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Poster Abstracts

Abstract No. 1

Scenarios for efficient intracellular bidirectional transport

C. Appert-Rolland[a], M. Ebbinghaus[b] and L. Santen[b]

a Laboratory of Theoretical Physics, Univ. Paris-Sud, CNRS UMR 8627
Bat 210, 91405 Orsay cedex, France
b Laboratory of Theoretical Physics, Univ. of Saarland,
D-66123 Saarbrucken, Germany
** Cecile.Appert-Rolland@th.u-psud.fr*

Transport by molecular motors has been successfully modeled by cellular automata models, as far as uni-directional transport is concerned (cf in vitro experiments [1]). However, within cells, transport is bi-directional and there is no clear picture yet how nature regulates the motion of motors in order to have efficient transport. Simple extensions of cellular automata models to bi-directional transport exhibit strong cluster formation [2] – a phenomenon that cannot be expected to be realistic.
Here, we explore several scenarios that could play a role in the organization of neuronal bi-directional transport. In particular, we shall consider
the possibility of lane formation under motor-motor interactions [3,4];
the role of the dynamics of the underlying lattice [5,6].
We shall show that different factors could act cooperatively to promote efficient transport [3].

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Abstract No. 2

Bringing the gap between ecophysiology and molecular system biology: The « Fruit Integrative Modeling » project

V. Baldazzi [1], G. Vercambre [1], M. Génard[1], Mark Poolman[2], A.C. Balakrishnan [2], D. Fell[2]

[1] *INRA PACA, Unité Plantes et Systèmes de Culture Horticoles, Avignon, France*
[2] *Oxford Brookes University, School of Life Science, Oxford, United Kingdom*

Understanding and predicting how phenotypic changes emerge from genetic and molecular basis is a topic of primary importance both in plant biology and agronomy. Indeed, recent years have witnessed an increased use of molecular techniques in fundamental research but also in plant breeding: omics data are currently used to screen a large population of plants selecting for specific traits, over a range of environmental conditions. To date, however, it is still difficult to link changes at the molecular level to the actual plant behaviour.

Ecophysiology historically aims at understanding the mechanisms that control the plants adaptation to environment factors. Classical ecophysiological models make use of a process-based description of plant growth and development. Each of the processes involved in plant growth is quantified in relation to environmental and developmental factors and the results summarized in the form of mathematical functions. Different processes are then combined together. The main limit of this approach relies in the empirical description of the single processes: mathematical expressions used to fit the experimental data are often simple (linear if possible) and the action of the different environmental factors is usually represented as additive or multiplicative terms, even in absence of a real biological foundation. As a consequence, changes in parameters values cannot be easily interpreted, and the predictive power of the model is significantly reduced as soon as the experimental conditions depart from the ones used for calibration.

In the last years many authors have claimed for an improved description of the underlying biological mechanisms, taking advantage of available omics data [1,3]. The ambition of the so-called "crop system biology" is to overcome the gap between ecophysiology and molecular system biology, providing a biological basis to current crop systems [2]. The interest is twofold. From an ecophysiological perspective, the integration of cellular and molecular levels can help to refine plant models, shading light into the complex interplay between different spatial and temporal scales in the emerging system response. From the point of view of molecular biology, the existence of a multi-level ecophysiological model could offer an useful framework in which interpreting omics data, in relation to environmental factors and agricultural practices.

Started in June 2010, the Fruit Integrative Modelling (FRIM) project (EraNet EraSysBio+ funding, E.U. 7FP) represents a concrete step in this direction. Focusing on tomato, the project will collect information on architecture and metabolism at the cellular, organ and plant scale under a variety of environmental situations. This information will be integrated in a multi-scale model, generated by the coupling of an ecophysiological model of the plant-fruit growth to a cellular kinetic model of metabolism.

The aim of the ecophysiological model is to describe the growth of a tomato plant (and fruits) over a whole season, under the control of available resources (water, carbon etc) and environmental factors (temperature, light). The model take the form of an ODE system where physical laws or empirical functions, based on experimental data, are used to describe source-sink relationships, flux exchanges and thermodynamic constraints behind the main processes of plant functioning (e.g. photosynthesis, sugar and acid accumulation etc).

Cell volume and metabolite concentrations computed by the fruit module provide the boundary

conditions of the cellular model. Here the aim is to accurately describe the carbon and energy metabolism of a typical pericarp cell, taking into account enzymes properties and transport between internal compartments. Modelling strategy will rely on the use of simplified kinetic functions and on the use of metabolic control coefficients to prioritize enzymes and reactions having the largest influence on key metabolite concentrations [4].

The integration between the cellular and the ecophysiological level will be performed using an appropriate reduction strategy, based on time-scales approximation (quasi-steady state) and simplification of cellular network topology, based on the results of the above sensitivity analysis.

At term, the FRIM integrative model will improve the understanding of fruit metabolism, by pinpointing crucial steps as related to sometimes complex but realistic environmental inputs. In particular, it will allow to analyse the consequences of variations in enzymes and/or membrane transporters on fruit functioning and quality.,

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Abstract No. 3

Randomization of metabolic networks: a measure of evolutionary significance

Georg Basler[a,*], Oliver Ebenhöh[b], Sergio Grimbs[a], Joachim Selbig[a,c], and Zoran Nikoloski[a,c]

a Institute for Biochemistry and Biology, University of Potsdam, Potsdam, Germany
b Institute of Medical Sciences, University of Aberdeen, Aberdeen, United Kingdom
c Max-Planck-Institute for Molecular Plant Physiology, Potsdam, Germany
** basler@mpimp-golm.mpg.de*

Complex networks have been successfully employed to represent different levels of biological systems, ranging from control of gene expression and protein-protein interactions to signal transduction and metabolism. The aim of network research in biology is to develop system representations capable of explaining diverse functional behavior. Network-based research has mainly focused on identifying unifying structural properties, such as small average path length, large clustering coefficient, heavy-tail degree distribution, and hierarchical organization, viewed as requirements for efficient and robust system architectures. However, for biological networks, it is unclear to what extent these properties reflect the evolutionary history, and, consequently, the diverse functions of the represented systems. Here, we show that salient structural properties of metabolic networks encode biologically relevant information by employing a new method for network randomization under mass balance constraints. We investigate the metabolic networks of six model organisms from all kingdoms of life, and determine the network properties which are inherently related to the evolution and functional organization of metabolism. Contrary to the results from the common switch randomization, our findings demonstrate the evolutionary importance of the small-world hypothesis as a fundamental design principle of complex networks. Our approach allows the extraction of biologically meaningful properties which result from evolutionary pressure imposed on metabolism, such as the impact of reaction knockouts on the viability of organisms.

Abstract No. 4

Dynamical membrane curvature instability controlled by intermonolayer friction

Anne-Florence Bitbol[a,*], Jean-Baptiste Fournier[a], Miglena I. Angelova[a,b] and Nicolas Puff[a,b]

a Laboratoire Matière et Systèmes Complexes (MSC)
Université Paris Diderot, Paris 7 et UMR CNRS 7057
10 rue Alice Domon et Léonie Duquet, F-75205 Paris Cedex 13, France
b Université Pierre et Marie Curie, Paris 6
4 place Jussieu, F-75252 Paris Cedex 05, France
** anne-florence.bitbol@univ-paris-diderot.fr*

Far from being static, the shape of a cell membrane undergoes constant remodeling during the life of a cell, for instance in processes such as vesicle budding or cell division. Giant unilamellar vesicles (GUVs) are model membranes constituted of lipid molecules that self-assemble into closed bilayers in water. We have carried out experiments in which a GUV is submitted to a local pH increase created by microinjecting a basic solution close to the membrane. This local pH increase causes a local deformation of the membrane, which grows and relaxes in a few seconds when the injection is stopped [1].

The local pH increase induces a chemical modification of the head groups of some lipids in the external monolayer of the membrane, which results in a change of the plane-shape equilibrium density and of the spontaneous curvature of the external monolayer. We have shown that both of these effects produce a destabilizing normal force density in the membrane, so they both lead to a shape instability [1].

We have developed a theoretical description of the dynamics of this instability [1, 2]. In our dynamical equations, we have taken into account the elastic force densities in each monolayer. These elastic force densities have been obtained from the monolayer free-energy densities through the virtual work priniciple [3]. Solving these dynamical equations, written at first order and in a one-mode approximation, gives the time evolution of the height of the membrane deformation, which features two timescales. The longest one (about 3 s) involves the slow relative sliding between the two monolayers: the instability is controlled by intermonolayer friction.

The change of the plane-shape equilibrium density and the change of the spontaneous curvature induced by the chemical modification yield different dynamics. Therefore, the dynamical study of the instability should allow for distinguishing these two types of modifications of the membrane properties. In contrast, when a global modification of the environment of a vesicle is considered, studying the change of its equilibrium shape does not allow to distinguish these two effects.

We have compared our experimental results and our theoretical predictions by fitting the time evolution of the height of the membrane deformation to the solution of our dynamical equations. We have obtained a good agreement between theory and experiment. We have extracted estimates of the intermonolayer friction coefficient b from these fits, with values $b = 2 - 8\ 10^8$ J.s/m^4 [1]. These values are consistent with previous measurements carried out using different methods.

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Abstract No. 5

Gene autoregulation via intronic microRNAs and its functions

Carla Bosia[a,*], Matteo Osella[b], Mariama El Baroudi[a], Davide Cora'[c] and Michele Caselle[a]

a Department of Theoretical Physics, University of Torino, Torino, Italy
b Génomique des Microorganismes, Université Pierre et Marie Curie, Paris, France
c Institute for Cancer Research and Treatment (IRCC), University of Torino, Torino, Italy
**cbosia@to.infn.it*

While many microRNAs are transcribed from their own genes, nearly half map within introns of "host" protein-coding genes. Eventually these intronic microRNAs may regulate the expression of their host genes forming a microRNA-mediated self-loop. Recent analysis of this phenomenon suggest that autoregulation mediated by intronic microRNAs may be under positive selective pressure but the functions of this regulatory circuit are currently unknown. Using a stochastic and a deterministic analysis of the circuit validated via simulations, we suggest that microRNA-mediated self-regulation, despite its simple topology, can perform different regulative tasks. Firstly it can alter the response time of gene expression to upstream signals, secondly it can implement fold-change detection and finally it can confer robustness to noise. We compare the features of this circuit with the analogous transcriptional self-regulation, which is an ubiquitous network motif in different species, to highlight in what situations a post-transcriptional self-regulation can be advantageous for the cell.

Abstract No. 6

Diauxic shift in single cells

Sarah Boulineau[a], Filipe Tostevin[a] and Sander Tans[a*]
a FOM-Institute AMOLF, Amsterdam, the Netherlands
** tans@amolf.nl*

Growth of Escherichia coli cells in a mixture of two carbon sources is often diauxic [1]. A classical example is growth of E. coli on glucose and lactose. In this case, growth consists of two distinct exponential phases separated by a lag phase (diauxic lag, during which growth stops). These two growth phases reflect the sequential consumption of the two sugars. Despite numerous studies on gene regulation and dynamics during diauxic shift [2-4], little is known on growth dynamics. For instance, questions relative to delays and variability in growth rate changes upon shift have remained uninvestigated.

Here, we monitored both growth and expression of the *lac* genes over time for each cell in a colony. We find that the diauxic lag also happens at the single cell level for the majority of the cells and can last up to three generations after the shift. However, for a small fraction of the population there seems to be no lag at all. The same variability is observed for time delays in gene expression and we show that these delays correlate with the delays in growth rate. In addition, this variability can be well explained by a stochastic model of the *lac* operon induction [5].

