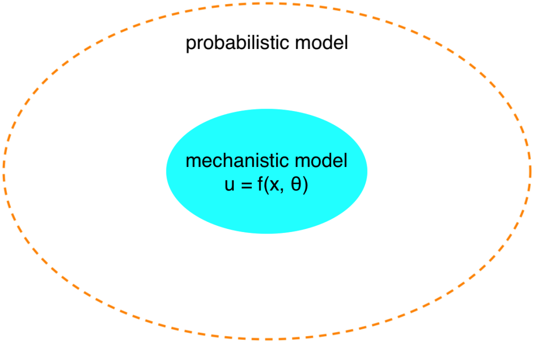
# Solving ODEs in a Bayesian Model

$F_\omega(\alpha + m)!$ 2022

Charles Margossian

- Outline:
  - ODE-based Bayesian models
  - Solving ODEs across the parameter space
  - Propagating derivatives through ODEs

# Integrating mechanistic models inside probabilistic models



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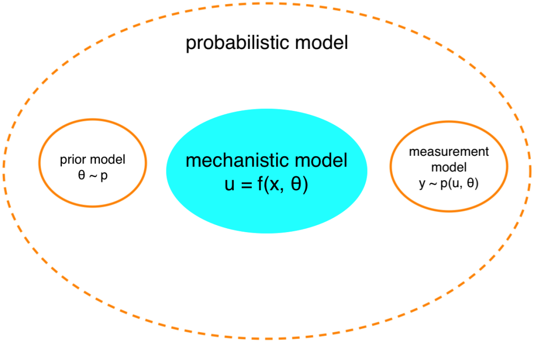
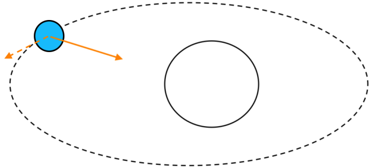



- Goal: learn the latent variables via $p(\theta \mid y)$.

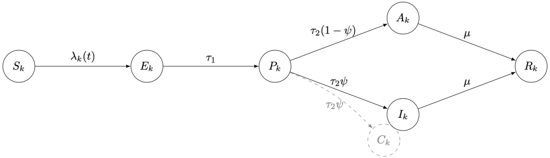
## Example 1: "textbook" model of planetary motion[1]

- $k$: star-planet gravitational interaction
- position $q(t, k)$ and momentum $p(t, k)$ solve Hamilton's equations.
- observations: $y(t) = q(t, k) + \epsilon$, with $\epsilon \sim \text{normal}(0, \sigma^2)$.



1: Gelman et al. (2020) *Bayesian Workflow*, preprint

# Example 2: SEIR model for Covid-19 to estimate mortality rate[2,3]




Mechanistic model:

- ODE model for disease transmission, stratified by age.

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2: Riou et al. (2020) *Estimation of SARS-CoV-2 mortality during the early stages of a pandemic*, PLOS Medicine

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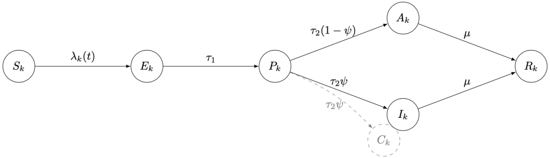


Mechanistic model:

- ODE model for disease transmission, stratified by age.

Probabilistic model:

- Combine multiple (biased) data sources
- Use prior on symptomatic rate for identifiability

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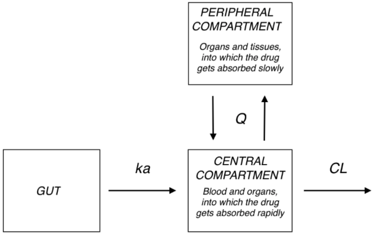
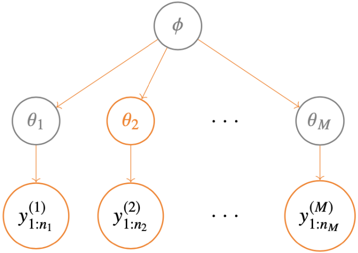
# Example 3: Population pharmacokinetic model[4,5]

