Sensitivity Analysis of Wnt Signaling Pathway

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***Abstract*—Wnt pathway plays a vital role in embryonic and early development , cell differentiation , cell polarity generation, stem cell maintenance, tissue repair, tissue development, and in cancer initiation. A group of proteins regulate the level of β-catenin inside the cell. Disregulation of this pathway becomes a cause of many human diseases like bone diseases and colorectal cancer. In this paper modal analysis is carried out for an existing mathematical model of Wnt Pathway. By modal analysis, time constants of proteins or protein complexes are calculated, states which do not satisfy the required criteria, have been proposed to be ignored for further analysis. Sensitivity analysis for this Pathway is conducted to identify most effective (hence important) parameters, for which the system's response is most sensitive. We have carried out different variations in parameters and studied change in the course of concentrations. The sensitivity analysis and simulation studies guide us towards the fact that system output is more sensitive to axin dependent destruction complex rate constant.**

I. Introduction

Wnt Signaling Pathway is a focus of intense research nowadays, as it is involved in many biological processes. Wnt is a group of signaling proteins made up of amino acids. These proteins are active in making canonical and non canonical pathways in the cell. Components of this pathway have a great degree of evolutionary conservational behavior in organisms,i.e from worms to mammals including humans, which makes it an important pathway [1]. Wnt signaling pathway Plays a vital role in embryonic development, stem cell maintenance , cell differentiation and Tissue development and Cell polarity generation [2]. Its dis regulation may cause colorectal cancer initiation [3].

In this paper the study of mathematical model of Wnt pathway is presented, and by conducting parametric sensitivity analysis we are investigating about the key parameters/variable of the pathway and their effect on the output (β-catenin). Before moving further the working principle of this pathway is explained;

Wnt proteins are secreted by Wnt secretion cells in extracellular space. Wnt binds to the frizzled receptor at the surface hence starts a sequence of events to initiate, which constitute this signaling pathway [4]. In the absence of Wnt stimulus level of transcriptional co activator β-catenin is regulated by a destruction complex made up of GSK/Axin/APC. This destruction complex continuously phosphorylates, ubiquitinates and destroys β-catenin. Due to which concentration of β-catenin inside the cell is kept low, and it is not able to enter nucleus, as described by Figure 1.

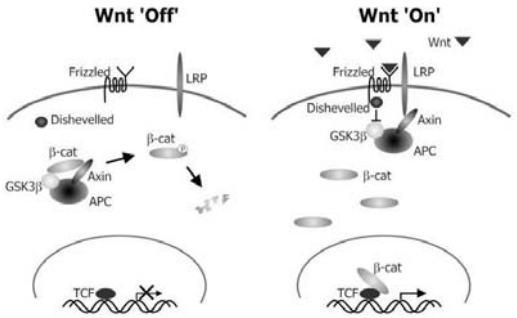

Fig. 1. Overview of the Wnt Pathway; In the OFF state (Left) Wnt Ligand is absent, the complex containing APC, Axin and GSK3β is active and regulates level of β-catenin by phosphorylation, ubiquitination and degrading β-catenin, In the ON state (Right) Wnt ligand binds to Frizzled and LRP receptors, the destruction complex becomes inactive due to deshevelled, β-catenin enters the nucleus and interacts with the TCF/LEF to start transcription [5].

In the presence of Wnt stimulus, it binds to the Frizzled and LRP receptor. Destruction complex becomes inactive due to activation of deshevelled protein. β-catenin accumulates in the cytoplasm, Finally enters in to the nucleus and binds to TCF. Which activates the transcription of over 100 genes, resulting into various gene expressions [4]. Figure 1 shows the function of Wnt pathways in presence and absence of Wnt Ligand.

Both experimental and theoretical studies of these pathways are crucial in our understanding of the processes, mathematical modeling of the Wnt signaling pathway has always been difficult. Firstly because of its complexity and secondly due to the non-availability of experimental data.Lee. et al, [5] developed a mathematical model consisting of system of ordinary differential equations parameterized by the experimental data obtained from Xenopus extracts. This model successfully replicates the experimental results, and is a great breakthrough in understanding and analyzing insights of the pathway. This model can be used to simulate experimental data, to predict the future behavior, and phenomena not yet encountered. Afterwards lee's coworkers expanded and explained the mathematical phenomena [6].

