

Theory and Modeling of Complex Systems in Life Sciences

Monday	18/09/2017
8:30 – 9:15	Registration
9:15 – 9:30	Opening
9:30 – 10:15	Ralf Metzler <i>Anomalous diffusion in membranes and cytoplasm of living cells (p. 23)</i>
10:15 – 11:00	Eli Barkai <i>Fluctuations of Single-Molecule Diffusivity (p. 5)</i>
11:00 – 11:30	Coffee break
11:30 – 12:15	Remi Monasson <i>Fast transitions between spatial maps in the rat hippocampus: theoretical models and analysis of multi-electrode recordings (p. 24)</i>
12:15 – 13:00	Aleksey Chechkin <i>Brownian yet non-Gaussian diffusion (p. 8)</i>
13:00 – 15:00	Lunch
15:00 – 15:45	Raphael Voituriez <i>First-passage times of Markovian and non Markovian random walks (p. 41)</i>
15:45 – 16:30	Sergey Traytak <i>Boundary effects for diffusion of particles in finite arrays of traps: Does the classical mean field theory really work? (p. 38)</i>
16:30 – 17:00	Coffee break
17:00 – 17:45	Sergei Nechaev <i>From geometric optics to plants: eikonal equation for buckling (p. 25)</i>
18:00 – 20:00	Welcome wine party
Tuesday	19/09/2017
9:30 – 10:15	Doris Heinrich <i>Dynamics of the cellular interior – from insight to control (p. 16)</i>
10:15 – 11:00	Davide Calebiro <i>Single-molecule analysis of G protein-coupled receptor signaling (p. 7)</i>
11:00 – 11:30	Coffee break
11:30 – 12:15	Maxime Dahan <i>Single molecule approach to intracellular dynamics (p. 10)</i>
12:15 – 13:00	Eugene Katrukha <i>Resolving passive and active transport in crowded environment of cell (p. 18)</i>
13:00 – 15:00	Lunch
15:00 – 15:45	Stanislav Smirnov <i>How the lizard got its colors (p. 35)</i>
15:45 – 16:30	Vladimir Teif <i>Microdomain formation in chromatin (p. 37)</i>
16:30 – 17:00	Coffee break
17:00 – 18:30	Poster Session
19:00 – 22:00	Conference Dinner

Wednesday	20/09/2017
9:30 – 10:15	David Holcman <i>Statistical analysis of super-resolution single trajectories in cell biology (p. 17)</i>
10:15 – 11:00	Agnieszka Wylomanska <i>Statistical investigation of anomalous diffusion processes (p. 44)</i>
11:00 – 11:30	<i>Coffee break</i>
11:30 – 12:15	Vladik Avetisov <i>Ultrametricity in the context of biology (p. 4)</i>
12:15 – 13:00	Mikhail Tamm <i>Rouse-like dynamics of the topologically stabilized polymer states (p. 36)</i>
13:00 – 15:00	<i>Lunch</i>
15:00 – 18:00	<i>Free/Social program</i>
Thursday	21/09/2017
9:30 – 10:15	Jacques Prost <i>Active behavior in tissues (p. 29)</i>
10:15 – 11:00	Thomas Franosch <i>Non-equilibrium dynamics of active agents (p. 13)</i>
11:00 – 11:30	<i>Coffee break</i>
11:30 – 12:15	Bernard Sapoval <i>Complexity in human respiration (p. 32)</i>
12:15 – 13:00	Marcel Filoche <i>Non linear transport of fluids into the tracheobronchial tree (p. 12)</i>
13:00 – 15:00	<i>Lunch</i>
15:00 – 15:45	Valery Kiselev <i>MRI as a probe of tissue microstructure (p. 19)</i>
15:45 – 16:30	Dmitry Novikov <i>The mesoscopic physics of diffusion MRI (p. 26)</i>
16:30 – 17:00	<i>Coffee break</i>
17:00 – 17:45	Carlo Manzo <i>Benefits of diversity: from molecular organization to cell signaling (p. 22)</i>
Friday	22/09/2017
9:30 – 10:15	Maria Samsonova <i>Reverse engineering of genotype-phenotype map using individual genetic variation (p. 31)</i>
10:15 – 11:00	Vitaly Volpert <i>Reaction-diffusion waves in biological applications (p. 42)</i>
11:00 – 11:30	<i>Coffee break</i>
11:30 – 12:15	Alexander Serov <i>The Itô-Stratonovich Dilemma and the Inverse Problem for the Overdamped Langevin Equation: A Bayesian Approach (p. 33)</i>
12:15 – 13:00	Kirill Polovnikov <i>Memory-dependent action for fractal Brownian motion and application to chromatin dynamics (p. 28)</i>
13:00 – 13:05	<i>Conference closing</i>

List of Posters

Anatoly S. Buchelnikov	<i>Theory of interceptor-protector action as a tool to study biomedical synergism of drugs mixture in combination chemotherapy (p. 6)</i>
A. A. Chertkova	<i>Functional rearrangements of the Drosophila gap gene regulatory sequences in a computational simulation of their evolution under elevated mutational pressure (p. 9)</i>
Andrey Dmitrenko	<i>Stochastic simulation of transcription factor binding in the Drosophila gap gene regulatory regions (p. 11)</i>
Maria Götz	<i>Tracer Size Dependent Anomalous Transport in Living Cells (p. 15)</i>
Janusz Gajda	<i>First passage times of accelerating subdiffusion in field of external potential (p. 14)</i>
Yann Lanoiselée	<i>Unravelling intermittent features in single particle trajectories by a local convex hull method (p. 20)</i>
Alexey A. Polotsky	<i>Adsorption of random and periodic copolymers: a theoretical study using simple model (p. 27)</i>
Marco Saltini	<i>Microtubule reorientation driven by severing: a competition model (p. 30)</i>
Alexander S. Serov	<i>Abortive Initiation as a Bottleneck for Transcription in the Early Drosophila Embryo (p. 34)</i>
Liubov Tupikina	<i>Heterogeneous continuous time random walk approach for analysis of diffusion in porous media (p. 39)</i>
Patrick Witzel	<i>Universal Scaling Law in Intracellular Dynamics (p. 43)</i>

Ultrametricity in the context of biology

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An ultrametric is a metric stronger than the familiar "weak" metric of Euclidian space surrounding us. In general, any metric must satisfy the triangle inequality, which requires each side of a triangle be no longer than the sum of the other two sides. The "weak" metric admits equilateral, isosceles, or scalene triangles, and it satisfies Archimedes' principle that states that a long distance can always be traversed step by step. Newtonian ideas about describing movements using differential equations are based precisely on Archimedes' principle. The "strong" metric, i.e. ultrametric, obeys the *strong* triangle inequality that requires that any side of a triangle be no longer than the longest of the other two sides. An ultrametric admits only equilateral or isosceles triangles (with smaller basis). An ultrametric space possesses an unusual geometry. Archimedes' principle is not fulfilled in an ultrametric space: a path that is done step-by-step never exceeds a single step length. Any point on an ultrametric ball can be regarded as its center. If two ultrametric balls share a common point, the smaller of them is entirely contained within the larger. Overall, an image of ultrametric space is not a straight line: it is a branching tree of balls embedded one within the other, and a branching tree is the most attractive feature of ultrametric distances.

