Model inference from protein time-course in Hematopoietic Stem Cells (HSC)

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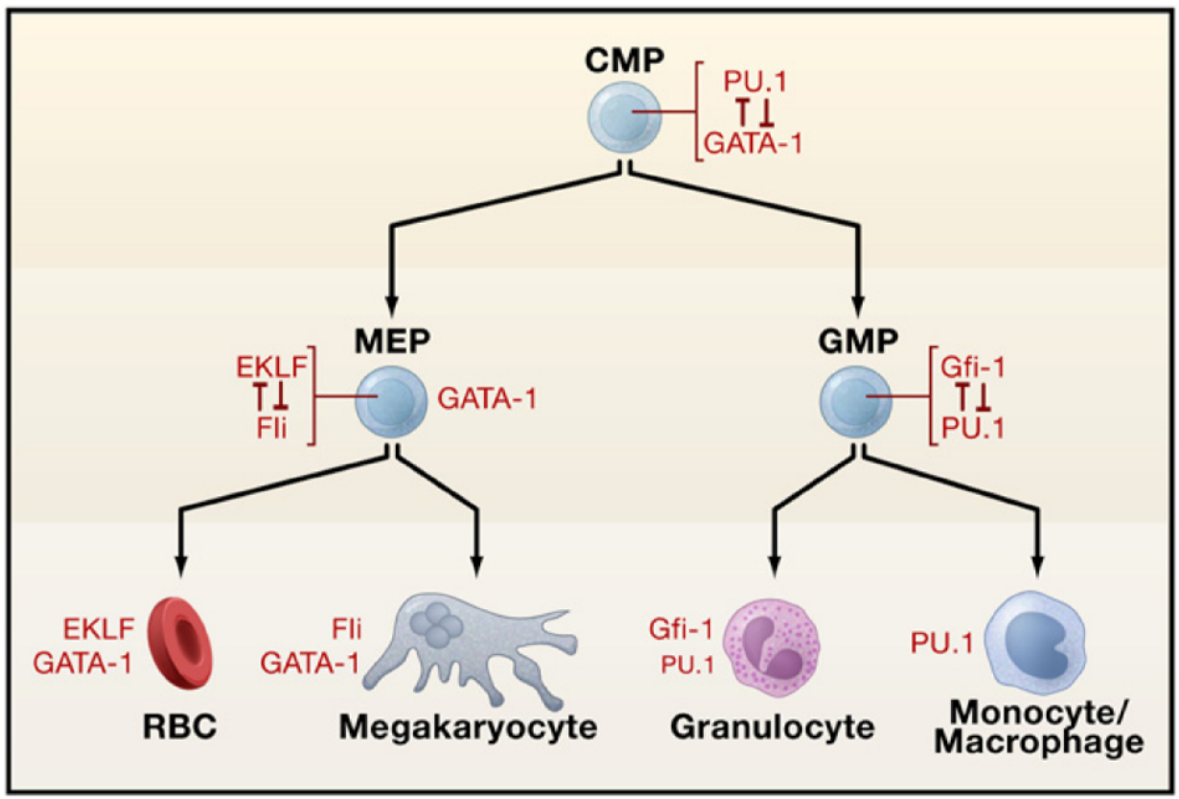
Introduction

- Dynamics of hematopoetic stem cell maturation cell from Common Myeloid Progenitor (CMP) to Megakaryocyte-Erythroid Progenitor (MEP) and Granulocyte-Macrophage Progenitor (GMP)