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Abstract No. 7

Modulation of HIV-1 pleomorphism by the presence of PSI-RNA: an Atomic Force Microscopy study

Cendrine Moskalenko[a], Audrey Thomas[b], Yvonne Beck[a], Julien Bernaud[a], Delphine Muriaux[b] and Martin Castelnovo[a*]

a Laboratoire de Physique CNRS UMR 5672, ENS Lyon, 46 Allée d'Italie 69464 Lyon cedex 07, France.
b Laboratoire de Virologie Humaine, Inserm U758, ENS Lyon, 46 Allée d'Italie 69464 Lyon cedex 07, France.

We are interested in the physical characterization of HIV-1 Virus-Like Particles (VLP) and purified capsid cores towards a better understanding of HIV-1 assembly. Here we focus on the modulation of their pleomorphic properties, i.e. the various global shapes of VLP or cores observed within common environmental and biological conditions. Using an original combination of biochemical approach, Atomic Force Microscopy (AFM) imaging and sophisticated image analysis, we quantitatively characterized the pleomorphism observed for HIV-1 VLP, as well as for purified viral cores. Analyzing three-dimensional high resolution AFM images of un-fixed VLP and viral cores, we conducted a complete morphological characterization of mature and immature particles at statistic levels. In addition, we revealed that the presence of the HIV-1 Psi-RNA inside viral cores is decisive for HIV-1 morphology.

Abstract No. 8

Theoretical aspects of mRNA degradation

Carlus Deneke*, Angelo Valleriani and Reinhard Lipowsky

Department of Theory and Bio-Systems, Max-Planck-Institute of Colloids and Interfaces, Potsdam, Germany
** deneke@mpikg.mpg.de*

In the process of gene expression, one important determinant of the protein level is the stability of messenger RNA. Most theoretical models of gene expression consider mRNA degradation by assigning a constant decay rate.
Experimentally, the stability can be analyzed by the decay of the mRNA level over time after the inhibition of further mRNA synthesis. However, numerous cases exist where the decrease of the mRNA level does not follow an exponential decay. This implies that a constant degradation rate does not suffice to fully describe the degradation process. Furthermore, a variety of putative mechanisms and responsible enzymes for degradation have been revealed in the different organisms. It was found that for effective degradation typically several modifications have to be performed to the mRNA. This can be viewed as an aging of the mRNA.
In this contribution, we establish the relation between the decaying mRNA level and the messages' lifetime distribution. The theoretical framework is general as we do not restrict to a particular degradation process. We introduce a general model based on a continuous-time Markov chain. Here, modifications of the mRNA are recognized as transitions which can alter the degradation efficiency. In addition, we show how the aging of the mRNA chains becomes manifest in a non-stationary age distribution and also in the change of capacity to synthesize proteins.
As a result, the presented approach allows to extract information about the underlying degradation mechanisms from the experimentally observed decay patterns. For example, it allows to distinguish between exo- and endonucleolytic degradation pathways. Moreover, our method is suitable to improve the analysis of mRNA lifetime experiments and provides additional aspects for models of gene expression.

Abstract No. 9

Double strand break repair in single *Escherichia coli* cells

M. El karoui [(1)(2)], B. Okumus[(2)], B. Lau[(2)] and J. Paulsson[(2)]

[(1)] INRA, UMR 1319 MICALIS, 78350, Jouy-en Josas, France.

[(2)] Department of Systems Biology, Harvard University, Boston, Massachusetts, USA.

It has been shown in recent years that even genetically identical cells behave differently because many central processes involve molecules present in small numbers. The inherent randomness of chemical reactions then generates spontaneous fluctuations that can enslave all dependent processes. Such 'noise' has been shown to randomize developmental pathways, disrupt cell cycle control, or even be exploited when heterogeneity is advantageous – allowing populations of cells to "hedge their bets".

Double Strand Breaks are one of the most deleterious types of DNA damage because they lead to loss of genetic information and eventually death if not repaired. In *Escherichia coli*, the main repair pathway involves the multifunctional RecBCD enzyme which salvages broken chromosomes by catalyzing the first step of homologous recombination. RecBCD is a heterotrimeric complex that is reportedly present in very low numbers in bacterial cells. This should lead to spontaneous fluctuations in RecBCD levels and non genetic heterogeneity in the population. Qualitative studies based on population averages show that bacterial cells that do not express RecBCD are barely viable, while over-expression of the RecBCD protein leads to less efficient DNA repair. This suggests that the level of RecBCD expression needs to be tightly controlled, and raises the question of how bacterial cells cope with potentially large cell-to-cell fluctuations in this complex. We have quantified cell to cell variability of RecBCD expression using chromosomal transcriptional fusions and observed significant fluctuations that are consistent with very low levels of transcription. As previously reported in the literature, we do not observe induction after DNA damage suggesting that RecBCD remains at very low levels even after SOS induction. Quantification of the RecD and recC subunit using translational fusions to GFP indicates that they are present in very low numbers. We are currently trying to quantify the level of RecB subunit in order to build a stochastic model of the RecBCD complex formation. This should allow us to better understand the impact of stochastic complex formation on double strand break repair in *E. coli*.

Abstract No. 10

Engineering reaction networks outside the cell: reactions and reactors

André Estévez-Torres*, **Ibtissam el Abdouni, Jean-Christophe Galas**

Laboratory for photonics and nanostructures, CNRS, Marcoussis, France
** aestevez@lpn.cnrs.fr*

Reaction networks with well-defined dynamics and topology are fundamental elements in the emergence of complex biological behaviors. With the tools of synthetic biology we start to understand how to engineer those networks inside the cell. We know, however, very little about how to implement them outside the cell.

We carry out a long-term effort towards the engineering of such networks in vitro. Our poster first attempts to give a chemist's point of view of the network description used in systems biology. Second, it introduces the toolboxes that we think we need for engineering reaction networks with interesting functions outside the cell. Namely, a controllable set of reactions and a tunable reactor. Finally, we show recent results on a nanoliter-scale continuous reactor for studying oscillatory reactions.

Abstract No. 11

The Two Regime Method for optimizing stochastic reaction-diffusion simulations

MB Flegg[a*], SJ Chapman[a] and R Erban[a]

a Mathematical Institute, University of Oxford, Oxford, United Kindom
** mark.flegg@maths.ox.ac.uk*

The computer simulation of stochastic reaction-diffusion processes in biology is often done using either compartment-based (spatially discretized) simulations or molecular- based (Brownian dynamics) approaches. Compartment-based approaches can yield quick and accurate mesoscopic results but lack the level of detail that is characteristic of the more computationally intensive molecular-based models. Often microscopic detail is only required in a small region but currently the best way to achieve this detail is to use a resource intensive model over the whole domain. We introduce the Two Regime Method (TRM) in which a molecular-based algorithm is used in part of the computational domain and a compartment-based approach is used elsewhere in the computational domain. We apply the TRM to two test problems including a model from developmental biology. We thereby show that the TRM is accurate and subsequently may be used to inspect both mesoscopic and microscopic detail of reaction-diffusion simulations according to the demands of the modeller.

Abstract No. 12

Dynamical model for DNA-protein interactions and facilitated diffusion

A.-M. Florescu[a,b,*] and M. Joyeux[c]

a-Max Planck institute for the Physics of Complex Systems, Dresden, Germany
b-Institute de Recherche Interdisciplinaire, Lille, France
c- Laboratoire Interdisciplinaire de Physique,Université Joseph Fourier Grenoble 1, Grenoble, France
** florescu@pks.mpg.de*

We present a dynamical model for non-specific DNA protein interactions, which is based on a previously developed "bead-spring" model for DNA with elastic, bending and Debye-Hückel electrostatic interactions [1] and where the protein interacts with DNA through electrostatic and excluded-volume forces. We studied the properties of this model using a Brownian dynamics algorithm that takes hydrodynamic interactions into account and obtained results that essentially agree with experiments and most predictions of kinetic models. For example, we showed that the protein samples DNA by a combination of 3D diffusion in the buffer and 1D sliding along the DNA chain. This model evidences the presence, in a certain range of values of the effective protein charge, of facilitated diffusion, i.e. a combination of the two types of diffusion that leads to faster-than-3D-diffusion sampling of DNA [2,3]. Moreover, analysis of single sliding events showed that the number of base pairs visited during sliding is comparable to that deduced from single molecule experiments. This model furthermore enabled us to discuss to what extent the combination of 1D and 3D diffusion can lead to faster DNA sampling than pure 3D diffusion of the protein. In contrast to some kinetic models, which predict that the maximum acceleration of DNA sampling due to facilitated diffusion may be as large as one hundred, our model suggests that this rate is in fact much smaller, of the order of two or even less. This is in agreement with recent reconsideration of experimental results, which concludes that observed large DNA protein reaction rates are not due to facilitated diffusion but rather to the very low salt concentration in the corresponding experiments[4].

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Abstract No. 13

A first principles calculation of oxygen consumption in strong exercise

Aurélie Foucquier[1*], Marcel Filoche[1,2] and Bernard Sapoval[1,2]

1 Laboratoire de Physique de la Matière Condensée, Ecole Polytechnique, CNRS, 91128 Palaiseau, France

2 Centre de Mathématiques et de Leurs applications, ENS Cachan, CNRS, 94235 Cachan Cedex, France

**aurelie.foucquier@polytechnique.edu*

Introduction: The pulmonary acinus is the gas exchange unit in the human lung. Several mechanisms occur in the oxygen transfer: the convective and diffusive transport into the acinar tree, the diffusive transfer across the alveolar membrane to the blood, the binding by hemoglobin and the equilibration between air and blood pressure. We present here a numerical calculation of the oxygen flux and alveolar pressure in a “machine acinus” for strong exercise conditions. What we call “machine acinus” is a system in which the blood is supposed to flow so rapidly that no hemoglobin equilibration occurs. Otherwise, this machine acinus has the same geometry and motion during the respiratory cycle as the real acinus. In this “machine” the so-called capillary pressure keeps constant and equal to the venous pressure. The gas exchange at the alveolar blood interface is described by a phenomenological quantity that we call the “integrative membrane permeability”. This is a top-down approach which restrict the values of this “integrative membrane permeability” to a narrow range of values compatible with the experimental values of VO2 and PAO2 in measured in strong exercise conditions.

Materials and Methods: The oxygen flux and partial pressure are computed as a function of time and space along the respiratory cycle by solving numerically the convection-diffusion equations in the acinar space for arbitrary values of the integrative membrane permeability. In our approach the entries are the oxygen partial pressure in air, the average veinous oxygen pressure, the acinus geometry and the duration of the respiratory cycle. For each value of this permeability, the global oxygen consumption VO2 and the average oxygen alveolar pressure PAO2 are obtained by integration in space and time. One then search for the values of permeability compatible with physiological data.

Results and Discussion:

First, the solutions of the convection-diffusion equations along the respiratory cycle indicate that both the oxygen partial pressure and flux across the membrane are distributed in space and varies with time.

Second, the machine acinus functioning is entirely governed by the integrative membrane permeability.

Third and significative: both VO2max and PAO2 depend in a non-linear manner of the membrane permeability. The fact that, even in this *simplified* machine acinus, the oxygen consumption VO2 is *not* proportional to the membrane permeability is important to stress because it shows that in no way the acinus works like is a simple gas exchanger. The non-linearity is due to the complex dynamics during the respiratory cycle of the screening effects due to diffusion limitations in the acinar space. Due to this screening effect, part of the alveolar surface is not fully used for gas exchange depending on space and time.

Fourth: A strong non-linearity is also found for the dependence of PAO2 on the permeability.

Finally, the “integrative permeability” value that we determine, encompass the fact that in reality hemoglobin equilibration occurs. We propose a scheme to relate that value to the real permeability of the membrane. Following this scheme, we find for the real permeability a value significantly smaller than that usually admitted in the literature but compatible with the experimental value of DLNO.

