Analysis of Markovian Population Models

Dissertation Defense

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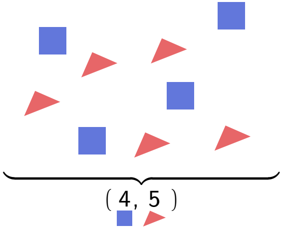
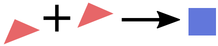
Motivation

- stochastic concentration changes
- systems biology: switches,
- applications: queueing, metabolic networks, bio-switches, traffic etc.
- goal: do *rigorous* analysis on such models

Markovian population models

Framework





- populations of identical agents
- state space ~ population sizes
- often huge to infinite

- continuous time
- exponential jump times / CTMC dynamics
- Kolmogorov equation for probabilities:

$$\frac{d}{dt}\pi(t) = \pi(t)Q$$

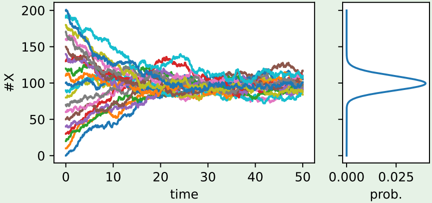
Markovian population models

How they behave

Example (birth-death process)

$$X \to \varnothing, \quad \alpha_1(x) = 0.1 \cdot x$$

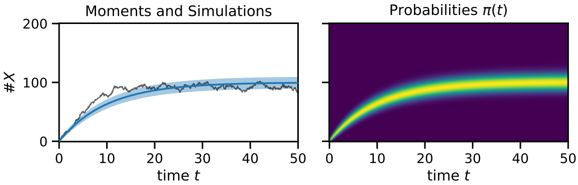
$$\varnothing \to X, \quad \alpha_2(x) = 10$$



- changes depend on current state only
- ergodic chains converge to unique distribution ($t \to \infty$)
- Foster-Lyapunov functions for bounds

Markovian population models

Approaches to their analysis

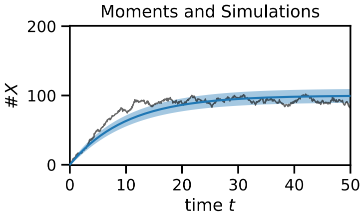


Moment equation

Moments such as mean $\mathrm{E}\left(X_t\right)$ and variance $\mathrm{E}\left(X_t^2\right) - \mathrm{E}\left(X_t\right)^2$ are described by (often linear) ODEs.

$$\frac{d}{dt}\mathrm{E}\left(f(\vec{X}_t)\right) = \sum_{j=1}^{n_R} \mathrm{E}\left(\left(f(\vec{X}_t + \vec{v}_j) - f(\vec{X}_t)\right)\alpha_j(\vec{X}_t)\right)$$

Moment-Based Methods



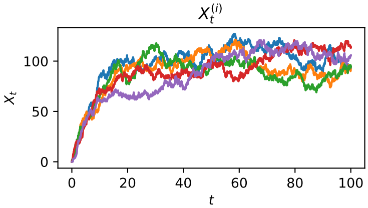
Markovian Population Models

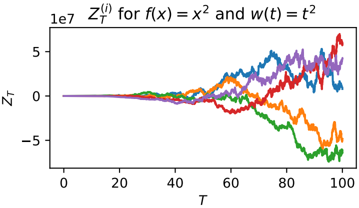
Martingale process

- start with the moment ODE
- multiply time-weighting: $w(t) = t^k$, $k \in \mathbb{N}$ or $w(t) = \exp(\lambda t)$
- analytic integration results in a martingale

$$Z_T := w(T) f(\vec{X}_T) - w(0) f(\vec{X}_0) - \int_0^T \frac{dw(t)}{dt} f(\vec{X}_t)\, dt - \sum_{j=1}^{n_R} \int_0^T w(t) (f(\vec{X}_t + \vec{v}_j) - f(\vec{X}_t)) \alpha_j(\vec{X}_t)\, dt$$

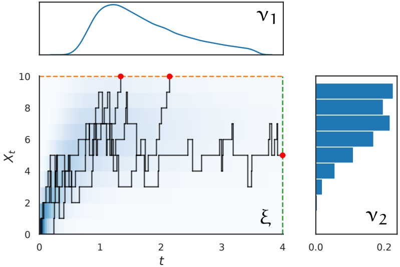
- known expectation: $\mathrm{E}(Z_T) = 0$, $\forall T \geqslant 0$





