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Dynamic Systems Laboratory 3

A. Derive Model Equations

A.1. Injection of Evans Blue – Prediction of *E(t)*

A.1.1. Define system to be modeled

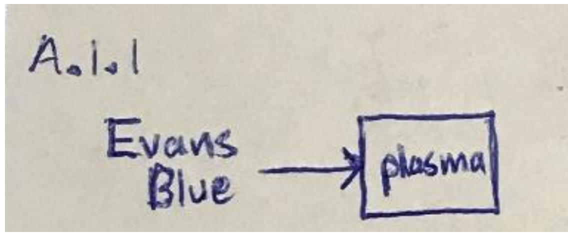

Figure 1: Schematic Diagram of System for Evans Blue

A.1.2. Define input-output

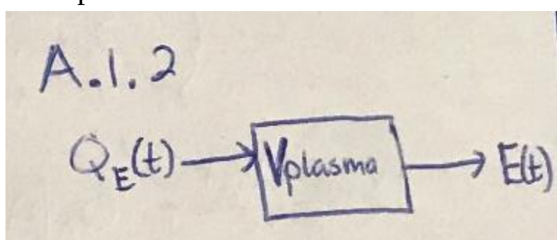

Figure 2: Diagram of Input-Output Relationship for Evans Blue

A.1.3. Derive model equation

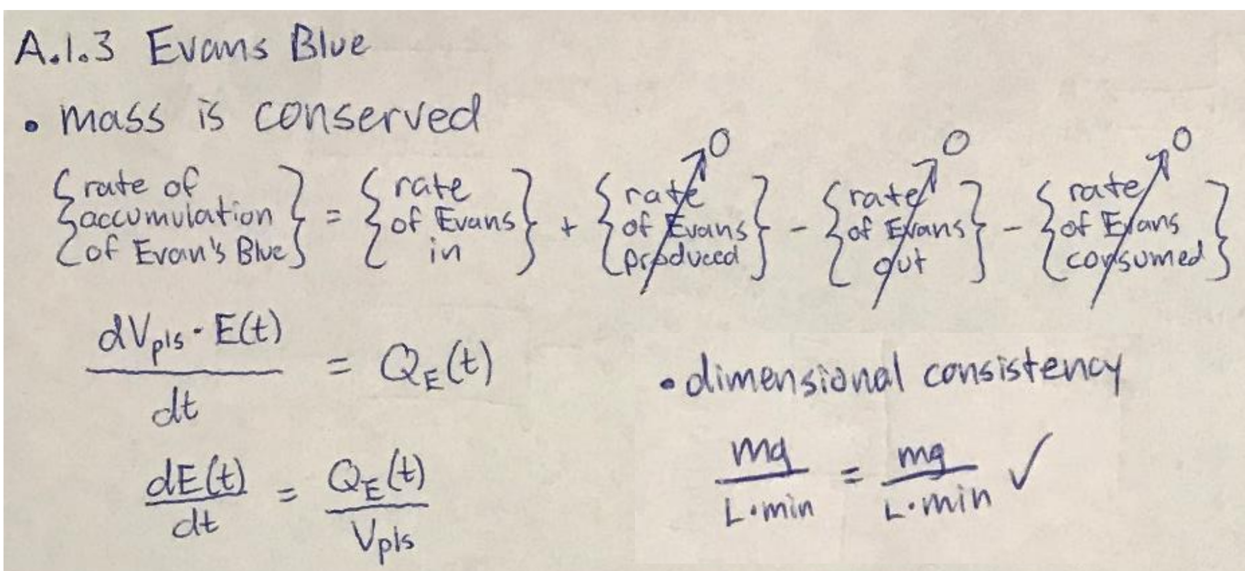

Figure 3: Derivation of Equation for Evans Blue

A.2. Injection of Inulin – Prediction of *I(t)*

A.2.1. Define system to be modeled

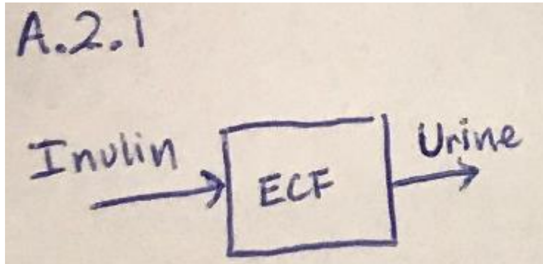

Figure 4: Schematic Diagram of System for Inulin

A.2.2. Define input-output

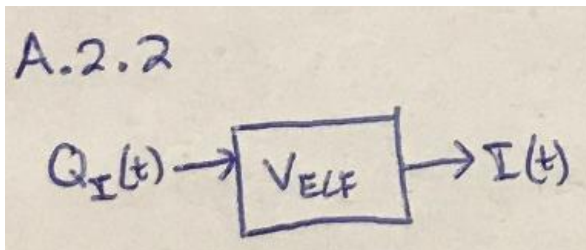

Figure 5: Diagram of Input-Output Relationship for Inulin

A.2.3. Derive model equation

A.2.3 Inulin

- mass is conserved

$$\left\{\begin{matrix}\text{rate of}\\\text{accumulation}\\\text{of Inulin}\end{matrix}\right\} = \left\{\begin{matrix}\text{rate of}\\\text{Inulin}\\\text{in}\end{matrix}\right\} + \cancelto{0}{\left\{\begin{matrix}\text{rate of}\\\text{Inulin}\\\text{produced}\end{matrix}\right\}} - \left\{\begin{matrix}\text{rate of}\\\text{Inulin}\\\text{out}\end{matrix}\right\} - \cancelto{0}{\left\{\begin{matrix}\text{rate of}\\\text{Inulin}\\\text{consumed}\end{matrix}\right\}}$$

$$\frac{d\,V_{ECF} \cdot I(t)}{dt} = Q_I(t) - K_{Iu} \cdot I(t)$$

$$\frac{dI(t)}{dt} = \frac{Q_I(t)}{V_{ECF}} - \frac{K_{Iu} \cdot I(t)}{V_{ECF}}$$

- dimensional consistency

$$\frac{mg/L}{min} = \frac{mg/min}{L} - \frac{L/min \cdot mg/L}{L}$$

$$\frac{mg}{L \cdot min} = \frac{mg}{L \cdot min} - \frac{mg}{L \cdot min} \quad \checkmark$$

Figure 6: Derivation of Equation for Inulin

A.3. Injection of Antipyrine – Prediction of *A(t)*

A.3.1. Define system to be modeled

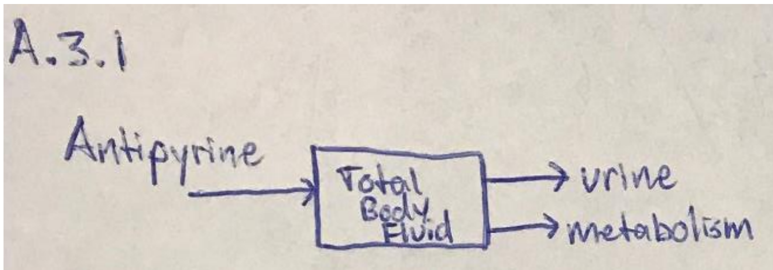

Figure 7: Schematic Diagram of System for Antipyrine

A.3.2. Define input-output

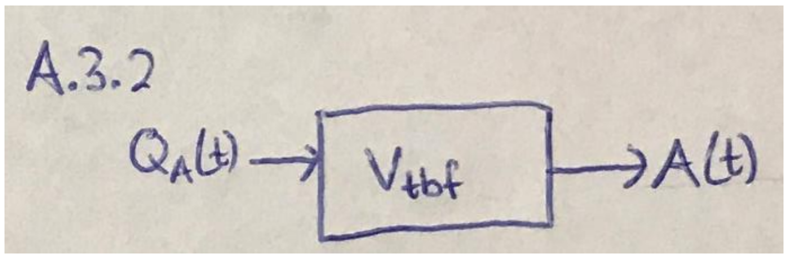

Figure 8: Diagram of Input-Output Relationship for Antipyrine

A.3.3. Derive model equation

A.3.3 Antipyrine

- mass is conserved

$$\left\{\begin{matrix}\text{rate of}\\\text{accumulation}\\\text{of Antipyrine}\end{matrix}\right\} = \left\{\begin{matrix}\text{rate of}\\\text{Antipyrine}\\\text{in}\end{matrix}\right\} + \overbrace{\cancel{\left\{\begin{matrix}\text{rate of}\\\text{Antipyrine}\\\text{produced}\end{matrix}\right\}}}^{0} - \left\{\begin{matrix}\text{rate of}\\\text{Antipyrine}\\\text{out}\end{matrix}\right\} - \left\{\begin{matrix}\text{rate of}\\\text{Antipyrine}\\\text{consumed}\end{matrix}\right\}$$

$$\frac{dV_{tbf}\cdot A(t)}{dt} = Q_A(t) - K_{AU}\cdot A(t) - K_{AM}\cdot A(t)$$

$$\frac{dA(t)}{dt} = \frac{Q_A(t)}{V_{tbf}} - \frac{K_{AU}\cdot A(t)}{V_{tbf}} - \frac{K_{AM}\cdot A(t)}{V_{tbf}}$$

$$\frac{dA(t)}{dt} = \frac{Q_A(t)}{V_{tbf}} - \frac{A(t)}{V_{tbf}}(K_{AU} + K_{AM})$$

