Embedding Machine Learning in Formal Stochastic Models of Biological Processes

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Outline

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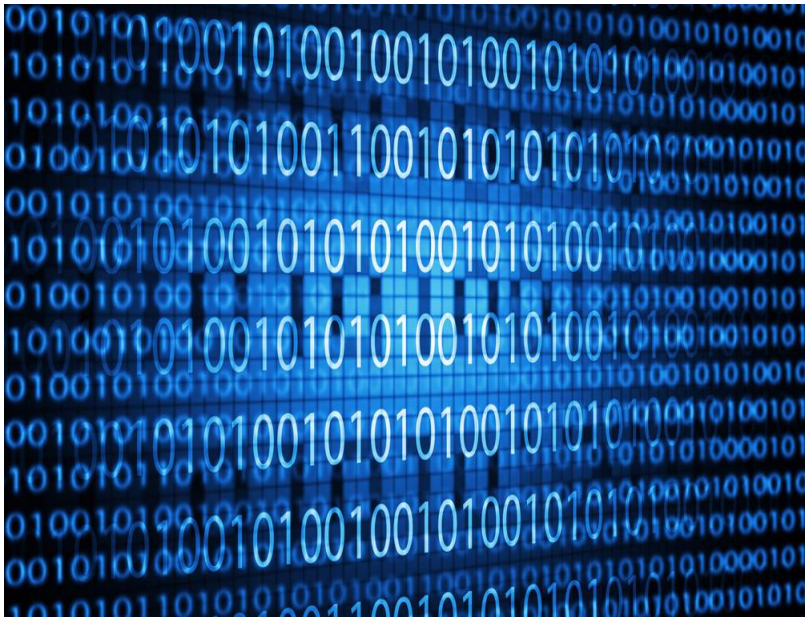
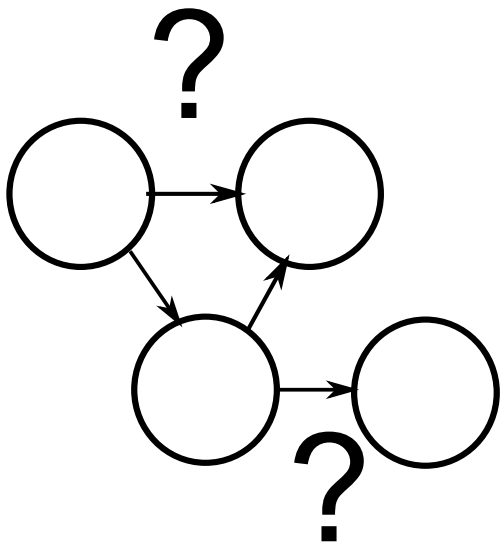
Formal modelling

- Formal languages (process algebras, Petri nets, rule-based) provide a convenient interface for describing complex systems.
- High-level abstraction makes writing and manipulating models easier.
- They can capture different kinds of behaviour: deterministic, stochastic, ...
- Formal nature lends itself to automatic, rigorous methods for analysis and verification.

- ...but what if parts of the system are unknown?

Alternative perspective





Model creation is data-driven

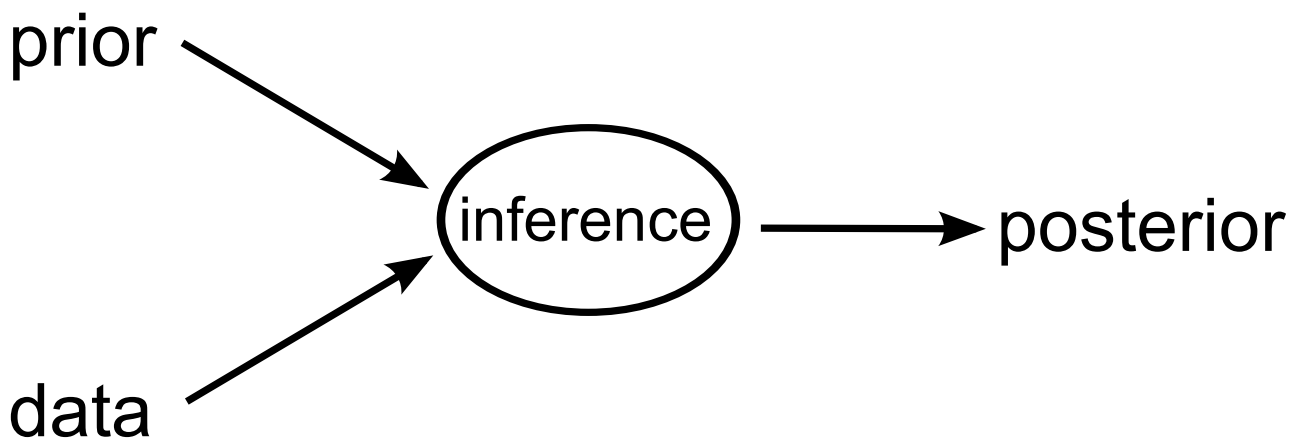
Modelling

There are two approaches to model construction:

Machine Learning: extracting a model from the data generated by the system, or refining a model based on system behaviour using statistical techniques.

Mechanistic Modelling: starting from a description or hypothesis, construct a model that algorithmically mimics the behaviour of the system, validated against data.

Machine Learning



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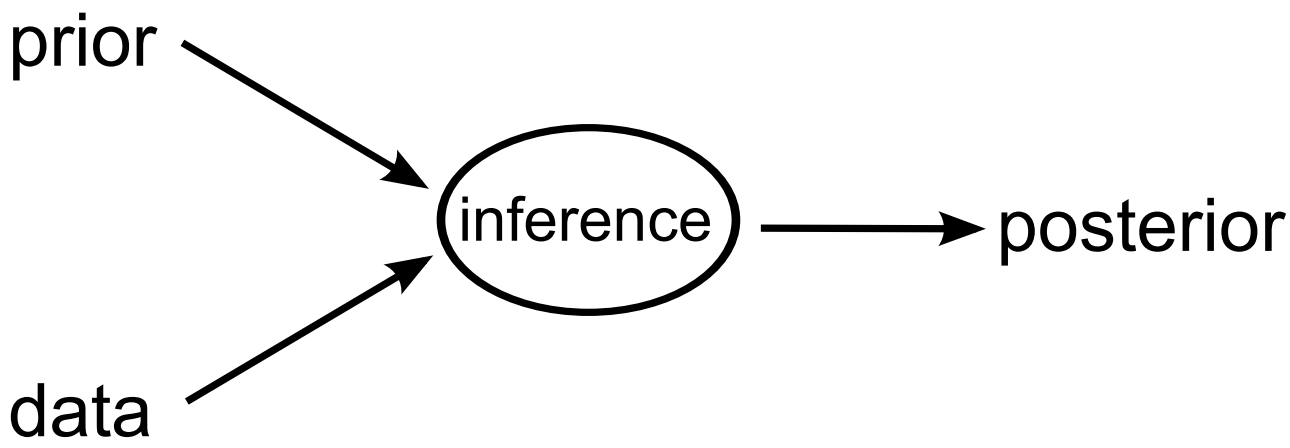


