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Nonlinear Dynamics of Notch -Delta Signalling

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Abstract
This paper a standard model of Notch-Delta mediated lateral inhibition was considered and investigated the effect that transactivation of Notch by Delta and the inhibition threshold of Delta by Notch signaling (i.e. the dimensionless thresholds a and b) would have on the dynamics of lateral inhibition for a system of two cells. It was observed that, provided there exist a degree of variability in signaling thresholds between cell pairs, the cell fates can be determined by Notch-Delta mediation and the dynamics is highly dependent on the thresholds.

Keywords: Notch-Delta signalling, nonlinear dynamics thresholds, variability of signaling, cell fate determination

1. Introduction

Dynamics is the study that deals with the changes that occur with systems that evolve in time. A system that exhibits dynamics could be one that settles down in equilibrium, keeps repeating in cycles (i.e. periodic) or portrays a more complex behavior (chaotic). Such system is known as a dynamical system. In simpler words, a dynamical system is a system that exhibits certain behavior in a particular pattern. Dynamical systems in the physical world often evolve from dissipative systems; whereby the dissipation may come from internal friction, thermodynamic losses, among many other causes. Examples if dynamical systems include the mathematical models that describe; the swinging of a clock pendulum, the flow of water in a pipe, the Lorenz system etc.

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Chaos theory is a developing mathematical theory and a subfield of dynamics that deals with the behavior of certain nonlinear dynamical and deterministic systems which exhibit chaotic behavior under certain physical conditions. It is the study in which apparently random events are inherently predictable from straightforward deterministic equations.

In chaos theory, approaches designed to control chaos are based on certain observed system behaviors. Any chaotic attractor contains an infinite number of unstable, periodic orbits. Chaotic dynamics then, consists of a motion where the system state moves in the neighborhood of one of these orbits for a while, then falls close to a different unstable periodic orbit where it remains for a limited time, and so forth. This results in a complicated and unpredictable wandering over long periods of time.

Control of chaos is the stabilization, by means of small system perturbations of one of these unstable periodic orbits. The result is to render an otherwise chaotic motion more stable and predictable, which is often of an advantage. The perturbation must be tiny compared to the overall size of the system to avoid significant modification of the system's natural dynamics.

The methods describing chaotic behavior occur in many areas of science and technology and sometimes are more suitable for describing oscillations and indeterminacy than the stochastic, probabilistic methods.

The non-feedback control is referred to as the control of chaos by 'perturbation' or 'program signal'. It involves changing the behavior of a nonlinear system by applying a properly chosen external excitation. The excitation can reflect the influence of some physical action such as an external force/field, or it can be some parameter perturbation (modulation). This approach to controlling chaos is attractive because of its simplicity; i.e. no measurements nor extra sensors are needed and it is generally advantageous for ultrafast processes e.g. at the molecular or atomic level where np possibility of measuring system variables exists.

The possibility of transformation of periodic motion into chaotic motion and vice versa by an external harmonic excitation was first studied in the 1980s in Moscow State University by Dudnik, et al (1983) and Kuznetsov, et al (1985) for the Lorenz system and by Alekseev and Loskutov (1985, 1987) for a fourth-order system describing dynamics of two interacting populations; these results were based on computer simulations.

Recently, investigations were aimed at better suppression of chaos using smaller values of excitation amplitude and providing convergence of the system trajectories to the desired periodic orbit (limit cycle). Belhaq and Houssni (1991) considered the case of quasi-periodic excitation by reducing it to the periodic case, so also did Basios, et al (1999) studied the case of parametric excitation by Melnikov analysis. Since a chaotic attractor contains trajectories close to periodic orbits with different periods, a proper choice should be made to minimize the amplitude of excitation.

2. Methodology

The Notch signaling pathway is a highly conserved ell signaling system present in most multicellular organisms. Mammals for example possess four different notch receptors, referred to as NOTCH1, NOTCH2, NOTCH3, and NOTCH4. The Notch receptor is a single-pass transmembrane receptor protein that coordinates a signaling system known as the Notch pathway. It is a protein required for the coordination and regulation of biological pattern formation in all multicellular animal species- from worms to humans. It is also needed for the mediation and determination of cell fates. For instance, it is required for the wing outgrowth of insects. Notch, being an unusual transmembrane protein functions both at the cell surface to receive extracellular signals and in the nucleus to regulate gene expression in animals.