- dimensional consistency

$$\frac{mg}{L\cdot min} = \frac{mg}{L\cdot min} - \frac{mg/L}{L}\cdot\left(\frac{L}{min} + \frac{L}{min}\right)$$

$$\frac{mg}{L\cdot min} = \frac{mg}{L\cdot min} - \frac{mg}{L^2}\left(\frac{L}{min} + \frac{L}{min}\right)$$

$$\frac{mg}{L\cdot min} = \frac{mg}{L\cdot min} - \frac{mg}{L\cdot min}\ \checkmark$$

Figure 9: Derivation of Equation for Antipyrine

B. Solve Model Equations Using SimuLink

Nominal Values: V_{tbf} = 42 L; V_{ecf} = 14 L; V_{pls} = 3.5 L; V_{int} = 10.5 L; V_{icf} = 28 L; k_{Iu} = 1.4 L min^{-1}; k_{Au} = 2.1 L min^{-1}; k_{Am} = 0.84 L min^{-1}.

B.1. Injection of Evans Blue – Prediction of *E(t)*

B.1.1. Construct the graphical process diagram for solving the model differential equation

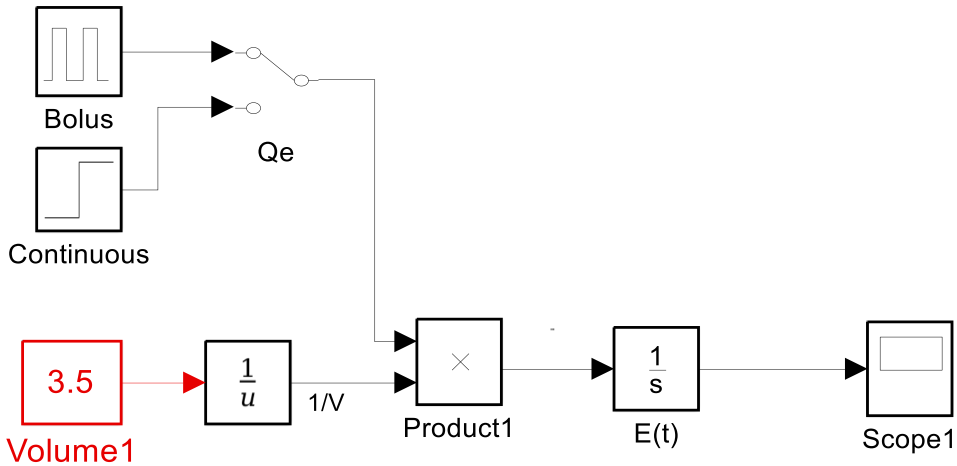

Figure 10: SimuLink Block Diagram for Evans Blue Model Equation

B.1.2. Find *E(t)* solution for 100 mg bolus of Evans Blue (impulse input) at t = 0 min and solution time interval = 0 to 100 min

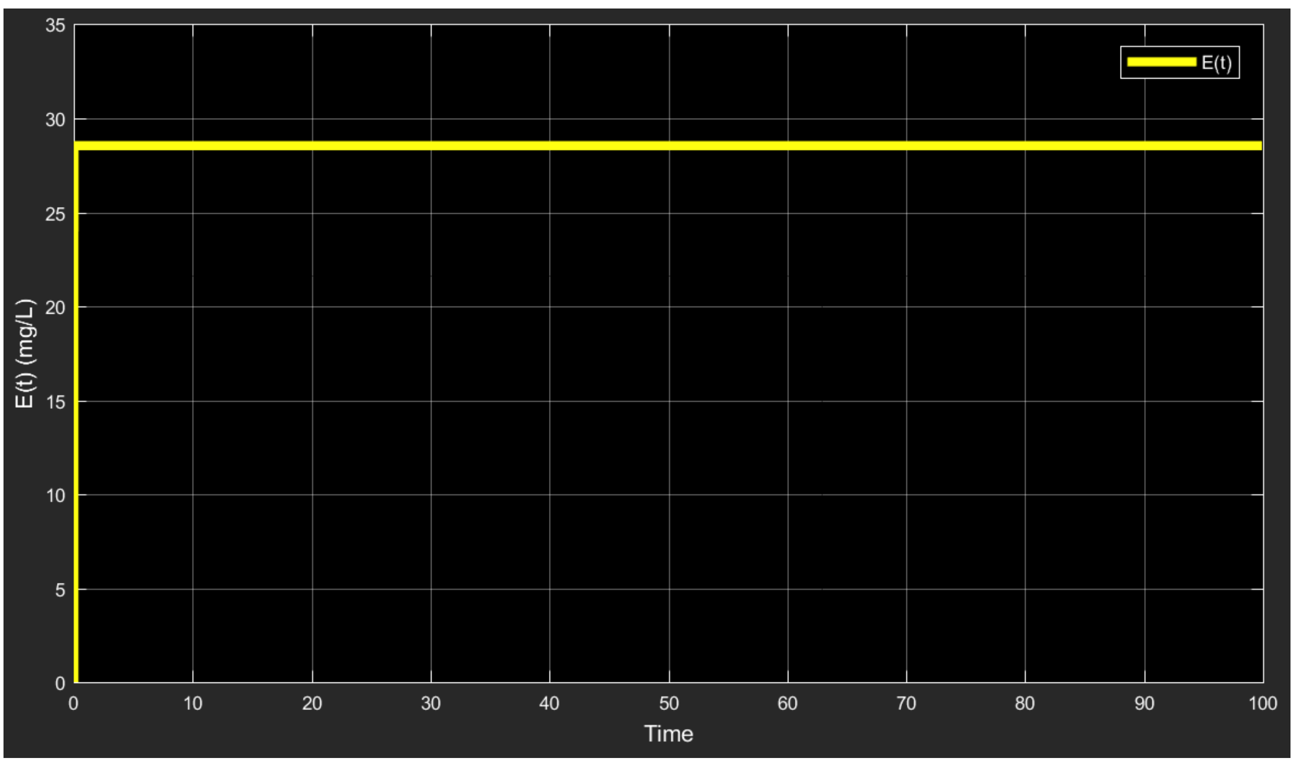

Figure 11: E(t) for 100mg Bolus of Evans Blue from Time 0 to 100min

B.1.3. Find *E(t)* solution for 1 mg/min continuous infusion of Evans Blue (step input) starting at t = 0 min and solution time interval = 0 to 100 min

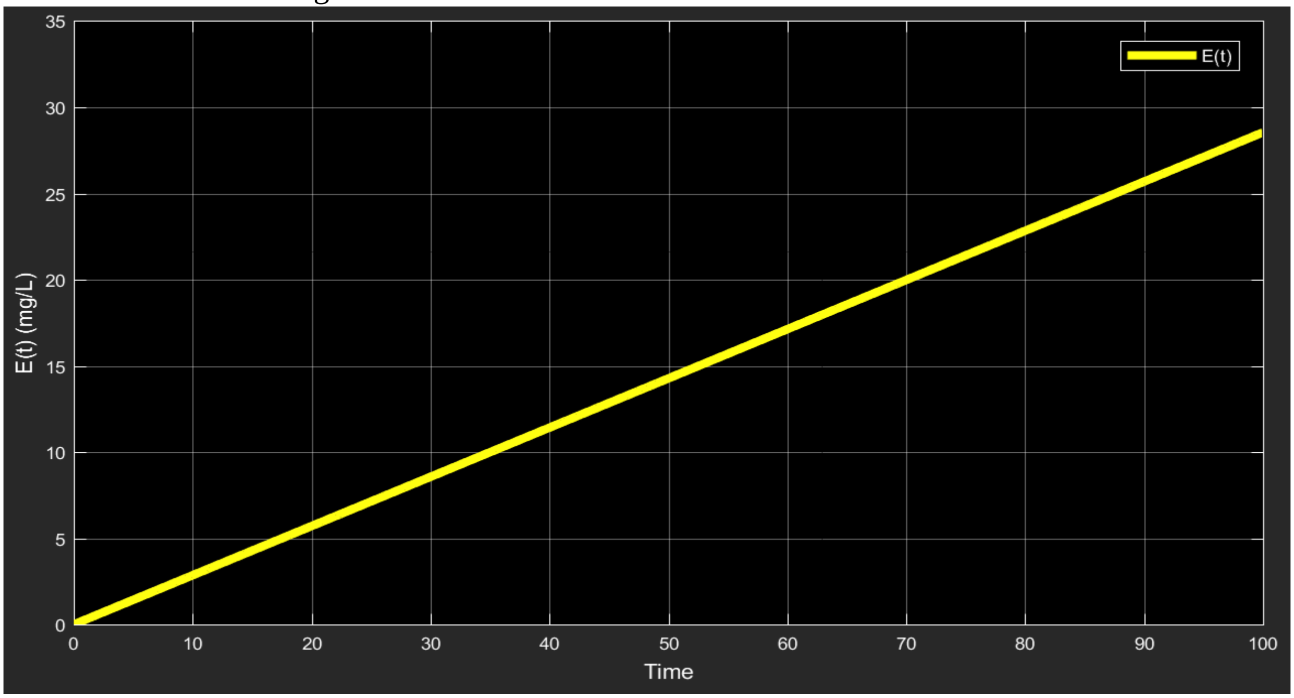

Figure 12: E(t) for 1mg/min Continuous Infusion of Evans Blue from Time 0 to 100min

