

Home Assignment 3: Glucose Dynamics

November 1, 2016

In this assignment we will study glucose dynamics. The model we will be using is based upon a metabolic simulation model developed at University of Padova and University of Virginia. The model is 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. For 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

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

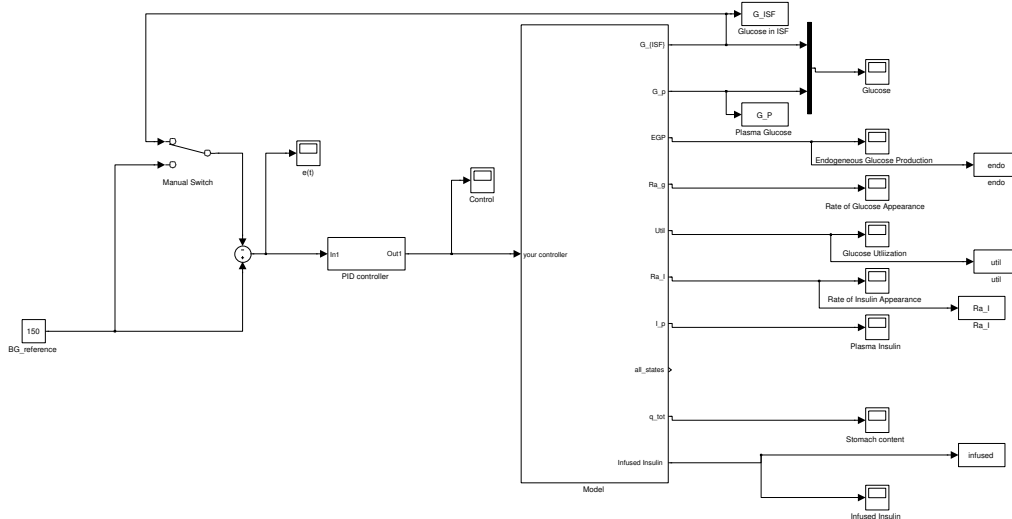


Figure 1 The simulink interface `DiabetesSimulation.mdl` to the Padova Simulation Model.

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*.

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

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

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

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

and

$$r_U = r_{Uii} + r_{Uid} \quad (4)$$

$$r_{Uii} = \text{constant} \quad (5)$$

$$r_{Uid} = \frac{V_m(X(t))G_t(t)}{K_m + G_t(t)} \quad (6)$$

$$V_m(X(t)) = V_{m0} + V_{mx}X(t) \quad (7)$$

$$\dot{X}(t) = -p_{2u}X(t) + p_{2u}(I(t) - I_b) \quad (8)$$

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 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 (look it up if you need to): Post-Prandial, Inhibit, Facilitate, 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

$$\dot{G} = r_{EGP} - r_{U_{id}} + \dots \quad (9)$$

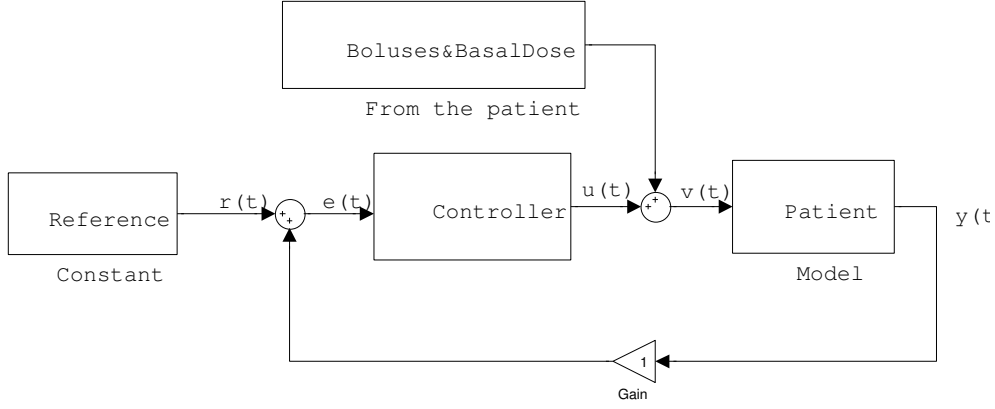


Figure 2 The system block diagram, including controller.

Some criticise the model, saying it overestimates glucose effectiveness $\partial\dot{G}/\partial G$. 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 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 ($G(t) < 70\text{mg/dl}$), 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.

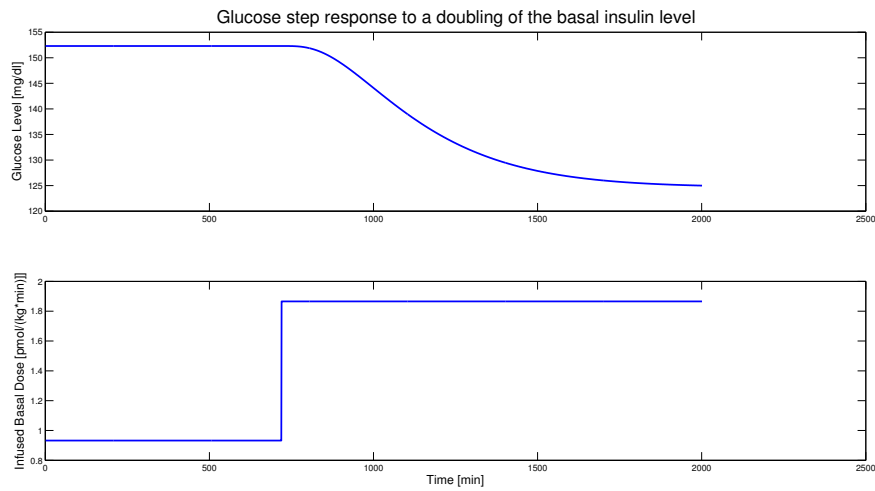


Figure 3 Step response of the glucose to a doubling of the insulin basal level.

- (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)?
- (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)?