Autodiff-based estimation of kinetic trap rate constants

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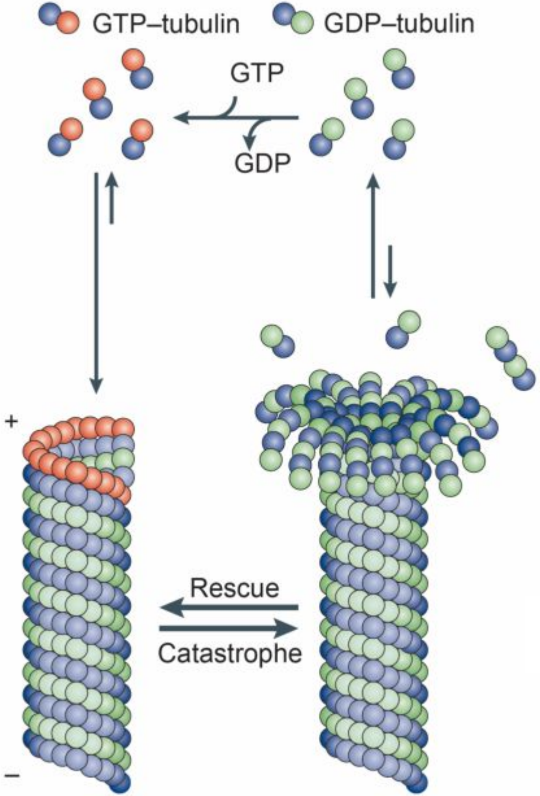
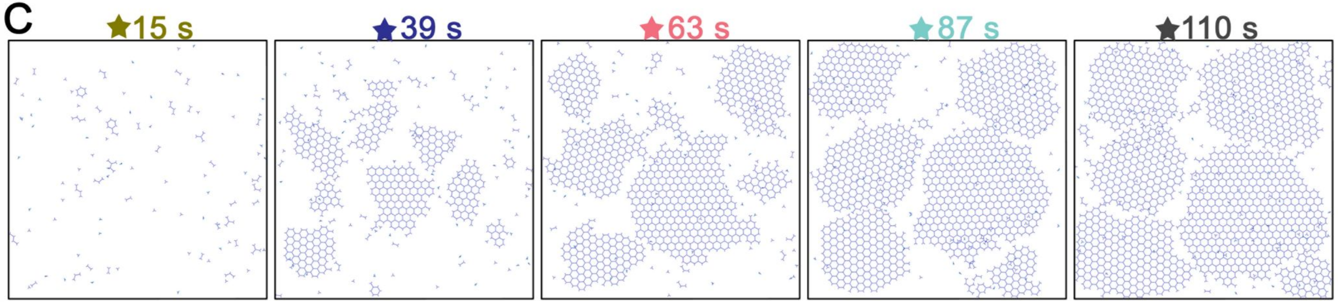
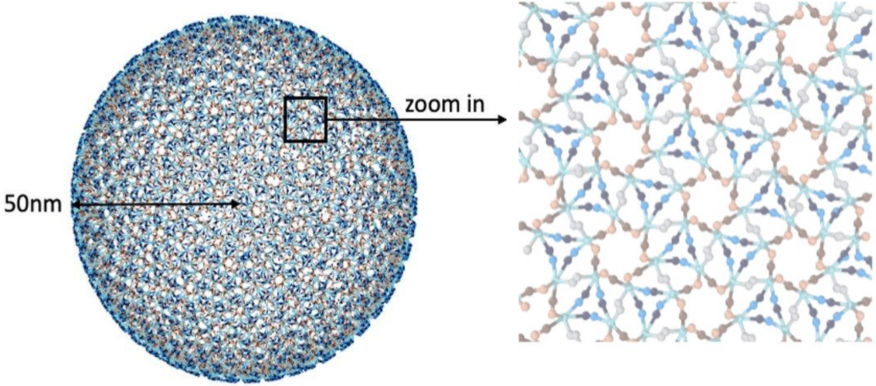
Molecular self-assembly is ubiquitous in cell biology



Cheeseman and Desai 2008,
Nat. Rev. Mol. Cell Biol.

