Proceedings of the XXXVIIIth Seminar of the French-Speaking Society for Theoretical Biology; Saint-Flour (Cantal), France, 11–13 June, 2018

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The annual seminar of the *French-speaking Society For Theoretical Biology* (SFBT) was held in its traditional ground of Saint-Flour (France) from 11 to 13 June 2018. For its XXXVIIIth edition, the seminar welcomed Franck Delaplace (University Evry Val d’Essonne—IBISC Laboratory) and Fabien Crauste (University of Bordeaux—CNRS UMR5221—Institute of Mathematics of Bordeaux) as invited speakers. F. Delaplace has spent many years expanding his expertise on systems biology; Fabien Crauste is renowned for his interdisciplinary work on blood cells.

The talk *Inferring the Causes of Cell Reprogramming by Abduction* given by F. Delaplace perfectly introduced one of the leading themes of this seminar: formal networks in biological systems. This theme is often represented in SFBT annual seminars, but we noticed this year a clear decline of the *Living viewed as a Machine* paradigm, which maintains a mechanistic and computer-like vision of living systems and, on the contrary, a step towards more soft and fuzzy, but also more versatile, more adaptable and more resilient formalisms to describe biology. In theoretical biologists’ minds, living organisms are no more robots driven by rigid programs. Indeed, their perception of living matter has evolved, and so have their models: they express the fact that biological networks are not networks, except in our mind, that cell processes, tissue morphogenesis or ecological systems do not systematically follow an ODE-driven behavior, which is so deterministic, but are rather delayed or noisy. Cells can “reprogram” themselves ! Is this ability to travel in a large phenotype landscape in order to escape deleterious conditions the result of another control

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inscribed as a “biological program” providing cell awareness to environmental changes, or something less defined, more uncertain, that derives from fragile interactions between cell components, making regulatory pathways in a single cell more diverse and versatile than expected? As F. Crauste proclaimed in his talk *Mathematical Immunology : Towards a Multi-Scale Approach of the T CD8 Immune Response*, immunological differentiation pathways are also not as clearly defined as taught in university: instead of a unique pathway, several differentiation trajectories could co-exist that give rise to activated, effector or memory T cells from naive cells.

The articles published in these proceedings of the XXXVIIIth SFBT 2018 seminar follow this trend, revisiting several aspects of biology, often proposing alternate views rather than focusing on biological data interpreted through the prism of a single paradigm. Biological modeling helps to consider alternate visions of cell, organism or ecosystem functioning.

Three papers focusing on genetic or metabolic regulated systems explore variations on regulatory networks, thus revisiting cell regulation: Liu and Bockmayr in *Formalizing Metabolic-Regulatory Networks by Hybrid Automata* integrate in a hybrid model the metabolism and its transcriptional regulation, so as to relax the strict control of Boolean networks. Mossé and Rémy in *A Combinatorial Exploration of Boolean Dynamics Generated by Isolated and Chorded Circuits* use the classical formalism of Boolean networks to model biological regulatory networks but propose a wider analysis of their behaviors including transient states generally ignored to the profit of asymptotic states, thus increasing the understandable richness of genetic regulatory pathways. Finally Christen et al. in *On Computing Structural and Behavioral Complexities of Threshold Boolean Networks*, by expressing the relationship between structure and function in threshold Boolean networks in terms of complexity, exhibit the availability of different strategies for Nature to implement the same functions and suggest to consider a set of related networks instead of single models to represent regulatory systems.

During the seminar, many discussions were related to cell tissue morphogenesis and homeostasis and a common aim rapidly emerged to control them by gene and metabolic regulation. Such hybrid numerical models are costly, firstly to develop and secondly to simulate. Recent numerical computation frameworks take advantage of all available CPU and GPU resources in a computer, and also facilitate and accelerate the programming of numerical models of cells and tissues. Among them, the *SimCells* software presented by Douillet and Ballet in *A GPU Algorithm for Agent-Based Models to Simulate the Integration of Cell Membrane Signals*. In this article, the authors focus on how to fastly compute 2 or 3D cell tissue membranes by using the computing power of a GPU. Collaborations emerged during the seminar to include biomechanical features as well as gene and protein networks to control cell behavior and how they sense and integrate their surrounding cellular and environmental neighborhood by chemical and biomechanical feedback.

Relatedly, *Holon-Lymphocytes*, a distributed, non-local, living tissue is shown to be also capable of integration and of self-assertion. This small living system behaves as and clearly belongs to ecosystems, as explained by Thomas-Vaslin in *Individuation and the Organization in Complex Living Ecosystem: Recursive Integration and Self-assertion by Holon-Lymphocytes*. In this dynamic system, self-maintained and

capable of immunoception, the immune system gains in complexity, thus behaving as an organism. However, awareness is not required for an ecosystem to self-maintain. In *New Schemes of Dynamic Preservation of Diversity: Remarks on Stability and Topology*, Sanchez-Palencia and Françoise show indeed that diversity of species can be maintained in an ecosystem even in conditions of non-existence of equilibrium, notably by processes of predation or by competitive exclusion.

The SFBT promotes a large spectrum of fields in which mathematics and numerical computation are required and this special issue demonstrates once again the huge diversity of approaches that make theoretical biology such a fascinating field of research.

For example, phylogeny! A good use of powerful mathematics and computational power applied to phylogeny is shown in the paper written by Lespinats et al., *Phylogeny and Sequence Space: A Combined Approach to Analyze the Evolutionary Trajectories of Homologous Proteins. The Case Study of Aminodeoxychorismate Synthase*. The authors improve a method that combines the representation of proteins in a high dimensional sequence space computed by using a Data-Driven High-Dimensional Scaling method, and their distances seen as a phylogenetic tree. This is a manner to connect the structure of proteins to their evolution and to understand how both relate.

Physiology, from cell differentiation to heart functioning, is also represented, with Paquin-Lefebvre and Bélair's mathematical study of blood cell differentiation in *On the Effect of Age-Dependent Mortality on the Stability of a System of Delay-Differential Equations Modeling Erythropoiesis*, and with a model reduction method applied to coagulation, by Ratto et al.'s *Clustering of Thrombin Generation Test Data Using a Reduced Mathematical Model of Blood Coagulation*. Finally, at a larger scale, i.e. heart physiology, Le Rolle et al. provide a *Sensitivity Analysis of a Left Ventricle Model in the Context of Intraventricular Dyssynchrony*.

Annual seminars of the SFBT are a breeding ground to share research, ideas and methods, in a comfortable but efficient way. Their success and longevity are clearly related to the long partnership we maintained for more than 20 years with *Acta Biotheoretica*. Thanks to the efficiency and responsiveness of the editorial team, we wrapped this issue up in the best conditions. For these reasons, we would like to thank all *Acta Biotheoretica*'s editorial staff, in particular its editor in chief, Frans Jacobs.

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