

Pre-CDC Workshop.
University of California, Santa Barbara
December 11, 2006

Munsky 2006



A Reduced Model Solution for the Chemical Master Equation Arising in Stochastic Analyses of Biological Networks.

Brian Munsky and Mustafa Khammash

UCSB Department of Mechanical Engineering

Outline

1. Introduction
2. The Finite State Projection (FSP)
3. Model Reduction of the FSP
4. Examples
5. Conclusions



Introduction

- Much mathematical modeling of gene networks is done at the macroscopic level.
 - Thermodynamic Limit.
 - Deterministic Models.
- Some key chemical species are very rare.
 - genes, proteins, RNA molecules, etc.
 - Take on discrete values.
- Noise dominates the cellular environment.

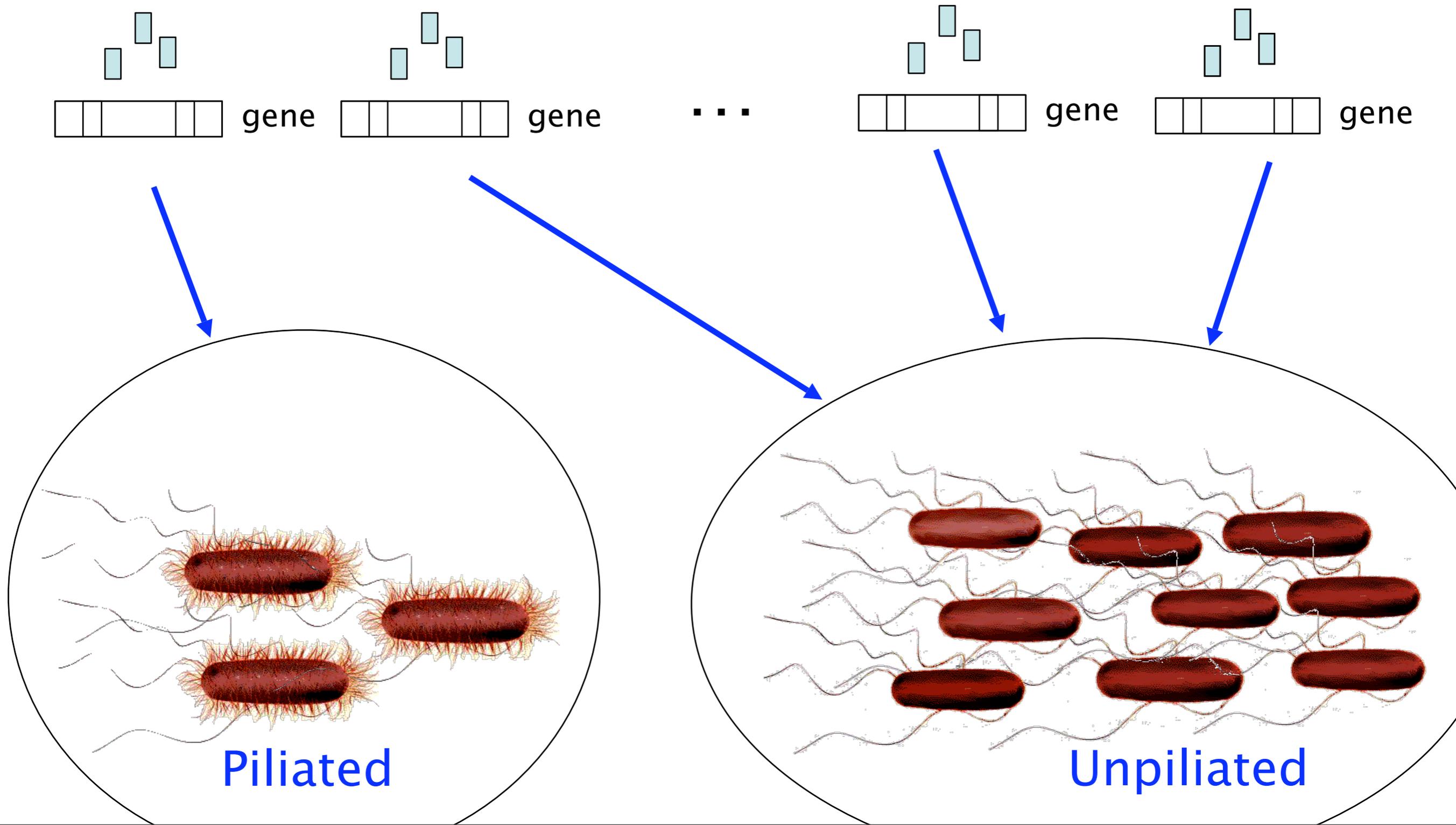
Stochastic Switching:

Identical genotype, identical environments, yet different phenotypes.



Stochastic Switching:

Identical genotype, identical environments, yet different phenotypes.



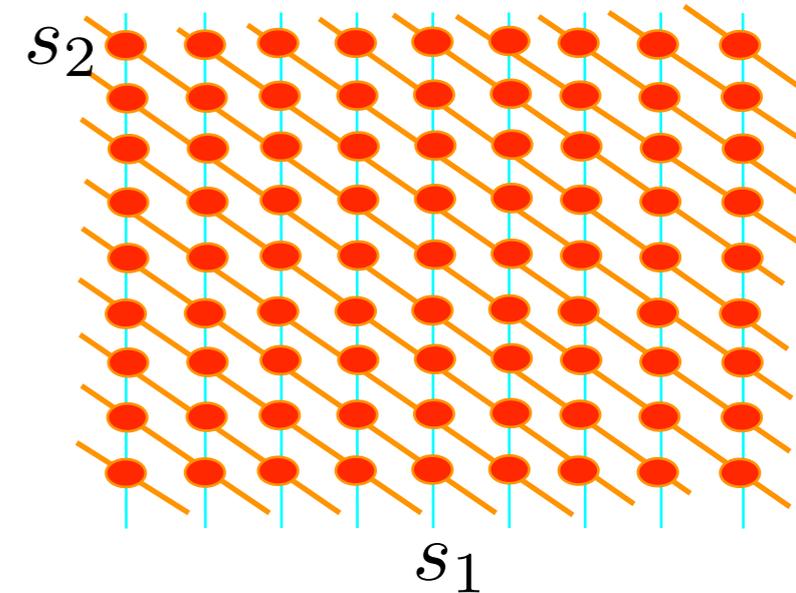


A Markov description of chemical kinetics

- At any time the system is in one of a countable number of configurations. $\mathbf{X}^T = [x_1, x_2, x_3, \dots]$
- Reactions are transitions from one configuration to another.
 - These reactions occur with exponentially distributed waiting times.
- The μ^{th} occurs in the next infinitesimal time step, with probability $a_\mu(\mathbf{x}_i)dt$.

The Chemical Master Equation

The probability that the system is in configuration \mathbf{x} at $t+dt$ is equal to the probability that the system is at \mathbf{x} at t , and no reaction occurs between t and $t+dt$ plus the probability that the system is one reaction removed from \mathbf{x} at t and that reaction occurs between t and $t+dt$.

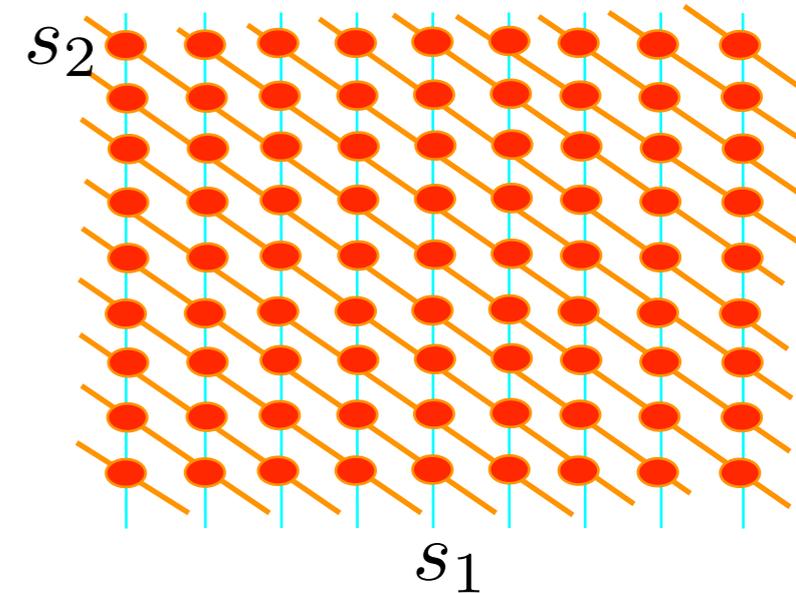


The Chemical Master Equation

The probability that the system is in configuration \mathbf{x} at $t+dt$ is equal to the probability that the system is at \mathbf{x} at t , and no reaction occurs between t and $t+dt$ plus the probability that the system is one reaction removed from \mathbf{x} at t and that reaction occurs between t and $t+dt$.

The CME (McQuarrie '67):

$$\dot{p}(\mathbf{x}, t) = -p(\mathbf{x}, t) \sum_{\mu=1}^M a_{\mu}(\mathbf{x}) + \sum_{\mu=1}^M p(\mathbf{x} - \nu_{\mu}, t) a_{\mu}(\mathbf{x} - \nu_{\mu})$$



The Chemical Master Equation

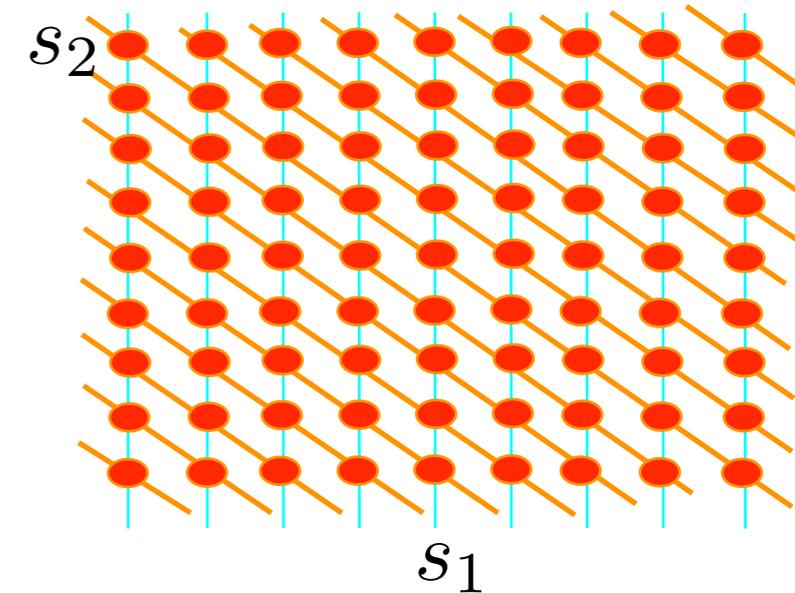
The probability that the system is in configuration \mathbf{x} at $t+dt$ is equal to the probability that the system is at \mathbf{x} at t , and no reaction occurs between t and $t+dt$ plus the probability that the system is one reaction removed from \mathbf{x} at t and that reaction occurs between t and $t+dt$.

The CME (McQuarrie '67):

$$\dot{p}(\mathbf{x}, t) = -p(\mathbf{x}, t) \sum_{\mu=1}^M a_{\mu}(\mathbf{x}) + \sum_{\mu=1}^M p(\mathbf{x} - \nu_{\mu}, t) a_{\mu}(\mathbf{x} - \nu_{\mu})$$

Define the probability density state

vector (pdv): $\mathbf{P}(\mathbf{X}, t) := [p(\mathbf{x}_1, t), p(\mathbf{x}_2, t), p(\mathbf{x}_3, t), \dots]^T$.



The Chemical Master Equation

The probability that the system is in configuration \mathbf{x} at $t+dt$ is equal to the probability that the system is at \mathbf{x} at t , and no reaction occurs between t and $t+dt$ plus the probability that the system is one reaction removed from \mathbf{x} at t and that reaction occurs between t and $t+dt$.

The CME (McQuarrie '67):

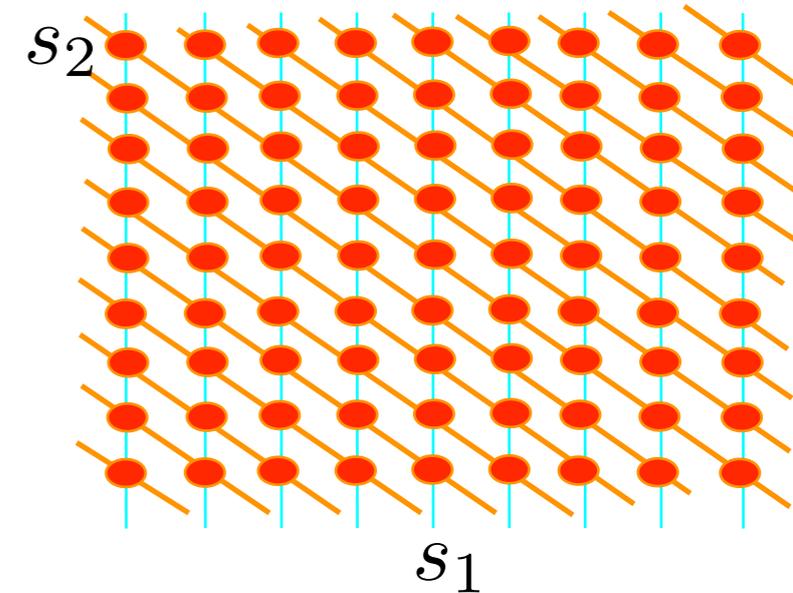
$$\dot{p}(\mathbf{x}, t) = -p(\mathbf{x}, t) \sum_{\mu=1}^M a_{\mu}(\mathbf{x}) + \sum_{\mu=1}^M p(\mathbf{x} - \nu_{\mu}, t) a_{\mu}(\mathbf{x} - \nu_{\mu})$$

Define the probability density state

vector (pdv): $\mathbf{P}(\mathbf{X}, t) := [p(\mathbf{x}_1, t), p(\mathbf{x}_2, t), p(\mathbf{x}_3, t), \dots]^T$.

$\mathbf{P}(\mathbf{X}, t)$ evolves according to the Linear Time Invariant ODE:

$$\dot{\mathbf{P}}(\mathbf{X}, t) = \mathbf{A} \cdot \mathbf{P}(\mathbf{X}, t).$$



The Chemical Master Equation

The probability that the system is in configuration \mathbf{x} at $t+dt$ is equal to the probability that the system is at \mathbf{x} at t , and no reaction occurs between t and $t+dt$ plus the probability that the system is one reaction removed from \mathbf{x} at t and that reaction occurs between t and $t+dt$.

The CME (McQuarrie '67):

$$\dot{p}(\mathbf{x}, t) = -p(\mathbf{x}, t) \sum_{\mu=1}^M a_{\mu}(\mathbf{x}) + \sum_{\mu=1}^M p(\mathbf{x} - \nu_{\mu}, t) a_{\mu}(\mathbf{x} - \nu_{\mu})$$

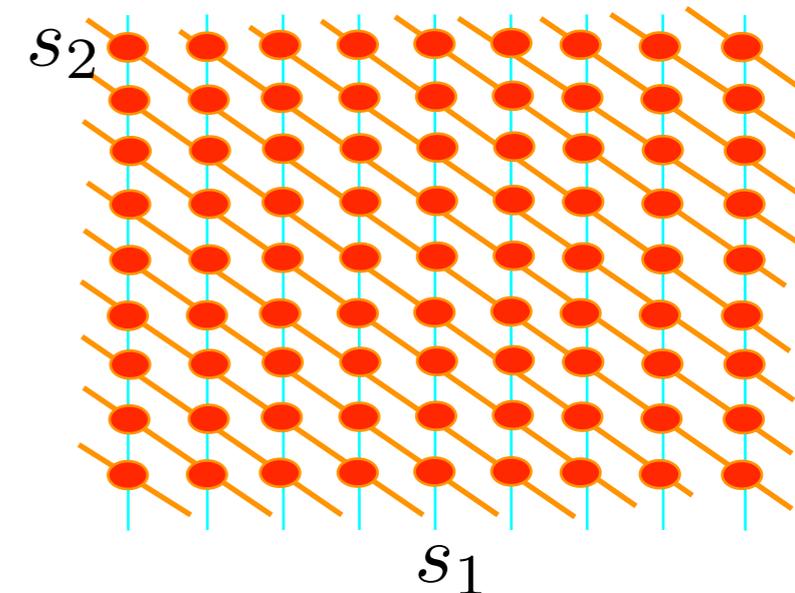
Define the probability density state

vector (pdv): $\mathbf{P}(\mathbf{X}, t) := [p(\mathbf{x}_1, t), p(\mathbf{x}_2, t), p(\mathbf{x}_3, t), \dots]^T$.

$\mathbf{P}(\mathbf{X}, t)$ evolves according to the Linear Time Invariant ODE:

$$\dot{\mathbf{P}}(\mathbf{X}, t) = \mathbf{A} \cdot \mathbf{P}(\mathbf{X}, t).$$

The matrix CME





Solving the CME

- Kinetic Monte Carlo algorithms.
 - SSA, τ leaping, System Partitioning Methods.

Solving the CME

- Kinetic Monte Carlo algorithms.
 - SSA, τ leaping, System Partitioning Methods.
 - May require many realizations (10^4 to 10^6) before one can achieve sufficient confidence in the solution of the CME.



Solving the CME

- Kinetic Monte Carlo algorithms.
 - SSA, τ leaping, System Partitioning Methods.
 - May require many realizations (10^4 to 10^6) before one can achieve sufficient confidence in the solution of the CME.
- Matrix Exponential Solution

$$\mathbf{P}(\mathbf{X}, t) = \exp(\mathbf{A}t)\mathbf{P}(\mathbf{X}, 0)$$



Solving the CME

- Kinetic Monte Carlo algorithms.
 - SSA, τ leaping, System Partitioning Methods.
 - May require many realizations (10^4 to 10^6) before one can achieve sufficient confidence in the solution of the CME.

- Matrix Exponential Solution

$$\mathbf{P}(\mathbf{X}, t) = \exp(\mathbf{A}t)\mathbf{P}(\mathbf{X}, 0)$$

- What if the configuration space is infinite?



Outline

1. Introduction
2. The Finite State Projection (FSP) solution of the Chemical Master Equation (CME)



The FSP: Finite Projection Bounds

Let $J = [j_1, j_2, \dots, j_N]$ be an indexing vector, defining $\mathbf{A}_J \in \mathbb{R}^{N \times N}$ to be the principle submatrix of \mathbf{A} .



The FSP:

Finite Projection Bounds

Let $J = [j_1, j_2, \dots, j_N]$ be an indexing vector, defining $\mathbf{A}_J \in \mathbb{R}^{N \times N}$ to be the principle submatrix of \mathbf{A} .

Theorem 1 [Munsky, Khammash JCP '06]: Consider any Markov Process in which the probability distribution evolves according to the ODE:

$$\dot{\mathbf{P}}(\mathbf{X}, t) := \mathbf{A} \cdot \mathbf{P}(\mathbf{X}, t)$$

If for an indexing vector $J: \mathbf{1}^T \exp(\mathbf{A}_J t_f) \mathbf{P}(\mathbf{X}_J; 0) \geq 1 - \epsilon$

then $\exp(\mathbf{A}_J t_f) \mathbf{P}(\mathbf{X}_J; 0) \leq \mathbf{P}(\mathbf{X}_J; t_f)$, and

$$\left\| \begin{bmatrix} \mathbf{P}(\mathbf{X}_J, t_f) \\ \mathbf{P}(\mathbf{X}_{J'}, t_f) \end{bmatrix} - \begin{bmatrix} \exp(\mathbf{A} t_f) \mathbf{P}(\mathbf{X}_J, 0) \\ \mathbf{0} \end{bmatrix} \right\|_1 \leq \epsilon.$$



The Benefits of an FSP Solution

- The FSP is a linear ODE.
 - Provides probability bounds on unlikely events.
 - Open to linear systems based model reductions.
 - Enables sensitivity and robustness analyses.

Outline

1. Introduction
2. The Finite State Projection (FSP)
3. FSP Model Reduction
 - Observability based minimal realizations.



Reducing Unobservable Configurations

- Often one is not interested in the entire probability distribution.



Reducing Unobservable Configurations

- Often one is not interested in the entire probability distribution.
- Instead one may wish only to estimate:
 - ★ a statistical summary of the distribution, e.g.
 - ◆ means, variances, or higher moments



Reducing Unobservable Configurations

- Often one is not interested in the entire probability distribution.
- Instead one may wish only to estimate:
 - ★ a statistical summary of the distribution, e.g.
 - ◆ means, variances, or higher moments
 - ★ probability of certain traits:
 - ◆ **switch rate**, extinction, specific trajectories, etc...



Reducing Unobservable Configurations

- Often one is not interested in the entire probability distribution.
- Instead one may wish only to estimate:
 - ★ a statistical summary of the distribution, e.g.
 - ◆ means, variances, or higher moments
 - ★ probability of certain traits:
 - ◆ **switch rate**, extinction, specific trajectories, etc...
- In each of these cases, one can define an output **y(t)**:

$$\dot{\mathbf{P}}(t) = \mathbf{A}\mathbf{P}(t)$$

$$\mathbf{y}(t) = \mathbf{C}\mathbf{P}(t)$$



Aggregation and Model Reduction

Given: Generic CME in the form of a linear ODE:

$$\dot{\mathbf{P}}(\mathbf{X}, t) = \mathbf{A} \cdot \mathbf{P}(\mathbf{X}, t)$$

The system begins in the set U at $t=0$ with pdv: $\mathbf{P}(X_U, 0)$.



Aggregation and Model Reduction

Given: Generic CME in the form of a linear ODE:

$$\dot{\mathbf{P}}(\mathbf{X}, t) = \mathbf{A} \cdot \mathbf{P}(\mathbf{X}, t)$$

The system begins in the set U at $t=0$ with pdv: $\mathbf{P}(X_U, 0)$.

Find: $\mathbf{P}(X_Y, t_f)$ for some set Y .



Aggregation and Model Reduction

Given: Generic CME in the form of a linear ODE:

$$\dot{\mathbf{P}}(\mathbf{X}, t) = \mathbf{A} \cdot \mathbf{P}(\mathbf{X}, t)$$

The system begins in the set U at $t=0$ with pdv: $\mathbf{P}(X_U, 0)$.

Find: $\mathbf{P}(X_Y, t_f)$ for some set Y .

Define:

R = set of configurations reachable from U .

R' = set of configurations unreachable from U .

O = set of configurations from which Y may be reached.

O' = set of configurations unobservable from Y .

