My Career in Mathematical Biology
A Personal Journey

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Many paths lead to Mathematical Biology. I started my journey by studying Chemistry at the Université Libre de Bruxelles (ULB). During my studies, I was much influenced by a series of remarkable teachers in the life sciences. A key bifurcation occurred after I presented my examination in Quantum Mechanics to the satisfaction of my teacher, who was a coworker of Ilya Prigogine. He asked me what my plans for the next year were, and when I told him that I intended to do my Master thesis in the field of enzymology and cellular regulation, he suggested me to talk to Prigogine, who had a long-standing interest in self-organization phenomena, and was turning, he said, to the study of biological systems. Thus, I went to see Ilya Prigogine, who was later to receive the Nobel Prize in Chemistry (in 1977). He was a formidable charismatic figure, enthusiastic, and generous with students. After listening to him for half an hour, I was so enthralled that I decided to do my Master thesis in his group, on the mathematical modeling of spatiotemporal organization in an enzymatic system. This I did under the guidance of René Lefever, who was only a few years older than me. I was hooked: instead of moving afterwards to biochemistry, I went on to do my PhD in Prigogine's group, on the analysis of an allosteric model for glycolytic oscillations, under the guidance of René Lefever and Grégoire Nicolis. My first article published on this work appeared in 1972. I remember that one referee wrote "the scientific value of this paper is nil", while the other two reviewers thought that the paper warranted immediate publication! I never forgot this initial experience, which taught me that referees should be constructive rather than destructive, and that one should not get too discouraged by negative comments!

At the end of my PhD I spent two years of post-doctoral work at the Weizmann Institute of Science, in Rehovot (Israel). Much of my time was devoted to the preparation of a review article with Roy Caplan on oscillatory enzymes. I was also fortunate to meet there Lee Segel, who had recently arrived as the new head of the department of Applied Mathematics. I was close to Lee for many years, and miss him dearly. With him I worked on the mechanism of oscillations and relay of cyclic AMP during the aggregation of Dictyostelium amoebae. Even if the period was initially not well suited to scientific research —I arrived one month before the Yom Kippur war—, the situation gradually changed and I fully benefited from this truly unique environment. I vividly remember the smell of orange trees when emerging around midnight from an evening of work at the computer center. During this period I also traveled to Germany where I briefly worked on glycolytic oscillations in yeast, both experimentally and theoretically, with Benno Hess at the Max-Planck Institute in Dortmund. From him I learned the importance of comparing theoretical predictions with available experimental data.

I returned to Brussels where I first had a non-tenured appointment at ULB. After a few years, at the end of the seventies, I decided to move again, this time to California, where I spent two memorable years in Berkeley, working with Dan Koshland. For the next decade I returned every summer to Berkeley, where I often worked in cafés around the campus. Initially I focused on models for adaptation in bacterial chemotaxis. In the course of this work we observed that sharp thresholds may occur in systems regulated through reversible phosphorylation. The paper describing this phenomenon, which we called "zeroorder ultrasensitivity", is one of my best research achievements: although it was barely noticed for some 20 years, with the rapid rise of Systems Biology it was cited hundreds of times in the last decade.

After my return from Berkeley I eventually secured a tenured position at ULB, where I built a unit of theoretical chronobiology within the department of Physical Chemistry headed by Ilya Prigogine. I was lucky to pursue my work on modeling biological oscillatory behavior with brilliant students over the years, thus focusing, with Olivier Decroly on chaos and multiple oscillatory regimes (birhythmicity), with Jean-Louis Martiel on the role of receptor desensitization in cyclic AMP signaling in Dictyostelium, and with Yue-Xian Li (now in UBC, Vancouver) on frequency coding in pulsatile intercellular communication.

A new chapter of activity opened when Michael Berridge came to Brussels for a series of lectures in 1988. We initiated a collaboration, which led to the publication of a minimal model for calcium oscillations based on the role of IP3 and calcium-induced calcium release. During this most fruitful collaboration, Geneviève Dupont joined us and did her PhD in my group, within which she pursues her work on modeling calcium oscillations and waves. Yet another great experience was the development of a minimal cascade model for the mitotic oscillator driving the early cell cycles in amphibian embryos. I soon left this topic (but later returned) to study models for circadian oscillations in Drosophila and to publish a book in 1996 on biochemical oscillations and cellular rhythms, of which a new edition is underway.

The next step was to extend with Jean-Christophe Leloup the Drosophila model to the mammalian circadian clock, while with Didier Gonze we investigated the robustness of circadian rhythms with respect to molecular noise. Using the mammalian model allows us to obtain insights into human syndromes associated with dysfunctions of the circadian clock.

I later worked with Olivier Pourquié, who discovered the segmentation clock, on modeling the role of bistability and oscillations in somitogenesis. More recently, I returned to modeling the dynamics of the cell cycle, this time in mammals. With Claude Gérard we analyzed a 39-variable model for the cell cycle, while with another PhD student, Atilla Altinok, and with a French oncologist, Francis Lévi, we used an automaton model for the cell cycle to probe the effect of circadian delivery of anticancer drugs.

My fascinating journey in Mathematical Biology thus brought me from one rhythm to another, and from surprise to surprise. What I like most in research are the encounters with colleagues and friends, and the interactions with experimentalists and students. Working in academia is a unique privilege: I cherish the freedom in selecting research topics and the creative aspects of the work. What I appreciate less is the pressure to submit more and more research proposals, too many of which eventually fail...

I never regretted my choice of focusing on the mathematical modeling of regulatory networks that underlie cellular rhythms. This topic exemplifies many aspects of the field now known as Systems Biology and possesses a strong aesthetic component. The mathematical approach gives a broad perspective and allows one to move easily from one topic to another, while retaining a global perspective. In selecting a research topic, the best is certainly to follow one's own deep interests, rather than obeying to transient, fashionable trends. As the French designer Coco Chanel said: fashion is what comes out of fashion!

Selected publications

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