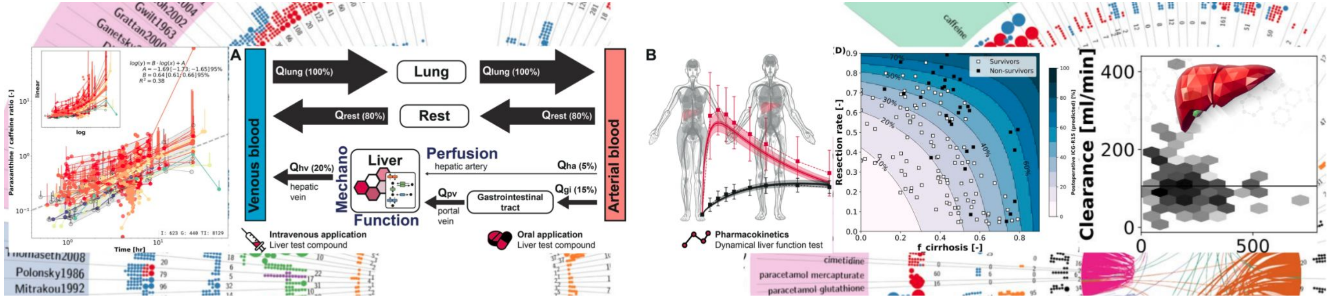

Pharmacokinetics Modeling Course

Ordinary Differential Equations (ODE) & Compartment Models

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🎯 Teaching Goals

By the end of this section, you should be able to:

1. **Understand the role of ODEs** in pharmacokinetic modeling to describe dynamic changes in drug concentration over time.
2. **Interpret ODEs** used in simple compartment models.
3. Gain **basic intuition for numerical integration methods**, such as Euler's method methods.
4. **Apply numerical integration techniques** to simulate drug concentration-time profiles.
5. **Understand how ODE-based models are implemented** in simulation tools and programming environments (e.g., Python).

Ordinary differential equations (ODE)

- a differential equation describes the **rate of change of a variable**
- **dC/dt** denotes the rate of change of the concentration over time
- differential equations require specification of the **initial value (C_0)**
- solution
  - Normally no analytic solution
  - Numerically approximation

$$\frac{dC}{dt} = -\frac{CL}{V} * C$$

$$C_0 = \frac{Dose}{V}$$

Mould DR, Upton RN. **Basic concepts in population modeling, simulation, and model-based drug development.** CPT Pharmacometrics Syst Pharmacol. 2012 Sep 26;1(9):e6. doi: 10.1038/psp.2012.4. PMID: 23835886; PMCID: PMC3606044.

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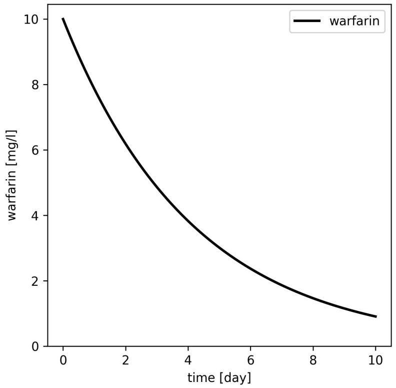
analytic solution

