Department of Electronic & Telecommunication Engineering

University of Moratuwa

BM 2101 – Analysis of Physiological Systems

ASSIGNMENT 04

USE OF MATLAB TO INVESTIGATE COMPARTMENTAL SYSTEMS

Name	**Index number**
Premathilaka H. D. M.	180497C

This report is submitted in partial fulfillment of the requirements for the module BM 2101 – Analysis of Physiological Systems.

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PART 1

Question 01

A simple plasma glucose/ insulin model can be expressed as:

$$\frac{di}{dt} = -0.8i + 0.2g$$

$$\frac{dg}{dt} = -5i - 2g + A(t)$$

where i is the deviation in insulin level from normal (in international units/kg) and g that for glucose (g/kg). The unit of time is hours. Enter the coefficients in the form $yp = ax + b$. For a step input $A(t)$ = 1 g/kg/h for $t > 0$, plot the changes in i and g over a 4 h period given that i and g are zero initially. Modify the equations to model a bolus input ($x = 1 - sign(t)$ is a delta function at $t = 0$). Now simulate a diabetic subject and a diabetic subject with insulin infusion of 100 mU/kg/h (both in response to the previous step input).

Solution 01

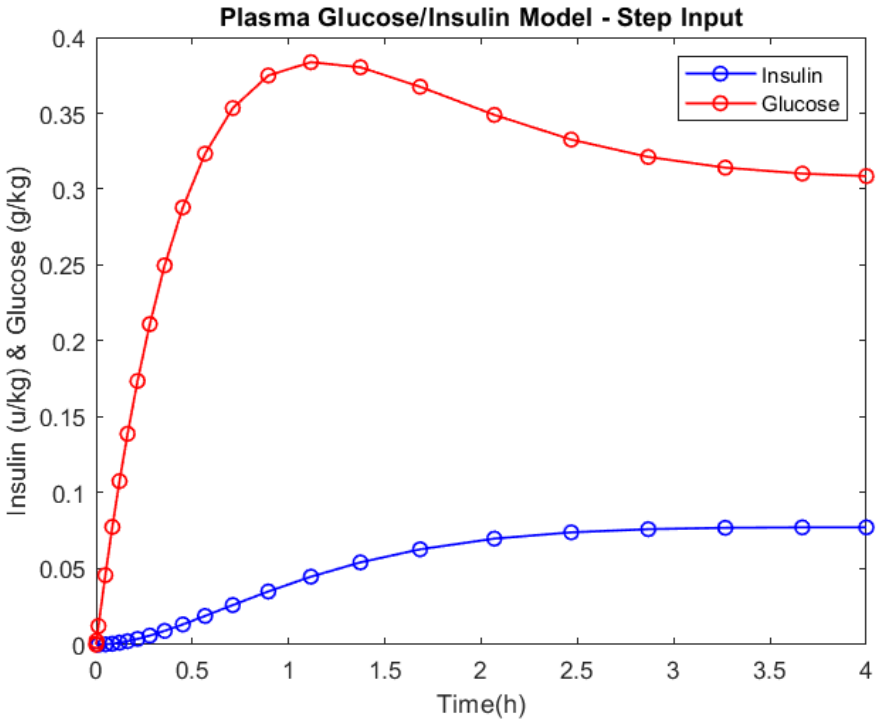
Plots obtained from the calculations are as follows.

a). When A(t) = 1 g/kg/h (t > 0)

Equations used;

$$\frac{di}{dt} = -0.8i + 0.2g$$

$$\frac{dg}{dt} = -5i - 2g + 1$$

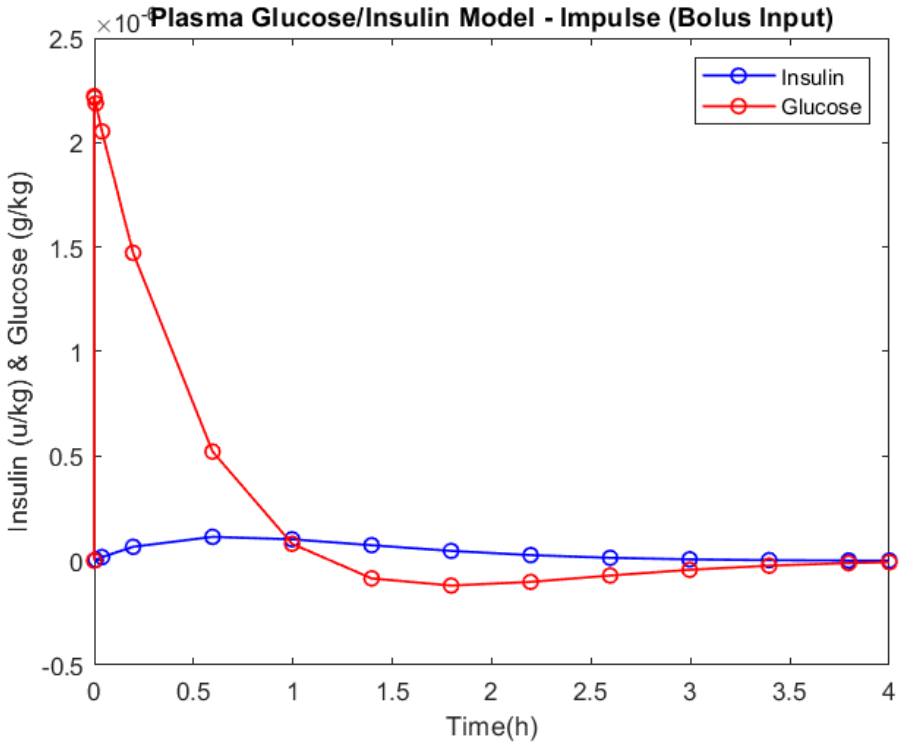


b). When A(t) = 1 – sign(t); Bolus input

Equations used;

$$\frac{di}{dt} = -0.8i + 0.2g$$

$$\frac{dg}{dt} = -5i - 2g + (1 - sign(t))$$

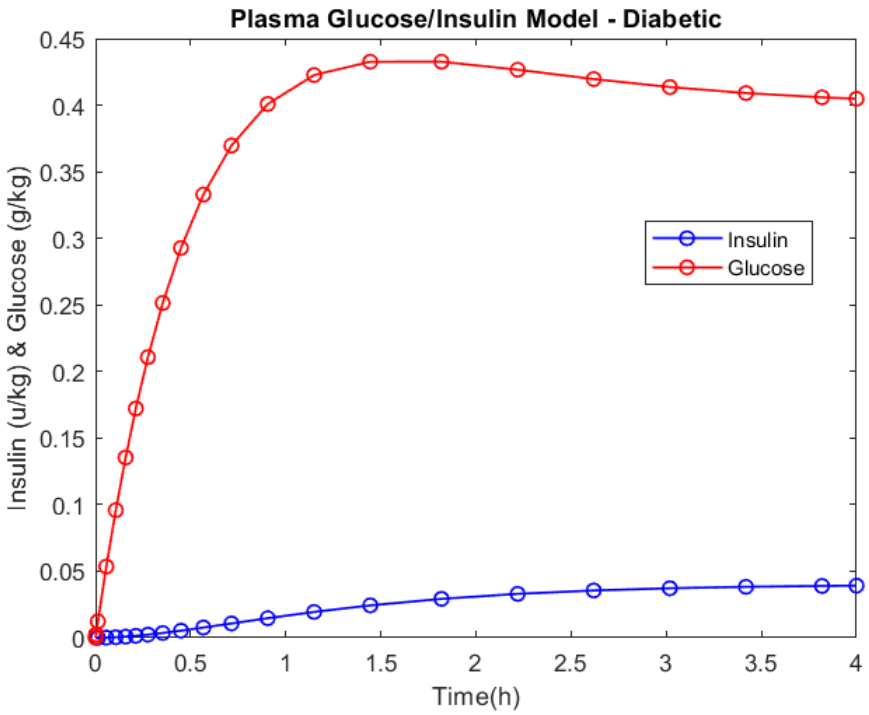


c). Diabetic Subject

- Generally, when the blood glucose levels are high in blood, the beta cells in the pancreatic islets will release insulin which would convert glucose into glycogen and then store them in the liver and other body tissues.
- But, in a diabetic patient, despite higher blood sugar levels, the beta cells won't release adequate insulin to convert glucose into glycogen.
- Thus, we can say that di/dt term is less dependent on the g term.
- Let's consider the following scenario.

$$\frac{di}{dt} = -0.8i + 0.08g$$

$$\frac{dg}{dt} = -5i - 2g + 1$$



d). Diabetic subject with insulin infusion of 100mU/kg/h

- When insulin is infused, the system of equations will take the form given below.

$$\frac{di}{dt} = -0.8i + 0.2g + B(t)$$

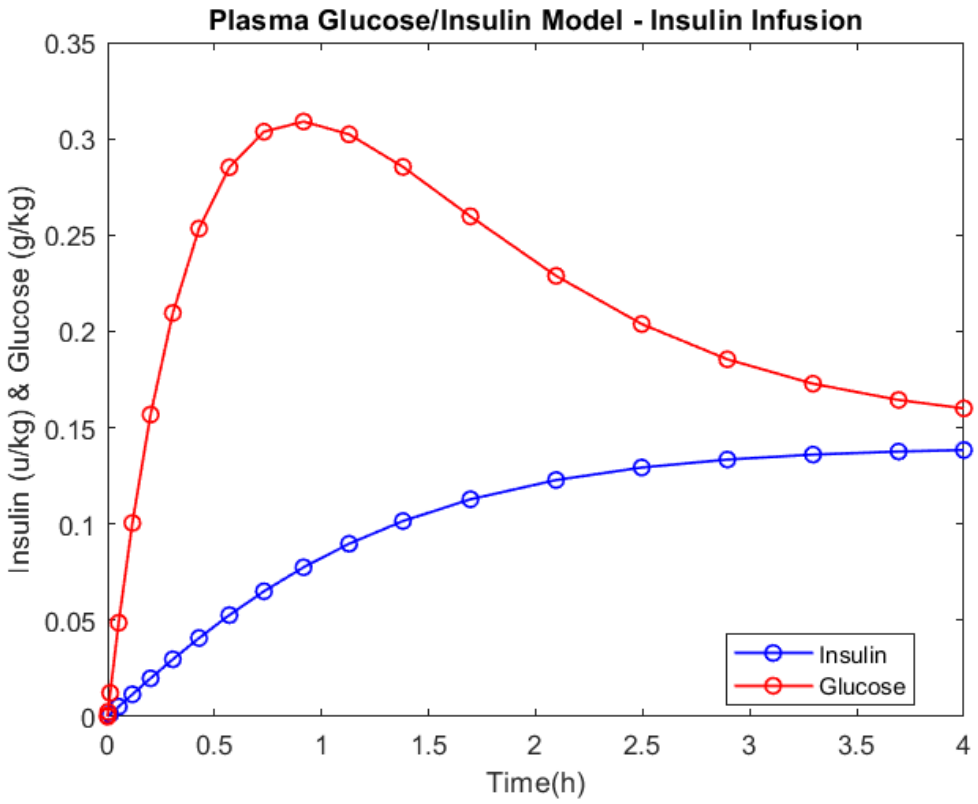
$$\frac{dg}{dt} = -5i - 2g + A(t)$$

where B(t) is the rate at which insulin is infused.

- In the question, we have considered B(t) = 100mU/kg/h
- Thus the set of equations corresponding to this system would be,

$$\frac{di}{dt} = -0.8i + 0.08g + 0.1$$

$$\frac{dg}{dt} = -5i - 2g + 1$$



Question 02

Set up an m-file to represent the Riggs model for iodine metabolism, then use ode23 to simulate the response to a sudden drop in iodine intake from 150 µg to 15 µg per day (this involves setting $B_n(t)$ to [15 0 0], at [150 0 0] no changes occur since this represents a steady-state). Produce plots for 0-10 days, then 0-300 days.

