Do not write in this margin

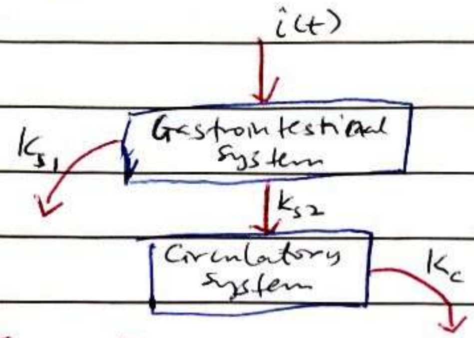
Question..........

Exp2 A The absorption of certain substances, e.g. drugs, in the body can be studied using compartmental models in which the input and output flow of the drug determines the concentration in each compartment. For instance for an oral administration medicine we can model its concentration in the stomach (i.e. the gastrointestinal system, in general) and its absorption to the circulatory system as

model equations

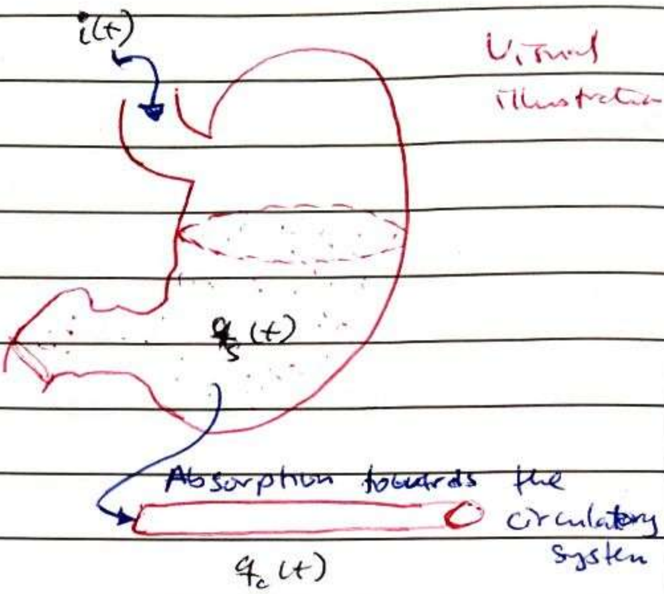
$$\frac{dq_s}{dt} = i(t) - (k_{s1} + k_{s2})\, q_s$$

$$\frac{dq_c}{dt} = k_{s2} q_s - k_c q_c$$



Schematic

Visual illustration



~~Another~~ Parameters k_{ij} are the transfer coefficients between the involved systems.

[Can you identify the modelling assumptions made?]

- q_s and q_c represent the concentration of the drug within the gastrointestinal system and circulatory system, respectively, $i(t)$ is the input flow, k_{s2} is the transfer coefficient between the gastrointestinal system and the circulatory system, and k_{s1} and k_c model the loss transfer coefficients.

~~Let ... input~~ Let $q_c(t)$ be the output.

We have state $q = \begin{bmatrix} q_s \\ q_c \end{bmatrix}$

State space model

and the system in state space form will ~~have~~ be

$$\dot{q} = Aq + Bu$$

$$y = Cq \qquad \text{where } y \text{ is the output.}$$

$$\left.\begin{aligned} \dot{q}_s &= -(k_{s1} + k_{s2})q_s + i(t) \\ \dot{q}_c &= k_{s2} q_s - k_c q_c \end{aligned}\right\} \text{(i)}$$

$$\dot{q} = \begin{bmatrix} \dot{q}_s \\ \dot{q}_c \end{bmatrix} = \begin{bmatrix} -(k_{s1}+k_{s2}) & 0 \\ k_{s2} & -k_c \end{bmatrix} \begin{bmatrix} q_s \\ q_c \end{bmatrix} + \begin{bmatrix} 1 \\ 0 \end{bmatrix} i(t)$$

$$y = \begin{bmatrix} 0 & 1 \end{bmatrix} \begin{bmatrix} q_s \\ q_c \end{bmatrix}$$

For the transfer function representation, taking laplace transforms of the differential equations (1) ~~...~~ above, we get

$$sQ_s(s) = -(k_{s1} + k_{s2})Q_s(s) + I(s) \quad \text{--- (ii)}$$

$$sQ_c(s) = k_{s2}Q_s(s) - k_c Q_c(s) \quad \text{--- (iii)}$$

Obtaining the transfer function model representation

We can combine both equations to form a single algebraic equation and from there obtain $\dfrac{Q_c(s)}{I(s)}$

~~Multiplying the second equation (iii) by s gives~~

$$\cancel{s^2 Q_c(s) = sk_{s2}Q_s(s) - sk_c Q_c(s)} \quad \text{--- (iv)}$$

~~Substituting the first equation (ii) into (iv)~~

$$\cancel{s^2 Q_c(s) = k_{s2}\left[-(k_{s1}+k_{s2})Q_s(s) + I(s)\right] - s}$$

Substitute the value $Q_s(s)$ from (ii) into (iii).

from (ii): $sQ_s + (k_{s1} + k_{s2})Q_s = I(s)$

$$Q_s(s + k_{s1} + k_{s2}) = I(s)$$

$$Q_s(s) = \frac{I(s)}{s + k_{s1} + k_{s2}}$$

Substitute into (iii)

$$sQ_c = \frac{k_{s2} I}{s + k_{s1} + k_{s2}} - k_c Q_c$$

$$sQ_c + k_c Q_c = \frac{k_{s2} I}{s + k_{s1} + k_{s2}}$$

$$(s + k_c)Q_c = \frac{k_{s2} I}{s + k_{s1} + k_{s2}}$$

Do not write in this margin

Question..........

$$\therefore \frac{Q_c(s)}{I(s)} = \frac{k_{s2}}{(s+k_c)(s+k_{s1}+k_{s2})}$$

For $k_{s1} = 0.02\ min^{-1}$, $k_{s2} = 0.1\ min^{-1}$, $k_c = 0.05\ min^{-1}$,

identify the poles and DC gain

$$Q_c(s) = \frac{0.1}{(s+0.05)(s+0.02+0.1)} I(s)$$

$$= \frac{0.1}{s^2 + 0.17s + 0.006} I(s)$$

$q_c(t) = \mathcal{L}^{-1}\{Q_c(s)\}$ (the system response for an arbitrary input)

The impulse response (i.e. for $I(s) = 1$) is given by

$$Q_c(s) = \frac{0.1}{s^2+0.17s+0.006} = \frac{0.1}{(s+0.05)(s+0.12)}$$

$$q_c(t) = \mathcal{L}^{-1}\{Q_c(s)\}$$

Plot the impulse response using Matlab/Octave

use the 'impulse' command

MATLAB

```
den = [1 0.17 0.006]; % enter the denominator of transfer function
roots(den) % obtain the poles,(roots of the denominator)

ans =
  -0.1200
  -0.0500

num = [0.1]; % enter the numerator of the Qc(s)
[r, p] = residue(num, den) % obtain the numerator of the partial
                           fraction expansion of Qc(s), called
  r = -1.4286              the residues 'r'. 'p' is for poles corres-
       1.4286              ponding to each residue
  p = -0.12
      -0.05                % notice roots are all real
```

Question......

