MODEL REDUCTION ON THE WNT PATHWAY LEADS TO BIOLOGICAL ADAPTATION

Casie Gaza

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Abstract

Complex systems are an unavoidable problem in the field of biology. One of the ways that scientists have tried to overcome this problem is by building mathematical models–manageable representations designed to look at specific physical phenomena. The Wnt Signaling Pathway is a complex system known to regulate cell-to-cell interactions, play a crucial role in Embryonic Development, and has been implicated in the study of cancer. The Wnt hormone regulates the behavior of a protein called β-Catenin. In 2003, Lee et al. built a model of the Wnt pathway in which β-Catenin increases overtime. However, in 2010, Jensen et al. built a different model of the Wnt pathway in which β-Catenin oscillates overtime. To investigate the Jensen et al. model, model reduction is employed to identify the phenomenological parameter combinations that determined features of the Wnt oscillations. The method used to reduce the model is called the Manifold Boundary Approximation Method which is a geometric, parameter-independent method of reducing the model by removing one parameter at a time. Reduction of the model showed that there were 5 variables and 8 parameters which drove the oscillating behavior of the system. After comparing to the Lee et al. reduced model of the Wnt pathway done by student Dane Bjork, a new minimal model combining elements of both systems is constructed, which predicts a novel class of behavior in the Wnt system: biological adaptation.

1 Introduction

1.1 Complex systems and the need for simple models

There are many examples of systems in the physical world which fall under the umbrella of a complex system. While there is no universally accepted definition of a complex system, they are often categorized by having a large number of heterogeneous components that interact in nonlinear ways. The complexity to these systems is nontrivial because within these mechanisms lies the heart of interesting phenomena yet, it is the major obstacle in advancing understanding. [6]

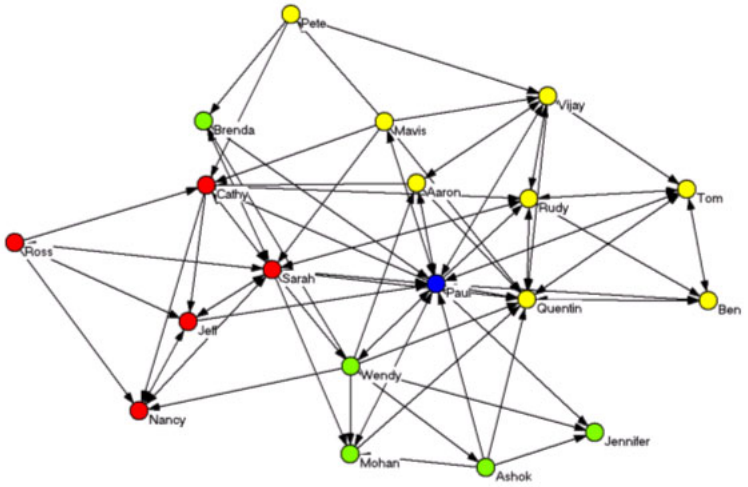

Figure 1: This is a representation of a social network. Each dot represents a different person. The colors represent a "type of person" meaning religious views, hobbies, and personalities. The segments represent ways in which the dots are connected. There are many segments and different colors which causes this system to be categorized as complex.

Figure 1 is a diagram of a social network. In this network, there are many segments and links that connect different people together. These segments represent interactions that are not well understood and are likely non-linear. If one were to pose the question, "How do the beliefs or preferences of some individuals influence the behavior of the system?" one would realize that this question is difficult for small systems, and especially for large systems in which the network continues to grow. Thus, it would be helpful to find a way to simplify a complex system in such a way that is both understandable and manageable.

1.2 Mathematical Models

Mathematical models are representations of complex systems designed to look at specific physical phenomena. While they are not complete representations, they serve as helpful tools in understanding specific portions of a complex system. These models are made out of variables and parameters. Variables are the "things" or entities interacting in the system while parameters are placeholders for constants–unknown values that describe the ways in which the variables interact. In many ways, one could imagine that parameters are like control knobs that can be tuned or adjusted to observe a specific behavior. Good mathematical models walk the fine line between exhibiting the system's complexity while remaining simple enough to reveal new insights which enable accurate predictions of the system's behavior. [6]

Nonetheless, the growth in modeling has created a divide amongst two groups of model builders and users: Those who build minimal models with simple representations for the way variables effectively interact with one another and those who build complex models with many parameters which describe the underlying mechanistic intricacies that cause the variables to change. The former are often known as top-down models or phenomenological models because they expose a system's phenomenology and are limited in mechanistic meaning. However, the problem with these models is that they are black-box approximations that are not immediately connected to the complicated mechanistic reality underlying the phenomena.

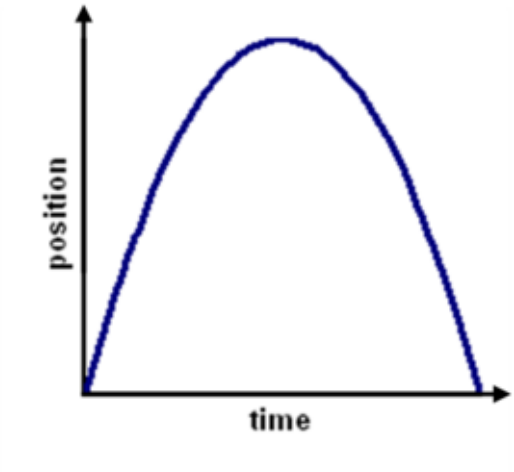

Figure 2: This graph can be modeled by a standard mechanics free-fall equation which describes the change in vertical position of the ball overtime. In the equation, there are two parameters, g–the acceleration due to gravity, and initial velocity, v_0 . If I pick certain parameter values for both g and v_0 then I am able to obtain the graph above which measures the macroscopic behavior of one variables, vertical position as a function of time

Figure 2 is an example of a non-complex system. It is represented by the mathematical model below.

$$y - y_0 = v_0 t + \frac{1}{2} g t^2 \tag{1}$$

In the figure, there is one variable being measured–position as a function of time. Although we can easily see how the change in time affects the position of the ball, it is not obvious whether air resistance affects the motion of the ball, nor is it obvious how the mass of the ball is changing its ability to move. Components like air resistance or the mass of the ball are examples of parameters that are not represented in the minimal model, yet they significantly affect the position of the ball as it changes overtime. While a person looking at the graph would be able to easily understand the behavior of this system, it is not clear whether or not this minimal model could generate accurate predictions or give an accurate approximation of the motion of the ball. Hence, the big problem with using phenomenological or minimal models.

In contrast to the top-down, phenomenological models are bottom-up or mechanistic models. These models contain a large number of parameters, which represent casual relationships in the system–oftentimes referred to as mechanistic parameters. Thinking back to our image of the social network (see Figure 1), the casual relationships are respective to each and every segment which connects one person to another. Oftentimes, these models give the feeling that they are "parts-lists" of the system. However, the problem with these models is that they require an unreasonable amount of information about the intricacies of the underlying mechanisms. This causes the models to be over-parameterized or sloppy. [6] [**?**]

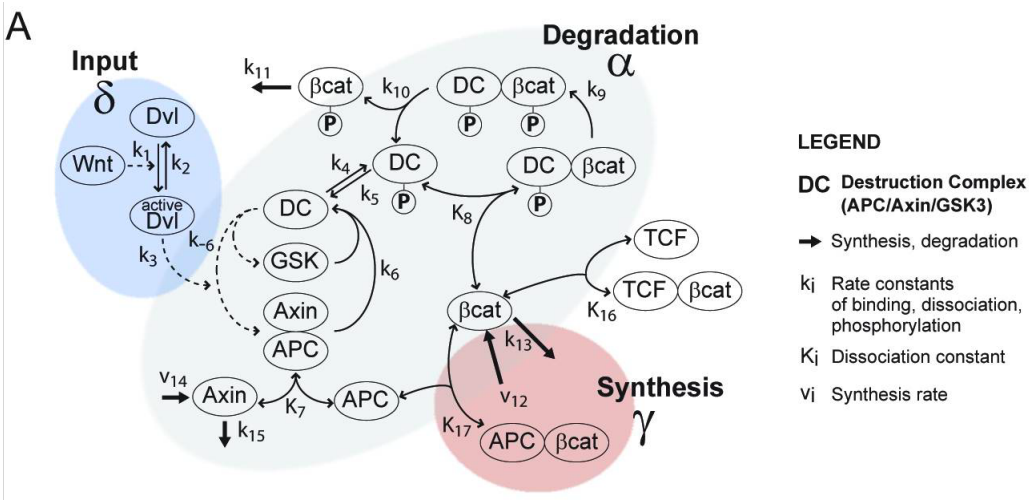

Figure 3: This is an example of a complex system that can be represented by a mathematical model. In this diagram, each casual interaction is represented with a parameter. For example, parameters k_4 and k_L represent the way Wnt is being input in the system. We can also see that there are numerous parameters which describe the formation of proteins DC, GSK, Axin and APC and how they are circulating throughout the system.We also have parameters which describe the mechanisms which cause a protein such as β-Catenin to enter and leave the system. All of these parameters, from k_4 to k_{17} describe the chemical reactions and interactions taking place which cause this system to behave a certain way (Image from Goentoro 2009).