Bayes' Theorem

For the distribution of a parameter θ and observed data D,

$$P(\theta \mid D) \propto P(\theta)P(D \mid \theta)$$

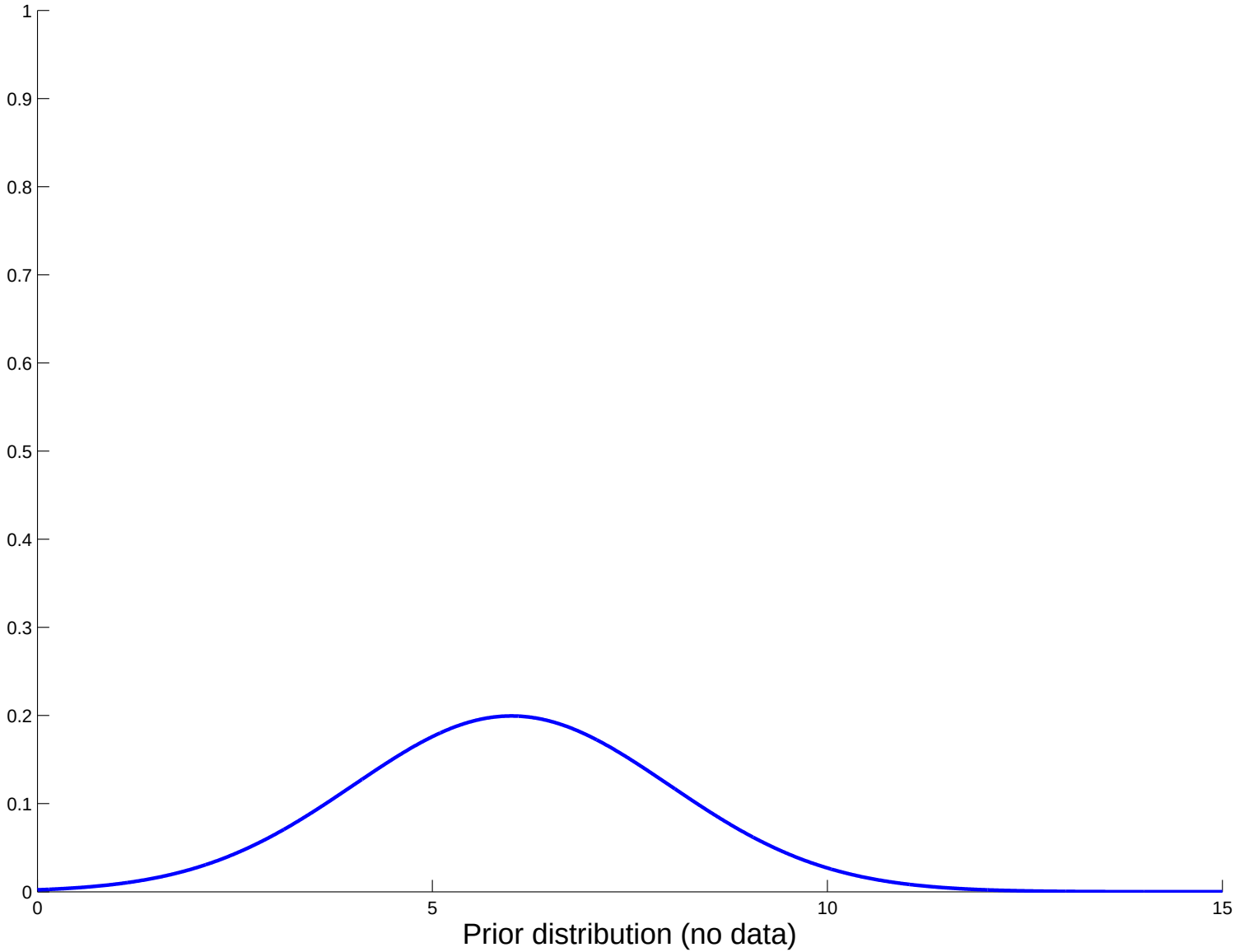
Bayesian statistics

- Represent belief and uncertainty as probability distributions (prior, posterior).
- Treat parameters and unobserved variables similarly.
- Bayes' Theorem:

$$P(\theta \mid D) = \frac{P(\theta) \cdot P(D \mid \theta)}{P(D)}$$

$$\text{posterior} \propto \text{prior} \cdot \text{likelihood}$$

Bayesian statistics



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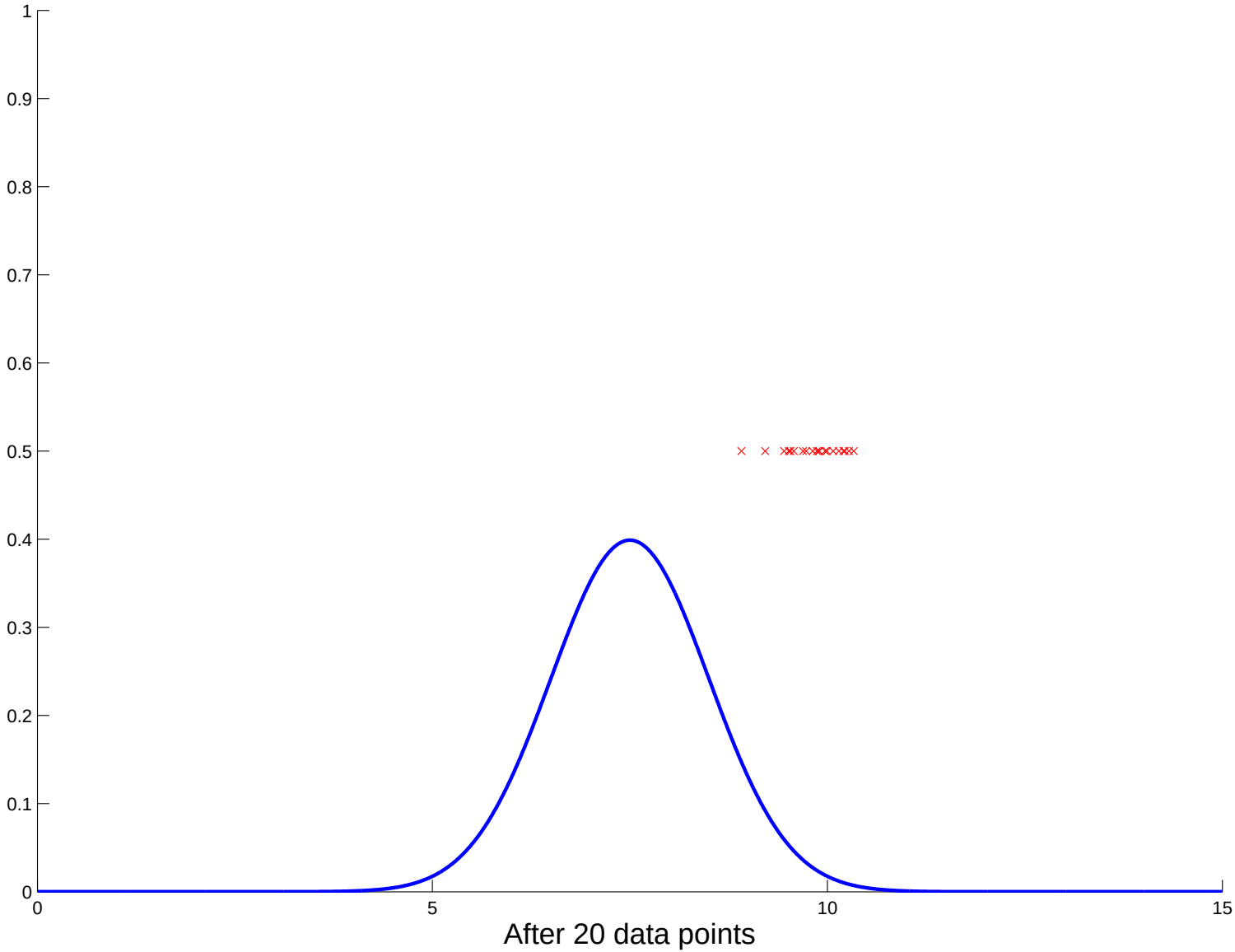