Where is the ultrametric geometry effective for modeling actual systems? Perhaps most natural ultrametric spaces emerge in the realm of complex systems characterized by high-dimensional, combinatorically large spaces of states and extremely complex landscapes of functions controlling a system's behavior. There is a rich variety of such systems in Life Sciences. One can even say that biological systems are always complex.

I will consider two examples that illustrate the natural emergence of ultrametricity when complexity and randomness are combined. The first example relates to sparse subsets chosen in a space of high dimensionality, and the second example illustrates the approximation of stochastic dynamics on complex energy landscapes via ultrametric random walks. In this presentation, I will refer to classical problems in biophysics such as protein dynamics and evolution.

Fluctuations of Single-Molecule Diffusivity

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In nature the time trace of a signal might be random however its long time average converges to the corresponding ensemble average (ergodicity). In the environment of the cell, time averaged diffusivities of single particles, e.g. mRNA in an E. Coli cell, remain random even in the long time limit [1]. This theme has been extensively studied in the context of random walks in random environments, where the time averaged procedure yields significantly different results if compared with the corresponding ensemble average [2]. Here we will briefly review the CTRW approach which exhibits aging effects which are observed in four experiments. This means that as the experiments proceeds, the particle is trapped in deeper traps, in such a way that the motion statistically slows down, and hence the time averaged procedure depends on the total time duration of the experiment (non-stationarity). Comparing this to random walks in quenched random environments, i.e. the quenched trap model, we show that the aging effect is replaced with a diffusivity which is system size dependent: the larger the system becomes the particle may encounter a deeper trap and hence slow down is related to size [3]. Further, the fluctuations of time averages in the quenched system are by far larger if compared with the mean field like CTRW theory.

References

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Theory of interceptor-protector action as a tool to study biomedical synergism of drugs mixture in combination chemotherapy

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Synergistic enhancement of biomedical activity of several antitumour aromatic drugs in the presence of another aromatic biologically active molecules, called ‘interceptors’ and being able to form stable non-covalent complexes with the drugs, is quite well-known fact in molecular biophysics which is used in combination chemotherapy. Evstigneev et al. analyzed experimental data accumulated by that time and formed the basic understanding of the competition between two fundamental molecular mechanisms governing such synergism, in the form of so-called theory of interceptor-protector action (IPA) [1]. In fact, this theory bridges the equilibrium physical parameters of intermolecular complexation with the data from biological experiments, i.e. with the response of biological system on the mixture administration. The main conclusions in the IPA theory can be made by the analysis of concentration dependence of so-called A_D factor which quantitatively expresses the fraction of the drug molecules displaced from DNA when interceptors are added.

Further development of the IPA theory led to the investigation of Drug – C_{60} fullerene – Cell systems, where fullerene is an interceptor and the biomedical effect is studied on human buccal epithelial cells [2]. The present work is devoted to study of a similar system where drug is antibiotic novatrone (mitoxantrone).

During the biological experiment we were calculating the quantity of heterochromatin granules (HGQ) in buccal epithelium cells administered with the mixture of novatrone and C_{60} fullerene at the different concentrations of the latter and then were re-calculating these data into A_D factor. An increase in HGQ indicates a decrease in the transcriptional activity of the cell nucleus. The obtained experimental dependences of the A_D factor on C_{60} fullerene concentration were fitted well within the framework of the IPA theory which indicates the applicability of the theory to study systems of this type. The theory of interceptor-protector action can be used as a kind of ‘calculator’ to regulate the effective concentration of the drug in a cell by adding C_{60} fullerene.

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2. Skamrova G.B., Laponogov I., Buchelnikov A.S., Shckorbatov Yu.G., Prylutska S.V., Ritter U., Prylutskiy Yu.I., Evstigneev M.P. Interceptor effect of C_{60} fullerene on the *in vitro* action of aromatic drug molecules. *Eur. Biophys. J.* 2014. V. 43. P. 265-176.

Single-molecule analysis of G protein-coupled receptor signaling

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G protein-coupled receptors (GPCRs) are the largest family of cellular receptors. They mediate the effects of several hormones and neurotransmitters and represent major pharmacological targets. In our lab we are developing single-molecule microscopy methods to investigate the organization of GPCR signaling cascades at the surface of living cells. Using this approach, we could show that three prototypical GPCRs have very different localization, mobility and tendencies to form supramolecular complexes. The formation of such complexes is due to transient receptor/receptor interactions, which can be directly visualized with our approach. Interactions between receptors and the underlying cytoskeleton seem to play an important role in defining the spatial arrangement of receptors. More recently, we have extended this approach to investigate the interactions between receptors and G proteins at single-molecule level. Our results reveal that GPCR signaling cascades are at the same time very dynamic and yet highly organized in space and time. These data suggest the existence of dynamic receptor nanodomains on the cell surface, which appears required for achieving high signaling efficiency and specificity.

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Sungkaworn, T., Rieken, F., Lohse, M. J., and Calebiro, D. High-resolution spatiotemporal analysis of receptor dynamics by single-molecule fluorescence microscopy. *J Vis Exp*, e51784 (2014).

Brownian yet non-Gaussian diffusion

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A growing number of biological, soft, and active matter systems are observed to exhibit normal diffusive dynamics with a linear growth of the mean-squared displacement, yet with a non-Gaussian distribution of increments. Based on the Chubinsky-Slater idea of a diffusing diffusivity, we here establish and analyze a minimal model framework of diffusion processes with fluctuating diffusivity. In particular, we demonstrate the equivalence of the diffusing diffusivity process with a superstatistical approach with a distribution of diffusivities, at times shorter than the diffusivity correlation time. At longer times, a crossover to a Gaussian distribution with an effective diffusivity emerges. Specifically, we establish a subordination picture of Brownian but non-Gaussian diffusion processes, which can be used for a wide class of diffusivity fluctuation statistics. Our results are shown to be in excellent agreement with simulations and numerical evaluations.

Reference:

A.V. Chechkin, F. Seno, R. Metzler, and I.M. Sokolov, Phys. Rev. X 7, 021002 (2017).

Functional rearrangements of the *Drosophila* gap gene regulatory sequences in a computational simulation of their evolution under elevated mutational pressure

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The regulatory DNA sequences involved in *Drosophila melanogaster* embryo segmentation during early development are often composed of many low-affinity transcription factor binding sites (TFBSs). Their functional role in regulation of developmental gene networks is an open question, especially considering the fragility of such sites with respect to possible mutations. We investigate the stability of the *cis*-regulatory logic based on low-affinity TFBSs by simulating the evolution of regulatory sequences controlling expression of four gap genes [1]. The purifying selection evaluates gene expression dynamics produced by a computational model of the developmental gene network [2]. Under the high mutation rate conditions, we observe a dramatic decrease in the total number of TFBSs through the course of evolution. The regulatory sequences tend towards organisations containing TFBSs with both increased binding affinity and higher functional importance (the strength of influence on gene expression). We demonstrate ubiquitous mutual correlations through time between the functional scores of TFBSs. Fewer than 10% of initial TFBSs are maintained throughout the entire simulation, deemed ‘core’ sites. These sites have increased functional importance as assessed under wild-type conditions and their binding energy and functional score distributions are highly conserved. Furthermore, TFBSs within proximity of core sites exhibit increased longevity, reflecting functional regulatory interactions with core sites. Our results demonstrate that, in response to elevated mutational pressure, evolution tends to sample regulatory sequence organisations with fewer, albeit on average stronger functional TFBSs. These organisations are also shaped by the regulatory interactions among core binding sites with sites in their local vicinity.

