



UvA-DARE (Digital Academic Repository)

Use of prior knowledge in biological systems modelling

Reshetova, P.V.

[Link to publication](#)

License
Other

Citation for published version (APA):
Reshetova, P. V. (2017). *Use of prior knowledge in biological systems modelling*.

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.

Polina Reshetova

Use of prior knowledge in biological systems modelling

P. Reshetova

Use of prior knowledge in biological systems modelling

2017

Use of prior knowledge in biological systems modelling

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. ir. K.I.J. Maex
ten overstaan van een door het College voor Promoties ingestelde commissie,
in het openbaar te verdedigen in de Agnietenkapel

op donderdag 2 maart 2017, te 10.00 uur

door

Polina Vladimirovna Reshetova
geboren te Terentyevskoye, Rusland

Promotiecommissie:

Promotor:

- Prof. dr. A. H. C. van Kampen Universiteit van Amsterdam
- Prof. dr. A. K. Smilde Universiteit van Amsterdam

Copromotor:

- dr. J. A. Westerhuis Universiteit van Amsterdam

Overige leden:

- Prof. dr. S. Brul Universiteit van Amsterdam
- Prof. dr. A. H. Zwiderman Universiteit van Amsterdam
- Dr. P. L. Klarenbeek Universiteit van Amsterdam
- Dr. J. E. Guikema Universiteit van Amsterdam
- Prof. dr. R. M. H. Merks Leiden Universiteit
- Prof. dr. J. Heringa Vrije Universiteit Amsterdam
- Prof. dr. H. V. Westerhoff Universiteit van Amsterdam

Faculteit der Natuurwetenschappen, Wiskunde en Informatica

The research reported in this thesis was carried out at the Swammerdam Institute for Life Sciences, Faculty of Science, University of Amsterdam (Science Park 904, 1098 XH Amsterdam, The Netherlands) and was supported by the BioRange programme of the Netherlands Bioinformatics Centre (NBIC).

Contents

1	Introduction	5
1.1	Modelling approaches	5
1.1.1	Statistical models for high-throughput data analysis.	7
1.1.2	Challenges using prior knowledge in high-throughput data analysis.	8
1.1.3	Network-based models of biological systems	9
1.1.4	Mathematical models of biological systems	10
1.2	Scope and outline of the thesis	11
2	Use of prior knowledge for the analysis of high-throughput transcriptomics and metabolomics data	13
2.1	Background	13
2.2	Two phases of the analysis of high dimensional data	14
2.3	Exploratory methods	16
2.3.1	Component models	16
2.3.2	Cluster models.	18
2.4	Supervised classification methods	22
2.5	Covariance matrices	25
2.6	Discussions and Conclusions	26
2.7	Supplementary Material 1. Additional figures.	29
2.8	Supplementary Material 2. Tables.	34
3	Using Petri nets for experimental design in a multi-organ elimination pathway	39
3.1	Introduction	39
3.2	Results	41
3.2.1	Fraction estimation from simulated reference profiles for all places.	41
3.2.2	Fraction estimation from simulated reference profiles for gut and liver places.	44
3.2.3	Inclusion of other constraints.	45
3.3	Discussion	49
3.4	Conclusion	50
3.5	Materials and Methods	51
3.5.1	Experimental data	51
3.5.2	A Petri net model of genistein elimination pathway	51
3.6	Appendix	55

4	Computational model reveals limited correlation between germinal centre B-cell subclone abundancy and affinity: implications for repertoire sequencing	67
4.1	Introduction	68
4.2	Material and Methods.	69
4.2.1	Sample and experimental data.	69
4.2.2	The mathematical model	70
4.2.3	Identification of expanded subclones	76
4.2.4	Comparison of simulated and experimental data	77
4.3	Results	79
4.3.1	Subclonal diversity.	80
4.3.2	Subclonal expansion.	81
4.3.3	BCR affinity of (un)expanded subclones	81
4.4	Discussion	85
4.5	Supplementary Material	88
5	The evolution of B-cell lineage trees during affinity maturation	91
5.1	Background.	91
5.2	Methods	93
5.2.1	Software	93
5.2.2	Computational model	93
5.2.3	Lineage tree construction	96
5.3	Results	98
5.3.1	Visualization of lineage tree development during the GCR.	98
5.3.2	Subclonal expansion and affinity in the context of lineage trees	102
5.4	Discussion	103
6	Discussion	105
6.1	Prior knowledge in statistical models	105
6.2	Prior knowledge to model genistein elimination pathway with Petri nets	106
6.3	Prior knowledge to model B-cell affinity maturation with differential equations	108
6.4	Databases as stores of prior knowledge	108
6.5	Biomedical text mining as a source of prior knowledge	109
7	Summary	111
8	Samenvatting	113
	References	115