Notch signaling was first genetically discovered in by John, (1914) when he noticed the appearance of a Notch in the wings of the fruit/mutant fly "Drosophila melanogaster". Notch signaling pathway describes an evolutionary conserved cell-cell communication mechanism which plays a crucial role in mediating cell-fate differentiation during embryonic development and wound healing. It consists of the notch trans-membrane protein receptor and its protein ligands, Delta and Jagged. Biological pattern formation is enabled by molecular mechanisms of cell-cell signaling, which permits cells to influence each other's fate and behavior. One of the most important mechanisms of cell signaling is mediated by Notch.

The interaction between the Notch receptor and both ligands of the same cell leads to the degradation of both interacting proteins (i.e. receptor and ligand), as a result does not generate signal, and is known as cis-inhibition. The interaction that exists between the receptor of a cell and both ligands pf a neighboring cell leads to the cleavage of the Notch receptor which releases the Notch Intracellular Domain (NCID) signal into the cytoplasm in the cell nucleus to modify gene expression and is called trans-activation.

The following are the numerous functions of notch signaling in multicellular organisms:

i. Neuronal function, development and control
ii. Homoeostasis of the cardiac valve as well as implications in other human disorders involving the cardiovascular system (the circulatory system that permits the circulation of blood and transport of nutrients within the body)
iii. Timely cell lineage specification of both endocrine and exocrine pancreas
iv. Regulation of embryo polarity, where the absence of notch signaling causes abnormal anterior-posterior polarity in somite (a somite is a division of the body of an embryo)
v. Involvement of Notch signaling in cancers has led to the investigation of notch inhibitors used as cancer treatments.

Lateral Inhibition Mediated by Notch-Delta Interaction (The Model) is described as an emergent property of the Delta-Notch signaling network. For this model, we considered that the rate of Notch activation in a cell is an increasing function of Delta concentration on its neighbor (signaling), and that the rate if Delta expression is a decreasing function of the level of activated Notch in the same cell (inhibition). These interactions are represented by a means of a standard mathematical model of Notch-delta signaling between cell pairs, which are given by:

$$\frac{dN_1}{dt} = \alpha f(D_2) - \delta_N N_1 \quad (1)$$

$$\frac{dD_1}{dt} = \beta f(N_1) - \delta_D D_1 \quad (2)$$

$$\frac{dN_2}{dt} = \alpha f(D_1) - \delta_N N_2 \quad (3)$$

$$\frac{dD_2}{dt} = \beta f(N_2) - \delta_D N_2 \quad (4)$$

Where $N_{1,2}$ represent the levels of Notch activity in cells 1 and 2, and $D_{1,2}$ are the concentrations of Delta in each cell. α and β are the maximal production rates of Notch and Delta respectively. δ_N and δ_D are their corresponding degradation rates.

For ease of calculation, equations (1 - 4) are written in dimensionless form as:

$$\frac{dN_{1,2}}{dt} = \frac{D_{2,1}^r}{a^r + D_{2,1}^r} - N_{1,2}$$

$$\frac{dD_{1,2}}{dt} = v\left(\frac{1}{1+\left(\frac{N_{1,2}}{b}\right)^h} - D_{1,2}\right)\frac{D_{2,1}^r}{a^r + D_{2,1}^r} - N_{1,2} \qquad (5)$$

Where the parameter v is the ratio between the degradation rates of Delta and Notch δ_D / δ_N. a and b are the dimensionless thresholds for Notch activation by Delta in the neighboring cell, and Delta inhibition by Notch in the same cell respectively.

$$a \equiv \frac{k_N \delta_D}{\beta} \text{ and } b \equiv \frac{k_D \delta_N}{\alpha} \qquad (6)$$

a and b are referred to as the activation and inhibition thresholds respectively. k_N is the threshold of Notch activation by neighboring Delta, k_D is the threshold of Delta inhibition by Notch in the same cell, and the coefficients r and h represent the cooperative character of the two aforementioned processes.

We investigate the temporal evolution of the model by solving numerically the equations (5).

