Bayesian nonparametrics

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STAT 615 - Iowa State University

December 5, 2017

Outline

- Stochastic kinetic models
- Approximate Bayesian computation

Stochastic kinetic models

Imagine a *well-mixed* system in *thermal equilibrium* with

- N species: $S_1, \ldots, S_N$ with
- number of molecules $X_1, \ldots, X_N$ with elements $X_j \in \mathbb{Z}^+$
- which change according to M reactions: $R_1, \ldots, R_M$ with
- propensities $a_1(x), \ldots, a_M(x)$.
- The propensities are given by $a_j(x) = \theta_j h_j(x)$
- where $h_j(x)$ is a known function of the system state.
- If reaction j occurs, the state is updated by the stoichiometry ν_j with
- elements $\nu_{ij} \in \{-2, -1, 0, 1, 2\}$, i.e. reaction orders 0,1, and 2.

Michaelis-Menton System

The Michaelis-Menton system has $N = 4$ species:

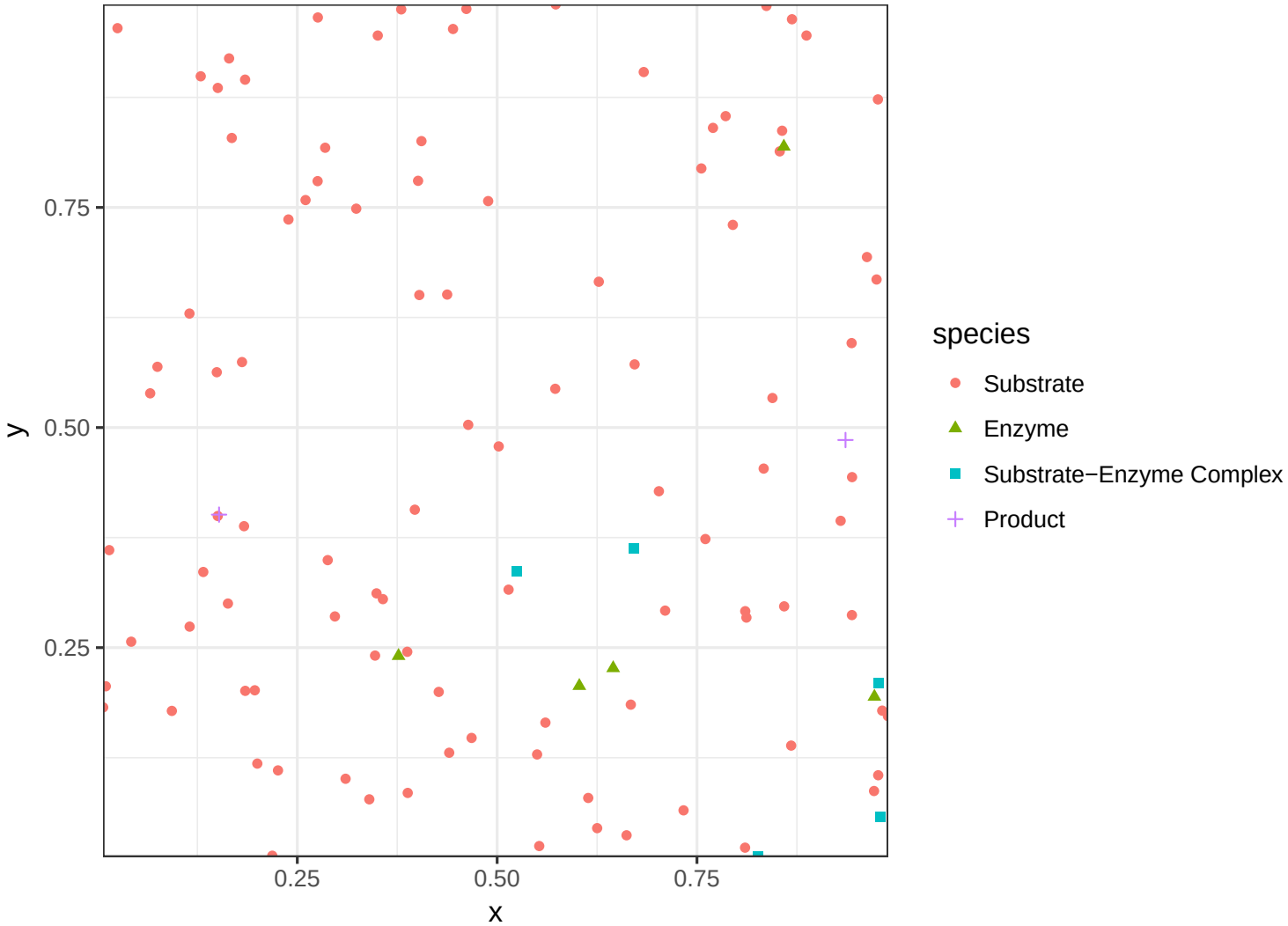
- Substrate (S),
- Enzyme (E),
- Substrate-Enzyme Complex (SE), and
- Product (P).

The $M = 3$ reactions as well as their propensities and stoichiometries are

Reaction	Propensity	Stoichiometry S	E	SE	P
S + E $\longrightarrow$ SE	$\theta_1 X_S X_E$	-1	-1	1	
SE $\longrightarrow$ S + E	$\theta_2 X_{SE}$	1	1	-1	
SE $\longrightarrow$ P+E	$\theta_3 X_{SE}$		1	-1	1

where $\theta = (\theta_1, \theta_2, \theta_3)$ is the parameter of interest.