Certain thyroid diseases can be simulated by altering some of the parameters. Simulate the following diseases and provide notes and plots.

a. Hypothyroidism due to autoimmune thyroid disease

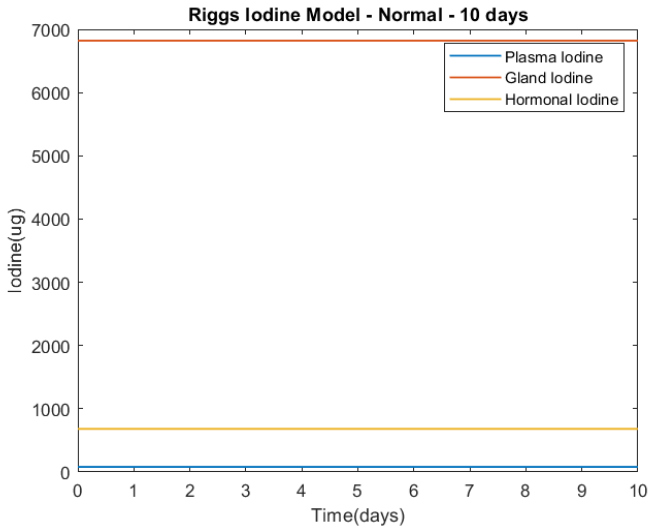
b. Hypothyroidism due to low Iodine intake

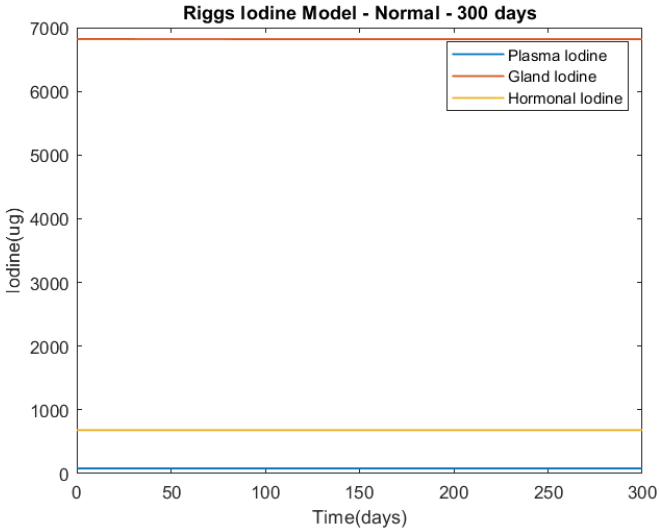
c. Hyperthyroidism due to Grave's disease

d. What are some common causes of goitre and tumors and how can they be simulated in the Riggs' model?

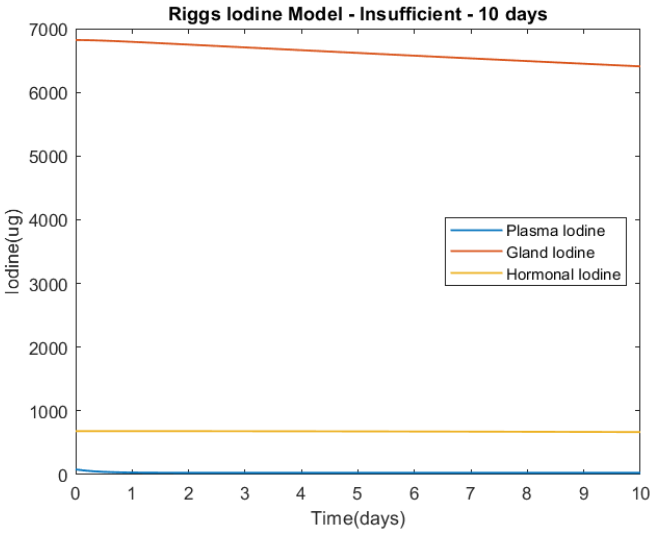
Solution 02

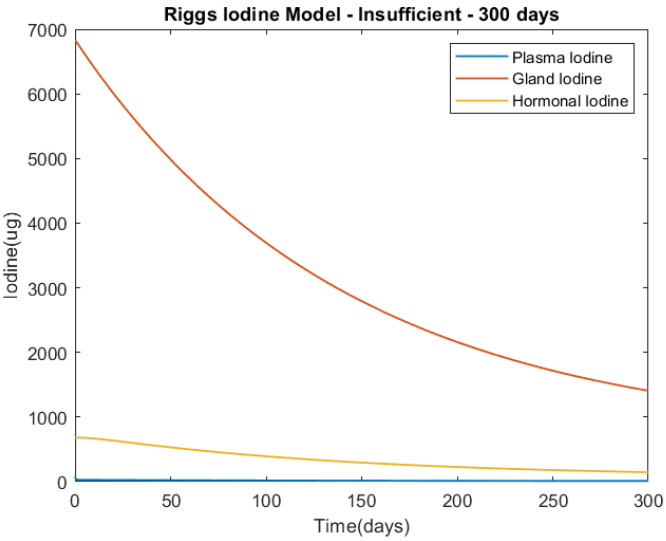
- When the daily intake is 150ug.





- When the daily intake is 15ug.

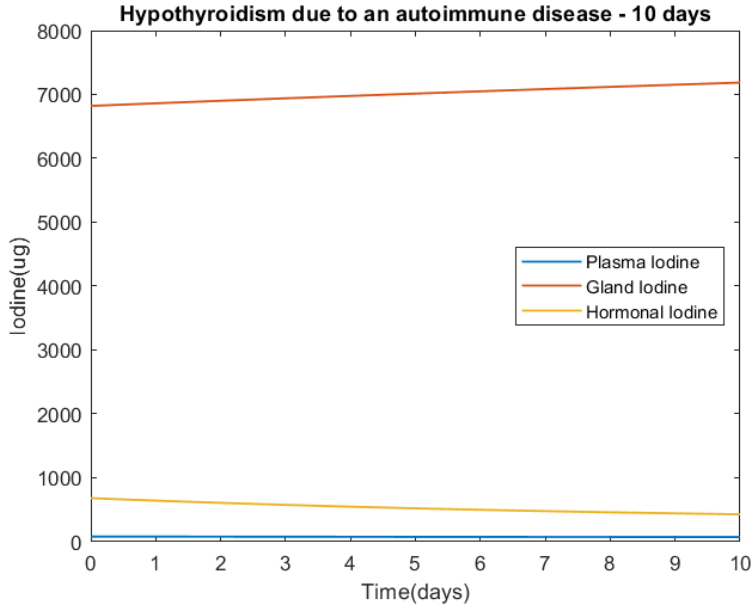


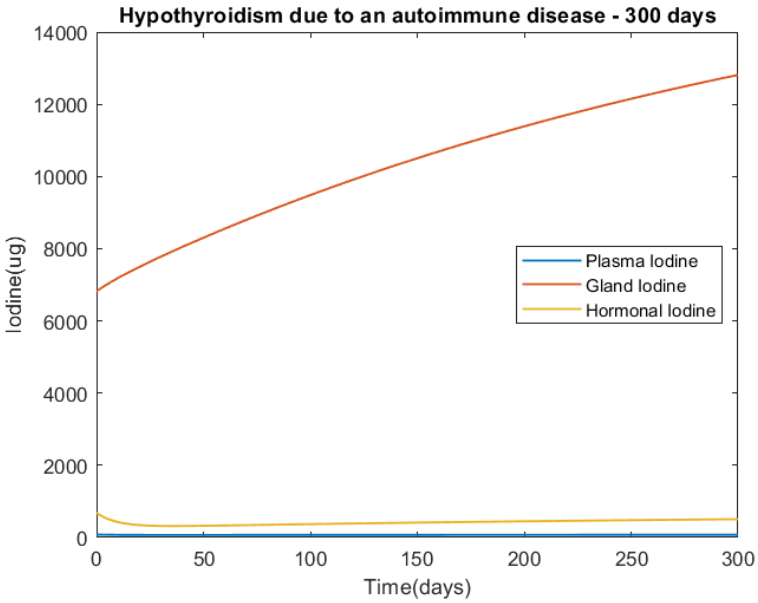


a). <u>Hypothyroidism due to autoimmune thyroid disease</u>

- Hypothyroidism is an endocrine disorder caused due to the prolonged deficiency of thyroid hormones.
- Autoimmune thyroid disease is a common cause of hypothyroidism.
- In that case, the immune system starts attacking the thyroid gland and when the thyroid is severely damaged, it won't be able to produce the required amount of thyroid hormones.
- If left untreated for a prolonged period, this might lead to hypothyroidism.

- One of the most common autoimmune disorders which causes hypothyroidism is Hashimoto's disease.
- In the Riggs' model for iodine metabolism, we can model the effect of hypothyroidism due to an autoimmune disease by decreasing the transfer rate parameter of the thyroid gland.
- Thus we should decrease the k_2 parameter.
- In the plots given below, in contrast to the default values used in the simulation, only k_2 is changed to 0.004 from 0.01.

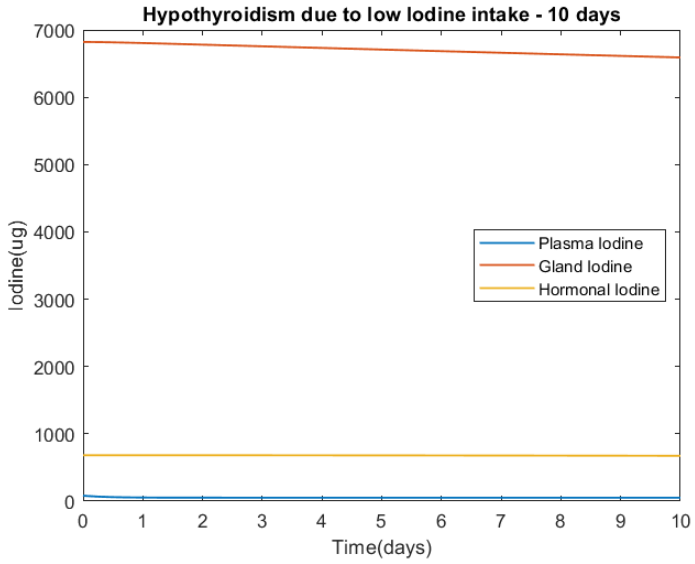


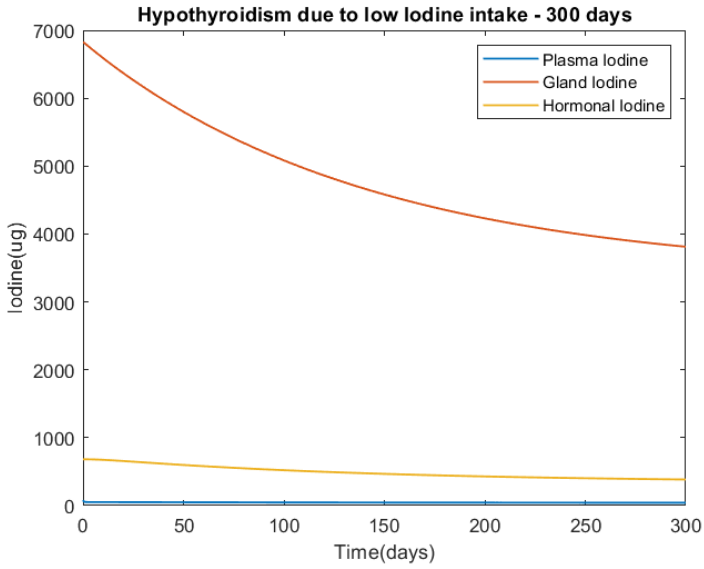


- As observed in the above diagrams, the gland iodine level increases over time but the hormonal and plasma iodine levels decline as the functions of the thyroid gland are hampered by the autoimmune disease.

b). Hypothyroidism due to low Iodine intake

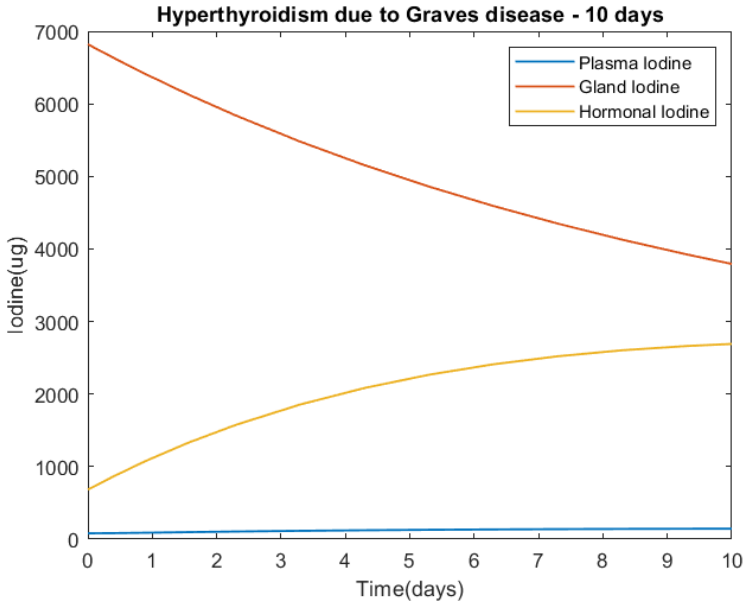
- Another cause for hypothyroidism is the inadequate consumption of Iodine.
- Iodine is the main raw material that is required to produce thyroid hormones.
- Thus, when Iodine is found in inadequate quantities in the circulation, less Iodine will be absorbed by the thyroid gland and therefore, the amount of thyroid hormones produced will be low.
- Over time, this might lead to hypothyroidism
- This scenario can be modelled using the Riggs' model by reducing the Iodine intake parameter ($B_1(t)$) while keeping the other parameters at the default values.
- In the following graphs, the $B_1(t)$ value used is 75ug/day.
- As observed in the graphs below, the gland iodine levels go down with time as less Iodine is found in the circulation.
- Moreover, as a result of the low quantities of Iodine found in the thyroid gland, there is a decline in the hormonal iodine as well.