The study was supported by the RFBR grant 16-01-00648-a.

References:

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Single molecule approach to intracellular dynamics

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Single molecule imaging constitute a powerful tool to probe the organization and dynamics of living systems. Here, we will illustrate the interest of single molecule approaches in two cellular contexts. First, we will describe the results of measurements in which we have probed the characteristics of the cell cytosol by tracking nanoprobe with various colloidal properties. We found that, contrary to common belief, the diffusion dynamics in the cytosol is not much controlled by crowding but by non-specific interactions. For well passivated probes, it resembles that measured in an homogeneous medium, slightly more viscous than water. Yet, increasing non-specific interactions lead to reduced mobility and anomalous diffusion. Second, we will discuss the search properties of DNA-binding proteins in the nucleus and highlight the role of non specific interactions in the search kinetics.

Stochastic simulation of transcription factor binding in the *Drosophila* gap gene regulatory regions

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Site-specific transcription factors (TFs) regulate gene activity through binding to some regions on the DNA called enhancers or *cis*-regulatory modules. Possible combinations of bound proteins form molecular configurations of the regulatory regions, which determine the transcription rate of target genes. In this study, we stochastically simulate the formation of these configurations by extending previously proposed models [1] and applying the extended model to the gap gene regulatory system in *Drosophila*. The model implements the agent-based modeling approach and assumes the facilitated diffusion mechanism for the TF search for its target site on the DNA, which is a combination between 3D diffusion of the TF molecules and their 1D sliding on the DNA. The TF molecules are represented as objects able to perform different types of movements on and near the DNA molecule. The search process is divided into several stochastic reactions associated with the binding of a free TF molecule to a non-specific site on the DNA, the sliding of a TF molecule along the DNA, different hops and jumps in a vicinity of the binding site, and the unbinding from the DNA. The extended model additionally takes into account specific properties of regulatory proteins participating in *Drosophila* segmentation, such as the short-range repression mechanism for inhibiting TFs and experimental data on the open chromatin states for more accurate prediction of the binding sites [2, 3]. The simulation results demonstrate a significant influence of the short-range repression mechanism on the formation of molecular configurations. This influence leads to the decreasing of both the TF sliding lengths and the resulting average occupancy times of the target sites. The short-range repression also increases the noise level for the number of occupied binding sites. We demonstrate absence of a simple map between the binding energy of a site and the occupancy time. This result necessitates accounting for the dynamic properties of the molecular configurations in gene expression models.

The study was supported by the Russian Foundation for Basic Research, grant 16-01-00648a.

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Non linear transport of fluids into the tracheobronchial tree

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In the human lung, the distribution system transporting the inhaled air from the upper pulmonary airways down to the exchange area between air and blood (the acinar region) is a highly branched structure comprising on average 15 generations: the *tracheobronchial tree*. Millions of years of evolution have led to this transport structure working almost linearly and optimized for standard conditions of rest or moderate exercise. However, procedures and therapeutics performed in the clinical setting can significantly deviate from this optimal framework, leading to a highly non linear and non homogeneous transport. We will show in two specific cases, forced exhalation maneuver and surfactant replacement therapy (SRT), that the fluid-structure interaction with the airway walls, and the fluid splitting in the bifurcations of the tree play a major role in understanding the global transport performance. In the case of SRT, this performance is governed by a double constraint [1]. This constraint is easily fulfilled in the newborn but in adults, it narrow considerably the window of acceptable delivery parameters (dose, concentration, posture). This can lead to dramatic clinical failures regardless of the underlying biochemistry of the delivered drugs.

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Non-equilibrium dynamics of active agents

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Various challenges are faced when animalcules such as bacteria, protozoa, algae, or sperms move autonomously in aqueous media at low Reynolds number. These active agents are subject to strong stochastic fluctuations, that compete with the directed motion. So far most studies consider the lowest order moments of the displacements only, while more general spatio-temporal information on the stochastic motion is provided in scattering experiments. Here we derive analytically exact expressions for the directly measurable intermediate scattering function for a mesoscopic model of a single, anisotropic active Brownian particle. The mean-square displacement and the non-Gaussian parameter of the stochastic process are obtained as derivatives of the intermediate scattering function. These display different temporal regimes dominated by effective diffusion and directed motion due to the interplay of translational and rotational diffusion which is rationalized within the theory.

Reference:

C. Kurzthaler and T. Franosch, Scientific Reports (2016)

First passage times of accelerating subdiffusion in field of external potential

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We discuss first passage time (FPT) statistics for the phenomenon of accelerating subdiffusion [1, 2, 3]. Models of such systems are characterized through MSD which exhibits different behavior in two regimes of time. It is worth to mention that one can consider a scenario with an arbitrary number of the accelerating MSD scalings. We investigate further model considered in [4] (see also [5]). We provide n-tuple distributed order time fractional diffusion equation (DOFDE) for probability density function (PDF) $p(x; t)$ of an accelerated process, and derive its FPT properties. Moreover we also discuss the underlying stochastic representation of the considered phenomenon.

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Tracer Size Dependent Anomalous Transport in Living Cells

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Transport within living cells from small molecules to big structures like organelles is crucial for all living organisms. The heterogeneous crowded environment as well as the variety of the cargos affects the transport behavior enormously. By choosing tracers, which are chemically identical but varying in dimension, cellular dynamics and structure can be probed on different length scales. Single particle tracking in living cells and time-resolved local mean squared displacement (LMSD) analysis reveal the impact of intracellular architecture and dynamics on transport processes. We tracked fluorescent beads with various diameters within living cells of *Dictyostelium discoideum* cells by high resolution microscope. By these means, size dependent active directed transport along microtubules can be distinguished and quantified. Moreover, considering solely diffusive motion of the beads, properties like mesh size, vesicle dimension surrounding the particle or crowding characteristics within cells can be revealed. Our results show a decrease in active velocities and diffusion coefficients for bigger particles. Furthermore, particles smaller than 400 nm in diameter show two modes of motion with two distinct diffusion coefficients. This type of analysis is not just an excellent tool to detect dynamics and architecture of living cells but consequently a method for medical applications, e.g. targeted drug delivery or innovative diagnostic assays.

Dynamics of the cellular interior – from insight to control

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The living cell's interior is a highly dynamic material system. Within this cytoplasmic space a complex interplay between crowding and ATP-driven cytoskeleton dynamics controls most cellular functions. Many features of anomalous transport within the cell interior have been revealed during the last decades and we gained a comprehensive understanding of the active cell mediated transport by motor proteins. Still, we lack a deeper understanding of the driving forces and underlying dynamics of the passive material and information transport within the cell.

We investigate the cytoplasmic space of eukaryotic cells by single-particle tracking of micro- and nano-tracers. Based on the analysis of the local mean squared displacement, on directional persistence and correlations, we are able to determine specific dynamics and to reliably separate active from passive motion phases of particle transport, which we analyse in terms of a two-state motility model: this yields the distribution of active and passive state durations as well as the distribution of the state parameters, i.e. the velocity during active phases and the diffusion coefficient of the passive motion.