Bounding mean first-passage times

Linear moment constraints



- $\tau = \inf\{X_t \geqslant H \mid t \geqslant 0\} \wedge T$
- time weighting $w(t) = t^k$
- exp. occupation measure ξ
- exit location measures ν_1, ν_2

Linear moment constraint

$$0 = E(Z_T) = T^k \overbrace{E(X_\tau^m; \tau = T)}^{\nu_1} + H^m \overbrace{E\left(\tau^k; \tau < T, X_\tau = H\right)}^{\nu_2}$$

$$- 0^k x_0^m + \sum_i c_i \underbrace{E\left(\int_0^\tau t^{k_i} X_t^{m_i}\, dt\right)}_{\xi}$$

[BBW20]

Moment matrices

The *moment matrix* must be *positive semi-definite*.

$$\mathrm{E}\begin{pmatrix} X^0 & X^1 & X^2 & \dots & X^n \\ X^1 & X^2 & \ddots & \ddots & \vdots \\ \vdots & \ddots & \ddots & \ddots & \vdots \\ X^n & X^{n+1} & \dots & \dots & X^{2n} \end{pmatrix} \succeq 0\,,$$

where $M \succeq 0$ iff. $\forall v \in \mathbb{R}^n . v^\top M v \geqslant 0$.

Example

Let $M = \begin{pmatrix} 1 & \mathrm{E}(X) \\ \mathrm{E}(X) & \mathrm{E}(X^2) \end{pmatrix}$. Then $\det M = \mathrm{E}(X^2) - \mathrm{E}(X)^2 = \sigma^2 \geqslant 0$.

[BBW20]

- measure support can be restricted using semi-definite constraints
- resulting SDPs can be solved using off-the-shelf software.

Semi-definite program (SDP)

An optimization problem with

1. *linear constraints* on moments and
2. *positive semi-definite constraints* on certain matrices.

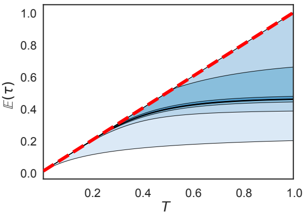
- alternative: linear *Hausdorff constraints* instead of semi-definite constraints

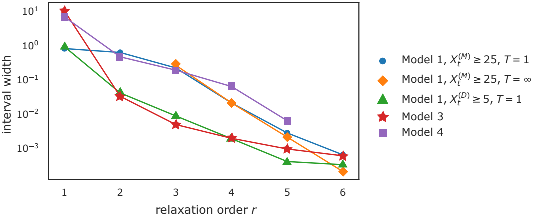
$$\int_{[0,1]^{\vec{n}}} \vec{x}^{\vec{\ell}}(1-\vec{x})^{\vec{k}}\, d\mu(\vec{x}) \geqslant 0$$

[BBW20]

Bounding mean first-passage times

Results



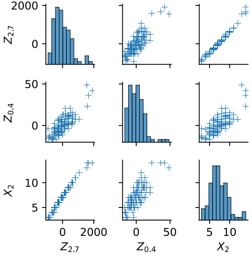


- fast convergence of bounds with increasing order
- SDPs are usually solved within seconds
- numerically challenging (inherent stiffness)
- scaling state-space / model size is difficult

[BBW20]

Linear control variates

Using correlated RVs with known expected value



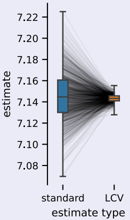
- improve MC estimates using Z_T
- use correlations between Z_T and X_T
- $\mathrm{E}\left(X_T + bZ_T\right)$ instead of $\mathrm{E}\left(X_T\right)$ (recall $\mathrm{E}\left(Z_T\right) = 0$)
- time-weighting $w(t) = \exp(\lambda t)$

Linear control variates

Given a control variate vector $\vec{Z}$, the estimator

$$\hat{V} - (\hat{\Sigma}_{\vec{Z}}^{-1}\hat{\Sigma}_{\vec{Z}V})^{\mathsf{T}}\hat{\vec{Z}}$$

has lower or equal variance as $\hat{V}$.



