Compartment Models

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Introduction

- Early work by Teorell and Widmark on propagation of alcohol in the body 1920
- Teorell coined the term compartment model around 1937
- Extensive application in pharmacokinetics Dost 1953
  - Models required for FDA approval of new drugs
  - Sheppard and Householder 1953
- Pulse testing
  - Standard technique in ecological systems
  - Measurement of blood volume and blood flow in vessels
  - Extensive use in industry

A Practical View

Doctors need simple models for the daily work. Key questions:

- How much drug should be administered?
- How should it be taken: inhalation, intravenously, intramuscularly, orally?
- How quickly will it act?
- How long will it act?

These questions all relate to the dynamics of propagation of drugs in the body.

A Single Compartment Model

Consider a single compartment with volume V and flow q. Assume that the amount m is injected into the volume. The concentration is then given by

$$\frac{dc}{dt} = -\frac{q}{V}c$$

where the initial concentration is $c(0) = m/V$. Solving the differential equation we find that the concentration decays exponentially

$$c(t) = \frac{m}{V}e^{-qt/V}$$

The dynamics can be captured by two quantities

- Volume of distribution V $[m^3]$ o
- Clearance q $[m^3/s]$

The ratio q/V $[s^{-1}]$ is called the elimination constant

Volume of Distribution

Assume that there are two volumes V_1 and V_2 with concentrations c_1 and c_2 with strong interaction. Furthermore assume that the volume V_1 is the one that is accessible to other compartments. If we represent the system with one compartment having the same mass, concentration c_1 and volume V we find that

$$c_1 V = c_1 V_1 + c_2 V_2$$

Hence

$$V = V_1 + \frac{c_2 V_2}{c_1}$$

The volume V can be very large even if V_2 is small if the ratio c_2/c_1 is large

Finding the Parameters

The concentration is given by

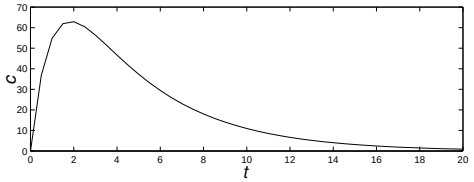
$$c(t) = \frac{m}{V}e^{-qt/V}$$

If the clearance and the volume of distribution are known it is easy to determine the concentration as a function of time t and dose m. The parameters q and V can be determined experimentally in the following way

- The volume of distribution can be determined from the dose m and the initial concentration $c(0)$ using the formula $V = m/c(0)$
- The elimination constant q/V can be determined by observing that $\log c(t) = -qt/V$. Plotting $\log c(t)$ versus time gives a straight line with slope t

Back to Reality

Unfortunately the simple model does not agree with experiments. The concentration curve typically looks like this



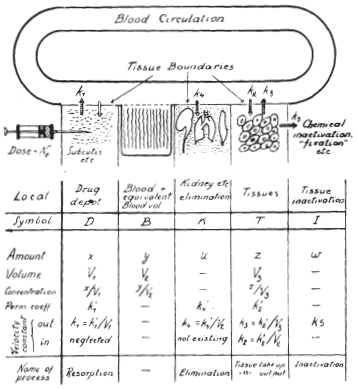
which indicates that the first order model is too simplistic. In practice it is still used by neglecting the initial part of the curve and approximating the tail by a single exponential

Compartment Models

Compartment Models

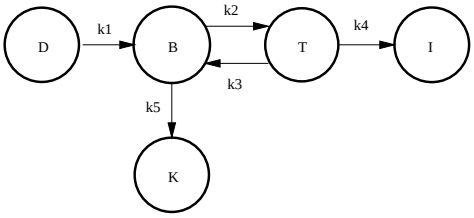
- Widmark 1920 Effect of alcohol on the human
- Teorell 1937 How drug injection propagates in the body
- Pharmacokinetics
- A special class of linear dynamical systems
- Nowadays required for FDA registration of medicines
- Advanced dosage (2 aspirin 3 times per day)
- Indirect measurements of volume and flow
- Use of radioactive tracers

Teorell's Model



Propagation of Drugs in the Body

T. Teorell (1937) Kinetics of Distribution of Substances Administered to the Body I and II. Arch. Int. de Pharm. et de Therapies 57(205-225), 57(226-240).



