Insulin Regulation and Control: We're Going to Need a Bigger Needle

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BACKGROUND

HOMEOSTASIS, the implicit goal of almost every biological system, is a constant regulation problem performed by the human body (and all living things). The body moves. It heats up. Lactic acid builds. Energy is consumed. A great number of parameters are constantly monitored and maintained by various organ systems, but sometimes those systems go awry.

Take the glucose-insulin system. It regulates blood glucose levels which is an essential function as cells uptake glucose in the presence of insulin to generate ATP for the energy to perform myriad tasks. If the blood glucose levels rise too high (hyperglycemia) or too low (hypoglycemia), the body is harmed. This can be controlled, however, by the pancreas varying levels of insulin to accelerate or decelerate glucose uptake.

This pancreatic control is impaired in diabetes wherein the pancreas produces little to no insulin. This significantly reduces cellular uptake of glucose which causes any meal to result in spiking blood glucose levels. Modern management of diabetes introduces external devices to supplement the body's insulin production. These are commonly referred to as "insulin pumps" that measure the blood glucose levels and deliver insulin as appropriate.

In this case study, the President of the United States has personally spoken offhandedly to a senator, and that senator has mentioned to council, and that council has dictated the budget of the NIH, and the NIH has therefore placed a premium on diabetic insulin control models. We have taken up the president's call and have set to the task of designing an insulin pump to rake in the grant funding from an RO1.

The Dynamical System

We used the following differential equations to numerically model the simplified glucose-insulin system:

$$\frac{dG(t)}{dt} = -p_1\left(G(t) - G_b\right) - X(t)G(t) + D(t) \tag{1}$$

$$\frac{dI(t)}{dt} = -nI(t) + u(t) \tag{2}$$

$$\frac{dX(t)}{dt} = -p_2X(t) + p_3\left(I(t) - I_b\right) \tag{3}$$

where $G(t)$ is the blood glucose concentration, $I(t)$ is the plasma insulin concentration, $X(t)$ is the insulin action, G_b is the baseline glucose concentration, I_b is the baseline plasma insulin concentration, $p_1p_2p_3$ are positive system parameters describing insulin sensitivity and glucose dynamics, and $u(t)$ is the input insulin delivery rate [1].

Equation 1, above, describes how the blood glucose concentration changes. The first term,

$$-p_1\left(G(t) - G_b\right), \tag{4}$$

represents a restoring influence with any deviation from the baseline blood glucose concentration resulting in a push back to that baseline. The second term,

$$-X(t)G(t) \tag{5}$$

represents the blood glucose concentration decreasing due to insulin uptake and is proportional to both the current level of glucose and the level of insulin action. The third term,

$$+D(t) \tag{6}$$

represents a disturbance. In our case, this will be due to eating meals that get metabolized and increase the blood glucose concentration. As a patient eats a meal, metabolism ramps up quickly and tends to taper off slowly as more of the food is digested in the stomach. We, therefore, chose to model the disturbance with a sawtooth input signal:

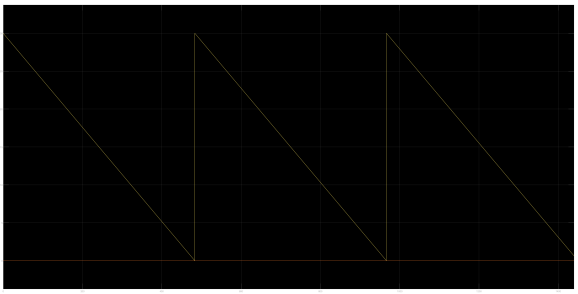

Fig. 1. Disturbance signal,$D(t)$, peak = 30, frequency = 3/day.

We chose the frequency to correspond to three instances in our period "day." In Simulink we let 1 second represent 1 minute and ran the simulation for the equivalent of one day. We chose the amplitude to be 30 since that resulted in a blood glucose spike of about 30 mg/dL which is typical after a meal [2].

