MODEL REDUCTION ON WNT PATHWAY LEADS TO BIOLOGICAL ADAPTATION

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INTRODUCTION

Complex systems are unavoidable in the field of biology. One of the ways that scientists have tried to overcome this problem is by building overparameterized, mechanistic mathematical models. However, these models become problematic when trying to further understanding about these systems or identify a systems macroscopic behavior. The Wnt Signaling Pathway is an example of a complex system which has multiple models, all of which encompass different behaviors. Our goal is to look at one model of the Wnt pathway, perform model reduction to identify combinations of phenomenological parameters and combine it with another minimal model of the Wnt pathway to identify a new feature of the Wnt pathway—biological adaptation.

THE WNT PATHWAY

The Wnt pathway is observed through the behavior of a protein B-Catenin.

LEE 2003 MODEL

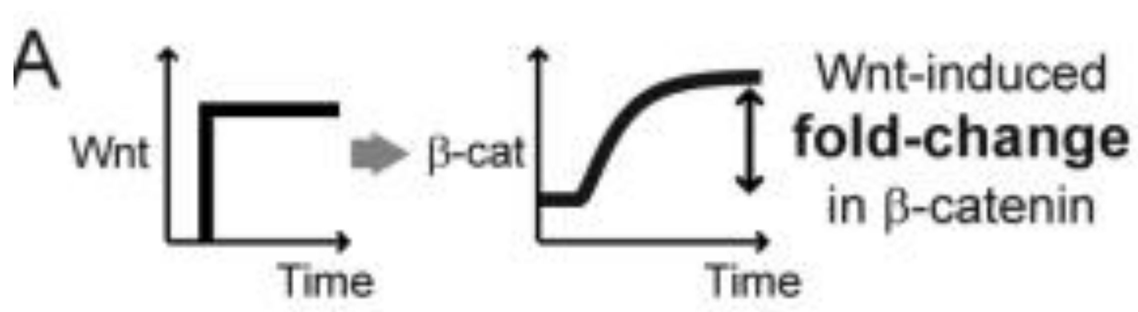

Figure 1: This is a graph of the behavior B-Catenin due to the Lee et al. model of the Wnt pathway. In the figure on the left we see that under the influence of the Wnt signal, the system settles into a new steady state. The right figure shows us that there is some initial concentration of B-Catenin which then begins to increase once the Wnt signal enters the pathway (Lee et al. 2003).

In 2003, Lee et al. built a model of the Wnt pathway which caused B-Catenin to increase overtime. Dane Bjork reduced this model and identified the phenomenological parameters which drove this specific behavior.