Cho et al, [7] extended Lee's model by studying the effect of APC mutants for β-catenin. They suggest that due to more mutated APC degradation of β-catenin is decreased, Limitation of this assumption is that there are more than one

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mutated copies of APC gene, which was not encountered, because cancer may carry more than one copies of APC gene [8]. Wawra et.al. introduced time delays in [7] model and showed that the oscillations in the β-catenin level may be caused by the time delays involved in the transcription and translation of Axin2. Mirams et. al. [8] tried to reduce Lee's [5] model, by performing a systematic asymptotic analysis. They have highlighted operation of Pathway components over different timescales, and reduced the model to a simpler one, having similar behavior as the original model.

Cho et. al. [9] proposed a sensitivity analysis approach for TNFα, NF-κB Signaling Pathway, and discussed about some important parameters of that pathway. Some parameters which plays a critical role in the pathway are selected for further analysis. Doing this requires a great prior knowledge about the pathway. Main reason to select only a few parameters, was to avoid simulation complexity. Now, due to advancements in technology, it is suitable to check all of the parameters, on the basis of this simulation we can decide which parameters should be selected for further analysis. We have used this approach for the Wnt signaling pathway.

This paper is organized as; Section I gives an overview about the literature related to the topic of this paper, Section II discusses the Mathematical modeling, simplification and Nondimensionalization of the model. Section III gives a discussion about Linearization of the Model, which is required for Modal analysis. Modal analysis is discussed in Section IV. Section V describes importance and preliminaries for Parametric Sensitivity Analysis. After identifying key parameters for this pathway, we analyze how the behavior of pathway changes with respect to changing variables/parameters, simulation results are shown in Section VI, and final discussion and conclusion is described in Section VII.

II. Mathematical Model

A. The Lee et al. Mathematical Model

Mathematical model of the Wnt pathway is a great breakthrough in understanding the operation of this pathway, firstly achieved by [5]. Mathematical modeling is done by first defining the reaction scheme, and constituting a set of ordinary differential equations, based on a series of balance equations describing concentrations of proteins, and their complexes. Protein synthesis are modeled as constant rates, and other processes are modeled as linear and bilinear rate equations [6]. *Lee et al's*. model contained 15 ordinary differential equations; each equation shows either a protein or a protein complex, as shown in Fig 2.

B. Model Simplification

To simplify the mathematical model, [6] used rapid equilibrium approximations or quasi-steady-state approximations for very fast processes. Only processes having timescales of hours are entertained, very slow processes are also neglected due to conservation relations [10]. By using these assumptions some differential equations are converted in to simple algebraic equations.

In the reduced model seven variables ($x_1, x_6, x_7, x_8, x_{13}, x_{14}$ and x_{15}), taken as dependent variables, are expressed as functions of other seven independent variables (x_2, x_3, x_4, x_9, x_{10}, x_{11} and x_{12}). x_5 is taken as a parameter. Deshevelled, APC, GSK3β and TCF are assumed to retain their level throughout the pathway operation as no degradation is detected in several hours [6], they are denoted by a 0 in their superscript.

The governing differential equations for the reduced, dimensional model are written below, notations for rate constants are kept same as used by [5] for simplicity.

$$\begin{aligned}
\dot{x_2} &= k_1 W(D_{sh}^0 - x_2) - k_2 x_2 \\
\dot{x_3} &= (k_4 x_4 - k_5 x_3 - \frac{k_9 x_{11} x_3}{k_8} + k_{10} x_9 \\
&\quad - \frac{1}{1 + K_8/x_3} v_{12} - (\frac{k_9 x_3}{k_8} + k_{13}) x_{11})/\gamma \\
\dot{x_4} &= -(k_3 x_2 + k_4 + k_{-6}) x_4 + k_5 x_3 + \kappa \\
\dot{x_9} &= \frac{k_9 x_3 x_{11}}{K_8} - k_{10} x_9 \\
\dot{x_{10}} &= k_{10} x_9 - k_{11} x_{10} \\
\dot{x_{11}} &= (k_4 x_4 - k_5 x_3 - (\frac{k_9 x_{11} x_3}{k_8}) + k_{10} x_9 - \\
&\quad \frac{K_8}{x_{11}} + 1)(v_{12} - (\frac{k_9 x_3}{k_8} + k_{13}) x_{11})/(\frac{x_3}{x_8}) \\
&\quad -(\frac{K_8}{x_{11}} + 1)(1 + \frac{x_3}{K_8} + \mu)) \\
\dot{x_{12}} &= (k_3 x_2 x_4 - (\frac{k_6 GSK^0 APC_0 K_{17} x_{12}}{K_7(K_{17} + x_{11})}) + k_{-6} x_4 \\
&\quad + v_{14} - k_{15} x_{12} + \dot{x_{11}}(\frac{APC^0 K_{17} x_{12}}{K_7(K_{17} + x_{11})^2}))/\nu
\end{aligned} \tag{1}$$