The partial fraction expansion becomes

$$Q_c(s) = \frac{0.1}{s^2+0.17s+0.006} = \frac{0.1}{(s+0.05)(s+0.12)}$$

$$= \frac{-1.4286}{s+0.12} + \frac{1.4286}{s+0.05}$$ (residues with corresponding real poles)

Using Laplace (Inverse Laplace) transform tables, (see experience controls app or other sources)

$$q_c(t) = \mathcal{L}^{-1}\{Q_c(s)\} = -1.4286\,e^{-0.12t} + 1.4286\,e^{-0.05t}$$

MATLAB:
```
t = 0:0.1:250;
y=-1.4286*exp(-0.12*t)+1.4286*exp(-0.05*t);
plot(t,y)
```

Compare the above plot with that obtained from using the 'impulse' function in matlab.

[Recall how to enter transfer function and state space models in MATLAB/octave?]

Exp L B

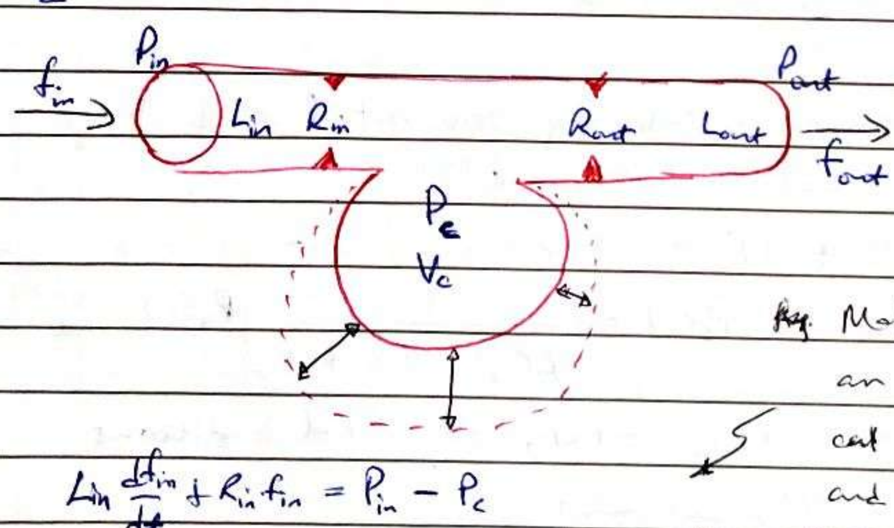


Fig. Mathematical model of an artery with mechanical resistance, inductance and capacitance elements

$$L_{in}\frac{df_{in}}{dt} + R_{in}f_{in} = P_{in} - P_c$$

$$L_{out}\frac{df_{out}}{dt} + R_{out}f_{out} = P_c - P_{out}$$

$$\frac{dV_c}{dt} = f_{in} - f_{out}$$

The f terms are flow rates
The P terms relate to pressure

Do not write in this margin

ExPLD

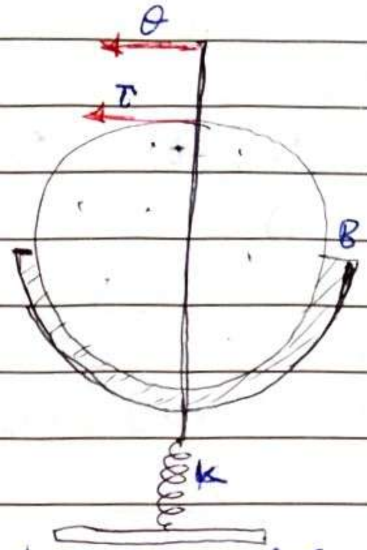
Question..

Do not write in this margin

Obtain the transfer function of the Westheimer model for the saccadic movements of the human eye, given by:

$$J\frac{d\theta^2}{dt} + B\frac{d\theta}{dt} + k\theta(t) = k_\tau \tau(t)$$

in which $\theta(t)$ is the output, i.e. the angular position of the eye, and $\tau(t)$ represents the input generated by the eye muscles.



A model of the human eye

Taking Laplace transforms (assuming zero initial conditions)

$$Js^2\theta(s) + Bs\theta(s) + k\theta(s) = k_\tau \tau(s)$$

$$\therefore \frac{\theta(s)}{\tau(s)} = \frac{k_\tau}{Js^2 + Bs + k}$$

For parameters

$J=2,\ B=3,\ k=1,\ k_\tau=6,$

the transfer function becomes

$$G(s) = \frac{\theta(s)}{\tau(s)} = \frac{6}{2s^2+3s+1}$$

To compute the step response, let $\tau(s) = \mathcal{L}\{\tau(t)\} = \frac{1}{s}$

$$\therefore \theta(s) = \left(\frac{1}{s}\right)\left(\frac{6}{2s^2+3s+1}\right) = \frac{6}{2s^3+3s^2+s}$$

$$= \frac{k_1}{s} + \frac{k_2}{s+p_1} + \frac{k_3}{s+p_2}$$ (partial fraction expansion)

Matlab code:

```
num = [6] ; den = [2  3  1  0];
[r, p] = residue (num, den)   % Calculating the residues and poles
                              which we shall use to obtain
                              the partial fraction expansion
    r =  6
        -12
         6

    P = -1
        -0.5
         0
```

and the partial fraction expansion becomes

$$\theta(s) = \frac{6}{s} + \frac{6}{s+1} - \frac{12}{s+0.5}$$

$$\theta(t) = \mathcal{L}^{-1}\{\theta(s)\} = 6 + 6e^{-t} - 12e^{-0.5t}$$

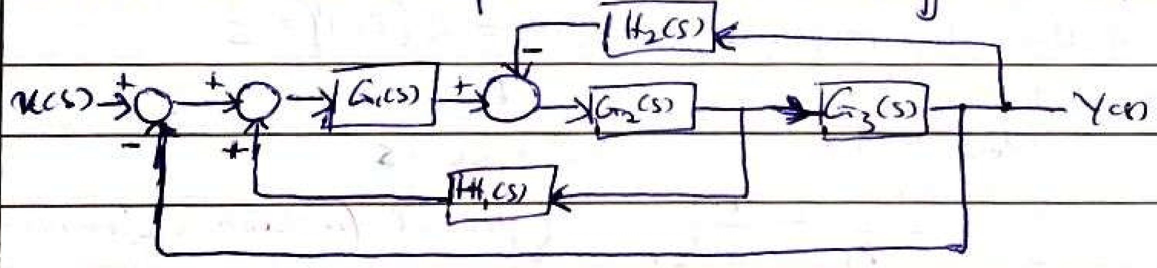
(via the inverse Laplace transform)

Matlab code for the step response:

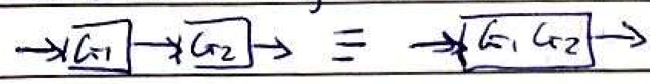
```
t = 0:0.1:15
y = 6+6*exp(-t) - 12*exp(-0.5*t);
plot (t,y)
        Alternatively
s = tf('s')
G= 6/(2*s^2+3*s+1)
Step(G, 15)
impulse (G, 15)        % produces the impulse response over
                         15 seconds)
```

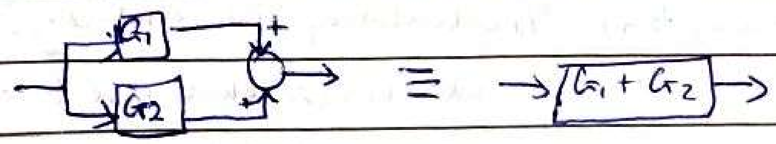
EXPL D

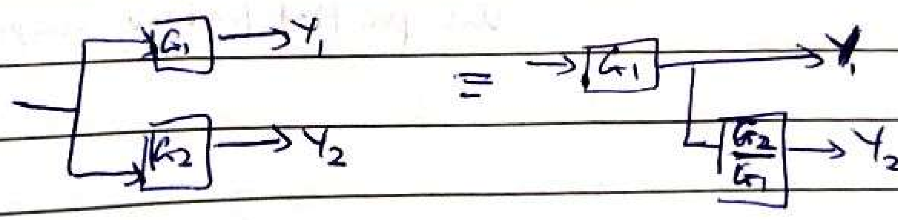
Reduce the block diagram below to a single transfer function.