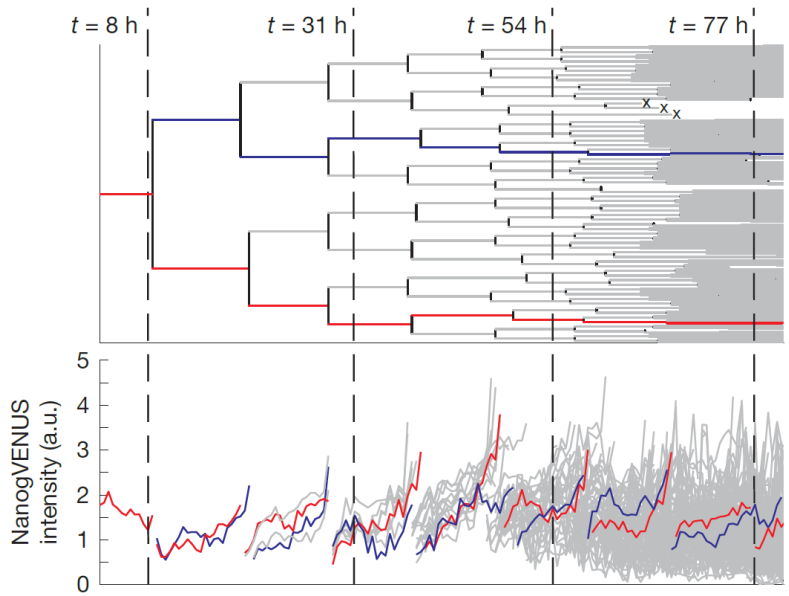


[1]

[1] Graf & Enver, 2009, *Nature*

Introduction (cont'd)

- Assumed corss-inhibition dynamics between `Pu.1` and `Gata1` in cell maturation fate:
  - Dynamics is assumed to be a bistable toggle-switch system
  - Lineage decision is a stochastics process resulting in uneven yield of MEP and GMP (70% : 30%)
- Analysis on single-cell time-lapsed data to infer parameters of this dynamics



[2]

[2] Feigelman, 2016, Ph.D. Thesis

Problems

- Stochaticity in single cell resolution is more punctuated
- Tree structure of the data add ore complexity: inheritance of information during inference process is not trivial

Ideas

- Sequential Monte Carlo simulations along the time-apsed data to infer "good" parameters

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- **problem:** Overfitting due to single-cell biased
- **solution:** Inference across cell lineages
- Inferred parameters from all simulated lineages are represented as distribution
- Final inferred parameters are expected value E of the distribution

Particle Filtering

- **Particle** A particle K is defined as a triple of previous simulation trajectory X, parameter set θ and assumed model M,

$$K := (X, \theta, M) \tag{1}$$

- **Particle filtering** is an parameters inference method that consists of: (1) *sequentially* performing simulations using *particles*, (2) *updating* the *prior* assumptions of the model using the results of the simulations and (3) rerunning the simulations using updated assumptions (*posterior*).

Particle Filtering: update rule

- **Posterior**
  After each simulation step, a posterior describes the probability of having the trajectory X and parameter θ given the observation D from real data,

$$P(X, \theta|D) \overset{\text{Bayes}}{=} \frac{P(D|X, \theta)P(X, \theta)}{P(D)} \tag{2}$$

  This Bayesian update rule is used to update parameters by looking at how well does the simulation follow the real data. I.e. after an iteration we will choose parameters belonging to particles that simulate the trajectory well w.r.t. experimental data.
- **Gamma Distribution** is used as prior since a posterior of a gamma is in turn gamma distributed (*prior conjugate*).

Particle Filtering: algorithm

1. Initialization of parameters θ.
2. Input of data $\mathcal{D}$.
3. Particle filtering routine:
   - 3.1 Generation of initial particles for step i

