

Geometry, Functionality and Robustness: Exploring the Parameter Space of the Segment Polarity Network

Madalena Chaves¹, Adel Dayarian^{2,3,*}, Anirvan Sengupta^{2,3}, Eduardo D. Sontag^{2,4}

1. Project COMORE, INRIA, Sophia-Antipolis, France
2. BioMaPS Institute for Quantitative Biology, Rutgers University, Piscataway, NJ USA
3. Department of Physics, Rutgers University, Piscataway, NJ USA
4. Department of Mathematics, Rutgers University, Piscataway, NJ USA

*E-mail: dayarian@eden.rutgers.edu

In a biological context, robustness often expresses the idea that a system remains functional under a variety of conditions. In mathematical models, the concept has often been associated to the volume of the space of admissible parameters. Our point of view is that not only volume, but also the geometry and topology of the space of admissible parameters contain information on essential aspects of the network. As an illustration, we analyze the segment polarity network, based broadly on the model developed by [1].

Many of the interactions between the components of the segment polarity network are qualitatively known, and have been used to develop a variety of mathematical models. Some of these models use Boolean idealizations in which genes can be either ON or OFF ([2, 3]), but no kinetic parameters need to be defined, while others use systems of differential equations for concentrations of proteins and mRNAs ([1]). We propose an approach which retains the information contained in the kinetic parameters but reduces the model to a logical form with various possible ON levels and species-dependent activation parameters. Then, we characterize the space of admissible set of parameters for our model by writing it as a semialgebraic set.

In the model presented in [1], two new regulatory interactions were added to the network to be able to reproduce the right pattern in computer simulation. Our analysis completely explains the two “missing links” in [1]. One of these new interactions suggest a new mechanism for the activation of Wingless, one of the components of segment polarity network. We noticed that this new interaction is problematic in the sense that now Wingless is always activated via the added self-activation and the other way to activate Wingless (via the CI-CN module) never contributes to the pattern. This is in contrast with experimental data. Thus, we decided to included another component in our analysis: *sloppy-paired* protein (previous research by others had also already suggested the contribution of sloppy-paired). With sloppy-paired added, the two new introduced interactions are not necessary anymore, and also CI-CN cycle contributes to the expression of Wingless.

After constructing a cylindrical algebraic decomposition of the admissible set of parameters, we considered the question of robustness of our system. One way to explore the space of admissible parameters is to consider a random point and follow a random walk in space. The random walk represents parameter fluctuations due to mutations, and the probability of exiting after t steps represents the probability that the network is no longer capable of correctly performing its function. Our analysis showed that only a very small number of parameters are responsible for the majority of network failures. The present approach shows that, in contrast to volume-only estimates, the geometry of this set provide reliable

quantitative measures of robustness.

The analysis developed in our research can be applied to many other systems and regulatory networks, to systematically characterize and explore the admissible space of parameters and its topology.

References

- [1] G. von Dassow, E. Meir, E.M. Munro, and G.M. Odell. The segment polarity network is a robust developmental module. *Nature*, 406:188-192, 2000.
- [2] R. Albert and H. G. Othmer. The topology of the regulatory interactions predicts the expression pattern of the *Drosophila* segment polarity genes. *J. Theor. Biol.*, 223:118, 2003.
- [3] M. Chaves and R. Albert and E.D. Sontag. Robustness and fragility of Boolean models for genetic regulatory networks. *J. Theor. Biol.*, 235: 431-449, 2005.