Abstract No. 14

Investigation of the ciliary beat frequency (CBF) and wave propagation on wildtype cells and RNAi-mediated striatine 6 mutants of *Paramecium tetraurelia* using microfluidics

Anette Funfak[a*], Hatem Ghanem[a], Cathy Fisch[b], Julien Diener[c], Laurent Combettes[d], Pascale Dupuis-Williams[b,e] and Charles Baroud[a]

a Laboratoire d'Hydrodynamique (LadHyX) and Department of Mechanics, Ecole Polytechnique, CNRS, 91128 Palaiseau, France
b ATIGE "Centriole et Pathologies Associées" UMR-U829 INSERM/UEVE, Université d'Evry Val d'Essonne
c I3S-Pole MDSC-equipe BioInfo, Sophia-Antipolis
d INSERM, UMR-S 757, UPS-Orsay
e ESPCI, 10 rue Vauquelin 75005 PARIS
**anette@ladhyx.polytechnique.fr*

Cilia are subcellular organelles which are present in many eukaryotic cells. In vertebrates they play an important role in the fluid transport of the reproductive system, the respiratory tract or the brain, in the mechanical and biochemical signal transduction in the kidneys and eyes as well as in the embryonic left-right asymmetry and intercellular communication[1]. Genetic disorders in the cilia or the basal body are known to be at the root of several diseases, such as the Meckler-Gruber syndrome, the Bardet-Biedl syndrome or primary ciliary dyskinesia (PCD)[2-4]. Moreover, there is a strong interest in understanding the role of cilia beating for locomotion of microswimmers or for fluid transport in the human body. The structure of cilia is preserved across species, which makes *Paramecium tetraurelia* a useful model for several genetic human pathologies.

We used RNA interference (RNAi) for the inhibition of gene expression and generated specific knockdown mutants with a suppression of the striatine 6 protein. This protein family is seen to play an important role in assembling and positioning the basal body[5].

In this study, we applied microfluidic and high-speed microscopy techniques for the analysis of the cilia activity around a swimming cell, in the case of wildtype cells and knockdown mutants (Fig 1). These images provide access to the cell velocity, the ciliary beating frequency (CBF), and the spatio-temporal organization of the ciliary beating.

For the knockdown mutants we found a reduced swimming velocity compared to the wildtype. However the dominant beating frequency was found to be similar for the two cell types, and did not correlate with the swimming velocity.

Measurements of the CBF showed the presences of different frequencies along different regions of a single cell. The strongest difference that was observed between the two cell types was in the propagation of waves in the beating pattern. Wild-type cells display long-range wave propagation which are difficult to identify on the Striatine 6 mutants. This suggest that the spatio-temporal organization of the beating patterns plays a role in defining the swimming velocity.

With the developed method, combining the advantages of RNAi- and microfluidic techniques as well as a simple model organism, we expect to gain a tool to investigate and characterize local CBF as well as temporarily and spatial wave propagation to study ciliary diseases.

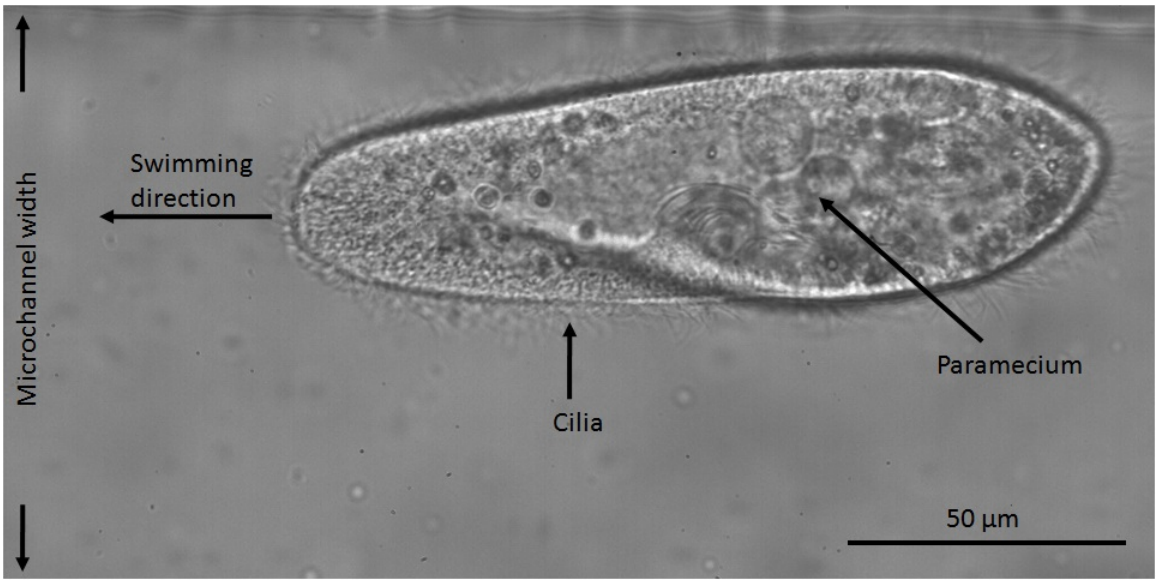

Fig 1: Forward swimming wildtype cell of *Paramecium tetraurelia* within a microchannel.

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Abstract No. 15

Stochastic simulations of a bistable frustrated unit

Ashok Garai[a], Bartlomiej Waclaw[b] and Hildegard Meyer-Ortmanns[a*]

a School of Engineering and Science, Jacobs University, P.O. Box 750561, 28725 Bremen, Germany
b School of Physics & Astronomy, University of Edinburgh , UK
** Email: h.ortmanns@jacobs-university.de*

The bistable frustrated unit (bfu) consists of a self activating loop which triggers the production of a repressor that provides negative feedback control on the self activating loop. The self activating loop produces proteins which can exist in two stable states with high or low concentrations. The presence of the negative feedback loop makes this bistable system frustrated [1]. In its deterministic realization the system is excitable in two regimes which are separated by Hopf bifurcations from an intermediate oscillatory regime with limit cycles [2]. In this work we study a stochastic realization of this unit, since the protein numbers in biological realizations of this model are not high, so that the stochastic effects may be pronounced. We both numerically integrate the corresponding master equation and simulate the system with the Gillespie algorithm. It is found that the stochastic fluctuations not only extend the oscillatory regime as compared to the deterministic case; they can even lead to oscillatory behavior in the space of protein concentrations for parameters, which are deeply in the fixed point regime in the deterministic version. In this case, however, the oscillations come as some kind of rare events. We locate the transition points via the change in the decay of the autocorrelation function. The large-volume limit is treated within the van Kampen expansion. Due to the possible coexistence of cyclic and deterministic behavior for one and the same set of parameters, the stochastic realization appears even more flexible than the deterministic one.

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Abstract No. 16

A model to move a low-grade glioma back in time

C. Gerin[a, b], B. Grammaticos[a], C. Deroulers[b,a], J. Pallud[c,e], E. Mandonnet[e,f,g] and M. Badoual[b,a]

a CNRS, UMR 8165, IMNC, Paris, France
b Univ Paris Diderot, Sorbonne Paris Cité, F-75013 Paris, France
c Department of Neurosurgery, Sainte-Anne Hospital, Paris, France
d University René Descartes Paris-V, Paris, France
e REG, Réseau d'Etudes des Gliomes, Groland, France
f INSERM, UMR 894
g Department of Neurosurgery, Lariboisière Hospital, Paris, France
** gerin@imnc.in2p3.fr*

Low-grade glioma is a slowly evolving tumour of the brain which always evolves into an aggressive tumour. Definitive surgical treatment is hindered by the cells infiltration into healthy tissue where they are invisible by the classical imaging techniques.
A recent clinical study showed that the growth of low grade glioma appears linear [1]. Is it possible to assume that it is always true ? Using this property, can we extrapolate the date of birth of the tumour ?
To answer these questions, we use a diffusion-proliferation model, employed with success for high-grade gliomas [2, 3].It is a simple model (few parameters) that can explain the constant velocity at large times of the front visible on MRI examinations.

The model predicts the existence of a "silent period": the tumour is growing, but remains under the detection threshold and thus it is not visible. A consequence of this phase is that the extrapolation always underestimates the age of the tumour predicted by the diffusion-proliferation model.

We apply this model to a series of non-treated patients and we deduce the median age of the birth of the glioma and the median age of the “clinical birth” (when the glioma becomes visible with MRI).

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Abstract No. 17

Gene regulatory networks in development and evolution of the mammalian neocortex

Tanay Ghosh and Matthias Groszer

Institut du Fer à Moulin, UMR-S 839 Inserm UPMC

The evolutionary enlargement of the mammalian cerebral cortex is thought to provide the substrate for much of our higher cognitive functions, social abilities, and ultimately language development. The cellular architecture of the cerebral neocortex is organized into six layers and especially neurons in upper layers appear to have contributed disproportionally to the enlargement in the primate lineage. During embryogenesis cortical neurons arise sequentially from intermediate progenitor cells (IPCs), early born neurons are destined for lower layers and later borns for upper ones. We intend exploring gene regulatory networks (GRN) specifically involved in upper layer neurogenesis. To this end we use comprehensive functional genomics approaches on in-vivo isolated IPCs and IPC specific transcription factors at developmental time points of lower and upper layer neurogenesis. Mathematical approaches should enable to parse these intricate GRNs into relevant functions.

Abstract No. 18

Nonlinear Fitness Landscape of a Molecular Pathway

Lilia Perfeito[a,b], Stéphane Ghozzi[b,*], Johannes Berg[b], Karin Schnetz[a], and Michael Lässig[b]

a Institut für Genetik, Universität zu Köln, Cologne, Germany
b Institut für Theoretische Physik, Universität zu Köln, Cologne, Germany
** ghozzi@thp.uni-koeln.de*

Genes are regulated because their expression involves a fitness cost to the organism. In bacteria, the production of proteins is a well-known cost factor, but their activity can also reduce growth. We map the fitness costs of a key metabolic network, the lactose utilization pathway in *Escherichia coli*. We measure the growth of several regulatory *lac* operon mutants in different environments inducing expression of the *lac* genes. We find a strikingly nonlinear fitness landscape, which depends on the production rate and on the activity rate of the *lac* proteins. A simple fitness model of the *lac* pathway, based on elementary biophysical processes, predicts the growth rate of all observed strains. The nonlinearity of fitness is explained by a feedback loop: production and activity of the *lac* proteins reduce growth, but growth also affects the density of these molecules. This nonlinearity generates a cliff in the fitness landscape, beyond which populations cannot maintain growth, as well as multistability. Furthermore, it determines how genotype and environment interact. Such feedback and nonlinearities are expected to be generic features shaping the evolution of metabolic pathways.

Abstract No. 19

Stochastic analysis of a miRNA-protein toggle switch

E. Giampieri[1], D. Remondini[1], L. De Oliveira[1], G. Castellani[1], P. Liò[2]

1.Physics dept., University of Bologna, Viale B. Pichat 6/2, Bologna, IT
2.Computer Science dept, University of Cambridge, JJ Thomson rd, Cambridge, UK

Complex cellular responses, an area of growing interest for system biology studies, are often modeled as switching between phenotype states and, despite the large body of deterministic studies some aspects still remain unclear, in particular the effect of the intrinsic and extrinsic noise, due to the low copy numbers of important cellular components. This give rise to noticeable stochasticity in gene expression and protein synthesis, and it is a fundamental aspect to be taken into account for studying such biochemical models.

To address this issue we are going to use the chemical master equation (CME) approach, with it's numerical counterpart, the Stochastic simulation algorithm (SSA), usually called the Gillespie method. The CME describe the evolution in time of the probability of occupancy of each state of the system, and it's associated with a continuous time Markov chain (CTMC) evolution. Similarly to the deterministic case, only simple systems are analytically tractable in the stochastic approach, i.e. the full probability distribution for the state of the biological system over time can be calculated explicitly, becoming computationally infeasible for systems with distinct processes operating on different timescales.

