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Evaluating the robustness of a biochemical network model

Reza Ghaemi and Domitilla Del Vecchio

Abstract— **Mathematical models of robust biological systems are expected to be robust against small variations in the model's parameters. In this paper, we investigate the robustness of the model proposed by Laub and Loomis for the molecular network underlying adenosine 3',5'-cycle monophosphate (cAMP) oscillations observed in populations of Dictyostelium cells 4 hours after the initiation of development. This is performed by using bifurcation analysis. In particular, we reduce the problem to study the persistence of the periodic orbit that arises from Hopf bifurcation as one key parameter is varied. By introducing an optimization problem, we determine the maximum allowed parameter variation under which the oscillatory behavior of the system persists. We obtain maximum allowed variation of 0.51% and show that this bound is tight.**

I. Introduction

Biological systems such as complex molecular networks, must reliably operate under significantly different environmental conditions, which can lead to large changes in the parameters of the system. For biological systems to work reliably under different conditions, it is important that prominent characteristics of the system, such as oscillatory behavior, are preserved despite changes in the operating environment. This property is called robustness.

Some biological systems are clearly experimentally proved to be robust [1], [2], [3]. If a biological system is robust, it should be expected that its mathematical model is also robust to parameter variations [4]. In this paper, we investigate the robustness of the model proposed by Laub and Loomis for the molecular network underlying adenosine 3',5'-cycle monophosphate (cAMP) oscillations observed in populations of Dictyostelium cells 4 hours after the initiation of development. Since such molecular network is experimentally known to be robust, the robustness of the model can be considered as a tool to check the validity of the model. To evaluate the robustness of the model we need objective measures. One technique is to compute parameter sensitivities which can be evaluated analytically for simple systems and computationally for complex networks like Laub and Loomis model.

Although single parameter insensitivity is necessary for a robust system, it is not sufficient due to interactions between several parameters, especially when parameters simultaneously differ from their nominal values. In this case, systematic change of many parameters, which is 14 in the Laub and Loomis (L-L) model, suffers from exponential increase of computation in the number of parameters that need to be changed. Therefore, sensitivity to the parameters has been traditionally considered through randomly varying all parameters. Because of random change of parameters, robustness is not guaranteed.

In [6], one of the robustness computational tools in control theory, known as the structural singular value (SSV), is employed to calculate the region for parameters where the oscillatory behavior of the L-L model is preserved. In the proposed method, first the limit cycle is determined using first order Fourier expansion of the states with nominal parameters. Then, the system is linearized around the approximated steady-state periodic solution and SSV is applied on the linearized system to determine the maximum parameter variation. In [7], the integral of the square of the derivative of the state, considered as a measure of the occurrence of oscillations, is minimized with respect to parameter variations using hybrid Genetic Algorithm (HGA) [9], to achieve the region in the parameter space that corresponds to oscillations. The previously mentioned methods result in 8.3% and 0.6% variation in the parameters, respectively, under which the oscillatory behavior of the system is preserved.

In this paper, we investigate the robustness of the L-L model using bifurcation analysis. In particular, we exploit the fact that the equilibria of this system can be explicitly computed as a function of the parameters. Thus, we can employ the Routh-Hurwitz criterion to infer that Hopf bifurcation occurs with respect to one parameter only, μ. As a consequence, we can study the persistence of the periodic orbit as this parameter, μ, which encompasses all other parameters, is changed. This significantly reduces the complexity of the problem. We then introduce an optimization problem whose solution determines the maximum parameter variation under which the model oscillates. The result is 0.51% variation and simulation results show that with a slightly higher variation the system does not oscillate. The difference between the amount of maximum variation calculated in this paper and that of previous ones is justified as follows. In previous papers either the model of the system is approximated by a linearized one or a random search method is employed to determine the maximum allowed parameter variation. In this paper the maximum variation is calculated based on an analytic approach. Since the proposed method requires an analytic expression of the equilibrium point, it can be employed only when the equilibrium is an explicit function of the parameters.