Aggregation and Model Reduction

The full pdv evolves according to:

$$\begin{bmatrix} \dot{\mathbf{P}}(\mathbf{X}_{RO}, t) \\ \dot{\mathbf{P}}(\mathbf{X}_{R'O}, t) \\ \dot{\mathbf{P}}(\mathbf{X}_{RO'}, t) \\ \dot{\mathbf{P}}(\mathbf{X}_{R'O'}, t) \end{bmatrix} = \begin{bmatrix} \mathbf{A}_{RO,RO} & \mathbf{A}_{RO,R'O} & \mathbf{A}_{RO,RO'} & \mathbf{A}_{RO,R'O'} \\ \mathbf{A}_{R'O,RO} & \mathbf{A}_{R'O,R'O} & \mathbf{A}_{R'O,RO'} & \mathbf{A}_{R'O,R'O'} \\ \mathbf{A}_{RO',RO} & \mathbf{A}_{RO',R'O} & \mathbf{A}_{RO',RO'} & \mathbf{A}_{RO',R'O'} \\ \mathbf{A}_{R'O',RO} & \mathbf{A}_{R'O',R'O} & \mathbf{A}_{R'O',RO'} & \mathbf{A}_{R'O',R'O'} \end{bmatrix} \begin{bmatrix} \mathbf{P}(\mathbf{X}_{RO}, t) \\ \mathbf{P}(\mathbf{X}_{R'O}, t) \\ \mathbf{P}(\mathbf{X}_{RO'}, t) \\ \mathbf{P}(\mathbf{X}_{R'O'}, t) \end{bmatrix}$$

Aggregation and Model Reduction

The full pdv evolves according to:

$$\begin{bmatrix} \dot{\mathbf{P}}(\mathbf{X}_{RO}, t) \\ \dot{\mathbf{P}}(\mathbf{X}_{R'O}, t) \\ \dot{\mathbf{P}}(\mathbf{X}_{RO'}, t) \\ \dot{\mathbf{P}}(\mathbf{X}_{R'O'}, t) \end{bmatrix} = \begin{bmatrix} \mathbf{A}_{RO,RO} & \mathbf{A}_{RO,R'O} & \mathbf{A}_{RO,RO'} & \mathbf{A}_{RO,R'O'} \\ \mathbf{A}_{R'O,RO} & \mathbf{A}_{R'O,R'O} & \mathbf{A}_{R'O,RO'} & \mathbf{A}_{R'O,R'O'} \\ \mathbf{A}_{RO',RO} & \mathbf{A}_{RO',R'O} & \mathbf{A}_{RO',RO'} & \mathbf{A}_{RO',R'O'} \\ \mathbf{A}_{R'O',RO} & \mathbf{A}_{R'O',R'O} & \mathbf{A}_{R'O',RO'} & \mathbf{A}_{R'O',R'O'} \end{bmatrix} \begin{bmatrix} \mathbf{P}(\mathbf{X}_{RO}, t) \\ \mathbf{P}(\mathbf{X}_{R'O}, t) \\ \mathbf{P}(\mathbf{X}_{RO'}, t) \\ \mathbf{P}(\mathbf{X}_{R'O'}, t) \end{bmatrix}$$

The unreachable configurations cannot be excited by reachable ones (may be removed!)

Aggregation and Model Reduction

The full pdv evolves according to:

$$\begin{bmatrix} \dot{\mathbf{P}}(\mathbf{X}_{RO}, t) \\ \dot{\mathbf{P}}(\mathbf{X}_{R'O}, t) \\ \dot{\mathbf{P}}(\mathbf{X}_{RO'}, t) \\ \dot{\mathbf{P}}(\mathbf{X}_{R'O'}, t) \end{bmatrix} = \begin{bmatrix} \mathbf{A}_{RO,RO} & \mathbf{A}_{RO,R'O} & \mathbf{A}_{RO,RO'} & \mathbf{A}_{RO,R'O'} \\ 0 & \mathbf{A}_{R'O,R'O} & 0 & \mathbf{A}_{R'O,R'O'} \\ \mathbf{A}_{RO',RO} & \mathbf{A}_{RO',R'O} & \mathbf{A}_{RO',RO'} & \mathbf{A}_{RO',R'O'} \\ 0 & \mathbf{A}_{R'O',R'O} & 0 & \mathbf{A}_{R'O',R'O'} \end{bmatrix} \begin{bmatrix} \mathbf{P}(\mathbf{X}_{RO}, t) \\ \mathbf{P}(\mathbf{X}_{R'O}, t) \\ \mathbf{P}(\mathbf{X}_{RO'}, t) \\ \mathbf{P}(\mathbf{X}_{R'O'}, t) \end{bmatrix}$$

The unreachable configurations cannot be excited by reachable ones (may be removed!)

Aggregation and Model Reduction

The full pdv evolves according to:

$$\begin{bmatrix} \dot{\mathbf{P}}(\mathbf{X}_{RO}, t) \\ \dot{\mathbf{P}}(\mathbf{X}_{R'O}, t) \\ \dot{\mathbf{P}}(\mathbf{X}_{RO'}, t) \\ \dot{\mathbf{P}}(\mathbf{X}_{R'O'}, t) \end{bmatrix} = \begin{bmatrix} \mathbf{A}_{RO,RO} & \mathbf{A}_{RO,R'O} & \mathbf{A}_{RO,RO'} & \mathbf{A}_{RO,R'O'} \\ 0 & \mathbf{A}_{R'O,R'O} & 0 & \mathbf{A}_{R'O,R'O'} \\ \mathbf{A}_{RO',RO} & \mathbf{A}_{RO',R'O} & \mathbf{A}_{RO',RO'} & \mathbf{A}_{RO',R'O'} \\ 0 & \mathbf{A}_{R'O',R'O} & 0 & \mathbf{A}_{R'O',R'O'} \end{bmatrix} \begin{bmatrix} \mathbf{P}(\mathbf{X}_{RO}, t) \\ \mathbf{P}(\mathbf{X}_{R'O}, t) \\ \mathbf{P}(\mathbf{X}_{RO'}, t) \\ \mathbf{P}(\mathbf{X}_{R'O'}, t) \end{bmatrix}$$

The unreachable configurations cannot be excited by reachable ones (may be removed!)

The unobservable configurations may not excite the observable ones

Aggregation and Model Reduction

The full pdv evolves according to:

$$\begin{bmatrix} \dot{\mathbf{P}}(\mathbf{X}_{RO}, t) \\ \dot{\mathbf{P}}(\mathbf{X}_{R'O}, t) \\ \dot{\mathbf{P}}(\mathbf{X}_{RO'}, t) \\ \dot{\mathbf{P}}(\mathbf{X}_{R'O'}, t) \end{bmatrix} = \begin{bmatrix} \mathbf{A}_{RO,RO} & \mathbf{A}_{RO,R'O} & 0 & 0 \\ 0 & \mathbf{A}_{R'O,R'O} & 0 & 0 \\ \mathbf{A}_{RO',RO} & \mathbf{A}_{RO',R'O} & \mathbf{A}_{RO',RO'} & \mathbf{A}_{RO',R'O'} \\ 0 & \mathbf{A}_{R'O',R'O} & 0 & \mathbf{A}_{R'O',R'O'} \end{bmatrix} \begin{bmatrix} \mathbf{P}(\mathbf{X}_{RO}, t) \\ \mathbf{P}(\mathbf{X}_{R'O}, t) \\ \mathbf{P}(\mathbf{X}_{RO'}, t) \\ \mathbf{P}(\mathbf{X}_{R'O'}, t) \end{bmatrix}$$

The unreachable configurations cannot be excited by reachable ones (may be removed!)

The unobservable configurations may not excite the observable ones

Aggregation and Model Reduction

The full pdv evolves according to:

$$\begin{bmatrix} \dot{\mathbf{P}}(\mathbf{X}_{RO}, t) \\ \dot{\mathbf{P}}(\mathbf{X}_{R'O}, t) \\ \dot{\mathbf{P}}(\mathbf{X}_{RO'}, t) \\ \dot{\mathbf{P}}(\mathbf{X}_{R'O'}, t) \end{bmatrix} = \begin{bmatrix} \mathbf{A}_{RO,RO} & \mathbf{A}_{RO,R'O} & \mathbf{0} & \mathbf{0} \\ \mathbf{0} & \mathbf{A}_{R'O,R'O} & \mathbf{0} & \mathbf{0} \\ \mathbf{A}_{RO',RO} & \mathbf{A}_{RO',R'O} & \mathbf{A}_{RO',RO'} & \mathbf{A}_{RO',R'O'} \\ \mathbf{0} & \mathbf{A}_{R'O',R'O} & \mathbf{0} & \mathbf{A}_{R'O',R'O'} \end{bmatrix} \begin{bmatrix} \mathbf{P}(\mathbf{X}_{RO}, t) \\ \mathbf{P}(\mathbf{X}_{R'O}, t) \\ \mathbf{P}(\mathbf{X}_{RO'}, t) \\ \mathbf{P}(\mathbf{X}_{R'O'}, t) \end{bmatrix}$$

The unreachable configurations cannot be excited by reachable ones (may be removed!)

The unobservable configurations may not excite the observable ones

The Full system reduces to

$$\begin{bmatrix} \dot{\mathbf{P}}(\mathbf{X}_{RO}, t) \\ \dot{\mathbf{P}}(\mathbf{X}_{RO'}, t) \end{bmatrix} = \begin{bmatrix} \mathbf{A}_{RO,RO} & \mathbf{0} \\ \mathbf{A}_{RO',RO} & \mathbf{A}_{RO',RO'} \end{bmatrix} \begin{bmatrix} \mathbf{P}(\mathbf{X}_{RO}, t) \\ \mathbf{P}(\mathbf{X}_{RO'}, t) \end{bmatrix}$$

The Observability Aggregated FSP.

Theorem 2: Consider any Markov Process in which the probability distribution evolves according to the ODE:

$$\begin{bmatrix} \dot{\mathbf{P}}_Y \\ \dot{\mathbf{P}}_{Y'} \end{bmatrix} = \begin{bmatrix} \mathbf{A}_Y & \mathbf{0} \\ \mathbf{A}_{Y'Y} & \mathbf{A}_{Y'} \end{bmatrix} \begin{bmatrix} \mathbf{P}_Y \\ \mathbf{P}_{Y'} \end{bmatrix}.$$

If for an indexing vector: $J \in Y$,

$$\mathbf{1}^T \exp \begin{bmatrix} \mathbf{A}_J t_f & \mathbf{0} \\ \mathbf{1}^T \mathbf{A}_{Y'J} t_f & \mathbf{0} \end{bmatrix} \begin{bmatrix} \mathbf{P}_J(0) \\ \mathbf{1}^T \mathbf{P}_{Y'}(0) \end{bmatrix} \geq 1 - \varepsilon,$$

then

$$\left\| \begin{bmatrix} \mathbf{P}_J(t_f) \\ \mathbf{1}^T \mathbf{P}_{Y'}(t_f) \end{bmatrix} - \exp \begin{bmatrix} \mathbf{A}_J t_f & \mathbf{0} \\ \mathbf{1}^T \mathbf{A}_{Y'J} t_f & \mathbf{0} \end{bmatrix} \begin{bmatrix} \mathbf{P}_J(0) \\ \mathbf{1}^T \mathbf{P}_{Y'}(0) \end{bmatrix} \right\|_1 \leq \varepsilon.$$

The Observability Aggregated FSP.

Theorem 2: Consider any Markov Process in which the probability distribution evolves according to the ODE:

$$\begin{bmatrix} \dot{\mathbf{P}}_Y \\ \dot{\mathbf{P}}_{Y'} \end{bmatrix} = \begin{bmatrix} \mathbf{A}_Y & \mathbf{0} \\ \mathbf{A}_{Y'Y} & \mathbf{A}_{Y'} \end{bmatrix} \begin{bmatrix} \mathbf{P}_Y \\ \mathbf{P}_{Y'} \end{bmatrix}.$$

If for an indexing vector: $J \in Y$,

$$\mathbf{1}^T \exp \begin{bmatrix} \mathbf{A}_J t_f & 0 \\ \mathbf{1}^T \mathbf{A}_{Y'J} t_f & 0 \end{bmatrix} \begin{bmatrix} \mathbf{P}_J(0) \\ \mathbf{1}^T \mathbf{P}_{Y'}(0) \end{bmatrix} \geq 1 - \varepsilon,$$

then

$$\left\| \begin{bmatrix} \mathbf{P}_J(t_f) \\ \mathbf{1}^T \mathbf{P}_{Y'}(t_f) \end{bmatrix} - \exp \begin{bmatrix} \mathbf{A}_J t_f & 0 \\ \mathbf{1}^T \mathbf{A}_{Y'J} t_f & 0 \end{bmatrix} \begin{bmatrix} \mathbf{P}_J(0) \\ \mathbf{1}^T \mathbf{P}_{Y'}(0) \end{bmatrix} \right\|_1 \leq \varepsilon.$$

We need only keep track of the unobservable states as a single aggregate.

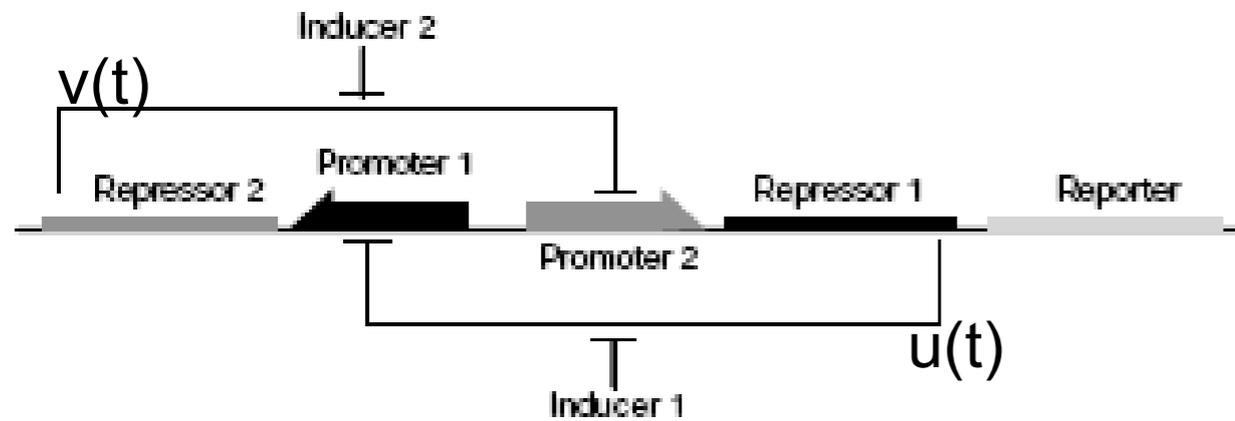


Outline

1. Introduction
2. The Finite State Projection (FSP)
3. Model Reduction Techniques
4. Example

Example: Genetic Toggle Model:

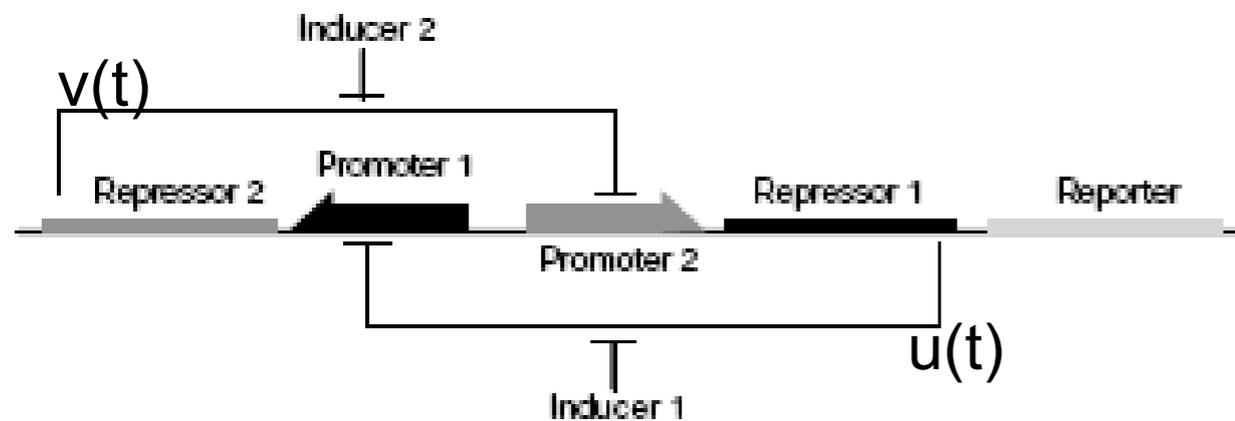
Gardner, *et al.*, *Nature* 403, 339-342 (2000)



Two repressors, u and v .

Example: Genetic Toggle Model:

Gardner, *et al.*, *Nature* 403, 339-342 (2000)



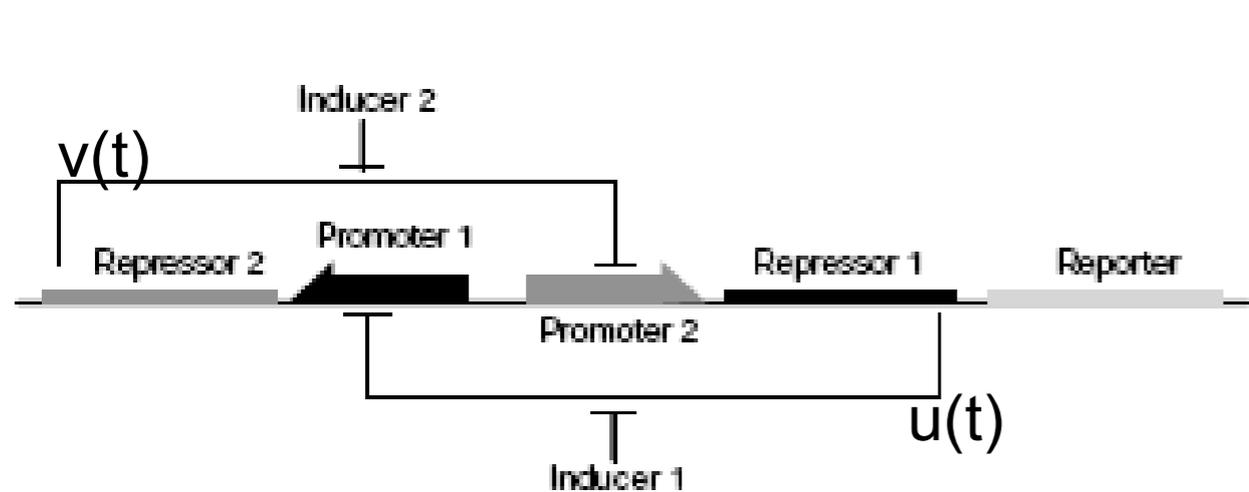
$$a_1(u, v) = \frac{\alpha_1}{1 + v^\beta} \quad \nu_1 = \begin{bmatrix} 1 \\ 0 \end{bmatrix}$$

Two repressors, u and v .

v inhibits the production of u .

Example: Genetic Toggle Model:

Gardner, *et al.*, *Nature* 403, 339-342 (2000)



$$a_1(u, v) = \frac{\alpha_1}{1 + v^\beta} \quad \nu_1 = \begin{bmatrix} 1 \\ 0 \end{bmatrix}$$

$$a_3(u, v) = \frac{\alpha_2}{1 + u^\gamma} \quad \nu_3 = \begin{bmatrix} 0 \\ 1 \end{bmatrix}$$

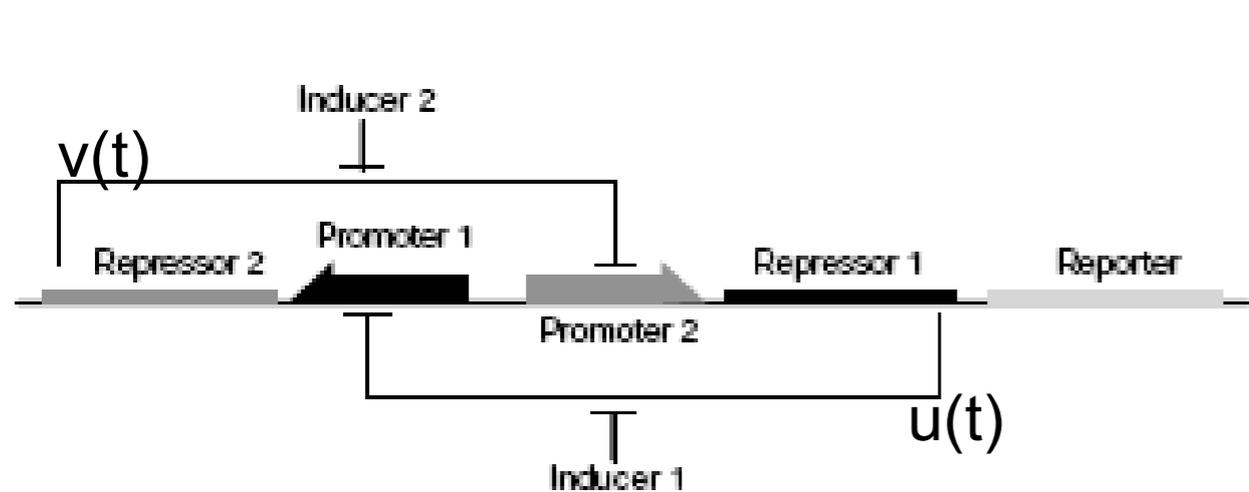
Two repressors, u and v .

v inhibits the production of u .

u inhibits the production of v .

Example: Genetic Toggle Model:

Gardner, et al., *Nature* 403, 339-342 (2000)



Two repressors, u and v .

v inhibits the production of u .

u inhibits the production of v .

Both u and v degrade exponentially.

$$a_1(u, v) = \frac{\alpha_1}{1 + v^\beta} \quad \nu_1 = \begin{bmatrix} 1 \\ 0 \end{bmatrix}$$

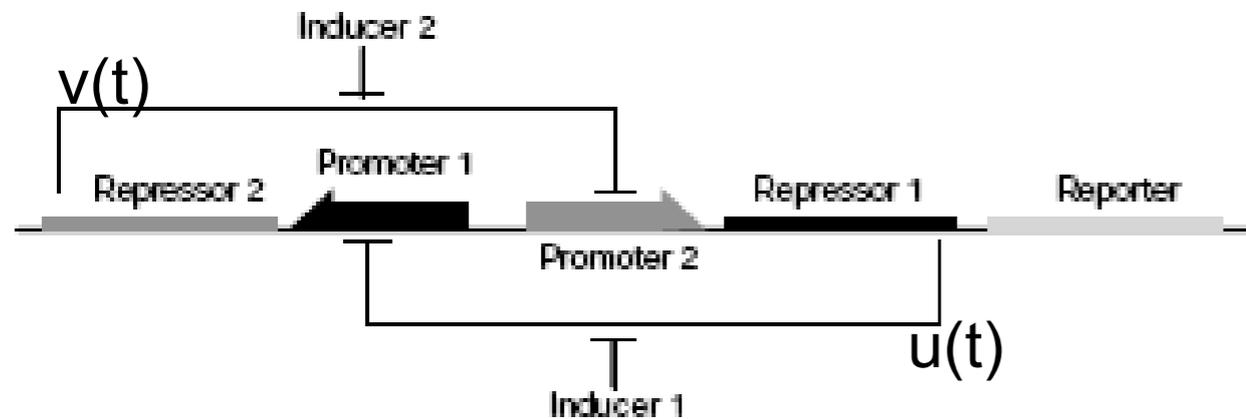
$$a_3(u, v) = \frac{\alpha_2}{1 + u^\gamma} \quad \nu_3 = \begin{bmatrix} 0 \\ 1 \end{bmatrix}$$

$$a_2(u, v) = u \quad \nu_2 = \begin{bmatrix} -1 \\ 0 \end{bmatrix}$$

$$a_4(u, v) = v \quad \nu_4 = \begin{bmatrix} 0 \\ -1 \end{bmatrix}$$

Example: Genetic Toggle Model:

Gardner, et al., *Nature* 403, 339-342 (2000)



Two repressors, u and v .

v inhibits the production of u .

u inhibits the production of v .