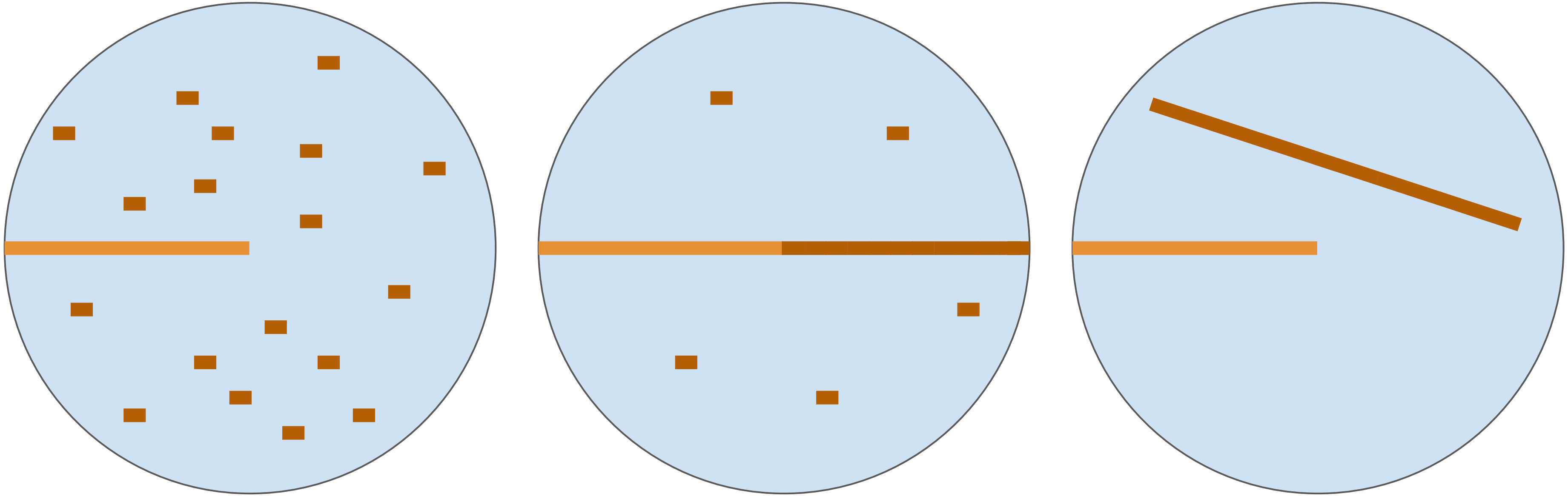


Guo et al. 2022, *PLoS Comput. Biol.*



Qian and Evans et al. 2023, *Biophys. J.*

Kinetic trapping inhibits molecular self-assembly

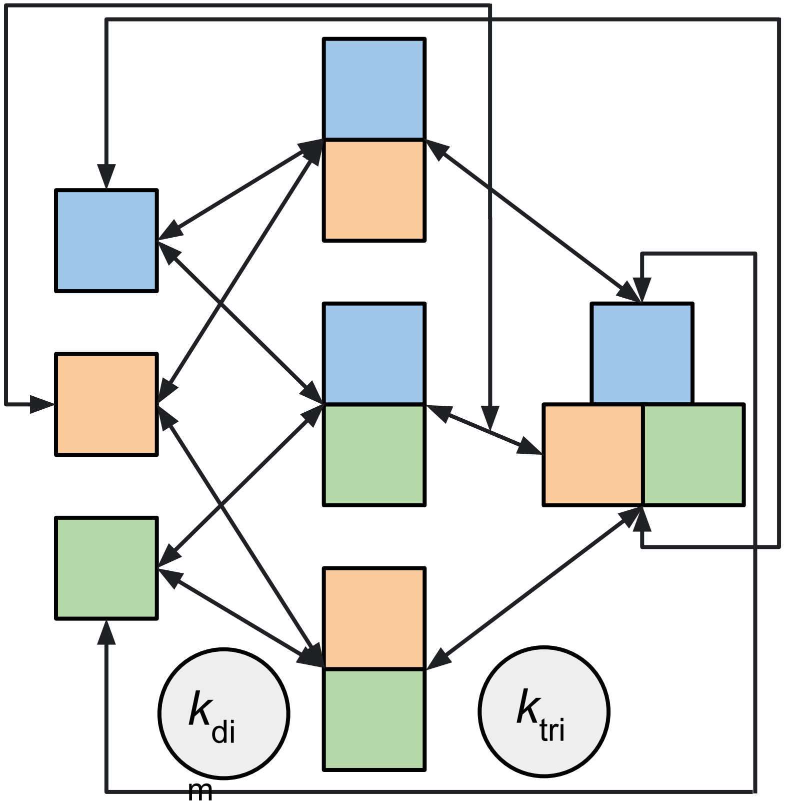


Cell seeks to span self with microtubule

Tubulin subunits bind to existing microtubule: No kinetic trapping

Tubulin subunits form new microtubule: Kinetic trapping

Fully connected hetero-*n*-mers provide a model system



$$\mathrm{X} + \mathrm{Y} \underset{k_{dim\_off}}{\overset{k_{dim\_on}}{\rightleftharpoons}} \mathrm{XY}$$