For this purpose, we use the fourth order Runge-Kutta method. In our calculations, we consider $r = h = 2$ and $\delta_D = \delta_N$, and using a time span of (0-300), we consider the cells initially as negative for Notch activation, with similar initial levels of Notch and Delta ($N_{1,0}, D_{1,0}, N_{2,0}, D_{2,0}$) = (0.05,0.90;0.06,0.91) in dimensionless units.

3. Results And Discussion

The sets of differential equations in equation (5) were solved using the fourth order Runge-Kutta scheme as presented in each of the plots in the figure below. In the calculation I used a step size of 0.001. The initial conditions are ($N_{1,0}, D_{1,0}, N_{2,0}, D_{2,0}$) = (0.05,0.90;0.06,0.91) in dimensionless units with computation over the interval {0, 300}. I studied the steady state behavior of a standard model of lateral inhibition for the case of two cells namely; Notch and Delta. The steady states of this system are dependent on two parameters a and b which are the dimensionless activation and inhibition thresholds respectively. As seen in figures 1, 2, 3, 4 below, we allow the values of a and b to vary across the population of the cell pairs.

Thus, for a population of cell pairs with variable activation and inhibition thresholds (a and b), the possible signaling states were generated and presented in Figs. 1, 2, 3, and 4 by time series depicting the dynamic behavior of the solved system. Put in another way, but expressing the same meaning, Figs. 1, 2, 3, and 4 through time series show the stable solutions of the system which are classified according to their resulting signaling states. This is done for varying values of a and b (i.e. for $a = 0.1$ and $b = 0.1$, $a = 1$ and $b = 0.01$, $a = 0.001$ and $b = 0.1$, $a = 10$ and $b = 1$) as previously said in the preceding paragraph.

In the figures below, Notch 1 and 2 represent the levels of Notch activity in cells 1 and 2. And delta 1 and 2 are the concentration of Delta in each cell.

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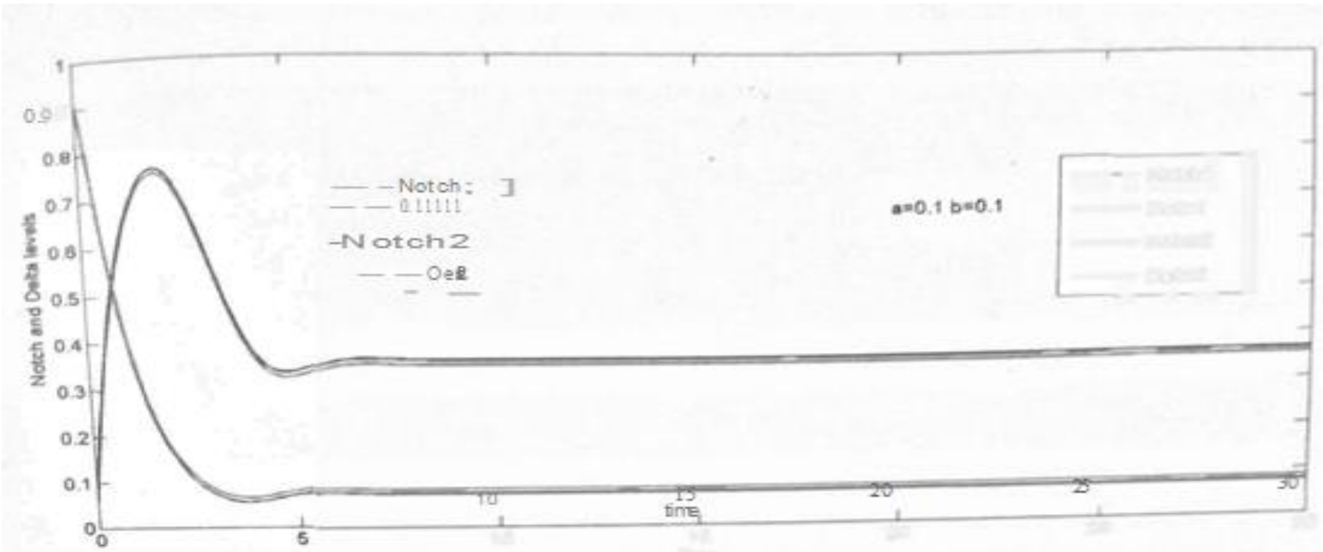

