

Constraint-based Modeling and Kinetic Analysis of the Smad Dependent TGF- β Signaling Pathway

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Traditionally, the quantitative models are validated by fitting a few experimental data. Due to the complexity of the model and the quality of the data, over-fitting is a common problem for parameter estimation. When the model has many estimated parameters and the corresponding data is a few, the over-fitting problem might lead to some unwarranted conclusions because the parameter set in the model might be a special domain of possible parameter sets which can similarly fit the data well, but result in different predictions. Since constraint-based modeling is an effective method to narrow the range of the possible parameter space for quantitative models, we proposed a constraint-based modeling method to build a comprehensive mathematical model for the Smad-dependent TGF- β signaling pathway by fitting experimental data and incorporating the qualitative constraints from the experimental analysis.

We established a comprehensive model for Smad dependent TGF- β signaling pathway in mammalian cells, which includes three modules: receptor trafficking and signaling; Smad nucleocytoplasmic shuttling and signaling and I-Smad negative regulation. Most parameter values in the model are derived from experimental analysis in epithelial cells. Seven unknown parameter values are estimated by using a modified version of the tool SBML-PET [1], which incorporates stochastic ranking evolution strategy (SRES) for parameter estimation jobs. The objective of the parameter estimation is to find the most feasible parameters in the model that reproduce the quantitative experimental data for the TGF- β signaling pathway. At the same time, the model with the estimated parameters should satisfy some qualitative experimental observation of this pathway.

The performance of the model generated by constraint-based modeling method is significantly improved compared to the model obtained by only fitting the quantitative data. The model agrees well with the experimental analysis of TGF- β pathway, such as the time course of nuclear phosphorylated Smad, the subcellular location of Smad and signal response of Smad phosphorylation to different doses of TGF- β (Figure 1). The simulation results show that the TGF- β signal response is regulated by the balance between the strength of signal initiation from clathrin dependent endocytosis and the strength of negative feedback in the venue of non-clathrin mediated endocytosis (Figure 2).

Figure 1: Comparison of experimental analysis and simulation results from the model obtained by constraint-based modeling method. (A-B) for “in-sample fit”. (C-D) for “out-sample fit”.

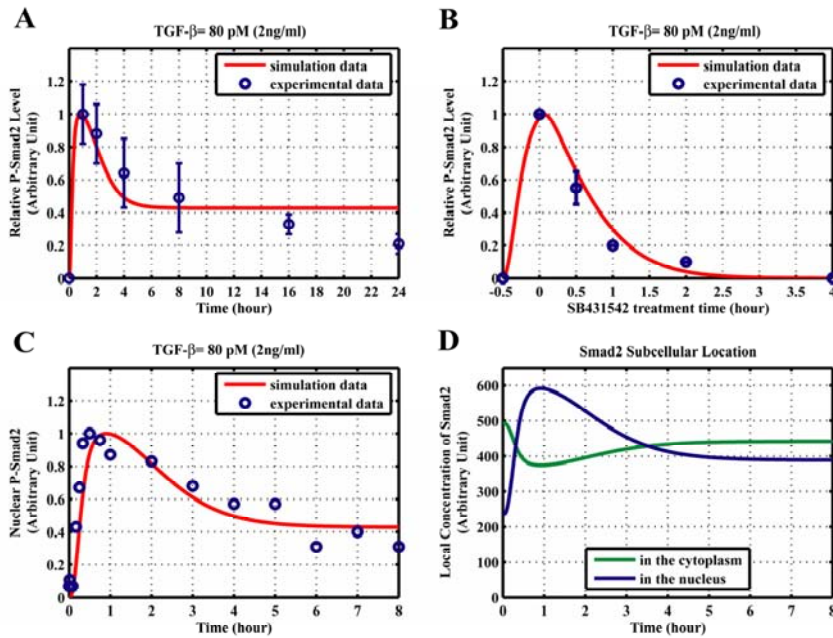
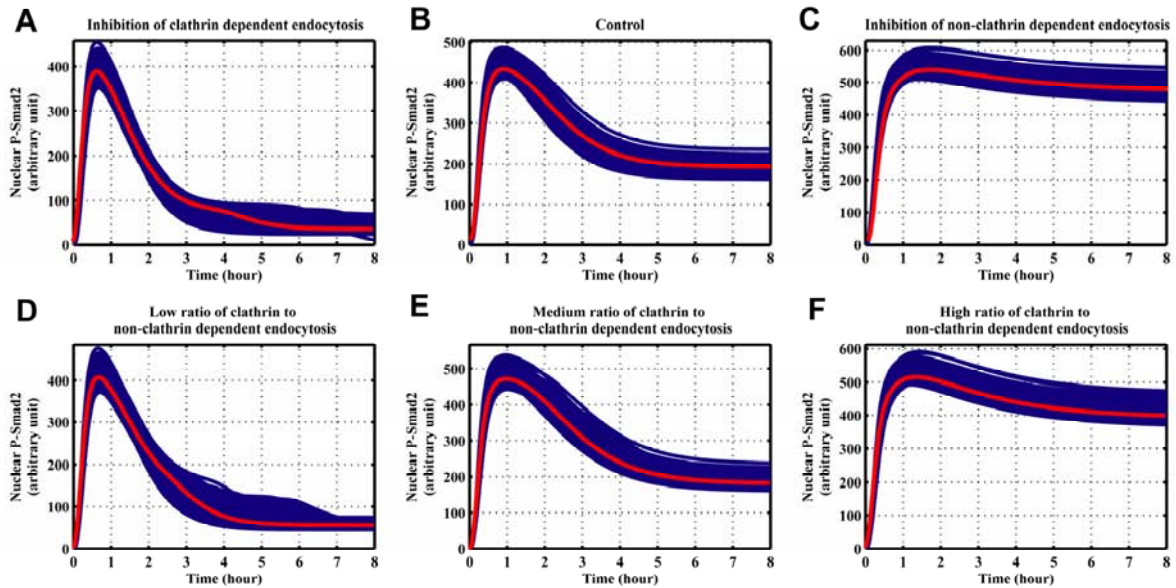


Figure 2: Computational simulations of the time course of nuclear phosphorylated Smad2 by the inhibition of different receptor endocytosis.



References

1. Zi Z, Klipp E (2006) SBML-PET: a Systems Biology Markup Language-based parameter estimation tool. *Bioinformatics* 22: 2704-2705.
2. Zi Z, Klipp E (2007) Constraint-based Modeling and Kinetic Analysis of the Smad Dependent TGF-β Signaling Pathway. *PLoS ONE* (in press).