



**UNIVERSITÀ
DEGLI STUDI
DI BERGAMO**

Dipartimento
di Ingegneria Gestionale,
dell'Informazione e della Produzione

Lesson 11.

Pharmacokinetic models

**CONTROL AND MODELING OF
BIOLOGICAL SYSTEMS**

**MASTER DEGREE IN
MEDICAL ENGINEERING**

TEACHER

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Drug dosing

Control engineering impacts modern medicine through robotic surgery, electrophysiological devices (pacemakers, artificial hearts, artificial pancreas) and image-guided therapies.

Another area where control theory has an impact is clinical pharmacology, in which mathematical modeling plays an important role.

In particular, the problem of drug dosing is a potential application of control theory.

Drug dosing can be made more precise by using pharmacokinetic and pharmacodynamics modeling.



A drug enters the body. What happens?

When a drug is taken and enters the body:

1. A portion of it binds to proteins in various areas of the organism (**bound fraction**).
2. A portion remains unbound (**free fraction**) and distributes by diffusion into biological fluids (**body water**).
3. A portion is removed by metabolization and transformed in other substances (metabolites) or by physiological excretion.



Body water

The average adult human body water is approximately 60% of the body weight.

Body water can be broken down into the following **compartments**:

1. **Intracellular fluid** (2/3 of body water) is the fluid contained within cells.
2. **Extracellular fluid** (1/3 of body water) is the fluid contained in areas outside of cells.
This includes:
 - ✓ Plasma: 20% of extracellular fluid.
 - ✓ Interstitial fluid: 80% of extracellular fluid.
 - ✓ Transcellular fluid contained inside organs, such as the gastrointestinal, cerebrospinal, peritoneal and ocular fluids (normally ignored in calculations)

A drug enters the body. What happens?

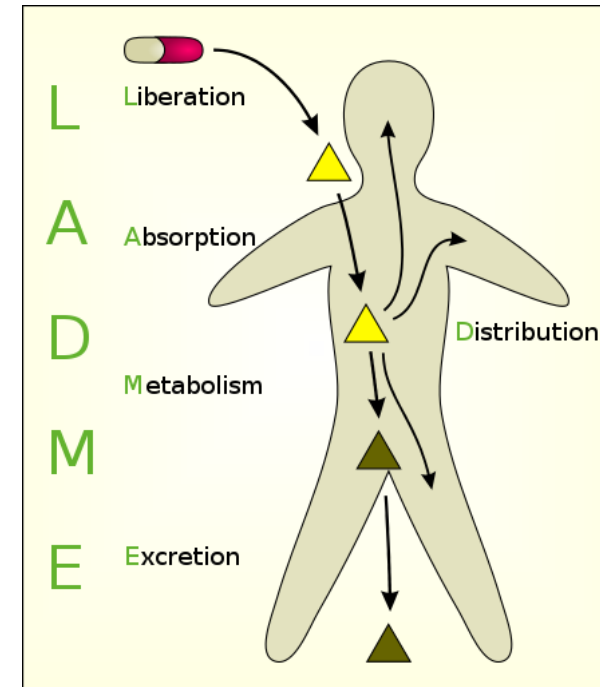
A drug has the same concentration in the body water (free fraction).

The concentration of drug bound to tissues (the real drug concentration) may change, but in general it is proportional to the free fraction.

To deliver the desired effects, a drug after its administration has to reach an adequate concentration in the **biophase**, that is the effect site of the drug.

Drug concentrations depend on posology (kind of dosing and quantity) and on the **ADME** velocity of the drug.

ADME: Absorption, Distribution, Metabolism, Excretion.



Drug dosing

Pharmacokinetics is the study of the time evolution of the ADME. It analyzes the concentration of drugs in tissue as a **function of time and dose schedule**.

Pharmacodynamics on the other hand is the study of the relationship between **drug concentration and drug effect**.

By relating the dose to the resultant concentration (**pharmacokinetics**) and concentration to effect (**pharmacodynamics**), it is possible to obtain a model for drug dosing.



Modelling

The concentration of drug inside the **biophase** is in general unknown since it is not easy to measure, or it is difficult to know the exact drug location in the tissues.

However, in general, the effects of a drug can be related to the time evolution of the **concentration in the plasma** (so in the body water).

By mathematical modelling one can then estimate the drug concentration in the tissues.

Compartmental models are a widely used tool to model these processes.



Pharmacokinetics models

Pharmacokinetics compartmental models assume that the body is comprised of more than one compartment.

Inside each compartment, the drug concentration is assumed to be **uniform** (perfect instantaneous mixing).

The instantaneous mixing is an idealization, but it has a little effect on the accuracy of the model.

Transport to other compartments and elimination from the body occur by metabolic processes.

The transport rate is assumed to be proportional to the drug concentration.



Compartments

The human body can be seen as composed by one or more compartments. In each compartment the drug is absorbed, distributed, metabolized, and eliminated (ADME).

The compartments do not necessarily represent physiological or anatomical entities. They should be considered as ideal spaces inside which the drug enters, moves, is eliminated with a velocity proportional to its concentration.

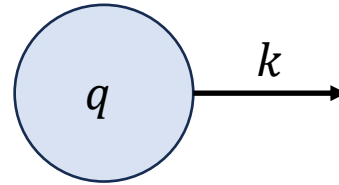
It's a first order dynamic!

(typical of compartments in compartmental models.)



Compartmental modelling

The simplest pharmacokinetic model is a 1-compartment model. This kind of model assume that the drug distributes uniformly and instantaneously in the whole body and all the tissues.



q represents the amount of a certain drug suddenly placed in the body. The elimination of drug from the body can be modeled as:

$$\dot{q}(t) = -kq(t)$$

With k described in time unit. If for instance $k = 0.1 [h^{-1}]$, this means that the amount of the drug decreases of the 10% every hour.

Parameters

The biological **half-life** (or half-time) $T_{\frac{1}{2}}$ measures the velocity of the elimination process.

It represents the time necessary to eliminate the half of the initial amount of the drug, that is the time necessary to reduce the concentration to half of its value.

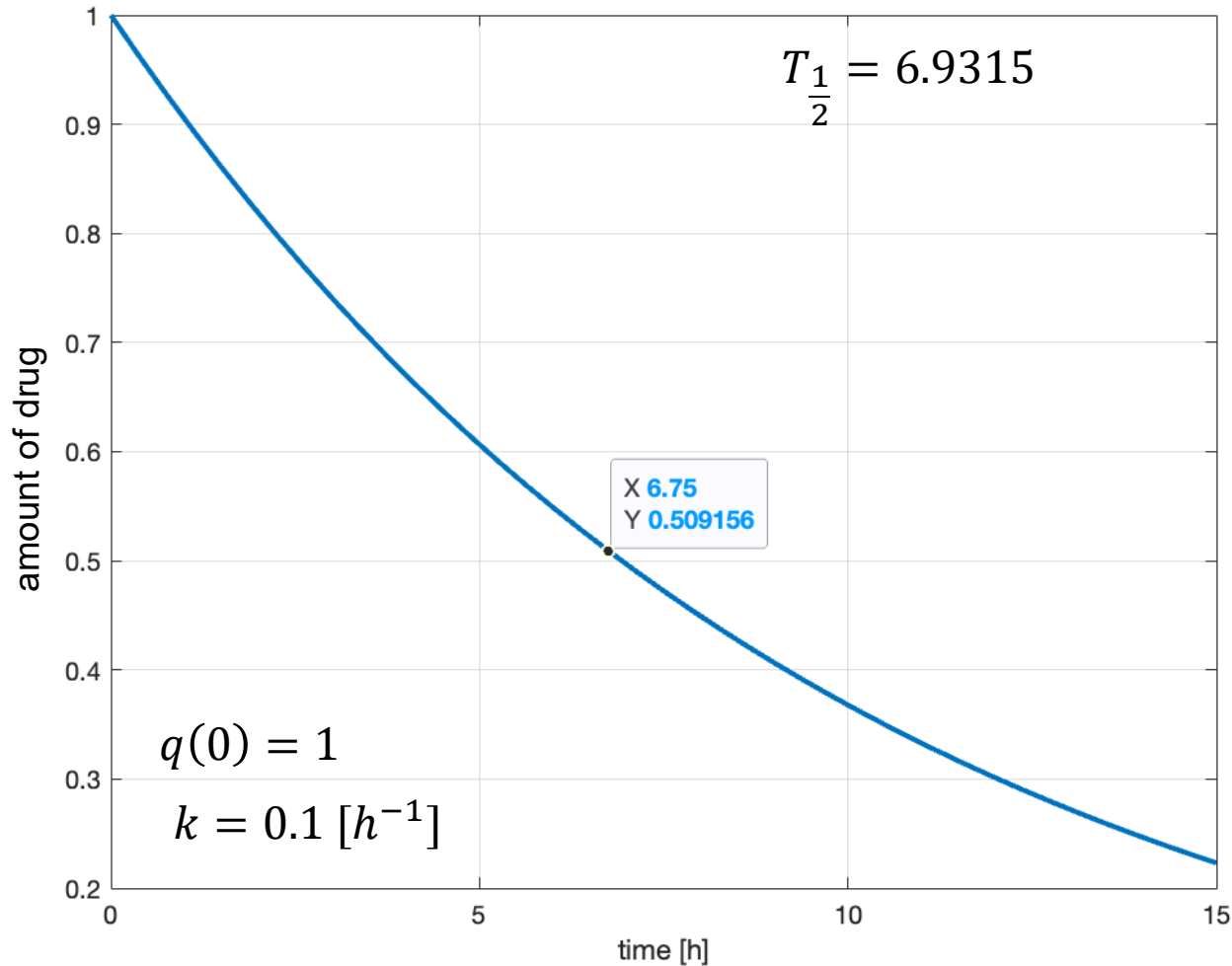
It's a measure of the capacity of the human body to eliminate the drug.

This parameter is of crucial importance to determine the right time interval between two successive administration of the drug.

It depends on the drug and the patient.



Half-life



$$\dot{q}(t) = -kq(t) \quad q(t) = q(0)e^{-kt}$$

This curve represents the time evolution of $q(t)$.

After almost 6.9 hours, the half of the drug amount is eliminated.

This is what we called **the half-life** and it can easily be computed:

$$T_{\frac{1}{2}} = \frac{\ln(2)}{k} = \frac{0.693}{k}$$

Half-life analysis

The time evolution of $q(t)$ is given by the equation of the model

$$\dot{q}(t) = -kq(t)$$

From which the **free movement** can be computed

$$q(t) = q(0)e^{-kt}$$

At time $T_{\frac{1}{2}}$ the amount of drug is half the initial amount:

$$q(T_{\frac{1}{2}}) = q(0)e^{-kT_{\frac{1}{2}}} = \frac{q(0)}{2}$$

Then:

$$e^{-kT_{\frac{1}{2}}} = \frac{1}{2} \quad \longrightarrow \quad -kT_{\frac{1}{2}} = \ln\left(\frac{1}{2}\right) = -\ln(2) \quad \longrightarrow \quad T_{\frac{1}{2}} = \frac{\ln(2)}{k}$$

Parameters

The transfer of drug from one compartment to another can be represented as a **flow** parameterized by a certain coefficient of transfer.

- The flow is considered proportional to the quantity of material inside the compartment.

The so-called **clearance** (CL) characterizes the process of elimination of the drug from a certain compartment. It represents the quote of volume excreted in a time unity.

- In a first order dynamical process, it is considered as constant.



Parameters

The apparent **volume of distribution** is a ratio of the total amount of drug in the body to the plasma concentration of the drugs.

$$V_d = \frac{\textit{amount of drug in body}}{\textit{plasma drug concentration}}$$

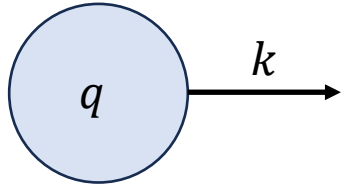
It represents the volume of biological fluids inside which the drug should distribute to obtain a certain value of concentration, assuming that the concentration of drugs in all tissues is uniform and equal to the one in the plasma.

It is called **apparent** since in general it's an approximation and does not correspond to the real volume of fluids in the body.



