
Adaptive moment closure for parameter inference of biochemical reaction networks

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Road Map

Problems

Parameter inference

Likelihood computation

Approximation choice

Solutions

MCMC algorithm

Moment closure approximation

Adaptive algorithm

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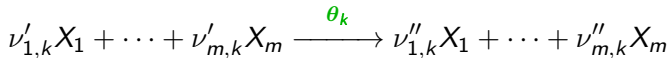
Moment closure approximation

Adaptive algorithm

Parameter inference

Given

- **Parametric model** of **chemical reaction network** with unknown rate **parameters** θ

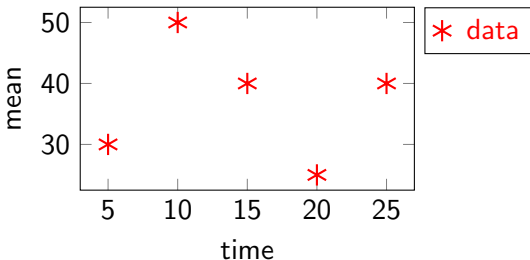


Here: **continuous-time Markov chain** (CTMC)

Model prediction $M(\theta)$ (output): **mean** and **variance**

- **Data** μ

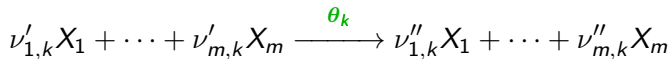
Here: **mean** and **variance** of population measurements



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Goal (Maximum likelihood estimation problem)

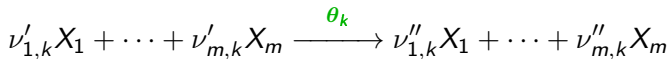
- Find **parameters** θ^* maximizing **likelihood** \mathcal{L} between **data** and **model prediction**

$$\theta^* = \arg \max_{\theta} \mathcal{L}(\mu, M(\theta))$$

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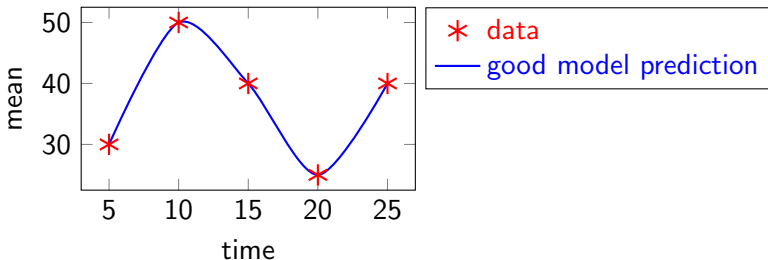


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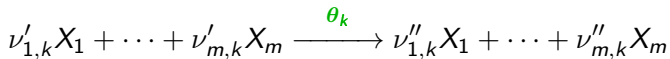
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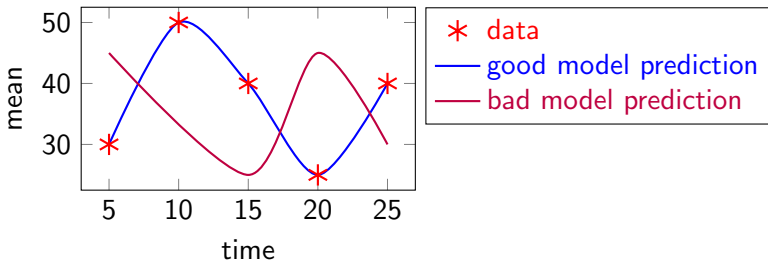


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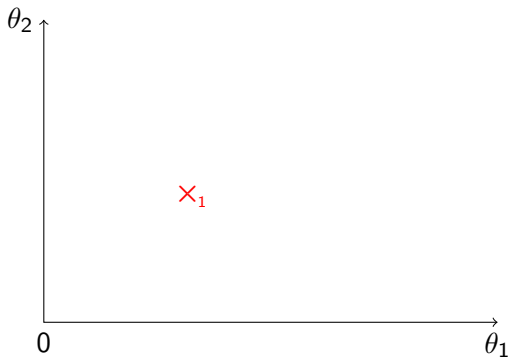
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Adaptive algorithm



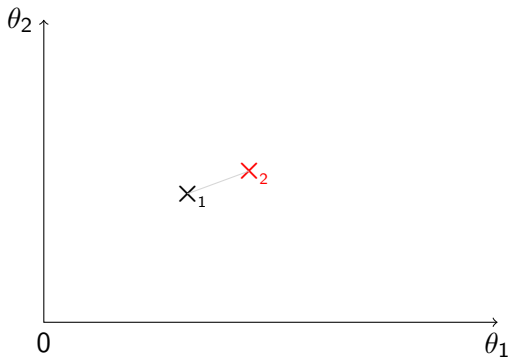
Markov chain Monte Carlo (MCMC) algorithm