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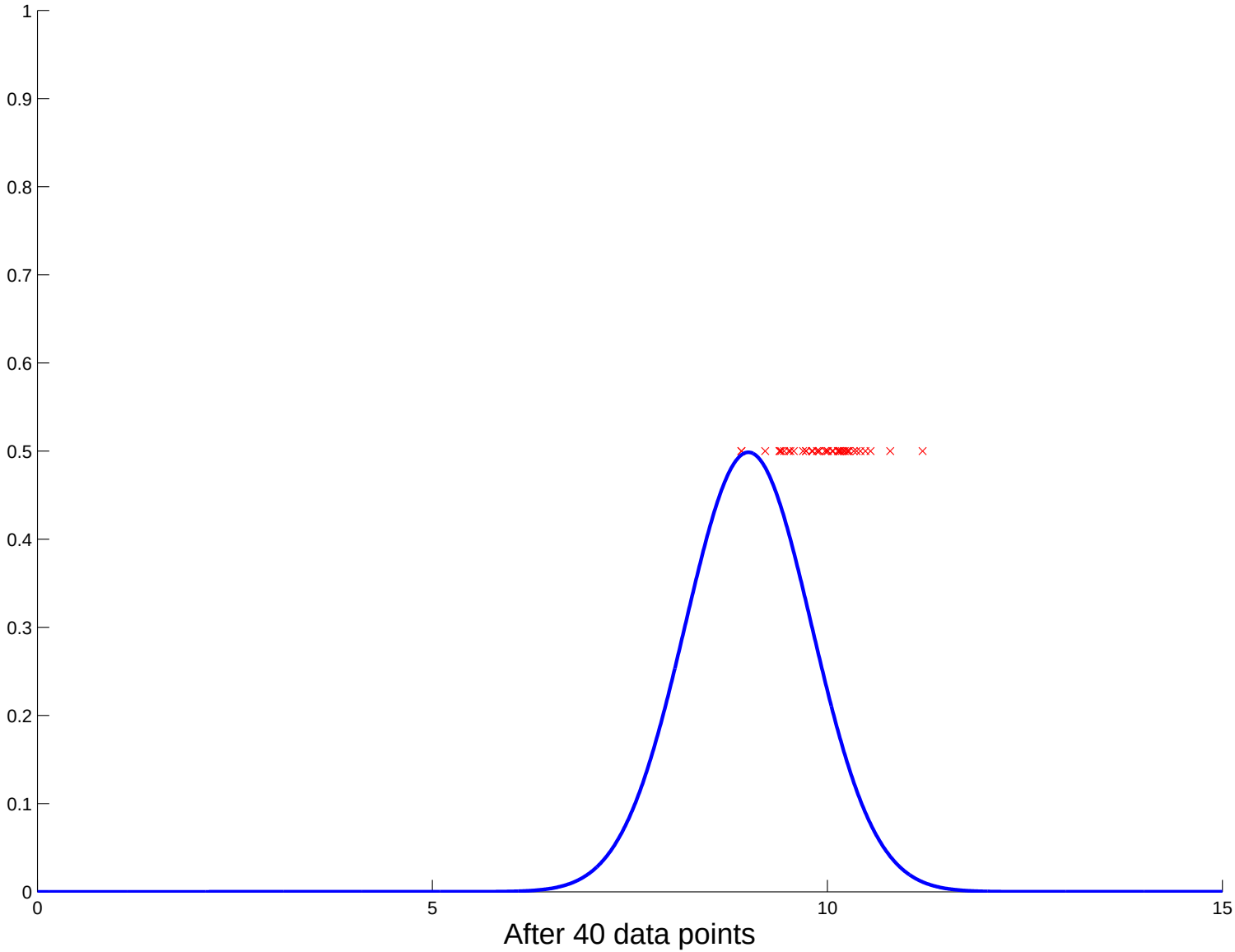

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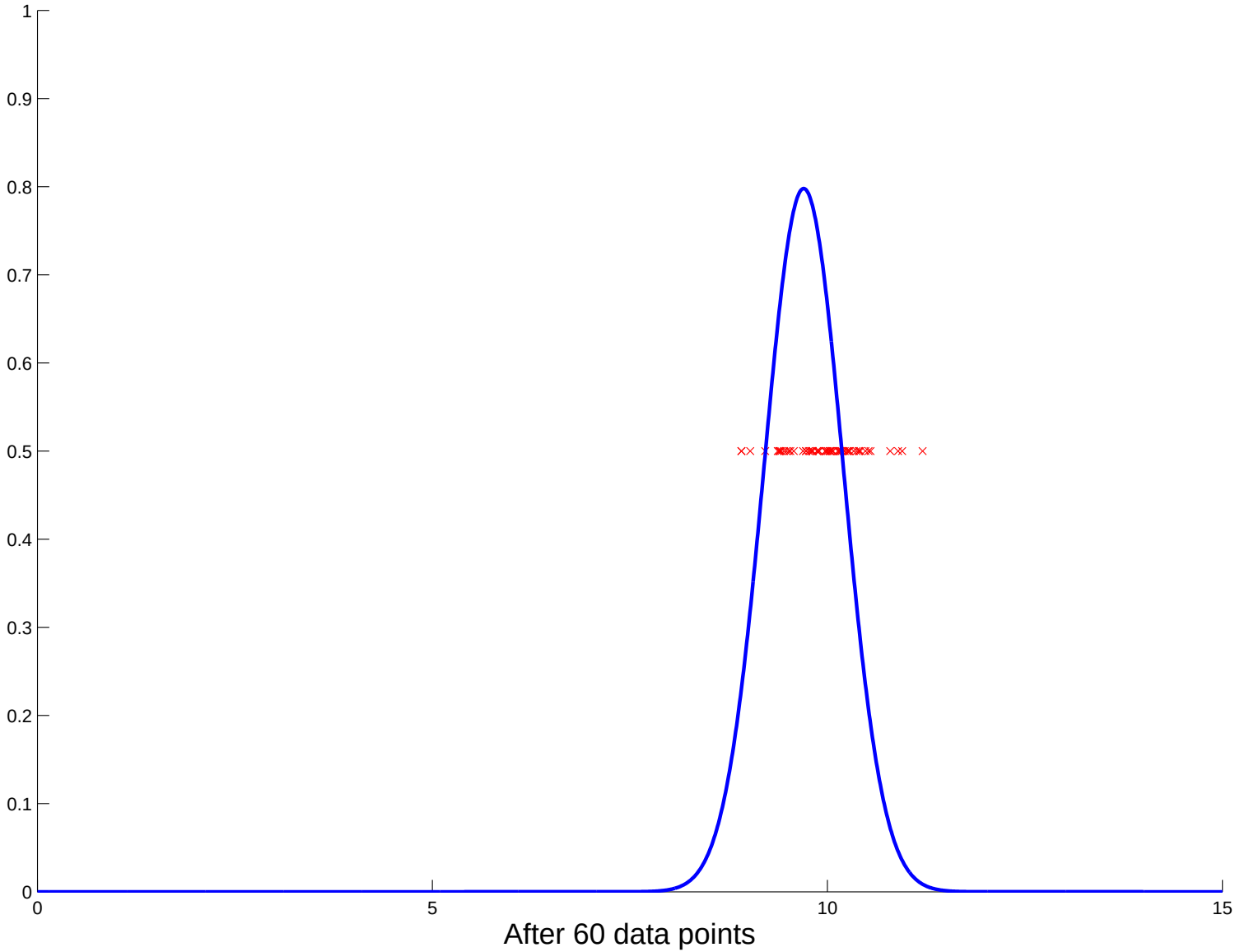

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Models are constructed reflecting what is known about the components of the biological system and their behaviour.

