

# Analysis of Markovian Population Models

Dissertation Defense

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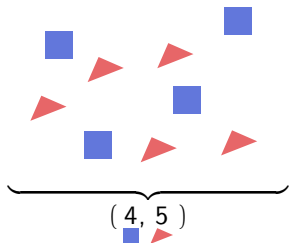
September 20, 2022

# Motivation

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

# Markovian Population Models

## Semantics



- ▶ state space  $\sim$  population sizes
- ▶ often huge to infinite



- ▶ continuous time
- ▶ exponential jump times / CTMC dynamics

# Markovian Population Models

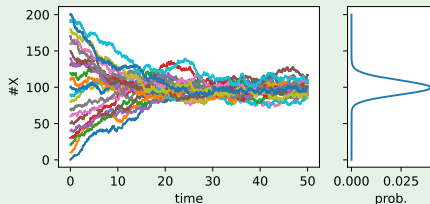
## Stationary Distribution – Foster-Lyapunov Functions

- ▶ ergodic chains converge to unique distribution ( $t \rightarrow \infty$ )

### Example

$$X \xrightarrow{0.1 \cdot \#X} \emptyset, \quad \alpha_1(x) = 0.1x$$

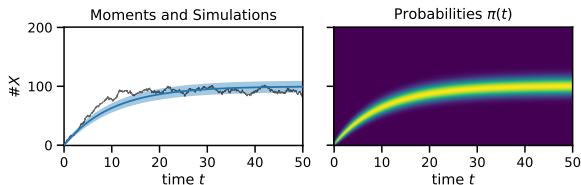
$$\emptyset \xrightarrow{10} X, \quad \alpha_2(x) = 10$$



- ▶ how does this distribution look like for infinite state-spaces?
- ▶ use Foster-Lyapunov function to bound sets
- ▶ locally augment functions for tighter sets / bounds

# Markovian Population Models

## Moment Dynamics



## Moment formula

Moments such as mean  $E(X_t)$  and variance  $E(X_t^2) - E(X_t)^2$  are described by (often linear) ODEs.

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

# Markovian Population Models

## Martingale Process

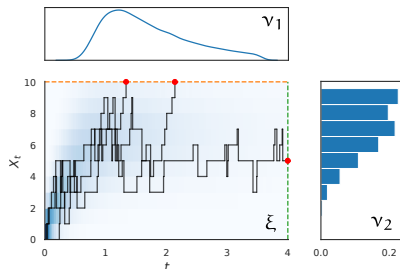
- ▶ multiply time-weighting:  $w(t) = t^k$ ,  $k \in \mathbb{N}$  or  $w(t) = \exp(\lambda t)$
- ▶ analytic integration and resulting martingale process

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

- ▶ known expectation:  $E(Z_T) = 0$ ,  $\forall T \geq 0$

# Bounding Mean First-Passage Times

## Linear Moment Constraints



- ▶  $\tau = \inf\{X_t \geq H \mid t \geq 0\} \wedge T$
- ▶ exp. occupation measure  $\xi$
- ▶ exit location measures  $\nu_1, \nu_2$

$$\begin{aligned}
 0 = \mathbb{E}(Z_T) &= T^k \overbrace{\mathbb{E}(X_\tau^m; \tau = T)}^{\nu_1} + H^m \overbrace{\mathbb{E}(\tau^k; \tau < T, X_\tau = H)}^{\nu_2} \\
 &\quad - 0^k x_0^m + \underbrace{\sum_i c_i \mathbb{E}\left(\int_0^\tau t^{k_i} X_t^{m_i} dt\right)}_{\xi}
 \end{aligned}$$

# Bounding Mean First-Passage Times

## Moment Matrices

### Moment Matrices

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

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

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

### Example

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

[BBW20]



# Bounding Mean First-Passage Times

## Semi-Definite Program

- ▶ 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

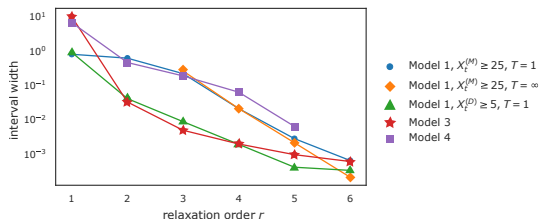
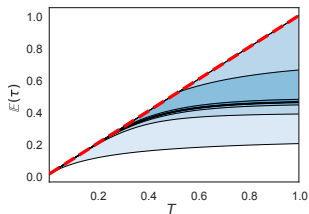
1. *linear constraints* on moments and
  2. *positive semi-definite constraints* on certain matrices.
- ▶ alternative: linear *Hausdorff constraints* instead of semi-definite constraints

