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Computational modelling of mycobacterium infection and innate immune response in zebrafish

Viana de Carvalho, R.

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Author: Viana de Carvalho, Rafael

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Summary

The modeling of biological systems is an important issue in the research of living organisms in the live sciences. In Health, biological models are essential to study treatment and solutions for infectious and contagious diseases. Therefore, researches use animal models that are closely related to human. At the same time, many ethical, legal and financial aspects have a strong influence on research using animal models. Along that line, computational models represent an alternative, and an addition, in order to minimize the impact of such aspects. Moreover, it can help in the research of infectious diseases performing experiments that are not feasible in lab.

Tuberculosis (*Tb*) is a contagious bacterial infectious disease, through *Mycobacterium tuberculosis*, that is still killing millions of people worldwide. In order to gain understanding of tuberculosis infection, several studies in *Tb* use *Mycobacterium marinum* infection in zebrafish (*Mtb*) as basis for their research. One reason is related to the fact of similarity of the infection behaviour between *Mtb* and *Tb* in humans. Moreover the impact of zebrafish on the ethical, legal and financial aspects for animal model research is low. Another reason to study mycobacterial infection process using zebrafish is the advantage on the data acquisition due to the transparency of zebrafish embryos and larva, so that a considerable data volume that can be generated in a short period of time.

In mycobacterial infection diseases, several components represent a biological process that interacts with each other and the environment through complex networks interconnected in a layered fashion. This thesis is presenting the computational modeling aspects of the mycobacterial infection process, in particular the infection through *Mycobacterium marinum* and the response of the innate immune system in zebrafish (*Danio rerio*). In the computational modeling process, both the qualitative and quantitative aspects of the models discussed have been addressed, together with simulations using different scenarios as well as validation of the results.

Each chapter represents a part of the modeling process, which in a modular fashion gradually establishes a model capable of representing the interactions between the principal components involved in the behaviour of the biological phenomenon. The objective of the research presented in this thesis is to introduce a more precise model that can represent the initial stages of a mycobacterium bacterial infection.

In Chapter 1, an overview on modeling methods used to model biological system is presented. The relevant aspects and characteristics of modeling process are raised as well as an extended discussion on the Petri net method, which is used in the models presented in this thesis.

Chapter 2 presents a qualitative model that represents the phases related to the dynamics of the mycobacterial infection process and the reaction of the innate immune system. From a macroscopic

perspective it is possible to visualize the dynamics of the infection process from the moment the bacteria is inoculated, detected and phagocytosis by the macrophages, the migration and bacterial proliferation, granuloma formation, as well as the dissemination of the infection to other regions in the host organism.

In Chapter 3 another qualitative model is introduced which represents one of the stages related to the infection process from a microscopic perspective. The model described in this chapter is composed of a range of components, in fact sub-models, that represent the interactions between the bacteria and the macrophage. This is organized in different hierarchical levels; i.e. intracellular and molecular. It is possible to visualize the regulatory pathways explored by the bacteria for survival and proliferation in the immune cell. Moreover, it is described how it is possible to simulate different scenarios through which the macrophage is able to prevent the proliferation through the process of bacterial digestion or apoptosis.

In Chapter 4 an important step in the process of modeling biological systems is introduced; that is, the merging of independent models that are, however, inter-related. The model that is presented in this chapter combines, in a hierarchical fashion, the models described in Chapters 2 and 3 in a unique structure that is able to visualize the infection process from the dynamics of the process, i.e. the macroscopic perspective, to the regulatory pathways, i.e. the molecular perspective. It is possible to simulate the infection process and correlate with the observed behaviour in nature, i.e. *in vivo* experiments. Besides, a 3D visualization tool is added in order to provide a better interpretation of the behaviour of the infection. This facilitates to relate the *in silico* to the *in vivo* observation.

Chapter 5 introduces a quantitative extension to the model that was previously described in Chapter 4 as a qualitative model. In this chapter integration is accomplished between the qualitative model and a quantitative model, defined by probabilistic functions on the processes related to the distribution of the granulomas over the host organism. As a result, a stochastic model is introduced which is able to simulate the behavior of bacterial infection in zebrafish. Data from laboratory experiments are used as a basis for a quantitative analysis of the model as well as simulations, verification and validation of the results.

In our studies, we emphasize the importance of the identification of the characteristics of the biological system to be modelled. The importance of collecting and connecting data as well as how they influence the modeling decision is essential to create a computational model that can represent the biological phenomenon. By modeling bacterial infection with a Petri net, we learned about the value of simplification, modularization and extension of the modeling process. It is, important to emphasize that the methodology introduced in this thesis can be used for the representation of other biological phenomena, i.e. diabetes. We hope that the techniques and methods that have been discussed in this thesis can then serve as a basis for future research in the modeling process of biological systems, using stochastic and hierarchical models implemented in Petri nets.