[BBW19]

Linear control variates

Efficiency trade-off

- infinite possible Z
- different time-weighting $\lambda \to$ different correlation
- the trade-off:

cost: slowdown

$$\text{cost}_{\text{old}} \big/ \text{cost}_{\text{new}}$$

- computing $\int_0^T w(t) X_t^m \, dt$
- computing the estimate

benefit: variance reduction

$$\sigma^2_{\text{new}} \big/ \sigma^2_{\text{old}}$$

- highly correlated variates

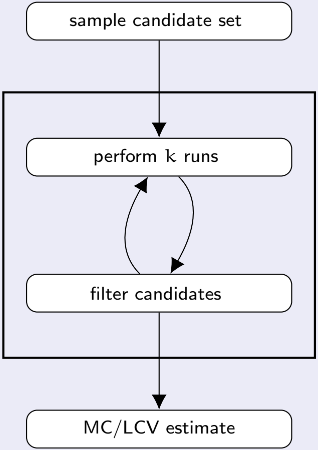
- approach: correlations between candidates and the target RV

[BBW19; BBW22]

Linear control variates

Selection by filtering

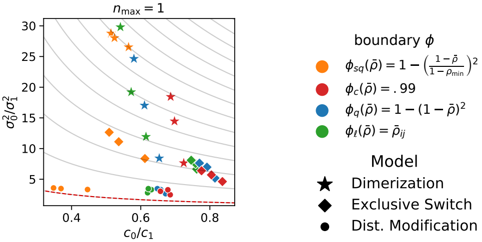
Algorithm 1



[BBW19]

filter criteria:

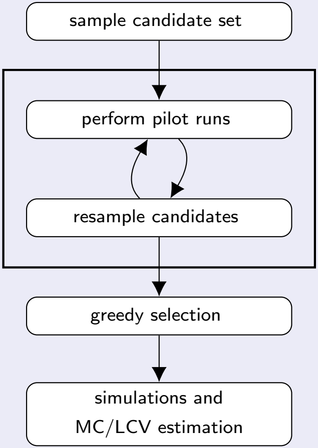
1. low target correlation
2. various redundancy heuristics



Linear control variates

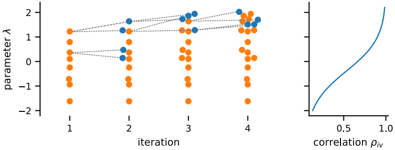
Selection by resampling

Algorithm 2



[BBW22]

- *resampling*: proportional to improvement

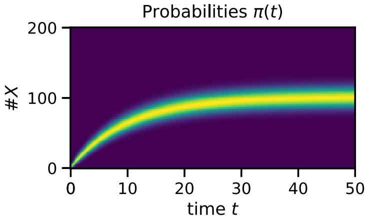


- *selection*: greedy by improvement

Results:

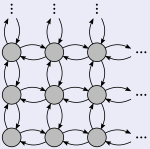
- performance equal/better than Alg. 1
- less hyper-parameter headaches

Aggregation & refinement



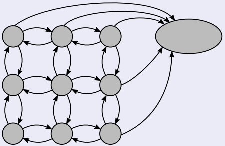
Finite-space projection

Original



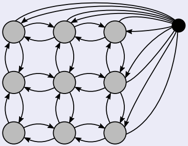
- very large/infinite
- impossible to analyze

Sink state



- transient analysis
- keep track of approx. error

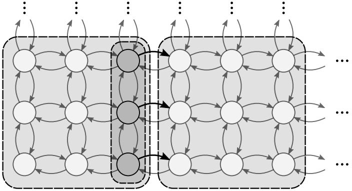
Redirection



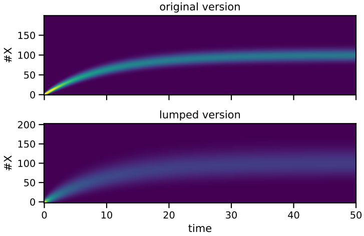
- stationary dist.
- dependent on redirection

State-space aggregation

Treating hyper-cubes of states as one



- hyper-cube macro-states
- *assumption*: uniform dist. within
- closed-form transition rates



- resulting distribution more "flat"
- locate main probability mass

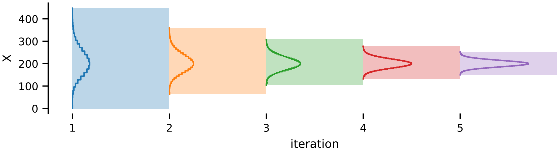
[Bac+21a]

