Home Assignment 3: Glucose Dynamics

2018

Preparation: exercises in Chapter 6 of the exercise manual.

In this assignment we will study glucose dynamics and try to regulate the glucose level with a PID controller. We will use a model that is based upon a metabolic simulation model developed at the University of Padova and the Univeristy of Virginia. The model is approved by the Food and Drug Administration (FDA), U.S., for the purpose of simulation studies, in place of animal studies, in the development of closed-loop insulin pumps. In this assignment, the model has been implemented in Simulink [1].

The Simulink model consists of a number of submodels. However, you will mainly work with the interface seen in Fig. 1. The right block is the submodel that contains 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 is on in Fig. 1).

1. Endogenous Glucose Production and Glucose Utilization: Start Simulink and open `DiabetesSimulation.mdl`. Make sure the controller is turned off (the switch is in the lower position). Load the data set `nominal.mat` (type `load nominal`) and run the simulation. This simulation represents a time period of two days for a patient with type 1 diabetes that is using a subcutaneous insulin pump with rapid-acting insulin and a subcutaneous continuous glucose sensor (CGM). The patient is 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 CIR refers to that the patient takes a fixed number of insulin units per digested grams of carbohydrates. Three meals and three corresponding insulin bolus doses are taken each day, as can be seen in scopes *Glucose* and *Infused Insulin* after the simulation is done.

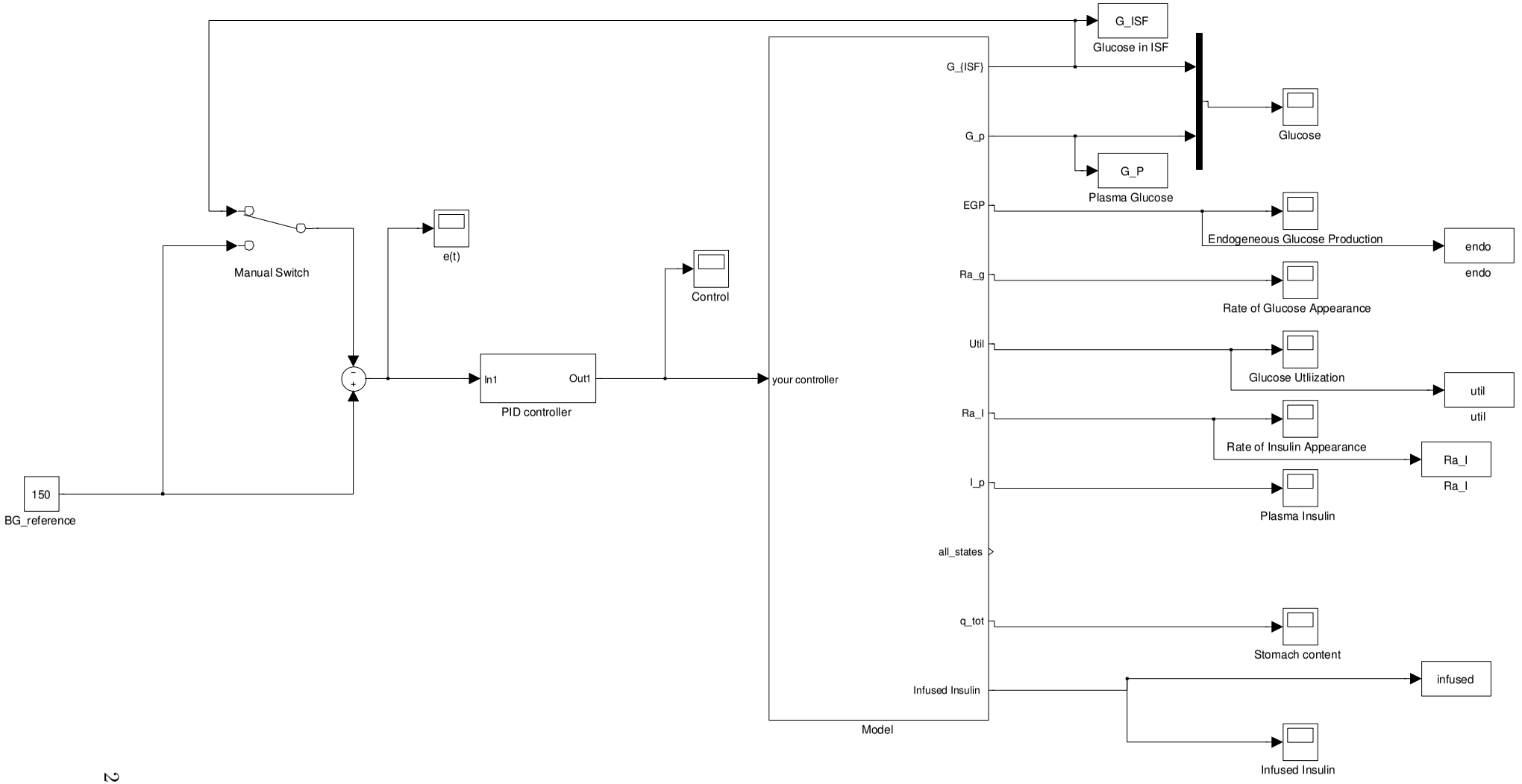
   Look at scopes *Endogenous Glucose Production* and *Glucose Utilisation*. The Endogenous Glucose Production r_{EGP} and the Glucose Utilisation r_U are governed by the following model