We also manipulate intracellular transport states via controlled external stimuli. By applying spatially and temporally defined external boundary conditions to these cells, like precisely monitored chemotaxis gradients or by cell motility essays on pre-ordered 3D topologies, we induce changes in cellular function and therefore aim to control cell functions, e. g. adhesion and migration.

Statistical analysis of super-resolution single trajectories in cell biology

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We will discuss our past and present efforts to extract biophysical parameters from the statistical analysis of large amount of single particle trajectories (SPTs), originating from super-resolution microscopy. SPTs have revealed features such diffusion tensors, potential wells, jump-drift and organized flows. The analysis is based on stochastic processes such as the Langevin equation for extracting drift and diffusion tensor at few tens of nanometers precision. The statistical method relies on constructing optimal estimators, deconvolving data and estimating first passage and narrow escape times from asymptotics of PDEs and stochastic simulations in empirical domains. The main applications are to determine sub-cellular functions from the heterogeneous organization of microdomains. We will discuss GAG viral assembly, topological flow organization in the endoplasmic reticulum and pre- and post- synaptic terminals of neuronal cells.

Resolving passive and active transport in crowded environment of cell

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The cytoplasm of a eucaryotic cell is a highly complex and mechanically composite medium that is structured by the cytoskeleton. How efficient is intracellular transport in this environment? How does it depend on polymer meshwork of F-actin and microtubules? We use small and photostable quantum dots (QDs) as probes for active and passive intracellular transport. Rapid imaging of non-functionalized QDs reveals two populations with a 100-fold difference in diffusion constant, with the faster fraction increasing upon actin depolymerization. When QDs are targeted to different kinesin motor proteins, their trajectories do not display strong actin-induced transverse displacements, as suggested previously using larger probes. Only kinesin-1 displays subtle directional fluctuations, because the subset of microtubules used by this motor undergoes prominent undulations. Using actin-targeting agents reveals that F-actin suppresses most microtubule shape remodeling, rather than promoting it. We show that the spatial heterogeneity of the cytoskeleton allows considering cell as simultaneously liquid, porous and elastic material.

MRI as a probe of tissue microstructure

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Among all scales of biology, the cellular scale (of the order of a micrometer) is accessible for modern microscopy techniques. Medicine, however, poses a unique unresolved challenge to access the cellular scale *in vivo*, deep inside human body. Such information can revolutionize clinical diagnostics, but so far characterization of cellular tissue structure is a prerogative of histology, an *ex vivo* technique. In contrast to microscopy, magnetic resonance imaging (MRI) can access virtually all MR-responding nuclei within the human body, *in vivo* and non-invasively. While the spatial resolution of MRI (of the order of a millimeter) is about three orders of magnitude coarser than the cell size, the currently booming microstructural MRI aims at evaluation of cell properties that remain imprinted in the MRI signal after the massive averaging due to the macroscopic imaging resolution. Transverse relaxation and water self-diffusion in biological tissues are the most informative in this respect. Water diffusion, in particular, offers the diffusion length scale commensurate with the structure at the cellular level. Varying MRI acquisition parameters enables observation of the transient effects in the transverse relaxation and diffusion, which manifest themselves in non-Gaussian diffusion, non-exponential transverse relaxation, as well as in the interference between relaxation and diffusion phenomena in the observed MR signal. The aim of this talk is to sketch the main physical principles of microstructural MRI and to connect them to the disorder averaging techniques adopted in describing transport phenomena in condensed matter physics.

Unravelling intermittent features in single particle trajectories by a local convex hull method

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Many biological transport processes are intermittent [1, 2], with two or several alternating phases of motion. These phases can be distinguished by a change in their dynamical properties e.g. change in diffusivity, in drift, in autocorrelations, in distribution of increments or in dimensionality. Identification of such distinct phases is of major importance for describing relevant properties such as biochemical reaction rates, or biophysical mechanisms as translocation, transcription or drug delivery. This identification is challenging by two factors: the amount of experimental data is limited and different phases are not known *a priori*. We address the problem of identification of change points between distinct phases in a single random trajectory without prior knowledge of the underlying stochastic model.

We introduce two model-free estimators based on a local convex hull (LCH) constructed over trajectory points [3]. The basic idea consists in considering a weighted *local* functional of the trajectory, $S(n)$, which depends on 2τ points around a point x_n . When applied to successive points along the trajectory, this local functional transforms the trajectory into a new time series, which can then be used to discriminate between different phases. The points x_n with $S(n)$ below some threshold are assigned to one phase while the remaining points are assigned to the other phase. We consider two functionals based on the local convex hull, the volume and the diameter (the largest distance in the hull).

Being based on purely geometrical properties of a trajectory, this method is sensitive to various changes in the dynamics and can be applied to a trajectory in any dimension. Its integral-like form makes it robust even in very noisy situations. We validate the LCH method by applying it to several models of intermittent processes. The recognition score R (the fraction of correctly recognized points) was computed by averaging over 1000 independent trajectories. Figure 1 illustrates one example of heterogeneous diffusion, in which the particle diffuses in a composite medium with high and low diffusivities.

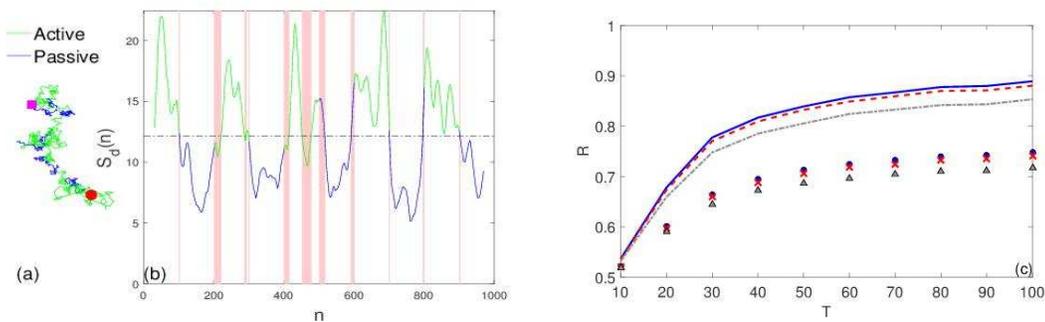


Figure 1: (a) A single trajectory with 1000 points of planar Brownian motion alternating a “slow” phase ($D_1 = 1/4$, dark blue) and a “fast” phase ($D_2 = 1$, light green), each phase duration $T=100$.

(b) The weighted LCH diameter $S_d(n)$ with the window size $\tau = 10$, applied to this trajectory. Pink shadow highlights the false identification zones. Dashed horizontal line shows the empirical mean S_d over that trajectory. (c) Recognition score R of the diameter-based discriminator $S_d(n)$ as a function of the mean phase duration T . Lines show the results for the case $D_2 = 1/4$ with three noise levels σ_n : 0 (blue solid), 0.5σ (red dashed), and σ (gray dash-dotted) (σ being the empirical standard deviation of increments calculated for each trajectory). Symbols correspond to the case $D_2 = 1/2$ with the same levels of noise.

