Mathematical Modeling of a Branch of the Leptin Signaling Pathway

Final Report for VIGRE Summer 2009 Research Workshop

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Introduction

Leptin is an adipose-derived hormone which regulates energy balance and contributes to the sensation of satiety in an organism. The study of leptin and its signaling pathways within the cell is of biological importance, to list a single reason, due to its obvious implications in the understanding of human appetite and metabolism. Leptin's associated signaling pathway is responsible for the expression of a number of genes, just a subset of which will be considered in the mathematical models presented in this paper. Analysis of leptin signaling component levels in experimental data collected from mice has indicated that the percentage of all genes expressed following a circadian rhythm (the periodic light/dark cycle affecting many organisms) may exceed the accepted upper bound of 10-15 percent. This suggests that the role of circadian oscillation in gene expression has been underestimated [1]. Thus, more important than leptin's role in metabolism is the evidence that the manner in which biological pathways are modeled and understood may be improved by considering the timing of regulation, interaction or signal transduction as well as the oscillatory phase at which a particular event takes place [1]. The purpose of this work is to develop an accurate analytical model representing the dynamics, which are mostly oscillatory according to [1], of the leptin signaling pathway as a feedback system and to compare the periodicities inherent to this system to the periodicities seen in the data. A model meeting these criteria will serve as a valuable tool for future experimental design in researching the leptin signaling pathway and possibly other signaling pathways.

Leptin Signaling Pathway

The modeling problem presented considers only part of the leptin signaling pathway. A nonmathematical description of the pathway considered involves leptin (LEP), leptin receptor (LEPR), leptin receptor complex (LRec), Janus-kinase 2 (JAK2), phosphorylated Janus-kinase 2 (JAK2*), signal transducer and activation of transcription (STAT3), phosphorylated signal transducer and activation of transcription (STAT3*), and suppressor of cytokine signal (SOCS3). The signal begins when leptin (LEP) outside the cell crosses through the cell wall by binding to leptin receptor (LEPR) to form the leptin receptor complex (LRec). At this point, LRec

phosphorylates available JAK2 to form JAK2*. This JAK2* in turn phosphorylates available STAT3 to form STAT3*, which then activates the transcription of SOCS3 in the nucleus. The suppressor SOCS3 serves to attenuate this signal by repressing both JAK2 and LEPR. A diagram of this process can be found in [1]. It is evident from this description that any dynamical system accurately modeling this pathway must be a feedback system, so it can be expected that a solution to such a system would have inherent periodicities. These periodicities represent the oscillatory behavior we hope to match to the data. While any model accurately portraying the behavior seen in the data and admitting an analytical solution would be of enormous use, it is simply the periodicities of such a solution that are of primary interest in this problem.

A Linear Model for the Leptin Signaling Pathway

A linear dynamical system model of the leptin signaling transduction pathway is a good first observation of the system, as it provides a relatively concise picture of the dynamics to be further modeled. The linear system is set in a 5-dimensional vector space ($\mathbb{R}^5$ for simplicity) whose components, a subset of the components of the signal pathway described above, are as follows:

R – Abundance of free leptin receptors (LEPR)

C – Abundance of leptin receptor complexes (LRec)

J – Abundance of JAK2 available to phosphorylate STAT3

T – Abundance of STAT3 available for activating transcription of SOCS3

S – Abundance of SOCS3 available to bond to Leptin receptor or JAK2.

The key assumption to observe in this model, aside from linearity, concerns the phosphorylation of JAK2 and STAT3. The phosphorylated variants of each of these components (JAK2* and STAT3*) are omitted in favor of letting their unmodified versions represent the signal transduction at either of these components as the population of that particular component. In other words, the signal in this model is considered to move along the entire component chain as a transfer from population to population. This assumption is not appropriate for an employable model but is, again, useful for the purpose of introducing the dynamics mathematically. The general linear model with non-homogeneous oscillatory growth/decay terms φ_X is as follows:

$$\frac{dR}{dt} = -b_C R - n_R S + \varphi_R$$

$$\frac{dC}{dt} = b_C R - p_J C + \varphi_C$$

$$\frac{dJ}{dt} = b_J C - p_T J - n_J S + \varphi_J$$

$$\frac{dT}{dt} = p_T J + \varphi_T$$

$$\frac{dS}{dt} = t_S T - \left(n_R + n_J\right) S + \varphi_S \ .$$

The role of the φ_X terms is to model the combined effects of periodic synthesis and/or decay due to effects outside of the system being modeled. It is possible that these terms can be constant and even zero. In fact, it is likely that most are zero and the circadian periodicities of the whole system are partially regulated by the oscillations of one or two of the components in the pathway. The coefficients in the system can be interpreted as population transfer rate constants. Specifically, b_X represents the bond rate of the current equations component to the next component in the pathway,X; similarly, p_X represents the phosphorylation rate of the current component to the next pathway component, X. The values n_X represent the percentage of the population of SOCS3 that binds to component X. Observe this model assumes there is an unlimited supply of leptin ready to bind to LRec, so leptin does not appear as a component in the state space.