A Mathematical Model

- Consider the body as a collection of compartments.
- Rate of transport between two compartment is proportional to the difference in concentration. For a system with two compartments we have

$$\frac{dx_1}{dt} = k(c_2 - c_1) = k\left(\frac{x_2}{V_2} - \frac{x_1}{V_1}\right) = -k_1 x_1 + k_2 x_2$$
$$\frac{dx_2}{dt} = k(c_1 - c_2) = k\left(\frac{x_1}{V_1} - \frac{x_2}{V_2}\right) = k_1 x_1 - k_2 x_2$$

  where x_1 is the number of molecules in compartment 1, and V_1 its volume, and c_1 the concentration in compartment 1, etc.
- Nonlinear transfer mechanism can also be used
- Notice that this particular model is closed!

Two Ways to Write the Models

In terms of the extensive variable mass x as

$$\frac{dx_1}{dt} = -\frac{k}{V_1}x_1 + \frac{k}{V_2}x_2$$
$$\frac{dx_2}{dt} = \frac{k}{V_1}x_1 - \frac{k}{V_2}x_2$$

or in terms of the intensive variable concentration c

$$\frac{dc_1}{dt} = -\frac{k}{V_1}c_1 + \frac{k}{V_1}c_2 = k_1(c_1 - c_2)$$
$$\frac{dc_2}{dt} = \frac{k}{V_2}c_1 - \frac{k}{V_2}c_2 = k_2(c_2 - c_1)$$

Notice structure of equations and coefficients

$$\frac{dx}{dt} = \begin{pmatrix} -k/V_1 & k/V_2 \\ k/V_1 & -k/V_2 \end{pmatrix} x, \quad \frac{dc}{dt} = \begin{pmatrix} -k/V_1 & k/V_1 \\ k/V_2 & -k/V_2 \end{pmatrix} c$$

Left Eigenvalues and Invariants

$$\frac{dx}{dt} = Ax = \begin{pmatrix} -k/V_1 & k/V_2 \\ k/V_1 & -k/V_2 \end{pmatrix} x$$

We have

$$\begin{pmatrix} 1 & 1 \end{pmatrix} \begin{pmatrix} -k/V_1 & k/V_2 \\ k/V_1 & -k/V_2 \end{pmatrix} = \begin{pmatrix} 0 & 0 \end{pmatrix}$$

A left eigenvector has zero eigenvalue. Physical interpretation

The audience is thinking!

Conclusion

A left eigenvector $v = \begin{pmatrix} 1 & 1 \end{pmatrix}$ with eigenvalue $\lambda = 0$ to the matrix A implies that

$$v\frac{dx}{dt} = \frac{dx_1}{dt} + \frac{dx_2}{dt} = 0$$

Hence

$$x_1 + x_2 = constant$$

conservation of mass!

Right Eigenvalues and Eigenvectors

$$\frac{dc}{dt} = Ac = \begin{pmatrix} -k/V_1 & k/V_1 \\ k/V_2 & -k/V_2 \end{pmatrix}$$

We have

$$\begin{pmatrix} -k/V_1 & k/V_2 \\ k/V_2 & -k/V_2 \end{pmatrix} \begin{pmatrix} 1 \\ 1 \end{pmatrix}$$

A right eigenvector has zero eigenvalue. Physical interpretation?

The audience is thinking!

Conclusion

A right eigenvector $v = \begin{pmatrix} 1 \\ 1 \end{pmatrix}$ with eigenvalue $\lambda = 0$ to the matrix A implies that if the initial condition is

$$c(0) = v$$

it follows that

$$\frac{dc}{dt} = Ac$$

and we have $Av = 0$ and the solution

$$x(t) = v = \begin{pmatrix} 1 \\ 1 \end{pmatrix}$$

is an equilibrium

The General Case of the Mass Balance

The general case of the mass balance is

$$\frac{dx_i}{dt} = \sum_{j \neq i} k_{ij} x_j - \sum_{i \neq j} k_{ji} x_i + u_i = \sum_{j \neq i} k_{ij} x_j - k_{ii} x_i + u_i$$

where x_i is the mass in compartment i, and k_{ij} is the rate constant for transport from compartment j to compartment i.
Notice that $k_{ij} \geq 0$ when $i \neq j$.

