



UvA-DARE (Digital Academic Repository)

Use of prior knowledge in biological systems modelling

Reshetova, P.V.

Publication date

2017

Document Version

Other version

License

Other

[Link to publication](#)

Citation for published version (APA):

Reshetova, P. V. (2017). *Use of prior knowledge in biological systems modelling*. [Thesis, fully internal, Universiteit van Amsterdam].

General rights

It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations

If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: <https://uba.uva.nl/en/contact>, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.

Chapter 7

Summary

Use of prior knowledge to plan experiments or to compare results with already known details has always been a crucial step in scientific research. Quick development of high-throughput experimental techniques and information technologies allows to evolve the use of prior knowledge even further. This work explored the use of prior knowledge as a basis for biological systems modelling and analysis. We discussed (1) the incorporation of prior knowledge in the analysis of high-throughput data in transcriptomics and metabolomics, and (2) the use of incomplete prior knowledge to build models of biological systems.

Chapter 2 reviews methods in transcriptomics and metabolomics that incorporate prior knowledge in the analysis of high throughput data. We specifically focused on a collection of methods that incorporated prior knowledge to estimate model parameters; we excluded methods that used prior knowledge to verify or validate the final results of a model or analysis. We divided the reviewed methods into three groups based on the underlying mathematical model: exploratory methods, supervised methods, and estimation of covariance matrices. By defining relationships among variables in high throughput data based on known *a priori* knowledge the reviewed methods reduce the solution space and/or focus the analysis on biological meaningful results. In this way the methods lead the analysis towards underlying biology. Despite this advantage, incorporation of prior knowledge into a model is not widely used. We concluded that the definition and acceptance of a common test framework to test methods incorporating prior knowledge and to test the prior knowledge influence on results is missing and urgently needed. The test framework would help to understand when and how to optimally apply prior knowledge in data analysis methods. Moreover, it should help to understand when prior knowledge is not correct or not appropriate for the analysed system.

Next, in Chapter 3 we used incomplete and scattered knowledge about the human genistein elimination pathway to build a Petri net model. Scattered knowledge in conjunction with the complicated nature of alternative genistein elimination routes hampers building and parameterization of quantitative models. For this reason, we suggested that the network structure alone might contain enough information to study the system dynamics. Using the Petri net model we showed that widely used metabolic profiles solely measured in venous blood were not sufficient to uniquely parameterize the model. Additional simulations based on the model suggested that gut epithelium metabolite profiles would allow to infer the relative contributions of concurrent elimination routes with higher accuracy, and to improve the reconstruction of concentration profiles of all metabolites in this pathway. Overall, we showed that a Petri net model based on scarce prior knowledge may be used to explore the pathway properties and to assist in the design of future experiments to complete missing knowledge.

In Chapter 4 we built an ODE model to determine the affinity distribution among B-cell populations measured with RNA repertoire sequencing during an immune response. While a lot is known about B-cell maturation, many important details remain to be elucidated. Particularly, while the lack of specific details about B cells, T cells, and antigen interactions prohibit the implementation of a precise model, these interactions determine which B-cells survive and, therefore, determine the affinities observed in the B-cell population. To overcome this lack of knowledge but also to avoid an overly complex model we suggested a simplification through a general sigmoidal function that imposes competition between B cells without the implementation of mechanistic details of B cells, T cells and antigen interactions. Despite this simplification, the model successfully generated valuable insights in the B-cell affinity distribution during affinity maturation. The result is intriguing because we show that expanded clones, widely used for further downstream analysis, might not be the highest affinity cells. We hope that this result will get experimental validation in the near future and will have impact in future clinical strategies for selection and characterization of B cells.

In Chapter 5 we used the ODE model of B-cell maturation to explore and visualize the evolution of B-cell lineage trees during affinity maturation. We followed changes in lineage tree parameters such as total number of nodes, node outgoing degrees and tree length, with progression of the immune response. Our simulations showed that lineage tree sizes largely varied while the range of the observed outgoing degrees became much smaller with proceeding affinity maturation. Moreover, our model allowed to investigate the B-cell affinity maturation in a novel way that is currently virtually impossible to obtain using experimental data. Particularly, the model allowed to simultaneously follow affinity changes and subclonal abundance (cell counts) in the context of B-cell lineage trees. It showed that the affinity maturation is not necessarily a linear process and high cell counts of a subclone do not guarantee the production of high affinity or highly expanded descendants. In general, the work in Chapters 4 and 5 expanded our understanding of the B-cell maturation.