extending the existing methodologies, including intra-layers/scales renormalizations [1].

With the advent of working with and development of complex systems pertinent methodologies of analysis and modeling, the awareness is increasing of the need to look at the parts of systems not as being universal and the way parts "work together" being specific for each system, but rather the parts working together and interacting be considered and studied in general, and by doing so to be gaining unified insights into every kind of systems that exist – from physics and meteorology, over biochemistry and health, to societal and sptiritual processes.

Since all the systems can ultimately be reduced down to atoms and the pertinent 'particles', and having in mind that physics in that domain had been strongly influenced by the already some more of four centuries old Kepler's and subsequent Newton's works, enough thorough analysis and scrutinizing [2] reveals intrinsic deficiencies, which can be traced back to formulation of gravitational, and later electric and magnetic fields, as the so-called (single, to be more specific) potential fields, that is force fields in which work over closed path (i.e. over the orbital body/particle trajectory) is zero. Furthermore, due to essentially non-oscillatory form of the pertinent non-linear differential equation of motion, to arrive at the pragmatically satisfying trajectory solutions the two so-called First Integrals (of Energy and Angular Momentum Conservation, i.e. time-independence) have essentially been postulated, based on which – along indispensable initial conditions – produced are solutions which actually do not satisfy those !?

By introduction of another, explicitly centrifugal central force/acceleration term proportional to 1/r^3 (besides the 1/r^2 centripetal one), the non-linear differential equation is produced, the solution of which reveals the non-recursive i.e. 'chaotic' behavior, along the possibly inherent multiscaledness and bifurcativity. Based on full support of universality of such modeling that comes from the consistently developed and very compelling Aetherodynamics of V.A. Atsukovsky (reference 7. in [2]) and W.M. Bauer [3], in the upcoming presentation will be contrasted and to a certain extent elaborated the complex systems relevant topics, as are:
Non-conservativeness versus Conservativeness; Morphysm/Negentropysm versus Enthropysm; Asymmetry versus Symmetry; Multi-scaling versus Multi-dimensionality, and the Unpredictable Determinism versus Probabilistic and Stochasticity.

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Brainstem Median Ternary Pattern Analysis in Early Mild Cognitive Impairment using Radial Basis Function Based Support Vector Machine

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Early Mild Cognitive Impairment **(**EMCI) represents the preclinical stage of Alzheimer's disease (AD) that may or may not progress to dementic condition. Postmortem studies reveal that brainstem shows earliest neuronal loss and thus it is considered to be a significant pathological substrate for early diagnosis of AD. The objective of this work is to differentiate EMCI from normal and Alzheimer's condition by analyzing the textural alterations of brainstem using Median Ternary Pattern.

Raw T1-weighted images comprising of 200 normal, 232 EMCI and 200 AD are considered from Alzheimer's Disease Neuroimaging Initiative database. These images are pre-processed and fuzzy 'C' means is used to cluster the brain tissue into gray matter, white matter and cerebrospinal fluid. Considering the white matter tissue, brainstem is segmented using connected component labelling technique. Texture analysis is carried out on the segmented brainstem images by extracting median ternary patterns. Median ternary pattern is an extension of local ternary pattern. It encodes the texture information of a local neighbourhood by defining a window around each pixel and calculating median gray-scale value. The intensity values of the neighbourhood is quantized into three different levels by defining a threshold. The local window is now transformed to 3 state-space, namely 0, 1 and -1. To reduce the complexity to 2 state-space, the ternary pattern is split into its corresponding positive and negative parts. Histograms are calculated for the positive and negative parts and are analysed. The two histograms are concatenated and are used as feature vector to differentiate EMCI subjects using radial basis function based support vector machine (RBF-SVM).

Results show that the combination of Fuzzy 'C' means with connected component labelling technique is able to segment the brainstem from all the considered images. Extracting the median ternary patterns from the segmented brainstem structure resulted in 512 features, comprising of 256 from the positive ternary pattern and 256 from the negative ternary pattern. It is observed that there are no intraclass variations between the mean value of positive and negative ternary pattern, while interclass variations are present. The mean values are observed to be 3.18, 3.32 and 3.26 for normal, EMCI and AD. As the mean values are close to 0, it shows that the brainstem structure is majorly comprised of flat texture. Further, using median ternary pattern as feature vector, RBF-SVM is able to differentiate EMCI from normal and AD with an accuracy of 82.6%. Its precision and recall measures are obtained to be as 82.4% and 82.3% respectively.

