ETH
Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

Seminar for Applied Mathematics SAM

Tensor-structured approach to the Master Equation

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based on joint works with

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What is a Reaction Network

- system: d components $S = (S_1, \ldots, S_d)$ with copy numbers $X = (X_1, \ldots, X_d) \in \mathcal{Z} = \mathbb{N}^d_{\geq 0}$, spatially homogeneous:
  - "well stirred"
  - "thermally equilibrated"
- reaction network: R elementary reaction channels

$$\nu_{s1} S_1 + \ldots + \nu_{sd} S_d \underset{\omega_s}{\longrightarrow} \nu'_{s1} S_1 + \ldots + \nu'_{sd} S_d, \quad 1 \leq s \leq R$$

- *stoichiometric vectors:* $\eta_s = \nu'_s - \nu_s \in \mathbb{Z}^d$
- *stoichiometric subspace:* $\Sigma = \operatorname{span}\{\eta_s\}_{s=1}^{R}$

Stochastic Dynamics and Master Equation

- reaction rates ("cross section values") are given by *propensity functions* $\omega_s : \mathcal{Z} \to \mathbb{R}_{\geq 0}$, $1 \leq s \leq R$
- càdlàg process $X(t)$: for a single elementary reaction at the moment t

$$X(t) = X(t-) + \eta_s,$$

then

$$X(t) = X(0) + \sum_{s=1}^{R} \eta_s \, Z_s \left(\int_0^t \omega_s(X(\tau)) \, \mathrm{d}\tau \right),$$

where Z_s, $1 \leq s \leq R$, are independent rate-one Poisson processes

Stochastic Dynamics and Master Equation

$$X(t) = X(0) + \sum_{s=1}^{R} \eta_s \, Z_s \left(\int_0^t \omega_s(X(\tau)) \, \mathrm{d}\tau \right)$$

- transition operator $\boldsymbol{P}(t) : [0,1]^{\mathcal{Z}} \to [0,1]^{\mathcal{Z}}$

$$\boldsymbol{P}_{ij}(t) = \mathbb{P}\{X(t) = j \mid X(0) = i\} \quad \text{for} \quad i, j \in \mathcal{Z}$$

- $\{\boldsymbol{P}(t)\}_{t \geq 0}$ is a commutative semi-group
- infinitesimal generator $\boldsymbol{Q} : [0,1]^{\mathcal{Z}} \to \mathbb{R}^{\mathcal{Z}}$:

$$\boldsymbol{Q}_{ij} = \lim_{t \downarrow 0} \frac{\boldsymbol{P}_{ij}(t) - \delta_{ij}}{t}, \quad \text{where} \quad i, j \in \mathcal{Z}$$

- for the CME we have [Ethier and Kurtz, 2005] :

$$(\boldsymbol{Q}\boldsymbol{q})_i = \sum_{s=1}^{R} \left(\omega_s(i) \; \boldsymbol{q}_{i+\eta_s} - \omega_s(i) \; \boldsymbol{q}_i \right), \quad i \in \mathcal{Z}$$

Stochastic Dynamics and Master Equation

- assume $\boldsymbol{p}^0 \in \mathcal{Z}$:

$$\boldsymbol{p}^0{}_i = \mathbb{P}\{X(0) = i\}$$

- for $t \geq 0$ consider $\boldsymbol{p}(t) \in \mathcal{Z}$:

$$\boldsymbol{p}_i(t) = \mathbb{P}\{X(t) = i\}$$

- forward Kolmogorov equation:

$$\begin{cases} \dot{\boldsymbol{p}} &= \boldsymbol{A}\boldsymbol{p}, \\ \boldsymbol{p}(0) &= \boldsymbol{p}^0, \end{cases}$$

where

$$\boldsymbol{A} = \boldsymbol{Q}^* = \sum_{s=1}^{R} (\boldsymbol{S}_{\eta_s} - \mathbb{I}) \cdot \operatorname{diag} \boldsymbol{\omega}_s$$

Stochastic Dynamics and Master Equation

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Stochastic Dynamics and Master Equation

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depending on the propensity functions, describes:

- chemical systems,
- biological, systems $\rightarrow$ "*systems biology*",
- population models,
- distributed systems and queueing networks.

Stochastic Dynamics and Master Equation

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✓autonomous ODEs, analytic solutions

♠ spatial supports of the solutions may be unfeasibly LARGE ("curse of dimensionality")

♠ transients may require careful treatment

Kinetics models

We consider

$$\omega_s(i) = \kappa_s \frac{\theta(i)}{\theta(i-\nu_k)} \prod_{k=1}^{d} \mathbf{1}_{\mathcal{X}_{sk}}(i_k), \quad i \in \mathcal{Z},$$

- $\kappa_s > 0$ is the *rate* of the sth reactions
- $\mathcal{X}_{sk} = \mathbb{Z}_{\geq \nu_{sk}}$ for $1 \leq k \leq d$

Kinetics models

Further, we assume

$$\theta(i) = \prod_{k=1}^{d} \prod_{j_k=1}^{i_k} \theta_k(j_k), \quad i \in \mathcal{Z},$$

- θ_k represents the interaction rate of the kth species

Then

$$\omega_s(i) = \kappa_s \prod_{k=1}^{d} 1_{\mathcal{X}_{sk}}(i_k) \cdot \omega_{sk}(i_k), \quad i \in \mathcal{Z},$$

where, for $1 \le s \le R$ and $1 \le k \le d$,

$$\omega_{sk}(i_k) = \prod_{j_k=0}^{\nu_{sk}-1} \theta_k(i_k - j_k), \quad i_k \in \mathbb{Z}_{\ge 0}.$$

Kinetics models

Mass-action kinetics

$$\theta_k(i_k) = i_k, \quad i_k \in \mathbb{Z}_{\geq 0},$$

$$\omega_{sk}(i_k) = \nu_{sk}! \binom{i_k}{\nu_{sk}} = \frac{i_k!}{(i_k - \nu_{sk})!}, \quad i_k \in \mathbb{Z}_{\geq 0}.$$

Michaelis–Menten kinetics

$$\theta_k(i_k) = \frac{\vartheta_k i_k}{\upsilon_k + i_k}, \quad i_k \in \mathbb{Z}_{\geq 0},$$

with a constant $\vartheta_k > 0$ and an integer constant $\upsilon_k \geq 0$

$$\omega_{sk}(i_k) = \vartheta_k^{\nu_{sk}} \prod_{j_k=0}^{\nu_{sk}-1} \frac{i_k - j_k}{\upsilon_k + i_k - j_k}, \quad i_k \in \mathbb{Z}_{\geq 0}.$$

Recent advances in solving CME I

- van Kampen's Linear Noise Approximation (LNA)
  [van Kampen, 1992]
- Moment Closure methods
  [Hespanha and Singh, 2005, Gomez-Uribe and Verghese, 2007]
- Chemical Langevin Equation (CLE) approximation
  [Gillespie, 2000, Ethier and Kurtz, 2005]
- closed-form solutions [Jahnke and Huisinga, 2007]
- Finite State Projection [Munsky and Khammash, 2006] and the sliding window abstraction [Henzinger et al., 2009]
- adaptive bases, aggregation [Engblom, 2009, Deuflhard et al., 2008, Hegland et al., 2007, Jahnke and Udrescu, 2010]

Recent advances in solving CME II

- Krylov subspace sparse exponential integrators

  [MacNamara et al., 2008]
- tensor methods: CP

  [Jahnke and Huisinga, 2008, Hegland and Garcke, 2011]
- tensor methods: TT, QTT

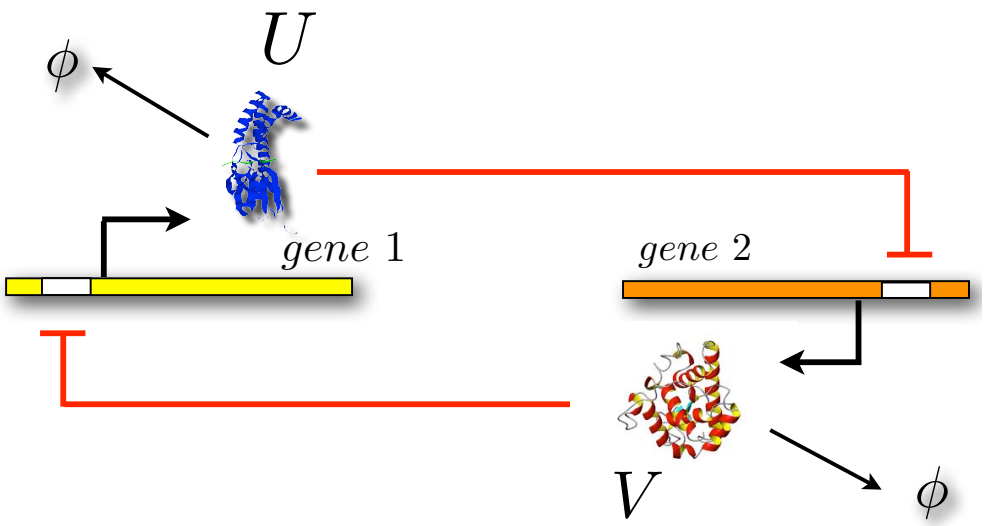
  [Dolgov and Khoromskij, 2012, KKNS, 2013, K. and Schwab, 2013]

  adaptive extraction of “principal”, “effective” components: **economical** and **robust**

Chemical Master Equation: Example

synthetic gene-regulatory circuit [Gardner et al., 2000]

$$\varnothing \xrightarrow{\frac{\alpha_1}{1+V^\beta}} \mathrm{U}, \quad \varnothing \xrightarrow{\frac{\alpha_2}{1+U^\gamma}} \mathrm{V},$$
$$\mathrm{U} \xrightarrow{\delta_1} \varnothing, \qquad \mathrm{V} \xrightarrow{\delta_2} \varnothing.$$

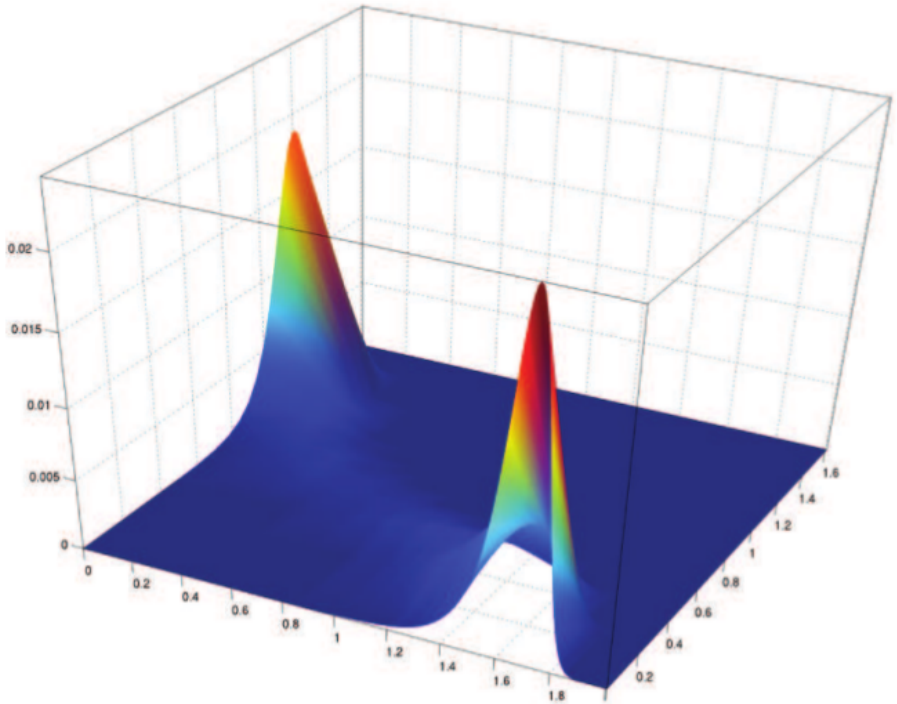


[KKNS, 2013]

Chemical Master Equation: Example

synthetic gene-regulatory circuit [Gardner et al., 2000]

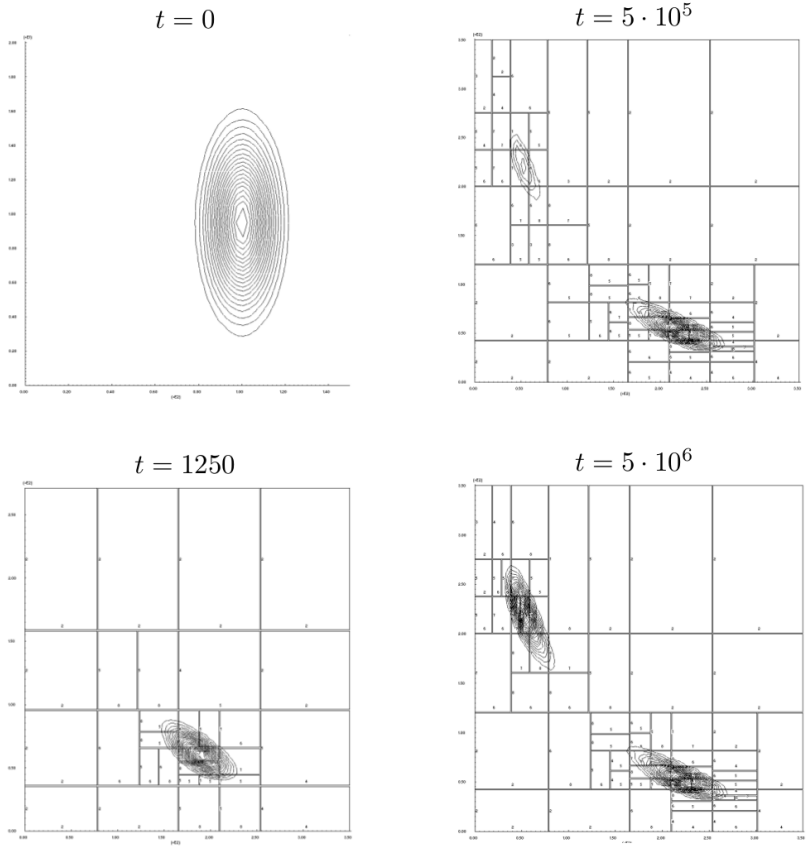
bimodal solutions



[Iglesias et al., 2007]