In this paper we consider the stochastic properties of a toggle switch, involving a protein compound and a miRNA cluster, known to control the eukaryotic cell cycle and possibly involved in oncogenesis, recently proposed in the literature within a deterministic framework.
Due to the inherent stochasticity of biochemical processes and the small number of molecules involved, the stochastic approach should be more correct in describing the real system: we study the agreement between the two approaches by exploring the system parameter space. We address the problem by proposing a simplified version of the model that allows analytical treatment, and by performing numerical simulations via a modified SSA method for the full model. We observed optimal agreement between the stochastic and the deterministic description of the circuit in a large range of parameters, but some substantial differences arise in at least two cases: 1) when the deterministic system is in the proximity of a transition from a monostable to a bistable configuration, and 2) when bistability (in the deterministic system) is "masked" in the stochastic system by the distribution tails. The approach provides interesting estimates of the optimal number of molecules involved in the toggle. Our discussion of the points of strengths, potentiality and weakness of the chemical master equation in systems biology and the differences with respect to deterministic modeling are leveraged in order to provide useful advice for both the bioinformatician practitioner and the theoretical scientist.

Abstract No. 20

Out of equilibrium dynamic of DNA replication

Arach Goldar[a*]

[a] *Commissariat à l'Energie Atomique (CEA), iBiTec-S, 91191 Gif-sur-Yvette, France*

** arach.goldar@cea.fr*

The replication of DNA in eukaryotic cells initiates at multiple chromosomal positions, called "replication origins" according to a spatiotemporal program, which depends on the tissue and/or the developmental stage. Despite the great importance of these replication origins, mechanisms that control their locations and their activation times are still poorly understood.

Since about ten years, experimental breakthroughs have allowed measurements of the replication state of the chromatin: it is then possible to follow the replication kinetics of a given DNA sequence over a cell population. So far, analysis of these experimental data was based on an equilibrium hypothesis: in average, the dynamics of replication of all chromosomal loci was assumed to be the same, and fluctuations were considered as negligible compared to the average behavior. Here, on the contrary, we demonstrate that DNA replication is an out of equilibrium process by using an analogy between the temporal evolution of DNA replication in *Saccharomyces cerevisiae* and the equation of motion of an overdamped particle in a quadratic potential. We extract from experimental data the distribution of replication time, the mean replication time and the rate of entropy production for every chromosomal position. We calculate an analytical form of the replication of a chromosomal position over the time using two parameters: the rate of entropy production and the genome-wide chromatin structure. We show that the chromatin structure extracted from replication timing profiles is in good accordance with experimentally measured chromatin structure. This finding allows us to establish a predictive and quantifiable relation between the structure of the chromatin and the mechanisms that control the locations and activation times of replication origins.

Abstract No. 21

Mechanical studies of morphogenesis at cellular and tissue levels validate a description of an epithelium as a continuous medium

I. Bonnet [a#], F. Bosveld [a#], F. Graner [a*], B. Guirao [a], P. Marcq [b], S. Tlili [a], Y. Bellaïche [a]

a - Biologie du Développement, Institut Curie, INSERM U934,
CNRS UMR 3215, UPMC, Paris, France
b - Physico-Chimie, Institut Curie,
CNRS UMR 168, UPMC, Paris, France
 # These authors contributed equally to this work
** francois.graner@curie.fr*

Tissue morphogenesis is fundamental to the formation of functional organs. To understand how a tissue acquires its shape, we use live imaging of a fly back during its metamorphosis (*Drosophila* pupal dorsal thorax epithelium). We non-invasively observe a monolayer of cells over large length scales (10^4 cells) and long time scales (>24 hr). Our time (5 min / frame) and space (200 pixels / cell) resolutions are adapted to the details of cell shape and dynamics: displacement, growth, and division.

We obtain detailed, multi-scale information on several mechanical quantities, which describe the tissue: deformation, speed, and velocity gradient. We determine full space-time measurements of their magnitude, direction and anisotropy. As controls, we compare two sides of each fly and observe a good symmetry of these quantities; we compare different flies and observe a good reproducibility. Their variations in time and space are smooth: this is a first step towards the mechanical description of the tissue as a continuous medium.

To look for causes of these morphogenetic movements, we perform laser ablations. A disk-shaped domain, of the size of ~10^2 cells, is severed from the surrounding epithelium and observed during its relaxation. We thus accurately measure the stress and strain in the tissue prior to ablation: this is a second step towards the mechanical description of the tissue as a continuous medium.

We fit to the relaxation data a model of an active, viscoelastic, anisotropic solid subject to external friction. We find that on the length scales considered the internal viscosity dominates the external friction. Finally, we obtain an estimate of the viscoelastic time scale of the epithelium. This third step validates the description of this epithelium as a linear, continuous medium.

Abstract No. 22

Motion Reversal of Molecular Motor Assemblies due to Weak Noise

Thomas Guérin* [a], **Jacques Prost** [b,c], **Jean-François Joanny** [b]

a Laboratoire de Physique Théorique de la Matière Condensée, UPMC Univ Paris 06, CNRS-UMR 7600, Paris, France
b Physicochimie Curie, Institut Curie/CNRS-UMR168/UPMC, Paris, France
c ESPCI, Paris, France
** tguerin@lptmc.jussieu.fr*

In many examples of intracellular transport, cargoes transported by molecular motors display a motion that is bidirectional rather than unidirectional [1]. This type of motion, also observed in acto-myosin systems, typically appears in the presence of two groups of motors with opposite polarity, and enables an object to move efficiently in two directions. Bidirectional motion can be seen as a consequence of the collective behavior of molecular motors. We propose an analytic theory for the calculation of the reversal time. We consider the bidirectional motion as a first exit problem in a non-equilibrium system. We identify the noise strength by doing an expansion of a master equation and apply the Wentzell-Freidlin theory to define an effective nonequilibrium potential and provide analytical estimates of the reversal time [2]. Our results match very well with the results of stochastic simulations. With high probability, a reversal event takes place along an "most probable exit trajectory" in the space of configurations.

We also discuss another collective effect (an oscillatory instability) appearing in the same model and compare our results to a recent experiment indicating that the acto-myosin system can become self-oscillatory when subjected to an elastic load [3]. Instabilities due to molecular motors might be relevant for describing mechanical oscillations in a variety of biological systems, including muscles, sensory hair-cell bundles of the inner ear, and flagella.

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Abstract No. 23

Combined local search strategy for learning in networks of binary synapses

Haiping Huang[a,*] **and Haijun Zhou**[a,b]

a Laboratory of Frontiers in Theoretical Physics, Institute of Theoretical Physics, Chinese Academy of Sciences, Beijing 100190, China
b Kavli Institute for Theoretical Physics China, Institute of Theoretical Physics, Chinese Academy of Sciences, Beijing 100190, China
** hphuang@itp.ac.cn*

Learning in networks of binary synapses is known to be an NP-complete problem. A smart combined stochastic local search strategy in the synaptic weight space is constructed to further improve the learning performance of a single random walker. In practice, we apply two communicating random walkers guided by their Hamming distance and associated energy costs to learn a same large set of patterns. Each walker first learns a small part of the whole pattern set (partially different for both walkers but with the same constraint density) and then explores its weight space to find a solution to classify the whole pattern set correctly. The desired solution locates at one of the common parts of weight spaces explored by these two walkers. The efficiency of this smart strategy is supported by our extensive numerical simulations and the typical Hamming distance as well as energy cost is predicted by an annealed computation.

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Abstract No. 24

Weber's Law in Autocatalytic Reaction Networks

Masayo Inoue[a], Kunihiko Kaneko[b]

a Cybermedia Center, Osaka University, Osaka, Japan
b Graduate School of Arts and Sciences, University of Tokyo, Tokyo, Japan
** inoue@cp.cmc.osaka-u.ac.jp*

Biological responses often obey Weber's law, according to which the magnitude of the response depends only on the fold change in the external input. In this study, we demonstrate that a system involving a simple autocatalytic reaction shows such response when a chemical is slowly synthesized by the reaction from a faster influx process. We also show that an autocatalytic reaction process occurring in series or in parallel can obey Weber's law with an oscillatory adaptive response. Considering the simplicity and ubiquity of the autocatalytic process, our proposed mechanism is thought to be commonly observed in biological reactions.

Abstract No. 25

Growth rate dependence of gene expression in bacteria

Stefan Klumpp[a,b*], Zhongge Zhang[c] and Terence Hwa[b,c]

a Max Planck Institute of Colloids and Interfacesm Potsdam, Germany
b Center for Theoretical Biological Physics and Department of Physics, University of California at San Diego, La Jolla, California, USA
c Division of Biological Sciences, University of California at San Diego, La Jolla, California, USA
** klumpp@mpikg.mpg.de*

The expression level of any gene is unavoidably coupled to the physiological state of the cell, which for bacteria during exponential growth is first and foremost characterized by the growth rate. Parameters that affect gene expression such as the availability of RNA polymerases and ribosomes, and the gene copy number are known to be growth-rate dependent. Therefore the expression level of a gene depends not only on its regulation, but also on the growth conditions, and a quantitative understanding of gene expression also requires an understanding of the global effects due to growth. We studied these effects for various genetic circuits involving positive and negative control as well as feedback using a model for gene expression and synthetic genetic circuits in *E. coli* grown in various media.

We show that the growth-rate dependence of constitutive expression can be explained by the growth-rate dependence of several cellular parameters. Our model predicts and our experiments confirm that this dependence, a reduction of the protein concentration at fast growth, is enhanced for genes under positive control and vanishes for genes controlled by a negative autoregulator.

If the growth rate depends on the concentration of a particular protein, e.g. a 'bottleneck enzyme' or a 'toxin', the growth-rate dependence of its expression results in feedback mediated by growth. For positive feedback this may lead to growth bistability, i.e. to a mixed population with one fraction of cells growing faster than the others. We hypothesize that this type of feedback plays a role in metabolic control and tolerance to antibiotics.

Furthermore, the growth rate dependence of cellular parameters and parameters of plasmid replication is used to obtain information about the control system for plasmid replication and to deduce the form of the control function, supporting exponential control over hyperbolic control [2].

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Abstract No. 26

Modified fluctuation-dissipation theorem and applications to molecular motors

G. Verley[a], K. Mallick[b] and D. Lacoste[a,*]

a Laboratoire Physico-Chimie Théorique, ESPCI, Paris, FRANCE
b Institut de Physique Théorique, Saclay, FRANCE
** david.lacoste@gmail.com*

It is a general rule that as a system gets smaller its fluctuations increase. As a consequence, in small systems, like a molecular motor, thermodynamic quantities like work or heat are only defined in a statistical sense. Exact relations exist between the statistical distributions of thermodynamic quantities which are known as fluctuations relations [1].
Within the linear regime, these fluctuations relations lead to a modified fluctuation dissipation theorem valid for systems close to non-equilibrium steady-states and obeying a markovian dynamics. We present here a compact derivation of this result which we apply to a model of molecular motors [2].

