

# Noise in Life 2006: Stochastic Dynamics in Cell Biology

## Final Report

### 1. Summary

The workshop “*Noise in Life 2006: Stochastic Dynamics of Cell Biology*”, was held in the Science Museum “CosmoCaixa” of the city of Barcelona, Spain, from June 15th to June 17th, 2006. The meeting gathered 60 participants from 7 countries, including 33 speakers and 5 organizers. The final list of participants has been submitted online through the ESF website.

The main funding source of the workshop has been the European Science Foundation, to which we are deeply indebted for their kind support. Additional funding was provided by two local universities, the Universitat de Barcelona and Universitat Politècnica de Catalunya, and by the Fundació La Caixa, who allowed us the use of their conference facilities at CosmoCaixa free of charge. The recently renovated Science Museum provided a welcoming and stimulating atmosphere for our scientific meeting. The dates of the conference had to be shifted one week (from the originally planned dates from June 8th to June 10th) due to scheduling restrictions of the Museum. We also note that since part of the additional funding came from a university (the Universitat de Barcelona) different from the one handling the ESF funds (the Universitat Politècnica de Catalunya), some of the expenses have been processed by the former. Only expenses and funding handled by the Universitat Politècnica de Catalunya have been listed in the financial form that has been submitted electronically with this report.

Detailed information about the event is available in the workshop’s website, which can be found at <http://www-fen.upc.es/donll/nil06>, and which will be kept active in the foreseeable future.

### 2. Description of the scientific content and discussion

The workshop aimed to provide a unified forum for discussion and exchange of ideas addressed to researchers interested in studying the effects of random fluctuations in cellular functions. The topics covered by the meeting were:

- Regulation of gene expression (Elowitz, Höfer, Metzler, van Oudenaarden)
- Intra- and inter-cellular spatiotemporal dynamics (Falcke, van Oudenaarden)
- Development and differentiation (Elowitz, Howard, Lewis)
- Biological rhythms (Gonze)
- Molecular motors (Casademunt, Mikhailov)
- Cell network dynamics (van Oudenaarden, Paulsson)

In parenthesis, we have specified those invited speakers whose talks dealt with the specific issues listed.

As can be seen in the final program described in detail in Sec. 4, the contributed talks also covered all of the topics listed above. We now present briefly the contents of each of the invited talks and list the specific topics covered by all contributed talks.

**Michael Elowitz**, pioneer of experimental studies published in 2002 that initiated the interest of the scientific community at large on the effects of noise on gene regulation, opened the conference with an exposition of recent experimental results showing that noise can have a beneficial role in the stress response of bacteria, by triggering transient differentiation.

**Martin Falcke** described wide-ranging theoretical efforts towards the understanding of calcium spatio-temporal dynamics within cells. His findings show that noise plays a fundamental role in the behaviour of channels that gate the calcium buffers, and exhibit a satisfactory agreement with experimental results.

**Alexander van Oudenaarden** discussed experimental observations and theoretical insight in two examples of cellular decision making based on feedback regulation. The first situation dealt with galactose metabolism in budding yeast, where persistent memory states have been reported. The second example concentrated on the control of spontaneous cell polarization in budding yeast. Experimental results show that bud site selection proceeds via traveling waves that provides a mechanism of random exploration of the cell periphery.

**Martin Howard** proposed in his talk a mechanism, on the basis of theoretical considerations, for the reliable determination of spatial position in the development of multicellular organisms. His proposal is based on two morphogen gradients, corresponding respectively to an activator stemming from the anterior end of the organism, and a corepressor originating from the posterior end.

**Julian Lewis** reviewed his far-reaching experimental and theoretical work on the mechanism of the somite segmentation clock, the transcriptional oscillator that controls the spacing of somites (body segments) in the vertebrate embryo. In particular he concentrated on the influence of random fluctuations on this process.

**Jaume Casademunt** described his theoretical work on the collective dynamics of interacting molecular motors in the presence of external forcing. His results show, for instance, that a collection of motors works more efficiently in the presence of coupling between the motors than in the case where the motors function independently from each other.

**Alexander Mikhailov** presented an evolutionary optimization process that allows the design of elastic networks with specific relaxation properties, that could represent the behavior of protein machines. His proposal might provide a useful procedure for the efficient design of molecular motors and other types of nano-devices.

**Didier Gonze** described the work performed at the group of Albert Goldbeter in Bruxelles, regarding the robustness to noise of well-established models of circadian oscillators. He reviewed the different types of models used since the mid 1990s for the modeling of circadian clocks in different types of or-

ganisms, and analyzed the response of these models to intrinsic fluctuations, arising from the randomness of the biochemical reactions underlying the gene regulation processes that lie at the heart of biochemical clocks.

