Efficient Simulations of Genetic Networks in Cells

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Abstract

Genetic networks play a key role in the current study of protein synthesis in cells. The experimental work carried out in this area is accompanied by extensive theoretical research based on computer simulations. These simulations are currently done using rate equations which are highly efficient and compact. Yet due to the low copy numbers of the reactive proteins in each cell, the mean-field approximation, upon which the rate equations are based, fails, and some critical phenomena are overlooked. Thus, in order to properly simulate these networks stochastic methods, such as Monte Carlo simulations or direct integration of the master equation, are required. However the number of equations in the master equation proliferates, making it infeasible for complex reaction networks. Here we present two methods which provide a dramatic reduction in the number of equations. First is the multiplane method, which maintains the structure of the master equation, but consists of much less equations. The second method, based on moment equations, further reduces the number of equations to the absolute minimum required for a stochastic simulation. These methods have been well established for networks consisting of protein-protein interactions, and in the future we hope to apply them for networks including additional processes.

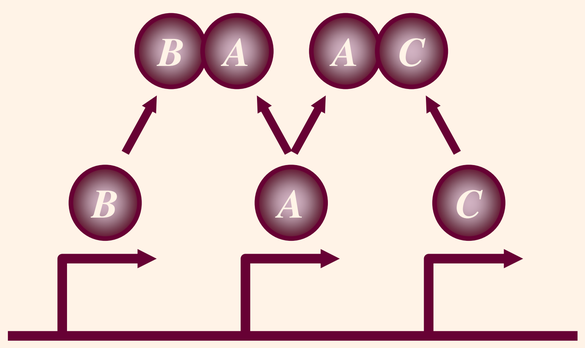
The Rate Equations:

$$\frac{d\langle N_A\rangle}{dt} = g - d\langle N_A\rangle - \gamma\langle N_A\rangle\langle N_B\rangle - \gamma\langle N_A\rangle\langle N_C\rangle$$

Generation — Degradation — Interaction

Rate equations are highly efficient – just one equation per protein

The mean-field approximation is not valid when copy numbers are low



gene

The network:

The gene produces the proteins A, B and C, at a rate of g. Degradation occurs at a rate of d. The reactions A+B → AB and A+C →AC have a reaction rate of γ.

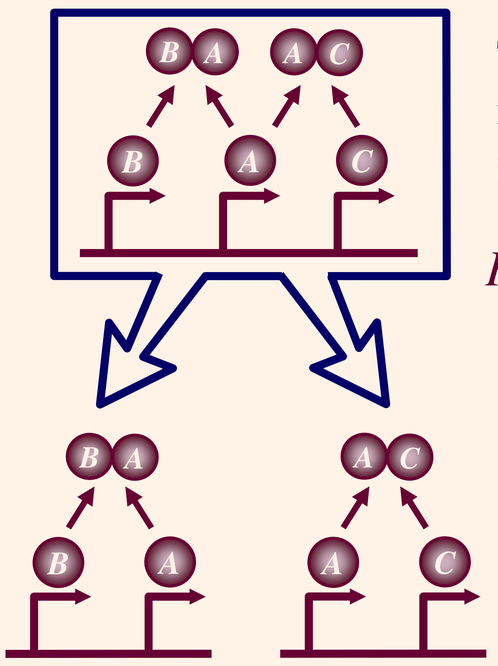
The Master Equation:

The master equation describes the full probability distribution $P(N_A,N_B,N_C)$.

Highly accurate under any conditions. Uncovers phenomena that the rate equations overlook

The number of equations grows exponentially with the number of reactive proteins – infeasible for complex networks

The Multiplane Method:



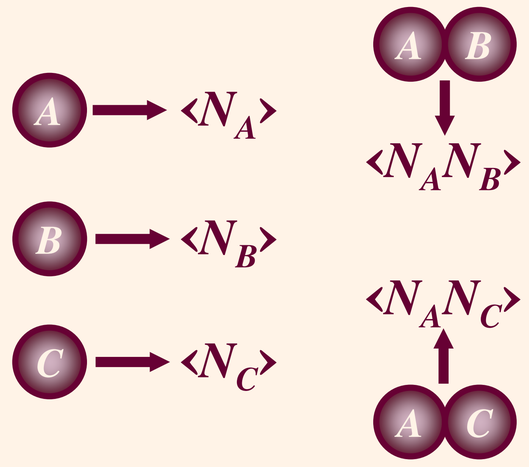
The multiplane method splits the network into a set of fully interacting sub-networks.