Chemical Master Equation: Example

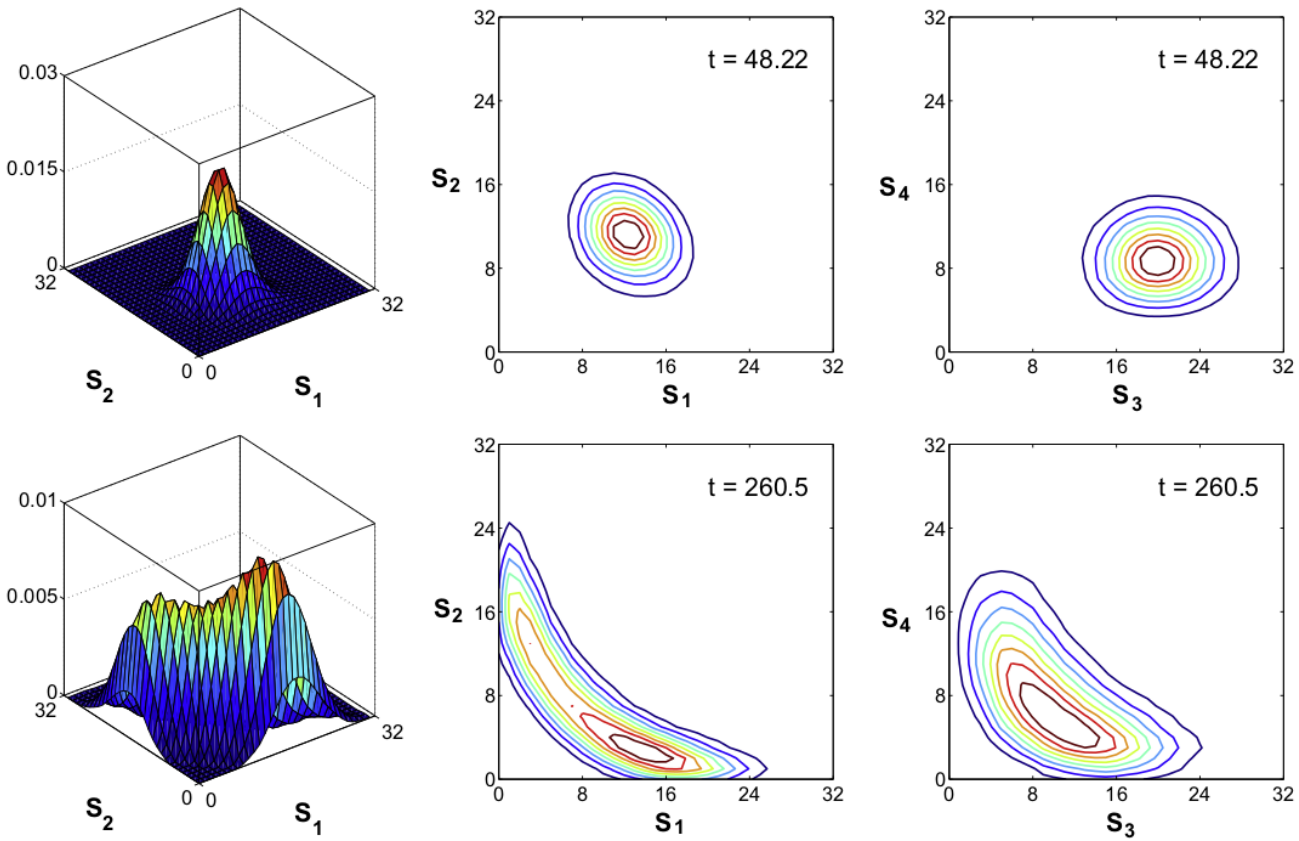
synthetic gene-regulatory circuit [Gardner et al., 2000]



adaptive approach, [Deuflhard et al., 2008]

Chemical Master Equation: Example

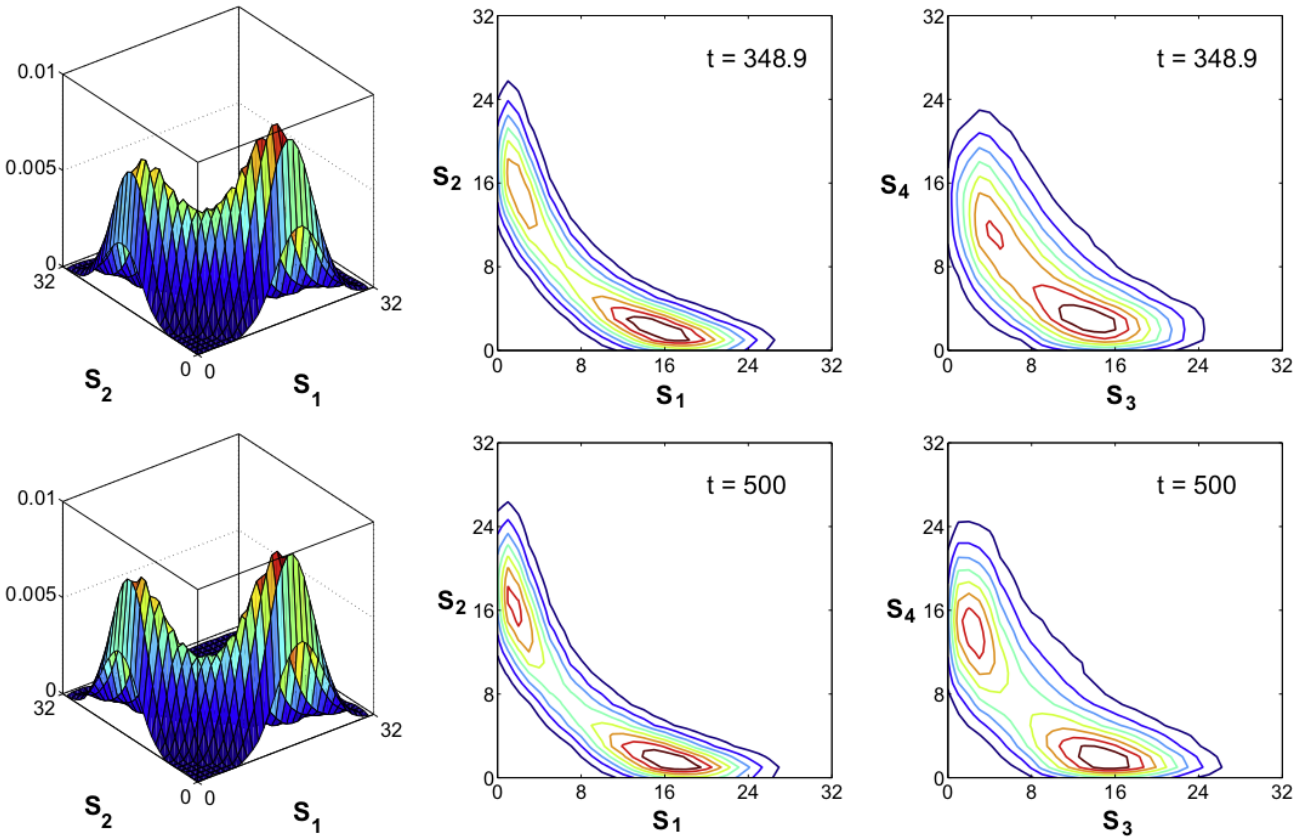
synthetic gene-regulatory circuit [Gardner et al., 2000]



4D toggle switch [Jahnke and Udrescu, 2010]

Chemical Master Equation: Example

synthetic gene-regulatory circuit [Gardner et al., 2000]



4D toggle switch [Jahnke and Udrescu, 2010]

Tensor Train representation

[Oseledets and Tyrtyshnikov, 2009a, Oseledets, 2009b, Oseledets and Tyrtyshnikov, 2009b, Oseledets, 2011]

- $\boldsymbol{x}$ is a d-dimensional $n_1 \times \ldots \times n_d$-vector;
- the *TT decomposition* of $\boldsymbol{x}$ through the *cores* $U_1, U_2, \ldots, U_d$ with *ranks* $r_1, \ldots, r_{d-1}$:

$$\boldsymbol{x}_{j_1,\ldots,j_d} = \sum_{\alpha_1=1}^{r_1} \ldots \sum_{\alpha_{d-1}=1}^{r_{d-1}} U_1(j_1, \alpha_1) \cdot U_2(\alpha_1, j_2, \alpha_2) \cdot \ldots \cdot U_{d-1}(\alpha_{d-2}, j_{d-1}, \alpha_{d-1}) \cdot U_d(\alpha_{d-1}, j_d)$$

- $U_1, U_2, \ldots, U_d$ are 2- and 3-dimensional arrays

Tensor Train representation

$$\boldsymbol{x}_{j_1,\ldots,j_d} = \sum_{\alpha_1=1}^{r_1} \cdots \sum_{\alpha_{d-1}=1}^{r_{d-1}} U_1(j_1,\alpha_1)\cdot U_2(\alpha_1,j_2,\alpha_2)\cdot\ldots$$
$$\cdot U_{d-1}(\alpha_{d-2},j_{d-1},\alpha_{d-1})\cdot U_d(\alpha_{d-1},j_d)$$

- for $k=1,\ldots,d-1$ implies a rank-r_k representation of the *unfolding matrix* $\boldsymbol{X}^{(k)}$:

$$\boldsymbol{X}^{(k)}_{\overline{j_1,\ldots,j_k};\,\overline{j_{k+1},\ldots,j_d}} = \boldsymbol{x}_{j_1,\ldots,j_k,j_{k+1},\ldots,j_d}$$

- TT ranks $=$ ranks of the unfolding matrices,

  see Theorem 2.1 in either of

  [Oseledets and Tyrtyshnikov, 2010, Oseledets, 2011]

Tensor Train representation

$\Longrightarrow$ a robust and efficient algorithm for the low-rank TT approximation of vectors,

[Oseledets and Tyrtyshnikov, 2010] or [Oseledets, 2011]

$\ldots$ if $\operatorname{rank}_{\|\cdot\|_{\mathrm{F}},\varepsilon_k} \boldsymbol{X}^{(k)} = r_k$ for $k = 1, \ldots, d-1$, then $\boldsymbol{x}$ has a TT ε-approximation of ranks $r_1, \ldots, r_{d-1}$ with $\varepsilon = \sqrt{\sum_{k=1}^{d-1} \varepsilon_k^2}$.

- the storage cost and complexity are formally linear in d:

$$d \cdot n \cdot \mathtt{poly}\left(r_1, \ldots, r_{d-1}\right),$$

where $n \geq n_1, \ldots, n_d$

WHAT ARE THE RANKS?

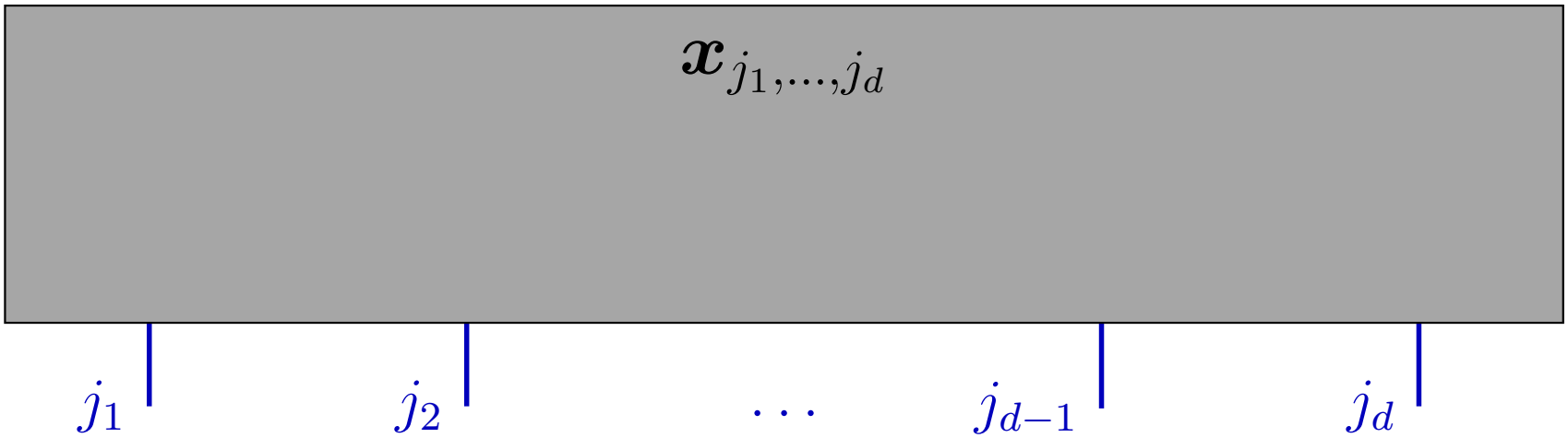
Tensor Train representation

- analogously for matrices and higher-order tensors:

