UNIVERSITÀ DEGLI STUDI DI BERGAMO
Dipartimento di Ingegneria Gestionale, dell'Informazione e della Produzione

Lesson 9.

Compartmental models

CONTROL AND MODELING OF BIOLOGICAL SYSTEMS

MASTER DEGREE IN MEDICAL ENGINEERING

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Compartmental models

Many nonnegative systems can be modelled as **compartmental models.**

These models are conceptually simple and thus very widespread in medicine, biology, economics, genetics, engineering.

The key idea is that any system can be described by a decomposition into a number of interacting subsystems, called **compartments,** which are coupled through some exchange of material.

Each compartment is assumed to be kinetically homogeneous, that is any material entering the compartment is **instantaneously mixed** with the material of the compartment.

Compartmental models

They are based on the **conservation of the mass** principle

«in a closed chemical reaction system, the total mass of all reactants will be equal to the total mass of all products»

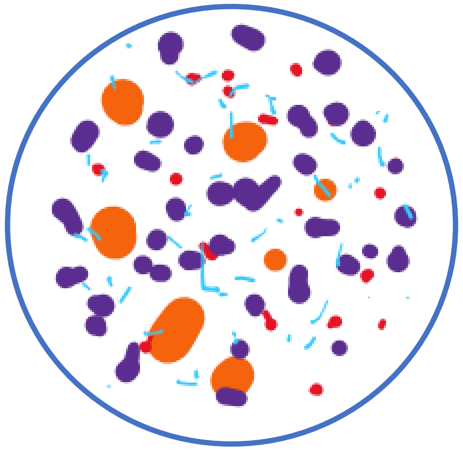
They are widely employed in medicine, biology, pharmacy. Examples may include:

- pharmacokinetics, lipoprotein kinetics
- metabolic systems, endocrine systems (i.e. blood glucose regulation)
- epidemic dynamics
- anesthesia
- etc.

Compartment

Compartment: **homogeneous** set of elements of the same nature behaving in the same way

Compartment



Not a compartment

Example:
same matter in different space (blood glucose in plasma, blood glucose in tissues,..)
Two different matters in the same space (blood glucose and insulin in plasma)

Compartments

Compartments depend on:

- the specific system they represent.
- The physiological/physical knowledge on the system.
- The experiments and the richness of data.

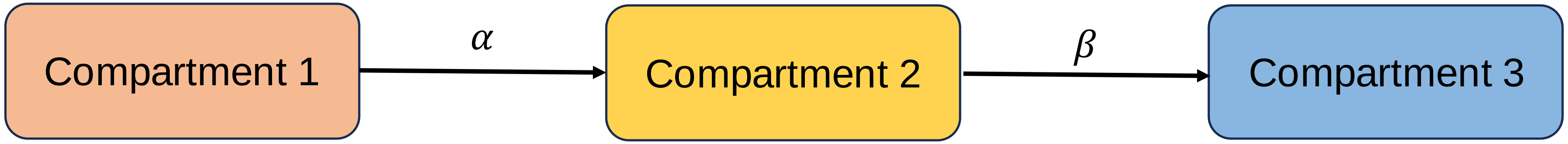
When defining the compartments, it is important to evaluate which quantities are accessible (and measurable) and which are not.

A compartment can be sometimes a physical space, but in other situation it can be just a theorical construction representing a set of homogeneous elements located in different places of the organism.

Compartmental models

Compartmental models are composed by a certain number of **compartments**, that are interacting subsystems whose connections are **flows** of matter from one compartment to another

Each compartment can be modelled as a first order system (1 state).

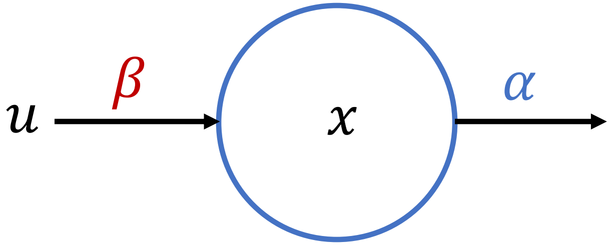


The states of each compartment are element of the same nature/properties.

The flow from one compartment to another convert the elements of each compartment into elements of the other one.

