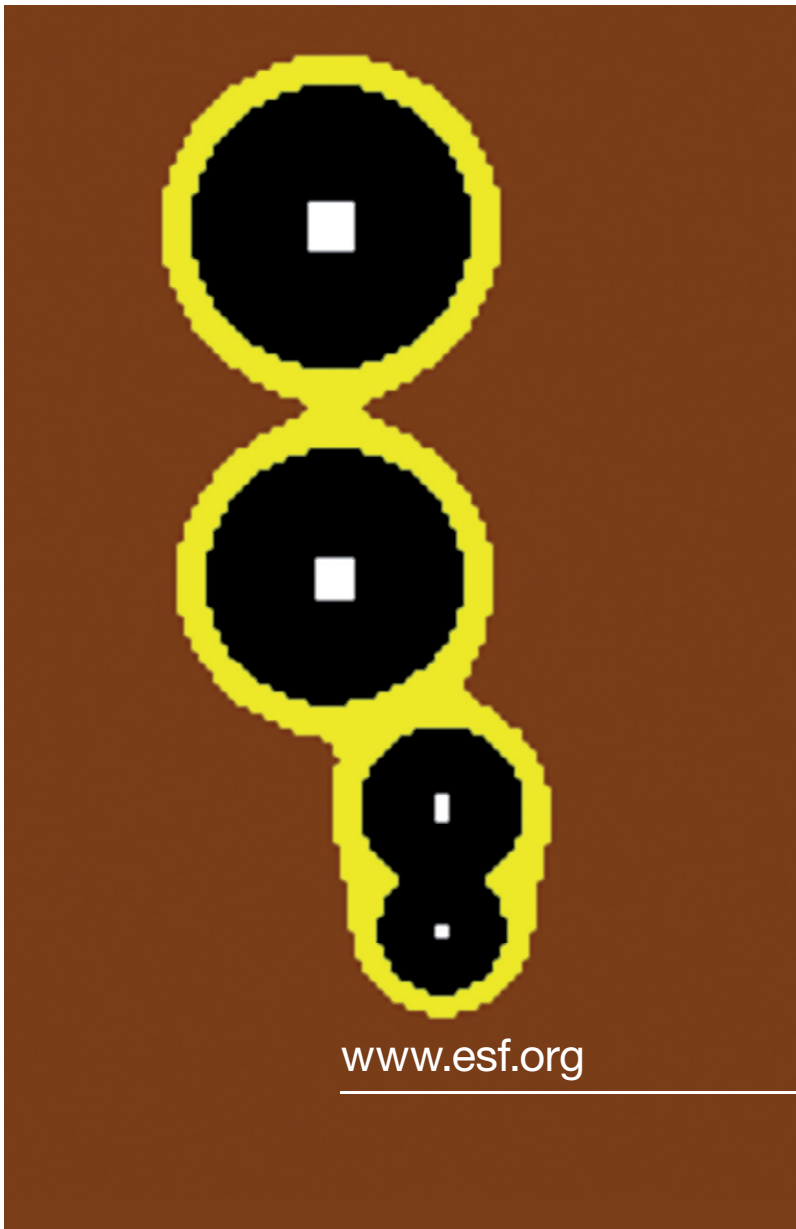
EUROPEAN SCIENCE FOUNDATION

SETTING SCIENCE AGENDAS FOR EUROPE

RESEARCH NETWORKING PROGRAMME

FUNCTIONAL DYNAMICS IN COMPLEX CHEMICAL AND BIOLOGICAL SYSTEMS (FUNCDYN)

Standing Committee for Life, Earth and Environmental Sciences (LESC)
Standing Committee for Physical and Engineering Sciences (PESC)



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Introduction

The European Science Foundation (ESF) is an independent, non-governmental organisation of national research organisations.
Our strength lies in the membership and in our ability to bring together the different domains of European science in order to meet the scientific challenges of the future. ESF's membership currently includes 77 influential national funding agencies, research-performing agencies and academies from 30 nations as its contributing members.
Since its establishment in 1974, ESF, which has its headquarters in Strasbourg with offices in Brussels and Ostend, has assembled a host of research organisations that span all disciplines of science in Europe, to create a common platform for cross-border cooperation.
We are dedicated to supporting our members in promoting science, scientific research and science policy across Europe. Through its activities and instruments ESF has made major contributions to science in a global context. The ESF covers the following scientific domains:
- **Humanities**
- **Life, Earth and Environmental Sciences**
- **Medical Sciences**
- **Physical and Engineering Sciences**
- **Social Sciences**
- **Marine Sciences**
- **Nuclear Physics**
- **Polar Sciences**
- **Radio Astronomy Frequencies**
- **Space Sciences**