The variations in brainstem texture, studied using median ternary pattern correlates with the neuropathology of the disease condition. These texture variations seems to be clinically significant and could be used for the early detection of AD.

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Генетические аспекты ассортативности брака

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Ассортативностью называется неслучайное заключение браков на основе сходства по любым факторам [1]. Актуальность изучения закономерностей ассортативного подбора супружеских пар обусловлена способностью феномена изменять наследуемость генетически детерминированных заболеваний и признаков, влиять на их вариабельность в популяции [2]. Методом ПЦР обследовано 196 супружеских пар (392 чел.) из 3 групп изученных семей с наличием аддиктивных расстройств, нормативной выборки и группы популяции. Анализ частот генотипов генов дофаминовой системы головного мозга *ANKK1/DRD2* и *DAT1* супружеских пар в каждой из групп сравнения выявил отсутствие статистически достоверных различий и высокую степень сходства распределения полиморфных вариантов анализируемых генов у супругов с наличием аддиктивных расстройств в форме алкогольной зависимости и феномена созависимости

ген *ANKK1/DRD2* χ^2Йейтс=0.139, p=0.426, φ=0.03 и ген *DAT1* χ^2Йейтс=0.152÷2.034, p=0.151÷0.5, φ=0.04÷0.13 ,

в выборке семей фенотипической нормы

ген *ANKK1/DRD2* χ^2Йейтс=0.1 , p=0.5 , φ=0.03 и ген *DAT1* χ^2Йейтс=0.086÷0.3, p=0.357÷0.5, φ=0.03÷0.05 ,

и в популяционной группе

ген *ANKK1/DRD2* χ^2Йейтс=0.035 , p=0.5, φ=0.02, и ген *DAT1* χ^2Йейтс=0÷2.027, p=0.183÷0.577, φ=0÷0.12 .

Однотипный характер распределения полиморфных вариантов анализируемых генов в супружеских парах всех исследованных групп свидетельствует о наличии ассортативности браков по изученным молекулярно-генетическим характеристикам с учётом специфики обследованных групп.

Генетическое значение феномена ассортативности браков заключается в том, что при постоянно высокой в течение многих поколений гомогамии в популяции постепенно формируются субпопуляции, в пределах которых заключаются браки, более однородные и менее схожие с другими субпопуляциями. Знание закономерностей формирования супружеских пар будет способствовать объективизации выбора тактики прегравидарной профилактики наследственной патологией и снижению темпов формирования субпопуляций с наличием генетически детерминированных расстройств, в частности, расстройств поведения зависимого характера.

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Genetic Aspects of Assortative Marriage

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Assortivity is a nonrandom marriage based on similarities for any factors [1]. The relevance of studying the laws of assortative selection of married couples is due to the ability of the phenomenon to change the heredity of genetically determined diseases and signs, to affect their variability in the population [2]. Using polymerase chain reaction (PCR) 196 married couples (392 people) from 3 groups of the studied families were examined with the presence of dependencies, a normative sample, and a population group. An analysis of the frequencies of the genotypes of the ANKK1/DRD2 and DAT1 brain dopamine system genes of the married couples in each of the comparison groups revealed the absence of statistically significant differences and a high degree of similarity in the distribution of polymorphic variants of the analyzed genes

(1) in spouses with the presence of addictive disorders in the form of alcohol dependence and the dependence phenomenon, χ^2Йейтс=0.139 (p=0.426, φ=0.03) and χ^2Йейтс=0.152÷2.034 (p=0.151÷0.5, φ=0.04÷0.13) for *ANKK1/DRD2* and *DAT1*, respectively,

(2) in the sample of families of phenotypic norm, χ^2Йейтс=0.1 (p=0.5, φ=0.03) and χ^2Йейтс=0.086÷0.3 (p=0.357÷0.5, φ=0.03÷0.05) for *ANKK1/DRD2* and *DAT1*, respectively, and

(3) in the population group, χ^2Йейтс=0.035 (p=0.5, φ=0.02) and χ^2Йейтс=0÷2.027 (p=0.183÷0.577, φ=0÷0.12) for *ANKK1/DRD2* and *DAT1*, respectively.

The uniform type of distribution of polymorphic variants of the analyzed genes in the married couples of all the studied groups indicates the presence of assortative marriages according to the studied molecular genetic characteristics, taking into account the specifics of the examined groups.