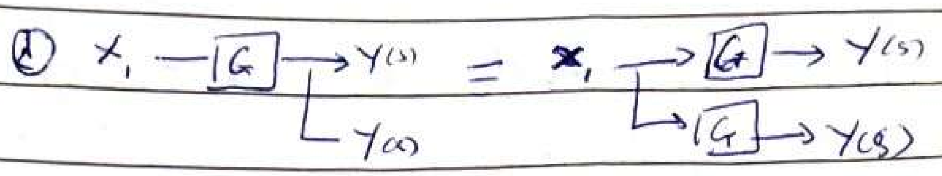
» Rules commonly used to reduce block diagrams:

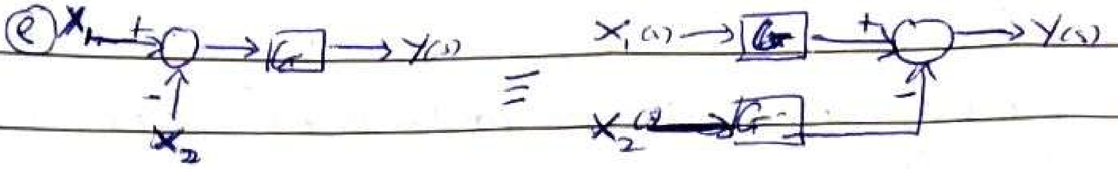
(a) 

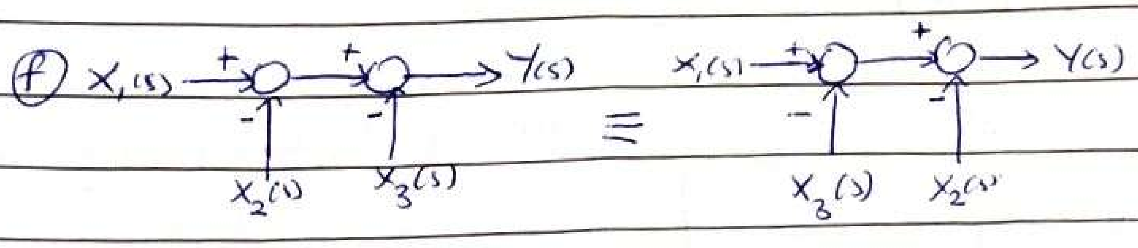
(b) 

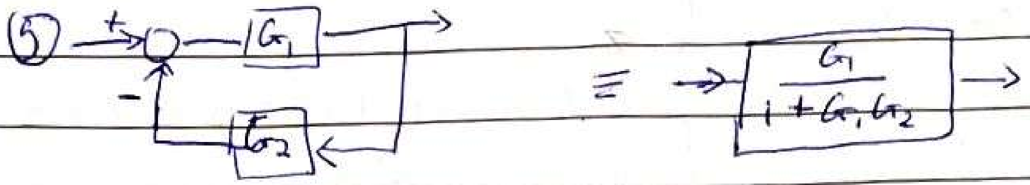
(c) 

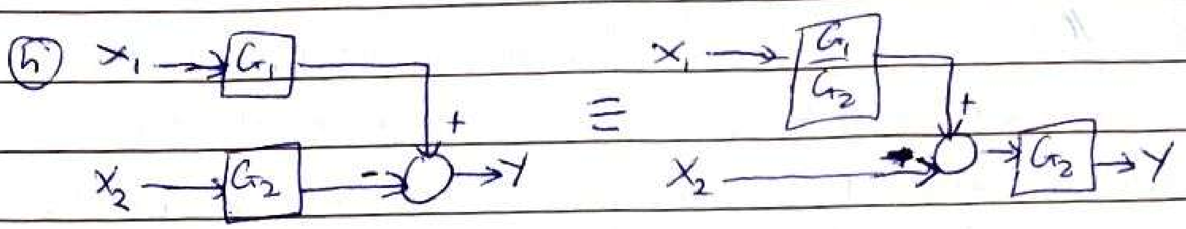
Question..



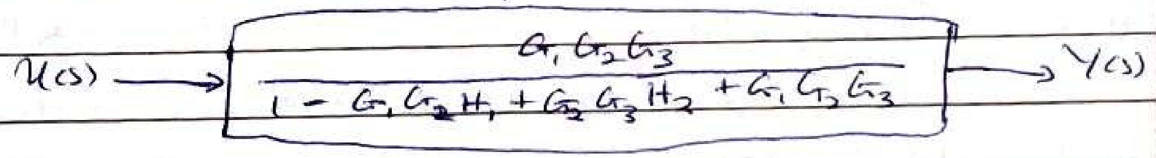








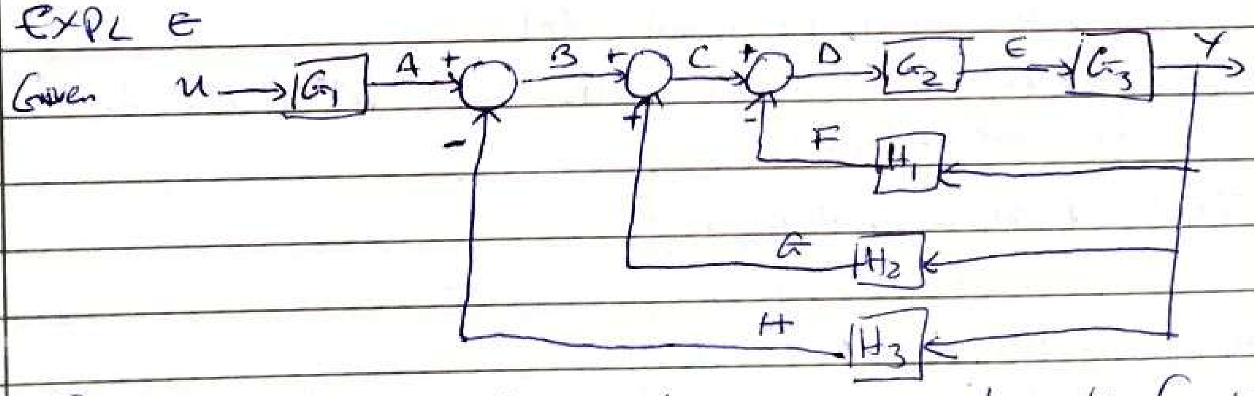
Applying the logic of the relevant reduction rules to the problem yields, the following as the answer to the question:



* See tutorials provided 5/03/2020.

EXPL E

Given



For the above system, reduce ~~it~~ it to a single transfer function by applying the necessary MATLAB commands for

Commands: tf, sumblk, connect, feedback, series,

Do not write in this margin

Question..........