Michaelis-Menton snapshot



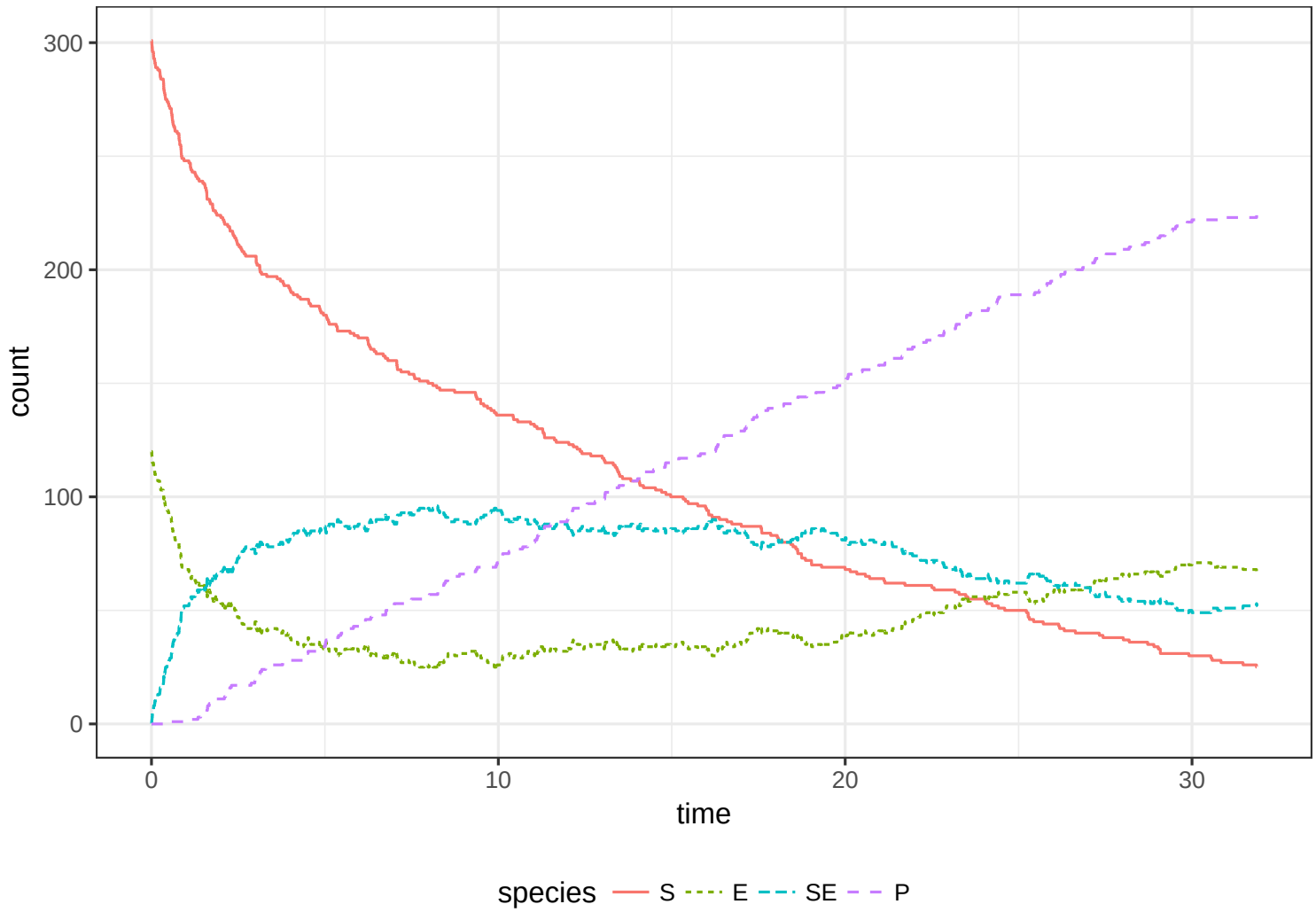
Gillespie algorithm

- If reaction $j \in \{1, \ldots, M\}$ has the following probability

$$\lim_{dt \to 0} P(\text{reaction } j \text{ within the interval } (t, t+dt)|X_t) = a_j(X_t)dt,$$

  then this defines a continuous-time Markov jump process.
- Then a realization from this model can be obtained using the Gillespie algorithm:
  1. For $j \in \{1, \ldots, M\}$, calculate $a_j(X_t)$.
  2. Calculate $a_0(X_t) = \sum_{j=1}^{M} a_j(X_t)$.
  3. Simulate a reaction time $\tau \sim Exp(a_0(X_t))$
  4. Simulate a reaction id $k \in \{1, \ldots, M\}$ with probability $a_k(X_t)/a_0(X_t)$
  5. Update X according to v_k and time by τ.