$$Ki := (K_{i1}, K_{i2}, \ldots, K_{im}) \tag{3}$$

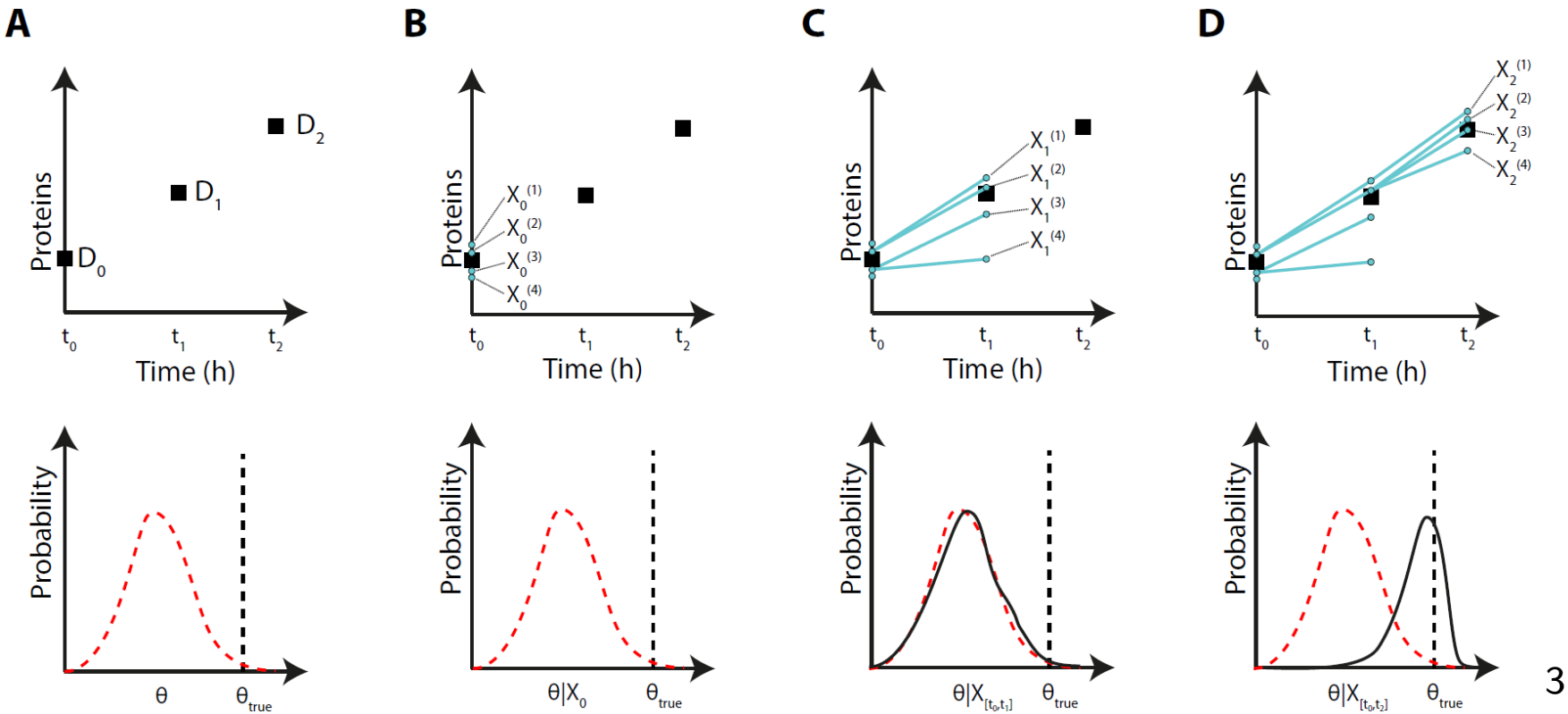
   - 3.2 Simulation run of each particle K_{ij}
   - 3.3 Weighting of each particle. The weight is a function of the probability of observing the data given the simulation result.