Figure 3 is a diagram of a signaling pathway called Wnt, described in the section below. In this diagram, we can see that there are many different mechanisms which create the functionality of this pathway. From these mechanisms, we can calculate the behavior of all the variables at all times. However, it is not obvious which are necessary or relevant for explaining those behaviors.

Both of these approaches to modeling have strengths and weaknesses. Phenomenological models contain parameters that can be inferred by much less data but, they do not give many mechanistic insights. This becomes problematic because the ability to engineer or control a system typically operates on a mechanistic level. For example, mutations operate on individual genes or drugs target specific biological molecules–none of which are represented in a reduced model, alone. Contrary, mechanistic models, such as the biological one above, derive the mechanistic interactions but they require an unreasonable amount of data to understand. The contradiction between both types of models create a divide amongst model builders and users. On one hand, we have simple, phenomenological models which are easily understood and require a reasonable amount of data to understand, yet we question their ability to generate accurate predictions and make proper approximations. On the other, we have complex, mechanistic models which represent the deeper, intimate details of the system yet, they are not easily understood and require an unreasonable amount of data.

The solution to this problem requires a method that explicitly reveals how the behavior of variables can be described by just a few parameters. Thus making the overarching goal of this thesis an attempt to bridge this gap between these two types of models by learning or deriving combinations of mechanistic parameters that can be described as phenomenological. Essentially, this thesis is going to demonstrate how we can apply a method called the Manifold Boundary Approximation Method (described in Chapter 3) to create "grey box" approximations of the Wnt pathway.

2 Background

2.1 Biology

In recent decades, many scientists have began to build complex mathematical models that describe mechanistic intricacies of a complex system. In the field of biology, this proves paradoxical because, as stated before, "The complexity is the origin of the richness of biological phenomena and the biggest hurdle in advancing mechanistic understanding of a behavior" [6]. One example of a complex system is a signaling pathway. We can imagine signaling pathways as being information highways–roads that our cells turn on depending on what it wants to create. Every cell has a finite number of pathways that contain sequences of chemical reactions and interactions which help to transfer and process information between cells and their environments to create a functioning system. One of these signaling pathways is called Wnt, and will be the focus of this thesis.

The Wnt signaling pathway helps to regulate cell-to-cell interactions, plays a crucial role in embryonic development, and has been implicated in the study of cancer [3]. The effects of the Wnt signaling pathway is observed through the behavior of a protein called β-Catenin. There is a signal called Wnt that is input into the pathway that operates much like a computer. The pathway will do some calculation and provide an output. The output, in this case is β-Catenin and is believed to be the end product of the computer algorithm for the Wnt signal. This was evident when "β-Catenin was very sensitive to relatively small perturbations in the Wnt pathway parameters" [1]. However, what makes this pathway interesting is that it can have two different behaviors given two different sets of variables and parameters.

In some cases, Wnt behaves in such a way that β-Catenin is bound by a group of proteins, a macromolecule, called the destruction complex. The destruction complex consists of Axin, APC, GSK3B and β-Catenin. When β-Catenin attaches to the destruction complex, it degradates, lowering its concentration. Thus preventing the target genes from being expressed at improper times or at harmful levels [1]. Figure 4 below demonstrates the difference of the Wnt pathway without the Wnt signal and under the influence of the Wnt signal.

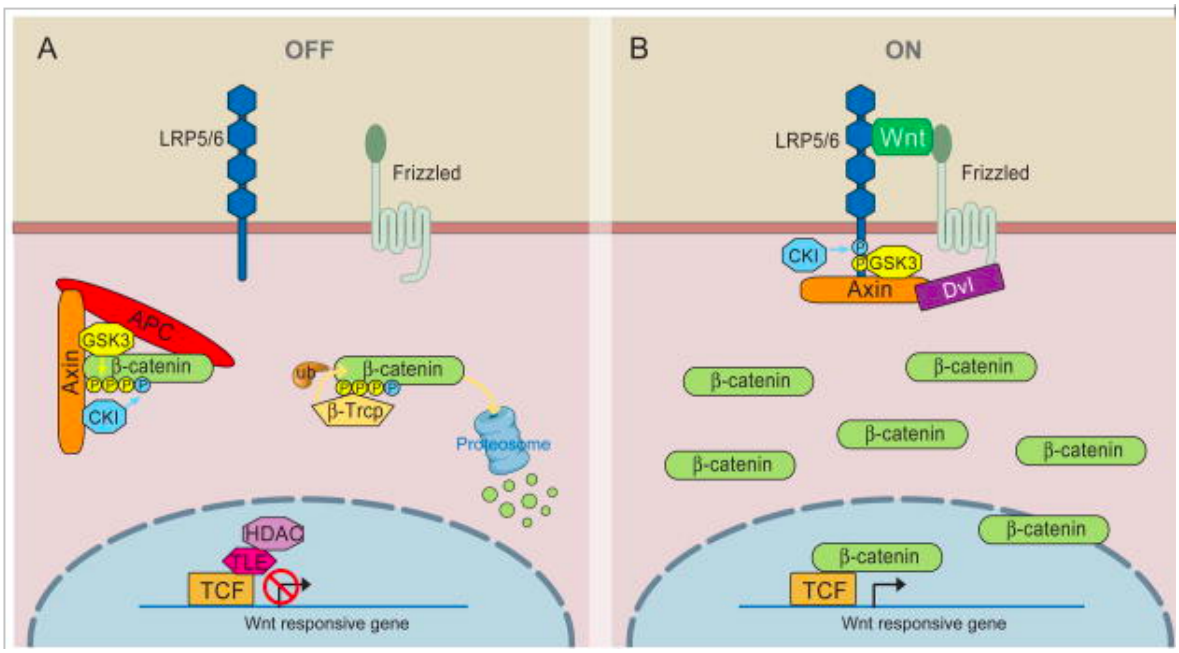

Figure 4: This figure compares the behavior of the Wnt pathway without the Wnt signal in comparison to the behavior of the pathway under the influence of the Wnt signal. In the case that the Wnt signal is not input into the system, we see the proper behavior of β-Catenin. It attaches to the destruction complex and then becomes phosphorylated causing the target gene expression to remain unaffected. Contrary, under the presence of the Wnt signal, we see that β-Catenin accumulates and thus alters the proper expression of target genes (Image taken from MacDonald 2009).

In 2003, Lee et al. built a model of the Wnt pathway which included fifteen variables and nineteen parameters. In this model, the Wnt signal enters the pathway, a receptor is activated which causes the degradation of the destruction complex. This creates a build up of β-Catenin which eventually leads to transcription of specific genes [3]. Figure 5 below is a diagram of this process.

