Distribution of a bifurcation parameter in a genetic network with uncertain parameters

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Introduction

The vast amount of gene expression data nowadays at hand offers the possibility to learn the genetic networks of the organisms by theoretical methods. For gene expression time series data dynamical modelling of the genetic network with differential equations is a natural way. Learning the network then means finding those parameters of the differential equations that encode the network structure. But parameter estimation is in most cases the limiting step in modelling of non-linear systems. Parameters might not be identifiable or are unreliable because the data is too scarce. Uncertaintites in parameters entail not only quantitative but also qualitative uncertainty in the system's behaviour. For this reason we change standpoint and explore for a small genetic network to what extent the structure itself determines the system's behaviour.

Approach

The presented approach is to assume that the parameters are not fixed or estimated, but drawn from a distribution, which has to be specified [6] [7]. This parameter distribution, together with the fixed network structure, leads to distributions of the observables. Repeated simulations of the model, with parameters drawn from their distributions, will yield many realisations of the dynamic profiles and observable quantities of the system. If the distribution of a quantity is sharp, we conclude that this quantity is strongly determined by the network structure, at least for the ensemble of parameters considered. This allows to study which kind of quantitative and qualitative behaviour can be expected from the model.

Monte Carlo simulations with random parameters have been used to compute the distributions of metabolic concentrations, metabolic fluxes, control coefficients, and other variables [6] [2]. The same approach has been applied to gene regulatory circuits [5] and a MAP kinase cascade [3]. Here we focus on another feature of dynamic systems, namely the location of a bifurcation point. We study a simple genetic network as has been analysed by Elowitz and Leibler [4]. It shows a parameter-dependent transition from a stable steady state to stable oscillations, known as a Hopf bifurcation. The Hill coefficient in the kinetic equations is a critical parameter. By sampling all other parameters from predefined distributions, we compute the distribution of the critical value.

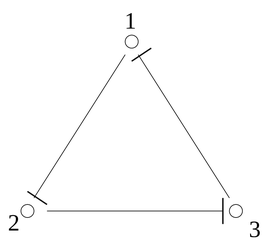
Dynamical network model

The type of network considered here consists of N genes. The simplification made is that mRNA and protein concentrations are merged into a single quantity. For each gene there is a production and a degradation term. The interaction among the genes via their respective products makes the production term a Hill kinetic:

$$\frac{\mathrm{d}x_i}{\mathrm{d}t} = -\alpha_i x_i + \frac{\beta_i}{\prod_{j=1}^{N}(1+(\frac{x_j}{k_{ij}})^{h_{ij}})}$$

where x_i is the concentration of mRNA of gene i, α_i is the degradation constant of the mRNA of gene i, β_i is the full strength of the promoter of gene i, and k_{ij} and h_{ij} are the dissociation constant and Hill coefficient for the binding of the product of gene j to the promoter of gene i. The sign of h_{ij} determines the type of interaction, i.e. activation or inhibition.

The repressilator

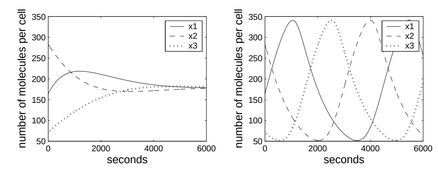


The repressilator [4] is a network of three genes forming a negative-feedback loop. The results presented here are from an analysis of the symmetric repressilator, i.e. $\alpha_i = \alpha$, $\beta_i = \beta$, $k_{ij} = k$ and $h_{ij} = h$. Thus the model equation are as follows:

$$\frac{\mathrm{d}x_1}{\mathrm{d}t} = -\alpha x_1 + \frac{\beta}{1+(\frac{x_3}{k})^h}$$
$$\frac{\mathrm{d}x_2}{\mathrm{d}t} = -\alpha x_2 + \frac{\beta}{1+(\frac{x_1}{k})^h}$$
$$\frac{\mathrm{d}x_3}{\mathrm{d}t} = -\alpha x_3 + \frac{\beta}{1+(\frac{x_2}{k})^h}$$

Bifurcation

Given values for α, β, and k, this system can show a Hopf bifurcation at a certain value $h = h_{\mathrm{crit}}(\alpha, \beta, k)$: for values $h < h_{\mathrm{crit}}$, the system has a stable steady state, while for $h > h_{\mathrm{crit}}$, the steady state becomes unstable and a stable limit cycle shows up. For the values $\alpha = 0.001$, $\beta = 0.5$, $k = 100$, we find $h_{crit} \approx 2.78$. The figure below shows the two behaviours of the symmetric repressilator for $h = 1 < h_{crit}$ and $h = 4 > h_{crit}$.