## Pharmacokinetic model:




## Hierarchical model:

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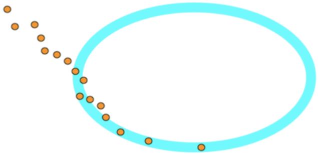
4: Wakefield (1996) *The Bayesian analysis of pop. PK models* JASA

5: M et al. (2022) *Pharmacometrics modeling using Stan and Torsten...* CPT: Pharmacometrics & Systems Pharmacology

Bayesian inference: probing $p(\theta \mid y)$ with MCMC



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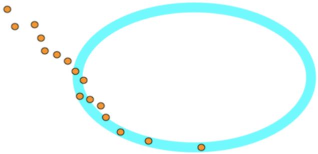

- Probabilistic programming languages are expressive and allow us to specify ODE-based likelihoods (e.g. `Stan`, `Turing`, `TensorFlow Probability`, ...)
- Across the parameter space:
  - Evaluate the likelihood, $\log p(y \mid \theta)$.
  - Evaluate the gradient, $\nabla_\theta \log p(y \mid \theta)$.

- Outline:
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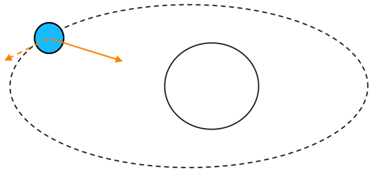
Model of planetary motion



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|---|---|
| 1 | 10.56 |
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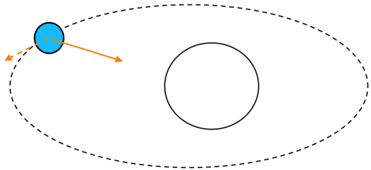

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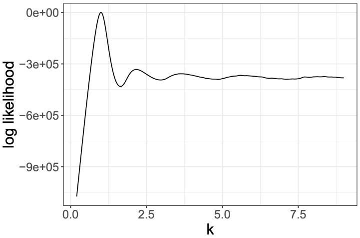

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$$\begin{aligned} q'(t) &= \frac{p}{m} \\ p'(t) &= -\frac{k}{r^3}(q - q_\odot) \end{aligned}$$

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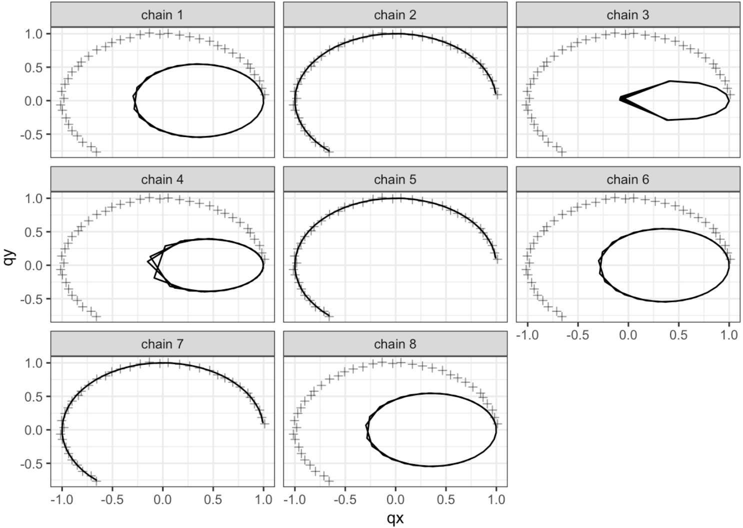
- use a numerical integrator.
  e.g. Euler's method (for simplicity):

$$u(t+\epsilon) \leftarrow u(t) + \epsilon u'(t+\epsilon)$$

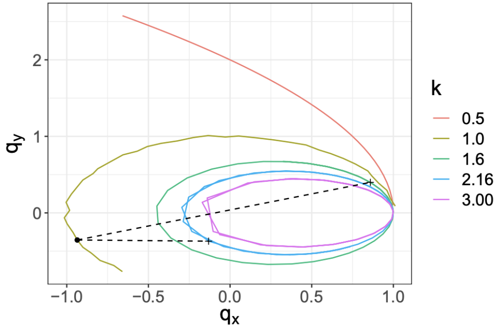
  - Error: $\mathcal{O}(\epsilon^2 |u''(t)|)$
  - In practice, set the error tolerance and tune $\epsilon$.