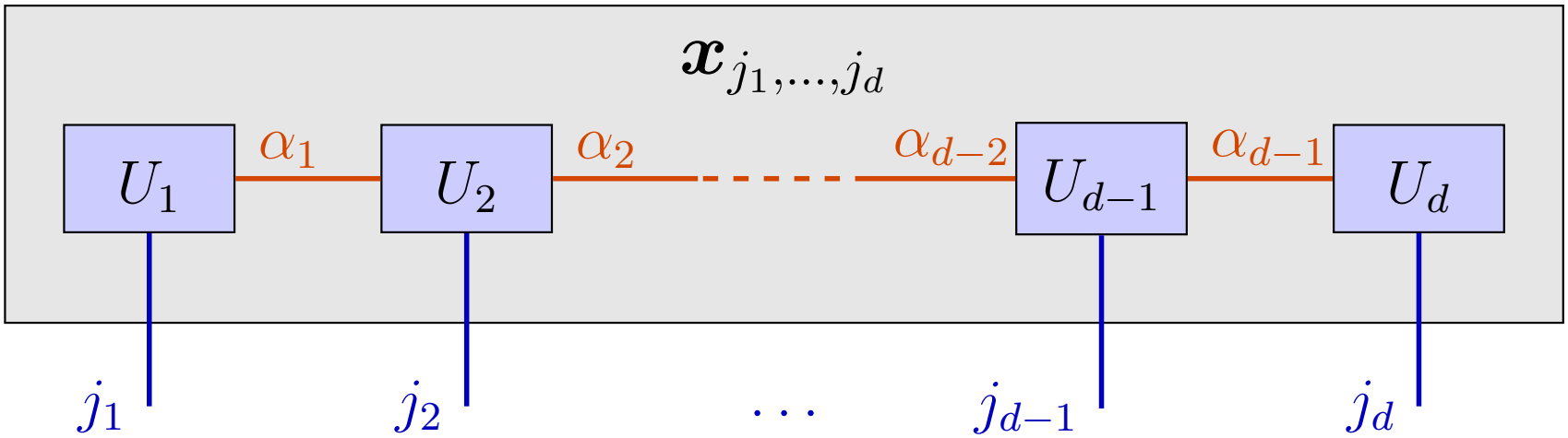
$$\boldsymbol{A}_{\substack{i_1,\ldots,i_d \\ j_1,\ldots,j_d}} = \sum_{\alpha_1=1}^{r_1} \cdots \sum_{\alpha_{d-1}=1}^{r_{d-1}} V_1(i_1, j_1, \alpha_1) \cdot V_2(\alpha_1, i_2, j_2, \alpha_2) \cdot \ldots$$
$$\cdot V_{d-1}(\alpha_{d-2}, i_{d-1}, j_{d-1}, \alpha_{d-1}) \cdot V_d(\alpha_{d-1}, i_d, j_d)$$

$\rightarrow$ vectorize $\boldsymbol{A}$
$\rightarrow$ permute the indices
$\rightarrow$ TT
$\rightarrow$ reshape $V_1, \ldots, V_d$

Tensor Train representation



Tensor Train representation



Tensor Train representation

- Tensor Train = *Matrix Product States (MPS)*

  [White, 1992, White, 1993, Verstraete et al., 2004]
- *Hierarchical Tensor Representation* is closely related

  [Hackbusch and Kühn, 2009, Grasedyck, 2010a, Ballani and Grasedyck, 2012, Kressner and Tobler, 2010, Kressner and Tobler, 2011]

✓A textbook and an up-to-date survey of publications on low-rank tensor methods are available

[Hackbusch, 2012, Grasedyck et al., 2013]

Quantized Tensor Train representation

[Oseledets, 2009a, Khoromskij, 2011, Oseledets, 2010a]

- assume $n_k = n_{k1} \cdot n_{k2} \cdot \ldots \cdot n_{kl_k} \qquad (n_{k1}, \ldots, n_{kl_k} \geq 2)$
- "quantize" the kth "physical" dimension:

$$j_k = \overline{j_{k1}, \ldots, j_{kl_k}} \rightarrow (j_{k1}, \ldots, j_{kl_k}),$$

where $1 \leq j_{km_k} \leq n_{km_k}$ for $m_k = 1, \ldots, l_k$.

$$\Longrightarrow \quad j_1 = \overline{j_{11}, \ldots, j_{1l_1}}, \ldots, j_d = \overline{j_{d1}, \ldots, j_{dl_d}}$$

$$\downarrow$$

$$\underbrace{j_{11}, \ldots, j_{1l_1}}_{\text{1st dimension}}, \ldots\ldots, \underbrace{j_{d1}, \ldots, j_{dl_d}}_{\text{dth dimension}}$$

- d "physical" dimensions
  $\rightarrow l_1 + \ldots + l_d$ "virtual" dimensions
- vector: $n_1 \times \ldots \times n_d$
  $\rightarrow n_{11} \times \ldots \times n_{1l_1} \times \ldots\ldots \times n_{d1} \times \ldots \times n_{dl_d}$

Quantized Tensor Train representation

$$\underbrace{j_{1,1},\ldots,j_{1,l_1}}_{\text{1st dimension}},\underbrace{j_{2,1},\ldots,j_{2,l_2}}_{\text{2nd dimension}},\ldots\ldots,\underbrace{j_{d,1},\ldots,j_{d,l_d}}_{\text{dth dimension}}$$

TT decomposition $\rightarrow$ QTT decomposition

TT cores $\rightarrow$ QTT cores

TT ranks $\rightarrow$ QTT ranks

$$\underbrace{r_{1,1},\ldots,r_{1,l_1-1}}_{\text{1st dimension}},\mathbf{r_1},\underbrace{r_{2,1},\ldots,r_{2,l_2-1}}_{\text{2nd dimension}},\mathbf{r_2},\ldots\ldots,\mathbf{r_{d-1}},\underbrace{r_{d,1},\ldots,r_{d,l_d-1}}_{\text{dth dimension}}$$

the TT ranks of the original tensor are in boldface

- **logarithmic** storage cost and complexity:

$$d\cdot l\cdot \mathtt{poly}\left(r_{1,1},\ldots,r_{1,l_1-1},\mathbf{r_1},\ldots\ldots,\mathbf{r_{d-1}},r_{d,1},\ldots,r_{d,l_d-1}\right)$$

if $l \geq l_1,\ldots,l_d$

$\boldsymbol{A}$ under the Finite State Projection

Finite State Projection set

$$\mathcal{Z}_n = \{i \in \mathcal{Z} : 0 \le i_k < n_k \quad \text{for} \quad 1 \le k \le d\} \subset \mathcal{Z}$$

instead of $\mathcal{Z} = \mathbb{N}^d_{\ge 0}$. Approximation:

$$\{\boldsymbol{\omega}_k^s\} \approx \{\tilde{\boldsymbol{\omega}}_k^s\} \Rightarrow^{?} \boldsymbol{A} \approx \tilde{\boldsymbol{A}}$$

$\{\tilde{\boldsymbol{\omega}}_k^s\}$ are of low rank $\Rightarrow^{?}$ $\tilde{\boldsymbol{A}}$ is of low rank

- [Dolgov and Khoromskij, 2012] gives the TT structure of $\boldsymbol{A}$ in the case of a signaling cascade with monomial propensities
- [KKNS, 2013, K. and Schwab, 2013] analyze the general QTT structure of $\boldsymbol{A}$ for the mass-action and Michaelis–Menten kinetics

Approximation of $\boldsymbol{A}$

Theorem (Th. 17 in [K. and Schwab, 2013])

For all $s = 1, \dots, R$ *and* $k = 1, \dots, d$, *assume that* $\|\tilde{\boldsymbol{\omega}}_k^s - \boldsymbol{\omega}_k^s\|_{\ell_2} \leq \frac{\delta}{d\sqrt{R}} \|\boldsymbol{\omega}_k^s\|_{\ell_2}$, *where* $\tilde{\boldsymbol{\omega}}_{sk}$ *has a QTT representation of ranks bounded by* r_{sk}.

Then $\left\|\tilde{\boldsymbol{A}} - \boldsymbol{A}\right\|_{\mathrm{F}} \leq \delta \|\boldsymbol{A}\|_{\mathrm{F}}$ *and* $\tilde{\boldsymbol{A}}$ *has a QTT decomposition of ranks*

$$q_1, \dots, q_1, \hat{q}_1, q_2, \dots, q_2, \hat{q}_2, \dots, \dots, \hat{q}_{d-1}, q_d, \dots, q_d$$

with $\hat{q}_k = R$ *for* $1 \leq k \leq d-1$ *and*

$$q_k = \sum_{\substack{s=1,\dots,R: \\ \nu_{sk}=\nu'_{sk}=0}} 2 \quad + \sum_{\substack{s=1,\dots,R: \\ \nu_{sk}+\nu'_{sk}\neq 0}} 3\, r_{sk}$$

for $1 \leq m_k \leq l_k - 1$ *and* $1 \leq k \leq d$.

In particular, $\nu_{sk} = \nu'_{sk} = 0$ implies $r_{sk} = 1$.

Approximation of A

The number of parameters to store A:

- full format: $\mathcal{O}\left(2^{2dl}\right)$
- sparse format: $\mathcal{O}\left(2^{dl}R\right)$
- QTT approximation: $\mathcal{O}\left(d\,l R^2 r^2\right)$, where $r_{sk} \leq r$ and $l_k \leq l$ for all s, k

Example (polynomial propensities)

ω_k^s is a polynomial of small degree p_k^s, then $r_k^s = 2\left(p_k^s + 1\right)$ uniformly in l_k, see [Grasedyck, 2010b] or [Oseledets, 2013] .
For a fixed R, we achieve a logarithmic reduction

Approximation of propensity factors

Lemma (Lm. 18 in [K. and Schwab, 2013])

Let $l \in \mathbb{N}$, $\nu \in \mathbb{Z} : \ 1 \leq \nu < 2^l - 1$.
Then the 2^l*-component vector* $\boldsymbol{u}$ *with the entries*

$$\boldsymbol{u}_i = \begin{cases} 0, & 0 \leq i < \nu \\ \frac{i!}{(i-\nu)!}, & \nu \leq i \leq 2^l - 1, \end{cases}$$

can be represented in the QTT format with ranks bounded by $2(\nu + 1)$.

Approximation of propensity factors

Lemma (Lm. 19 in [K. and Schwab, 2013])

Let $\upsilon, \nu \in \mathbb{N}$. Assume that $\tau, \mu \in \mathbb{R}$ are such that $\tau \geq 1$ and $\mu > 1$. Consider the function $g : [\nu - 1 + \tau, \nu - 1 + \mu\tau] \to \mathbb{R}$ given by

$$g(x) = \prod_{j=0}^{\nu-1} \frac{x-j}{\upsilon + x - j} \quad \text{for} \quad x \in [\nu - 1 + \tau, \nu - 1 + \mu\tau] .$$

Then for every $p \in \mathbb{N}$ there exists a polynomial $\mathcal{P}$ of degree p such that

$$\|\mathcal{P} - \lambda\|_{\mathcal{C}[\nu-1+\tau,\nu-1+\mu\tau]} \leq C\rho^{-p},$$

where $\rho = \frac{\mu+\sqrt{2\mu-1}}{\mu-1}$ and $C = 2\frac{1}{\rho-1} = 2\frac{\mu-1}{\sqrt{2\mu-1}+1}$.

QTT ranks of A

Michaelis–Menten kinetics

$$r_{sk} = \mathcal{O}\left(\log \frac{1}{\varepsilon_{sk}} \cdot \log n_k\right) + \mathcal{O}\left(\log^2 n_k\right),$$

To achieve a relative accuracy δ, we set

$$\varepsilon_{sk} = \frac{\delta}{2d\sqrt{R}} \|\boldsymbol{\omega}_{sk}\|,$$

then

$$r = \mathcal{O}\left(\left(\log \frac{1}{\delta} + \log d + \log R + \log n\right) \log n\right),$$

$$3Rr = \mathcal{O}\left(R\left(\log \frac{1}{\delta} + \log d + \log R + \log n\right) \log n\right)$$

bounds the QTT ranks of $\boldsymbol{A}$

QTT ranks of $\boldsymbol{A}$

Mass-action kinetics

If the kth species reacts under the mass-action kinetics,

$$3Rr = 6R\,(\nu + 1)$$

bounds the corresponding $l_k - 1$ QTT ranks of $\boldsymbol{A}$

$\nu \geq \nu_{sk}$, $1 \leq s \leq R$

Mixed kinetics

$\rightarrow$ the maximum of the two

hp-DG discretization

Let $\mathcal{M} = \{J_m\}_{m=1}^{M}$ be a partition of $J = (0, T)$ into subintervals $J_m = (t_{m-1}, t_m)$, $1 \le m \le M$, and $\underline{\rho} \in \mathbb{N}_{\ge 0}^{M}$.

$$\mathcal{P}^{\underline{\rho}}(\mathcal{M}, X) = \{\boldsymbol{p} : J \to X : \ \boldsymbol{p}|_{J_m} \in \mathcal{P}^{\rho_m}(J_m, X),\ 1 \le m \le M\}$$

The Discontinuous Galerkin FEM formulation: find $\boldsymbol{p} \in \mathcal{P}^{\underline{\rho}}(\mathcal{M}, X)$ such that

$$\sum_{m=1}^{M} \int_{J_m} \langle \dot{\boldsymbol{p}} - \boldsymbol{A}\boldsymbol{p},\ \boldsymbol{q} \rangle \, \mathrm{d}t + \sum_{m=1}^{M} \left\langle \boldsymbol{p}_{m-1}^{+} - \boldsymbol{p}_{m-1}^{-},\ \boldsymbol{q}_{m-1}^{+} \right\rangle = 0$$

for all $\boldsymbol{q} \in \mathcal{P}^{\underline{\rho}}(\mathcal{M}, X)$, where $\boldsymbol{p}_0^{-} = \boldsymbol{p}_0$,

$$\boldsymbol{p}_m^{+} = \lim_{t \downarrow t_m} \boldsymbol{p}(t), \quad \boldsymbol{p}_m^{-} = \lim_{t \uparrow t_m} \boldsymbol{p}(t).$$

... as a time stepping method

If $\boldsymbol{p}|_{J_m} \in \mathcal{P}^{\rho_m}(J_m, X)$ are known for $1 \leq m \leq \widehat{m} - 1$, then $\boldsymbol{p}|_{J_{\widehat{m}}} \in \mathcal{P}^{\rho_{\widehat{m}}}(J_{\widehat{m}}, X)$ can be found as the solution to

$$\int_{J_{\widehat{m}}} \langle \dot{\boldsymbol{p}} - \boldsymbol{A}\boldsymbol{p}, \boldsymbol{q} \rangle \, \mathrm{d}t + \left\langle \boldsymbol{p}^+_{\widehat{m}-1} - \boldsymbol{p}^-_{\widehat{m}-1}, \boldsymbol{q}^+_{\widehat{m}-1} \right\rangle = 0$$

for all $\boldsymbol{q} \in \mathcal{P}^{\rho_{\widehat{m}}}(J_{\widehat{m}}, X)$.