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Executing the model generates data that can be compared with biological data.

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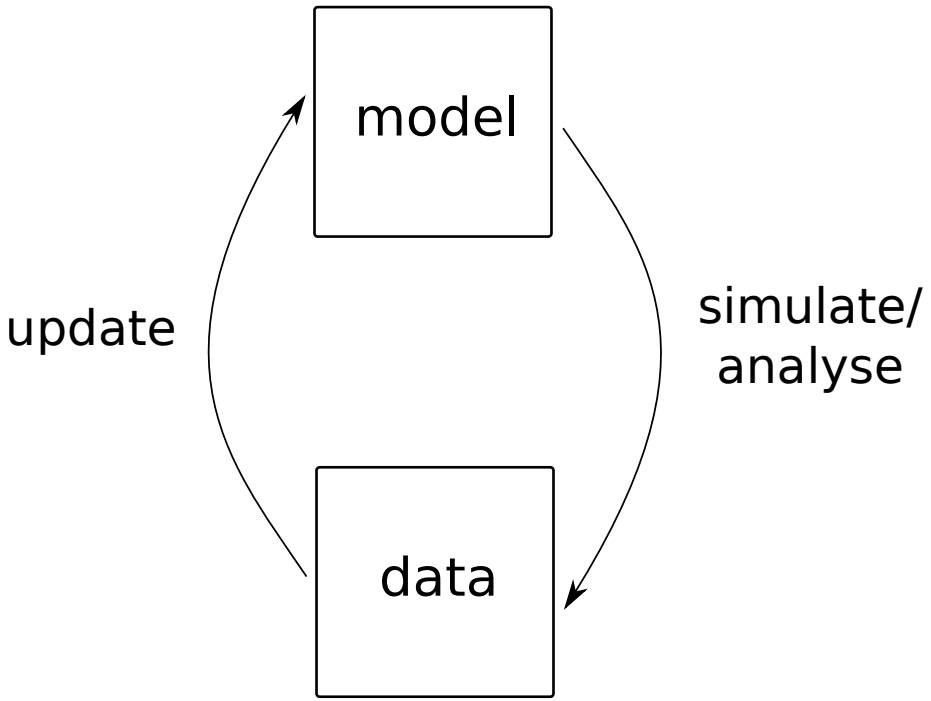
Optimizing models

Usual process of parameterising a model is iterative and manual.



Comparing the techniques

Data-driven modelling:

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Mechanistic modelling:

+ general execution "engine" (deterministic or stochastic) can be reused for many models
+ models can be used speculatively to investigate roles of parameters, or alternative hypotheses
- parameters are assumed to be known and fixed, or costly approaches must be used to seek appropriate parameterisation

Developing a probabilistic programming approach

What if we could...

- include information about uncertainty in the model?
- automatically use observations to refine this uncertainty?
- do all this in a formal context?

Starting from an existing process algebra (Bio-PEPA), we have developed a new language **ProPPA** that addresses these issues[2].

[2] Anastasis Georgoulas, Jane Hillston, Dimitrios Milios, Guido Sanguinetti: *Probabilistic Programming Process Algebra*. QEST 2014: 249-264.

Outline

Probabilistic programming

A programming paradigm for describing incomplete knowledge scenarios, and resolving the uncertainty.

- Describe how the data is generated in syntax like a conventional programming language, but leaving some variables uncertain.

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- Specify observations, which impose constraints on acceptable outputs of the program.
- Run program forwards: Generate data consistent with observations.
- Run program backwards: Find values for the uncertain variables which make the output match the observations.

Outline

Molecular processes as concurrent computations

Concurrency	**Molecular Biology**	**Metabolism**	**Signal Transduction**
Concurrent computational processes	Molecules	Enzymes and metabolites	Interacting proteins
Synchronous communication	Molecular interaction	Binding and catalysis	Binding and catalysis
Transition or mobility	Biochemical modification or relocation	Metabolite synthesis	Protein binding, modification or sequestration

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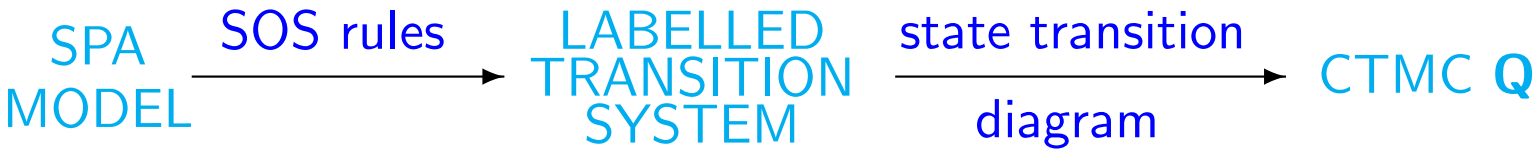

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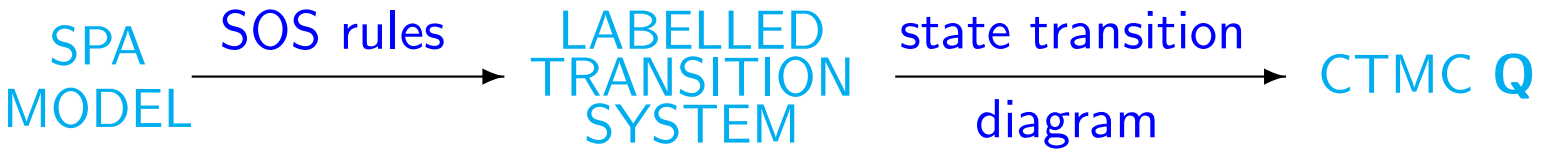

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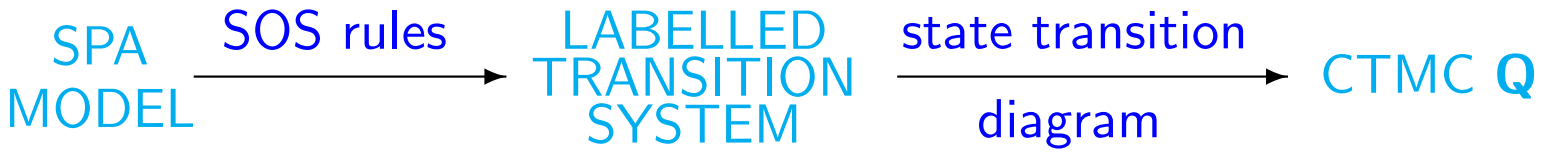

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Models are typically executed by simulation using Gillespie's Stochastic Simulation Algorithm (SSA) or similar.

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- The local states of components are quantitative rather than functional, i.e. biological changes to species are represented as distinct components.
- A component varying its state corresponds to it varying its amount.
- This is captured by an integer parameter associated with the species and the effect of a reaction is to vary that parameter by a number corresponding to the stoichiometry of this species in the reaction.

The abstraction

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The species components (now quantified) are then composed together to describe the behaviour of the system.

The semantics

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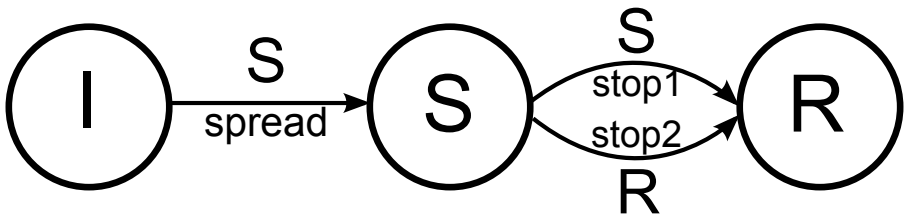
The labelled transition system generated by the stochastic relation formally defines the underlying CTMC.