Compartmental modelling

Let's analyze the system



$$\dot{q}(t) = -kq(t) \quad q(t) = D e^{-kt}$$

$q(0) = D$ Initial condition: initial quantity of drug. In the example we took $q(0) = 1$

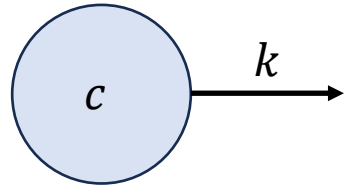
Assume that the apparent volume is V . The drug concentration is given by:

$$c(t) = \frac{q(t)}{V} = \frac{D}{V} e^{-kt}$$

The initial concentration is given by $c(0) = \frac{D}{V}$

Compartmental modelling

The same model can be also written looking at the concentration:

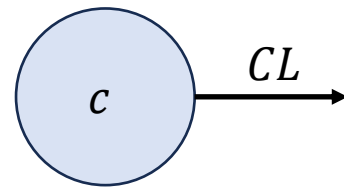


$$\dot{c}(t) = -kc(t)$$

$$c(t) = c(0)e^{-kt}$$

$$c(0) = \frac{D}{V}$$

If we express the elimination rate as the clearance of the drug, then



$$\dot{c}(t) = -\frac{CL}{V}c(t)$$

$$c(t) = c(0)e^{-\frac{CL}{V}t}$$

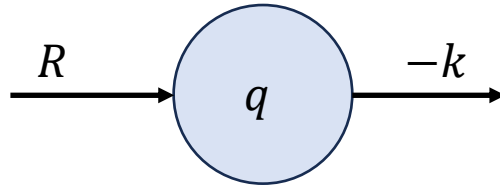
$$T_{\frac{1}{2}} = \frac{\ln(2)}{CL/V} = \frac{0.693 * V}{CL}$$

$$c(0) = \frac{D}{V}$$

$$k = \frac{CL}{V}$$

Pharmacokinetics models

Suppose to also have a fixed rate of injection of the drug R , in unit per time (for instance [mg/h]) (for instance a drip-feed).



R (which is a velocity) represents the input amount of a certain drug in the body. The accumulation of drug in the body can be now modeled as:

$$\dot{q}(t) = -kq(t) + R$$

R is a sort of step input signal (of amplitude R). The amount of drug in the body will increase until the rate of elimination equals the rate of infusion R . It's like the water tank example....

Stationary point

The stationary (equilibrium) point is reached when the amount of drug administered in a certain period is identically equal to the amount of drug eliminated in the same period.

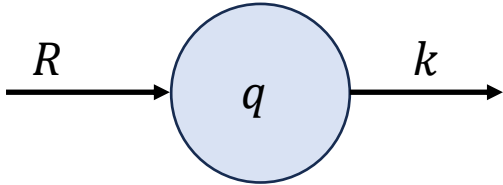
In the stationary condition **the concentration of the drug is constant.**

The time necessary to reach a stationary point depends on the half-life of the drug.

Dosing: depending on the characteristic and the effects of a drug, its administration can be done by a single dose (bolus) or in periodic repeated shots (like an antibiotic).

Stationary conditions

Let's analyze the system



$$\dot{q}(t) = -kq(t) + R \quad q(0) = 0$$

$$q(t) = \frac{R}{k} (1 - e^{-kt})$$

$$x(t) = e^{At}x(0) + \int_0^t e^{A(t-\tau)} Bu(\tau) d\tau$$
$$q(t) = e^{-kt}q(0) + \int_0^t e^{-k(t-\tau)} R d\tau$$

At the equilibrium: $\dot{q}(t) = 0$. Then

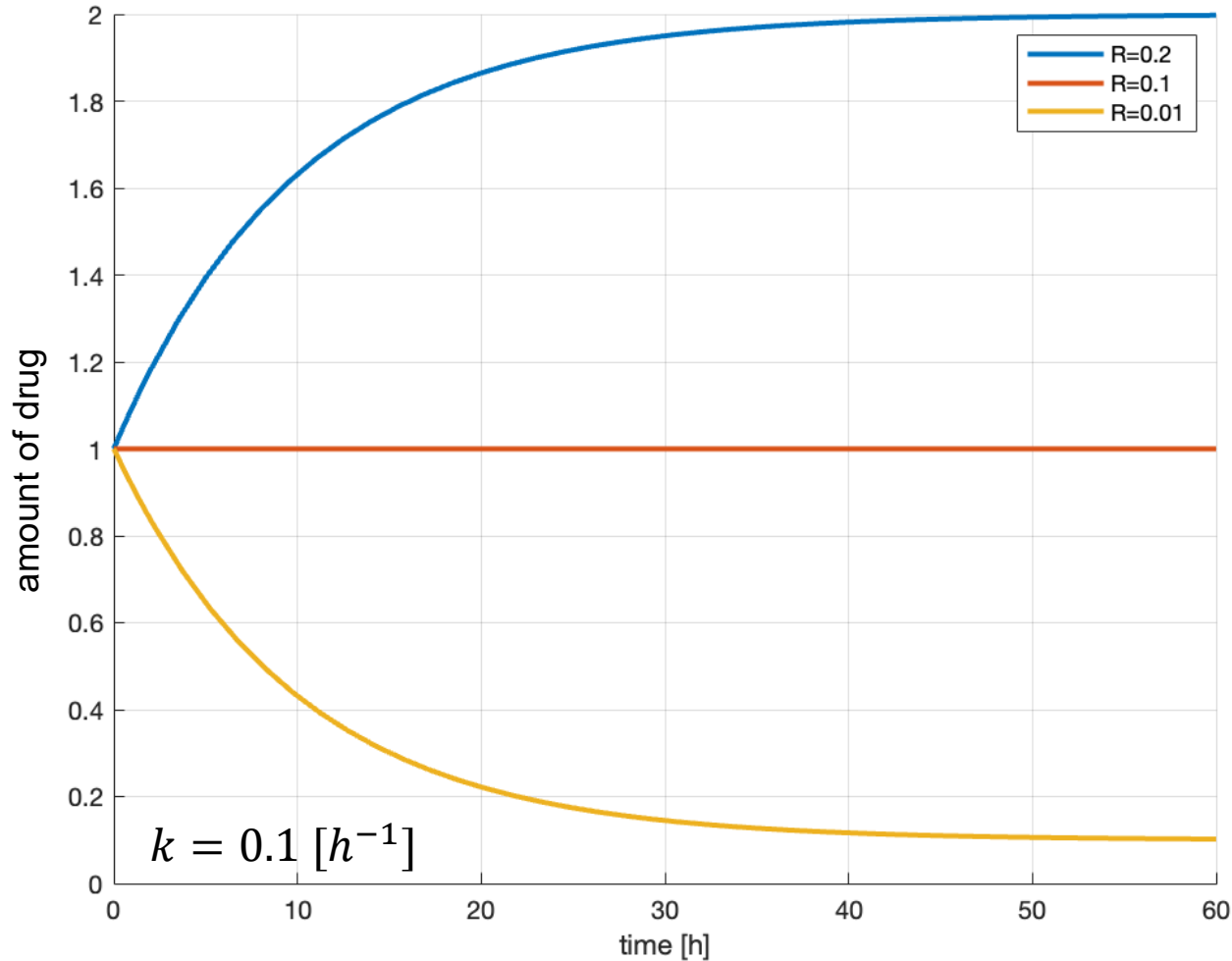
$$\bar{q} = \frac{R}{k}$$

Assume that the apparent volume is V . The drug concentration at the equilibrium is given by:

$$c(t) = \frac{q(t)}{V} \longrightarrow \bar{c} = \frac{R}{kV} = \frac{R}{CL}$$

$$k = \frac{CL}{V}$$

Pharmacokinetics models



$$\dot{q}(t) = R - kq(t)$$

For different values of R the body either accumulates or eliminates the drug

This depends on the value of the inflow rate R , since the equilibrium concentration is given by:

$$\bar{q} = \frac{R}{k}$$

Two compartments model

In a pharmacokinetic 2-compartments model, the human body is described as composed by two elements: the central compartment and the peripheral compartment.

This kind of model assumes that the drug, after its administration in the central compartment, distributes uniformly between the two compartments without instantaneously reaching an equilibrium.

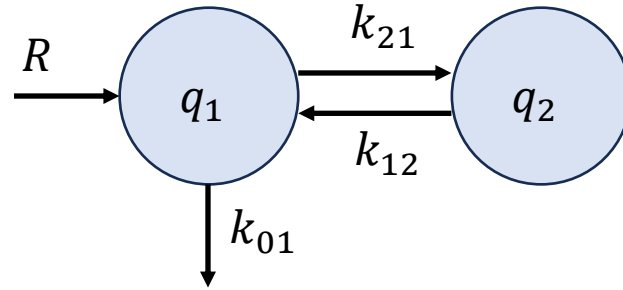
Assumption:

- **Central compartment:** high perfusion tissues (plasma, heart, lungs, kidney, liver, brain).
- **Peripheral compartment:** low perfusion tissues (muscles, fat, and skin)



Two compartments model

A pharmacokinetic 2-compartments model is of the form:



q_1 represents the amount of a certain drug in the central compartment. q_2 represents the amount of the drug in the peripheral compartment. The elimination of drug from the body is modeled by k_{01} :

$$\dot{q}_1(t) = -(k_{01} + k_{21})q_1(t) + k_{12}q_2(t)$$

$$\dot{q}_2(t) = k_{21}q_1(t) - k_{12}q_2(t)$$

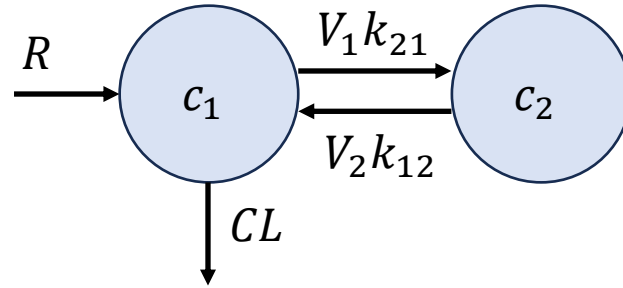
$$q_1(0) = R$$

$$q_2(0) = 0$$

$$c_1(t) = \frac{q_1(t)}{V_1}$$

Two compartments model

Considering the concentration as the state of the system:



$$V_1 k_{21} = V_2 k_{12} = Q \quad k_{01} = \frac{CL}{V_1}$$

$$V_2 = \frac{k_{21}}{k_{12}} V_1$$

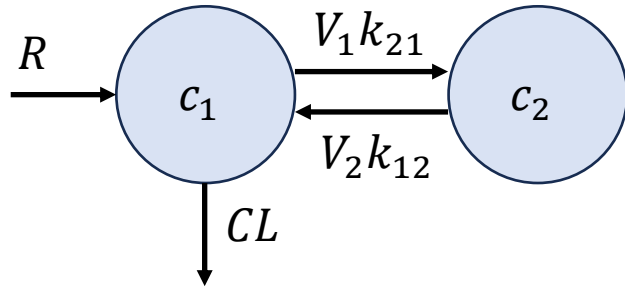
c_1 represents the concentration of drug in the central compartment. c_2 represents the concentration of the drug in the peripheral compartment. The clearance of drug from the body is modeled by CL :

$$\dot{c}_1(t) = -\frac{(CL + Q)}{V_1} c_1(t) + \frac{Q}{V_1} c_2(t) \quad c_1(0) = \frac{R}{V_1}$$

$$\dot{c}_2(t) = \frac{Q}{V_2} c_1(t) - \frac{Q}{V_2} c_2(t) \quad c_2(0) = 0$$

Stationary conditions

Suppose to have a constant infusion rate R :



$$\begin{aligned} \dot{c}_1(t) &= -\frac{(CL + Q)}{V_1} c_1(t) + \frac{Q}{V_1} c_2(t) + \frac{R}{V_1} \\ \dot{c}_2(t) &= \frac{Q}{V_2} c_1(t) - \frac{Q}{V_2} c_2(t) \end{aligned}$$

$$\begin{aligned} V_1 k_{21} &= V_2 k_{12} = Q \\ V_2 &= \frac{k_{21}}{k_{12}} V_1 \quad k_{01} = \frac{CL}{V_1} \end{aligned}$$

$$c_1(0) = 0$$

$$c_2(0) = 0$$

At the equilibrium: $\dot{c}_1(t) = 0$ and $\dot{c}_2(t) = 0$. Then from the second equation:

$$0 = \frac{Q}{V_2} \bar{c}_1 - \frac{Q}{V_2} \bar{c}_2 \quad \longrightarrow \quad \bar{c}_1 = \bar{c}_2$$