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Abstract No. 27

Spatial organization of the cell cytoplasm: Protein gradients and liquid-liquid phase separation in the *C. elegans* embryo

Chiu Fan Lee[a,*], Clifford P. Brangwynne[a,b], Zdeněk Petrášek[c], Jöbin Gharakhani[a], Anthony A. Hyman[b], and Frank Jülicher[a]

a Max Planck Institute for the Physics of Complex Systems, Dresden, Germany
b Max Planck Institute of Molecular Cell Biology and Genetics, Dresden, Germany
c Biotechnologisches Zentrum der TU Dresden, Dresden, Germany
** cflee@pks.mpg.de*

During the asymmetric division of the one-cell stage embryo of the nematode *C. elegans*, germ line granules (P-granules) segregate and localize in the posterior half of the cell in order to be unequally distributed to the two daughter cells. Segregation occurs via a spatial gradient of supersaturation of P-granule components which nucleate in droplets on in the posterior side and dissolve in the anterior side. This supersaturation gradient is generated by a concentration gradient of the protein Mex-5. Using a combined experimental and theoretical approach, we show that the Mex-5 gradient is established by a modulation of the diffusivity of Mex-5 via reactions that occur at the cell cortex and within the cytoplasm. We propose that Mex-5 may control P-granule phase separation via its competitive RNA binding activity, by which the local Mex-5 concentration influences the saturation point of the phase transition that triggers P-granule formation.

Abstract No. 28

Architecture of the Bacteriophage Genome: Polymorphism and Phase Transitions

A. Leforestier[1*], BK. Sung[1,2], A. Siber[3], R. Podgornik[4], F. Livolant[1]

[1] *Laboratoire de Physique des Solides, CNRS UMR8502, Bât 510, Université Paris-Sud, 91405 Orsay Cedex, France*
[2] *Biomedical Physics Laboratory, Department of Physics and Astronomy, Seoul National University, Seoul 151-747, Republic of Korea*
[3] *Institute of Physics, Bijenicka cesta 46, 10000 Zagreb, Croatia*
[4] *Theoretical Physics Department, J. Stefan Institute, SI-1000 Ljubljana, Slovenia*
[*] *Correspondence: leforestier@u-psud.fr*

Double-stranded DNA bacteriophage genomes are densely packaged into capsids until the ejection is triggered upon interaction of the tail with the bacterial receptor. Using cryo-electron microscopy, we describe the organization of the genome in the full capsid of T5, and explore its conformational changes as a function of the ionic and aqueous environment as well as the length of molecule. In the full capsid, monodomains of hexagonally crystallized DNA segments initially form a 3D lattice of defects. Upon progressive ejection, the genome undergoes a series of phase transitions, turning liquid crystalline and finally isotropic. The addition of a DNA condensing agent (either multivalent cations that diffuse through the capsid wall or polymers such as PEG that does not permeate the capsid) provokes the condensation of the DNA chain into toroidal globules. We show that the nature and the concentration of the condensing agent tune both the DNA-DNA interactions between segments of the chain and the interactions between the capsid proteins and the DNA molecule, leading to a variety of shapes and compactness. We'll discuss these results with respects to the different forms that may be assumed by a DNA molecule inside the capsid at different stages of the infectious cycle of the phage (ejection, packaging).

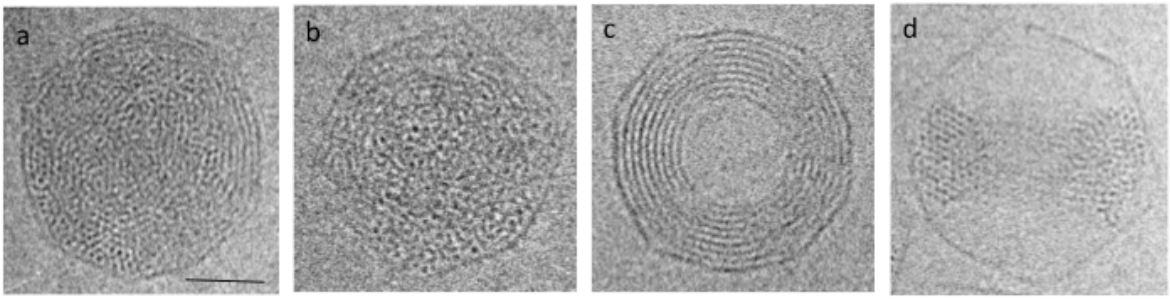

Image gallery of DNA conformations inside the T5 bacteriophage capside. (a) Full capsid. (b) Capsid after partial ejection (40%) of the genome showing a cholesteric organisation. (c, d) Partially filled capsid after DNA condensation by spermine, showing toroidal conformations in top and side views. Scale bar 20 nm.

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Abstract No. 29

Electrostatics of a partially formed, charged spherical shell in salt solution: the weak and strong coupling limits

A. Lošdorfer Božič[a,*], A. Šiber[b] and R. Podgornik[a,c]

a Department of Theoretical Physics, Jozef Stefan Institute, Ljubljana, Slovenia
b Institute of Physics, Zagreb, Croatia
c Faculty of Mathematics and Physics and Institute of Medicine, University of Ljubljana, Ljubljana, Slovenia
** anze.bozic@ijs.si*

We study the electrostatics of a partially formed, charged spherical shell in a salt solution. We investigate the problem in two different limits, the weak [1] and strong coupling regimes [2]. The former is described by the Poisson-Boltzmann (PB) theory (and its linearised Debye-Hückel (DH) version) [2], based on the mean-field approximation, and is applicable for low ion valencies, small charge densities, high medium dielectric constant, or high temperatures. The limitations of the PB approximation become practically important only in highly charged systems (especially ones with high ion valencies), where ion-ion correlation effects begin to affect the electrostatic properties of the system. There, one has to give up the idea of a mean-field description altogether, taking recourse in a fundamentally different reformulation of the electrostatic theory, based on the concept of strong coupling [3]. Since our system in this regime includes both monovalent salt and polyvalent counterions, we describe it by using the strong coupling dressed counterions theory. Thus, the monovalent salt is treated in the DH limit, giving rise to a strong coupling description of dressed polyvalent counterions interacting via a screened DH pair potential.

For each of the two cases described above we numerically calculate the dependence of the free energy on the parameters of the system, and derive analytical approximations to clarify its behaviour. From the results on the energetics of partially formed shells we then examine the stability of tethered (crystalline) and fluid shells towards rupture. We delineate different regimes of stability, where, for fluid shells, we also include the effects of the bending elasticity of the shells. We then show how these results apply to the stability of both viruses and vesicles, drawing out phase diagrams for the rupture of spherical capsids and the poration of vesicles.

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Abstract No. 30

Statistics for clustering in gene expression data: from statistical significance to biological relevance

Marta Łuksza[a,b], Michael Lässig[a] and Johannes Berg[a]

a Institute for Theoretical Physics, Cologne, Germany
b Max Planck Institute for Molecular Genetics, Berlin, Germany
** luksza@molgen.mpg.de*

The identification of groups of co-expressed genes is a key step in gene expression analysis. Clustering is used widely to infer putative functional relationships between genes, with gene expression clusters arising for instance through common biological pathways or shared modes of regulation.

But could such clusters have arisen simply by chance, without an underlying biological mechanism? Even unrelated objects can form cluster-like structures simply due to density fluctuations. To distinguish such random clusters from biological signals, we compute the cluster score *p*-value: the probability that a random data set contains a cluster with similarity score equal or higher than a given score *S*. We develop a probabilistic model for high dimensional gene expression data, which incorporates possible dependencies between experimental conditions. Using methods from statistical mechanics, we obtain an analytical solution to the cluster significance problem. Based on our model, we develop a new clustering method, which finds clusters with significant scores only and optimizes the number of clusters.

We apply significance-based clustering to genome-wide expression data in yeast with samples corresponding to various environmental stress conditions. Tracking the dependence of co-expression clusters on cluster scoring parameters and cluster sizes, we find a striking correspondence between cluster *p*-value and the biological significance of a cluster (quantified by enrichment in Gene Ontology terms).

Abstract No. 31

Trade-offs and constraints in allosteric sensing

Bruno M.C. Martins[a,b,*] and Peter S. Swain[a]

a Centre for Systems Biology at Edinburgh, University of Edinburgh, Edinburgh, UK
b PDBC, Instituto Gulbenkian de Ciência, Oeiras, Portugal
** bruno.martins@ed.ac.uk*

Sensing extracellular changes is the first stage in the process of cellular decision making, but why different biochemical networks use different sensing mechanisms is not yet clear. To gain a better insight into this question we studied one of the simplest sensors, common in both eukaryotes and prokaryotes: allosteric transcription factors. Such proteins directly transduce information about sensed changes in the environment to changes in gene expression. Our purpose is to understand the 'design' of allosteric sensors. Using the Monod-Wyman-Changeux (MWC) model [1] and following on the approach initiated by Detwiler et al. [2], we defined and calculated a set of six sensing characteristics – the dynamic range, the Hill number, the static gain, the response time, and, by analytically solving the stochastic version [3] of the MWC model, the intrinsic noise and the information transmission capacity [4] – as a function of the biochemical parameters of individual sensors and of the number of sensors.

We found that optimizing one characteristic strongly constrains the performance of the system with regards to other characteristics. For example, a high Hill number implies both a high dynamic range and a high capacity, the static gain and the Hill number are anti-correlated and reducing the intrinsic noise also reduces the dynamic range and the Hill number. We can also calculate the probability distributions of the numbers of input molecules and active sensors that maximize information transmission and, thus, show that a population of one hundred allosteric sensors can *a priori* distinguish between four bands of input concentrations. Finally, and perhaps surprisingly, we found that most of the space of characteristics is inaccessible given plausible biochemical parameters.

These results suggest that allosteric sensors are unlikely to be selected for high performance in one sensing characteristic but for a compromise in the performance of many. Our approach provides both quantitative and qualitative insights about the function and robustness of allosteric sensors and is therefore useful to both the study of endogenous systems and the design of circuits in synthetic biology.

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Abstract No. 32

Epistasis in signalling cascades

Philippe Nghe[1], Manjunatha Kogenaru[1], and Sander J. Tans[1]

[1]Biophysics group, AMOLF, 1098XG Science Park, Amsterdam, Netherlands. E-mail: nghe@amolf.nl

Short Abstract — **We study how the structure of a gene network gives rise to evolutionary constraints. Focusing on signalling cascades, we show theoretically that functional relations between network components generate interactions between mutations (epistasis) and classify the different epistatic scenarios according to cascade structure. We show the existence of situations in which there is a preferential order of mutations, and situations in which two components require mutual adequacy leading to separate optima. We test our predictions on a synthetic cascade in Escherichia Coli by mutating separate components of our network and measuring the performance of combinatorial mutants.**

I. Motivation

Evolutionary constraints have recently been analyzed in detail at the level of physical interactions between molecular components [1,2], revealing the presence of epistatic interactions restricting evolution to a only a few possible paths [3]. On the other hand, studies of mutational effects in gene networks report synergistic or antagonistic interactions in a statistical sense [4,5] and are thought to be related to network topology [6,7]. We propose here to study mechanistically the interactions between mutations generated by functional relations within gene networks, focusing on the case of signalling cascades and show how such interactions can constraint gene networks evolutionary pathways [8].

II. Theoretical analysis

We consider linear cascades made of successive down or up-regulating steps. We evaluate the performance of a network based on the range of the output provided at steady-state in response to a given input signal. Epistatic interactions between mutations can be predicted based on maps of metwork performance as a function of network parameters. More precisely, mutations affecting two genes which are functionally but not physically related represent orthogonal paths on the performance map, which correspond to local paths in the genotype to fitness landscape.

We show that the dependence of the optimum of one parameter on the value of another generates evolutionary constraints. For example in the case of two successive repressors, there is a domain in the space of binding constants for which all paths to maximum performance exhibit sign epistasis, implying a preferential order of mutations. When these two repressors are downstream another repressor, all paths relating two optima exhibit reciprocal sign epistasis. This requirement for mutual adequacy potentially results in the existence of local fitness optima. More generally, we classify epistatic scenarios for cascades of arbitrary length and composition.

III. Experimental evolution

We test the relevance of our simplified model on a synthetic signaling cascade in E. Coli. This cascade is made of an input control system based on *arabinose* and two successive repressor proteins (*TetR* and *LacI*) with a fluorescence reporting system for each step. We mutate individually each repressor proteins and create a librairy of all combinations of mutants between the two genes. We first observe that mutants diversity is well described by considering the parameter space of binding constants. Measuring the performance of combinatorial cascades,

we explore exhaustively two steps mutational paths and show that they follow the predicted epistatic patterns.

