Analytical study of an exclusive genetic switch

Juan Venegas-Ortiz[1] and Martin R. Evans[2]

***Short Abstract* — The nonequilibrium stationary state of an exclusive genetic switch is considered. The model comprises two competing species and a single binding site which, when bound to by a protein of one species, causes the other species to be repressed. Mean field theory and numerical simulations reveal that generically bistability occurs and the system is in a symmetry broken state. An exact perturbative solution which in principle allows the nonequilibrium stationary state to be computed is also developed and computed to first and second order.**

***Keywords* — Genetic switch, nonequilibrium stationary state, statistical mechanics, gene regulation, exact solution, mean field theory, bistability.**

I. Model

Genetic networks are interacting, many-component systems of genes, RNA and proteins, that control the functions of living cells [1-2]. They exhibit complex, nonlinear behaviour due to the feedback between the expression of different genes. At a simplistic level of description the gene sequence, through transcription by RNA and translation by mRNA, leads to the production of proteins. These proteins may themselves act as transcription factors which may switch on or off the activity of other genes [3] . A particularly simple example of a genetic network is a toggle switch formed from pairs of genes that mutually repress each other's expressions [4]. Such switches serve as microscopic models for bistable and oscillatory states [5-6] and importantly may be synthesized [7].

We consider the simplest toggle switch introduced by Warren and ten Wolde [5] which we will refer to as the Exclusive Switch. The model comprises two genes labelled 1 and 2 each leading to the production of proteins X_1 and X_2. These proteins also degrade stochastically. There is a single mutual binding site to which either an X_1 or X_2 may bind and when bound repress the production of the other protein. Thus when an X_1 is bound, the X_1 population fluctuates around some steady state value determined by the balance of production and degradation while the X_2 population degrades towards zero.

II. Results

Simulations show that the system is always bistable, that is, the system is always functioning as a switch, with two opposite states in which one population is much more abundant than the other. This holds generically except in the limit where the unbinding/binding rates $u,b\to\infty$ where the state is symmetric. As the relevant parameters for the switch become smaller, the probability of finding bound proteins decreases, but the distributions always remain asymmetric, showing no transition between asymmetric and symmetric states.

The mean field theory we have developed is based on exact moment equations which are factorised at the level of second moments. The approximation scheme is constructed to be exact in the limiting parameter case of vanishing b, u with the binding constant k = b/u held constant. The theory shows good agreement with some quantities obtained from the simulation, but there are some other quantities whose agreement varies and depends on the value of the parameters. The mean-field theory could be improved upon by systematically considering higher order moments and correlations.

As a first attempt, to our knowledge, at an exact solution of this nonequilibrium system we have developed an exact perturbative approach which consists of an expansion in the unbinding rate u . We computed the expansion to first order and this has allowed us to obtain the whole probability distribution for the typical E. coli and other values, in good agreement with the simulations. Higher orders can be obtained systematically by iterating the proposed method.

III. Conclusion

The techniques that we have developed should be applicable to the understanding of other related systems and properties of genetic switches in general. The factorisation of the moment equation hierarchy is straightforward to implement to obtain a mean field theory; the exact perturbative approach is more involved but can be used in general for problems with similar probability distributions. Thus the techniques represent standard procedures to analyse this class of systems.

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[1] Institute for Condensed Matter and Complex Systems. School of Physics and Astronomy. University of Edinburgh E-mail: J.Venegas-Ortiz@sms.ed.a.uk

[2] Institute for Condensed Matter and Complex Systems. School of Physics and Astronomy. University of Edinburgh E-mail: mevans@staffmail.ed.ac.uk

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