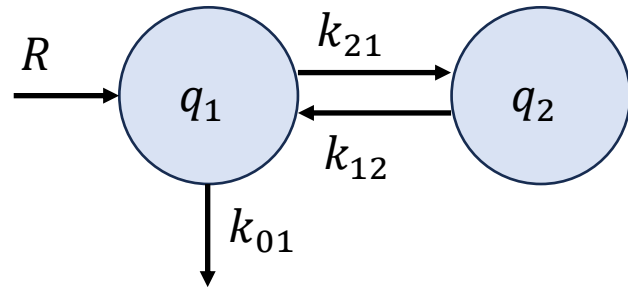
And from the first equation:

$$0 = -\frac{(CL + Q)}{V_1} \bar{c}_1 + \frac{Q}{V_1} \bar{c}_2 + \frac{R}{V_1} \quad \longrightarrow \quad \bar{c}_1 = \frac{R}{CL}$$

(As in the 1 compartment case)

Stationary conditions

If we consider the drug amount model:



$$\dot{q}_1(t) = -(k_{01} + k_{21})q_1(t) + k_{12}q_2(t) + R$$

$$\dot{q}_2(t) = k_{21}q_1(t) - k_{12}q_2(t)$$

$$q_1(0) = 0$$

$$q_2(0) = 0$$

$$V_1 k_{21} = V_2 k_{12} = Q$$

$$V_2 = \frac{k_{21}}{k_{12}} V_1 \quad k_{01} = \frac{CL}{V_1}$$

At the equilibrium: $\dot{q}_1(t) = 0$ and $\dot{q}_2(t) = 0$. Then from the second equation:

$$0 = k_{21}\bar{q}_1 - k_{12}\bar{q}_2 \quad \longrightarrow \quad \bar{q}_2 = \frac{k_{21}}{k_{12}}\bar{q}_1$$

And from the first equation:

$$0 = -(k_{01} + k_{21})\bar{q}_1 + k_{12}\frac{k_{21}}{k_{12}}\bar{q}_1 + R \quad \longrightarrow \quad \bar{q}_1 = \frac{R}{k_{01}}$$

(As in the 1 compartment case)

Multicompartmental models

In this kind of model, the human body is described as composed by more than two compartments.

For each compartment, we can define a specific dynamic, that is a state variable. This implies that the system is described by several states.

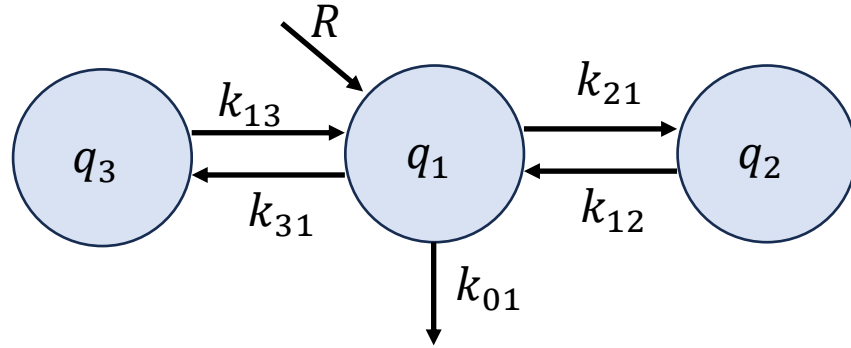
The most employed model consider three compartments:

- **Central compartment**
- **Superficial peripheral compartment**
- **Deep peripheral compartment**



Three compartments model

A pharmacokinetic 3-compartments model is of the form:



The mathematical model can be given by :

$$\dot{q}_1(t) = -(k_{01} + k_{21} + k_{31})q_1(t) + k_{12}q_2(t) + k_{13}q_3(t)$$

$$\dot{q}_2(t) = k_{21}q_1(t) - k_{12}q_2(t)$$

$$\dot{q}_3(t) = k_{31}q_1(t) - k_{13}q_3(t)$$

$$q_1(0) = R$$

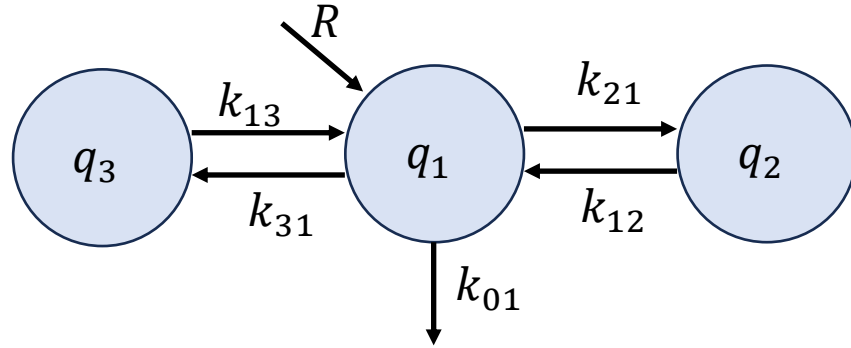
$$q_2(0) = 0$$

$$q_3(0) = 0$$

$$c_1(t) = \frac{q_1(t)}{V_1}$$

Three compartments model

This model can be rewritten in matrix form:



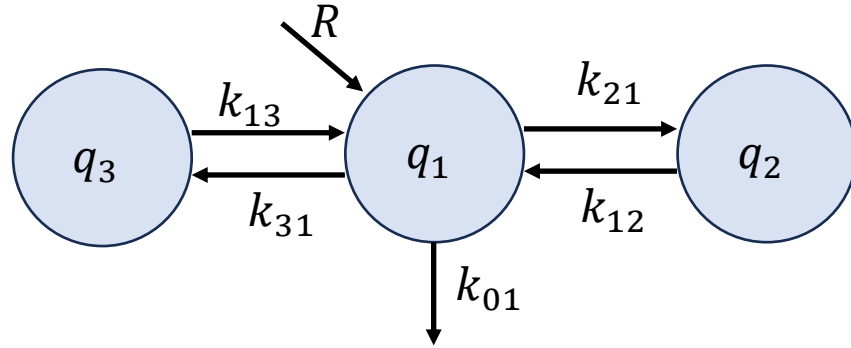
The mathematical model can be given by :

$$\begin{bmatrix} \dot{q}_1(t) \\ \dot{q}_2(t) \\ \dot{q}_3(t) \end{bmatrix} = \begin{bmatrix} -k_{01} & -k_{21} & -k_{31} & k_{12} & k_{13} \\ & k_{21} & & -k_{12} & 0 \\ & k_{31} & & 0 & -k_{13} \end{bmatrix} \begin{bmatrix} q_1(t) \\ q_2(t) \\ q_3(t) \end{bmatrix} \quad \begin{array}{l} q_1(0) = R \\ q_2(0) = 0 \\ q_3(0) = 0 \end{array}$$

$$c_1(t) = \frac{q_1(t)}{V_1}$$

Three compartments model

If we consider an external constant infusion R



The mathematical model can be given by :

$$\dot{q}_1(t) = -(k_{01} + k_{21} + k_{31})q_1(t) + k_{12}q_2(t) + k_{13}q_3(t) + R$$

$$\dot{q}_2(t) = k_{21}q_1(t) - k_{12}q_2(t)$$

$$\dot{q}_3(t) = k_{31}q_1(t) - k_{13}q_3(t)$$

$$q_1(0) = 0$$

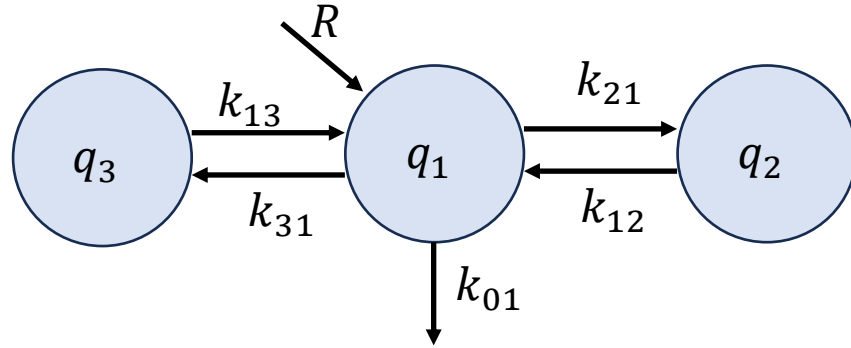
$$q_2(0) = 0$$

$$q_3(0) = 0$$

$$c_1(t) = \frac{q_1(t)}{V_1}$$

Three compartments model

Also this model can be rewritten in matricial form:



The mathematical model can be given by :

$$\begin{bmatrix} \dot{q}_1(t) \\ \dot{q}_2(t) \\ \dot{q}_3(t) \end{bmatrix} = \begin{bmatrix} -k_{01} & -k_{21} & -k_{31} & k_{12} & k_{13} \\ & k_{21} & & -k_{12} & 0 \\ & k_{31} & & 0 & -k_{13} \end{bmatrix} \begin{bmatrix} q_1(t) \\ q_2(t) \\ q_3(t) \end{bmatrix} + \begin{bmatrix} R \\ 0 \\ 0 \end{bmatrix} \quad \begin{array}{l} q_1(0) = 0 \\ q_2(0) = 0 \\ q_3(0) = 0 \end{array}$$

$$c_1(t) = \frac{q_1(t)}{V_1}$$

Stationary conditions

Given the constant infusion rate R , the stationary conditions can be computed by setting $\dot{q}_1(t) = \dot{q}_2(t) = \dot{q}_3(t) = 0$.

Then from the second and the third equation we have:

$$\bar{q}_2 = \frac{k_{21}}{k_{12}} \bar{q}_1 \quad \bar{q}_3 = \frac{k_{31}}{k_{13}} \bar{q}_1$$

Finally from the first equation we have:

$$-(k_{01} + k_{21} + k_{31})\bar{q}_1 + k_{12} \frac{k_{21}}{k_{12}} \bar{q}_1 + k_{13} \frac{k_{31}}{k_{13}} \bar{q}_1 + R = 0 \quad \longrightarrow \quad \bar{q}_1 = \frac{R}{k_{01}}$$

Considering the concentration:

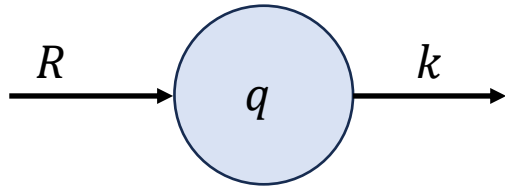
$$\bar{c}_1 = \frac{\bar{q}_1}{V_1} = \frac{R}{k_{01} V_1} = \frac{R}{CL}$$

$$k_{01} = \frac{CL}{V_1}$$



Dosing

In the previous slides we have supposed a constant venous infusion rate R . Take a 1 compartment model:



$$\dot{q}(t) = -kq(t) + R$$

$$q(0) = 0$$

The administration of a drug can also be a single (intra- or extravenous) dosis (bolus):

$$\dot{q}(t) = -kq(t) + R\delta(t)$$

$$q(0) = 0$$

Where $\delta(t)$ is the Dirac delta function, representing an impulse. The extravenous administration may have a dynamic of absorption (first or second order).

Dosing

In the extravenuous administration of the drug, not all the dose reaches the venous circulation.

The fraction of the doses that effectively reaches the venous circulation is called bioavailable fraction, or **bioavailability**.

We indicate it with a real number $F \in (0,1)$. Indeed, for the intravenous administration $F = 1$.

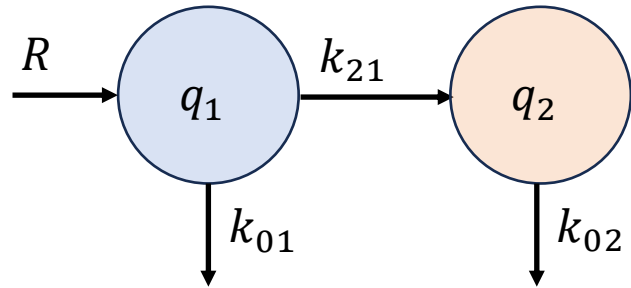
The bioavailable doses is given by $F * R$.

The bioavailability is an important parameter to be taken into account when designing a pharmacokinetic model of a drug. The right doses amount depends on this parameter.