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Benefits of diversity: from molecular organization to cell signaling

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Cellular signaling is regulated by biochemical interactions that are ultimately controlled by molecular diffusion. Recent advances in fluorescence microscopy have allowed the visualization of single molecules in living cells at unprecedented spatiotemporal resolution, revealing that the heterogeneity of the cellular environment produces exotic molecular motions that deviate from Brownian behavior [1]. These findings have stimulated new questions about the mechanisms generating these phenomena, as well as regarding their implications for cell biology. In this context, we have studied a transmembrane receptor involved in the capture of pathogens, which motion exhibits anomalous diffusion with signatures of weak ergodicity breaking [2]. Through the study of receptor mutants, we have been able to correlate the receptors motion to its molecular structures, lateral organization and interactions, thus establishing a link between nonergodicity and biological function. In addition, we have quantitatively interpreted the receptor dynamics through a stochastic model of random motion with random diffusivity on scale-free media [3,4], and we are attempting to gain further insight into the molecular causes of this complex diffusion. Our work highlights the role of heterogeneity in cell membranes and proposes a connection with function regulation. In addition, our models offer a theoretical framework to interpret anomalous transport in complex media, such as those found, e.g., in soft condensed matter, geology, and ecology.

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Anomalous diffusion in membranes and cytoplasm of living cells

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Lipid molecules are amphiphilic molecules with a hydrophilic head group and two hydrophobic tail groups. In water the lipids self-organise into micelles or bilayer sheets in order to avoid contact between the tail groups and the water molecules. Such bilayers form the basis of all biological membranes in living cells, and they are also at the heart of bio-compatible containers envisaged in drug delivery into biological cells.

This talk will focus on the dynamics of lipid molecules in lipid bilayer membrane systems as well as that of proteins embedded in the bilayer. It combines information from extensive all atom and coarse grained Molecular Dynamics simulations as well as single potassium channel trajectories measured in the membranes of living human cells. Particular focus is laid on deviations of the lipid and protein motion from normal diffusion. Such anomalous diffusion, characterised by a non-linear power-law scaling of the mean squared displacement will be demonstrated to characterise both lipids and proteins. While in a pure lipid system at room temperature this anomalous diffusion crosses over to normal diffusion at around 10 nanoseconds, it will be shown that the addition of disorder in the form of membrane-embedded cholesterol or protein molecules extends the range of the anomalous diffusion regime by several orders of magnitude.

In the case of the membrane of the living cell, the anomalous diffusion reaches macroscopic time scales, at least of the order of hundreds of seconds. The stochastic motion of both lipids and proteins corresponds has its origin in the viscoelastic nature of the lipid bilayer-protein system, similar to the motion of a monomer in a Rouse chain.

When the concentration of proteins in the lipid bilayer becomes appreciable (protein crowding) it will be shown that the previously Gaussian nature of the probability density function of the particles is replaced by a stretched Gaussian form. This is shown to be connected with strongly varying mobilities in the system. Remarkably, very similar features are observed in a simple two dimensional argon systems, and thus a major contribution of the complexity of the motion is due to geometric constraints. In the protein motion in the living cell, the anomalous diffusion is dominated by waiting time motion with diverging time scale, and thus the motion becomes both ageing and non-ergodic.

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Fast transitions between spatial maps in the rat hippocampus: theoretical models and analysis of multi-electrode recordings

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Hippocampus can store spatial representations, or maps, which are recalled each time a subject is placed in the corresponding environment. These representations, or the collective firing of the so-called place cells in the hippocampus, contain precise information about the current animal position. In this talk, I will consider the issue of fast transitions between these maps, from both theoretical and experimental points of view. As far as modelling is concerned, I will show how an extension of the celebrated Hopfield model for memories, where D-dimensional continuous attractors rather than fixed activity configurations are stored, can be studied and shown to exhibit spontaneous transitions, through several distinct mechanisms. I will then present some recent experimental results by Jezek et al. on a 'teleportation' experiment in rats, and show how spatial representations can be decoded by inferring effective Ising models from the neural data. Remarkably, the animal maintains a very robust representation of its positions, though spatial representations vary back and forth on very short time scales (~100 msec). This study sheds some light on how space representations efficiently code not only for position but also for contextual information, a crucial feature for episodic memories.

From geometric optics to plants: eikonal equation for buckling

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Optimal embedding in the three-dimensional space of exponentially growing squeezed surfaces, like plants leaves, or 2D colonies of exponentially reproducing cells, is considered in the framework of conformal approach. It is shown that the boundary profile of a growing tissue is described by the 2D eikonal equation, which provides the geometric optic approximation for the wave front propagating in the media with inhomogeneous refraction coefficient. The variety of optimal surfaces embedded in 3D is controlled by spatial dependence of the refraction coefficient which, in turn, is dictated by the local growth protocol.

The mesoscopic physics of diffusion MRI

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The fundamental scientific challenge, and an unmet clinical need of MRI, is to become sensitive and specific to tissue structural changes at the cellular level of micrometers, given its nominally coarse millimeter-level imaging resolution. This "super-resolution" can be only achieved indirectly, by virtue of biophysical modeling, which links diagnostic radiology with the modern physics methodology. Brownian motion of water molecules provides an essential length scale, the diffusion length, that can be experimentally controlled within the micrometer range, commensurate with cellular dimensions. This opens up a unique window for quantifying tissue properties *in vivo* using diffusion MRI. The goal of this presentation is to outline biophysical modeling of non-Gaussian water diffusion in different tissue types from the overarching perspective of coarse-graining over an increasing diffusion length scale. Coarse-graining enables application of far-reaching ideas of universality, borrowed from condensed-matter and mesoscopic physics, originally developed for describing transport in disordered systems. I will identify distinct structural universality classes in living tissues, and will connect them to the observed time-dependent diffusive dynamics measured with MRI in brain and body, both in healthy tissues and in pathologies.

Adsorption of random and periodic copolymers: a theoretical study using simple model

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Adsorption of heteropolymers - polymers composed of monomer units of two and more types, onto chemically heterogeneous surfaces - was intensively studied in the last decades. A particular interest to this problem is motivated to its connection to the question of molecular recognition, playing a crucial role in living organisms and in various biomedical/biotechnological applications. To understand the mechanisms of the polymer adsorption and polymer-surface recognition, the problem was extensively investigated from different angles by using relatively simple and physically transparent models.

In the present work, adsorption of ideal random and periodic lattice copolymers on homogeneous substrates is studied. An analytical solution of the problem is based on the *generation functions* (GFs) method (or the grand canonical approach) [1]. This technique allows obtaining an *exact* solution in the infinite chain limit.

For random copolymers (RC) with monomer sequence modeled as the first-order Markov chain, an equation for finding the smallest singularity of the GF is derived [2]. The solution of this equation gives access to the free energy of the adsorbed RC and various observables. Although the annealed approximation gives an unphysical result with respect to the quenched case, it is a key starting point for studying more realistic cases. For quenched RC we use the constrained annealed approximation introduced by Morita in 1964 that takes into account the constraints on the first two [2] and higher moments of monomer units distributions. Comparison with the direct numerical simulations of lattice chains averaged over many realizations of random sequences shows very good quantitative agreement.

For periodic copolymers, a periodic sequence of monomer units can be represented as a first order Markov chain with the transition matrix of special circulant form [3]. For both random and regular (periodic) cases the adsorption transition temperature is analyzed and the temperature dependences of the main conformational and thermodynamic characteristics of the adsorbed chain, such as adsorbed fraction, energy, entropy, heat capacity are obtained.

