METRUM
RESEARCH GROUP

Differential Equation Based Models in Stan

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Stan Con

21 January 2017

mc-stan.org

Why do we need Differential Equations?

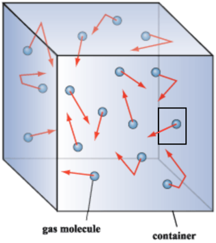


Figure: Gas Leaking out of a Box (edited from http://www.daviddarling.info/encyclopedia/G/gas.html)

- The rate at which the gas exits the box depends on the amount of gas itself.

$$y'(t) = -\lambda y(t)$$

Compartment Models in Pharmacometrics

- Pharmacokinetic (PK): science of what the body does to the drug
- Pharmacodynamic (PD): science of what the drug does to the body

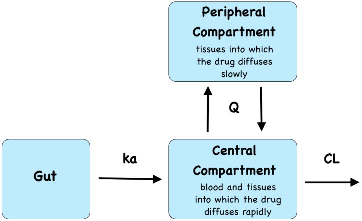


Figure: Two compartment Model with absorption from the Gut

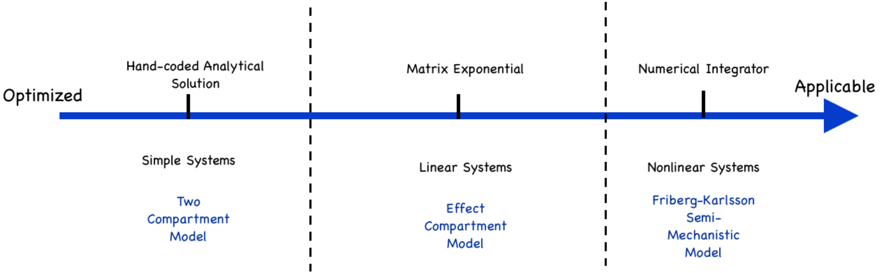
System of ODEs

$$\frac{dy_{\mathrm{gut}}}{dt} = -k_a y_{\mathrm{gut}}$$

$$\frac{dy_{\mathrm{cent}}}{dt} = k_a y_{\mathrm{gut}} - \left(\frac{CL}{V_{\mathrm{cent}}} + \frac{Q}{V_{\mathrm{cent}}}\right) y_{\mathrm{cent}} + \frac{Q}{V_{\mathrm{peri}}} y_{\mathrm{peri}}$$

$$\frac{dy_{\mathrm{peri}}}{dt} = \frac{Q}{V_{\mathrm{cent}}} y_{\mathrm{cent}} - \frac{Q}{V_{\mathrm{peri}}} y_{\mathrm{peri}}$$

Overview: Tools for solving systems of ODEs in Stan



Effect Compartment Model

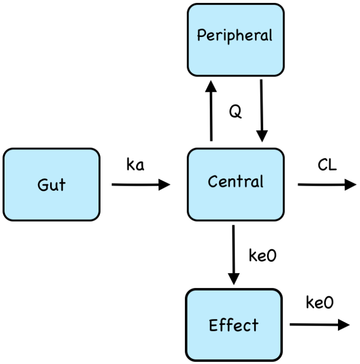


Figure: Effect Compartment Model

System of ODEs

$$\frac{dy_{\mathrm{gut}}}{dt} = -k_a y_{\mathrm{gut}}$$

$$\frac{dy_{\mathrm{cent}}}{dt} = k_a y_{\mathrm{gut}} - \left(\frac{CL}{V_{\mathrm{cent}}} + \frac{Q}{V_{\mathrm{cent}}}\right) y_{\mathrm{cent}} + \frac{Q}{V_{\mathrm{peri}}} y_{\mathrm{peri}}$$

$$\frac{dy_{\mathrm{peri}}}{dt} = \frac{Q}{V_{\mathrm{cent}}} y_{\mathrm{cent}} - \frac{Q}{V_{\mathrm{peri}}} y_{\mathrm{peri}}$$

$$\frac{dy_{\mathrm{eff}}}{dt} = k_{e0} y_{\mathrm{cent}} - k_{e0} y_{\mathrm{eff}}$$

Matrix Expression

$$
\begin{aligned}
\frac{dy_{\mathrm{gut}}}{dt} &= -k_a y_{\mathrm{gut}} \\
\frac{dy_{\mathrm{cent}}}{dt} &= k_a y_{\mathrm{gut}} - \left(\frac{CL}{V_{\mathrm{cent}}} + \frac{Q}{V_{\mathrm{cent}}}\right) y_{\mathrm{cent}} + \frac{Q}{V_{\mathrm{peri}}} y_{\mathrm{peri}} \\
\frac{dy_{\mathrm{peri}}}{dt} &= \frac{Q}{V_{\mathrm{cent}}} y_{\mathrm{cent}} - \frac{Q}{V_{\mathrm{peri}}} y_{\mathrm{peri}} \\
\frac{dy_{\mathrm{eff}}}{dt} &= k_{e0} y_{\mathrm{cent}} - k_{e0} y_{\mathrm{eff}}
\end{aligned}
$$

Equivalently:

$$
\vec{y}' = A\vec{y}
$$

$$
A = \begin{bmatrix} -k_a & 0 & 0 & 0 \\ ka & -\left(\frac{CL}{V_{\mathrm{cent}}} + \frac{Q}{V_{\mathrm{cent}}}\right) & \frac{Q}{V_{\mathrm{peri}}} & 0 \\ 0 & \frac{Q}{V_{\mathrm{cent}}} & -\frac{Q}{V_{\mathrm{peri}}} & 0 \\ 0 & k_{e0} & 0 & -k_{e0} \end{bmatrix}
$$