B.2. Injection of Inulin – Prediction of *I(t)*

B.2.1. Construct the graphical process diagram for solving the model differential equation

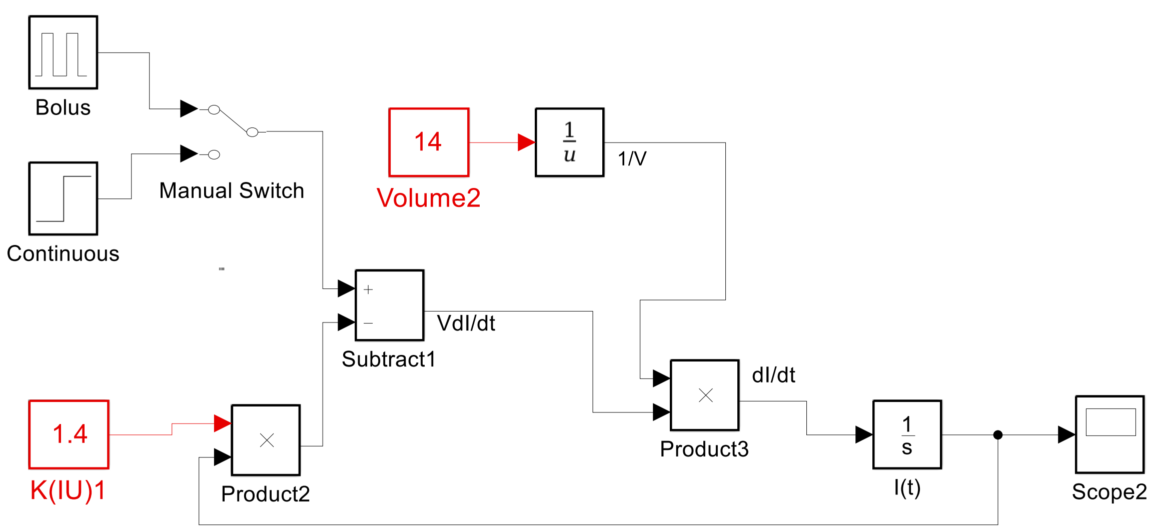

Figure 13: SimuLink Block Diagram for Inulin Model Equation

B.2.2. Find *I(t)* solution for 100 mg bolus of Inulin (impulse input) at t = 0 min and solution time interval = 0 to 100 min

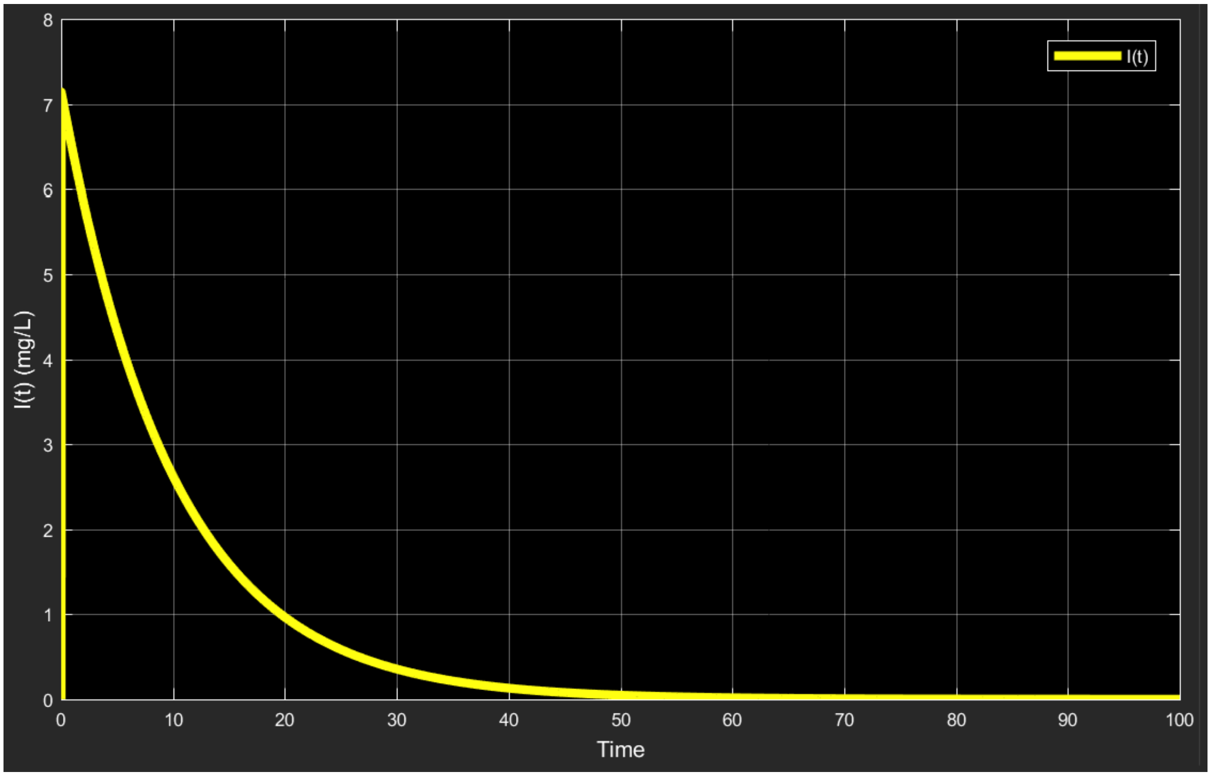

Figure 14: I(t) for 100mg Bolus of Inulin and Solution from Time 0 to 100min

B.2.3. Find *I(t)* solution for 1 mg/min continuous infusion of Inulin (step input) starting at t = 0 min and solution time interval = 0 to 100 min