IV. Conclusion

Functional relations between gene network components lead to predictible epistatic interactions between mutations based on the knowledge of network structure. These epistasic properties arise from phenotypic functional dependence between mutated components and provide insights into accessible evolutionary paths.

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Abstract No. 33

Intermittent depolymerization of actin filaments is caused by local transitions at random sites

Thomas Niedermayer[a,*], Antoine Jégou[b], Emmanuele Helfer[b], Guillaume Romet-Lemonne[b], Marie-France Carlier[b], Reinhard Lipowsky[a]

[a] *Theory and Bio-Systems, Max Planck Institute of Colloids and Interfaces, 14424 Potsdam, Germany*

[b] *Cytoskeleton Dynamics and Motility Group, Laboratoire d'Enzymologie et Biochimie Structurales, CNRS, 1 Avenue de la Terrasse, 91198 Gif-sur-Yvette, France*

** thomas.niedermayer@mpikg.mpg.de*

After the polymerization of actin monomers into filaments, the actin-bound ATP is hydrolyzed into ADP, a process that was believed to decrease the filament stability. Recent experiments suggest the opposite behavior, however, namely that the actin filaments become increasingly stable with time [1]. Several mechanisms for this stabilization have been proposed, ranging from structural transitions of the whole filament helix to surface attachment of the filament ends. We performed novel fluorescence microscopy experiments on single filaments and found that filaments do indeed cease to depolymerize in an abrupt manner. We also calculated the distributions of a easily accessible observable for many possible stabilization mechanisms. A comparison of theory and experiment reveals that the sudden truncation of the shrinkage process does neither arise from blocking of the ends nor from a collective transition of the whole filament. Instead, we predict a local transition process occurring at random sites within the filament.

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Abstract No. 34

A Mathematical Model of 6S RNA Regulation of Gene Expression

Mor Nitzan[a*], Karen M. Wassarman[b], Ofer Biham[a] and Hanah Margalit[c]

a Racah Institute of Physics, The Hebrew University, Jerusalem, Israel
b Department of Bacteriology, University of Wisconsin-Madison, Madison, WI, USA
c Department of Molecular Genetics and Biotechnology, Faculty of Medicine, The Hebrew University, Jerusalem, Israel
** mor.nitzan@mail.huji.ac.il*

E. coli's 6S RNA is a type of noncoding, small RNA that is ubiquitously expressed in the cell and is the key component in a unique global RNA polymerase (RNAP) - mediated regulation mechanism [1]. 6S RNA was shown to differentially inhibit σ-70 dependent promoters during stationary phase by binding and forming a stable complex with the housekeeping form of RNAP, blocking the ability of RNAP to bind to promoter DNA. Surprisingly, when stationary phase cells are exposed to high enough levels of nucleotide-triphosphate (NTP), they enter outgrowth phase at which time 6S RNA is used as a template for product RNA (pRNA) synthesis. 6S RNA interactions with RNAP are destabilized during the pRNA synthesis reaction, leading to the dissociation of the 6S RNA-RNAP complexes. The released 6S RNA becomes highly unstable and the released RNAP enables increased transcription of genes. Many of the dynamic properties and the promoter specificity which characterize this regulation mechanism are still unclear.

Using a mathematical model of this biological system we study the dynamics of the system components and specifically mRNAs transcribed by σ-70 dependent promoters (during exponential phase, stationary phase and outgrowth) [2]. We find that this global regulation mechanism exhibits unique properties; RNAP level returns to steady state subsequent to its inhibition, and stored inactive RNAPs bound by 6S RNA accumulate over late stationary phase and can return to their active form rapidly upon the introduction of newly available nutrients. We show that a gene's sensitivity to 6S RNA regulation varies according to its inherent effective promoter parameters- affinity to RNAP and clearance rate. We also compare 6S RNA regulation to other global RNAP-mediated regulation mechanisms and deduce several of its properties, including its energetic efficiency, its robustness to noise, and the competitive edge of cells carrying it at the transition to a new environment.

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Abstract No. 35

Exploring the links between nucleoid physical state, growth rate and gene expression

Matteo Osella[a,*], Vittore F. Scolari[a], Mina Zarei[a] and Marco Cosentino Lagomarsino[a]

Génophysique – Genomic Physics Group
UMR 7238 CNRS-Université Pierre et Marie Curie , Paris, France
** matteo.osella@upmc.fr*

Bacterial cells rely on a strong link between transcription program, chromosome physical organization and growth conditions. Growth rate is coupled to cellular macromolecular composition, and thus to the main global parameters of gene expression (such as ribosome and RNA polymerase abundance). While locally it relies on specific transcription-factor binding, transcription depends globally on the state of the mesoscopic protein/genome complex called nucleoid; the main proteins shaping the nucleoid have growth-dependent expression. Finally, nucleoid organization and growth are also linked by the process of replication. Our work, in direct collaboration with experiments, focuses on the characterization of these links at different levels using data analysis and models. This poster presents the intermediate results of different subprojects.

1.Integrating several data sources (microarrays, ChIP-on-chip) we identified clusters of genes sensitive to nucleoid-perturbation that correlate with large structured regions along the chromosome that typically demix in the cell (macrodomains). In particular, we found indications that the switch between the motile and biofilm lifestyle might depend on nucleoid-mediated regulation in two large regions containing the flagella regulons.

2.More generally, we considered how gene functions and transcriptional interactions are influenced by chromosomal coordinate. We found that essential genes preferentially cluster in specific chromosome domains and, analyzing the transcriptional regulatory network, we found significant correlation between link topology and chromosome organization.

3.Finally, we are investigating how global physiological parameters such as growth rate and nucleoid organization can contribute to the cell-to-cell variability of gene expression. Starting from quantitative estimates of the cellular macromolecular composition, we find a non-trivial scaling of expression fluctuations with growth rate.

Abstract No. 36

Robustness of circadian clocks to daylight fluctuations

B. Pfeuty, Q. Thommen, M. Lefranc

Universite de Lille 1, PhLAM, CNRS UMR8523

The daily life of most living organisms is orchestrated by an endogeneous biological clock, the so-called circadian clock, which provides them with information about the time of day. Loss of synchronization between the circadian clock and the day/night cycle is known as "jet lag". Circadian clocks are built with networks of genes and proteins which interact so as to generate biochemical oscillations with a period close to 24 hours. Perfect synchronization with the day/night cycle is achieved through parametric forcing, by having one or more properties of the clock depend on light intensity. For example, a clock protein may be strongly degraded at night and stabilized by light. However, daylight intensity can display strong fluctuations from day to day, which could potentially reset the clock erratically.

The analysis of time series of the activity of two recently identified clock genes of a small microscopic alga, Ostreococcus tauri, has shed light on this paradox. Remarkably, no signature of coupling to light can be detected in time series in condition of stable entrainment [1,2]. This indicates that when the clock is on time, coupling to light is scheduled at the precise time when it has no effect on the core circadian oscillator, just as when one experiences zero resistance when pushing a swing [1]. As a consequence, fluctuations in daylight are completely absorbed. Proper synchronization is however ensured by the fact that if the clock is not on time, coupling to light affects the clock at a time where it is responsive and thus can be reset [1].

Moreover, what makes a clock robust to daylight fluctuations can be analyzed in terms of its phase response curve, which characterizes how it reacts to a light perturbation at different times of the day. Depending on characteristic properties of this curve, such as curvature, a clock will be robust or not, and this can be quantified by analytical criteria [3]. Remarkably, phase response curves measured in a number of real organisms satisfy these criteria supporting the idea that robustness to daylight fluctuations is an evolutionary imperative for suitable clock functioning [3].

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Abstract No. 37

From a to alpha surfing microtubules: quantitative insight into budding yeast mating

Antonio Politi[a,*], Romain Gibeaux[b], Claude Antony[a], Michael Knop[b], and François Nédélec[a]

a European Molecular Biology Laboratory, Heidelberg, Germany
b Center for Molecular Biology (ZMBH), Heidelberg University, Germany
** politi@embl.de*

In yeast mating, two haploid cells of opposing mating type fuse to form a diploid cell. Cells first polarize and orient their nuclei, so that their microtubule organizing centers (SPB) face each other. After fusion of the plasma membrane the two nuclei congress and fuse. Although it is known that nuclear movement is mediated by cytoplasmic microtubules the exact mechanism of karyogamy remained so far unresolved. Two mechanisms have been proposed in the literature, microtubule plus-end coordinated depolymerization [1] and sliding of opposed microtubules [2]. We will show that a third way, where MT are captured by motors located on the partner SPB, may occur instead. Using mathematical modeling the efficiency of the different proposed mechanisms is compared and the role of motors on the plus-tip of microtubules is investigated.

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Abstract No. 38

A Phyllotactic approach to the structure of collagen fibrils

Jean Charvolin and Jean-François Sadoc

Laboratoire de Physique des Solides, Université Paris-Sud, CNRS UMR 8502, F-91405 Orsay,cedex, France.
sadoc@lps.u-psud.fr

Collagen fibrils, cable-like assemblies of long biological molecules, are dominant components of connective tissues. Their determinant morphological and functional roles motivated a large number of studies concerning their formation and structure. However, these two points are still open questions and, particularly, that of their organization which is certainly dense but not strictly that of a crystal. We examine here how the algorithm of phyllotaxy could contribute to the analysis of the structure of collagen fibrils. Such an algorithm indeed leads to organizations giving to each element of the assembly the most homogeneous and isotropic dense environment in a situation of cylindrical symmetry. The scattered intensity expected from a phyllotactic distribution of triple helices in collagen fibrils well agrees with the major features observed along the equatorial direction of their X ray patterns. Following this approach, the aggregation of triple helices in fibrils should be considered within the frame of soft condensed matter studies rather than that of molecular crystal studies.

Abstract No. 39

Replica symmetry in evolution under thermal noise

Ayaka Sakata[a,*], Koji Hukushima[b] and Kunihiko Kaneko[b]

a Department of Computational Intelligence and Science, Tokyo Institute of Technology, Yokohama, Japan
b Department of Basic Science, University of Tokyo, Tokyo, Japan
** ayaka@sp.dis.titech.ac.jp*

Biological functions are determined by phenotype, which is expressed through a dynamical process governed by genotypes. The genotypes that can achieve phenotypes with higher fitness are selected through the evolution. The expression dynamics of the phenotype is generally stochastic due to thermal noise, and the phenotypes of isogenetic organisms are not necessarily identical. To maintain the biological functions under the noisy environment, the phenotype should be insensitive to the noise. The evolution of the robustness considering the phenotypic fluctuation is an interesting subject.

We study the evolutionary process by introducing a statistical-mechanical model of spin-glass system. In our model, the configuration of spin variables $\boldsymbol{S}$ and their interaction variables $\boldsymbol{J}$ represent a phenotype and genotype, respectively. Time scales associated with $\boldsymbol{J}$ is extremely slow in comparison to that associated with $\boldsymbol{S}$, and it is considered that the interactions are fixed during the time evolution of the spins. Therefore, the equilibrium distribution of the spins is given by temperature T_S and Hamiltonian under a given $\boldsymbol{J}$. The interactions evolve to increase their fitness, which is given by the probability that specific spin configurations (target configurations) appear. We assume that the equilibrium state of the interactions given by temperature T_J and fitness is achieved after a long time evolution.