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

[BBW20]

# Bounding Mean First-Passage Times

## Results

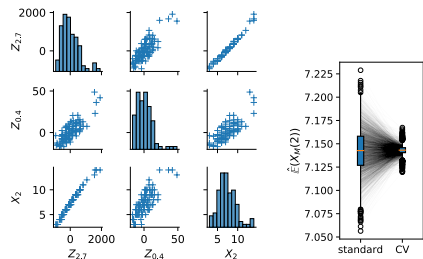


- ▶ fast convergence of bounds with increasing order
- ▶ numerically challenging (inherent stiffness)

[BBW20]

# Linear Control Variates

Using Correlated RVs with Known Expected Value



- ▶ improve MC estimates using  $Z_T$
- ▶ use correlations between  $Z_T$  and  $X_T$
- ▶  $E(X_T + bZ_T)$  instead of  $E(X_T)$  (recall  $E(Z_T) = 0$ )

## Linear Control Variates

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

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

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

[BBW19]

# Linear Control Variates

## Efficiency Trade-off

### cost: slowdown

$$c_{\text{old}}/c_{\text{new}}$$

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

### benefit: variance reduction

$$\sigma_{\text{new}}^2/\sigma_{\text{old}}^2$$

- ▶ highly correlated variates

Approach: Assess correlations between  $k$  candidates and the target RV  $V$

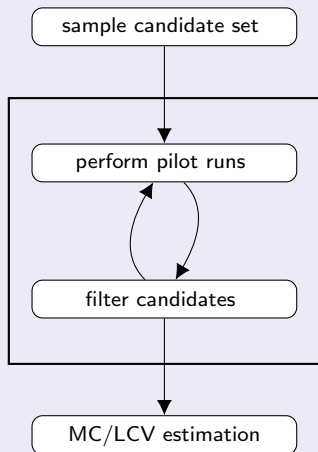
$$\begin{bmatrix} 1 & \dots & \rho_{1k} & \rho_{1v} \\ \vdots & \ddots & \vdots & \vdots \\ \rho_{k1} & \dots & 1 & \rho_{kv} \\ \rho_{v1} & \dots & \rho_{vk} & 1 \end{bmatrix}.$$

[BBW19; BBW22]

# Linear Control Variates

## Selection by Filtering

### Algorithm 1

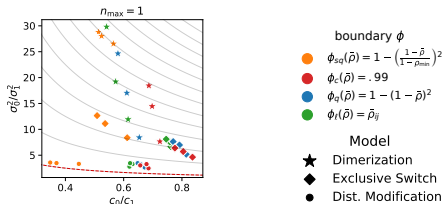


Filter criteria:

1. low target correlation

$$\rho_{iv} < \max \left( 0.1, \frac{\max_j \rho_{jv}}{k_{\min}} \right)$$

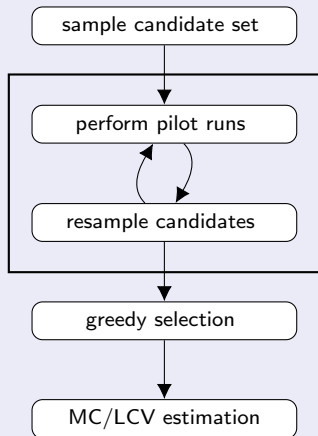
2. various redundancy heuristics



# Linear Control Variates

## Selection by Resampling

### Algorithm 2



Filter criteria:

1. *resampling* proportional to improvement

$$\gamma_{kv} = (1 - \rho_{kv}^2)^{-1}$$

2. *selection* by best improvement of one CV

$$\arg \max_{1 \leq i \leq |P_{\text{all}}|} \hat{\gamma}_{iv} \prod_{\substack{1 \leq j \leq |P_{\text{all}}| \\ (m_j, \lambda_j) \in P^*}} \hat{\gamma}_{ij}^{-1}$$

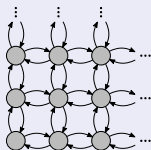
# Linear Control Variates

## Results

- ▶ best example?