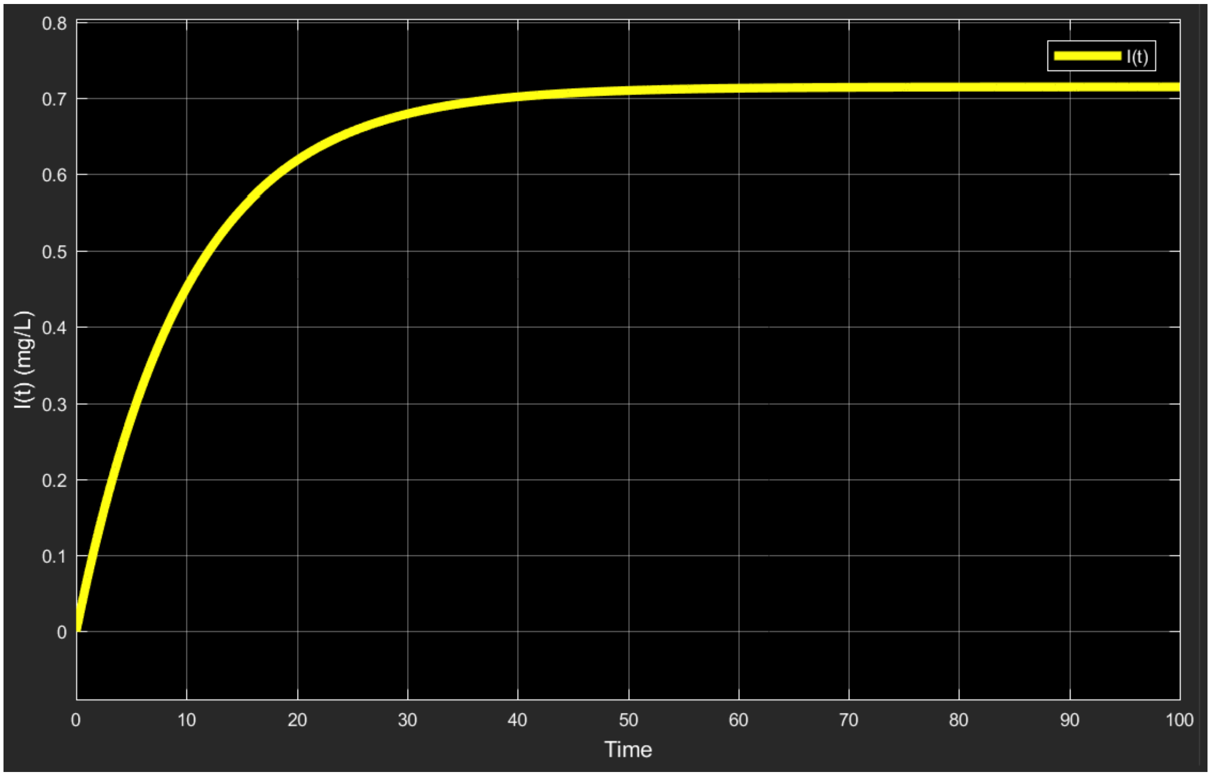

Figure 15: I(t) for 1mg/min Continuous Infusion of Inulin from Time 0 to 100min

B.3. Injection of Antipyrine – Prediction of *A(t)*

B.3.1. Construct the graphical process diagram for solving the model differential equation

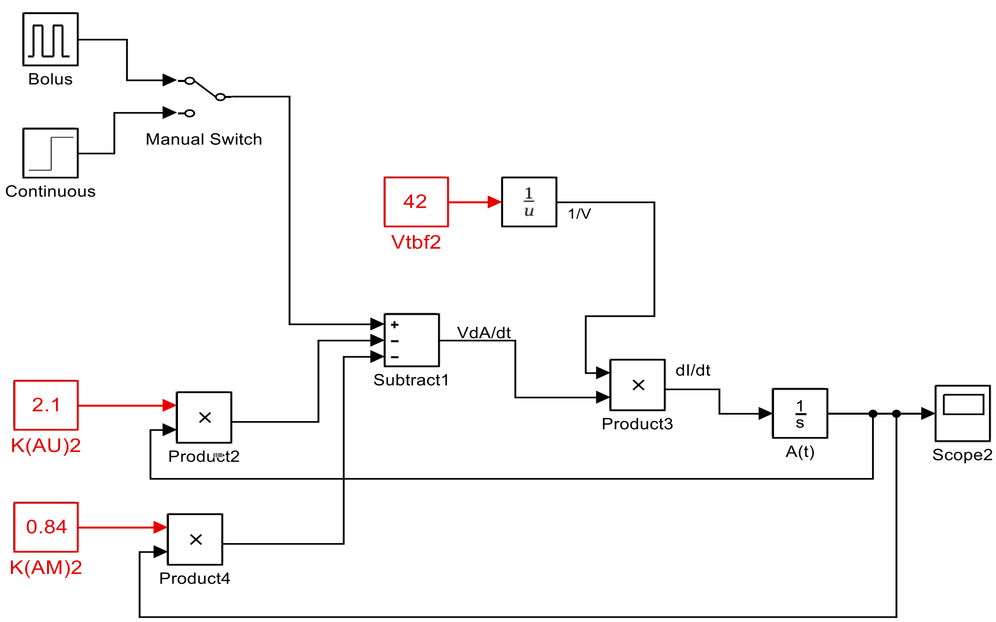

Figure 16: SimuLink Block Diagram for Antipyrine Model Equation

B.3.2. Find *A(t)* solution for 100 mg bolus of Antipyrine (impulse input) at t = 0 min and solution time interval = 0 to 100 min

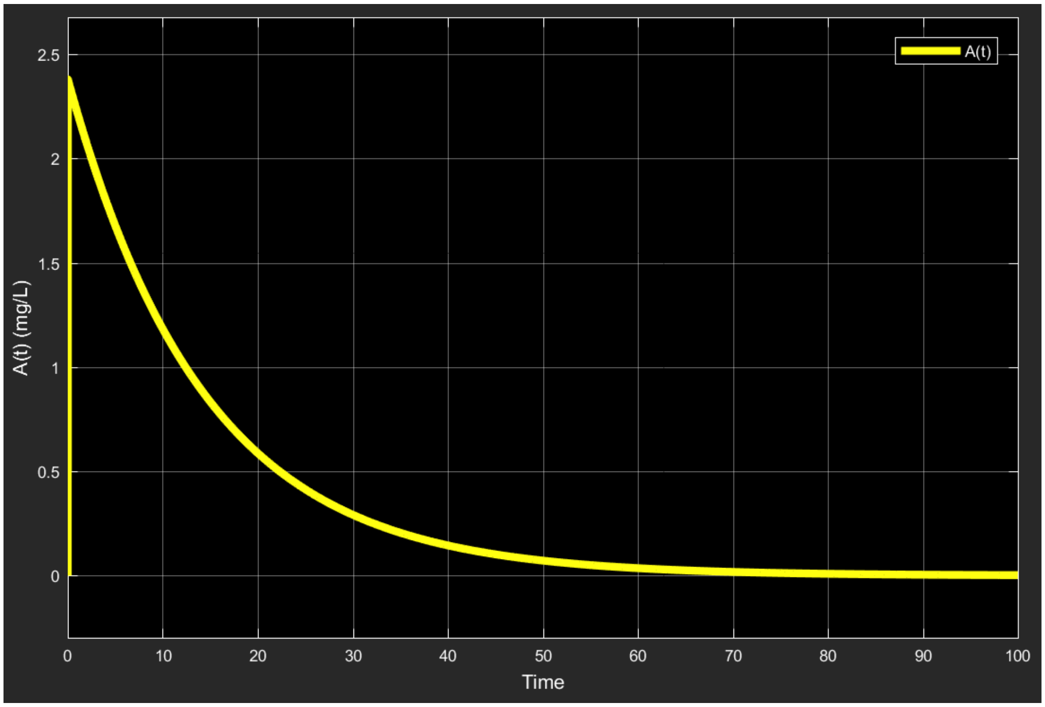

Figure 17: A(t) for 100mg Bolus of Antipyrine and Solution from Time 0 to 100min

B.3.3. Find *A(t)* solution for 1 mg/min continuous infusion of Antipyrine (step input) starting at t = 0 min and solution time interval = 0 to 100 min

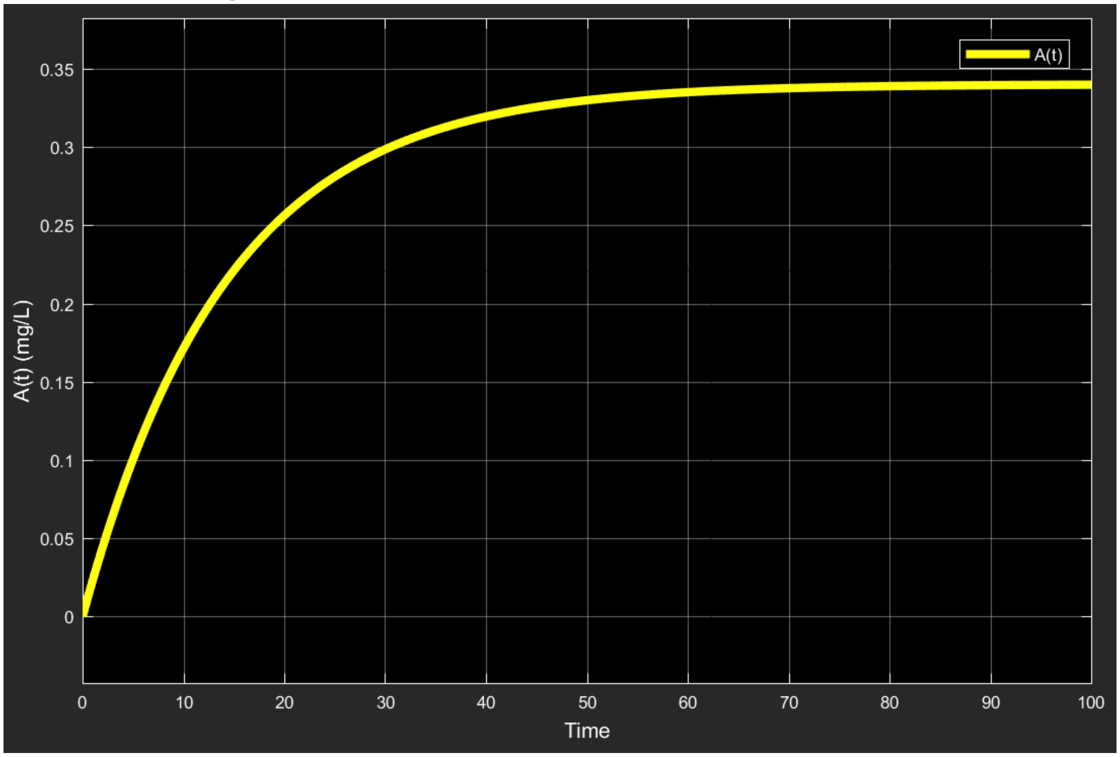

Figure 18: A(t) for 1mg/min Continuous Infusion of Antipyrine from Time 0 to 100min

