

Bifurcation Analysis of a Self-Repressing Gene

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Utilizing bifurcation theory to analyze a simple gene network, the self repressing gene, permits understanding the behavior of the system in a wide region of parameter space. This point of view is extremely helpful to serve as a guideline for the design of synthetic networks which display a desired behavior, see [1] and [2].

A detailed mechanistic model composed of tens of differential equations, first derived in [3], [4] and further developed in [5], proves to be intractable for bifurcation analysis, due to the high number of equations. Because of this, a simplified mathematical model which formulates protein synthesis in terms of time delays is constructed in a systematic fashion by performing approximations on the original mechanistic system. This simplified model circumvents the problem mentioned and permits the use of bifurcation analysis. The necessity of incorporating details arising from time delays has been shown, as discussed in [6], [7] and [8], as it accounts for dynamical behavior not possible in models that fail to incorporate these time delays. The derivation of the simplified model differs from the time-delay model of [5] and from time-delay models in other contexts in that it is derived directly from a detailed description of the process being modelled, as opposed to being postulated.

The equations of [3] and [5] for an mRNA with N codons are expressed in terms of the probability that each is occupied by the front of a ribosome. Biochemical and probabilistic considerations were used to derive a mechanistic model consisting of a system of ODEs for these quantities. Experimental work shows, [9], that initiation is the rate limiting step of translation and simulations of the mechanistic model under such conditions, [5], reveal steady state solutions with small and slowly varying amplitude along the chain.

Under initiation limited conditions, a parameter measuring the smallness of the initiation rate constant permits the application of perturbation analysis directly on the mechanistic model. The leading order terms of this analysis yields a PDE approximation valid in the low packing, slowly varying conditions which are of physiological relevance. The solution to the simple hyperbolic PDE is combined with the boundary condition to give a simplified model in the form of an integral equation over the history for the initiation rate. A simple ansatz transforms this integral equation into a single delay differential equation.

The mechanistic delay model obtained is then used to perform bifurcation analysis of a self-repressing gene, with repression of the hill type. The region of self-sustained oscillations (Hopf boundary) in the two parameter space of dimensionless protein degradation rate (κ_p) and time delay (τ_E) is found and compared with the equivalent boundary of a heuristic, time-delay model proposed elsewhere for the same system. Qualitative differences are found and explained in terms of the undergoing biological process. Modelling the same system with the set of fully mechanistic ODE's developed in [3], [4] and [5] permits us to determine the region where the mechanistic model yields oscillations or a decay to steady state. Very

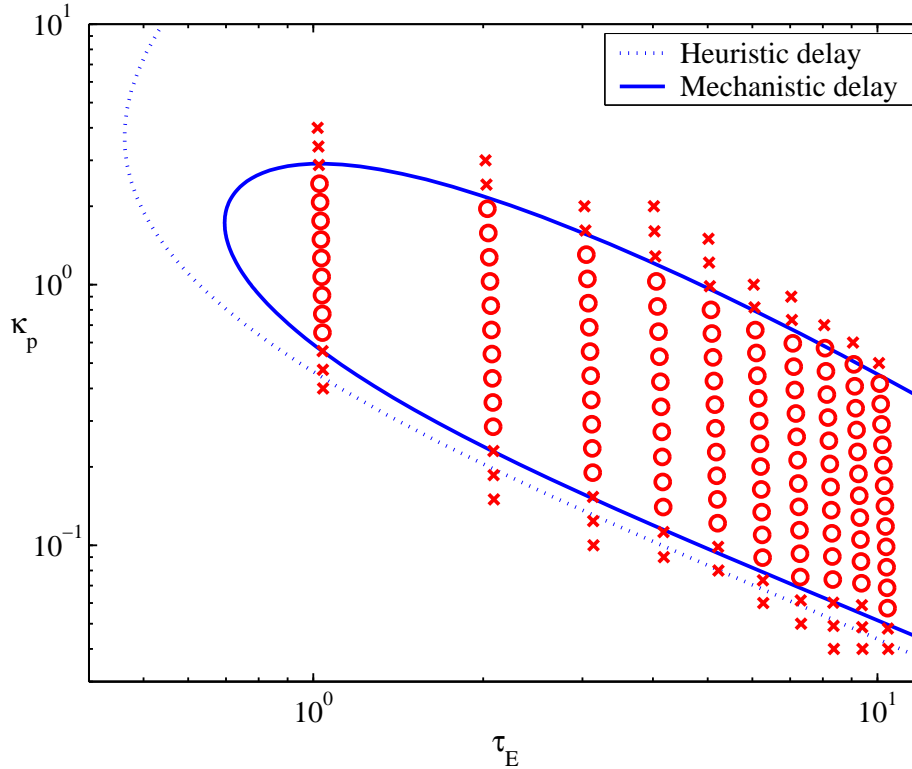


Figure 1: Region of sustained oscillations for the heuristic delay model (broken) and the systematically derived, mechanistic delay model (continuous) in two parameter space. Parameters that yield oscillations for the mechanistic ODE model are marked by (\circ) and those that yield decay to steady state by (\times).

good agreement is found for the region of oscillations as given by the mechanistic ODE and time-delay models. See Fig. 1.

References

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