

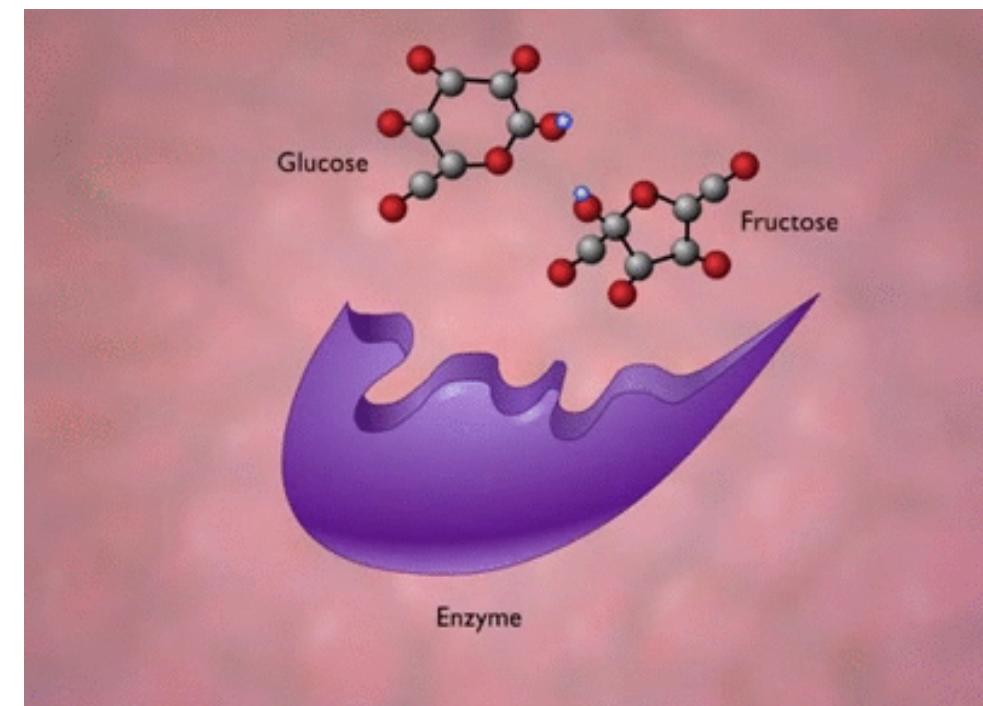
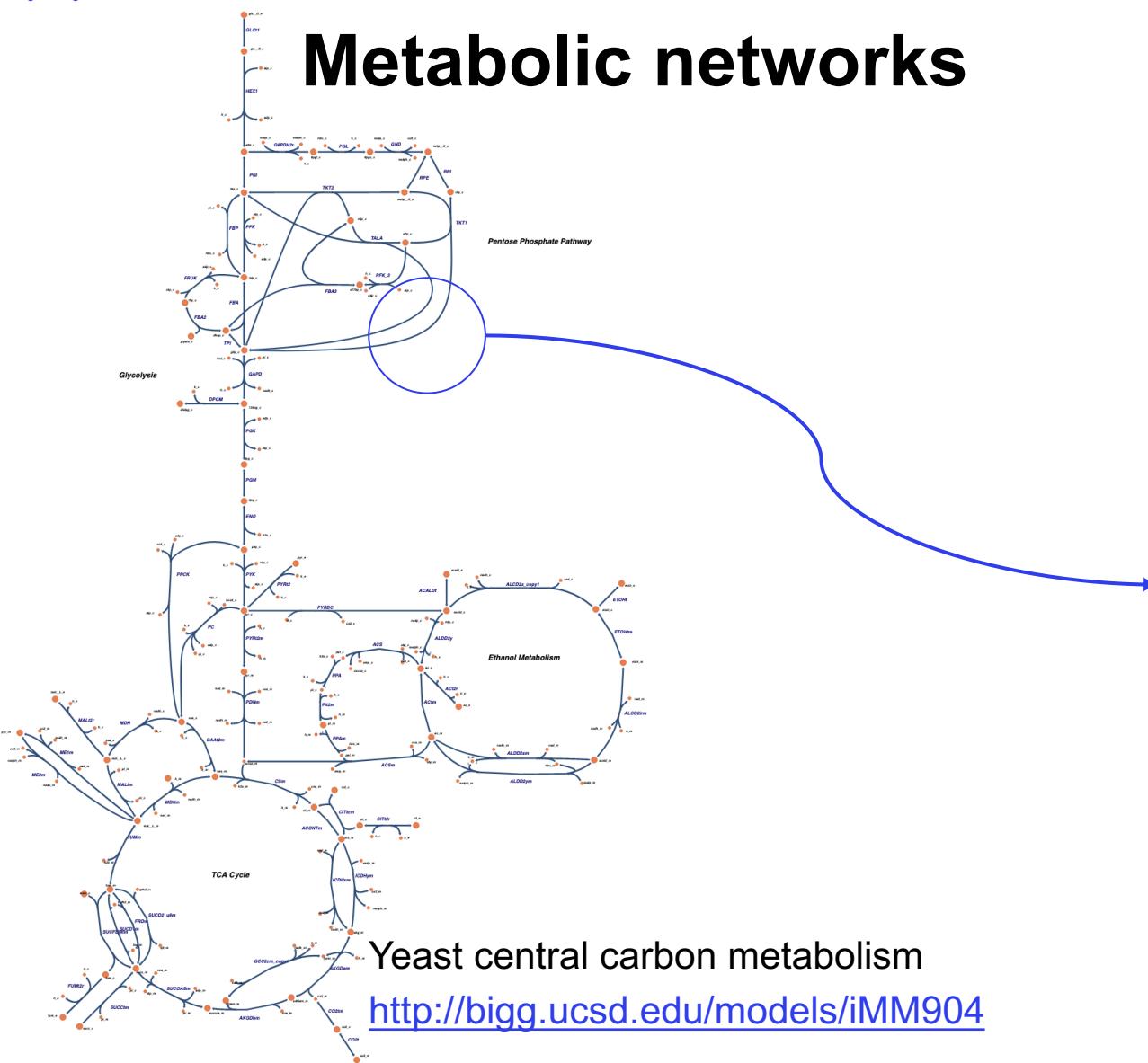
Teddy Groves