2 compartments model with absorption

The extravenous administration may have a dynamic of absorption (first or second order).



$$\dot{q}_1(t) = -(k_{01} + k_{21})q_1(t) + R\delta(t)$$

$$q_1(0) = 0$$

$$\dot{q}_2(t) = k_{21}q_1(t) - k_{02}q_2(t)$$

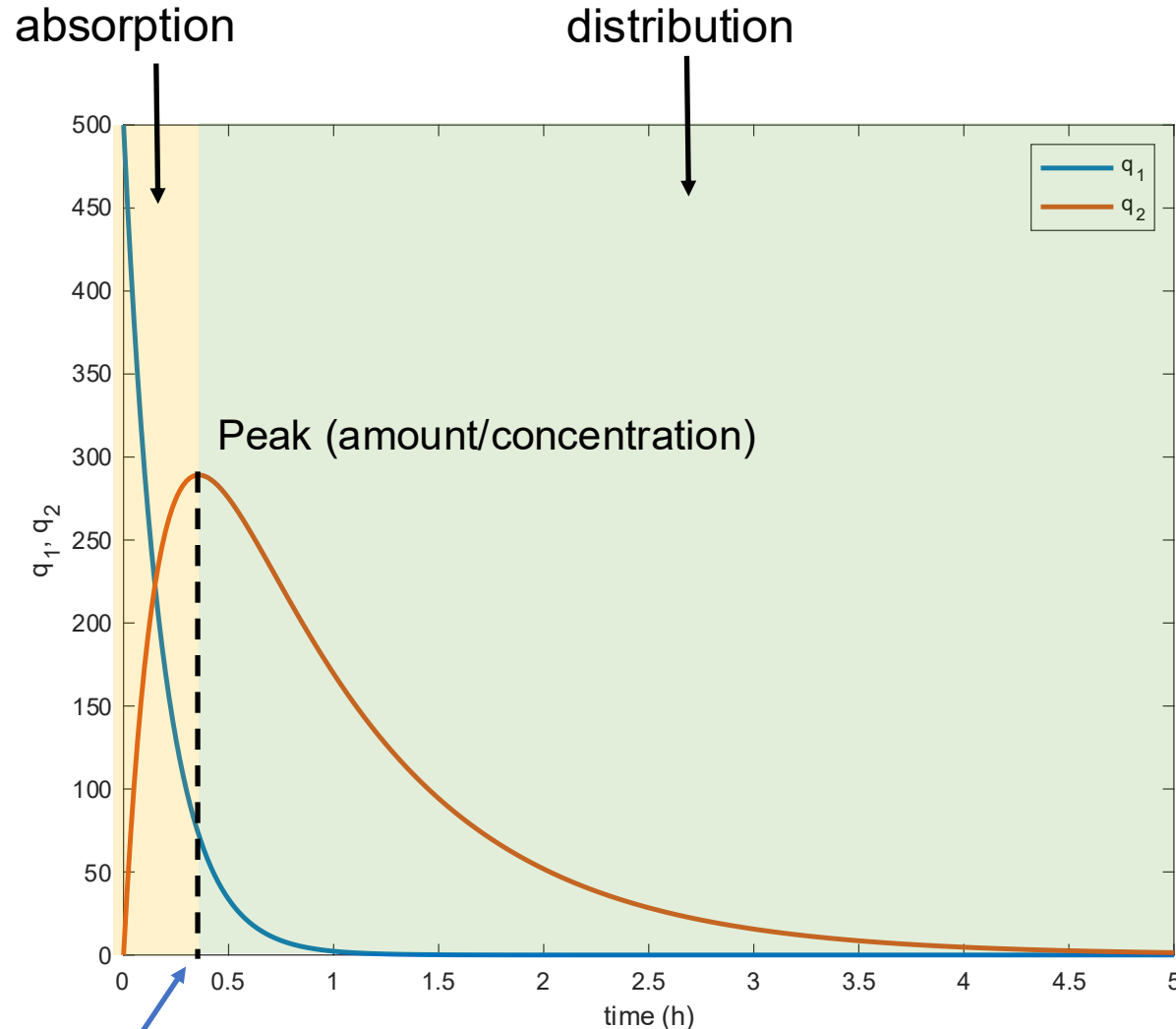
$$q_2(0) = 0$$

Compartment 1: administration compartment. Only a fraction of the doses reaches the venous circulation. It's the dynamic of the absorption.

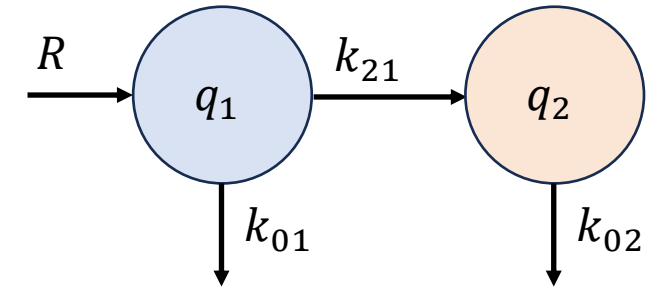
Compartment 2: central compartment. Drug concentration:

$$c_2(t) = \frac{q_2(t)}{V_2}$$

2 compartments model with absorption



Peak time (measure of velocity of absorption)



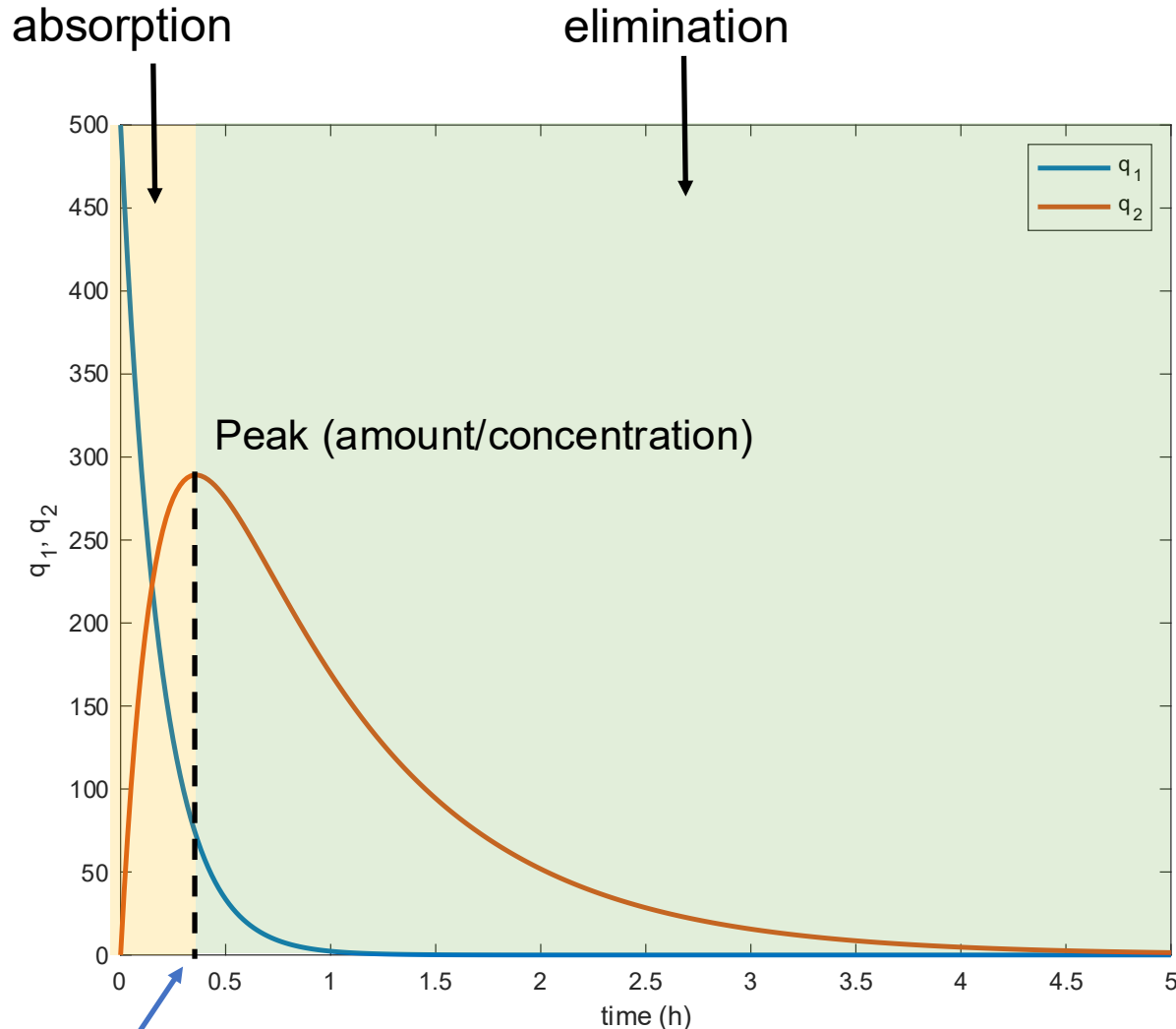
The absorption constant is:

$$k_a = k_{01} + k_{21}$$

The bioavailability is: $F = \frac{k_{21}}{k_{01} + k_{21}}$

The bioavailable doses is : $F * R$

2 compartments model with absorption



Absorption phase:

$$q_1(t) = R e^{-k_a t}$$

Elimination phase:

$$q_2(t) = R \frac{k_{21}}{k_{02} - k_a} (e^{-k_a t} - e^{-k_{02} t})$$

Peak: absorption rate equals the elimination rate

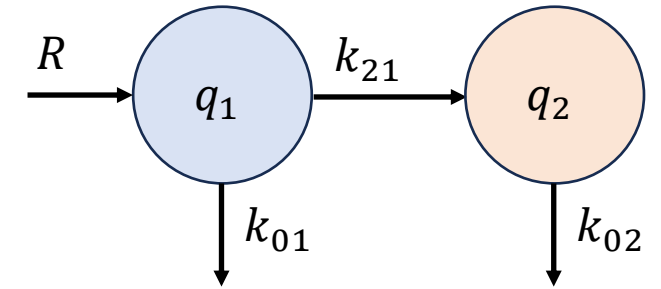
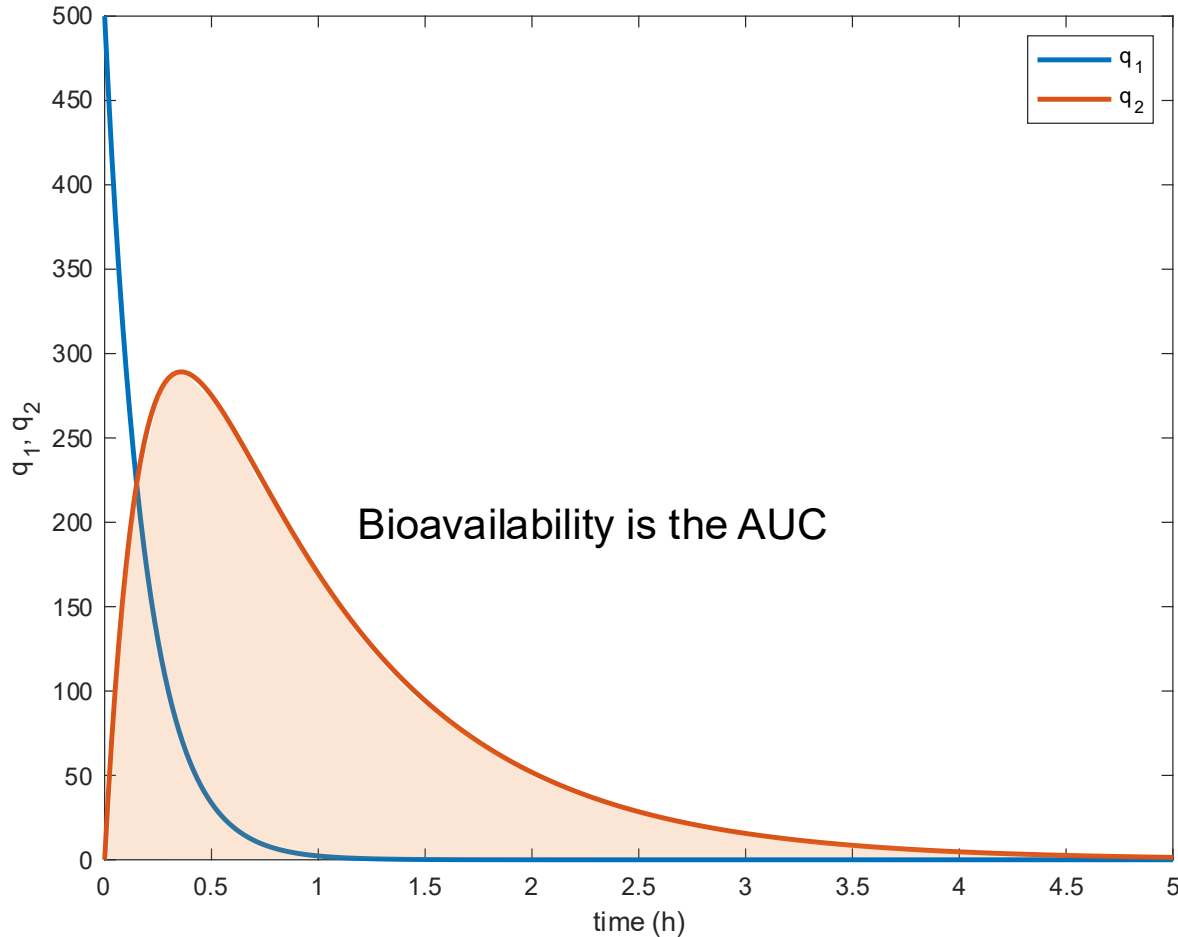
$$t_{peak} = \frac{\ln(k_{02}) - \ln(k_a)}{k_{02} - k_a}$$

$$q_{peak} = q_2(t_{peak}) \quad c_{peak} = \frac{q_{peak}}{V_2}$$

Peak time (measure of velocity of absorption): when absorption rate equals elimination rate



