CHAPTER 2

Identifiability of Compartmental Models

In this chapter, we attack the inverse problem: Given a solution, what are the properties of the flow rates? The discussion held in this chapter is mainly based in [5] where the reader can find some additional theoretical results if needed. In our model the input f to a compartmental system can be to a single compartment or in certain circumstances, be mixed before it is distributed to input compartments. In general, we assume that the input to the system is of the form

$$\boldsymbol{f} = Bu\,(t) \tag{2.0.17}$$

where B has as many rows as there are compartments. In general a donor controlled system is written as

$$\frac{d\boldsymbol{x}}{dt} = A\mathbf{x} + Bu(t) \tag{2.0.18}$$

with initial conditions

$$\mathbf{x}(0) = \mathbf{x}_0 \tag{2.0.19}$$

For example, in a two-compartment system, the matrix $B = [1\ 1]^T$ would be used to indicate that the input is shared equally by compartments1 and 2, and the matrix $B = [1\ 0]^T$ means that the input is applied only the compartment denote as 1. Since our system is assumed donor controlled, the output will have the form

$$y = C\boldsymbol{x} \tag{2.0.20}$$

in which the output of the compartments is directed to one or more measuring devices with measurements $y(t)$. These outputs are observations rather than flows out of the system. A Bolus input can be modeled either as an initial value $\mathbf{x}(0)$ or incorporated into $Bu(t)$ as an input delta δ centered at $t = 0$, and the Perfusion is modeled as a constant in time input $u(t) = u$. However, the flow rates in the matrix A are unknown and must be determined from a knowledge of the input $u(t)$ and the measure $y(t)$. The problem of determining such an A is known as the identification problem.

Definition 2.1. Identifiable System

A system

$$\frac{d\boldsymbol{x}}{dt} = A\mathbf{x} + f(t) \tag{2.0.21}$$

is identifiable if from a knowledge of the input $f(t)$ and the measure $y(t)$ there is a unique solution to the flow rates in the matrix A .

However, this problem does not always have a single solution and even when it does, it may be difficult to find. The problem of actually estimating the parameters of an identifiable problem is an ill-posed problem; that is, the output may be close to the true output, whereas the parameters are still quite different than the true parameters; that is, such parameters are usually sensitive to slight perturbations of the data.

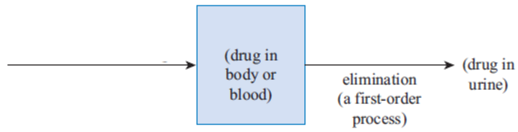

FIGURE 2.1.1. One compartment Bolus case

2.1. Examples of a Identifiable System

2.1.1. One dimensional case. Lets consider the system associated by the Figure 2.1.1. This configuration implies that our model is

$$\frac{dx}{dt} = -a_{10}x \tag{2.1.1}$$

and a dose D can be introduced as an initial condition (the bolus) as

$$x(0) = D \tag{2.1.2}$$

its solution is given by

$$x(t) = D\exp\left(-a_{10}t\right) \tag{2.1.3}$$

and measuring (in the only existing compartment) means $C = 1$, then

$$y\left(t\right) = D\exp\left(-a_{10}t\right) \tag{2.1.4}$$

and it is clear that knowing $y\left(t\right)$for a given $t = t_1$

$$a_{10} = -\frac{1}{t_1}\ln\left(\frac{y\left(t_1\right)}{D}\right) \tag{2.1.5}$$

we find the only parameter we have in our model (a_{10}) in a unique way, making the system identifiable.