Mathematical formulation

Given a compartment

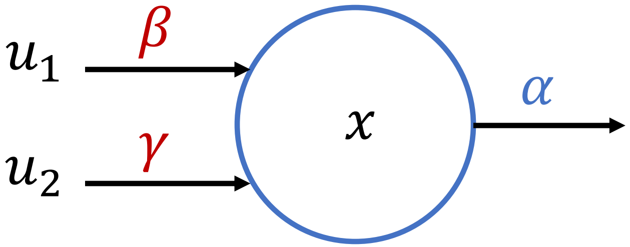


Where x represents the amount of material, the mathematical equation for this compartment can be written as:

$$\dot{x}(t) = -\alpha x(t) + \beta u(t)$$

With: $\alpha > 0$ and $\beta > 0$.

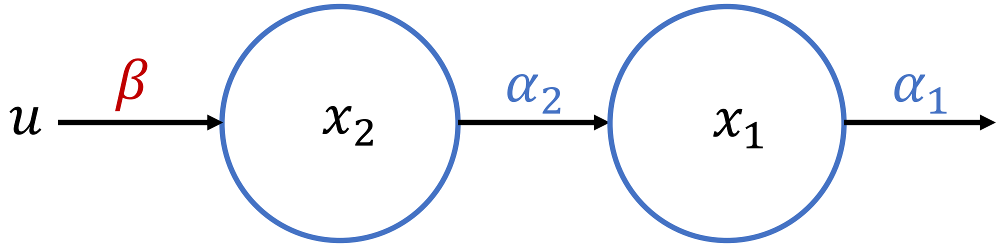
If there are more than one input:



$$\dot{x}(t) = -\alpha x(t) + \beta u_1(t) + \gamma u_2(t)$$

Mathematical formulation

Suppose to have two compartments



$$\dot{x}_1(t) = -\alpha_1 x_1(t) + \alpha_2 x_2(t)$$
$$\dot{x}_2(t) = -\alpha_2 x_2(t) + \beta u(t)$$

Total system mass: $x_1 + x_2$

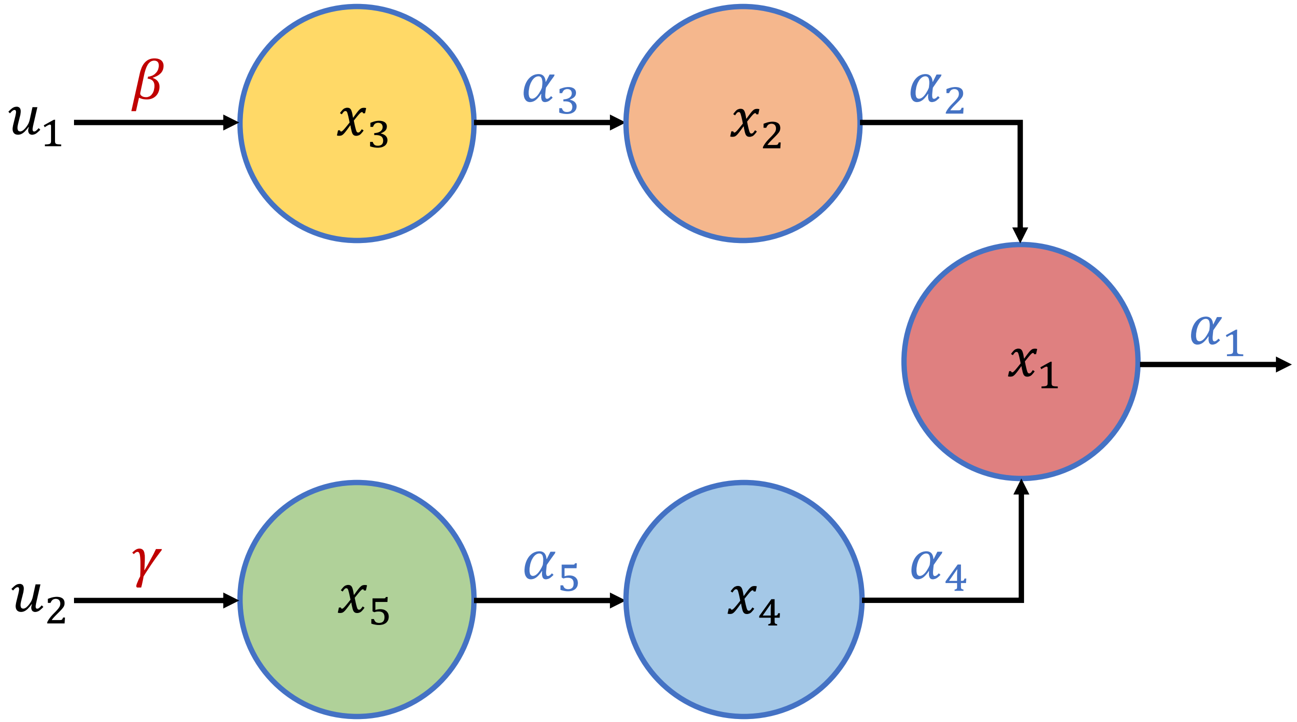
Total mass variation : $\dot{x}_1 + \dot{x}_2$