JENSEN 2010 MODEL

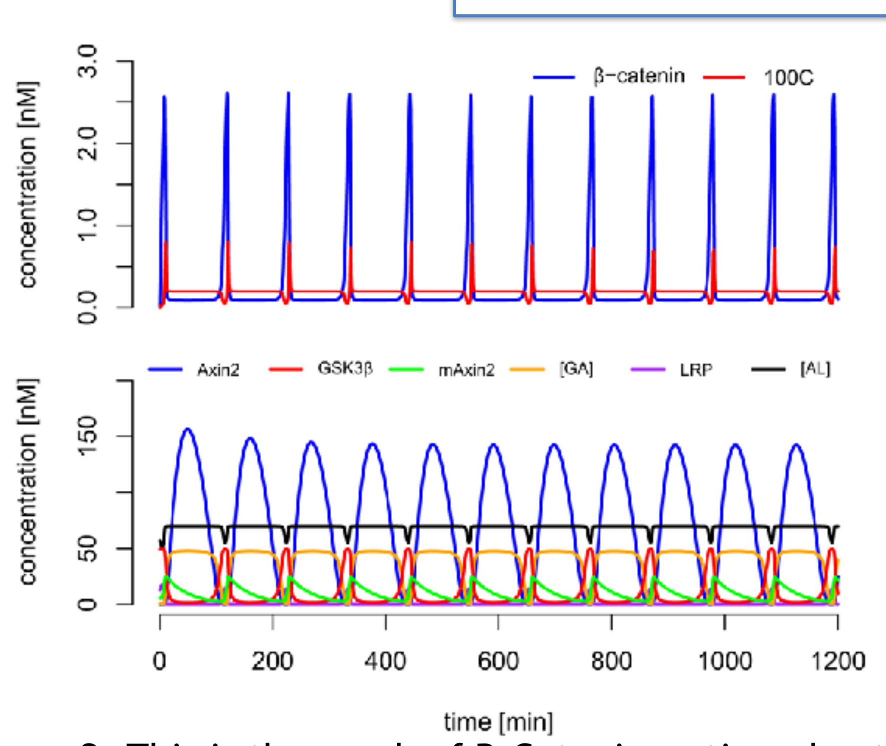

Figure 2: This is the graph of B-Catenin vs time due to the Jensen et al. model of the Wnt pathway. The first graph shows us that the concentration of B-Catenin oscillates overtime as a result of the Wnt signal—a completely different behavior from that observed from the Lee et al. model (Jensen et al. 2010).

In 2010, Jensen et al. built a different model of the Wnt pathway which caused B-Catenin to oscillate overtime. We want to reduce this model and identify the combinations of parameters which drive this behavior.

MANIFOLD BOUNDARY APPROXIMATION METHOD (MBAM)

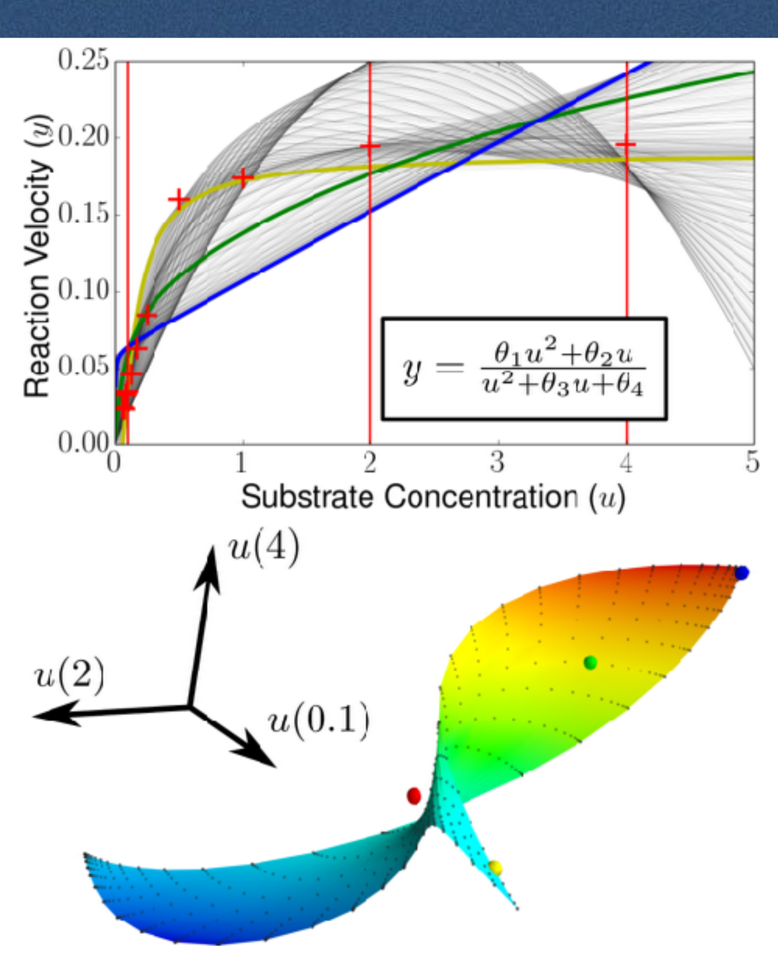

Figure 3: How inputs and outputs correspond to each other to build the model manifold. Here, the blue lines correspond to the blue surfaces on the manifold, green paths correspond to green surfaces on the manifold, etc. (Transtrum et al. 2015)

MBAM is a model reduction technique which begins by building a Model Manifold. This manifold which takes an input in parameter space (derived from the finite number of parameter values) and generates a corresponding output vector in data space which is motivated by observing the way B-Catenin is changing overtime. If we do this enough, we can sweep through all of the inputs and outputs to create a complete model manifold.