Fig: 1 Time Series Showing the Stable Solutionas of the System at a=0.1 and b=0.1

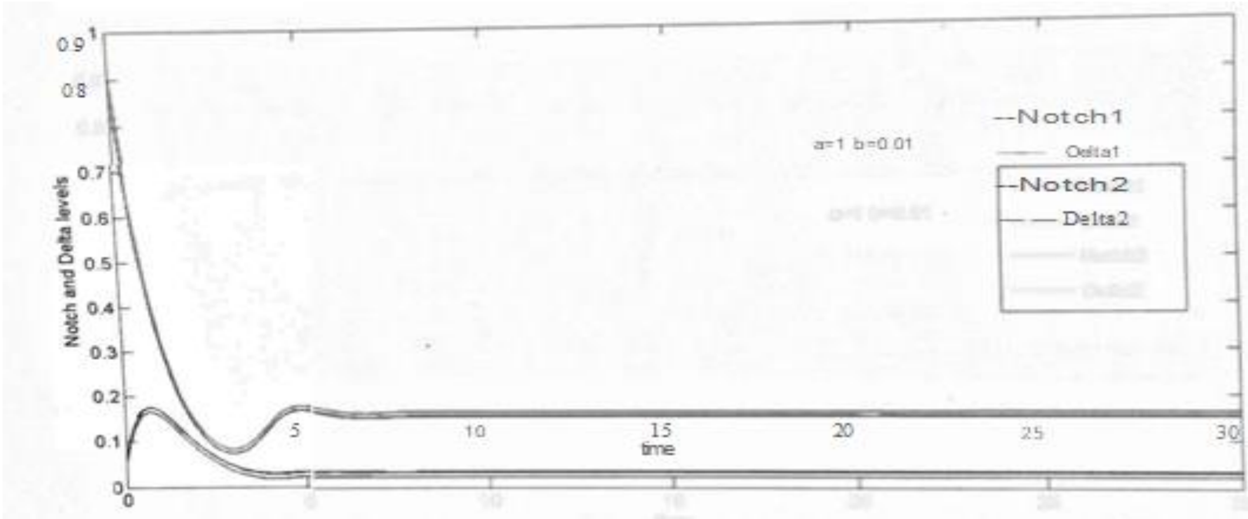

Fig: 2 Time Series Showing the Stable Solutionas of the System at a=0.1 and b=0.1