Modelling metabolic networks with Stan

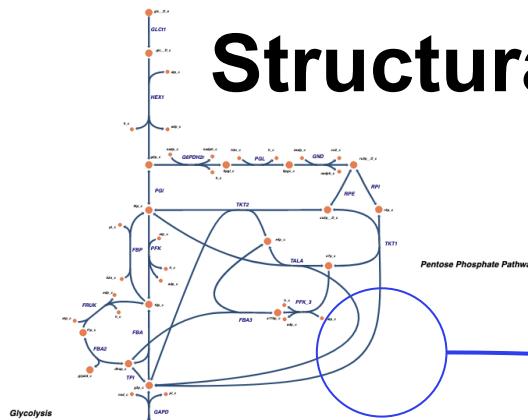
Cell factories



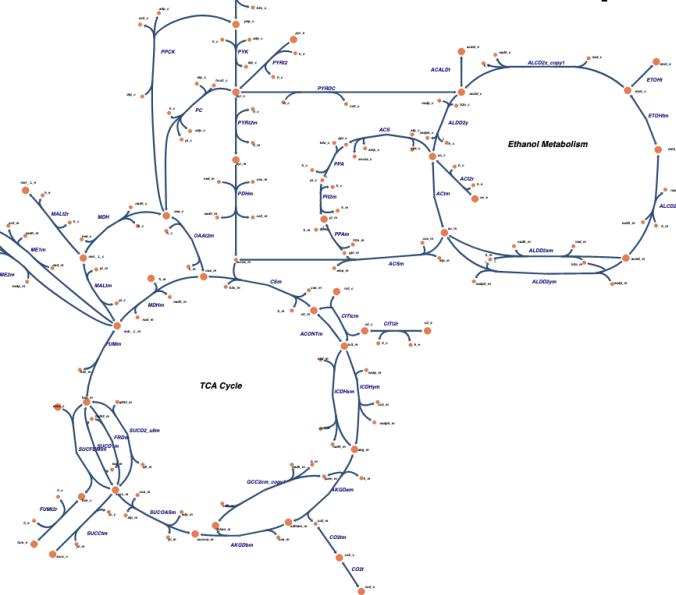
Metabolic networks



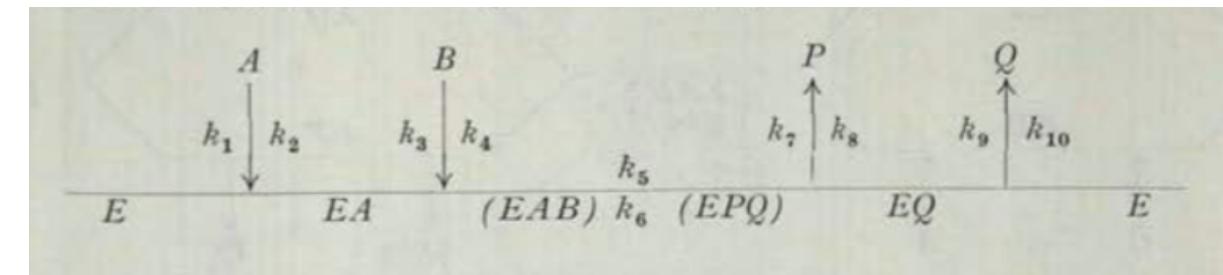
Structural information



Network topology



Mechanism



Rate equation

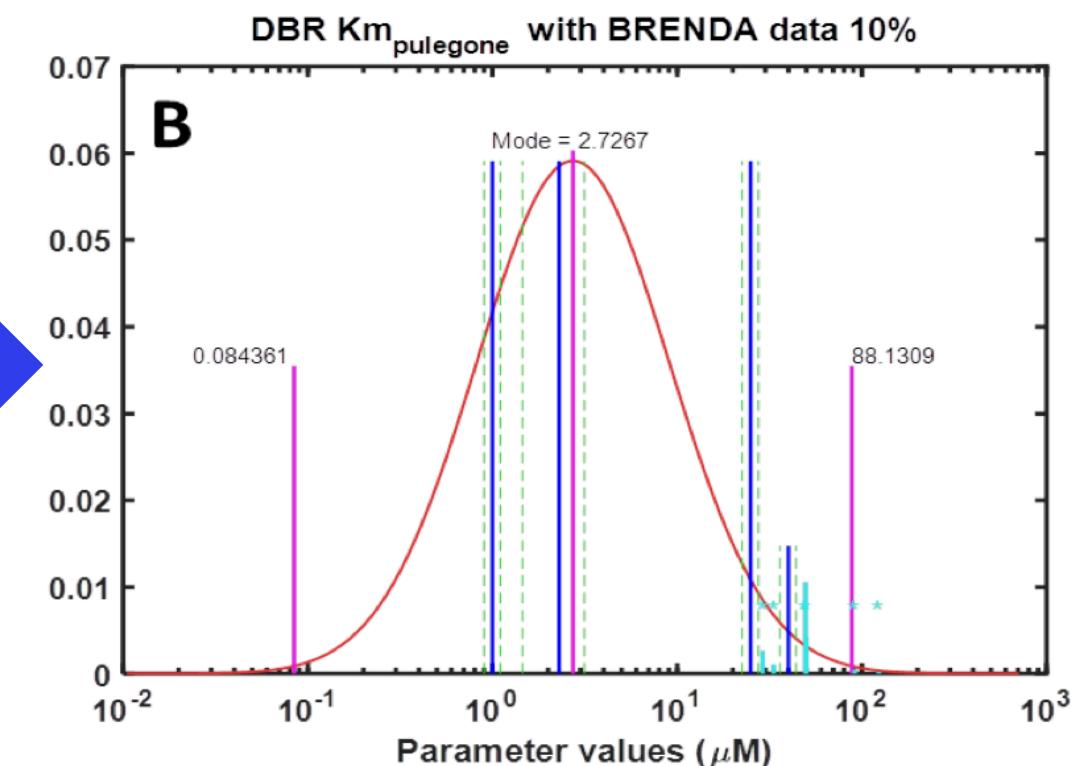
$$v = \frac{V_1 V_2 \left(AB - \frac{PQ}{K_{\text{eq}}} \right)}{K_{1a} K_b V_2 + K_b V_2 A + K_a V_2 B + V_2 AB + \frac{K_q V_1 P}{K_{\text{eq}}} + \frac{K_p V_1 Q}{K_{\text{eq}}}} + \frac{V_1 PQ}{K_{\text{eq}}} + \frac{K_q V_1 AP}{K_{1a} K_{\text{eq}}} + \frac{K_a V_2 BQ}{K_{1q}} + \frac{V_2 ABP}{K_{1p}} + \frac{V_1 BPQ}{K_{1b} K_{\text{eq}}}$$