Time step systems

$$(\boldsymbol{C}_m \otimes \mathbb{I} - \boldsymbol{G}_m \otimes \boldsymbol{A}) \cdot \boldsymbol{P}_m = \boldsymbol{\phi}_{m-1} \otimes \boldsymbol{p}^-_{m-1} ,$$

Properties [Schötzau and Schwab, 2000] :

- Once the partition is fine enough, the DG formulation is uniquely solvable.
- Exponential convergence: a prescribed level of accuracy ε can be reached with $\rho M = \mathcal{O}\left(\log \varepsilon^{-1}\right)$ temporal degrees of freedom.

Theorem

Assume that $\boldsymbol{A}$ is represented in the QTT or QT3 format in terms of $\tilde{d}$ cores with ranks $r_1, \ldots, r_{\tilde{d}-1}$. Then the matrix of the DG system can be represented in the corresponding format in terms of $\tilde{d}+1$ cores with ranks $2, r_1+1, \ldots, r_{\tilde{d}-1}+1$.

Summary & Implementation

hp-DG-QTT algorithm proposed in [K., Reichmann and Schwab, 2012] , implemented in MATLAB:

- implicit, exponentially convergent spectral time discretization of discontinuous Galerkin type
- TT-structured arithmetics and linear system solution rely on the **TT Toolbox**

hp-DG-QTT solver + MATLAB 7.12.0.635 (R2011a) + a laptop 2.7 GHz dual-core CPU, 4 GB RAM

vs.

SPSens beta 3.4 [Sheppard et al., 2013] + up to 1500 cores of BRUTUS,

Birth-death processes I

d independent birth-death processes: $X_1, \ldots, X_k$ are mutually independent,

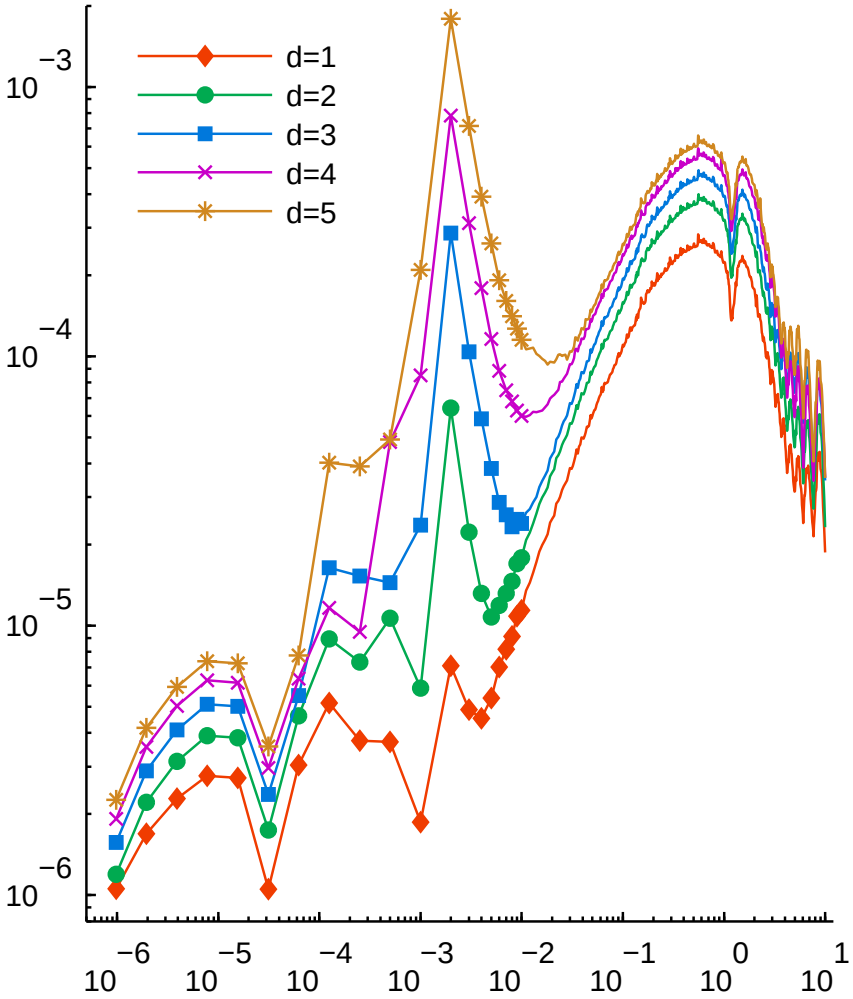
$$\varnothing \underset{d_k}{\overset{b_k}{\rightleftharpoons}} \mathrm{X}_k$$

Perfectly separable, a closed-form solution is available [Jahnke and Huisinga, 2007]

$$\boldsymbol{p}(t) = \prod_{k=1}^{d} p_k(t)$$

$b_k = 1000$ and $d_k = 1$, $l_k = 12$, $d = 1, 2, 3, 4, 5$, $r_{\text{max}}\left[\boldsymbol{A}\right] \leq 8$ for accuracy $5 \cdot 10^{-15}$. $T = 10$, $M = 569$ steps.
$r_{\text{max}}\left[\boldsymbol{p}_M^-\right] = 6$ for all d

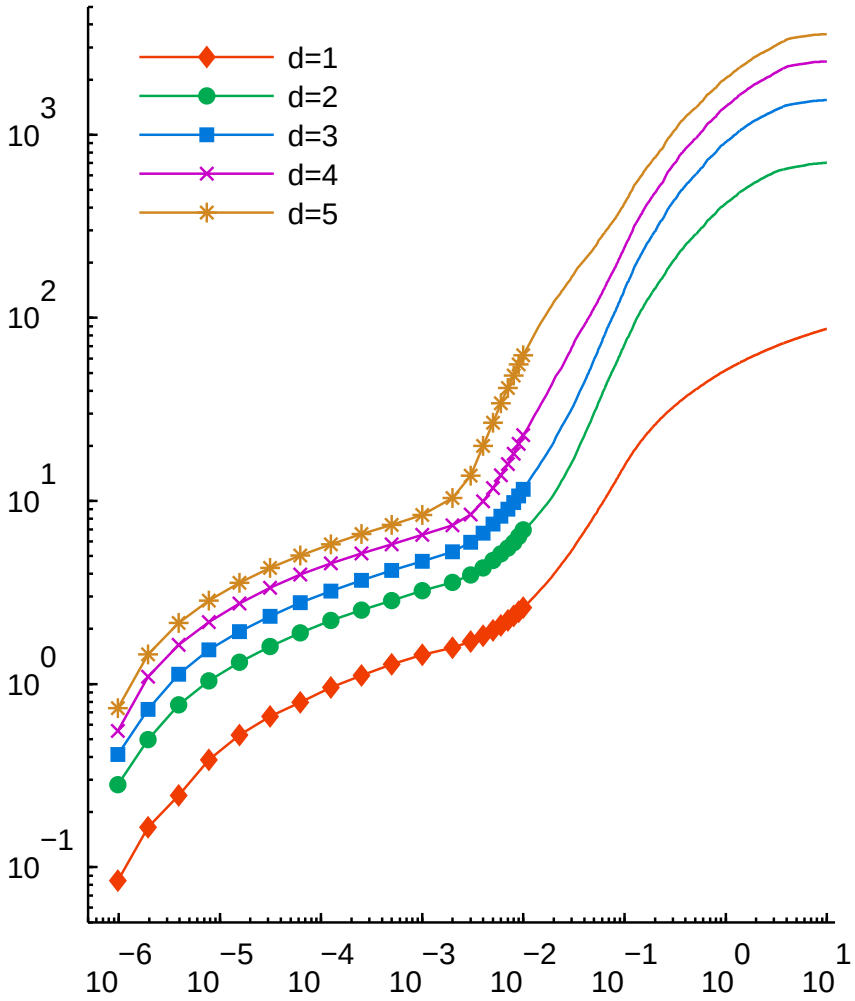
Birth-death processes



$$\Delta_{\ell_2}\left[\boldsymbol{p}_m^-\right] / \left\|\boldsymbol{p}_M^-\right\|$$

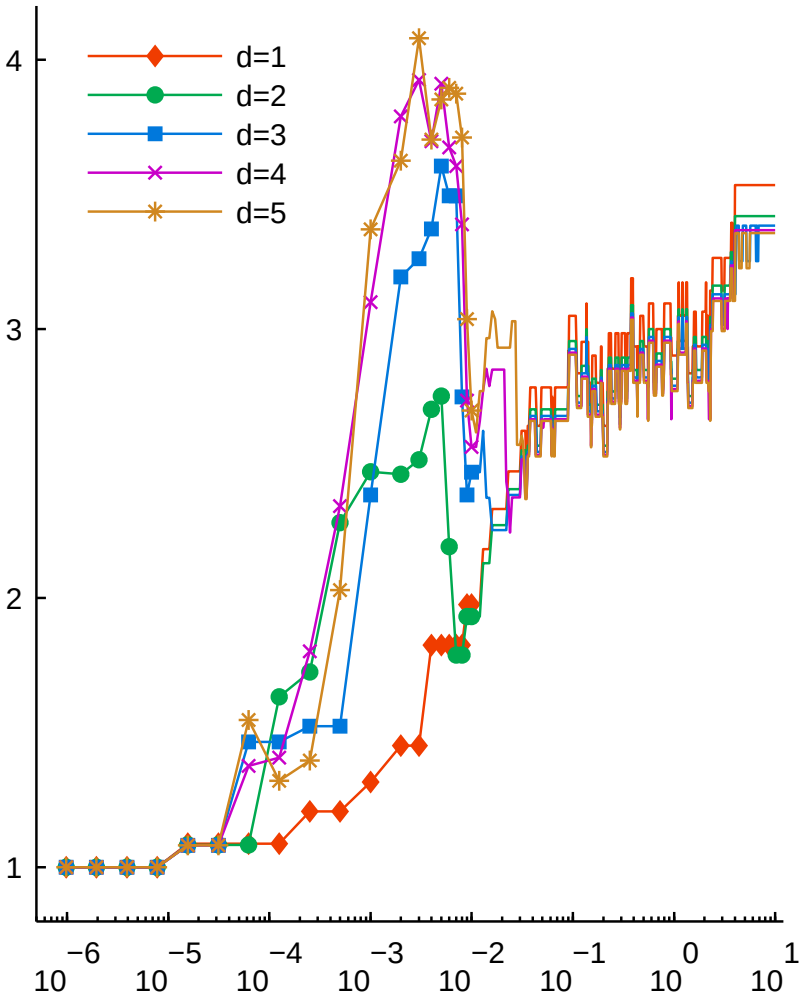
(after truncation) vs. t_m

Birth-death processes



cumulative computation time (sec.) vs. t_m

Birth-death processes

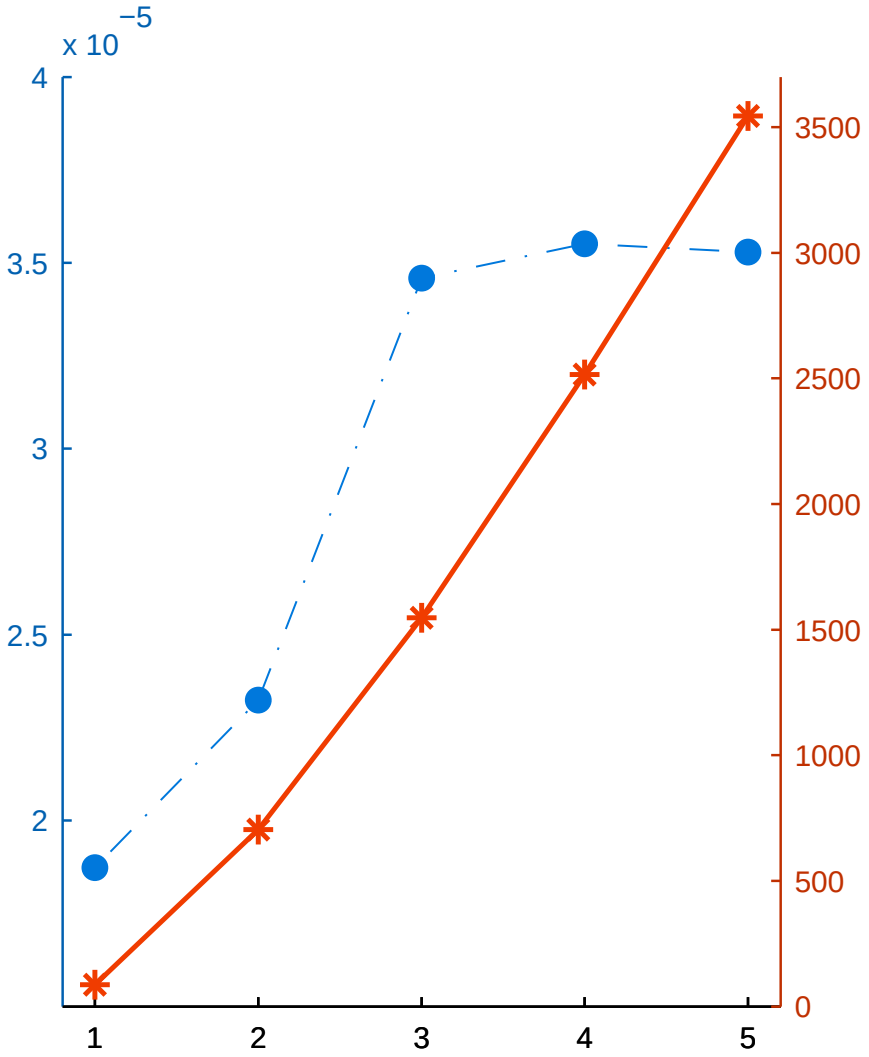


effective QTT rank

$$r_{\text{eff}}\left[\boldsymbol{p}_m^-\right]$$

(after truncation) vs. t_m

Birth-death processes



relative discrepancy

$$\Delta_{\ell_2}\left[\boldsymbol{p}_M^-\right] / \left\|\boldsymbol{p}_M^-\right\|$$

