Parameter inference for small biochemical systems

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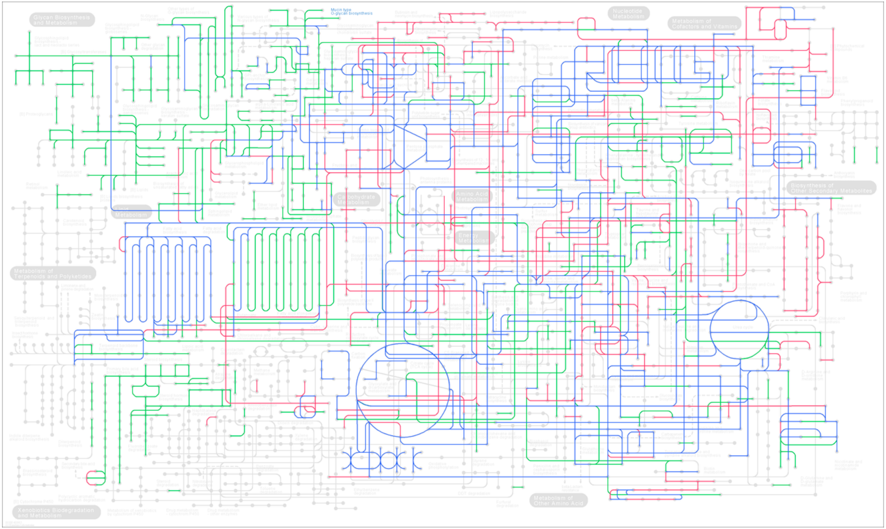
Paper

Darren Wilkinson's "Parameter inference for stochastic kinetic models of bacterial gene regulation," a book chapter in [1].

Problem


Glycan Biosynthesis and Metabolism
Nucleotide Metabolism
Metabolism of Cofactors and Vitamins
Carbohydrate Metabolism
Amino Acid Metabolism
Energy Metabolism
Metabolism of Terpenoids and Polyketides
Biosynthesis of Other Secondary Metabolites
Xenobiotics Biodegradation and Metabolism
Metabolism of Other Amino Acid

Problem

Cast of Characters

- r_j is a customer behavior pattern in a restaurant.
- $R_j(t)$ counts occurrences of r_j up to time t.
- c_j is the rate at which r_j happens.
- $X(t)$ is the restaurant state: customers, orders, cash register.
- $\mathcal{D}_t$ is an incomplete observation of $X(t)$ with error.
- τ governs measurement error.
- θ is τ and c together.

Problem

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r_2: sick customer, healthy customer, hotcakes $\xrightarrow{c_3}$ 2 sick customers

$$R_3(t) \sim PP(c_3 \binom{X_1(t)}{1} \binom{X_2(t)}{1} \binom{X_3(t)}{1})$$

Assume pattern r_j occurs independently of other patterns except when the contents of the restaurant changes.

Problem

Given $\mathcal{D}_t$, find c.

Problem

Given $\mathcal{D}_t$, find c. Also, switching to ODE's is not allowed: stochastic models are biologically necessary ([2] and references therein).

Problem

Likelihood:

$$P(X(\vec{t}), \vec{t}|c) = \prod_{i=1}^{n} c_{\nu_i} \prod_{j=1}^{u} \binom{X_j(t_{i-1})}{p_{\nu_i j}} \exp\left(-c_{\nu_i} \int_0^T \binom{X_j(t)}{p_{\nu_i j}} dt\right)$$

Other work

- Approximate MJP with SDE [3, 4, 5]
- Method of moments [6, 7]
- Variational inference with mean-field approximation [8]
- Approximate Bayesian Computation (ABC) and MCMC [9, 10, 11, 12]
- EM with a sample average replacing the E-step expectation or similar [13, 14, 15, 16, 17]

Likelihood Free MCMC

To produce a chain of samples from $P(\theta|D)$, using a proposal $q(\theta^*|\theta)$, accept with probability $p_{rej}(\theta^*|\theta) \equiv \min\{1, A\}$ if