BUILDING THE MODEL MANIFOLD

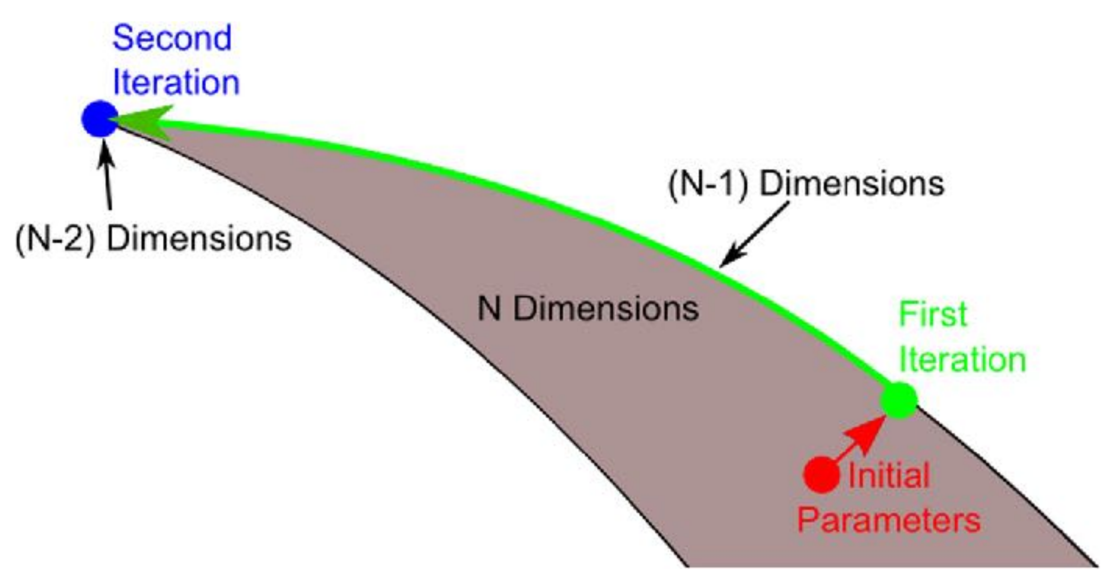

Figure 4: In this figure the red vector corresponds to the geodesic that is being ran along the manifold. It starts by running to a boundary and then identifies a limit represented by the green dot.The process is then iterated to the second boundary in blue (Transtrum and Qiu 2014).

After building the model manifold, we want to create a series of approximations by reducing our model one parameter at a time. In order to do this, we use a geodesic—a path of least distance—to locate the nearest boundary on the manifold. In this method, we are relying on the fact that as we go through the process of model reduction, each boundary will be N-1 dimensions less than the one before it.

