Adaptive moment closure for parameter inference of biochemical reaction networks

Christian Schilling, Andreas Podelski

University of Freiburg, Germany

Sergiy Bogomolov, Jakob Ruess, Thomas A. Henzinger

IST Austria, Austria

CMSB 2015 — September 16th, 2015 — Nantes, France

Road Map

Problems

Solutions

Parameter inference

MCMC algorithm

Likelihood computation

Moment closure approximation

Approximation choice

Adaptive algorithm

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Parameter inference

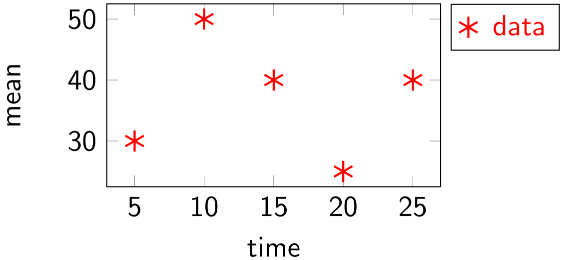
Given

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

$$\nu'_{1,k}X_1 + \cdots + \nu'_{m,k}X_m \xrightarrow{\theta_k} \nu''_{1,k}X_1 + \cdots + \nu''_{m,k}X_m$$

  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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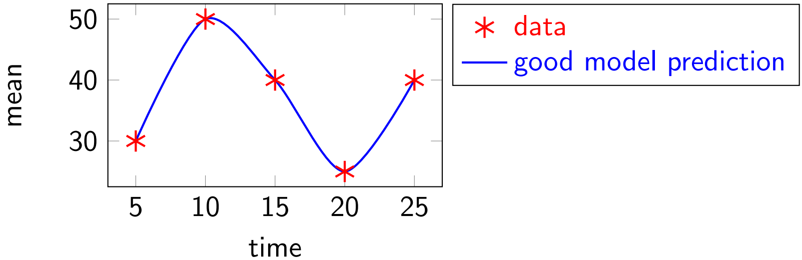

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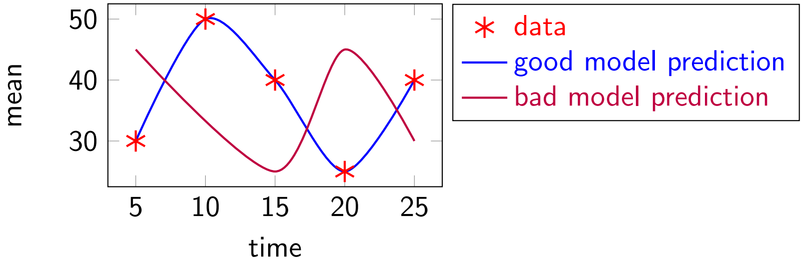

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Parameter inference → **MCMC algorithm**

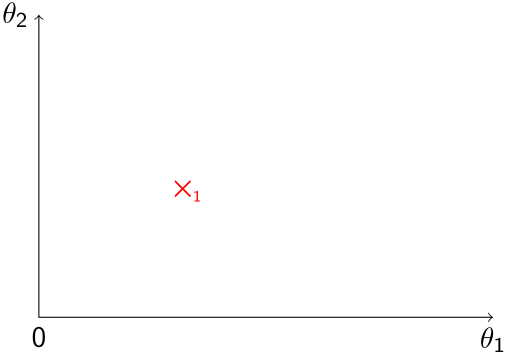
Likelihood computation

Moment closure approximation

Approximation choice

Adaptive algorithm

Markov chain Monte Carlo (MCMC) algorithm



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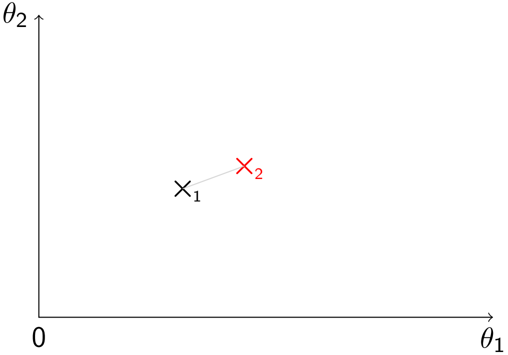

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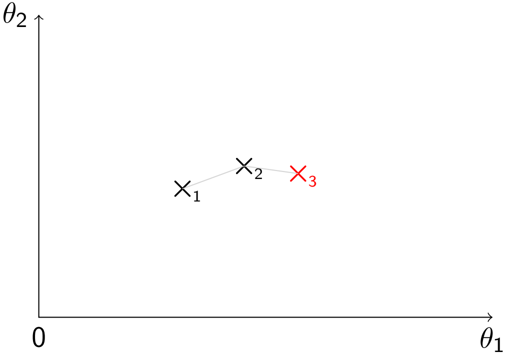