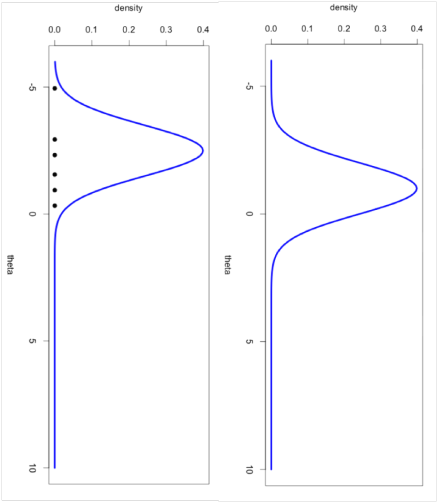
$$A = \frac{q(\theta, x|\theta^*, x^*)}{q(\theta^*, x^*|\theta, x)} \times \frac{P(\theta^*, x^*|\mathcal{D})}{P(\theta, x|\mathcal{D})}$$

Likelihood Free MCMC

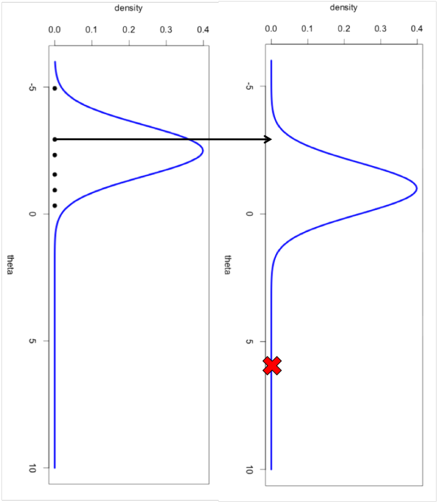
$$
\begin{aligned}
&\frac{q(\theta^*, x^*|\theta, x)}{q(\theta, x|\theta^*, x^*)} \times \frac{P(x|\theta)}{P(x^*|\theta^*)} \frac{P(\theta)}{P(\theta^*)} \frac{P(\mathcal{D}|x, \theta)}{P(\mathcal{D}|x^*, \theta^*)} \\
&= \frac{f(\theta^*|\theta)}{f(\theta|\theta^*)} \frac{P(x^*|\theta^*)}{P(x|\theta)} \times \frac{P(x|\theta)}{P(x^*|\theta^*)} \frac{P(\theta)}{P(\theta^*)} \frac{P(\mathcal{D}|x, \theta)}{P(\mathcal{D}|x^*, \theta^*)} \\
&= \frac{f(\theta^*|\theta)}{f(\theta|\theta^*)} \times \frac{P(\theta)}{P(\theta^*)} \frac{P(\mathcal{D}|x, \theta)}{P(\mathcal{D}|x^*, \theta^*)}.
\end{aligned}
$$

This approach due to Marjoram et al. (paper title: “MCMC Without Likelihoods”) [18].

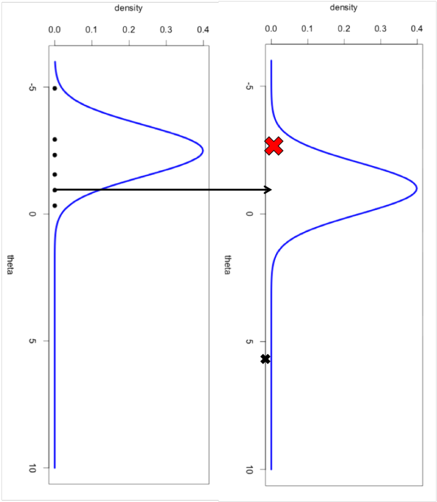
Likelihood Free Particle MCMC



Likelihood Free Particle MCMC



Likelihood Free Particle MCMC



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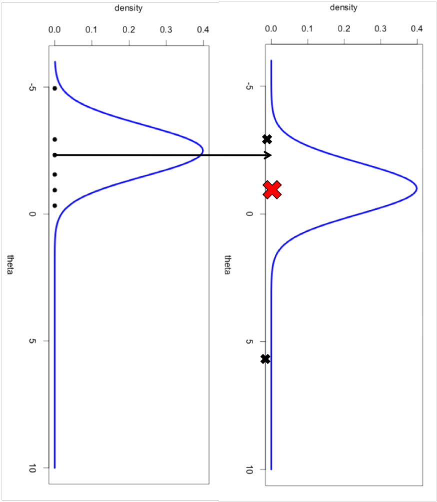