The genetic significance of the assortment of marriages is that, with homogamy constantly high over many generations, subpopulations are gradually formed in the population, within which marriages are concluded that are more homogeneous and less similar to other subpopulations. Knowledge of the laws governing the formation of married couples will help to objectify the choice of pregravid prophylaxis tactics in the presence of genetically determined disorders and reduce the rate of formation of subpopulations with the presence of genetically determined disorders, in particular, disorders of behavior of a dependent nature.

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Медицинские приложения одномерной модели гемодинамики

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Важную роль в развитии недостаточности мозгового кровообращения играют два патологических фактора: атеросклероз и извитость сонных и позвоночных артерий (CVA). Они производят потери энергии и снижение скорости. Одной из современных проблем в сосудистой хирургии является неинвазивная оценка гемодинамической значимости сосудистой окклюзии, обусловленной атеросклерозом [1, 2]. Виллизиев круг (CW) перераспределяет кровоток из здоровых сосудов через головной мозг при стенозе CVA [3, 4]. Сосуды, образующие CW, достаточно малы и сложны для визуализации с помощью компьютерной томографии (CTA) и для сегментации [5]. Существует множество анатомических вариаций, которые заключаются в отсутствии какой-либо части CW. Таким образом, реальный клинический набор данных, включающий CTA, как правило, является неполным. В данной работе продемонстрирован вычислительный инструмент для индивидуального гемодинамического моделирования мозгового кровотока с учетом анатомических особенностей CW при стенозе CVA на основе 1D моделей [6, 7, 8].

Возможным побочным эффектом патологической извитости (PT) является снижение кровотока при гипотонии. Эта патология занимает второе место после заболевания атеросклерозом. Она наблюдается в 30% случаев летальных исходов от инсульта. Для изучения влияния PT в данной работе мы вводим параметризацию силы трения вдоль сосуда или сосредоточенную модель для потери давления. Влияние силы трения состоит в уменьшении систолических значений давления и скорости потока [9]. С помощью математического моделирования мы сравниваем случаи прямого сосуда, извитости C-типа, S-типа, перегиб/койлинг, и реальной извитости на основе анатомических данных. Отметим, что одномерная сетевая модель гемодинамики является хорошей основой для моделирования специфических для пациента условий кровотока в норме и при наличии сосудистых патологий. Вычислительная реализация использует разумное количество вычислительных ресурсов и хорошо подходит для использования в клинической практике.

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Medical applications of 1D model of cerebral haemodynamics

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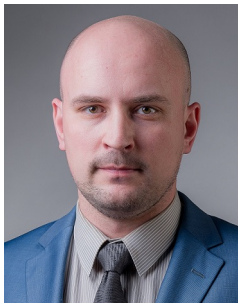

The two pathological factors play important role in the development of insufficiency in the cerebral circulation: atherosclerosis and tortuosity of the carotid and vertebral arteries (CVA). They produce energy losses and velocity decrease. Contemporary problem in vascular surgery is non-invasive evaluation of the haemodynamic importance of vascular occlusion, which is produced by the atherosclerosis [1, 2]. The Circle of Willis (CW) redistributes blood flow from healthy vessels through the brain during stenosis of CVA [3, 4]. The CW vessels are rather small and are difficult for the computed tomography angiography (CTA) visualization and segmentation [5]. There are a lot of anatomical variations, which are the absence of some part of CW. Thus, the real clinical datasets are incomplete. We demonstrate a computational tool for individual simulations of the cerebral blood flow variations accounting the anatomical features of the Circle of Willis during stenosis of CVA based on 1D models [6, 7, 8].

The possible side-effect of the pathological tortuosity (PT) is the blood flow decrease during hypotension. This pathology takes the second place after the atherosclerosis disease. It is observed in 30% cases of the deaths from stroke. To study the effect of the PT we introduce parametrization of the friction force along the vessel and lumped model of the pressure drop. It decreases the systolic values of the downstream pressure and velocity [9]. We compare straight vessel case (no tortuosity), C-type, S-type, kinking/coiling types and real patient anatomical case. We conclude, that the 1D network dynamical model of haemodynamics is a good basis for modeling patient-specific blood flow conditions in normal case and in the presence of vascular pathologies. The computational implementation uses reasonable computational resources and suits well for the use in clinical practice.

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Validation of Electro-Dermal Activity signals with EEG responses: Issues and Challenges

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Emotions are the fundamental intellectual capacity of human that is characterized by perception, attention, and behavior. Emotions are described using two-dimensional arousal and valence scales. Arousal represents the emotion while valence scale defines the pleasantness of the emotion perceived [1,2]. Emotion regulation involves a complex interplay of cortical and subcortical regions of the brain. Emotional state analysis using physiological signal can provide relevant information for better diagnostics. However, human emotion and its electrophysiological correlates are still poorly understood [3].