$$\mathrm{X} + \mathrm{Z} \underset{k_{dim\_off}}{\overset{k_{dim\_on}}{\rightleftharpoons}} \mathrm{XZ}$$

$$\mathrm{Y} + \mathrm{Z} \underset{k_{dim\_off}}{\overset{k_{dim\_on}}{\rightleftharpoons}} \mathrm{YZ}$$

$$\mathrm{XY} + \mathrm{Z} \underset{k_{tri\_off}}{\overset{k_{tri\_on}}{\rightleftharpoons}} \mathrm{XYZ}$$

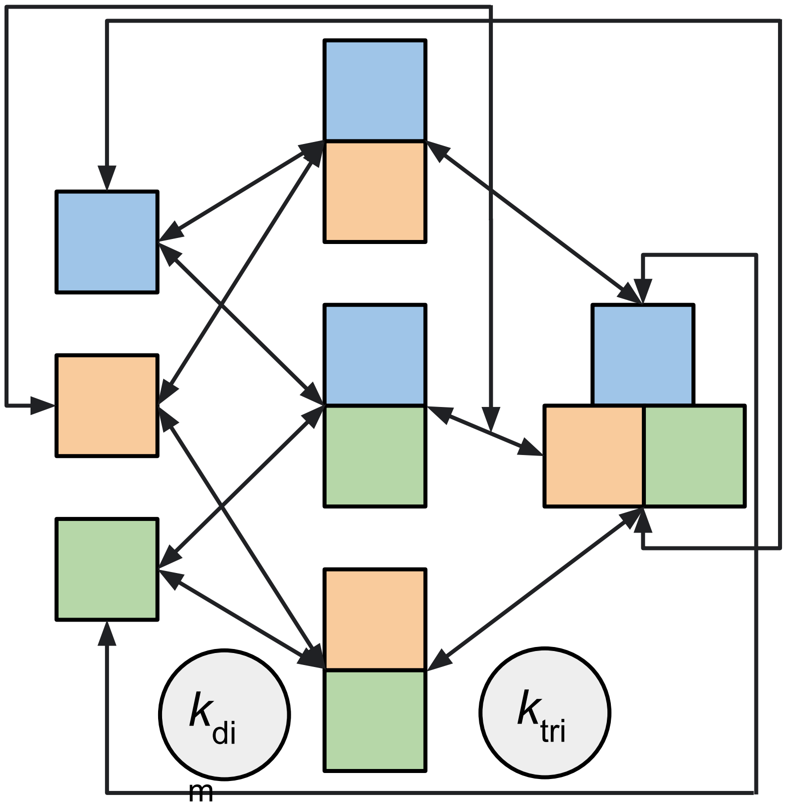
$$\mathrm{XZ} + \mathrm{Y} \underset{k_{tri\_off}}{\overset{k_{tri\_on}}{\rightleftharpoons}} \mathrm{XYZ}$$