2.1.2. Two dimensional Bolus (no outfluxes). Lets consider a two compartmental model where there are not physical outfluxes from the system as shown in Figure 2.1.2. The corresponding matrix representation to this system is

$$A = \begin{pmatrix} -a_{12} & a_{21} \\ a_{12} & -a_{21} \end{pmatrix} \tag{2.1.6}$$

so the system is written as

$$\frac{d}{dt}x_1 = -a_{12}x_1 + a_{21}x_2 \tag{2.1.7}$$

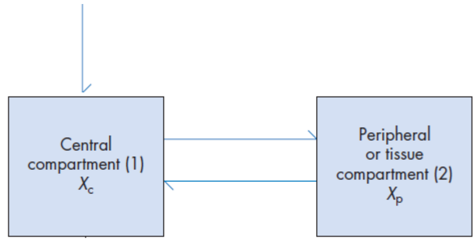

FIGURE 2.1.2. Two compartments (no outputs)

$$\frac{d}{dt}x_2 = a_{12}x_1 - a_{21}x_2 \tag{2.1.8}$$

where the input, and the measure are in the compartment 1 as

$$B = \begin{pmatrix} 1 \\ 0 \end{pmatrix}, \; C = \begin{pmatrix} 1 & 0 \end{pmatrix} \tag{2.1.9}$$

Now we ask ourselves if a_{12} and a_{21} are identifiable. Lets define the input as

$$u(t) = \delta(t - \epsilon) \tag{2.1.10}$$

a known Bolus input immediately ϵ after the system is started then the solution (Appendix.- Analytic Solution) is given by

$$x(t) = \exp(At)\, x(0) + \int_0^t \exp A(t-s)\, Bu(s)\, ds \tag{2.1.11}$$

that reduces to

$$x(t) = \exp(A(t-\epsilon))\, B \tag{2.1.12}$$

and the measure $y(t)$ is written as

$$y(t) = C \exp(A(t-\epsilon))\, B \tag{2.1.13}$$

taking $\lim_{\epsilon \to 0} y(t)$ we get

$$y(t) = C \exp(At)\, B \tag{2.1.14}$$

which is our general solution. As discussed in Appendix.- The Exponential of a Matrix, the computation of $\exp(At)$ can be done as

$$y(t) = CK \begin{pmatrix} \exp(\lambda_1 t) & 0 \\ 0 & \exp(\lambda_2 t) \end{pmatrix} K^{-1} B \tag{2.1.15}$$

where the eigenvalues are given by

$$det(A - \lambda \mathbf{1}) = 0 \tag{2.1.16}$$

and **1** denotes the Identity matrix so (2.1.16) leads to

$$(-a_{12} - \lambda)(-a_{21} - \lambda) - a_{12}a_{21} = 0 \tag{2.1.17}$$

obtaining the equation

$$\lambda(\lambda + a_{12} + a_{21}) = 0 \tag{2.1.18}$$

which implies that the eigenvalues are

$$\begin{array}{c} \lambda_1 = 0 \\ \lambda_2 = -(a_{12} + a_{21}) \end{array} \tag{2.1.19}$$

and the eigenvectors define the matrix K as

$$K = \begin{pmatrix} a_{21} & 1 \\ a_{12} & -1 \end{pmatrix}, \; K^{-1} = \frac{1}{detK} \begin{pmatrix} -1 & -1 \\ -a_{12} & a_{21} \end{pmatrix} \tag{2.1.20}$$

and its determinant is

$$detK = -(a_{12} + a_{21}) \tag{2.1.21}$$

multiplying (2.1.15) by K^{-1} we get

$$y_1(t) = \frac{1}{det(K)} CK \begin{pmatrix} -\exp(\lambda_1 t) & -\exp(\lambda_1 t) \\ -a_{12}\exp(\lambda_2 t) & a_{21}\exp(\lambda_2 t) \end{pmatrix} B \tag{2.1.22}$$

and by K

$$y_1(t) = \frac{1}{det(K)} C \begin{pmatrix} -a_{21}\exp(\lambda_1 t) - a_{12}\exp(\lambda_2 t) & -a_{21}\exp(\lambda_1 t) + a_{21}\exp(\lambda_2 t) \\ -a_{12}\exp(\lambda_1 t) + a_{12}\exp(\lambda_2 t) & -a_{12}\exp(\lambda_1 t) - a_{21}\exp(\lambda_2 t) \end{pmatrix} B \tag{2.1.23}$$

using that the input and measure (2.1.9) are in the compartment1 gives

$$y_1(t) = \frac{1}{det(K)} C \begin{pmatrix} -a_{21}\exp(\lambda_1 t) - a_{12}\exp(\lambda_2 t) \\ -a_{12}\exp(\lambda_1 t) + a_{12}\exp(\lambda_2 t) \end{pmatrix} \tag{2.1.24}$$

and then

$$y_1(t) = \frac{-a_{21}\exp(\lambda_1 t) - a_{12}\exp(\lambda_2 t)}{det(K)} \tag{2.1.25}$$

