Home Assignment 3: Glucose Dynamics

October 29, 2014

This assignment is based upon the metabolic simulation model developed at the Padova and Virginia universities, approved by the Food and Drug Administration (FDA) U.S., for simulation studies in place of animal studies for the purpose of closed-loop insulin pump development. Here, this model has been implemented as a Simulink model [1]. The Simulink model consists of a number of submodels, but you will mainly work with the interface seen in Fig. 1. The right block is the submodel containing the Padova model. From this block several outputs emerge, connected to scopes and export sinks to the workspace. To the left of the model block, a connection to a controller can be seen. This in turn is connected to a reference signal and a negative feedback from the interstitial glucose measurement. The controller is switched on and off by double-clicking the manual switch (it's on in the picture).

1. Endogenoeus Glucose Production and Glucose Utilization: Load the data set `nominal.mat` (type `load nominal`). Start Simulink and load the `DiabetesSimulation.mdl` model. Make sure the controller is turned off (the switch in the lower position). Run the simulator with these data and look at the different output scopes. This experiment represents two days for a patient with type 1 diabetes using a subcutaneous insulin pump with rapid-acting insulin and a subcutaneous continuous glucose sensor (CGM). The patient is

[1] Based on a model and parameter values generously supplied by C.Dallaman

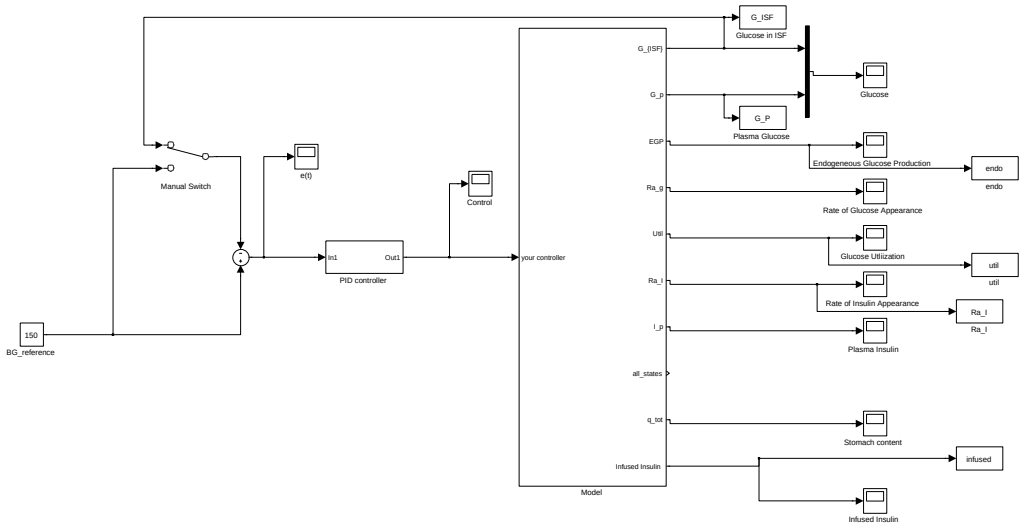

Figure 1 The simulink interface `DiabetesSimulation.mdl` to the Padova Simulation Model.

using a fixed therapy regime with a constant Carbohydrate-to-Insulin Ratio (CIR) and a constant basal insulin infusion to cover the basic metabolism. The Carbohydrate-to-Insulin ratio refers to that the patient takes a fixed number of insulin units per digested grams of carbohydrates. Three meals and corresponding insulin bolus doses are taken each day.

Look at the different output scopes. Imagine that you and a physician are looking at the plots together. How would you explain the behavior to him? Try to explain in words the behavior of the Endogeneus Glucose Production r_{EGP} and the Glucose Utilization $r_U = r_{Uii} + r_{Uid}$ during the simulation, i.e., what is their relationship to the glucose and insulin levels, and how and why do they deviate from their fasting values? Partition your analysis into the postprandial and the fasting stages. Can you recognize the type of relationship r_{Uid} is dependent upon? Useful terminology (look it up if you need to): Post-Prandial, Inhibit, Facilitate, Positive/Negative Feedback. Consider the model:

$$r_{EGP} = k_{p1} - k_{p2}G_p(t) - k_{p3}I_d(t) \tag{1}$$
$$\dot{I}_1 = -k_i(I_1(t) - I(t)) \tag{2}$$
$$\dot{I}_d = -k_i(I_d(t) - I_1(t)) \tag{3}$$

and

$$r_{Uii} = constant \tag{4}$$
$$r_{Uid} = \frac{V_m(X(t))G_t(t)}{K_m + G_t(t)} \tag{5}$$
$$V_m(X(t)) = V_{m0} + V_{mx}X(t) \tag{6}$$
$$\dot{X}(t) = -p_{2u}X(t) + p_{2u}(I(t) - I_b) \tag{7}$$

where

- G_p is glucose in plasma.
- G_t is glucose in 'slowly equilibrating tissue'.
- $I(t)$ is the plasma insulin concentration and I_b is the basal value.
- $X(t)$ is the 'remote' insulin.
- I_d is the delayed insulin signal.
- I_1 intermediate delayed insulin signal.

2. Glucose Effectiveness: Load the data set `nobolus1.mat` and run the simulation. Make sure the controller is turned off (the switch in the lower position). In this data set we simulate that the patient forgets, or is unable to, administer the bolus doses of day 1. Look at the glucose plot. During the lecture, some critisism that the model may overestimate glucose effectiveness $\partial\dot{G}/\partial G$ was touched upon. Consider that:

$$\dot{G} = r_{EGP} + r_{U_{id}} + \dots \tag{8}$$

Based on this simulation—Do you think that is a valid point? Explain why.