An Alternative Representation

The equation can also be written as

$$\frac{dx}{dt} = Ax + Bu$$

with

$$a_{ij} \geq 0 \quad \text{for } i \neq j, \quad a_{ii} \leq 0, \quad |a_{ii}| \geq \sum a_{ij}, \quad b_i \geq 0$$

Notice that we can always obtain a system with

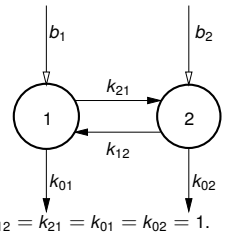
$$\sum a_{ij} = 0$$

by including sources and sinks as extra compartments (a closed system)

Graphical Representation

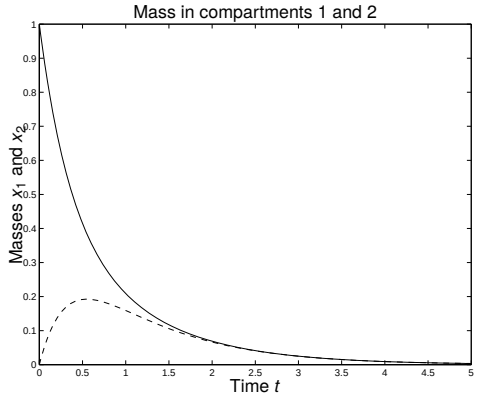
Mathematical model
mass balance

$$\frac{dx_1}{dt} = -(k_{01} + k_{21})x_1 + k_{12}x_2 + b_1 u$$
$$\frac{dx_2}{dt} = k_{21}x_1 - (k_{02} + k_{12})x_2 + b_2 u$$

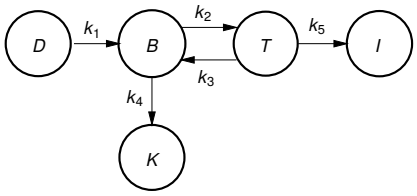


Assume the following numerical values $k_{12} = k_{21} = k_{01} = k_{02} = 1$.
What happens if an impulse is injected to compartment 1.

Results

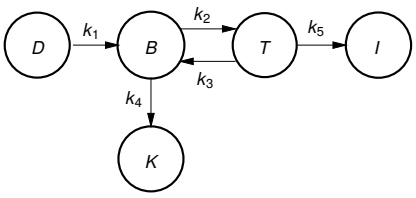


Teorells Model



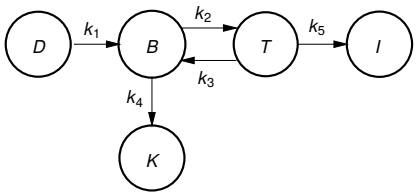
- D Tissue where drug is injected
- B Blood
- T Tissue where drug should work
- K Kidney
- I Drug inactivation

Teorells Model



$$A = \begin{pmatrix} -k_1 & 0 & 0 & 0 & 0 \\ k_1 & -(k_2 + k_4) & k_3 & 0 & 0 \\ 0 & k_2 & -(k_3 + k_5) & 0 & 0 \\ 0 & k_4 & 0 & 0 & 0 \\ 0 & 0 & k_5 & 0 & 0 \end{pmatrix}, \quad B = \begin{pmatrix} 1 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}$$

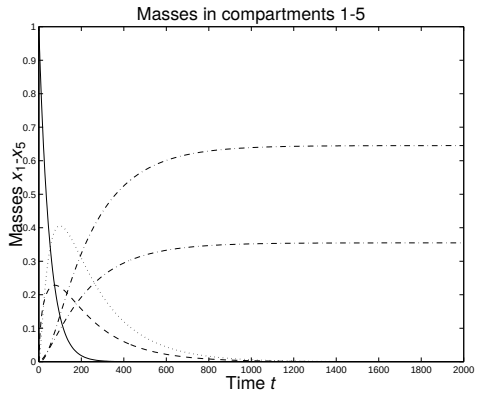
A Simplified Model



$$A = \begin{pmatrix} -k_1 & 0 & 0 \\ k_1 & -(k_2 + k_4) & k_3 \\ 0 & k_2 & -(k_3 + k_5) \end{pmatrix}, \quad B = \begin{pmatrix} 1 \\ 0 \\ 0 \end{pmatrix}$$

$$C = \begin{pmatrix} 0 & 1/V_b & 0 \\ 0 & 0 & 1/V_t \end{pmatrix}, \quad D = \begin{pmatrix} 0 \\ 0 \end{pmatrix}$$