Equation 2 describes how the plasma insulin concentration changes. The first term,

$$-nI(t) \tag{7}$$

represents the insulin clearing out of the blood plasma. The second term,

$$+u(t) \tag{8}$$

represents the input term derived from the control scheme. Determining this term will be the focus of the case study. In relation to the context of the problem, an insulin pump would act to increase plasma insulin concentration and would be a positive input value.

Equation 3 describes the pharmacokinetics of the insulin delivery - how the exogenous insulin will act in the body. The first term,

$$-p_2 X(t) \tag{9}$$

represents the decay of the insulin action. Over time, the effect will fall off. The second term,

$$+p_3 \left(I(t) - I_b\right) \tag{10}$$

represents a threshold of insulin required before it begins to increase glucose uptake. An insulin plasma concentration below the threshold will not increase the insulin action.

The State-Space System

The following equation is the general form of our model:

$$\dot{\alpha} = A\alpha + Bu(t) + D(t), \tag{11}$$

where α is the vector containing the state variables, $\dot{\alpha}$ is the vector that describes how the state variables change. u(t) is our input into the system, and D(t) is a disturbance introduced to our system. The disturbance is an influx of glucose from a meal a patient has consumed. We had three state variables: G(t) the blood glucose concentration (mg/dL), I(t) the plasma insulin concentration (mU/L), and X(t) the insulin action. Thus, our state vector is as follows:

$$\alpha = \begin{bmatrix} G(t) \\ I(t) \\ X(t) \end{bmatrix} \tag{12}$$

For each of our states, we had a baseline values given to us: $G_b = 100[mg/dL], I_b = 10[mU/L], and X_b = 0[mU]$. The following vector contains equations, given by our client, describing how the state variable vector changes:

$$\dot{\alpha} = \begin{bmatrix} -p_1(G(t) - G_b) - X(t)G(t) + D(t) \\ -nI(t) + U(t) \\ -p_2 X(t) + p_3(I(t) - I_b) \end{bmatrix} \tag{13}$$

Thus, our non-linearized $A\alpha$ and Bu matricies are as follows:

$$A\alpha = \begin{bmatrix} -p_1(G(t) - G_b) - X(t)G(t) \\ -nI(t) \\ -p_2 X(t) + p_3(I(t) - I_b) \end{bmatrix} \tag{14}$$

$$Bu = \begin{bmatrix} 0 \\ u(t) \\ 0 \end{bmatrix} \tag{15}$$

Dynamics Analysis

Linearization

We linearized our model by taking the Jacobian of $\dot{\alpha}$ (eq. 13) and chose our equilibrium to be at the baseline values of our states. We decided that our equilibrium would be about the baseline values of our state variables because we wanted our system to trend toward our desired (baseline) values of glucose, insulin, and insulin action. For a vector $f(x_1, x_2)$ with two rows, the Jacobian takes the form:

$$\frac{\partial f}{\partial x} = \begin{bmatrix} \frac{\partial f_1}{\partial x_1} & \frac{\partial f_1}{\partial x_2} \\ \frac{\partial f_2}{\partial x_1} & \frac{\partial f_2}{\partial x_2} \end{bmatrix} \tag{16}$$

The Jacobian of equation (14) turned out to be

$$\tilde{A} = \begin{bmatrix} -p_1 - x & 0 & -G \\ 0 & -n & 0 \\ 0 & P_3 & -p_2 \end{bmatrix}, \tag{17}$$

while the Jacobian of equation (15) turned out to be

$$\tilde{B} = \begin{bmatrix} 0 \\ 1 \\ 0 \end{bmatrix} \tag{18}$$

We evaluated our Jacobian matrices at the baseline values, obtaining our model as shown below:

$$\dot{\alpha} = \begin{bmatrix} -0.03 & 0 & -100 \\ 0 & -0.1 & 0 \\ 0 & 0.01 & -0.02 \end{bmatrix} \alpha + \begin{bmatrix} 0 \\ 1 \\ 0 \end{bmatrix} u \tag{19}$$

To see if our linearized system is controllable and observable, we used the following equations:

$$M_C = \begin{bmatrix} B & AB & A^2B & A^{n-1}B \end{bmatrix}, \tag{20}$$

where C is the controllability matrix.

$$M_O = \begin{bmatrix} C \\ CA \\ CA^2 \\ CA^{n-1} \end{bmatrix} \tag{21}$$

where n is the number of state variables. If M_C is full rank, then the system is controllable. If M_O is full rank, then the system is observable. in our case, our linearized system is both controllable and observable.