$$C_{(t)} = \frac{Dose}{V} e^{-\frac{CL}{V}.t}$$



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Euler Method

Euler method is the simplest **numerical method to solve ODEs**

Ordinary differential equation

$$\frac{d\vec{x}}{dt} = \vec{f}(\vec{x}, \vec{p}, t)$$

Single state variable, initial condition

$$\frac{dx}{dt} = f(x) \quad \text{with} \quad x(t=0) := x_0$$

1. **Approximate rate of change**

$$f(x) = \frac{dx}{dt} \approx \frac{x(t+\Delta t) - x(t)}{\Delta t}$$

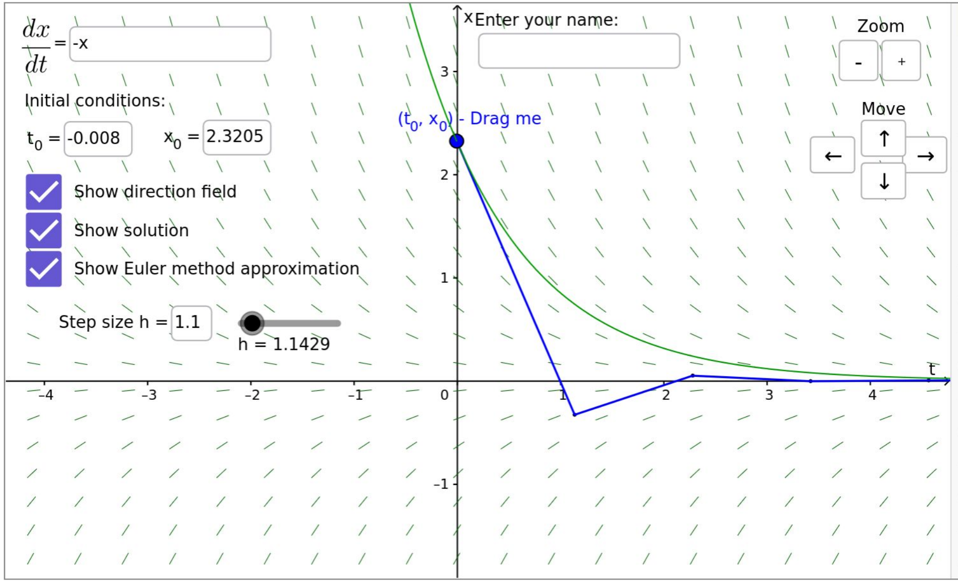
2. Get next solution value

$$x(t+\Delta t) \; = \; x(t) \; + \; \Delta t \; f(x(t)) \; + \; O(\Delta t^2)$$

3. Goto 1

🏃 Euler Method 🏃

https://melbapplets.ms.unimelb.edu.au/2021/07/08/exploring-an-ode-with-euler-method/



t	x(t)
-0.00845	2.32058
1.13445	-0.33161
2.27735	0.04739
3.42025	-0.00677
4.56315	0.00097
5.70605	-0.00014
6.84895	0.00002
7.99185	0
9.13475	0
10.27765	0
11.42055	0
12.56345	0
13.70635	0
14.84925	0
15.99215	0
17.13505	0
18.27795	0

$$\frac{dC}{dt} = -\frac{CL}{V} * C$$

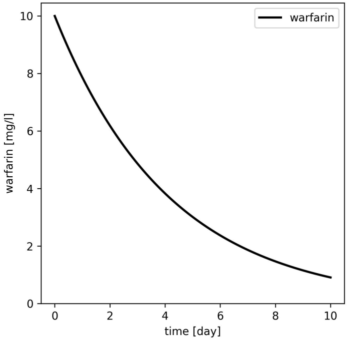
$$C_0 = \frac{Dose}{V}$$

Numerical integration in Python

- ODEs can be solved via numerical integration
- e.g. Euler method as simplest case
- solving a system of equations is computationally expensive

$$\frac{dC}{dt} = -\frac{CL}{V} * C$$

$$C_0 = \frac{Dose}{V}$$




```python
from scipy.integrate import odeint
from matplotlib import pyplot as plt
import numpy as np

# Parameter
V = 10  # [l]
CL = 0.1  # [L/hr]
Dose = 100  # [mg]


def ydot(y, t):
    """ODE system: dx/dt"""
    C = y[0]
    return np.array([-CL/V * C])


# initial condition
y0 = np.array([Dose/V, ])  # [mg/l]

# Numerical integration
t = np.linspace(start=0, stop=10*24, num=200)  # [hr]
C = odeint(ydot, y0, t)

f, ax = plt.subplots(nrows=1, ncols=1, figsize=(5, 5), dpi=300)
ax.plot(t/24.0, C[:, 0], label="warfarin", color="black", linewidth=2.0)
ax.set_xlabel("time [day]")
ax.set_ylabel("warfarin [mg/l]")
ax.set_ylim(bottom=0)
ax.legend()
plt.show()
```

Compartment models

- Pharmacokinetics can be modeled via compartment models
- Simple pharmacokinetic models have proven useful in many applications
- Main processes (**ADME**)
  - **A**bsorption
  - **D**istribution
  - **M**etabolization
  - **E**xcretion

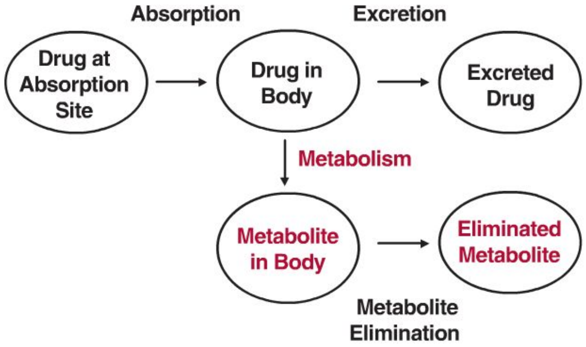
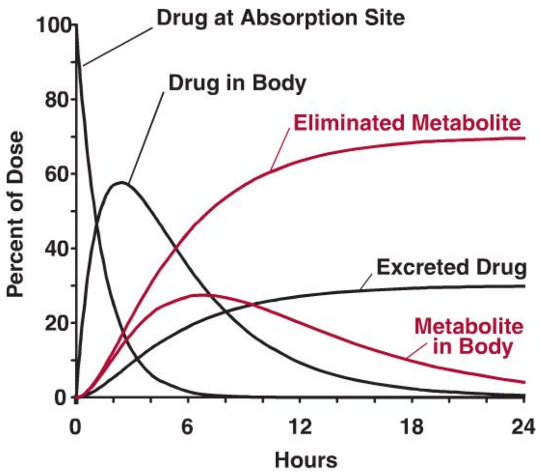