Do not write in this margin

$G_1 = 10$, $G_2 = \frac{s+2}{s+10}$, $G_3 = \frac{1}{s+2}$, $H_1 = 5$, $H_2 = -2s$, $H_3 = \frac{3}{s+2}$.

Additionally, draw the impulse response for the equivalent transfer function.

(Note that the intermediate inputs/outputs are named: A, B, C, D, E, F, G, H.)

Solutions

```
% Define transfer functions
s = tf('s')
G1 = tf(10,1);
G2 = (s+2)/(s+10);
G3 = 1/(s+2);
H1 = tf(5,1);
H2 = -2*s
H3 = 3/(s+2);
% Specify inputs/outputs by branches   Labels
G1.u = 'U'; G1.y = 'A';
G2.u = 'D'; G2.y = 'E';
G3.u = 'E'; G3.y = 'Y';
H1.u = 'Y'; H1.y = 'F';
H2.u = 'Y'; H2.y = 'G';
H3.u = 'Y'; H3.y = 'H';
% Specify inputs/outputs of sum blocks
Sum1 = sumblk('B = A - H');
Sum2 = sumblk('C = B + G');
Sum3 = sumblk('D = C - F');
% Connect the model. The 'connect' command returns the state-variable representation
T = connect(G1, G2, G3, H1, H2, H3, sum1, sum2, sum3, 'U', 'Y');
% Convert the result to transfer function form
Ttf = tf(T)
```

Alternatively, having defined the transfer functions G_1, G_2, G_3, H_1, H_2, and H_3,

```
% Calculate the series product of G2 & G3
G23 = G2*G3
% We want the H1, H2, H3 together to form a negative feedback configuration with G23. ∴ Group H1, H2, H3 in a parallel way
H123 = H1 - H2 + H3
% Reduce the negative feedback configuration formed by G23 & H123
Gfeed_G23_H123 = feedback(G23,
                 H123, -1)
% Compute the series of the resulting transfer function above with G1
G_reduced = G1*Gfeed_G23_H123
```

Compartmental Modelling Continued. TUTORIALS

Example: Insulin – Glucose Dynamics.

It is important that the blood glucose concentration is regulated to be in the range 70 – 110 mg/L. The blood glucose concentration is influenced by body constitution, food intake, digestion, stress, and exercise

- The pancreas secretes the hormones insulin and glucagon. Insulin to lower the glucose level by causing the liver and other cells to take up more glucose when the glucose level in the blood is too high. Glucagon to increase the glucose level in the blood when it is too low, by acting on cells in the liver so as to release glucose
  - There are also other hormones that influence glucose concentration.
- Long exposure to high blood sugar concentration may result in cardiovascular diseases, stroke, chronic kidney disease, foot ulcers, and blindness.
- Low blood sugar can give headaches, fatigue, dizziness, lethargy, and blurred vision. Very low blood sugar levels can result in coma
- Diabetes: Type 1:- where production of insulin is impaired
  Type 2:- where the ability of the body to absorb insulin can be reduced.

Diabetes is a disease where the body's ability to produce or respond to insulin is impaired, resulting in blood sugar levels that are too high

Models of different complexity have been developed to try to mathematically represent the complicated mechanisms that regulate glucose and insulin in the body

- The models are typically tested with data from experiments where glucose is injected intravenously and insulin and glucose concentrations are measured at regular time intervals.

Impulse response

System ID & validation

Refer to diagram fig 4.19c in Åström/Murray 2019

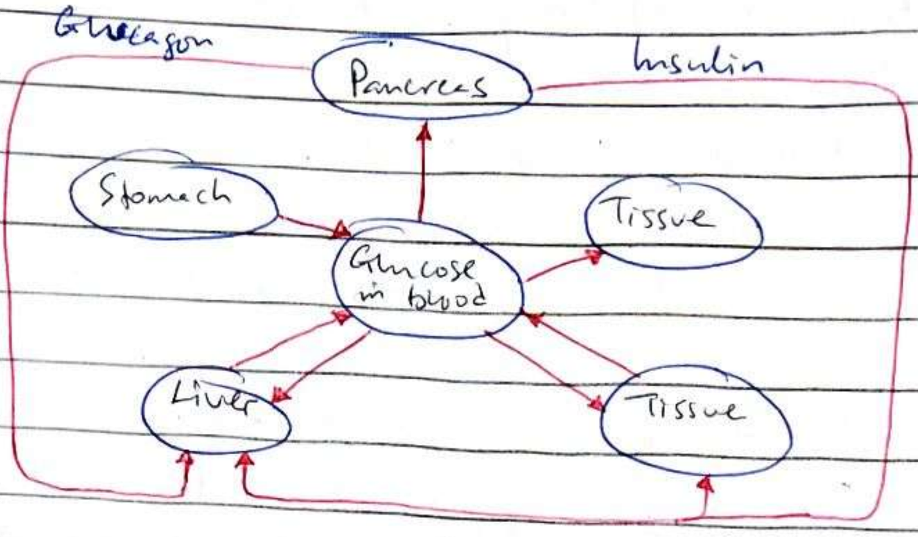


fig 4.196:- A schematic picture of the relevant mechanisms that regulate glucose concentration in the blood. (From which a compartmental may be developed.)

In an article, "R. N. Bergman. Toward physiological understanding of glucose tolerance: Minimal model approach. Diabetes, 38:1512-1527, 1989", a simple minimal model the insulin-glucose dynamics is suggested:

Evaluate o/p a state space form?

$$\frac{dG}{dt} = -P_1(G - G_e) - XG + u_G$$

$$\frac{dX}{dt} = -P_2 X + P_3 (I - I_e)$$

$G \triangleq$ concentration of glucose in the blood plasma

2 states not 3? G, X, (I)

$X \triangleq$ the effect of insulin on glucose removel, which is proportional to the concentration of insulin I in the interstitial fluid

$I \triangleq$ concentration of insulin in the interstitial fluid

- The "variables" with subscript 'e' are equilibrium values

Equilibrium

- If the external input u_G is zero and $I = I_e$ there is an equilibrium with $G = G_e$ and $X = 0$

— The second equation represents how the variable X depends on the insulin concentration I in the interstitial fluid.

initial conditions

*(Assignment: Form the compartment model)

No insulin dynamics

- The first equation is a compartment model for glucose.
  The right-hand side has three terms:
  >> a linear clearance term that models glucose removal at a rate proportional to $G - G_e$,

nonlinearity transcendental functions

  >> The nonlinear term XG captures the fact that removal rate of glucose is enhanced by insulin.
  >> u_G is the external input glucose concentration rate

Read last three paragraphs

Exercises 4.8 & 4.9 Aström & Murray 2024 pp 4-30.