C. Mathematical Characterization of Model Equations

C.1. Characterization Table

Table 1: Characterization of Model Equations

	Dynamic Order	Linear or Nonlinear	Time-varying or Time-invariant	Autonomous Part
Evans Blue model	1	Linear	Invariant	$\frac{dE(t)}{dt} = 0$
Inulin model	1	Linear	Invariant	$\frac{dI(t)}{dt} = -\frac{k_{Iu}}{V_{ecf}}\mathrm{I(t)}$
Antipyrine model	1	Linear	Invariant	$\frac{dA(t)}{dt} = -\left(\frac{k_{Au}}{V_{tbf}} + \frac{k_{Am}}{V_{tbf}}\right)\mathrm{A(t)}$

C.2. Design an experiment to test whether or not the inulin model is linear. Provide results of the experiment to support your conclusion

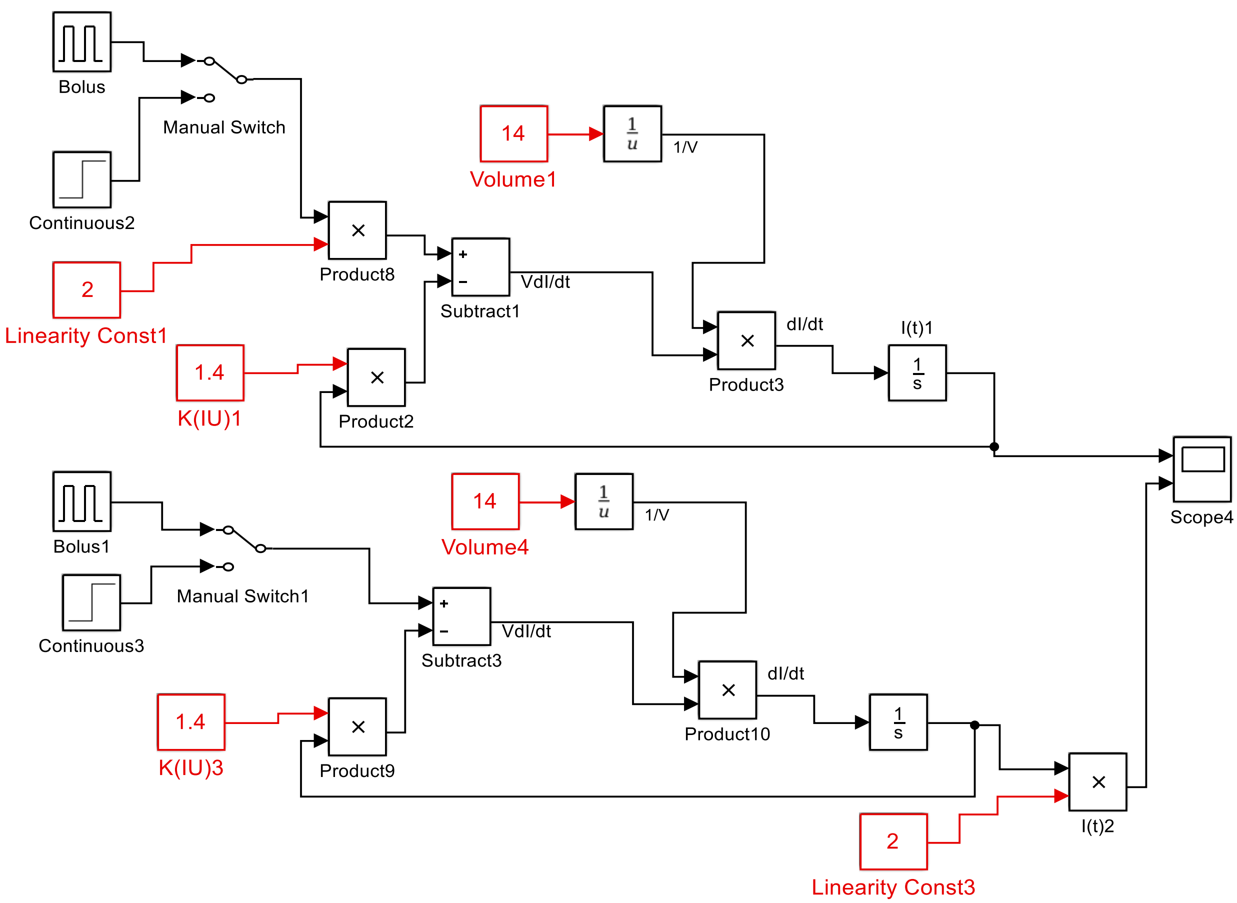

Figure 19: SimuLink Block Diagram for Linearity Test of Inulin Model (Design: input*2 = output*2)

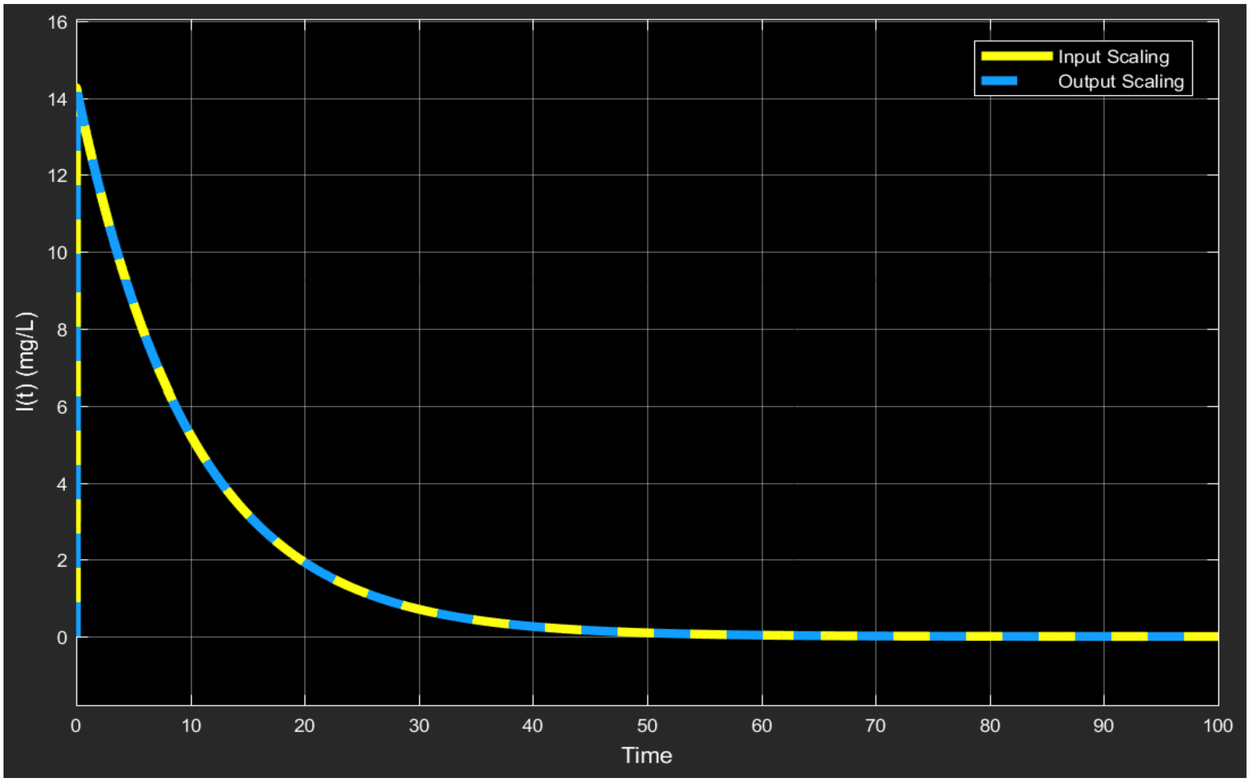

Figure 20: Plot for Inulin Linearity Test (input*2 = output*2)

To prove linearity, we scaled the input Q(t) by a factor of 2 and plotted the output. Then we input Q(t) and scaled the output I(t) also by a factor of 2 and plotted it. Because the graphs are perfectly superimposed, we were able to conclude that the system is homogeneous and therefore linear.