Finding K and L values in Observer Feedback

Because we were only given a sensor to measure the glucose of our patient, we do not have a direct way to measure our other state variables, specifically the level of insulin and the level insulin action. Thus, we decided to use a state observer to estimate our state variables. The general form of a state observer is as follows (tilde means linearized and the hat means it is an observer):

$$\dot{\hat{\alpha}} = \tilde{A}\hat{\alpha} + \tilde{B}u + L(y - \hat{y}), \tag{22}$$

where $u = -k^t\alpha$.

$$\hat{y} = c\hat{x} \tag{23}$$

To ensure that our system is stable and that the error between the output of the observer ($\hat{y}$) and the glucose sensor reading is approximately zero, we have to find values for our k and L matrices such that the eigenvalues for matrices $\tilde{A} - \tilde{B}k^T$, which determines how the system variables evolve, and $\tilde{A} - LC$, which determines how our estimated states evolve. The magnitude of our eigenvalues will depend on our frequency analysis using the Nyquist Criterion for Stability.

Frequency Domain Analysis

We used the ”tf()” function in Matlab to obtain the transfer function for our state observer. Then, we used the ”nyquist()” function to analyze if our system was stable or not. Our system was stable if there are zero encirclements of the point (-1, 0). In our case, wanted a gain margin of around 25%, meaning if the actual model deviates from our predicted model by about 25%, then our system is still stable. Using the ”place()” function in Matlab, we were able to obtain k and L values for specific eigenvalues. In essence, the ”place()” function accepts the matrices that describe the feedback of the system, and our desired eigenvalues for the feedback. Then, the ”place()” function returns the gain values corresponding eigenvalues we gave the function. In the end, we chose the eigenvalues $\lambda = [-1.2, -1.205, -1.210]$ and obtained the L vector:

$$L = \begin{bmatrix} 3.4650 \\ -1.3492 \\ -0.0393 \end{bmatrix} \tag{24}$$

We determined the eigenvalues for our k vector to be less negative than the eigenvalues corresponding to our L vector because we wanted our observer to determine values of the state variables slightly quicker than the system which is under observation. Thus, we decided on eigenvalues of $\lambda = [-1.1, -1.105, -1.110]$ and obtained our gain vector:

$$k = \begin{bmatrix} -1.2423 & 3.1650 & 349.92 \end{bmatrix} \tag{25}$$

From figures (2 and 3), we see the Bode plot and the Nyquist plot, respectively, of the system without a controller; that is, u(t) = 0.

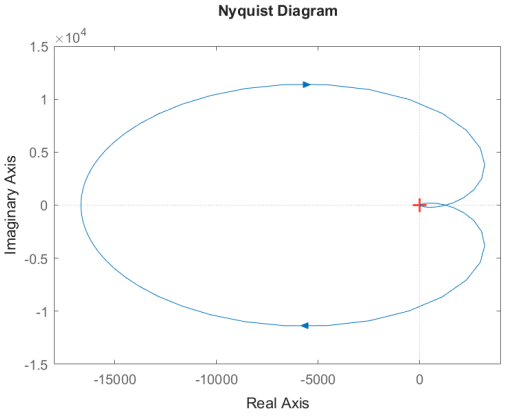

Fig. 3. Nyquist Plot of insulin system Without a Controller $u(t) = 0$

In figure (3), we observed an encirclement of the point (-1, 0), meaning that the system is unstable. To stabilize the system, we can adjust the gain, the k vector, of our state feedback so that the Nyquist plot excludes the point (-1, 0).