$$r_{EGP} = k_{p1} - k_{p2}G_p(t) - k_{p3}I_d(t) \tag{1}$$

$$\dot{I}_1 = -k_i(I_1(t) - I(t)) \tag{2}$$

$$\dot{I}_d = -k_i(I_d(t) - I_1(t)) \tag{3}$$

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


G_ISF
Glucose in ISF
G_{ISF}
G_p
Glucose
G_P
Plasma Glucose
EGP
Endogeneous Glucose Production
endo
endo
Ra_g
Rate of Glucose Appearance
Util
Glucose Utlization
util
util
Ra_I
Rate of Insulin Appearance
Ra_I
Ra_I
I_p
Plasma Insulin
all_states
q_tot
Stomach content
Infused Insulin
infused
Infused Insulin
Model
your controller
Manual Switch
e(t)
Control
In1
Out1
PID controller
150
BG_reference

and

$$r_U = r_{Uii} + r_{Uid} \tag{4}$$
$$r_{Uii} = constant \tag{5}$$
$$r_{Uid} = \frac{V_m(X(t))G_t(t)}{K_m + G_t(t)} \tag{6}$$
$$V_m(X(t)) = V_{m0} + V_{mx}X(t) \tag{7}$$
$$\dot{X}(t) = -p_{2u}X(t) + p_{2u}(I(t) - I_b) \tag{8}$$

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 is the intermediate delayed insulin signal.

Try to explain in words the simulated behavior of r_{EGP} and r_U based on the following questions

- 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 post-prandial and the fasting stages.
- Can you recognise the type of relationship r_{Uid} is dependent upon?

Useful terminology: Post-Prandial (time during or relating to the time after food intake), Inhibit (prevent), Facilitate (make a process easier), Positive/Negative Feedback.

2. Glucose Effectiveness: Load the data set `nobolus1.mat` and run the simulation. Again, make sure the controller is turned off (the switch is 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 scope *Glucose* and consider that the rate of change of glucose $\dot{G} = dG/dt$ is modeled as

$$\dot{G} = r_{EGP} - r_{U_{id}} + \dots \tag{9}$$

Some criticise the model, saying it overestimates glucose effectiveness defined as $\partial\dot{G}/\partial G$, i.e., how the rate of change of glucose is dependent on the presence of glucose. Based on the simulation, do you think that it is a valid point?

