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Article 4

**2007; Artyomov; Purely stochastic binary decisions in cell signaling models without underlying deterministic bistabilities**

1. What are the conclusions of this paper about their model for bistability, and how are these conclusions distinct from previous work?

The authors of this paper were able to create bistability in a system driven purely by stochastic fluctuations in a system that, under normal conditions, would converge to a single steady state value. Unlike other papers that model gene regulatory balance to create a bistable system, this paper shows how bistability can be created when reducing the number of molecules in a system, which causes stochastic effects to come into play.

Previous works, such as the Gardner paper we read, showed that when the regulation is balanced, the steady state value is entirely deterministic on the initial concentration values. However, in the paper, they used a small number of signaling molecules to model their system, which means that stochastic influences cannot be ignored and actually cause significant changes in the system trajectory.

1. What are the conclusions of this paper related to T‐cell signaling?

Their model describes T cell responses to a diverse range of stimuli, particularly in regards to positive (agonism) and negative (antagonism) feedback. With stochastic fluctuations driving the concentration of signaling product to be at two extremes, it enables the T-cell to make a decision to be either on or off, whereas in systems with a large number of molecules, there is a bimodal distribution of signaling product at neither extreme therefore no decision can be made.

1. Discuss validation and any other relevant issues to analyze the level of certainty for the two conclusions you described above.

The authors described a model that was purely computationally driven, with no experimental complement to reinforce their conclusions, perhaps due to difficulties surrounding creating and measuring a system with a very few number of molecules. However, their initial equation to model the feedback regulation was very general and commonly used, and they were able to compare the results between a large number of molecule vs a few number within this known model, which provides merit to their findings.