By following the replica method, the equilibrium property of the model is analyzed. It is found that the adaptation phase, in which target configurations appear, is obtained at $T_S < T_S^{RS}$. In particular, the replica symmetric adaptation phase appears in the intermediate T_S region, $T_S^{RSB} < T_S < T_S^{RS}$, when $T_J < 1$ [1]. The evolved interactions in this phase are less frustrated compared with the randomly constituted one. The results are consistent with our previous study with Monte Carlo simulation, in which the evolution of less-frustrated genotypes that provide a smooth expression of phenotype is implied [2].

The model at an intermediate temperature T_S describes the situation that the phenotype is not determined uniquely from the genotype. Our result implies the evolutional significance of the fluctuation in the phenotype expression. We will make a presentation about the detailed analysis of the model and the evolutional meanings of the replica symmetry in the intermediate temperature region.

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Abstract No. 40

Biological functionalisation of polymer surfaces for use in microresonator based biosensors

M. Salsac[a,*], H. Leh[a], C. Nogues[a], M. Buckle[a], J. Lautru[b], C. Delezoide[c], I. Ledoux[c], J. Zyss[c] and C.T. Nguyen[c].

a. Laboratory of Biology and Applied Pharmacology (LBPA), CNRS, Institut d'Alembert, ENS de Cachan.
b. Institut d'Alembert, ENS de Cachan.
c. Laboratory of Quantum and Molecular Photonics (LPQM) CNRS, Institut d'Alembert, ENS de Cachan.
** msalsac@lbpa.ens-cachan.fr*

The ability to detect, quantify and subsequently understand molecular interactions is essential for drug profiling, diagnostics, treatment and many major medical applications. Over recent years there has been an emergence of ever more compact, sensitive and fast biosensors [1, 2, 3, 4]. Our project is part of this trend, and has as its principal goal the development of a new biosensor based on optical microresonators. In collaboration with a research group in physics (LPQM – ENS Cachan) working on components and materials for photonics we are developing the optical detector/biological material interface.

Preliminary tests carried out on optical devices have confirmed that we have a sensitive signal in response to the presence of molecules on the microresonator surface. Our objective now is to functionalise these surfaces with appropriate detecting molecules, to ensure accurate and specific detection. A surface chemistry based on silane monolayers has been developed in our laboratory and will be adapted to the microresonator material for that purpose.

The developed biosensor is designed for a range of diverse applications, from the study of DNA-protein interactions –which constitutes a main interest in our research team – to other kinds of interactions, such as peptide-proteins, antigen-antibody, amongst others.

We aim to offer an efficient new tool, with a reduced time response for monitoring interaction process in real-time, together with the possibility to providing hitherto inaccessible information about conformational changes thanks to the use of the polarization properties of light that allow analysis of phase changes at a surface.

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Abstract No. 41

Environmental versatility promotes modularity in genome-scale metabolic networks

Areejit Samal[1,2,*], Andreas Wagner[3] and Olivier C. Martin[1,4]

[1] *Laboratoire de Physique Théorique et Modèles Statistiques, CNRS and Univ Paris-Sud, UMR 8626, F-91405 Orsay Cedex, France*
[2] *Max Planck Institute for Mathematics in the Sciences, Inselstr. 22, 04103 Leipzig, Germany*
[3] *Institute of Evolutionary Biology and Environmental Studies, University of Zurich, Winterthurerstrasse 190, CH-8057 Zurich, Switzerland*
[4] *INRA, UMR 0320/UMR 8120 Génétique Végétale, Univ Paris-Sud, F-91190 Gif-sur-Yvette, France*
** samal@mis.mpg.de*

The ubiquity of modules in biological networks may result from an evolutionary benefit of a modular organization. For instance, modularity may increase the rate of adaptive evolution, because modules can be easily combined into new arrangements that may benefit their carrier. Conversely, modularity may emerge as a by-product of some trait. We here ask whether this last scenario may play a role in genome-scale metabolic networks that need to sustain life in one or more chemical environments. We call a metabolic network viable in a given chemical environment, if it can synthesize all of an organism's biomass compounds from nutrients in this environment. An organism's metabolism is highly versatile if it can sustain life in many different chemical environments. We here ask whether versatility affects the modularity of metabolic networks.

Using recently developed techniques [1] to randomly sample large numbers of viable metabolic networks from a vast space of metabolic networks, we use flux balance analysis to study in silico metabolic networks that differ in their versatility. We find that highly versatile networks are also highly modular [2]. They contain more modules and more reactions that are organized into modules. Most or all reactions in a module are associated with the same biochemical pathways. Modules that arise in highly versatile networks generally involve reactions that process nutrients or closely related chemicals. We also observe that the metabolism of E. coli is significantly more modular than even our most versatile networks.

Our work shows that modularity in metabolic networks can be a by-product of functional constraints, e.g., the need to sustain life in multiple environments. This organizational principle is insensitive to the environments we consider and to the number of reactions in a metabolic network. Because we observe this principle not just in one or few biological networks, but in large random samples of networks, we propose that it is a generic principle of metabolic network organization.

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Abstract No. 42

Imaging domains and protein-lipid interactions in mixed lipid vesicles

Barbara Sarri*, Peter G. Petrov, Julian Moger and C. Peter Winlove

School of Physics, University of Exeter, Exeter EX4 4QL, United Kingdom
** bcms202@exeter.ac.uk*

The mechanical properties of cell membranes arise from their remarkable structural organisation. In order to better understand the origins of membrane elasticity, we study protein-lipid interactions in simple model lipid bilayer systems (giant vesicles). We investigate protein-lipid interactions and the effect of proteins on the membrane (micro)domain organisation of giant vesicles consisting of several lipid species. We use a label-free imaging technique, Coherent Anti-Stokes Raman Scattering (CARS), to image the lipid species, and Two-Photon Fluorescence (TPF) to visualise autofluorescent proteins. Protein adsorption onto the lipid membrane can thus be studied and 3D reconstruction allows the protein distribution around the vesicles to be investigated. The effects of proteins on the lateral lipid microdomain structure can also be studied.

CARS is a four-wave mixing process that uses vibrational signatures of atomic groupings [1]. To differentiate between different lipid species we use deuterated lipids whose carbon atoms have been replaced by deuterium atoms. This substitution does not change the chemical properties of the molecule but allows distinguishing between two fatty acid chains containing CH_2 and CD_2, respectively, because their vibrational modes are differents [2]. The model lipid membranes used are composed of lipid mixtures (DOPC, DPPC(d62) and cholesterol in varying amounts) and are phase-separated into microdomains of different composition.

The protein studied in this work is α-elastin. Elastin is a protein of the extra-cellular matrix and forms elastic fibres found in different tissues [3]. Lipid-elastin interactions are poorly understood but are important for the processes of secretion of tropoelastin and the early stages of fibril formation. In a more general context, understanding the interactions between proteins and bilayer lipid membranes is important for better appreciation of membrane mechanical properties [4].

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Abstract No. 43

Fragmented neutral spaces lead to contingency in evolution

Steffen Schaper*, Iain G. Johnston and Ard A. Louis

Rudolf Peierls Centre for Theoretical Physics, University of Oxford, Oxford, United Kingdom
** steffen.schaper@physics.ox.ac.uk*

Neutral networks (NNs) are sets of genotypes encoding the same phenotype which are connected by point mutations[1]. They provide the space that evolving populations can explore through neutral drift [2]. Many studies have highlighted the importance of these networks for evolutionary dynamics, linking them for example to robustness [3], evolvability [4] and speciation [5]. Central to their role in shaping fitness landscapes is their connectivity. Here we study a genotype-phenotype map in which the fragmentation of NNs is evident, namely RNA secondary structures. Compensatory mutations, an instance of reciprocal sign epistasis [6], lead to the existence of many neutral components (NCs). We argue that this fragmentation leads to contingency in evolution by demonstrating two facts: First, neither energy (fitness) nor entropy (abundance in genotype space) favours one NC over all others in an NN. Second, the potential for future innovations depends critically on the particular NC from which an population recruits its genotypes. Taken together, this implies that the course of evolution is contingent on random events (and initial conditions) which drive populations to specific areas of genotype space.

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Abstract No. 44

RNA Polymerase II Dynamics and Effects of Cohesin in Fission Yeast

Margarita Schlackow[a,*], Radek Erban[a] and Monika Gullerova[b]

a Oxford Centre for Collaborative Applied Mathematics, Oxford University, Oxford, UK
b Sir William Dunn School of Pathology, Oxford University, Oxford, UK
** margarita.schlackow@keble.ox.ac.uk*

RNA polymerase II (Pol II) transcribes DNA nucleotide sequence information into RNA sequence information called messenger RNA (mRNA). In order to dissociate from the DNA the polymerase needs to receive a signal. This signal is not well defined in the fission yeast *Schizosaccharomyces pombe.* Previous studies have shown that the cohesin (the protein responsible for binding the sister-chromatids) concentrates between convergent genes (genes facing each other) of the fission yeast [1]. The aggregation of cohesin forces the polymerase to terminate. However, the role of cohesin in Pol II kinetics remains poorly understood. It has been hypothesized that the cohesin can be pushed by RNA polymerase II along the chromosomes. We present a preliminary kinetic model for the interaction between cohesin and Pol II, which are written in terms of systems of differential equations or stochastic simulations [2]. We are currently evaluating how cohesin influences the transcription rate in time. The Gillespie Stochastic Simulation Algorithm can be used to study the effect of experimental noise on the model and indicate ways to optimise the experiments [3]. Experiments such as ChIP-on-chip, nuclear run-on assays and plasmid transformations are being used to parametrise the developed model.

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Abstract No. 45

How do cells perform arithmetic division?

Antonio Scialdone[a*], Martin Howard[a] , Sam Mugford[b] and Alison Smith[b]

a Dept. of Computational and Systems Biology, John Innes Centre, Norwich, UK
b Dept. of Metabolic Biology, John Innes Centre, Norwich, UK
** antonio.scialdone@bbsrc.ac.uk*

Cells are able to make vital decisions by sophisticated processing of molecular inputs. In some cellular processes the implementation of arithmetic operations on two molecular inputs can be required, e.g., to eventually produce a molecule at a concentration that is proportional to the sum or the product of the concentrations of two different molecular inputs. An important question to address concerns what mechanisms can lead to the implementation of the desired arithmetic operation.

Recent work [1] has shown that arithmetic division plays a fundamental role in the normal growth of the model plant *Arabidopsis thaliana*. In order to support its growth during the night, the plant relies on starch reserves that have been accumulated throughout the day: the starch is then linearly degraded during the night, at a rate that ensures the exhaustion of starch reserves at the time of expected dawn, when photosynthesis begins again. Remarkably, the plant adjusts the degradation rate in response to an unexpected early or late night: the degradation rate d, is set on the basis of the amount of starch stored, S, and the time to next dawn, t, such that $d=S/t$. How is the plant able to perform such arithmetic division?

We present different general mechanisms that the cell can exploit to implement arithmetic division between two molecular inputs, both at transcriptional and post-translational levels. Experiments to assess the specific mechanism that is working *in vivo* are discussed, with a focus on the case of *Arabidopsis.*

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Abstract No. 46

DnaA and the timing of DNA replication in E. coli as a function of growth rate

Matthew Grant [a], Chiara Saggioro [b], Ulisse Ferrari [c], Bruno Bassetti [d], Bianca Sclavi [b,*], Marco Cosentino Lagomarsino [e]

a Department of Physics, Cambridge University, Cambridge, UK
b LBPA, UMR 8813, CNRS/ENS Cachan, Cachan, France
c Dip. Fisica, Università La Sapienza, Rome, Italy
d Fisica Teorica, Università degli Studi di Milano, Milano, Italy
e Genomic Physics Group, FRE 3214 CNRS/UPMC, Paris, France
** sclavi@lbpa.ens-cachan.fr*

In *Escherichia coli* overlapping rounds of DNA replication allow the bacteria to achieve doubling times that are faster than the time required to copy the genome. The precise timing of initiation of DNA replication is determined by a regulatory circuit that depends on the binding of a critical number of DnaA-ATP proteins at the origin of replication resulting in the melting of the DNA and the assembly of the replication complex. The synthesis of DnaA in the cell is controlled by a growth-rate dependent, negatively autoregulated gene found near the origin of replication. The activity of the protein depends on its nucleotide bound state and its availability compared to the number of nonspecific binding sites on the genome, both of which are dependent on the rate of DNA replication.