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Memory-dependent action for fractal Brownian motion and application to chromatin dynamics

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In recent years there have seen plethora of new theoretical and experimental studies of chromosome structure and dynamics, both in eukaryotic and prokaryotic cells. Combination of theoretical considerations (e.g., necessity that chromosome parts disentangle easily during the transcription) and experimental observations (presence of distinct chromosome territories, locus-locus contact maps obtained by the Hi-C method) make us believe that at least in many cases spatial organization of chromosome is self-similar on different lengthscales, and resembles the so-called fractal globule. In Gaussian approximation the conformation of chromatin is a fractal Brownian motion (fBm) with Hurst exponent $H = 1/3$.

Despite an intensive investigation of the role of proteins equilibrating chromatin folding, a consensus on the interactions leading to abovementioned statistics is lacking. Here we propose the action of a fBm particle, that generalizes the Brownian local action by introducing the memory kernel to the coupling of velocities at different times [1]. It can be shown that such an action implies the Lagrangian of a self-similar polymer chain with specific quadratic long-range interactions. The important feature of this potential is a power-law decay of the rigidities with increase of chemical distance between the monomers. The low-frequency spectrum of this elastic network turns out to be equivalent to the one of the beta-model [2] in which power-law relaxation times of normal modes in the chain control equilibrium statistics of the conformation.

Moreover, in the framework of quadratic interactions we analyze dynamics of the chain packed with arbitrary fractal dimension and surrounded by viscoelastic medium, described by the generalized Langevin equation [3]. We show that the presence of viscoelasticity does not change the fractal dimension of the equilibrium polymer conformation, but simply slows down relaxation in the system. The characteristic relaxation times of the chain are calculated and concrete forms of locus-locus correlation functions are obtained. These results allow to disentangle the effects of topological interactions and influence of medium viscoelasticity, and provide a way to recover both *fractal dimension* of packing and *characteristics of the medium* from the experiments on one-point and two-point DNA locus tracking.

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Active behavior in tissues

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After introducing the notion of homeostatic pressure, I will subsequently introduce dynamical equations, which exhibit fluid like behavior on time scales long compared to duplication and apoptosis times, in the vicinity of homeostatic conditions. Subsequently, I will describe stress-clamp experiments, which provide numbers on the effects of stress on cell division and apoptosis and introduce the idea of "active" tissue, which allows us to understand some aspects of experimental results. Then I will describe a dynamical transition in nematic epithelia which we predicted about ten years ago in active gels. Eventually, I will shortly give some conjectures about long time electric effects on polar tissues.

Microtubule reorientation driven by severing: a competition model

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Reorganization of the cortical microtubule array in plant cells plays an important role in controlling the direction of anisotropic cell expansion and hence in directing plant morphogenesis. A striking example of such a reorganization consists of the reorientation of the array driven by katanin-mediated severing of microtubules at microtubule crossovers, in response to the perception of blue light. This severing mechanism creates a new population of microtubules orthogonal to the initial array [1]. We show that this mechanism can be fully explained by a model based on the competition between the waiting time for the stochastic severing event at a crossover between two orthogonal microtubules, and the disappearance of the crossover through shrinkage of either of the two microtubules due to dynamic instability. This model exhibits a critical relationship between its parameters and the microtubule reorientation probability [2].

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Reverse engineering of genotype-phenotype map using individual genetic variation

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Gene networks control organism phenotype in health and disease by dynamically processing information introduced by genotype and environment. We are rapidly entering an era of “personal genomics” wherein data on gene structure and expression will be available for large numbers of individuals. Such experiments demonstrated the existence of abundant variation in individual DNA, however a fundamental challenge, critical for realizing the promise of personalized medicine, is discerning how and why some individual variations lead to phenotypic changes, while others do not.

We develop the concepts and models necessary to advance this goal using *Drosophila*, where the molecular tools are precise and quantitative predictions are verifiable. A developmental process - early embryo segmentation - is ripe for attack. This network is well-characterized and a wealth of functional data is available, including DNA binding sites and cellular resolution concentrations of critical transcription factors (TFs). In this study, using a thermodynamic modeling framework, we provide both analytical and computational descriptions of how single-nucleotide variants (SNPs) affect gene expression. The analysis reveals that SNPs increase (decrease) gene expression if located within binding sites of repressors (activators). We show that the sign of SNP influence (activation or repression) may change in time and space and elucidate the origin of this change in specific examples. Our approach predicts non-local and nonlinear effects arising from SNPs, and combinations of SNPs, in individual fly genotypes.

Simulation of individual fly genotypes using our model reveals that this non-linearity reduces to almost additive inputs from multiple SNPs. Further, we see signatures of the action of purifying selection in the gap gene regulatory regions. To infer the specific targets of purifying selection, we analyze the patterns of polymorphism in the data at two phenotypic levels: the strengths of binding and expression. We find that combinations of SNPs show evidence of being under selective pressure, while individual SNPs do not. The model predicts that SNPs appear to accumulate in the genotypes of the natural population in a way biased towards small increases in activating action on the expression pattern. Taken together, these results provide a system level view of how genetic variation translates to the gene expression level.

Complexity in human respiration

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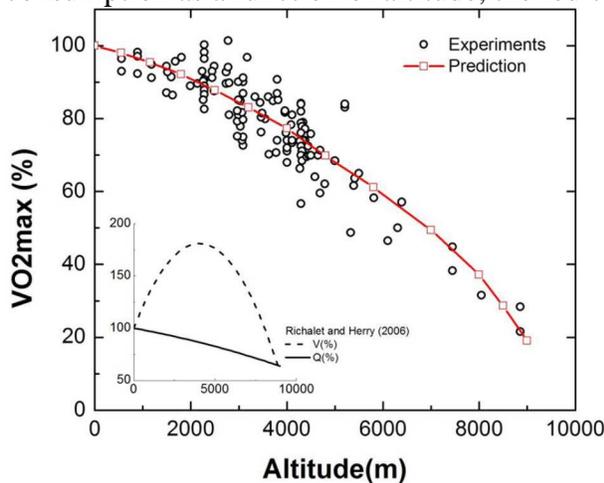
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The role of the mammal's respiratory system is to capture oxygen from the ambient air and transfer it to blood. This is accomplished by two complex geometrical systems in series. First, the bronchial tree; second, each small bronchia feeds a small arborescent structure called an "acinus". The capture of oxygen to blood occurs through the acinus walls. Each acinus plays a double role: first it is a small hydrodynamic pump, and second it is a chemical reactor. Besides the geometrical complexity, there exists a mathematical complexity caused by the non-linearity of the equations governing the gas exchanges.

The quantities that drive respiration are the cyclic ventilation, the cardiac output in the pulmonary artery with its oxygen partial pressure. During breathing, the acini dilate and contract, then they drive the ventilation. The spatial dependence of the oxygen concentration at the interior of the acinus is then governed by a convection-diffusion-permeation equation. The permeation is the diffusion of oxygen from the gas phase to the hemoglobin molecules inside the red blood cells that flow inside the capillary vessels. There, oxygen is trapped by hemoglobin, following a non-linear chemical reaction.

The results are obtained by solving interactively the coupled equations for O_2 convection-diffusion-permeation dynamics in the breathing airways and oxygen-hemoglobin dynamics in the capillaries. An example of the results is given in the figure that represents the maximal oxygen consumption as a function of altitude, the red curve representing the theoretical prediction.