Example — in Bio-PEPA



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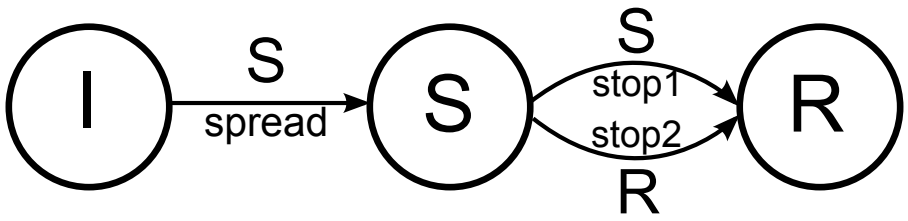


```
k_s = 0.5;
k_r = 0.1;

kineticLawOf spread : k_s * I * S;
kineticLawOf stop1 : k_r * S * S;
kineticLawOf stop2 : k_r * S * R;

I = (spread,1) ↓ ;
S = (spread,1) ↑ + (stop1,1) ↓ + (stop2,1) ↓ ;
R = (stop1,1) ↑ + (stop2,1) ↑ ;

I[10] ⋈*  S[5] ⋈*  R[0]
```

A Probabilistic Programming Process Algebra: ProPPA

The objective of ProPPA is to retain the features of the stochastic process algebra:

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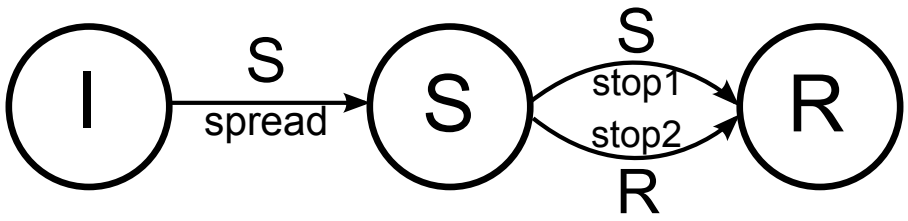
The objective of ProPPA is to retain the features of the stochastic process algebra:

- simple model description in terms of components
- rigorous semantics giving an executable version of the model...

... whilst also incorporating features of a probabilistic programming language:

- recording uncertainty in the parameters
- ability to incorporate observations into models
- access to inference to update uncertainty based on observations

Example Revisited

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```

Additions

Declaring uncertain parameters:

- `k_s = Uniform(0,1);`
- `k_t = Uniform(0,1);`

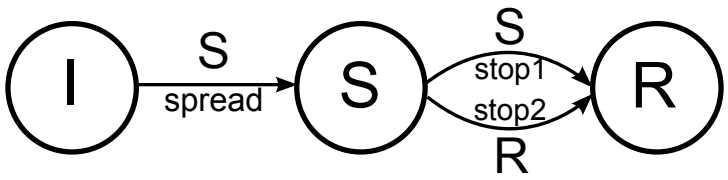
Providing observations:

- `observe('trace')`

Specifying inference approach:

- `infer('ABC')`

Additions

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observe('trace')
infer('ABC') //Approximate Bayesian Computation
```
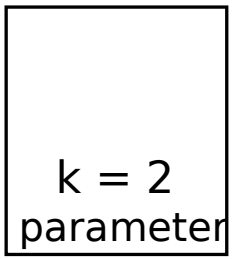
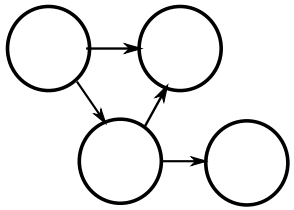

Semantics

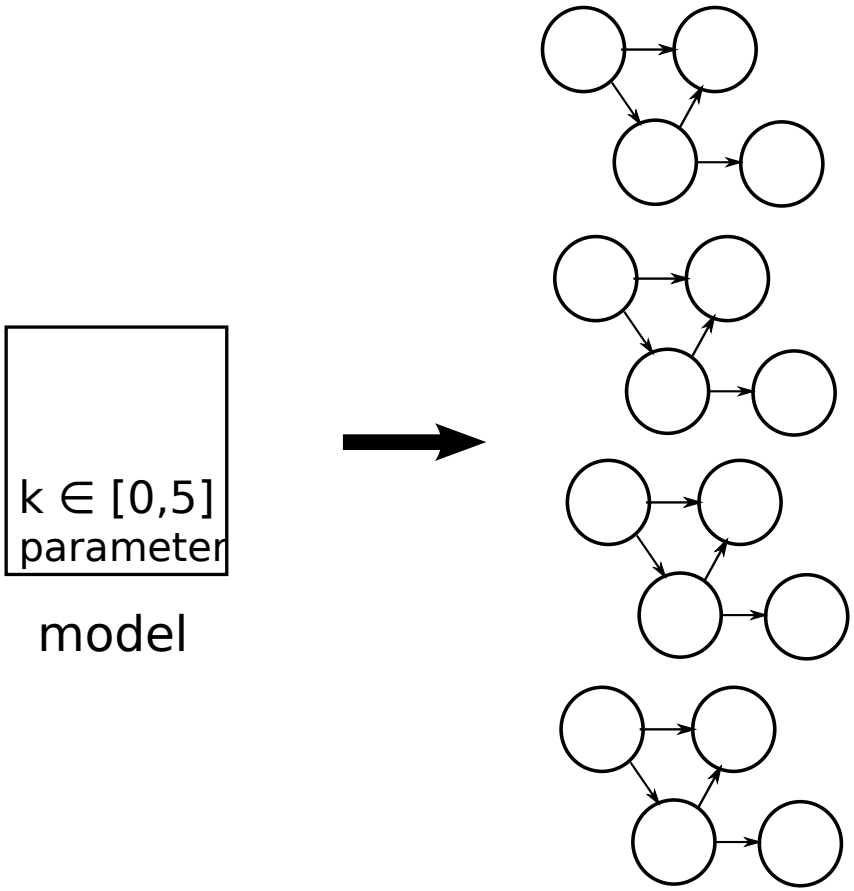
- A Bio-PEPA model can be interpreted as a CTMC; however, CTMCs cannot capture uncertainty in the rates (every transition must have a concrete rate).
- ProPPA models include uncertainty in the parameters, which translates into uncertainty in the transition rates.
- A ProPPA model should be mapped to something like a distribution over CTMCs.

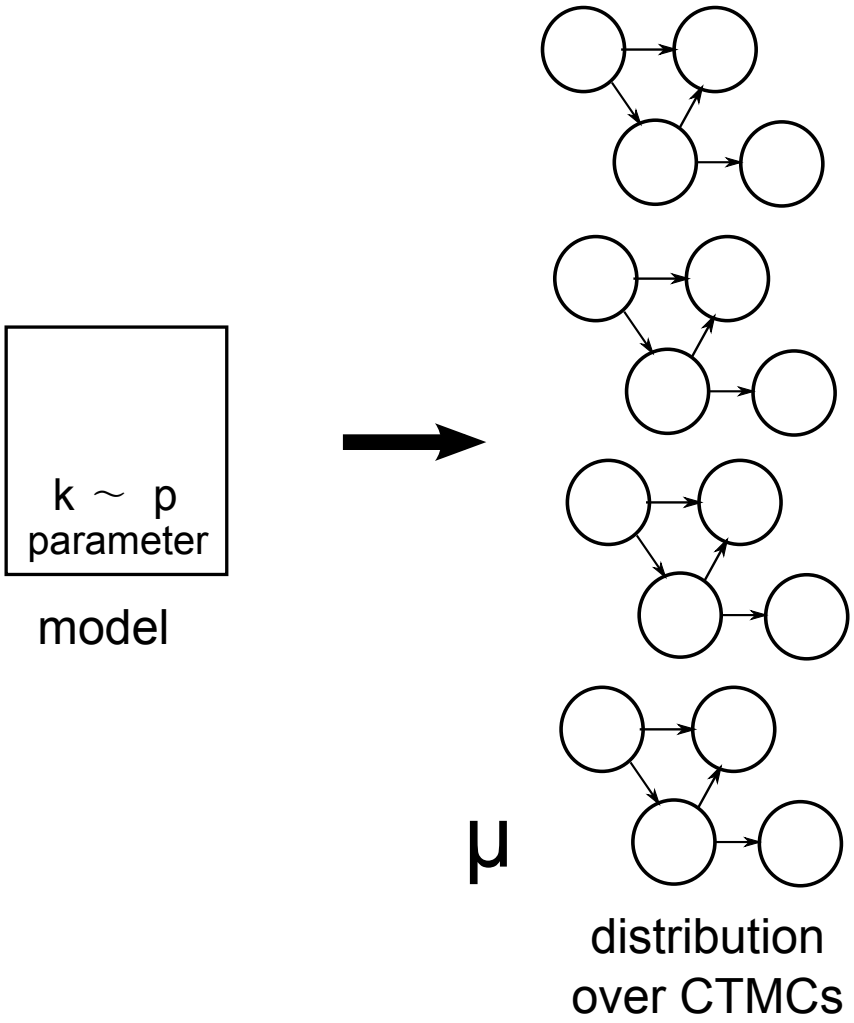


model



CTMC


k ∈ [0,5]
parameter
model
set
of CTMCs


k ~ p
parameter
model
μ
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Constraint Markov Chains

Constraint Markov Chains[3] (CMCs) are a generalization of DTMCs, in which the transition probabilities are not concrete, but can take any value satisfying some constraints.

Constraint Markov Chain

A CMC is a tuple $\langle S, o, A, V, \phi \rangle$, where:

- S is the set of states, of cardinality k.
- $o \in S$ is the initial state.
- A is a set of atomic propositions.
- $V : S \to 2^{2^A}$ gives a set of acceptable labellings for each state.
- $\phi : S \times [0,1]^k \to \{0,1\}$ is the constraint function.

[3] Caillaud *et al.*, *Constraint Markov Chains*, Theoretical Computer Science, 2011

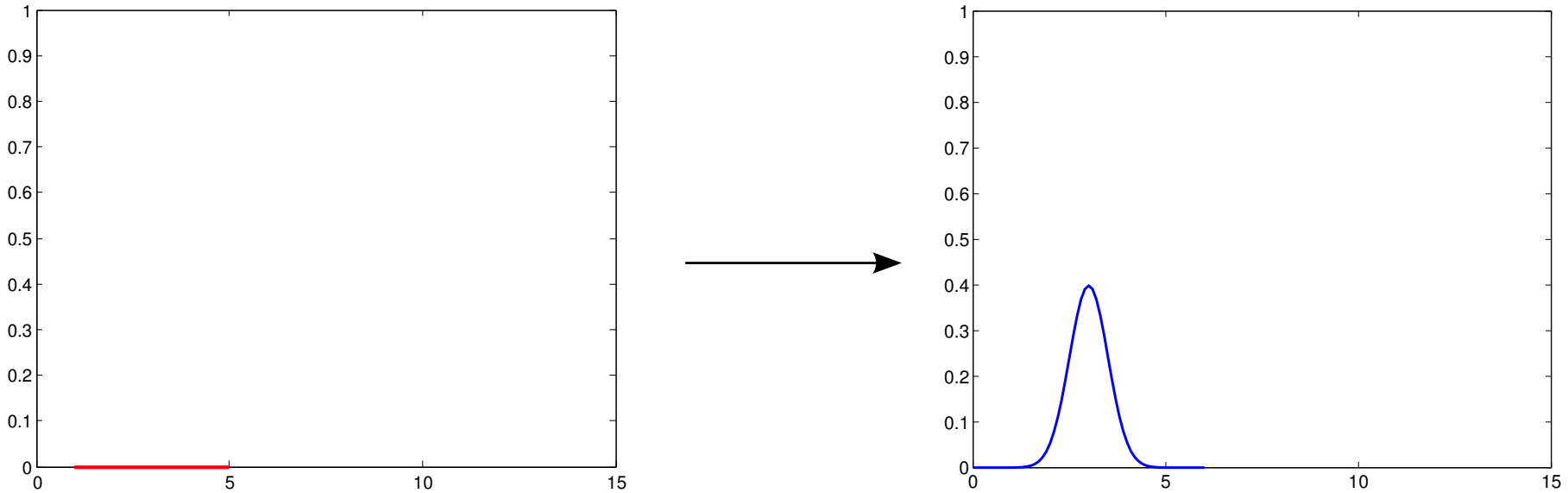
Constraint Markov Chains

In a CMC, arbitrary constraints are permitted, expressed through the function ϕ: $\phi(s, \vec{p}) = 1$ iff $\vec{p}$ is an acceptable vector of transition probabilities from state s.

However,

- CMCs are defined only for the discrete-time case, and
- this does not say anything about how likely a value is to be chosen, only about whether it is acceptable.

To address these shortcomings, we define **Probabilistic Constraint Markov Chains**.


1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
1
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15

Probabilistic CMCs

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- $\phi : S \times [0, \infty)^k \to [0, \infty)$ is the constraint function.

- This is applicable to continuous-time systems.
- $\phi(s, \cdot)$ is now a probability density function on the transition rates from state s.

