Chapter 3
In Silico Biology:
Making the Most of Parallel Computing

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ABSTRACT

Biological systems are typically complex and adaptive, involving large numbers of entities, or organisms, and many-layered interactions between these. System behaviour evolves over time, and typically benefits from previous experience by retaining memory of previous events. Given the dynamic nature of these phenomena, it is non-trivial to provide a comprehensive description of complex adaptive systems and, in particular, to define the importance and contribution of low-level unsupervised interactions to the overall evolution process. In this chapter, the authors focus on the application of the agent-based paradigm in the context of the immune response to HIV. Explicit implementation of lymph nodes and the associated lymph network, including lymphatic chain structure, is a key objective, and requires parallelisation of the model. Steps taken towards an optimal communication strategy are detailed.

INTRODUCTION

Biological systems are typically complex and adaptive. They are complex, involving large numbers of organs, cells, molecules, as well as their interactions. They are adaptive, because their behaviour evolves over time, and can change and learn from experience, e.g. through memory in the context of immune responses.

Key principles of complex adaptive systems, (e.g. RNA folding or immune response), are *emergence* and *self-organisation*. Emergence refers to patterns of system evolution arising from an abundance of simple, low-level, interactions, (see e.g. Corning (2002)). For the immune system, this is particularly relevant, as the response is obtained from multiple cell interactions throughout the body. Self-organisation refers to increased complexity obtained without intervention from outside sources, (e.g. De Wolf and Holvoet (2005)). Again, this is an obvious property of both the infection mechanisms of HIV and the immune response to those.

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Given these two properties, a full description of a complex adaptive and definition of the way in which low-level unsupervised interactions, (and their relative importance), lead to its overall evolution, are far from trivial.

In this chapter, we introduce concepts and approaches designed to gain insight into complex systems, focusing on immune models. Concepts of bottom-up and top-down programming are explained. Approaches include mathematical, shape-space models, cellular automata and agent-based models.

We, subsequently, further detail the agent-based paradigm, which is very suited to biological systems. Limitations of existing agent-based immune models are analysed, forming a basis for the model objectives as case study.

The model structure is detailed next, with particular emphasis on the importance of the balance between agent diversity and agent population size, and on the need for an explicit implementation of the lymph network.

Due to the computational requirements of such a model, a parallel implementation is necessary. Efforts towards an optimal parallel implementation are detailed, along with a presentation of MPI, (*de facto* standard for parallel programs).

Finally, we present some important model results, and reflect on the applicability of a similar development framework for other biological systems.

MODELLING COMPLEX SYSTEMS

Two categories of complex system modelling are discussed, *top-down* and *bottom-up* designs (Bohringer and Rutherford, 2008). The main concept of a top-down design is to break down a system into several components, expected to be easier to manipulate and understand. The overall system is formulated and specified, but without going into details of its parts. In an iterative process, each component is then defined in more detail and, if necessary, split into lower-level subsystems. This process, repeated until the entire specification is obtained for its base elements, involves use of black boxes which facilitate model development, but may also hinder model validation if these fail to elucidate elementary mechanisms of the system studied.

In a bottom-up approach, individual base components are detailed and designed, and then linked together. These form more complex systems, which are again linked, in an iterative process, and the top-level model increasingly emerges. This approach is, therefore, particularly suited to complex adaptive systems, which in their structure demonstrate both emergence and self-organisation. The remainder of this Section considers several examples of top-down/bottom-up design, grouped in three families: mathematical, shape-space, and agent-based models.

In the context of HIV research, mathematical models were first introduced to study the epidemiological aspect of infection, (i.e. spread in a human population). This early focus was motivated by the need to understand dynamics of the infection and population threat, but also by a lack of detailed biological information, which ruled out models of pathogenesis. Although data, even on spread of HIV, were sparse, models were developed, which focused on specific "at risk" groups, e.g. early work by Anderson (1988). More accurate medical information and improved computing resources have now led to considerably more advanced epidemiological models, e.g. Naresh et al. (2006). In the context of this research, the mathematics of pathogenesis are directly relevant. Models using differential equations (DE), to reproduce variations of cell counts and viral loads appeared in the late 1990s, (see e.g. Perelson and Nelson (1999)) and are typical of top-down designs. These have been refined for each count variation by detailing different DEs to account for viral production, and drug therapies such as RT inhibitors or protease inhibitors. These models, however, can not currently cover whole infection