Cover figure:
Eyespot patterns of the butterfly *Lopinga achine* (family *Satyridae*). The pigments (papiliochrome and melanin, yellow and black, respectively) are large molecules that do not significantly diffuse inside tissues. The mechanism associated with eyespot pattern formation can be described by the diffusion of a morphogen that reacts with pigment precursors. The morphogen concentration vanishes asymptotically in time, inducing the formation of the eyespot. This reaction-diffusion model consistently predicts the major features of the development of butterfly eyespot patterns, including their structural organisation, their phenotypic plasticity and seasonal variability [Dilão and Sainhas, Proc. R. Soc. London B, 271 (2004) 1565. Picture taken by Kumon Takashi, with permission].

The aim of the ESF Research Networking Programme FUNCDYN is to establish and support a competitive European research community in functional dynamics. The intention of FUNCDYN is twofold:
- To promote systematic investigations on the dynamics of biological and chemical systems, where the dynamical behaviour in itself is part of the function.
- To encourage the development of new tools and methods for modelling the dynamics, the development and the morphology of biological systems, with special emphasis on the incorporation of dynamic information.

Living organisms are characterised by a plethora of chemical, structural and physical details at several levels of complexity. As a consequence, the comprehensive understanding and modelling of processes and mechanisms on every spatial and temporal scale is a difficult task. One of the aims of the FUNCDYN programme is the development and the dissemination of systematic methods of reduction of model complexity. Without losing the quantitative predictability of models, this can be done by restricting the modelling of the relevant temporal and spatial scales to the phenomena under analysis. During the last 30 years, in the fields of physics and chemistry, analogous spatio-temporal problems have been successfully approached by the implementation of theoretical and experimental methods derived from the theories of non-linear dynamics and dynamical systems.

Studies of non-biological systems, which are dynamically similar to living cells, such as interacting oscillators operating far from equilibrium, are equally within the scope of the FUNCDYN programme. These studies serve as inspiration for similar approaches in bio-systems and are essential for testing the feasibility of new analytic and experimental ideas.

Moreover, the ESF FUNCDYN programme aims, at the European level, to promote the integration of researchers from the field of non-linear dynamics with researchers from biochemistry and biology. The programme intends to encourage the integrated use of expensive equipment scattered over Europe for in vivo large-scale data collection.

The running period of the ESF FUNCDYN Research Networking Programme is for five years from November 2006 to October 2011.

Aims and Objectives

With the advent of novel methods in spectroscopy, microscopy, molecular biology, and chemometry, an increasing body of detailed data on function, mechanisms and composition of biological, biochemical and chemical systems is becoming available. In contrast, data on the dynamics of biological systems remain scant. The establishment of systems biology as a new branch of biology reflects the fact that the dynamics are more and more often taken into account. In other scientific disciplines such as physics, chemistry and mathematics, the study of complex dynamical systems is a well-established area of research.

The ESF FUNCDYN programme aims at bringing together the vast expertise and methods developed over the years in the study of dynamic non-linear systems with the increasing amount of data made available by proteomics, metabolomics and transcriptomics. It is expected that this methodology will provide a more complete and detailed understanding of the dynamics of complex biological and chemical systems. We call this approach **'functional dynamics'**. In fact, FUNCDYN provides support for the emerging scientific community on functional dynamics in Europe. To this purpose, FUCNDYN provides grants for supporting the exchange of scientists between European laboratories and offers a series of scientific meetings devoted to functional dynamics.

Thanks to the diversity of the complex dynamics of biological, biochemical and chemical systems, functional dynamics covers a broad scope of investigated systems and applied methods. However, they share two common principles:

- The dynamical behaviour has been found to be an integral part of the function of the system. This function may be biological, technical or of any other nature. Studies focus on unravelling both the different types of dynamic behaviour shown and their underlying molecular mechanisms. Efforts will be made to identify the possible different functions associated with different types of dynamics.
- The dynamics shown in biological and model systems is often complex. Our objective is to systematically construct useful models for the dynamics of complex functional systems. This requires the use of non-linear evolution equations. Often the dynamic behaviour is robust and does not depend essentially on the entire micro-complexity of the individual system. Hence, the task taken up often consists of reducing this complexity to a manageable level while keeping the key regulations responsible for the observed behaviour. This can be done in a systematic way by using the experience from non-linear dynamics.