$$w_i^k = P(D_i|X_i^k) = \mathcal{N}(\mathcal{D}_i|X_i^k) \tag{4}$$

   - 3.4 Parameter update for every K,

$$\theta^k \propto P(\theta|X_{[to,ti]}^k) \tag{5}$$

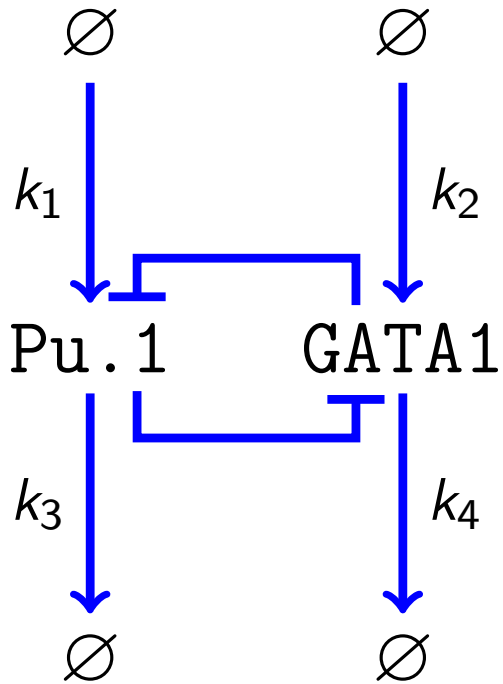
Particle Filtering: visualization



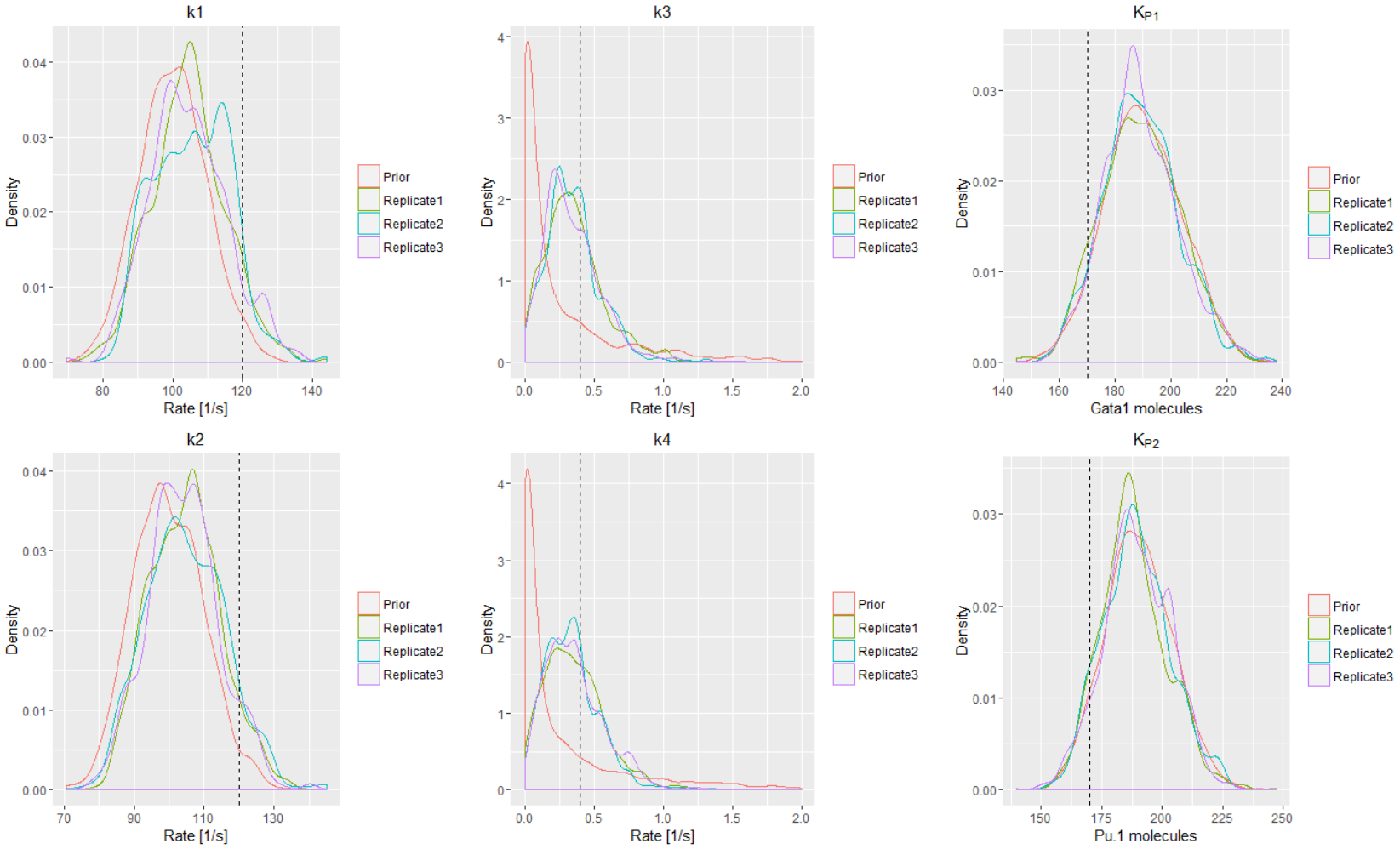
[3] Feigelman, 2016, Ph.D. Thesis

Reaction Model

- Simple model in line with cross inhibiton assumption
- Inhibiton modeled trough inverse michaelis menten kinetik
- Parameterize production and degredation rates as well as inhibition half point



Testing


k1
Density
Rate [1/s]
Prior
Replicate1
Replicate2
Replicate3
k3
Density
Rate [1/s]
Prior
Replicate1
Replicate2
Replicate3
K_{P1}
Density