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Rules are expressed as state-to-function transition systems (FuTS[4]).

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This gives rise the underlying PCMC.

[4] De Nicola *et al.*, *A Uniform Definition of Stochastic Process Calculi*, ACM Computing Surveys, 2013

Simulating Probabilistic Constraint Markov Chains

Probabilistic Constraint Markov Chains are open to two alternative dynamic interpretations:

1. For each trajectory, for each uncertain transition rate, sample once at the start of the run and use that value throughout;
2. During each trajectory, each time a transition with an uncertain rate is encountered, sample a value but then discard it and re-sample whenever this transition is visited again.

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Our current work is focused on the Uncertain Markov Chain case.

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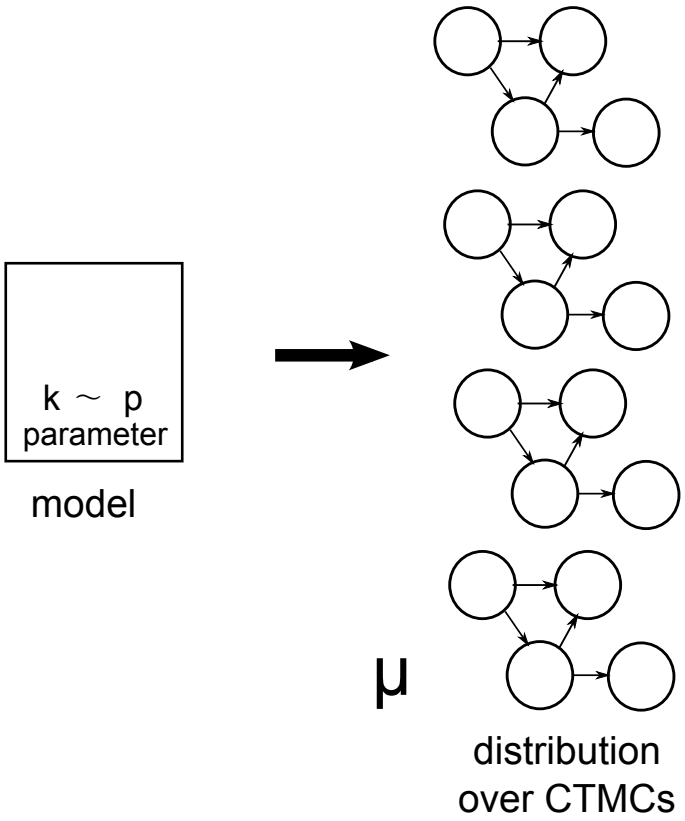
Inference



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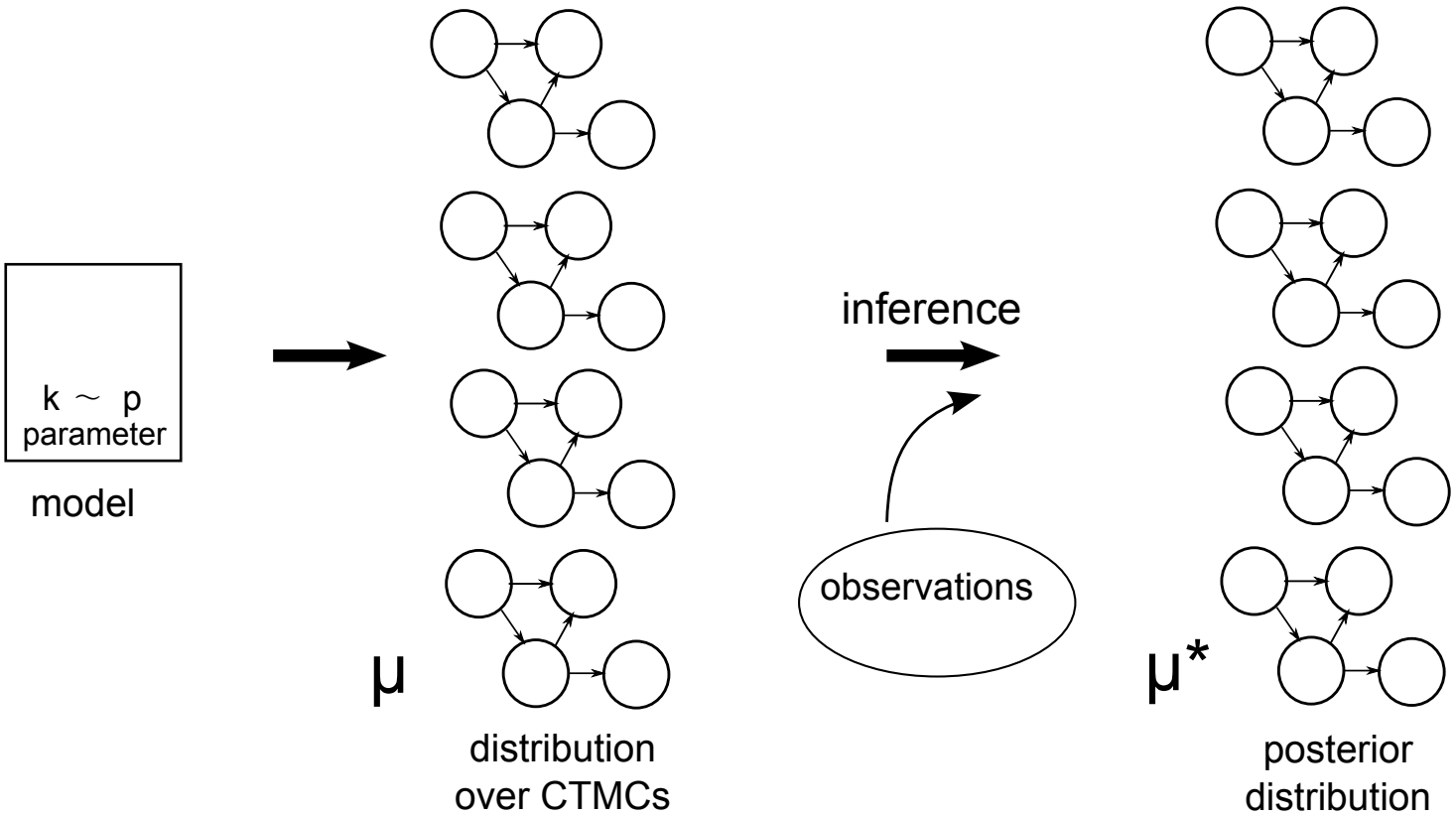
k ~ p
parameter
model
μ
distribution
over CTMCs
inference
observations
μ*
posterior
distribution

Inference

$$P(\theta \mid D) \propto P(\theta)P(D \mid \theta)$$

- The ProPPA semantics does not define a single inference algorithm, allowing for a modular approach.
- Different algorithms can act on different input (time-series *vs* properties), return different results or in different forms.
- Exact inference is often impossible, as we cannot calculate the likelihood.
- We must use approximate algorithms or approximations of the system.

Inferring likelihood in uncertain CTMCs

Transient probabilities can be expressed as:

$$\frac{dp_i(t)}{dt} = \sum_{j \neq i} p_j(t) \cdot q_{ji} - p_i(t) \sum_{j \neq i} q_{ij}$$

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$$\frac{dp_i(t)}{dt} = \sum_{j \neq i} p_j(t) \cdot q_{ji} - p_i(t) \sum_{j \neq i} q_{ij}$$

The probability of a single observation (y, t) can then be expressed as

$$p(y, t) = \sum_{i \in \mathcal{S}} p_i(t) \pi(y \mid i)$$

where $\pi(y \mid i)$ is the probability of observing y when in state i.

Inferring likelihood in uncertain CTMCs

Transient probabilities can be expressed as:

$$\frac{dp_i(t)}{dt} = \sum_{j \neq i} p_j(t) \cdot q_{ji} - p_i(t) \sum_{j \neq i} q_{ij}$$

The probability of a single observation (y, t) can then be expressed as