Stationary distribution

Iterative refinement algorithm

A simple refinement based on approximate solutions:

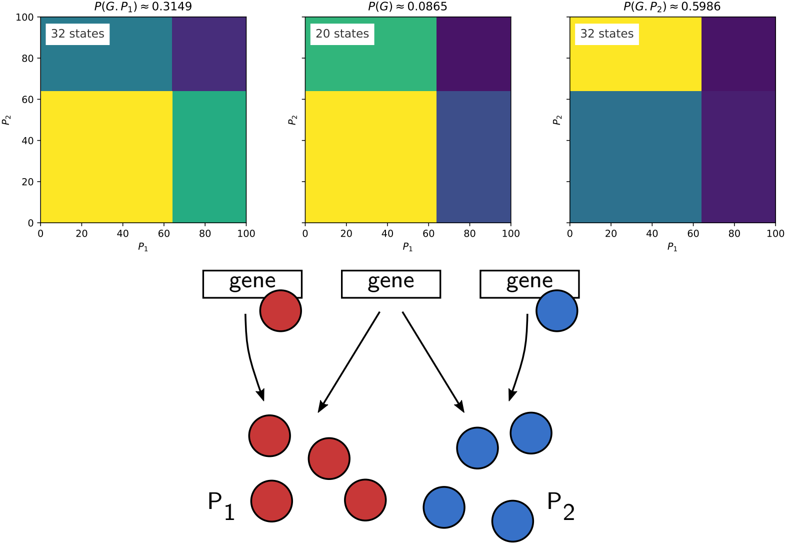
1. start with macro-states of size 2^k
2. compute approximate distribution
3. remove states with low probability
4. split the remaining states
5. go to step 2



[Bac+21b; Bac+21a]