C.3. Design an experiment to test whether or not the Antipyrine model is time-invariant. Provide results of the experiment to support your conclusion

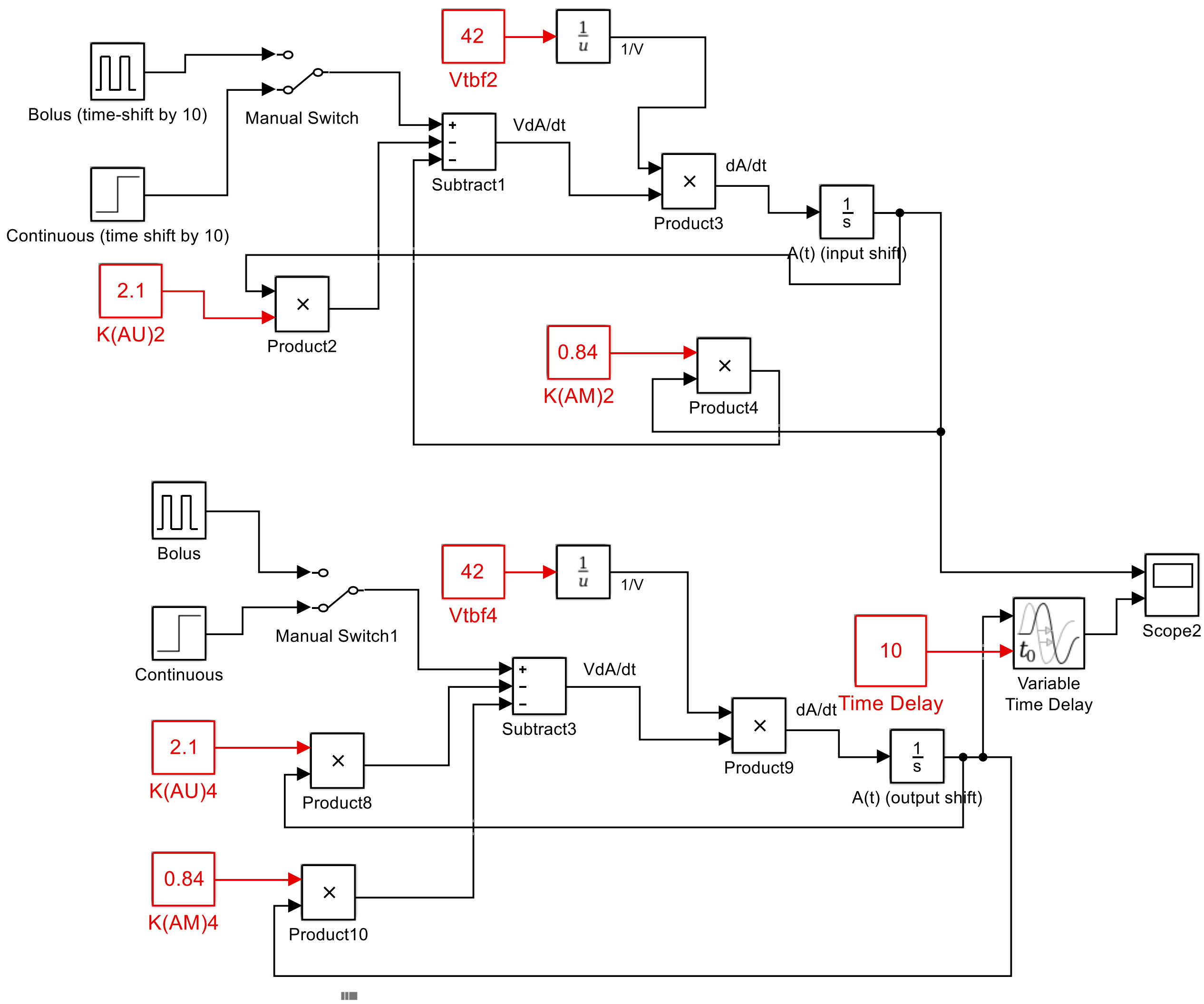

Figure 21: SimuLink Block Diagram for Time Invariance Test of Antipyrine

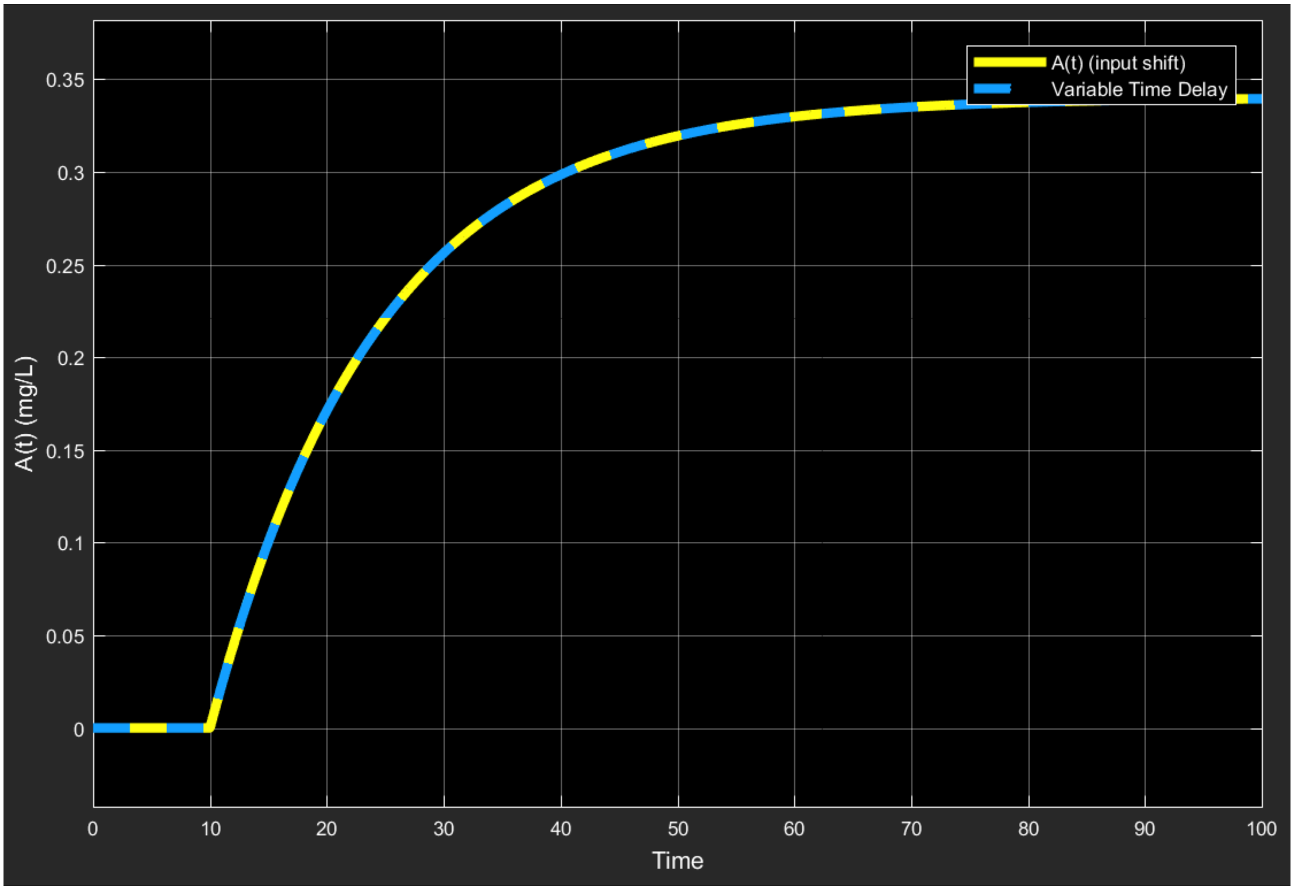

Figure 22: Graphical Solution for Time Invariance Test of Antipyrine

To prove time invariance, we introduced a 10-minute phase shift to the system and plotted the result. Then on the same graph, we plotted the system solution with no phase shift on the input, but instead on the output. Because both exhibited the same behavior we can conclude that the system is time invariant.

