Towards Executable Biology

Exceptional scientific breakthroughs of the last century and the advent of high-throughput technologies in the early 2000s have catapulted molecular biology in the realm of systems biology. Systems biology inherited the denotational language proper of control theory. However, the necessity of a new language for biology, able to capture and express biological processes on the level of software explanation, is clearly perceived by the biological community.

The need to define a framework built upon complementary and yet coherent formal languages for systems biology repeatedly emerged during my studies. In this dissertation we showed several examples of how formal model definitions of biological processes ensure a consistent interpretation and help to clearly define problems and hypotheses. In Chapter 2, we explain the notion of executable models for biological processes as introduced by Fisher et al. and we present two formalism based on Petri nets. The first formalism was built to model signalling networks which analysis is based on simulations and Monte Carlo model checking. The second formalism focuses on gene regulatory networks and exploring the model state space in search of attractors.

In Chapter 3, we demonstrate a large scale application of our Petri net formalism for signal transduction to multi-cellular pattern formation. Our modelling approach to the well-studied process of C. elegans vulval development, showing that our model correctly reproduced a large set of in vivo experiments with statistical accuracy. Also Chapter 4 focuses on signalling networks. We investigated the effect of proteolysis after nutrient starvation in S. cervisiae. Particularly, we showed how computational models, bioinformatics analyses, and in vivo observations can be integrated in order to formulate and validate novel biological hypotheses.

The last case study is presented in Chapter 5. We constructed a regulatory network model based on the functionality of cis-regulatory elements in order to generate
fundamental insights into cellular fate differentiation during haematopoiesis. Particularly, we took advantage of state space analysis techniques, explained in Chapter 2, to guide \textit{in vivo} validation of the novel inhibitory link between the proteins Gata1 and Fli1.

Finally, in Chapter 6, I argue that in order to reach a software-like description of biological behaviors, we should be able to abstract from the physical effects of chemical reactions towards the functions accomplished by such chemical changes in a systemic perspective. It is already necessary, and it will be even more in the future, given the incredible extent and speed of knowledge gain, to reduce the vast amount of complex molecular and systemic interactions to human understandable terms and, therefore, to create a sound and solid abstraction framework for the construction of biological models.