Electrodermal Activity (EDA) is a non-invasive, and easily recordable technique to measure emotions. It refers to the variations in electrical properties of the skin due to the changes in emotions. These signals can be recorded from several parts of the human body such as palmer, forehead and sole. EDA signals are composed of two components, namely skin conductance level or tonic component and skin conductance response or phasic component. The tonic component represents the slow varying changes over time, whereas the phasic component refers to the fast-varying changes over time. Several time, frequency and time-frequency analysis has been performed on the EDA signal in the past for the analysis of emotions [2,3]. However, due to variation in recording sites, inter and intra-subject variability, low frequency and complexity makes the analysis of EDA signals challenging.

Other than EDA, Electroencephalography (EEG) signals of the cortical region have been used to determine different emotional states. EEG is a technique that measures voltage fluctuations resulting the ionic current flows within the neurons of the brain. It can be recorded with several electrodes over scalp. EEG Signals has been analyzed in time, frequency and time-frequency domains for the recognition of emotions [4]. Although EEG is non-invasive and fast but there are several challenges in EEG for emotion detection like poor spatial resolution, wearability, portability and huge amount of data from multiple electrodes [5,6].

This talk is aimed at discussing the issues and challenges associated with validating EDA response with EEG which includes localization of sub-anatomic region in the brain and the relevance of frequency bands recorded by EEG electrodes in those areas in response to the emotional stimuli.

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Research of the Template Comparison Method of Body Tissue Node's Diffusion Coefficient Determination

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Перспективы улучшения моделей почвы геномными данными

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Биогеохимические модели почвы могут быть улучшены за счет явного описания микробной активности и нелинейных эффектов их метаболизма на цикл С. Однако современные микробные модели почв не имеют сколько-нибудь реалистичного представления микробного сообщества в различных типах почв и изменений в его биоразнообразии и функциях со временем, типом землепользования или экологическими условиями [1]. За исключением очень немногих попыток [2] современные микробные модели используют только общие экспериментально оцениваемые количества биомасс бактерий и грибов или абстрактные группы микроорганизмов с различными стратегиями роста. Применение молекулярно-генетических методов в настоящее время является одним из необходимых этапов анализа природных микробиомов. Использование этих подходов при исследовании почвенных микробных комплексов перспективно для выявления таксономических маркеров и микробиологических драйверов педогенеза. Однако адекватные способы обработки высокопроизводительных данных секвенирования для микробиомов почвы по-прежнему отсутствуют. Цель этого исследования состояла в том, чтобы продемонстрировать перспективу развития моделей почв знаниями о микробиоме, получаемыми молекулярно-генетическими методами.

Исследование включало анализ микробных сообществ в двух типах почвы под двумя видами растений и с 6 сортами. Так же исследование включало анализ микробных сообществ, связанных с генетическими горизонтами, развивающимися в течение длительной эволюции почвы в средней зоне тайги в хронорядах подзолистых почв: 1) первоначальное почвообразование (1-2, 15-20, 30-35 лет) и 2) развитие подзола (почвы 70-, 145-, 455, 1590 лет). Все образцы почвы анализировали физико-химическими методами, выделение ДНК проводили с использованием PowerGround® (MO BIO, USA). Амплификацию V4 участка 16S рРНК проводили с помощью универсальных праймеров (F515 и R806). Секвенирование библиотек ампликонов выполнялось ILLUMINA MiSeq. Обработку данных последовательностей осуществляли с использованием "Trimomatic" [3] и "QIIME" [4]. Кластеризацию образцов и анализ микробного таксономического состава проводили с использованием карты Кохонена (SOM) [5], со специфической обработкой данных: удаление контаминатов и ненадежных данных, выделение доминантных видов.

Были выявлены характерные закономерности состава микробных таксонов для различных типов почв, растений, глубины и возраста почв в сукцессиях подзолистых почв. Подробная биологически значимая информация (характерные паттерны, адаптивные и эволюционные стратегии микроорганизмов в процессе формирования и управления почвой) может быть получена и применена для развития моделей почв.