Now substituting that one eigenvalue λ_1 is zero we obtain that

$$y_1(t) = \frac{-a_{21} - a_{12}\exp(\lambda_2 t)}{-(a_{12}+a_{21})} \tag{2.1.26}$$

or

$$y_1(t) = \frac{a_{21} + a_{12}\exp(\lambda_2 t)}{a_{12}+a_{21}} \tag{2.1.27}$$

So, for identification we need a unique solution for a_{12} and a_{21}.Taking $t \to \infty$ we get

$$\lim_{t\to\infty} y(t) = \frac{a_{12}}{a_{12}+a_{21}} \tag{2.1.28}$$

we can find $\frac{a_{12}}{a_{12}+a_{21}}$ which together with

$$\frac{d}{dt}y_1(t) = \frac{\lambda_2 a_{21}\exp(\lambda_2 t)}{a_{12}+a_{21}} \tag{2.1.29}$$

using (2.1.29) at $t = 0$ simplifies to

$$\frac{d}{dt}y_1(0) = -a_{21} \tag{2.1.30}$$

so the system is identifiable. It is interesting to point out that as consequence of not having any output one eigenvalue is zero, and the concentration level will always increase making the $\int_0^\infty y_1(t)\,dt$ to diverge.

2.2. An Example of a Non- Identifiable System

2.2.1. Two dimensional Bolus (measure in 2). Lets consider now the two compartmental model with elimination in compartment 1 represented in Figure 1.2.1 and with matrix representation given by (2.1.6). But this time the measure it is taken only in the $2nd$ compartment. This meas that

$$C = \begin{pmatrix} 0 & 1 \end{pmatrix} \tag{2.2.1}$$

and the solution has the starting level in 2

$$y_2(0) = 0 \tag{2.2.2}$$

the integral equation

$$\int_0^\infty y_2(t)dt = \int_0^\infty (C\exp(At)\,B)\,dt \tag{2.2.3}$$

provides

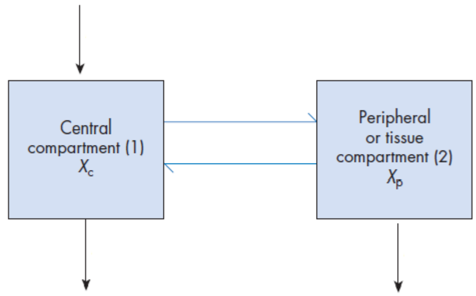

FIGURE 2.2.1. Two compartments (2 outputs)

$$C\exp(At)\,B\,|_0^\infty = -CA^{-1}B = \frac{a_{12}}{(a_{21}a_{10})} \tag{2.2.4}$$

from where we can not identify any parameter directly. But making use of the derivatives of $y(t)$ we find that

$$a_{12} = \frac{d}{dt}y(0) \tag{2.2.5}$$

obtaining a_{12}, and from the second derivative

$$a_{12}(-a_{12} - a_{10}) - a_{21}a_{12} = \frac{d}{dt^2}^2 y(0) \tag{2.2.6}$$

getting 2 equations, but further differentiation doesn't provide more information about the system . Now, defining the constants $\alpha := \frac{1}{a_{12}}\frac{d}{dt^2}^2 y(0) + a_{12}$, and $\beta := \frac{a_{12}}{\int_0^\infty y(t)dt}$ we have that the system is written as

$$(a_{10} + a_{21}) = \alpha \tag{2.2.7}$$

and

$$a_{21}a_{10} = \beta \tag{2.2.8}$$

from where we can see that there are two solutions (interchanging the values of a_{21} and a_{10}).

