

Chapter 7

Agent–Based Modelling in Multicellular Systems Biology

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ABSTRACT

*This chapter aims at discussing the content of multi-agent based simulation (MABS) applied to computational biology i.e., to modelling and simulating biological systems by means of computational models, methodologies, and frameworks. In particular, the adoption of agent-based modelling (ABM) in the field of multicellular systems biology is explored, focussing on the challenging scenarios of developmental biology. After motivating why agent-based abstractions are critical in representing multicellular systems behaviour, MABS is discussed as the source of the most natural and appropriate mechanism for analysing the self-organising behaviour of systems of cells. As a case study, an application of MABS to the development of *Drosophila Melanogaster* is finally presented, which exploits the ALCHEMIST platform for agent-based simulation.*

INTRODUCTION

The chapter reviews the role of *agent-based modelling* (ABM) in the simulation of biological systems, focussing on the simulation of multicellular systems. Modelling multicellular systems requires tools that can support multi-scale models, where different cells form large-scale, dynamic networked systems – as, e.g., in tissues of cells, organs, and even full embryos – and where both the biochemical reactions that occur inside each cell and the molecules diffusion along the tissue (mediating the interaction among nuclei/cells) can be reproduced (Dada & Mendes, 2011; Deisboeck, Wang, Macklin, & Cristini, 2011).

Despite its recognised value for modelling complex systems (Bonabeau, 2002), and also for modelling biological systems (Holcombe et al., 2012), ABM is still not completely accepted as a suitable modelling approach in the literature on multicellular systems—whereas, dually, multicellular systems are not usu-

DOI: 10.4018/978-1-5225-1756-6.ch007

ally considered as a valid application domain in the ABM literature. This provides the first motivation behind this chapter: that is, pointing out the potential of ABM in the context of multicellular systems.

ABM grounds on top of the three fundamental abstractions for multi-agent systems (MAS) (Zambonelli & Omicini, 2004):

- **Agent:** The autonomous source of activity in the system,
- **Society:** A group of interacting agents, and
- **Environment:** The context where agents and societies live and interact. As such, agent-based models are perfectly suited for studying the systemic and emergent properties that characterise a multicellular system, meant to be reproduced *in virtuo*.

ABM looks a promising approach in this context given the direct mapping between agent-based abstractions and multicellular systems: agent-cell (with internal and interacting behaviour), agent society-multicellular system, environment-extracellular matrix.

As an example, *developmental biology* is used as a reference scenario to demonstrate the power of *multi-agent based simulation* (MABS). Developmental biology is a challenging branch of life science that studies the process by which organisms develop, focussing on the genetic control of cell growth, differentiation and movement: as such, it analyses multicellular systems during their formation and development. In particular, the chapter illustrates the application of MABS to the development of *Drosophila Melanogaster* based on the ALCHEMIST agent-based simulation framework (Pianini, Montagna & Viroli, 2013; Montagna, Omicini & Pianini, 2016). In the overall, the contribution of the chapter can be articulated as follows:

1. Reviewing the actual state-of-the-art in MABS applied to multicellular systems biology, as well as making an argument for the value of agent-based approaches in the field;
2. Reporting on a case-study of agent modelling and simulation;
3. Discussing the specific issue of developmental biology – that is, one of the hottest and most challenging field in biology –, and verifying which specific achievements were obtained in the last years by adopting the agent metaphor within biological studies;
4. Providing an example of MABS platform for biological systems; and
5. Supplying biologists with a tool possibly helping them finding insights into the biological phenomena, experimenting working hypotheses, performing the so called *what-if* analysis, and making prediction on system behaviour.

BACKGROUND

The field of research devoted to understanding biological cell functionalities by means of modelling and simulation techniques is called *Systems Biology*. The field originally emerged around year 2000, in particular the pioneering work of Kitano (2002). Systems biology is grounded on the idea that the high complexity of phenomena and mechanisms regulating biological system dynamics cannot be understood by *in-vivo* experiments alone—mostly, due to the limitation of experimental techniques in investigating the coordinated activities among system components. In order to understand biological systems, other concepts and tools are required that could enable the execution of *in-silico* experiments, *i.e.*, modelling

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