$$\mathrm{YZ} + \mathrm{X} \underset{k_{tri\_off}}{\overset{k_{tri\_on}}{\rightleftharpoons}} \mathrm{XYZ}$$

Fully connected:
Every reactants binds to every other reactant

Rate-growth:
Every reaction at a given level of assembly has the same association rate, which determines a single dissociation rate

Fully connected hetero-n-mers provide a model system



Catalyst.jl

$$\frac{\mathrm{d}X(t)}{\mathrm{d}t} = k_{dim\_off}\mathrm{XY}(t) + k_{dim\_off}\mathrm{XZ}(t) + k_{tri\_off}\mathrm{XYZ}(t) - k_{dim\_on}Y(t)X(t) - k_{dim\_on}X(t)Z(t) - k_{tri\_on}X(t)\mathrm{YZ}(t) \tag{1}$$

$$\frac{\mathrm{d}Y(t)}{\mathrm{d}t} = k_{dim\_off}\mathrm{XY}(t) + k_{dim\_off}\mathrm{YZ}(t) + k_{tri\_off}\mathrm{XYZ}(t) - k_{dim\_on}Y(t)X(t) - k_{dim\_on}Y(t)Z(t) - k_{tri\_on}Y(t)\mathrm{XZ}(t) \tag{2}$$

$$\frac{\mathrm{dXY}(t)}{\mathrm{d}t} = -k_{dim\_off}\mathrm{XY}(t) + k_{tri\_off}\mathrm{XYZ}(t) + k_{dim\_on}Y(t)X(t) - k_{tri\_on}\mathrm{XY}(t)Z(t) \tag{3}$$