(blue) and total computation time (red) vs. d

Birth-death processes

d	N	$\frac{\|\boldsymbol{A}\boldsymbol{p}_0\|_2}{\|\boldsymbol{p}_0\|_2}$	$\frac{\|\boldsymbol{A}\boldsymbol{p}_M^-\|_2}{\|\boldsymbol{p}_M^-\|_2}$	r_{eff}	Δ_{ℓ_2}	TIME
1	2^{12}	$1.4_{+\mathbf{3}}$	$1.0_{-\mathbf{3}}$	3.53	$1.9_{-\mathbf{5}}$	87
2	2^{24}	$2.4_{+\mathbf{3}}$	$1.4_{-\mathbf{3}}$	3.42	$2.3_{-\mathbf{5}}$	704
3	2^{36}	$3.5_{+\mathbf{3}}$	$1.8_{-\mathbf{3}}$	3.38	$3.5_{-\mathbf{5}}$	1548
4	2^{48}	$4.5_{+\mathbf{3}}$	$2.0_{-\mathbf{3}}$	3.37	$3.6_{-\mathbf{5}}$	2516
5	2^{60}	$5.5_{+\mathbf{3}}$	$2.3_{-\mathbf{3}}$	3.36	$3.5_{-\mathbf{5}}$	3544

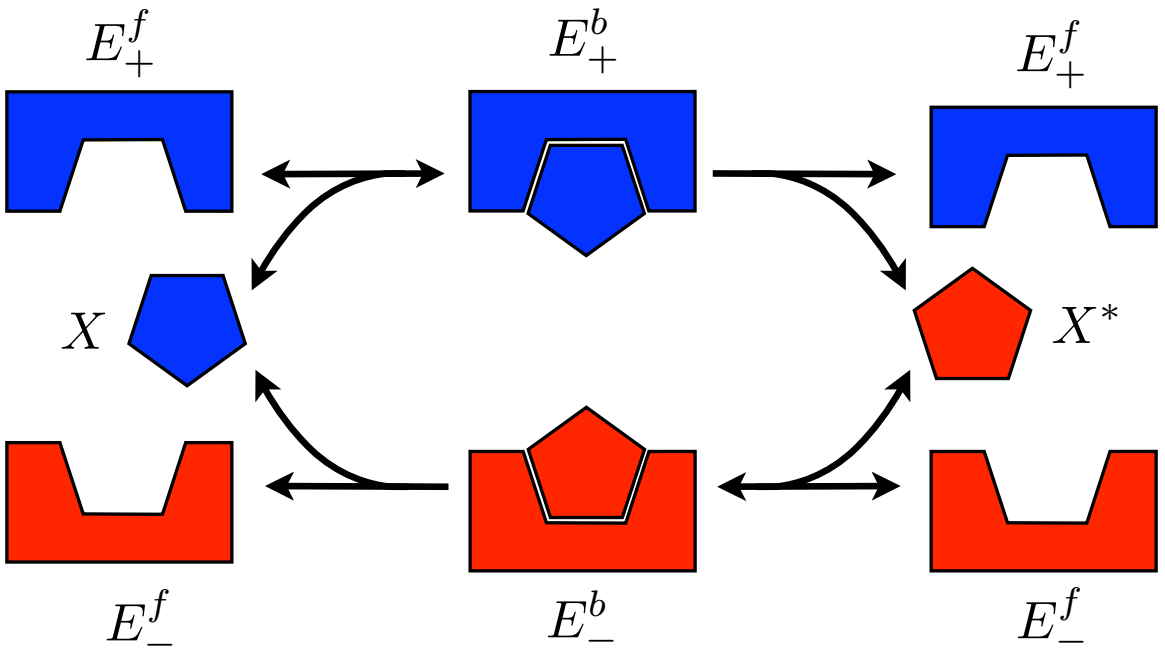
$r_{\text{eff}} = r_{\text{eff}}\left[\boldsymbol{p}_M^-\right]$, $\Delta_{\ell_2} = \Delta_{\ell_2}\left[\boldsymbol{p}_M^-\right]$, computational TIME in seconds; N is the number of states taken into account

Enzymatic futile cycle

Enzymatic futile cycle [Schwender et al., 2004, Samoilov et al., 2005]

$$\mathrm{X} + \mathrm{E}^{\mathrm{f}}_{+} \underset{k_{+2}}{\overset{k_{+1}}{\rightleftharpoons}} \mathrm{E}^{\mathrm{b}}_{+}, \quad \mathrm{X}^{*} + \mathrm{E}^{\mathrm{f}}_{-} \underset{k_{-2}}{\overset{k_{-1}}{\rightleftharpoons}} \mathrm{E}^{\mathrm{b}}_{-},$$

$$\mathrm{E}^{\mathrm{b}} \xrightarrow{k_{+3}} \mathrm{E}^{\mathrm{f}}_{+} + \mathrm{X}^{*}, \quad \mathrm{E}^{\mathrm{b}}_{-} \xrightarrow{k_{-3}} \mathrm{E}^{\mathrm{f}}_{-} + \mathrm{X}.$$



Transposed QTT, "QT3" [Oseledets, 2010b]

Instead of the ordering

$$\underbrace{j_{1,1}, \ldots, j_{1,l}}_{\mathbf{1}\text{st dimension}}, \underbrace{j_{2,1}, \ldots, j_{2,l}}_{\mathbf{2}\text{nd dimension}}, \ldots\ldots, \underbrace{j_{d,1}, \ldots, j_{d,l}}_{\boldsymbol{d}\text{th dimension}},$$

we may use

$$\underbrace{j_{1,1}, j_{2,1}, \ldots, j_{d,1}}_{1\text{st level}}, \ldots\ldots, \underbrace{j_{1,l}, j_{2,l}, \ldots, j_{d,l}}_{\boldsymbol{l}\text{th level}}$$

Transposed QTT, "QT3" [Oseledets, 2010b]

Example

a 2-dimensional $n \times n$-vector

$$\boldsymbol{x} = \begin{pmatrix} 1 & & & \\ & 1 & & \\ & & \ddots & \\ & & & 1 \end{pmatrix} = \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix}^{\otimes l}$$

$$\text{rank}_{\textbf{QTT}} = n, \; \text{rank}_{\textbf{QT3}} = 1.$$

Transposed QTT, "QT3" [Oseledets, 2010b]

Theorem (Th. 2.5 in [KKNS, 2013])

Assume that for every $s = 1, \ldots, R$ *and* $k = 1, \ldots, d$ *the one-dimensional propensity vector* $\boldsymbol{\omega}_k^s$ *is given in a QTT decomposition of ranks bounded by* r_k^s*. Then for* $\boldsymbol{A}$ *there exists a QT3 decomposition of ranks bounded by*

$$\sum_{s=1}^{R} \left(1 + \prod_{k \in \mathcal{K}^s} 2\right) \left(\prod_{k \in \mathcal{K}^s} r_k^s\right),$$

where $\mathcal{K}^s = \{k \in \mathbb{N} : \ 1 \leq k \leq d$ *and* $\nu_{sk} + \nu'_{sk} \neq 0\}$*.*

Enzymatic futile cycle

Runs

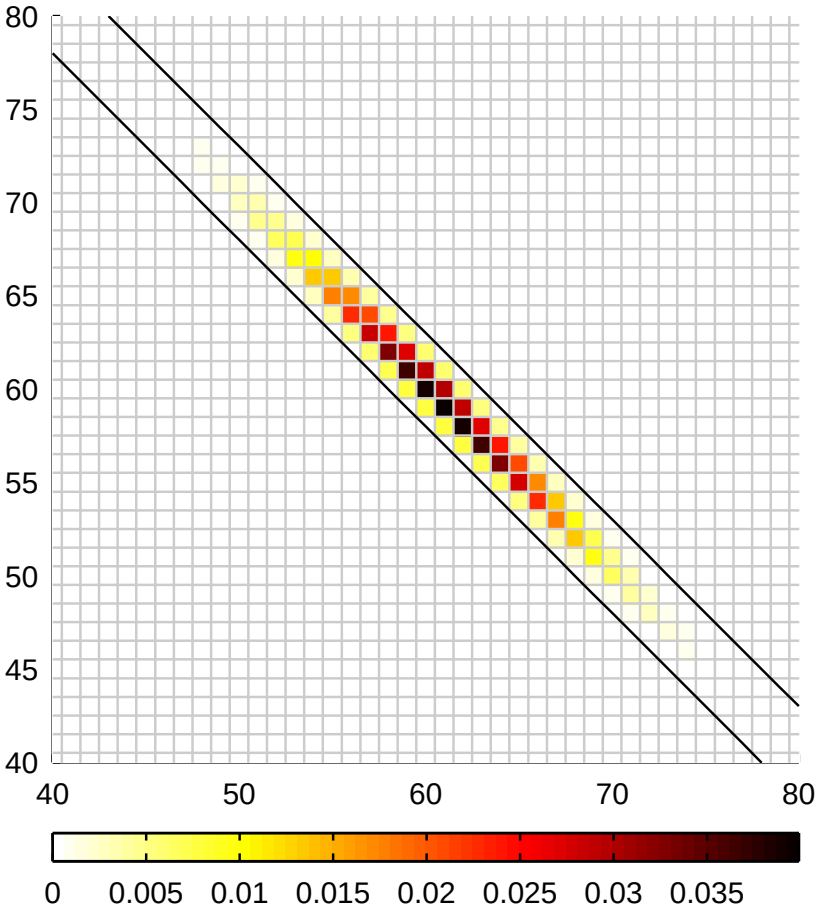
- (A) transposed QTT
- (B) transposed QTT, higher accuracy parameters
- (C) transposed QTT, lower accuracy parameters
- (D) standard QTT, the same accuracy parameters

$\max_{0 \le t_m \le 0.1} r_{\mathsf{max}} \left[\boldsymbol{P}_m \right]$ reaches

- 51 for (A)
- 359 for (D)

We compare the marginal distribution $\sum_{E_{\pm}^{\mathrm{b,f}}} \boldsymbol{p}_m^-$ to that based on $18.6 \cdot 10^9$ Monte Carlo simulations (110 seconds / 10000 draws, over $2 \cdot 10^8$ seconds of CPU time overall).

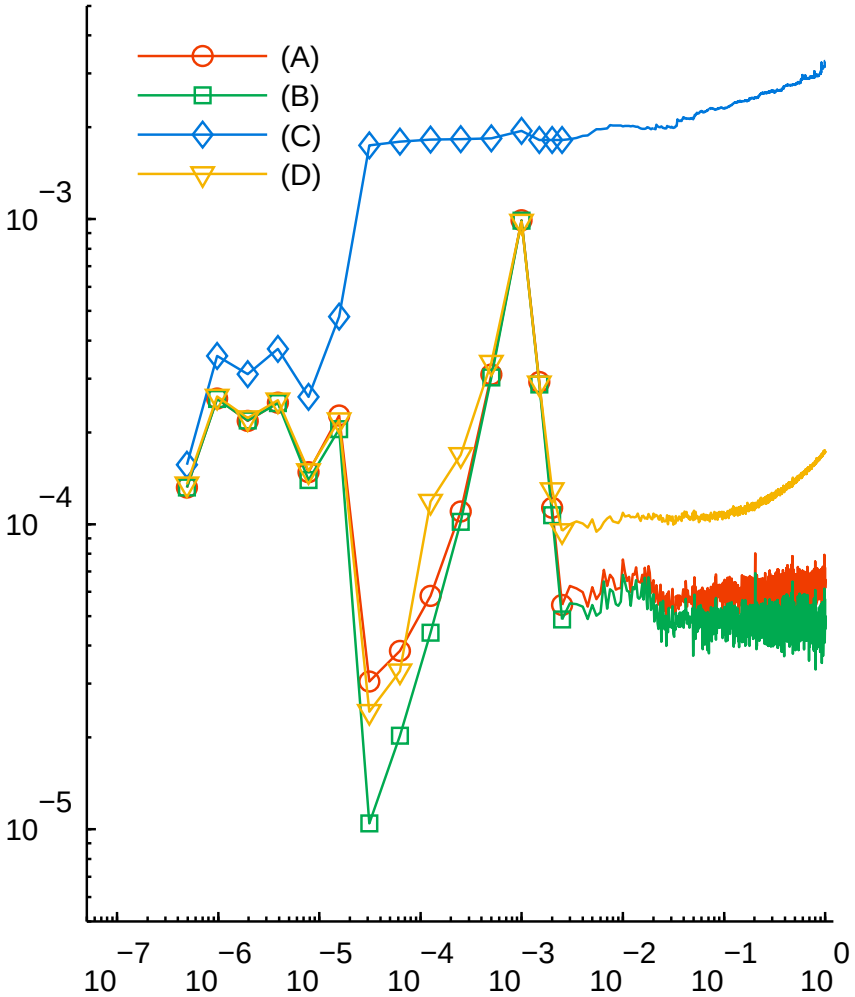
Enzymatic futile cycle



the marginal PDF for $m = 20$, $t_m = 5 \cdot 10^{-3}$, X (vert.) vs. X^* (hor.)

