

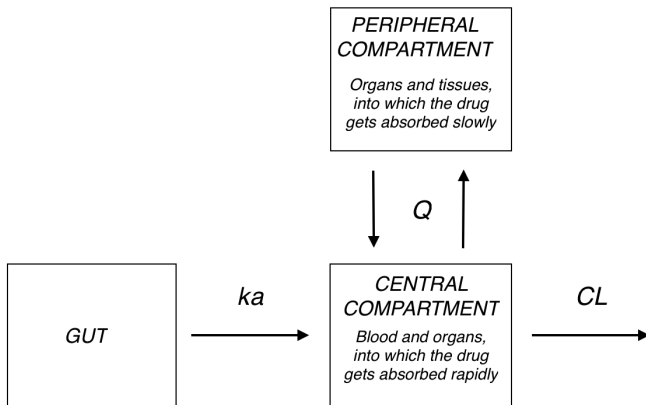
II

## Models in pharmacometrics

What is the effect of a treatment on a patient?

- ▶ *pharmacokinetics (PK)*: how is the drug absorbed in the body?
- ▶ *pharmacodynamics (PD)*: once it is absorbed, what are its effects?

# Example: Two compartment model



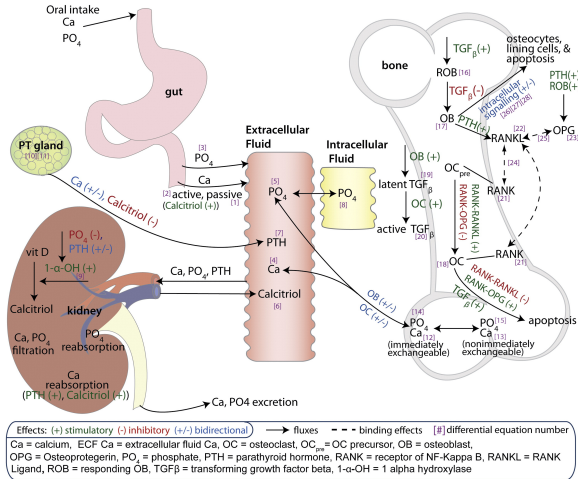
# Two compartment model

$$y'_{\text{gut}} = -k_a y_{\text{gut}}$$

$$y'_{\text{cent}} = k_a y_{\text{gut}} - \left( \frac{CL}{V_{\text{cent}}} + \frac{Q}{V_{\text{cent}}} \right) y_{\text{cent}} + \frac{Q}{V_{\text{peri}}} y_{\text{peri}}$$

$$y'_{\text{peri}} = \frac{Q}{V_{\text{cent}}} y_{\text{cent}} - \frac{Q}{V_{\text{peri}}} y_{\text{peri}}$$

# Example 2: Bone mineral density model from [Peterson and Riggs, 2012]



# Two compartment model

Denote  $\theta = \{CL, Q, VC, VP, K_a\}$ , the ODE coefficients. Then

$$y' = f(y, t, \theta)$$

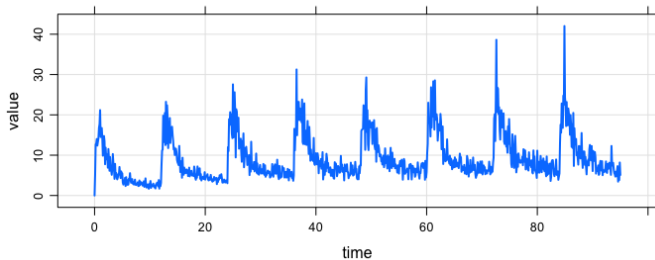
Given an initial condition  $y_0 = y(t_0)$ , solving the above ODE gives us the *natural evolution* of the system at any given time point.

# The event schedule

An event can be:

- ▶ **State changer**: an (exterior) intervention that alters the state of the system; for example a bolus dosing or the beginning of an infusion.
- ▶ **Observation**: a measurement of a quantity of interest at a certain time.

# Drug concentration in a patient's blood

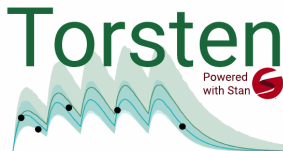




# The event schedule

- ▶ There is no general theory for the event schedule :(
- ▶ The modeling software NONMEM® proposes a convention for pharmacometrics, which we adopt in Torsten.

Torsten offers additional built-in functions to simulate data from a compartment model.



Each Torsten function requires users to specify:

- ▶ a system of ODEs and a method to solve it.
- ▶ An event schedule.

# Torsten function

```
pmx_solve_twocpt(time, amt, rate, ii, evid,  
                 cmt, addl, ss,  
                 theta, biovar, tlag)
```

# Torsten function

```
pmx_solve_twocpt(time, amt, rate, ii, evid,  
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                 theta, biovar, tlag)
```

- ▶ analytically solve the ODEs for the two cpt model.

# Torsten function

```
pmx_solve_twocpt(time, amt, rate, ii, evid,  
                 cmt, addl, ss,  
                 theta, biovar, tlag)
```

- the event schedule

# Torsten function

```
pmx_solve_twocpt(time, amt, rate, ii, evid,  
                 cmt, addl, ss,  
                 theta, biovar, tlag)
```

- the ODE coefficients  $\theta = \{CL, Q, VC, VP, ka\}$

# Torsten function

```
pmx_solve_twocpt(time, amt, rate, ii, evid,  
                 cmt, addl, ss,  
                 theta, biovar, tlag)
```

- bio-availability fraction and lag times.

# Example

Clinical trial:

- ▶ Single patient
- ▶ Bolus doses with 1200 mg, administered every 12 hours, for a total of 15 doses.
- ▶ Many observations for the first, second, and last doses.
- ▶ Additional observation every 12 hours.

Note: the observation are plasma drug concentration measurement.

See `data/twoCpt.data.r`.



## Model:

- ▶ two compartment model with first-order absorption
- ▶ prior information based on clinical trial conducted on a large population
- ▶ normal error for the plasma drug concentration measurement.

Prior:

$$CL \sim \text{logNormal}(\log 10, 0.25)$$

$$Q \sim \text{logNormal}(\log 15, 0.5)$$

$$VC \sim \text{logNormal}(\log 35, 0.25)$$

$$VP \sim \text{logNormal}(\log 105, 0.5)$$

$$ka \sim \text{logNormal}(\log 2.5, 1)$$

$$\sigma^2 \sim \text{half - Cauchy}(0, 1)$$

Likelihood:

$$\log(cObs) \sim \text{Normal}\left(\log\left(\frac{y_2}{VC}\right), \sigma^2\right)$$

*Exercise 1: write and fit this model, using `twoCptModel.r` and `model/twoCptModel.stan`.*

*Exercise 2: Write a generated quantities block and do posterior predictive checks.*

# Resources

- ▶ Torsten repository:  
<https://github.com/metrumresearchgroup/Torsten>
- ▶ Torsten User manual (on GitHub and in the workshop folder).

# References I



Peterson, M. and Riggs, M. (2012).

Predicting nonlinear changes in bone mineral density over time using a multi scale systems pharmacology model.

*CCPT Pharmacometrics, Systems pharmacology.*