Topic Areas

Based on the current research efforts, six interlinked lines of research have been identified as integral constituents of the present proposal. These areas represent key examples and do not aim for exclusivity:

a. Oscillations in biological systems

Many biological systems show oscillatory behaviour, which is a consequence of the underlying metabolic processes. In some cases, oscillatory or rhythmic dynamics have been identified as serving some biological function. Classical examples are the information encoded in calcium oscillations and associated signal transduction pathways, or the behaviour of circadian clocks. Furthermore, oscillatory dynamics in the peroxidase-oxidase reaction have recently been identified as the mechanism for enzyme protection against deactivation by reactive intermediates. Oscillations also appear in strongly coupled networks when their operating point reaches an instability region. Glycolytic oscillations in a population of yeast cells belong to this class of systems. Studies of the dynamics of such oscillations have yielded valuable new mechanistic information on the control of glycolytic flux in yeast cells.

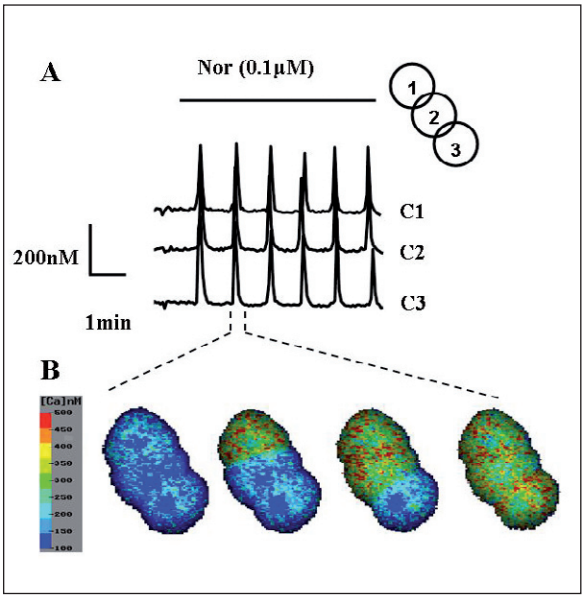

Figure 1. Tightly coordinated calcium oscillations and intercellular calcium wave in a group of hepatocytes (liver cells). Although the stimulating hormone (vasopressin) is globally added in the bath containing the cells, sequential calcium spiking occurs in the three cells, which are connected through gap junctions; this spiking is unidirectional as the calcium spikes always occur sequentially in cells 1, 2 and 3 (panel A). Expanded time resolution (panel B) shows that such sequential spiking results in the appearance of repetitive intercellular calcium waves, leading to bile secretion. The colour coding shows the cytosolic calcium concentration [Dupont, Swillens, Clair, Tordjmann, and Combettes, Biochim. Biophys. Acta 1498 (2000) 134].

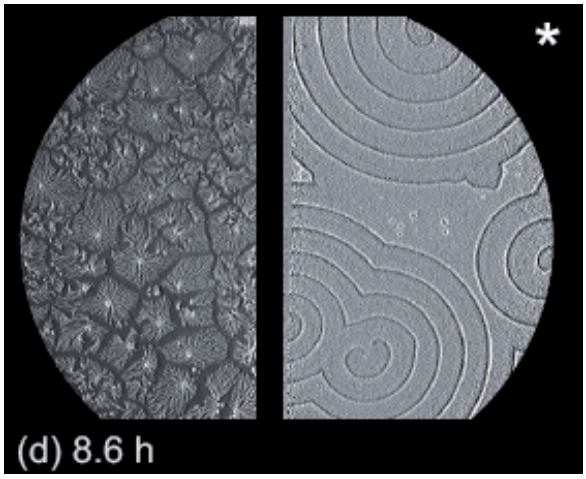

Figure 2. Aggregation of *Dictyostelium discoideum* cells after 8.6 h of aggregation. Left: territories with central cell mounds and cell streams; right: travelling waves of the chemoattractant cAMP. While the cells on the left grow on a normal medium, a small concentration of a receptor blocker has been introduced in the medium on the right side [Hilgardt, Čejková, Hauser, and Ševčíková, Biophys. Chem. 132 (2008) 9].

Figure 3. Tomographic reconstruction of a scroll wave in the Belousov-Zhabotinsky reaction. The scroll wave is subject to an instability which is also found in the transition form cardiac tachycardia to cardiac fibrillation. The line around which the scroll rotates increases in length and gets more and more distorted. Eventually, the scroll wave breaks up into many fragments, leading to a turbulent regime [Luengviriya, Storb, Lindner, Müller, Bär, and Hauser, Phys. Rev. Lett. 100 (2008), 148302].

b. Spatio-temporal patterns in biological systems

Dynamical processes are often spread over extended areas. The coupling of non-linear dynamical behaviour and transport processes gives rise to a series of new phenomena, such as the emergence of waves. These waves transport information, as in the case of amoeba of the slime mould *Dictyostelium discoideum*, where cell aggregation is crucially dependent on the emergence of waves of the chemo-attractant cAMP. Other examples are waves in calcium as encountered in cardiomyocytes, hepatocytes, oocytes, or in neutrophils. It is noteworthy that a vast arsenal of techniques has been developed and is being currently employed in theoretical studies of the dynamics of biological systems in space and time, and on their functions.

