

Self-assembly and Self-organization in Computer Science and Biology

Edited by

Vincent Danos¹ and Heinz Koepl²

1 University of Edinburgh, GB, vdanos@inf.ed.ac.uk

2 TU Darmstadt, DE, heinz.koepl@bcs.tu-darmstadt.de

Abstract

This report documents the program and the outcomes of Dagstuhl Seminar 15402 “Self-assembly and Self-organization in Computer Science and Biology”. With the trend of technological systems to become more distributed they tend to resemble closer biological systems. Biological systems on all scale are distributed and most often operate without central coordination. Taking the morphogenesis as an example, it is clear that the complexity and precision of distributed mechanisms in biology supersedes our current design attempts to distributed systems. The seminar assembled together researchers from computer science, engineering, physics and molecular biology working on the problem of decentralized coordination of distributed systems. Within every domain different terms have been coined, different analysis methods have been developed and applied and the seminar aims to foster the exchange of methods and the instantiation and alignment of important problem statements that can span across the disciplines. A representative example for a problem that is studied across domains through different methods is self-assembly. For example, computer scientists consider abstract self-assembly models such as Wang tiles to bound shape complexities while polymer physicists and biologists use molecular dynamics simulations to characterize self-assembly by means of energy and entropy. Because of its well-definedness, we deliberately placed emphasis on self-assembly that is otherwise entailed in the more general term self-organization. Within the domain of self-organization various research threads were represented at the seminar and a certain convergence of underlying concepts was possible. The seminar helped to exchange techniques from different domains and to agree on certain problem statements for future collaborations.

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1 Executive Summary

Heinz Koepl

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The Seminar brought together researchers from molecular biology, molecular modeling and theoretical computer scientists with interest in formal models of molecular computation and self-organization. Molecular biology provides a rich substrate to implement molecular computation and complex self-assembly algorithms. The Seminar featured several talks



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on DNA-assembly systems, that to-date represents the most advanced molecular substrate for self-assembly. The increase in the achievable complexity of such molecular structures asks for a formal description and analysis of those systems using methods from theoretical computer science. The Seminar was successful in identifying common problem statements and in establishing a common scientific language. Apart from self-assembly, the broader term self-organization was mostly represented by research on swarming or self-propelled particle (SPP) models. The common feature of SPP systems and self-assembly is the emergence of global structures through local interaction rules (self-assembled structure vs swarms or flocks). One contribution also featured the combination of swarming and self-assembly system in terms of nucleation studies. Moreover, novel methodological overlap between simulation algorithms for molecular self-assembly and simulation algorithms for SPP systems were identified and elaborated during the workshop.

The seminar was structured as a regular workshop with morning and afternoon sessions but plenty of time was allocated for discussions after each talk. For the first such Dagstuhl Seminar no working groups were defined. For follow-up Seminars on the same topic we aim to additionally define working groups that may also deliver preliminary research results and initiation of new collaborations.

Although the workshop was very interdisciplinary we were able to arrange the presentations into sessions of a coherent theme. The feedback of participants was extremely positive, stating that they could really profit from the technical discussions that accompanied every presentation and that were performed in the free time. Correspondingly, several new collaborations across disciplines were initiated at the seminar.

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3 Overview of Talks

3.1 Engineering Self-Organization: From Networking to Synthetic Biology

Jacob Beal (BBN Technologies – Cambridge, US)

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Emerging methods for aggregate programming can greatly simplify the engineering of complex self-organizing systems. The foundation of this approach is field calculus, which provides guaranteed local-to-global mapping and encapsulation of distributed processes. Building on this foundation, composable “building block” algorithms provide resilience guarantees, and are then packaged into accessible APIs that can make the engineering of complex self-organizing systems as simple as the engineering of single-machine programs. These methods are already being applied into electronic networked systems. In order to effectively engineer complex self-organization behaviors with biological organisms, however, the performance and predictability of cellular information processing must be improved. Toward this end, I will review key recent advances in the enabling technologies of biological design automation, CRISPR-based repressor families, and device modeling based on calibrated flow cytometry.