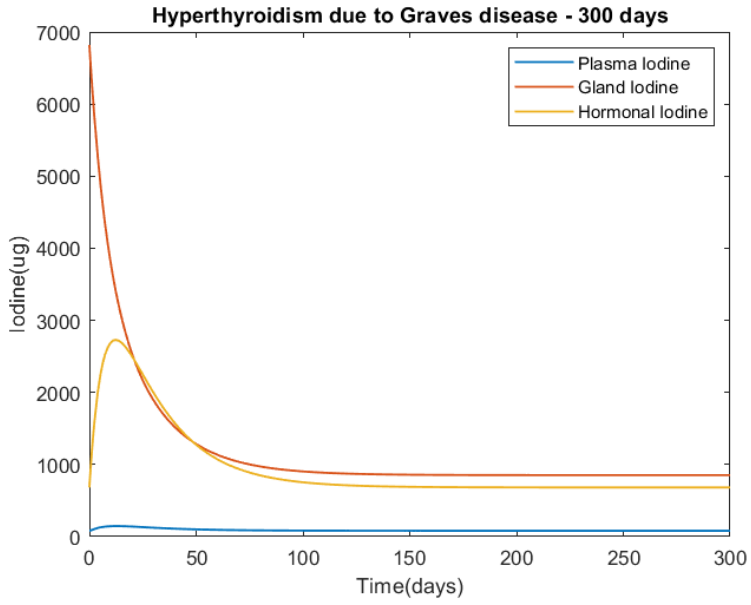




c). Hyperthyroidism due to Grave's disease

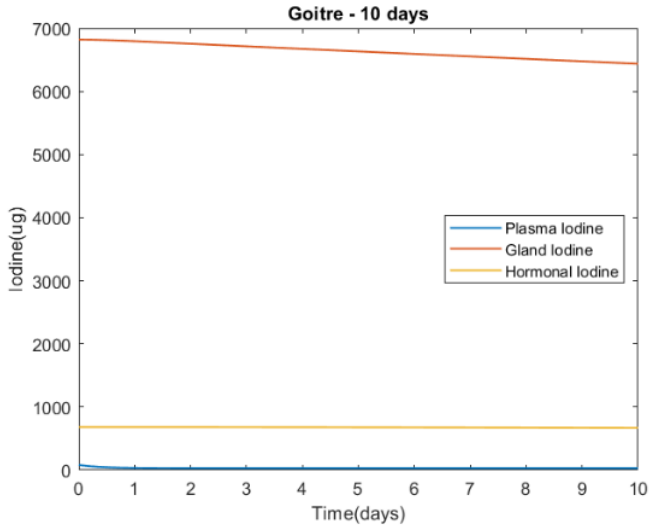
- Hyperthyroidism is a condition in which the body produces more thyroid hormones than the required amounts.
- As the thyroid hormones directly affect the metabolic rate, it is clear that excess of these hormones would increase the metabolic rate beyond the normal range.
- An extremely high state of metabolism is called a hypermetabolic state.
- A common cause for hyperthyroidism is the Grave's disease.
- Grave's disease is an autoimmune disease in which the immune system produces antibodies known as thyroid stimulating immunoglobulins.
- These immunoglobulins latch on to the thyroid cells which prompt the thyroid gland to produce excess thyroid hormones.
- This phenomenon can be modelled using the Riggs' Iodine model.
- In contrast to the default values, to model hyperthyroidism, a greater value should be used for the k_2 parameter.

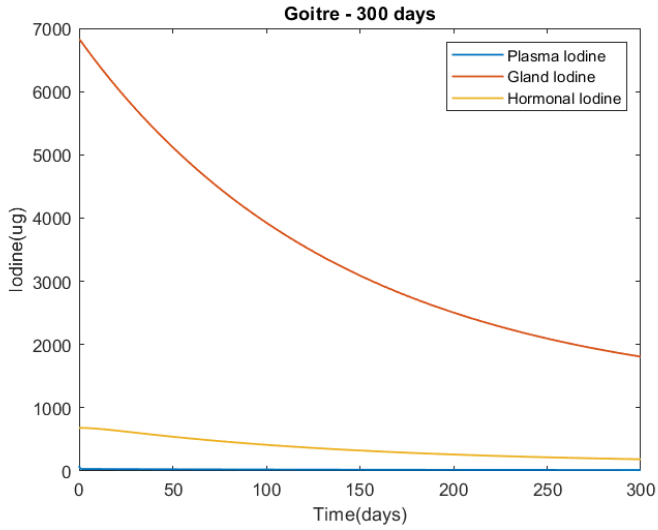




d). Goitre

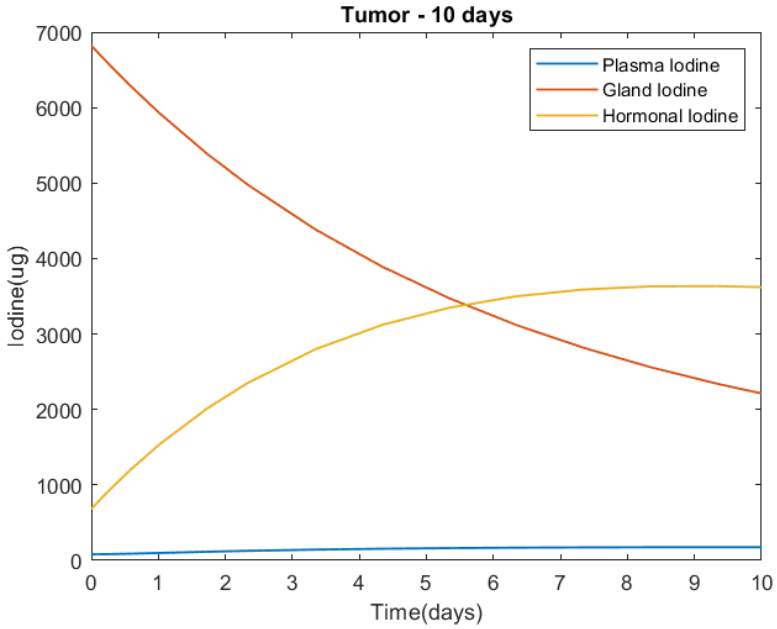
- The thyroid hormones; *Thyroxine(T4) and Triiodothyronine(T3)* are iodinated molecules of a key amino acid; *Tyrosine*. Hence, Iodine acts as an essential raw material for thyroid hormone synthesis.
- Dietary iodine is absorbed by the intestine which then enters the circulation.
- The negative feedback effect on '*Thyroid stimulating hormone(TSH)*' is reduced in severe iodine deficient environments or in cases of prolonged iodine deficiencies. As a compensatory mechanism, the *Hypothalamus* triggers an increased secretion of TSH from the *Pituitary gland*.
- As a consequence of increased TSH, thyroid follicular epithelial cells undergo hypertrophy and hyperplasia. In other words, the thyroid gland enlarges remarkably which is commonly known as '*goitre*'.
- This compensatory increase in thyroid mass or the enlargement of the thyroid gland occurs in order to overcome T3 and T4 deficiencies by extracting more iodine from the circulation.
- As Goitre is mainly caused due to the low Iodine intakes, we can model such cases using the Riggs' model by decreasing the $B_1(t)$ parameter.
- For the simulation purposes, the used $B_1(t)$ value is 25ug/day.

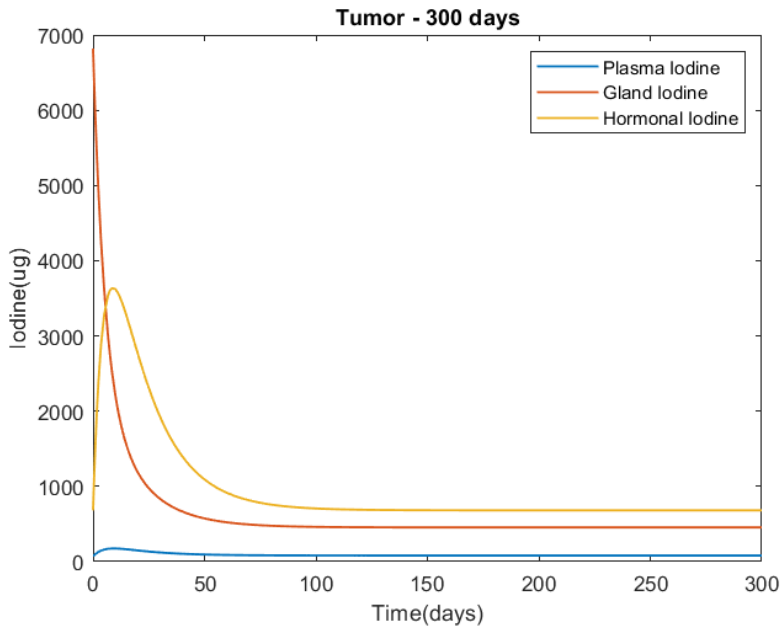




Tumor

- Thyroid tumors are lump like structures that are formed within the thyroid gland.
- Thyroid tumors can cause either hyperthyroidism or hypothyroidism.
- It has been found that Iodine deficiency too plays a role in causing tumors in the thyroid gland.
- Nevertheless, let's consider a case where severe hyperthyroidism is caused due to a tumor in the thyroid gland.
- In that case, the body will produce more and more thyroid hormones. Thus, to simulate such a case, let's increase the k_2 parameter.
- In the graphs shown below, the k_2 value used is 0.15.





PART 2

Question 01

The Simulink diagram below represents following equations (used to solve numerically in Part 1).

$$\frac{di}{dt} = -0.8i + 0.2g + B(t)$$

$$\frac{dg}{dt} = -5i - 2g + A(t)$$

The step input $A(t)$ is set at 1 g/kg/h for $t > 1$, $B(t)$ is presently set at 0 for all time. The slider gain is a quick way of altering the height of the step. Start the simulation and then stop it after a few hrs have elapsed. The plots should look similar to those in part 1.

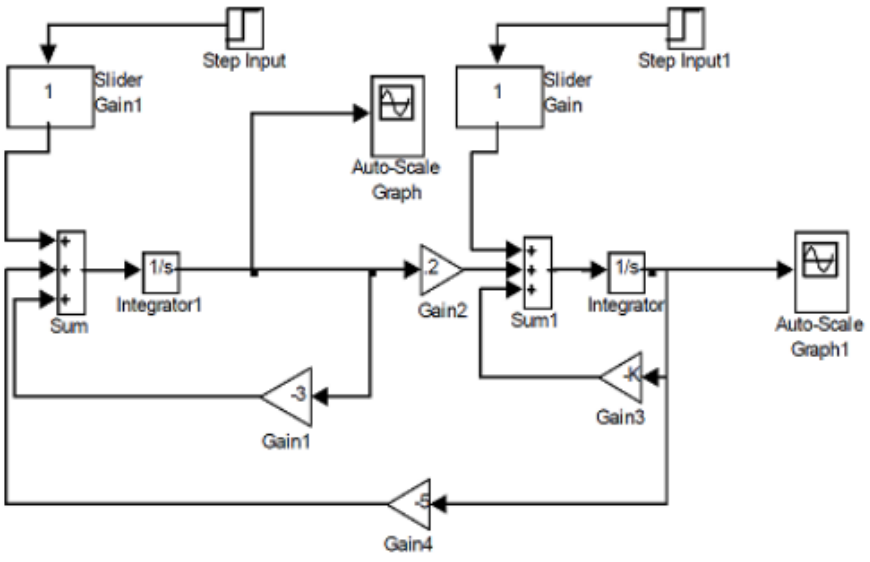
Now try:

$$\frac{di}{dt} = -0.63i + 0.13g \text{----------(01)}$$

$$\frac{dg}{dt} = -5i - 2.5g + A(t)$$

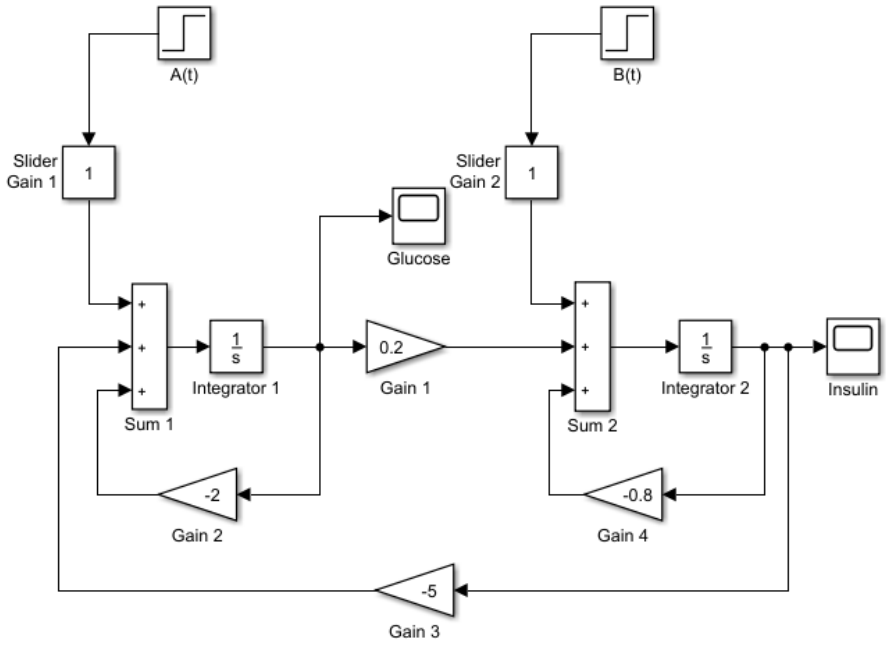
which correspond to an alternative set of coefficients, determined by a different procedure in the original article (Bolie, J Appl Physiol, 16:783). What difference does this make?