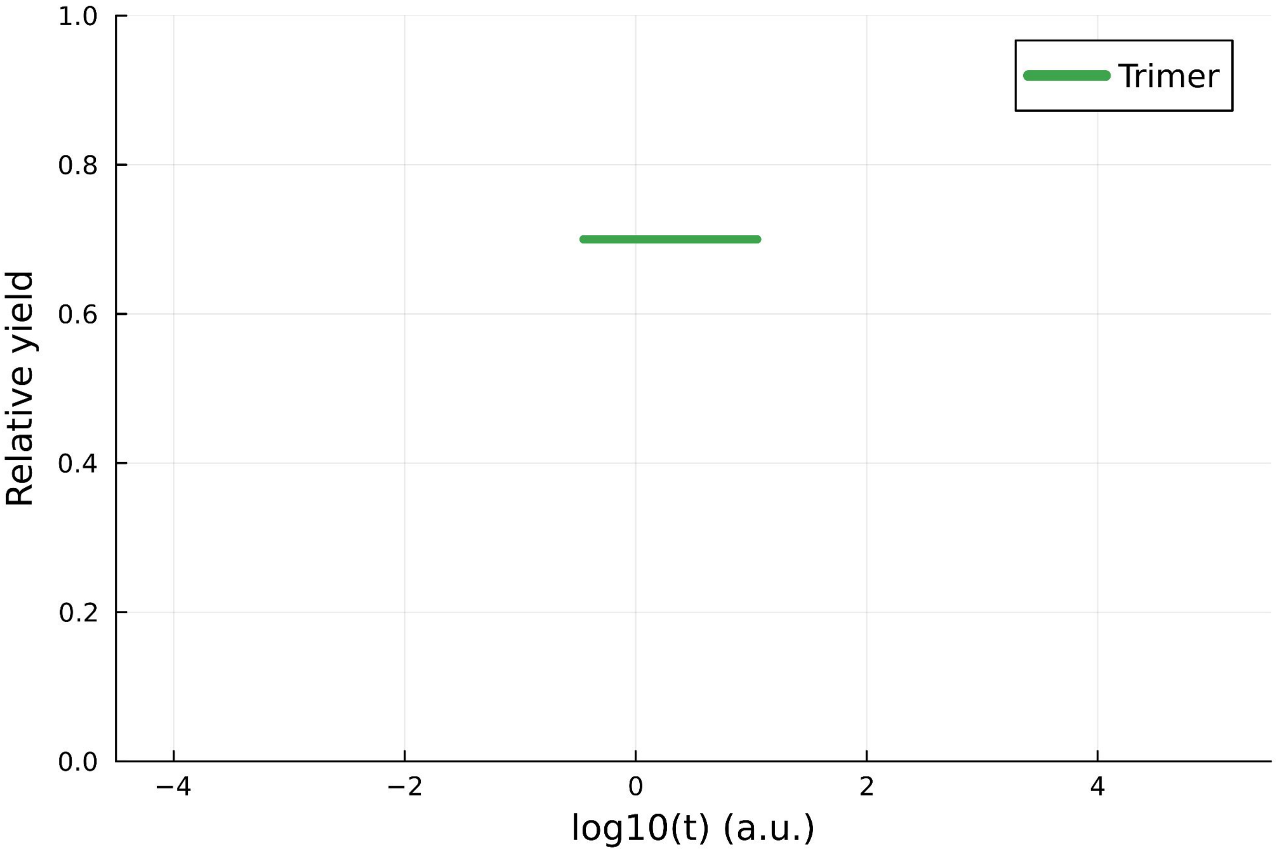
$$\frac{\mathrm{d}Z(t)}{\mathrm{d}t} = k_{dim\_off}\mathrm{XZ}(t) + k_{dim\_off}\mathrm{YZ}(t) + k_{tri\_off}\mathrm{XYZ}(t) - k_{dim\_on}Y(t)Z(t) - k_{dim\_on}X(t)Z(t) - k_{tri\_on}\mathrm{XY}(t)Z(t) \tag{4}$$

$$\frac{\mathrm{dXZ}(t)}{\mathrm{d}t} = -k_{dim\_off}\mathrm{XZ}(t) + k_{tri\_off}\mathrm{XYZ}(t) + k_{dim\_on}X(t)Z(t) - k_{tri\_on}Y(t)\mathrm{XZ}(t) \tag{5}$$

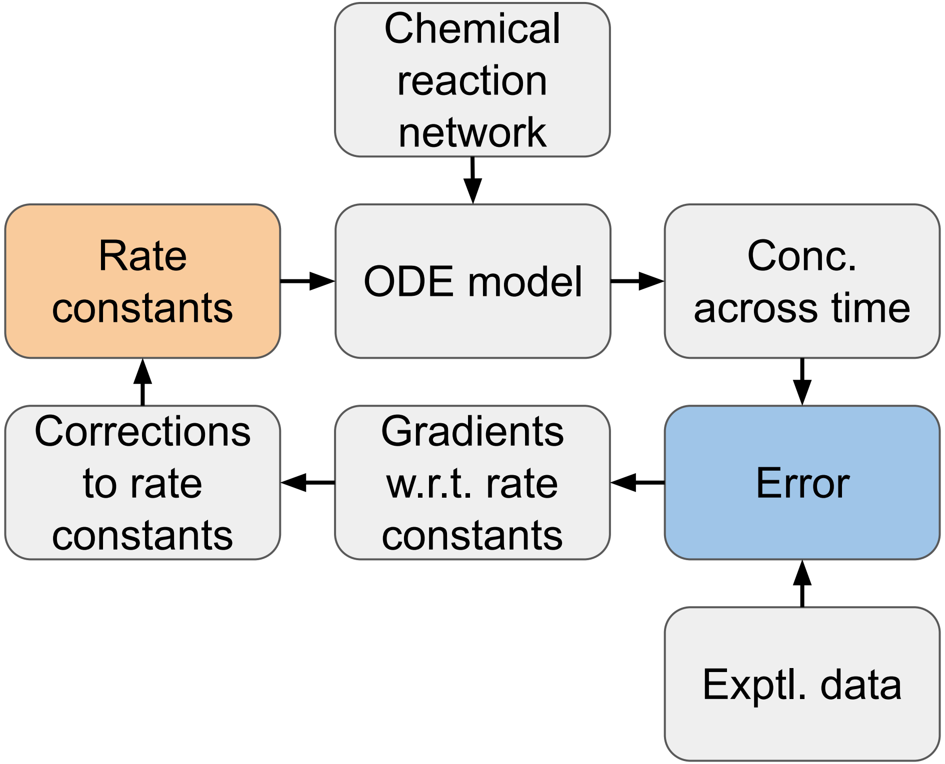
$$\frac{\mathrm{dYZ}(t)}{\mathrm{d}t} = -k_{dim\_off}\mathrm{YZ}(t) + k_{tri\_off}\mathrm{XYZ}(t) + k_{dim\_on}Y(t)Z(t) - k_{tri\_on}X(t)\mathrm{YZ}(t) \tag{6}$$

