In Silico Manipulation of Qualitative Biological Behaviour using Sparsity Enforcing Regularization

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Abstract

Qualitative dynamical behaviour such as bistability and oscillation is ubiquitous in biological systems and due to corresponding building-block patterns in the underlying network architecture. For instance, bistability is generated by positive feedback or mutual inhibition and the associated abidance in an alternative stable state even after the removal of a transient stimulus is a recurring motif in cell differentiation, proliferation and death. Mathematical models of these phenomena can be derived from mass action kinetics, and their qualitative repertoire can be studied by means of numerical bifurcation analysis. Malfunction in bistability and oscillations is implicated in numerous diseases including cancer and Parkinson's disease and - according to one of the postulates of systems biology - is caused by a genetic or environmental perturbation of the biological network. In this concept, understanding of disease and measures for rational network manipulation are to be gained by means of a combined use of experimental and computational techniques.

In this talk we consider the intrinsic apoptotic signalling pathway and suppose that the threshold at which the mitochondrial stimulus irreversibly triggers the suicidal pogramme needs to be altered in order to counteract suppressed or excessive cell death. The formulation of the corresponding qualitative inverse problem leads to an underdetermined nonlinear operator equation

$$F(q) = z$$

where z denotes desired locations of limit points in the bifurcation diagram and q represents deviations from parameters of the currently malfunctional network. By means of sparsity enforcing regularization key intervention points can be revealed, then serving as manageable candidates for drug targets. Based on ℓ_1-penalization we suggest a convergent iterative procedure

$$q^{k+1} = q^k + d^k$$

that involves linear programs for the generation of sparse corrections d^k of the iterates q^k and outperforms standard SQP approaches in our numerical examples since only first order derivative information is used.