This paper is organized as follows. In Section II we introduce the model of the system and the associated parameters. The analytic expression of the fixed point of the system is derived in Section III. Using the derived fixed point expression, the Hopf Bifurcation analysis is introduced in

Reza Ghaemi and Domitilla Del Vecchio are with Department of Electrical Engineering and Computer Science at the University of Michigan, Ann Arbor, MI 48109, Email: ddv@eecs.umich.edu, ghaemi@umich.edu.

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Section IV. According to the analysis introduced in Section IV, an optimization problem is introduced in Section V, which determines the maximum allowed parameter variation to maintain oscillation.

II. Laub-Loomis Model

In [5], Laub and Loomis propose a model of the molecular network underling adenosine 3',5'-cyclic monophosphate (cAMP) oscillations observed in populations of Dyctyostelium cells. The model, based on the network depicted in Figure 1, induces spontaneous oscillations in cAMP observed during the early development of Dictyostelium discoideum. In this model, changes in the enzymatic activities

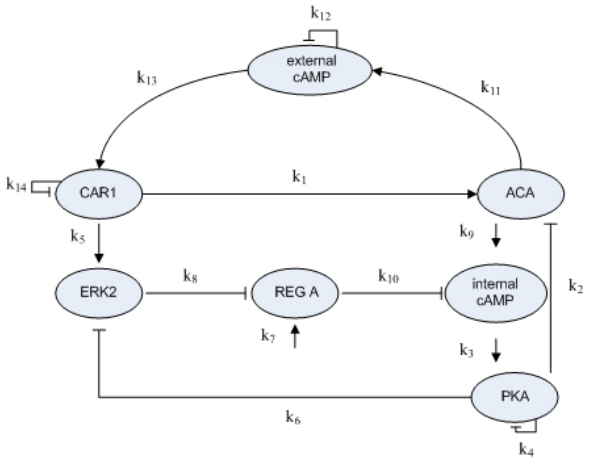

Fig. 1. Laub and Loomis model.

of these proteins are described by the following system of seven non-linear differential equations,

$$\dot{x} = f(x,k) = \begin{bmatrix} k_1 x_7 - k_2 x_1 x_2 \\ k_3 x_5 - k_4 x_2 \\ k_5 x_7 - k_6 x_2 x_3 \\ k_7 - k_8 x_3 x_4 \\ k_9 x_1 - k_{10} x_4 x_5 \\ k_{11} x_1 - k_{12} x_6 \\ k_{13} x_6 - k_{14} x_7 \end{bmatrix}, \qquad (1)$$

where the state variable $x = [x_1, \cdots, x_7]$ represents the concentration of the seven proteins: $x_1 = [ACA]$, $x_2 = [PKA]$, $x_3 = [ERK2]$, $x_4 = [REGA]$, $x_5 = [Internal\ cAMP]$, $x_6 = [External\ cAMP]$ and $x_7 = [CAR1]$. The fourteen different coefficients $k_i,\ i = 1, \cdots, 14$, are system parameters, and we have denoted $k = (k_1, \cdots, k_{14})$.

It is shown in [5] that oscillations appear at the nominal parameter values in Table 1.

Table I: Nominal values for each parameter

Parameter	Units	Nominal Value
k_1	min^{-1}	2.0
k_2	$Mol^{-1}min^{-1}$	0.9
k_3	min^{-1}	2.5
k_4	min^{-1}	1.5
k_5	min^{-1}	0.6
k_6	$Mol^{-1}min^{-1}$	0.8
k_7	$Mol^{-1}min^{-1}$	1.0
k_8	$Mol^{-1}min^{-1}$	1.3
k_9	min^{-1}	0.3
k_{10}	$Mol^{-1}min^{-1}$	0.8
k_{11}	min^{-1}	0.7
k_{12}	min^{-1}	4.9
k_{13}	min^{-1}	23.0
k_{14}	min^{-1}	4.5

In the next section, the equilibria of the model are calculated analytically.