In compact form: $\dot{x}(t) = Ax(t) + Bu(t)$, with

$$x = \begin{bmatrix} x_1 \\ x_2 \end{bmatrix} \qquad A = \begin{bmatrix} -\alpha_1 & \alpha_2 \\ 0 & -\alpha_2 \end{bmatrix} \qquad B = \begin{bmatrix} 0 \\ \beta \end{bmatrix}$$

Mathematical formulation

Suppose to have a five compartments model with two inputs



$$\dot{x}_2(t) = -\alpha_2 x_2(t) + \alpha_3 x_3(t)$$
$$\dot{x}_3(t) = -\alpha_3 x_3(t) + \beta u_1(t)$$

$$\dot{x}_1(t) = -\alpha_1 x_1(t) + \alpha_2 x_2(t) + \alpha_4 x_4(t)$$

$$\dot{x}_4(t) = -\alpha_4 x_4(t) + \alpha_5 x_5(t)$$
$$\dot{x}_5(t) = -\alpha_5 x_5(t) + \gamma u_2(t)$$

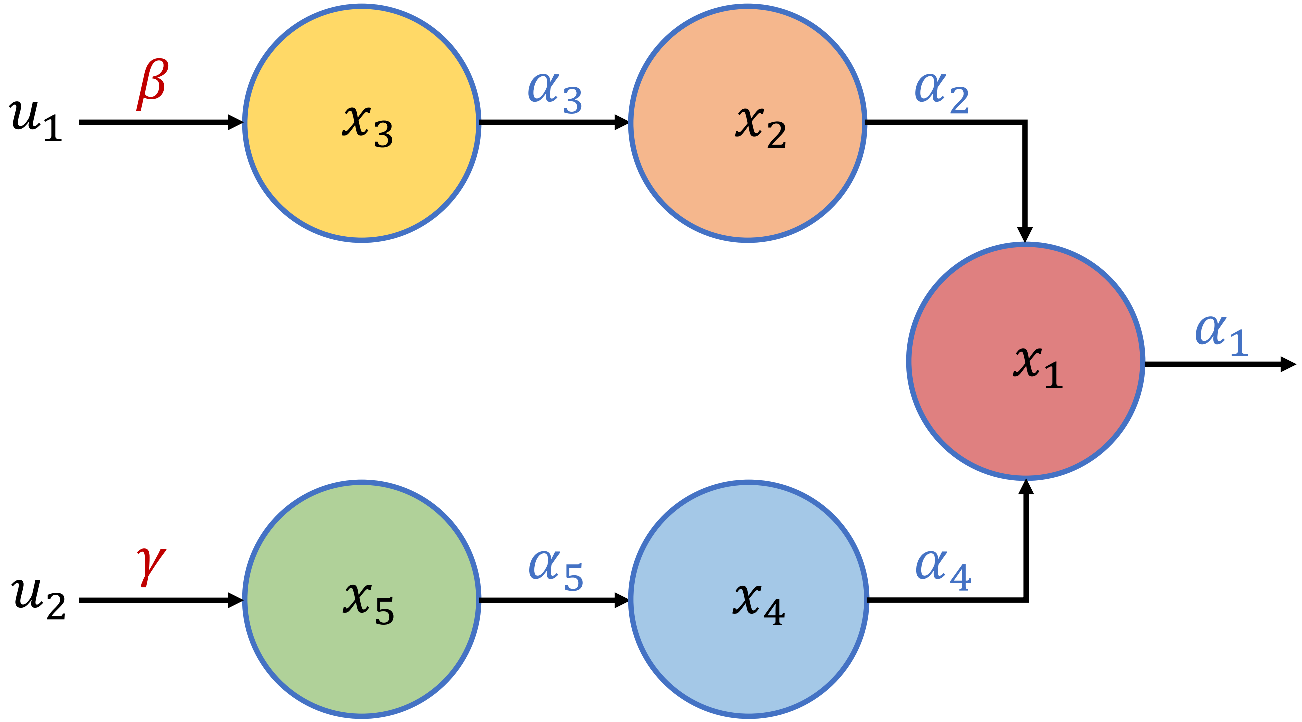
Total system mass: $\sum_{i=1}^{5} x_i$

Total mass variation: $\sum_{i=1}^{5} \dot{x}_i$

Mathematical formulation

In compact form: $\dot{x}(t) = Ax(t) + Bu(t)$, with

$$x = \begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \\ x_5 \end{bmatrix} \qquad u = \begin{bmatrix} u_1 \\ u_2 \end{bmatrix}$$



$$A = \begin{bmatrix} -\alpha_1 & \alpha_2 & 0 & \alpha_4 & 0 \\ 0 & -\alpha_2 & \alpha_3 & 0 & 0 \\ 0 & 0 & -\alpha_3 & 0 & 0 \\ 0 & 0 & 0 & -\alpha_4 & \alpha_5 \\ 0 & 0 & 0 & 0 & -\alpha_5 \end{bmatrix}$$

$$B = \begin{bmatrix} 0 & 0 \\ 0 & 0 \\ \beta & 0 \\ 0 & 0 \\ 0 & \gamma \end{bmatrix}$$

Five compartments model with two inputs

Analysis

In the expression: $\dot{x}(t) = Ax(t) + Bu(t)$, $u(t)$ represents exogenous supply of a certain material.

It the input is constant $u(t) = \bar{u}$, for the mass conservation principle we have $\dot{x}(t) = 0$. Then:

$$\bar{u} = \begin{bmatrix} \bar{u}_1 \\ \bar{u}_2 \end{bmatrix}$$

$$\dot{x}(t) = 0$$

$$\Rightarrow$$

$$0 = -\alpha_1 x_1(t) + \alpha_2 x_2(t) + \alpha_4 x_4(t)$$
$$0 = -\alpha_2 x_2(t) + \alpha_3 x_3(t)$$
$$0 = -\alpha_3 x_3(t) + \beta \bar{u}_1$$
$$0 = -\alpha_4 x_4(t) + \alpha_5 x_5(t)$$
$$0 = -\alpha_5 x_5(t) + \gamma \bar{u}_2$$

We can compute the equilibrium of the system (no mass variation)

Analysis

From the third and fith equations we get

$$\bar{x}_3 = \frac{\beta}{\alpha_3}\bar{u}_1 \qquad \bar{x}_5 = \frac{\gamma}{\alpha_5}\bar{u}_2$$

From the second and forth equations we get

$$\bar{x}_2 = \frac{\beta}{\alpha_2}\bar{u}_1 \qquad \bar{x}_4 = \frac{\gamma}{\alpha_4}\bar{u}_2$$

Finally from the first equation we get

$$\bar{x}_1 = \frac{\beta}{\alpha_1}\bar{u}_1 + \frac{\gamma}{\alpha_1}\bar{u}_2$$

Properties

1. All diagonal elements are of the form $-\alpha_i$, $\alpha_i > 0$. So A has **non-positive** diagonal elements.

2. All non-diagonal elements are of the form α_i, $\alpha_i > 0$. So A has **non-negative** off-diagonal elements.

3. Then matrix A is a **Metlzer matrix** (nonzero matrix with nonnegative off-diagonal elements). Then –A is a Z-matrix.

4. Matrix A is column-wise **diagonally dominant**

$$|A_{ii}| - \sum_{j \neq i, j=1}^{n} A_{ji} \geq 0$$

in each column of A, the absolute value of the element on the main diagonal is greater than the sum of the values of the other elements in that column

Properties

Any square matrix enjoying the previous property is called a **compartmental matrix**.