Michaelis-Menton Gillespie Simulation



Complete observations

Suppose you observe all system transitions:

- n reactions occur in the interval $[0, T]$
- $t_1, \ldots, t_n$ are the reaction times
- $r_1, \ldots, r_n$ are the reaction indicators, $r_i \in \{1, \ldots, M\}$

Then inference can be performed based on the likelihood

$$L(\theta) \propto \prod_{j=1}^{M} \theta_j^{n_j} \exp\left(-\theta_j I_j\right)$$

where

$$n_j = \sum_{i=1}^{n} \mathrm{I}(r_i = j) \quad \# \text{ of } j \text{ reactions}$$

$$I_j = \int_0^T h_j(X_t)dt = \sum_{i=1}^{n} h_j(X_{t_{i-1}})(t_i - t_{i-1}) + h_j(X_{t_n})[T - t_n]$$

Inference

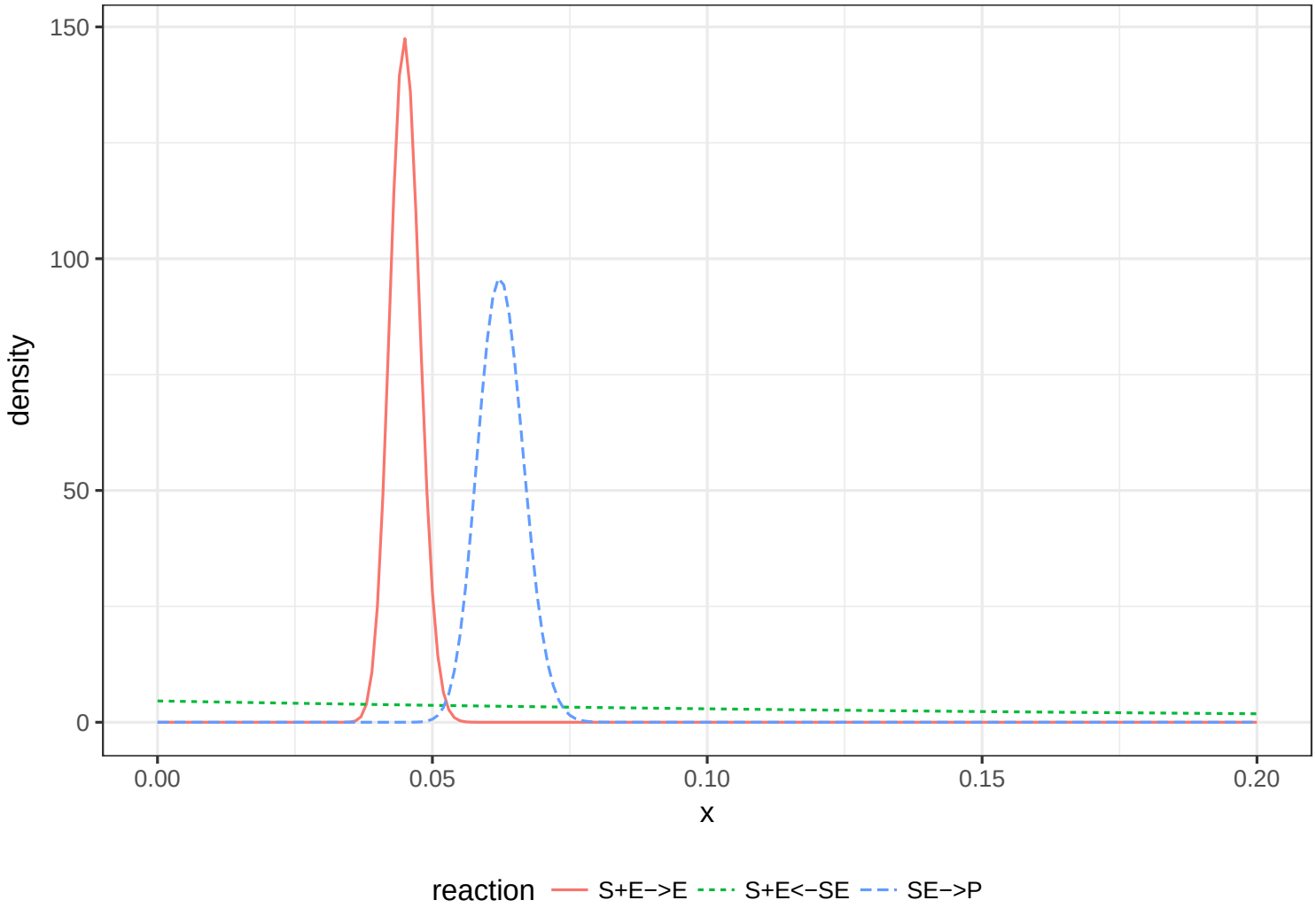
- Maximum likelihood estimation

$$\hat{\theta}_j = \frac{n_j}{I_j}$$

- Conjugate Bayesian inference

$$\begin{aligned} p(\theta) &= \prod_{j=1}^{M} Ga(\theta_j; \alpha_j, \beta_j) \\ p(\theta|X) &= \prod_{j=1}^{M} Ga(\theta_j; \alpha_j + n_j, \beta_j + I_j) \\ E[\theta_j|X] &= \frac{\alpha_j + n_j}{\beta_j + I_j} \end{aligned}$$