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 it incorporates a controller that 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. Instead, 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

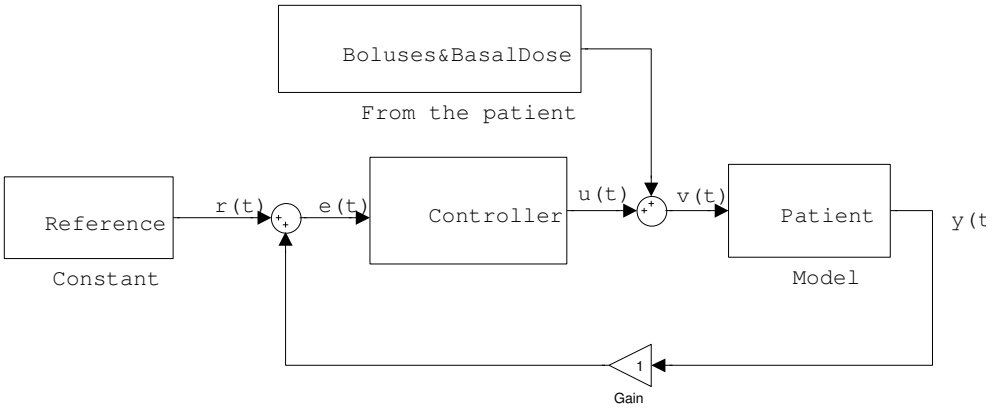


Figure 2 The system block diagram, including controller.

($G(t) < 70$mg/dl), by trying to keep the glucose at the reference level $r(t)$. A block diagram of the overall system can be seen in Fig. 2 where $u(t)$ is the control signal emerging from the controller and $v(t)$ is the total insulin infusion, adding the basal and bolus doses administered by the patient (if any) to $u(t)$. The controller acts on the difference $e(t)$ between the reference signal $r(t)$ and the true measurement output $y(t)$. Find where the signals $r(t)$, $u(t)$, $e(t)$ and $y(t)$ are located in Fig. 1. The controller is a PID-controller, where P stands for proportional, I stands for integral and D stand for derivative. The controller calculates $u(t)$ based on these three different terms

$$u_P(t) = Ke(t), \quad u_I(t) = K_i \int_0^t e(\tau)d\tau \quad \text{and} \quad u_D(t) = K_d\dot{e}$$
$$\rightarrow u(t) = u_P + u_I + u_D$$

where parameters K, K_i and K_d can be tuned. The proportional part u_P gives a control signal that is directly proportional to $e(t)$. The integral term u_I gives an accumulated response to $e(t)$ that is persistent. Finally, the derivative term u_D gives a contribution that is acting on the direction of $e(t)$, 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 make sure the controller is turned on. This data set models the food intake as in the previous simulations but with no basal or bolus injection of insulin, i.e., $v(t) = 0$. Instead, it is the controller that administrates the insulin injection. Run the simulation and look at scope *Glucose*. Is the glucose level kept at decent values?

(b) Try changing the proportional gain K (double-click on the controller block to open this subsystem) and simulate again. What happens to the glucose levels if you make it much larger (like 10 times larger)?

(c) 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)?

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

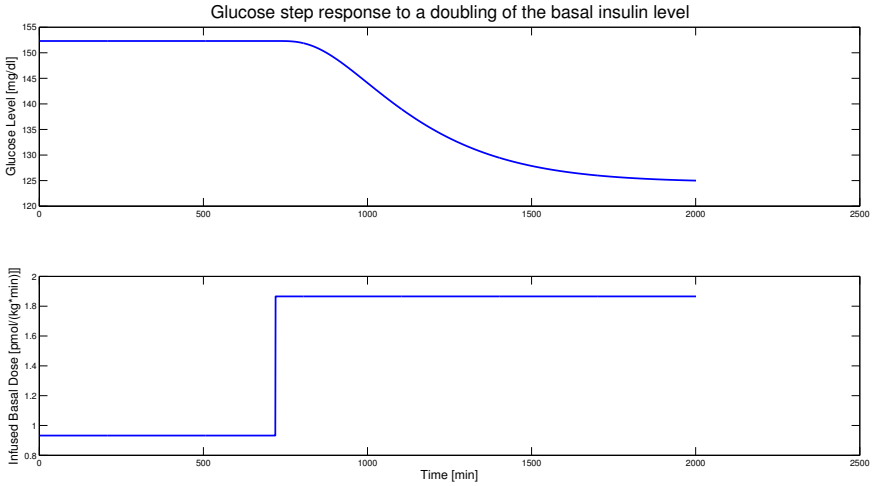


Figure 3 Step response of the glucose to a doubling of the insulin basal level.

(e) What do you think is the main challenge to controlling this system (using feedback control)? Hint: Consider the open-loop system behavior shown in Fig. 3.