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Perspectives of Soil Model Development With Genomic Data

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Soil biogeochemical models have been shown to be improved by explicit simulation of microbial activity and nonlinear effects on soil C cycle related to their metabolism. However, current soil microbially-explicit models lack any realistic microbiome representation in different types of soils and changes in its diversity and functions with time, soil management or environmental conditions [1]. Except for very few attempts [2] current microbial models operate total quantities of bacterial and fungal biomass estimated experimentally, or abstract groups of microorganisms with different growth strategies. The application of molecular-genetic methods is currently one of the necessary steps in the natural microbiomes analysis. The use of these approaches in the study of soil microbial complexes is promising in identifying taxonomic markers and microbiological drivers of pedogenesis. However, relevant ways of processing high-throughput sequencing data for soil microbiome are still lacking. The aim of this study was to demonstrate the potential of soil modeling advances upon integration of a more detailed knowledge about soil microbiome obtained with molecular-genetic methods.

The study included analysis of the microbial composition associated with two soil types (chernozem and sod-podzolic) under two different plants species (wheat and maize) and with 6 plant varieties. As well the study included analysis of microbial compositions associated with the genetic horizons developing during the long-term soil evolution in the middle taiga zone in a podzol soils chronosequences: 1) the initial soil formation (samples of 1-2, 15–20, 30-35 years) and 2) the ongoing podzol pedogenesis (soils of 70-, 145-, 455, 1590 years). All soil samples were analyzed by classical methods (physic-chemical), DNA isolation was performed using the PowerSoil® DNA Isolation Kit (MO BIO, USA). Amplification of a V4 variable region of the 16S rRNA was carried out with universal primers (F515 and R806). Amplicon libraries sequencing was performed by ILLUMINA MiSeq. Sequence data processing was carried out using “Trimmomatic” [3] and “QIIME” [4]. Samples clustering and concurrent microbial taxonomic composition analysis was carried out using an artificial neural network that is trained using unsupervised learning - Kohonen's self-organizing map (SOM)[5] with a specific data pre-processing: contamination removal, dominant species selection and unreliable data elimination.

Characteristic patterns of the microbial taxa composition were revealed for different soil types, plants, soil depth and age of podzolic soils succession. Detailed biologically relevant information (characteristic patterns, adaptive and evolutional strategies of microorganisms during soil formation and management) can be obtained and used for developing soil models.

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Осликавање молекуларних механизама у живим ћелијама

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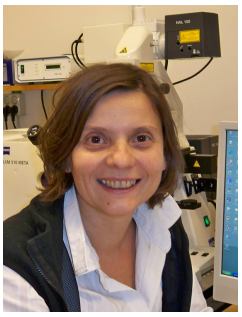

Жива ћелија је отворен динамички систем који непрестано размењује материју и енергију са околином. Локална концентрација и положај молекула се у живим ћелијама контролишу путем хемијских реакција и транспортних процеса. Кроз хемијске реакције и транспортне процесе биомолекули у живим ћелијама су интегрисани у простору и времену у реакционе мреже, односно биохемијске путеве. Интеграцијом сложених биохемијских путева долази до самоорганизације на већим растојањима и дужим временским скалама, и до настајања нових особина које нису својствене неживој материји већ само живим ћелијама, као што су способност транскрипције гена и трансдукције сигнала. Кроз ове сложене процесе, живе ћелије се прилагођавају на промене у околини и размножавају се. Да бисмо на молекуларном нивоу разумели процеса на којима се заснивају сложене биолошке функције и да бисмо могли да их математички опишемо и симулирамо, потребне су методе које нам омогућавају да концентрацију и мобилност биолошких молекула меримо у живим ћелијама и у њиховој непосредној околини.

Флуоресцентна корелациона спектроскопија (ФКС) је једина до данас постојећа техника која нам омогућава да у живим ћелијама детектујемо појединачне молекуле и меримо њихову концентрацију и мобилност [1-3]. Међутим, класична ФКС има један велики недостатак – мерно поље је ограничено на веома малу запремину $(0.2 – 2)\times10^{-15}$ l. Да бисмо превазишли овај недостатак, развили смо масовно паралелну ФКС (мпФКС) [4-7]. мпФКС нам омогућава квантитативно конфокално осликавање без скенирања са временском резолуцијом од 11 μs/слици. У свом излагању, представићу мпФКС и њену примену; даљи развој методе који укључује мерење времена живота молекула у побуђеном стању како би се добиле информације о променама у непосредној околини флуоресцентног молекула (мпФКС/ФЛИМ), и двоканалну масовно паралелну флуоресцентну крос-корелациону спектроскопију (дк-мпФККС), која нам омогућава квантитативну карактеризацију хемијских реакције у живим ћелијама. Ове информације су неопходне за развој математичких модела који са високим степеном поузданости могу да опишу процесе у живим ћелијама и предвиде квалитативне промене у њиховој динамици.

