Using low-rank tensor formats to enable computations of cancer progression models in large state spaces

Simon Pfahler[1], Peter Georg[1], Y. Linda Hu[2], Stefan Vocht[2], Rudolf Schill[2,3], Andreas Lösch[2], Kevin Rupp[2,3], Stefan Hansch[2], Maren Klever[4], Lars Grasedyck[4], Rainer Spang[2], Tilo Wettig[1]

[1]Department of Physics, University of Regensburg
[2]Department of Informatics and Data Science, University of Regensburg
[3]Department of Biosystems Science and Engineering, ETH Zürich
[4]Institute for Geometry and Applied Mathematics, RWTH Aachen University

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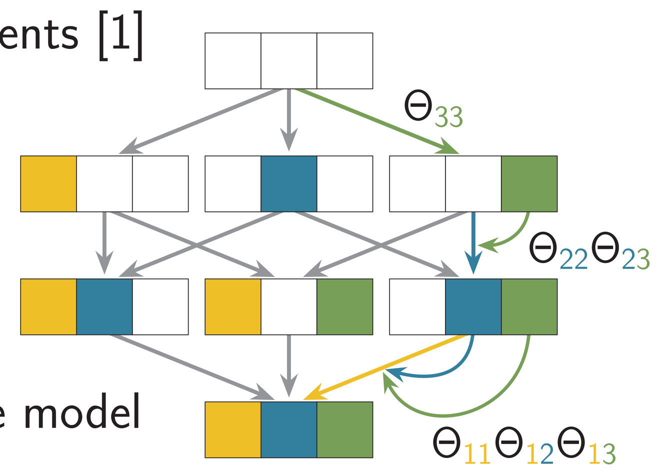
Summary

- Comprehensive cancer progression models should include a large number d of genomic events
- Mutual Hazard Networks model the progression process using only d^2 parameters [1]
  - Computational complexity of a straightforward implementation still scales exponentially in d
  - Calculations using $\gtrsim 25$ events are computationally infeasible [2]
- Tensor Trains allow for cost-effective storage and calculations for high-dimensional tensors
  - This method reduces the computational complexity from exponential to polynomial in d

Mutual Hazard Network (MHN) model

- MHN models tumor progression as a continuous-time Markov chain on the 2^d-dimensional state space of possibly active events [1]
- Events can only occur one at a time
- Transition rates are given by

$$(\mathbf{Q}_\Theta)_{\mathbf{x}\to\mathbf{x}_{+i}} = \underbrace{\Theta_{ii}}_{\text{base rate}} \prod_{x_j=1} \underbrace{\Theta_{ij}}_{\text{influences}}$$



- $\mathbf{Q}_\Theta \in \mathbb{R}^{2^d\times 2^d}$ is sparse, $\Theta \in \mathbb{R}^{d\times d}$ describes the model in compact form using only d^2 parameters
- Time marginal probability distribution from Θ:

$$\mathbf{p}_\Theta = (\mathbf{Id} - \mathbf{Q}_\Theta)^{-1}\,\mathbf{p}_\varnothing \qquad \mathbf{p}_\varnothing = (100\%, 0\%, 0\%, \dots, 0\%)^T$$

- Optimal Θ matrices are found by optimizing the time-marginalized Kullback-Leibler divergence from the given data distribution $\mathbf{p}_\mathcal{D}$:

$$S_{\mathrm{KL}}(\mathbf{p}_\Theta) = \sum_{\mathbf{x}} (\mathbf{p}_\mathcal{D})_{\mathbf{x}} \log\left((\mathbf{p}_\Theta)_{\mathbf{x}}\right)$$

- Gradients can be calculated analytically:

$$\frac{\partial S_{\mathrm{KL}}}{\partial \Theta_{ij}} = \sum_{\mathbf{y},\mathbf{z}} \underbrace{\sum_{\mathbf{x}} \frac{\partial S_{\mathrm{KL}}}{\partial(\mathbf{p}_\Theta)_{\mathbf{x}}} (\mathbf{Id} - \mathbf{Q}_\Theta)^{-1}_{\mathbf{xy}}}_{=:\mathbf{q}_{\mathbf{y}}} \left(\frac{\partial \mathbf{Q}_\Theta}{\partial \Theta_{ij}}\right)_{\mathbf{yz}} (\mathbf{p}_\Theta)_{\mathbf{z}}$$

- KL divergence and gradient calculation time is dominated by solution time of two linear equations:

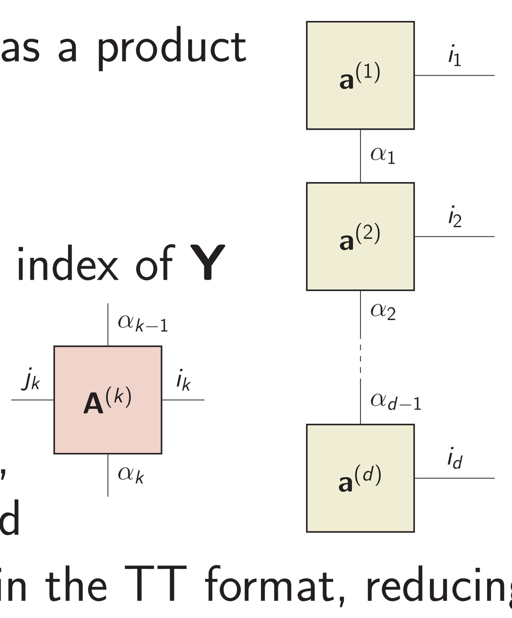
$$(\mathbf{Id} - \mathbf{Q}_\Theta)\,\mathbf{p}_\Theta = \mathbf{p}_\varnothing \qquad (\mathbf{Id} - \mathbf{Q}_\Theta)^T\,\mathbf{q} = \frac{\partial S_{\mathrm{KL}}}{\partial \mathbf{p}_\Theta}$$

Tensor Train (TT) representation

- A d-dimensional tensors $\mathbf{a} \in \mathbb{C}^{n_1\times\dots\times n_d}$ can be written as a product of d Tensor Train cores $\mathbf{a}^{(k)} \in \mathbb{C}^{r_{k-1}\times n_k\times r_k}$:

$$\mathbf{a} = \mathbf{a}^{(1)} \circ \dots \circ \mathbf{a}^{(d)}$$

  $\mathbf{X} \circ \mathbf{Y}$ denotes contraction of last index of $\mathbf{X}$ with first index of $\mathbf{Y}$
- Similar for operators $\mathbf{A} \in \mathbb{C}^{(m_1\times\dots\times m_d)\times(n_1\times\dots\times n_d)}$:
  TT cores $\mathbf{A}^{(k)} \in \mathbb{C}^{r_{k-1}\times m_k\times n_k\times r_k}$
- Storage cost is reduced from exponential to linear in d, but additional dependency on TT ranks r_k is introduced



- Many arithmetic operations can be performed directly in the TT format, reducing the computational complexity [3]:
  - Superposition $\lambda\mathbf{a} + \nu\mathbf{b}$: $\mathcal{O}\left(dn(r_{\mathbf{a}} + r_{\mathbf{b}})^2\right)$
  - Inner product $\langle\mathbf{a}, \mathbf{b}\rangle$: $\mathcal{O}\left(dnr_{\mathbf{a}}r_{\mathbf{b}}(r_{\mathbf{a}} + r_{\mathbf{b}})\right)$
  - Operator-by-Tensor product $\mathbf{Ab}$: $\mathcal{O}\left(dmn(r_{\mathbf{A}}r_{\mathbf{b}})^2\right)$

  $n := \max(n_k)$, $m := \max(m_k)$, $r_{\mathbf{X}} := \max((r_{\mathbf{X}})_k)$
- Linear equations $\mathbf{Ax} = \mathbf{b}$ can also be solved efficiently directly in this format

References

[1] R. Schill, S. Solbrig, T. Wettig, and R. Spang, *Modelling cancer progression using Mutual Hazard Networks, Bioinformatics* **36** (January, 2020) 241.

[2] P. Georg, L. Grasedyck, M. Klever, R. Schill, R. Spang, and T. Wettig, *Low-rank tensor methods for Markov chains with applications to tumor progression models, Journal of Mathematical Biology* **86** (December, 2022).

[3] P. Georg, *Tensor Train Decomposition for solving high-dimensional Mutual Hazard Networks*, PhD thesis, Universität Regensburg, October, 2022.