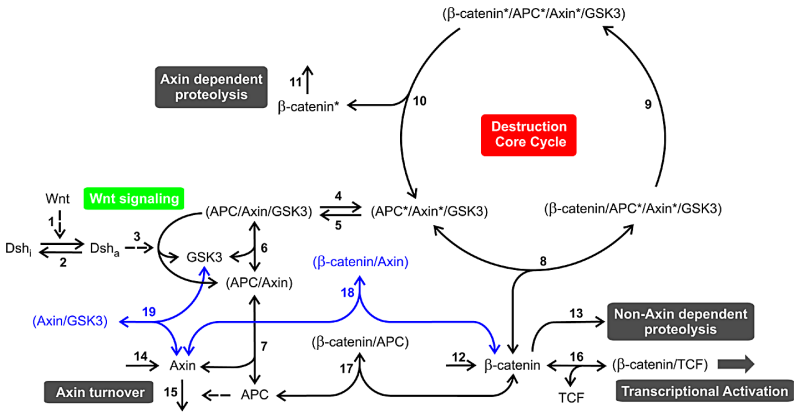

Figure 5: This is a diagram of the model of the Wnt pathway that was built in 2003 by Lee et al. In this diagram, the destruction complex is formed with proteins such as β-Catenin, Axin, APC and GSK3B but it is bound by the concentration of β-Catenin. In this figure, single arrowheads denote the direction for specific interactions, blue lines represent mechanisms that are only considered when there is a high Axin concentration, and double arrowheads denote binding equilibria (Image taken from Lee et al. 2003)

In 2015, Dane Bjork reduced this model which demonstrated that it could be approximated with four variables, nine parameters and included three conservation laws. Through this model reduction, we were able to verify that the 2003, Lee et al. model caused β-Catenin to increase overtime as shown in Figure 6.

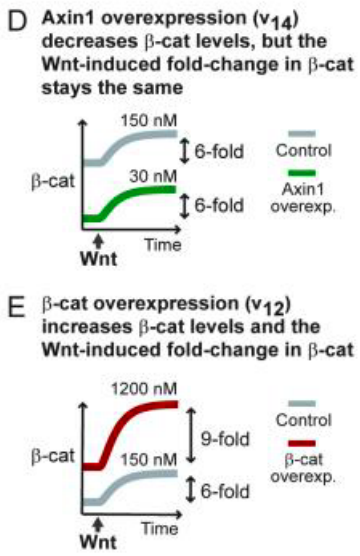

Figure 6: The graph of β-Catenin vs time for the Lee et al. model. Before the Wnt signal, there is a steady state of the concentration of β-Catenin. However, after the Wnt signal enters the pathway, the concentration of β-Catenin begins to significantly increase (Image taken from Geontoro 2009).

In 2010, Jensen et al. built a different model of the Wnt pathway which included eight variables and twenty parameters. The diagram of this model is shown below.

This model describes oscillatory behavior of β-Catenin which comes from a negative feedback loop within the system. In this diagram, the Wnt signal enters the pathway which causes β-Catenin to attach to a target protein called Axin2. When this occurs, the concentration of the destruction complex increases which promotes the degradation of β-Catenin and Axin2. However, lower concentrations of Axin2 decreases the amount of destruction complex which in turn, causes a build up of β-Catenin. This demonstrates the formation of a negative feedback loop centered around the target gene Axin2 and leads to an oscillating concentration of β-Catenin [2].

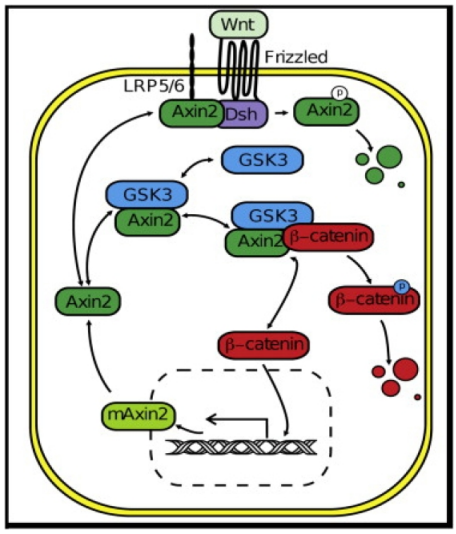

Figure 7: This is the diagram of the Wnt model created by Jensen et al. in 2010. It is comparatively different to the Lee et al. model because of the replacement of target gene Axin2 and Axin. In this diagram, red represents the protein β-Catenin, green represents the protein Axin2, blue represents the molecule GSK3 and yellow represents the mRNA for Axin2 (Image taken from Jensen et al. 2010).

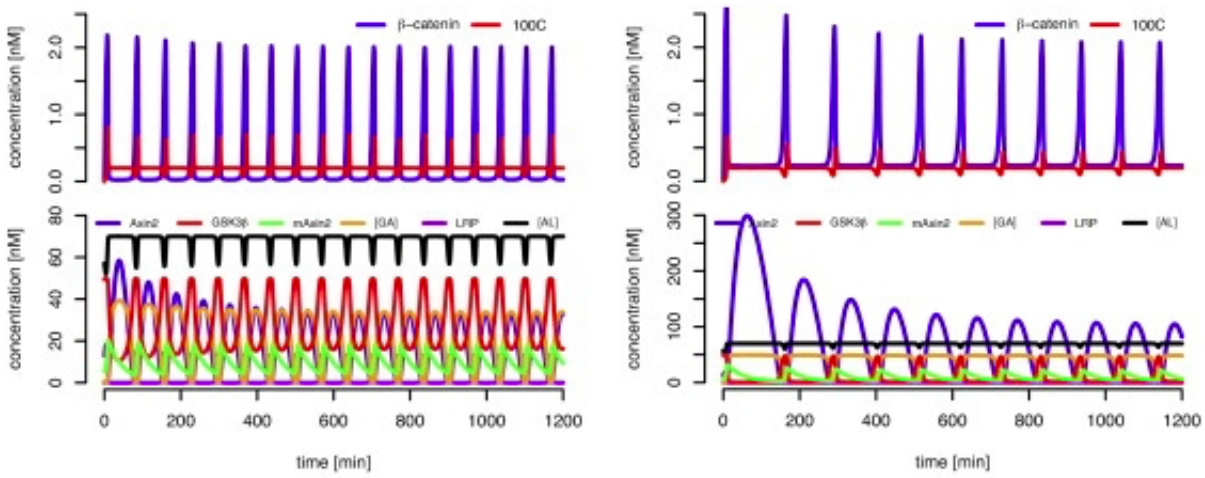

Figure 8: This is the graph of β-Catenin vs time for the Jensen et al. model of the Wnt signalling pathway. This model causes β-Catenin's concentration to oscillate which is different from the Lee et al. model where we saw β-Catenin increase overtime (Image taken from Jensen et al. 2010).

2.2 Goal of Thesis

The goal of this thesis is to first reduce the Jensen et al. model of the Wnt pathway to identify the phenomenological parameter combinations that determine features in the Wnt oscillations. Next, we will construct a minimal model which explains the transition between oscillatory and non-oscillatory behavior in the Wnt pathway and in doing so, predict a novel class of behavior for the Wnt system: Biological adaptation. The method we will use to reduce the Jensen et al. model is called the Manifold Boundary Approximation Method (described below). This analysis will also allow us to explore the use of MBAM on oscillatory models and determine whether there are any fundamental challenges to applying this methodology to such behaviors.

3 Methods

So, how do we reduce this complex model? The solution lies in a model reduction technique called the Manifold Boundary Approximation Method. However, before we begin to discuss the intimate details of this method, I will introduce a much simpler example of model reduction using the example of a bead on a rotating hoop.

$$mr\ddot{\theta} + b\dot{\theta} + mgsin(\theta) - mr\omega^2 \sin(\theta)\cos(\theta) = 0. \tag{2}$$

$$\frac{d^2\theta}{dt^2} = \frac{1}{T^2}\frac{d^2\theta}{d\tau^2} \tag{3}$$

Equation 1 above is a non-linear differential equation which contains a variable, θ and parameters m, r, b, g, ω, θ_0 and θ_0' where m is the mass of the bead, r is the radius of the loop, b is the damping coefficient, g is the acceleration due to gravity, ω is the angular velocity of the hoop and θ_0, θ_0' are initial conditions. These seven parameters determine the motion of a bead rotating along a hoop. The goal is for us to get to the equation,

$$\frac{d^2\theta}{d\tau^2} + \epsilon\frac{d\theta}{dt} + \sin(\theta)(a - \cos(\theta)) = 0. \tag{4}$$

We begin by first rescaling time $t = T\tau$.