In above model $\gamma = (1+(1-\frac{1}{1+\frac{K_8}{x_3}})\frac{x_{11}}{K_8})$, $\nu = \frac{APC^0 K_{17}}{K_7(K_{17}+x_{11})}$, $\kappa = k_6 GSK^0 \frac{K_{17} x_{12} APC^0}{K_7(K_{17}+x_{11})}$, $\mu = \frac{TCF^0 K_{16}}{(K_{16}+x_{11})^2} + \frac{APC^0 K_{17}}{(K_{17}+x_{11})^2}$, k_i's denote mass-action rate constants, x_i's denote concentration of the reactions, synthesis of β-catenin and Axin are assumed to be constants and are denoted by v_{12} and v_{14} respectively. K_i's are Michaelis-Menton dissociation constants. W represents the extracellular concentration of the Wnt Ligand. Dsh^0 , APC^0, $GSK3^0$ and TCF^0 are the total concentration of these proteins. By observing the model one can easily see that x_{10} is decoupled i.e it is not involved in any other equations, because x_{10} is amount of the phosphorylated β-catenin, which will now be ubiquitinated and degraded by proteosomes. As x_{10} have no further role in transcription so it can be neglected henceforth [8].

C. Non Dimensional Model

Model Nondimensionalization can recover system's interensic properties like Time constants in our case. By rescaling system parameters we are free from SI units, and can identify the reactions that dominate on a particular timescale of

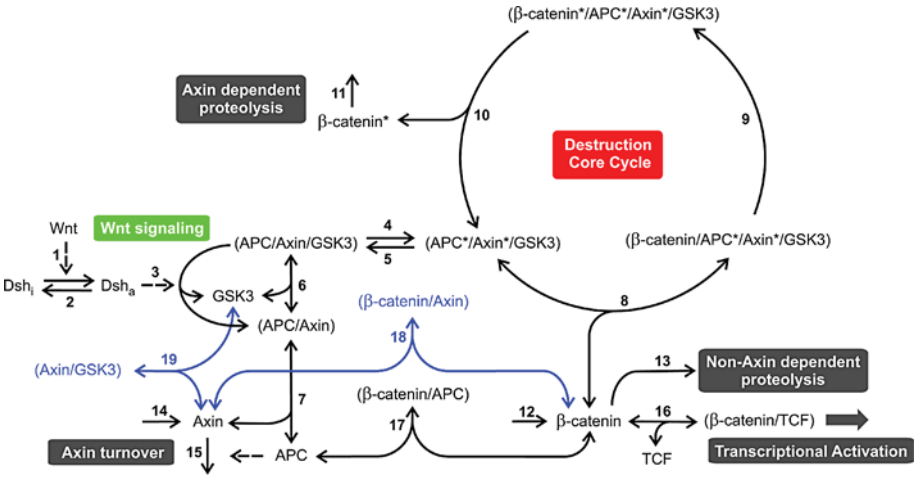

Fig. 2. Reaction scheme of the Wnt pathway; whole pathway is numbered in 19 steps, protein complexes are named by their components written in brackets, phosphorylated components are having an asterisk. Single headed arrows show uni directional reactions, and two sided arrows show binding equilibria. The broken arrow show that the components mediate, but do not act in the reaction scheme [5].

our interest. model nondimensionalization is done by scaling dimensional variables as shown in Table 1, time is scaled by $1/k_5$.

