APPLICATION OF CONTROL LAWS TO SYSTEMS OF NONLINEAR ODES REPRESENTING BIOLOGICAL PROCESSES

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1. Introduction

Synthethic biology draws from many fields, including control theory and engineering. Many principles from these disciplines have already been applied to help describe biological system and construct objects that have analogs in electrical and mechanical engineering. This new intersection with math and biology opens the door to many new questions. Such as can control laws be applied to biological systems to force produce a certain result? What can control theory teach us about naturally occurring control systems? What kind of object can we construct?

2. Method

In this paper we consider a special system of ordinary differential equations (ODEs) that represent a genetic circuit, a simple yet fundamentally important element. The model is a genetic circuit that functions as a bistable switch [3]. It is a system with two stable equilibrium point where each equilibrium point can represents a binary state: "on" or "off", "0" or "1" or "high" or "low". To facilitate this, the system allows for the supression of one protein by an inducer, enabling the an external input to force the system to switch states. The concentration of the two proteins are $p_A \geq 0$, $p_B \geq 0$, given some input I, the production rate parameter $\alpha > 0$ is how fast the proteins increases, and a cooperativity parameter $n > 1$ which represents how many proteins need to work together (i.e. cooperate) to turn off gene expresion.

$$\dot{p}_A = \frac{\alpha}{1 + (Ip_B)^n} - p_A$$
$$\dot{p}_B = \frac{\alpha}{1 + p_A^n} - p_B$$

Our goal is to solve the stabilization problem of getting the concentration of the different protiens, A and B to approach desired levels that might not necessarily be naturally possible. We will consider a MIMO sliding control for a modified version of the system above with noise, n_A, n_B, and added input, u_A, u_B.

$$\dot{p}_A = \frac{\alpha}{1 + p_B^n} - p_A + n_A + u_A$$
$$\dot{p}_B = \frac{\alpha}{1 + p_A^n} - p_B + n_B + u_B$$

The construction of the sliding controller comes from [1]. For the development of the first control law we will assume f is known and that the $|n_i| \leq n_{max}$

First we choose $s = [s_A \ s_B]^T = \vec{e}$, where $\vec{e} = \begin{bmatrix} p_A - p_A^d \\ p_B - p_B^d \end{bmatrix}$. Next we construct the following Lyapunov function $V = \frac{1}{2}s^T s$. Also let $\dot{p}_A = f_1(p_A, p_B) + n_A + u_A$, $\dot{p}_B = f_2(p_A, p_B) + n_B + u_B$, $f = \begin{bmatrix} f_1 \\ f_2 \end{bmatrix}$, $n = \begin{bmatrix} n_A \\ n_B \end{bmatrix}$. and $u = \begin{bmatrix} u_A \\ u_B \end{bmatrix}$. By differentiating V we get

$$\dot{V} = s^T \dot{s}$$

$$\dot{V} = s^T (f + n + u)$$

then choose $u = -f - \begin{bmatrix} n_{max} \\ n_{max} \end{bmatrix} - \begin{bmatrix} k_A \mathrm{sat}_\phi(s_A) \\ k_B \mathrm{sat}_\phi(s_B) \end{bmatrix}$

$$\dot{V} = s^T \left(- \begin{bmatrix} n_{max} \\ n_{max} \end{bmatrix} - \begin{bmatrix} k_A \mathrm{sat}_\phi(s_A) \\ k_B \mathrm{sat}_\phi(s_B) \end{bmatrix} \right)$$

$$\dot{V} = s_A(n_A - n_{max}) + s_B(n_B - n_{max}) - k_A \mathrm{sat}_\phi(s_A) s_A - k_B \mathrm{sat}_\phi(s_B) s_B \leq 0$$

Since V is positive definite and for properly chosen k the latter terms dominate the earlier terms making $\dot{V}$ negative definite, this is sufficient to say this system with this control law and properly chosen k converges asymptotically to zero.