So,

$$\frac{d\theta}{dt} = \frac{1}{T}\frac{d\theta}{d\tau}$$
$$\frac{d^2\theta}{dt^2} = \frac{1}{T^2}\frac{d^2\theta}{d\tau^2}$$

We can now substitute this into (1), which gives:

$$\frac{mr}{T^2}\frac{d^2\theta}{d\tau^2} + \frac{b}{T}\frac{d\theta}{d\tau} + mg\sin(\theta) - mr\omega^2\sin(\theta)\cos(\theta) = 0$$

If we divide everything by mr and then multiply both sides by T^2, we get:

$$\frac{d^2\theta}{d\tau^2} + \frac{Tb}{mr}\frac{d\theta}{d\tau} + \frac{g}{r}\sin(\theta)T^2 - \omega^2\sin(\theta)\cos(\theta)T^2 = 0$$

We want $T^2\omega^2$=1. Thus, T=$\frac{1}{\omega}$. So, by substitution,

$$\frac{d^2\theta}{d\tau^2} + \frac{b}{\omega mr}\frac{d\theta}{d\tau} + \frac{g}{r\omega^2}\sin(\theta) - \omega^2\sin(\theta)\cos(\theta)\frac{1}{\omega^2} = 0$$

This gives us,

$$\frac{d^2\theta}{d\tau^2} + \epsilon\frac{d\theta}{dt} + \sin(\theta)(a - \cos(\theta)) = 0 \tag{5}$$

where

$$\epsilon = \frac{b}{mr\omega} \tag{6}$$

$$a = \frac{g}{\omega^2 r} \tag{7}$$

By going through the process above, we were able to reduce our mathematical model (our differential equation) from seven parameters to two. The consequence of model reduction is the grouping of mechanistic parameters which we call ϵ and a. While we have not "gotten rid" of any parameters, we have reduced our model by creating combinations of parameters which drive the behavior of our system. Notice that equation 5 is equal to equation 1 behaviorally–in both equations, we still exhibit the behavior of the bead rotating along the hoop. However, in equation 5, we have two parameters and in (1) we have seven. This is an example of how mechanistic parameters b, m, g, r and ω can be grouped together or combined to create phenomenological parameters, ϵ and a and is the way we can analytically reduce a model.

Now imagine having a mathematical model with a system of eight equations and twenty parameters. It is obvious that the analytic model reduction game would be challenging to play because unlike this case, we would not know where we want to end up, nor would we be able to identify which parameters or groups of parameters were important. So, we need a numerical method that allows us to derive the combinations of parameters that are necessary for the behavior of the system. That is what the Manifold Boundary Approximation Method does.

The Manifold Boundary Approximation Method, also called MBAM, is a model reduction machine which takes systems of equations and generates a set of solutions which we call the model manifold. We can build this set of solutions by first considering the inputs and outputs. The inputs that we have are the original, finite number of parameter values. In the case of the rotating bead, these finite number of parameter values would be the values for all seven of our initial parameters: m, r, b, g, ω, θ_0 and θ_0'. If we were to generate a space which encompasses all of these parameters, it would be a 7 dimensional space called parameter space. Parameter space, by definition, is a space defined by the numerical values of the original parameters in our model. The outputs of this model are the solutions which the bead on a rotating hoop could take on, given different initial conditions. We call this space, behavior space, because it holds all of the possible behaviors for a given complex system. Thus, for every input or parameter value, there is a specific output and in total, the output would be the set of solutions for the bead on a rotating hoop.

We can imagine that each input is a vector and if we were to sweep across all of the vectors in our model, we would trace out a smooth surface as shown in Figure 9 below. If we mapped each input to a specific output, we would also trace out a smooth surface in behavior space. This smooth surface in behavior space is called the model manifold. As stated before, the model manifold is a set of solutions for all of our desired behaviors. In the case of the damped bead example, our manifold would hold solutions for all of the possible outcomes of the beads motion such as the bead not rotating, the bead under damped motion, the bead without damped motion, etc. This model manifold contains all of the solutions– all the combinations of parameters which cause our rotating bead to behave a certain way.

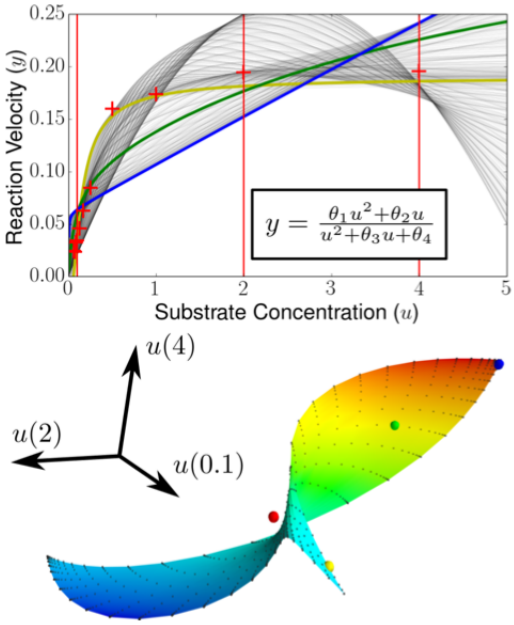

Figure 9: How inputs and outputs correspond to each other to build the model manifold. Here, the blue lines correspond to the blue surfaces on the manifold, green paths correspond to green surfaces on the manifold, etc. (Transtrum et al. 2015)

In the case specific to this thesis, the model manifold contains all of the solutions for the way β-Catenin behaves in the Wnt pathway. It contains the case for which β-Catenin oscillates, and for the case that it increases overtime. We will use this method because it is a numerical, computational machine which will tell us which parameters, or combinations of parameters are crucial to the behavior of the model. In this case, we want to focus on the result where β-Catenin oscillates. MBAM will help us do that by identifying combinations of parameters in our model which have no control over β-Catenin oscillating, thus allowing us to simulate the analytical method, like we did with the rotating bead on a hoop, and determine the few combinations of parameters which generate oscillations. So, how do we begin?

3.1 Building the Model Manifold

We begin by building the model manifold. The Manifold Boundary Approximation Method is a technique which takes sets of differential equations and transposes them into a geometric, parameter-independent set of solutions by building and analyzing a model manifold. As said before, MBAM is a computational machine which takes inputs (parameter values) and maps them to outputs which are solutions on the manifold. When we sweep through all the inputs in parameter space, we also sweep through all of the outputs in behavior space which gives us a smooth surface called the model manifold. The model manifold is a geometric set of solutions for all of the desired behaviors of β-Catenin in the Wnt pathway.

The dimensions for our parameter space are dictated by the number of parameters we begin with in our original model. If we are thinking about the Jensen et al. model of the Wnt pathway, there are twenty mechanistic parameters which means that our parameter space is a twenty-dimensional space. Since we are mapping the inputs from parameter space to outputs in behavior space, we also need to determine the dimensions in behavior space. The dimensions of our behavior space are determined by the number of different predictions our model can make. In our case, the dimensions of behavior space is the number of time points at which we predict β-Catenin concentration. While both of these spaces are nearly impossible to visualize because of their size, we can use computational differential geometry to explore them numerically. This leads into the next question which is, how do we begin to use the model manifold?

To begin using the manifold, we must first consider picking an initial point to start at. This initial point is the set of parameter values reported by Jensen et al. [2]. From this initial point in parameter space we can calculate a geodesic. Geodesics are the paths of least distance on a curved surface. We can imagine that they are the analogs of straight lines but on curved surfaces–one dimensional curves in parameter space. The initial direction is determined by decomposing the Jacobian matrix. These paths in parameter space also have a corresponding path in behavior space on the model manifold. Since these geodesics are the paths of least distance, we can use them to find the nearest boundary on the model manifold. These boundaries correspond to simplified models.

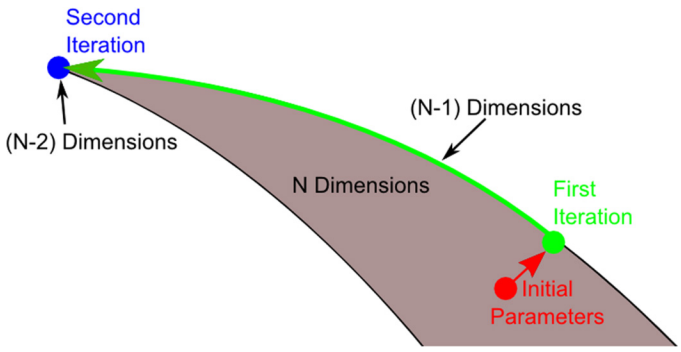

Figure 10: In this figure the red curve corresponds to the geodesic that is being run along the manifold. It starts by running to a boundary and then identifies a limit represented by the green dot.The process is then iterated to the second boundary in blue (Transtrum and Qiu 2014).