$$\frac{\mathrm{dXYZ}(t)}{\mathrm{d}t} = -3k_{tri\_off}\mathrm{XYZ}(t) + k_{tri\_on}Y(t)\mathrm{XZ}(t) + k_{tri\_on}\mathrm{XY}(t)Z(t) + k_{tri\_on}X(t)\mathrm{YZ}(t) \tag{7}$$

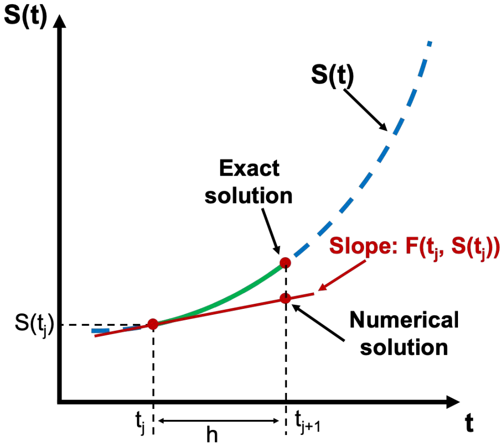
Kinetic trapping may encode information about reactions



Estimating rate constants requires expensive computation



$$\nabla \mathrm{Error} = \left(\frac{\partial \mathrm{Error}}{\partial k_{dim}}, \frac{\partial \mathrm{Error}}{\partial k_{tri}}, \dots \right)$$