The second control w3 will extend the previous control to deal with the possibility of varying parameters. Consider the additional conditions $|\alpha - \hat{\alpha}| \leq A$, $|n - \hat{n}| \leq N$ and $\|f - \hat{f}\| \leq F$. Which will make our control law $u = -\hat{f} - \begin{bmatrix} n_{max} \\ n_{max} \end{bmatrix} - \begin{bmatrix} k_A \mathrm{sat}_\phi(s_A) \\ k_B \mathrm{sat}_\phi(s_B) \end{bmatrix}$ and

$$\dot{V} = s_A(f_1 - \hat{f}_1) + s_B(f_2 - \hat{f}_2) + s_A(n_A - n_{max}) + s_B(n_B - n_{max}) - k_A \mathrm{sat}_\phi(s_A) s_A - k_B \mathrm{sat}_\phi(s_B) s_B$$

if we chose $k \geq F + M$ properly such that $\dot{V} \leq 0$, then we have asymptotic convergence of s.

3. Results

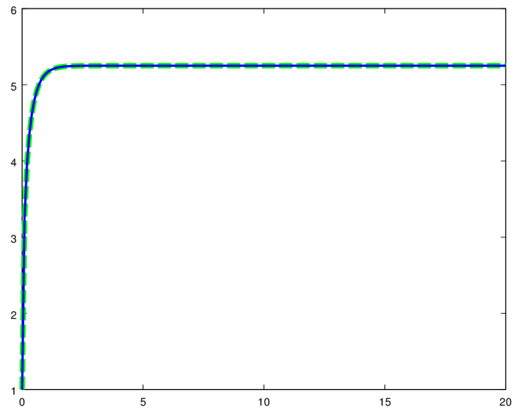
Given these $\alpha = 150$ and $n = 2$ parameters we expect to see both protein concentration reaching the same equilibruim point (i.e. 5.24) or one going to zero and the other to α as in Figure 1.

The first control law assumes f is known, we vary n_{max} and k, we chose $\alpha = 150$, $n = 2$, and $\vec{p}^{\,d} = [6 \ 2]^T$. The more noise the more gain k that we had to apply to reach equilibirum. Even if your actual value deviate slightly from the actual α when n is fixed, the controller can still bring you to equilibrium.

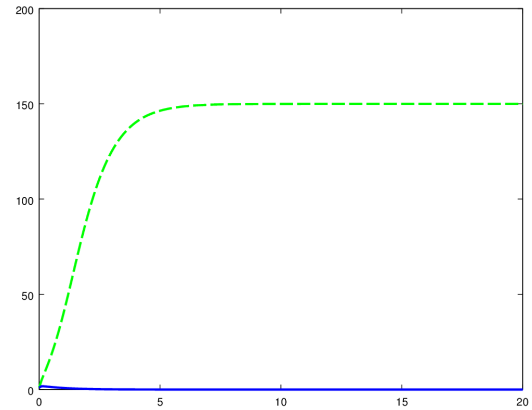
Next we applied a control law for varying parameters in the presence of additive noise, $a_{low} < a < a_{high}$ and $n_{low} < n < n_{high}$, where the lows and highs vary and we set $n_{max} = 3$ and $k = 15$, the rest of the values remain fixed as in the previous portion. Last since it has been observed that the system is very sensitive to changes in n, we fix n and only let a vary with time and find the results in Figure 5.

4. Discussion

One of the major issues in biology is noisy data, though many biological process are robust to noise, knowing that the control law is also not sensitive to noise is still important. Overall the control techniques seem to be somewhat effective on these systems of ODEs, even in the presence of noise. The goal of these experiments was to see if noise and unexpected