Michaelis-Menton Complete Data Inference

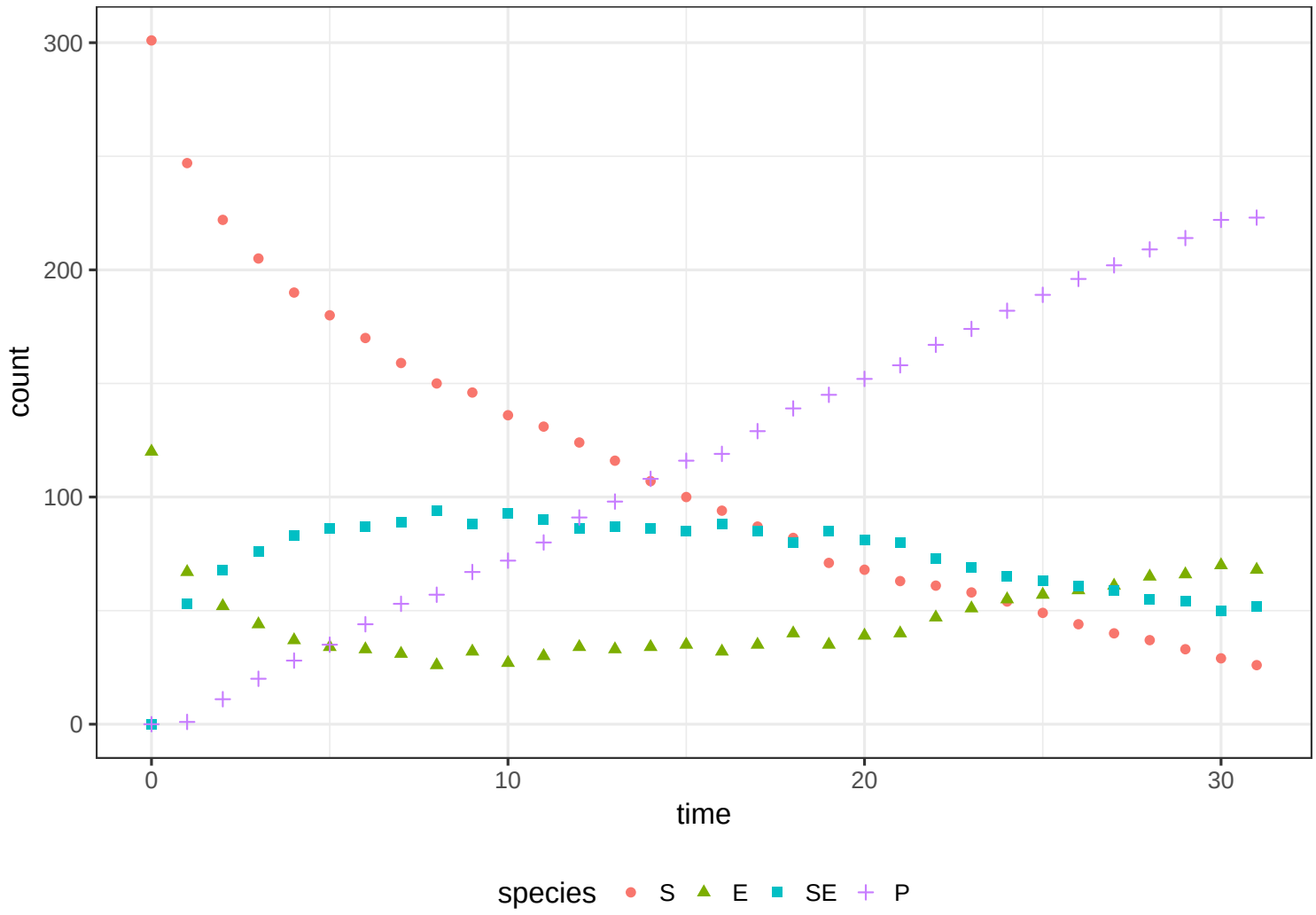


Discrete observations

Suppose you only observe the system at discrete-times:

- For simplicity, observe the system at times $t = 1, 2, \ldots, T$.
- At these times, we observe $y_t = X_t$ the system state.
- But do not observe the system between these times.

Michaelis-Mention discrete observations



Inference

Inference is still performed based on the likelihood

$$L(\theta) = p(y|\theta) = p(t, y)$$

but this is the solution to the chemical master equation

$$\frac{\partial}{\partial t}p(t, y) = \sum_{j=1}^{M} \left(a_j(y - v_m)p(t, y - v_m) - a_j(y)p(t, y)\right)$$