3.2 Interpreting the Boundaries as Approximations

In order to determine whether the geodesic has run sufficiently close to a boundary on the model manifold we can track the changes in parameter values as we move along its path as shown in Figure 10 above. Since the geodesic is bounded by the physical edges of the manifold, as it gets closer to a boundary it can be numerically defined to have some limit which it will asymptotically approach. As the geodesic approaches boundaries in behavior space, the parameters velocities exponentially increases which causes it to have extreme limit values such as zero or ∞. These extreme values result in outputs of the model which cannot be exceeded by any other parameter combination. They are the reason that we can interpret the boundaries of the model manifold as limits of the model parameters.

3.3 The Method

Now that we have gone through some of the intimate details of our model reduction method, let's walk through the process of how it helps us reduce a sloppy model. We first begin by gathering an over-parameterized model such as the Jensen et al. model of the Wnt pathway. We then want to apply the MBAM to this model in order to find simplified, approximate models.

We start by inputting our mathematical model into the MBAM program. It then runs a geodesic which identifies a boundary as shown in Figure 11.

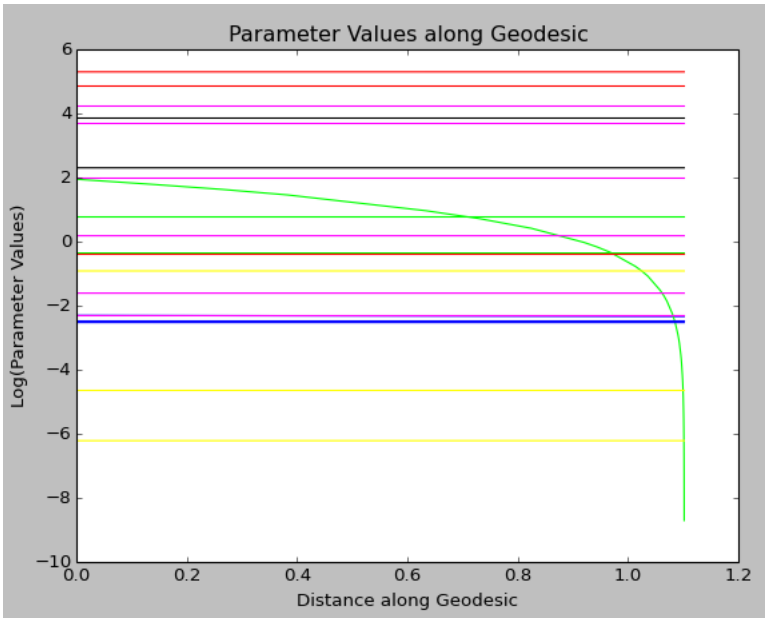

Figure 11: This is one of the figures coming from the MBAM program. In this figure, every colored line represents a different parameter in our model. One of the parameters, c_{bc}, in bright green, is asymptotically approaching zero at approximately x=1.15. This allows us to conclude that (1) the Geodesic has found a boundary and (2) has given this parameter a numerical value of zero (log value being -∞) which we can substitute into our model.

We will also see the graph which looks like Figure 12 where we see the parameter velocities hitting a boundary which causes them to approach negative ∞ quickly.

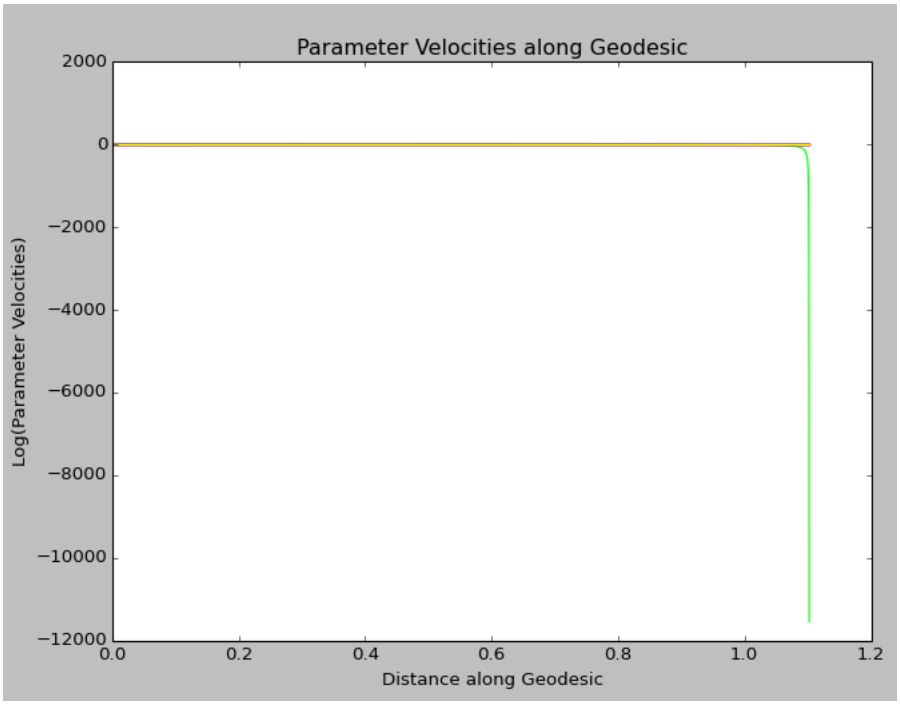

Figure 12: This figure from the MBAM program tells us that the velocity of this parameter approaches negative ∞ at the boundary. Hence the asymptotic approach towards zero. This allows us to conclude that this parameter is no longer relevant to the oscillatory behavior of β-Catenin.

Both of the figures above allow us to conclude that a specific parameter can become zero without significantly affecting the behavior of the model. This allows us to begin playing our analytical model reduction game, just like we did with our rotating bead above. Below is an example of the game we will play with our larger, Jensen et al. model.

In the larger model, the variables on the left hand side describe the different entities within our system. So, C describes the destruction complex–the macromolecule which inhibits the concentration of β-Catenin and the parameters on the right hand side describe the way it is changing overtime. c_{fc} describes the formation of the destruction complex, c_{bc} describes the breakdown of the destruction complex, and α is a parameter which tells us that some of the destruction complex goes away by other natural processes.

We begin with the equation 8 below where c_{fc}, c_{bc}, and α are three mechanistic parameters in our model.

$$\frac{dC}{dt} = c_{fc}BGA - c_{bc}C - \alpha C. \tag{8}$$

Since MBAM told us that the parameter c_{bc} goes to zero, we can now substitute that value into our original model to give us:

$$\frac{dC}{dt} = c_{fc}BGA - \alpha C \tag{9}$$

Later in the model reduction process, we find that the parameters α and c_{fc} go to ∞. This causes us to begin the process by which we combine mechanistic parameters into identifiably phenomenological combinations.

Since MBAM tells us that α goes to ∞, lets divide the equation by α.

$$\frac{dC}{dt} \cdot \frac{1}{\alpha} = \frac{c_{fc}BGA}{\alpha} - \frac{\alpha C}{\alpha}. \tag{10}$$

By doing so, reduce the model by deriving meaningful combinations of parameters.

$$0 = BGA - \frac{c_{fc}C}{\alpha} - C, \tag{11}$$

where identify $\frac{c_{fc}}{\alpha}$ a new parameter This process allowed us to reduce the model from two parameters to one.

The iteration of this process is the way we use MBAM as a model reduction tool and also the way we play the analytical reduction game similar to that of a bead on a rotating hoop.

3.4 Periodicity

One of the questions that this thesis explores relates to model reduction techniques for oscillatory regimes. One of the big questions we consider is "How does periodicity affect the results of reduction?" In order to answer this question, geodesics were run using predictions for both one period and two periods.

4 Data

As we iteratively remove parameters from our model, we will have a series of paths which allow us to go from our original twenty mechanistic parameters to the minimal model with nine phenomenological parameters. Since we wanted to explore how the periodicity of the oscillations affected our model reduction techniques, we used the MBAM in two different cases. One which looked at two periods of time, and another which only looked at one period of time. The sequence of approximations for each case are summarized in Figure 13.