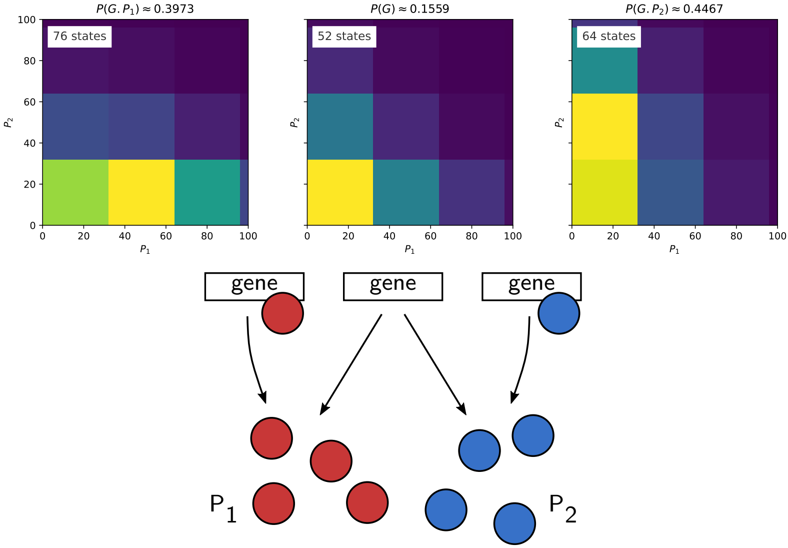
Stationary distribution

Example

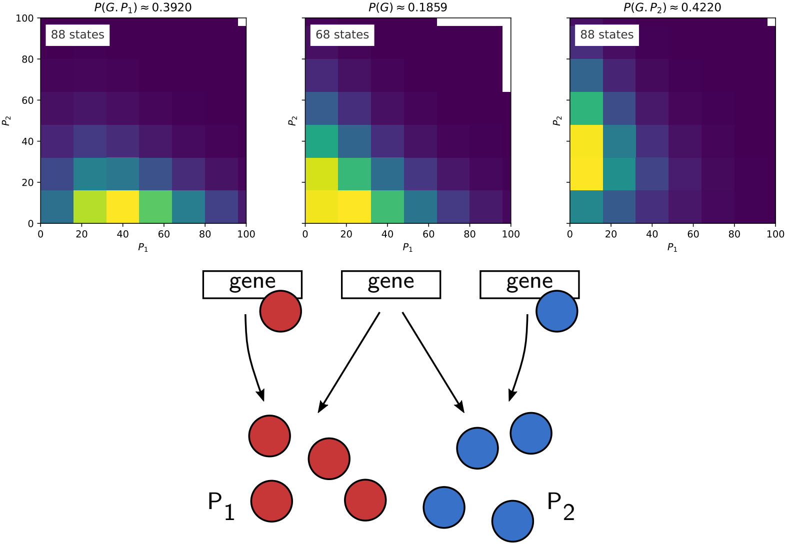


Stationary distribution

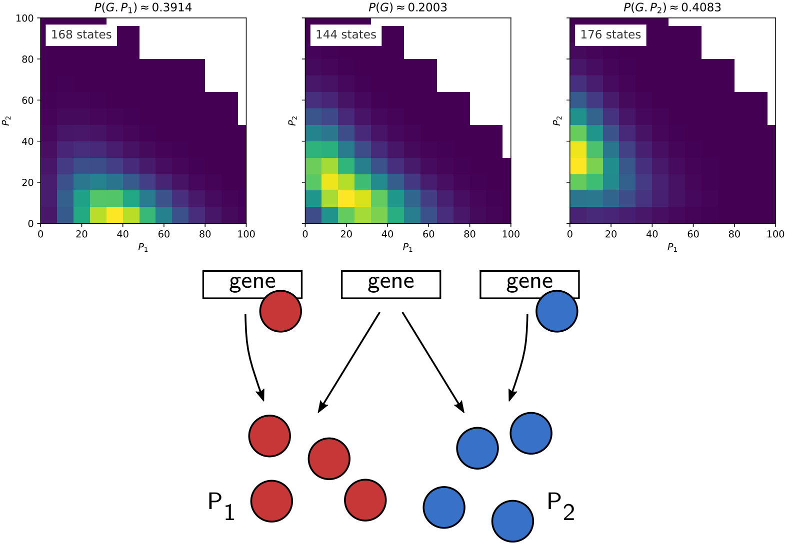
Example



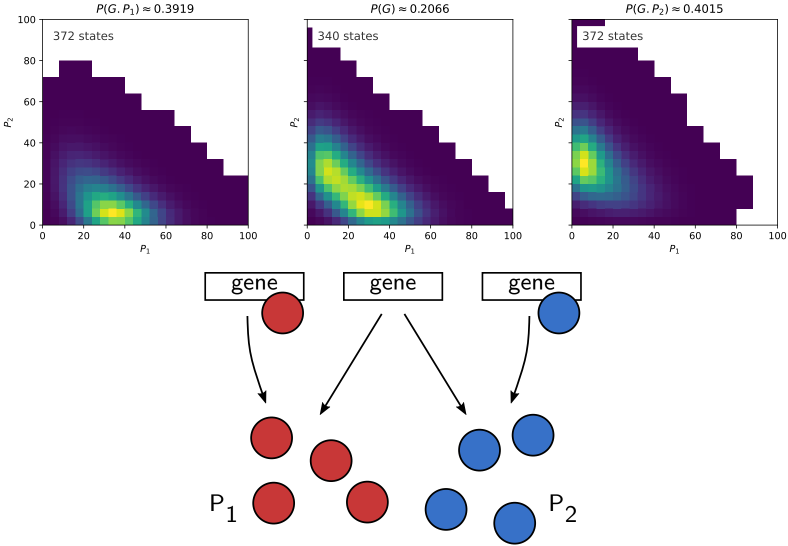
Stationary distribution
Example



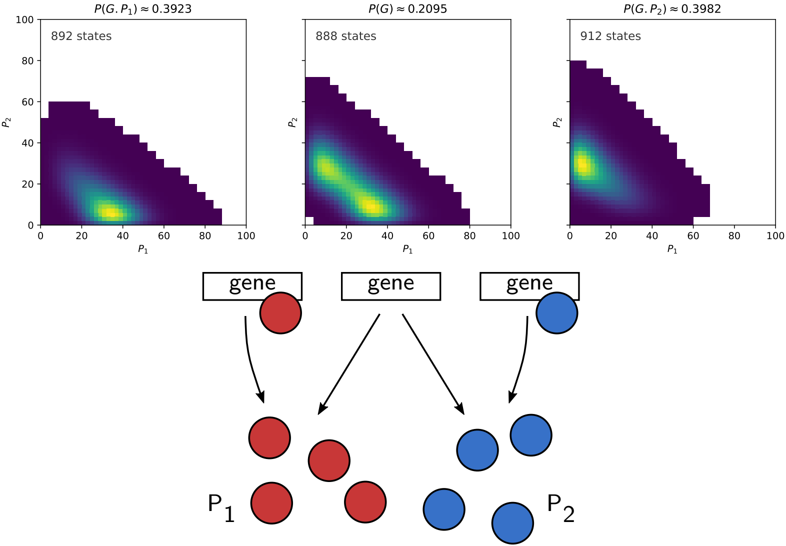
Stationary distribution
Example



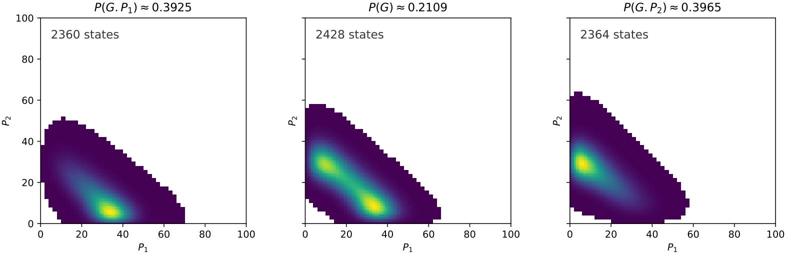
Stationary distribution
Example

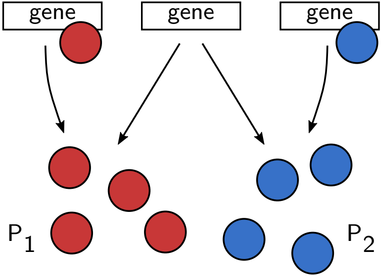


Stationary distribution
Example



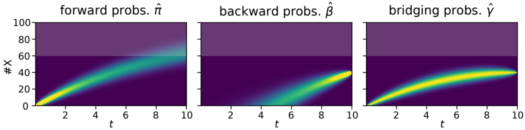
Stationary distribution
Example





Bridging problem

Dynamical analysis under initial *and* terminal constraints



Forward probabilities π

How the process evolves with time: $\Pr(X_t = x \mid X_0 = 0)$