1. A compartmental LTI system is a **nonnegative** system.

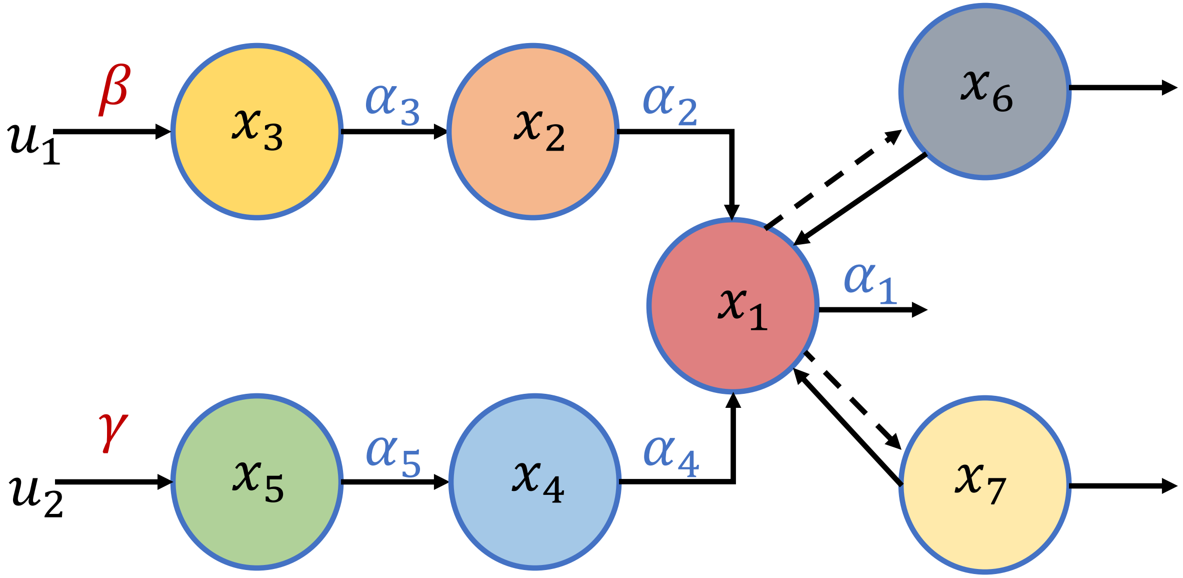
2. Since A is diagonally dominant and has **non-positive** diagonal elements, then all eigenvalues of matrix A are negative (or at most one of them is null).

3. For this reason any LTI compartmental system is asymptotically stable (or at least stable).

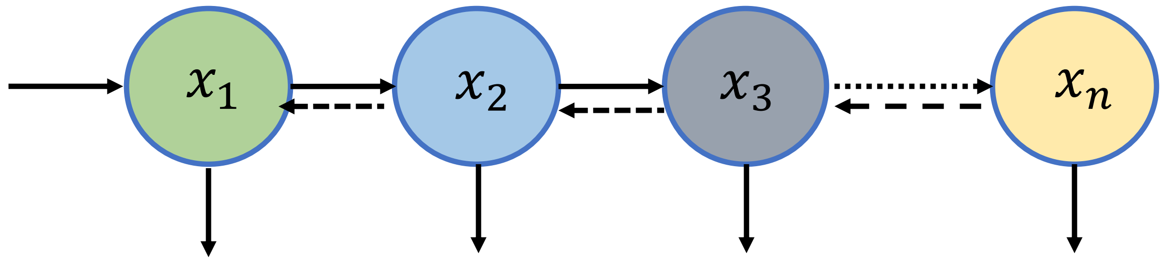
4. Notice that, then, –A is an M-matrix.

Structures

In general, for mammillary and chain structure, the eigenvalues are always real.