4.8 (Drug administration) The metabolism of alcohol in the body can be modelled by the nonlinear compartment model

$$V_b \frac{dc_b}{dt} = q(c_l - c_b) + q_{iv}$$

$$V_l \frac{dc_l}{dt} = q(c_b - c_l) - q_{max}\left(\frac{c_l}{c_0 + c_l}\right) + q_{gi}$$

where $V_b = 48L$ and $V_l = 0.6L$ are the apparent volumes of distribution of body water and liver water, c_b and c_l are the concentration of alcohol in the compartments, q_{iv} and q_{gi} are the injection rates for intravenous and gastrointestinal intake. $q = 1.5$ L/min is the total hepatic blood flow, $q_{max} = 2.75$ mmol/min and $c_0 = 0.1$ mmol/L.

i Simulate the system and compute the concentration in the blood for oral and intravenous doses of 12g and 40g of alcohol

4.9 (Insulin-glucose dynamics) The following model for insulin glucose dynamics by Gaetano et al ("Mathematical models and state observation of the glucose-insulin homeostasis, ... 2005.) has three states:

- glucose concentration in the blood plasma G [mg/dL]
- insulin concentration in the interstitial fluid I [$\mu UI/ml$]

equations which are from compartment models? - the increased removal rate of glucose due to insulin X [min^{-1}]

The state X is proportional to the concentration of interstitial insulin. The dynamics are

3-state model

$$\frac{dG}{dt} = -(P_1 + X)G + P_1 G_b + u_G$$

$$\frac{dX}{dt} = -P_2 X + P_3 (I - I_b)$$

$$\frac{dI}{dt} = P_4 \max(G - P_5, 0) - P_6 (I - I_b) + u_I$$

- Use the parameters

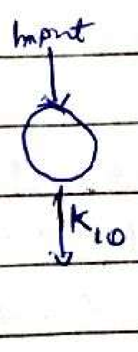
$G_b = 87$, $I_b = 37.9$, $P_1 = 0.05$, $P_2 = 0.5$, $P_3 = 10^{-4}$, $P_0 = 399$

$P_4 = 10^{-5}$, $P_5 = 150$, $P_6 = 0.05$, $P_7 = 199$

initial conditions * i. Simulate the system with initial conditions $G(0) = 400$, $I(0) = 200$ and $X(0) = 0$. This corresponds to a person having taken a large initial dose of glucose.

A notational convention: The convention used in writing the transfer rate (k) between compartments is given by k_{ij}, which describes the flow of solute leaving compartment i, and entering compartment j. All transfer rates ~~are~~ are given by $k_{ij} \geq 0$.

> Response of a One Compartment Model.



Following from the conservation of mass,

Accumulation ($\dot{C}_1$) = Input ($f(t)$) − output ($k_{10} C_1$)

i.e. $\dot{M}_1 = f(t) - k_{10} M_1$

* For a unit step input of size B, the solution to the above differential equation, for non zero initial condition $C_1(0)$ is

~~unit~~ step

$$M_1 = \left\{ \frac{B}{k_{10}} - \left(\frac{B}{k_{10}} - M_1(0) \right) e^{-k_{10} t} \right\} u(t)$$

impulse

* For a bolus injection input, $f(t)$, the solution is given by
$$m_1 = \{e^{-k_{10}t}\} u(t)$$

pulse

* If the input is a hypodermic needle injection, $u(t) - u(t-t_1)$ with zero initial conditions, the response (based on superposition) is
$$m_1 = \frac{1}{k_{10}}\left(1 - e^{-k_{10}t}\right)u(t) - \frac{1}{k_{10}}\left[1 - e^{-k_{10}(t-t_1)}\right]u(t-t_1)$$

Example

The figure shows a block diagram of an ultrafiltration dialysis process. The "patient" system can be modelled by three subsystems or blocks ("trunk", "arms" and "legs"). In each of these blocks, there is a volume of liquid (plasma) defined, respectively, by $V_T(t)$, $V_A(t)$, and $V_L(t)$. There is a transfer of liquid (plasma) among blocks, according to the transfer constants k_{TA}, k_{TL}, k_A and k_L. Finally, the ultrafiltration process removes a quantity of liquid defined by $UFR(t)$ from the "trunk" block.

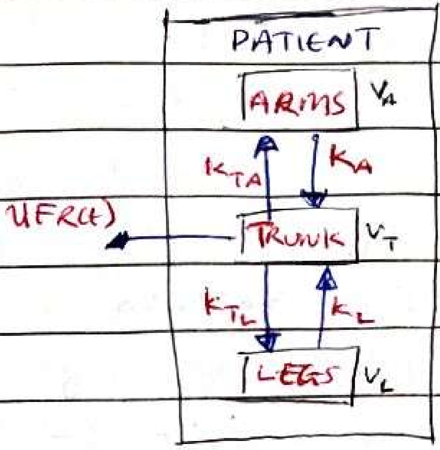


fig: Scheme of an ultrafiltration dialysis process

The dynamic equations defining the transfer of liquid between blocks are as follows:

$$\frac{dV_T(t)}{dt} = -(k_{TA} + k_{TL})V_T(t) + k_A V_A(t) + k_L V_L(t) - UFR(t)$$

$$\frac{dV_A(t)}{dt} = -k_A V_A(t) + k_{TA} V_T(t)$$

$$\frac{dV_L(t)}{dt} = -k_L V_L(t) + k_{TL} V_T(t)$$

(a) Obtain the block diagram in the s domain that form the "patient" system, considering $UFR(t)$ the input and $V_T(t)$ the output

(b) Obtain the transfer function for the "patient" system.

(c) Transform the block diagram until it is in the form of a simple feedback system in terms of transfer function blocks.

(d) Determine the transfer function, its zeros and poles and plot a map of zeros and poles, when the transfer constants have the following values:

$k_{A} = 0.15$; $k_L = 0.25$; $k_{TA} = 0.33$; $k_{TL} = 0.28$

(e) The system is controlled by a feedback closed loop, where the quantity UFR of liquid to be removed is proportional to the difference between the trunk volume V_T and its desired value R (the reference trunk volume) according to the expression $UFR = k(V_T - R)$. Obtain the closed-loop transfer function when $k = 2$

(f) Plot the closed-loop impulse and step responses.

Solution

(a) We want to put the given system in the form

$$UFR(s) \longrightarrow \boxed{G(s)} \longrightarrow V_T(s)$$

Patient

and determine $G(s)$ (~~pro~~ problem (b))

Moving the system equations to the s-domain by taking Laplace transforms of the equations:

$$sV_T(s) = -(k_{TA} + k_{TL})V_T(s) + k_A V_A(s) + k_L V_L(s) - UFR(s)$$

$$sV_A(s) = -k_A V_A(s) + k_{TA} V_T(s)$$

$$sV_L(s) = -k_L V_L(s) + k_{TL} V_T(s)$$

Grouping terms according to the variables on the left-hand sides: ~~[illegible]~~

$$sV_T(s) + k_{TA}V_T(s) + k_{TL}V_T(s) = k_A V_A(s) + k_L V_L(s) - UFR(s)$$

$$sV_A(s) + k_A V_A(s) = k_{TA} V_T(s)$$

$$sV_L(s) + k_L V_L(s) = k_{TL} V_T(s)$$

$$(s + k_{TA} + k_{TL}) V_T(s) = k_A V_A(s) + k_L V_L(s) - UFR(s)$$

$$\therefore \quad V_T(s) = \frac{k_A V_A(s)}{s + k_{TA} + k_{TL}} + \frac{k_L V_L(s)}{s + k_{TA} + k_{TL}} - \frac{UFR(s)}{s + k_{TA} + k_{TL}} \quad \text{---(i)}$$

$$(s + k_A) V_A(s) = k_{TA} V_T(s)$$

$$\therefore \quad V_A(s) = \frac{k_{TA} V_T(s)}{s + k_A} \quad \text{---(ii)}$$

$$(s + k_L) V_L(s) = k_{TL} V_T(s) \quad \text{---(iii)}$$

$$\therefore \quad V_L(s) = \frac{k_{TL} V_T(s)}{s + k_L}$$

It therefore appears that V_T has three inputs: V_A, V_L, and UFR (i); likewise V_A and V_L appear to have input as V_T from (ii) and (iii) above.