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1. **Compute likelihood** for **current parameters**
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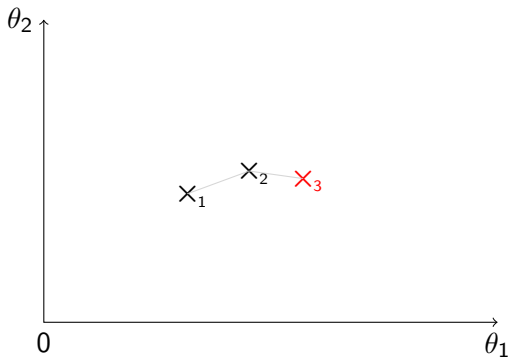
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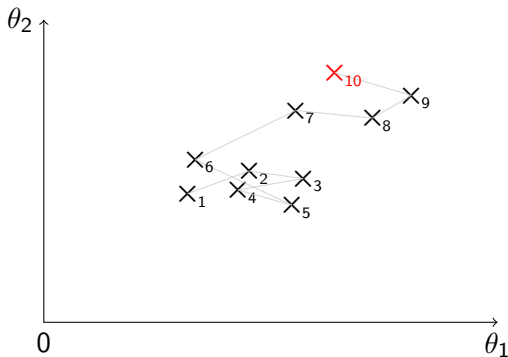
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Likelihood computation

Likelihood given via **chemical master equation** (CME):

$$\frac{\partial}{\partial t} p(x, t) = -p(x, t) \sum_{k=1}^K a_k(x, \theta) + \sum_{k=1}^K p(x - \nu_k, t) a_k(x - \nu_k, \theta)$$

But: Usually **impossible to compute directly**

Approximations

1. Apply a **stochastic simulation algorithm** (SSA)
2. Solve a system of **moment equations** (ODEs)

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Moment closure approximation (MCA)

We can derive a **system of moment equations** from the CME

$$\frac{\partial}{\partial t} \boldsymbol{\nu}(\mathbf{t}) = A(\theta) \boldsymbol{\nu}(\mathbf{t}) + B(\theta) \bar{\boldsymbol{\nu}}(\mathbf{t})$$

where $\bar{\boldsymbol{\nu}}(\mathbf{t})$ depends on moments of higher order

Apply **moment closure approximation** (MCA)

$$\frac{\partial}{\partial t} \tilde{\boldsymbol{\nu}}(\mathbf{t}) = A(\theta) \tilde{\boldsymbol{\nu}}(\mathbf{t}) + B(\theta) \varphi(\tilde{\boldsymbol{\nu}}(\mathbf{t}))$$

where $\tilde{\boldsymbol{\nu}}(\mathbf{t})$ approximates $\boldsymbol{\nu}(\mathbf{t})$

Precision of the approximation and **computational complexity** to solve the ODE system determined by the **closure order** and the **choice of function** φ

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Approximation choice

Observation 1

The **approximation precision** depends on the **model**

Consider an evaluation of three **MCAs** in three **parameter regions**

(+ = good, - = bad)

MCA	region 1	region 2	region 3
MC ₁	+	-	-
MC ₂	+	+	-
MC ₃	+	-	+

Observation 2

The **approximation precision** depends on the **parameter region**

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Adaptive algorithm for MCA choice

Iterative MCMC algorithm (recalled)

Start at **initial parameters** and repeat:

1. **Compute likelihood** for **current parameters**
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Proposed approach for step 1 (MCA choice)

Use the **most precise MCA** for some **particular parameters θ**
for **all likelihood computations** in the **parameter region** of θ

Rationale

If an MCA is the **most precise** approximation available **at some point**, it should be a **precise** approximation in the **region** around