Source of uncertainty: experiments

- Metabolomics
- Proteomics
- Fluxomics



Source of uncertainty: online databases



The plan



The plan

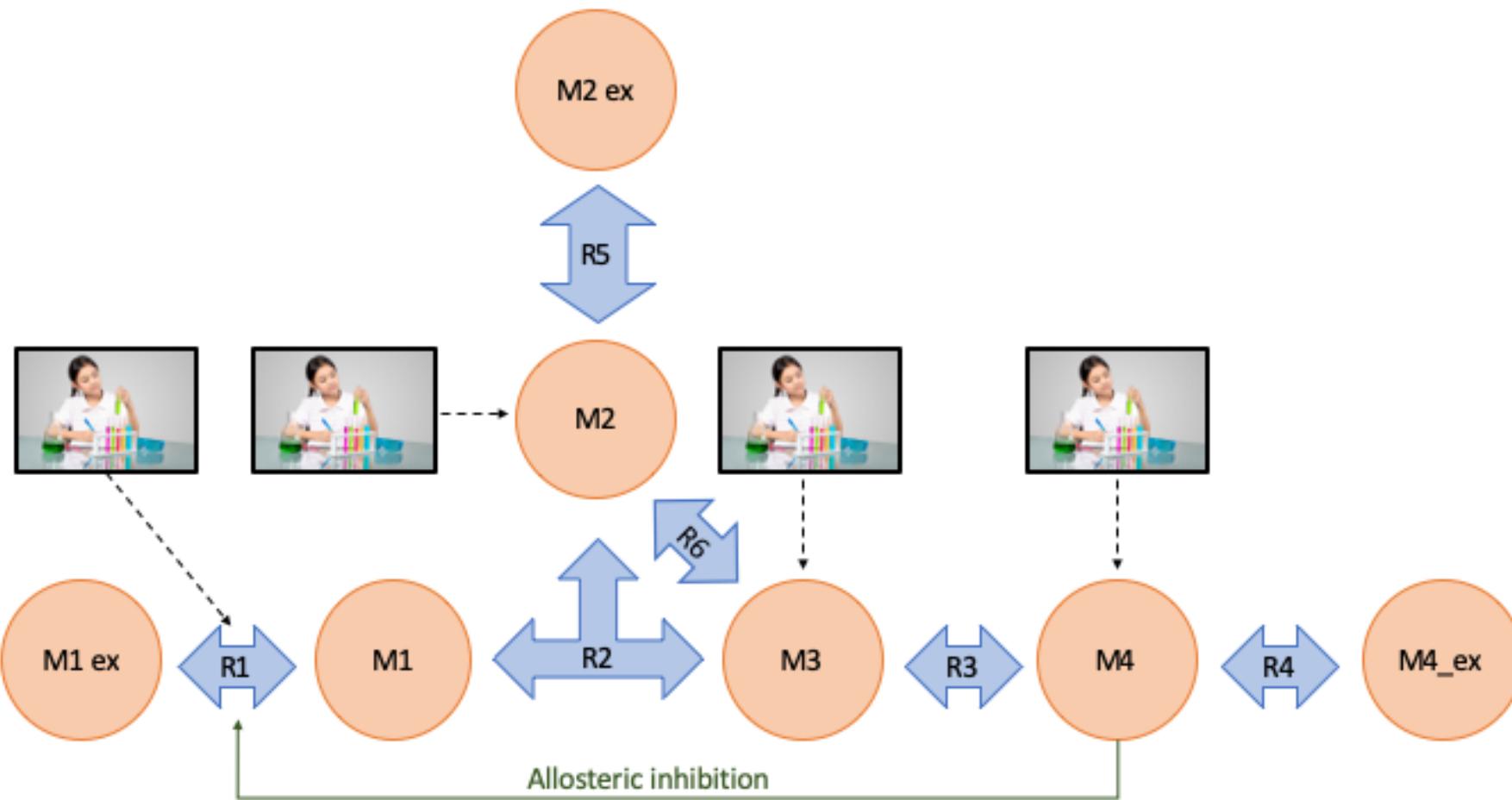


Challenges

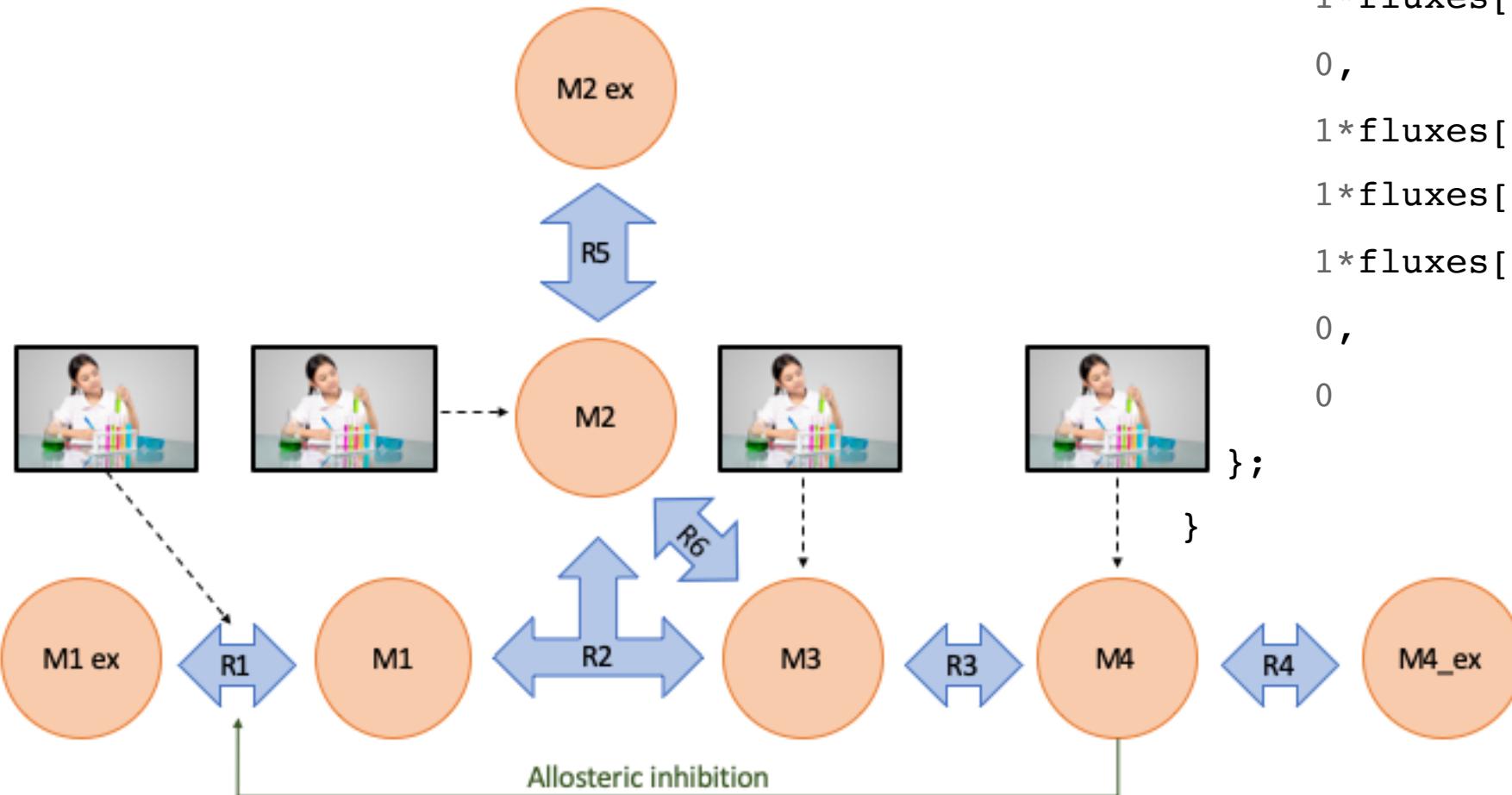
- Allosteric regulation
- Thermodynamics
- Big, stiff system of ODEs



