# Linear Compartmental Systems-The Basics

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## 0.1 The Model

Consider material flowing among n compartments labeled $1, 2, \cdots, n$. Assume to begin that no material flows into any compartment from the external environment but that material can flow out of a compartment to the external environment and be lost. Material may flow between compartments. In Pharmacokinetics, the material is a drug, administered to the body, say orally, and the compartments might include stomach, intestines, blood, kidney, liver,etc. Wherever the drug might be.

We want to model

$$x_i(t) = \text{amount material in compartment i at time t}$$

Define for $i \neq j$

$$k_{ij} = \text{ rate of flow of material from j to i per unit material in i}$$

and

$$k_{0i} = \text{ rate of flow of material from i to the outside per unit material in i}$$

By definition, $k_{ij} \geq 0$ and $k_{oi} \geq 0$.

Then $x_i(t)$ satisfies the differential equation

$$x_i'(t) = -k_{oi}x_i(t) + \sum_{j\neq i} k_{ij}x_j(t) - \sum_{j\neq i} k_{ji}x_i(t)$$

The first term represents loss to the outside environment, the second term represents gain from other compartments, and the final term is loss due to material flowing out of $i$ to other compartments.

If we define

$$k_{ii} = k_{oi} + \sum_{j \neq i} k_{ji}$$

then we may write the system as

$$x_i' = -k_{ii}x_i + \sum_{j \neq i} k_{ij}x_j$$

or, as

$$x' = Ax \tag{1}$$

where

$$a_{ij} = k_{ij},\ i \neq j,\ a_{ii} = -k_{ii}. \tag{2}$$

Obviously, $A$ is a quasipositive matrix so solutions of our system that start positive ($x(0) \geq 0$) stay positive in the future ($x(t) \geq 0,\ t \geq 0$).

The total amount of material in the system at time $t$ is

$$N(t) = \sum_i x_i(t) = 1 \cdot x(t)$$

where $1 = (1, 1, \cdots, 1)$. Our hypothesis that there is no material coming into our system from the outside and that there is possibly material flowing out from the compartments to the outside make it obvious that

$$N'(t) = 1x'(t) = 1Ax \leq 0$$

In order to see the last inequality in mathematical terms, note that the row vector $1A$, made up of the column sums of $A$, is nonpositive:

$$-k_{ii} + \sum_{j \neq i} k_{ji} = -k_{oi} \leq 0 \tag{3}$$

This has important implications-namely that $N$ cannot increase so $x = 0$ must be stable for (1).

**Proposition 1.** *$s(A) \leq 0$ so $x = 0$ is stable for (1) relative to $R_+^n$. If, in addition, $A$ is irreducible and $k_{oi} > 0$ for some $i$ or if $A$ is nonsingular then $s(A) < 0$ so $x = 0$ is asymptotically stable.*

*Proof.* Let $k_o = (k_{o1}, k_{o2}, \cdots, k_{on})$ so $k_o \geq 0$ and let 1 denote the row vector of ones. Let $v > 0$ be an (column) eigenvector for $A$ corresponding to eigenvalue $s(A)$, normalized so $1v = 1$. The nonpositivity of column sums noted in (3) can be express as

$$1A = -k_o.$$

So, using $Av = s(A)v$, we have

$$s(A) = s(A)1v = 1Av = -k_o v \leq 0.$$

It follows that $x = 0$ is stable for (1) relative to $R^n_+$ since we may use $N = 1 \cdot x$ as a Lyapunov function. We showed above that $\dot{N} = 1Ax \leq 0$ and note that $N \geq 0$ for solutions starting in $R^n_+$. Therefore $0 \leq N(t) \leq N(0),\ t \geq 0$.

If $v >> 0$, which is the case when $A$ is irreducible, and if some $k_{oi} > 0$, then clearly $s(A) < 0$ so $A$ is a stable matrix. If instead $A$ is nonsingular then 0 is not an eigenvalue so $s(A) < 0$. □

## 0.2 Mean Residence Time

Let $x_0 > 0$ be such that $1 \cdot x_0 = 1$. We call $x_0$ a probability vector. If we start the system off at $x_0$, then $x(t) = e^{At}x_0$. Note that the amount of material in the system $N(t) = 1 \cdot x(t)$ satisfies $N(0) = 1$, $N'(t) \leq 0$, and if $s(A) < 0$ then $N(t) \to 0$ as $t \to \infty$. The probability of leaving the system in the interval $(t, t + \Delta t)$ is

$$N(t) - N(t + \Delta t) \approx -N'(t)\Delta t$$

So the mean residence time (MRT) of material in our system is given by

$$\begin{aligned} MRT(x_0) &= -\int_0^\infty tN'(t)dt \\ &= -\int_0^\infty t1 \cdot Ax(t)dt \end{aligned}$$