2.2.2. Two dimensional Bolus with 2 out fluxes. We now consider the same example and hypothesize that both compartments have fluxes to the outside. The system of equations has matrices

$$A = \begin{pmatrix} -a_{12} - a_{10} & a_{21} \\ a_{12} & -a_{21} - a_{20} \end{pmatrix} \tag{2.2.9}$$

where the input comes only in the compartment1, the measured output it is taken only in the same compartment (number 1). And we have 4 parameters to estimate.

The solution still is (2.1.18) so that

$$y(0) = 1 \tag{2.2.10}$$

and its derivatives

$$\frac{d^n y}{dt^n}(t) = CA^n \exp(At) B \tag{2.2.11}$$

provide more equations for the system as

$$\frac{d^n y}{dt^n}(0) = CA^n B \tag{2.2.12}$$

from where we obtain 2 equations as

$$\frac{dy}{dt}(0) = -(a_{12} + a_{10}) \tag{2.2.13}$$

and

$$\frac{d^2 y}{dt^2}(0) = (a_{12} + a_{10})^2 + a_{21} a_{12} \tag{2.2.14}$$

but successive differentiation after the $2nd$ derivative don't provide new equations. This two equations together with the equation that comes from the integration

$$\int_0^\infty y(t)\,dt = \int_0^\infty C \exp(At) B dt \tag{2.2.15}$$

gives

$$= CA^{-1} \exp(At) B \,|_0^\infty = -CA^{-1} B \tag{2.2.16}$$

and the inverse is given by

$$A^{-1} = \begin{pmatrix} -\frac{a_{20}+a_{21}}{a_{10}a_{20}+a_{10}a_{21}+a_{12}a_{20}} & -\frac{a_{21}}{a_{10}a_{20}+a_{10}a_{21}+a_{12}a_{20}} \\ -\frac{a_{12}}{a_{10}a_{20}+a_{10}a_{21}+a_{12}a_{20}} & -\frac{a_{12}+a_{10}}{a_{10}a_{20}+a_{10}a_{21}+a_{12}a_{20}} \end{pmatrix} \tag{2.2.17}$$

so

$$\int_0^\infty y(t)\,dt = \frac{a_{20} + a_{21}}{a_{10}a_{20} + a_{10}a_{21} + a_{12}a_{20}} \tag{2.2.18}$$

and the system is not identifiable. Including another measure (in compartment 2) as

$$C = \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} \tag{2.2.19}$$

makes the system identifiable. This can also be shown with the Laplace transform approach.

2.2.3. Using Laplace Transform. The Laplace transform is defined as

$$L\left(f\left(t\right)\right)=\int\limits_{0}^{\infty}\exp\left(-st\right)f\left(t\right)dt \tag{2.2.20}$$

so that

$$L\left(\frac{d}{dt}f\left(t\right)\right)=sF\left(s\right)-f\left(0\right) \tag{2.2.21}$$

then we get

$$Y\left(s\right)=C\left(\int\limits_{0}^{\infty}\exp\left(At\right)\exp\left(-s1t\right)dt\right)B \tag{2.2.22}$$

which becomes

$$Y\left(s\right)=C\left(s1-A\right)^{-1}B \tag{2.2.23}$$

Now,

$$s1-A=\begin{pmatrix} s+a_{12}+a_{10} & -a_{21} \\ -a_{12} & s+a_{21}+a_{20} \end{pmatrix} \tag{2.2.24}$$

its determinant is

$$det\left(s1-A\right)=\left(s+a_{12}+a_{10}\right)\left(s+a_{21}+a_{20}\right)-a_{12}a_{21} \tag{2.2.25}$$

$$=s^{2}+s\left(a_{12}+a_{10}+a_{21}+a_{20}\right)+a_{10}a_{21}+a_{12}a_{20}+a_{10}a_{20} \tag{2.2.26}$$

so the Laplace Transform

$$C\left(s1-A\right)^{-1}B=\frac{1}{det\left(s1-A\right)}\begin{pmatrix} 1 & 0 \end{pmatrix}\begin{pmatrix} s+a_{21}+a_{20} & a_{21} \\ a_{12} & s+a_{12}+a_{10} \end{pmatrix}\begin{pmatrix} 1 \\ 0 \end{pmatrix} \tag{2.2.27}$$