$P(N_A,N_B,N_C) \rightarrow P(N_A,N_B);\ P(N_A,N_C)$

In a complex network, the multiplane method reduces a multi-dimensional equation into a set of two or three dimensional ones.

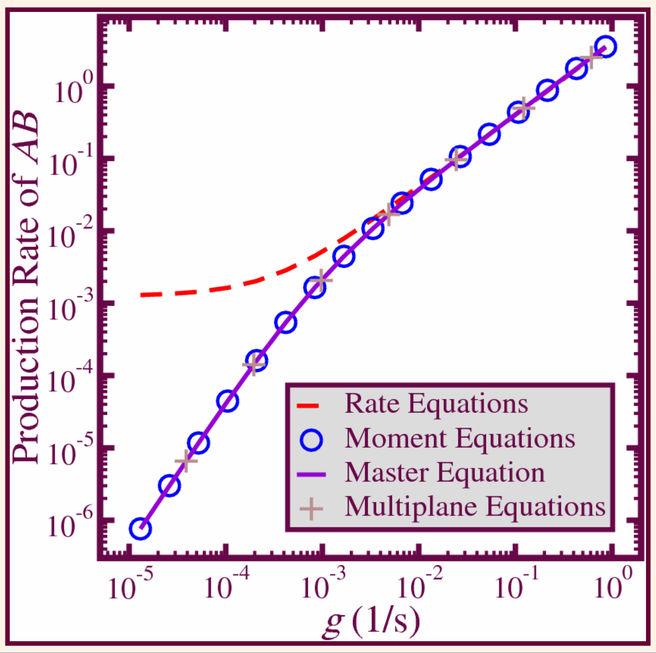
The Moment Equations:

By summing over the master equation one obtains equations for the moments of the distribution, $P(N_A,N_B,N_C)$. One must only write equations for moments that are directly related to a protein or to an interaction.



The number of equations is minimal for a stochastic simulation- one for each protein, and one for each interaction.

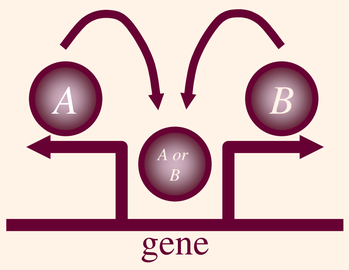
The Results



The production rate of the AB dimmer vs. g, the generation rate of the proteins A, B and C, as obtained from the master equation (solid line). The results of the multiplane (pluses) and the moment equations (circles) are in full agreement with those of the full master equation. The results of the rate equations (dashed line) deviate for small population sizes.

Can We Solve This?

The exclusive switch:

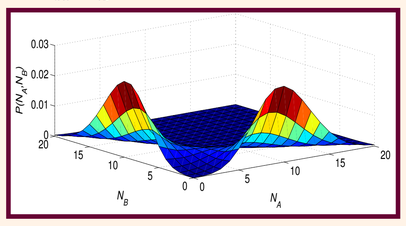


gene

The proteins A and B have a common promoter site, which they cannot occupy simultaneously. Each of the proteins represses the production of the other.

The master equation shows that this network has two steady states – bi-stability.
This circuit is a genetic switch.

The results of the master equation for the exclusive switch display two distinct peaks of the probability $P(N_A,N_B)$.



The Challenge:

We attempt to adjust the multiplane method and the moment equations to solve such networks.

References:

A. Lipshstat, A. Loinger, N.Q. Balaban and O. Biham, Genetic Toggle Switch without Cooperative Binding, Phys. Rev. Lett. 96,188101 (2006)

B. Barzel and O. Biham, Efficient Simulations of Genetic Networks in Cells (to be published).

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