3.2 Self-Organized Actin Patterns in Motile Amoeboid Cells

Carsten Beta (Universität Potsdam, DE)

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Joint work of Beta, Carsten; Gerhardt, Matthias; Nagel, Oliver; Walz, Michael; Ecke, Mary; Stengl, Andreas; Gerisch, Günther

Main reference M. Gerhardt, M. Ecke, M. Walz, A. Stengl, C. Beta, G. Gerisch, “Actin and PIP3 waves in giant cells reveal the inherent length scale of an excited state”, *Journal of Cell Science*, Vol. 127, pp. 4507–4517, 2014.

URL <http://dx.doi.org/10.1242/jcs.156000>

Main reference M. Gerhardt, M. Walz, C. Beta, “Signaling in chemotactic amoebae remains spatially confined to stimulated membrane regions,” *Journal of Cell Science*, Vol. 127, pp. 5115–5125, 2014.


URL <http://dx.doi.org/10.1242/jcs.161133>

Numerous cellular functions like cell motility, phagocytosis, and division depend on the coordinated formation of functional cytoskeletal structures that exhibit characteristic length and time scales. Here, we focus on self-organized wave patterns that emerge in the substrate-attached actin cortex of motile cells of the social amoeba *Dictyostelium discoideum*. We use electric pulse-induced cell fusion to generate giant polynuclear *Dictyostelium* cells that allow us to observe the wave patterns in a large spatially extended actin cortex, independent of confinement due to limited cell size. We found that waves consist of a PIP3-rich band enclosed by an actin-rich border, i.e., they are composite structures involving both the actin cortex and the composition of the adjacent membrane. They travel across the substrate-attached membrane with a constant speed and display a self-organized width on the order of μm that remains constant independent of the cell size. Also the formation of rotating spiral waves was observed. Upon head-on collision, they mutually annihilate and, thus, show all the typical properties of an excitable system. To investigate whether localized receptor stimuli can induce the spreading of excitable waves, we delivered spatially confined stimuli of the chemoattractant cAMP to the cell membrane. To generate localized cAMP stimuli, either

particles coated with covalently bound cAMP molecules were brought into contact with the cell membrane or a patch of the membrane was aspirated into a glass micropipette to shield this patch against freely diffusing cAMP molecules in the surrounding medium. By imaging the spatiotemporal dynamics of fluorescent markers for PIP3, PTEN and filamentous actin, we observed that the signaling activity remained spatially confined to the stimulated membrane region. Neighboring parts of the membrane that were not exposed to cAMP did not show any sign of excitation, i.e., no receptor-initiated spatial spreading of excitation waves was observed. Finally, we showed data on the transport of micron-sized objects by Dictyostelium cells, demonstrating that motile amoeboid cells can function as small trucks that transport micro-cargo to a desired location.

3.3 Optimizing the Assembly of Stacked Rings

Koan Briggs (University of Kansas, US)

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Joint work of Briggs, Koan; Deeds, Eric

Many macromolecular machines inside the cell exhibit a stacked ring architecture, with multiple uniform-length rings of protein subunits bound to one another. The majority of these machines must adopt their fully assembled quaternary structure in order to function, making the assembly process vital for cellular function and survival. The assembly of protein complexes containing stable substructures has been shown to suffer from a type of kinetic trapping that we term assembly deadlock, which occurs when smaller intermediates are exhausted from the system before all of the fully functional structures have formed. Deadlock can result in plateaus in the assembly dynamics, leading to delays in reaching maximum complex assembly and a reduced final complex concentration. While these plateaus have been extensively studied for simple rings, the effect of assembly deadlock on more general structures like stacked rings remains to be fully investigated. In this work, we focused on the case of a stacked homotrimer; this structure contains both three- and four-member rings as substructures, but is simple enough to allow for extensive investigation. Our mathematical models revealed that this structure could suffer from extreme deadlock that significantly reduces the efficiency of assembly. Using a computationally efficient deterministic simulation approach, we exhaustively analyzed the parameter space of self-assembly for this case, and found that the number and duration of plateaus in the assembly dynamics depended strongly on the pattern of affinities in this structure. Since these complexes are generally only functional when fully assembled, we hypothesized that existing stacked ring architectures would evolve to utilize the most efficient assembly pathways predicted by our models. Analysis of interfaces in solved crystal structures of stacked homotrimers confirmed this prediction. Our findings have important implications for understanding how assembly dynamics have influenced the structural evolution of large macromolecular machines.