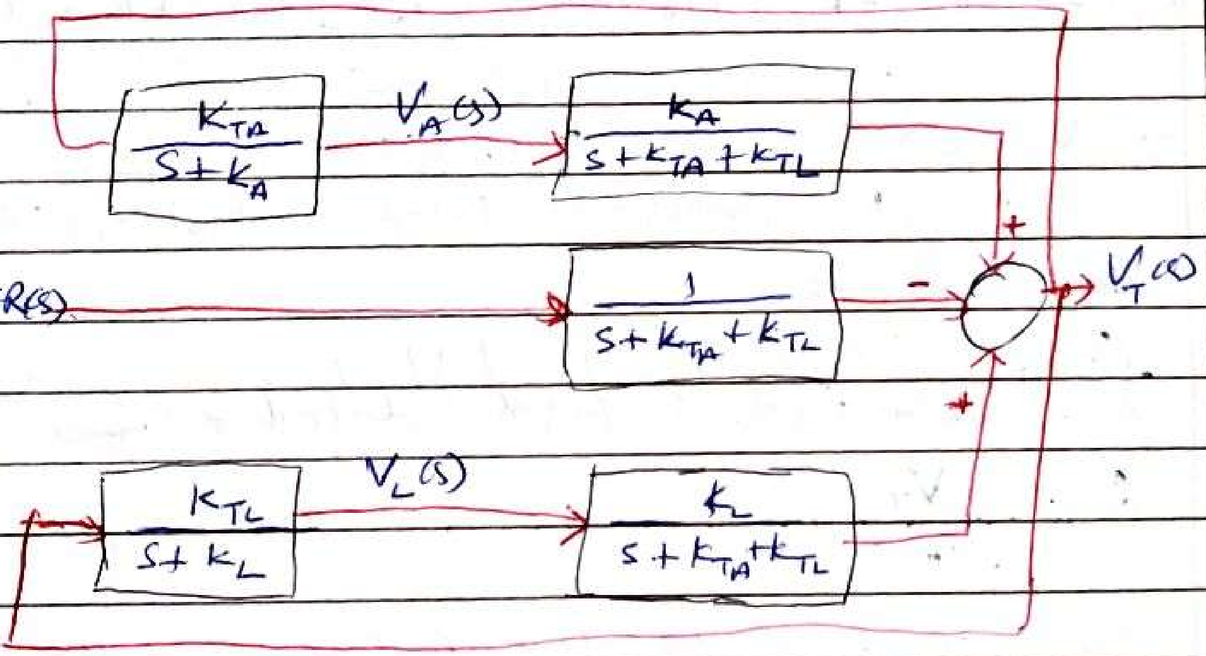


fig: Graphical representation of the system equations.

(3) To obtain the transfer function of the system $G(s)$, we can substitute the expression of $V_A(s)$ in (ii) and $V_L(s)$ in (iii) into (i):

$$V_T(s) = \left(\frac{k_A}{s+k_{TA}+k_{TL}}\right)\left(\frac{k_{TA}}{s+k_A}\right)V_T(s) + \left(\frac{k_L}{s+k_{TA}+k_{TL}}\right)\left(\frac{k_{TL}}{s+k_L}\right)V_T(s)$$

$$- \left(\frac{1}{s+k_{TA}+k_{TL}}\right)uFR(s)$$

$$= V_T(s)\left[\frac{k_A k_{TA}}{(s+k_{TA}+k_{TL})(s+k_A)} + \frac{k_L k_{TL}}{(s+k_{TA}+k_{TL})(s+k_L)}\right]$$

$$- \left(\frac{1}{s+k_{TA}+k_{TL}}\right)uFR(s)$$

$$V_T - V_T\left[\frac{k_A k_{TA}}{(s+k_{TA}+k_{TL})(s+k_A)} + \frac{k_L k_{TL}}{(s+k_{TA}+k_{TL})(s+k_L)}\right]$$

$$= -\left(\frac{1}{s+k_{TA}+k_{TL}}\right)uFR$$

Multiplying through by $(s+k_{TA}+k_{TL})(s+k_A)(s+k_L)$ yields

$$V_T(s+k_{TA}+k_{TL})(s+k_A)(s+k_L) - V_T\left[k_A k_{TA}(s+k_L) + k_L k_{TL}(s+k_A)\right]$$

$$= -(s+k_A)(s+k_L)\,uFR$$

$$V_T\left[-(s+k_{TA}+k_{TL})(s+k_A)(s+k_L) + k_A k_{TA}(s+k_L) + k_L k_{TL}(s+k_A)\right]$$

$$= (s+k_A)(s+k_L)\,uFR$$

$$\therefore \frac{V_T}{uFR} = \frac{(s+k_A)(s+k_L)}{k_A k_{TA}(s+k_L) + k_L k_{TL}(s+k_A) - (s+k_{TA}+k_{TL})(s+k_A)(s+k_L)}$$

~~when expanded~~

$$G(s) = \frac{V_T}{uFR}$$

You can expand the above equation to get the numerator and denominator of $G(s)$ as polynomials.

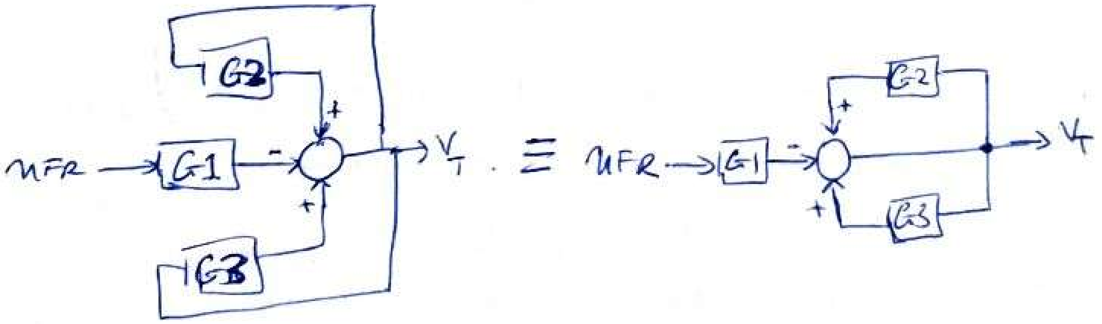
$$G(s) = \frac{s^2 + s(k_A + k_L) + k_A k_L}{s^3 + (k_A + k_L + k_{TA} + k_{TL})s^2 + (k_A k_L + k_A k_{TL} + k_L k_{TA})s}$$

MATLAB

```
%% Obtaining the transfer function from the system's equations
% Define symbolic variables
syms s VT VA VL uFR KTA KTL KA KL
% Define systems equations
VA = KTA/(s+KA)*VT;
VL = KTL/(s+KL)*VT;
eq = VT == (KA/(s+KTA+KTL))*VA + (KL/(s+KTA+KTL))*VL - ...
        (1/(s+KTA+KTL))*uFR;
% Solve the system's equations, obtaining VT as a function of UFR
   VT = solve(eq, VT);
% obtain system transfer function
   G = VT/uFR;
   G = collect(G); % write G as a quotient of polynomials
   pretty(G);
```

