

Chapter 6

Conclusion

In this thesis we have shown that rewriting systems are suitable for modelling and analysing biological systems quantitatively. Calculi of Looping Sequences, which is a class of formalisms based on rewriting systems, is used to model all biological systems described in this thesis.

We have used rewriting system not only at the modelling level, but also at the implementation level. We have used Maude, a rewriting logic based formalism, to implement, simulate and model-check our models. Our approach is discrete and stochastic and models system states by using terms and system behaviour by using rewrite rules. In this sense our approach differentiates itself from most approaches used in systems biology, which are continuous and deterministic, and mostly use differential equations to define the behaviour of the system.

Calculi of Looping Sequences consists of several variants, each equipped with formal syntax and semantics. However, such syntax and semantics cannot be directly used for implementation. Models of biological systems at molecular level usually contain a large number of molecules, which yield a very large state space. In Chapter 3 we have defined a compact representation for system states and an operational semantics based on such representation. To handle the state explosion problem we have chosen to perform statistical model-checking by sampling the state space of the system. Using this approach we were able to show that rewriting systems, especially Calculi of Looping Sequences, support not only modelling quantitative aspects of biological systems, but also analysis using simulation and model-checking.

We have realised that *in silico* biology requires not only a model of biological systems at molecular level, but also an integrative model at all possible levels. In Chapter 4 we have proposed an approach to integratively model biological systems using different levels of representation. We have also provided a mechanism to link models at different levels of representation, so that the behaviour of the system of interest at a given level of representation depends on the behaviour of the system at lower levels. Our approach also supports visualisation of the system behaviour at a high level. Visualisation is important to compare the system behaviour with what we observe in real biological processes, especially when the behaviour is related with spatiality, as in the growth of an organ.

When we model a biological system, we often have to take into account the interaction between organisms and the environment where they live. The environment provides resources which are needed by organisms to sustain their lives. Many approaches in modelling biological systems do not consider the environment as part of the model in order to keep the model simple. Sometimes we cannot take this kind of approach, since the environment is a crucial factor in the evolution of the biological system of interest. This phenomenon is shown in Chapter 5, where we model the dynamics of a population of organisms. The development of each organism depends on many environmental factors, thus we have to consider the environment as part of our model. These environmental factors are usually weather related events, such as rainfalls and temperature changes. We model them as external events. Our approach supports incorporating real weather data into the model. In this way we can use the data to validate our model.

We believe that the approach we have presented in this thesis is general and supports the integrative paradigm of systems biology. The generality of our approach is shown by applying it to different domains: from cell biology both at molecular and microscopic levels to population biology. The integrative paradigm has been illustrated by modelling the cell cycle at different levels of representation, which are linked with each other.

Interesting future work could be the combination of our approach to model a system at different levels of representation with our approach to model external events. The resulting approach could be used to model population dynamics of animals, especially spatial aspects of the dynamics. In this way we could use visualisation to observe some high level behaviour of the population as a whole, such as *population dispersal*. This phenomenon is useful for modelling the spread of a disease by an animal that acts as a vector.

The tools we are using in this thesis are based on Maude. The behaviour of a system is modelled using Maude rewrite rules. This requires the modeller to understand Maude syntax. The development of tools that provide a user friendly interface for a modeller to input the model would be an interesting future work. These tools should also be equipped with the capability to visualise the output using either charts or animation. In this way we can provide a set of tools for biologists, who are non experts in computer science, to perform *in silico* experiments with biological systems.

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