In order to obtain an improved understanding of the contribution of the different regulatory processes in the timing of initiation of DNA replication as a function of growth rate we formulate a minimal quantitative model of the initiator circuit that includes the key ingredients known to regulate the activity of the DnaA protein. This model can describe the oscillations in DnaA-ATP/DNA as a function of the cell cycle, achieving the same maximum value at the time of initiation independently of the growth rate by a continuous change in the value of the parameters controlling the rate of DnaA synthesis. We compare different possible scenarios to characterize the roles of DnaA autoregulation and of the DnaA-bound ATP-hydrolysis regulatory process under different growth conditions.

A continuous increase in the rate of DnaA gene expression dependent on the growth rate of the cell can account for the timing of initiation of DNA replication at different cell doubling times. Auto-repression of the DnaA gene is not required for this model to work and the rate of RIDA can be varied 10 fold without significantly affecting the outcome. Both RIDA and auto-repression however can contribute to dampen the amplitude of the oscillations of DnaA-ATP/DNA during the cell cycle and result in a smaller range in the change of the average amount of DnaA-ATP per genome equivalent as a function of growth rate. This is required if DnaA's activity as both the initiator of DNA replication and as a transcription factor is to reflect the status of the DNA replication process in response to perturbations of the replication forks independently of the growth rate.

Abstract No. 47

Long-term Evolutionary Constraints on Signaling Pathways Implicated in Cancer

Param P. Singh[a *] & Hervé Isambert[a]

a *Institut Curie, Physico-Chimie Curie, UMR 168 (CNRS-UPMC), 11 P. & M. Curie, 75005 Paris, France*
** Param-Priya.Singh@curie.fr*

Gene duplication and subsequent diversification are believed to play a major role in evolution. The continuous process of duplication-divergence has made it possible to create complex organisms like vertebrates from relatively simple unicellular organisms [1]. Among one of the most striking events in the evolutionary history of an organism are whole genome duplication (WGD) events, which have now been firmly established in all major eukaryote kingdoms. WGDs are rare but dramatic genome doubling transitions leading to two fold genetic redundancy. It has now been established by comparative genomic studies that the common ancestor of vertebrates also underwent two WGDs some 500 MY ago. These WGDs have shaped vertebrate genomes and bio-molecular networks. More generally, duplication and deletion processes at various genomic scales have restricted, by construction, the emergent properties of biomolecular networks at a broad systemic level [2–5].

In the present work[6], we explore the evidence supporting the role of non-adaptive functional auto-inhibition constraints on the evolution of signaling pathways implicated in cancer development and progression. We have analyzed the consequences of oncogenic mutations on the evolutionary fates of gene duplicates arising from two WGDs. Our preliminary results, suggest that signaling pathways implicated in cancer have been largely shaped by these two WGDs with significant retention of ohnologs. Furthermore, oncogenes in these pathways with functional auto-inhibitory constraints appear to have retained more ohnologs than the ones without such constraints suggesting that the expansion and the emergent properties of these signaling pathways have been largely shaped by non-adaptive constraints.

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Abstract No. 48

Photocontrol of protein activity in a single cell of a live organism

Deepak Kumar Sinha[a *], David Bensimon[a,b] Ludovic Jullien[c] and Sophie Vriz[d]

a Ecole Normale Sup´erieure, Laboratoire de Physique Statistique, Paris, France.
b Department of Chemistry and Biochemistry, UCLA, Los Angeles, USA
c Ecole Normale Sup´erieure, D´epartement de Chimie, Paris 05, France.
d Collège de France, paris and Université Paris 7 - Denis Diderot
** emaildks@gmail.com*

Each cell in multicellular organisms constantly responds to external signals by modifying it's internal state and environment. For example, during development, cellular differentiation and intra-cellular signaling are essential for the coordinated development of the organism. The spatio-temporal dynamics of these complex interaction networks is one of the most challenging problems in biology. An era of developmental biology has revealed a repertoire of molecules playing crucial roles during development. However, advancing the quantitative assessment of their interactions (affinities, rate constants, strength of non linearities etc.) and the rules governing them, require not only visualization of these proteins at the single cell level in the living organism through various stages of development but also the means to control or interfere spatially and temporally with the activity of these proteins.

In this poster, I will describe a multidisciplinary non-invasive optical strategy to control protein activity and gene expression in live zebrafish embryos as well as cells in culture with the spatial resolution down to single cell.

Our method constitutes of three components: 1) the dependence of biological activity of a protein fused to estrogen receptor on the binding state of the estrogen to its chaperone, 2) the chemical inertness and the permeability of the cell membrane to non-endogeneous caged inducers and 3) the selective optical uncaging of inducers in zebrafish embryos with up to single cell resolution using two photon microscopy.

We demonstrate the use of this technique to control protein activity in two different contexts: 1) the activation of the nuclear translocation of two different fluorescent proteins in zebra fish embryo and cell cultures, and 2) the activation of the Cre recombinase activity in an appropriate transgenic animal to genetically label a single cell of the embryo.

We believe that the ability of our method to change the protein activity or genetic map of selective cells in embryos could be applied more widely to investigate physiological processes (in embryogenesis, organ regeneration and carcinogenesis) with high spatio-temporal resolution.

Abstract No. 49

Path Influence Quantification for signaling networks and its application for mathematical modeling of Ewing sarcoma

Gautier Stoll[a,b,c,*], Emmanuel Barillot[a,b,c] and Andrei Zinovyev[a,b,c]

a Institut Curie, 26 rue d'Ulm, Paris, F-75248 France;
b INSERM, U900, Paris, F-75248 France;
c Mines ParisTech, Fontainebleau, F-77300 France.
** gautier.stoll@curie.fr*

Ewing sarcoma is the second most frequent pediatric bone tumor. It is shown that most of Ewing tumors share the same genetic abnormality: a chromosomal translocation inducing the expression a chimeric transcription factor, EWS-FLI1. In addition, EWS-FLI1 alone appears to be able to induce tumorigenesis in cellular models.

In this context, a signaling network downstream of EWS-FLI1 has been constructed [1]. It describes EWS-FLI1 effects on proliferation and apoptosis. It has been build using selection of genes from experiments on inducible cellular systems. Qualitative connections between genes were introduced by mining biological literature and the network was further refined by applying reverse engineering methods to data on systematic knock-down perturbations of the network. The resulting influence network is available in the form of a Cytoscape file.

The size of the network (107 nodes) precludes from applying the traditional mathematical modeling approaches (ODEs, Boolean models, etc.). Because of this, a simple method for confronting biological data with an influence network has been developed: Path Influence Quantification (PIQuant).

This method is implemented as a part of BiNoM Cytoscape plugin [2]. Briefly, it sums up influences along all possible paths in the network. Path influence is defined from the activity value of its source node, path length and path sign.

PIQuant was applied in the context of Ewing sarcoma, using the influence network (and its refined version), gene expression data from inducible cell-lines and from tumor biopsies. It produced:

- Coherence tests between influence network (and refined version) and cell-lines data
- Coherence tests between refined influence network and tumor biopsies
- Extraction of sub-network for further mathematical modeling
- Potential therapeutic targets

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Abstract No. 50

Learning the nonlinear interactions from particle trajectories

Pavel M. Lushnikov[a], Petr Šulc [b*] and Konstantin S. Turitsyn[c]

a) Department of Mathematics and Statistics, University of New Mexico, Albuquerque, NM, 87131, USA
b) Rudolf Peierls Centre for Theoretical Physics, University of Oxford, Oxford OX1 3NP, UK
c) Department of Mechanical Engineering, Massachusetts Institute of Technology, Cambridge, MA, 02139, USA
** p.sulc1@physics.ox.ac.uk*

Nonlinear interaction of membrane proteins with cytoskeleton and membrane leads to non-Gaussian structure of their displacement probability distribution. We propose a statistical analysis technique for learning the characteristics of the nonlinear potential from the cumulants of the displacement distribution. The efficiency of the approach is demonstrated on the analysis of kurtosis of the displacement distribution of the particle traveling on a membrane in a cage-type potential. Results of numerical simulations are supported by analytical predictions. We show that the approach allows robust identification of the potential for the much lower temporal resolution compared with the mean square displacement analysis.

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Abstract No. 51

NF-kB inflammatory response and excitable media

Pernille Yde[a], Mogens H. Jensen[a] , Sandeep Krishna[a], Benedicte Mengel and Ala Trusina[a*]

a CMOL, Niels Bohr Institute, Copenhagen, Denmark
** trusina@nbi.dk*

Waves propagating in “excitable media” is a reliable way to transmit signals in space. A fascinating example where living cells comprise such a medium is Dictyostelium D. which propagates waves of chemoattractant to attract distant cells. While neutrophils chemotax in a similar fashion as Dictyostelium D., it is unclear if chemoattractant waves exist in mammalian tissues and what mechanisms could propagate them.
We propose that chemoattractant cytokine waves may naturally develop as a result of NF-κB response. Using a heuristic mathematical model of NF-κB-like circuits coupled in space we show that the known characteristics of NF-κB response favor cytokine waves.
While the propagating wave of cytokines is generally beneficial for inflammation resolution, our model predicts that there exist special conditions that can cause chronic inflammation and re-occurrence of acute inflammatory response.

Abstract No. 52

Matching of RNA-type sequences and statistical analysis of random RNA

Nechaev S.K.[a], Tamm M.V.[b] and Valba O.V.[a*]

a LPTMS, Univescity Paris Sud, Orsay, France
b Physics Department, Moscow State University, Moscow, Russia
** valbaolga@gmail.com*

We developed and implemented a new statistical algorithm for quantitative determination of the binding free energy of two heteropolymer sequences under the supposition that each sequence can form a hierarchical cactus–like secondary structure, typical for RNA molecules. We offered a constructive way to build a "cost function" characterizing the matching of two RNAs with arbitrary primary sequences. The substantial difference of this procedure from the convenient sequence comparison is that in RNA case we not only align the sequences of nucleotides which constitute pairs between two RNAs, but also take into account the secondary structure of the parts of RNA between the aligned nucleotides. The proposed algorithm is based on two facts: i) the standard alignment problem can be reformulated as a zero–temperature limit of more general statistical problem of binding of two associating heteropolymer chains; ii) the last problem can be straightforwardly generalized onto the sequences with hierarchical cactus–like structures (i.e. of RNA–type). Taking zero–temperature limit at the very end we arrive at the desired ground state free energy with account for entropy of side cactus–like loops [1].

Using this algorithm we studied different statistical properties of random RNA sequences such as average free energy, fluctuation and loop distribution for both linear and cactus–like structures formed by two interacting RNA. We received that without limitation on the minimal loop length cactus-like structures are characterized by the very high possibility of binding of about 0.92. For explanation this effect a new hierarchical model for determination average free energy of two interacting random RNA was proposed. The model showed a good agreement with the numerical experiments for cactus-like structures and allowed us to suppose a critical behavior for approaching the possibility of binding in alphabetic sequences to 1. We found that if number of different letters in alphabetic sequences "c" is more than the critical value of 4, average free energy will be always less than 1. The interesting effect is observed for the critical "c"; for finite sequence length the possibility of binding in cactus-like structures is always less than 1, but it equals 1 at infinity.

Fluctuation for both linear and cactus-like structures belongs to the KPZ universality class. It allowed us to firstly detect phase transition for random RNA by temperature behavior of fluctuation.

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