Gata1 molecules
Prior
Replicate1
Replicate2
Replicate3
k2
Density
Rate [1/s]
Prior
Replicate1
Replicate2
Replicate3
k4
Density
Rate [1/s]
Prior
Replicate1
Replicate2
Replicate3
K_{P2}
Density
Pu.1 molecules
Prior
Replicate1
Replicate2
Replicate3

Model Comparison

- Compare different models via Bayes Factors

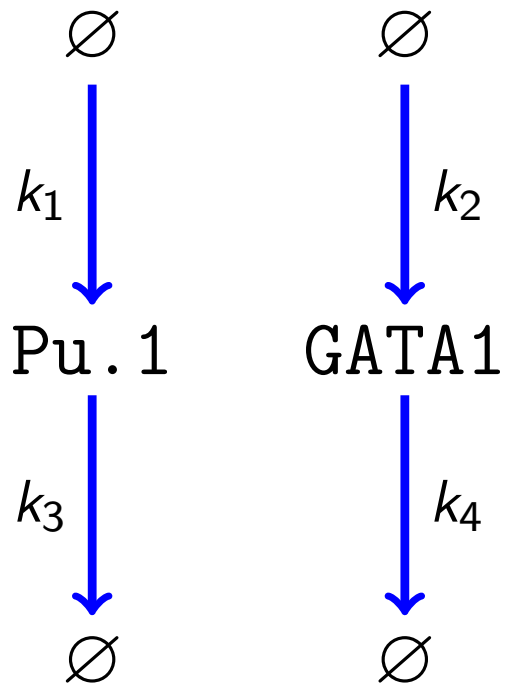
$$B_{M1,M2} = \frac{P(M_1|\mathcal{D})}{P(M_2|\mathcal{D})} \overset{\text{Bayes}}{=} \frac{P(M_1)P(\mathcal{D}|M_1)}{P(M_2)P(\mathcal{D}|M_2)} \tag{6}$$

- The average weight of the particle trajectories are used as Bayes Factor

$$P(\mathcal{D}|M) = P(\mathcal{D}_l) \prod_{l=1}^{N} P(\mathcal{D}_{i+1}|\mathcal{D}_{0:i}, M) \tag{7}$$