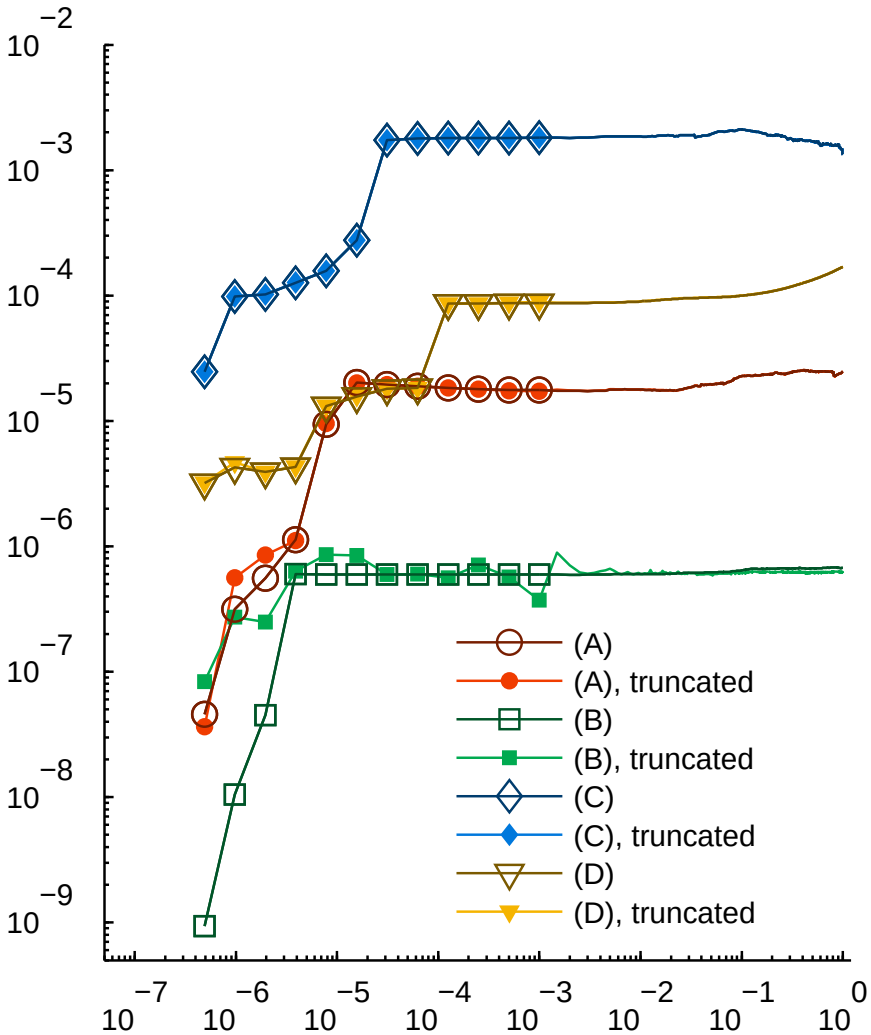
the transposed QTT format automatically exploits this sparsity pattern *of the full PDF* for compression without special input from the user

Enzymatic futile cycle



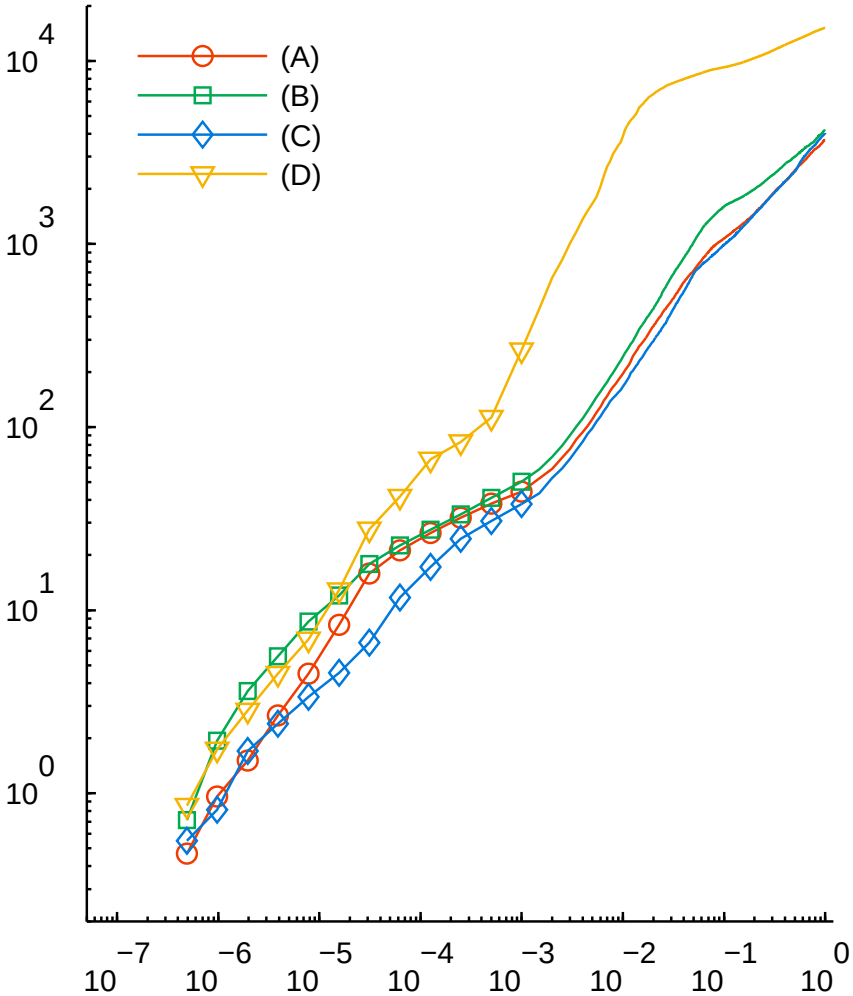
discrepancy Δ_{ℓ_1} (before truncation) from the marginal PDF based on Monte Carlo simulations vs. t_m

Enzymatic futile cycle



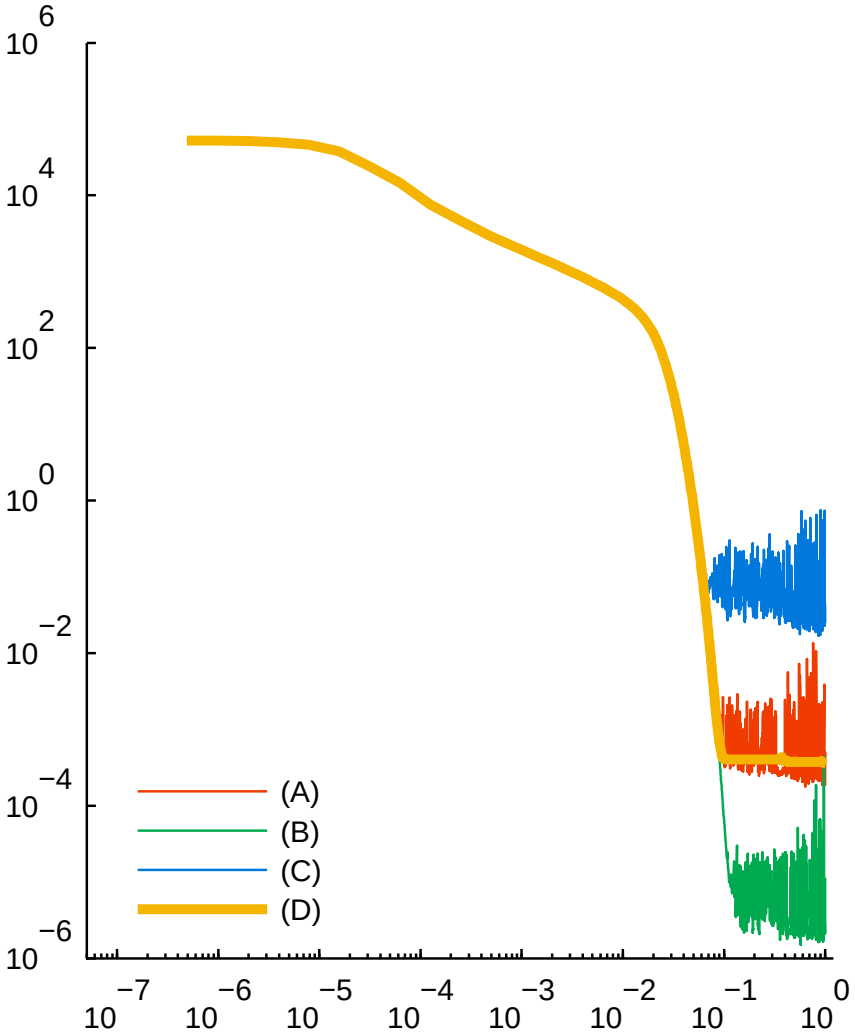
probability deficiency $\mathrm{ERR}_{\Sigma}\left[\boldsymbol{p}_m^-\right]$ vs. t_m

Enzymatic futile cycle



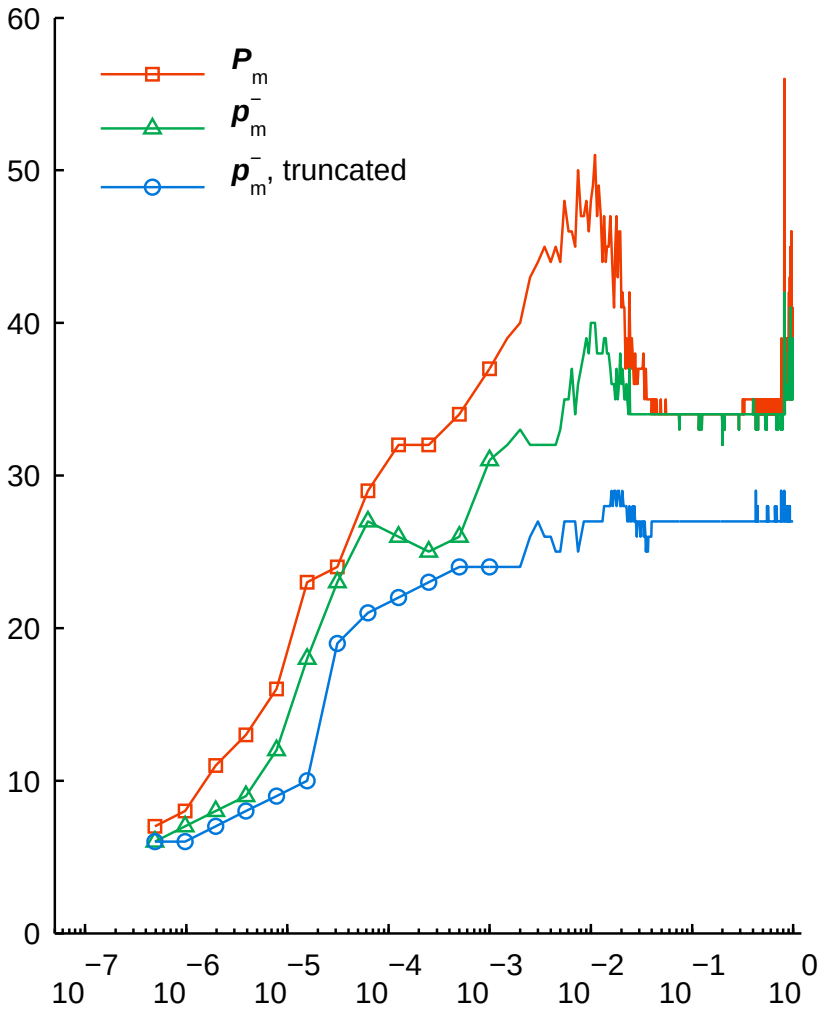
cumulative computation time (sec.) vs. t_m