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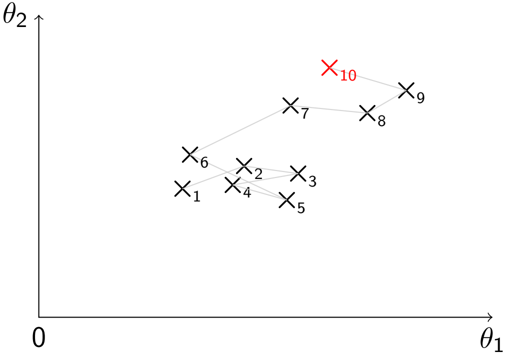

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Likelihood given via **chemical master equation** (CME):

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

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

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

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

Apply **moment closure approximation** (MCA)

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

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

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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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

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Approximation choice

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<table>
<tr><th>Problems</th><th>Solutions</th></tr>
</table>

Parameter inference

MCMC algorithm

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Adaptive algorithm for MCA choice

Iterative MCMC algorithm (recalled)

Start at **initial parameters** and repeat:

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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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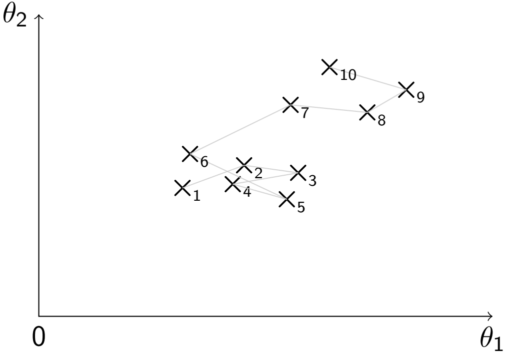

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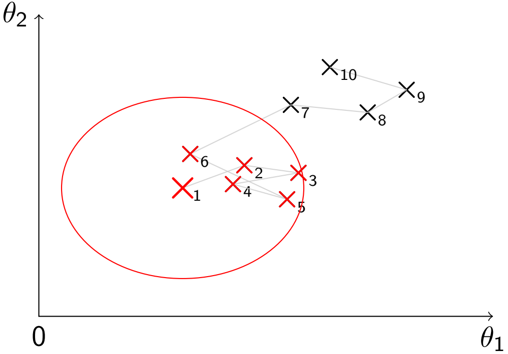

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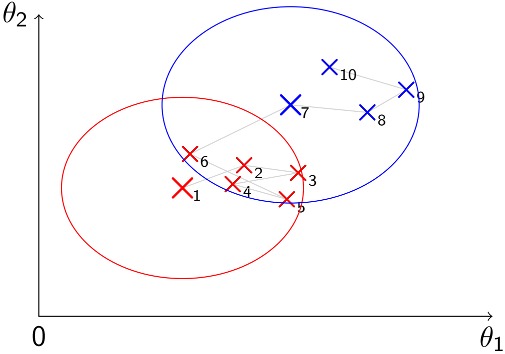

Pseudocode

Input

parametric CTMC, data, MCAs, initial parameter choice

1. Run **simulation** (SSA) and **evaluate all MCAs**
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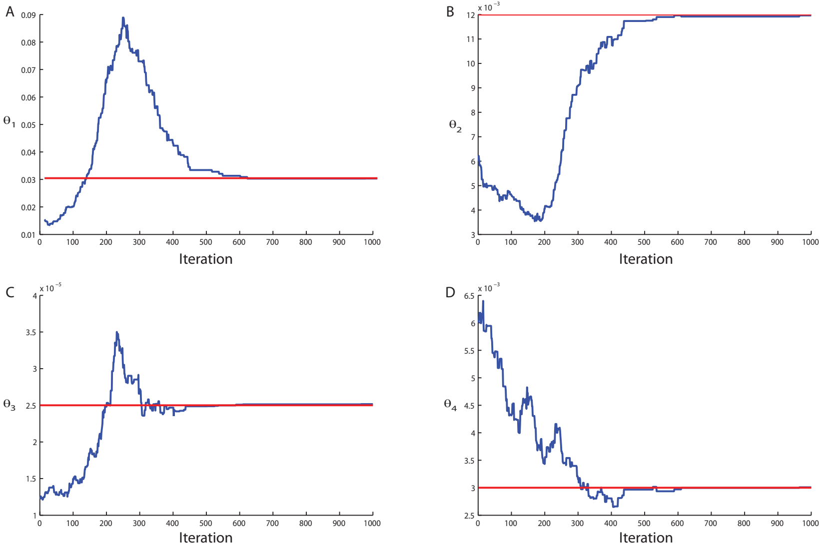
Evaluation

Model

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

[1] derivative 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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approxi-mation	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
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Region criterion influence

SSA approach

fixed MCA approach

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- **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