Tensor Trains for MHN

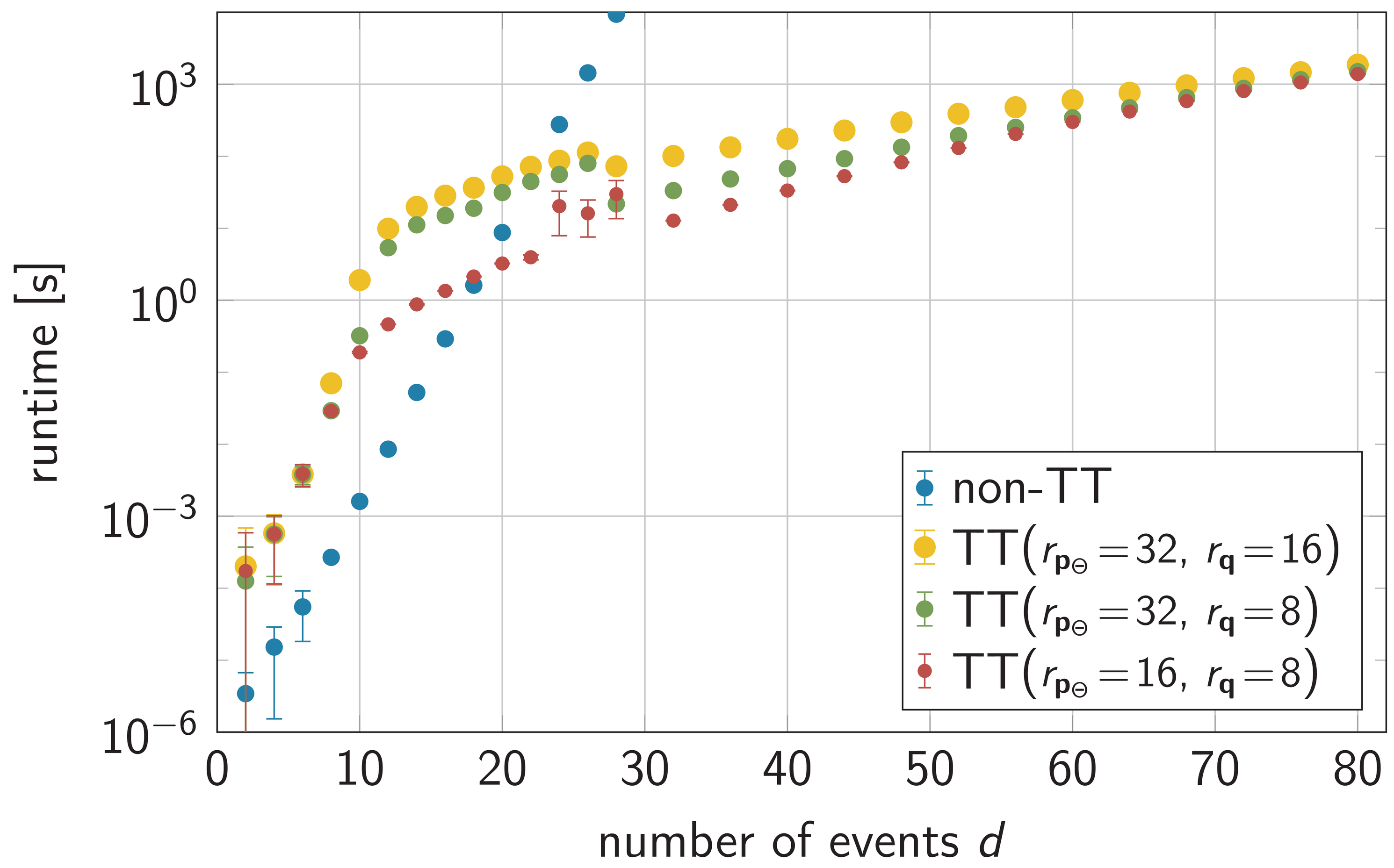
- Events are binary $\to n_k = 2$ for all mode sizes
- $\mathbf{Q}_\Theta$ can naturally be written as a Tensor Train [1]:

$$\mathbf{Q}_\Theta = \sum_{i=1}^{d}\left(\bigotimes_{j=1}^{i-1}\underbrace{\begin{pmatrix}1 & 0\\ 0 & \Theta_{ij}\end{pmatrix}}_{\in\mathbb{R}^{1\times2\times2\times1}} \otimes \underbrace{\begin{pmatrix}-\Theta_{ii} & 0\\ \Theta_{ii} & 0\end{pmatrix}}_{\in\mathbb{R}^{1\times2\times2\times1}} \otimes \bigotimes_{j=i+1}^{d}\underbrace{\begin{pmatrix}1 & 0\\ 0 & \Theta_{ij}\end{pmatrix}}_{\in\mathbb{R}^{1\times2\times2\times1}}\right)$$

  - $\mathbf{Q}_\Theta$ is a sum of d rank-1 Tensor Trains
  - All TT-ranks of $\mathbf{Q}_\Theta$ are equal to d
- $\mathbf{p}_\varnothing$ is a canonical unit Tensor Train, with all TT-ranks equal to 1
- $\mathbf{p}_\Theta$ and $\mathbf{q}$ can be calculated in the TT format (max. TT ranks $r_{\mathbf{p}_\Theta}$ and $r_{\mathbf{q}}$)
- For gradients, each nonzero entry in $\mathbf{p}_\mathcal{D}$ has to be treated individually
  - One linear equation has to be solved for each nonzero entry (usually $\sim$1000)
  - This can be parallelized trivially