3.4 Swarming Models with Repulsive-Attractive Effects

Jose Antonio Carillo (Imperial College London, GB)

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I gave an overview of the different levels of description of collective behavior models highlighting some of the interesting mathematical open problems in the subject. Calculus of variations, dynamical systems, mean-field limits for PDEs, kinetic and aggregation-diffusion equations naturally show up as necessary tools to solve some of these questions.

3.5 Three-Dimensional Swarming States Induced by Hydrodynamic Interactions

Maria Rita D'Orsogna (California State University – Northridge, US)

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Swarming patterns arising from self-propelled particles have been extensively studied, particularly in two-dimensions and in the absence of an embedding medium. We consider the dynamics of more realistic three dimensional self-propelled particles interacting in a fluid medium. The fluid interaction terms generated by direct short-ranged pairwise interactions may impart much longer-ranged hydrodynamic forces, effectively amplifying the coupling between individuals. We consider two limiting cases of fluid interactions, a “clear fluid” where particles have direct knowledge of their own velocity, that of others and of the fluid, and an “opaque fluid” where particles are able to determine their velocity only in relation to the surrounding fluid flow. We discuss emergent patterns that are unstable in fluid-free environments and that become stabilized by opaque fluid couplings such as rotating mills.

3.6 If I had a Hammer . . .


Hanno Hildmann (NEC Laboratories Europe – Heidelberg, DE)

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My talk is about the proverbial hammer with which one would like to address all proverbial nails, and specifically and in the context of this seminar, about the nature inspired mechanisms used to design self-organization into the solutions we have worked on at NEC and at BT's EBTIC. I will talk about a variety of projects which have all been approached with a few different techniques. I will also discuss these techniques and highlight their common elements as well as the parts in which they differ. The “if” part of the title refers to the fact that the aim of this seminar is to discuss a variety of techniques and that I am interested to engage in a discussion with the other participants about other / new techniques I could learn.

3.7 Porphyrins, Pyrazinacenes and Oxoporphyrinogens: Supramolecular (and other) Effects

Jonathan P. Hill (National Institute for Materials Science – Ibaraki, JP)

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Self-assembly of molecules implies intermolecular processes that can involve hydrogen bonding, van der Waals interactions (e. g. pi-pi stacking), amphiphilicity, coordination chemistry and combinations of these. Here, we will discuss assembly processes of porphyrins, pyrazinacenes and oxoporphyrinogens (amongst others) including how their structures affect the final self-assembly form and any dynamic processes occurring in the structures. These include investigations of supramolecular activity at surfaces and in solutions. For instance, charge transfer within a supramolecular manifold, surface assembly of porphyrin trimers and chiral processes at surfaces and in solution will be presented.

3.8 Statistical Inference of Cellular Behaviour from Heterogeneous Single-Cell Data

Heinz Koepl (TU Darmstadt, DE)

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Modeling and inferring stochastic biomolecular processes based on single-cell data requires an extension of the traditional Markov chain description to account for the random molecular environment into which the process of interest is embedded. In particular, we seek an isolated process model that behaves as if the process was still embedded into the molecular environment. Based on that novel process model we develop a Bayesian inference framework that resorts to traditional MCMC schemes in combination with sequential Monte Carlo techniques. We apply the framework to live-cell imaging data of a inducible gene expression system in budding yeast and show that it allows to separate intrinsic from extrinsic noise components from single measurements without the need for dedicated dual-color constructs.

3.9 Self-propelled Chimeras

Nikita Kruk (TU Darmstadt, DE)

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Joint work of Kruk, Nikita; Maistrenko, Yuri; Wenzel, Nicolas; Koepl, Heinz
Main reference N. Kruk, Y. Maistrenko, N. Wenzel, H. Koepl, “Self-propelled Chimeras,” arXiv:1511.04738v1 [nlin.AO], 2015.