Biologically relevant spatio-temporal behaviour is not restricted to two dimensions. In fact, dynamical self-organisation in three dimensions is of paramount importance in the heart tissue. Here generic non-linear instabilities play an imminent role in the generation of cardiac arrhythmias and ventricular fibrillation. Therefore considerable efforts are devoted to related theoretical and experimental studies on model systems.

c. Biomimetic systems

As a rule, biological systems possess a high degree of complexity resulting in a finely tuned biological action, which, however, often obscures the origins and sources of some dynamical function. One way to gain insight into the driving forces of such complex behaviour is the study of biomimetic systems. These fully artificial systems are specially designed so that they mimic some characteristic features of the structure, reactivity and dynamics of their natural counterparts. Biomimetic systems are considerably simpler and, therefore, may point to the essential features to be retained for the understanding of how the natural systems work. Examples are the study of the dynamics of enzyme reactions in a compartmented environment, as well as the quest for new mechanisms for the development of stationary and dynamic patterns in responsive gels and membranes subjected to reactions, where chemo-mechanical couplings plays an important role.

d. Chemical systems: models for coherent behaviour in biological systems

Chemical and electrochemical systems are ideal models for studying the laws of oscillations, chaos and pattern formation since the parameters affecting the exotic dynamics can be easily controlled. Another advantage of working with chemical systems is that the 'laws of motion' responsible for the dynamics are easy to define in forms of differential equations that can then be 'routinely' analysed with exact mathematical or numerical methods.

Complex biological systems (e.g., tissues) are built of large numbers of cells, and thus the global and/or local coupling of the units plays an essential role in generating the collective dynamics. Therefore, the nonlinear dynamics of coupled chemical systems should be further investigated in order to learn about general laws governing the emergence of coherent dynamics as

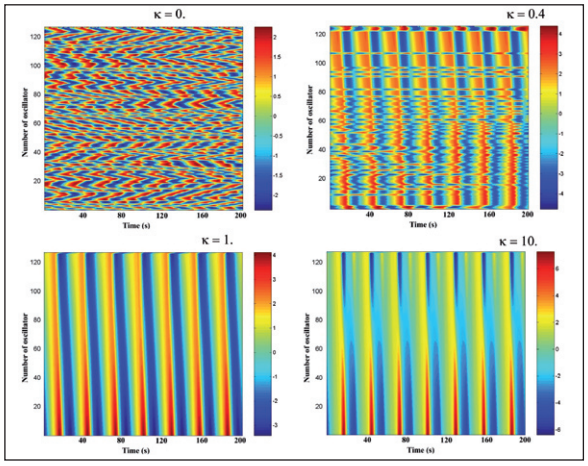

Figure 4. Results of simulations showing the emergence of coherent oscillatory dynamics of 128 globally coupled non-identical Zn electrodes by increasing the coupling strength κ during Zn-electrodeposition. Colour coding is applied to visualise the current oscillations of each Zn electrode. Independent oscillations are observed with no coupling (κ = 0), while the synchronised dynamics becomes more and more pronounced as the coupling strength is increased [Birzu and Gáspár, unpublished results].

well as to develop algorithms for achieving controlled (synchronised) behaviour in both chemical and biological model systems.

e. Theoretical and experimental methods of functional dynamics

The development of a tool-box of computational methods to analyse and model the temporal and spatio-temporal behaviour during self-organisation processes is an ongoing and challenging task. One of the aims of the modelling efforts is the search for systematic methods for establishing low dimensional, quantitative models for complex biological systems. These efforts will be supplemented with experimental techniques for establishing realistic parameter values for such models.

f. Modeling mechanisms and processes in biology

During the development of organisms, the basic processes and transformations that occur inside tissues and cells are of a (bio)chemical nature. These transformations occur sequentially in time and are described by genetic regulatory networks. The regulatory mechanisms are described by the graphs containing the information of the activation and the inhibition processes of the network. It is therefore important to develop and use mathematical and computational tools in order to describe the time evolution and the asymptotic states of protein concentrations in complex genetic regulatory networks. Tools for calibration and validation of models are being developed and applied to specific biological processes.