Backward probabilities β

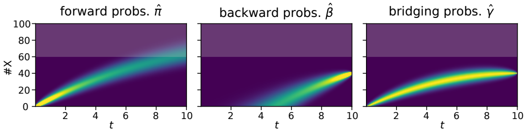
Probability of ending up in a given state: $\Pr(X_T = 40 \mid X_t = x)$

Bridging probabilities γ

In between: $\Pr(X_t = x \mid X_0 = 0, X_T = 40)$

[Bac+21b]

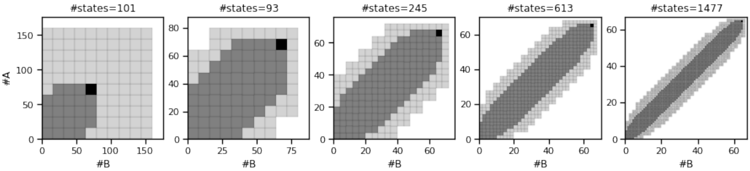
Bridging problem
Refinement



- bridging distribution:

$$\gamma(x_i, t) = \pi(x_i, t)\beta(x_i, t)/\pi(x_g, T)$$

- record intermediary times
- remove or split based on $\hat{\gamma}(x_i, t)$



[Bac+21b]

Bridging problem

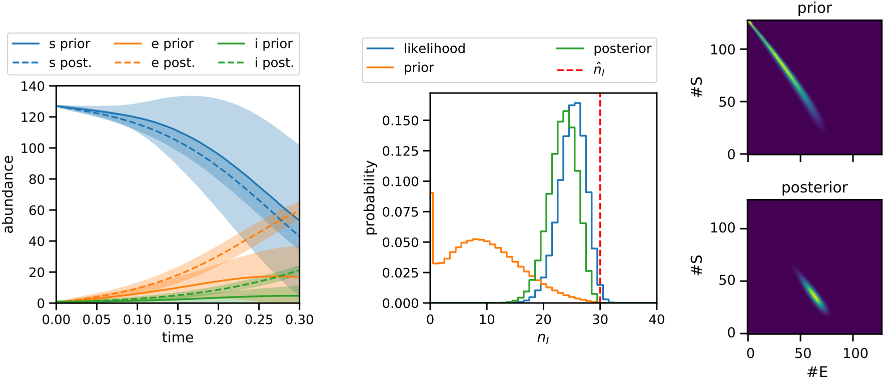
Bayesian filtering in an SEIR model

$$S + I \to E + I \qquad E \to I \qquad I \to R$$

We know:

- initial state
- uncertain measurement of I at $T = 0.3$

We are interested in the posterior at T.



