

Genetic Networks Show Strong Differential Dynamical Properties

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We propose a mathematical framework to study the differential dynamical property of genetic networks between normal and abnormal cells, as the dynamical counterpart of differentially expressed genes. Existing methods of discovering differentially expressed genes are statically in nature and fail to account for dynamical behaviors and dynamical interactions. As the dynamics of interacting genes (genetic networks) are increasingly recognized to play an important role in cell functions, there is an urgent need to study differential dynamical behaviors of genetic networks. Therefore we propose to model the regulation of genetic networks as a control problem, and to study the dynamical property of genetic networks.

The framework consists of three steps: choosing underlying model, parameter estimation, and dynamical analysis. We first modeled genetic networks as state-space equations which are versatile and have a lot of analytic tools available, and then applied a constrained Expectation-Maximization (EM) algorithm to estimate parameters in the model. Based on estimated state-space models, we analyzed four dynamical properties of genetic networks: stability and relative stability. We applied our methods to three biological systems: the SOS DNA repair system under different dosages of radiation, the GSH redox cycle in mice exposed to either normal air or poison. We found that the genetic networks in two biological systems exhibited differential dynamical properties between normal and abnormal cells.

The SOS system is found to be stable under low level of radiation and unstable under high dosage. A similar pattern exists in the GSH redox cycle, stable in mice exposed to normal air and unstable in those exposed to poison. It is not surprising that systems under normal condition are stable and become unstable under sufficiently perturbed conditions. The step responses of GSH redox cycle are shown in Figure 1 and 2.

Related to stability is relative stability, how far to disturb the system for it to become unstable. Root-locus plots can show how much the output can be amplified and fed back while the overall system remains stable, and this margin of stabilizing gains can be taken as a measure of the relative stability of the original system. In the SOS system, the *recA* to *uvrA* system shows differential relative stability. Under low radiation, it has a large margin for positive feedback and a narrow margin for negative feedback; under high radiation, the exact opposite is true. In the GSH redox cycle, the *ALDH2A1* to *IDH2* system is stable for a great swath of gains, when exposed to normal air, but if exposed to poison, not only is it unstable itself but cannot be stabilized by any gain value. This means GSH redox cycle in damaged mice lungs is very difficult to control as it has no relative stability and no stability.

Difference in stability and relative stability between normal and abnormal cells means considerable difference in dynamical behaviors and that difference imply fundamental

difference in biological systems and different functioning of cells. Therefore differential dynamical properties can be a valuable tool in all aspects of biomedical research.

Figures

Figure 1: This is the step response of GSH redox cycle exposed to normal air. All genes show stable behaviors and converge to steady states.

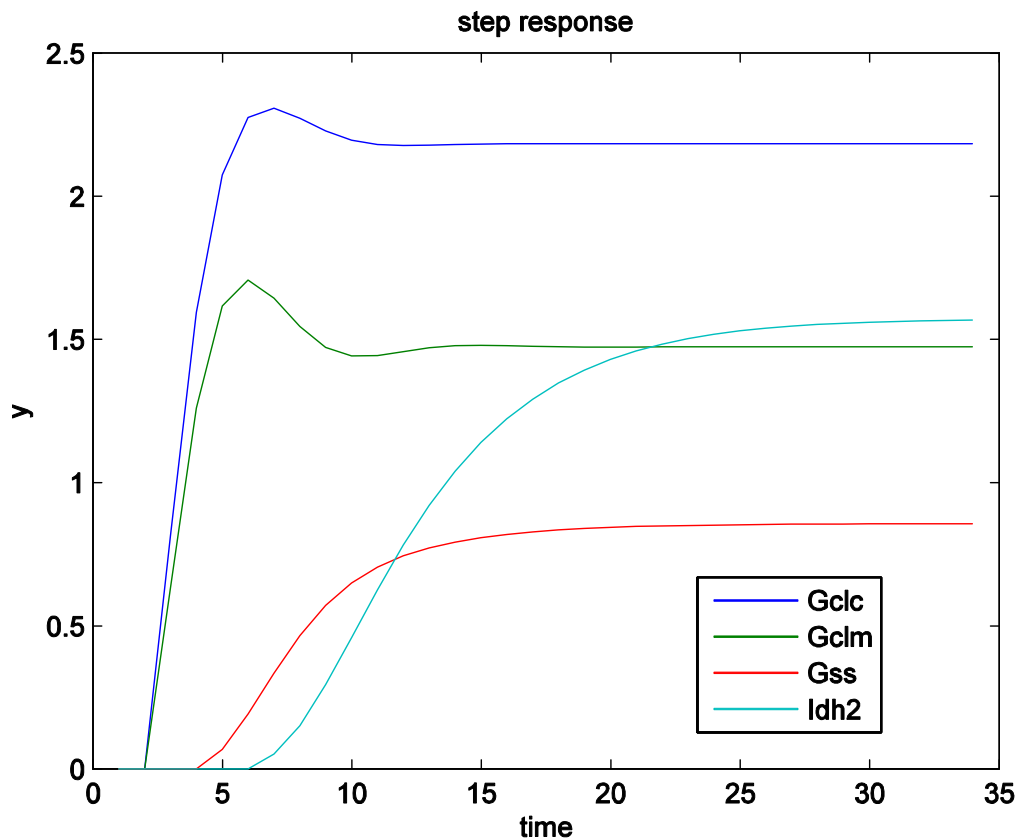


Figure 2: This is the step response of GSH redox cycle when exposed to poison. The gene Gclc shows unstable behavior as it diverges toward negative infinity.