Now try $B(t)$ = 0.1 U/kg/h in a normal subject and a diabetic subject (change last term in equation (1) to $0.01g$).

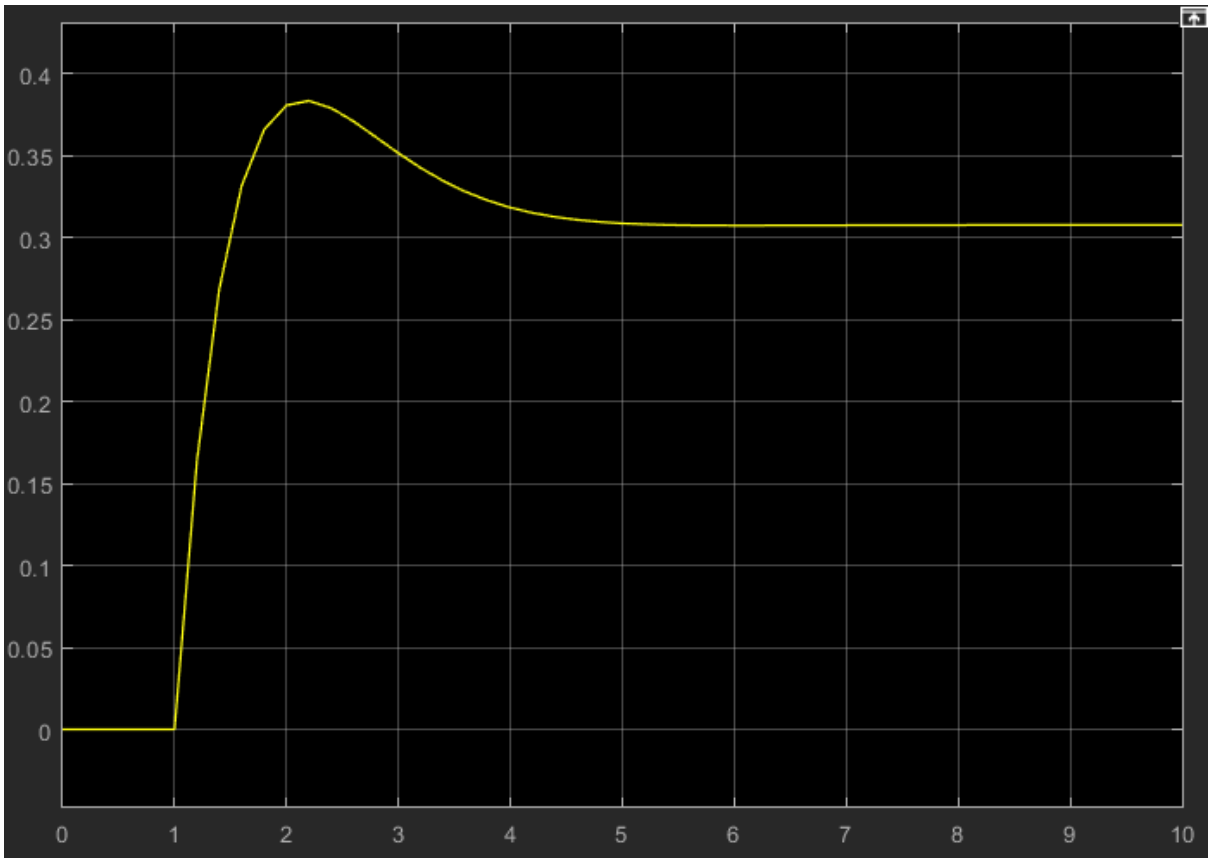


Solution 01

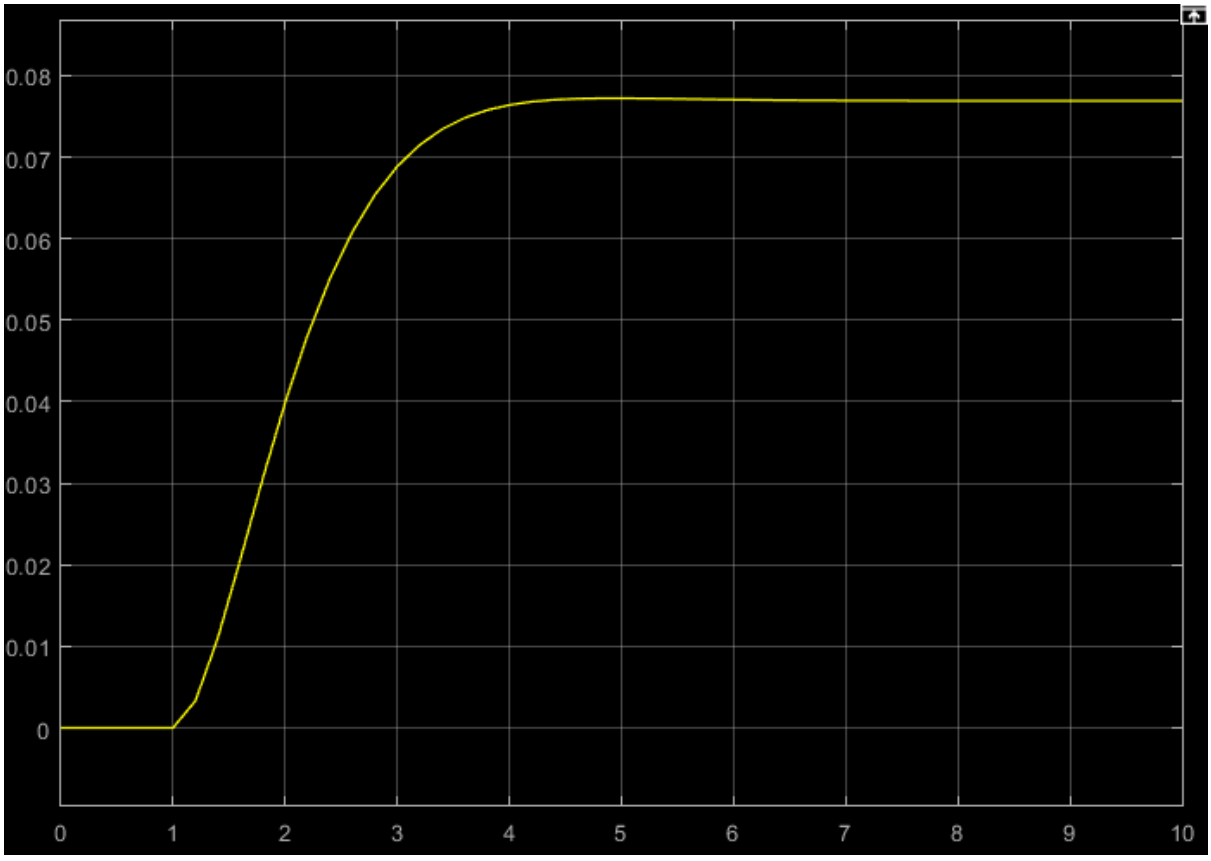
Simulation 01



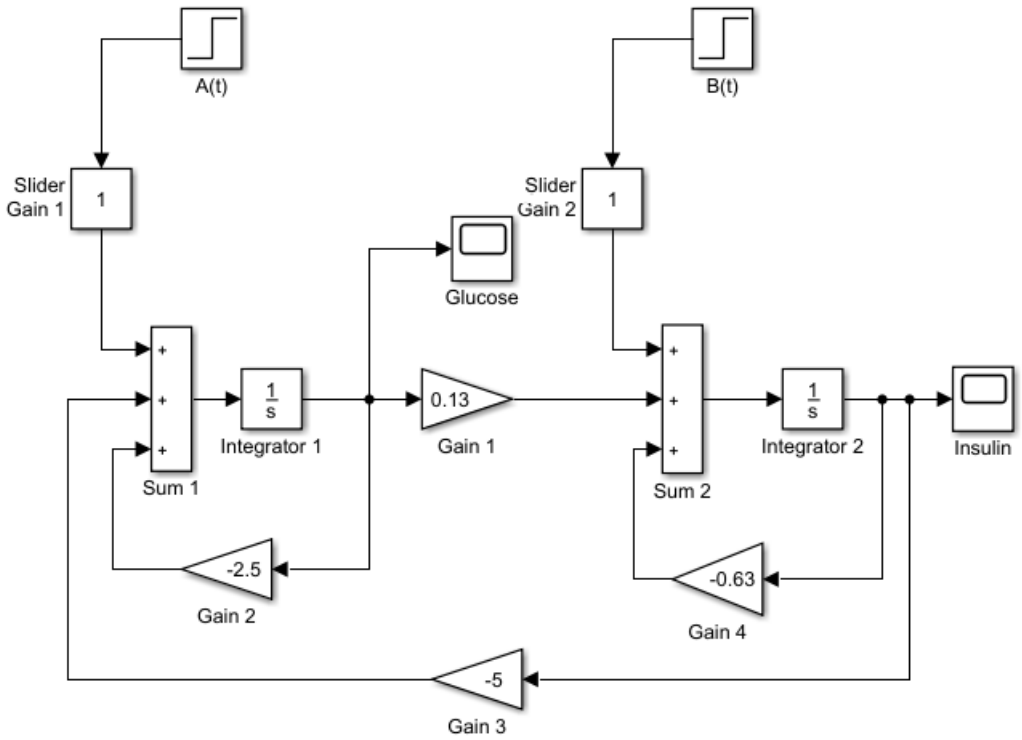
- Glucose



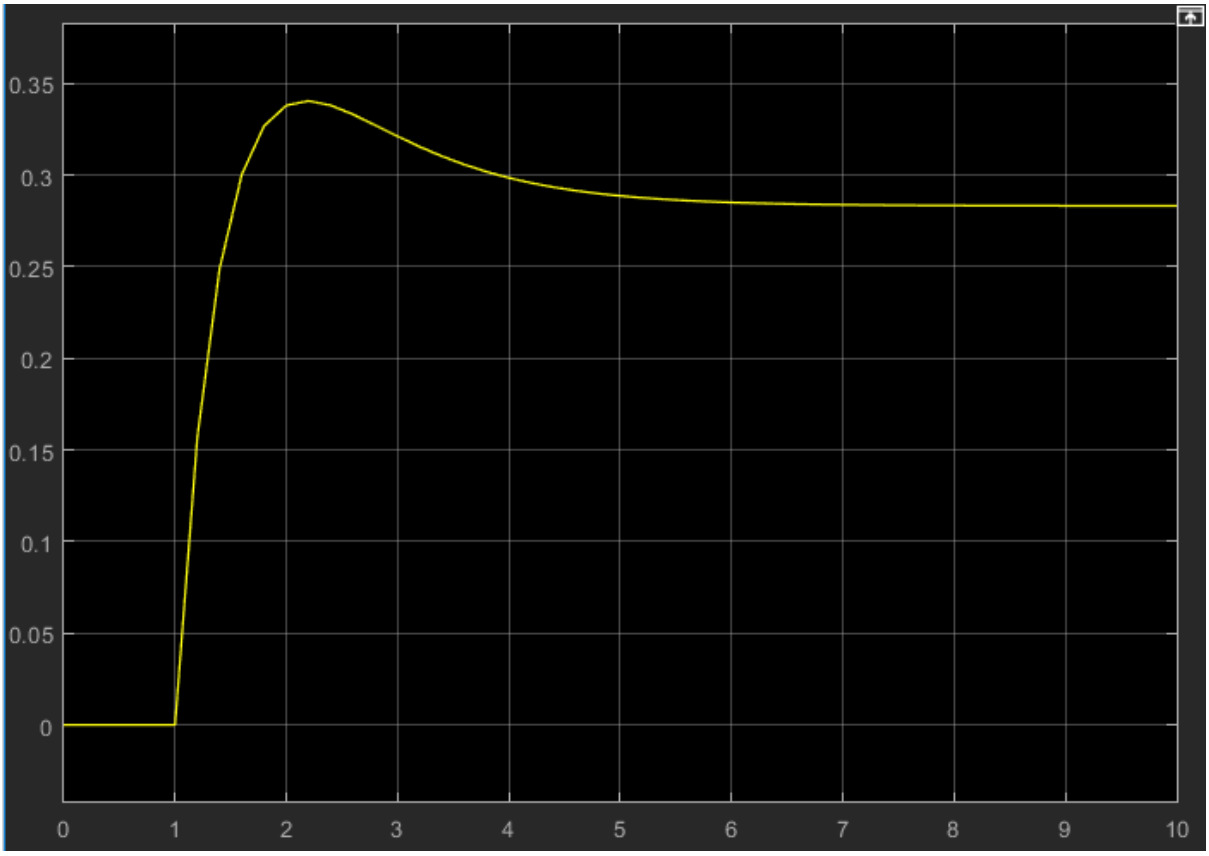
- Insulin



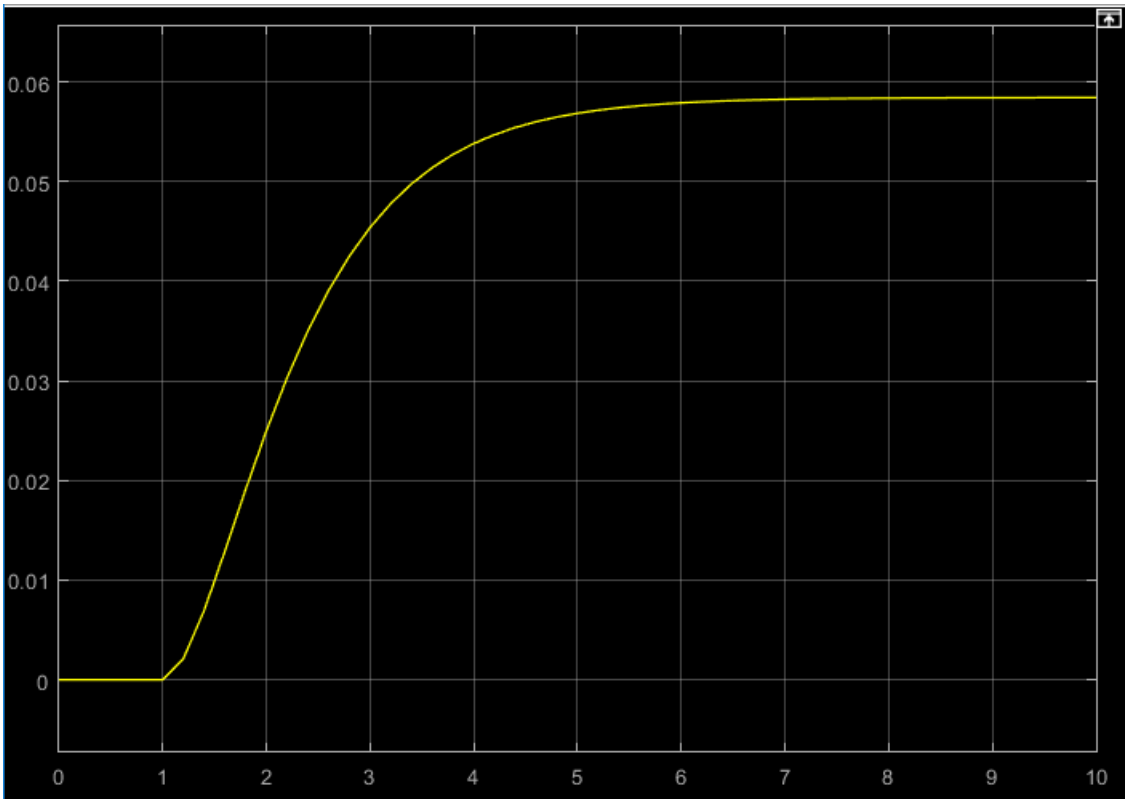
Simulation 02



- Glucose



- Insulin



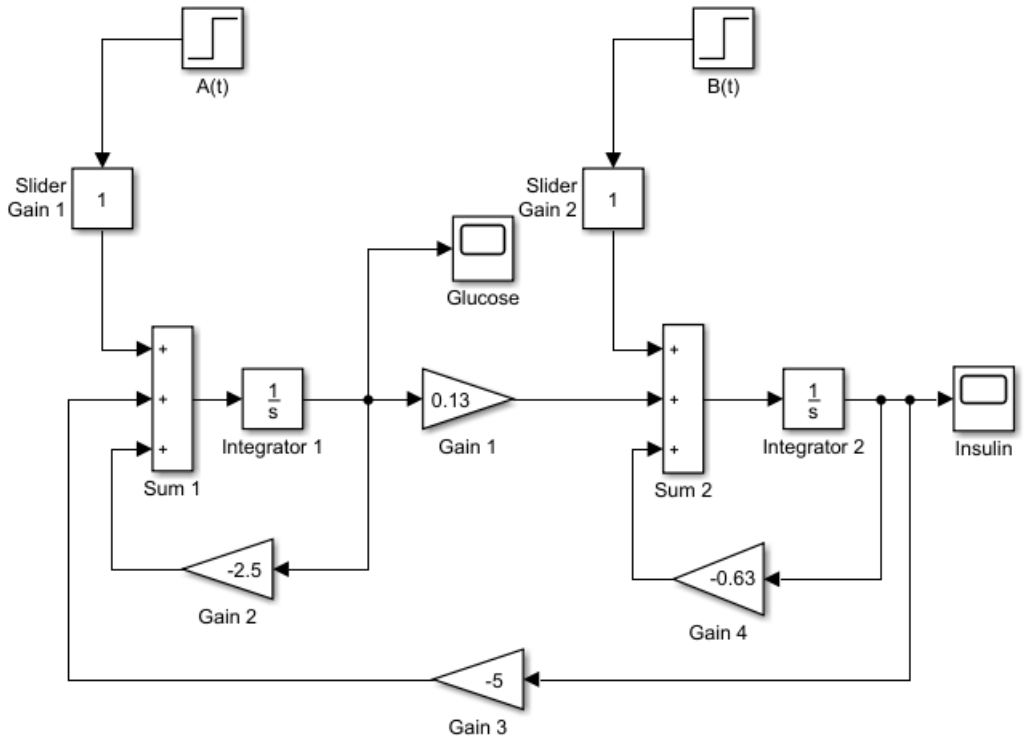
Comparison of simulation 01 and simulation 02

- In simulation 01, the insulin curve has plateaued at a level closer to 0.08 whereas in simulation 02, the curve has plateaued at a level closer to 0.06.
- Comparing the two glucose curves, we can observe that the peak as well as the steady state level of glucose is greater in simulation 01.
- Let's now briefly discuss the changes in the parameters that have caused the changes in curves in simulation 01 and simulation 02.
- Parameter that governs the basal removal of glucose in plasma to cells is increased from 2 to 2.5.
- Moreover, the rate at which insulin is broken down is decreased from 0.8 to 0.63
- Even though the glucose stimulated release of insulin factor is reduced, due to the aforementioned reasons, glucose is converted into glycogen at a faster rate in case II compared to case I.