Both u and v degrade exponentially.

$$a_1(u, v) = \frac{\alpha_1}{1 + v^\beta} \quad \nu_1 = \begin{bmatrix} 1 \\ 0 \end{bmatrix}$$

$$a_3(u, v) = \frac{\alpha_2}{1 + u^\gamma} \quad \nu_3 = \begin{bmatrix} 0 \\ 1 \end{bmatrix}$$

$$a_2(u, v) = u \quad \nu_2 = \begin{bmatrix} -1 \\ 0 \end{bmatrix}$$

$$a_4(u, v) = v \quad \nu_4 = \begin{bmatrix} 0 \\ -1 \end{bmatrix}$$

$$\alpha_1 = 50 \quad \beta = 2.5$$

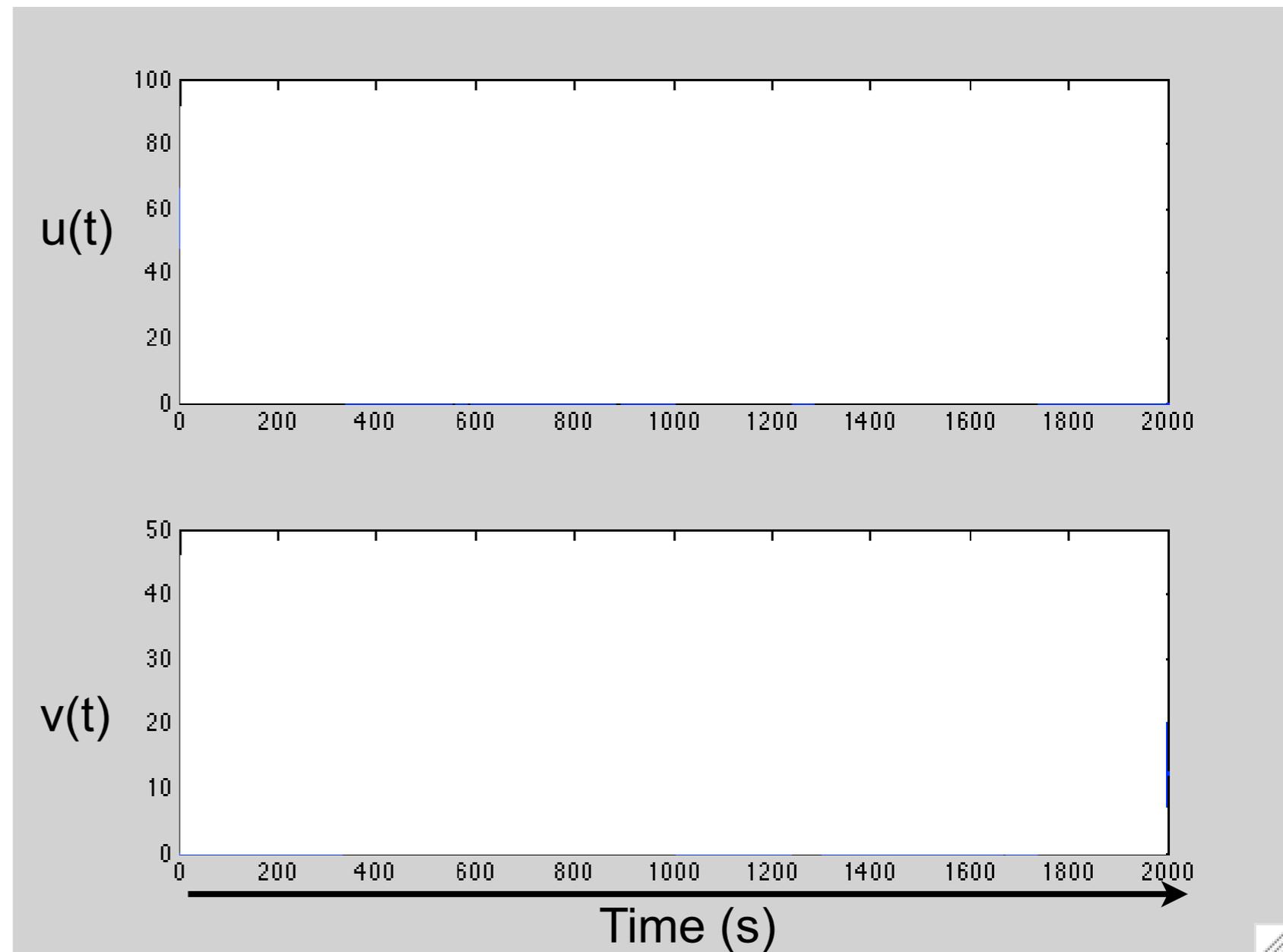
$$\alpha_2 = 16 \quad \gamma = 1$$

A Sample Trajectory

We begin with an initial condition:

$$\begin{bmatrix} u(t) \\ v(t) \end{bmatrix} = \begin{bmatrix} 60 \\ 0 \end{bmatrix}$$

and consider a sample trajectory.

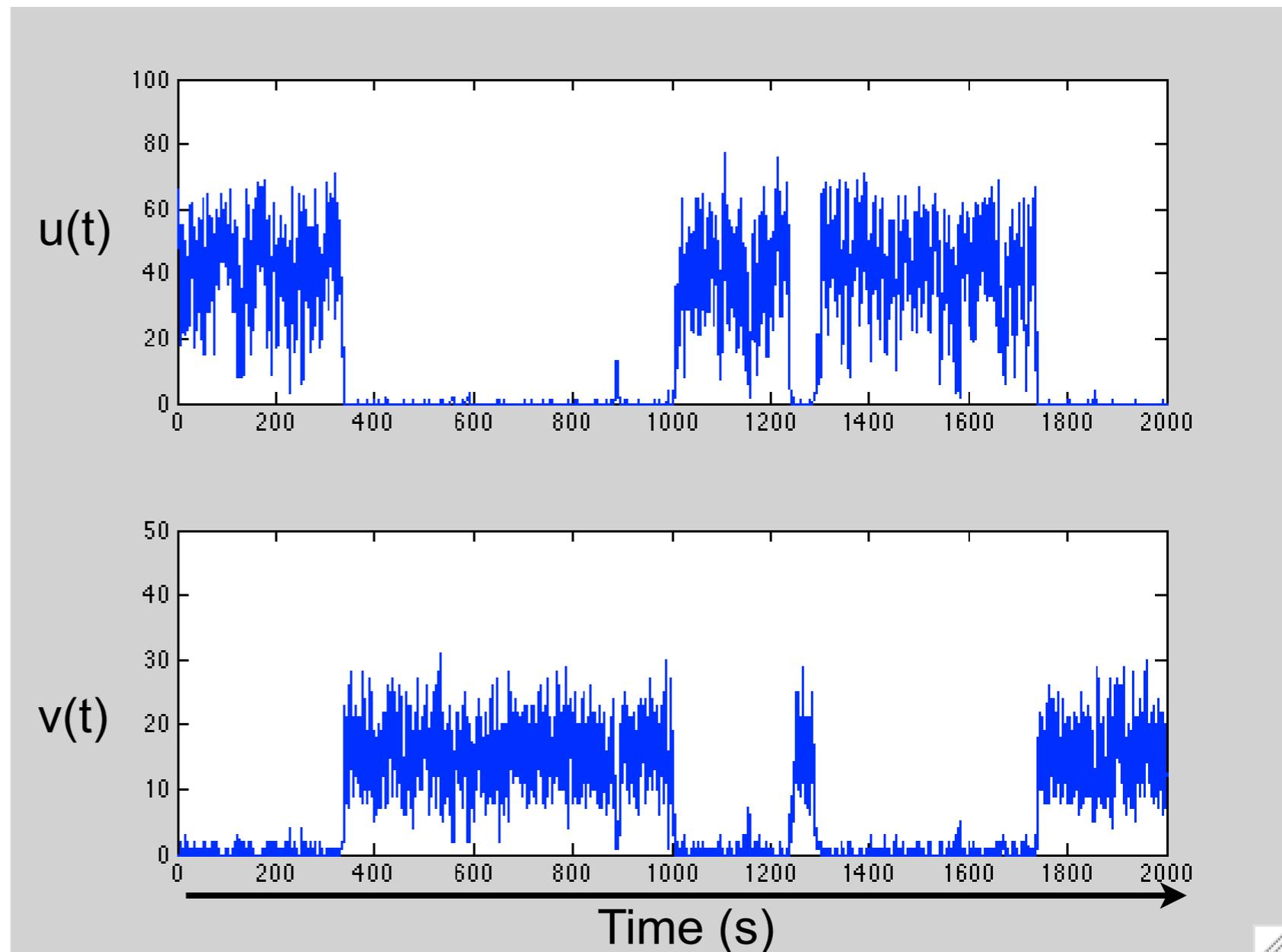


A Sample Trajectory

We begin with an initial condition:

$$\begin{bmatrix} u(t) \\ v(t) \end{bmatrix} = \begin{bmatrix} 60 \\ 0 \end{bmatrix}$$

and consider a sample trajectory.

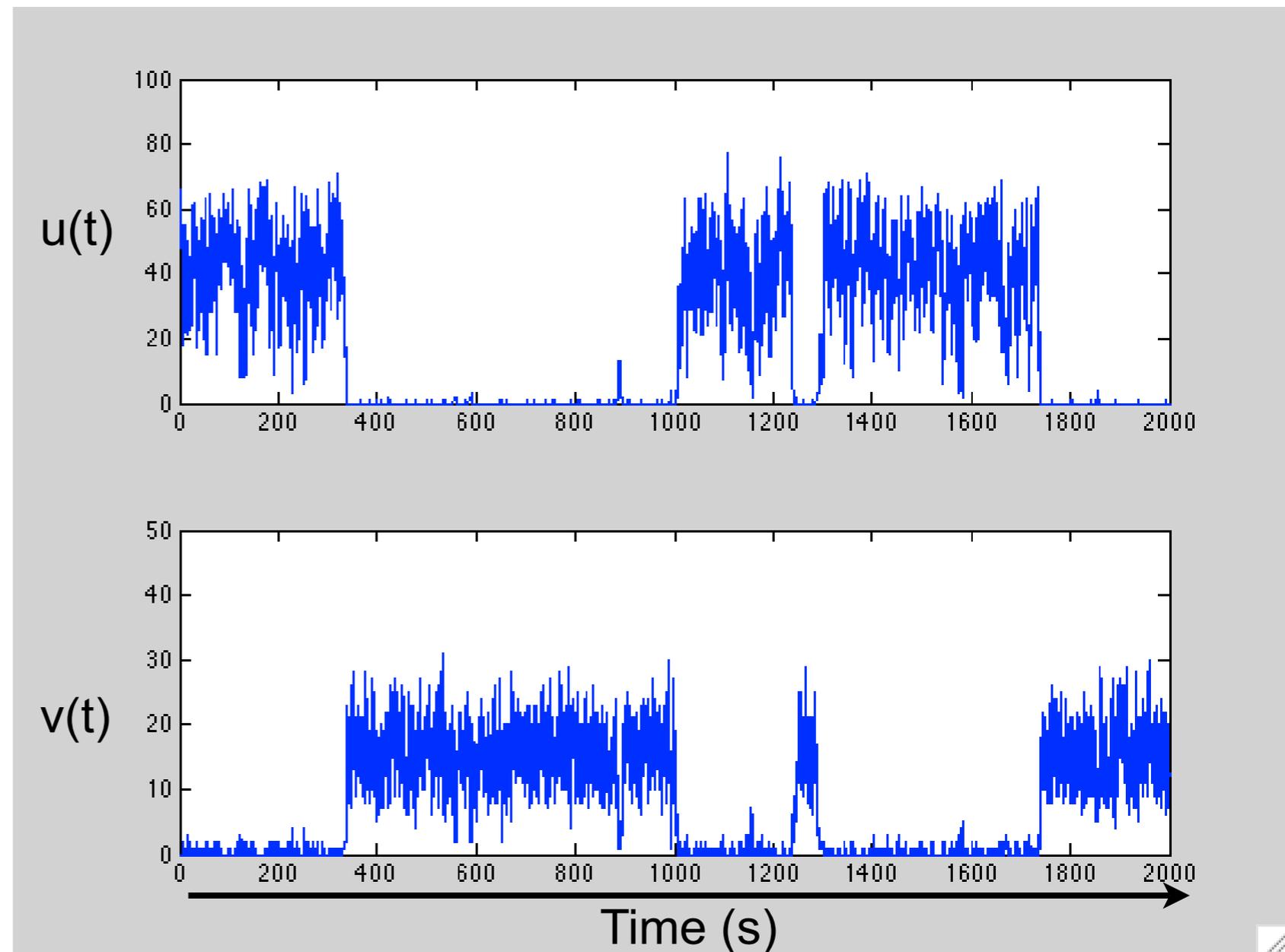


A Sample Trajectory

We begin with an initial condition:

$$\begin{bmatrix} u(t) \\ v(t) \end{bmatrix} = \begin{bmatrix} 60 \\ 0 \end{bmatrix}$$

and consider a sample trajectory.



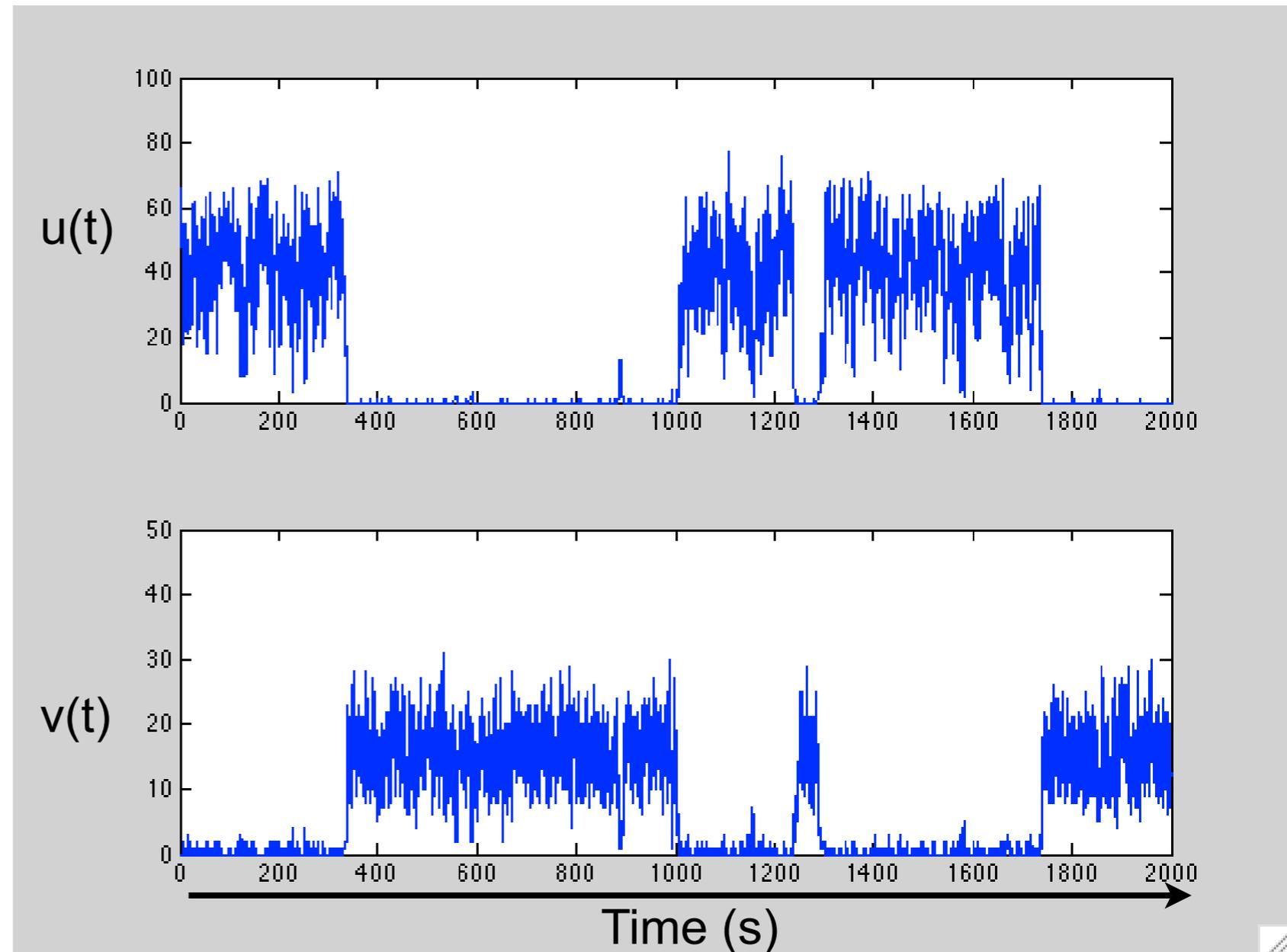
A Sample Trajectory

We begin with an initial condition:

$$\begin{bmatrix} u(t) \\ v(t) \end{bmatrix} = \begin{bmatrix} 60 \\ 0 \end{bmatrix}$$

and consider a sample trajectory.

Define the switch to be OFF when $v(t) > 5$ and $u(t) < 20$.



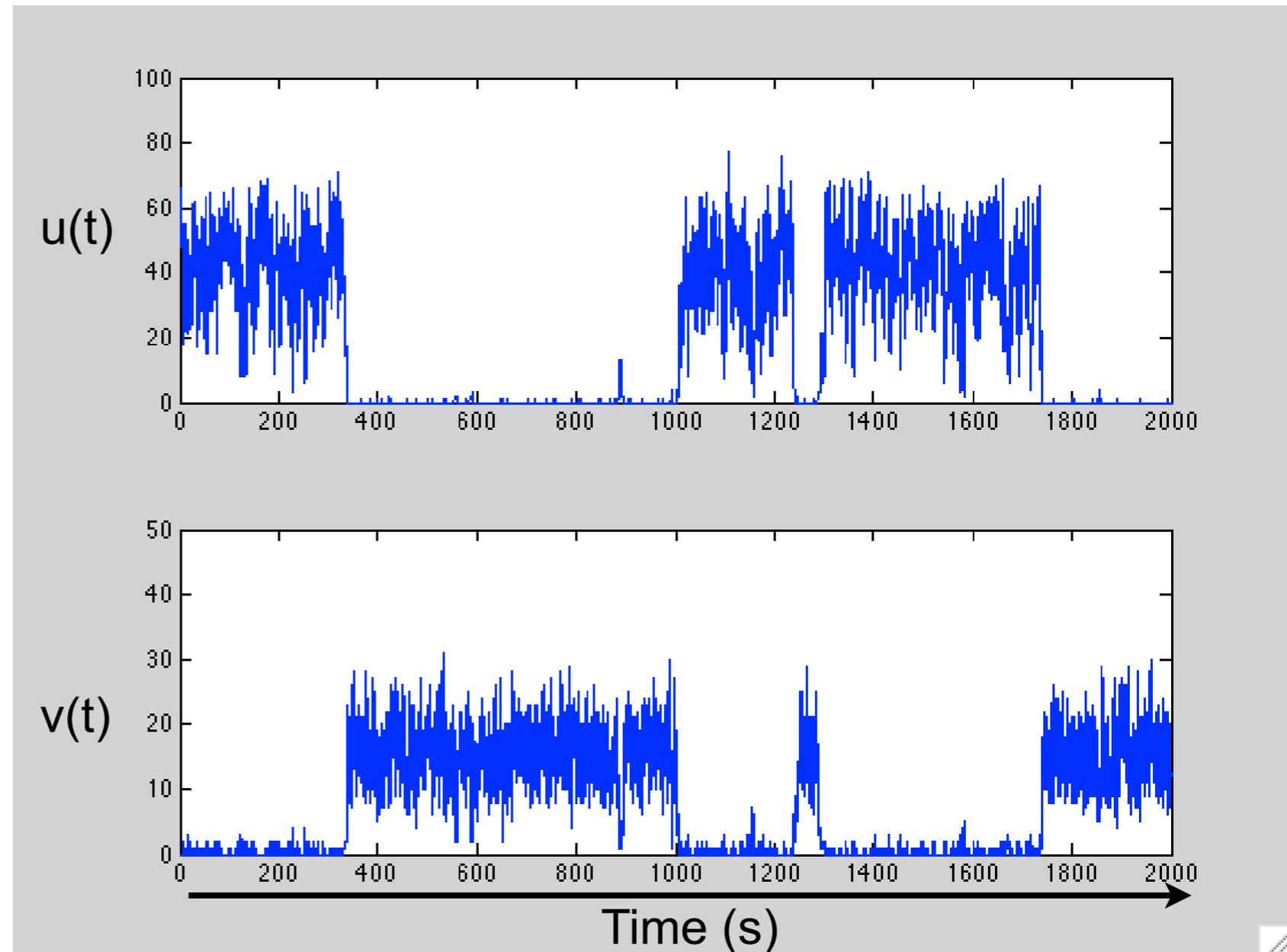
A Sample Trajectory

We begin with an initial condition:

$$\begin{bmatrix} u(t) \\ v(t) \end{bmatrix} = \begin{bmatrix} 60 \\ 0 \end{bmatrix}$$

and consider a sample trajectory.

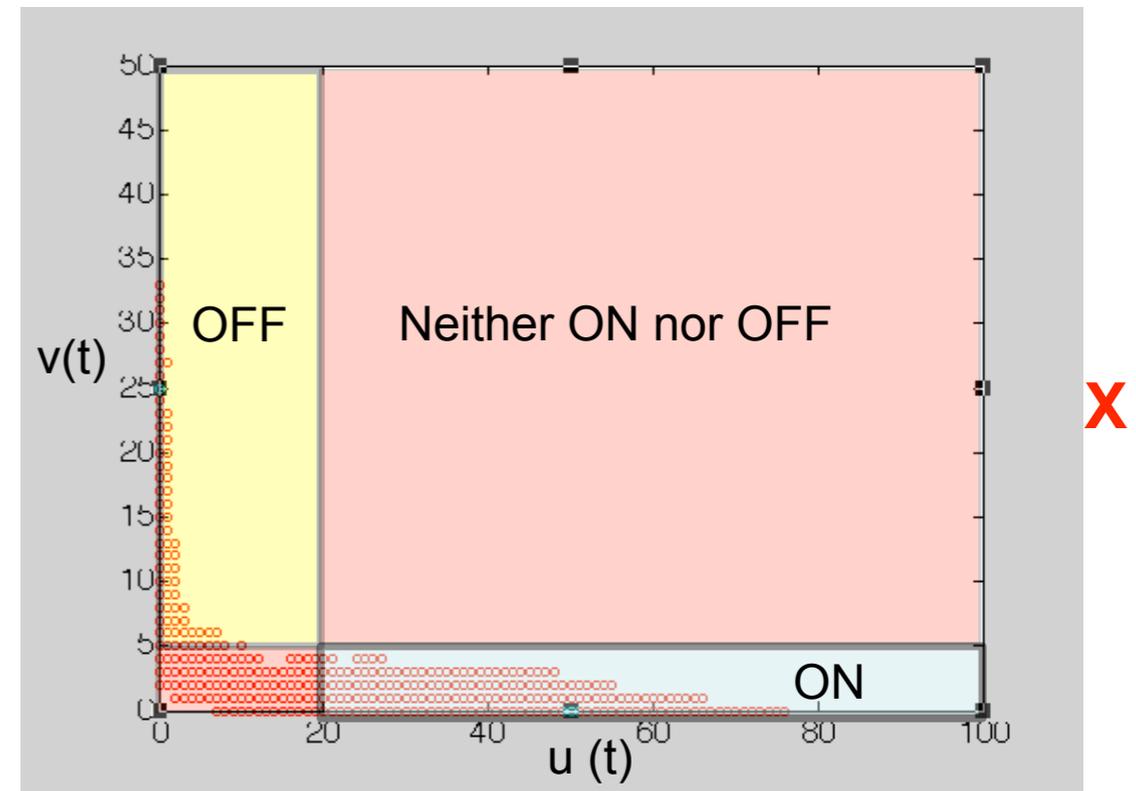
Define the switch to be OFF when $v(t) > 5$ and $u(t) < 20$.



Find: The time at which 99% have turned OFF.

Partitioning the Configuration Space

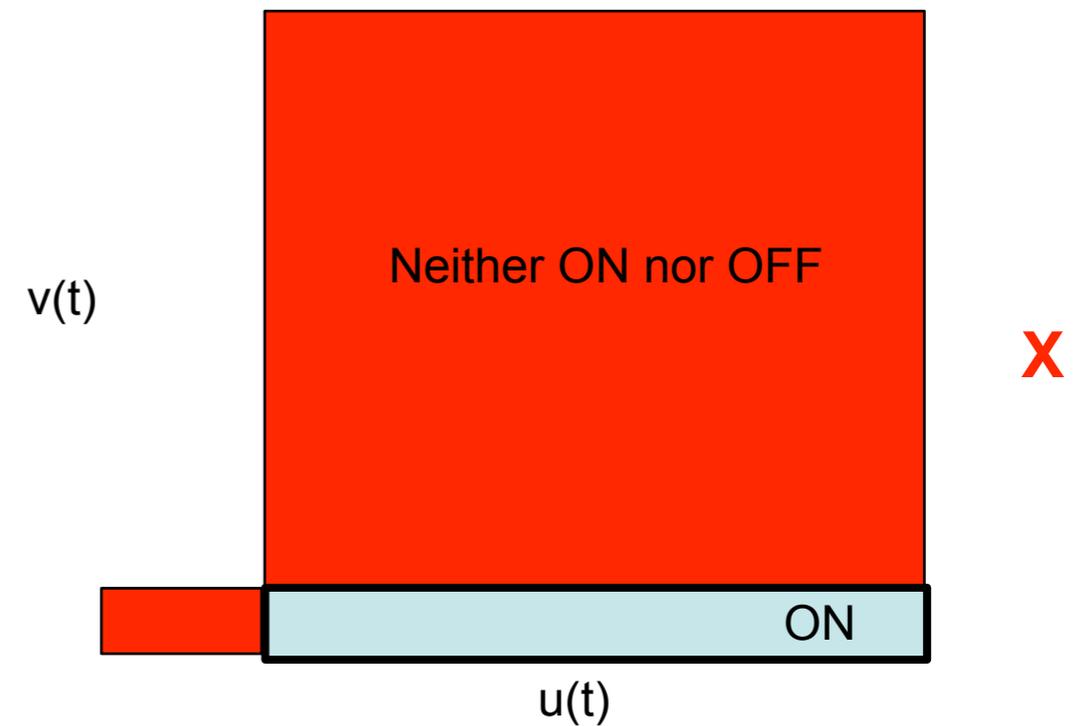
For convenience, we define some configuration subsets.