The Itô-Stratonovich Dilemma and the Inverse Problem for the Overdamped Langevin Equation: A Bayesian Approach

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The Overdamped Langevin Equation (OLE) is a ubiquitous model used to describe stochastic phenomena in heterogeneous environments, such as biomolecule diffusion in living cells, numerical simulations of protein structures or financial time-series. However, when diffusivity is not uniform, the solution of the OLE depends on the interpretation of the stochastic term that appears in it. The OLE can thus be considered a family of statistical models rather than a single model, with each member corresponding to a different interpretation of the stochastic noise term. The problem of choosing the interpretation of the OLE that provides the correct total force given the active force and the diffusivity gradient became known as Itô-Stratonovich dilemma. For physical systems in equilibrium, the dilemma is resolved by requiring that the long-time distribution of particle locations follow the Boltzmann distribution, but for other systems the question remains open. This leads to ambiguity in the inverse problem for these systems, when the active and diffusive components of the observed total force have to be correctly identified. Lack of knowledge on the dynamical properties of the analyzed processes does not allow one to choose a single interpretation.

In this talk we address the inverse problem of inferring the parameters of the OLE from the dynamics of individual tracers and propose a Bayesian approach that incorporates the uncertainty about the correct model in the statistical analysis. Direct integration over all possible models allows us to obtain a posterior distribution and provide an interpretation-independent estimation of the active force. Applications to single-particle tracking experiments, molecular dynamics and hydrodynamic simulations are discussed.

Abortive Initiation as a Bottleneck for Transcription in the Early *Drosophila* Embryo

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The standard totally asymmetric simple exclusion process model of transcription (TASEP) predicts the existence of a gene-independent limit on the maximal rate of transcription as a result of polymerase “traffic jams” in the bulk of the gene at sufficiently high polymerase concentrations. Recent experiments in living *Drosophila* embryos provide quantitative access to the transcriptional dynamics of genes in the high polymerase concentration limit. Our analyses suggest uniformity of the maximal rate of transcription in the genes *Hunchback*, *Snail*, and *Knirps*, and their modified constructs. Intriguingly, the observed maximal rate of transcription is ~40 % of the one predicted by the TASEP model. We propose that the appearance of a gene-independent maximum rate of transcription indeed hints at fundamental physical constraints on the process due to traffic jams, but that the observed reduction in the maximal rate reflects jamming in the promoter region where the polymerase elongation rate is lower due to cycles of abortive initiation. As a result, the transcription bottleneck shifts from the bulk of the gene to its promoter region, and we suggest experiments that would test this hypothesis [arXiv: 1701.06079].

How the lizard got its colors

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In vertebrates, skin colour patterns emerge from nonlinear dynamical microscopic systems of cell interactions. Here we show that in ocellated lizards a quasi-hexagonal lattice of skin scales, rather than individual chromatophore cells, establishes a green and black labyrinthine pattern of skin colour. We analysed time series of lizard scale colour dynamics over four years of their development and demonstrate that this pattern is produced by a cellular automaton (a grid of elements whose states are iterated according to a set of rules based on the states of neighbouring elements) that dynamically computes the colour states of individual mesoscopic skin scales to produce the corresponding macroscopic colour pattern. Using numerical simulations and mathematical derivation, we identify how a discrete von Neumann cellular automaton emerges from a continuous Turing reaction-diffusion system. Skin thickness variation generated by three-dimensional morphogenesis of skin scales causes the underlying reaction-diffusion dynamics to separate into microscopic and mesoscopic spatial scales, the latter generating a cellular automaton. Our study indicates that cellular automata are not merely abstract computational systems, but can directly correspond to processes generated by biological evolution.

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Rouse-like dynamics of the topologically stabilized polymer states

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It has been known for some time that apart from traditional equilibrium states of polymer systems, such as swollen polymer coils and melts of linear polymer chains, which have been studied by classical polymer physics, there exist a class of states whose properties are mostly controlled by the topological interactions of the chains. The archetypical system where topological interactions play such a crucial role is a melt of non-concatenated polymer rings, but it became more and more clear in recent years that such states can be observed, at least as metastable ones, in various other contexts including, for example, rapid collapse of a linear chain under external force (in this context they are often called crumpled or fractal globules), and conformation-dependent polymerization. Most importantly, such states seem to be a good candidate for the description of chromosome packing in living cells.

Naturally, the study of polymer dynamics in this novel class of states is of substantial interest. In my talk I will present our recent advances in scaling and semi-analytical generalizations of the classical Rouse model of polymer dynamics, which allow us to describe the relaxation times, self-diffusion and dynamical correlation functions in the fractal globule and similar polymer states. I will also discuss the generalization of the theory for the dynamics of a polymer surrounded by a viscoelastic environment subject to the generalized Langevin equation with scale-free memory. In conclusion, I will briefly talk about alternative theories of the fractal globule dynamics, based on the generalization of the reptation theory, and discuss possible applicability limits of different theories.

Microdomain formation in chromatin

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Epigenetic regulation in chromatin is responsible for a large degree of variation in the expression level. However, the understanding of the underlying molecular mechanisms is still far from being complete. Among such mechanisms, DNA methylation, nucleosome positioning, 3D genome organization and covalent histone modifications have been addressed in several recent theoretical works. In this talk a new model will be presented, where nucleosome positioning and histone modifications are coupled to the 3D genome organization through physical changes of chromatin compaction. We take into account that chromatin exists in several states that are distinguished not only by covalent epigenetic modifications but also by the physical structure (an assumption, supported by very recent experimental studies). A biophysical lattice model for chromatin is formulated and parameterized using available experimental data such as nucleosome repositioning, protein binding to chromatin fibers *in vitro* and heterochromatin domains *in vivo*. The main new feature of the proposed model is taking into account physical interaction between neighbouring chromatin elements (not just colouring them with covalent histone modifications as in other models of this type). The model is also based on our previous prediction that nucleosomal arrays can be converted between different states of compaction through nucleoprotein assembly governed by specific proteins such as for example HP1 or CTCF. One of our new predictions is that a locally introduced heterochromatic state would spread only to a finite domain – a prediction which we verify using the sequencing data for mouse embryonic stem cells. The model also predicts the establishment of microdomains in 3D consistent with experiments in the interphase cell nucleus.

Boundary effects for diffusion of particles in finite arrays of traps: Does the classical mean field theory really work?

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The problem on diffusion of small particles among static ideally absorbing traps randomly located in 3D domains serves as a common framework for the theoretical description of a wide range of different applications throughout chemistry, physics, and biology. After a long hiatus interest in this problem was rekindled mostly in biological applications like enzyme catalysis, nutrient consumption due to diffusion including oxygen consumption by human tissue cells, calcium uptake by intestinal cells, bacterial absorption of various sugars etc. [1].

For many years it was commonly accepted that theoretical description based on the well-known classical mean field approximation with respect to so called coarse-grained concentration field inside the given array of traps is the best suited to the posed problem [1-3]. It is expedient to recall here the famous S. Lec saying: “To get to the source, we must swim against the flow”. Therefore in this paper we present critical review of a great quantity of existing studies on the problem. Particularly we have shown that widely used mean-field equation for the coarse-grained particle concentration works only deep inside the spherical array of randomly distributed traps.