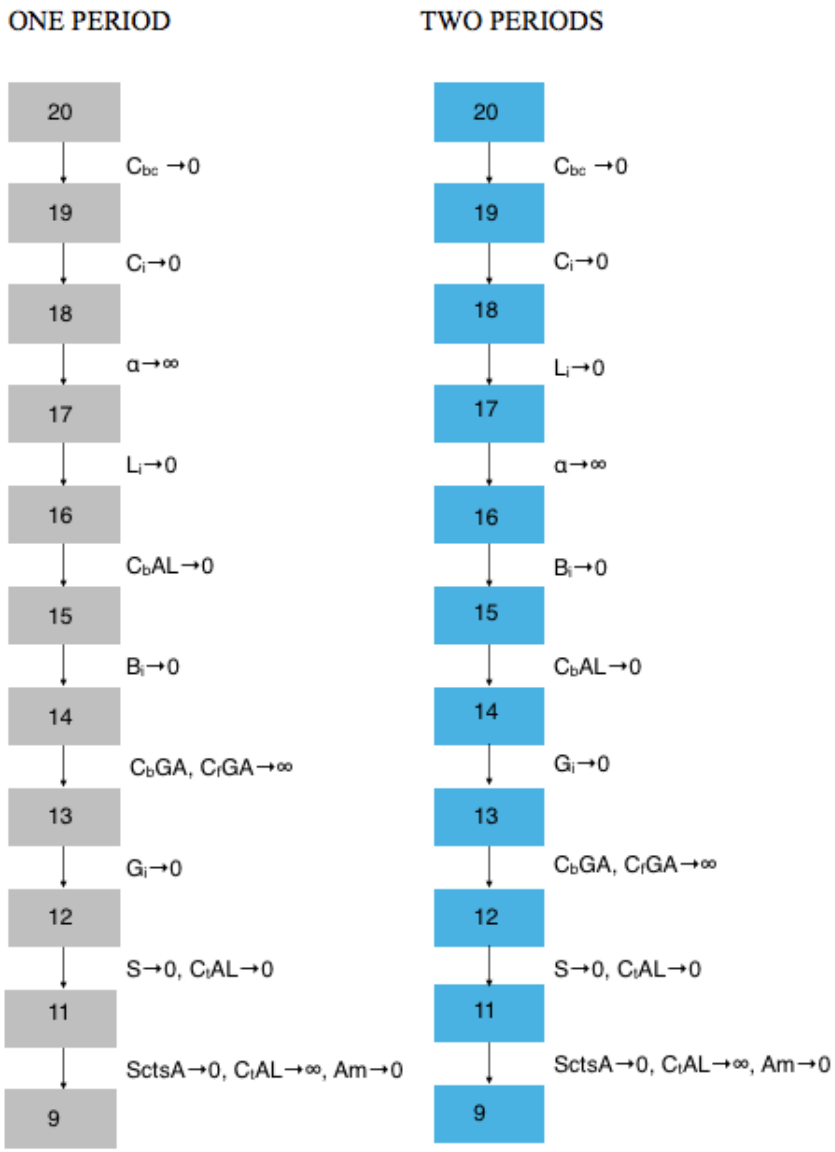

Figure 13: The flow chart above summarizes the different reduction paths for the one-period and two period data sets. Notice that the two sequences are nearly identical with the biggest difference being the order in which the limits are identified.

In the flow chart above, it is evident that the Manifold Boundary Approximation Method did not generate identical paths of model reduction for the two cases. However, it is important to note that the final nine parameters are the same in both cases. This allows us to conclude that our results are not dependent on the choice of model predictions. It further shows that MBAM can successfully reduce oscillatory models without additional techniques.

5 Data Analysis

5.1 Model Reduction for Oscillatory Regimes

From the flow chart in Figure 13, it is evident that the periodicity did not affect the minimal model derived from reduction. Although different paths were taken to arrive at a model with nine parameters, the same model resulted in both cases. This allowed us to assume that there was no information lost from having too little data. It also allowed us to infer that the MBAM generates accurate predictions for oscillating models, and that the specific behavior space used does not strongly affect the final outcome.

5.2 Comparing Two Models

Now that we have a minimal model for the oscillating Wnt signaling pathway (left), we can compare it to the non-oscillatory reduced model made by Dane Bjork in 2015 (right).

$$\dot{B} = \tilde{\tilde{S}} - c_{fc}\tilde{\tilde{B}}[GA_2] \tag{12}$$

$$\dot{Am} = \tilde{\tilde{B}}^2 - \frac{\tilde{Am}}{\tau_{A_2m}} \tag{13}$$

$$\dot{A}_2 = \frac{(KGA_2 + A_2)(-c_{fAL}A_2L + \tilde{A_2m})}{KGA_2 + G + A_2} \tag{14}$$

$$\dot{GA}_2 = \frac{-c_{fAL}A_2LG + \tilde{A_2m}\dot{G}}{KGA_2 + G + A_2} \tag{15}$$

$$\dot{AL} = -c_{fAL}A_2L - \nu A_2L = \dot{-L} \tag{16}$$

$$\dot{B} = -k_{13}X_{11} - X_8 + k_{12} \tag{17}$$

$$\dot{C} = -\tilde{k_9}\frac{\tilde{X_8}}{X_{11}}(1 + X_2) + \frac{\tilde{\tilde{k_9}}}{X_{11}} \tag{18}$$

$$\dot{X}_1 = -W * X_1 + \tilde{X}_2F(W) = \dot{X}_2 \tag{19}$$

The equations on the left hand side make-up the final, minimal, reduced model for oscillating concentration of β-Catenin created by Jensen et al. Equations 12-16 make up the simplified model which is behaviorally equivalent to the original oscillating model with 14 variables and 20 parameters.

In this model, Equation 12 describes the parameters which affect the concentration of β-Catenin. The parameter $\tilde{\tilde{S}}$ or $SctsA$ represents the production rate of β-Catenin and c_{fc} represents the formation rate of the destruction complex denoted by $\tilde{\tilde{B}}[GA_2]$. Equation 13 describes the way $Axin_2$'s mRNA concentration is being controlled. Equation 14 describes the components of the $Axin_2$ protein.The parameters KGA_2 and $\tilde{A_2m}$ control the production rate of $Axin_2$ while the parameter $-c_{fAL}$ controls its degradation. Equation 15 describes the dynamics of the destruction complex and Equation 16 describes a conservation law between AL and L. Although the typical student reading this paper may not understand the mechanistic intricacies of the parameters in the model, it is important to notice that in our model reduction process, we have been able to identify the parameter combinations which make this minimal model equivalent to our original model. Just like the original Jensen model that we looked at, this model encompasses some variable which describes the formation of β-Catenin, a variable which describes the concentration of $Axin_2$ and the way it is being produced in a negative feedback loop, the destruction complex and the way Wnt is entering into our pathway.

On the right side, Equations 17-19, make up the final, minimal, reduced model for the non-oscillating concentration of β-Catenin created by Lee et al. This model was similarly derived from a complicated mechanistic model by Dane Bjork. In the model, there are three variables which drive the behavior of increasing β-Catenin–the concentration of β-Catenin, the destruction complex, and a conservation law which describes how Wnt is being input into the pathway. More specifically, in Equation 17, the parameter k_{12} is the production rate of β-Catenin and the parameter k_{13} is the degradation rate, analogous to c_{fc}. Likewise, Equation 18 has a parameter $\tilde{\tilde{k}}_9$, which is the formation rate of the destruction complex and $\tilde{k}_9$ is the degradation rate.

These two models are not designed to represent the same functions of the Wnt pathway. They are distinct, separate models, with several common elements which we can generalize to be functionally equivalent in the pathway.

The final goal of this thesis is to combine the relevant elements from the minimal Jensen model (Equations 12-16) with those of the minimal Lee model (Equations 17-19) in order to build a new hybrid model that predicts novel Wnt behaviors. While the models above model two separate behaviors of β-Catenin, we can make general conclusions about the mechanisms they are describing.

In both cases, there is an equation describing the way β-Catenin is changing overtime.

$$\dot{B} = \tilde{\tilde{S}} - c_{fc}\tilde{\tilde{B}}[GA_2] \quad (20) \qquad \dot{B} = -k_{13}X_{11} - X_8 + k_{12} \quad (21)$$

The Jensen and Lee model do not match; however, there are similarities in the equations. Generalizing the commonalities in both models is crucial for building the combined minimal model because they describe the same underlying mechanisms. In the $\dot{B}$ equation, both models have a parameter describing a mechanism which causes the amount of β-Catenin to decrease (-c_{fc} from (20) and -k_{13} from (21)) and a parameter that causes β-Catenin to incrase ($\tilde{\tilde{S}}$ from (20) and k_{12} from (21)). Since these mechanisms appear in both minimal models separately, we can infer that they should also appear in our combined minimal model.