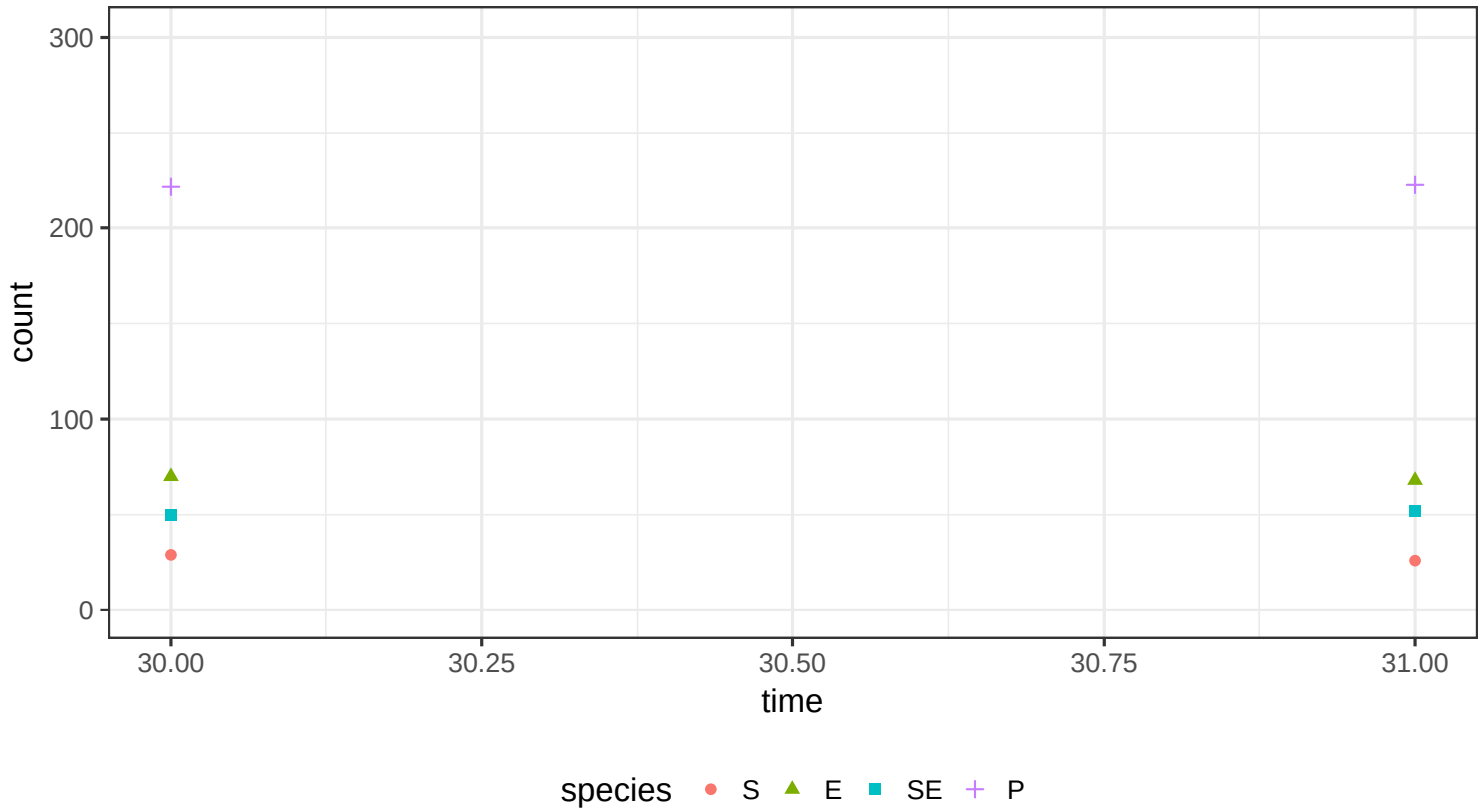
For constitutive production $h(X_t) = 1$ and $a(X_t) = \theta$, we still have

$$L(\theta) \propto \theta^n \exp\left(-\theta I\right)$$

with

$$n = y_T - y_0 \qquad I = \int_0^T 1dt = T$$

Reversible isomerization



- How many reactions occurred in the interval $[30, 31]$?
- What is $\int_{30}^{31} X_{SE} dt$?

Summary

- With complete observations and independent gamma priors, the posterior is

$$p(\theta|X) = \prod_{j=1}^{M} Ga(\theta_j; \alpha_j + n_j, \beta_j + I_j)$$

where

$$\begin{aligned} n_j &= \textstyle\sum_{i=1}^{n} \mathrm{I}(r_i = j) \\ I_j &= \textstyle\int_0^T h_j(X_t)dt = \sum_{i=1}^{n} h_j(X_{t_{i-1}})(t_i - t_{i-1}) + h_j(X_{t_n})[T - t_n] \end{aligned}$$

- For discrete observations, the likelihood is analytically intractable and therefore no closed form exists for the posterior (or MLEs).