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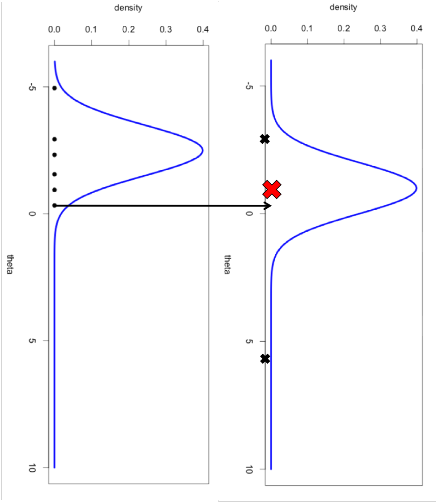

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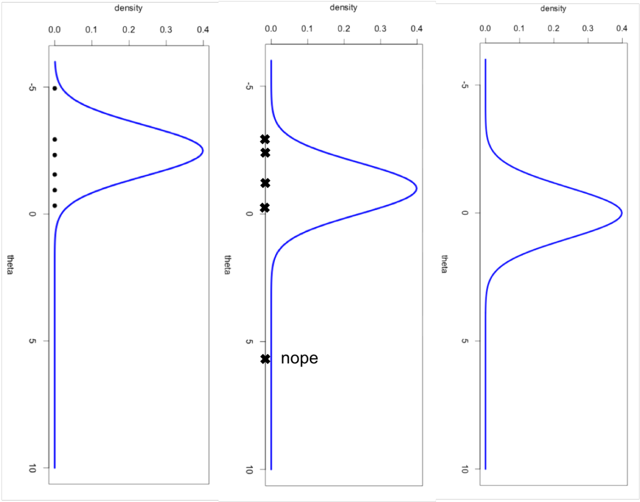
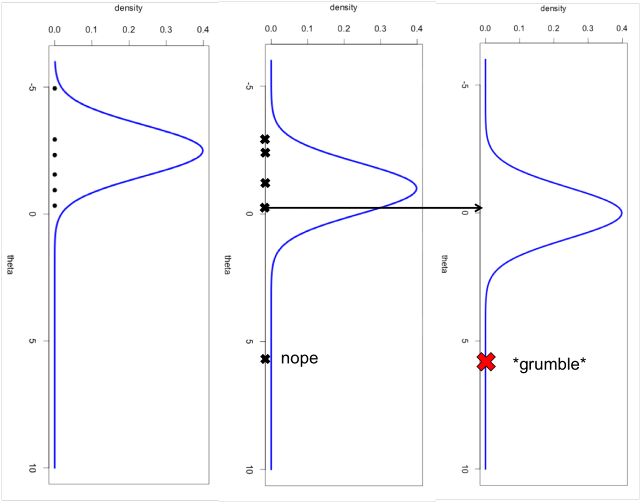


Likelihood Free Particle MCMC



Likelihood Free Particle MCMC

Likelihood Free Particle MCMC

Given a hidden continuous-time Markov process $\{x_t\}_{t=0}^T$ with:

- Unknown parameters θ and known initial state x_0
- Data points $\mathcal{D}_{t_i}$ at times t_i, $i \in \{1, ...I\}$
- A simple, tractable error model $P(\mathcal{D}_{t_i}|x_{t_i}, \theta)$
- A simulator for paths of x given θ
- An array B_0 of 1,000,000 samples from a prior on θ, x_0
- Empty arrays B_i of the same length

For each time point (for $i \in \{1, ...I\}$):

- Until B_i is full:
  - Draw $(\theta^*, x^*_{t_{i-1}})$ from B_{i-1} or a KDE of its contents
  - Using $(\theta^*, x^*_{t_{i-1}})$, simulate up to $x^*_{t_i}$, the state at time t_i
  - Set $A = \min(1, \frac{P(\mathcal{D}_{t_i}|x^*_{t_i}, \theta^*)}{P(\mathcal{D}_{t_i}|x_{t_i}, \theta)})$
  - With probability A, overwrite (θ, x_{t_i}) with $(\theta^*, x^*_{t_i})$
  - After burn-in and thinning, add (θ, x_{t_i}) to B_i