FIGURE 2-5. A drug is simultaneously absorbed into the body and eliminated from it, by excretion and metabolism. The processes of absorption, excretion, and metabolism are indicated with arrows and the compartments with ovals. The compartments represent different locations and different chemical species (color = metabolite). Metabolite elimination may occur by further metabolism or excretion.

FIGURE 2-6. Time course of drug and metabolite in each of the compartments shown in Fig. 2-5. The amount in each compartment is expressed as a percentage of the dose administered. In this example, all the dose is absorbed. At any time, the sum of the molar amounts in the five compartments equals the dose.



Example of compartment model

- system of ODEs
- Solved numerically
- A(D)ME
  - Absorption (v_a)
  - Metabolism (v_m)
  - Elimination ($v_{u,A}$, $v_{u,B}$)
- Mass action equations with rate constants k_a, k_m, k_e

Physiologically based pharmacokinetic (PBPK) modeling for dynamical liver function tests and CYP phenotyping. Jan Grzegorzewski (supervisor: **Matthias König**). PhD Thesis, Jan 2023

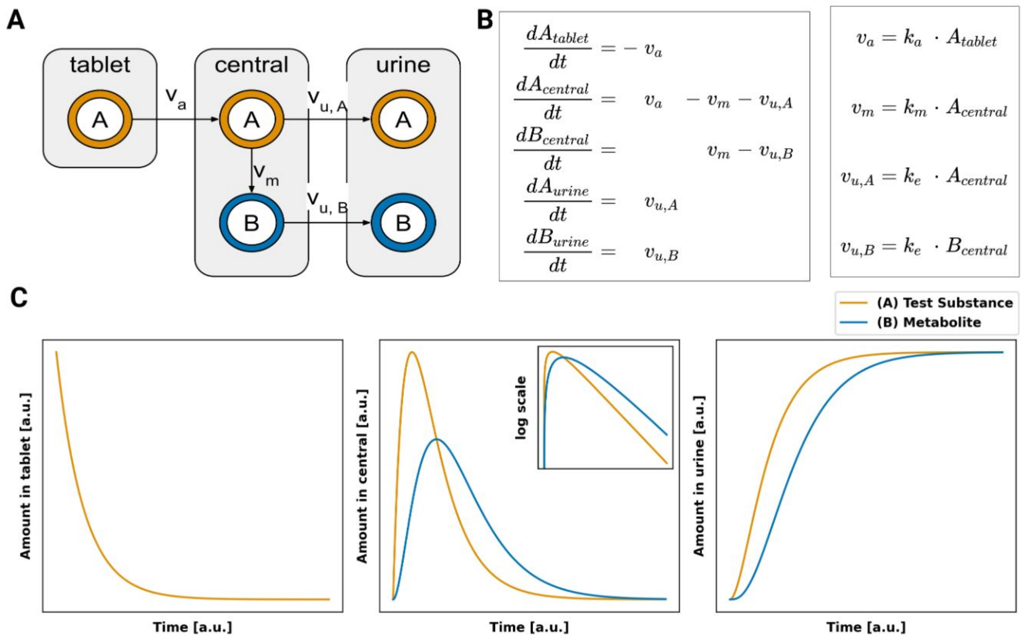


FIGURE 2.3: **Simple ODE-based pharmacokinetics model. A)** The system consists of three compartments (tablet, central, urine) that are connected via transport reactions. The model contains two substances the test substance A (orange); and the metabolite B (blue). The test substance A is metabolized to metabolite B in the central compartment. **B)** The resulting system of ordinary differential equations (ODEs). The rate of absorption, metabolism, and excretion (v_a, v_m, $v_{u,A}$, $v_{u,B}$) are modeled via irreversible mass-action kinetics. **C)** With an initial amount of $A_{tablet} = 10$ and rates $k_a = 1$, $k_m = 1$, and $k_e = 1$, all in [a.u.], the resulting amounts over time of the substances in the tablet, central, urine compartments are depicted.

spyder

The Scientific Python Development Environment