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Genetic regulatory networks inference : modeling, parameters estimation & model validation

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Publication date
2010

[Link to publication](#)

Citation for published version (APA):

Fomekong Nanfack, Y. (2010). *Genetic regulatory networks inference : modeling, parameters estimation & model validation*.

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English Summary

In many animals, morphogen gradients specify different structures starting from a single cell at early embryo development. The morphogens provide spatial information by forming concentration gradients that subdivide the developing embryo in different regions. Distinct cell types and structures emerge as a consequence of the different combinations of morphogen gradients. This is a general mechanism by which a cell can generate cell type diversity and structures in body plan formation.

Understanding the body plan formation also requires understanding the underlying biochemical process. This is the level at which genes influence the transcription of other genes. Genetic regulatory networks (GRNs) are an ensemble of interconnected genes that dynamically control the level of expression for each gene in the genome. Understanding how GRNs control the mechanism that leads to a specific phenomena such as body patterning requires knowledge of the active genes and the architecture of the network.

In some cases the genome and sometimes the genes' connectivity are known from experimental studies. An additional option to study GRNs is to use mathematical models and simulation studies. Qualitative and quantitative models may provide insights in the causal relationships between components of a network as well as the mechanisms behind the network dynamics.

It is possible to use a quantitative model to infer the mechanism behind pattern formation ruled by GRNs. Assuming that all parameters are known from literature or experimental measurements (i.e., all initial conditions, kinetic coefficients in the biochemical system, diffusion coefficients, transcription-binding factors, and the spatial domain is specified), the inference problem consists in solving the equations and is called the *direct problem*. Then, by means of sensitivity analysis, one can analyze the model robustness with respect to the

parameters. Unfortunately, in practice many parameters are unknown and estimation of these parameters from experimental data is needed for quantitative modelling of GRNs. This is called the *inverse problem*. In such a case, only the governing equations describing the system and possibly some of the parameters therein are given.

Inverse modelling of GRNs capable of simulating a continuous spatio-temporal biological process requires accurate data and a good description of the system and ultimately an efficient method to estimate the unknown parameters. These problems are typically ill-posed. In the case of spatial and temporal data, the fitting procedure can be computationally very expensive and inaccurate. Complexity may come from the uncertainty laying in the experimental data measurement or/and the dimensionality of the model. Therefore the choice of an appropriate optimisation technique is crucial. Nevertheless, finding a set of parameters that reproduces the observation does not necessarily imply that the network structure has been identified. In some cases, the network inference can lead to an unique network, while in many cases, the optimisation can lead to circuits with different topology. It is therefore necessary to find the true or most plausible network out of the multiple candidates. Systematic analysis such as model uncertainty or sensitivity analysis should be considered to assess the validity of the reverse-engineered model.

In the current thesis, we investigate several aspects of the inference of GRNs capable of simulating spatio-temporal pattern in development. The main focus is the parameter estimation and model validation. As a case study we use a quantitative spatio-temporal model of the regulatory network for early development in *Drosophila melanogaster*. First we present a method based on evolutionary algorithm, an hybrid (μ, λ) -ES used to estimate the parameters of the investigated model. Compared to previous methods applied to the same problem, this method is much faster and it is becoming possible to obtain a larger set of circuits that simulate with very good accuracy the gene expression profiles.

Once parameters have been estimated, it is essential to address their reliability. We investigated the sensitivity and robustness of circuits obtained from reverse engineering of the regulatory network for early development in the fruit fly; *Drosophila melanogaster*. We analyse the uniqueness of the predicted network and the model stability. We show that amplitude variation and defects within the simulated gene expression can be identified by clustering the simulated gene expression profiles. The analysis demonstrates that the model-solutions lead to several networks having different stability behaviour. Parameter sensitivity analysis allows one to discriminate between circuits having significant parameter differences but exhibiting the same quantitative pattern. Furthermore, we show that using a stochastic model derived from a deterministic solution, one can introduce fluctuations within the model to analyze the circuits' robustness. Ultimately, we show that there is a close relation between circuit sensitivity

and robustness. The current study shows that reverse engineering of GRNs should not only focus on estimating parameters by minimizing the difference between observation and simulation but also on other model properties. Our study suggests that multi-objective optimization based on robustness, stability and sensitivity analysis has to be considered