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Imaging of molecular mechanism in living cells

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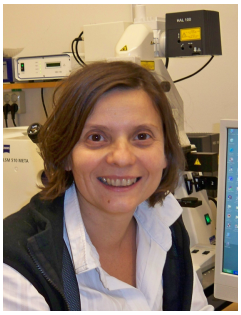

Living cells are open dynamical systems that continuously exchange matter and energy with their surroundings. In living cells, biomolecules are integrated *via* chemical reactions and transport processes into self-regulated networks. Through these networks life-sustaining biological functions, such as gene transcription and signal transduction, emerge at the higher level of organization and at longer spatio-temporal scales. To be able to understand and model how specialized biological functions consistently arise through the random motion of molecules and their stochastic interactions, and how robust and specific responses are obtained under the influence of the external environment that is noisy and changes unpredictably, the concentration and mobility of biological molecules need to be measured in live cells and in their immediate surroundings.

Fluorescence Correlation Spectroscopy (FCS), a quantitative and non-destructive fluorescence technique with single-molecule sensitivity, has proven to be indispensable for such purpose [1-3]. However, classical single-point FCS (spFCS) has one serious shortcoming – limited overview, as it provides information in an observation volume element that is about $(0.2 – 2)\times10^{-15}$ l. In order to overcome this limitation, we have developed massively parallel FCS (mpFCS) [4-7]. mpFCS allows time-resolved (11 µs/frame) confocal fluorescence microscopy imaging without scanning that is suitable for quantitative characterization of fast reaction-transport processes in solution and in live cells. In my talk, I will present mpFCS and give examples of its applications; its integration with fluorescence lifetime imaging microscopy (mpFCS/FLIM) and our ongoing work on the development of dual color massively parallel Fluorescence Cross-Correlation Spectroscopy (dc-mpFCCS). These techniques combined in one instrumental setup for functional Fluorescence Microscopy Imaging (fFMI), allow us to measure properties that are tightly linked to biomolecules activity at functional sites and are crucial for understanding their mechanisms of action. Such information is indispensable for the development of mathematical models with good predictive value.

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青藏高原人群的遗传起源与适应性演化

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人类征服青藏高原的历程悠久而曲折。徐书华团队之前的研究表明，青藏高原人群的遗传起源可追溯至距今 4-6 万年前的旧石器时代中晚期，早期进入青藏高原的人类族群间发生广泛的基因交流，并与后期进入青藏高原的族群发生进一步遗传混合，最终形成了一个包含现代智人和早期智人多个谱系（包括考古学已经发现的阿尔泰尼安德特人和丹尼索瓦人等，以及其他未知古人类）的遗传构成极其复杂的混合人群[1]。这个过程中，一些曾经帮助人类适应高原环境的古人类基因片段得以保留下来，因高原极端环境的选择作用，在现今高原人群中积累到较高的频率[2-4]。

我们最近在全基因组水平对藏族人群的高原适应性变异进行了系统性梳理，充分利用深度基因组测序数据的优势，构建了藏族人群全基因组尺度上的适应性遗传变异图谱，鉴定了有相对明确功能的关键遗传变异，包括 63 个错义突变、7 个失活性变异、1298 个进化保守性变异，以及 509 个基因表达数量性状变异；这些分布在基因组范围的功能性变异不一定都与藏族人群的高原适应直接相关，但是大多数都与藏族人群的适应性演化密切相关。高原适应涉及到一系列复杂性状——涉及到的基因可能比医学中研究的一些复杂疾病更为错综繁杂。我们团队进一步发展了一个新统计量（*FIS*）对鉴定出的适应性遗传变异的相对重要性进行加权排序，发现排在首位的并不是通常认为的 *EPAS1*，而是位于 *EPAS*1 下游的一个跨膜蛋白编码基因 *TMEM247*；尤其是发现藏族人群基因组中的 *TMEM247* 存在一个高频关键错义变异（rs116983452），可能对藏族人群高原适应具有重要贡献和意义。论文新发现的 *TMEM247* 基因关键突变（rs116983452）导致平原人群中高频存在的丙氨酸（Ala）（野生型）与青藏高原人群特有的缬氨酸(Val)（突变型）之间的显著分化，其中 94%的藏族人都携带突变型，而在世界其他现代人群体中的频率非常低或者完全缺失，是迄今为止在青藏高原人群基因组中发现的最高频的错义突变。我们通过计算推断藏族人群中携的 *TMEM247*-rs116983452 适应性变异可追溯至距今约 6 万年前，这个藏族高频突变可能继承自早期进入高原的具有古人类血统的祖先并传承至今。