III. Equilibria of the system

Let us denote by $\bar{x} = [\bar{x}_1, \cdots, \bar{x}_7]$ an equilibrium of the system, that is $f(\bar{x}, k) = 0$. From the 7th and 6th differential equations of the model of the system in equation (1) we have

$$\bar{x}_7 = \frac{k_{13}}{k_{14}}\bar{x}_6, \quad \bar{x}_6 = \frac{k_{11}}{k_{12}}\bar{x}_1, \qquad (2)$$

and therefore

$$\bar{x}_7 = \frac{k_{13}k_{11}}{k_{14}k_{12}}\bar{x}_1. \qquad (3)$$

Substituting expression (3) in the first differential equation of (1), we have the following result

$$\bar{x}_1 = 0 \qquad (4)$$

or

$$\bar{x}_2 = \frac{k_1 k_{11} k_{13}}{k_2 k_{14} k_{12}}. \qquad (5)$$

Equation (4) and $f(\bar{x}, k) = 0$ implies that

$$\begin{aligned} &\bar{x}_1 = \bar{x}_2 = \bar{x}_5 = \bar{x}_6 = \bar{x}_7 = 0 \\ &\bar{x}_3 \bar{x}_4 = \frac{k_7}{k_8}. \end{aligned} \qquad (6)$$

For the nonzero equilibrium, from equation (5) we have that

$$\bar{x}_5 = \frac{k_4}{k_3} \cdot \frac{k_1 k_{11} k_{13}}{k_2 k_{14} k_{12}}. \qquad (7)$$

From the 3rd differential equation of (1), equation (3) and equation (5) we observe that

$$\bar{x}_3 = \frac{k_2 k_5}{k_1 k_6}\bar{x}_1. \qquad (8)$$

From the 5th differential equation of (1) and equation (7) we have that

$$\bar{x}_4 = \frac{k_9 k_3 k_2 k_{14} k_{12}}{k_{10} k_4 k_1 k_{11} k_{13}} \cdot \bar{x}_1. \qquad (9)$$

Substituting equations (8) and (9) in the 4th differential equation of the equation (1) we have that

$$\bar{x}_1 = \left(\frac{k_{10} k_4 k_6 k_7 k_{11} k_{13}}{k_9 k_3 k_5 k_8 k_{14} k_{12}} \right)^{1/2} \cdot \frac{k_1}{k_2}. \qquad (10)$$

Employing equation (10) in equations (2), (3), (8) and (9) we have that

$$\bar{x}_3 = \left(\frac{k_{10}k_4k_5k_7k_{11}k_{13}}{k_9k_3k_6k_8k_{14}k_{12}}\right)^{1/2} \quad (11)$$

$$\bar{x}_4 = \left(\frac{k_9k_3k_6k_{14}k_{12}k_7}{k_{10}k_4k_5k_{11}k_{13}k_8}\right)^{1/2} \quad (12)$$

$$\bar{x}_6 = \frac{k_1k_{11}}{k_2k_{12}} \cdot \left(\frac{k_{10}k_4k_6k_7k_{11}k_{13}}{k_9k_3k_5k_8k_{14}k_{12}}\right)^{1/2} \quad (13)$$

$$\bar{x}_7 = \frac{k_{13}k_{11}k_1}{k_{14}k_{12}k_2}\left(\frac{k_{10}k_4k_6k_7k_{11}k_{13}}{k_9k_3k_5k_8k_{14}k_{12}}\right)^{1/2}. \quad (14)$$

Therefore, the system has two equilibrium points. One is determined by equation (6) which we do not consider for Hopf bifurcation, because for the states $x_1, \cdots, x_7$ negative values, which would result from oscillations, have no physical meaning. The other equilibrium with all positive elements is determined by equations (5-7-10-11-12-13-14), which are used for analyzing the persistence of a periodic orbit in the next section.