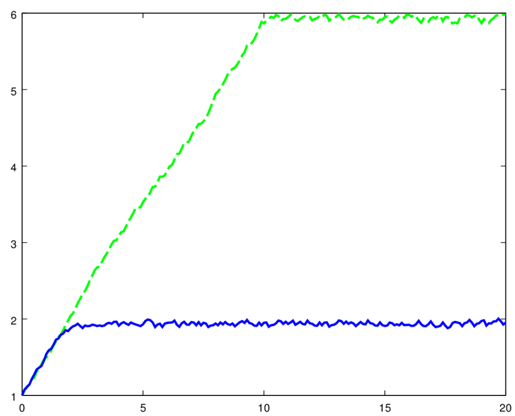


(A) p_A and p_B versus time when $I = 1$

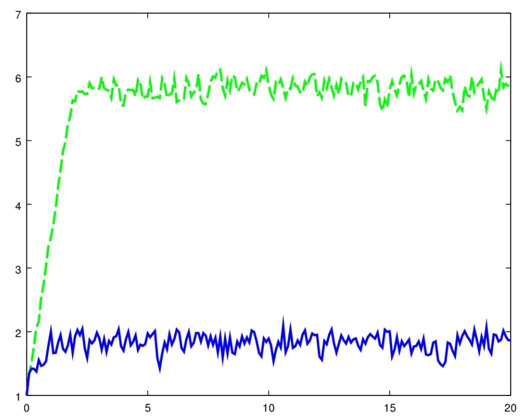


(B) p_A and p_B versus time when when $I > 1$

FIGURE 1. Graphs of the original system without control



(A) p_A and p_B versus time when $n_{max} = 1$ amd $k = 1$



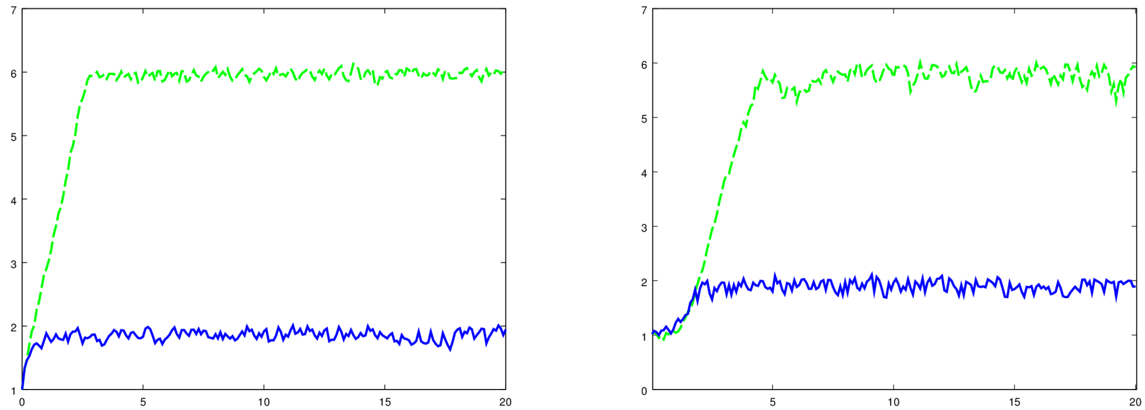
(B) p_A and p_B versus time $n_{max} = 5$ and $k = 15$

FIGURE 2. Graphs of the p_A and p_B versus time given the first controller

variations would gravely effect the outcome. Noise obfuscated the signal, but did not disable the controller from performing it's task, given the proper parameters. Another thing to mention is that even though it might seem impratical to assume that f is known, there are many parameter identification techniques, that can be used to find sufficiently close parameters. Also in Figure 4 and 5 we see that varying n can create much work for the controller and disrupt it's effectiveness. It seems given an assorted number of situations controllers can be adjusted to work with the bistable switch.

5. Further Work

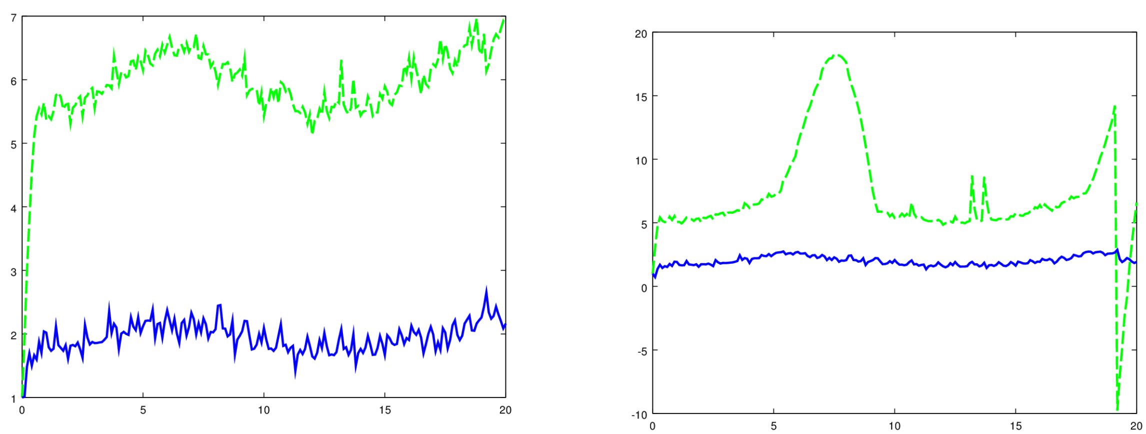
Since we only considered this control problem from a mathematical perspective we didn't consider implementation issues. How could we relate these theoretical control laws to our systems using the many built-in control systems biology. Also it would be more expedient to apply the control laws to a more general version of this same paired relationship. Another