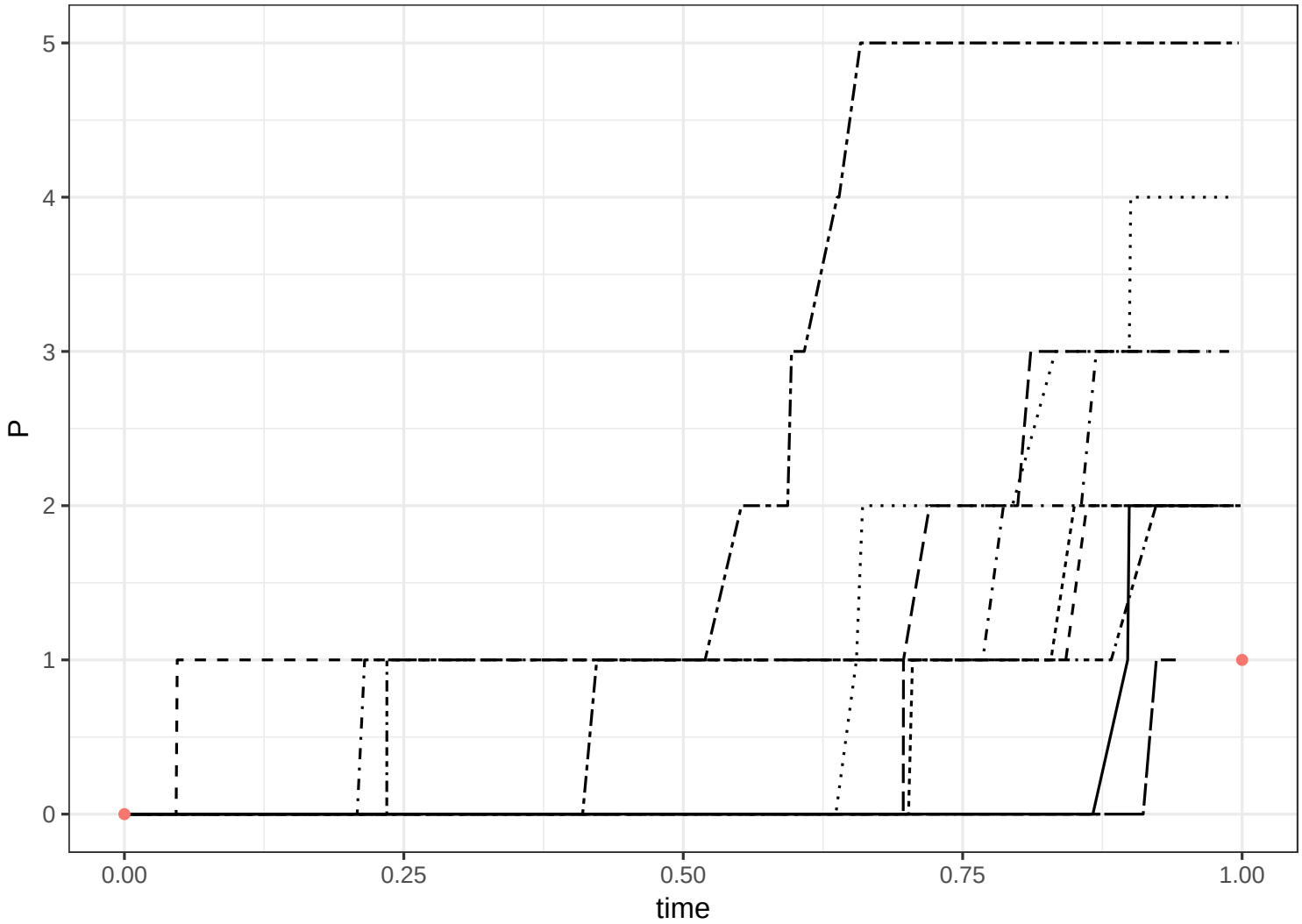
The idea

- But we can simulate from the model using the Gillespie algorithm!!
- Intuitively, if we
  1. pick a set of parameters,
  2. simulate a realization using these parameters,
  3. and it matches our data,
  4. then these parameters should be reasonable.

Our goal is to formalize this through

1. Rejection sampling
2. Gibbs sampling

Simulations from the prior



Rejection sampling

Our objective is samples from the posterior

$$\begin{aligned} p(\theta|y) &= \int p(\theta, X|y)dX \propto \int p(y|X)p(X|\theta)p(\theta)dX \\ &= \int \prod_{t=1}^{n} \mathrm{I}(y_t = X_t)p(X|\theta)p(\theta)dX \end{aligned}$$

A rejection sampling procedure is

1. Sample $\theta \sim p(\theta)$.
2. Sample $X \sim p(X|\theta)$ a.k.a. Gillespie
3. If $y_t = X_t$ for $t = 1, 2, \ldots, T$, then
4. θ is a sample from $p(\theta|y)$ and
5. θ, X is a sample from $p(\theta, X|y)$.

Gibbs sampling

Our objective is samples from the posterior

$$p(\theta|y) = \int p(\theta, X|y)dX \propto \int p(y|X)p(X|\theta)p(\theta)dX$$

A Gibbs sampling procedure is

1. Start with $\theta^{(0)}, X^{(0)}$
2. For $k = 1, \ldots, K$,
   a. Sample $\theta^{(k)} \sim p(\theta|X^{(k-1)})$
   b. Sample $X^{(k)} \sim p(X|\theta^{(k)}, y)$ a.k.a. rejection sampling

$\theta^{(k)}, X^{(k)}$ converge to samples from $p(\theta, X|y)$

An approximate posterior

- Intuitively, if we
  1. pick a set of parameters,
  2. simulate a realization using these parameters,
  3. and it is similar to our data,
  4. then these parameters should be reasonable.

- We can formalize this using
  - Approximate Bayesian computation

Approximate Bayesian computation (ABC)

Our approximate objective is samples from the posterior

$$p(\theta|y) = \int p(\theta, X|\rho \leq \epsilon)dX \propto \int \mathrm{I}(\rho \leq \epsilon)p(X|\theta)p(\theta)dX$$

where $\rho = \rho(y, X)$ is a measure of the difference between your data y and simulations X.

- Choice of ϵ reflects tension between computability and accuracy.
  - As $\epsilon \to \infty$,
    - $p(\theta|\rho \leq \epsilon) \xrightarrow{d} p(\theta)$
    - acceptance probability converges to 1
  - As $\epsilon \to 0$,
    - $p(\theta|\rho \leq \epsilon) \xrightarrow{d} p(\theta|y)$
    - acceptance probability decreases

ABC rejection sampling

Let $\rho = \sum_{t=1}^{n} |y_t - X_t|$ and $\epsilon = n$,

An ABC rejection sampling procedure is

1. Sample $\theta \sim p(\theta)$
2. Sample $X \sim p(X|\theta)$ a.k.a. Gillespie
3. If $\rho(y, X) \leq \epsilon$, then
4. θ is a sample from $p(\theta|\rho \leq \epsilon)$ and
5. θ, X is a sample from $p(\theta, X|\rho \leq \epsilon)$.