Results



Some Interesting Problems

- Modeling: Determine number of compartments and transfer coefficients
- Effectiveness of the drug. How much comes to the right organ?
- Use of tracers
- Patient to patient variations
- Dosage: Assume that a certain concentration of drug is desired. How should it be administered.
- Discrete or continuous injection
- Tablets versus injections
- Nonlinear transfer mechanisms

General Properties

- Compartment models are linear systems with special properties
- Related to positive matrices (Frobenius theorem)

  All elements except the diagonal are positive
- Compartment systems are always stable (possibly an eigenvalue $\lambda = 0$)
- With some technical assumptions (irreducibility) it can be concluded that:
  - All eigenvalues of the system matrix A are in the left half plane or at the origin
  - For closed systems one eigenvalue is at the origin
  - For open systems all eigenvalues are in the left half plane

An Example

Consider the simple cyclic system

$$A = \begin{pmatrix} -1 & 0 & 1 \\ 1 & -1 & 0 \\ 0 & 1 & -1 \end{pmatrix}$$

The characteristic polynomial is

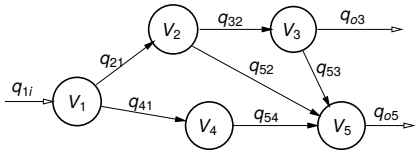
$$\det \lambda I - A = (\lambda + 1)^3 - 1 = \lambda(\lambda^2 + 3\lambda + 3)$$

The eigenvalues are $\lambda = 0$, and $\lambda = -3/2 \pm i\sqrt{3/2}$. This system has complex eigenvalues and consequently oscillatory behavior.

Compartment Models

Flow Systems

A collection of tanks with perfect mixing connected by pipes



Problems of measuring flows and volumes using tracers will now be investigated. Typical applications are

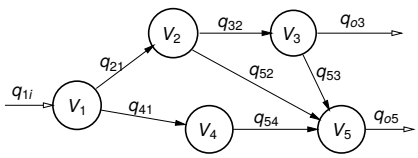
- Biomedical
- Industrial

Classification of Flow Systems

- Open
- Closed
- Completely connected
- Catenary
- Circular
- Mammilar
- Symmetric

Flow Systems

A collection of tanks with perfect mixing connected by pipes



- V_i Volume [m^3] of ith tank
- q_{kl} Flow rate [kg/m^3] from tank l to tank k
- q_{ki} Inflow [kg/m^3] to tank k
- q_{ol} Outflow [kg/m^3] from tank l

The Tracer Equations

Let c_k be the concentration of a tracer substance in tank V_k. Assume that the tracer moves in the same way as the fluid. Then

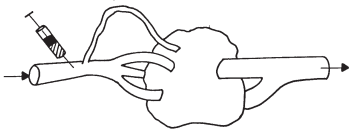
$$V_k \frac{dc_k}{dt} = \sum_{l=1, l\neq k}^{n} q_{kl} c_k - \sum_{l=0, l\neq k}^{n} q_{lk} c_l + q_{ki} c_i$$

where

$$\sum_{l=1, l\neq k}^{n} q_{kl} + q_{ki} = 0$$

Compartment Models

Tracer Experiments



Idea: Inject a tracer in the system. Measure tracer concentration at some point in the system. Determine volumes and flows.
Compare with counting of animals in the wood!