The result should be the same as obtained by hand previously

(c) The figure (previously shown) shows the graphical/schematic arrangement of the transfer function can be ~~[illegible]~~ reproduced as



where $G1(s) = \dfrac{1}{s + k_{TA} + k_{TL}}$; $G3(s) = \dfrac{k_{TL}}{s + k_L} \cdot \dfrac{k_L}{s + k_{TA} + k_{TL}}$

$G2(s) = \dfrac{k_{TA}}{s + k_A} \cdot \dfrac{k_A}{s + k_{TA} + k_{TL}}$

We can simplify this using block diagram algebra or alternatively,

$$V_T(s) = -G1(s)uFR(s) + G2(s)V_T(s) + G3(s)V_T(s)$$

$$= -G1(s)uFR + [G2(s) + G3(s)]V_T(s)$$

$$V_T(s) - [G2(s) + G3(s)]V_T(s) = -G1(s)uFR$$

$$V_T(s)[1 - G2(s) - G3(s)] = -G1(s)uFR$$

$$\frac{V_T(s)}{uFR(s)} = \frac{-G1(s)}{1 - G2(s) - G3(s)} \equiv \frac{G1(s)}{G2(s) + G3(s) - 1}$$

¿ Confirm using MATLAB that the resulting transfer function is the same?

(d) Given that $k_A = 0.15$; $k_L = 0.25$; $k_{TA} = 0.33$; $k_{TL} = 0.28$

$$G(s) = \frac{V_T}{uFR} = \frac{-(s^2 + 0.4s + 0.0375)}{s^3 + 1.01s^2 + 0.162s} = \frac{-(s^2 + 0.4s + 0.0375)}{s(s^2 + 1.01s + 0.162)}$$

* ! determine the poles and zeros by hand, and confirm using Matlab!

There's a shorter way to do this than what follows, but since we've been doing symbolic computing, it is instructive use this method.

```
%% Obtaining numeric transfer function from symbolic, and then its
%% poles, zeros, and a pole-zero map

% Substituting the transfer constraints by their values
 G= subs(G, [KA,KL,KTA,KTL],[0.15, 0.25, 0.33, 0.28]);
[numGs, denGs] = numden(G); % obtains num. and den. of G(s)

% convert symbolic G(s) to transfer function object
 numG = sym2poly(numGs);
denG=sym2poly (denGs);
 % ie. obtaining the numerator and denominator of G(s) as a
 % numeric vector
 G = tf(numG, denG); % obtain G(s) as a transfer-function object
G=minreal(G); % obtain the minimal realisation of G(s)
 display(G);
```

% obtain poles and zeros of G(s)

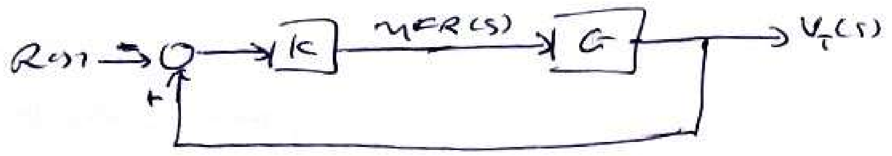
```
zerosG = zero(G)
polesG = pole(G)
```

% plot the pole-zero map

```
pzmap(G)
```

Compare your results to hand calculated values.

(e) We have the closed-loop ultrafiltration dialysis process diagram:



where $UFR(s) = K(V_T - R)$ as ~~defined~~ given/shown ; $K = 2$

let $\frac{V_T}{R} = M$; the closed-loop transfer function

$$V_T = G \cdot UFR = GK(V_T - R)$$

$$V_T - GKV_T = -GKR$$

$$V_T(1 - GK) = -GKR$$

$$\frac{V_T}{R} = \frac{-GK}{1-GK} \equiv \frac{GK}{GK-1} = M(s)$$

$$M(s) = \frac{2s^2 + 0.8s + 0.075}{s^3 + 3.01s^2 + 0.962s + 0.075}$$

% obtaining the closed loop transfer function

```
> k=2;
> M=k*G/(k*G-1)
> M=minreal(M);
> display(M);
```

(f) %% obtain the closed-loop impulse and step responses

% obtaining ~~impulse~~ the responses

```
[ir, t] = impulse(M); % obtaining the impulse response
sr= step(M,t); % obtaining the step response
```

```
% Plotting the responses
figure;
plot(t, ir, 'b', t, sr, 'r');
axis tight;
legend({'Impulse response', 'Step response'}, 'Location', 'Best');
xlabel('Time');
ylabel('V_T(t)');
```

Example Drug administration / Compartment model

Extravascular administration of drugs (oral, rectal, intramuscular, transdermal, subcutaneous) can be modelled by two connected compartments. In the first of these compartments, for example the digestive tract, there is an amount of drug $x(t)$ which increases with the administration of the drug and decreases by the absorption of the drug in the blood plasma, which is reflected in the following equation:

$$\frac{dx(t)}{dt} = q(t) - k_a x(t)$$

where $q(t)$ is the rate of administered drug, and k_a is the absorption constant.

In the second compartment, which represents the blood plasma, there is an amount of drug $p(t)$ which increases with absorption and decreases by elimination of the drug, which is reflected in the following equation

$$\frac{dp(t)}{dt} = k_a x(t) - k_e p(t)$$

where k_e is the elimination constant.

Finally, the plasmatic concentration $c(t)$ is the amount of drug in the plasma per unit volume, i.e.

$$c(t) = \frac{p(t)}{V_d}$$

where V_d is a constant called the apparent volume of distribution.

(a) Obtain the block diagram of the system and derive its transfer function.

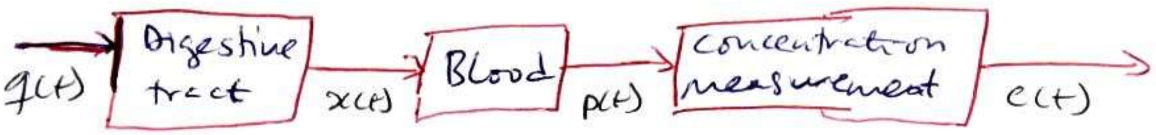


fig: functional diagram of the extravascular administration of drugs system

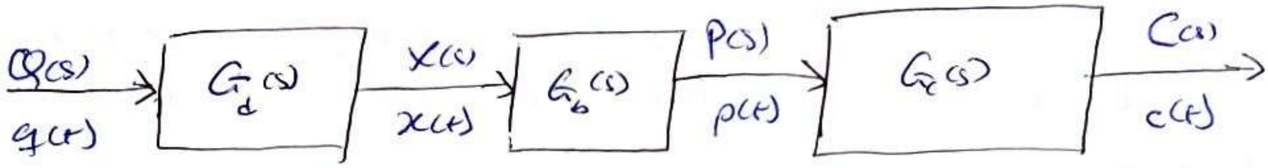


fig: Block diagram in the s domain

$$\dot{x}(t) = q(t) - k_a x(t)$$ for the first block

$$\Rightarrow \quad s X(s) = Q(s) - k_a X(s)$$

$$(s + k_a) X(s) = Q(s)$$

$$\frac{X(s)}{Q(s)} = \frac{1}{s + k_a} = G_d(s)$$

$$\dot{p}(t) = k_a x(t) - k_e p(t)$$ for the second block

$$s P(s) = k_a X(s) - k_e P(s)$$

$$(s + k_e) P(s) = k_a X(s)$$

$$G_b(s) \equiv \frac{P(s)}{X(s)} = \frac{k_a}{s + k_e}$$

for the third block

$$c(t) = \frac{P(t)}{V_d}$$

$$\therefore \quad C(s) = \frac{P(s)}{V_d}$$

$$G_c(s) = \frac{C(s)}{P(s)} = \frac{1}{V_d}$$

The overall transfer function

$$G(s) = \frac{C(s)}{Q(s)} = G_d(s)\, G_b(s)\, G_c(s)$$

$$= \frac{1}{s+k_a} \cdot \frac{k_a}{s+k_e} \cdot \frac{1}{V_d}$$

$$G(s) = \left(\frac{k_a}{V_d}\right)\left[\frac{1}{(s+k_a)(s+k_e)}\right]$$

(b) Find the order, undamped natural frequency, and damping ratio of the system. Derive the values of the constants required for the system to be undamped.