Dimensional Variable (nM)	Nondimensional Variable	Scaling	Description
X_2	$V(t^{'})$	$\frac{1}{Dsh^0}$	Dishevelled
X_{11}	$Ba(t^{'})$	$\frac{1}{K_{16}}$	β-catenin(active)
X_{10}	$Bp(t^{'})$	$\frac{k_5 k_{10}}{v_{14} k_{11}}$	β-catenin (Phosphorylated)
X_3	$Da(t^{'})$	$\frac{k_5}{v_{14}}$	Destruction Complex (active)
X_9	$Db(t^{'})$	$\frac{k_5}{v_{14}}$	Destruction Complex (bound)
X_4	$Di(t^{'})$	$\frac{k_5}{v_{14}}$	Destruction Complex (inactive)
X_{12}	$X(t^{'})$	$\frac{k_5}{v_{14}}$	Axin

TABLE I
DIMENSIONAL AND NONDIMENSIONAL VARIABLES [8]

After scaling previous model with the identified variables in table 1, the nondimensional model becomes;

$$\begin{aligned}
\dot{V}(t^{'}) &= k_1^{'} W(1-V) - k_2^{'} V \\
\dot{Di}(t^{'}) &= -(k_3^{'} V + k_4^{'} + k_{-6}^{'}) Di + D_a + \frac{k_6^{'} X}{1 + K_{16}^{'} B_a} \\
\dot{Db}(t^{'}) &= k_9^{'} B_a D_a - k_{10}^{'} Db \\
\dot{X}(t^{'}) &= (k_3^{'} V Di + k_{-6} Di - (\frac{k_6^{'}}{1 + K_{16}^{'} B_a} + k_{15}^{'}) X + 1 \\
&\quad + \frac{K_{16}^{'} K_7^{'} X \dot{Ba}(t^{'})}{(1 + K_{16}^{'} B_a)^2}) / (1 + \frac{K_7^{'}}{1 + K_{16}^{'} B_a})
\end{aligned} \tag{2}$$

$$\begin{aligned}
\dot{Da}(t^{'}) &= ((k_4^{'} Di - D_a - (k_9^{'} D_a B_a - k_{10}^{'} D_b)) \\
&\quad - (\frac{D_a K_8^{'} (v_{12}^{'} - k_{14}^{'} D_a B_a) - k_{13}^{'} B_a}{1 + k_6^{'} v_{14}^{'} D_a + \frac{TCF^0}{(1+B_a)^2} + \frac{APC^{0'}}{(1+K_{16}^{'} B_a)^2}})) \\
&\quad / (1 + K_8^{'} B_a - \frac{K_8^{'} v_{14}^{'} B_a D_a}{\sigma}) \\
\dot{Ba}(t^{'}) &= (\frac{v_{14}^{'}}{K_8^{'}} (k_4^{'} D_i - D_a - (k_9^{'} D_a B_a - k_{10}^{'} D_b)) \\
&\quad - \frac{1 + K_8^{'} B_a}{K_8^{'} B_a} (v_{12}^{'} - k_{14}^{'} D_a B_a - k_{13}^{'} B_a)) / \\
&\quad (v_{14}^{'} D_a - \frac{1 + K_8^{'} B_a}{K_8^{'} B_a} (1 + k_6^{'} v_{14}^{'} D_a \\
&\quad + \frac{TCF^0}{(1 + B_a)^2} + \frac{APC^{0'}}{(1 + K_{16}^{'} B_a)^2}))
\end{aligned} \tag{3}$$

In above nondimensional model $\sigma = 1 + k_6^{'} v_{14}^{'} D_a + \frac{TCF^0}{(1+B_a)^2} + \frac{APC^{0'}}{(1+K_{16}^{'} B_a)^2}$ W is dimensionless Wnt concentration, we will assume its two levels W = 0 (Off state) and W = 1 (On state) for simulation purpose. Parameters with prime represents nondimensional form, their values are taken from [8] Table 2.

III. LINEARIZATION OF THE MODEL

Modal analysis is used to determine important states of the system, having a key role in the behavior of the system. This technique is a linear technique so linearization of the system is performed.

Mostly our concern is when Wnt accumulates in the extracellular space, and hence effects the degradation of β-catenin, so system is linearized by taking Wnt stimulus On ($W = 1$). Linearization is done around the equilibrium points, which are closer to the steady state values of all the states.