Figures (4 and 5) show the Bode plot and the Nyquist plot, respectively, of the system with a controller that has a gain vector k as seen in equation (25); that is, $u(t) = -k^T\hat{\alpha}$. The eigenvalues, and equivalently, the poles of our feedback system that corresponded to the values in vector k were $\lambda = [-1.1, -1.105, -1.110]$.

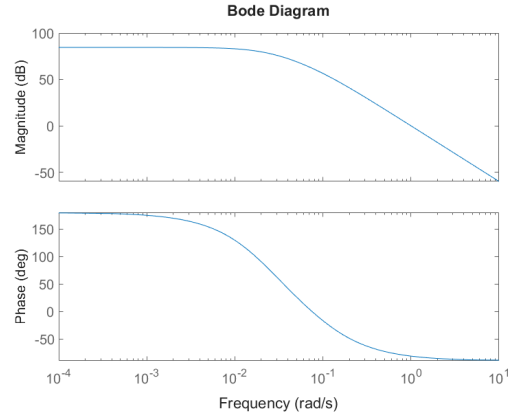

Fig. 2. Bode Plot of insulin system Without a Controller $u(t) = 0$

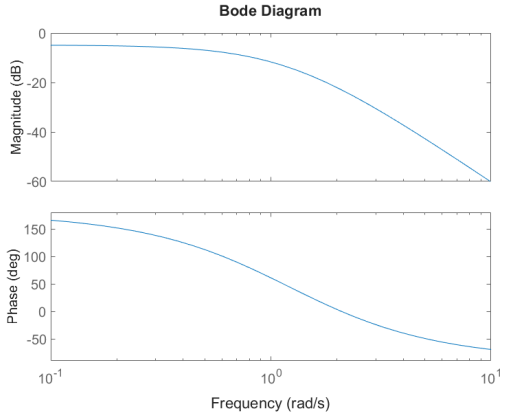

Fig. 4. Bode Plot of insulin system with Controller $u(t) = -k^T\hat{\alpha}$

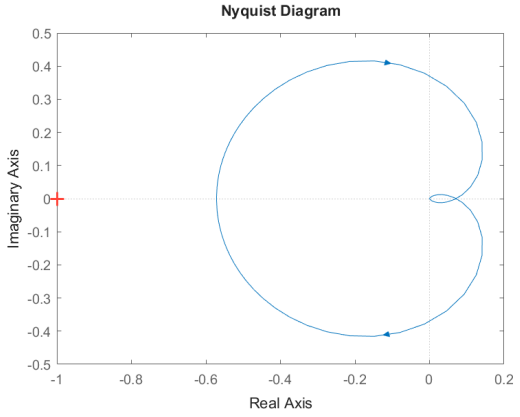

Fig. 5. Nyquist Plot of insulin system with Controller $u(t) = -k^T\hat{\alpha}$

From figure (5), we observed that there were zero encirclements of the point (-1, 0), meaning that our closed-loop system was stable. The gain margin of our system was around 25%, meaning that if the actual values in our k vector drop by 25%, then our system will still be stable as there would still be zero encirclements of the point (-1, 0). Figure (6) shows a 25% decrease in the k vector values. Although the Nyquist plot has expanded, it does not encompass the (-1, 0) point.

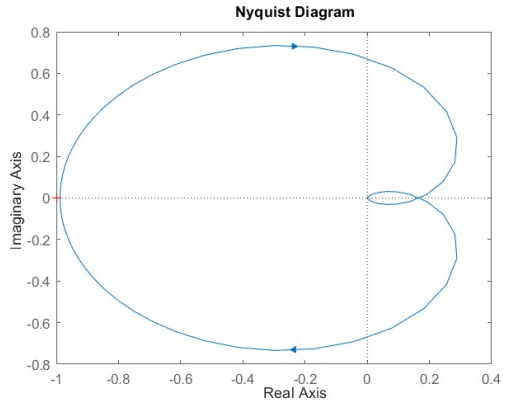

Fig. 6. Nyquist Plot of insulin system with Controller $u(t) = -k^T\hat{\alpha}$ but with 25% less gain

The phase margin of our system is infinite as long as we stay within the 25% gain margin. We can say that the phase margin is infinite because no matter how much we rotate the Nyquist plot seen in figure (6), it will never encompass the (-1, 0) point.