To describe the behavior of coarse-grained concentration within the diffusion layer near the array’s boundary, we developed a new approach based on the renormalization group. The diffusive interaction between sinks are taken into account by employing the monopole approximation, which proved to be good for spherical traps. A new equation with respect to the coarse-grained concentration nearby the boundary was derived. Our theory predicts that the characteristic penetration length is longer than what follows from the standard mean-field approximation. To elucidate the problem at issue from the physical point of view, we carried out a dimensional analysis of appropriate control parameters. It was found that the criterion numbers for the strength of diffusion interaction and for the smallness of the penetration length have simple and, at the same time, fundamental meanings. With the aid of the proposed new equation, we calculated the time-dependent particles concentration outside the spherical ensemble of traps and the total flux of particles on the boundary of this array. The future extension of this study may include the diffusion and absorption of particles to arrays of traps randomly distributed in domains other than spherical.

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Heterogeneous continuous time random walk approach for analysis of diffusion in porous media

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Solute transport and, particularly, diffusion of particles in porous media is a long standing problem [1]. The general random walks framework has been shown to describe quantitatively the anomalous transport patterns frequently observed in fractured and heterogeneous porous media [2]. One of the major conceptual difficulties consists in a very broad range of time and length scales in the dynamics that prohibits using conventional theoretical approaches or numerical simulation methods. To overcome this problem and bridge various scales, we suggest to represent a porous medium by an equivalent “porous graph” (Fig. 1, see also [3]) and then to model the complex dynamics of a particle in the porous medium by a continuous time random walk (CTRW) on that porous graph. The graph structure accounts for the inter-connectivity of pores, whereas their geometric properties (shapes of pores and of connectivity regions) are, to some extent, captured through the CTRW characteristics, hence connecting the topological and dynamical properties of the system.

In our CTRW approach, the space and time characteristics of individual jumps on a graph are coupled that requires developing new theoretical tools. We present several preliminary results on the long-time asymptotic behavior of a particle on a porous graph. To validate the proposed coarse-graining scheme, we compare the asymptotic behavior of the CTRW on a porous graph with the original continuous dynamics in several models of porous media. In particular, we investigate how topology of an underlying graph and inter-connectivity of pores can affect the long-time behavior.

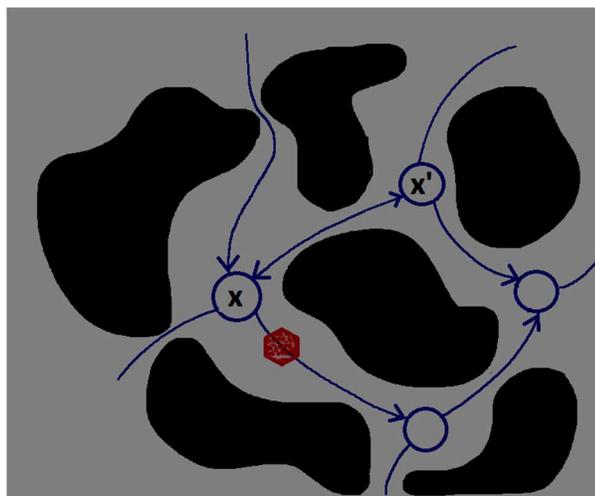


Figure 1: Diffusion of a particle (red) in a porous medium is modeled by a continuous time random

walk on a porous graph with directed edges.

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First-passage times of Markovian and non Markovian random walks

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The first-passage time is a key quantity for evaluating the kinetics of various processes, and in particular chemical reactions involving "small" numbers of particles. A striking example is given by gene transcription, where specific proteins search for target sequences on DNA.

I will present asymptotic results which enable the evaluation of the first-passage time statistics to a target site for a wide range of random processes in confined domains, and show how these results can be extended to non Markovian processes, which are often needed to model transport in complex environments.

Reaction-diffusion waves in biological applications

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The theory of reaction-diffusion waves develops under the influence of various applications such as flame propagation in combustion, ecological invasions in population dynamics or tumor growth in biomedical applications. The mathematical theory of reaction-waves includes the investigation of their existence, stability, speed of propagation. These questions are well studied for the scalar equation and for some particular classes of systems but in many cases they remain open. Last years, nonlocal and delay reaction-diffusion equations are intensively studied in relation with some new applications. In this lecture we will present the classical theory of reaction-diffusion waves and its recent developments for some biomedical and ecological models.

Universal Scaling Law in Intracellular Dynamics

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Intracellular information and material transport is vital for all living cells. Within this intracellular space a complex interplay between cytoplasmic crowding and ATP-driven dynamics controls most cellular functions. Whereas the active transport due to motor proteins, e.g. along microtubules, is well understood, we still lack a comprehensive picture of the passive transport processes. Here, we show a universal scaling of non-Gaussian increment distributions from intracellular nanoparticle transport in eukaryotic cells in different cytoskeleton states (wild type, without actin cortex, without microtubules, and lacking both). These distributions collapse to a single master curve with exponential tails for these four cytoskeleton states, indicating a generic intracellular transport feature. We find that the different cytoskeleton components regulate the efficiency of intracellular transport, but not the underlying dynamics. These anomalous intracellular dynamics are attributed to spatio-temporal heterogeneities of the cytoplasm. This opens up new theoretical modelling developments on intracellular transport beyond the conventional Gaussian realm and, on the practical level, medical perspectives in getting mechanistic insight into targeting and degenerative diseases to improve therapy.

Statistical investigation of anomalous diffusion processes

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Anomalous diffusion in crowded fluids, e.g., in cytoplasm of living cells, is a frequent phenomenon. A common tool by which the anomalous diffusion of a single particle can be classified is the time-averaged mean square displacement (TAMSD). However there are also different statistics that can be useful in this problem. A validation of anomalous diffusion processes for single-particle tracking data is of great interest for experimentalists. In this presentation we demonstrate statistical methods useful in the anomalous diffusion property recognition. One of the example is the rigorous statistical test based on TAMSD for classical anomalous diffusion process, namely fractional Brownian motion (FBM) or visual test based on the dynamical functional which is useful in the problem of differentiation between FBM and continuous time random walk, the second classical model of anomalous diffusion. We demonstrate also the role of codifference, the general measure of dependence, adequate for processes with infinite variance, in the problem of the anomalous diffusion property exhibition.

	Monday 18/09	Tuesday 19/09	Wednesday 20/09	Thursday 21/09	Friday 22/09
8:30 – 9:15	<i>Registration</i>				
9:15 – 9:30	<i>Opening</i>				
9:30 – 10:15	Metzler	Heinrich	Holcman	Prost	Samsonova
10:15 – 11:00	Barkai	Calebiro	Wylomanska	Franosch	Volpert
11:00 – 11:30	<i>Coffee break</i>	<i>Coffee break</i>	<i>Coffee break</i>	<i>Coffee break</i>	<i>Coffee break</i>
11:30 – 12:15	Monasson	Dahan	Avetisov	Sapoval	Serov
12:15 – 13:00	Chechkin	Katrukha	Tamm	Filoche	Polovnikov
13:00 – 15:00	<i>Lunch</i>	<i>Lunch</i>	<i>Lunch</i>	<i>Lunch</i>	<i>Lunch</i>
15:00 – 15:45	Voituriez	Smirnov	<i>Free time</i>	Kiselev	
15:45 – 16:30	Traytak	Teif		Novikov	
16:30 – 17:00	<i>Coffee break</i>	<i>Coffee break</i>		<i>Coffee break</i>	
17:00 – 17:45	Nechaev	Poster session		Manzo	
17:45 – 18:30	<i>Wine reception</i>	<i>Conference Dinner</i>			