**Johan Paulsson** presented a general theory that gives fundamental limits to noise suppression, affecting the well-established homeostatic regulation mechanism via negative feedback. These limits are due to the opposing mechanisms that underlie different sources of noise, which require often counteracting noise-reduction strategies. His results show that an efficient noise reduction might require non-trivial strategies, such as counteracting feedback loops and non-Markovian molecular memory.

**Thomas Höfer** described the effects of multi-stability and noise in the proliferation and differentiation of immune cells. A theoretical model based on experimental observations shows that depending on the strength of feedback, the expression of T-cell growth factor receptors on a cell can follow an all-or-none or a graded pattern. The model allows for a consistent interpretation of what were previously considered conflicting experimental findings.

**Ralf Metzler** presented a model for the opening and closing dynamics of DNA bubbles, and discussed target search approaches that might be employed by DNA binding proteins. In particular, he compared different search strategies such as three-dimensional diffusion with directed one-dimensional searches after non-specific DNA binding, including in the latter strategy Lévy-flight components at DNA loops.

The contributed communications included development questions addressed by J. Buceta, F. Tostevin and M. Ibañes, differentiation studies described by H. Chang, J. Poyatos and A. Zaikin, methodological issues on stochastic modeling presented by M. Hemberg, V. Rouilly, M. Dobrzynski and J. Vidal, studies on robustness, tunability and precision described by L. Morelli, C. Gómez-Urbe and L. Mirny, DNA and RNA studies presented by D. Hennig, M. Manosas and L. Saiz, a study on molecular motors given by A. Ciudad, and several dynamical issues addressed by R. Guantes, A. Politi, E. Ullner, T. Veretchaguina and A. Wagemakers.

A discussion session ranging from 5 to 10 minutes followed each talk. In all talks the discussion was very active, with several questions by the audience. We do not describe here the specific content of the discussions due to lack of space. In any case, discussions continued after the talks, during coffee and lunch breaks.

### **3. Assessment of the results and future impact**

The main goal of the workshop was to bring together two communities that have been separately working on the influence of noise in cell biology. On the one hand a theoretical community, stemming from decades of research in stochastic and nonlinear dynamics, has recently turned its attention to problems in cell physiology. On the other hand an experimental group of researchers, coming from the fields of molecular and cell biology, has become recently interested in the influence of noise on several cellular processes, including gene regulation and signaling. These two communities have been working mostly in isolation from each other since their interests began to converge in the last five years, ap-

proximately. *Noise in Life 2006* has succeeded in providing a first bridge between these two overlapping endeavours, helping establish preliminary contacts between the two communities. We hope that this first contact will lead to a closer collaboration in the mid term, that will provide the experimentalists with the theoretical expertise already existing in the stochastic dynamics community. We are confident that such a synergetic strategy will be successful in establishing the importance of noise in living systems, including how noise is avoided in certain biological processes, while it is used by others.

#### 4. Final programme of the meeting

	<b>Thursday June 15</b>		<b>Friday June 16</b>	<b>Saturday June 17</b>
<b>8:30-9:15</b>	Registration	<b>9:00-9:50</b>	Julian Lewis	Johan Paulsson
<b>9:15-9:30</b>	Opening remarks	<b>9:50-10:10</b>	Leonid Mirny	Dirk Hennig
<b>9:30-10:20</b>	Michael Elowitz	<b>10:10-10:25</b>	Antonio Politi	Hannah Chang
<b>10:20-10:40</b>	Luis G. Morelli	<b>10:25-10:40</b>	Leonor Saiz	A. Wagemakers
<b>10:40-11:10</b>	Coffee	<b>10:40-11:10</b>	Coffee	
<b>11:10-12:00</b>	Martin Falcke	<b>11:10-12:00</b>	Jaume Casademunt	Thomas Höfer
<b>12:00-12:15</b>	Raúl Guantes	<b>12:00-12:15</b>	Martin Hemberg	Aleix Ciudad
<b>12:15-12:30</b>	Vincent Rouilly	<b>12:15-12:30</b>	C. Gómez-Uribe	Filipe Tostevin
<b>12:30-12:45</b>	Ekkehard Ullner	<b>12:30-12:45</b>	T. Verechtchaguina	J. Vidal Rodriguez
<b>12:45-13:00</b>	María Manosas	<b>12:45-13:00</b>	Juan F. Poyatos	Maciej Dobrzynski
<b>13:00-15:30</b>	Lunch	<b>13:00-15:30</b>	Lunch	
<b>15:30-16:20</b>	Alexander van Oudenaarden	<b>15:30-16:20</b>	Alexander Mikhailov	Ralf Metzler
<b>16:20-16:40</b>	Javier Buceta	<b>16:20-16:40</b>	Marta Ibañes	Alexei Zaikin
<b>16:40-17:10</b>	Coffee	<b>16:40-17:10</b>	Coffee	
<b>17:10-18:00</b>	Martin Howard	<b>17:10-18:00</b>	Didier Gonze	