Likelihood Free Particle MCMC

$$\frac{P(x^*_{t_i}|x^*_{t_{i-1}},\theta^*,\mathcal{D}_{t_{i-1}})}{P(x_{t_i}|x_{t_{i-1}},\theta,\mathcal{D}_{t_{i-1}})}\frac{P(x^*_{t_{i-1}},\theta^*|\mathcal{D}_{t_{i-1}})}{P(x_{t_{i-1}},\theta|\mathcal{D}_{t_{i-1}})}\times$$

$$\frac{P(x_{t_i}|x_{t_{i-1}},\theta,\mathcal{D}_{t_{i-1}})}{P(x^*_{t_i}|x^*_{t_{i-1}},\theta^*,\mathcal{D}_{t_{i-1}})}\frac{P(x_{t_{i-1}},\theta|\mathcal{D}_{t_{i-1}})}{P(x^*_{t_{i-1}},\theta^*|\mathcal{D}_{t_{i-1}})}\frac{P(\mathcal{D}_{t_i}|x_{t_i},\theta)}{P(\mathcal{D}_{t_i}|x^*_{t_i},\theta^*)}$$

Likelihood Free Particle MCMC

$$\frac{P(x^*_{t_i}|x^*_{t_{i-1}}, \theta^*, \mathcal{D}_{t_{i-1}})}{P(x_{t_i}|x_{t_{i-1}}, \theta, \mathcal{D}_{t_{i-1}})} \frac{P(x^*_{t_{i-1}}, \theta^*|\mathcal{D}_{t_{i-1}})}{P(x_{t_{i-1}}, \theta|\mathcal{D}_{t_{i-1}})} \times$$

$$\frac{P(x_{t_i}|x_{t_{i-1}}, \theta, \mathcal{D}_{t_{i-1}})}{P(x^*_{t_i}|x^*_{t_{i-1}}, \theta^*, \mathcal{D}_{t_{i-1}})} \frac{P(x_{t_{i-1}}, \theta|\mathcal{D}_{t_{i-1}})}{P(x^*_{t_{i-1}}, \theta^*|\mathcal{D}_{t_{i-1}})} \frac{P(\mathcal{D}_{t_i}|x_{t_i}, \theta)}{P(\mathcal{D}_{t_i}|x^*_{t_i}, \theta^*)}$$

$$P(x_{t_i}|x_{t_{i-1}}, \theta, \mathcal{D}_{t_{i-1}})P(x_{t_{i-1}}, \theta|\mathcal{D}_{t_{i-1}})P(\mathcal{D}_{t_i}|x_{t_i}, \theta)$$

Likelihood Free Particle MCMC

$$\frac{P(x^*_{t_i}|x^*_{t_{i-1}},\theta^*,\mathcal{D}_{t_{i-1}})}{P(x_{t_i}|x_{t_{i-1}},\theta,\mathcal{D}_{t_{i-1}})}\frac{P(x^*_{t_{i-1}},\theta^*|\mathcal{D}_{t_{i-1}})}{P(x_{t_{i-1}},\theta|\mathcal{D}_{t_{i-1}})}\times$$

$$\frac{P(x_{t_i}|x_{t_{i-1}},\theta,\mathcal{D}_{t_{i-1}})}{P(x^*_{t_i}|x^*_{t_{i-1}},\theta^*,\mathcal{D}_{t_{i-1}})}\frac{P(x_{t_{i-1}},\theta|\mathcal{D}_{t_{i-1}})}{P(x^*_{t_{i-1}},\theta^*|\mathcal{D}_{t_{i-1}})}\frac{P(\mathcal{D}_{t_i}|x_{t_i},\theta)}{P(\mathcal{D}_{t_i}|x^*_{t_i},\theta^*)}$$

$$P(x_{t_i}|x_{t_{i-1}},\theta,\mathcal{D}_{t_{i-1}})P(x_{t_{i-1}},\theta|\mathcal{D}_{t_{i-1}})P(\mathcal{D}_{t_i}|x_{t_i},\theta)$$

$$= P(x_{t_i},x_{t_{i-1}},\theta|\mathcal{D}_{t_{i-1}})P(\mathcal{D}_{t_i}|x_{t_i},\theta,x_{t_{i-1}},\mathcal{D}_{t_{i-1}})$$

$$= P(x_{t_i},x_{t_{i-1}},\theta|\mathcal{D}_{t_i})P(\mathcal{D}_{t_i}|\mathcal{D}_{t_{i-1}})$$

Questions? I

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Questions? VII