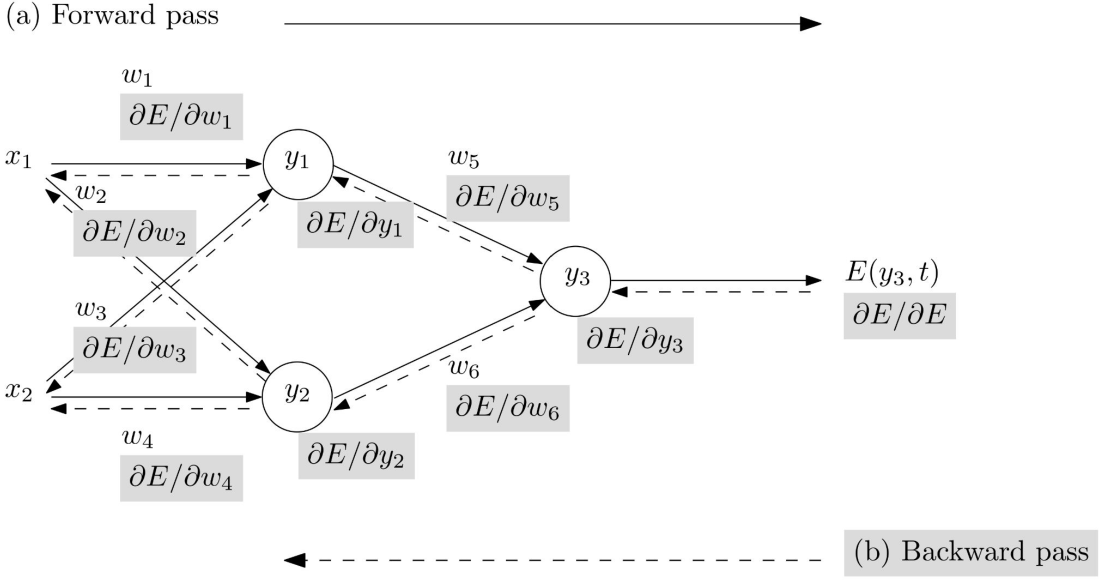


$$\frac{\partial [X]_n}{\partial t} = f([X]_n, [Y]_n, [Z]_n, \dots)$$

Kong et al. 2020, *Academic Press*

$$[X]_{n+1} \approx f([X]_n, [Y]_n, [Z]_n, \dots) \times (t_{n+1} - t_n)$$

Automatic differentiation accelerates gradient calculation



Baydin et al. 2018, *arXiv*

Reverse-mode autodiff excels when the ratio of inputs to outputs is high

Forward-mode autodiff requires less memory

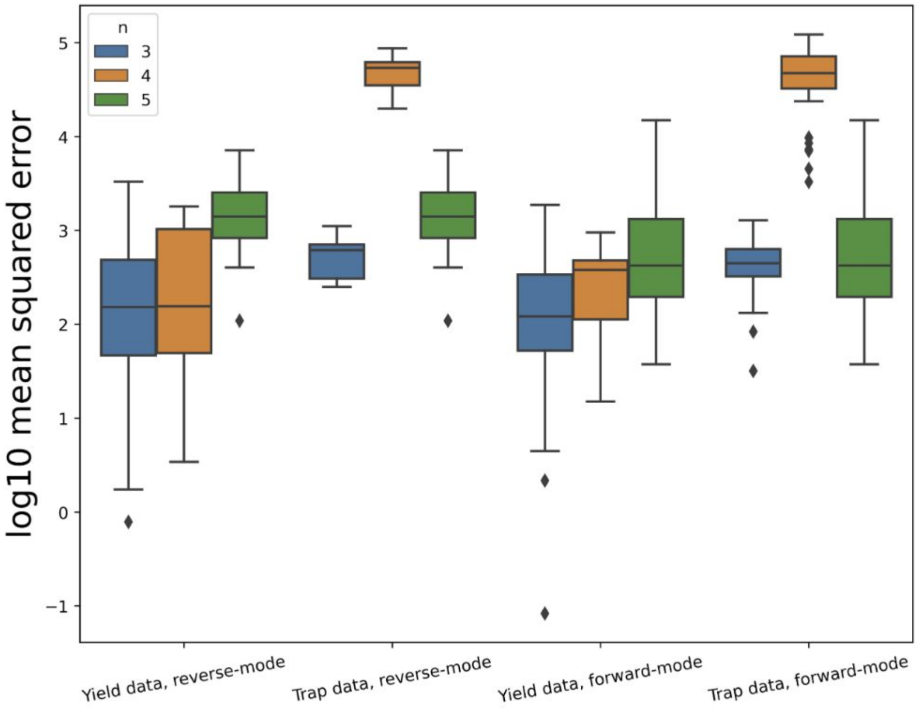
Zygote

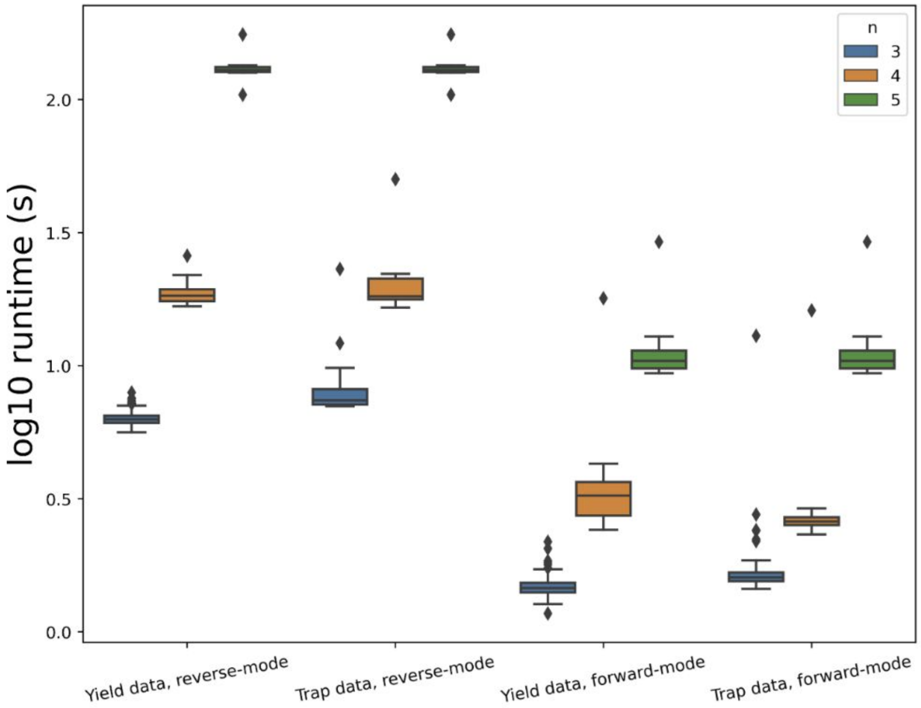
ForwardDiff.jl

What information does kinetic trapping encode about rate constants?

Can autodiff help us to extract that data machine learning?

Forward-mode is faster, yield data provides more accuracy





Next steps

1. Perform non-autodiff control experiments
2. Examine memory consumption of forward- and reverse-mode autodiff
3. Examine more realistic chemical reaction networks and data

Acknowledgements

Johnson lab

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Error regression

```
Call:
lm(formula = error ~ autodiff_mode + exp_type + n + autodiff_mode:exp_type,
    data = df)

Residuals:
   Min     1Q Median     3Q    Max
-30533 -13018    848   2682  99715

Coefficients:
                              Estimate Std. Error t value Pr(>|t|)
(Intercept)                     -10004       4709  -2.124   0.0341 *