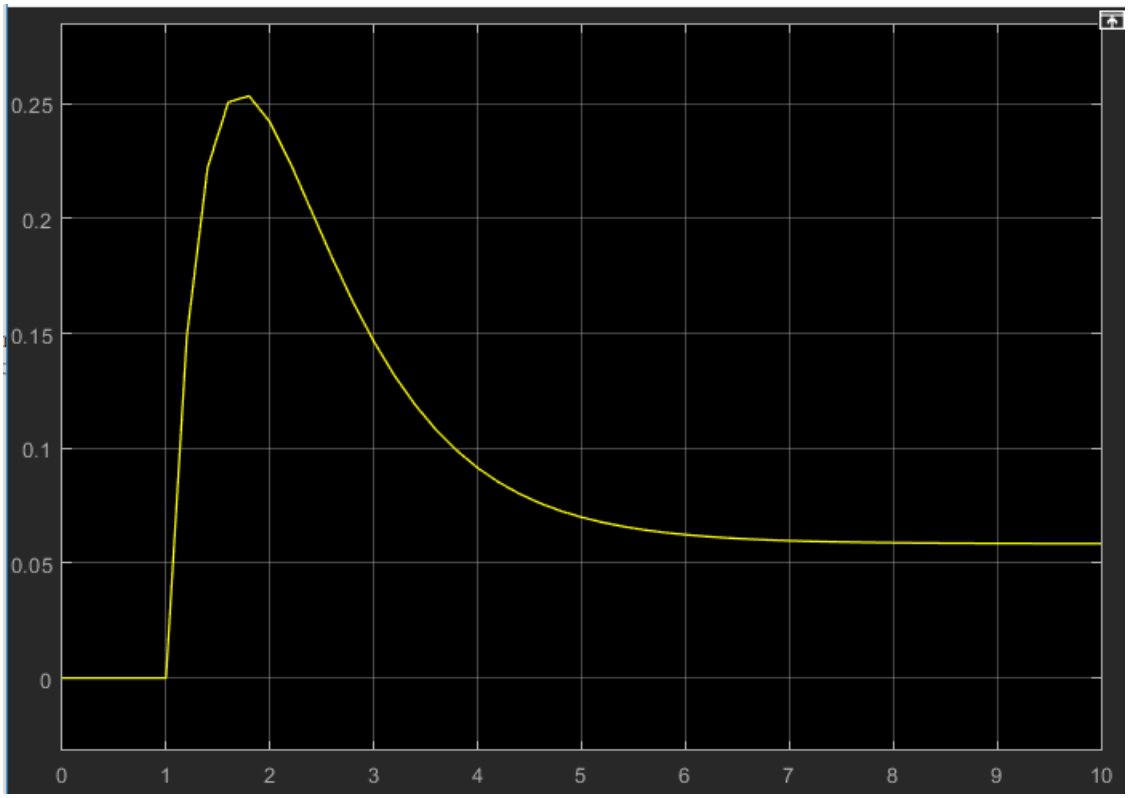
Simulation 03 – Normal Subject

$$\frac{di}{dt} = -0.63i + 0.13g + 0.1$$

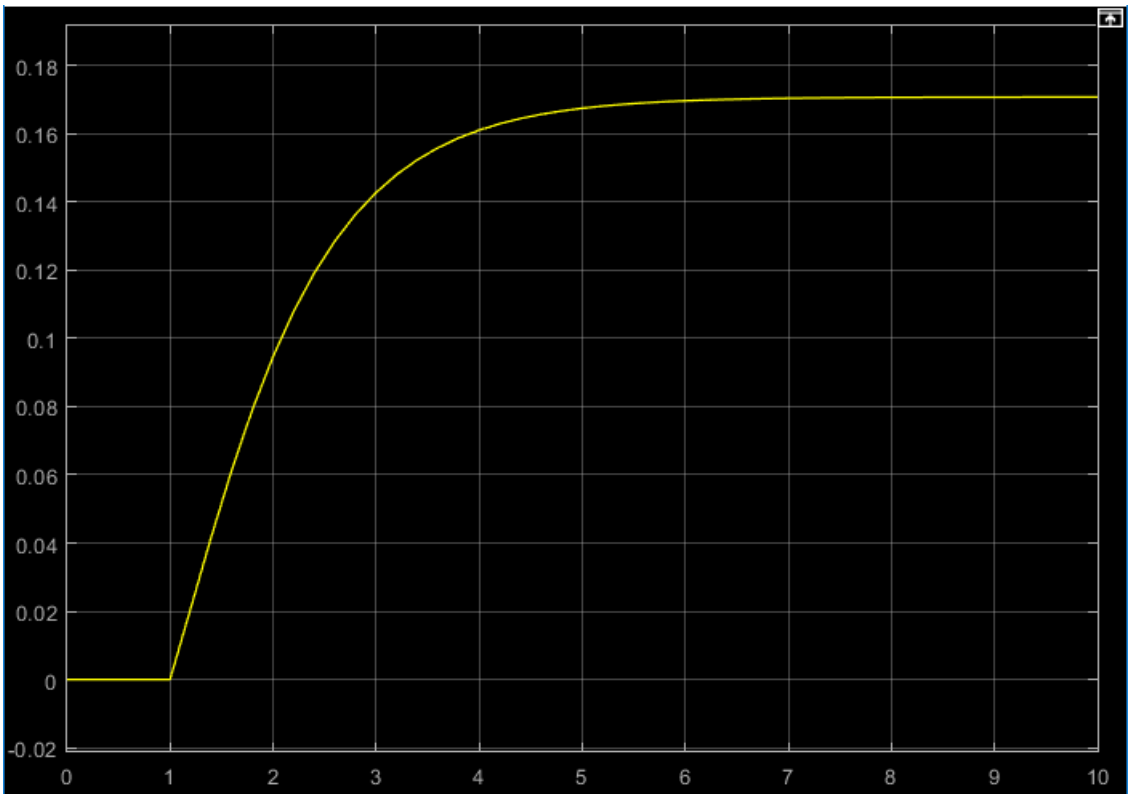
$$\frac{dg}{dt} = -5i - 2.5g + 1$$



- Glucose



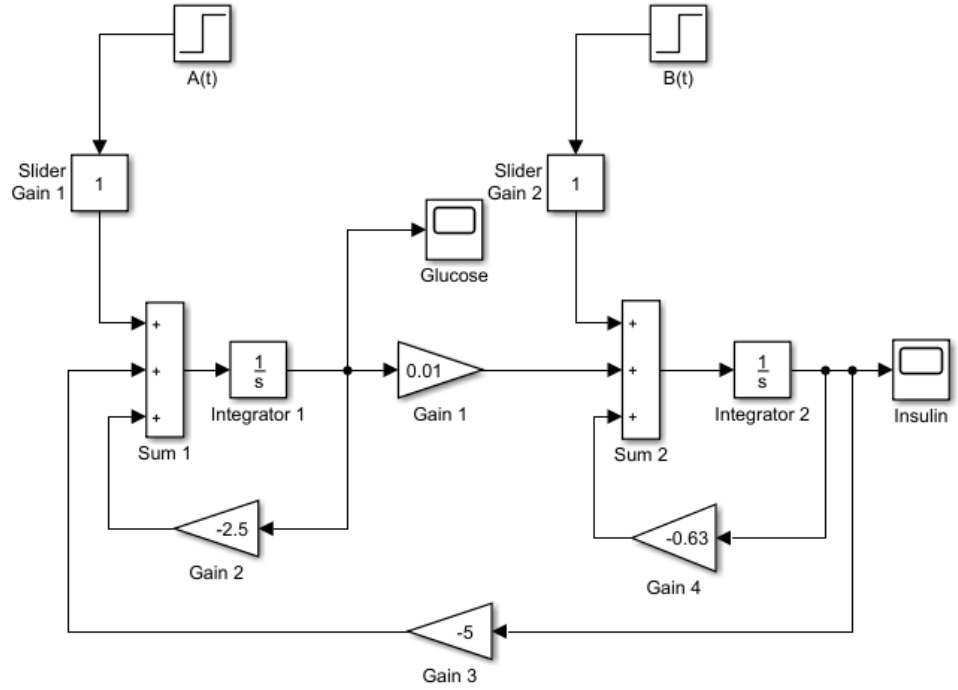
- Insulin



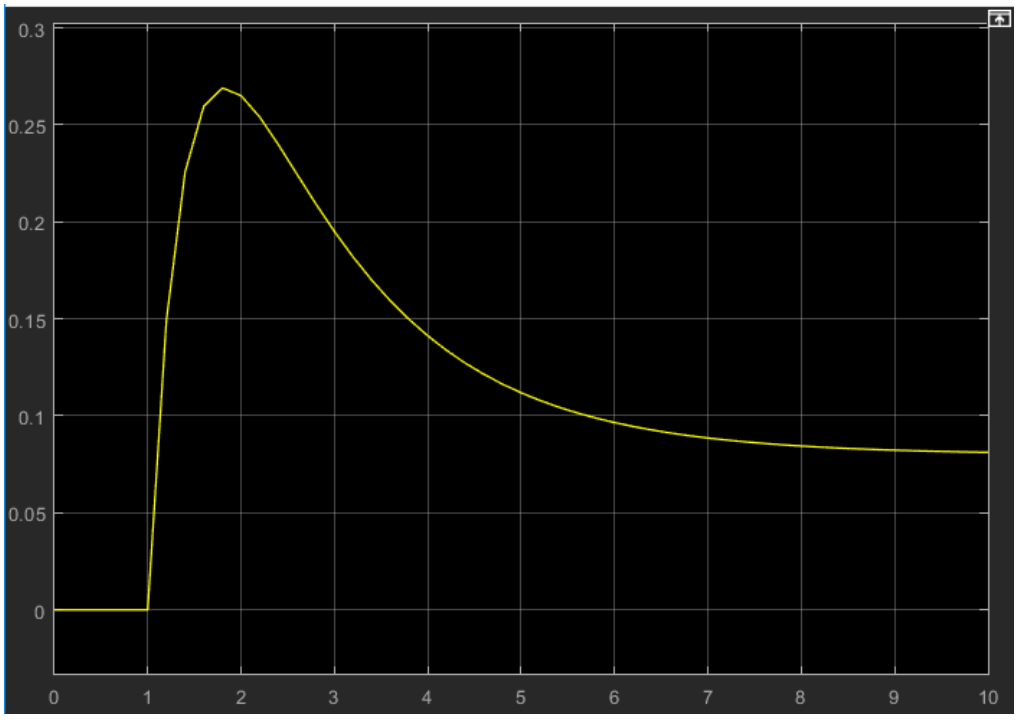
Simulation 04 – Diabetic Subject

$$\frac{di}{dt} = -0.63i + 0.01g + 0.1$$

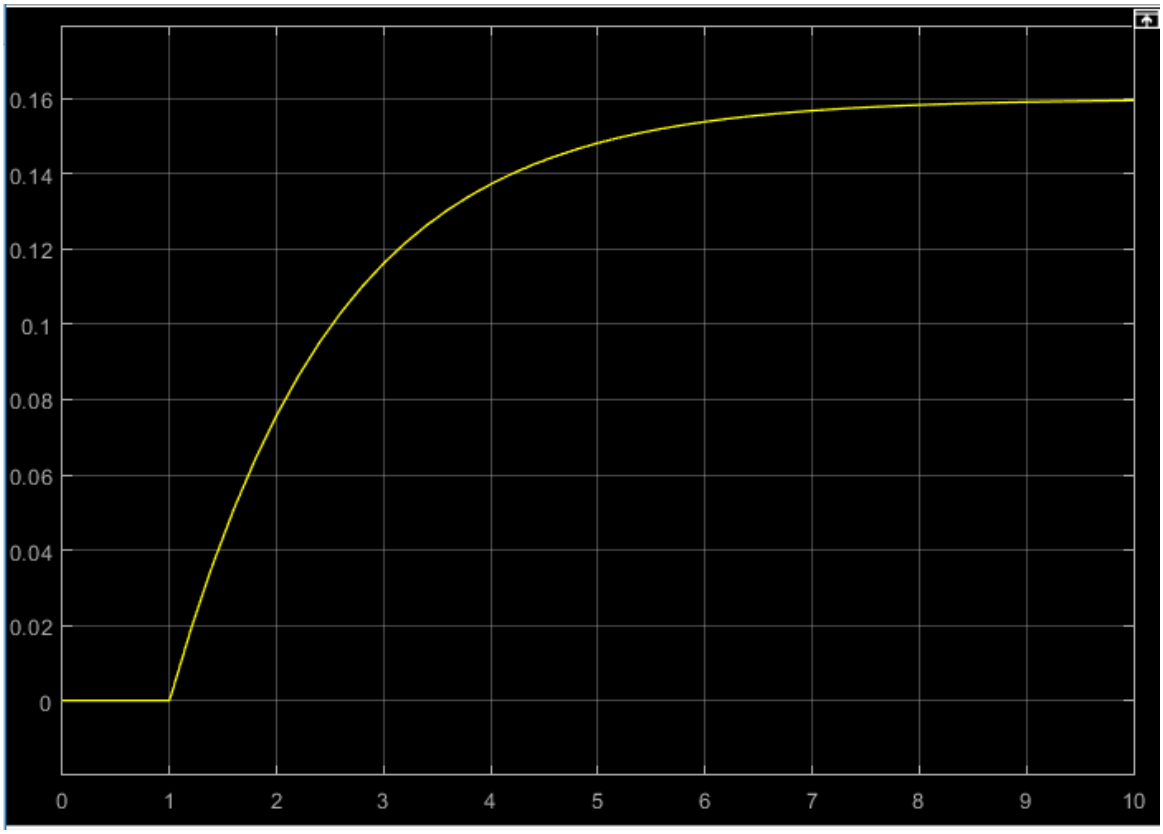
$$\frac{dg}{dt} = -5i - 2.5g + 1$$



- Glucose



- Insulin



Question 02

Using a similar Simulink model to simulate the Riggs iodine model in Part 1.