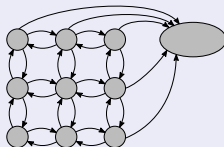
# Finite-Space Projection

## Original



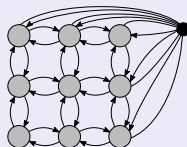
- infinite

## Sink state



- transient analysis
- keep track of approx. error

## Redirection

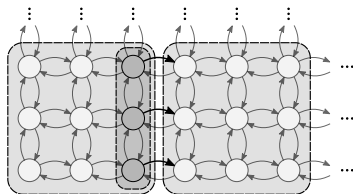


- stationary dist.
- dependent on redirection

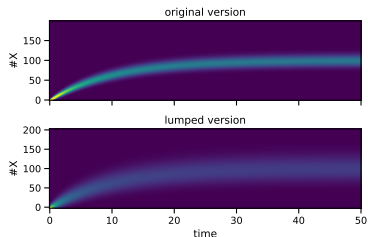


# State-Space Aggregation

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

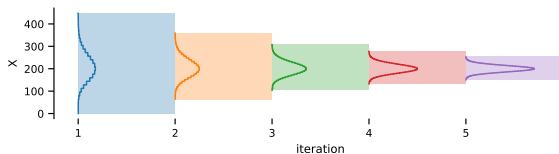
[Bac+21a; Bac+21b]

# Stationary Distribution

## Iterative Refinement Algorithm

A simple refinement based on approximate solutions:

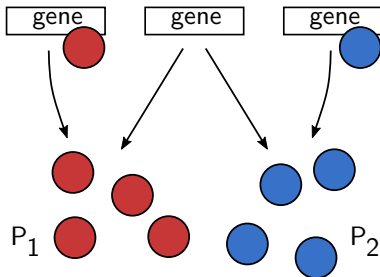
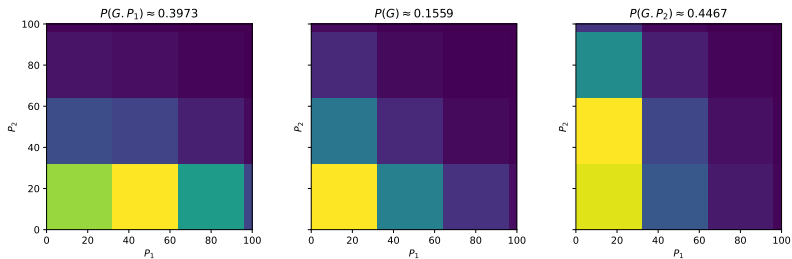
1. start with macro-states of size  $2^k$
2. compute approximate distribution
3. remove states with low probability
4. split the remaining states
5. go to step 2



[Bac+21a; Bac+21b]

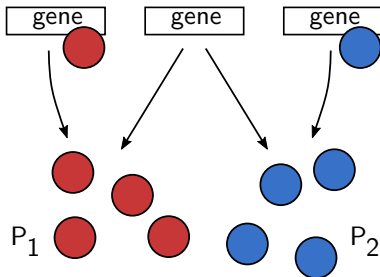
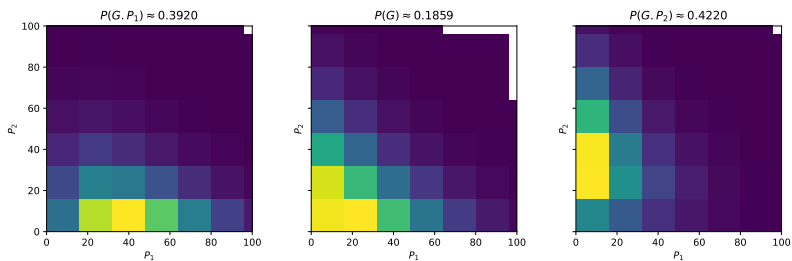
# Stationary Distribution

## Examples



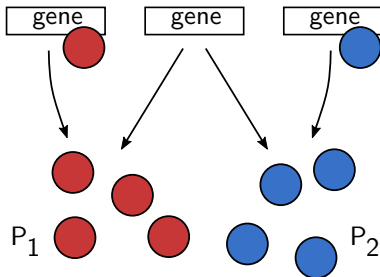
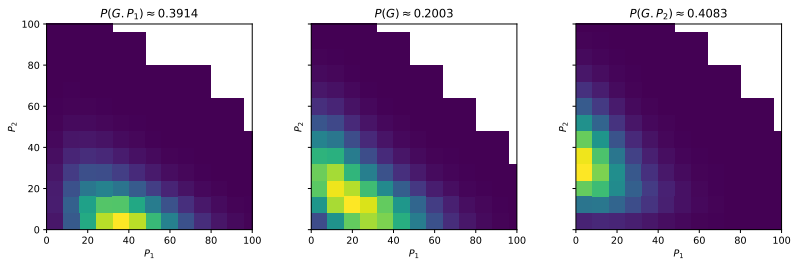
# Stationary Distribution

