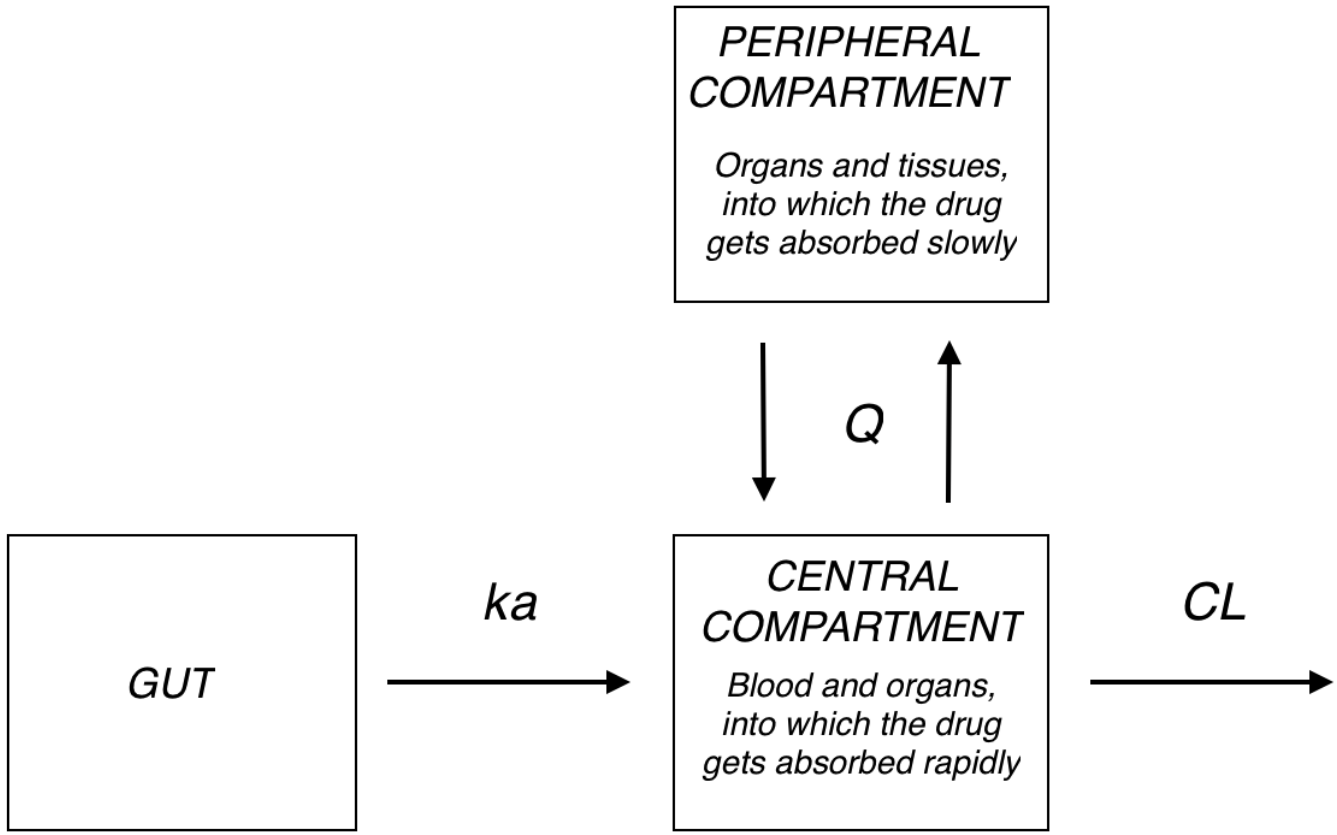
II

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?