COMBINED MINIMAL MODEL

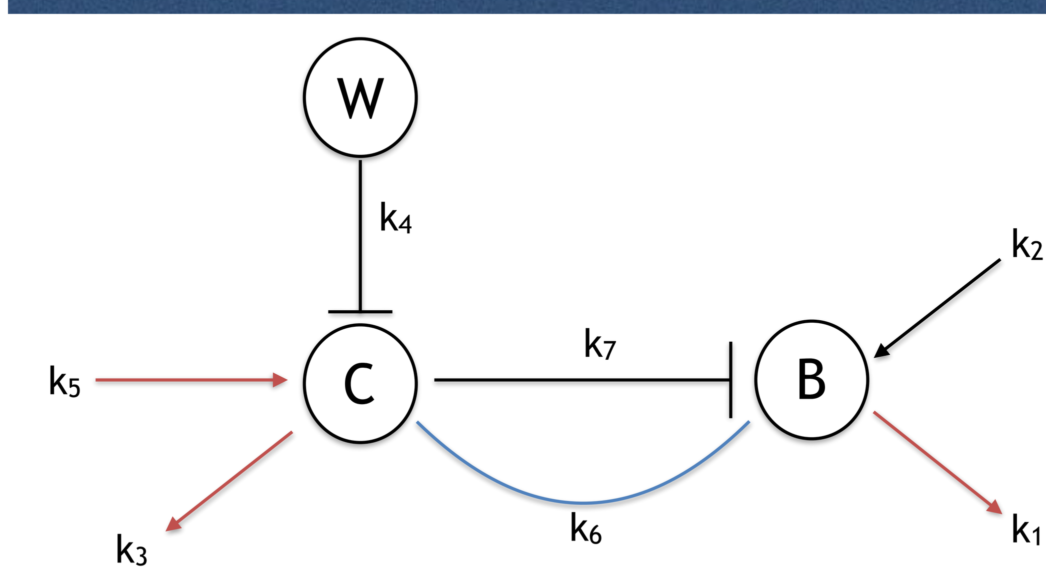

Figure 5:This is the diagram of our new combined model. Red lines signify parameters which are derived from the Lee et al. model, blue lines from the Jensen et al. model and black lines are parameters incorporated into both models.

After performing model reduction on the oscillating Wnt model, we were able to generate a new, minimal model which encompasses the behavior of both the Lee et al. and Jensen et al. model and explains the transition in their different behaviors.

FINDING ADAPTATION

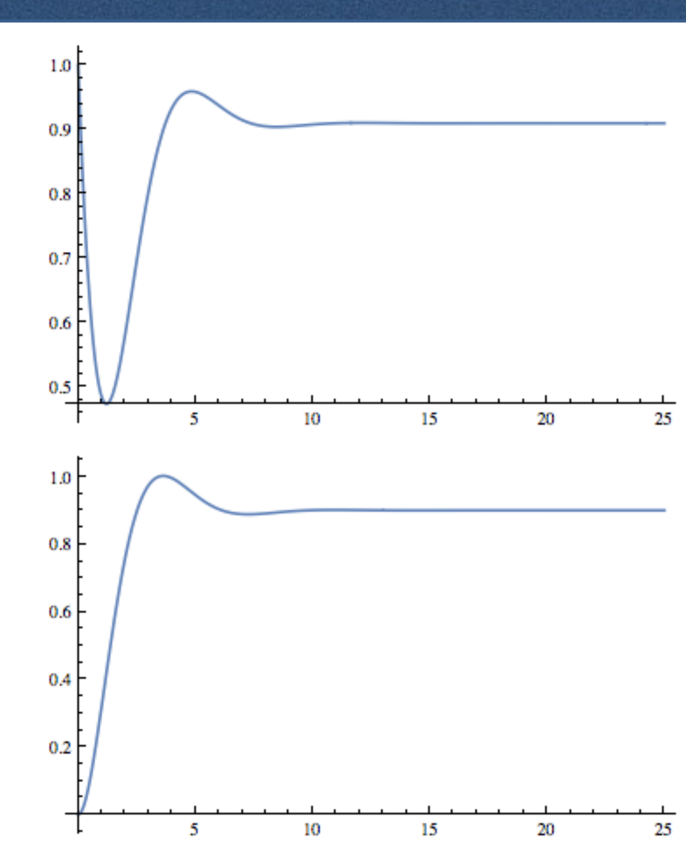

Figure 6: Graphs of B-Catenin (y-axis) vs time (x-axis) and its partner, the destruction complex (y-axis) vs. time (x-axis) which settle into new steady states and take upon them adaptive features

Using our combined, minimal model, we were able to derive the steady states from the model, and thus look for new behaviors such as adaptation. From the figure on the left, it is clear that although the adaptation curve is not steep, there is evidence of B-Catenin settling into a new behavioral state.

FUTURE RESEARCH

In the future, it would be interesting to attempt to experimentally find this new adaptation by the Wnt pathway.

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