2 compartments model with absorption



The bioavailability can be seen as the Area Under the Curve (AUC) of the drug amount (concentration) from t_0 to t_{end}

The bioavailable doses is : $F * R$

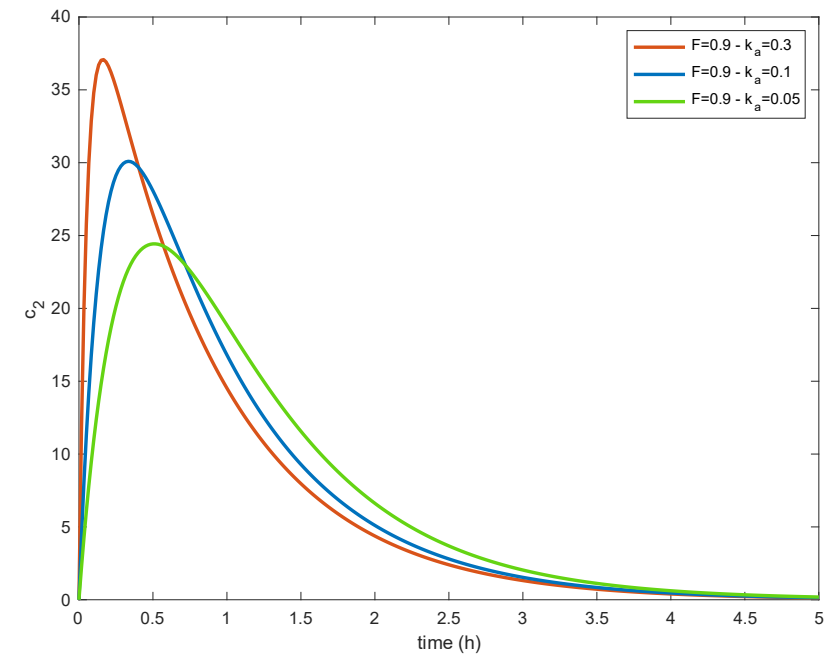
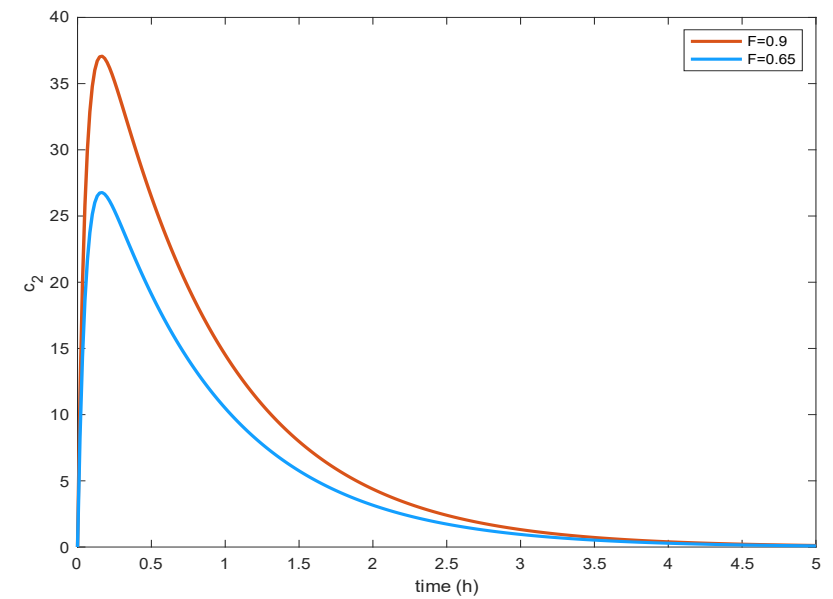
Dosing

The concentration of a drug administered by extravenuous infusion depends on the doses, but also on the absorbed fraction F and from the velocity of absorption (the constant k_a).

If the absorption is too slow, the plasma concentration won't be sufficiently high.

The ideal situation is to reach a desired concentration as fast as possible and to remain in that state as much as possible.

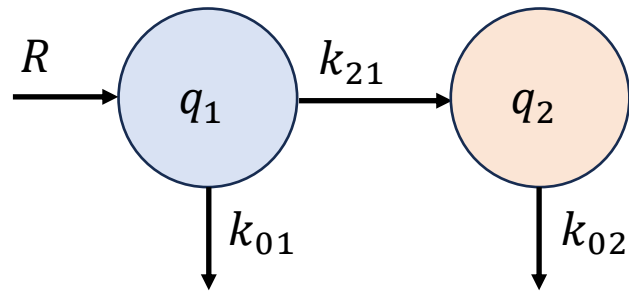
$$F = \frac{k_{21}}{k_{01} + k_{21}} = \frac{k_{21}}{k_a}$$



Example

A pharmacokinetic system consists of a first-order absorption compartment and a first-order central compartment. A patient receives a dose of 500 mg of an oral medication.

After administration, the bioavailable fraction of the drug is 90%. The drug is eliminated with elimination constant $k_{02} = 0.2 [h^{-1}]$



$$R = 500 [mg]$$

$$F = 0.9$$

$$k_{02} = 0.2 [h^{-1}]$$

$$\dot{q}_1(t) = -(k_{01} + k_{21})q_1(t) + R\delta(t)$$

$$\dot{q}_2(t) = k_{21}q_1(t) - k_{02}q_2(t)$$

$$q_1(0) = 0$$

$$q_2(0) = 0$$

Three hours after intake, the remaining dose of drug in the absorption compartment is 250mg.

Example

1. Calculate the bioavailable dose.

The bioavailable doses is : $F * R = 450 [mg]$

2. Calculate the absorption constant k_a .

$$\begin{aligned} \dot{q}_1(t) &= -(k_{01} + k_{21})q_1(t) & q_1(0^+) &= R & k_a &= (k_{01} + k_{21}) \\ \dot{q}_2(t) &= k_{21}q_1(t) - k_{02}q_2(t) & q_2(0) &= 0 \end{aligned}$$

Note that:

$$q_1(t) = q_1(0)e^{-k_a t} \quad q_1(3) = 250 [mg]$$

This means that : $T_{\frac{1}{2}} = 3 [h]$ $T_{\frac{1}{2}} = \frac{\ln(2)}{k_a}$ \longrightarrow $k_a = \frac{\ln(2)}{T_{\frac{1}{2}}} = 0.23 [h^{-1}]$

Example

3. Calculate the peak time and peak concentration value if the apparent volume is 3 L.

$$t_{peak} = \frac{\ln(k_{02}) - \ln(k_a)}{k_{02} - k_a} \quad q_{peak} = q_2(t_{peak}) \quad c_{peak} = \frac{q_{peak}}{V_2}$$

Where $V_2 = 3 [L]$

$$t_{peak} = \frac{\ln(k_{02}) - \ln(k_a)}{k_{02} - k_a} = \frac{\ln(0.2) - \ln(0.23)}{0.2 - 0.23} = \frac{-0.14}{-0.03} = 4.67 [h]$$

Then

$$\begin{aligned} q_2(t_{peak}) &= R \frac{k_{21}}{k_{02} - k_a} (e^{-k_a t_{peak}} - e^{-k_{02} t_{peak}}) = R \frac{F k_a}{k_{02} - k_a} (e^{-k_a t_{peak}} - e^{-k_{02} t_{peak}}) \\ &= 450 \frac{0.23}{0.2 - 0.23} (e^{-0.23 \cdot 4.67} - e^{-0.2 \cdot 4.67}) = -3450(0.342 - 0.393) = 175.95 [mg] \end{aligned}$$

And $c_{peak} = \frac{q_{peak}}{V_2} = \frac{175.95}{3} = 58.65 [mg/L]$



Repeated Dosing

Most prescription drugs are administered repeatedly for a limited duration (for acute illnesses) or for an extended period of time (for chronic conditions).

An example of repeated dosing for acute illnesses can be represented by antibiotic.

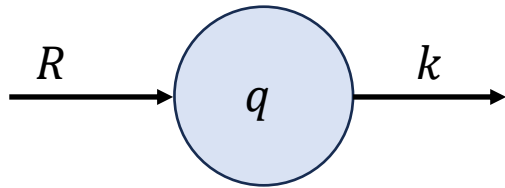
An example of repeated dosing for chronic diseases can be represented by insulin.

As such, it is important to understand the pharmacokinetic (PK) behavior of drugs when they are administered according to repeat-dose regimens.



Repeated Dosing

Suppose to have a single administration of a drug as a starting point, for instance we administer $R=500mg$ of a drug in a single compartment.



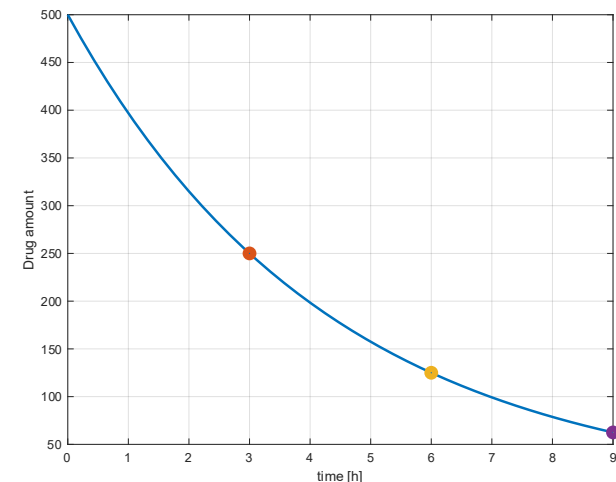
$$\dot{q}(t) = -kq(t)$$

$$q(0) = R$$

Immediately after the administration, the drug amount in the body (and its concentration) begins to decrease in terms of half-life.

If the half-life is 3 hours, we will observe that:

- After 3 hours: $q(3) = 250mg$
- After 6 hours: $q(6) = 125mg$
- After 9 hours: $q(9) = 62.5mg$
- After 12 hours: $q(12) = 31.25mg$



Repeated Dosing

What if we administer a second dose of 500mg after six hours?