ABC Gibbs sampling

Let $\rho = \sum_{t=1}^{n} |y_t - X_t|$ and $\epsilon = n$,

A Gibbs sampling procedure is

1. Start with $\theta^{(0)}, X^{(0)}$
2. For $k = 1, \ldots, K$,
   a. Sample $\theta^{(k)} \sim p(\theta | X^{(k-1)})$
   b. Sample $X^{(k)} \sim p(X | \theta^{(k)}, \rho \leq \epsilon)$ a.k.a. rejection sampling

$\theta^{(k)}, X^{(k)}$ converge to samples from $p(\theta, X | \rho \leq \epsilon)$

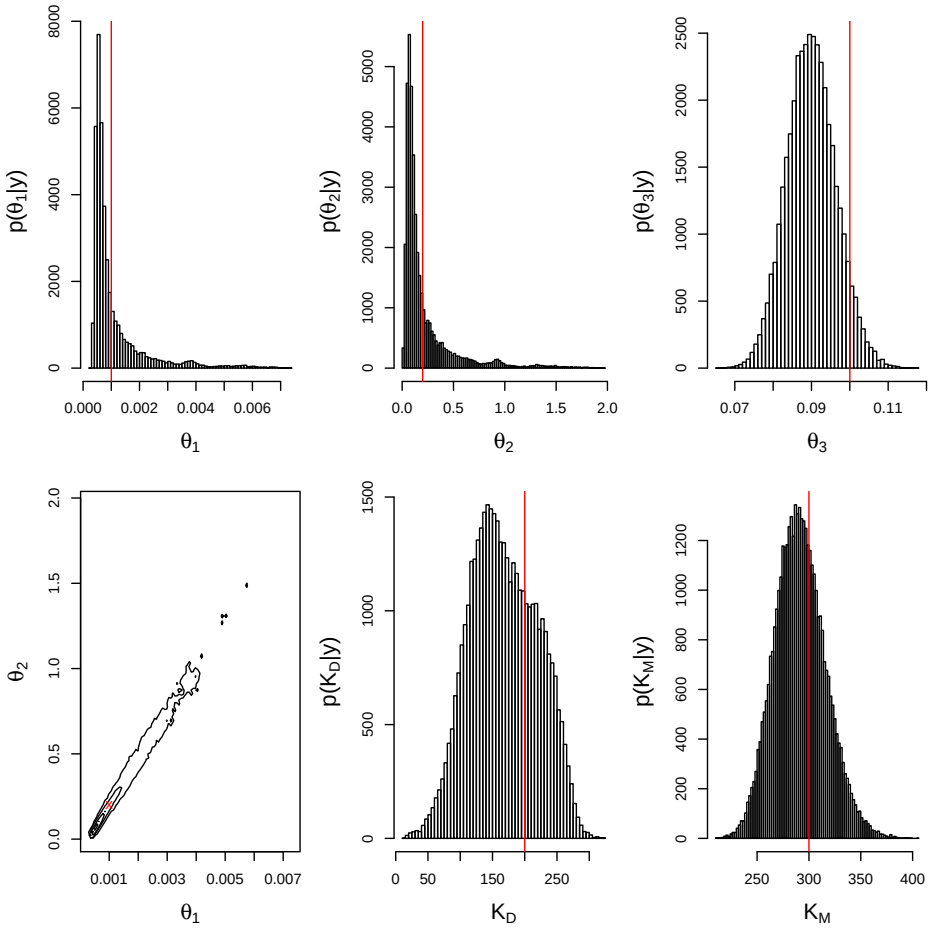
Michaelis-Menton system

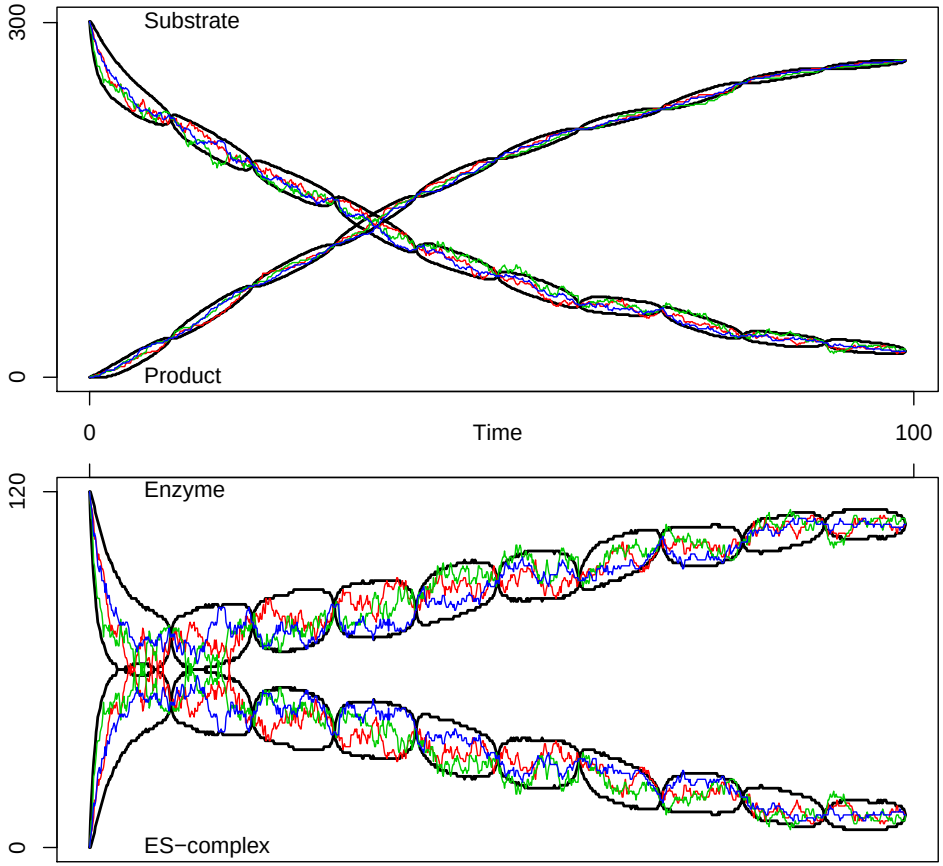
$$E + S \underset{\theta_2}{\overset{\theta_1}{\rightleftharpoons}} ES \xrightarrow{\theta_3} E + P$$

Table: Measurements taken from a simulated Michaelis-Mention system with parameters $\theta_1 = 0.001$, $\theta_2 = 0.2$, and $\theta_3 = 0.1$.