IV. Hopf bifurcation analysis

In this section we employ the explicit representation of the equilibria computed in the previous section to perform Hopf bifurcation analysis, which leads to determination of the region in the parameter space corresponding to oscillations. To determine the conditions under which the system undergoes a Hopf bifurcation, we linearize the system about the non-zero equilibrium. This renders the following linearization matrix

$$\bar{A}=\begin{bmatrix} -k_2\bar{x}_2 & -k_2\bar{x}_1 & 0 & 0 & 0 & 0 & k_1 \\ 0 & -k_4 & 0 & 0 & k_3 & 0 & 0 \\ 0 & -k_6\bar{x}_3 & -k_6\bar{x}_2 & 0 & 0 & 0 & k_5 \\ 0 & 0 & -k_8\bar{x}_4 & -k_8\bar{x}_3 & 0 & 0 & 0 \\ k_9 & 0 & 0 & -k_{10}\bar{x}_5 & -k_{10}\bar{x}_4 & 0 & 0 \\ k_{11} & 0 & 0 & 0 & 0 & -k_{12} & 0 \\ 0 & 0 & 0 & 0 & 0 & k_{13} & -k_{14} \end{bmatrix}. \quad (15)$$

The characteristic polynomial of the matrix $\bar{A}$ can be written in the following form

$$F(s) = s^7+z_6s^6+z_5s^5+z_4s^4+z_3s^3+z_2s^2+z_1s+z_0, \quad (16)$$

where $z_i,\ i = 0, \cdots, 6$, are calculated analytically in terms of $k_1, \cdots, k_{14}$. To analyze how the values of the parameters z_i affect the stability of the equilibrium, we use the Routh-Hurwitz criterion. The Routh-Hurwitz table is given by the following expression

s^7	1	z_5	z_3	z_1
s^6	z_6	z_4	z_2	z_0
s^5	$T_1 = \frac{z_6z_5-z_4}{z_6}$	$T_2 = \frac{z_6z_3-z_2}{z_6}$	$T_3 = \frac{z_6z_1-z_0}{z_6}$	0
s^4	$U_1 = \frac{T_1z_4-z_6T_2}{T_1}$	$U_2 = \frac{T_1z_2-z_6T_3}{T_1}$	z_0	0
s^3	$V_1 = \frac{U_1T_2-T_1U_2}{U_1}$	$V_2 = \frac{U_1T_3-T_1z_0}{U_1}$	0	0
s^2	$W = \frac{V_1U_2-U_1V_2}{V_1}$	z_0	0	0
s^1	$R = \frac{WV_2-V_1z_0}{W}$	0	0	0
s^0	z_0	0	0	0

(17)

According to Routh-Hurwitz criterion, the number of eigenvalues of $\bar{A}$ with positive real part is determined by the number of sign changes in the vector $C = [1\ z_6\ T_1\ U_1\ V_1\ W_1\ R\ z_0]$. Note that each of the components of C is a function of $k \in \mathbb{R}^{14}$. In particular, we obtain that R is the only parameter that takes both positive and negative signs in a region $B_{\delta^*}(k^*)$ of interest. The reason why this is the region of interest will be specified in the next section.

Claim 4.1: Let us define

$$B_{\delta^*}(k^*) := \{k \in \mathbb{R}^{14} | k = [k_1^*+\delta_1k_1^*, \cdots, k_{14}^*+\delta_{14}k_{14}^*], |\delta_i| \leq \delta^*\}, \quad (18)$$

and $\delta^* = 0.0051$. Then in $B_{\delta^*}(k^*)$ the functions z_6, T_1, U_1, V_1, W_1 and z_0 are always positive and the only function that accepts both positive and negative values is R.

Proof 4.1: To evaluate the values of the functions z_6, T_1, U_1, V_1, W_1, R and z_0 over the ball $B_{\delta^*}(k^*)$ we solve the following optimization problem for each function $T \in \{z_6, T_1, U_1, V_1, W_1, z_0\}$, which gives us the minimum value that these functions take in $B_{\delta^*}(k^*)$. This is provided by

$$\begin{aligned} \min_{\Delta} \quad & T(k_1^*+\delta_1k_1^*, \cdots, k_{14}^*+\delta_{14}k_{14}^*) \\ \text{subject to:} \quad & |\delta_i| \leq \delta^*,\ i = 1, \cdots, 14, \end{aligned} \quad (19)$$

which is solved using gradient descent method. By performing the proposed method we obtain the minimum values 15.38, 76.13, 184.64, 225.73, 128.74, 93.87 for the functions z_6, T_1, U_1, V_1, W_1 and z_0, respectively. □

Remark 4.1: Another approach for calculating the optimal value of the functions is griding and performing exhaustive search. For each parameter, we consider the points $\{k_i^* - \delta^*k_i^*, k_i^*, k_i^*+\delta^*k_i^*\}$. Therefore, to perform exhaustive search we need to evaluate each of the functions for 3^{14} points and find the minimum value of each function. The resulting optimal solutions are the same as what is obtained using gradient descent method.