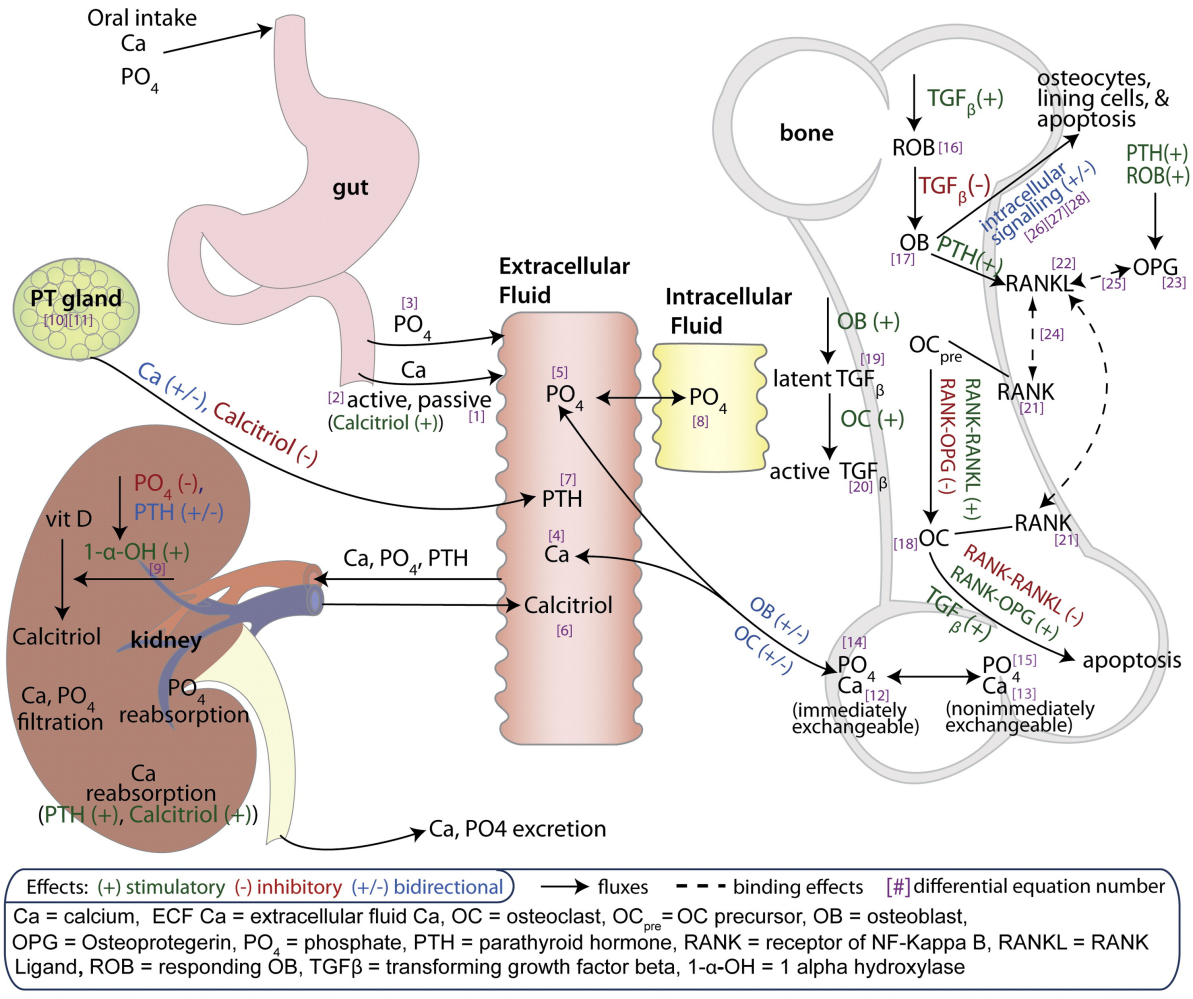
Example: Two compartment model



Two compartment model

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

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

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

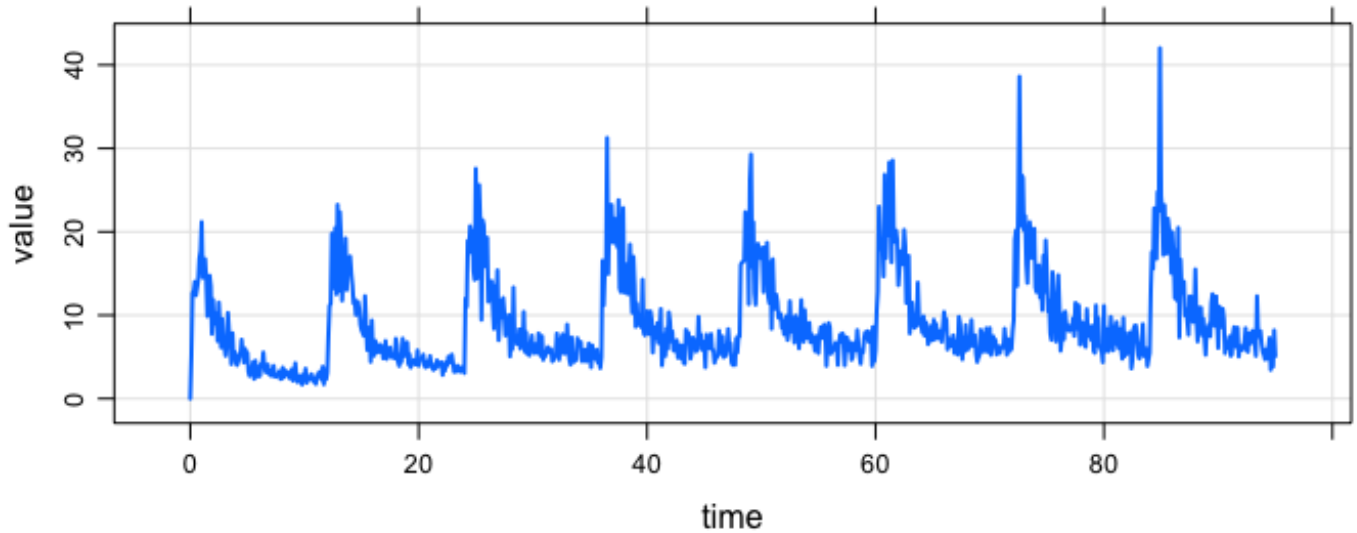
Given an initial condition $y_0 = y(t_0)$, solving the above ODE gives us the *natural evolution* of the system at any given time point.

The event schedule

An event can be:

- Sate 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.

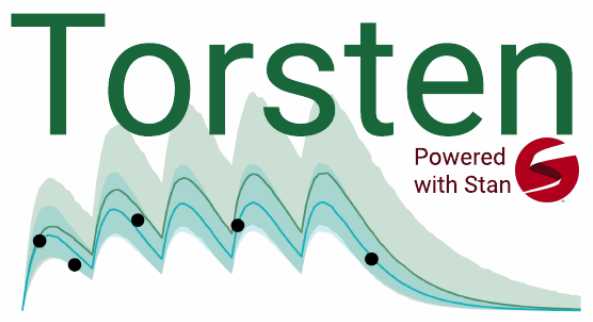
Drug concentration in a patient's blood



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

Torsten function

```
pmx_solve_twocpt(time, amt, rate, ii, evid,
                 cmt, addl, ss,
                 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-availibility 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:

$$
\begin{aligned}
CL &\sim \text{logNormal}(\log 10, 0.25) \\
Q &\sim \text{logNormal}(\log 15, 0.5) \\
VC &\sim \text{logNormal}(\log 35, 0.25) \\
VP &\sim \text{logNormal}(\log 105, 0.5) \\
ka &\sim \text{logNormal}(\log 2.5, 1) \\
\sigma^2 &\sim \text{half} - \text{Cauchy}(0, 1)
\end{aligned}
$$

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.