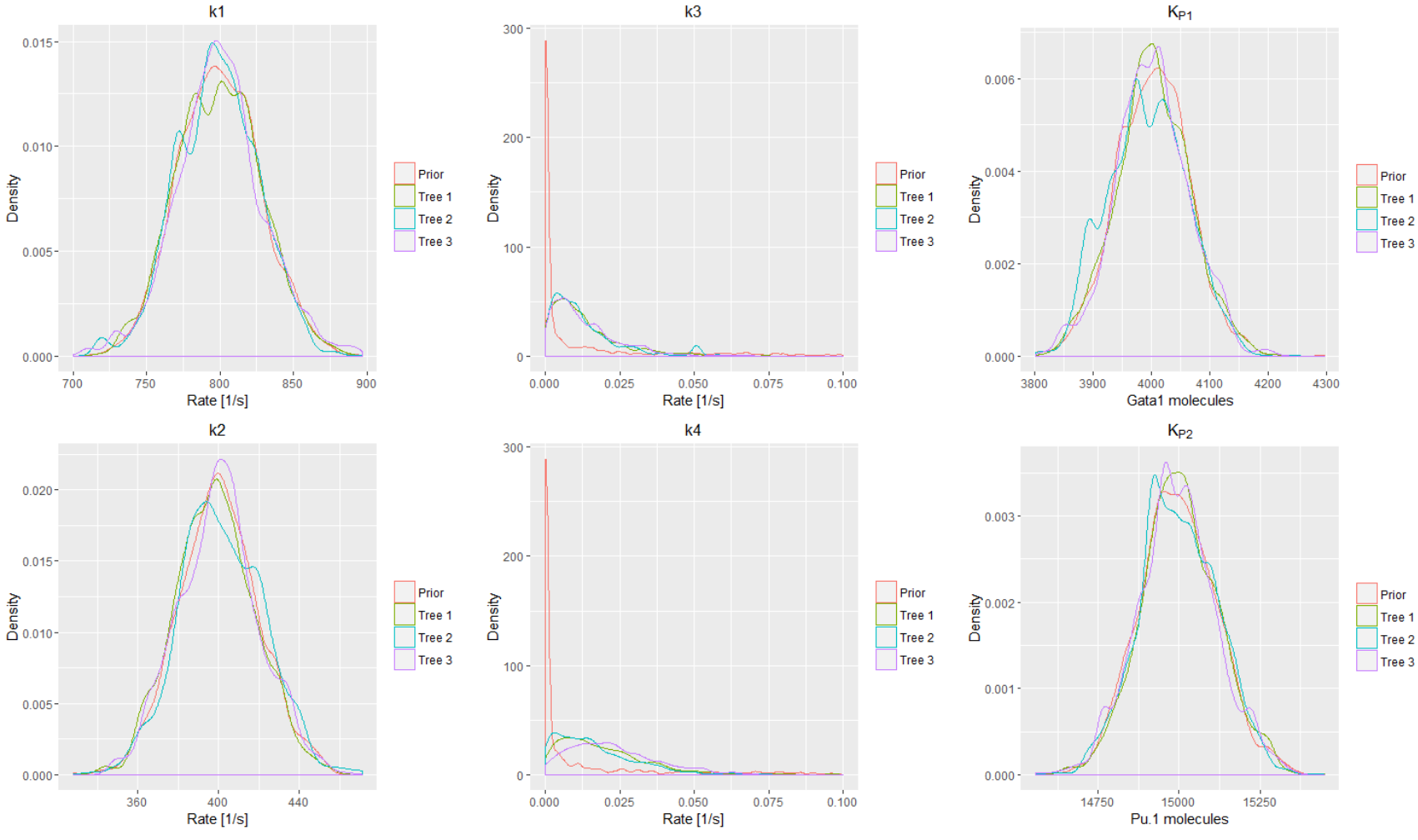
Model Comparison Test

- Independent model used on synthetic data set
- Model comparison by Bayes factors



$$B_{M1,M2} = \frac{P(\mathcal{D}|M_{inhibitory})}{P(\mathcal{D}|M_{indepent})} = \frac{10^{-2221.498}}{10^{-2234.828}} \approx 2.14 \cdot 10^{13} \qquad (8)$$

Single cell time lapse data



Interpretation

- Parameters of reaction model have varying susceptibility to fitting trough particle filtering
- Model cannot accuratly describe the dynamic of the transcript factors
- Recent finding (Hoppe et al. 2016) on the same data suggest the lineage choice to be independent from the transcription factor ratios
- Particle filtering cannot infer the prescene of the external decision factor

Conclustion & Outlook

- Particle filtering enable the paramterization of models using time lapse data of cell lineage trees
- Using the weight of particle trajectories models can be compared, allowing quantified comparison of theories
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Questions

Questions?