Partitioning the Configuration Space

For convenience, we define some configuration subsets.

X = set of all configurations that have never been OFF.

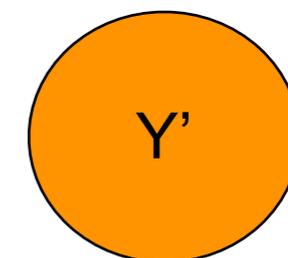
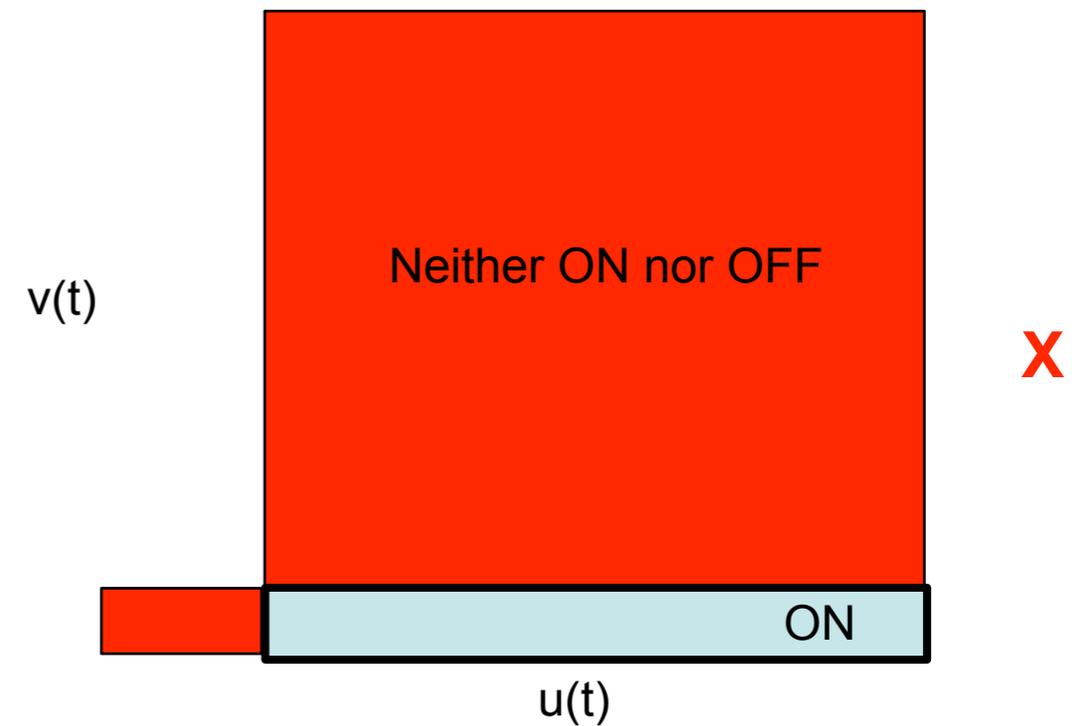


Partitioning the Configuration Space

For convenience, we define some configuration subsets.

X = set of all configurations that have never been OFF.

Y' = set of all configurations which have ever been OFF.



Partitioning the Configuration Space

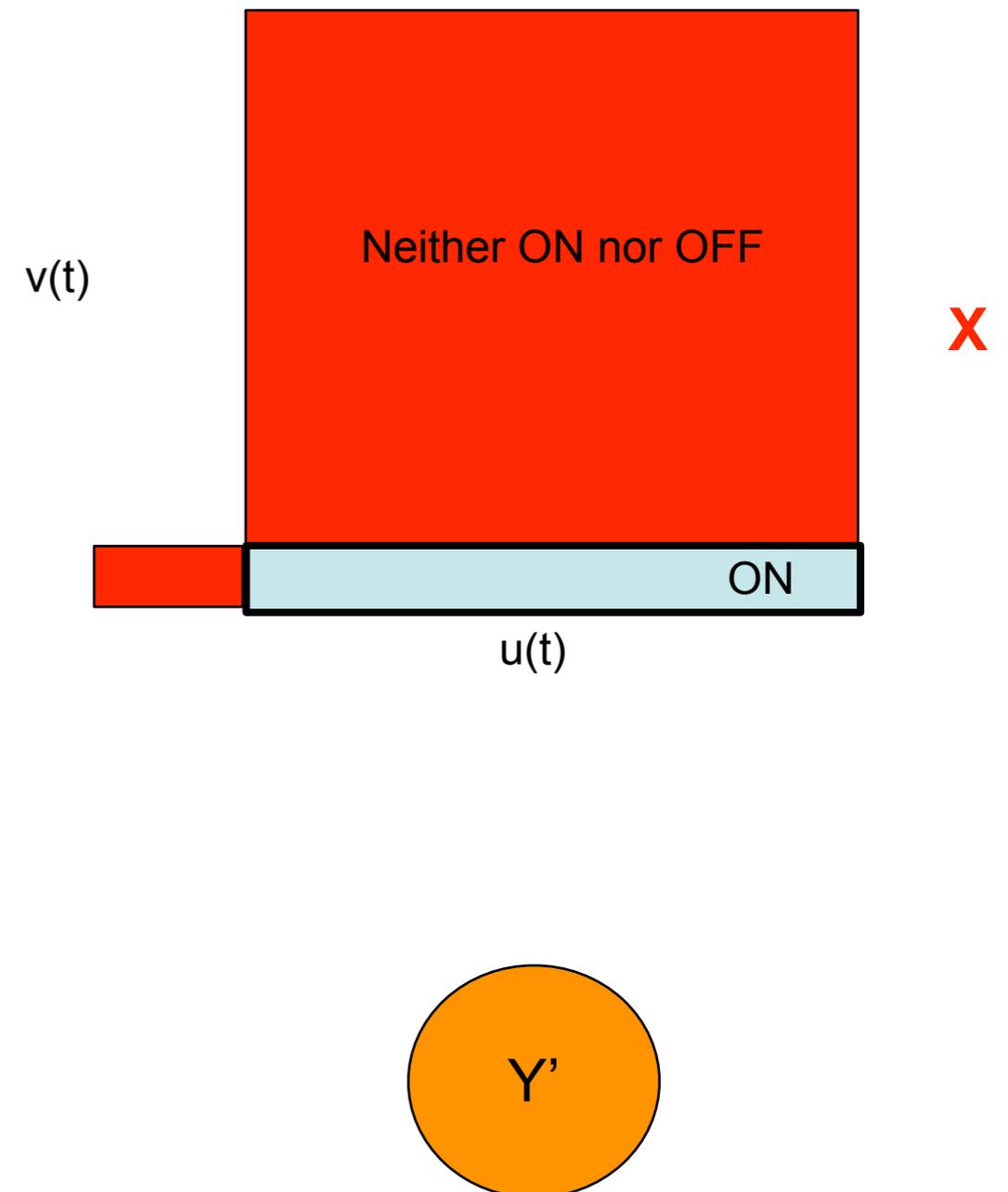
For convenience, we define some configuration subsets.

X = set of all configurations that have never been OFF.

Y' = set of all configurations which have ever been OFF.

Relationships:

X is unreachable from **Y'**, and therefore **Y'** is unobservable from **X**.



Partitioning the Configuration Space

For convenience, we define some configuration subsets.

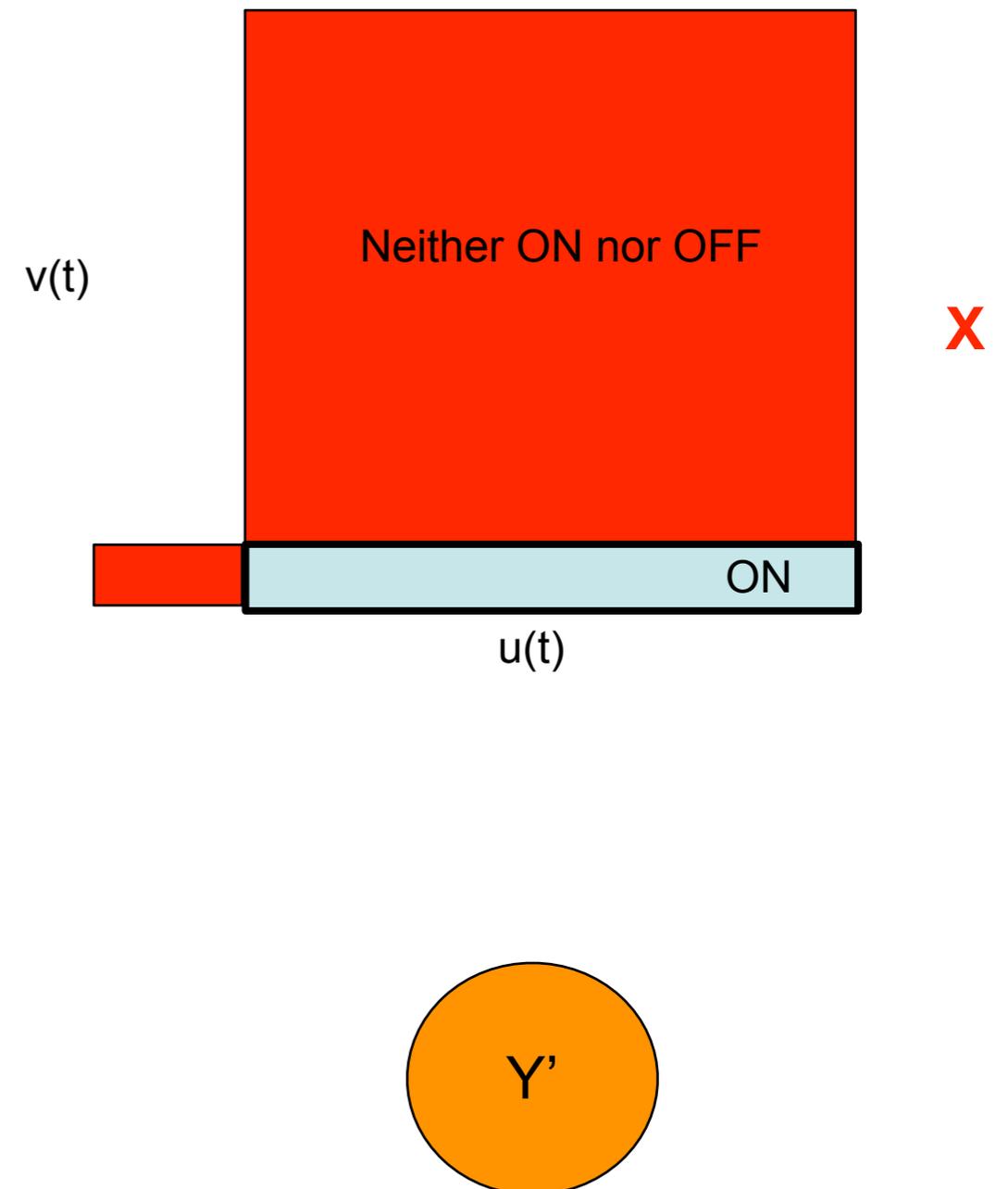
X = set of all configurations that have never been OFF.

Y' = set of all configurations which have ever been OFF.

Relationships:

X is unreachable from **Y'**, and therefore **Y'** is unobservable from **X**.

We can therefore treat **Y'** as a single aggregate.



Partitioning the Configuration Space

For convenience, we define some configuration subsets.

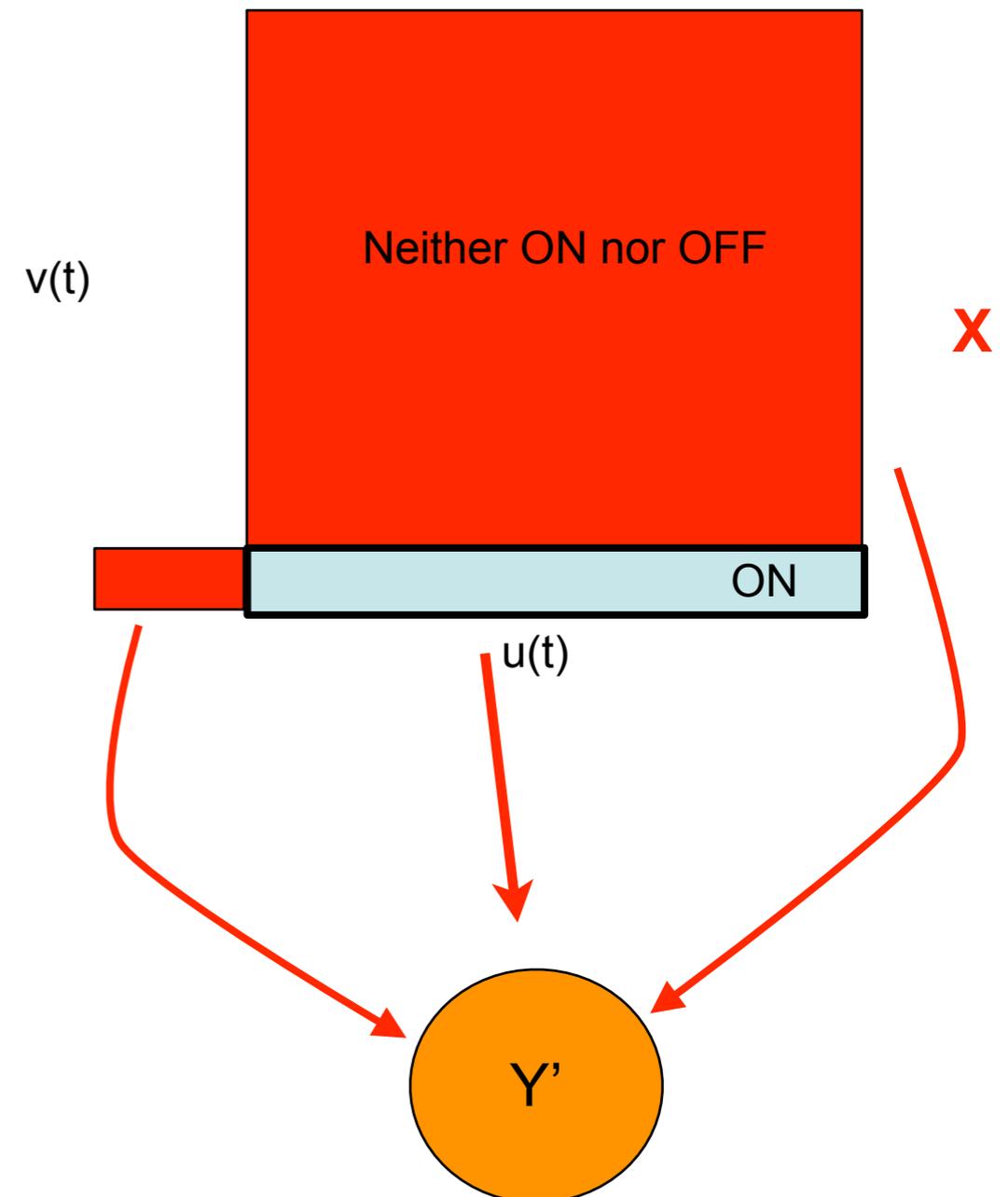
X = set of all configurations that have never been OFF.

Y' = set of all configurations which have ever been OFF.

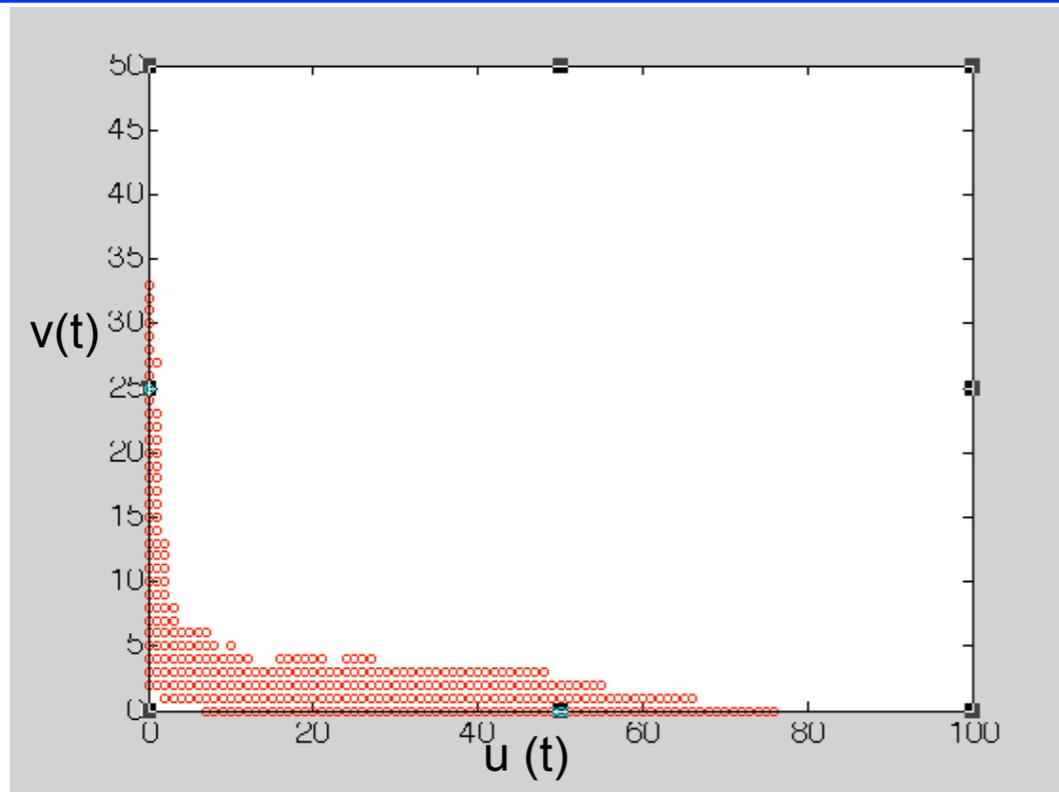
Relationships:

X is unreachable from **Y'**, and therefore **Y'** is unobservable from **X**.

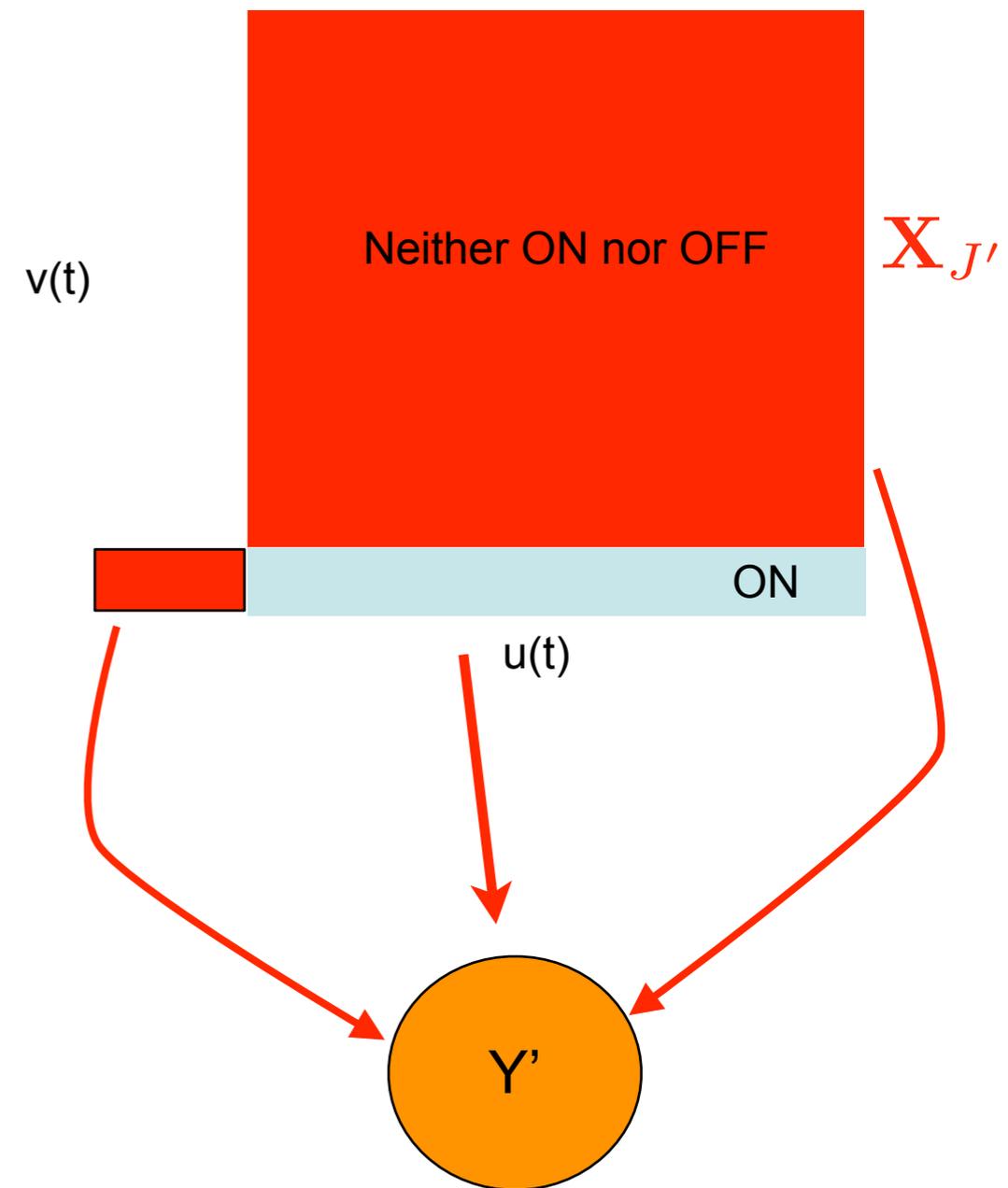
We can therefore treat **Y'** as a single aggregate.