An analytical solution to this system is a task for a mathematical software package capable of complicated symbolic manipulation. Even with all the bond and phosphorylation constants set equal to unity, the assumption $1 - n_R = n_J$, and $\varphi_X = 0$ for all X except T with $\varphi_T = -T$, *Mathematica* will not yield a sensible, more less manageable output. The next step is to seek a numerical solution.

Simulation of the Linear Model

In order to simulate the linear model, the assumptions made at the end of the last section are carried over to a numerical consideration of the problem with two modifications. First, a constant decay rate for STAT3 is assumed with $\varphi_T = -kT$, where k is a parameter ranging from 0 to 1 according to user input in the simulation. Second, the percentage n representing the bond rate of SOCS3 to LRec is varied between 0 and 1 according to user input. (The assumption

$1 - n_R = n_J$, from above, implies $n_J = 1 - n$.) A simple *MATLAB* program utilizing the built-in differential equation solver **ode45**, which employs a Runge-Kutta algorithm, provides the numerical solution once the initial conditions and the parameters are selected by the user. The system under these assumptions is given by the following:

$$\frac{dR}{dt} = -R - nS$$

$$\frac{dC}{dt} = R - C$$

$$\frac{dJ}{dt} = C - J - (1 - n)S$$

$$\frac{dT}{dt} = J - kT$$

$$\frac{dS}{dt} = T - S\ .$$

For ease of use, a *MATLAB* graphical user interface (GUI) is built to run the simulation (See figure 1 in the appendix). The GUI shown below contains period and amplitude sliders for the oscillatory terms φ_X. In the output plot (See figure 2 in the appendix), the amplitudes of these terms are set to zero, so the model being simulated is exactly the one listed in this section with variable parameters n and k whose values are listed in the upper left hand corner of the output plot. Note the oscillatory behavior of the solution to this feedback system.

A Nonlinear Model for the Leptin Signaling Pathway

With the linear model presented above serving as a guide for the dynamics, a more accurate model which involves physically likely nonlinear dynamics can be built. The nonlinear model under consideration is as follows:

$$\frac{dR}{dt} = -b_{SR}S + \varphi_R$$

$$\frac{dJ}{dt} = -b_{SJ}S + \varphi_J$$

$$\frac{dT}{dt} = \varphi_T$$

$$\frac{dS}{dt} = t_S T^* + \varphi_S$$

$$\frac{dR^*}{dt} = b_{LR}LR - R^*$$

$$\frac{dJ^*}{dt} = b_{R^*J} R^* J - J^*$$

$$\frac{dT^*}{dt} = b_{J^*T} J^* T - \varphi_{T^*} ,$$

where b_{XY} is the bond rate of component X to component Y, t_X is the rate of activation of transcription of X, X^* is the phosphorylated version of X, and φ_X is the growth/decay rate of X which may or may not be periodic and could be a function of X.

Simulation of the Nonlinear Model

The nonlinear model is simulated similarly to the linear model with a GUI to facilitate ease of use. To simplify the simulation, a few assumptions concerning the coefficients of the system are made. All bond and activation of transcription rates are set equal to unity, and the growth/decay terms are all set equal to the same arbitrary constant. The simulation, of course, can be written to accommodate user-varied versions of these parameters.

There has been little success in achieving an informative simulation of this model, the main obstacle being to choose the correct solver algorithm to implement.

Conclusion and Future Work

The task of modeling the leptin signaling pathway is still largely undone. The linear model does not capture enough complexity, namely the impulsive nature of the phosphorylation components of the pathway, but is easily simulated and qualitatively analyzed. The expected oscillatory behavior is readily observed in simulations of the linear model, but a practical analytical solution is still unavailable. Some future investigation may involve simplifying the complicated closed form of the solution as output by *Mathematica*, if such a consideration would provide insight for simplifying a more complex model's (e.g., a nonlinear model's) solution. Also, an attempt to characterize the inherent periodicities of the linear system without an analytical solution available may be the groundwork for doing the same to future models to be considered. It is not known how such an objective would be accomplished, but the motivation lies in the desire to identify circadian oscillators occurring naturally in the regulatory pathway. One suggestion might be to consider the eigenvalues of the linear system. It is a simple fact from the theory of linear differential equations that complex eigenvalues are associated with periodic solutions. A detailed investigation of this idea may prove fruitful for characterizing the oscillations of trajectories of the system.