We see that the $MRT(x_0)$ depends on $x_0$, the initial distribution among the compartments. It seems natural to define a residence time that is independent of the initial data and which depends only on the structure of the network. Let us try $x_0 = v$ where $v > 0$ is the dominant positive eigenvector ($Av = s(A)v$), normalized so that $1 \cdot v = 1$. Then since $x(t) = e^{s(A)t}v$ if

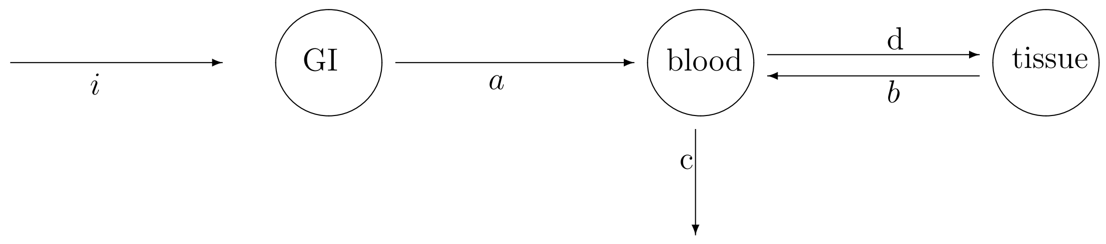


Figure 1: Route to site of infection in tissue of an orally administered drug. Vertical arrow from "blood" indicates metabolism in liver.

$x(0) = v$, we have $Ax(t) = s(A)e^{s(A)t}v$ and we may compute

$$MRT = MRT(v) = -\int_0^\infty ts(A)e^{s(A)t}dt = -\frac{1}{s(A)} \tag{4}$$

provided $s(A) < 0$.

A reasonable, initial condition-independent, Mean Residence Time for material in the system is given by the negative reciprocal of $s(A)$.

## 0.3 External Inputs

If we have constant rate inputs into our system, then (1) becomes

$$x' = Ax + r \tag{5}$$

where the components of the vector $r > 0$ give the rate of inflow from the outside into the compartments. It is not hard to see that solutions of this system that start positive stay positive in the future. Indeed, the variation of constants formula

$$x(t) = e^{At}x(0) + \int_0^t e^{A(t-s)}rds$$

implies that if $x(0) \geq 0$, then $x(t) \geq 0, t \geq 0$ since $e^{At} \geq 0,\ t \geq 0$ and $e^{A(t-s)} \geq 0,\ 0 \leq s \leq t$.

Consider the route an orally administered drug takes to the target tissue described in the Figure 0.3.

In this example, the matrix $A$ in the case depicted in Figure 0.3 is given by:

$$A = \begin{pmatrix} -a & 0 & 0 \\ a & -d-c & b \\ 0 & d & -b \end{pmatrix}$$

and

$$r = (i, 0, 0)$$

We assume that $s(A) < 0$ so then we know that $A^{-1} = -\int_0^\infty e^{At}dt < 0$. See homework problem #2. The steady state for this system is

$$\bar{x} = -A^{-1}r = [\int_0^\infty e^{At}dt]r > 0$$

a positive vector.

**Proposition 2.** *Every nonnegative solution of (5) converges to* $\bar{x}$ *if* $s(A) < 0$.

*Proof.* $y(t) = x(t) - \bar{x}$ satisfies $y' = Ay$ so $y(t) \to 0$ as $t \to \infty$ since $s(A) < 0$. Alternatively, take the limit in the variation of constants formula above. □

Note that the results of this section use only that the matrix $A$ is quasi-positive and that $s(A) < 0$; it is not important that $A$ is defined by (2).

## 0.4 The Gradostat

Consider $n$ tanks, each containing growth medium of volume $V$, in a linear array with nearest neighbor two-way flows between vessels:

$$\leftrightarrows \bigcirc \leftrightarrows \bigcirc \leftrightarrows \cdots \leftrightarrows \bigcirc \leftrightarrows$$

The circles represent the tanks and the arrows denote the flow between tanks and between the first and last tanks and the environment. Each arrow represents a flow of rate $F$ in units of volume per unit time (e.g., gallons per minute) of growth medium. The material of interest here is a nutrient supplied at concentration $N^0$ (weight per unit volume) in the inflow from the external environment to the left-most tank. The inflow from the environment to the right-most vessel contains only growth medium with no nutrient. Each tank is assumed to be well-mixed so its contents are homogeneously distributed. The outflow from the two end-tanks to the environment contains just the well-mixed contents of each vessel. Write down the differential equations for

$$N_i(t) = \text{concentration of nutrient in tank } i \text{ at time } t$$

**Note that here we use concentrations whereas above we have used weight!**

The system of equations satisfied by the vector $N(t)$ is

$$VN'(t) = FAN + FN^0 e_1$$

where $e_1 = (1, 0, \cdots, 0)^T$ and $A$ is the tridiagonal "diffusion matrix" with $-2$ on its main diagonal and 1 on the diagonals above and below the main diagonal. Notice from the graph above that $A$ is irreducible so by Proposition 1 $s(A) < 0$.