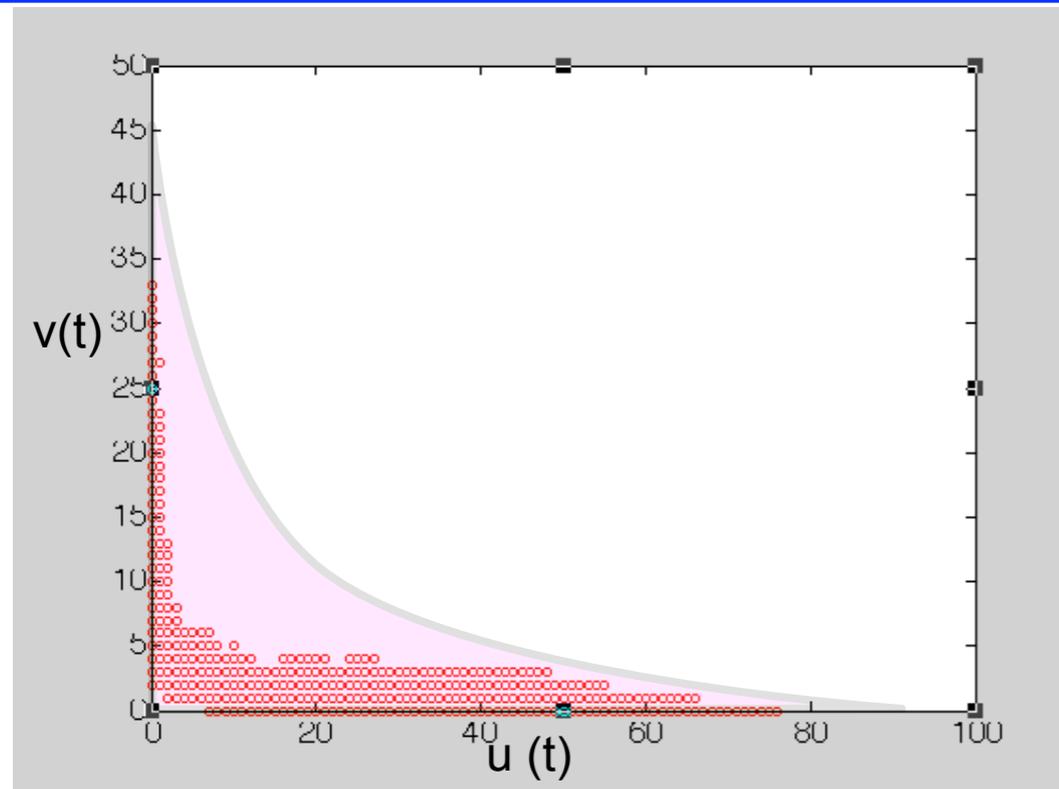
Applying the FSP.



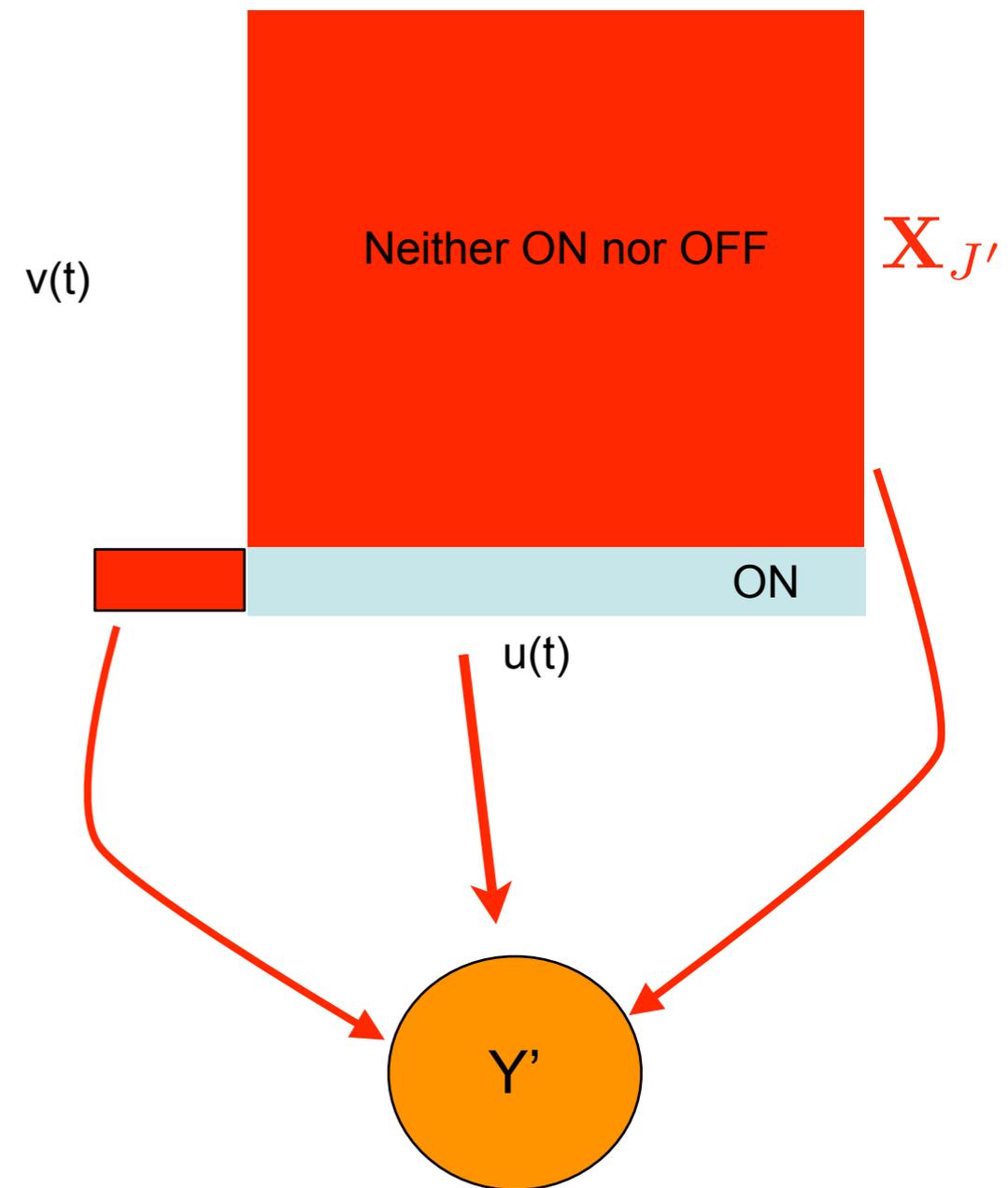
- From the simulation we saw that trajectories tend to remain in a small region of the configuration set: $u(t)v(t) < 260$.



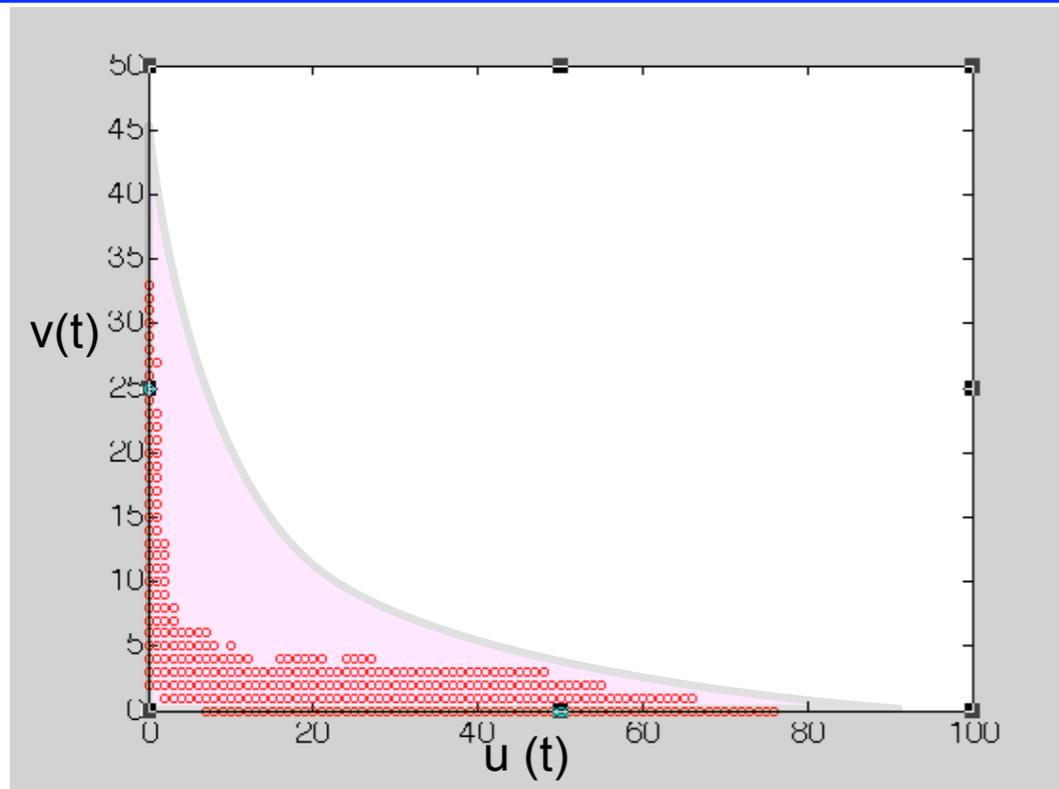
Applying the FSP.



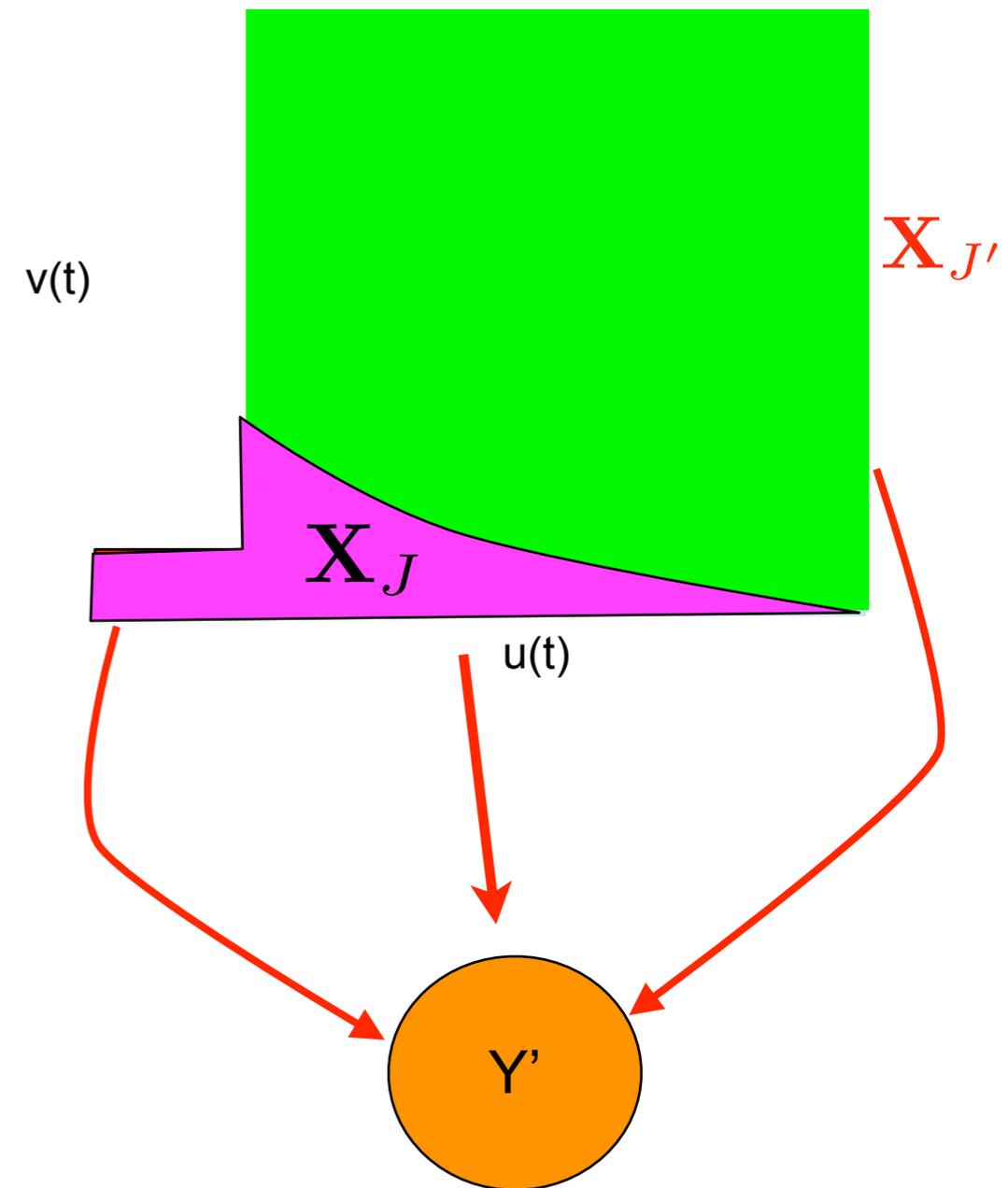
- From the simulation we saw that trajectories tend to remain in a small region of the configuration set: $u(t)v(t) < 260$.
- We will call this set X_J and its complement $X_{J'}$



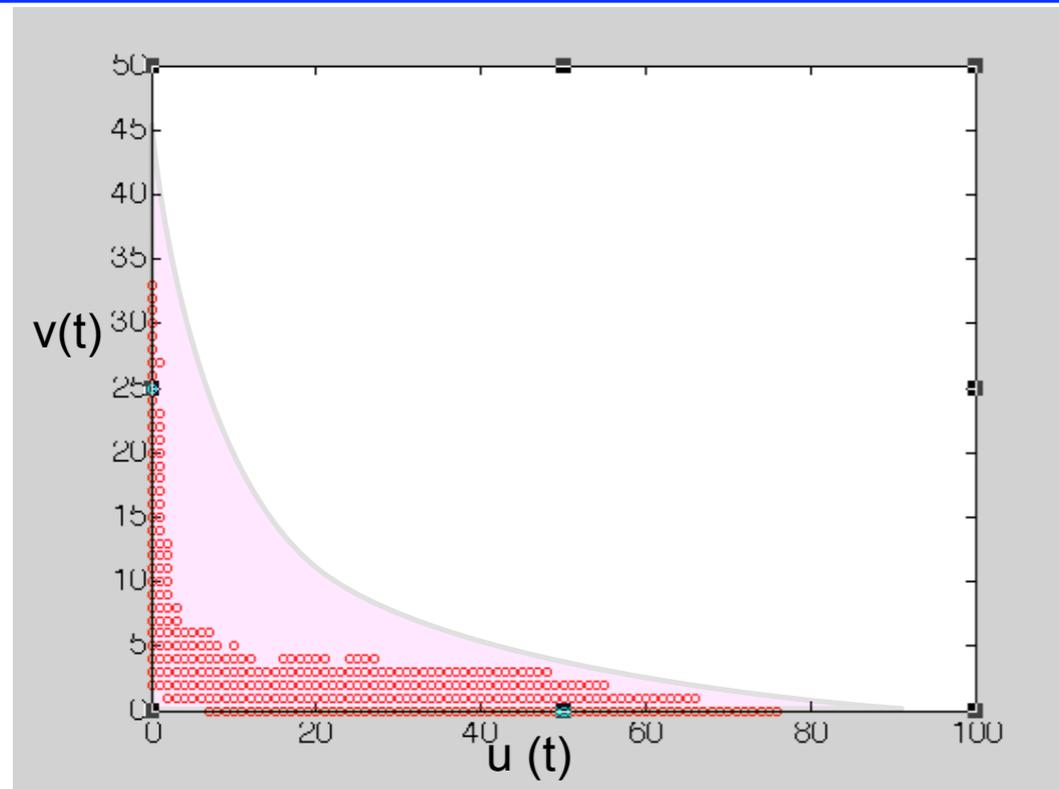
Applying the FSP.



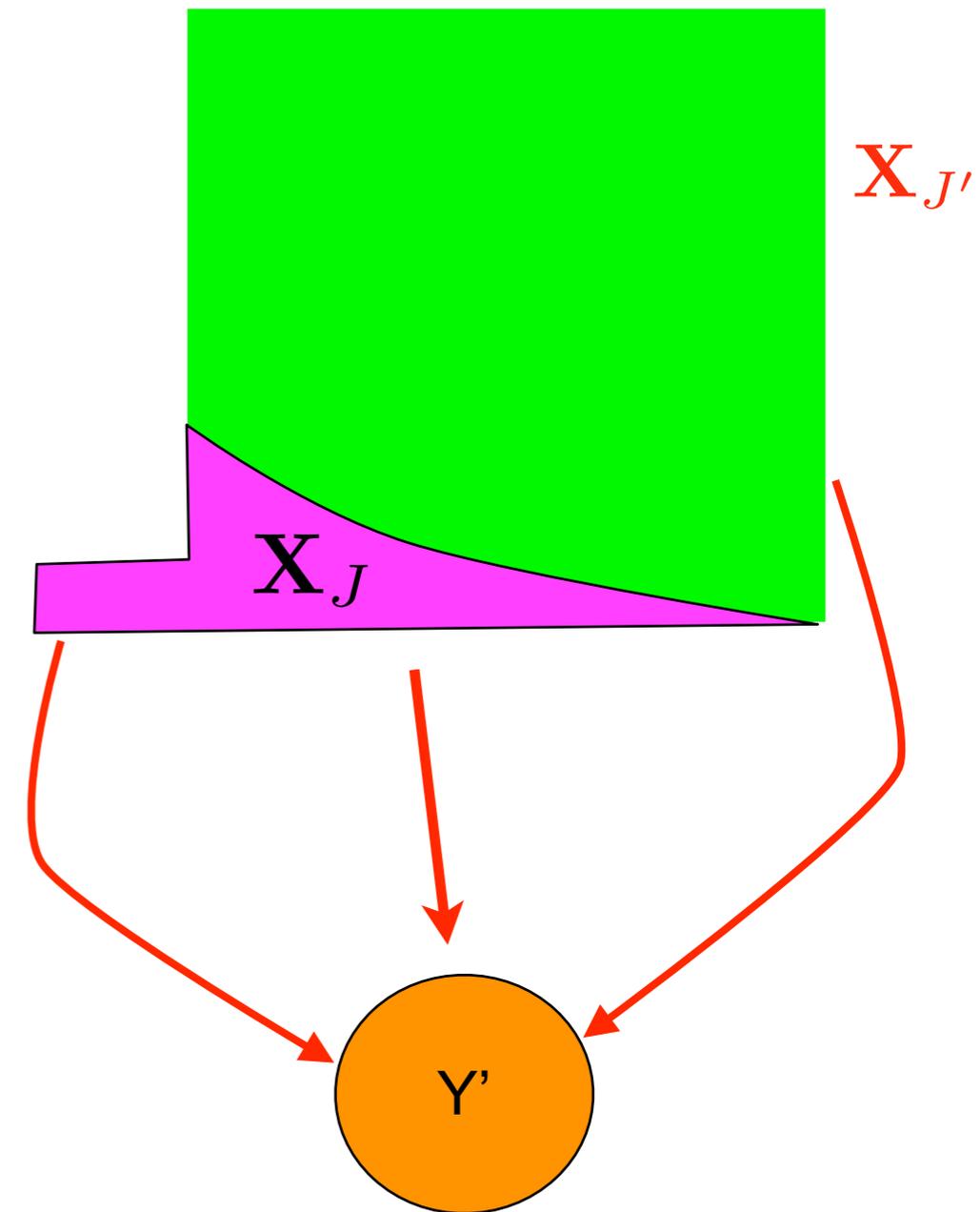
- From the simulation we saw that trajectories tend to remain in a small region of the configuration set: $u(t)v(t) < 260$.
- We will call this set X_J and its complement $X_{J'}$



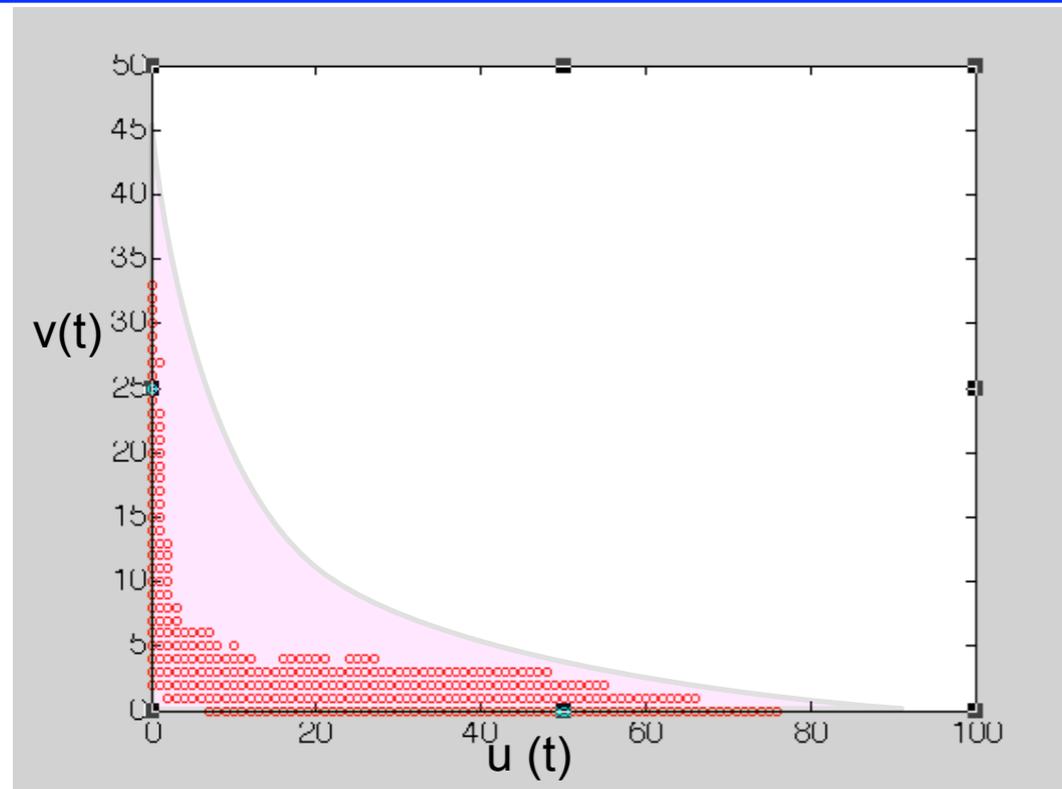
Applying the FSP.