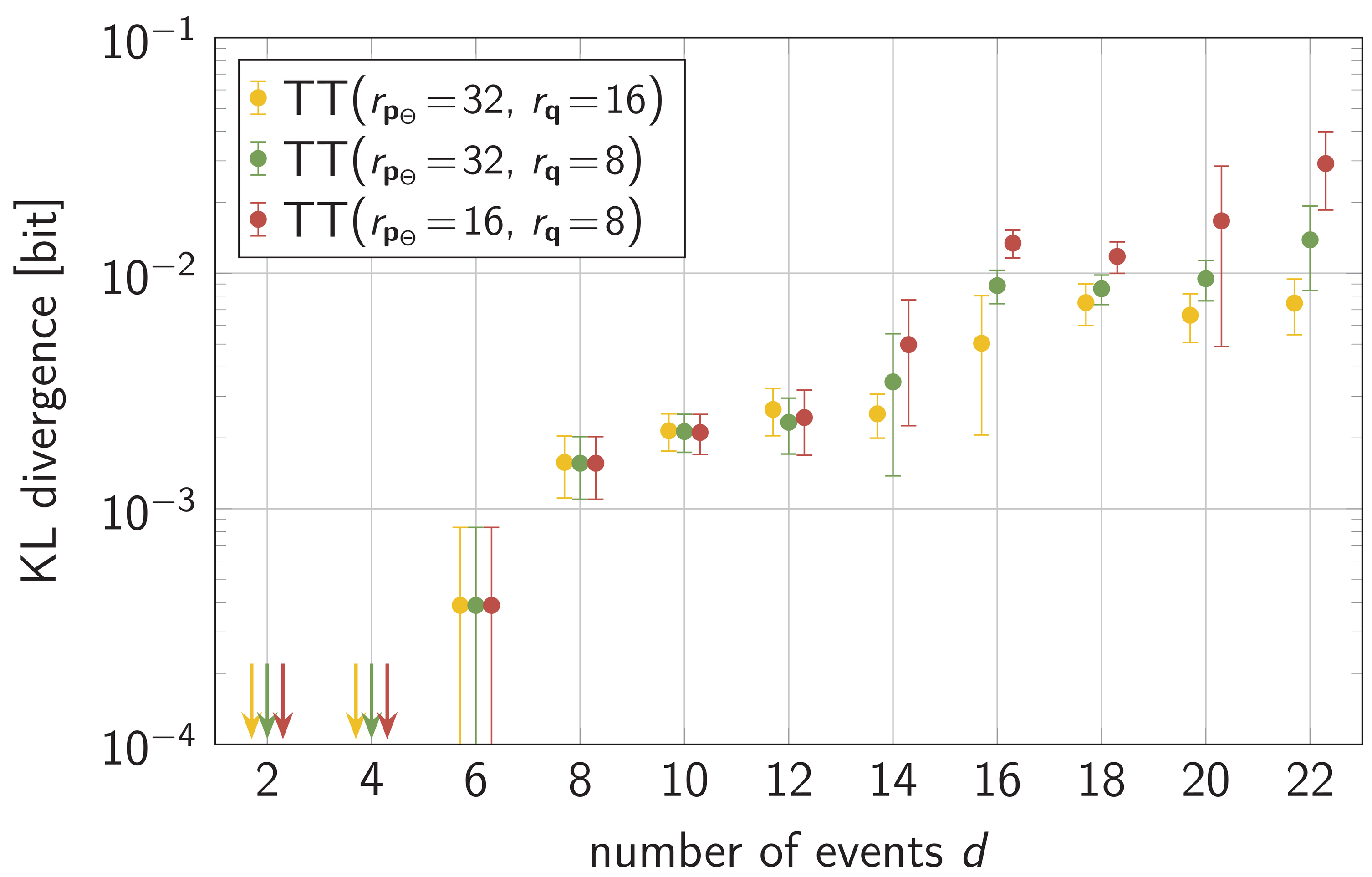
Results: Runtime speedup

- Runtime for one score and gradient evaluation at Θ = independence model
- $\mathbf{p}_\mathcal{D}$ constructed from 1000 random samples
- Runtime grows with $\sim d^{5.4}$ for large d $\Rightarrow$ **polynomial growth!**



Results: Accuracy of the TT solution

- KL divergence from exact result to TT solution after full optimization of Θ



Code availablility

- C++ library for TT-calculations `pRC`: gitlab.com/pjgeorg/pRC
- Application-specific C++ library `cMHN` that utilizes `pRC` for MHN-calculations: soon to be open-source

Future improvements

- Reduce runtime by accelerating solution of linear equations in TT format
- Include formation of metastases in the model

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Correspondence: simon.pfahler@ur.de