3. Artificial Pancreas: The patient has been admitted to a pilot study in an artificial pancreas project, i.e., an investigation of the possibility of closed loop control of the glucose dynamics. The patient's pump is modified such that

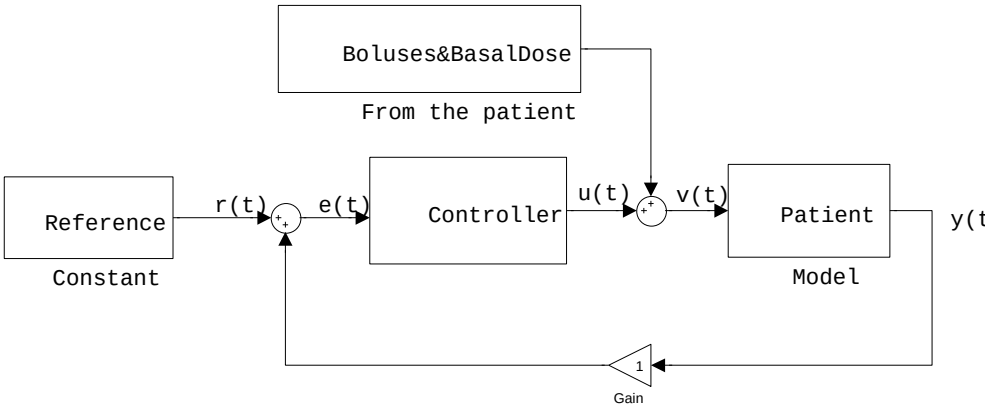

Figure 2 The system block scheme, including controller.

it incorporates a controller, which will automatically inject insulin based on the subcutaneous glucose feedback signal received from the CGM sensor. The patient is told that he will not need to take any bolus doses. The controller will automatically add (or possibly subtract down to 0) the amount of insulin to administer on a minute-to-minute basis. The purpose of the controller is to improve the glycemic control, i.e., reduce the mean of the glucose value $G(t)$ without increasing time spent in hypoglycemia ($G(t) < 70$ mg/dl), by trying to keep the glucose at the reference level $r(t)$. The overall system can be seen in Fig. 2. Here, $u(t)$ is the control signal emerging from the controller, $v(t)$ is the total insulin infusion, adding the basal and bolus doses administred by the patient (if any) to $u(t)$. The controller is a PID-controller, where P represents proportional, I stands for integrating and D is Derivative. The controller acts on the difference $e(t)$ between a reference signal $r(t)$ and the true measurement output $y(t)$, and calculates a control signal $u(t)$ based on three different terms

$$e(t) = r(t) - y(t) \tag{9}$$

$$u(t) = u_P + u_I + u_D \tag{10}$$

$$u_P = Ke(t) \tag{11}$$

$$u_I = K_i \int_{t_0}^{t} e(\tau)d\tau \tag{12}$$

$$u_D = K_d \dot{e} \tag{13}$$

where K, K_i and K_d are tunable controller parameters. The proportional term u_P gives a control signal that is directly proportional to the error between the output and the desired reference. Likewise, the integrating term u_I gives an accumulated response to an error that is persistent, and finally, the derivative term u_D gives a contribution that is acting on the direction of the error, thereby trying to foresee the development and act in advance. In Fig. 3, the step response of the glucose to a change of the insulin basal level can be seen. This may be useful to understand the behavior of the controller and the system for the questions below.

(a) Load the dataset `nobolus12.mat`, and run the simulation again, but with the controller turned on. Try changing the proportional gain K (double-click the controller block to open this subsystem). What happens if you make it much larger (like 10 times larger)?

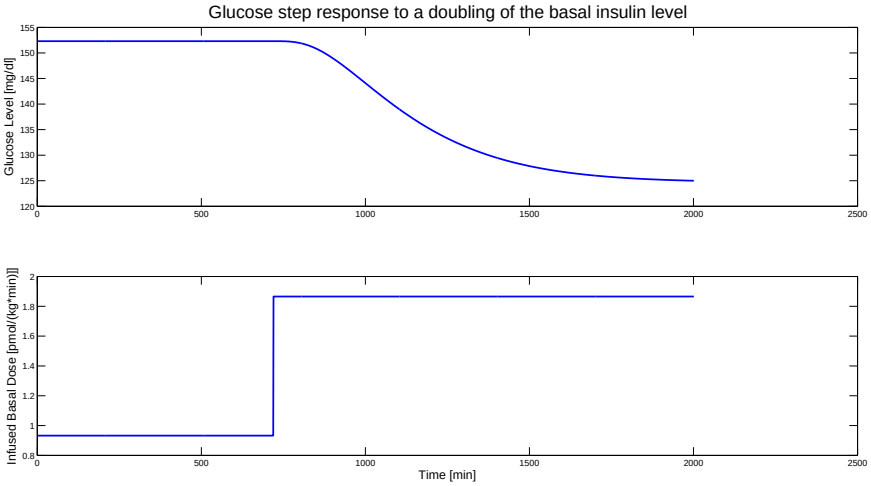

Figure 3 Step response of the glucose to a doubling of the insulin basal level.

(b) Reset the proportional gain K and instead increase the integrator parameter K_i. What happens if K_i is increased (say by a factor 15)?

(c) Reset both K and K_i. Double K_d. What happens?

(d) What do you think is the main challenge to controlling this system (using feedback control)?