[Bac+21b]

Contributions

- local augmentation of Foster-Lyapunov functions
- bounding of mean first-passage times [BBW20]
- variance reduction for MC estimation [BBW19; BBW22]
- state-space aggregation scheme
  - stationary distribution [Bac+21a]
  - bridging distribution [Bac+21b]
  - importance sampling

References I

[BBW20] Michael Backenköhler, Luca Bortolussi, and Verena Wolf. "Bounding Mean First Passage Times in Population Continuous-Time Markov Chains". In: *17th International Conference on Quantitative Evaluation of SysTems*. Vol. 12289. Lecture Notes in Computer Science. Springer, 2020, pp. 155–174.

[BBW19] Michael Backenköhler, Luca Bortolussi, and Verena Wolf. "Control Variates for Stochastic Simulation of Chemical Reaction Networks". In: *17th International Conference on Computational Methods in Systems Biology*. Vol. 11773. Lecture Notes in Computer Science. Springer, 2019, pp. 42–59.

[BBW22] Michael Backenköhler, Luca Bortolussi, and Verena Wolf. "Variance Reduction in Stochastic Reaction Networks using Control Variates". In: *Principles of Systems Design – Essays Dedicated to Thomas A. Henzinger on the Occasion of His 60th Birthday*. Vol. 13660. Lecture Notes in Computer Science. Springer, 2022.

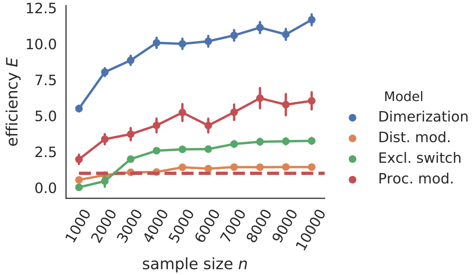
References II

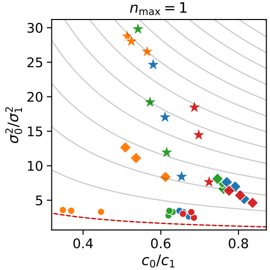
[Bac+21a] Michael Backenköhler et al. "Abstraction-Guided Truncations for Stationary Distributions of Markov Population Models". In: *18th International Conference on Quantitative Evaluation of SysTems*. Vol. 12846. Lecture Notes in Computer Science. Springer, 2021, pp. 351–371.

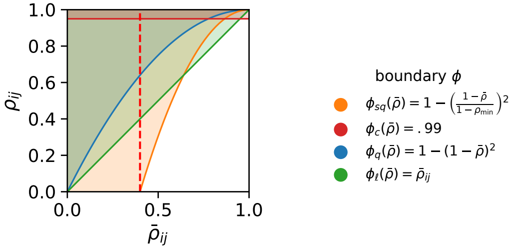
[Bac+21b] Michael Backenköhler et al. "Analysis of Markov Jump Processes under Terminal Constraints". In: *27th International Conference on Tools and Algorithms for the Construction and Analysis of Systems*. Vol. 12651. Lecture Notes in Computer Science. Springer, 2021, pp. 210–229.

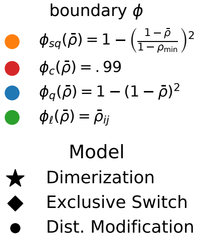
Linear control variates

Results



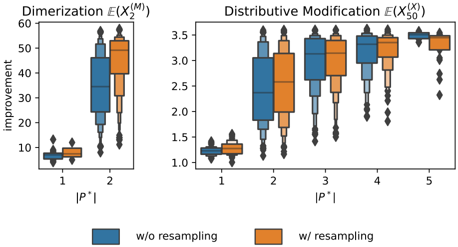






Linear control variates
Results

- SMC can improve variance reduction



- less dependence on initial covariates
- more consistent performance