我们的分析表明，*TMEM247*-rs116983452-T 的频率与人群居住地海拔呈显著正相关，提示与人类在青藏高原的适应可能有密切关系。进一步结合基因表达与多项生理生化表型及体质人类学特征，对高原藏族人群的适应性遗传变异进行了系统性评估；发现 *TMEM247*-rs116983452-T 与 *TMEM247* 及 *EPAS1* 的表达水平都有密切相关，并可能对藏族人群低氧环境下的血红蛋白和红细胞水平等高原适应性性状产生重要的调控。 对于平原人群而言，长期暴露于低氧环境中将诱发红细胞增生以提高血液携氧能力，但最终可能过度增生而导致“红细胞增多症”。相比之下，高原世居藏族人群的红细胞和血红蛋白水平保持在相对较低的水平，*TMEM247* 基因的功能突变可能就是产生这种保护性机制的重要遗传因素之一。通过统计模型分析，我们发现 *TMEM247*-rs116983452 对藏族高原适应性表型的解释度高于 *EPAS1* 的变异位点，但二者之间可能存在一定的相互作用，体现了高原适应的复杂性和多基因相互作用效应 。我们的研究和发现为后续进一步全面深入研究藏族适应高原的遗传基础和分子机制锁定了目标、为揭开人类征服高原极端环境的演化之谜开拓了新的视野[5]。

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The Genetic History and Adaptive Evolution of Tibetan Highlanders

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It was a long journey for human to conquer the Tibet Plateau where the average elevation is beyond 4,500 meters and the oxygen pressure is much lower than at sea level (~60%). We estimated that the genetic origin of the Tibetan highlanders could be traced back to around 40,000 to 60,000 years ago, in the middle-late Paleolithic. The early migrants to the plateau had extensive genetic admixture with each other, and had further gene flows with the latecomers, leading to the admixed descendants with very complex genetic makeup -- inherited from ancestral lineages of modern human and archaic hominins [1]. During this process, some archaic genomic segments that were advantageous to the high-altitude adaptation were retained, and reached to high frequencies due to natural selection [2-4].

Taking advantage of the whole-genome deep sequencing data, we constructed a map of adaptive genetic variants in Tibetans, including 1,877 key variants with known functions: 63 missense, 7 loss-of-function, 1,298 evolutionarily conserved variants and 509 expression quantitative traits loci. We further developed a statistic (*FIS*, functional importance score) to prioritize these identified adaptive genetic variants, and found that the top signal is not the well-known *EPAS1*, but *TMEM247*, a transmembrane protein coding gene. Especially, a missense variant (rs116983452) located in *TMEM247* showed rather high frequency specifically in Tibetans. This key variant may largely increase the genetic differentiation between the lowlanders and Tibetan highlanders, by transforming Alanine, the common wild type in the lowlanders, to Valine, the Tibetan-enriched mutant type. This mutant is carried by around 94% Tibetans, but is in low frequency or even missing in other world-wide modern human populations. It is so far the most highly differentiated missense variant between Tibetans and the lowlanders. We estimated the age of the adaptive Tibetan sequences carrying *TMEM247*-rs116983452-T to be about 60,000 years ago, implying that this Tibetan-specific variant could be inherited from early inhabitants of Tibet Plateau with archaic ancestry.

We found that the frequency of *TMEM247*-rs116983452-T is strongly and positively correlated with altitude. Further analyses revealed that this variant is significantly associated with the expression levels of *EPAS1* and *TMEM247*, and could possible regulate the concentrations of hemoglobin and red blood cell of Tibetans under hypoxia. By statistical modeling, we found that *TMEM247*-rs116983452 shows greater effect size and better predicts the phenotypic outcome than any *EPAS1* variants in the association with adaptive traits in Tibetans, but interactions were also observed between *TMEM247*-rs116983452 and *EPAS1* variants, indicating that multiple variants may jointly deliver the fitness of the Tibetans on the Plateau, where a complex model is needed to elucidate the adaptive evolution mechanism [5].