D. Sensitivity Analysis

D.1. On the basis of the inulin model equation and the continuous infusion protocol, provide qualitative answers to the questions in the following Table

Table 2: Sensitivity Analysis for Inulin Model

Perturbation(s)	Initial Value $I(t)$ at t=0 (mg L^{-1})	Final Value $I(t)$ at $t\to\infty$ (mg L^{-1})	Initial Rate $dI(t)/dt$ at t=0 (mg L^{-1} min^{-1})	Final Rate $dI(t)/dt$ at $t\to\infty$ (mg L^{-1} min^{-1})	Time constant (min)
1. ↑ Q_I	Unchanged	Increased	Increased	Unchanged	Unchanged
2. ↑ V_{pls}	Unchanged	Unchanged	Decreased	Unchanged	Increased
3. ↓ V_{int}	Unchanged	Unchanged	Increased	Unchanged	Decreased
4. ↑ V_{ecf}	Unchanged	Unchanged	Decreased	Unchanged	Increased
5. ↓ V_{icf}	Unchanged	Unchanged	Unchanged	Unchanged	Unchanged
6. ↑ V_{tbf}	Unchanged	Unchanged	Insufficient	Unchanged	Insufficient
7. ↑ k_{Iu}	Unchanged	Decreased	Unchanged	Unchanged	Decreased
8. ↑ Q_I &↑ k_{Iu}	Unchanged	Insufficient	Increased	Unchanged	Decreased
9. ↑ V_{ecf} &↑ k_{Iu}	Unchanged	Decreased	Decreased	Unchanged	Insufficient

D.2. Justify your responses to Items #1, #4, and #8 in Table 2

D.2.1. Item #1

The initial value (t=0) of the system subjected to the continuous infusion of Inulin is zero. Therefore, the initial value will not be affected by any change in the input variable Q_I since it does not depend on the input. At t=∞, I(t) approaches the value Q_I/k_{IU}, and is therefore directly proportional to the value of the input. Based on this relationship, we can say that the final value will increase if Q_i is increased. At t=0, the initial concentration is zero, and the initial rate is equal to Q_I/V_{ECF}. Again, this is directly proportional to the input value, and would also increase in response to this perturbation. The final rate is the rate at t=∞, and is zero in all cases, as the concentration of Inulin reaches a steady state. The time constant in this system is equal to V_{ECF}/k_{IU} and would remain unchanged since it does not depend on the input variable.

D.2.2. Item #4

At t=0, the initial value of the system is zero. As in the previous problem, no change in the input variable Q_I will have any effect on the initial value since it does not depend on the input. At t=∞, we know that the value of I(t) does not depend on V_{ECF} as mentioned in item #1, so the final value would remain unchanged. Since the initial rate is equal to Q_I /V_{ECF}, an increase in V_{ECF} would result in a decrease in the initial rate as it is inversely proportional. The final rate remains unchanged at zero. The time constant is again directly proportional to V_{ECF}, so it would increase in response to this perturbation.

D.2.3. Item #8

Similarly to items #1 and #4, the initial value of the system is zero, and is independent of both Q_I and k_{IU}, so therefore will not change. The initial rate is equal to Q_I/k_{IV} at time equals zero, so knowing that both Q_I and K_{IV} increase is insufficient information to predict the result, since it is unknown by how much each increases and they are a quotient. The initial rate depends directly on Q_I and not k_{IU} so we can say that it will increase in this case. The final rate remains zero as in the previous two items. Since the time constant is again equal to V_{ECF}/k_{IU}, an increase in k_{IU} would result in a decrease in the time constant.

E. Analytical Solutions

E.1. Derive analytical solutions for *E(t)*, *I(t)*, and *A(t)* for bolus infusion of M_E, M_I, M_A mg

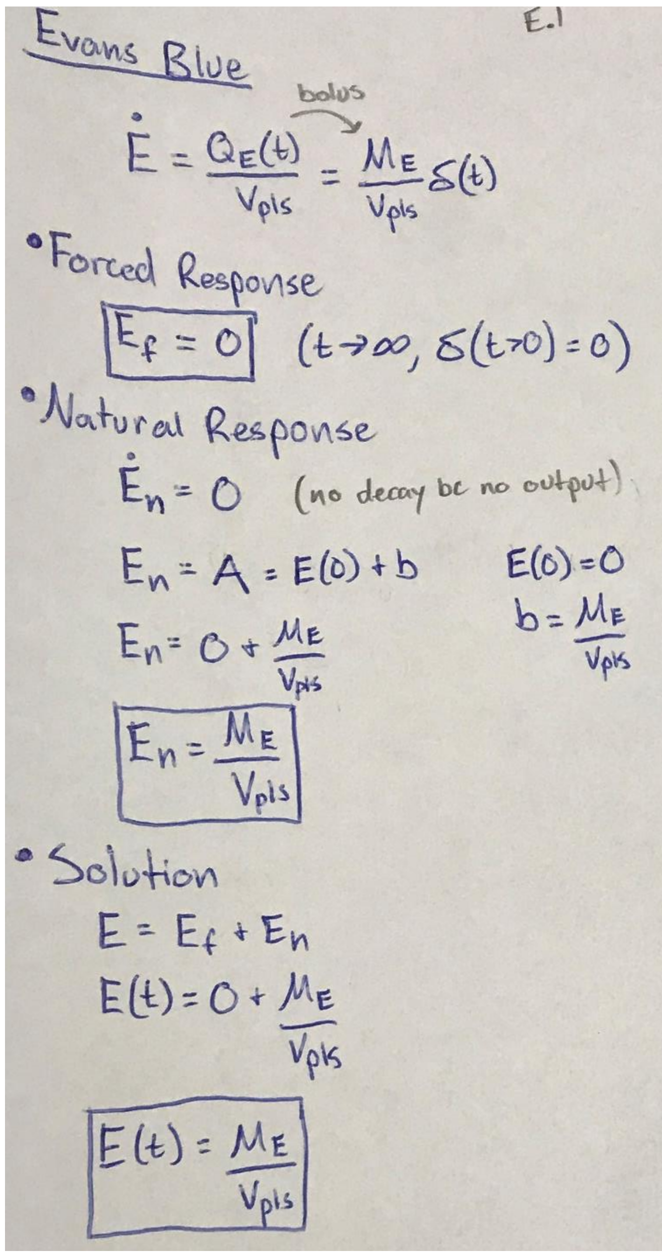

Figure 23: Analytical Solution for Bolus Injection of Evans Blue

Inulin

- Derived Equation

$$\dot{I} + \frac{k_{IU} I}{V_{ECF}} = \frac{Q_I(t)}{V_{ECF}} \overset{\text{bolus}}{=} \frac{M_I}{V_{ECF}} \delta(t)$$

- Forced Response

$$\boxed{I_f = 0} \quad (t \to \infty,\ \delta(t>0) = 0)$$

- Natural Response

$$\dot{I}_n + \frac{k_{IU} I_n}{V_{ECF}} = 0 \leftarrow \text{no input}$$

$$\dot{I}_n = \frac{-k_{IU}}{V_{ECF}} I_n$$

$$\frac{1}{I_n} \dot{I}_n = -\frac{k_{IU}}{V_{ECF}}$$

$$\frac{1}{I_n} \int dI_n = -\frac{k_{IU}}{V_{ECF}} \int dt$$

$$I_n = A e^{\frac{-k_{IU}}{V_{ECF}} t}$$

$$I(0) = 0$$

$$A = I(0) + b \qquad b = \frac{M_I}{V_{ECF}}$$

$$A = \frac{M_I}{V_{ECF}}$$

$$\boxed{I_n = \frac{M_I}{V_{ECF}} e^{\frac{-k_{IU}}{V_{ECF}} t}}$$

- Solution

$$I = I_f + I_n$$

$$I = 0 + \frac{M_I}{V_{ECF}} e^{\frac{-k_{IU}}{V_{ECF}} t}$$

$$\boxed{I(t) = \frac{M_I}{V_{ECF}} e^{\frac{-k_{IU}}{V_{ECF}} t}}$$

Figure 24: Analytical Solution for Bolus Injection of Inulin

E.1

Antipyrine

$$\dot{A} + \frac{A(t)}{V_{tbf}}\left(K_{AU} + K_{AM}\right) = \frac{Q_A(t)}{V_{tbf}} \overset{\text{bolus}}{=} \frac{M_A}{V_{tbf}}\,\delta(0)$$

- Forced Response

$$\boxed{A_f = 0} \quad (t \to \infty,\ \delta(t>0) = 0)$$

- Natural Response

$$\dot{A}_n + \left(\frac{K_{AU} + K_{AM}}{V_{tbf}}\right)A_n(t) = 0$$

$$\frac{1}{A_n}\dot{A}_n = -\left(\frac{K_{AU} + K_{AM}}{V_{tbf}}\right)$$

$$\frac{1}{A_n}\int dA = -\left(\frac{K_{AU} + K_{AM}}{V_{tbf}}\right)\int dt$$

$$A_n = Ce^{-\frac{(K_{AU} + K_{AM})}{V_{tbf}}t}$$

$$A(0) = 0$$

$$C = A(0) + b \rightarrow b = \frac{M_A}{V_{tbf}}$$

$$C = 0 + \frac{M_A}{V_{tbf}}$$

$$C = \frac{M_A}{V_{tbf}}$$

$$\boxed{A_n = \frac{M_A}{V_{tbf}}e^{-\left(\frac{K_{AU} + K_{AM}}{V_{tbf}}\right)t}}$$