autodiff_moderev                 -2286       3055  -0.748   0.4546
exp_typeyield                   -17008       2237  -7.603 1.45e-13 ***
n                                 8115       1273   6.377 4.14e-10 ***
autodiff_moderev:exp_typeyield    4192       3748   1.118   0.2639
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 17330 on 498 degrees of freedom
Multiple R-squared:  0.2557,	Adjusted R-squared:  0.2497
F-statistic: 42.77 on 4 and 498 DF,  p-value: < 2.2e-16
```

Time regression

```
Call:
lm(formula = time ~ autodiff_mode + exp_type + n + autodiff_mode:exp_type,
    data = df)

Residuals:
    Min      1Q  Median      3Q     Max
-31.729 -11.304  -3.051   7.536 118.899

Coefficients:
                               Estimate Std. Error t value Pr(>|t|)
(Intercept)                     -80.031      4.908 -16.305  < 2e-16 ***
autodiff_moderev                 32.209      3.184  10.115  < 2e-16 ***
exp_typeyield                     3.320      2.332   1.424    0.155
n                                23.560      1.326  17.762  < 2e-16 ***
autodiff_moderev:exp_typeyield -16.696      3.906  -4.274  2.3e-05 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 18.07 on 498 degrees of freedom
Multiple R-squared:  0.4973,    Adjusted R-squared:  0.4933
F-statistic: 123.2 on 4 and 498 DF,  p-value: < 2.2e-16
```