A simple reaction network



A simple reaction network



```
real[] get_odes(real[] fluxes){  
    return {  
        1*fluxes[1]-1*fluxes[2],  
        0,  
        1*fluxes[2]-1*fluxes[5]-1*fluxes[6],  
        1*fluxes[2]-1*fluxes[3]+1*fluxes[6],  
        1*fluxes[3]-1*fluxes[4],  
        0,  
        0  
    };
```

How we represent rate equations

```
real ordered_unibi(real A, real P, real Q, real V1, real V2, real Ka,
                    real Kp, real Kq, real Kia, real Kip, real Kiq, real Keq){
    real num = V1*V2*(A-P*Q/Keq);
    real denom = Ka*V2 + V2*A + Kq*V1*P/Keq + Kp*V1*Q/Keq + V1*P*Q/Keq + V2*A*P/Kip;
    return num / denom;
}
```

$$v = \frac{V_1 V_2 \left(A - \frac{PQ}{K_{eq}} \right)}{K_a V_2 + V_2 A + \frac{K_q V_1 P}{K_{eq}} + \frac{K_p V_1 Q}{K_{eq}} + \frac{V_1 P Q}{K_{eq}} + \frac{V_2 A P}{K_{ip}}}$$

How we represent thermodynamic constraints

```
real get_Kip_ordered_unibi(real Keq, real Kia, real Kq, real v1, real v2){  
    return Keq*Kia*v2 / (Kq*v1);  
}  
  
real get_Kiq_ordered_unibi(real Keq, real Ka, real Kp, real v1, real v2){  
    return Keq*v2*Ka / (v1*Kp);  
}
```

$$K_{\text{eq}} = \frac{V_1 K_{\text{ip}} K_{\text{q}}}{V_2 K_{\text{ia}}} = \frac{V_1 K_{\text{p}} K_{\text{iq}}}{V_2 K_{\text{a}}}$$

How we represent allosteric regulation

```
real get_regulatory_effect(real[] activator_concentration,
                           real[] inhibitor_concentration,
                           real free_enzyme_ratio,
                           real[] dissociation_constant_r,
                           real[] dissociation_constant_t,
                           real transfer_constant){

    real Q_num = size(inhibitor_concentration) == 0 ? 1 :
        1 + sum(to_vector(inhibitor_concentration) ./ to_vector(dissociation_constant_t));
    real Q_denom = size(activator_concentration) == 0 ? 1 :
        1 + sum(to_vector(activator_concentration) ./ to_vector(dissociation_constant_r));
    real Q = transfer_constant * free_enzyme_ratio * Q_num / Q_denom;

    return inv(1 + Q);
}
```