- Solution

$$A = A_f + A_n$$

$$\boxed{A = \frac{M_A}{V_{tbf}}e^{-\left(\frac{K_{AU} + K_{AM}}{V_{tbf}}\right)t}}$$

Figure 25: Analytical Solution for Bolus Injection of Antipyrine

E.2. Derive analytical solutions for *E(t)*, *I(t)*, and *A(t)* for continuous infusion of $Q_E(t)$, $Q_I(t)$, $Q_A(t)$ mg min^{-1}

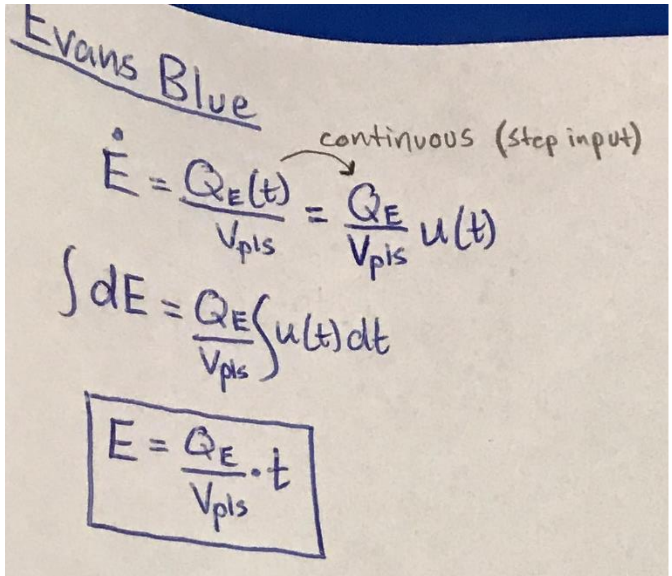

Figure 26: Analytical Solution for Continuous Injection of Evans Blue

Inulin

continuous (step input)

$$\dot{I} + \frac{k_{IU}}{V_{ECF}} I = \frac{Q_I(t)}{V_{ECF}} = \frac{Q_I}{V_{ECF}} u(t)$$

- Forced Response

$$I_f = B$$

$$\frac{dB}{dt} + aB = b \qquad \frac{dB}{dt} = 0 \qquad a = \frac{k_{IU}}{V_{ECF}} \qquad b = \frac{Q_I}{V_{ECF}}$$

$$0 + \frac{k_{IU}}{V_{ECF}} B = \frac{Q_I}{V_{ECF}}$$

$$B = \frac{Q_I}{k_{IU}}$$

$$\boxed{I_f = \frac{Q_I}{k_{IU}}}$$

- Natural Response

$$\dot{I}_n + \frac{k_{IU}}{V_{ECF}} I_n = 0 \leftarrow \text{no input}$$

$$\frac{1}{I_n}\int dI_n = -\frac{k_{IU}}{V_{ECF}}\int dt$$

$$I_n = Ae^{-\frac{k_{IU}}{V_{ECF}}t}$$

$$A = I(0) - \frac{b}{a}$$

$$A = 0 - \frac{Q_I}{V_{ECF}} \cdot \frac{V_{ECF}}{k_{IU}}$$

$$A = -\frac{Q_I}{k_{IU}}$$

$$\boxed{I_n = -\frac{Q_I}{k_{IU}} e^{-\frac{k_{IU}}{V_{ECF}}t}}$$

- Solution

$$I = I_f + I_n$$

$$\boxed{I(t) = \frac{Q_I}{k_{IU}}\left(1 - e^{-\frac{k_{IU}}{V_{ECF}}t}\right)}$$

Figure 27: Analytical Solution for Continuous Injection of Inulin

Antipyrine

continuous (step input)

$$\dot{A} + \left(\frac{K_{AU} + K_{AM}}{V_{tbf}}\right)A = \frac{Q_A(t)}{V_{tbf}} = \frac{Q_A}{V_{tbf}}u(t)$$

• Forced Response

$$A_f = B \quad \rightarrow \quad \frac{dB}{dt} + aB = b \qquad \frac{dB}{dt} = 0$$

$$a = \frac{K_{AU} + K_{AM}}{V_{tbf}}$$

$$B = \frac{Q_A}{K_{AU} + K_{AM}}$$

$$b = \frac{Q_A}{V_{tbf}}$$

$$\boxed{A_f = \frac{Q_A}{K_{AU} + K_{AM}}}$$

• Natural Response

$$\dot{A}_n + \left(\frac{K_{AU} + K_{AM}}{V_{tbf}}\right)A_n = 0 \leftarrow \text{no input}$$

$$\frac{1}{A_n}\int dA_n = -\left(\frac{K_{AU} + K_{AM}}{V_{tbf}}\right)\int dt$$

$$A_n = Ce^{-\left(\frac{K_{AU} + K_{AM}}{V_{tbf}}\right)t}$$

$$C = A(0) - \frac{b}{a}$$

$$C = 0 - \frac{Q_A}{V_{tbf}} \cdot \frac{V_{tbf}}{K_{AU} + K_{AM}}$$

$$C = -\frac{Q_A}{K_{AU} + K_{AM}}$$

$$\boxed{A_n = -\left(\frac{Q_A}{K_{AU} + K_{AM}}\right)e^{-\left(\frac{K_{AU} + K_{AM}}{V_{tbf}}\right)t}}$$

• Solution

$$A = A_f + A_n$$

$$\boxed{A(t) = \frac{Q_A}{K_{AU} + K_{AM}}\left(1 - e^{-\left(\frac{K_{AU} + K_{AM}}{V_{tbf}}\right)t}\right)}$$

Figure 28: Analytical Solution for Continuous Injection of Antipyrine

F. Model-Based Analysis and Interpretation of Data

F.1. Perform experiments to figure out the quantities listed in Table 2

Table 3: Quantities Determined from Experiments

	Case 1	Case 2
V_{pls} (L)	2	4.55
V_{int} (L)	8	13.63
V_{icf} (L)	19.9	36.12
V_{ecf} (L)	10	18.18
V_{tbf} (L)	29.9	54.3
k_{Iu} (L min^{-1})	1.21	1.57
$k_{Au} + k_{Am}$ (L min^{-1})	3.49	4

The MATLAB function patientSimulator() generated graphs from which we were able to estimate the values of time (t) and the concentration of the dye types (E(t), I(t), A(t)). Then, using the analytical solutions solved for in Part E, we were able to substitute in the time and concentration values which allowed us to solve for the unknowns.

To find V_{pls} we used the Evans Blue continuous equation, and for V_{ECF} we used the Inulin bolus equation. Because the total volume of extracellular fluid consists of volume of plasma and the volume of interstitial fluid, we used $V_{ECF} – V_{pls}$ to find V_{int}.

For V_{tbf} we used the Antipyrine bolus equation, and given that total body fluid consists of the extracellular fluid volume (known) and the intracellular fluid, we used $V_{tbf} – V_{ECF}$ to find V_{ICF}.

Using the values from patientSimulator() and the Inulin continuous equation we estimated that the final value at t=∞ was equal to the value at t=100 and were able to solve for K_{IU}. With the same method, but using the Antipyrine continuous equation, we were able to determine $K_{AU} + K_{AM}$.

F.2. $\mathbf{K_{AU} + K_{AM}}$

Antipyrine leaves the system through both urine and metabolism. Throughout our experiment we only measured the total elimination from the system, not the elimination from each component separately. An experiment where we measured Antipyrine in the urine would enable us to solve for K_{AU} and then K_{AM}.

F.3. Pros and Cons of the two Injection Protocols (bolus and continuous)

A benefit of the bolus method is that it allows us to inject a known amount of drug (nearly) instantaneously. Upon injection, we know the maximum concentration that the drug will reach in the body and can reason that the concentration will only decrease assuming that the body can eliminate the drug. Being able to rapidly raise the concentration of a drug in the body via a one-time injection is particularly useful for emergency medicine scenarios. This however can also be a drawback in cases of overdose. The continuous method is beneficial because we have a known, stable amount of drug entering the body. This is useful for administering medication over longer durations. However, if the ability of the body to eliminate this substance changes, then the concentration of the drug may rise to unsafe levels and be difficult to monitor.

F.4. Rules for calculating dynamic response profiles of indicator plasma concentrations

1. Administer three dyes such that one is unable to be eliminated from the body, one is excreted only, and one is excreted and metabolized. Make sure that each dye is administered with both the bolus and continuous method.
2. Monitor and record plasma concentrations of each dye over a relatively long duration (a few hours)
3. With the values recorded from part 2, use the differential equations modeling the injection and elimination of the dyes to solve for the desired variable.
4. Based on the values calculated in part 3, and using the relationships between body fluid volumes, calculate the desired plasma concentrations