Tracer Propagation - Example 1

Consider a tank with volume V. Assume that there is a flow with rate q through the tank. Inject a tracer with concentration c_{in} at the inlet. Assume that the tracer mixes perfectly with the fluid. A mass balance gives

$$V \frac{dc}{dt} = q(c_{in} - c)$$

where c is the concentration in the tank and in the outlet.
The relation between c and c_{in} is a dynamical system with impulse response

$$g(t) = e^{-\frac{qt}{V}}$$

and transfer function

$$G(s) = \frac{1}{1 + sV/q}$$

Tracer Propagation - Example 2

Consider a pipe with volume V. Assume that there is a flow with rate q through the pipe. Inject a tracer with concentration c_{in} at the inlet. Assume that the tracer mixes perfectly with the fluid. The concentration c_{out} at the outlet is then given by

$$c_{out}(t) = c_{in}\big(t - \frac{V}{q}\big)$$

The relation between c_{out} and c_{in} is a dynamical system with the impulse response

$$g(t) = \delta\big(t - \frac{V}{q}\big)$$

and the transfer function

$$G(s) = e^{-sq/V}$$

Tracer Propagation - General Properties

Consider a flow system with one inlet and one outlet. The propagation of a tracer through the system is a linear dynamical system with one input and one output. Let g be the impulse response of the system. The impulse response has the properties

$$g(t) \geq 0$$
$$\int_0^\infty g(t)dt = 1$$

The first equation says that the outlet concentration is never negative. The second equation says that all injected tracer must finally come out.

The Stewart Hamilton Equation

Consider a flow system with one inlet and one outlet. Let the inlet and outlet flows be q and let the volume of the system be V. Furthermore let g be the impulse response of the system. Then

$$\frac{V}{q} = \int_0^\infty t g(t)dt = T_{ar}$$

This formula has been used extensively in biology, ecology and engineering to determine volumes and flows. The quantity T_{ar} is called the average residence time.

Proof

The impulse response $g(t)$ can be interpreted as a probability density function for the time it takes a particle to pass through the system. Consider a collection of particle that enter the system at time t. The quantity $g(t)dt$ is the fraction of particles that enter the system in the time interval $(t, t + dt)$. These particles have traversed the volume qt. The total volume visited by all particles is thus

$$V = \int_0^\infty qtg(t)dt = q\int_0^\infty tg(t)dt$$

Dividing by q gives the Stewart-Hamilton equation.

Examples

Consider a tank having volume V $[m^3]$ and flow q $[m^3/s]$ with perfect mixing. The impulse response is

$$g(t) = \frac{q}{V} e^{-qt/V}$$

Integration gives

$$\int_0^\infty g(t)dt = \int_0^\infty \frac{q}{V} e^{-qt/V} dt = 1$$

Furthermore

$$\int_0^\infty tg(t)dt = \int_0^\infty t\frac{q}{V} e^{-qt/V} dt = \frac{V}{q}$$

Hence if the impulse response is measured and we know the flow the volume can be computed.

Computing Average Residence Times

Transfer functions are very convenient to use when computing average residence times. We have

$$G(s) = \int_0^t e^{-st} g(t)dt$$

Differentiating this with respect to s we get

$$G'(s) = -\int_0^t te^{-st} g(t)dt$$

Hence

$$T_{ar} = \int_0^t te^{-st} g(t)dt = -G'(0)$$

The average residence time T_{ar} is a useful characteristic.

Examples

Tank with perfect mixing

$$G(s) = \frac{1}{1 + sV/q}$$
$$G'(s) = -\frac{1}{(1 + sV/q)^2} \frac{V}{q}$$
$$T_{ar} = -G'(0) = \frac{V}{q}$$

Pipe with perfect mixing

$$G(s) = e^{-sV/q}$$
$$G'(s) = -\frac{V}{q} e^{-sV/q}$$
$$T_{ar} = -G'(0) = \frac{V}{q}$$

Series Connection of Tanks

The transfer function for a series connection is

$$G(s) = G_1(s)G_2(s)$$

Hence

$$G'(s) = G_1'(s)G_2(s) + G_1(s)G_2'(s)$$
$$T_{ar} = G'(0) = T_{ar1} + T_{ar2}$$

Since $G_i(0) = 1$

Measurement of Volume and Flow

Consider a flow system with volume V $[m^3]$ and through flow q $[m^3/s]$. Inject a given amount m of a tracer rapidly. If the injection time is so short that the injection can be regarded as an impulse. Let $c(t)$ $[kg/s]$ be the concentration of the substance at the outlet. We have