How we represent steady state quantities

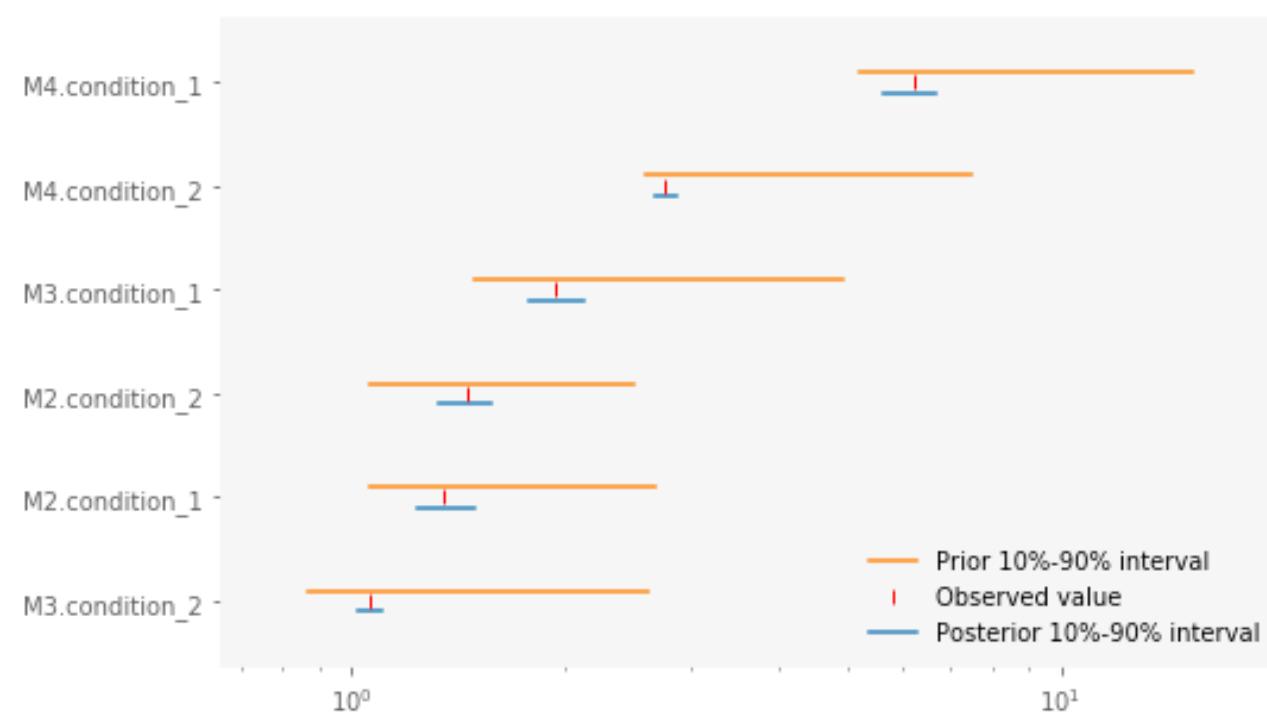
```
concentration[,e] = integrate_ode_bdf(steady_state_equation,  
                                      initial_concentration,  
                                      initial_time,  
                                      {steady_time},  
                                      kinetic_parameter,  
                                      known_reals[,e],  
                                      known_ints,  
                                      rel_tol, abs_tol, max_steps)[1];  
  
flux[,e] = get_fluxes(concentration[,e], kinetic_parameter, known_reals[,e]);
```