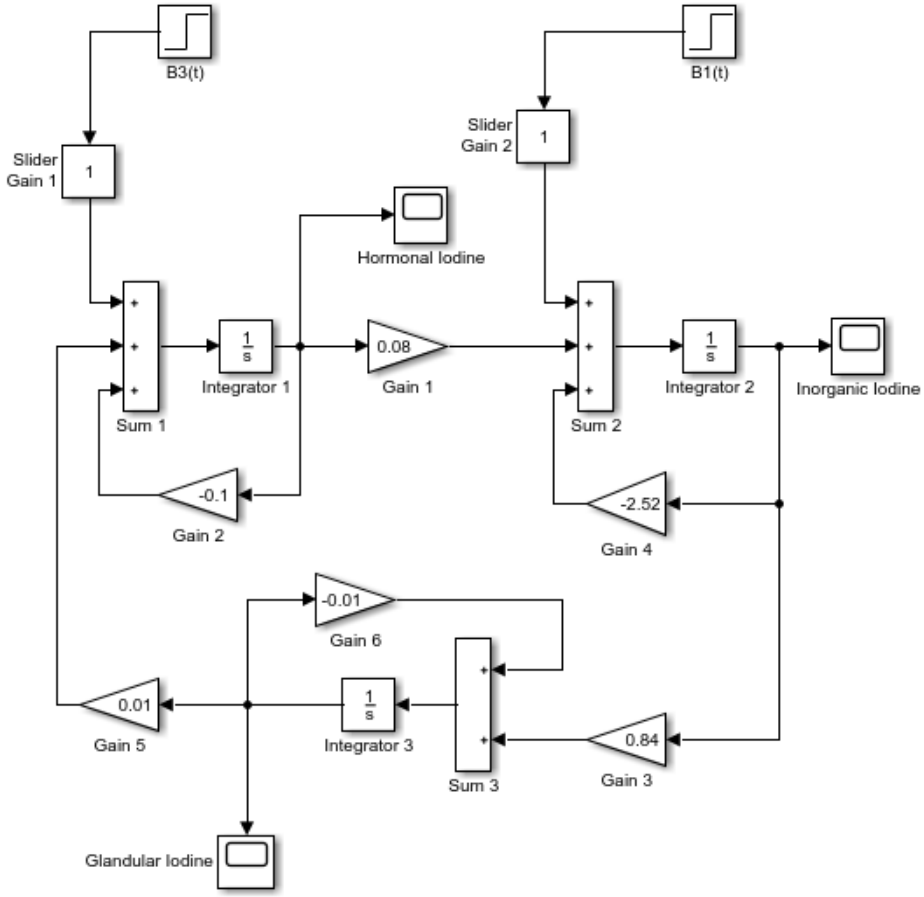
$$\frac{dI}{dt} = -2.52I + 0.08H + 15$$

$$\frac{dG}{dt} = 0.84I - 0.01G$$

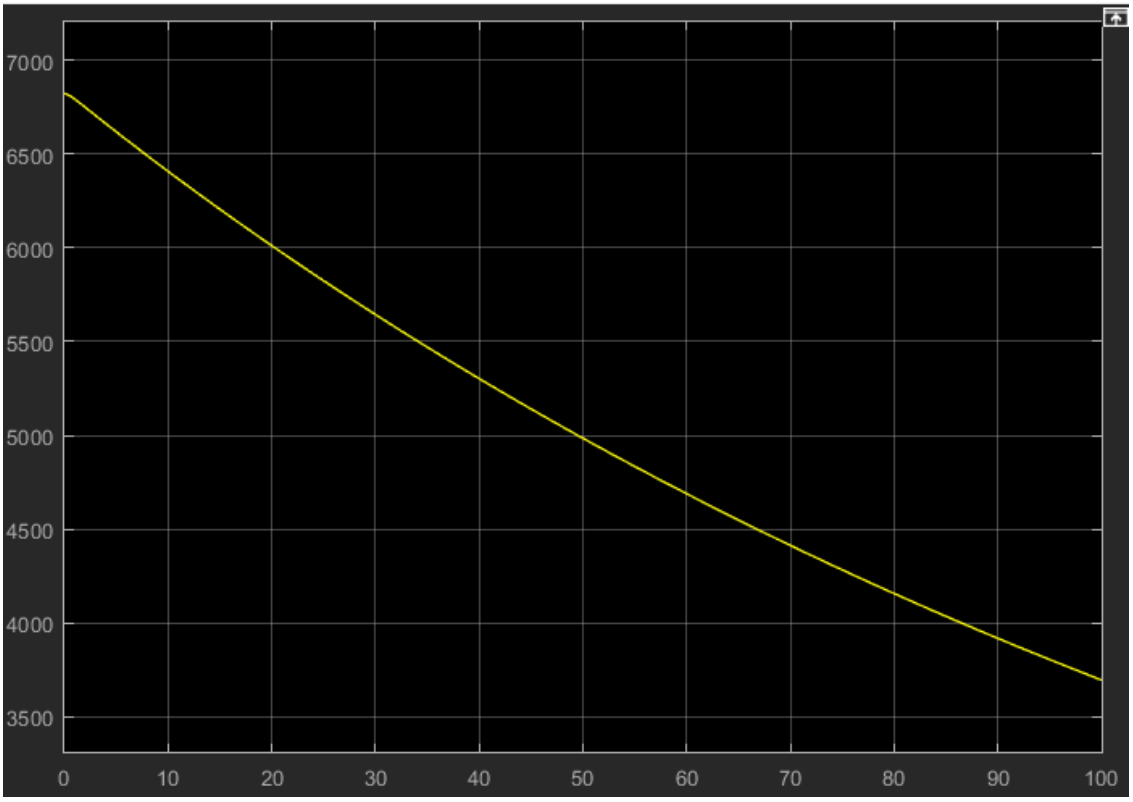
$$\frac{dH}{dt} = 0.01G - 0.1H$$

Solution 02

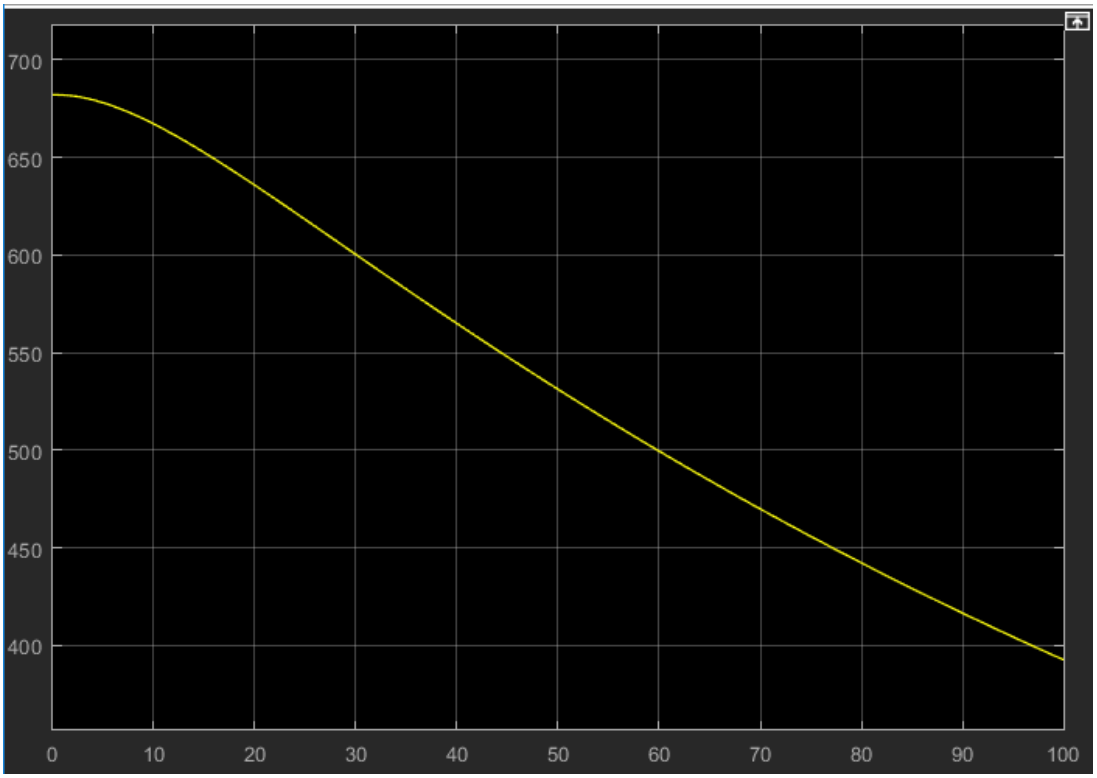
The Simulink design and the corresponding plots are in the following pages.



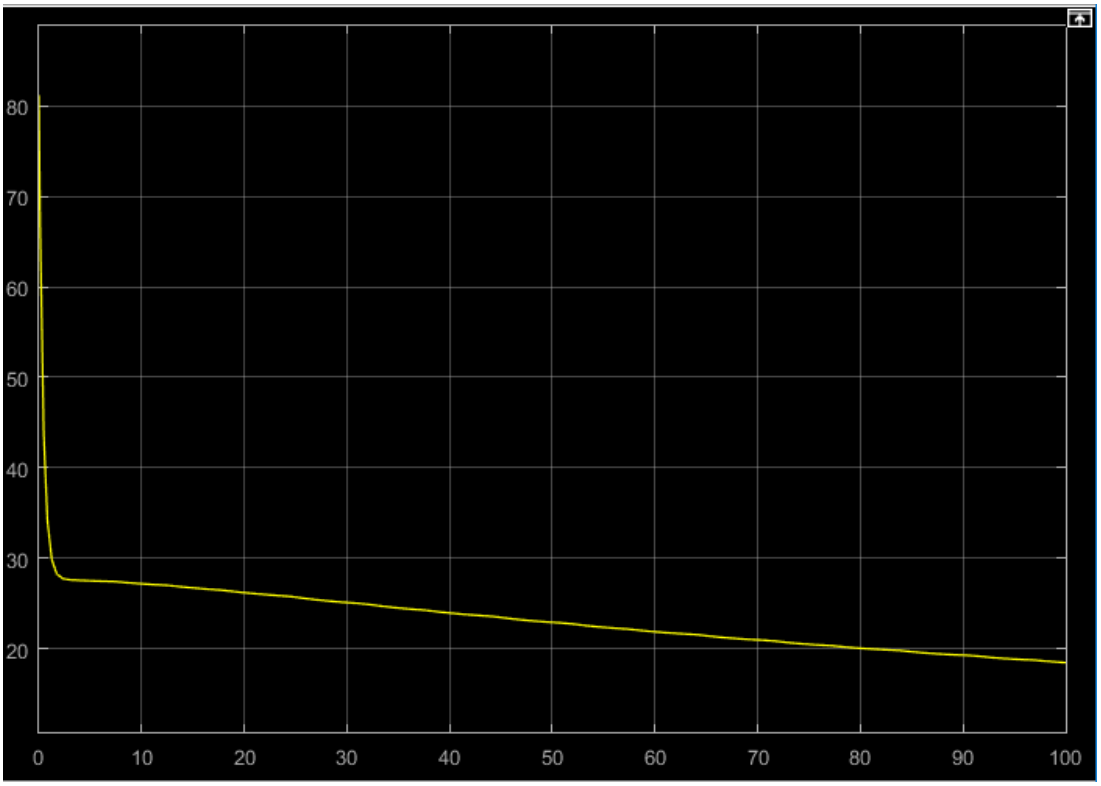
- Glandular Iodine



- Hormonal Iodine



- Inorganic Iodine



PART 3

Question 01

Derive the analytical solution for the Bolies' glucose $g(t)$, insulin $i(t)$ model (refer lecture notes). Answer should be explained in terms of the stability curve.

$$\frac{dg(t)}{dt} = -k_4 g(t) - k_6 i(t) + A(t) \quad where \quad A(t) = a.u(t)$$

$$\frac{di(t)}{dt} = -k_1 i(t) + k_3 g(t) + B(t) \quad where \quad B(t) = 0$$

Hint: to find *g(t),* solve $\frac{d^2g(t)}{dx^2} + (k_1 + k_4)\frac{dg(t)}{dt} + (k_1k_4 + k_3k_6)g = k_1.a + a.\frac{du(t)}{dt}$

Solution 01

- Let's consider the two base equations given in the question.

$$\frac{dg(t)}{dt} = -k_4 g(t) - k_6 i(t) + a.u(t) \quad ----------(01)$$

$$\frac{di(t)}{dt} = -k_1 i(t) + k_3 g(t) \quad ----------(02)$$

- When we differentiate equation (01) and then substitute equation (02) in the result, we get,

$$\frac{d^2g(t)}{dt^2} + (k_1 + k_4)\frac{dg(t)}{dt} + (k_1k_4 + k_3k_6)g(t) = k_1.a + a.\frac{du(t)}{dt}$$

- Note than for t ≠ 0,

$$\frac{du(t)}{dt} = 0$$

- Thus, we can reduce the above second order differential equation to,

$$\frac{d^2g(t)}{dt^2} + (k_1 + k_4)\frac{dg(t)}{dt} + (k_1k_4 + k_3k_6)g(t) = k_1.a$$

- Now, let's substitute for *k_1, k_3, k_4, k_6* and *a.* (The values are given in the lecture notes.)
- $k_1 = 0.8\ h^{-1}$, $k_3 = 0.2$ IU/h/g, $k_4 = 2\ h^{-1}$, $k_6 = 5$ g/h/IU and a = 1 g/l/h
- Then,

$$a = 1$$
$$k_1 = 0.8$$
$$(k_1 + k_4) = 2.8$$
$$(k_1k_4 + k_3k_6) = 2.6$$

- The resulting second order differential equation is as follows.

$$\frac{d^2g}{dt^2} + 2.8\frac{dg}{dt} + 2.6g = 0.8$$

- We can say that,

$$g(t) = g_c(t) + g_p(t)$$

where $g_c(t)$ *is the complementary solution and* $g_p(t)$ *is the particular solution.*

- The boundary conditions for this problem are as follows.

$$g(0) = 0$$

$$g'(0) = 1$$

- Using these conditions, we can solve the above differential equation using MATLAB.

```
syms g(t)

Dg = diff(g,t);

ode = diff(g,t,2) == -2.8*diff(g,t) -2.6*g + 0.8;
cond1 = g(0) ==  0;
cond2 = Dg(0) == 1;
conds = [cond1 cond2];
gSol(t) = dsolve(ode, conds);
gSol = simplify(gSol)
```

- The calculated solution is,

```
>> Finding_gt_it
gSol(t) =
(37*sin((4*t)/5)*exp(-(7*t)/5))/52 - (4*cos((4*t)/5)*exp(-(7*t)/5))/13 + 4/13
```

- Therefore,

$$g(t) = -\frac{4}{13}e^{-1.4t}\cos 0.8t + \frac{37}{52}e^{-1.4t}\sin 0.8t + \frac{4}{13}$$

- From equation 01, we know that,

$$\frac{dg(t)}{dt} = -2g(t) - 5i(t) + 1 \quad for\ t > 0$$

- Then,

$$i(t) = -\frac{1}{5}\frac{dg(t)}{dt} - \frac{2}{5}g(t) + \frac{1}{5} \quad for\ t > 0$$

- Again we can use MATLAB to simplify the above expression

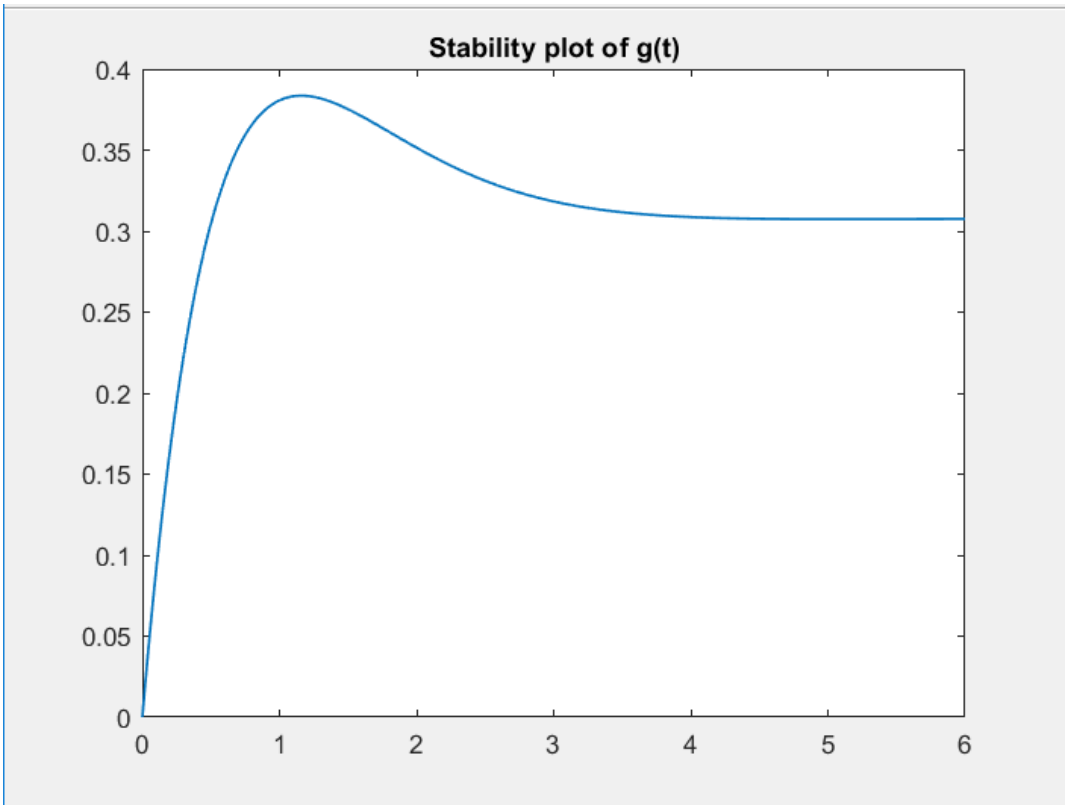
```
%%
% Finding i(t)
simplify(-0.2*diff(gSol,t) -0.4*gSol + 0.2)
```