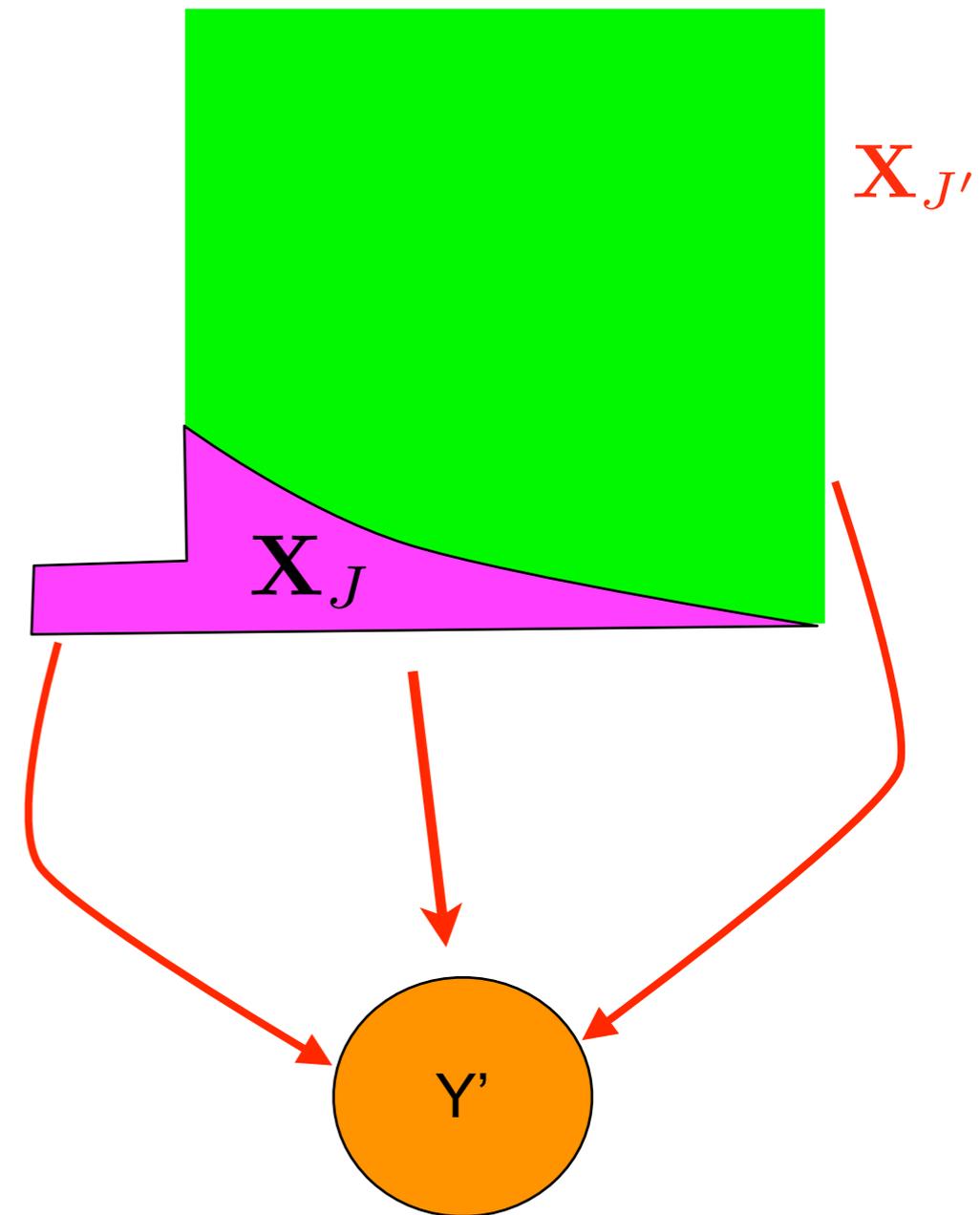
- From the simulation we saw that trajectories tend to remain in a small region of the configuration set: $u(t)v(t) < 260$.
- We will call this set X_J and its complement $X_{J'}$



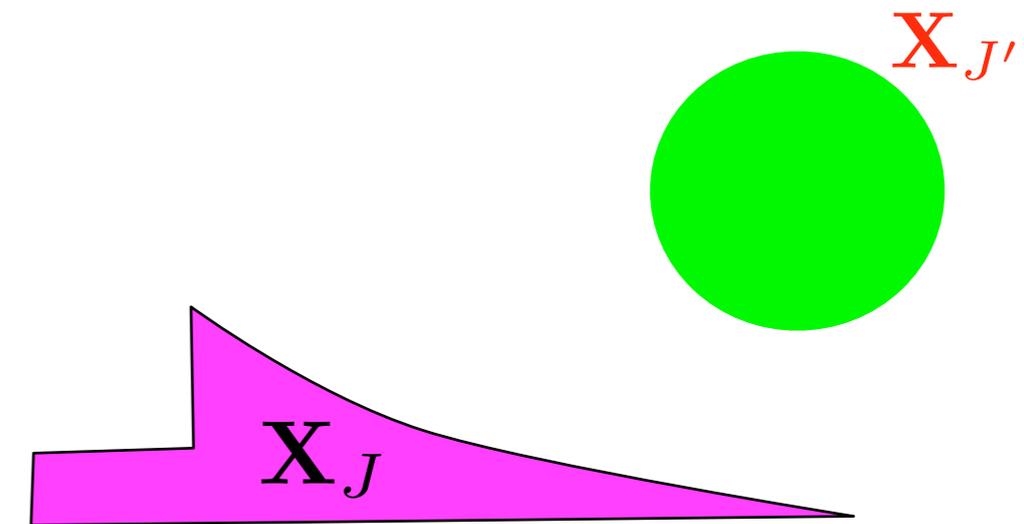
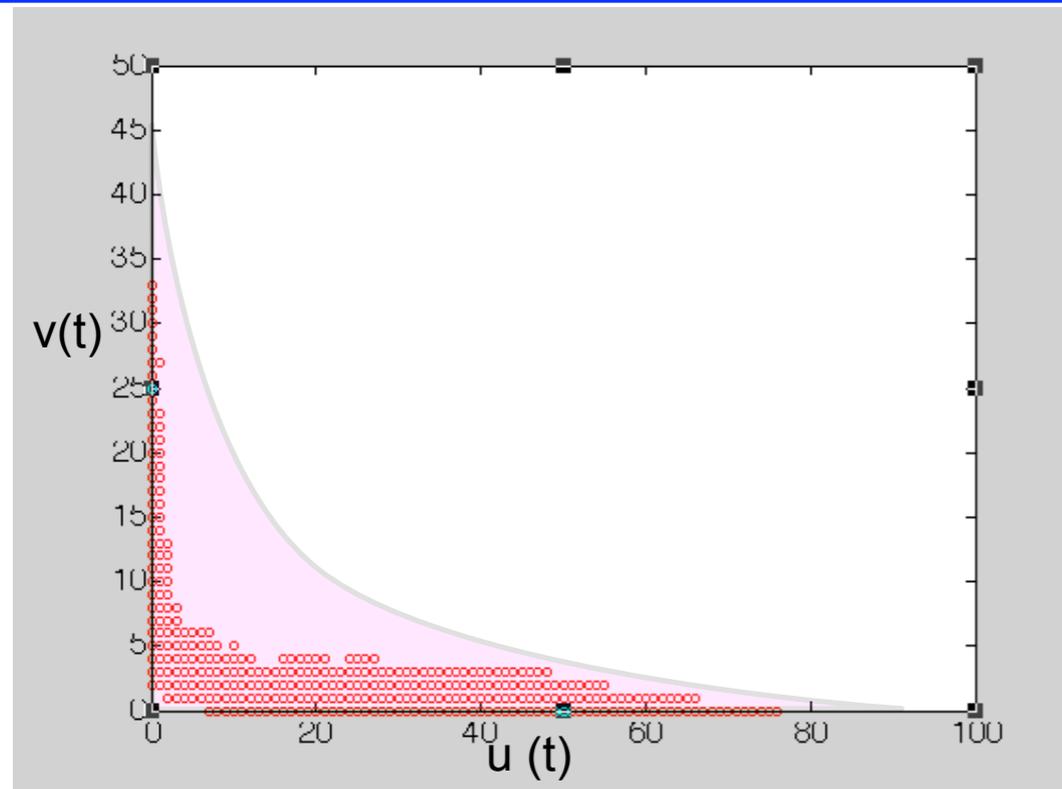
Applying the FSP.



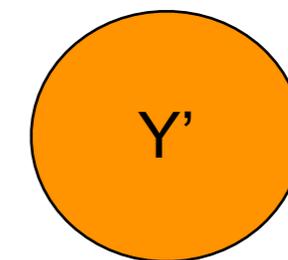
- From the simulation we saw that trajectories tend to remain in a small region of the configuration set: $u(t)v(t) < 260$.
- We will call this set X_J and its complement $X_{J'}$
- We project $X_{J'}$ to a single point.



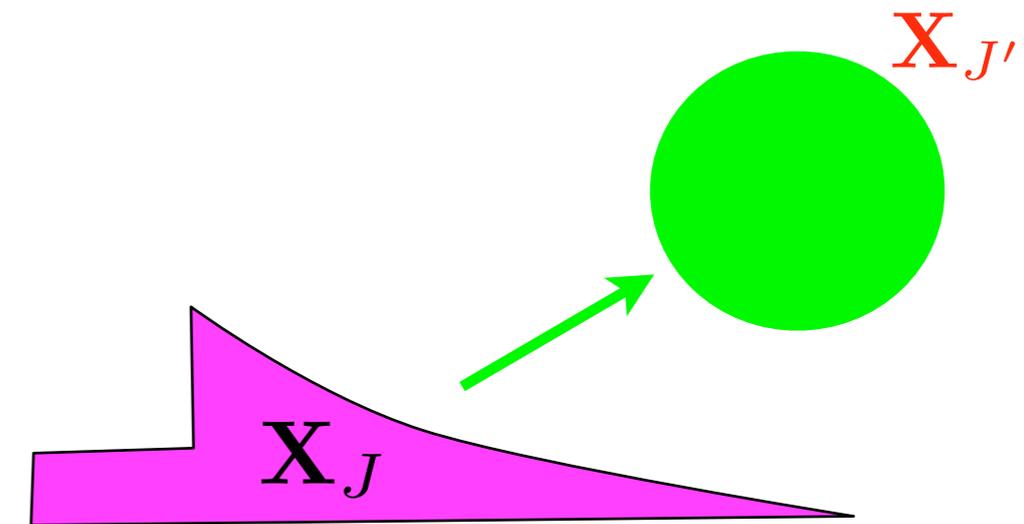
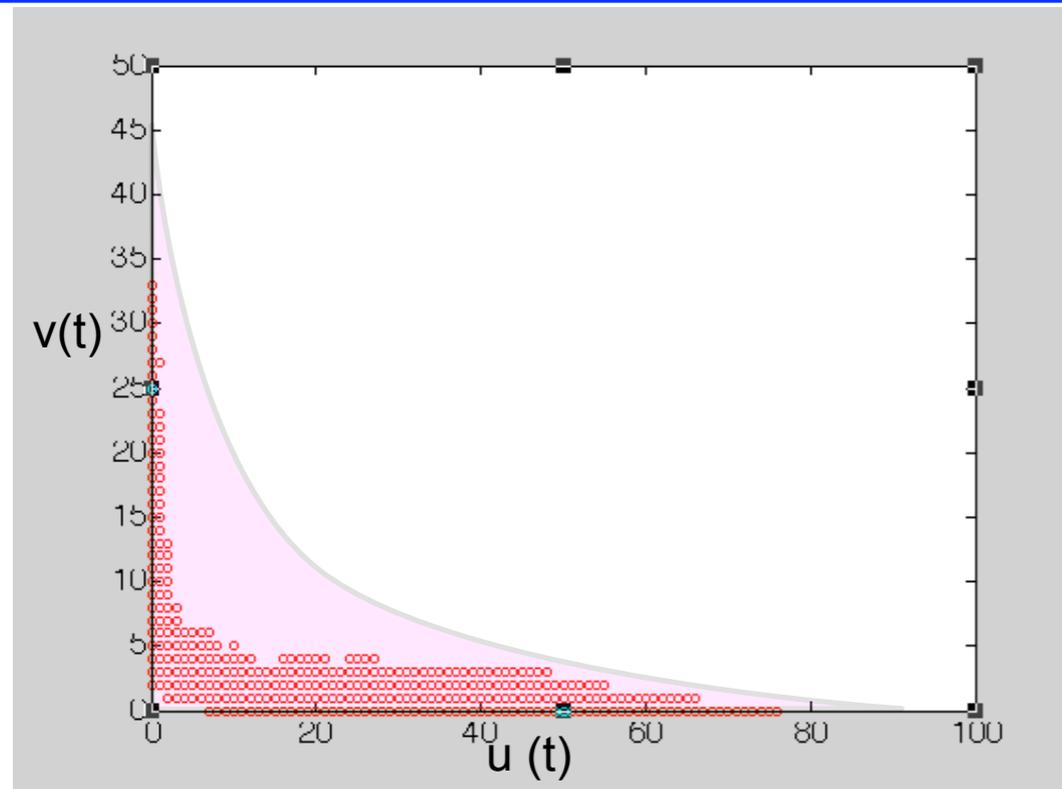
Applying the FSP.



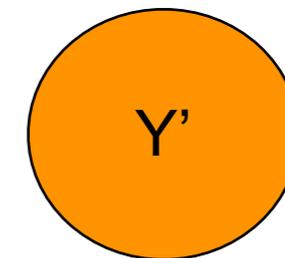
- From the simulation we saw that trajectories tend to remain in a small region of the configuration set: $u(t)v(t) < 260$.
- We will call this set X_J and its complement $X_{J'}$.
- We project $X_{J'}$ to a single point.



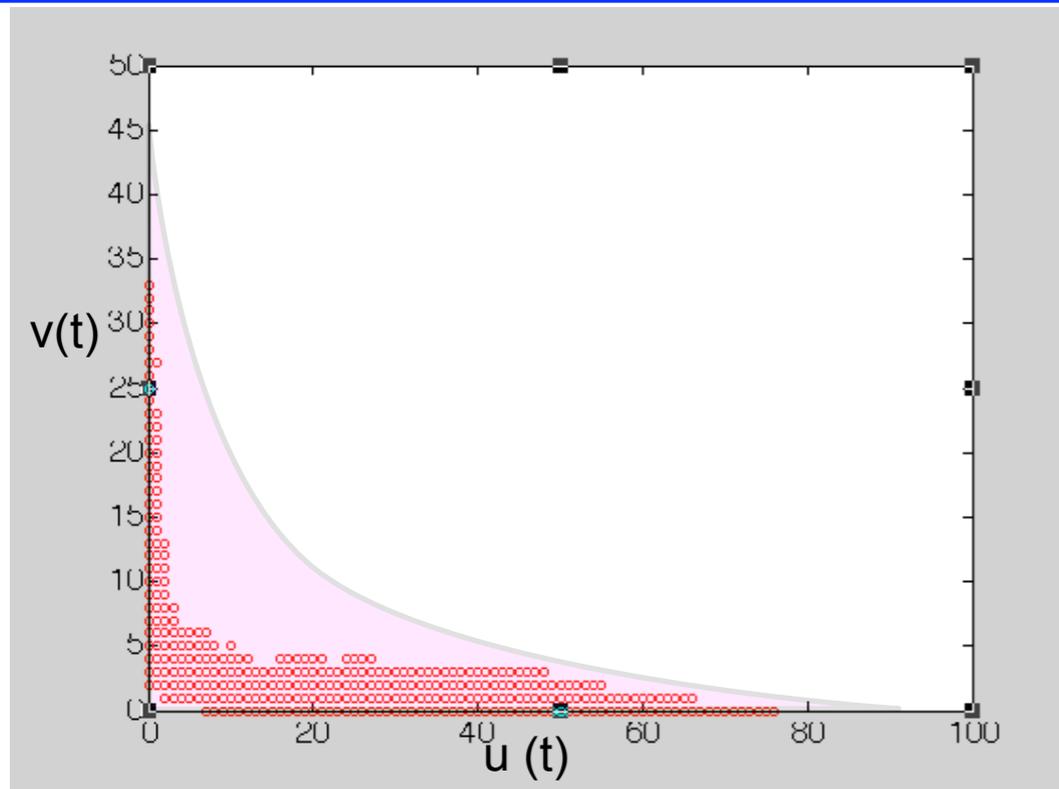
Applying the FSP.



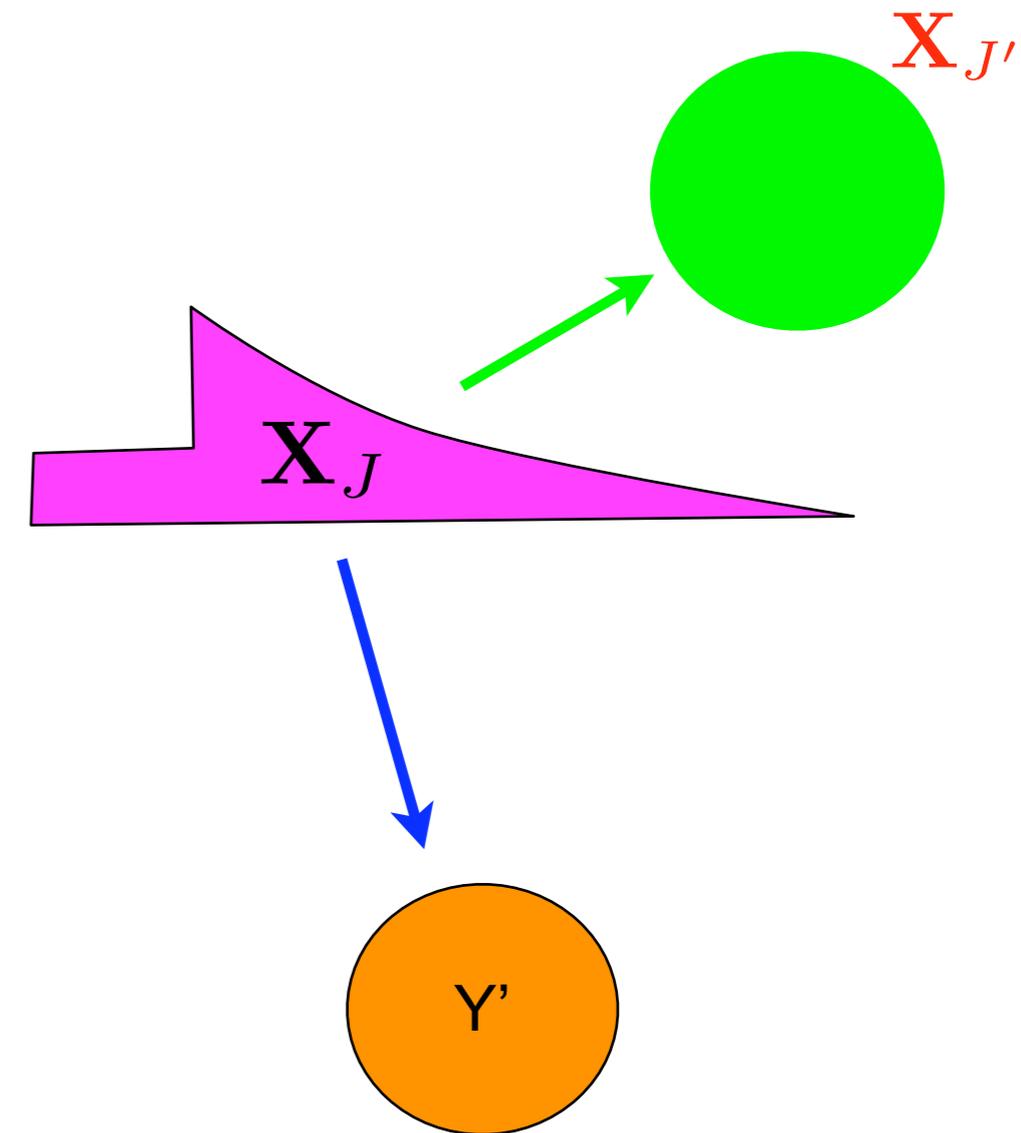
- From the simulation we saw that trajectories tend to remain in a small region of the configuration set: $u(t)v(t) < 260$.
- We will call this set X_J and its complement $X_{J'}$
- We project $X_{J'}$ to a single point.



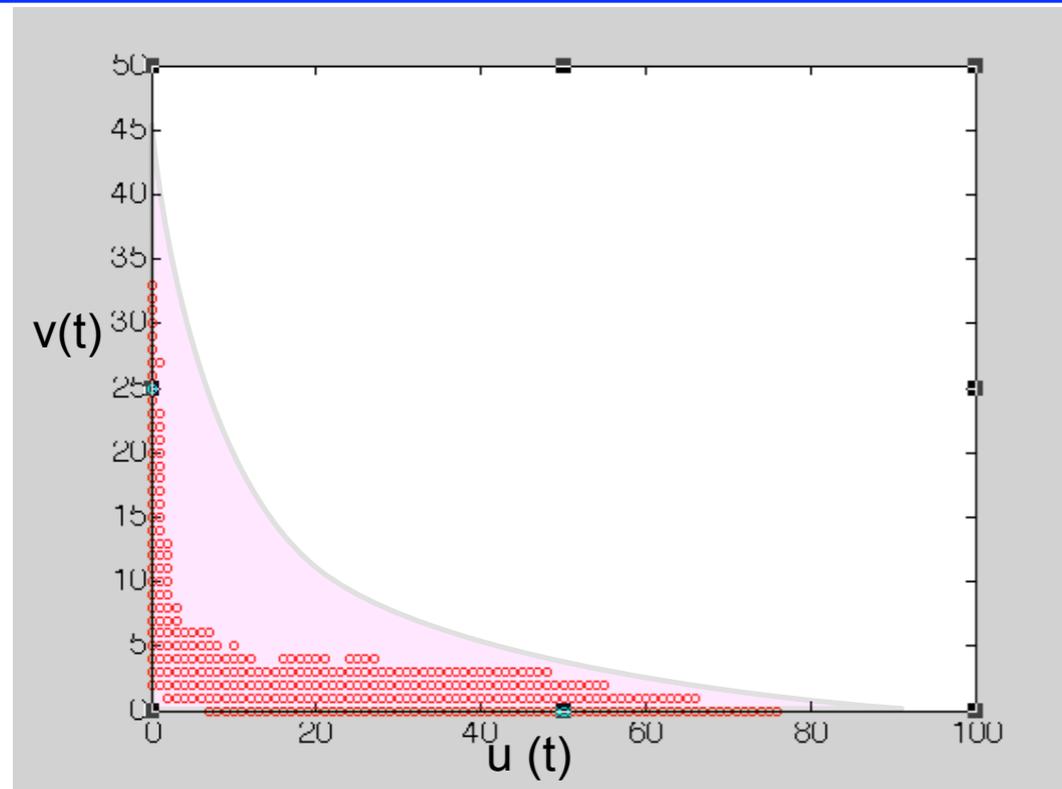
Applying the FSP.



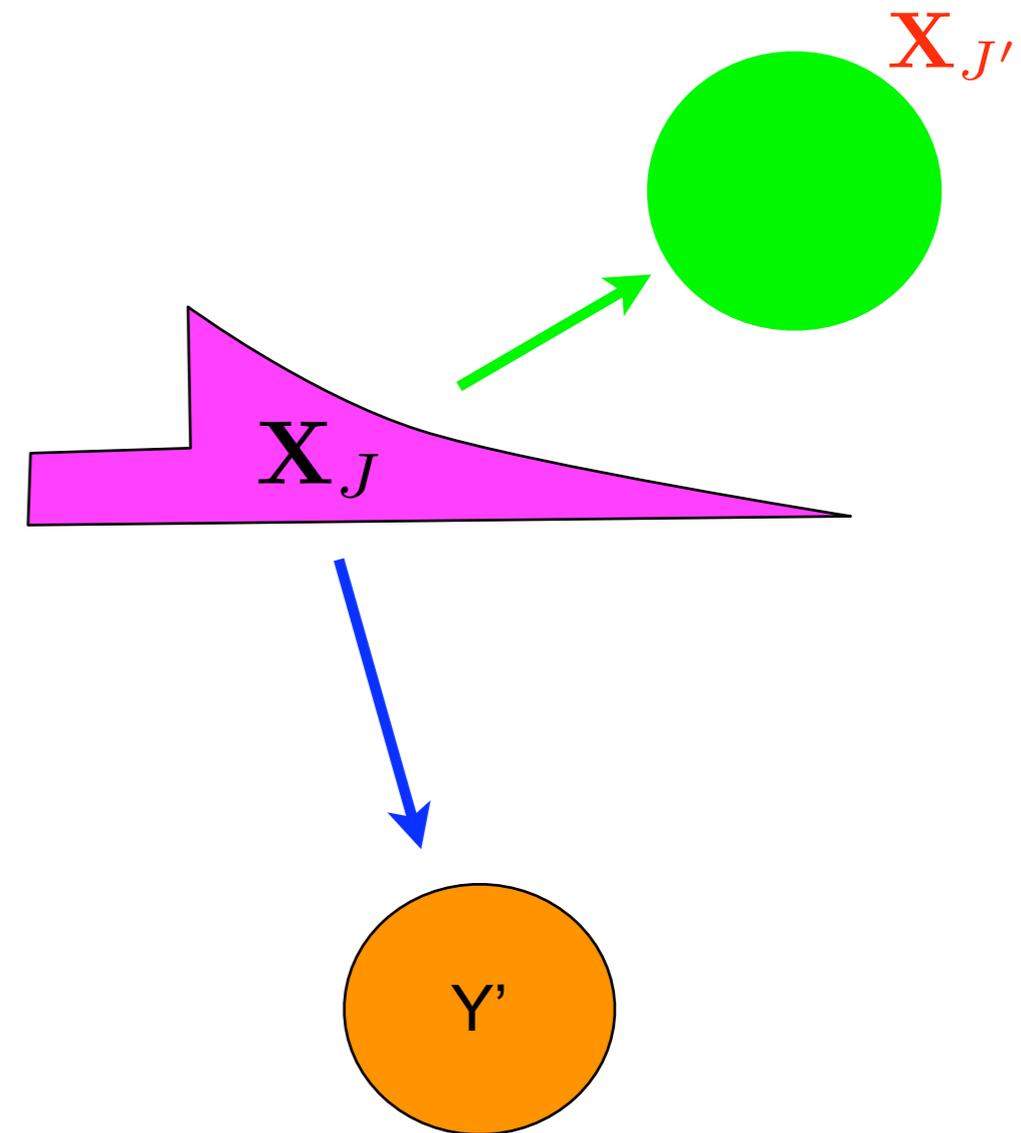
- From the simulation we saw that trajectories tend to remain in a small region of the configuration set: $u(t)v(t) < 260$.
- We will call this set X_J and its complement $X_{J'}$
- We project $X_{J'}$ to a single point.