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Гибридно-интегрированные устройства как эффективный инструмент борьбы с антибиотекирезистентностью

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Экспресс-тестирование антибиотикорезистентности (АБР) является чрезвычайно важным этапом микробиологической диагностики, поскольку позволяет принимать правильные оперативные решения по тактике антибактериальной терапии в условиях растущего уровня резистентных штаммов бактерий. Такое тестирование может быть основано на наблюдении за жизнеспособностью микроорганизмов под воздействием антибиотиков. В настоящее время такое тестирование завершено на выбранных штаммах, что занимает много времени (2–7 дней). Внедрение портативных (для оказания медицинской помощи) устройств для экспрессного (6–8 часов) микробиологического тестирования является ожидаемым событием среди врачей общей практики, специалистов по инфекционным заболеваниям, поставщиков и широкой общественности [1]. Эти ожидания основаны на развитии технологий нового поколения в МЭМС/НЭМС и междисциплинарных науках.

Здесь мы обсуждаем способы перестройки основанного на культуре классического метода микробиологического анализа, чтобы сократить время анализа, а также сделать анализ широко доступным для населения и медицинского персонала. Это может быть достигнуто путем внедрения таких устройств с использованием МЭМС/НЭМС и информационных технологий и принципов архитектуры лаборатории-на-чипе (ЛНЧ). Архитектура устройства должна включать в себя немало важных функциональных элементов, таких как: камера роста, модуль идентификации, модуль АБР, микрофлюидная транспортная подсистема, сенсорная система и другие.

Ростовая платформа изготовлена из нанопористого анодного оксида алюминия и позволяет однородной колонии достигать размера около 1000 КОЕ (колониеобразующих единиц) [2]. На следующем этапе анализа эти колонии перемещаются и транспортируются в подсистему идентификации, включая распознавание изображений [3], акустический анализ для различения G(+)/G(-), флуориметрический анализ. Стадия идентификации позволяет отбирать патогенные бактерии и доставлять их в подсистему для АБР. Это может быть реализовано с помощью клапанных механизмов, включая акустофлюидную актюацию. Заключительная стадия анализа АБР проводится по крайней мере для 2 видов микроорганизмов и до 10 антибиотиков. Жизнеспособность проверяется с использованием многоканального динамического рассеяния света [4], импедиметрическим или электрохимическим методами.

Представлена топология и конструкция гибридно-интегрированного ЛНЧ и особенности его основных функциональных элементов. Обсуждается архитектура этого миниатюрного устройства нового поколения для экспресс-идентификации и тестирования устойчивости к антибиотикам микроорганизмов, физические принципы и технологии для создания функциональных компонентов и их интеграции в единую систему.

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Hybrid-integrated Devices as an Efficient Tool of Fighting Antibiotic Resistance Problem

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An express-antibiotic susceptibility testing (AST) is an extremely important stage of microbiological diagnostics since it enables to make correct operative decisions on antibacterial therapy tactics under conditions of growing level of resistant bacterial strains. Such testing could be based on observation of viability of microorganisms under exposure of antibiotics. At present time such testing is completed over selected strains which is a time-consuming procedure (2–7 days). Introduction of portable (point-of-care) devices for express (6–8 hours) microbiological testing is a highly anticipated event among general practitioners, infectious diseases specialists, vendors and general public [1]. These expectations are based on development of new generation technologies in bioMEMS/NEMS and multidisciplinary sciences.

Here we discuss the ways of redesigning culture-based classical method of microbiological analysis in order to reduce the analysis time, as well as to make the assay widely available for population and medical staff. This could be achieved via implementation of such devices using MEMS/NEMS and information technologies and lab-on-a-chip (LoC) architecture principles. Architecture of the device should include quite a few important functional elements, such as: growth chamber, identification module, AST module, microfluidic transport subsystem, sensor system and others.

The growth platform was prepared of nanoporous anodic alumina and enables homogeneous colony to reach the size of about 1000 CFU (colony forming units) [2]. During the next analysis stage these colonies are displaced and transported into the identification subsystem, including image recognition [3], acoustic analysis to discriminate G(+)/G(-), fluorimetry assay. The identification stage enables pathogenic bacteria to be selected and delivered to the subsystem for AST. This could be realized via valve mechanisms, including acoustofluidic actuation. The final AST stage of assay is made for at least 2 species of microorganisms and up to 10 antibiotics. The viability is tested using multichannel dynamic light scattering [4], impedimetric or electrochemical methods.

The layout of hybrid-integrated LoC and features of its main functional elements are presented. The architecture of this new generation miniature device for express identification and antibiotic resistance testing of microorganisms, physical principles and technologies for creating functional components and their integration into a single system are discussed.

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