Matrix Exponential Solution

The solution is given by

$$\vec{y(t)} = e^{tA}\vec{y_0}$$

where e^{tA} is the matrix exponential, formally defined by the convergence series

$$e^{tA} = \sum_{n=0}^{\infty} \frac{(tA)^n}{n!} = I + tA + \frac{t^2A^2}{2!} + ...$$

Code in Stan:

```
matrix_exp(t * A)
```

Friberg-Karlsson semi-mechanistic model for drug-induced myelosuppression

- Friberg-Karlsson semi-mechanistic model for drug-induced myelosuppression [1, 2, 3, 4, 5, 6]

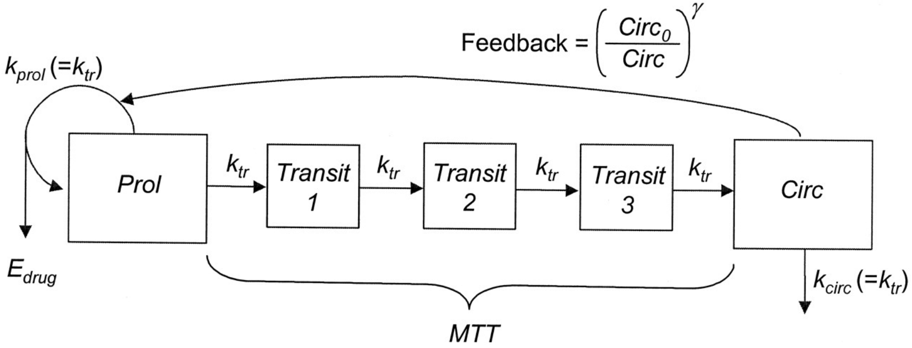


Figure 2 of reference [1]

Friberg-Karlsson semi-mechanistic model for drug-induced myelosuppression

$$\frac{dy_{\mathrm{prol}}}{dt} = k_{\mathrm{prol}} y_{\mathrm{prol}} (1 - E_{drug}) (\frac{Circ_0}{y_{\mathrm{circ}}})^{\gamma} - k_{\mathrm{tr}} y_{\mathrm{prol}}$$
$$\frac{dy_{\mathrm{trans1}}}{dt} = k_{\mathrm{tr}} y_{\mathrm{prol}} - k_{\mathrm{tr}} y_{\mathrm{trans1}}$$
$$\frac{dy_{\mathrm{trans2}}}{dt} = k_{\mathrm{tr}} y_{\mathrm{trans1}} - k_{\mathrm{tr}} y_{\mathrm{trans2}}$$
$$\frac{dy_{\mathrm{trans3}}}{dt} = k_{\mathrm{tr}} y_{\mathrm{trans2}} - k_{\mathrm{tr}} y_{\mathrm{trans3}}$$
$$\frac{dy_{\mathrm{circ}}}{dt} = k_{\mathrm{tr}} y_{\mathrm{trans3}} - k_{\mathrm{tr}} y_{\mathrm{circ}}$$

$$\begin{aligned} E_{drug} &= \alpha \widehat{c} \\ k_{prol} &= k_{circ} = k_{tr} \\ MTT &= \frac{n+1}{k_{tr}} \end{aligned}$$

$$\begin{aligned} \widehat{c} &\equiv \text{plasma drug concentration} \\ Circ &\equiv \text{absolute neutrophil count (ANC)} \end{aligned}$$

How do Numerical Integrators work?

- Euler's (now outdated) method sets the foundation for multiple algorithms.
- Consider the ODE equation, "evaluated" at x_n:

$$y'_n = f(y_n, x_n)$$

- Construct function step by step, with a step of length h.
  - $x_{n+1} = x_n + h$
  - $y_{n+1} \sim y_n + hy'_n$

Stiff and Non-stiff Equations

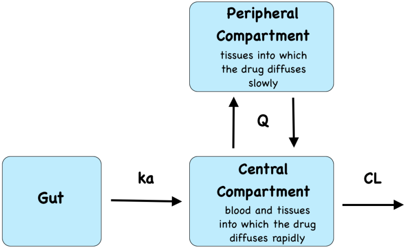
- In a stiff equation, the scale at which $y(x)$ varies w.r.t x changes
- Consider:

$$y = e^{-x} + e^{-1000x}$$

- What step should the integrator take?
- Need to pick between `integrate_ode_rk45()` and `integrate_ode_bdf()`

The Event Schedule

- The ODEs describe the *natural* evolution of the system – but how do we treat exterior interventions, for instance due to clinical treatments?



The Event Schedule

- Metrum is developing Torsten: a C++ extension of Stan with an event handler for pharmacometrics models.
- The package also includes analytical solutions for commonly used models.

- `https://github.com/charlesm93/example-models/tree/feature/issue-70-PKPDexamples-torsten/PKPD/torsten`
- `https://github.com/stan-dev/stan/wiki/Complex-ODE-Based-Models`

Q & A

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[3] J. E. Latz, M. O. Karlsson, J. J. Rusthoven, A. Ghosh, and R. D. Johnson.
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Phase i dose-finding study and a pharmacokinetic/pharmacodynamic analysis of the neutropenic response of intravenous diflomotecan in patients with advanced malignant tumours.
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[5] S. J. Kathman, D. H. Williams, J. P. Hodge, and M. Dar.
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References II

[6] Steven J Kathman, Daphne H Williams, Jeffrey P Hodge, and Mohammed Dar.
A bayesian population pk-pd model for ispinesib/docetaxel combination-induced myelosuppression.
Cancer Chemother Pharmacol, 63(3):469–476, 2009 Feb.