There is also an equation describing the way the destruction complex, C, is changing overtime.

$$\dot{GA_2} = \frac{-c_{fAL} * A_2 * L * G + \tilde{A_2 m} * \dot{G}}{KGA_2 + G + A_2} \quad (22) \qquad \dot{C} = -\tilde{k_9}\frac{\tilde{X_8}}{X_{11}}(1 + X_2) + \frac{\tilde{\tilde{k_9}}}{X_{11}} \quad (23)$$

Similar to the case of β-Catenin, there is a parameter which describes the mechanism that causes the concentration of destruction complex to decrease as well as a parameter which describes the increase of destruction complex in the system.

Using these similarities, we can begin to piece our combined minimal model together where we have a parameter describing Wnt entering the pathway, a parameter describing the destruction complex inhibiting the formation of β-Catenin, and a parameter describing the formation rate of β-Catenin. We can also identify differences in our model such as the negative feedback loop which cuases β-Catenin to oscillate from the Jensen et al. model and formation and degradation rates for the destruction complex from the Lee et al. model. These similarities and differences are shown in the combined minimal model in Figure 14 below.

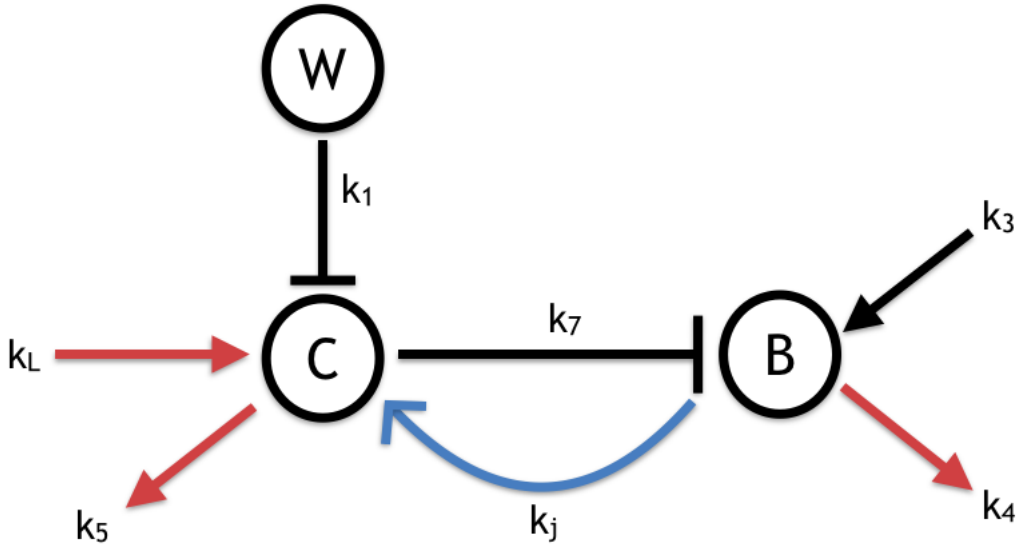

Figure 14: This is the diagram of our new combined model. Red lines signify parameters which are derived from the Lee et al. model, blue lines from the Jensen et al. model and black lines are parameters incorporated into both models.

In Figure 14, the red lines represent the variables derived from the Lee et al. model and the blue arrow represents the portion derived from the Jensen et al. model. The black lines are the parameters or mechanisms that are present in both models. This diagram summarizes the combined minimal model which embodies the transition between the Lee et al. and Jensen et al. model.

The mathematical model for this diagram is:

$$\dot{B} = -k_2 C + k_3 - k_4 \beta \tag{24}$$

$$\dot{C} = k_j \beta - k_1 W + k_L - k_5 C. \tag{25}$$

Now that we have our new mathematical model which encompasses both the case where we have increasing β-Catenin from the Lee et al. 2003 model and oscillating β-Catenin from the Jensen et al. 2010 model, we can now determine the steady states by solving the equations $\dot{C} = 0$ and $\dot{B} = 0$.

$$\begin{bmatrix} \dot{C} \\ \dot{\beta} \end{bmatrix} = \begin{bmatrix} -k_5 & k_j \\ -k_2 & -k_4 \end{bmatrix} \begin{bmatrix} C \\ \beta \end{bmatrix} + \begin{bmatrix} -k_1 W + k_L \\ k_3 \end{bmatrix}$$

where, $\det A_{Jensen} =$

$$\begin{bmatrix} 0 & k_j \\ k_2 & 0 \end{bmatrix}$$

Which gives us an oscillatory steady state.

$\det A_{Lee}=$

$$\begin{bmatrix} -k_5 & 0 \\ -k_2 & -k_4 \end{bmatrix}$$

gives us a stable steady state.

If we recall our minimal model:

$$\dot{B} = -k_L C + k_3 - k_4\beta \tag{26}$$

$$\dot{C} = k_j\beta - k_1 W + k_L - k_5 C \tag{27}$$

One will notice that recovering the minimal Lee 2003 model requires that we set the parameter k_j to ∞. However, it is also interesting to investigate the case where k_L, k_4, k_L, and k_j all approach ∞.

In that case,

$$\frac{\dot{C}}{k_L} = \frac{k_j\beta - k_4 W + k_L - k_5 C}{k_L}, \tag{28}$$

So,

$$\frac{\dot{C}}{k_L} = -\frac{C}{\beta} - \frac{k_4}{k_L}W(\frac{C}{\beta}) + \frac{k_L}{k_L} + \frac{k_5}{k_L}\beta. \tag{29}$$

Therefore, if k_L approaches ∞ then,

$$0 = -\frac{C}{\beta} - \frac{k_4}{k_L}W(\frac{C}{\beta}) + \frac{k_L}{k_L} + \frac{k_5}{k_L}\beta. \tag{30}$$

In this case, we know that we will have fractions which have the form $\frac{\infty}{\infty}$. However, we overcome this indeterminate form by remembering that the geodesic tells us the magnitude of our ∞. Thus, we are able to say that although the two parameters alone are infinitely large, their ratio is finite.

Thus,

$$\frac{C}{\beta} + \frac{k_4}{k_L}W(\frac{C}{\beta}) = \frac{k_L}{k_L} + \frac{k_5}{k_L}\beta \tag{31}$$

$$\frac{C}{\beta} + \frac{k_4}{k_L}W(\frac{C}{\beta}) = \frac{k_L}{k_L} + \frac{k_5}{k_L}\beta. \tag{32}$$

After doing some algebra, we arrive at,

$$C = \frac{\beta(\frac{k_L}{k_L} + \frac{k_5}{k_L}\beta)}{\frac{k_4}{k_L}W + 1}. \tag{33}$$

This is the process for which we solve the new steady state of our destruction complex, C. After we plug in this value of C into equation 20, we are able to determine our new steady state for B which is,

$$0 = k_L - \beta(k_4 - \frac{\frac{k_L}{k_L}}{1 + \frac{k_4}{k_L}W}) - \beta^2 \frac{\frac{k_j}{k_L}}{1 + \frac{k_4}{k_L}W}. \tag{34}$$

The roots of (33) can be found using the quadratic formula, to give steady state values to β-Catenin.

By finding the steady state in this model, we know that for some combinations of parameters that describe the input of the Wnt signal, we should expect that the system will fall into a new steady state which is not necessarily oscillating concentrations of β-Catenin or an increasing concentration of β-Catenin.

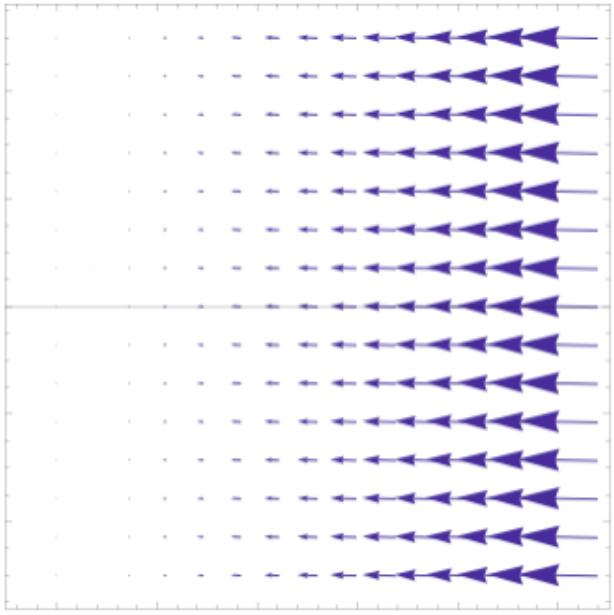

Figure 15: From the image above, we can see that the vector plots flows towards some new steady state. This steady state comes from the positive solution to Equation 33.