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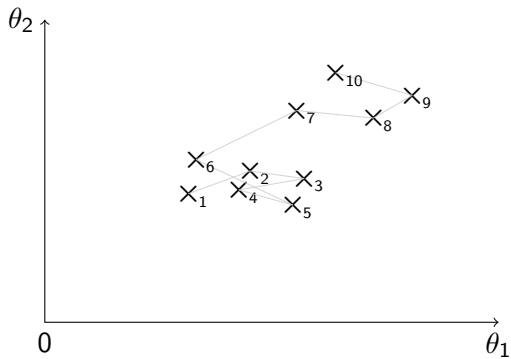
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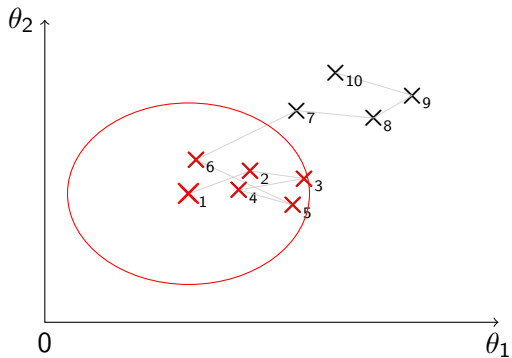
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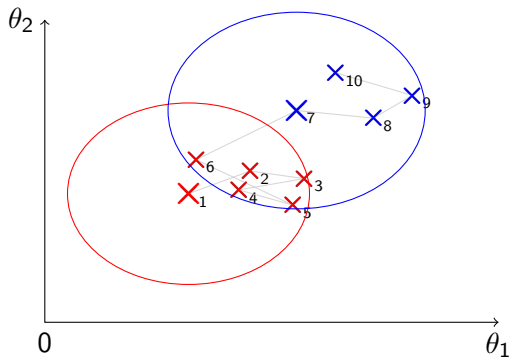
Re-evaluation during search



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Re-evaluation during search



Pseudocode

Input

parametric CTMC, data, MCAs, initial parameter choice

1. Run **simulation** (SSA) and **evaluate all MCAs**
Fix the **most precise MCA** and the **region**
2. **Compute likelihood** for current parameters
using the **current MCA**
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go to step 2 (keep **MCA**)
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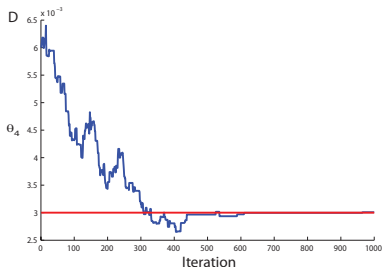
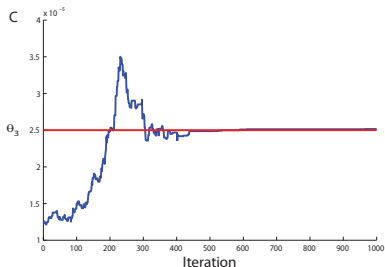
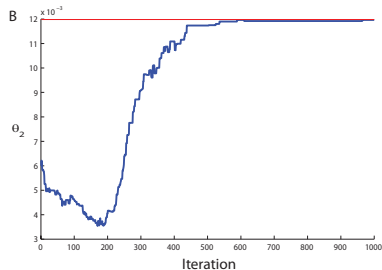
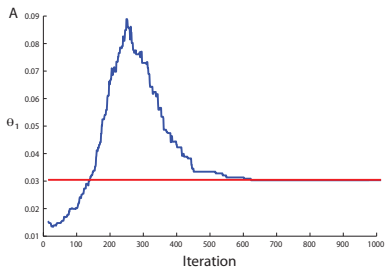
Evaluation

Model

- 4 parameters $\theta = (\theta_1, \theta_2, \theta_3, \theta_4)$
- 11 MCA choices¹
- MCMC algorithm run for 1,000 steps
 - One run for the adaptive algorithm
 - One run for each MCA fixed

¹derivative matching, zero cumulants, zero variance, low dispersion; each of order 2–4 (except low dispersion)

Adaptive algorithm run for $\theta = (\theta_1, \theta_2, \theta_3, \theta_4)$



— true parameters, — proposed parameters

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Adaptive algorithm statistics

- 23 **MCA evaluations**
- 19 times a **new MCA** was chosen
- 7 **different MCAs** were chosen in total

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approximation	relative distance to true parameters [%]				MCA use [%]
	θ_1	θ_2	θ_3	θ_4	
adaptive	0.44	0.31	0.65	0.29	
dm2	4.45	2.74	2.68	4.32	15
zc2	11.02	6.11	3.23	2.93	10
zv2	281.09	74.85	45.72	76.29	0
dm3	2.54	1.23	1.85	3.55	10
zc3	9.72	4.80	0.86	2.87	5
zv3	285.55	79.96	49.01	83.41	0
ld3	9.08	4.30	6.75	9.63	0
dm4	3.43	1.33	4.17	9.54	15
zc4	0.35	0.19	3.77	9.29	35
zv4	292.60	78.89	46.60	71.90	0
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Region criterion influence

SSA approach

fixed MCA approach

Observation

- Extreme **region criteria** result in the monolithic approaches
- **Trade-off** between **precision** and **efficiency**

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Conclusion

- **Parameter inference** problem, solved via **MCMC method**
- **Likelihood computation** problem, solved via approximation by **simulation** or **moment closure**
- **Adaptive algorithm** automatically chooses a **good approximation** for the **current parameter region**
- **Leverages** the strengths of two different approaches