Parameter inference for small biochemical systems using likelihood-free MCMC

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Paper

Darren Wilkinson's “Parameter inference for stochastic kinetic models of bacterial gene regulation,” a chapter of the proceedings in [1].

Problem

Cast of Characters

- Simulation begins at time 0 and proceeds in continuous time.
- $\mathcal{R}_j$ is a chemical reaction.
- $R_j(t) \in \mathbb{Z}_{\geq 0}$ counts occurrences of $\mathcal{R}_j$ up to time t.
- $\theta_j \in \mathbb{R}_{\geq 0}$ is the rate at which $\mathcal{R}_j$ happens. More on this in future slides.
- $X_i(t) \in \mathbb{Z}_{\geq 0}$ is the number of molecules of type i
- $\mathcal{D}_t \in \mathbb{R}$ is an incomplete observation of $X(t)$ with error.

Problem

a.png

$$R_3(t) \sim PP(\theta_3 \binom{X_1(t)}{1} \binom{X_2(t)}{1} \binom{X_3(t)}{1})$$

Assume reaction $\mathcal{R}_j$ occurs independently of other patterns except when the contents of the system 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

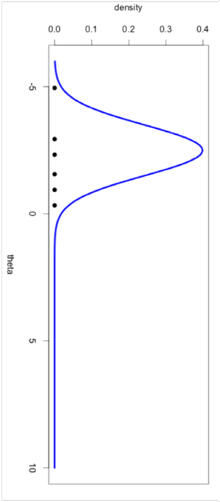
$$A = \frac{q(\theta, x|\theta^*, x^*)}{q(\theta^*, x^*|\theta, x)} \times \frac{P(\theta^*, x^*|\mathcal{D})}{P(\theta, x|\mathcal{D})}$$

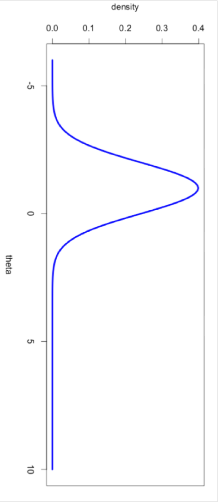
Likelihood Free MCMC

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

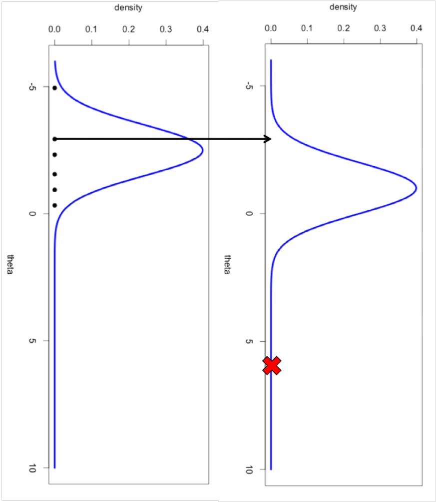
This approach due to Marjoram et al. (paper title: "MCMC Without Likelihoods") [18].

Likelihood Free Particle MCMC

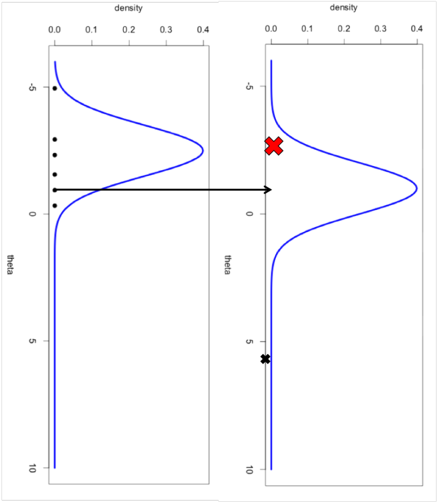




Likelihood Free Particle MCMC



Likelihood Free Particle MCMC



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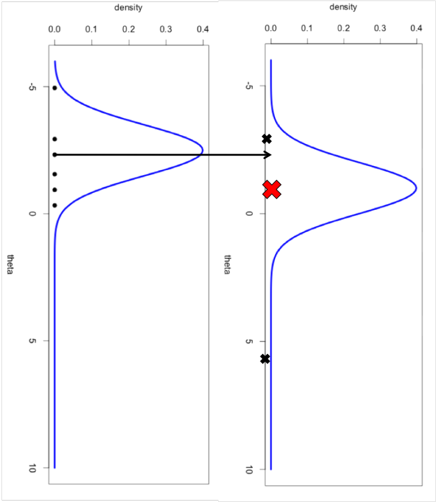

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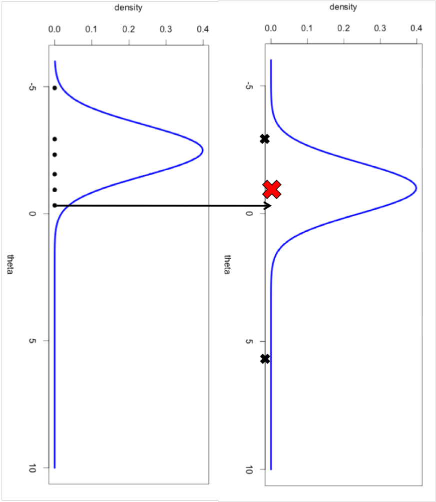

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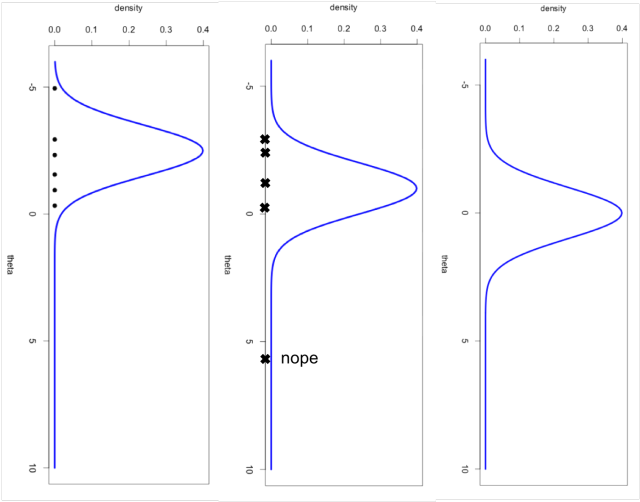

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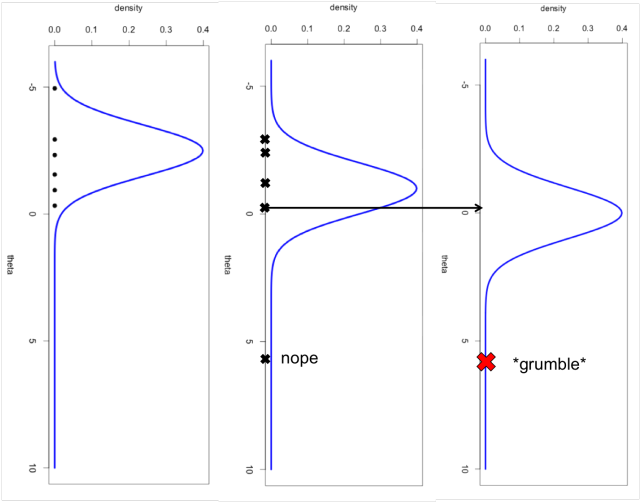

Likelihood Free Particle MCMC

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

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

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

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

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

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

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Questions? VII