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Preface

Biochemical processes are governed by non-linear kinetic laws. One important source of non-linearity is provided, besides cooperativity, by the multiple modes of cellular regulation exerted at the levels of gene expression, protein synthesis, enzyme activity, receptor function, and transport processes, to cite but the main examples. The goal of this special issue of *Biophysical Chemistry* is to explore some of the major consequences of non-linear kinetics for the dynamics of biochemical and cellular processes.

Through their link with instabilities, appropriate non-linearities may give rise to three main types of dynamic phenomena, which are seldom considered all together. First, instabilities in non-linear systems can give rise to sustained oscillations, which can be periodic or chaotic. Second, the same mechanisms which are responsible for oscillatory behavior in homogeneous conditions can, when coupled to diffusion, produce wavelike phenomena. A third type of phenomenon associated with non-linear kinetics pertains to the multiplicity of coexisting steady states, which is exemplified by the evolution, in the same conditions, to either one of two stable steady states (bistability). It becomes increasingly clear that the three types of dynamic phenomena mentioned here play significant roles in some of the most fundamental manifestations of life. These phenomena are best investigated by combining an experimental with a theoretical approach. Theoretical studies have indeed played an important role in establishing the conditions in which instabilities arise in regulated biological systems, and sometimes permit the prediction of phenomena which would not otherwise be easily observed or even searched for in the experiments.

This special issue of *Biophysical Chemistry* is based on the contributions to a workshop organized from 14–20 June 1997 at the Fondation des Treilles (Tourtour, France), on the theme ‘Oscillations, bistability and waves in biochemical and cellular systems’. The workshop, held in the presence of 22 participants, allowed the discussion of some of the main examples of oscillatory, bistable and wavelike behavior known at the biochemical and cellular levels, besides circadian rhythms and oscillatory phenomena observed in nerve cells and neural networks. The content of this issue largely reflects the program of the workshop. Two additional papers were included, to extend the scope of this issue.

That fact that similar mechanisms underlie oscillations, bistability and waves is reflected by the fact that often two or all of these phenomena occur in the same system, in closely related conditions. Thus, this issue of *Biophysical Chemistry* opens with three articles devoted to cyclic AMP (cAMP) oscillations and waves in *Dictyostelium discoideum*, which provide one of the best and most thoroughly studied examples of spatiotemporal organization at the supracellular level. After a presentation of the salient experimental and theoretical aspects of cAMP oscillations by Nanjundiah, their modeling is addressed by Halloy and Goldbeter, who consider the role of G proteins in cAMP signaling and further show how theoretical models can be used to generate concentric and spiral waves of cAMP in the course of *D. discoideum* aggregation. Weijer and coworkers examine, by means of a combined experimental and theoretical approach, how wavelike signals of cAMP control morphogenesis at the slug and culmination stages that follow aggregation.

Glycolysis in yeast and the horseradish peroxidase reaction provided, around the mid-1960s, the first two examples of biochemical oscillations. Lately, there has been a renewal of interest in these two experimental systems. Glycolytic oscillations have been found in new cell types, while both chaos and wavelike propagation have recently been observed in glycolyzing yeast extracts. Results on glycolytic waves are presented here by Müller and coworkers, together

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with data on the analysis of propagating cAMP waves in *Dictyostelium*. Sorensen and coworkers also investigate glycolytic oscillations in yeast, and focus on the occurrence of complex oscillations, including autonomous chaos, and on the quenching of simple oscillations. Chaos is also studied in the peroxidase reaction by Olsen and coworkers, who further discuss the possible function of peroxidase oscillations in vivo. A different type of synchronized activity resulting, on the much smaller time scale of catalytic cycles, from the stochastic operation of an enzyme reaction in small volumes is discussed by Hess and coworkers.

Next to the cAMP signaling system in *Dictyostelium* cells, but much more widespread, are the oscillations and waves of cytosolic calcium which represent the best known example of spatiotemporal organization at the cellular level. A series of articles deals with selected aspects of this phenomenon which is encountered in a large variety of cells, either spontaneously or after stimulation by a hormone or a neurotransmitter. Keizer and Smith address by means of a theoretical analysis and computer simulations the link between calcium sparks and the saltatory propagation of calcium waves in cardiac cells. Using similar methods as well as experimental results Sneyd and coworkers examine the mechanism of intercellular calcium wave propagation. The role of mitochondria in the generation of calcium spikes and oscillations is examined by Mazat and coworkers, by means of a theoretical model. Lechleiter et al. investigate the role of ATPases and calcium uptake in the generation of spiral waves of calcium in *Xenopus* oocytes. Turning to the role of periodic calcium signals in development, Sardet and coworkers review the occurrence of calcium oscillations and waves in eggs. Ozil shows that the encoding of these oscillations in terms of frequency is of key importance for egg development after fertilization. The resumption of cell division triggered by repetitive calcium spikes in the fertilized egg is examined by Dupont by means of a theoretical approach.

Few phenomena are as important in developmental biology as the cell division cycle. The dynamics of the cell cycle appears to rely on oscillations as well as bistability. Among the systems best studied in molecular terms for the dynamics of the cell cycle are the fission yeast and the amphibian embryo. In companion papers, Novak, Tyson and coworkers present the results of their latest theoretical studies bearing on these two systems. In particular, the model they propose for the yeast cell cycle encompasses the three types of checkpoint brought to light by recent experimental studies. The latter model is the most detailed one proposed so far for the ordered sequence of events underlying the eukaryotic cell cycle.

The last part of this issue deals with other examples of bistability at the biochemical and cellular levels. Guidi and Goldbeter examine a theoretical model for the isocitrate dehydrogenase reaction and provide evidence for both bistability and oscillations in this enzyme reaction system. Laurent extends his previous theoretical studies of the transition of prion proteins to their pathological conformation, and analyzes the consequences of bistability that arises from the self-amplified nature of this process. Finally, Segel examines the occurrence of multiple attractors in immunological models which suggest that transitions between coexisting states lie at the very core of the immune response, as a result of non-linear cellular interactions.

This issue underlines the richness of dynamic phenomena arising from the non-linear nature of cellular regulatory processes. The present collection of articles might not provide an exhaustive account of the field, which undergoes rapid developments. Rather, it offers insights into some of the most challenging aspects of oscillations, bistability and waves in biochemical and cellular systems, and provides examples of how theoretical models can be used to complement experimental studies of these phenomena.

I wish to thank the contributors to this volume, as well as the referees who reviewed the papers. Special thanks are due to the Fondation des Treilles for supporting and hosting the workshop on which this collection of articles is based. It is a particular pleasure to open this volume by reproducing as frontispiece a work by the painter Yves Nioré, who is closely associated with the Fondation des Treilles in Tourtour. The painting, after feedback from some of the participants in the workshop, was entitled ‘Branches non connectées’ (i.e. ‘Non-connected branches’). It can be viewed as a striking illustration of bistability, in the special case where the two branches of stable steady states cease to be connected, thus, preventing the possibility of hysteresis that generally accompanies bistable behavior. Amazing as this may seem, this painting was not prepared for the purpose of reproduction in this volume. Works of art illustrating oscillations and, even more frequently, waves (including spirals) are more abundant than those which pertain to bistability. Putting the latter phenomenon on equal footing with oscillations and waves among non-linear, self organization phenomena in the dynamics of biological systems fits one purpose of this volume.

Albert Goldbeter

'Branches non connectées', painting (1997) by Yves Nioré .