## Invited talks (speakers in alphabetical order)

“Cooperative dynamics of interacting motors”

J. Casademunt, O. Campàs, Y. Kafri, J. Brugués, K. Zeldovich, J.F. Joanny

“Transient Differentiation at the Single Cell Level”

G.M. Suel, J. Garcia-Ojalvo, L.M. Liberman, M.B. Elowitz

“Noise in calcium signalling”

M. Falcke, A. Skupin, R. Thul

“Circadian rhythms and molecular noise”

Didier Gonze and Albert Goldbeter

“Multistability and noise in T cell gene expression”

Thomas Höfer

“Finding the Center Reliably: Robust Patterns of Developmental Gene Expression”

Martin Howard and Pieter Rein ten Wolde

“Transcriptional noise and its manifestations in the somite segmentation clock”

Julian Lewis, François Giudicelli and Ertugrul Ozbudak

“Coupled dynamics of DNA conformations and DNA-binding proteins”

Ralf Metzler, Tobias Ambjörnsson, and Michael A. Lomholt

“Relaxation in nonlinear elastic networks and prototypes of molecular machines”

Yuichi Togashi and Alexander S. Mikhailov

“Noisy cellular decision making: from temporal to spatial choices”

Alexander van Oudenaarden

“Fundamental limits and trade-offs in negative feedback control”

Johan Paulsson

## Contributed talks (speakers in alphabetical order)

”Dorsoventral boundary formation in *Drosophila*’s wing imaginal disks”

J. Buceta

“Multistable and multistep dynamics in neutrophil differentiation”

Hannah H. Chang, Philmo Y. Oh, Donald E. Ingber, Sui Huang

“Kinesin as an electrostatic machine”

Aleix Ciudad, J.M. Sancho, and G.P. Tsironis

“Mesoscopic methods for noisy biochemical processes”

Maciej Dobrzynski, Jordi Vidal Rodríguez, Joke G. Blom, Jaap A. Kaandorp

“The covalent cycle as a tunable low-pass filter that is robust to noise”

C. Gomez-Uribe, L. Mirny, and G.C. Verghese

“Genetic design and dynamics of minimal cellular oscillators”

Raúl Guantes, Juan F. Poyatos

“Stochastic analysis of simple chemical reactions”

M. Hemberg and M. Barahona

“Cooperative escape dynamics of polymer chains under microcanonical conditions”

Dirk Hennig

“Cell lineage transport: a mechanism for molecular gradient formation”

M. Ibañes, D. Rasskin-Gutman, Y. Kawakami, J.C. Izpisua-Belmonte

“Force dependent fragility in RNA hairpins”

M. Manosas, D. Collin and F. Ritort

“Intrinsic fluctuations, robustness and tunability in signaling cycles”

Joseph Levine and Leonid Mirny

“The precision of genetic oscillators and clocks”

Luis G. Morelli and Frank Jülicher

“Frequency encoding, cycling and identification of feedbacks in Ca<sup>2+</sup>/IP3 signalling”

A. Politi, L.D. Gaspers, A.P. Thomas, and T. Hofer

“Robust stem cell fate control in *Drosophila*”

J. F. Poyatos

“A multiscale modelling framework for multi-cellular systems in Synthetic Biology”

Vincent Rouilly and Richard I. Kitney

“Stochastic dynamics of macromolecular-assembly networks”

L. Saiz and J. M. G. Vilar

“Min protein oscillations and segregation during cell division”

Filipe Tostevin and Martin Howard

“Dynamics of synthetic genetic networks with repressive cell-to-cell communication”

E. Ullner, A. Zaikin, J. Garcia-Ojalvo, E. Volkov

“Interspike interval densities in resonate and fire neurons”

T. Verechtchaguina, I.M. Sokolov, L. Schimansky-Geier

“Stochastic and spatial modelling of biochemical networks”

Jordi Vidal Rodriguez, Jaap Kaandorp, Joke Blom

“Noise-induced frequency locking in a simple genetic oscillator”

Alexandre Wagemakers, Luonan Chen, Miguel A.F. Sanjuan and K. Aihara

“Control of synchronization in noisy genetic oscillators coupled via quorum sensing”

A. Zaikin, A. Koseska, J. Kurths, J. Garcia-Ojalvo