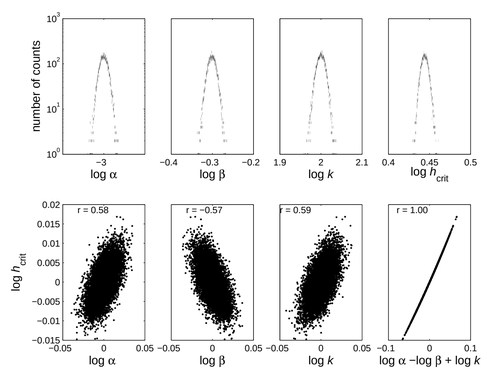


Parameter sampling and bifurcation analysis

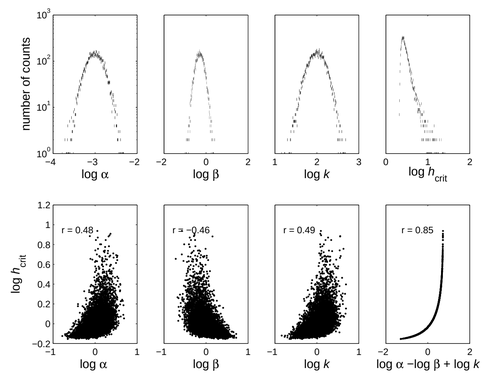
The parameters α, β, and k were drawn from log-normal distributions such that $\log_{10}\alpha$, $\log_{10}\beta$, and $\log_{10}k$ are independent and normally distributed with a standard deviation of σ and mean values $\bar{\alpha} = 0.001$, $\bar{\beta} = 0.5$, and $\bar{k} = 100$, respectively. We performed 10000 simulations for distributions with widths $\sigma = 0.01$ and $\sigma = 0.2$. By drawing a set of parameters, each time we obtain a realisation of the dynamic system in which the Hill coefficient h is still undetermined. For each realisation we run a bifurcation analysis to determine the critical value $h_{\mathrm{crit}}(\alpha, \beta, k)$ of the Hill coefficient. By repeating the drawing from the parameter distributions, we can sample the distribution of critical Hill coefficients. The critical parameter $h = h_{\mathrm{crit}}(\alpha, \beta, k)$ was determined using MATLAB with the package MATCONT [1] and searching at least the interval from 1 to 50.

Results

For a parameter width $\sigma = 0.01$ we were always able to determine the bifurcation points. In 10^4 simulations, no critical value lower than ~ 2.68 was found. For a parameter width $\sigma = 0.2$ we found a bifurcation point in 9779 out of 10^4 simulations.
We find positive correlation values for α and k, respectively, while β is negatively correlated with h_{crit}. This shows that a lower damping (small α) and a stronger coupling (high β or low k) between genes makes the system more prone to oscillations.
The qualitative behaviour of the cycle does not depend on the absolute scaling of time and concentration. This implies that h_{crit} can only depend the linear combination $\ln\alpha - \ln\beta + \ln k$ which is confirmed by our simulation results.
The two figures below show histograms for α, β, k and h_{crit}, and correlation plots for the three parameters α, β, k and the linear combination $\ln\alpha - \ln\beta + \ln k$ versus h_{crit}. In the left figure the distribution width is $\sigma = 0.01$, in the right one $\sigma = 0.2$.



$\sigma = 0.01$



$\sigma = 0.2$

Summary

Parameter estimation for complex dynamic models is a challenge in current systems biology. To study the potential dynamic behaviour of a given model with uncertain parameters, we use a Monte-Carlo sampling approach. We draw the parameters from a distribution and observe the distribution of the variables in the simulated system.
In the example model describing a small genetic network, the incidence of a Hopf bifurcation (a qualitative trait) and the distribution of the critical values of the Hill coefficient, at which the Hopf bifurcation occurs (a quantitative measure), have been determined. We may also ask a slightly different question: if all parameters (including the Hill coefficients) are drawn from distributions, what is the probability for the system to oscillate? Given our distribution of h_{crit}, this can be easily answered by sampling h and h_{crit} independently from their distributions and counting how often $h >$ crit .
The presented analysis can be considered as first step towards a thoroughly parameterized model. It gives hints, which types of qualitative behaviour can be expected at all and at which parameter combination. It enrolls which parameter values have a strong influence on the dynamics, which points points to parts of the model where exact measurements are necessary or where fluctuations are important or nonrelevant.

GK Dynamics Evolution

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