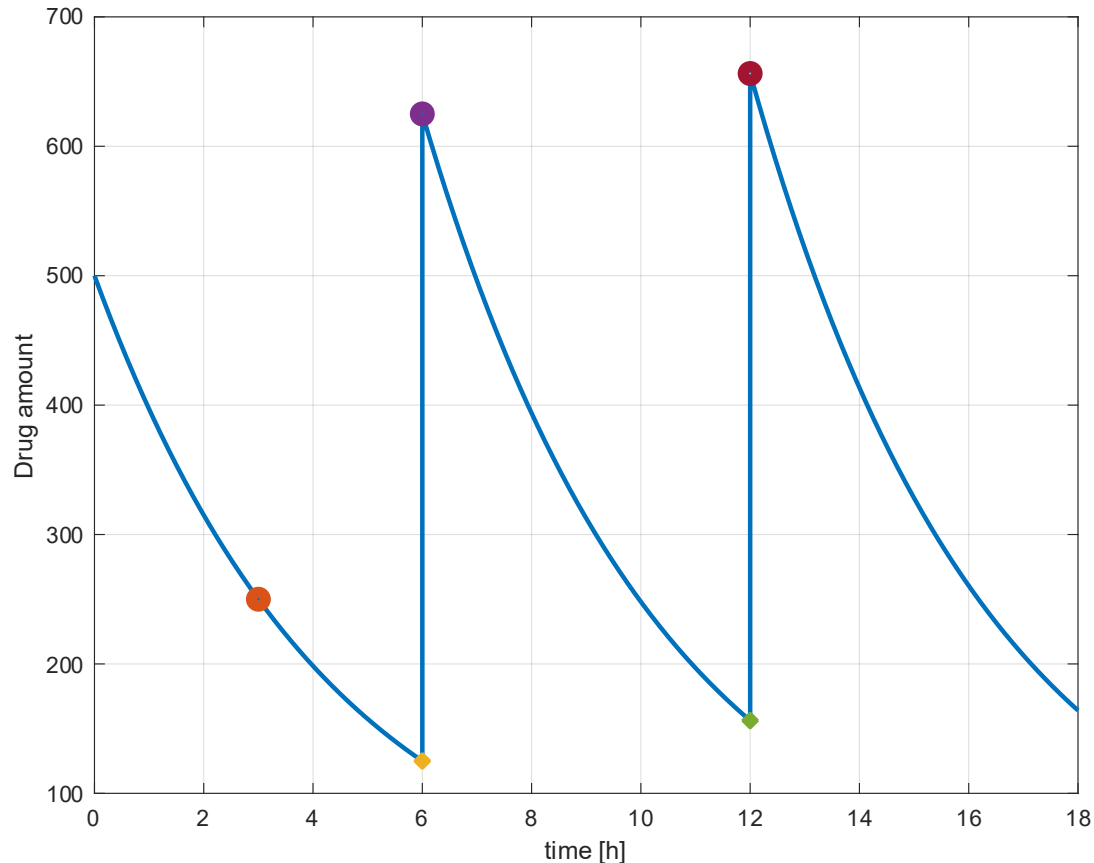
After 6 hours: $q(6) = 125mg$. If we administer an extra dose of 500mg, we get that the combined observed drug amount will be $q(6^+) = 625mg$.

If a third dose of 500mg is delivered after 12 hours, we will have a remaining amount from the second dose of $125mg$ plus the remaining amount from the first dose of $31.25mg$. Then, we get that the combined observed drug amount will be $q(12^+) = 656.25mg$. This is an additive combination of concentrations from the first, second, and third doses.

The process of adding concentrations from multiple doses to determine the observed concentrations is often referred to as the principle of superposition.



Repeated Dosing



- After 3 hours: $q(3) = 250mg$
- After 6 hours: $q(6^+) = 625mg$
- After 12 hours: $q(12^+) = 656.25mg$

The process of adding concentrations from multiple doses to determine the observed concentrations is often referred to as the principle of superposition.

The pattern of superposition described assumes that each dose behaves approximately the same.

This simple, additive superposition is approximately true for many drugs.

Repeated Dosing

Successive doses will result in increasing of the drug in the body until a plateau is reached. This plateau is called **steady state**.

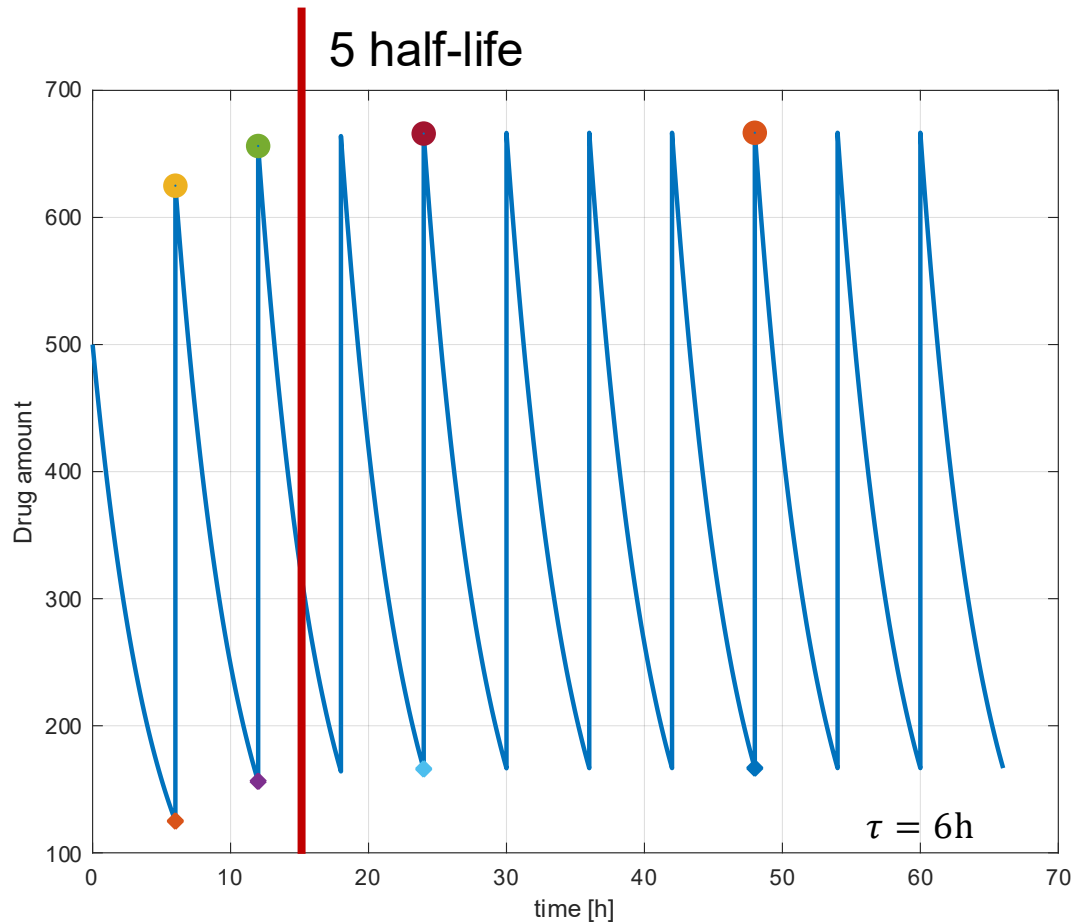
At steady state, the amount of drug administered on each dosing occasion is matched by an equivalent amount of drug leaving the body between each dose. Thus, drug amount will rise and fall according to a repeating pattern as long as we continue to administer drug at the same dose level and with the same time period between doses.

This repeated time period of dosing is often called the dosing interval and is in general denoted by τ .

For most drugs, it takes roughly **five half-lives** to reach an approximate steady state.



Repeated Dosing



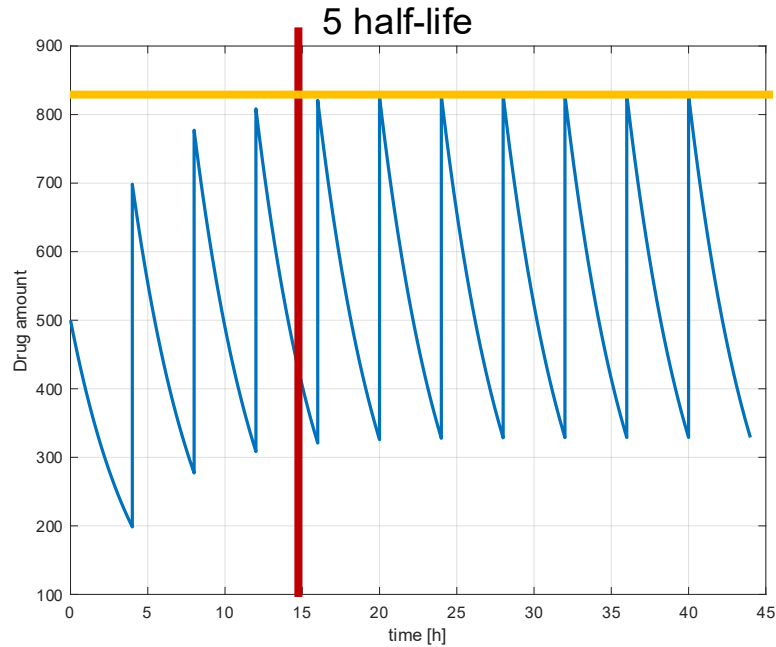
- After 6 hours: $q(6^+) = 625mg$
- After 12 hours: $q(12^+) = 656.25mg$
- After 24 hours: $q(24^+) = 666.02mg$
- After 48 hours: $q(48^+) = 666.66mg$

The time to steady state is dictated by the half-life of the drug.

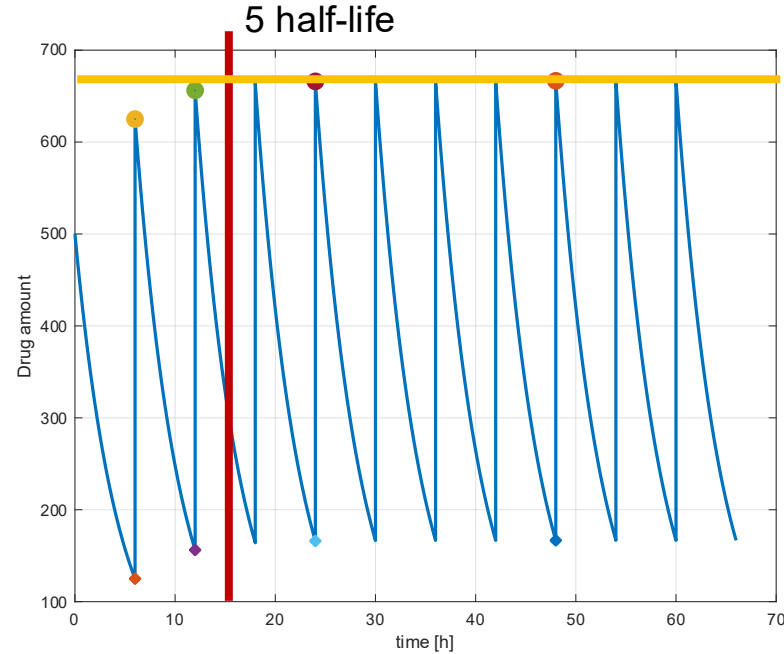
Intuitively we might think that increasing the dose or giving doses more frequently would accelerate attainment of steady state. However, neither of these changes will alter the speed at which steady state is achieved.

Changing the dose or dosing interval will affect the amount (concentration) achieved at steady state, but not the time required to achieve steady state.