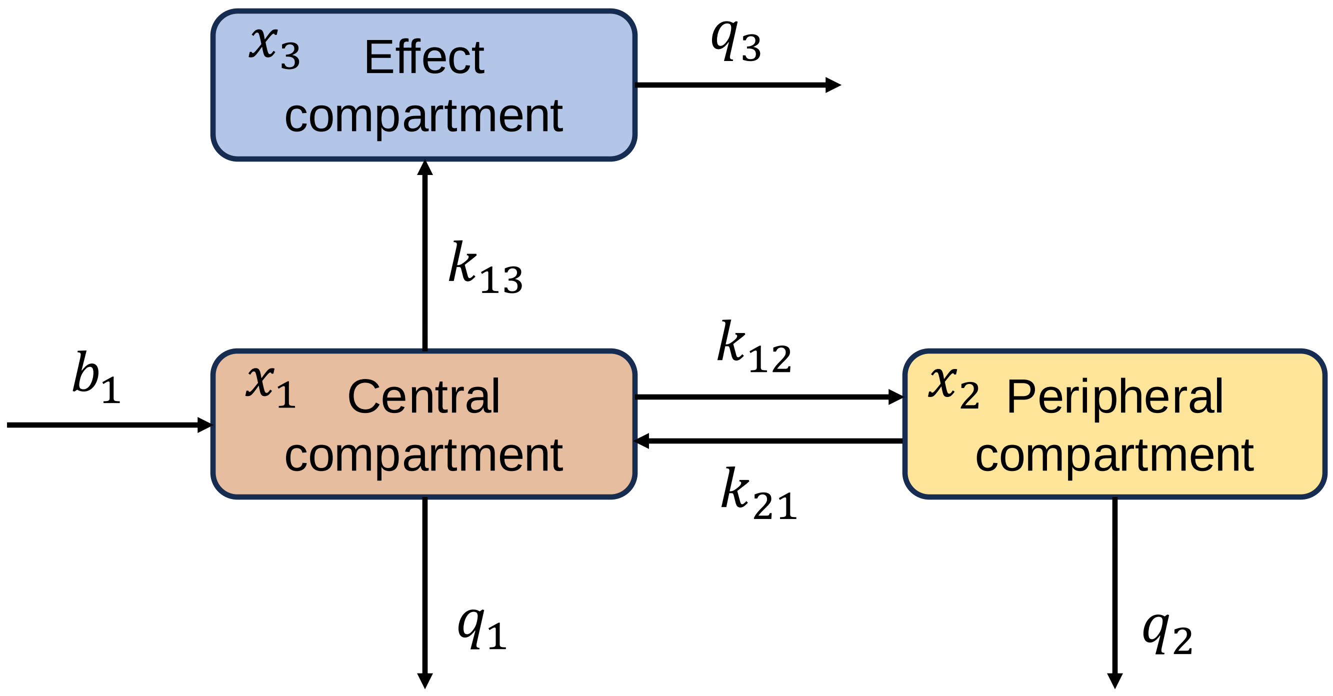
Mammillary structure



Chain structure

Example – Compartmental model for the effect of atracurium

Atracurium is a drug used to induce neuromuscular blockade during surgery or mechanical ventilation



Example – Compartmental model for the effect of atracurium

The equation of this model are given by

$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \end{bmatrix} = \begin{bmatrix} -q_1 - k_{12} - k_{13} & k_{21} & 0 \\ k_{12} & -q_2 - k_{21} & 0 \\ k_{13} & 0 & -q_3 \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix} + \begin{bmatrix} b_1 \\ 0 \\ 0 \end{bmatrix} u$$

With

$k_{12} = 0.1928, k_{13} = 0.0017, k_{21} = 0.1556$

$q_1 = 0.1047, q_2 = 0, q_3 = 0.0836, b_1 = 1$

Example – Compartmental model for the effect of atracurium

Then

$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \end{bmatrix} = \begin{bmatrix} -0.2992 & 0.1556 & 0 \\ 0.1928 & -0.1556 & 0 \\ 0.0017 & 0 & -0.0836 \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix} + \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix} u$$

1. $A_{ii} \leq 0$ ✓
2. $A_{ji} \geq 0$ ✓
3. Let's verify that $|A_{ii}| - \sum_{j\neq i,j=1}^{n} A_{ji} \geq 0$ for $i = 1$

$$|A_{11}| = 0.2992$$

$$\sum_{j\neq 1,j=1}^{n} A_{ji} = 0.1945$$

$$\rightarrow \quad |A_{ii}| - \sum_{j\neq i,j=1}^{n} A_{ji} = 0.1047 \geq 0$$ ✓

Example – Compartmental model for the effect of atracurium

$$\begin{bmatrix}\dot{x}_1\\ \dot{x}_2\\ \dot{x}_3\end{bmatrix} = \begin{bmatrix}-0.2992 & 0.1556 & 0\\ 0.1928 & -0.1556 & 0\\ 0.0017 & 0 & -0.0836\end{bmatrix}\begin{bmatrix}x_1\\ x_2\\ x_3\end{bmatrix} + \begin{bmatrix}1\\ 0\\ 0\end{bmatrix}u$$

4. Let's verify that $|A_{ii}| - \sum_{j\neq i,j=1}^{n} A_{ji} \geq 0$ for $i = 2$

$$|A_{22}| = 0.1556$$

$$\sum_{j\neq 2,j=1}^{n} A_{ji} = 0.1556$$

$$\Rightarrow \quad |A_{ii}| - \sum_{j\neq i,j=1}^{n} A_{ji} = 0 \geq 0$$

✅

Example – Compartmental model for the effect of atracurium

$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \end{bmatrix} = \begin{bmatrix} -0.2992 & 0.1556 & 0 \\ 0.1928 & -0.1556 & 0 \\ 0.0017 & 0 & -0.0836 \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix} + \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix} u$$