Figure 15 above corresponds to our quadratic equation above as we see two different steady states which our model could settle into. However, the quadratic equation which we solve for provides us with two different solutions–one which is negative and one which is positive. We disregard the solution that is negative because it is physically impossible for us to achieve–it does not make sense for us to have negative concentrations of either the protein β-Catenin or the macromolecule called the destruction complex.

We are then able to generate the next graph which demonstrates decaying oscillations.

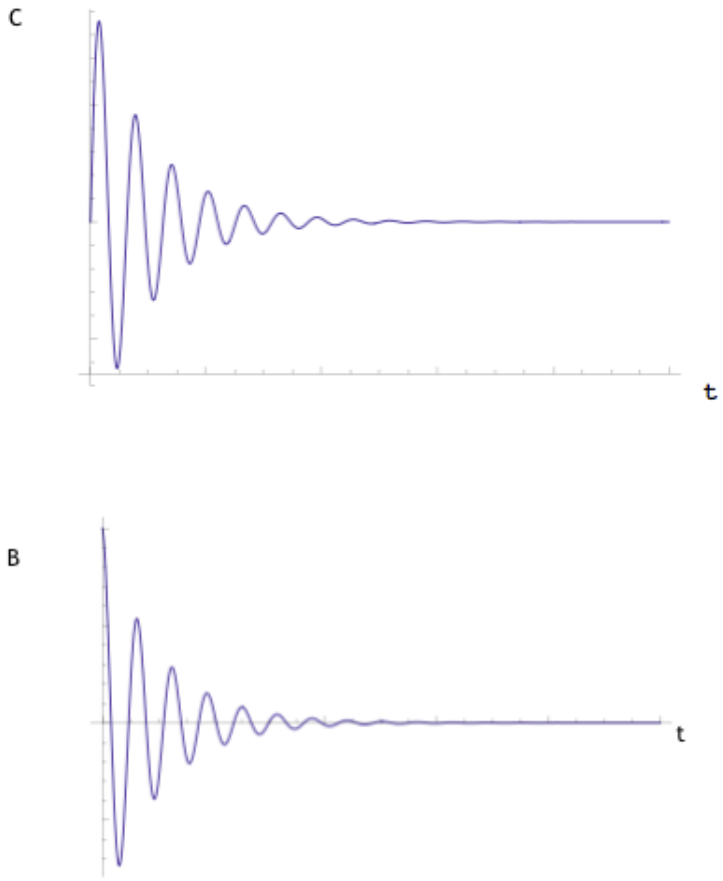

Figure 16: This graph is the graph of the concentration of β-Catenin as it changes overtime. In this graph, we see decaying oscillations as time continues to increase.

Figure 16 above is a graph with decaying oscillations. This implies that there is a new steady state under the Wnt signal because decaying oscillations implies that there is some finite amount of time for which oscillatory behavior exists.If we were to

look at the behavior of β-Catenin overtime as time ran towards infinity, we would not see the oscillatory behavior continue. In the Jensen et al. model of the Wnt signaling pathway, we saw a limit cycle where our oscillations continued as time ran towards infinity. However, these graphs tell us that there is some type of bifurcation point at which the oscillating concentration of β-Catenin ends and a new steady state that it begins to settle into.

This new steady state hints that there is a minimal model that exists which encompasses both behaviors of β-Catenin from the Lee et al. model and the Jensen et al. model of the Wnt pathway. We can now use this minimal model to generate new predictions about the Wnt pathway and other behaviors that it encompasses.

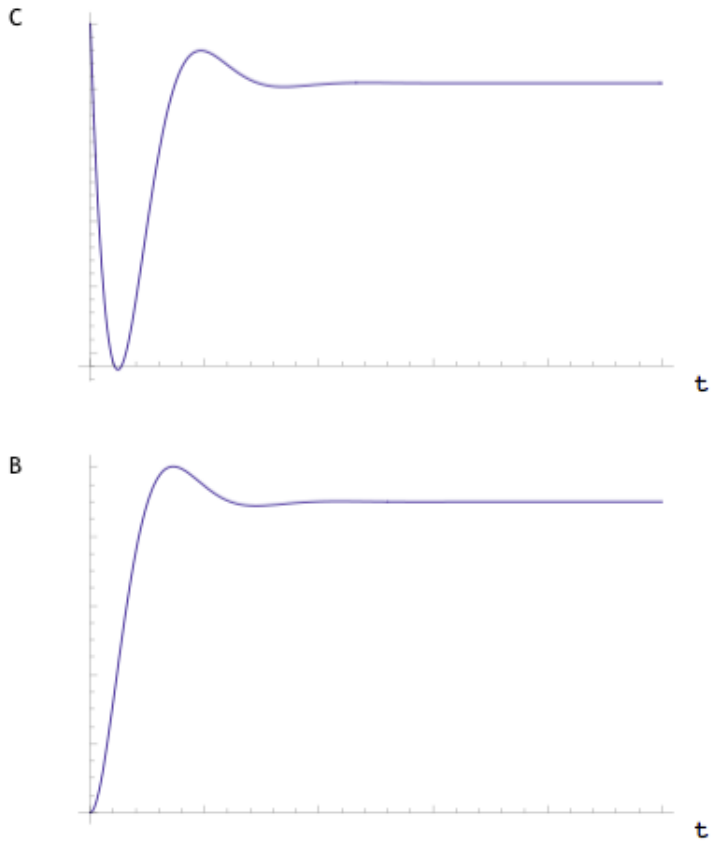

Figure 17: This image is a graph of the concentration of the destruction complex C and β-Catenin as it changes overtime. The first is related to the former and the second is related to the latter. The first curve, the curve which describes the destruction complex changing overtime has the features of an adaptation curve.

In this figure, we are able to see that the destruction complex, C, has a concentration which is adapting overtime. By definition, adaptation is the ability for

"something" to start out in one behavior, change and morph into a different state, and then return back to its original state which we are able to see in the first graph [4]. While this curve tells us that the destruction complex has the ability to adapt, we also know that since it inhibits the production of β-Catenin, that β-Catenin must also have the ability to settle into a new steady state. We also see that both C and B are settling into new steady states which implies that the Wnt pathway has some adaptive behavior which it is able to fall into and function under.

6 Conclusion

Lets recall the goals of this thesis. The first goal of this thesis was to reduce the Jensen et al. model of the Wnt pathway to identify the phenomenological parameter combinations. We did that by using the Manifold Boundary Approximation Method and playing the analytical reduction game analogous to a bead on a rotating hoop. By going through the reduction process, we were able to draw the conclusion that one, MBAM is able to successfully reduce oscillating models and two, our results were independent from the periodicity. The second goal of this thesis was to combine the Lee et al. minimal model with the Jensen et al. minimal model to build a new minimal model of the Wnt pathway. After analyzing our new minimal model, we were able to predict adaptive behavior for the destruction complex, and we were able to show the protein β-Catenin settling into a new steady state.

Moving forward, this project makes predictions that can be done experimentally. Our model predicts that Wnt regulates β-Catenin through an adaptation mechanism in the destruction complex. Adaptation is a survival function of cells and gives us reason to believe that this prediction of novel class behavior for the Wnt pathway is physically plausible. It would be interesting to observe this behavior experimentally as a validation for our model.

The ultimate goal of this thesis hinted at the need for minimal models which are complex enough to capture the intricacy of a complex system while remaining simple enough to generate new, accurate predictions. Through this project, we were able to show that we can bridge the gap between mechanistic models and phenomenological models by deriving combinations of mechanistic parameters which control the phenomenology. These results are particularly fascinating because we are able to combine mechanisms from two models and we were able to generate a new prediction which neither of those models could have predicted individually.

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