Using the Routh-Hurwitz rule, we know that when $R = 0$, there exist two pure imaginary poles $s_{1,2} = \pm j\sqrt{\frac{z_0}{W}}$ while the remaining eigenvalues have all negative real parts. In addition, it can be concluded that if $R > 0$, all eigenvalues have negative real parts while if $R < 0$, there exist two complex eigenvalues with positive real part with the others having negative real parts. Therefore, it can be concluded that independently of the specific combination of parameters $k_i, i = 1, \cdots, 14$, the sign of the function $R = g(k_1, \cdots, k_{14})$ is the only responsible for a change in the sign of real parts of the eigenvalues. Since the expression of the function R is so long, we avoid writing it. Instead, to provide a qualitative perception of the behavior of R as function of the parameters k, Figures (1-3) provide the 2-dimensional zero level set of the function R for different nominal values of k.

By Claim 4.1 and Routh-Hurwitz criterion it also follows that the only Hopf bifurcation that the system admits occurs at $R = 0$. As a consequence, by changing R directly and simulating the system as R changes, we could determine how negative R can be taken to have persistence of the periodic

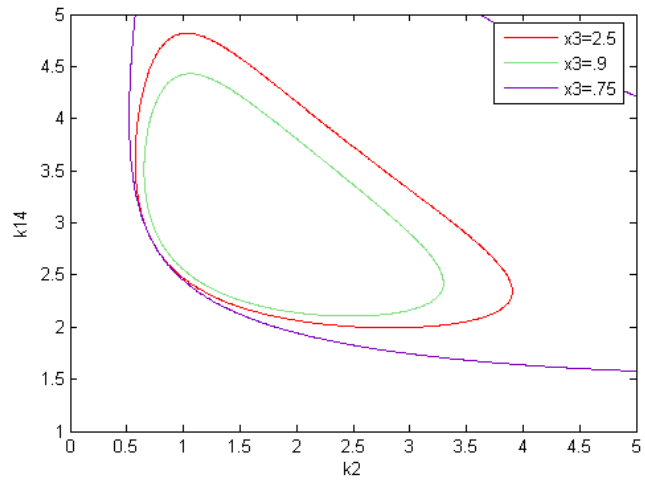

Fig. 2. Zero level set of the function R in the k_2, k_{14} plane for different values of k_3.

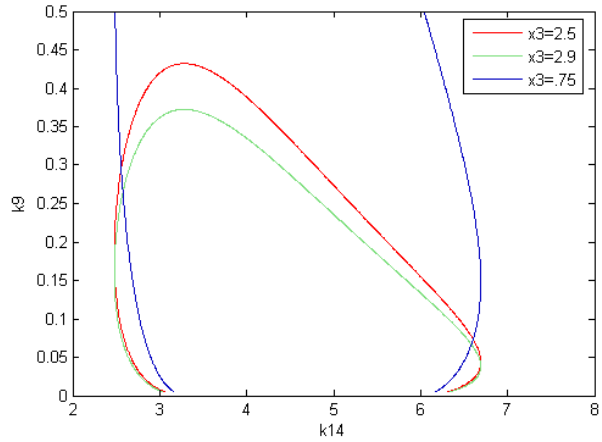

Fig. 3. Zero level set of the function R in k_{14}, k_9 plane for different values of k_3.

orbit arising when $R = 0$. In order to be able to perform this one-dimensional parameter study, we need to (a) express one of k_i in equation (1) as a function of R, (b) change the value of R indirectly by changing such k_i. Tasks (a) and (b) are possible only if we have that $g(\cdot)$ is locally invertible with respect to one k_i in the ball of interest $B_{\delta^*}(k^*)$. This is shown by the following claim.