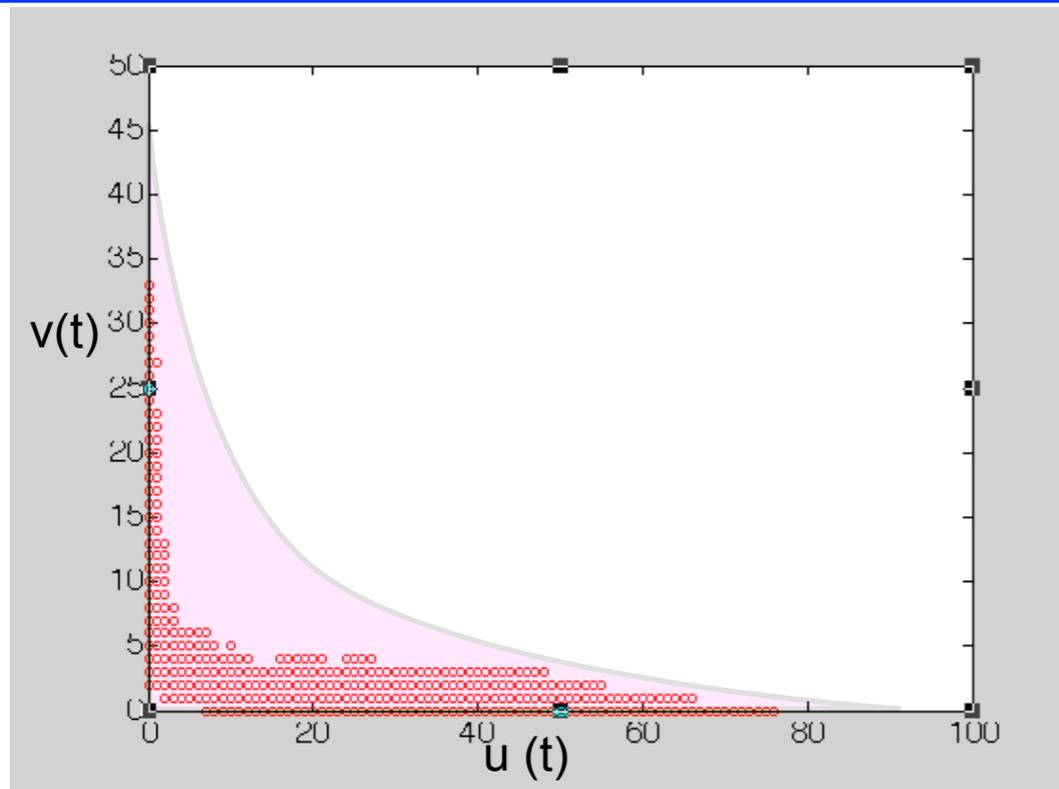
Applying the FSP.



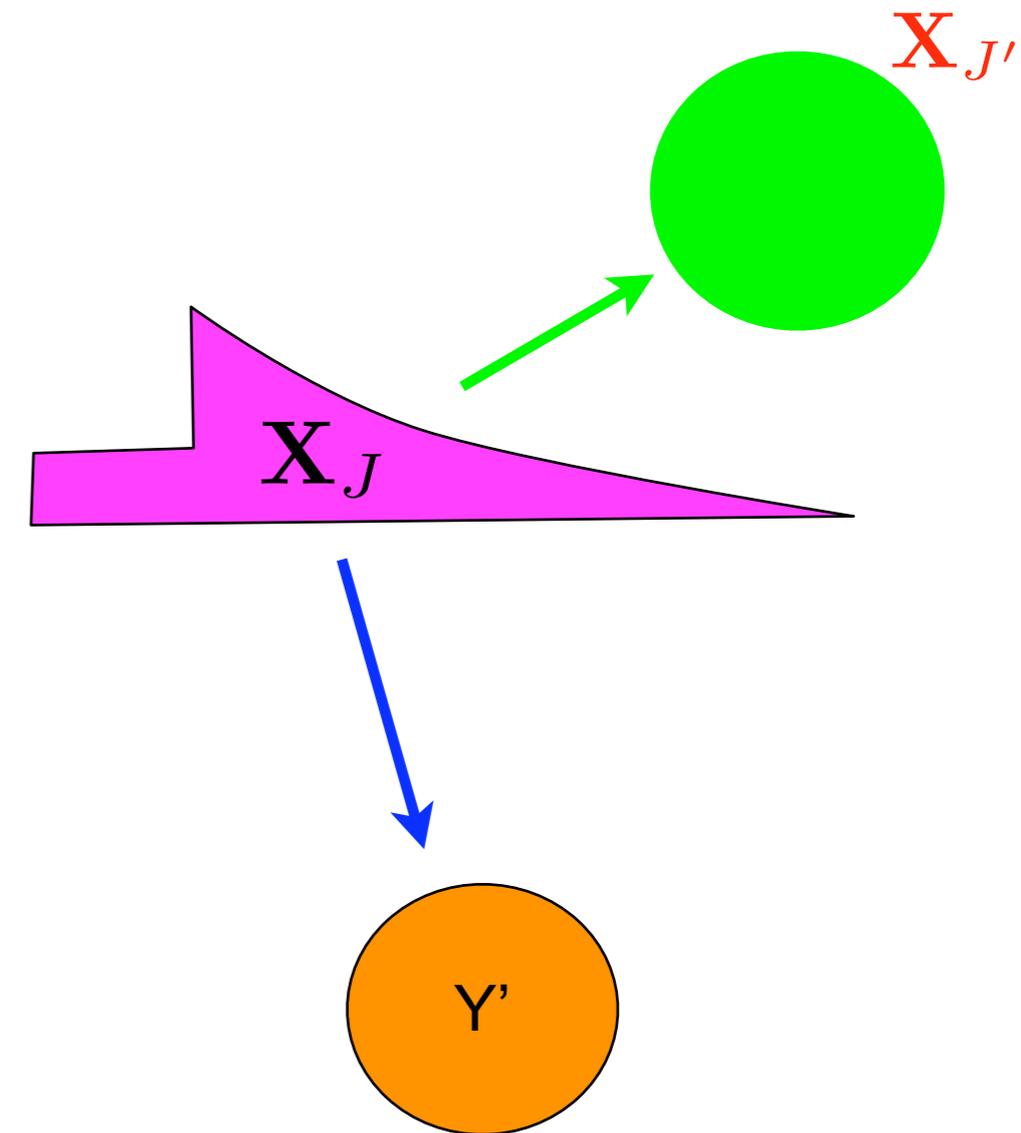
- From the simulation we saw that trajectories tend to remain in a small region of the configuration set: $u(t)v(t) < 260$.
- We will call this set X_J and its complement $X_{J'}$
- We project $X_{J'}$ to a single point.
- No transitions can leave $X_{J'}$



Applying the FSP.



- From the simulation we saw that trajectories tend to remain in a small region of the configuration set: $u(t)v(t) < 260$.
- We will call this set X_J and its complement $X_{J'}$
- We project $X_{J'}$ to a single point.
- No transitions can leave $X_{J'}$



We now have a small dimension, solvable system.



Applying the FSP.

Define:

$y'(t) = \mathbf{1}^T \mathbf{P}(Y', t)$: probability of having turned off.



Applying the FSP.

Define:

$y'(t) = \mathbf{1}^T \mathbf{P}(Y', t)$: probability of having turned off.

From Theorem 2, if $\mathbf{1}^T \exp \begin{bmatrix} \mathbf{A}_J t_f & 0 \\ \mathbf{1}^T \mathbf{A}_{Y' J} t_f & 0 \end{bmatrix} \begin{bmatrix} \mathbf{P}_J(0) \\ y'(0) \end{bmatrix} \geq 1 - \varepsilon,$

Applying the FSP.

Define:

$y'(t) = \mathbf{1}^T \mathbf{P}(Y', t)$: probability of having turned off.

From Theorem 2, if $\mathbf{1}^T \exp \begin{bmatrix} \mathbf{A}_J t_f & 0 \\ \mathbf{1}^T \mathbf{A}_{Y' J} t_f & 0 \end{bmatrix} \begin{bmatrix} \mathbf{P}_J(0) \\ y'(0) \end{bmatrix} \geq 1 - \varepsilon,$

then

$$\left\| \begin{bmatrix} \mathbf{P}_J(t_f) \\ y'(t_f) \end{bmatrix} - \exp \begin{bmatrix} \mathbf{A}_J t_f & 0 \\ \mathbf{1}^T \mathbf{A}_{Y' J} t_f & 0 \end{bmatrix} \begin{bmatrix} \mathbf{P}_J(0) \\ y'(0) \end{bmatrix} \right\|_1 \leq \varepsilon$$



Applying the FSP.

Define:

$y'(t) = \mathbf{1}^T \mathbf{P}(Y', t)$: probability of having turned off.

From Theorem 2, if $\mathbf{1}^T \exp \begin{bmatrix} \mathbf{A}_J t_f & 0 \\ \mathbf{1}^T \mathbf{A}_{Y', J} t_f & 0 \end{bmatrix} \begin{bmatrix} \mathbf{P}_J(0) \\ y'(0) \end{bmatrix} \geq 1 - \varepsilon,$

then

$$\left\| \begin{bmatrix} \mathbf{P}_J(t_f) \\ y'(t_f) \end{bmatrix} - \exp \begin{bmatrix} \mathbf{A}_J t_f & 0 \\ \mathbf{1}^T \mathbf{A}_{Y', J} t_f & 0 \end{bmatrix} \begin{bmatrix} \mathbf{P}_J(0) \\ y'(0) \end{bmatrix} \right\|_1 \leq \varepsilon$$

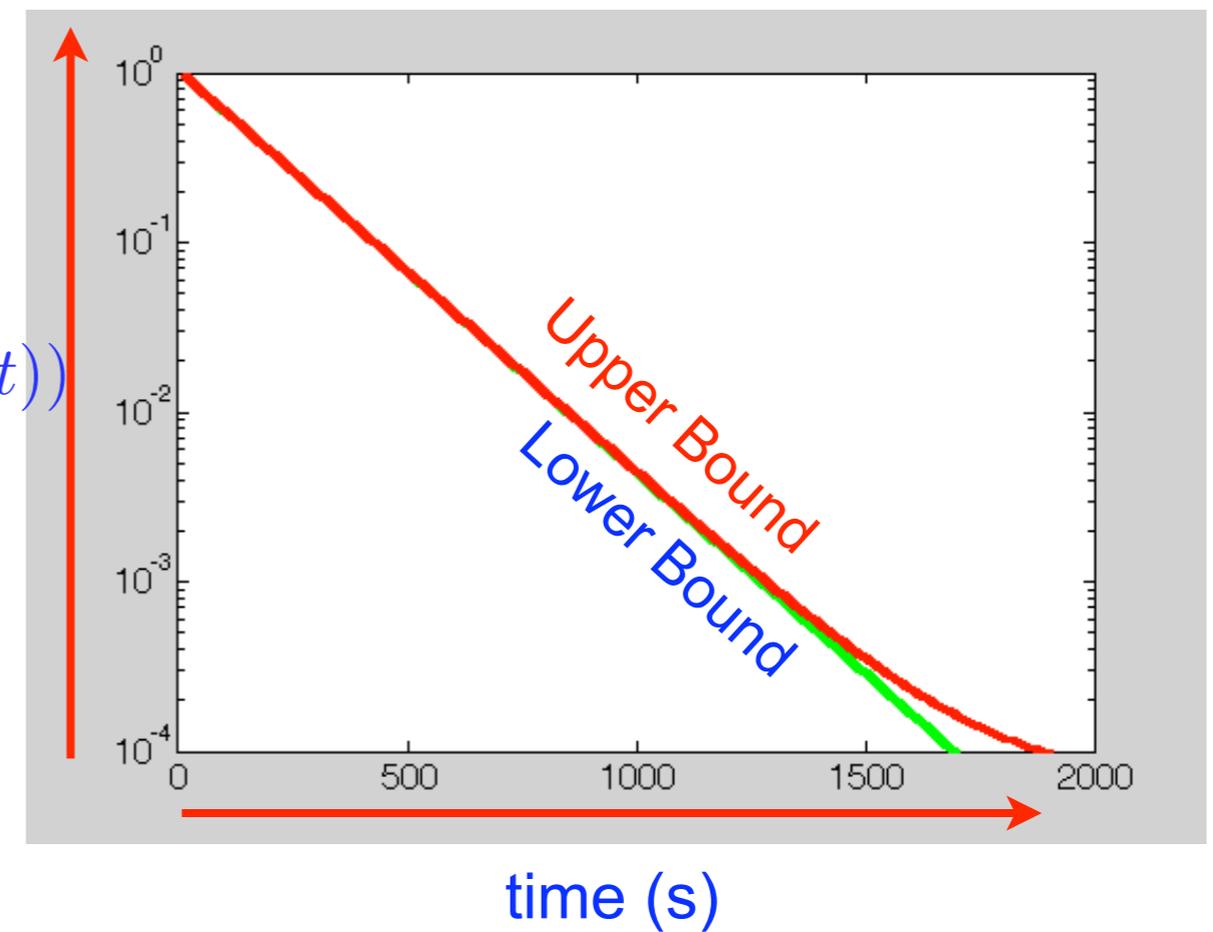
Most importantly, we have an estimate of the probability that of avoiding the OFF configurations, $(1-y'(t))$, which we were seeking to find.

Results

The reduced FSP solution takes only **1.9 seconds** to compute.

(1 - the probability of turning OFF) vs. time

$$(1 - y'(t))$$



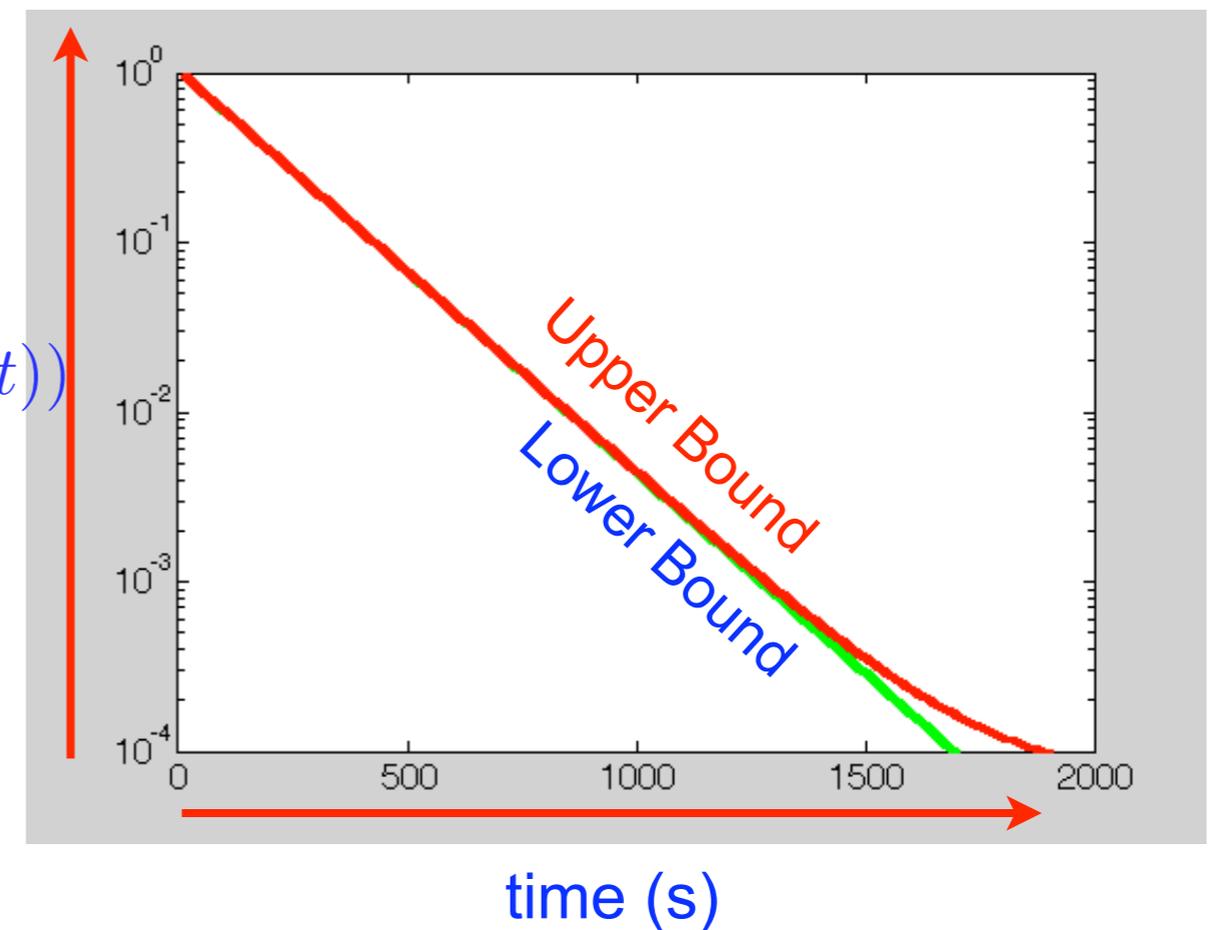
Results

The reduced FSP solution takes only **1.9 seconds** to compute.

Provides guaranteed bounds on the probability of switching.

$$(1 - y'(t))$$

(1 - the probability of turning OFF) vs. time



Results

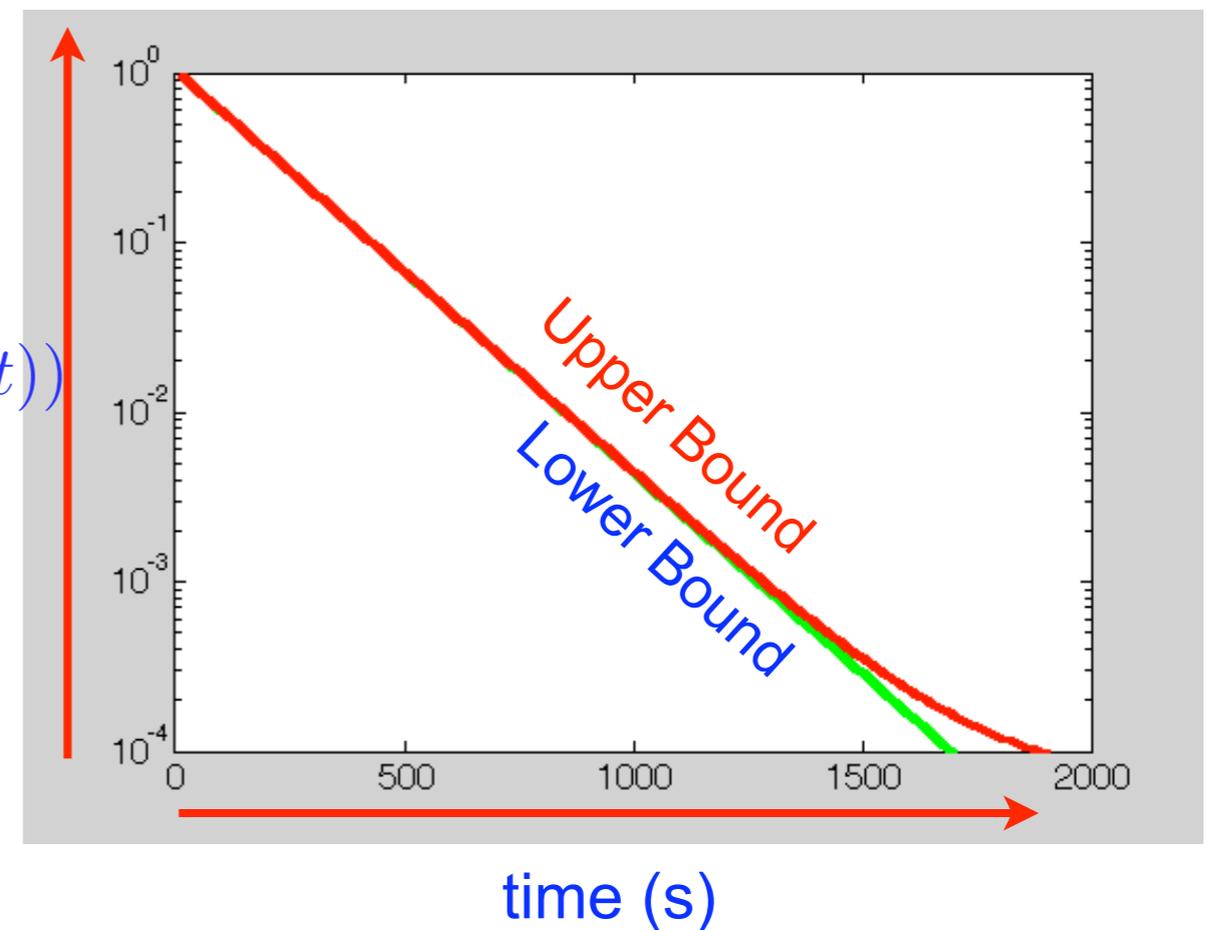
The reduced FSP solution takes only **1.9 seconds** to compute.

Provides guaranteed bounds on the probability of switching.

In comparison, Monte Carlo simulations (SSA) require many many runs to achieve comparable precision.

$$(1 - y'(t))$$

(1 - the probability of turning OFF) vs. time



Results

The reduced FSP solution takes only **1.9 seconds** to compute.

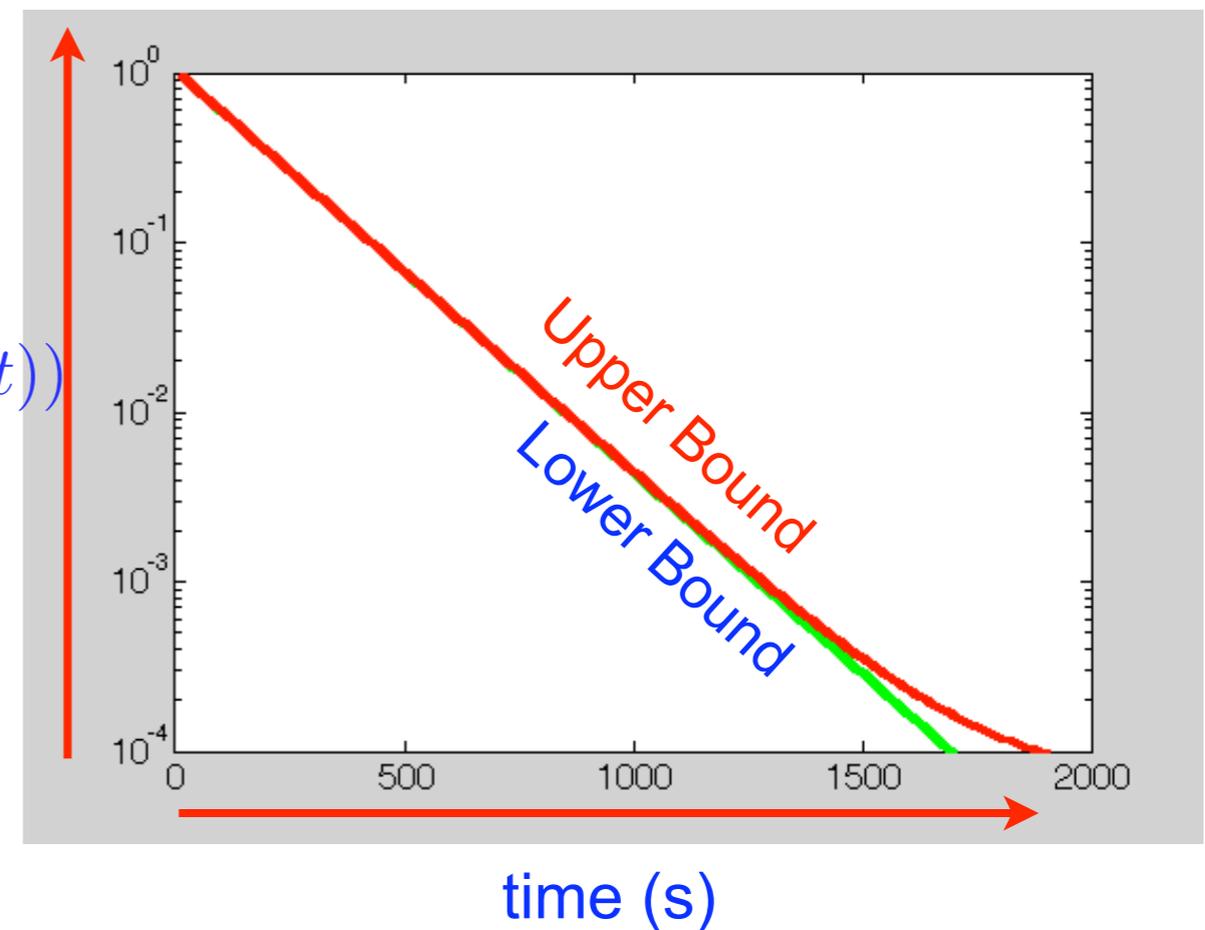
Provides guaranteed bounds on the probability of switching.