$$q \int_0^\infty c(t)dt = M$$

The flow can thus be determined by

$$q = \frac{M}{\int_0^\infty c(t)dt}$$

The quantity q which has dimension $[m^3/s]$ is called clearance

Measurement of Volume and Flow

We have

$$q = \frac{M}{\int_0^\infty c(t)dt}$$

It follows from the Stewart-Hamilton equation that

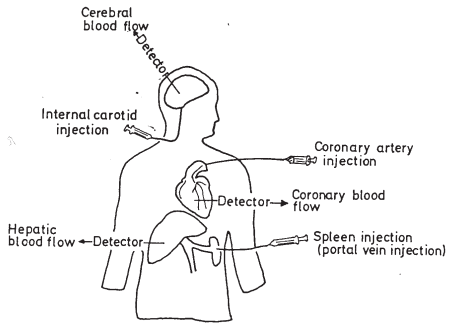
$$\frac{V}{q} = \frac{\int_0^\infty tc(t)dt}{\int_0^\infty c(t)dt}$$

Hence

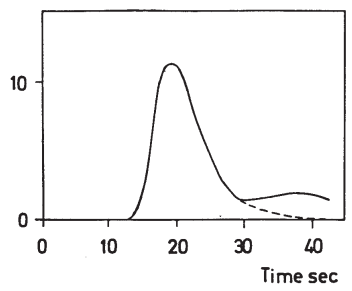
$$V = \frac{M \int_0^\infty tc(t)dt}{\left(\int_0^\infty c(t)dt\right)^2}$$

Pratical problems in computation of the infinite integrals

Many Examples

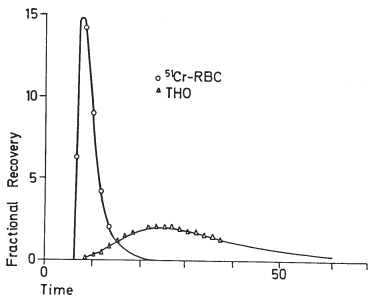


Impulse Response of the Heart



Notice the effect of recirculation.

Choice of Tracer is Important



Cr^{15} stays vascular, but THO penetrates extracellular

Volume of Distribution and Virtual Flow

In biological systems it is desirable to have a concept of volume for systems with very complicated flow patterns. The volume of distribution is such a measure. Assuming that the total amount of substance is m [kg] and that the system is in equilibrium. The concentration is then the same in all compartments and the volume of distribution is defined as

$$V_{dist} = \frac{m}{c}$$

This formula is often used in medicine to measure volumes. To apply it it is essential that the system is in equilibrium.
Since the concentration not necessarily is constant the volume is not necessarily equal to the true physical volume it is called *volume of distribution* or *apparent volume*.

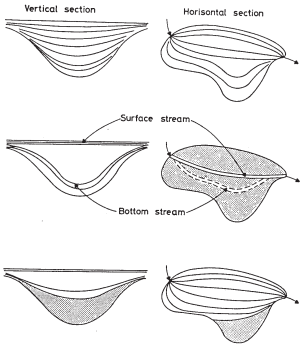
The Concept of Clearance

There are many different mechanisms that govern transport from one compartment to another. It is practical to have a simple way to describe removal of a substance from a compartment. Clearance or volumetric flow is such a measure. For a volume V with through-flow q $[\mathrm{m}^3/\mathrm{s}]$ the clearance is simply q. Clearance can also be defined as

$$q = \frac{w}{c}$$

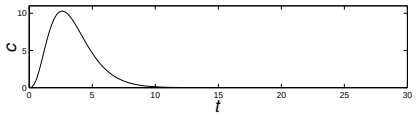
where w [kg/s] is the mass flow rate and c $[\mathrm{kg}/\mathrm{m}^3]$ the concentration.

Applications in Ecology

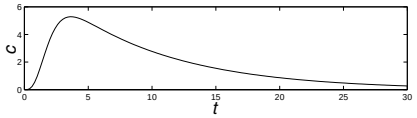


Applications in Industry

Tank volume 4000 m^3, flow 350 m^3/h, average residence time $T_{ar} = 11.4$.
Tank with 2 stirrers: $T_{ar} = 3.5\ h$, $V_e = 3.5 \times 350 = 1225$