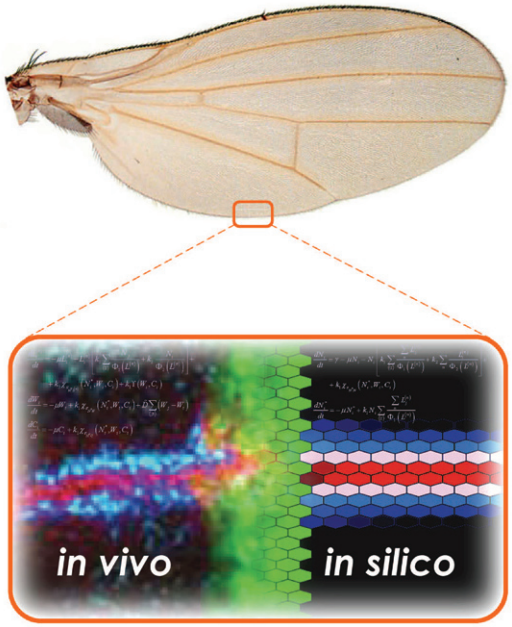

Figure 5. During development, the *Drosophila* wings are generated from a set of cells grouped into different segments or compartments that never mix with one another, and which enable the symmetrical construction of the dorsal (D) and ventral (V) parts starting from a given limit or border. This subdivision into compartments also takes place during the formation of the vertebrate central nervous system, and the genes and signalling pathways involved are conserved in both *Drosophila* and vertebrate species. This figure shows results of a study that by combining in silico (modelling and numerical simulations) and in vivo experiments explains how the formation of the DV boundary can be performed in a reliable way. [Buceta, Herranz, Canela-Xandri, Reigada, Sagués, and Milan, PLoS ONE 2(7) (2007) e602].

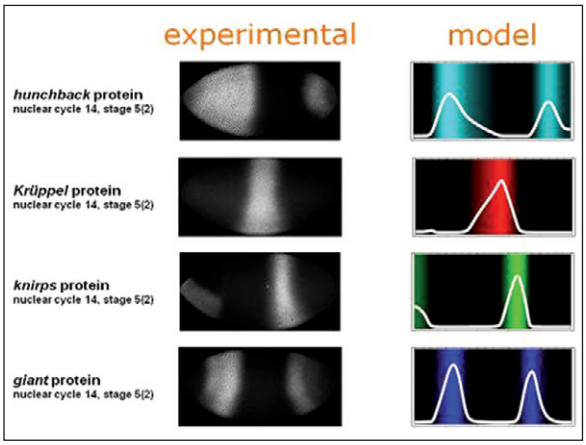

Figure 6. Pattern formation in early development of *Drosophila*. Left: shows the concentration of some proteins along the antero-posterior axis of the embryo. Right: shows the corresponding model predictions based on a model with a diffusion mechanism and interactions following the mass action law [Alves and Dilão, J. Theor. Biol. 241 (2006) 342].

FUNCDYN Activities

The ESF Research Networking Programme FUNCDYN operates through a variety of activities and opportunities. **Support** for **exchange visits** and **science meetings** are the most prominent instruments of the FUNCDYN programme. They aim at encouraging and supporting collaborative research, the transfer of know-how between the European groups, as well as the formation of a European scientific community studying functional dynamics.

Two types of **grants for exchange of scientists** are available:

- **Short visit grants** provide support for a visit of up to 15 days at a European partner laboratory located in a different European country than that of the applicant.
- **Exchange grants** provide support for a visit of up to two months at a European partner laboratory located in a different European country than that of the applicant. Exchange grants are intended especially for younger scientists.

In the area of **science meetings**, the FUNCDYN programme offers three opportunities:

- Major **workshops** will bring together the European functional dynamics community. They act as a platform for the presentation of ongoing achievements. The workshops will further encourage collaborative research and teaming-up between different research groups.
- **Theme schools** will focus on special issues within functional dynamics. They will provide a more in-depth training in selected areas of functional dynamics for younger staff and scientists. We feel the need for such theme schools, given that the emerging field of functional dynamics brings together researchers from many areas, which share similar tools, but are often prevented from complete and/or convenient interaction because of differences in glossaries and in 'local subject styles'.
- FUNCDYN also invites **proposals** from potential organisers of **workshops** and **science meetings** on topics with a clear connection to the programme.

Any further information and on-line application forms for grants and meetings can found in the FUNCDYN websites: **funcdyn.org** and **www.esf.org/funcdyn**

There are four deadlines for applications per year:
1 March, 1 June, 1 September and 1 December.

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