Enzymatic futile cycle



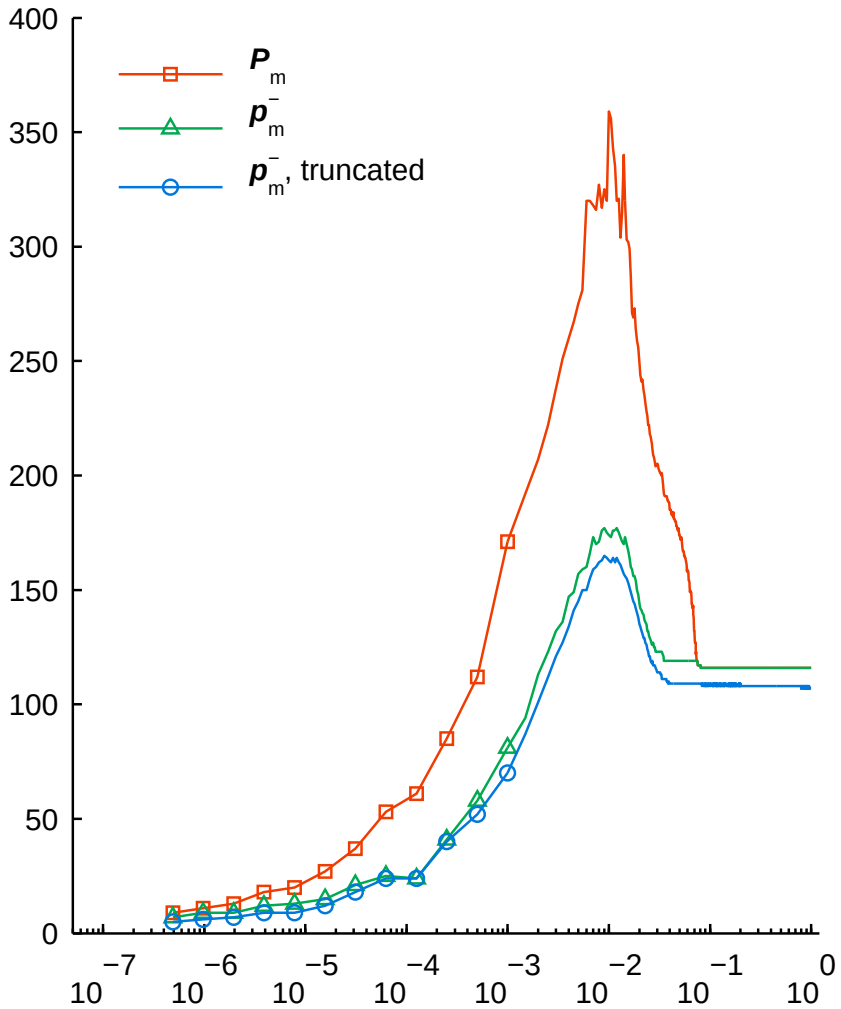
relative norm $\frac{\left\| \boldsymbol{A}\boldsymbol{p}_m^- \right\|_2}{\left\| \boldsymbol{p}_m^- \right\|_2}$ of the derivative vs. t_m

Enzymatic futile cycle



maximum QTT ranks $r_{\max}$ for (A) vs. t_m

Enzymatic futile cycle



maximum QTT ranks $r_{\max}$ for (D) vs. t_m

Enzymatic futile cycle

run	$\frac{\|\boldsymbol{A}\boldsymbol{p}_m^-\|_2}{\|\boldsymbol{p}_m^-\|_2}$	r_{eff}	r_{max}	Δ_{ℓ_1}	$\texttt{ERR}_\Sigma$	$\texttt{TIME}$
$m = 210,\ t_m = 0.1$						
(A)	3.5_{-4}	13.17	27	5.7_{-5}	2.3_{-5}	1.07_{3}
(B)	6.5_{-5}	12.14	25	4.6_{-5}	6.1_{-7}	1.60_{3}
(C)	1.3_{-1}	12.16	24	2.3_{-3}	2.1_{-3}	9.87_{2}
(D)	4.1_{-4}	60.06	109	1.1_{-4}	1.0_{-4}	9.23_{3}
$m = M = 1332,\ t_m = T = 1$						
(A)	1.8_{-4}	13.66	27	7.2_{-5}	2.5_{-5}	3.70_{3}
(B)	1.1_{-5}	12.06	25	5.7_{-5}	6.2_{-7}	4.21_{3}
(C)	2.5_{-2}	12.85	24	3.3_{-3}	1.3_{-3}	4.03_{3}
(D)	3.7_{-4}	58.97	107	1.7_{-4}	1.7_{-4}	1.52_{4}

$r_{\text{eff}} = r_{\text{eff}}\left[\boldsymbol{p}_m^-\right]$, $r_{\text{max}} = r_{\text{max}}\left[\boldsymbol{p}_m^-\right]$, $\Delta_{\ell_1} = \Delta_{\ell_1}\left[\sum_{E_\pm^{\text{b,f}}} \boldsymbol{p}_m^-\right]$, $\texttt{ERR}_\Sigma = \texttt{ERR}_\Sigma\left[\boldsymbol{p}_m^-\right]$

are given for the truncated solution $\boldsymbol{p}_m^-$; computational $\texttt{TIME}$ is given in seconds;

$$\frac{\|\boldsymbol{A}\boldsymbol{p}_0\|_2}{\|\boldsymbol{p}_0\|_2} = 5.2 \cdot 10^4$$

Gardner switch

Toggle Switch

[Sjöberg et al., 2009, Deuflhard et al., 2008, Munsky and Khammash, 2008]

$\alpha_1 = 5000$, $\alpha_2 = 1600$, $\beta = 2.5$, $\gamma = 1.5$, $\delta_1 = \delta_2 = 1$.

$l_U = 13$, $l_V = 12$.

The initial value is zero. No transposition.

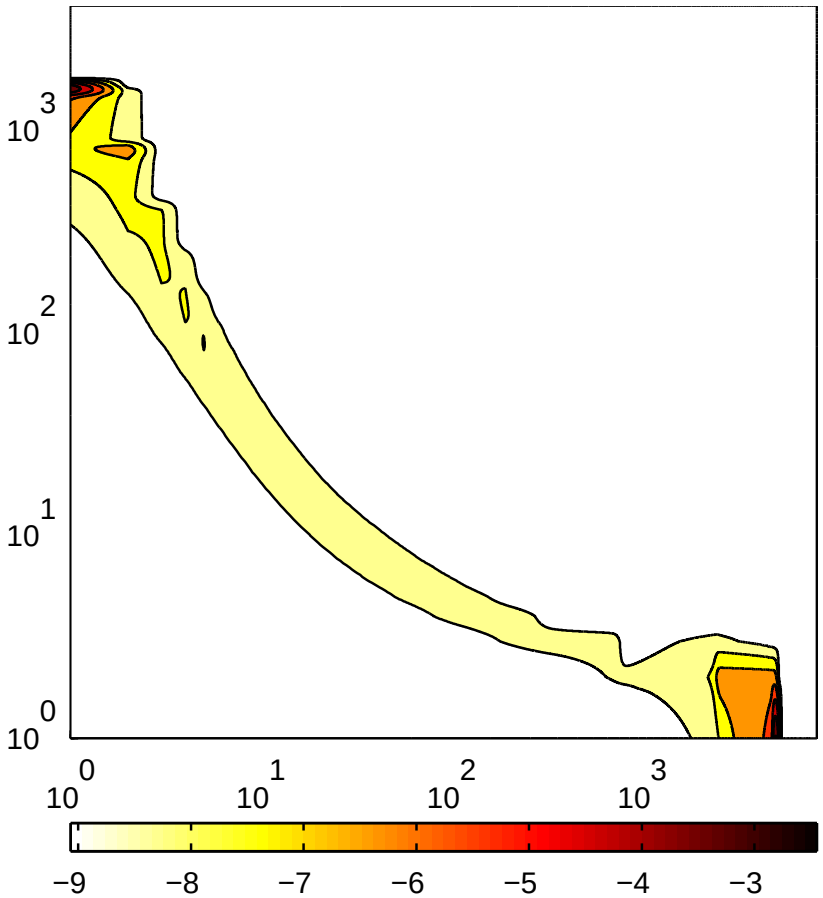
$r_{\mathsf{max}}[\boldsymbol{A}] = 14$ and $r_{\mathsf{eff}}[\boldsymbol{A}] = 10.89$ for accuracy 10^{-14}.

The evaluation accuracy is $\mathtt{EPS} = 10^{-8}$.

$T = 100$, $M = 1111$ steps overall.

at $t = T$: $\mathtt{ERR}_\Sigma\left[\boldsymbol{p}_M^-\right] = 3.17 \cdot 10^{-5}$, $\Delta_{\ell_1}\left[\boldsymbol{p}_M^-\right] = 8.34 \cdot 10^{-4}$ w.r.t. the PDF based on 816 million Monte Carlo simulations (360 seconds / 1000 draws, over $3 \cdot 10^8$ seconds of CPU time). $r_{\mathsf{eff}}\left[\boldsymbol{p}_M^-\right] = 8.74$, $r_{\mathsf{max}}\left[\boldsymbol{p}_M^-\right] = 13$.

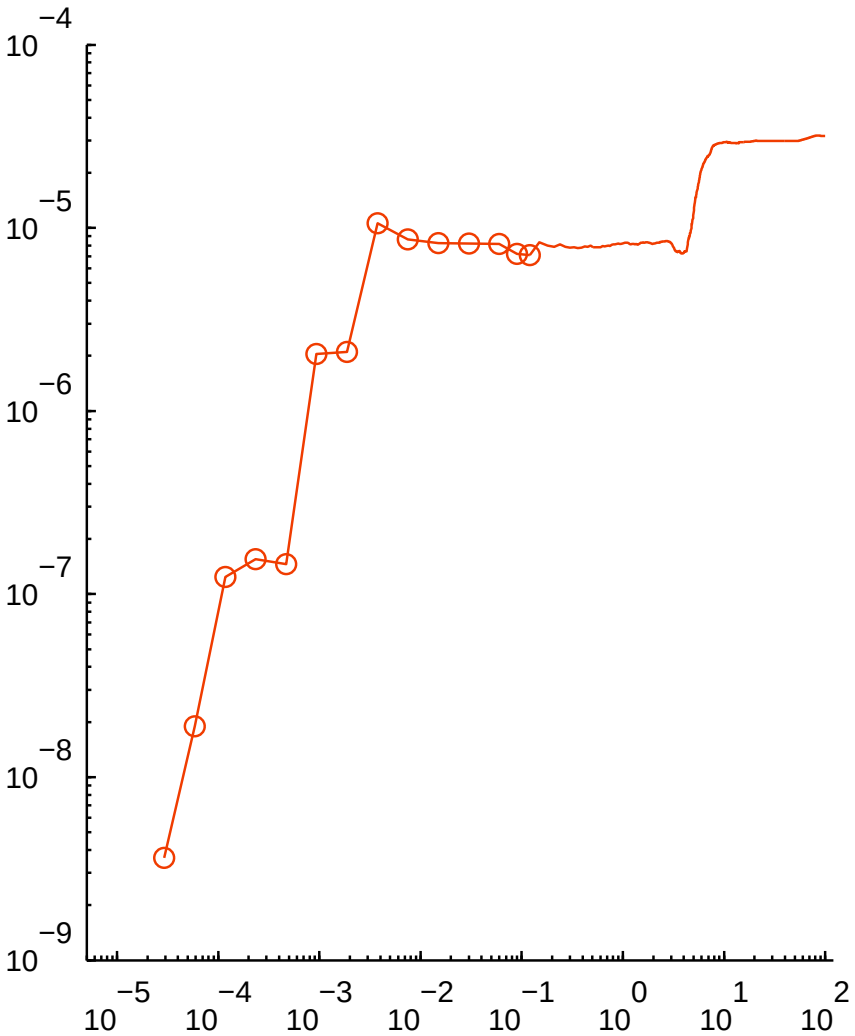
Gardner switch



the PDF for $m = 350$,
$t_m \approx 10.18$,
U (hor.) vs. V (vert.)

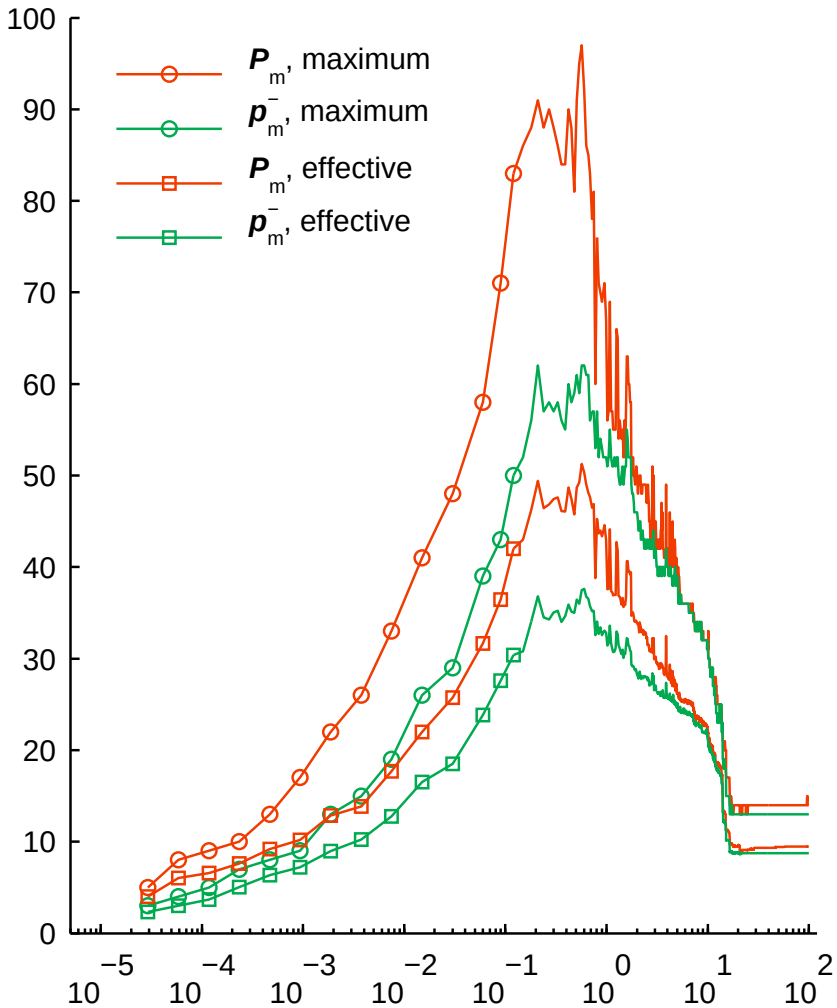
as the process evolves, the probability mass becomes concentrated in two distinct regions