leads to

$$C\left(s1-A\right)^{-1}B=\frac{s+a_{21}+a_{20}}{det\left(s1-A\right)} \tag{2.2.28}$$

using (2.2.22) we get

$$Y\left(s\right)=\frac{s+a_{21}+a_{20}}{s^{2}+s\left(a_{12}+a_{10}+a_{21}+a_{20}\right)+\left(a_{10}a_{21}+a_{12}a_{20}+a_{10}a_{20}\right)} \tag{2.2.29}$$

so we get

$$\begin{aligned}\alpha &= a_{21} + a_{20} \\ \beta &= a_{12} + a_{10} + a_{21} + a_{20} \\ \gamma &= a_{10}a_{21} + a_{12}a_{20} + a_{10}a_{20}\end{aligned} \tag{2.2.30}$$

there is no unique solution and the system is not identifiable. But, if we include a second measure (in compartment 2) C will be the $2x2$ identity matrix and we obtain

$$Y(s) = \frac{1}{det(s1 - A)} \begin{pmatrix} s + a_{21} + a_{20} \\ a_{12} \end{pmatrix} \tag{2.2.31}$$

and

$$\begin{pmatrix} Y_1(s) \\ Y_2(s) \end{pmatrix} = \frac{\begin{pmatrix} s + a_{21} + a_{20} \\ a_{12} \end{pmatrix}}{s^2 + s(a_{12} + a_{10} + a_{21} + a_{20}) + (a_{10}a_{21} + a_{12}a_{20} + a_{10}a_{20})} \tag{2.2.32}$$

Thus, from the numerator of $Y_1(s)$, we can find $a_{21} + a_{20}$, and from that of $Y_2(s)$, we can find a_{12}. The denominator gives us two additional equations which can be used to find a_{10} and a_{21} thereby making our new system identifiable.

2.2.4. The General Case. In a general model with n compartments, the associated compartmental matrix A is $n \, \mathrm{x} \, n$. If the model has p inputs and q outputs, then B will be a $n \, x \, p$ matrix and C a $q \, \mathrm{x} \, n$ matrix. The observed measurements $y(t)$ constitute a $q \, \mathrm{x} \, p$ matrix, again given by,

$$y(t) = C \exp(At) B \tag{2.2.33}$$

with Laplace transform

$$Y(s) = C(s1 - A)^{-1} B \tag{2.2.34}$$

The inverse may be shown, by expanding in minors, to be of the form

$$(s1 - A)^{-1} = \frac{Q(s)}{P(s)} \tag{2.2.35}$$

where $P(s)$ is the characteristic polynomial of A and $Q(s)$ is a polynomial of degree at most $(n - 1)$ with $q \, \mathrm{x} \, p$ matrix coefficients.Thus

$$Y(s) = \frac{CQ(s) B}{P(s)} \tag{2.2.36}$$

and the numerator has $q \, \mathrm{x} \, p$ matrix coefficients. If $Y(s)$ is known, then it gives us n equations in the coefficients in A from the denominator alone. The numerator gives us $n - 1$ equations for each element in the $q \, \mathrm{x} \, p$ matrix. The total number of equations is therefore $n + pq(n - 1)$. The total number of unknown flows may be as large as n^2 if each compartment has flows to every other and to the outside. This gives the negative result.

PROPOSITION 2.2. *If the total number of nonzero flows in the compartmental model exceeds n + $pq(n$ - $1)$, then the system is not identifiable: In particular, if the structure is not specified, the system is not identifiable if $n > pq$.*

The last inequality holds if $n^2 > n + pq(n-1)$. Sufficient conditions are usually quite technical since even if the number of equations is greater than or equal to the number of flows, there may be redundancy among the equations. This happens in the case of a cycle which has exactly $n-1$ flows (provided it has no excretions) but leads to $2n-2$ equations. For necessary and sufficient conditions, see, for example [7,8,9,10,11]