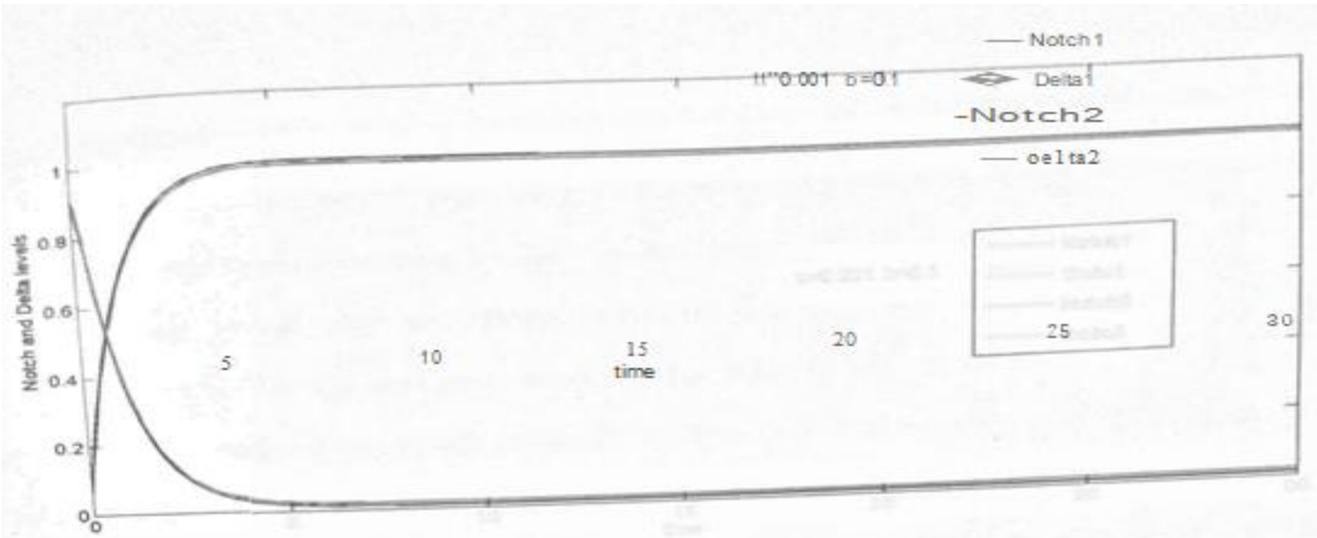

Fig: 3 Time Series Showing the Stable Solutionas of the System at a=0.1 and b=0.1

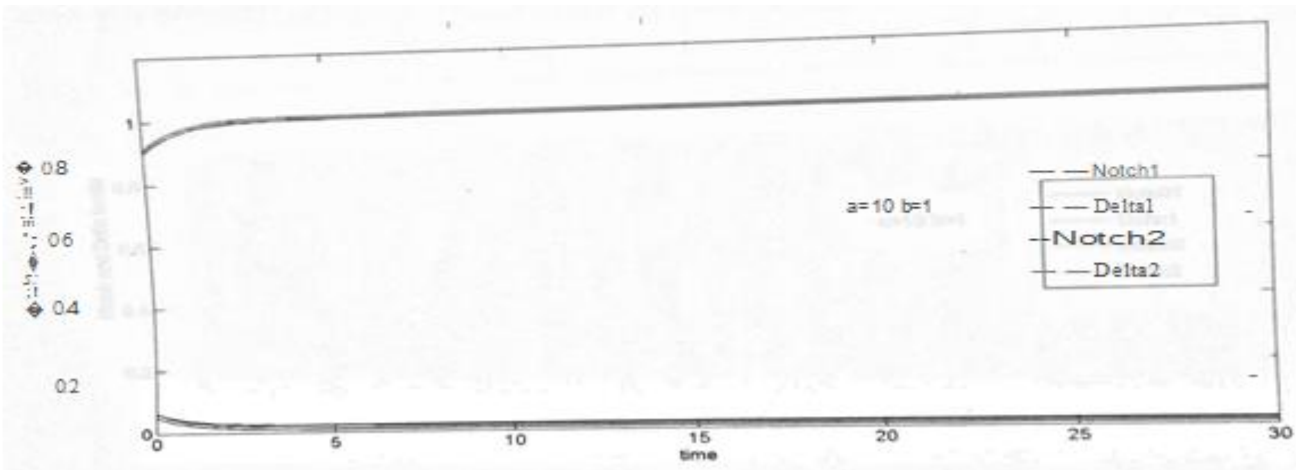

Fig: 4 Time Series Showing the Stable Solutionas of the System at a=0.1 and b=0.1

Comparing the figures, I observed that varying the threshold values a and b has effect of producing larger Notch with a maximum while presenting lower Delta values (as presented in Fig 1). In fig 2, the threshold values of $a = 1.0$ and $b = 0.01$ shows larger value of Delta with well-defined minimum compared to the Notch values. Fig 3 with $a = 0.001$ and $b = 0.1$ shows higher Notch values and low Delta values similar to Fig 1 without any defined minimum or maximum. Fig 4 also produced similar Notch-Delta relationship to Fig 2 with the exception of well-defined stationary points. This shows a complex temporal dynamics of the Notch-Delta signaling to the threshold values as the results are highly dependent on the values. This population level variability of signaling thresholds can be associated to diversity in the contact areas between cell pairs. The model reproduced the signaling outcomes observed in the Drosophila intestine.

Conclusion

Provided there exists a degree of variability in signaling thresholds between cell pairs, the cell fates can be determined by Notch-Delta mediation and the dynamics is highly dependent on the thresholds. The model reproduced outcomes observed in the Drosophila intestine, which results into cell differentiation versus self-renewal fates. The complex dynamics of cell-cell interactions can thus be explained using the temporal analysis of Notch-Delta signaling.

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