# Posterior predictive checks



$$\log p(y \mid \theta) = K + \frac{1}{2\sigma^2} \sum_{t=t_0}^{\tau} (u(t) - y_t)^2$$

## Potential Fixes

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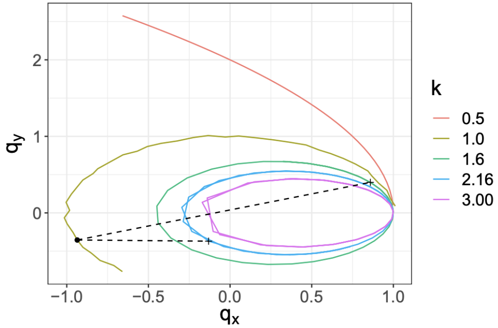


Potential Fixes

- Use a stronger prior (still multimodal)
- Correct samples in post-processing step
- Don't rely on default initializations! Draw inits from prior.
- Use "global" algorithms:
    - tempering
    - MCMC with normalizing flow[6,*]
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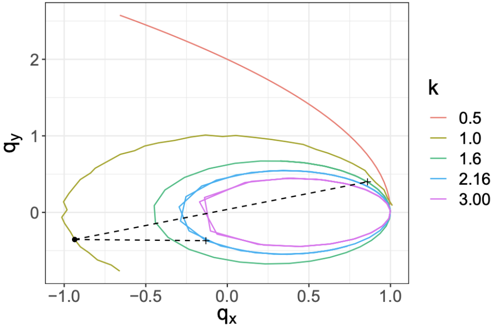


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What makes a good initialization for MCMC?

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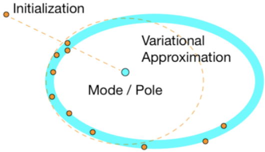
- Draw from an approximation $q(\theta) \approx p(\theta \mid y)$, e.g. using a

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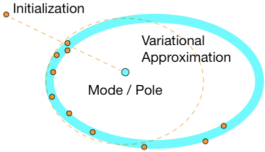


- Draw *overdispersed* initializations to make convergence diagnostics such as $\widehat{R}$ reliable.[8]
- How much overdispersion do we need? For unimodal target, the initial variance must be lower-bounded by a linear function of the initial squared bias.[9]

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## Study on Michaelis-Menten Pharmacokinetic model[10]

- Which numerical integrator should we use in `Stan`?
  - $RK4^{th}/5^{th}$ (non-stiff solver)
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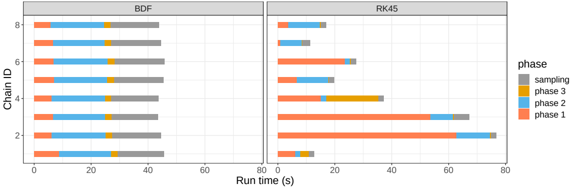


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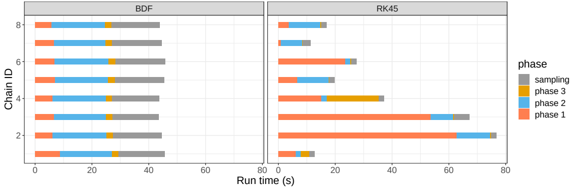


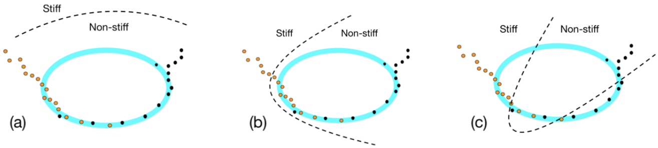


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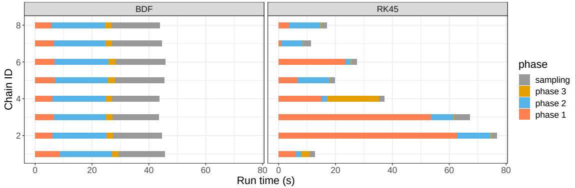


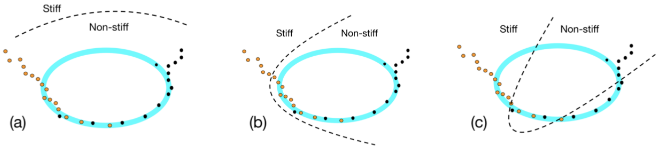


- Poses a challenge when running many chains in parallel (ongoing work with Stanislas Du Ché).