5. Let's verify that $|A_{ii}| - \sum_{j \neq i, j=1}^{n} A_{ji} \geq 0$ for $i = 3$

$$|A_{33}| = 0.0836$$

$$\sum_{j \neq 3, j=1}^{n} A_{ji} = 0$$

$$\Rightarrow \quad |A_{ii}| - \sum_{j \neq i, j=1}^{n} A_{ji} = 0.0836 \geq 0 \quad ✅$$

Example – Compartmental model for the effect of atracurium

As for the stability analysis of system

$$\begin{bmatrix}\dot{x}_1\\ \dot{x}_2\\ \dot{x}_3\end{bmatrix} = \begin{bmatrix}-0.2992 & 0.1556 & 0\\ 0.1928 & -0.1556 & 0\\ 0.0017 & 0 & -0.0836\end{bmatrix}\begin{bmatrix}x_1\\ x_2\\ x_3\end{bmatrix} + \begin{bmatrix}1\\ 0\\ 0\end{bmatrix}u$$

Let's check the spectrum (the eigenvalues) of matrix A

$$spec(A) = \{-0.0836; -0.0399; -0.4149\}$$

So the system is asymptotically stable.

Example – Compartmental model for the effect of atracurium

Notice that for $\bar{u} = 0$ we get

$$\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}$$

Meaning: no inlet flow of drug implies no drug mass in the compartments

From a physiological point of view, the objective in a system like this is to find the right amount of inlet flow, such that the total mass of drug in the compartments reaches a certain equilibrium value.

Example – Compartmental model for the effect of atracurium

Suppose that the desired equilibrium mass is $\bar{M} = 1.1169$. Then, at the equilibrium $\dot{x}(t) = 0$ and

$$\bar{M} = \bar{x}_1 + \bar{x}_2 + \bar{x}_3$$

Also, at the equilibrium the outlet flow must be equal to the inlet flow. Then

$$\bar{u} = q_1\bar{x}_1 + q_2\bar{x}_2 + q_3\bar{x}_3$$

Combining these two equations

$$\bar{u} = q_1\bar{x}_1 + q_2\bar{x}_2 + q_3(\bar{M} - \bar{x}_1 - \bar{x}_2)$$
$$= (q_1 - q_3)\bar{x}_1 + (q_2 - q_3)\bar{x}_2 + q_3\bar{M}$$

Example – Compartmental model for the effect of atracurium

From the first equation $(-k_{12} - k_{13} - q_1)\bar{x}_1 + k_{21}\bar{x}_2 + \bar{u} = 0$

$$(-k_{12} - k_{13} - q_1)\bar{x}_1 + k_{21}\bar{x}_2 + (q_1 - q_3)\bar{x}_1 + (q_2 - q_3)\bar{x}_2 + q_3\bar{M} = 0$$

Manipulating this equation we get

$$\bar{x}_1 = \frac{k_{21} + q_2 - q_3}{k_{12} + k_{13} + q_3}\bar{x}_2 + \frac{q_3}{k_{12} + k_{13} + q_3}\bar{M}$$

Example – Compartmental model for the effect of atracurium

From the second equation $k_{12}\bar{x}_1 - (k_{21} + q_2)\bar{x}_2 = 0$

$$\frac{k_{12}(k_{21} + q_2 - q_3)}{k_{12} + k_{13} + q_3}\bar{x}_2 + \frac{k_{12}q_3}{k_{12} + k_{13} + q_3}\bar{M} - (k_{21} + q_2)\bar{x}_2 = 0$$