(A) p_A and p_B versus time, $n_{max} = 3$ $k = 2$ and $\alpha = 145$

(B) p_A and p_B versus time $n_{max} = 3$, $k = 4$ and $\alpha = 155$

FIGURE 3. Graphs of the p_A and p_B versus time given the first controllerl



(A) $a_{low} = 149.5$, $a_{high} = 150.5$, $n_{low} = 1.5$ and $n_{high} = 2.5$

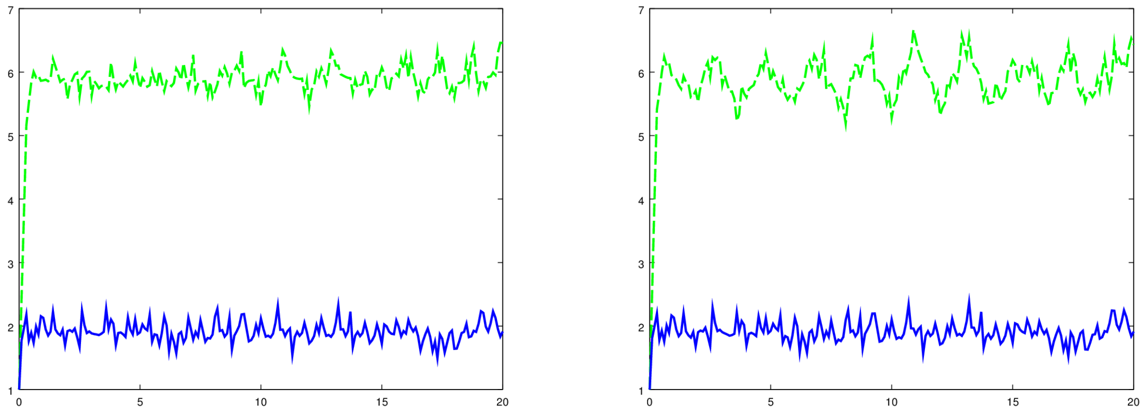
(B) $a_{low} = 149$, $a_{high} = 151$, $n_{low} = 1$ and $n_{high} = 3$

FIGURE 4. Graphs of the p_A and p_B versus time given the second controller

subject of interest would be going beyond this simple two part system while testing more theoretical control laws. It also seemed like it might be useful to create a control law that pushes a system into a limit cycle instead of a point.

References

[1] Benamor, Anouar, et. al. *Sliding Mode Control, with Integrator, for a Class of MIMO Nonlinear Systems* Engineering, 2011, 3, 435-444
[2] Go, T. *Lecture Notes* Summer 2015, Nonlinear Control Systems Class
[3] Murray, Richard M. and Dunlop, Mary J., *Towards Biological System Identification: Fast and Accurate Estimates of Parameters in Genetic Regulatory Networks*, 2006, Conference on Decision and Control
[4] Slotine, Jean-Jacque E *Video Lecture* Nonlinear Systems Class



(A) $a_{low} = 145$, $a_{high} = 155$, $n = 2$

(B) $a_{low} = 125$, $a_{high} = 175$, $n = 2$

FIGURE 5. Graphs of the p_A and p_B versus time given the second controller

[5] Slotine, Jean-Jacque E., Li, Weiping, *Applied Nonlinear Control* Prentice-Hall International, New Jersey, 1991.