The state vector is taken as

$$\begin{bmatrix} V & D_i & D_b & X & D_a & B_a \end{bmatrix}^T$$

System and input matrices are found to be;

$$A = \begin{bmatrix} -1.5 & 0 & 0 & 0 & 0 & 0 \\ -2.8 & -9.2 & 0 & 66 & 1.0 & -1.3 \\ 0 & 0 & -1549 & 0 & 340 & 5757 \\ 0.9 & 2.4 & 0 & -23.1 & 0 & 0.4 \\ 0 & 1.6 & 1269 & 0 & 279 & -4719 \\ 0 & 0 & 0 & 0 & 0 & -0.1 \end{bmatrix}$$

and

$$\text{B} = \begin{bmatrix} 0.1245 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}$$

The system is having 6 states, System matrix is of 6x6 dimension, as shown above, hence their will be 6 eigen values related to each state. By observing eigenvalues we can see that their are real as well as complex eigenvalues. Fortunately real parts of all eigenvalues in both cases i.e Wnt = 0, and Wnt = 1, are negative which ensures stability of the system.

IV. Modal Analysis

Modal analysis is a technique to analyze the behavior of a cellular system. Main theme of modal analysis technique is to first linearize the system, and then apply transformation to these equations so that they are decoupled and are moved on different timescales. Time constants in biological systems are defined as the time in which significant changes occur in a system normally after relieving from a steady state due to a perturbations. Time constants are found as;

$$\tau_i = \frac{1}{Re(\lambda_i)} \tag{4}$$

where λ_i are the eigenvalues of the Jacobin matrix. To decouple the system equations from each other similarity transform of the form stated below is applied.

$$WMW^{-1} = A \tag{5}$$

where M is the system matrix, A is a matrix having eigenvalues of M as its diagonal elements. W is a transformation matrix also called Modal matrix. It is having eigenvectors of the transposed system matrix M^T. Similarly inverse modal matrix M^{-1} consists of eigen vectors of system matrix as its columns. After transformation the old states "S" are converted to new states X;

$$X = WS \tag{6}$$

After finding the solution of transformed system X, each component of this vector is changed in time according to an exponential term having time constant -$\frac{1}{Re(\lambda_i)}$ [10].

In analyzing time constants for such systems we define a minimum time constant τ_m which is of our interest, and then eigenvalues are classified as

$$-\frac{1}{Re(\lambda_i)} < \tau_m \tag{7}$$

Generally minimum time constant for the pathways is defined as 1 Sec [10]. in our case time constants vary from ms range to Sec range; i.e

$$\begin{bmatrix} 0.0005 & 0.0326 & 0.4430 & 21.3266 & 21.3266 & 0.6636 \end{bmatrix}$$

Above is the range of time constants in Sec for the condition when Wnt ligand is On. When Wnt stimulus is Off time constant varies in the following range;

$$\begin{bmatrix} 0.0005 & 0.0326 & 0.4430 & 21.3266 & 21.3266 & 7.2993 \end{bmatrix}$$

By looking at above time constants we can conclude that when Wnt is On, Degradation of β-catenin (last element) is much slower(0.66 Sec) as compared to the time when Wnt stimulus is Off (7.3 Sec)

On the other hand first three states satisfy τ_m criteria in both conditions i.e Wnt On and Off, and last state satisfy this criteria only when Wnt is On. From here we can conclude that active deshevelled (V), inactive destruction complex (D_i) and destruction complex bound to β-catenin (D_b) are fast processes and can be replaced with the rapid equilibrium assumptions. As active β-catenin is the major target of Wnt pathway, so this protein is of more interest to us. We can see that first three states are on a shorter timescale as compared to β-catenin, so we can ignore these states. Other remaining states are Axin and active destruction complex, Wnt pathway is proven to be most sensitive to the concentration of Axin , and it is proposed to be the limiting factor for destruction complex [8].