In comparison, Monte Carlo simulations (SSA) require many many runs to achieve comparable precision.

Provide no accuracy guarantees.

(1 - the probability of turning OFF) vs. time

$$(1 - y'(t))$$



Results

The reduced FSP solution takes only **1.9 seconds** to compute.

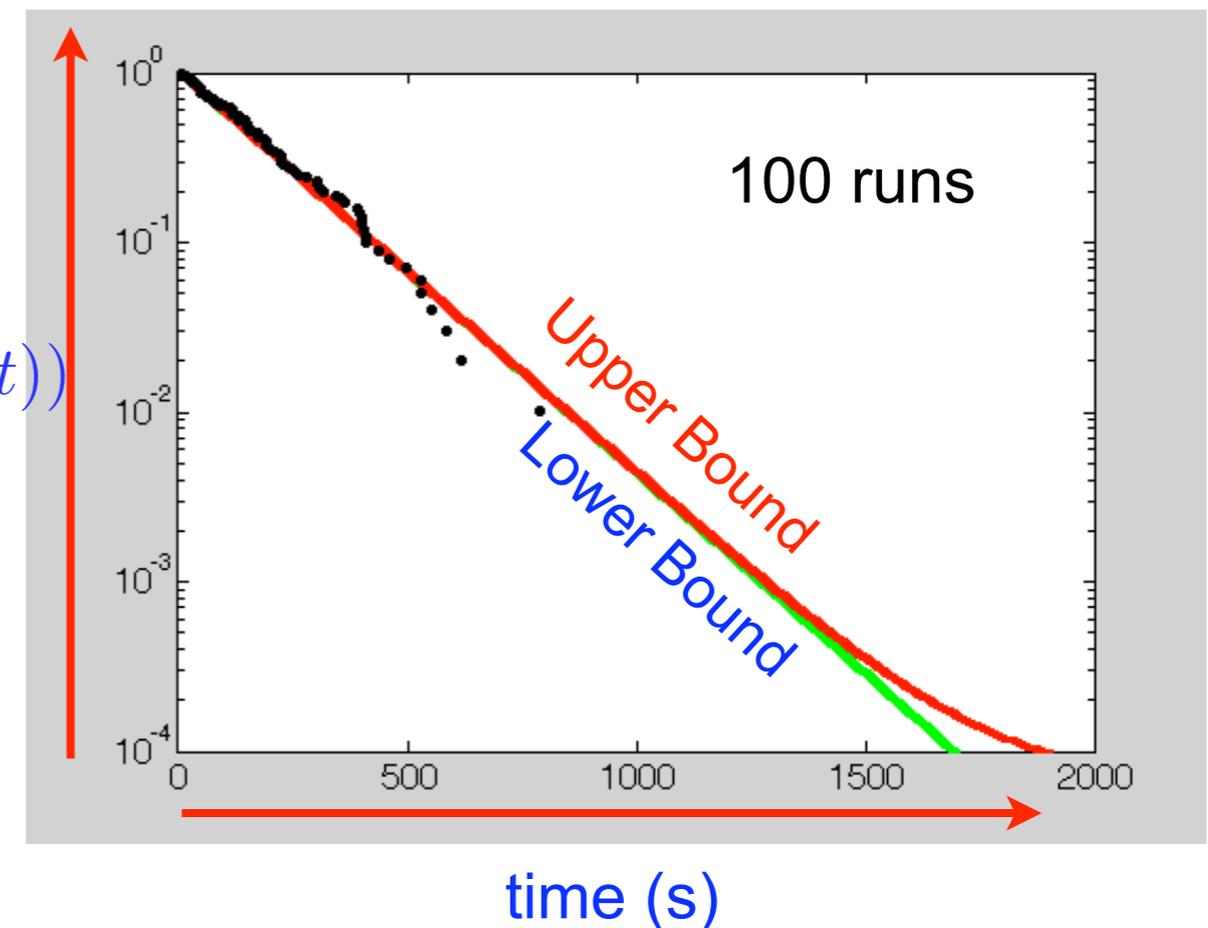
Provides guaranteed bounds on the probability of switching.

In comparison, Monte Carlo simulations (SSA) require many many runs to achieve comparable precision.

Provide no accuracy guarantees.

(1 - the probability of turning OFF) vs. time

$$(1 - y'(t))$$



Results

The reduced FSP solution takes only **1.9 seconds** to compute.

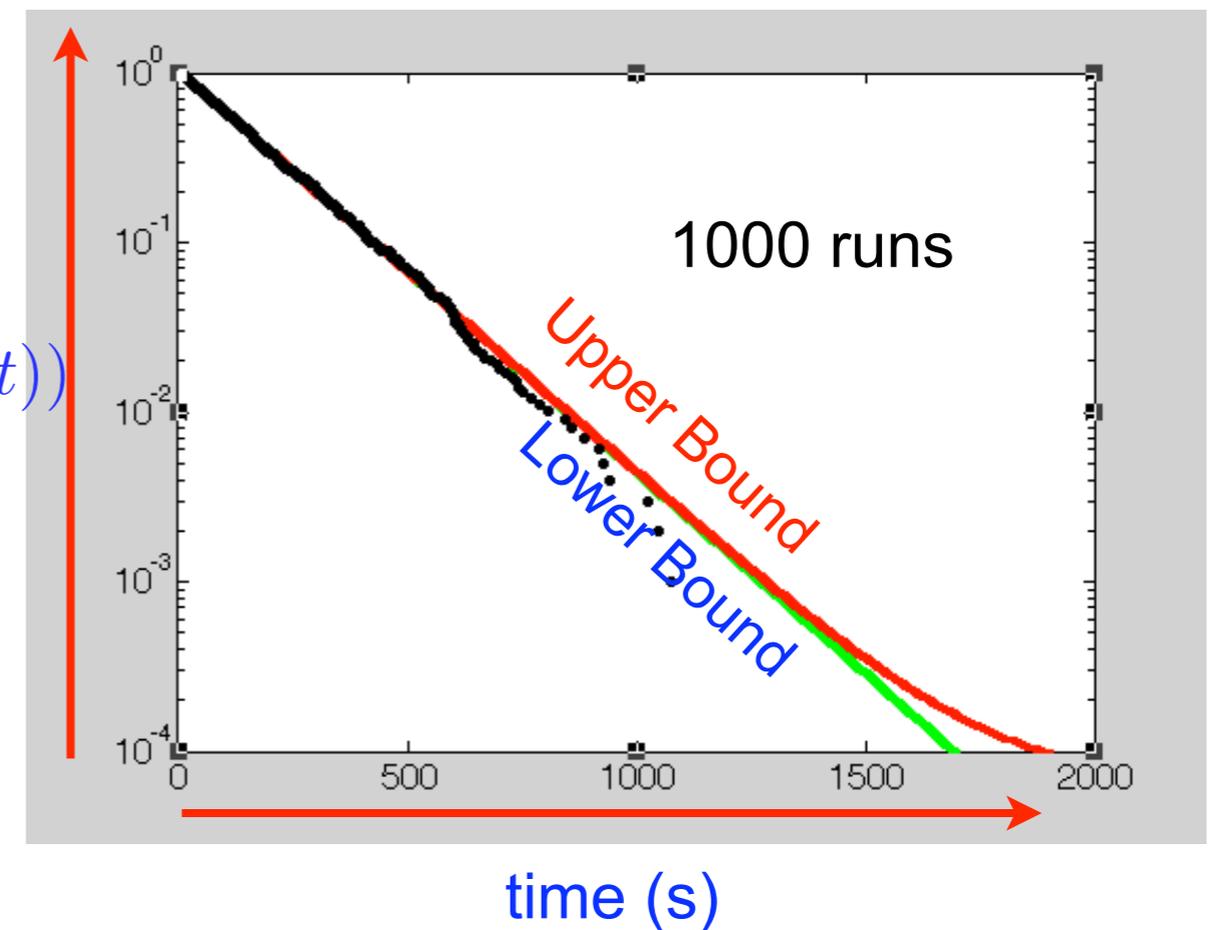
Provides guaranteed bounds on the probability of switching.

In comparison, Monte Carlo simulations (SSA) require many many runs to achieve comparable precision.

Provide no accuracy guarantees.

(1 - the probability of turning OFF) vs. time

$$(1 - y'(t))$$



Results

The reduced FSP solution takes only **1.9 seconds** to compute.

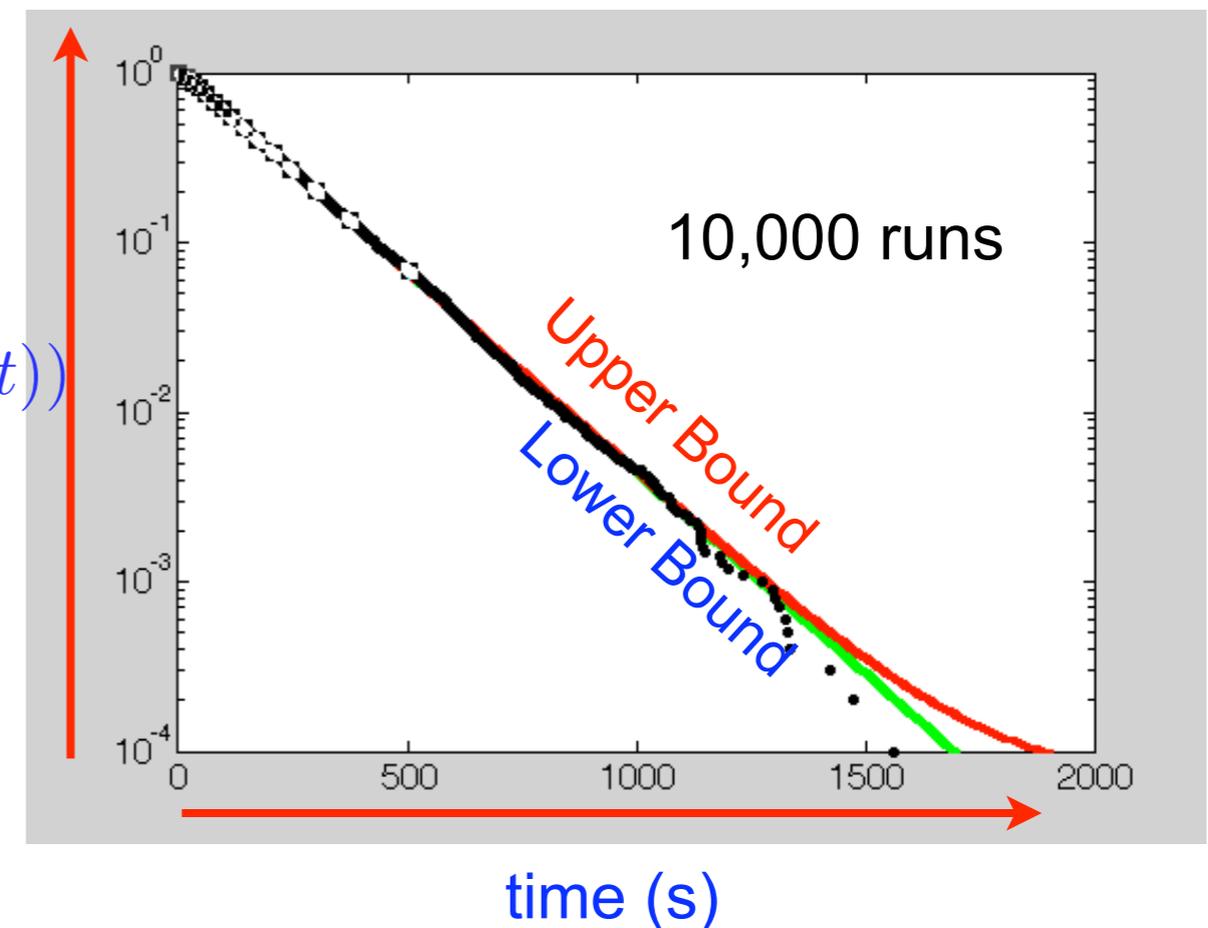
Provides guaranteed bounds on the probability of switching.

In comparison, Monte Carlo simulations (SSA) require many many runs to achieve comparable precision.

Provide no accuracy guarantees.

(1 - the probability of turning OFF) vs. time

$$(1 - y'(t))$$



Results

The reduced FSP solution takes only **1.9 seconds** to compute.

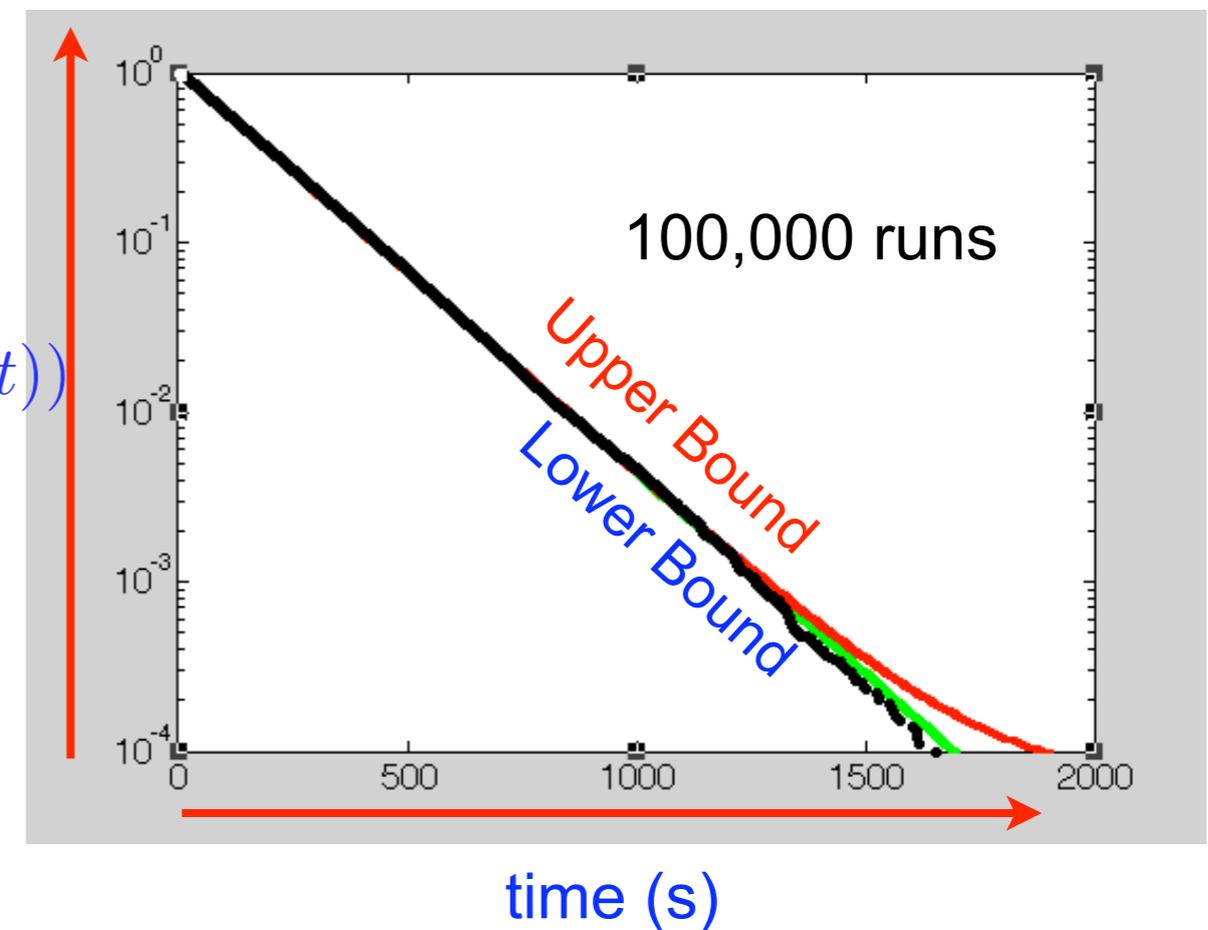
Provides guaranteed bounds on the probability of switching.

In comparison, Monte Carlo simulations (SSA) require many many runs to achieve comparable precision.

Provide no accuracy guarantees.

(1 - the probability of turning OFF) vs. time

$$(1 - y'(t))$$



Results

The reduced FSP solution takes only **1.9 seconds** to compute.

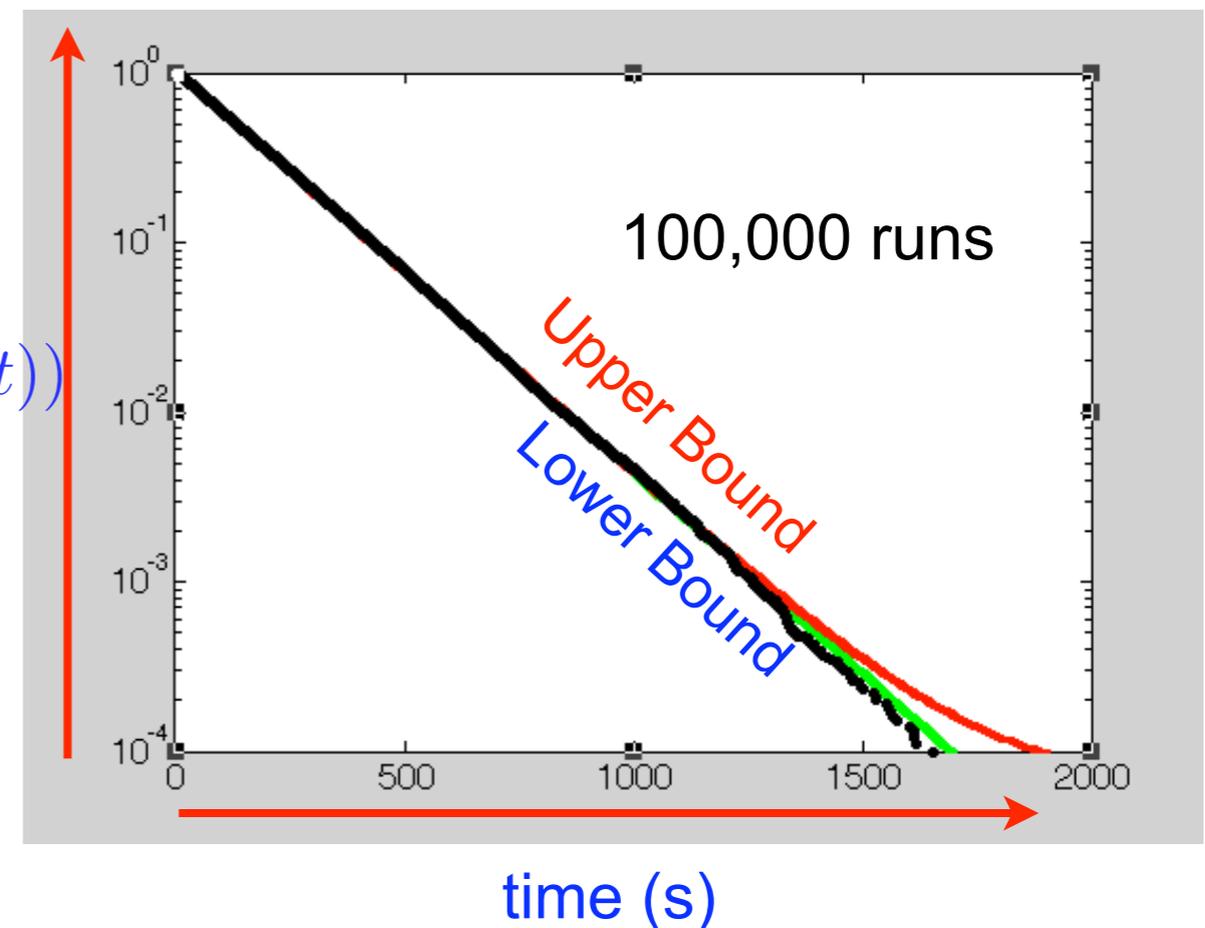
Provides guaranteed bounds on the probability of switching.

In comparison, Monte Carlo simulations (SSA) require many many runs to achieve comparable precision.

Provide no accuracy guarantees.

(1 - the probability of turning OFF) vs. time

$$(1 - y'(t))$$



The FSP approach also provides estimates of every other initial probability distribution supported on X_J .

Monte Carlo methods only consider a single individual initial distribution.

FSP vs. Monte Carlo Algorithm

Table 1: A comparison of the efficiency and accuracy of the FSP and SSA solutions to find the time at which 99 percent of cells will have reached the OFF state.

| Method | # Simulations | Comp. Time (s) ^a | t_{99} | Relative Error |
|-------------------|---------------|-----------------------------|------------|-------------------|
| Full Model | | | | |
| FSP | N.A. | 1.9 | 850 | < 0.12% |
| SSA | 10^3 | 33 | 789 | $\approx 7.3\%$ |
| SSA | 10^4 | 330 | 806 | $\approx 5.2\%$ |
| SSA | 10^5 | 3300 | 838 | $\approx 1.5\%$ |
| SSA | 10^6 | 3.3×10^4 | 845 | $\approx 0.6\%$ |

^aAll computations have been performed in Matlab 7.2 on a 2.0 MHz PowerPC G5.

Outline

1. Introduction
2. The Finite State Projection (FSP)
3. Model Reduction Techniques
4. Example
5. Conclusions



Conclusions

- Bio-networks are noisy due to small molecular populations.



Conclusions

- Bio-networks are noisy due to small molecular populations.
- The Chemical Master Equation describes the evolution of the system's probability distribution.

Conclusions

- Bio-networks are noisy due to small molecular populations.
- The Chemical Master Equation describes the evolution of the system's probability distribution.
 - Usually cannot be solved exactly,



Conclusions

- Bio-networks are noisy due to small molecular populations.
- The Chemical Master Equation describes the evolution of the system's probability distribution.
 - Usually cannot be solved exactly,
 - but it can be approximated using the Finite State Projection algorithm.

Conclusions

- Bio-networks are noisy due to small molecular populations.
- The Chemical Master Equation describes the evolution of the system's probability distribution.
 - Usually cannot be solved exactly,
 - but it can be approximated using the Finite State Projection algorithm.
- Often the FSP is both faster and more precise than Monte Carlo approaches.



Conclusions

- Bio-networks are noisy due to small molecular populations.
- The Chemical Master Equation describes the evolution of the system's probability distribution.
 - Usually cannot be solved exactly,
 - but it can be approximated using the Finite State Projection algorithm.
- Often the FSP is both faster and more precise than Monte Carlo approaches.
 - Allows additional analytical tools (robustness, sensitivity).



Conclusions

- Bio-networks are noisy due to small molecular populations.
- The Chemical Master Equation describes the evolution of the system's probability distribution.
 - Usually cannot be solved exactly,
 - but it can be approximated using the Finite State Projection algorithm.
- Often the FSP is both faster and more precise than Monte Carlo approaches.
 - Allows additional analytical tools (robustness, sensitivity).
 - Enables model reductions.



Acknowledgments

This material is based upon the work supported by the University of California, Santa Barbara Chancellor's Fellowship, the National Science Foundation under Grant NSF-ITR CCF-0326576, and the Institute for Collaborative Biotechnologies through Grant DAAD19-03-D-0004 from the U.S. Army Research Office.