Claim 4.2: The function $g(\cdot)$ is locally invertible with respect to k_1 over the ball $B_{\delta^*}(k^*)$ defined in (18) where $\delta^* = 0.0051$.

Proof 4.2: Let us define the function $H(\cdot)$ as follows

$$H(k) = \frac{\partial}{\partial k_1} g(k), \tag{20}$$

where $k = [k_1, \cdots, k_{14}]$. Then we define the following optimization problem

$$\begin{aligned} \max_{\Delta} \quad & H(k_1^* + \delta_1 k_1^*, \cdots, k_{14}^* + \delta_{14} k_{14}^*) \\ \text{subject to:} \quad & |\delta_i| \leq \delta^*, \ i = 1, \cdots, 14 \end{aligned} \tag{21}$$

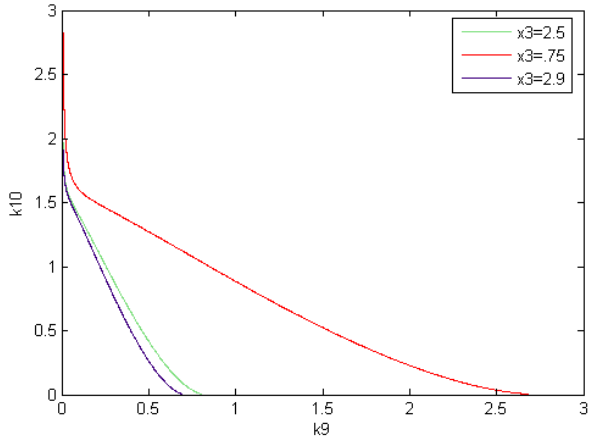

Fig. 4. Zero level set of the function R in k_9, k_{10} plane for different values of k_3.

where $\Delta = [\delta_1, \cdots, \delta_{14}]$. Using the gradient descent method, we obtain the maximum value of $H(k)$ over the ball $B_{\delta^*}(k^*)$ as -24.9152. Therefore, $\frac{\partial}{\partial k_1} g(k)$ is negative over the ball $B_{\delta^*}(k^*)$ which means that $g(\cdot)$ is monotonically decreasing with respect to k_1. Therefore, $g(k)$ is invertible with respect to k_1 over the ball $B_{\delta^*}(k^*)$. □

By virtue of Claim 4.2, we can write

$$k_1 = g^{-1}(R, k_2, \cdots, k_{14}), \ k \in B_{\delta^*}(k^*)$$

where $g^{-1}(\cdot)$ is continuous in R. As a result, equation (1) can be rewritten in the following form

$$\dot{x}(t) = f(R, k_2, \cdots, k_{14}, x(t)). \tag{22}$$

Letting $\mu = -R$, equation (22) can be written in the following form

$$\dot{x}(t) = \bar{f}(\mu, x(t)), \tag{23}$$

in which we did not explicitly express the dependence of f on $k_1, \cdots, k_{14}$ as we will study the behavior of the system only as μ varies.

It is worth noting that the parameter μ encompasses all parameters $k_1, \cdots, k_{14}$. For equation (23), we thus analyze the robustness of the orbit arising from Hopf bifurcation. Therefore, the parameter μ can be considered as a bifurcation parameter such that if $\mu = 0$ there are two imaginary eigenvalues and five eigenvalues with negative real parts; if $\mu < 0$, all the eigenvalues have negative real parts; if $\mu > 0$, there are only two eigenvalues with positive real parts. Thus Hopf bifurcation occurs at $\mu = 0$ independently of the values of all other coefficients. This is because all the elements of the first column of Routh-Hurwitz table is positive in the ball $B_{\delta^*}(k^*)$ except R. At this point, the existence of the Hopf orbit can be just investigated by varying one parameter (μ). In particular, we can take (23) to the following normal form on the center manifold

$$\begin{aligned} \dot{r}(t) &= -\mu \cdot dr(t) + ar(t)^3 + O(\mu^3, r(t)^5) \\ \dot{\theta}(t) &= \cdots \end{aligned} \tag{24}$$

with $d = \frac{d\lambda(\mu)}{d\mu}|_0 > 0$, in which μ will be varied (through varying k_1) to determine how positive it can be made and still have persistence of the periodic orbit.