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- *Hidden in this equation is a Fréchet derivative between $f$ and $u$, i.e. between two infinite-dimensional objects. Such a derivative cannot be stored on a finite computer, so we need to make sure we don't compute it.*[11]

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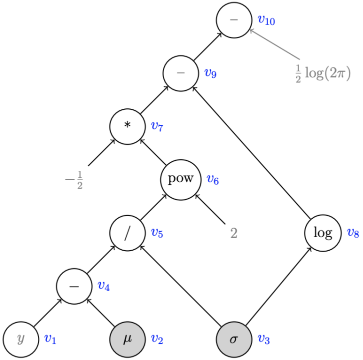
# Automatic differentiation of implicit functions

(1) Direct method

(2) Forward method

(3) Adjoint method



## Automatic differentiation of implicit functions

(1) Direct method

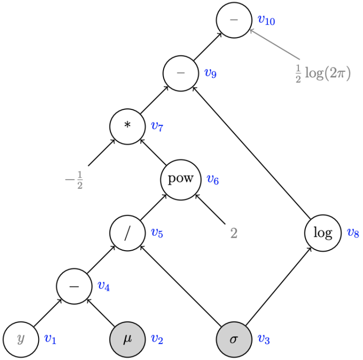
- Treat $u$ as a sequence of explicit functions, $u(t + \epsilon) \approx u(t) + \epsilon u'(t)$.

(2) Forward method

- Write an ODE solved by $\mathrm{d}u/\mathrm{d}\theta(t)$.

(3) Adjoint method

- Write an ODE solved by $\partial f / \partial u(t) \cdot \mathrm{d}u/\mathrm{d}\theta(t)$.



# Forward method

$$u'(t) = g(t, u, \vartheta) \in \mathbb{R}^N$$

- Let $K$ be the dimension of input which depend on $\theta$
  - $\vartheta$: explicit ODE parameters
  - $u_0$: initial condition if parameter dependent $\rightarrow$ Can rewrite the ODE as a deviation from a baseline and take $u_0 = \mathbf{0}$.
  - time steps: $t_0, t_1, \cdots$

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$$\frac{\mathrm{d}u}{\mathrm{d}\vartheta}(t) = \int_{t_0}^{\tau} \mathrm{d}t \frac{\mathrm{d}u'}{\mathrm{d}\vartheta}(t)$$

- Solve a system of $N + NK$ coupled ODEs.

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- Solve a system of $N + NK$ coupled ODEs.
- Our goal should be to minimize $K$.
  - In Covid-19 model, went from $K = 62$ to $K = 5$, meaning solving 3596 to 290 ODEs[3] $\rightarrow$ 3 days to 2 hours to fit model.

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## Adjoint method

- Construct an ODE which *directly* returns

$$\delta^\dagger \cdot \frac{\mathrm{d}u}{\mathrm{d}\theta}(t).$$

- Requires solving the ODE forward and backward in time.
- Solve a total of $2N + K$ coupled ODEs (rather than $N + NK$).

- Eligibly method is old;[12] popularized in Machine Learning by Neural ODEs.[13]
- Better scaling but not always better performance than forward method.[14]

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12: Pontryagin et al (1963) *The Mathematical Theory of Point Processes*, textbook
13: Chen et al (2018) *Neural Ordinary Differential Equations*, NeurIPS
14: Rackauckas et al (2021) *A comparison of Autodiff [...] for derivatives of differential equations* IEEE HPEC

## Arsenal of tools

- Prob languages which support ODEs:
  - `Stan`:
    - supports three ODE integrators (RK45, BDF, Adams).
    - supports forward and adjoint differentiation methods.
    - supports matrix exponential for linear ODEs.
    - supports several implicit functions.
  - `Torsten`:
    - extends Stan for pharmacometrics modeling.
    - solve ODEs within a clinical event schedule.
  - `TensorFlow Probability`
    - tip: use it with JAX, rather than TensorFlow.
    - ODE support exists but is limited.
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- Questions? Comments?

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