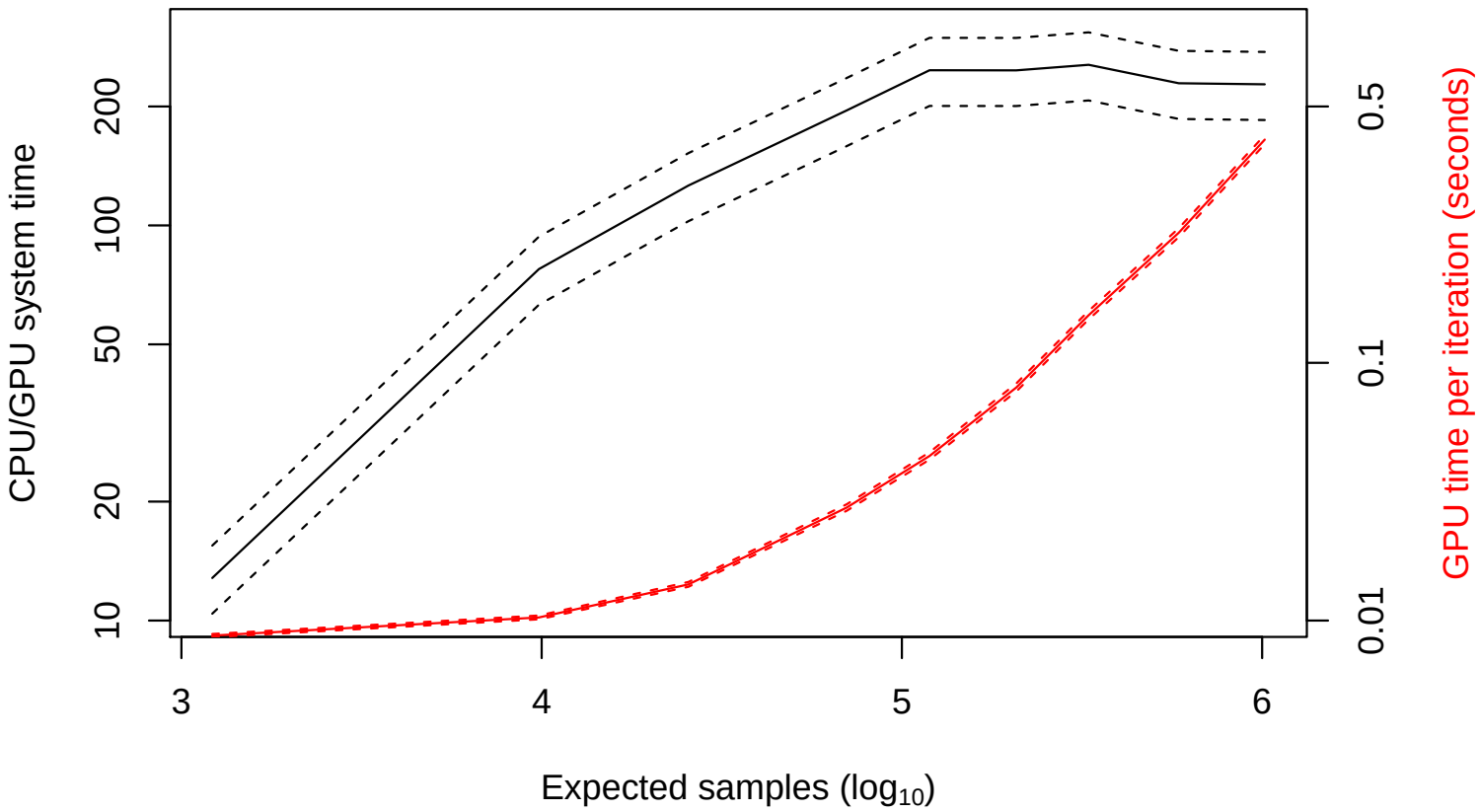
Time	0	10	20	30	40	50	60	70	80	90	100
E	120	71	76	81	80	90	90	104	103	109	109
S	301	219	180	150	108	86	61	52	35	29	22

With $\epsilon = 0$ (i.e. draws from $p(\theta|y)$),





Since rejection sampling is inherently parallel, run this algorithm on a graphical processing unit:



Summary

- Bayesian inference in discretely observed SCKMs
  - Goal: $p(\theta|y) \propto p(y|\theta)p(\theta)$
  - Likelihood, $L(\theta) = p(y|\theta)$, is analytically intractable
  - Sampling methods are required, e.g. rejection and/or Gibbs
  - Acceptance rate can be unacceptably low
- Approximate Bayesian computation (ABC) in SCKMs
  - Goal: $p(\theta|\rho \leq \epsilon) \propto p(\rho \leq \epsilon|\theta)p(\theta)$
  - $\rho = \rho(y, X)$ measures the difference between data and a simulation
  - ϵ balances computability with accuracy
  - Readily accommodates bounded errors, e.g. $y_t = X_t \pm \epsilon$
- ABC generally
  - More general than SKMs, e.g. phylogenetic trees
  - Building ρ is an art, often use sufficient statistics of the data
  - Not useful for unbounded errors, e.g. $y_t = X_t + \epsilon_t, \epsilon_t \sim N(0, \sigma^2)$
  - Current debate about usefulness for model selection