URL <http://arxiv.org/abs/1511.04738v1>

The appearance of chimera states in a minimal extension of the classical Vicsek model for collective motion of self-propelled particle systems is presented. Inspired by earlier works on chimera states in the Kuramoto model, a phase lag parameter in the particle alignment dynamics is introduced. Compared to the oscillatory networks with fixed site positions, the self-propelled particle systems can give rise to distinct forms of chimeras resembling moving flocks through an incoherent surrounding, for which their parameter domains are

characterized. More specifically, localized directional one-headed and multi-headed chimera states, as well as scattered directional chimeras without space localization are detected. Canonical generalizations of the elementary Vicsek model are discussed and chimera states for them indicating the universality of this novel behavior are shown. A continuum limit of the particle system is derived that preserves the chimeric behavior.

3.10 Principles of Protein Self-Assembly in the Cell

Emmanuel Levy (Weizmann Institute of Science – Rehovot, IL)

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A single yeast cell is a few microns in diameter and yet contains about a hundred million proteins. Interactions between these proteins are crucial for the self-organization of the cell and its ability to perform cellular functions. While much information exists on the identity of protein interactions and complexes, little is known about their higher-order organization in living cells. We will present work that aims to better understand this high-order organization. First, we will describe a strategy that we have been developing to probe the local environment of proteins in cells (functional interactions). Second, we will present an analysis where we assess the potential of single point mutations to trigger unwanted interactions, leading to uncontrolled protein super-assembly (dysfunctional interactions). Finally, we will present a minimal protein system that we engineered to model and better understand principles protein self-assembly at the micron scale.

3.11 Chimera State: A Novel Paradigm of Nonlinear Science

Yuri Maistrenko (National Academy of Sciences of Ukraine – Kiev, UA)

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Joint work of Larger, L.; Penkovsky, B.; Sudakov, O.; Osiv, O.; Maistrenko, V.

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URL <http://dx.doi.org/10.1088/1367-2630/17/7/073037>

Chimera is a rich class of self-organized solutions developed spontaneously in high dimensional networks with non-local and symmetry breaking coupling features, in which synchronous and asynchronous oscillations co-exist. Its accurate understanding is expected to bring important insight in many complex spatiotemporal phenomena, from living and mechanical systems to optics and turbulence. Chimera state was discovered in 2002 by Kuramoto and Battogtokh for the complex Ginzburg-Landau equation and its phase approximation, the Kuramoto model. Currently, this is an area of intense theoretical and experimental research, for now, chimeras have been found in many systems from various fields. In the lecture, different aspects of chimera state in one-, two- and three-dimensions have been discussed. The main attention was paid on a highly controllable experiment based on optoelectronic delayed feedback applied to a wavelength tunable semiconductor laser and modelled by a modified Ikeda equation. For the system, a wide variety of chimera patterns of different modality is found and interpreted.

The model simulations generate behavior in an excellent qualitative agreement with that exhibited in the experiment. The presentation is illustrated by 3-Dim videos of the complex spatiotemporal chimera dynamics.

3.12 Cell-Free Transcription-Translation: From Gene Circuits to Self-Assembly in a Test Tube

Vincent Noireaux (University of Minnesota – Minneapolis, US)

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Joint work of Noireaux, Vincent; Shin, Jonghyeon; Caschera, Filippo

Main reference J. Shin, V. Noireaux, “An E. coli Cell-Free Expression Toolbox: Application to Synthetic Gene Circuits and Artificial Cells,” *ACS Synthetic Biology*, 1(1):29–53, 2012.

URL <http://dx.doi.org/10.1021/sb200016s>

Cell-free transcription-translation (TX-TL) systems are becoming powerful platforms to construct biochemical systems in vitro through the expression of synthetic gene circuits. In the past decade, considerable efforts have been made to expand the capabilities of those systems. My lab has worked on expanding the transcription repertoire of cell-free expression systems, traditionally based on the T7 RNA polymerase and promoter, to go beyond just in vitro protein production. We developed an all E. coli platform so as to use 10s or 100s of regulatory parts for the construction, execution and characterization of gene circuits outside living cells in either test tube reactions, microfluidics or liposomes. New metabolisms energize gene expression for 8-10 hours to reconstruct complex active biological systems. For example, the phages T7 and phix174 are synthesized in cell-free TX-TL reactions from their genomes. Both phages serve as model systems to study the relationship information to self-assembly. Encapsulated inside cell-sized phospholipid liposomes, the cell-free TX-TL system is used to construct a minimal cell using a bottom-up approach. I will present this cell-free synthetic biology platform and our last experiments.