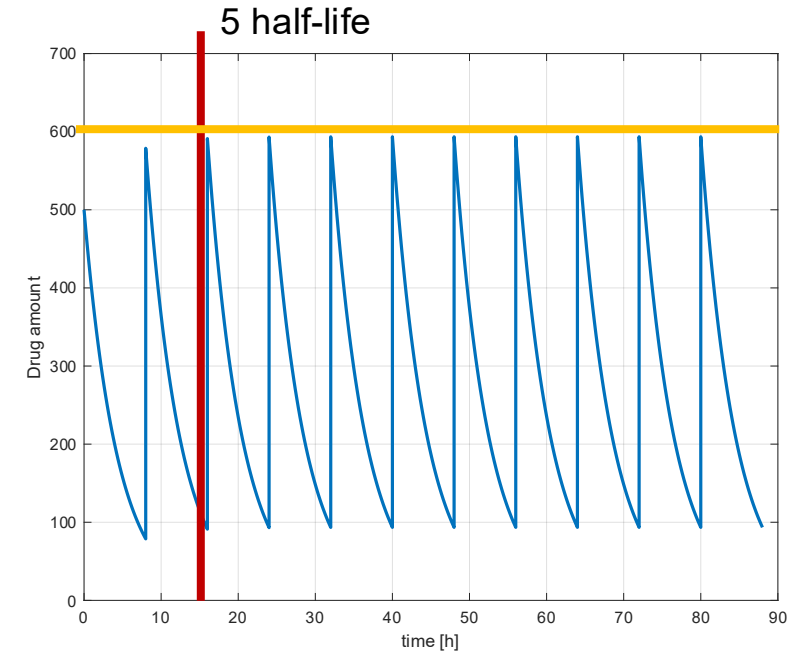
Comparison of different time-intervals



Time interval: $\tau = 4\text{h}$



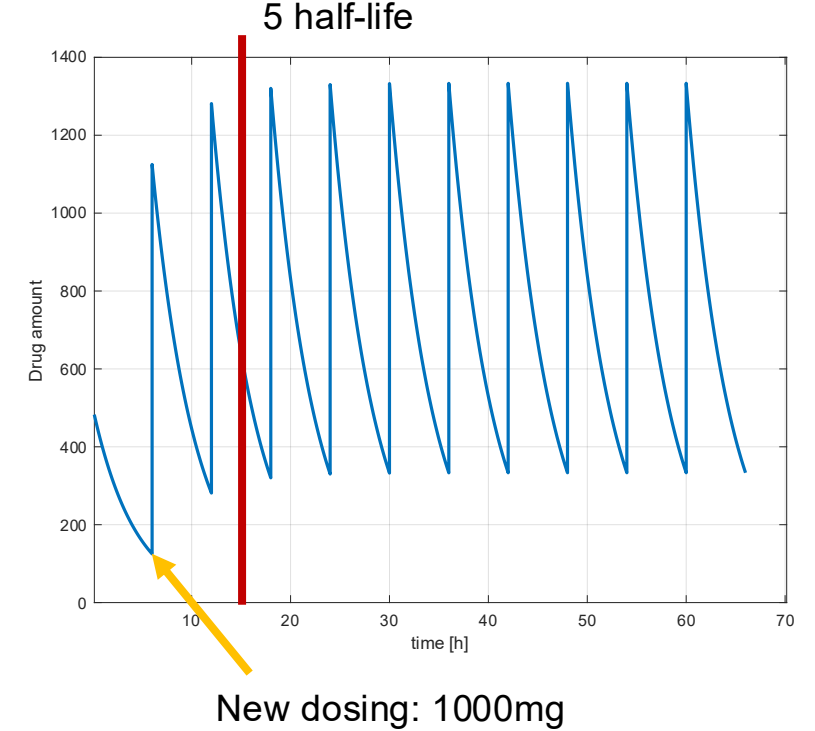
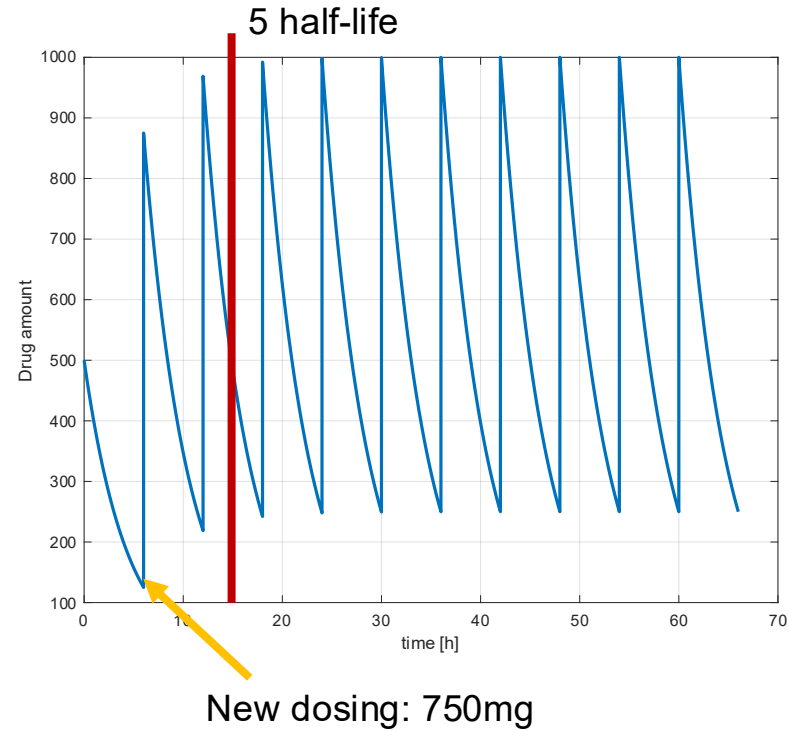
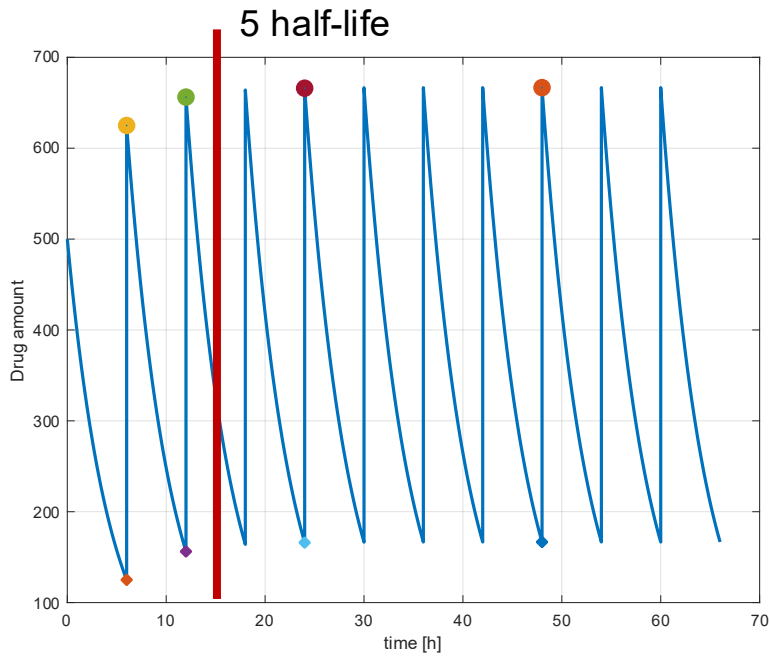
Time interval: $\tau = 6\text{h}$



Time interval: $\tau = 8\text{h}$

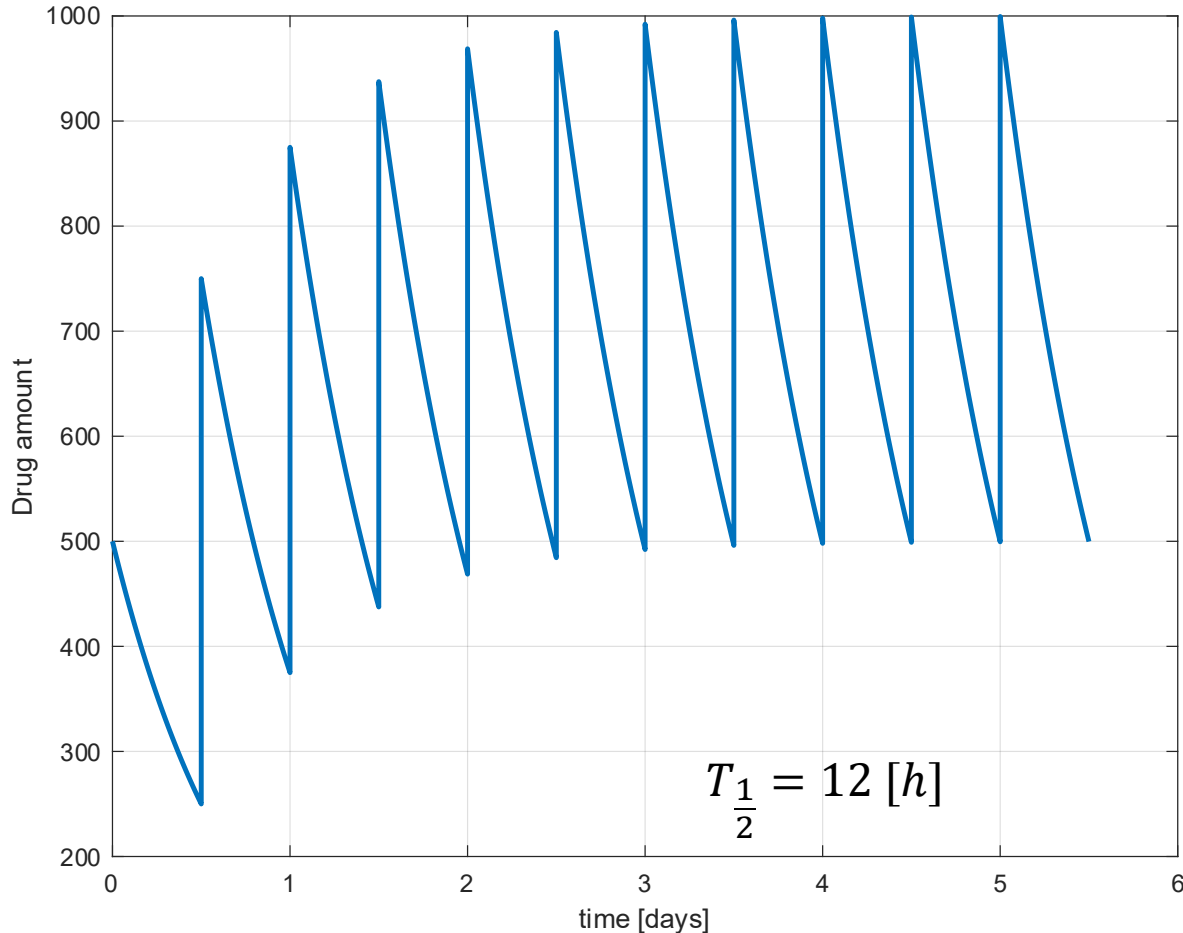
Different amounts at steady state, different administration times (absolute), but steady state after 5 half-life.

Comparison of different dosing



Different amounts at steady state, but steady state reached after 5 half-life.

Example: antibiotic



If for instance our model represents the pharmacokinetics of a 500mg antibiotic drug to be taken twice a day, and with half-life of 12 hours, simulating the model we can have a clue on how the concentration of the drug varies during the treatment.

By managing dose and half-life we have a tool to optimize in some sense the total amount of drug the patient have in the body any time.

Remarks

The average amount (concentration) of drug at the steady state is:

$$\bar{A}_{ss} = \frac{F * R}{k * \tau} \qquad \bar{C}_{ss} = \frac{F * R}{V * k * \tau} = \frac{F * R}{CL * \tau}$$

The bioavailability F is $F = 1$ for venous administration.

We define **accumulation factor** the ratio between the amount at steady state and the amount of the first dose (evaluated at the same administration moment).

To vary \bar{A}_{ss} (or \bar{C}_{ss}) one can only manage R or τ . The bioavailability and the total clearance ($V * k$) are properties of the drug and of the patient.

Pharmacodynamic models

Pharmacodynamics (PD) is the study of the relationship between drug concentration and drug effect.

Pharmacodynamics represents a broad discipline that seeks to identify drug- and system- specific properties that regulate acute and long-term biological responses to drugs.

It aims to characterize the temporal aspects of drug effects through mathematical modelling.

The term is typically used in the context of therapeutic effects, whereas ***toxicology or toxicodynamics*** relates to adverse drug reactions.



Pharmacodynamic models

The construction of a **pharmacodynamic (PD)** model is often strictly related to the construction of a **pharmacokinetic (PK)** model.

Depending on the complexity of the **pharmacodynamic** model/system, the **pharmacokinetic** model and associated parameters are often fixed to serve as a driving function for the pharmacodynamic model relating drug exposure to pharmacological/toxicological effects.

Although simultaneous PK/PD modeling is desirable, this can be quite challenging for complex models.

In what follows, we will study the simpler yet largely employed PD model, the so-called **Hill Equation**.



The Hill equation

The Hill equation assumes that drug effects (E) are directly proportional to the plasma concentration of the drug.

$$E(t) = E_0 \pm \frac{E_{max} * c(t)}{EC_{50} + c(t)}$$

This equation, also known as the E_{max} model, describes the concentration-effect relationship in terms of

- a baseline effect or E_0 (also known as placebo effect, often considered as null);
- the maximum possible effect (E_{max});
- the drug concentration producing half maximal effect (EC_{50}).

Note: it is a sort of *output transformation equation* of the PK model.



The Hill equation

EC_{50} can be seen as the concentration at which the effect of the drug is 50% beyond the placebo (or null) response.