Tank with 4 stirrers: $T_{ar} = 10.6\ h$, $V_e = 10.6 \times 350 = 3710$



Finding the Parameters of the System

We will first determine the input output relation between the injection and the concentration. The system is characterized by the matrices

$$A = \begin{pmatrix} -k_0 - k_1 & k_1 \\ k_2 & -k_2 \end{pmatrix}, \quad B = \begin{pmatrix} k_0 \\ 0 \end{pmatrix}, \quad C = \begin{pmatrix} 1 & 0 \end{pmatrix}$$

The transfer function for the system is

$$\begin{aligned} G(s) = C(sI - A)^{-1}B &= \begin{pmatrix} 1 & 0 \end{pmatrix} \begin{pmatrix} s + k_0 + k_1 & -k_1 \\ -k_2 & s + k_2 \end{pmatrix}^{-1} \begin{pmatrix} b_1 \\ 0 \end{pmatrix} \\ &= \frac{k_0(s + k_2)}{s^2 + (k_0 + k_1 + k_2)s + k_0 k_2} \end{aligned}$$

This calculation shows that the parameter combinations k_2, $k_0 + k_1 + k_2$ and $k_0 k_2$ can be determined which implies that all rate constants can be computed from the experiment

Finding the Parameters of the System

Consider an experiment where 10 g has been injected in compartment 1 and the following concentration has been measured in compartment 1.

$$c(t) = A_1 e^{-\lambda_1} + A_2 e^{-\lambda_2} = 0.38e^{-1.65t} + 0.18e^{-0.182t}$$

Taking Laplace transforms we find

$$C(s) = \frac{A_1}{s + \lambda_1} + \frac{A_2}{s + \lambda_2} = \frac{s(A_1 + A_2) + A_1\lambda_2 + A_2\lambda_1}{s^2 + (\lambda_1 + \lambda_2)s + \lambda_1\lambda_2}$$

Identifying this with the expression for $G(s)$ we find

$$\begin{aligned} k_2 &= \frac{A_1\lambda_2 + A_2\lambda_1}{A_1 + A_2} \\ k_0 + k_1 + k_2 &= \lambda_1 + \lambda_2 \\ k_0 k_2 &= \lambda_1\lambda_2 \end{aligned}$$

Finding the Parameters of the System

$$\begin{aligned} k_2 &= \frac{A_1\lambda_2 + A_2\lambda_1}{A_1 + A_2} \\ k_0 + k_1 + k_2 &= \lambda_1 + \lambda_2 \\ k_0 k_2 &= \lambda_1\lambda_2 \end{aligned}$$

Solution

$$\begin{aligned} k_0 &= \frac{\lambda_1\lambda_2(A_1 + A_2)}{A_1\lambda_2 + A_2\lambda_1} \\ k_1 &= \frac{A_1A_2(\lambda_1 - \lambda_2)^2}{(A_1 + A_2)(A_1\lambda_2 + A_2\lambda_1)} \\ k_2 &= \frac{A_1\lambda_2 + A_2\lambda_1}{A_1 + A_2} \end{aligned}$$

Inserting the numerical values $A_1 = 0.38$, $A_2 = 0.18$, $\lambda_1 = 1.65$ and $\lambda_2 = 0.182$ give $k_0 = 0.459$, $k_1 = 0.719$ and $k_2 = 0.654$.

Determining Volumes and Flows

Initial concentration $c_1(0) = 0.38 + 0.18 = 0.56$ $[kg/m^3]$, injected amount 0.010 kg. Assuming perfect mixing

$$V_1 = \frac{0.010}{0.56} = 0.0179[m^3]$$

The outflow from volume V_1 is $q_0 = V_1 k_0 = 0.008201$, furthermore we have

$$V_2 = \frac{k_1}{k_2} V_1 = 0.0196$$

The total volume is thus $V_1 + V_2 = 0.0375$. It can also be computed using the Stewart-Hamilton equation. This gives

$$V_t = q_0 T_{ar} = q_0 \frac{A_1 \lambda_1^{-2} + A_2 \lambda_2^{-2}}{A_1 \lambda_1^{-1} + A_2 \lambda_2^{-1}} = 0.0375$$

Compartment Models

Summary

- Compartment models
- An interesting special case of linear systems
- Many interesting properties
- Many applications industry, biology, medicine
- Measurement of “volumes” and “flows”
- The Stewart Hamilton Equation

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