## Examples



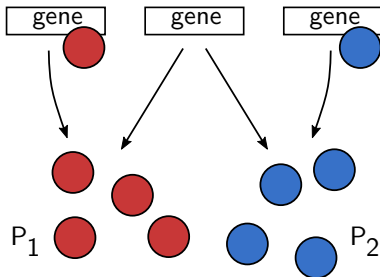
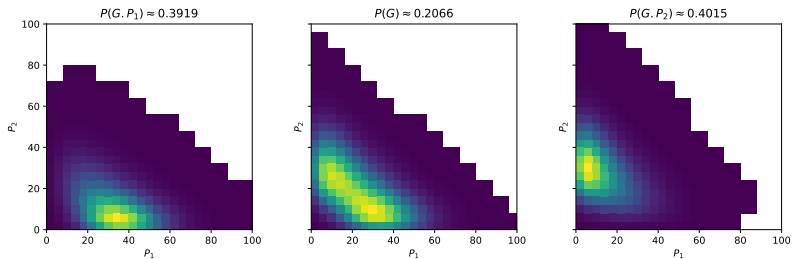
# Stationary Distribution

## Examples



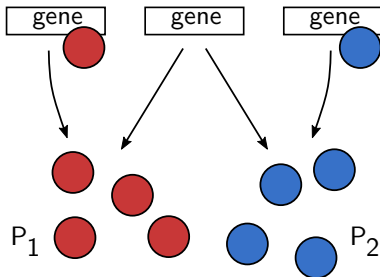
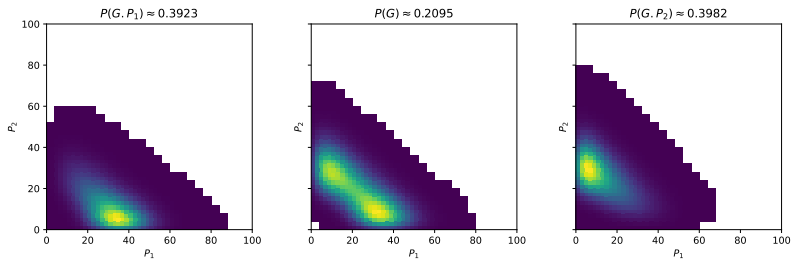
# Stationary Distribution

## Examples



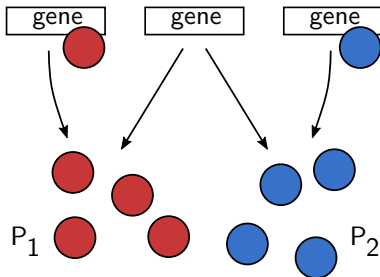
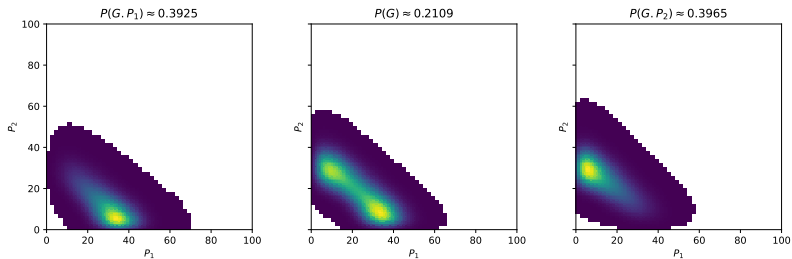
# Stationary Distribution

## Examples



# Stationary Distribution

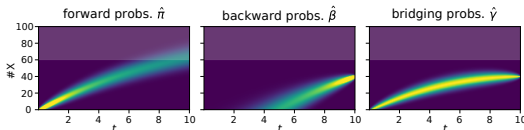
## Examples





# Bridging Problem

## Dynamical Analysis Under Initial *and* Terminal Constraints



### Forward Probabilities

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

### Backward Probabilities

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

### Bridging Probabilities

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

[Bac+21a]

# Bridging Problem

## Refinement

- ▶ Show that  $\text{bridge} = \text{forward} * \text{backwards}$
- ▶ Record intermediary times

# Bridging Problem

## Examples

# 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+21b]
  - ▶ bridging distribution [Bac+21a]
  - ▶ 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. “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.
- [Bac+21b] 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.