Gardner switch



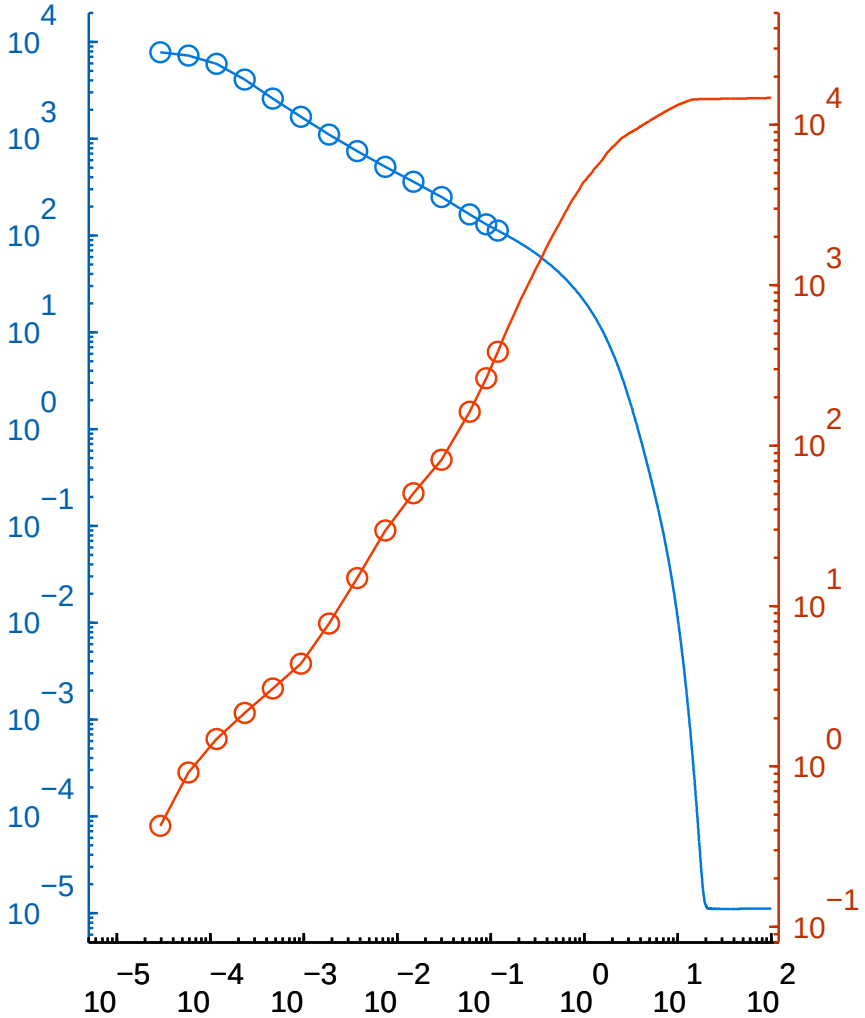
probability deficiency
$\mathrm{ERR}_{\Sigma}\left[\boldsymbol{p}_m^-\right]$ vs. t_m

Gardner switch



maximum and effective QTT ranks vs. t_m

Gardner switch



relative norm $\frac{\left\| \boldsymbol{A}\boldsymbol{p}_m^- \right\|_2}{\left\| \boldsymbol{p}_m^- \right\|_2}$ of the derivative (blue) and cumulative computation time (red, sec.) vs. t_m

Reversibility and Deficiency I

- a CRN $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ is *weakly reversible*:
  $\forall\,(\nu \to \nu') \in \mathcal{R} \quad \exists m \in \mathbb{N},\ \nu_1, \ldots, \nu_m \in \mathcal{C}$ such that

$$(\nu' \to \nu_1), (\nu_1 \to \nu_2), \ldots, (\nu_{m-1} \to \nu_m), (\nu_m \to \nu) \in \mathcal{R}$$

- a CRN $\mathcal{G} = \{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ is *reversible*:
  $(\nu \to \nu') \in \mathcal{R}$ implies $(\nu' \to \nu) \in \mathcal{R}$
- CRN $\leftrightarrow$ graph:
  - each complex $\nu \in \mathcal{C}$ is a node,
  - each reaction $(\nu \to \nu') \in \mathcal{R}$ is a directed edge.

Reversibility and Deficiency II

- each connected component of $\mathcal{G}$ is called a *linkage class*
- $\mathcal{G}$ is weakly reversible iff each linkage class of $\mathcal{G}$ is weakly reversible.
- *deficiency of the CRN* [Feinberg, 1979] :

$$\delta = (\#\mathcal{C} - \ell(\mathcal{G}) - \dim \Sigma) \in \mathbb{Z}_{\geq 0},$$

where $\ell(\mathcal{G})$ is the number of linkage classes

Stoichiometric compatibility classes

Recall:

- *stoichiometric vectors:* $\eta_s = \nu'_s - \nu_s \in \mathbb{Z}^d$,
- *stoichiometric subspace:* $\Sigma = \operatorname{span}\{\eta_s\}_{s=1}^{R}$.

Every $c \in \mathbb{R}^d$ induces:

- a *stoichiometric compatibility class*

$$c + \Sigma,$$

- a *positive stoichiometric compatibility class*

$$(c + \Sigma) \cap \mathbb{R}^d_{>0}.$$

Deterministic model I

- evolution of

  copy numbers $X = (X_1, \ldots, X_d)' \in \mathbb{Z}^d_{\geq 0}$

  $\downarrow$

  concentrations $x = (x_1, \ldots, x_d)' \in \mathbb{R}^d_{\geq 0}$

  [Kurtz, 1976, Kurtz, 1981, van Kampen, 1992]

- the stochastic model transforms to

$$x(t) = x(0) + \sum_{s=1}^{R} \eta_s \int_0^t f_s(x(\tau))\,\mathrm{d}\tau, \text{ or } \dot{x}(t) = \sum_{s=1}^{R} \eta_s f_s(x(t))\,,$$

for all $t > 0$. The rate functions: $f_s(x) = \kappa_s \prod_{k=1}^{d} x_k^{\nu_{sk}}$, $x \in \mathbb{R}^d_{\geq 0}$.

Deterministic model II

- $c \in \mathbb{R}^d_{\geq 0}$ is a *complex-balanced equilibrium*:

$$\sum_{\substack{1 \leq s \leq R: \\ \nu_s = \xi}} f_s(c) = \sum_{\substack{1 \leq s \leq R: \\ \nu'_s = \xi}} f_s(c) \quad \text{for all} \quad \xi \in \mathcal{C},$$

- if $\delta = 0$, then a steady state is admitted iff the CRN is weakly reversible
- if the CRN is weakly reversible, there is precisely one steady state *within each pos. stoch. comp. class*

[Feinberg, 1979]

Steady states of the stochastic model

Theorem (Th. 6.1 in [Anderson et al., 2010])

Let $c \in \mathbb{R}^d_{>0}$ be a c.-b.e., then

(a) *the stochastic model admits the stationary distribution $\boldsymbol{p}$:*

$$\boldsymbol{p}_i = M \prod_{k=1}^{d} \frac{c_k^{i_k}}{\prod_{j_k=1}^{i_k} \theta_k(j_k)}, \quad i \in \mathcal{Z},$$

provided that $\boldsymbol{p}$ is summable; if $\mathcal{Z}$ is an irreducible communicating class of X, then $\boldsymbol{p}$ is a unique stationary distribution;

(b) *for every closed, irreducible communicating class $\mathfrak{G} \subset \mathcal{Z}$ of X the stochastic model admits such a stationary distribution $\boldsymbol{p}$ on $\mathfrak{G}$.*

QTT ranks of the factors I

Theorem (Th. 22 in [K. and Schwab, 2013])

Let $\lambda > 0$, $\alpha = \pi \left(\sqrt{\frac{2}{5}} - \frac{1}{2} \right)$ and $1 \leq 2e^{\alpha}\lambda < 2^l - 1$,

$$g(x) = \lambda^x / \Gamma(x+1), \quad x \in \mathbb{R}, \quad \text{and} \quad \boldsymbol{u}_i = g(i), \quad 0 \leq i < 2^l.$$

Suppose $\varepsilon > 0$ and $K_\infty \in \mathbb{N}$ are such that

$$\begin{aligned} K_\infty &\geq \log_2 2e\lambda, \\ K_\infty &\geq \log_2 \left(2\log_2 \frac{1}{\varepsilon} + 1 - \log_2 \pi \right) - 1, \end{aligned}$$

and set $K_l = \min\{K_\infty, l\}$.

QTT ranks of the factors II

Then there exists $\boldsymbol{v}$ such that $\|\boldsymbol{v}-\boldsymbol{u}\|_{\ell_2} \leq \varepsilon$ and that can be exactly represented in the QTT format with ranks bounded by

$$r = r_0 + 3\left(K_l - k_0\right)\left(2 + \log_\rho \frac{2C_1}{\varepsilon}\right) + \frac{3}{4\beta}\left(K_l - k_0 - 1\right)\left(K_l - k_0\right),$$

where $r_0 = 2\sqrt{e^{\alpha+1}\lambda}$, $k_0 = \lceil \log_2 e^{\alpha+1}\lambda \rceil$ and

$$C_1 = \frac{2\,C}{\rho - 1}, \quad C = \frac{e^\alpha}{\sqrt{1-e^{-3\pi}}\sqrt{\pi}}\left(\frac{2}{5}\right)^{\frac{1}{4}},$$

$$\beta = \log_2 \rho, \quad \rho = 2 + \sqrt{3}$$

QTT ranks of the factors III

Lemma (Lm. 24 in [K. and Schwab, 2013])

Let $\vartheta, \lambda > 0$ and $\upsilon, l \in \mathbb{N}$. Then $\boldsymbol{u}$ with the entries

$$\boldsymbol{u}_i = \frac{\lambda^i}{\prod_{j=1}^{i} \theta(j)}, \quad 0 \leq i < 2^l,$$

where

$$\theta(x) = \frac{\vartheta x}{\upsilon + x} \quad \text{for all} \quad x > 0,$$

can be represented in the QTT format with ranks bounded by $\upsilon + 1$.

QTT ranks of p

Mass-action kinetics

$$r_{sk} = \mathcal{O}\left(\log \frac{1}{\varepsilon_{sk}} \cdot \log n_k\right) + \mathcal{O}\left(\log^2 n_k\right),$$

To achieve an accuracy ε, we set $\varepsilon_k = \frac{\varepsilon}{d} \frac{\|\boldsymbol{p}\|_{\ell_2}}{\|\boldsymbol{p}_k\|_{\ell_2}}$, then

$$r = \mathcal{O}\left(c^{\frac{1}{2}}\right) + \mathcal{O}\left(\log \frac{d}{\varepsilon} \cdot \log n\right) + \mathcal{O}\left(\log^2 n\right)$$

$n \geq n_1, \ldots, n_d$ and $c \geq c_1, \ldots, c_d$ For large n:

$$r = \mathcal{O}\left(c^{\frac{1}{2}}\right) + \mathcal{O}\left(\left(\log \frac{d}{\varepsilon}\right) \cdot \log\log \frac{d}{\varepsilon}\right)$$

QTT ranks of p

Michaelis–Menten kinetics

For the kth species:

$$r_k = \upsilon_k + 1$$

bounds the corresponding $l_k - 1$ QTT ranks of $\boldsymbol{p}$

Mixed kinetics

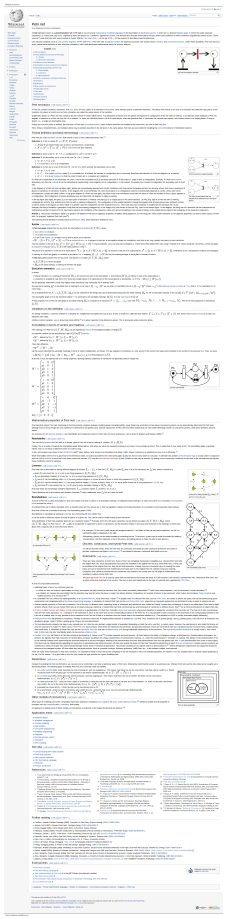
$\rightarrow$ the maximum of the two

Conclusion

- a novel, “ab-initio” computational methodology for the direct numerical solution of the CME was proposed and showed to be superior to existing approaches
- the low-rank QTT structure of the CME operator and, for weakly reversible CRNs of zero deficiency, of steady states is proved
- the use of tensor structure yields very efficient dynamic adaptation of the effective state space, (“principal components”, “basis elements”), outperforming the compression of the conventional methods

Petri Nets

PN



CRN

the same model,
in the theory of
distributed systems

zero-deficiency PNs:

[Angeli et al., 2007,

Mairesse and Nguyen, 2010]

Overview of tensor-structured solvers

Time discretization

1. low-order integration schemes: QTT-structured Euler θ-scheme, see [Dolgov et al., 2011, Gavrilyuk and Khoromskij, 2011]
2. adaptive high-order integration schemes: hp-DG-QTT [K., Reichmann and Schwab, 2012]
3. dynamics on TT manifolds: [Khoromskij et al., 2012, Lubich et al., 2012]

Solvers of linear systems

1. ALS [Holtz et al., 2010, Holtz et al., 2012, Uschmajew, 2012, Rohwedder and Uschmajew, 2012]
2. "DMRG" [Dolgov and Oseledets, 2011]
3. Alternating Minimal ENergy methods [Dolgov and Savostyanov, 2013a, Dolgov and Savostyanov, 2013b]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