Identifiability analysis and predictive power of the gene circuit model

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The correct prediction of system behavior is a necessary property of a mathematical model that is largely determined by the identifiability of model parameters. The number of parameters that are estimated by fitting to experimental data is typically large. For the comprehensive analysis of modeling results it is necessary to know how reliable the obtained estimates are, that constitutes the identifiability problem. Insufficient or noisy data, as well as the strong parameter correlation or even their functional relation may prevent the unambiguous determination of parameter values. In addition, some of parameters bearing certain biological sense however have estimates that do not essentially affect the model solution. The most common approach used in identifiability analysis is the study of the local sensitivity of the model to parameters [1].

A typical example of predictive model is a gene circuit model [2] that dynamically reconstitutes the set of interactions within the genetic network. In an ideal world the model is fitted to wild type (WT) data and the solution obtained by zeroing of parameters related to a target gene should show a good fit to data null mutant for this gene. However, the correct prediction of the model behavior at fixed values of some parameters is only possible if these parameters are identifiable. If there exist strong correlations between fixed parameters and those estimated by fitting, the prediction may become infeasible, as in this case the changes of parameter values cause the simultaneous changes in correlated parameters. But even in case of parameter independency good prediction may become infeasible if the model solutions fitted to mutants are highly sensitive to a certain subset of parameters to which the solutions fitted to WT are insensitive.

In this study we introduce a criterion of predictive power of the model that is based on measures of model sensitivity to parameters and apply it to the gene circuit model presented in [3] that describes the dynamics of segmentation gene expression in *Drosophila*

melanogaster. Two types of measures are considered: the first one reveals the biologically substantiated low sensitivity of the model to changes of parameters that are responsible for correct reconstruction of expression patterns in mutants, while the second one takes into account their correlation with the other parameters.

It is shown that the model solution, obtained by fitting to gene expression data in WT and Kr- mutants simultaneously, demonstrates much higher predictive power with respect to gene expression patterns in null mutants for *Kr* than those only fitted to WT data. The method makes it possible to predict the possibility to correctly reproduce the expression of other genes in mutants. Besides, the requirement of high values of the measures introduced in this work may be used as a necessary condition in the search of model solutions to provide the high predictive power.

1. M.Ashyraliyev, J.Jaeger, J.G. Blom (2008) On Parameter Estimation and Determinability for Drosophila Gap Gene Circuits, *BMC Systems Biology*, **2**:83.

2. J. Jaeger et al. (2004) Dynamic control of positional information in the early Drosophila embryo, *Nature*, **430**:368-371.

3. K.Kozlov et al. (2012) Modeling of Gap Gene Expression in Drosophila Kruppel Mutants. *PLoS Comput Biol* **8**(8): e1002635.