We repeated the process of obtaining values for our k and L vectors but for eigenvalues $\lambda = [-2.1, -2.105, -2.110]$ to see how our system behaves for more negative eigenvalues. The L vector turned out to be

$$L = \begin{bmatrix} 6.4650 \\ -9.3273 \\ -0.1380 \end{bmatrix} \tag{26}$$

and the k vector turned out to be

$$k = \begin{bmatrix} -8.9 & 6.2 & 1297.9 \end{bmatrix} \tag{27}$$

The resulting Bode plot and Nyquist plot are seen in figures (7 and 8).

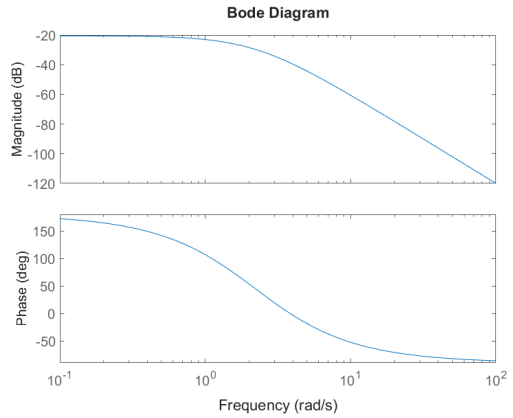

Fig. 7. Bode Plot of insulin system with Controller from -2 Eigenvalues

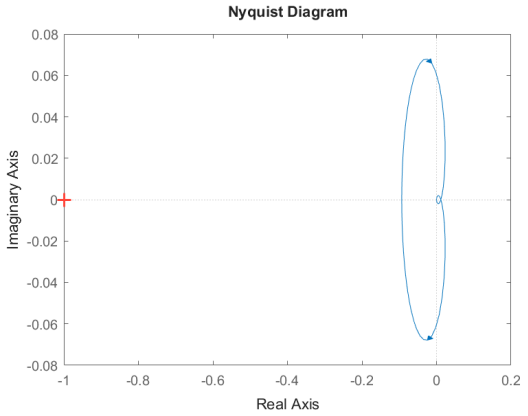

Fig. 8. Nyquist Plot of insulin system with Controller from -2 Eigenvalues

The main difference seen in our system when we increased our eigenvalues from around -1 to values around -2, is the increase in our L and k gain vectors.This is to be expected as the more negative a system's eigenvalues, the quicker the system reaches its equilibrium point. As the eigenvalues changed from -1 to -2, we observed an increase to the gain margin. With eigenvalues around -2, the gain margin increased from 25% to around 90% gain margin. Although a gain margin of approximately 90% sounds great, the values in the k vector that corresponds to a system with a gain margin of 90% is a bit much. Greater values in the k vector correspond to a greater amount of insulin being injected into the patient even if the the patient's glucose level is slightly off the baseline value. Because we hate to be the ones to say "We're gonna need a bigger needle", we will use the gains that correspond to eigenvalues around -1. While our system will have a gain margin that is only 25%, which seems minor when compared to a gain margin of 90%; if the actual model differs from our predicted model by more than 25%, then it would probably be more worthwhile to re-investigate our predicted model than to adjust our gain margin.

Transfer Function and State Space Analysis

Simulations: Using Simulink, we created a block diagram, seen in figure (9) of the state observer system.

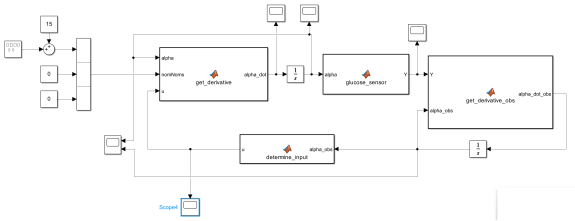

Fig. 9. Simulink block diagram of the observer state-space model.

