Dynamical systems analysis of the gene regulatory network: on example of Drosophila early segmentation

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Fruit flies (Drosophila) are model organisms for studying spatial pattern formation in animals. In the first few hours of development, a network of interacting genes forms expression patterns which determine the body plan (*bouplan*). Data shows that wild-type (WT) development is remarkably robust, with various initial trajectories canalizing to an attracting state [3]. Dynamical systems analysis of a core nonlinear model of the anterior-posterior (AP) segmentation gene network has shown how this WT stability can arise as a trajectory through phase space [1, 2]. The WT is stable only to a certain point, however. Once an embryo's buffering capacity is overwhelmed by a sufficiently severe perturbation, altered phenotypes can arise [4-6].

We work here with a gene circuit model of 4 gap genes (adapted from [1, 2]) - (hunchback; Kruppel, Kr; giant, gt; & knirps), under the control of the maternal Bicoid (Bcd) gradient. The 4-gap gene model provides a small very well characterized network for investigating this. Here, we specifically focus on robustness to the Bcd gradient perturbations. That is, we test to what degree the gap gene expression patterns are robust to variability in the Bcd gradient. Using the 'coarse-grained' reaction-diffusion modeling, we can study the robustness in the network via dynamical systems analysis and computations.

The extended dynamical analysis of the model [1, 2] reveals three classes of behavior associated with the qualitatively different expression patterns of genes Kr and gt in the anterior vicinity [7]. And only one of the classes corresponds to norm (WT).

Our further analysis of the model [1, 2] corroborates the results of [7] and suggests generally pathological character of the solutions of the model [1, 2] found so far [8]. Here we have studied all 23 published sets of equation parameters for the gap gene model that have

consistent network topology [1]. For further analysis, we have used the solution set studied in details in [1,2] and systematically altered (in small steps) each of the 24 T^{ij} values in the solution matrices ([1] Table S3). We find cases where small parameter changes cause abrupt changes in patterning, producing more severe defects from the initial solutions.

We have shown here how mutation of gene-gene interactions can lead a gene network to a bifurcation point, at which natural variability can push embryos into neighboring basins of attraction. Our work suggests a dynamical basis, in which a mutation takes the system to a bifurcation point, and the variable outcomes are a manifestation of natural variability in upstream control. It can explain how mutations decrease the robustness of gene networks to natural variability.

Our conclusion is that the search of for the 4-gene network solutions robust to the Bcd gradient variability does not accomplished yet.

This work was supported by the Joint NSF/NIGMS BioMath Program, 1-R01-GM072022, the National Institutes of Health, 2R56GM072022, 2-R01-GM072022, CRDF RUB1-33054-ST-12 and 13-04-02137a, RFBR.

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