In the next section, we will introduce the optimization problem which determines the radius of the ball $B_{\delta^*}(k^*)$, with respect to the norm $\|\cdot\|_\infty$, in which the function μ is positive.

V. Optimization solution for specification of the maximum allowed parameter variation

From equation (24) (the behavior of the trajectories on the local center manifold) we know that for small value of $\mu > 0$, there exist a periodic orbit and for $\mu < 0$ such orbit disappears. Thus we can investigate how large $\mu > 0$ can be before the $O(\mu^3, r^5)$ becomes relevant and fades the orbit away. Since this is related only to changing one parameter (μ), it can be simply performed by simulating the dynamics (23) for $\mu > 0$ and check the maximum allowed μ, which we call $\hat{\mu}$, before the periodic orbit disappears. Once the maximum radius of the ball $B_{\delta^*}(k^*)$ in which the function μ is positive is determined, we calculate the maximum amount that parameter μ varies within the ball and check, via simulation, whether the system has a periodic orbit over such an interval.

We propose the following procedure to determine the maximum allowed parameter variation to preserve the oscillatory behavior of the system. Let us first find the maximum percentage of the parameter uncertainty under which $\mu \geq 0$ via solving the following optimization problem:

$$\begin{aligned} \min_{\Delta} \quad & \|\Delta\|_\infty \\ \text{subject to} \quad & \mu = -g(k_1^* + \delta_1 k_1^*, \cdots, k_{14}^* + \delta_{14} k_{14}^*) \geq 0, \end{aligned} \tag{25}$$

where $\Delta = (\delta_1, \cdots, \delta_{14})$ and $k_1^*, \cdots, k_{14}^*$ are he nominal parameters. The optimization problem (25) is equivalent to the following one:

$$\begin{aligned} \min_{\Delta, c} \quad & c \\ \text{subject to:} \quad & |\delta_i| \leq c, \ i = 1, \cdots, 14 \\ & -g(k_1^* + \delta_1 k_1^*, \cdots, k_{14}^* + \delta_{14} k_{14}^*) \leq 0. \end{aligned} \tag{26}$$

This problem is solved numerically using SQP [8] method which is described in Appendix.

As stated in the beginning of the section, we calculate the maximum value of parameter μ over all the parameters k with allowed percentage of deviation from the nominal point. Then we check, via simulation, whether the system has a periodic orbit when μ varies from 0 to the calculated maximum value.

Now we show that the maximum allowed variation of parameters, for which the periodic orbit originating from Hopf bifurcation persists, is given by the set $B_{\delta^*}(k^*)$, where $\delta^* = 0.0051$.

Solving the optimization problem (25) results in $\delta^* = 0.0051$. Therefore, by Claim 4.1 we know that within the ball $B_{\delta^*}(k^*)$ the necessary condition for having the periodic orbit arising from Hopf bifurcation is satisfied. That is, there is one pair of eigenvalues, whose real part becomes positive. We find the largest value of μ within the ball $B_{\delta^*}(k^*)$ by solving the following optimization problem

$$\begin{aligned} \max_{\Delta} \quad & \mu = -g(k_1^* + \delta_1 k_1^*, \cdots, k_{14}^* + \delta_{14} k_{14}^*) \\ \text{subject to } & \delta_i \leq \delta^*, \ i = 1, \cdots, 14. \end{aligned} \tag{27}$$

This problem is solved using gradient decent method. Denoting the solution of (27) $\hat{\mu}$, we have $\hat{\mu} = 4.9828$. From Claim 4.2 we know that we can vary μ from 0 to $\hat{\mu}$ by varying parameter k_1. By changing parameter k_1 via simulation we check if the system has a periodic orbit over this interval. If this is the case, then the maximum percentage of parameter variation is determined under which the system oscillates. Simulation results show that the system has a periodic orbit over the interval $0 < \mu \leq \hat{\mu}$, which verifies that the maximum allowed percentage of parameter variation is $\delta^* = 0.51\%$.