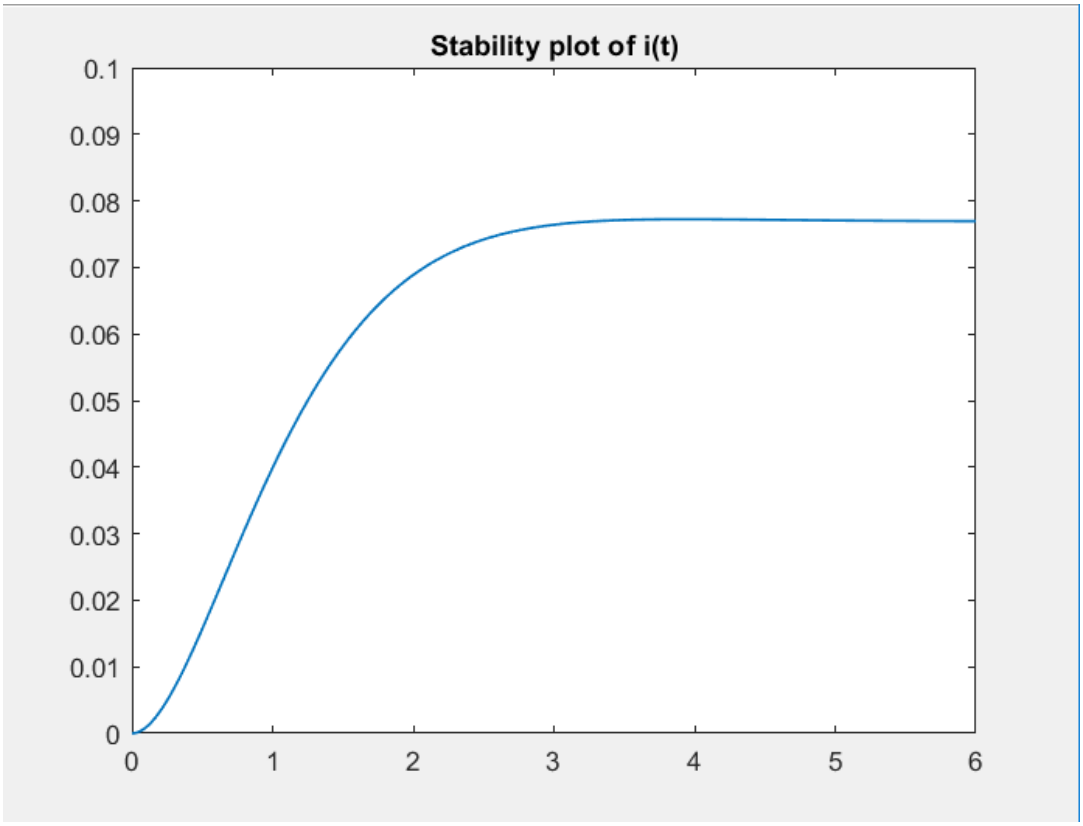
```
1/13 - (7*sin((4*t)/5)*exp(-(7*t)/5))/52 - (cos((4*t)/5)*exp(-(7*t)/5))/13
```

- Therefore,

$$i(t) = -\frac{1}{13}e^{-1.4t}\cos 0.8t - \frac{7}{52}e^{-1.4t}\sin 0.8t + \frac{1}{13}$$

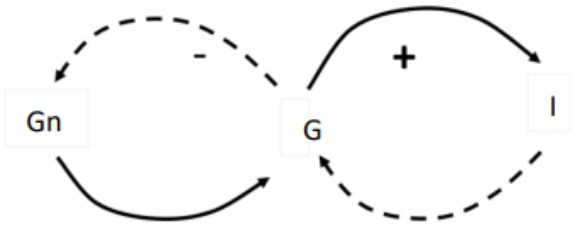
- Using the above equations, we can plot the stability curves of g(t) and i(t) for the Bolies' plasma glucose model.
- Note that the graphs shown below are quite similar to what we obtained in the previous parts of this assignment.





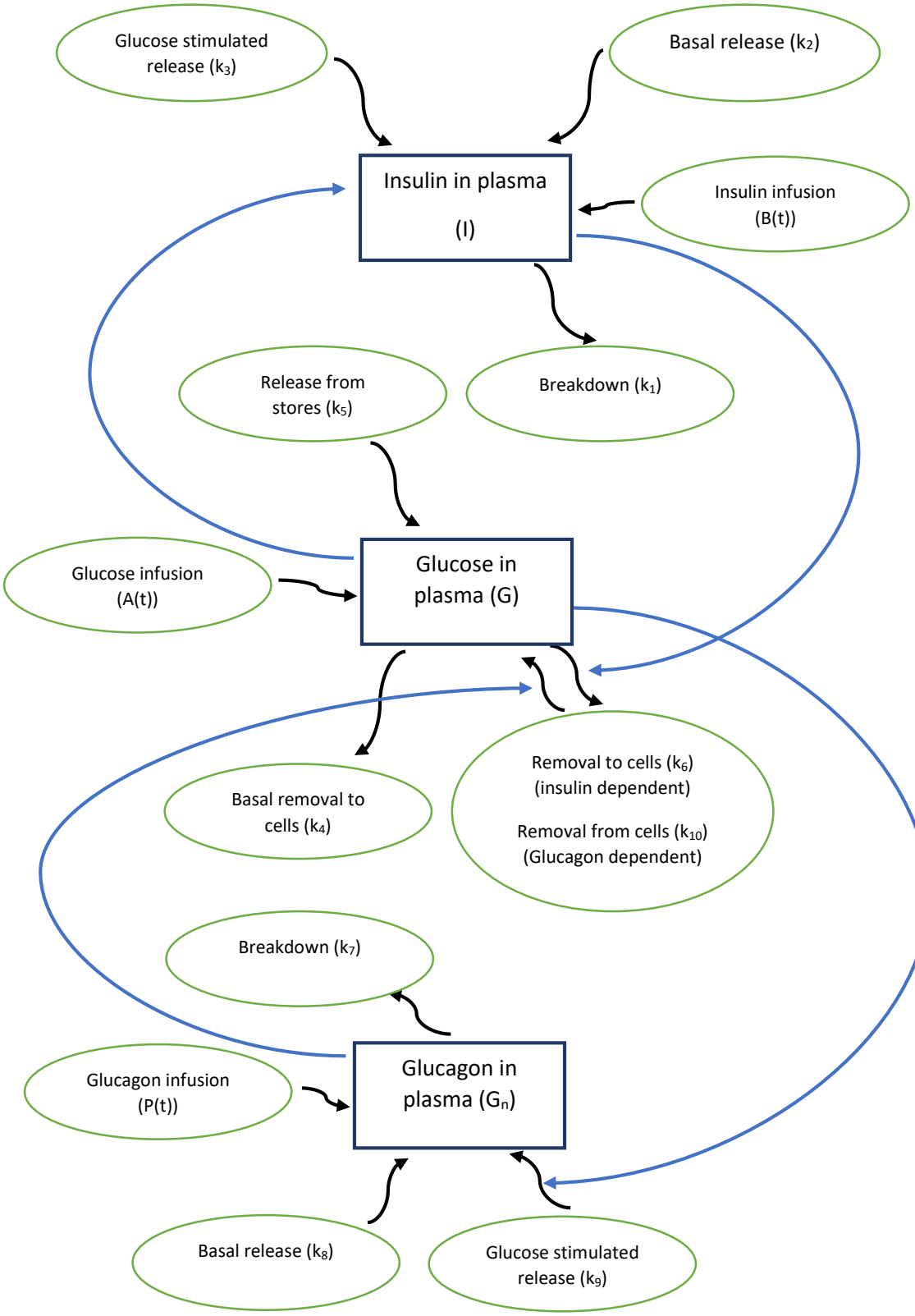
Question 02

Bolies' model considers only the reduction of plasma glucose levels with insulin. Expand this model by including the effects of glucagon which helps to increase the plasma glucose levels.



Solution 02

- Insulin and Glucagon are two complementary hormones produced by the pancreas.
- Insulin which is released by the beta cells of the pancreatic islets convert glucose into glycogen and store them in the liver and other body tissues when the blood glucose levels are high.
- Glucagon on the other hand, does the opposite.
- That is, when the blood glucose level is low or when the body needs extra energy (i.e. exercise), the alpha cells in the pancreatic islets release glucagon which converts glycogen in the liver and other body tissues, into glucose and then thus produced glucose is released to the bloodstream.
- The proposed compartmental model is given below.


Glucose stimulated release (k_3)
Basal release (k_2)
Insulin in plasma (I)
Insulin infusion (B(t))
Release from stores (k_5)
Breakdown (k_1)
Glucose infusion (A(t))
Glucose in plasma (G)
Basal removal to cells (k_4)
Removal to cells (k_6) (insulin dependent)
Removal from cells (k_{10}) (Glucagon dependent)
Breakdown (k_7)
Glucagon infusion (P(t))
Glucagon in plasma (G_n)
Basal release (k_8)
Glucose stimulated release (k_9)

- Let's apply mass conservation law and derive equations similar to the previous model.

$$\frac{dG(t)}{dt} = k_5 - k_4 G(t) - k_6 I(t) + k_{10} G_n(t) + A(t)$$

$$\frac{dI(t)}{dt} = k_2 - k_1 I(t) + k_3 G(t) + B(t)$$

$$\frac{dG_n(t)}{dt} = k_8 + k_9 G(t) - k_7 G_n(t) + P(t)$$

- Considering the equilibrium state, we can say that,

$$\frac{dG(t)}{dt} = \frac{dI(t)}{dt} = \frac{dG_n(t)}{dt} = 0$$

- Then,

$$k_5 = k_4 G_0 + k_6 I_0 - k_{10} G_{n0}$$

$$k_2 = -k_3 G_0 + k_1 I_0$$

$$k_8 = k_7 G_{n0} - k_9 G_0$$

- Let's do the following substitution

$$i = I - I_0$$

$$g = G - G_0$$

$$g_n = G - G_{n0}$$

- Moreover, assume that

$$A(t) = a.u(t)$$

$$B(t) = 0$$

$$P(t) = 0$$

- Thus, the system of equations for this modified model would be,

$$\frac{dg(t)}{dt} = -k_4 g(t) - k_6 i(t) + k_{10} g_n(t) + a.u(t)$$

$$\frac{di(t)}{dt} = -k_1 i(t) + k_3 g(t)$$

$$\frac{dg_n(t)}{dt} = k_9 g(t) - k_7 g_n(t)$$

- Note that,

$$i(0) = I_0 - I_0 = 0$$

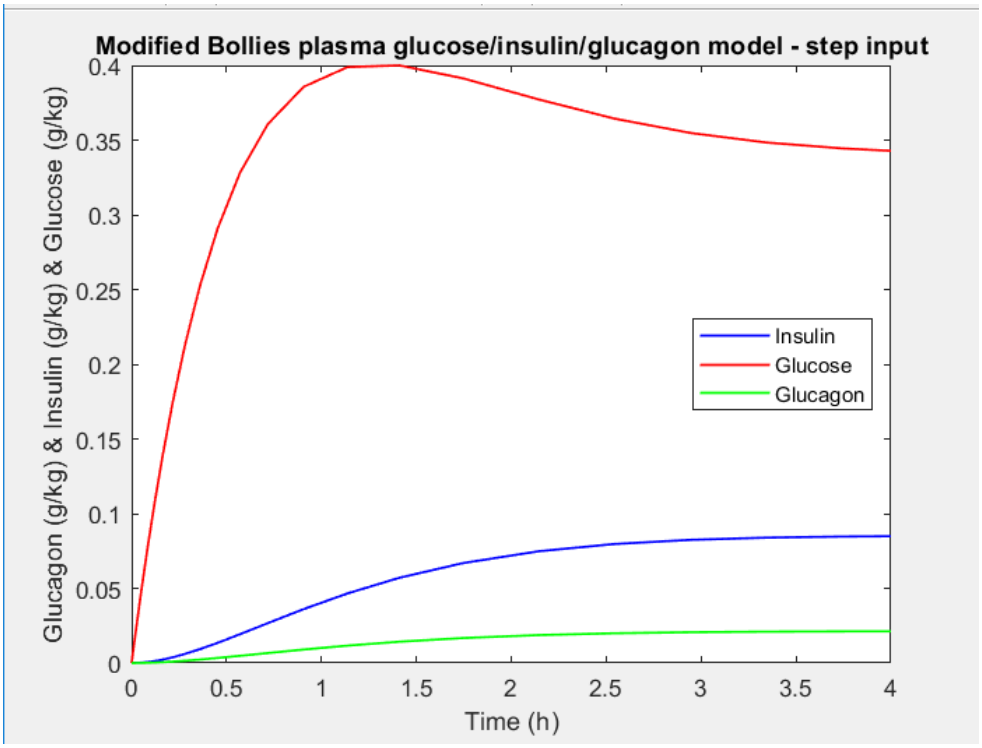
$$g(0) = G_0 - G_0 = 0$$

$$g_n(0) = G_{n0} - G_{n0} = 0$$

- For calculation purposes, let's assume that k and a values in this modified model are equal to those in the simple Bolies' model.
- Matrix representation of the set of equation is,

$$\begin{pmatrix} \frac{di(t)}{dt} \\ \frac{dg(t)}{dt} \\ \frac{dg_n(t)}{dt} \end{pmatrix} = \begin{pmatrix} -k_1 & k_3 & 0 \\ -k_6 & -k_4 & k_{10} \\ 0 & k_9 & -k_7 \end{pmatrix} \begin{pmatrix} i(t) \\ g(t) \\ g_n(t) \end{pmatrix} + \begin{pmatrix} 0 \\ a.u(t) \\ 0 \end{pmatrix}$$

- Since k_7, k_8, k_9 and k_{10} are undefined, let's pick some arbitrary values.
- Thus, the results obtained via the above model are shown in the graph below.



- When the blood glucose level is increased suddenly, there is an increase in the insulin level.
- The glucagon level of blood has remained more or less the same.
- Compared to the time at which the glucose level reaches its peak, the insulin level reaches its peak stage after a short delay.
- This small delay can be thought of as the time taken by the pancreatic islets to detect a change in the glucose level.
- The glucagon level as well as the insulin level have plateaued almost simultaneously.
- As there is more insulin in the circulation, the glucose level will drop gradually.
- This can be seen clearly, in the above graph.
- Furthermore, we can see that the curves obtained through this modified Bolies model are similar to the curves we obtained in part 1.

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