V. Parametric Sensitivity Analysis

Parametric sensitivity analysis is a systematic approach, to examine behavior of biochemical systems, and to simulate and predict how sensitive the observed system reacts to possible changes. Variations in the parameter definitely changes the dynamic behavior of the system. Sensitivity analysis is an approach to find, how much the model depends on a specific parameter. It guides us on what parameters should be emphasized for further research, and provide a guidance to the experimental biologists upon considering only those proteins or parameters for measurements which are important. This approach is important mainly, when values for some parameters

are not well known. Measurement of these parameters in vivo (inside a living organism) requires a lot expertise. Analyzing the effect of a specific parameter on the system can tell us whether this parameter brings significant changes to the system (hence it is important to be measured) or the system is nearly unaffected by this (hence a guess is sufficient).
Another reason to apply sensitivity analysis on biological systems is to find a method to change the behavior of the system. This approach can give an idea about the parameters, which can change the behavior of the system. Similarly robustness with respect to external stimuli or disturbances, is an important property of any system. Sensitivity analysis is a way to determine this property for a specific system [11].
In this work, Parametric sensitivity analysis approach is applied to well known biological system "Wnt Signaling Pathway". Parameters having higher sensitivity (hence greater influence on this pathways) are selected for detailed analysis. Simulations have been performed to understand effect of variations of these parameters on the pathway. First we must understand the concept behind this approach. A mathematical model can be written as;

$$\dot{X} = f(X, K, t), X(t_0) = X_0 \tag{8}$$

where $f(X, K, t)$ is a nonlinear function, depending upon states X, Parameters K and time t. Here

$$X = [x_1 x_2 .... x_6]^T \tag{9}$$

is the state vector, and

$$K = [k_1 k_2 .... k_{24}]^T \tag{10}$$

is a column vector for the parameters. Effect of variation in parameters k_j upon system states x_i is found by Taylor series expansion [12];

$$x_i(k_j + \delta k_j, t) = x_i(k_j, t) + \sum_{j=1}^{24} \frac{\partial x_i}{\partial k_j} \delta k_j + H.o.t \tag{11}$$

In Equation 11 $\frac{\partial x_i}{\partial k_j}$ are called local concentration sensitivity coefficients, Higher order terms are normally ignored. These coefficients are defined as;

$$s_{ij}(t) = \frac{\partial x_i(t)}{\partial k_j(t)} \tag{12}$$

Where, $x_i(t)$ denotes ith state, and $k_j(t)$ denotes jth parameter. In our case $i = 1, 2, ..., 6$ and $j = 1, 2, ..., 24$. In current case Sensitivity matrix is defined as [12], [13];

$$S = \frac{\partial X}{\partial K} = \begin{bmatrix} s_{1,1} & s_{1,2} & \cdots & s_{1,24} \\ s_{2,1} & s_{2,2} & \cdots & s_{2,24} \\ \vdots & \vdots & \ddots & \vdots \\ s_{6,1} & s_{24,2} & \cdots & s_{6,24} \end{bmatrix} \tag{13}$$

By finding the solution for the ODE's of the system 9, and then differentiating states with respect to parameters can give us required sensitivity matrix. Normally, signaling pathways have complex nonlinear equations, so numerical methods are preferred for this approach. We have used Internal Numerical Differentiation approach.

VI. Simulations and Results

For sensitivity analysis, non dimensional model 3 is used, nominal parameter values are taken from [8] Table 2. Looking at the results of modal analysis technique, sensitivity analysis is applied to three significant states, i.e Axin (X), Active Destruction Complex (D_a) and β-catenin (B_a). Simulation results are shown in Figure 3. There are total 24 parameters involved in this model, the parameters having strong effect on each protein/protein complex, are shown in the figure. Surprisingly all the states are most sensitive to the same four parameters, i.e k13 (rate constant for non-axin dependent proteolysis), k14(non dimensional rate constant for axin depending destruction complex), v12(Synthesis of β-catenin) and v14(Synthesis of axin).
The output for Wnt signaling pathway is β-catenin, hence variation in the course of concentration of β-catenin, due to above parameters is measured. To check parameter variance effect on any signaling pathway, it is suitable to take the actual value of parameter with five times bigger and five times smaller values [9]. For this analysis, we have used a special input, which remains on for the half time and then gets off for other half time. This is done to encounter the dynamics of the system in both presence and absence of the Wnt signal.
Figure 4 shows variation in the concentration of β-catenin by changing values of parameter k13 (rate constant for non-axin dependent proteolysis). Concentration of β-catenin is kept low on higher values of k13 and concentration increases for lower values of k13. This response is evident, as proteolysis of β-catenin decreases its level.
Figure 4 shows variation in the concentration of β-catenin by varying values of parameter k14 (non dimensional rate constant for axin depending destruction complex). Concentration of β-catenin is kept low on higher values of k14 and concentration of β-catenin increases significantly for lower values of k14. This response could be described as, k14 is a rate constant for destruction complex, so higher level for this rate tries to level off β-catenin.