The steady state solution satisfies

$$A\bar{N} = -N^0 e_1$$

and since $A$ is quasipositive and $s(A) < 0$,

$$\bar{N} = -N^0 A^{-1} e_1 \geq 0$$

In fact, straight forward algebra yields

$$\bar{N}_i = \frac{n+1-i}{n+1} N^0$$

Therefore, there is a negative linear gradient in concentration of nutrient as we go from the left vessel to the right one.

The eigenvalues $\lambda_k$ of this important matrix $A$ are known:

$$\lambda_k = -2 - 2\cos(\frac{k\pi}{n+1}), \ k = 1, 2, \cdots n$$

See e.g. page 197 of [3] (or work it out yourself). So

$$s(A) = -2 - 2\cos(\frac{n\pi}{n+1}) = -2 + 2\cos(\frac{\pi}{n+1})$$

Therefore, the mean residence time for a nutrient in the gradostat is

$$MRT = -\frac{V}{Fs(A)} = \frac{V}{2F} \frac{1}{1 - \cos(\frac{\pi}{n+1})}.$$

As expected, it gets bigger as $n$ gets bigger.

## 0.5 Periodic Input

Particularly in pharmacology, it is common to administer drugs in a periodic fashion: take 2 tablets every 6 hours. Therefore it is natural to consider compartmental systems

$$x' = Ax + r(t) \tag{6}$$

where $r(t+T) = r(t)$ is periodic of period $T$ and, of course, nonnegative $r(t) \geq 0$. Suppose that $A$ is a quasipositive matrix with $s(A) < 0$. The variation of constants formula

$$x(t) = e^{At}x(0) + \int_0^t e^{A(t-s)}r(s)ds.$$

implies that $x(t) \geq 0$ whenever $x(0) \geq 0$.

We want to find initial data $x(0)$ so that $x(0) = x(T)$, which will guarantee that the corresponding solution is $T$-periodic. Therefore we seek a solution $x(0)$ of the equation

$$x(0) = e^{AT}x(0) + \int_0^T e^{A(T-s)}r(s)ds$$

By the spectral mapping theorem, or elementary calculation,

$$\sigma(e^{AT}) = e^{\sigma(A)T}$$

where $\sigma(B)$ denotes the set of eigenvalues of matrix $B$. Since $s(A) < 0$, $\Re(\lambda) < 0$ for every eigenvalue of $A$. Since the eigenvalues of $e^{AT}$ are just $e^{\lambda T}$ where $\lambda \in \sigma(A)$, we see that these all have modulus less than one. In other words, the spectral radius of $e^{AT}$ is less than one. In particular, one is not an eigenvalue of $e^{AT}$ so $I - e^{AT}$ is invertible. Moreover, by the Neumann series,

$$(1 - e^{AT})^{-1} = \sum_{j=0}^{\infty} e^{AjT} \geq 0$$

We have

$$x(0) = (1 - e^{AT})^{-1} \int_0^T e^{A(T-s)}r(s)ds = \sum_{j=0}^{\infty} e^{AjT} \int_0^T e^{A(T-s)}r(s)ds \geq 0$$

Therefore, we see that if $s(A) < 0$ then there is a unique $T$-periodic solution $\bar{x}(t)$ of (6) and that it is nonnegative. In fact, it attracts all solutions.

**Proposition 3.** *If $s(A) < 0$, then the unique $T$-periodic solution $\bar{x}(t)$ attracts all solutions.*

*Proof.* We need only show that $x(nT) \to \bar{x}(0)$ as $n \to \infty$ for arbitrary $x(0)$. By the variation of constants formula, $x_n = x(nT)$ satisfies

$$\begin{aligned} x_{n+1} &= e^{AT}x_n + \int_{nT}^{(n+1)T} e^{A((n+1)T-s)}r(s)ds \\ &= e^{AT}x_n + \int_0^T e^{A(T-u)}r(u)du \\ &= Bx_n + R \end{aligned}$$

where $B = e^{AT}$, $R = \int_0^T e^{A(T-u)}r(u)du$ and where we have changed variables in the first integral ($u = nT + s$) and used the periodicity of $r$. Therefore, we have $x_1 = Bx_0 + R$, $x_2 = Bx_1 + R = B^2x_0 + BR + R$, and by induction:

$$x_n = B^n x_0 + \sum_{j=0}^{n-1} B^j R$$

since $B^n x_0 \to 0$ we have on taking limits

$$x_n \to \sum_{j=0}^{\infty} B^j R = \bar{x}(0).$$

□

# References


[1] J. Jacquez and C. Simon, Qualitative Theory of Compartmental Systems, SIAM Review 35 (1993) no.1 , pp 43-79.

[2] G. Walter and M. Contreras, Compartmental Modeling with Networks, Birkhäuser, 1999, Boston.

[3] R.M. May, Stability and Complexity in Model Ecosystems, Princeton Univ. Press, 1973.