While the nonlinear model better represents the impulsive nature of the phosphorylation components of the pathway, it will be useful to obtain a reliable numerical simulation to this system to qualitatively validate its consideration. An analysis of the equilibrium points and stability properties of this system is the next natural step to take. If a technique for the assessment of the periodicities of an unknown solution to a linear system is found in literature or derived, then this technique could be possibly extended to the nonlinear system.

Another type of model that could be considered for this problem is a spiking model or an impulsive system of differential equations. Presently, a review of the literature available is required before much can be said about such a model.

The problem will be carried over as a research project for the MATH 4020 math-modeling clinic in the fall 2009 semester in the LSU mathematics department. All future work discussed above will be considered to some extent in this project with an emphasis on a new spiking model.

Appendix

Figure 1

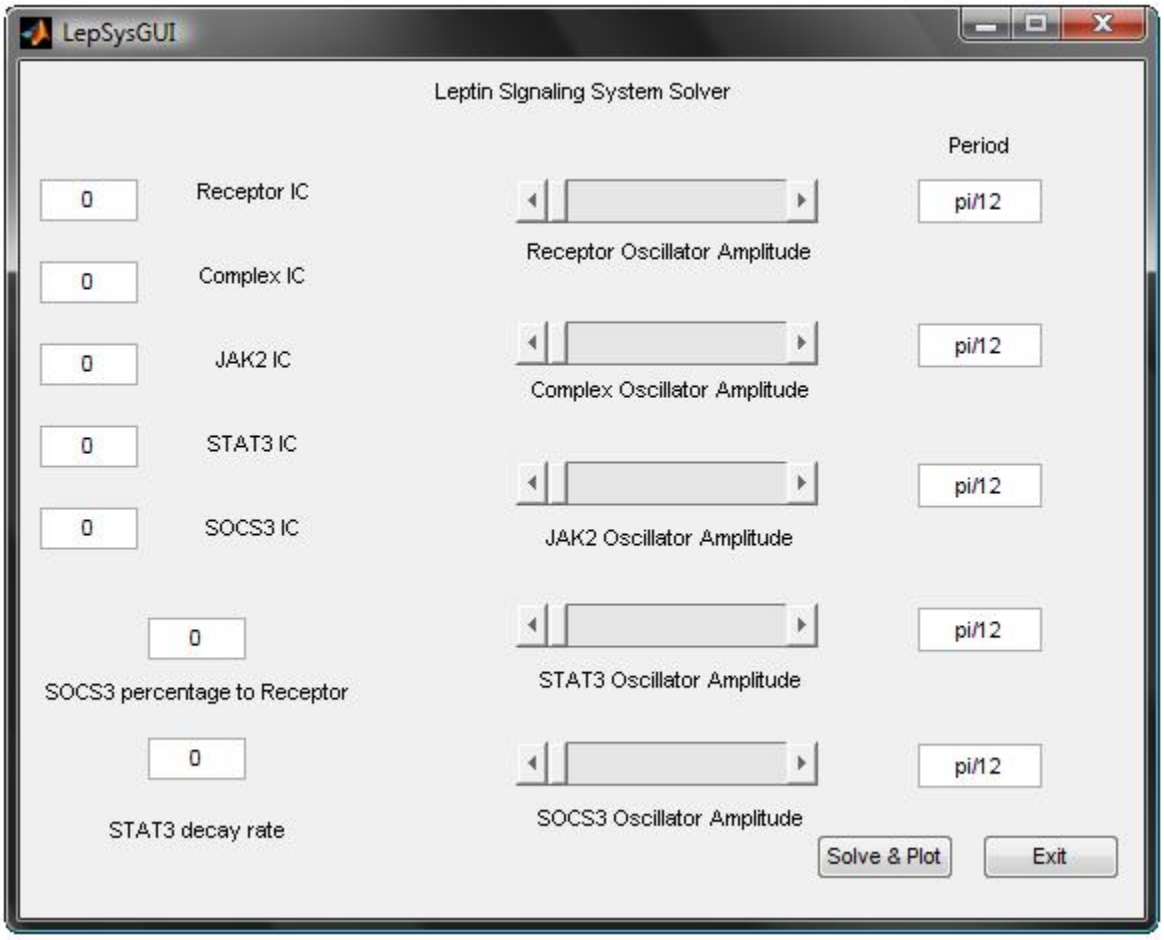
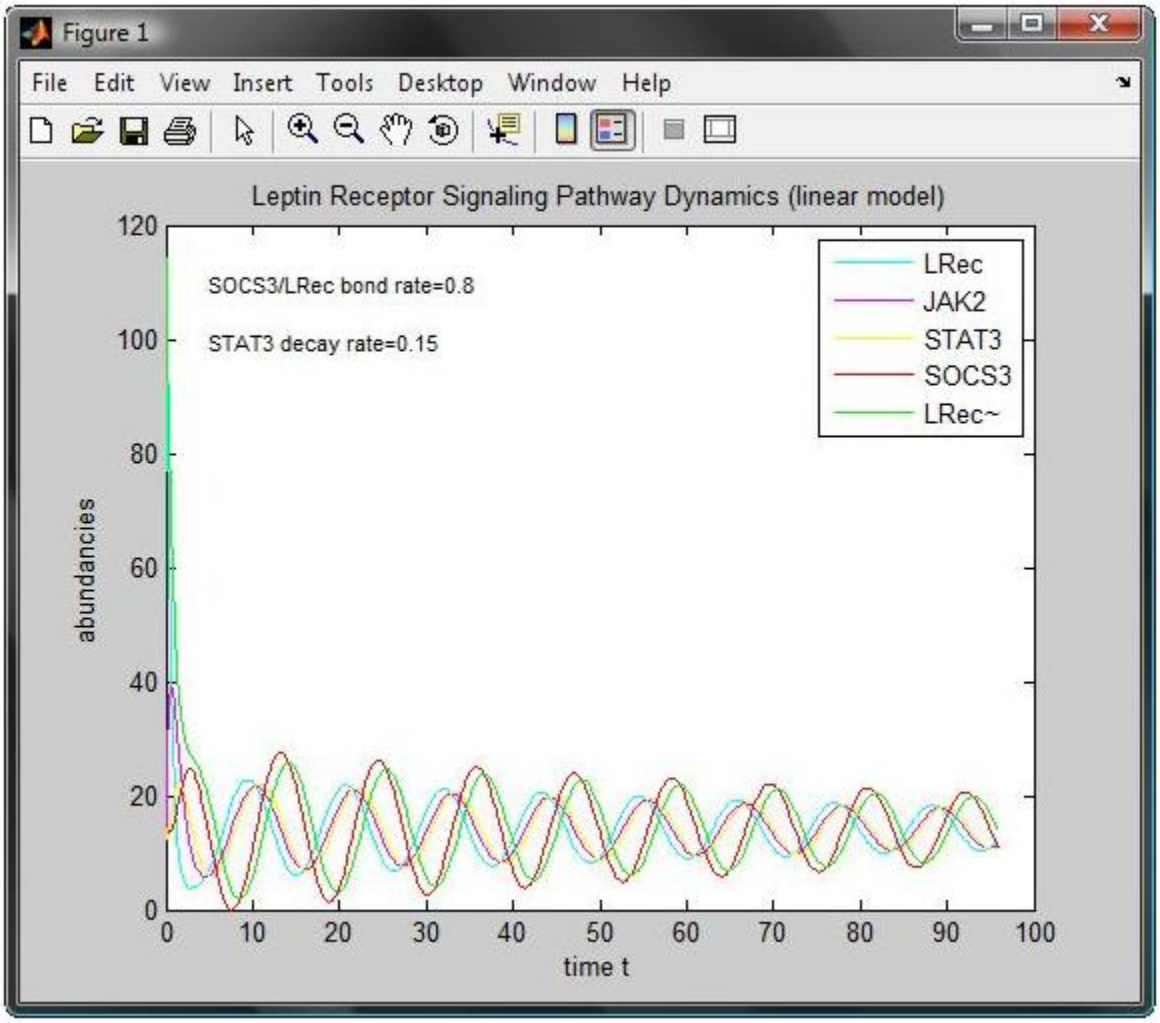

LepSysGUI
Leptin Signaling System Solver
Period
0
Receptor IC
pi/12
Receptor Oscillator Amplitude
0
Complex IC
0
JAK2 IC
pi/12
Complex Oscillator Amplitude
0
STAT3 IC
pi/12
0
SOCS3 IC
JAK2 Oscillator Amplitude
0
pi/12
STAT3 Oscillator Amplitude
SOCS3 percentage to Receptor
0
pi/12
SOCS3 Oscillator Amplitude
STAT3 decay rate
Solve & Plot
Exit

Figure 2



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References

1. Ptitsyn AA, Gimble JM: **Analysis of circadian pattern reveals tissue-specific alternative transcription in leptin signaling pathway**. *BMC Bioinformatics* 2007, **8**(Suppl 7):S15.