In general, we can define $EC_{\tilde{c}}$ as the value of the concentration such that

$$E(EC_{\tilde{c}}) - E_0 = \frac{\tilde{c}}{100} E_{max}$$

The full Hill equation incorporates a parameter γ , called the Hill coefficient, which describes the steepness of the concentration-effect relationship:

$$E(t) = E_0 \pm \frac{E_{max} * c(t)^\gamma}{EC_{50}^\gamma + c(t)^\gamma}$$

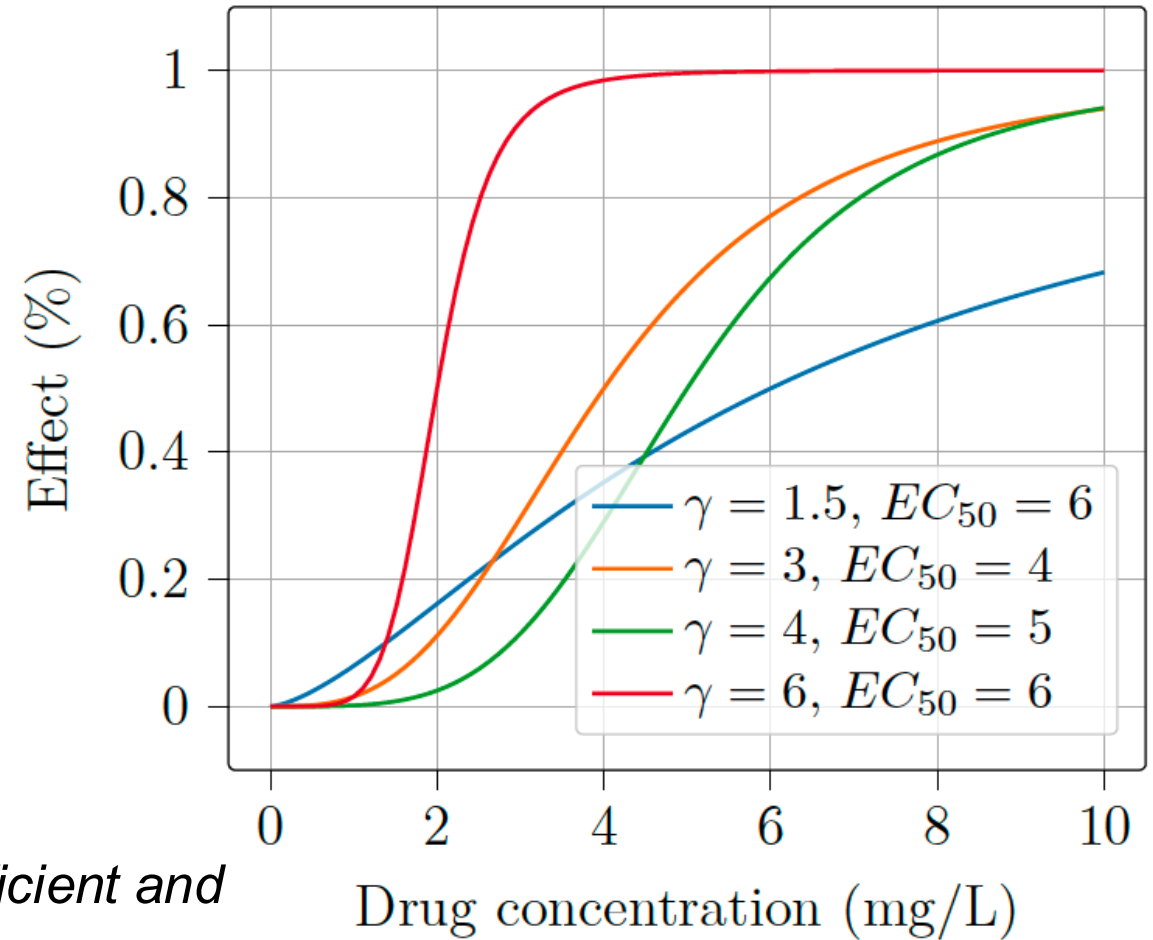
Remarks

Note that the previous expression (with $E_0 = 0$) can be written as

$$E(t) = E_{max} \frac{1}{\alpha^\gamma + 1}$$

with
$$\alpha = \frac{EC_{50}}{c(t)}$$

which is a sigmoid function.



(Sigmoid function for different values of the Hill coefficient and half-effect concentration).

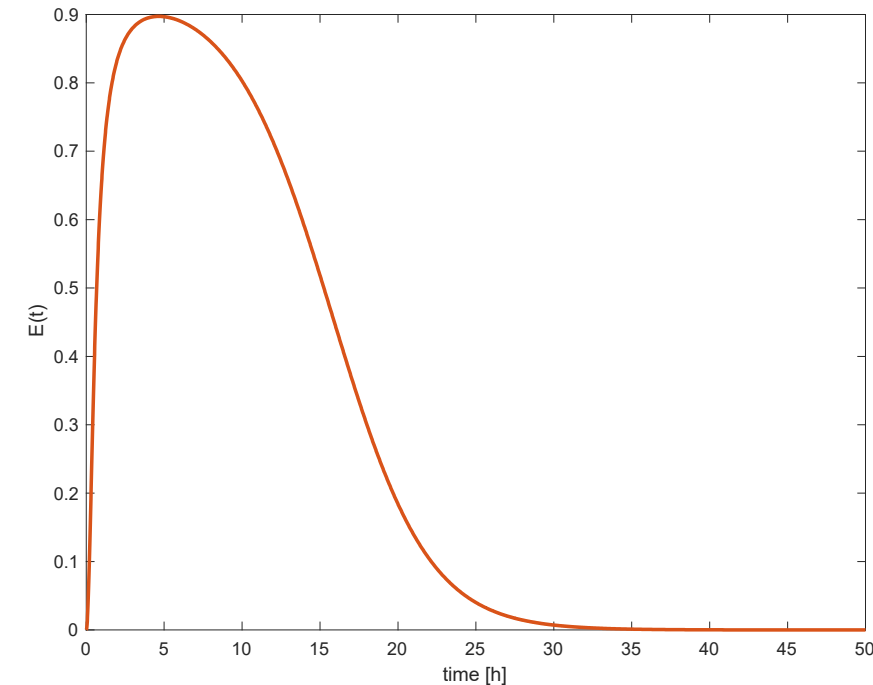
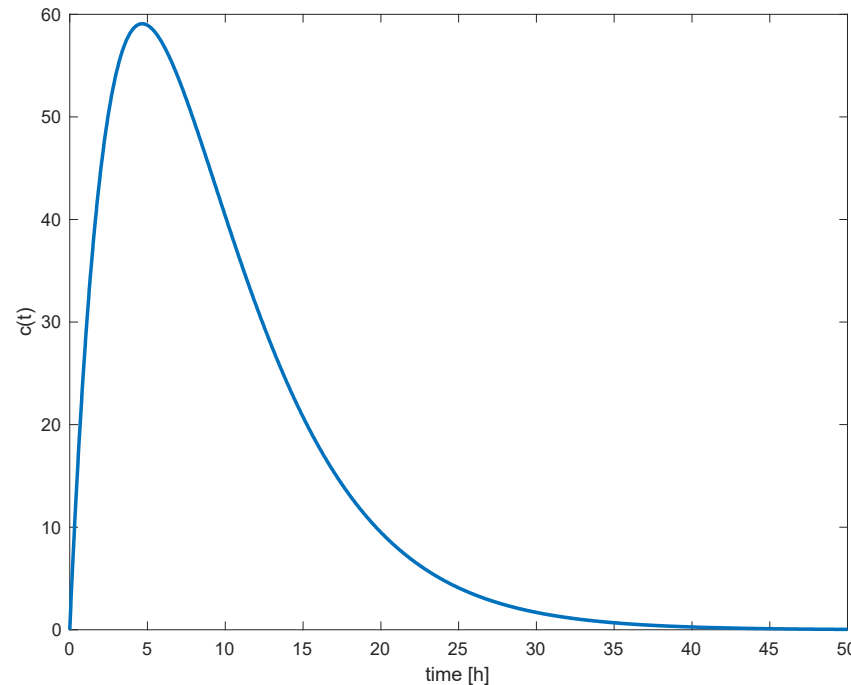
Example (continue...)

4. Calculate the effect of the drug when the concentration reaches its peak, assuming that $E_0 = 0$, $E_{max} = 1$, $\gamma = 2$ and $EC_{50} = 20$ [mg/L]

$$c_{peak} = \frac{q_{peak}}{V_2} = \frac{175.95}{3} = 58.65 \text{ [mg/L]} \quad t_{peak} = 4.67 \text{ [h]}$$

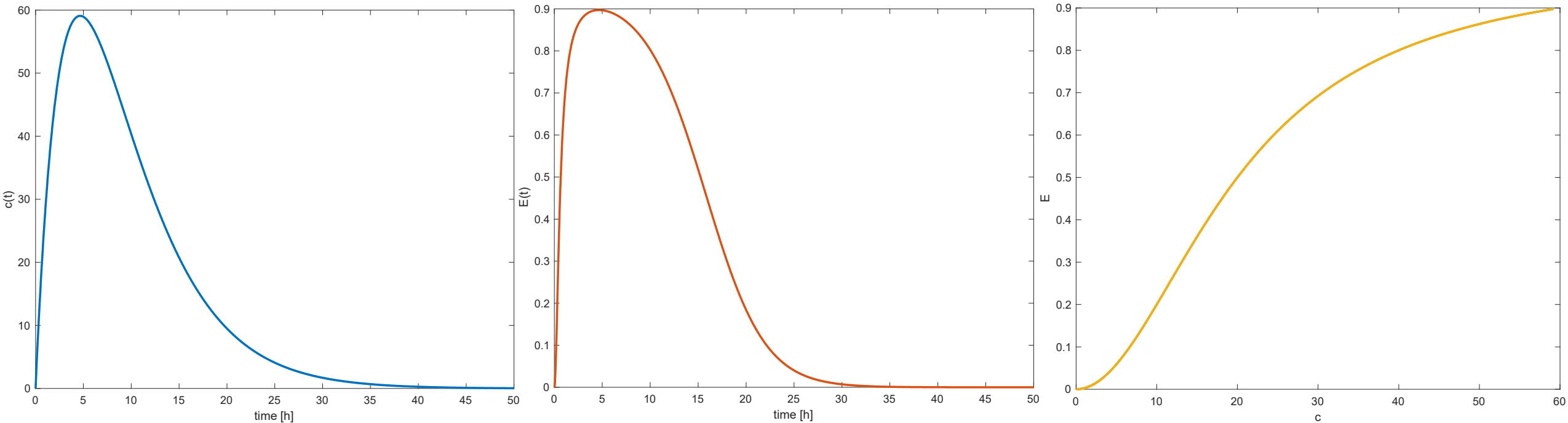
Then

$$\begin{aligned} E(t_{peak}) &= \frac{c_{peak}^\gamma}{EC_{50}^\gamma + c_{peak}^\gamma} \\ &= \frac{58.65^2}{20^2 + 58.65^2} \\ &= 0.896 \end{aligned}$$



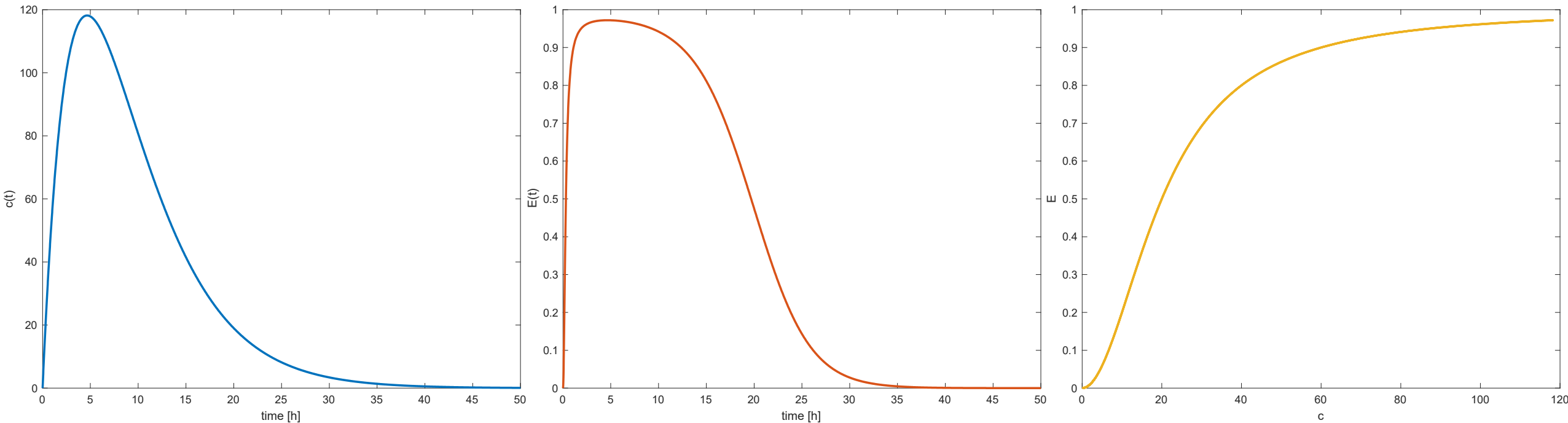
Example (continue...)

Time evolutions of concentration and effect, and plot of effect as a function of concentration.



Example (continue...)

If the patient receives a dose of 1000 mg of an oral medication, we get:



We need to double the dose to reach almost the 100% of the effect.



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