Table II shows the parameters that are different slightly more than 0.51% from the nominal parameters and are not associated with any limit cycle.

Table II: Perturbed values for each parameter

Parameter	Units	Perturbed Value
k_1	min^{-1}	1.9898
k_2	$Mol^{-1}min^{-1}$	0.8954
k_3	min^{-1}	2.5128
k_4	min^{-1}	1.5076
k_5	min^{-1}	0.5969
k_6	$Mol^{-1}min^{-1}$	0.8041
k_7	$Mol^{-1}min^{-1}$	1.0051
k_8	$Mol^{-1}min^{-1}$	1.2934
k_9	min^{-1}	0.3015
k_{10}	$Mol^{-1}min^{-1}$	0.8041
k_{11}	min^{-1}	0.6964
k_{12}	min^{-1}	4.9250
k_{13}	min^{-1}	22.8827
k_{14}	min^{-1}	4.5229

This shows that the bound we found for δ is tight.

VI. Conclusion

To validate the model of biological systems, robustness of the model can be considered as a key indicator. In this paper, we investigate the robustness of the Laub-Loomis model using bifurcation analysis. In previous work, μ analysis and global/hybrid optimization are used to evaluate the robustness of the model. Since these approaches are based on either approximation of the model of the system by a linear one or random search methods, the outcome of these methods are not guaranteed to determine the maximum allowed variation in the parameters of the model under which the system preserves oscillatory behavior. In this paper the fixed point of the system is derived explicitly as a function of parameters and a bifurcation analysis based on Routh-Hurwitz method is introduced, which determines maximum allowed uncertainty of 0.51%. This bound is tighter than the one that is found using μ analysis or global/hybrid optimization methods. This method can be applied on more general models where the

fixed point of the system can be explicitly represented as a function of parameters of the system. We will explore in future work the applicability of the proposed methodology to other problems in order to study its generality.

VII. Acknowlagements

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Appendix

The sequential quadratic programming (SQP) method is employed to solve the problem (26) numerically. According to this method, the nonlinear inequality is linearized around some feasible initial solution Δ^1 and the following LP is solved:

$$\begin{aligned} \min_{\Delta,c} \quad & c \\ \text{subject to:} \quad & |\delta_i| \le c,\ i = 1, \cdots, 14 \\ & - g(k_1^* + \delta_1^1 k_1^*, \cdots, k_{14}^* + \delta_{14}^1 k_{14}^*) \\ & - \nabla_k g(k_1^* + \delta_1^1 k_1^*, \cdots, k_{14}^* + \delta_{14}^1 k_{14}^*)^T \times \\ & [k_1^*(\delta_1 - \delta_1^1), \cdots, k_{14}^*(\delta_{14} - \delta_{14}^1)]^T \le 0. \end{aligned} \tag{28}$$

If we define

$$\begin{aligned} v &:= \begin{bmatrix} k_1^* & 0 & \cdots & 0 \\ 0 & k_2^* & \cdots & 0 \\ \vdots & & \ddots & \\ 0 & 0 & \cdots & k_{14}^* \end{bmatrix} \nabla_k g(k_1^* + \delta_1^1 k_1^*, \cdots, k_{14}^* + \delta_{14}^1 k_{14}^*) \\ w &:= -g(k_1^* + \delta_1^1 k_1^*, \cdots, k_{14}^* + \delta_{14}^1 k_{14}^*) + \Delta^1 v, \end{aligned} \tag{29}$$

then problem (28) can be written in the following form:

$$\begin{aligned} \min_{\Delta,c} \quad & c \\ \text{subject to:} \quad & |\delta_i| \le c,\ i = 1, \cdots, 14 \\ & w - \Delta v \le 0. \end{aligned} \tag{30}$$

If $w \le 0$ the problem has the trivial solution $\Delta = 0$. Otherwise, the problem has the following solution:

$$\begin{aligned} S &= \frac{w}{\sum_{j=1}^{14} |v_j|} \\ \delta_i^* &= sign(v_i) S. \end{aligned} \tag{31}$$

Using (31), we perform SQP iteration until the solutions converge to the optimal solution of the problem (25).