Without a controller, the dynamics of the system would allow the glucose level of our patient to drift in a fashion as seen in the figure (10).

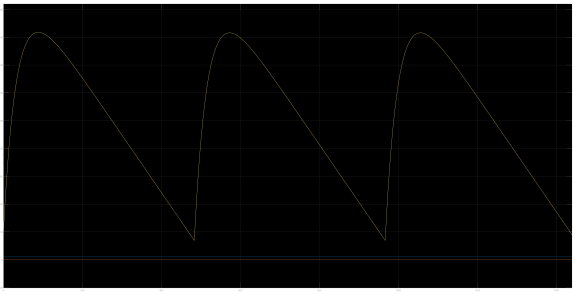

Fig. 10. Simulation of the System without Insulin Input

Although very small, we observed that glucose level of the patient remains well above the baseline of 100 [mU/dL]. Because the patient is still able to produce some insulin, although not much, the amount of glucose decreases slowly which is dangerous as remaining above a doctor specified baseline leads to hyperglycemia.

When we implemented our controller to introduce insulin, we see (in figure 11) that the glucose level in our patient decreases to the baseline value at the end of 12.3 Minutes, allowing the glucose level of our patient to remain at a safe level for an extended period of time before they enjoy their next meal. As bonus, the amount of insulin in our patient does not go into the negatives, meaning that we did not introduce so much insulin that our controller had to attempt to extract insulin from our patient; thus, also free us from having to deal with negative values in real life which are not possible.

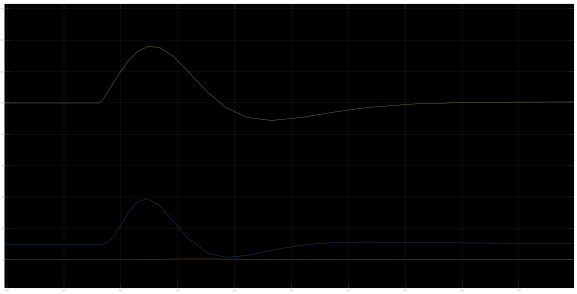

Fig. 11. Simulation of the System with Controller. -1 EigenValue.

Feasibility of Design

Overall, our controller would be challenging and expensive to implement. The primary concern would be that our controller allows for a negative insulin input. Although ”negative insulin” is meaningless in this context, the intended effect could be achieved by instead delivering some type of insulin R inhibitor. Insulin R inhibitors interfere with insulin receptor binding sites and therefore would function to reduce the amount of insulin action and glucose uptake.

Our insulin pump would need a dual drug design to administer both insulin and an insulin inhibitor. This would increase complexity, cost, maintenance, and would generally be a wasteful solution. The advantage of allowing negative insulin input (faster response to disturbance and more aggressive control) seems totally offset by the impracticality of implementing it.

Within the scope of the dual-drug delivery system, the first control scheme with poles about -1 is much more practical than the second control scheme with poles about -2. While the first scheme does have a worse peak glucose response to the disturbance (136 mg/dL vs. 119 mg/dL), both schemes settle the glucose level back to its baseline in less than fifteen minutes, while a typical modern insulin pump takes two to four hours to settle to baseline. The first control scheme has the additional advantages of a much lower peak insulin input (32 units vs. 118 units) and no negative insulin level in the simulation which suggests it is physically possible. These controllers are brutally efficient - they respond aggressively to any deviation from baseline glucose levels, but require significantly more insulin (measured in units/min vs. normal units/hr).

REFERENCES

[1] “Artificial Pancrease”, ESE 441 FL24, Washington University in St. Louis. Accessed DEC. 6, 2024.
[2] Duerden, S. (2024b, December 6). What is postprandial blood sugar?. US MED. https://www.usmed.com/blog/postprandial-blood-sugar/