- From the transfer function obtained above, the system is second order.
- Set $G(s) = \dfrac{K\omega_n^2}{s^2 + 2\zeta\omega_n s + \omega_n^2} = \dfrac{(k_a/V_d)}{s^2 + (k_a+k_e)s + k_a k_e}$

· this obviously works since corresponding terms can be matched.

$$G(s) = \frac{\frac{k_a k_e}{k_a k_e}\left(\frac{k_a}{V_d}\right)}{s^2 + (k_a+k_e)s + k_a k_e} = \frac{\left(\frac{1}{k_e V_d}\right) k_a k_e}{s^2 + (k_a+k_e)s + k_a k_e}$$

Hence we see that $K = \dfrac{1}{k_e V_d}$

- from $\omega_n^2 = k_a k_e$

$\omega_n = \sqrt{k_a k_e}$ this is the undamped natural frequency

- For the damping ratio

$$\zeta = \frac{k_a + k_e}{2\omega_n} = \frac{k_a + k_e}{2\sqrt{k_a k_e}}$$

- For the system to be underdamped, the damping ratio will be less than 1 i.e. $\zeta < 1$:

$$\frac{k_a + k_e}{2\sqrt{k_a k_e}} < 1$$

$$\frac{(k_a + k_e)^2}{4 k_a k_e} < 1$$

$$(k_a + k_e)^2 < 4 k_a k_e$$

$$(k_a + k_e)^2 - 4 k_a k_e < 0$$

$$k_a^2 + k_e^2 + 2 k_a k_e - 4 k_a k_e < 0$$

$$k_a^2 + k_e^2 - 2 k_a k_e < 0$$

Dividing through by k_a^2

$$1 + \frac{k_e^2}{k_a^2} - \frac{2 k_e}{k_a} < 0$$

$$1 + \left(\frac{k_e}{k_a}\right)^2 - 2\left(\frac{k_e}{k_a}\right) < 0$$

At this point it may not be clear how to interpret this. However, if we form fractions of k_a & k_e, we may simplify it sufficiently for interpretation

$$1 + R^2 - 2R < 0 \quad \text{where } R = \frac{k_e}{k_a}$$

rearranged,

$$R^2 - 2R + 1 < 0$$

$$(R - 1)^2 < 0$$

The above condition on R cannot be fulfilled for any real value of R, Hence no combination of constants $\frac{k_e}{k_a}$ will cause the system to have an underdamped behaviour.

(c) Obtain the evolution of plasma concentration ~~[illegible]~~ when a D_0 oral dose is administered.

- When an oral dose D_0 is administered, it is possible to model the rate of drug dispensed as an impulse:

$$q(t) = D_0 \delta(t)$$
$$Q(s) = D_0$$

So the plasmatic concentration is

$$C(s) = G(s)Q(s) = \left(\frac{k_a}{V_a}\right)\frac{1}{(s+k_a)(s+k_e)} \cdot D_0$$

- We can obtain $c(t) = \mathcal{L}^{-1}\{C(s)\}$ using the following matlab code:

```
%% Symbolic computation of plasmatic concentration
syms s ka ke Vd D0 % define symbolic variables & constants
G =(ka/Vd)/((s+ka)*(s+ke)); % system transfer function
Q = D0 % System's input in s-domain
C = G * Q
c = ilaplace(C); % system's output in time domain
```

$$c(t) = \frac{D_0 k_a}{V_d(k_a - k_e)}\left(e^{-k_e t} - e^{-k_a t}\right)$$

(d) Derive the peak plasma concentration c_p and the time t_p in which it occurs

- At the peak of the plasma concentration, it's derivative is zero, so at the time of the peak $t = t_p$

$$\left.\frac{dc(t)}{dt}\right|_{t=t_p} = 0$$

[do that by hand first]

To solve by MATLAB:

```
% Symbolic computation at peak plasma concentration
syms t tp
dc_dt = diff(c, t) % Plasmatic concentration time derivative
tp = solve(dc_dt == 0, t)
pretty(tp);
cp = subs(c, t, tp)'; % plasma concentration at peak time
pretty(cp);
```

$$t_p = \frac{\ln\left(\frac{k_a}{k_e}\right)}{k_a - k_e}$$

$$c_p = \frac{D_0 k_a}{V_d (k_a - k_e)}\left(e^{-k_e t_p} - e^{-k_a t_p}\right)$$

Now consider the case of a patient, with an apparent volume of $V_d = 10\,L$, to which an oral dose $D_0 = 500$ mg of a certain drug is administered. Under these circumstances, a peak concentration of $c_p = 30$ mg/L is reached 8 hours ~~[illegible]~~ after the drug administration.

(e) Obtain the values of the absorption and elimination constants

(f) Draw the evolution of plasmatic concentration.

(2) If we know c_p and t_p, it is possible to determine the constants k_a and k_e, by solving the above equations. Note that there is no analytical solution for them, so a numerical result will be obtained using the following MATLAB code:

```
%% Numerical computation of the absorption and elimination
    rates
D0=500;
Vd = 10;
Par.D0=D0;
Par.Vd = Vd;
Par.tp = 8; % Experimental value of peak time
Par.cp=30; % Experimental value of peak concentration
x = fsolve(@(x) AbsElimRateEquations(x, Par), [2, 1]); % solve
ka = x(1); % Absorption rate
ke = x(2); % elimination rate
display(ka);
display(ke);
%% Equation for absorption and elimination rates as a function of peak response
Function F= AbsElimRateEquations(x, Par)
                          absorption and elimination rates
ka= x(1)  % x: vector containing
ke= x(2)
D0 = Par.D0; % initial drug dose
Vd = Par.Vd;  % apparent volume of distribution
tp = log(ka/ke)/(ka-ke); % computed peak time value
A = D0*ka/(Vd*(ka-ke)); % An intermediate variable
cp = A*exp(-ke*tp) - A*exp(-ka*tp); % computed peak concentration
eq1 = tp - Par.tp ; % equation for peak time
eq2 = cp - Par.cp ; % equation for peak concentration
F= [eq1 eq2]; % set of equation's result (should be zero)
```

You should get $k_a = 0.2164\ h^{-1}$; $k_e = 0.0639\ h^{-1}$

(f) The evolution of the plasmatic concentration

```
> s=tf('s');
> G = (ka/Vd)/((s+ka)*(s + ke));
> [c, t]= impulse(G*D0);
> plot(t,c);
> xlim([0, t(end)]);
> xlabel('Time (hours)');
> ylabel('Plasmatic concentration (mg/mL)');
```