3.13 Theoretical Modeling of Algorithmic Self-Assembling Systems

Matthew J. Patitz (University of Arkansas – Fayetteville, US)

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An introduction to tile-based algorithmic self-assembly will be presented, starting with Winfree’s abstract Tile Assembly Model (aTAM). A series of aTAM results are surveyed, followed by a description of derivative models, such as the 2-Handed Assembly Model, along with related results. Special emphasis is given to results relating to computational universality and intrinsic universality.

3.14 DNA-Based Programmable Molecular Devices

John H. Reif (Duke University – Durham, US)

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My talk overviews the use of self-assembly techniques for the construction of DNA nanostructures from strands of synthetic DNA, and the use of chemical reactions on DNA (such as strand-displacement reactions) to allow for molecular devices to operate in a programmable manner. First we overview our prior work: - The self-assembly of DNA lattices from DNA tiles and its use for executing molecular computations is described. - Also, our experimental demonstrations of autonomous DNA devices that walk on DNA nanostructures are described. Then various techniques for executing molecular computations currently being developed in my lab will be overviewed, including: - Activatable tiles: which are initially inactive, and then can be activated when needed. - Time-responsive see-saw gates: which can be reset to be reused for multiple computations, - Analog gates: which compute (with inputs and outputs encoded as reactant concentrations) arithmetic operations over the reals. - DNA origami Transformers: which allow DNA origami to be transformed via strand-displacement reactions.

3.15 Thermostat Methods for Canonical Sampling

Matthias Sachs (University of Edinburgh, GB)

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Joint work of Leimkuhler, Benjamin; Matthews, Charles; Sachs, Matthias

The talk comprises a general introduction to stochastic thermostat methods for canonical sampling in molecular dynamics and beyond. I will introduce stochastic thermostats as ergodic extensions of Newton's equations. A particular focus will be on so-called adaptive thermostats i.e. thermostats which still maintain ergodicity with respect to the Gibbs-Boltzmann distribution even if the dynamics of the system are perturbed by external noise.

3.16 Models and Algorithms for Programmable Matter

Christian Scheideler (Universität Paderborn, DE)

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Joint work of Derakhshandeh, Zahra; Gmyr, Robert; Strothmann, Thim; Bazzi, Rida; Richa, Andrea; Scheideler, Christian

Consider programmable matter consisting of simple computational elements, called particles, that can establish and release bonds and can actively move in a self-organized way. I will present a basic model and first results concerning the feasibility of solving basic problems relevant for such programmable matter. As a model, I will use a general form of the amoebot model first proposed in SPAA 2014. Based on that model, efficient local-control algorithms for leader election and line formation requiring only particles with constant size memory are presented, and the limitations of solving these problems within the amoebot model are discussed. The details of this talk can be found in [1].

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3.17 Inverse Reinforcement Learning in Swarm Systems

Adrian Sosic (TU Darmstadt, DE)

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Inverse reinforcement learning (IRL) is the problem of recovering a system’s latent reward function from observed system behavior. In this paper, we concentrate on IRL in homogeneous large-scale systems, which we refer to as swarms. We show that, by exploiting the inherent homogeneity of these systems, the IRL objective can be reduced to an equivalent single-agent problem of constant complexity, allowing us to decompose a global system objective into local subgoals at the agent-level. Based on this, we reformulate the corresponding optimal control problem as a fix-point problem pointing towards asymmetric Nash equilibrium, which we solve using a novel heterogeneous learning scheme particularly tailored to the swarm setting. Results on the Vicsek model and the Ising model demonstrate that the proposed framework is able to produce meaningful reward models from which we can learn near-optimal local policies that replicate the observed system dynamics.