Manipulating the previous equation we obtain

$$\bar{x}_2 = \frac{k_{12}q_3}{k_{12}q_3 + (k_{21}+q_2)(k_{13}+q_3)}\bar{M}$$

Since $\bar{x}_2$ only depends on known values, we can compute the equilibrium

Example – Compartmental model for the effect of atracurium

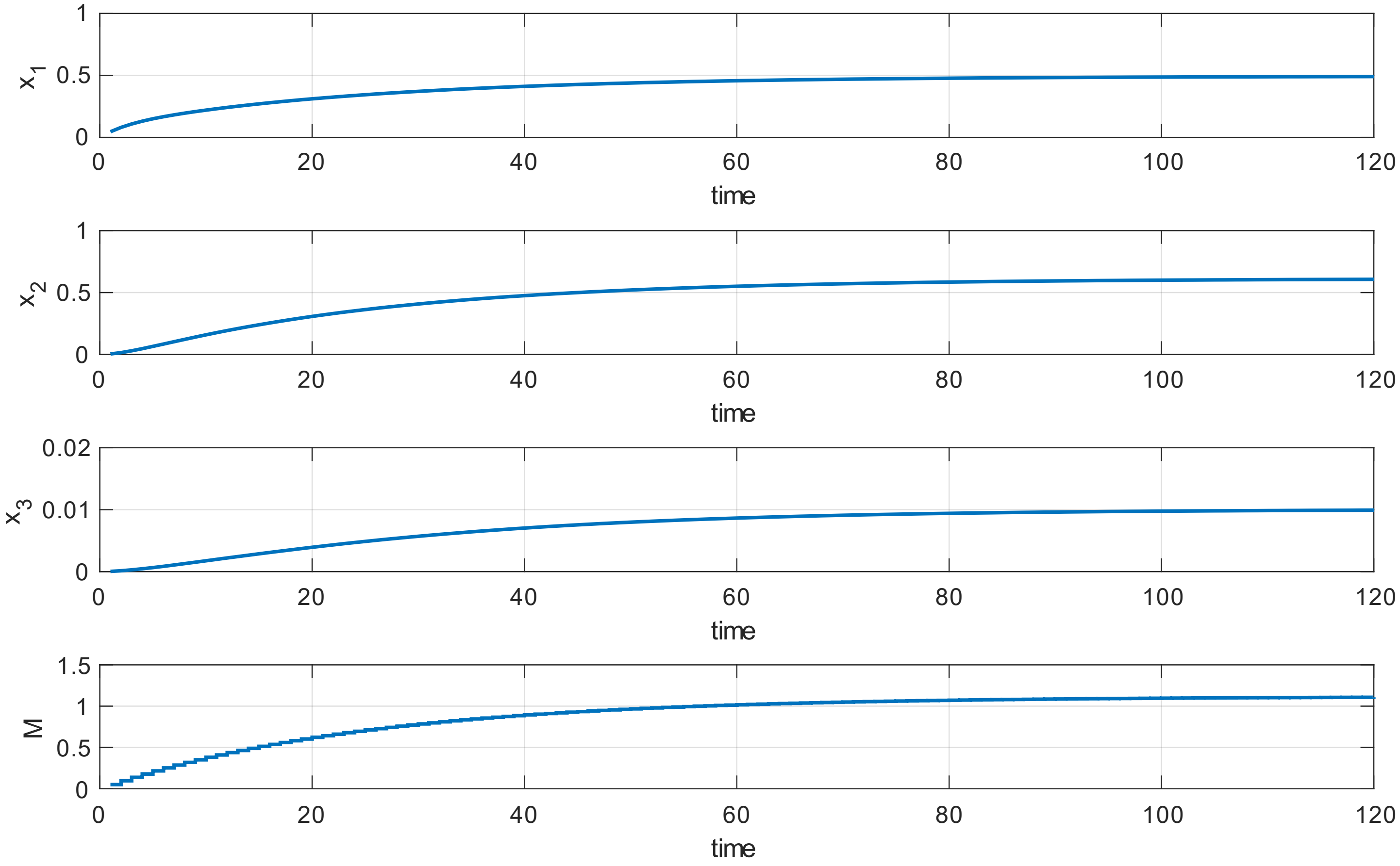
$$\bar{x}_2 = \frac{k_{12}q_3}{k_{12}q_3 + (k_{21}+q_2)(k_{13}+q_3)}\bar{M} = 0.6125$$

$$\bar{x}_1 = \frac{k_{21} + q_2 - q_3}{k_{12} + k_{13} + q_3}\bar{x}_2 + \frac{q_3}{k_{12} + k_{13} + q_3}\bar{M} = 0.4943$$

$$\bar{x}_3 = \bar{M} - \bar{x}_1 - \bar{x}_2 = 0.0101$$

$$\bar{u} = q_1\bar{x}_1 + q_2\bar{x}_2 + q_3\bar{x}_3 = 0.0526$$

Example – Compartmental model for the effect of atracurium



Simulation for $\bar{u} = 0.0526$

The total mass converges to the desired values

$\bar{M} = 1.1169$

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