Figure 6 is a plot of variation in the concentration of β-catenin by changing parameter v12. v12 is synthesis of β-catenin, hence change in concentration of β-catenin is directly proportional to change in v12. Figure 7 shows change in

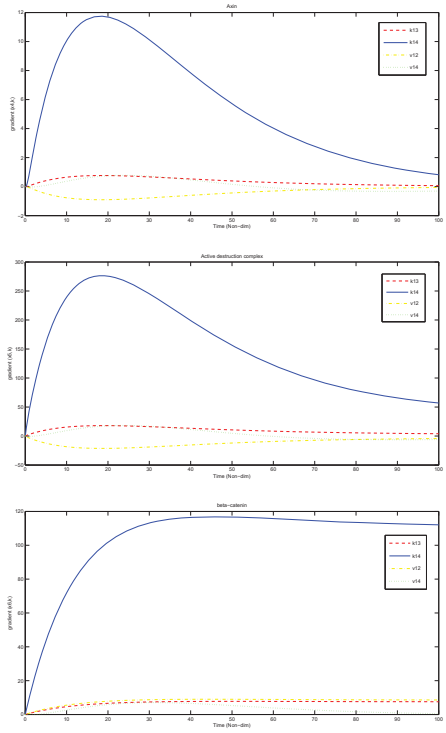

Fig. 3. Parametric Sensitivity Analysis results, vertical axis shows gradient of specific state with respect to parameters

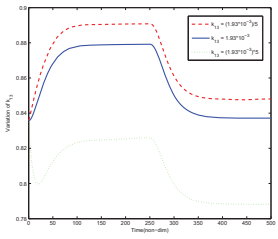

Fig. 4. variation in concentration of β-catenin with respect to k13

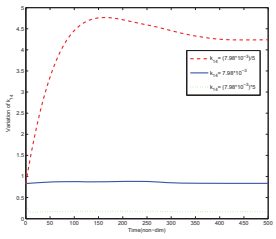

Fig. 5. variation in concentration of β-catenin with respect to k14

the concentration of β-catenin by varying parameter v14 (synthesis of axin). Axin has not a great effect on β-catenin, in its free form.

Conclusion

The model is linearized and stability of of the system is analyzed , by looking at the eigenvalues it is obvious that the system is stable. After this, Modal analysis is applied which states that time constants of the system varies from some milliseconds to several Seconds. This analysis also ensures us that rate of degradation of β-catenin is a lot more slower when Wnt signal is On. From above analysis, it can be concluded that active deshevelled (V), inactive destruction complex (D_i) and destruction complex bound to β-catenin (D_b) are fast processes and can be replaced with the rapid equilibrium assumptions.

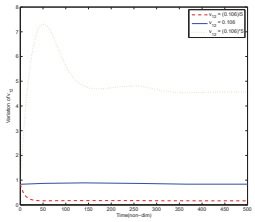

Fig. 6. variation in concentration of β-catenin with respect to variation in v12

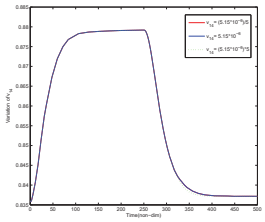

Fig. 7. variation in concentration of β-catenin by varying values of v14

The parametric sensitivity analysis is investigated, and k13 (rate constant for non-axin dependent proteolysis), k14 (non dimensional rate constant for axin depending destruction complex), v12 (Synthesis of β-catenin) and v14 (Synthesis of axin) are found to be the key parameters for this pathway. Then for variation in these parameters variations in concentration of output (β-catenin) is investigated. Results of this analysis helps the experimental biologists, to consider only those parameters/variable for measurement, which have a great significance for the pathway.

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