3.18 Rule-Based Modeling of Graph-Like Systems

Sandro Stucki (EPFL – Lausanne, CH)

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Joint work of Danos, Vincent; Heindel, Tobias; Honorato-Zimmer, Ricardo; Jaramillo-Riveri, Sebastian; Stucki, Sandro

Rule-based modeling (RBM) is a paradigm for describing combinatorially complex stochastic processes with an underlying network structure through a finite set of rewrite rules. In this talk, I will give an overview of RBM – illustrating how it can be used to model biological processes in particular – and present some recent work on generating rate-equations and ODEs tracking higher-order statistics from a large class of rule-based systems, as well as an extension of the formalism for modeling steric constraints in molecular self-assembly.

3.19 Coarse-Grained Modelling for Self-Assembly

Petr Šulc (*Rockefeller University – New York, US*)

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Joint work of Šulc, Petr; Romano, Flavio; Ouldrige, Thomas; Louis, Ard; Doye, Jonathan; Matek, Christian; Rovigatti, Lorenzo

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URL <http://dx.doi.org/10.1063/1.4881424>

We introduce coarse-grained models of DNA and RNA. The models are developed to capture the basic thermodynamics, mechanics and structural properties of DNA and RNA, including the formation of duplex from two single strands. The models are primarily developed for applications in DNA and RNA nanotechnology, but can be used as well for biophysical properties of the molecules. We describe the model development and parametrization, and provide estimates of computational efficiency. We further provide examples of applications of the models, including strand displacement reactions with DNA and RNA, DNA hybridization, the effects of secondary structure on duplex formation, RNA supercoiling, unzipping of an RNA hairpin and RNA pseudoknot folding thermodynamics.

3.20 Effects of Time-delays and Plasticity in Neural Networks

Serhiy Yanchuk (*Weierstraß Institut – Berlin, DE*)

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Joint work of Yanchuk, Serhiy; Popovych, Oleksandr; Tass, Peter

Main reference O. V. Popovych, S. Yanchuk, P. A. Tass, “Self-organized noise resistance of oscillatory neural networks with spike timing-dependent plasticity,” *Science Reports*, Vol. 3, Article No. 2926, 2013.

URL <http://dx.doi.org/10.1038/srep02926>

I split my talk into two parts. Part 1. I firstly review basic properties of systems with time-delays and their implementation with delay-differential equations. In large neural networks, delays can be important for determining spiking patterns and play crucial role for information processing. With the use of time-shift transformation, one can reduce the number of time-delays in the network to the number of independent cycles. In such a situation, the “effective delays”, which determine the dynamics, are given by the sums of time-delays along any independent closed cycle [1]. Part 2. The second topic, which I mention in my talk is the effect of STDP – spike timing-dependent plasticity on the dynamics of noisy neuronal networks. In particular, STDP may produce the resistance to noise. In such a situation, the network with STDP reacts to an application of noise by adjusting the average level of the coupling weights so that the necessary level of synchronization is maintained [2].

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Participants

- Jacob Beal
BBN Technologies –
Cambridge, US
- Carsten Beta
Universität Potsdam, DE
- Koan Briggs
University of Kansas, US
- José Antonio Carillo
Imperial College London, GB
- Matthew Cook
Universität Zürich & ETH
Zürich, CH
- Maria Rita D’Orsogna
California State University –
Northridge, US
- Vincent Danos
University of Edinburgh, GB
- Hanno Hildmann
NEC Laboratories Europe –
Heidelberg, DE
- Jonathan P. Hill
National Institute for Materials
Science – Ibaraki, JP
- Heinz Koepl
TU Darmstadt, DE
- Nikita Kruk
TU Darmstadt, DE
- Emmanuel Levy
Weizmann Institute of Science –
Rehovot, IL
- Yuri Maistrenko
National Academy of Sciences of
Ukraine – Kiev, UA
- Vincent Noireaux
University of Minnesota –
Minneapolis, US
- Matthew J. Patitz
University of Arkansas –
Fayetteville, US
- John H. Reif
Duke University – Durham, US
- Matthias Sachs
University of Edinburgh, GB
- Christian Scheideler
Universität Paderborn, DE
- Rebecca Schulman
Johns Hopkins University –
Baltimore, US
- Friedrich Simmel
TU München, DE
- Adrian Sosc
TU Darmstadt, DE
- Sandro Stucki
EPFL – Lausanne, CH
- Petr Šulc
Rockefeller University –
New York, US
- Serhiy Yanchuk
Weierstraß Institut – Berlin, DE