How we represent measurements

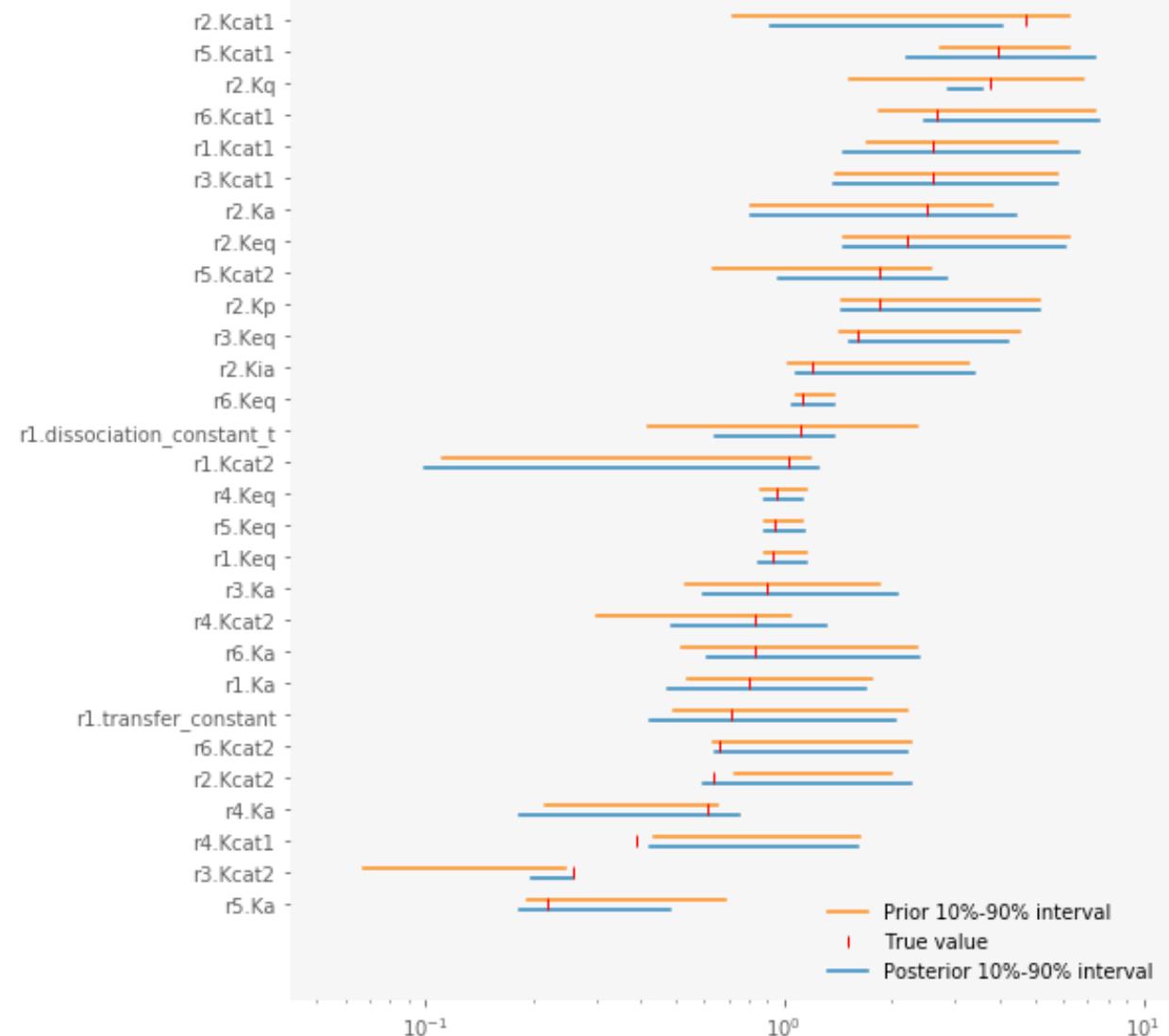
```
concentration_measurement ~ lognormal(log(concentration_hat), concentration_measurement_scale);  
  
flux_measurement ~ normal(flux_hat, flux_measurement_scale);
```

Results

Metabolite concentration results



Kinetic parameter results



Next hurdle: performance (please help!)

- How to exploit sparse ODE Jacobians?
- How to do fewer ODE solves?
- What can we parallelise?



References

Rate equations

- Cleland, W. W. (1963). The kinetics of enzyme-catalyzed reactions with two or more substrates or products: I. Nomenclature and rate equations. *Biochimica et Biophysica Acta (BBA) - Specialized Section on Enzymological Subjects*, 67(), 104–137. [http://dx.doi.org/10.1016/0926-6569\(63\)90211-63](http://dx.doi.org/10.1016/0926-6569(63)90211-63)

Enzyme kinetics in general

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<http://dx.doi.org/10.1016/j.biotechadv.2017.09.005>

Allosteric regulation

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- Saa, P., & Nielsen, L. K. (2015). A General Framework for Thermodynamically Consistent Parameterization and Efficient Sampling of Enzymatic Reactions. *PLOS Computational Biology*, 11(4), 1004195.
<http://dx.doi.org/10.1371/journal.pcbi.1004195>