$$p(y, t) = \sum_{i \in \mathcal{S}} p_i(t) \pi(y \mid i)$$

where $\pi(y \mid i)$ is the probability of observing y when in state i.

The likelihood can then be expressed as

$$P(D \mid \theta) = \prod_{j=1}^{N} \sum_{i \in \mathcal{S}} p_{(i|\theta)}(t_j) \pi(y_j \mid i)$$

Calculating the transient probabilities

For finite state-spaces, the transient probabilities can, in principle, be computed as

$$\mathbf{p}(t) = \mathbf{p}(0)e^{Qt}.$$

Likelihood is hard to compute:

- Computing $e^{\mathbf{Q}t}$ is expensive if the state space is large
- Impossible directly in infinite state-spaces

Basic Inference

- Approximate Bayesian Computation is a simple simulation-based solution:
  - Approximates posterior distribution over parameters as a set of samples
  - Likelihood of parameters is approximated with a notion of distance.

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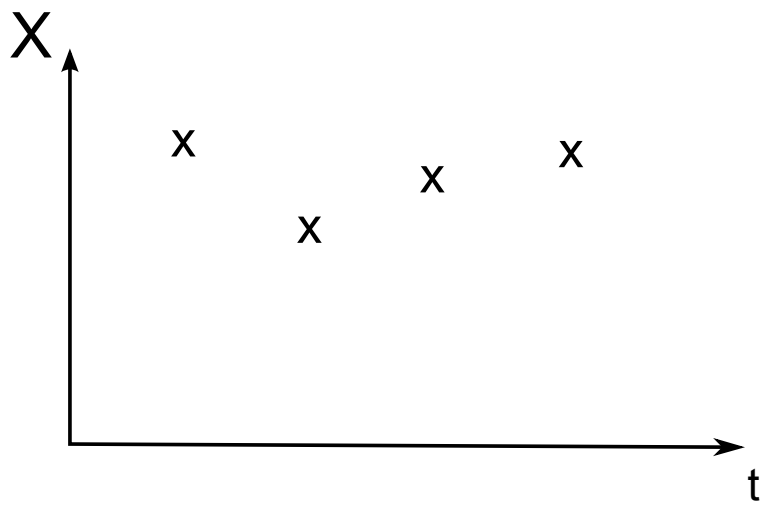

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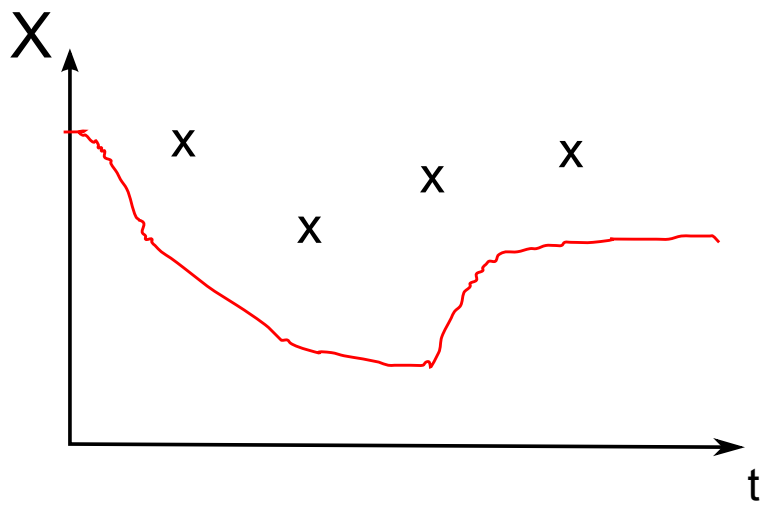

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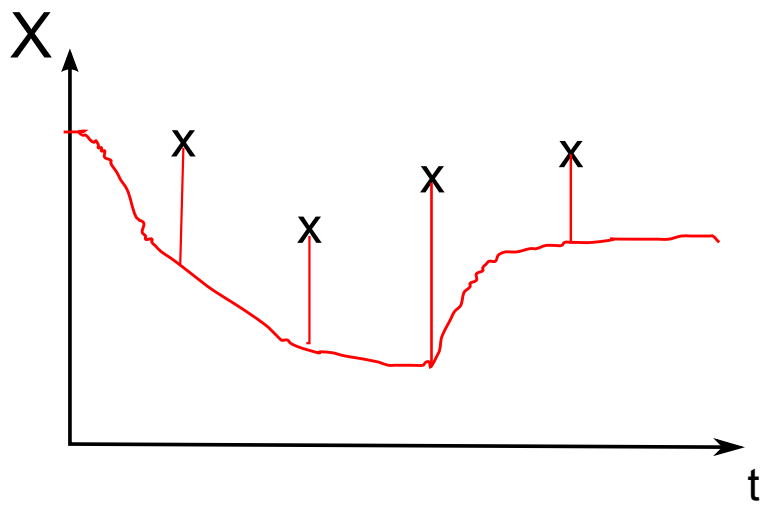

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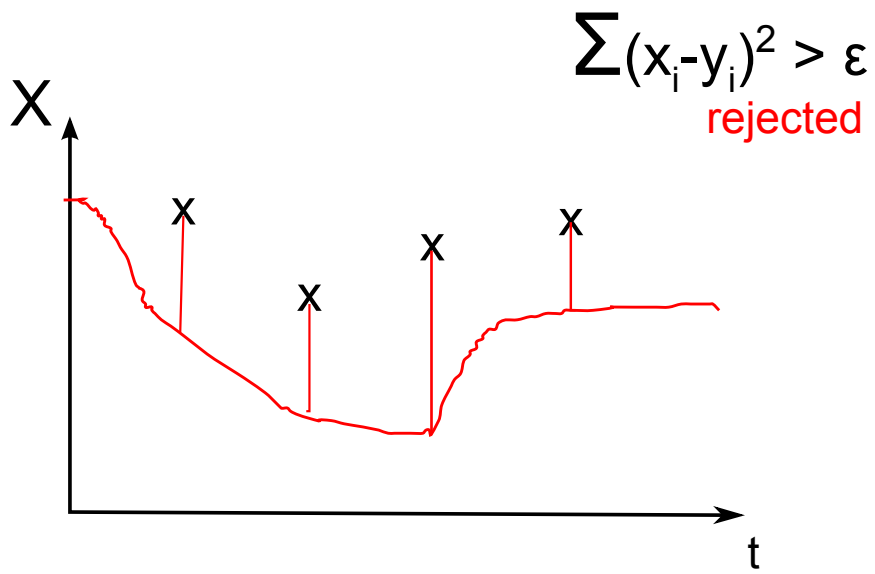

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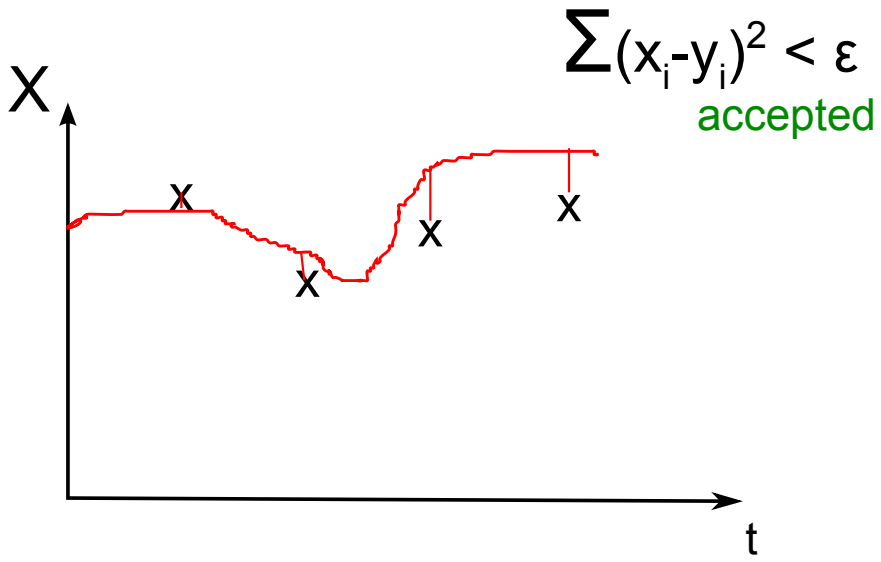

Approximate Bayesian Computation

ABC algorithm

1. Sample a parameter set from the prior distribution.
2. Simulate the system using these parameters.
3. Compare the simulation trace obtained with the observations.
4. If distance $< \epsilon$, accept, otherwise reject.

This results in an approximate to the posterior distribution.
As $\epsilon \to 0$, set of samples converges to true posterior.
We use a more elaborate version based on Markov Chain Monte Carlo sampling.

Inference for infinite state spaces

Various methods become inefficient or inapplicable as the state-space grows.

How to deal with unbounded systems?

- Multiple simulation runs
- Large population approximations (diffusion, Linear Noise,. . .)
- Systematic truncation
- **Random truncations**

Expanding the likelihood

The likelihood can be written as an infinite series:

$$p(x', t' \mid x, t) = \sum_{N=0}^{\infty} p^{(N)}(x', t' \mid x, t)$$
$$= \sum_{N=0}^{\infty} \left[f^{(N)}(x', t' \mid x, t) - f^{(N-1)}(x', t' \mid x, t) \right]$$

where

- $x^* = \max\{x, x'\}$
- $p^{(N)}(x', t' \mid x, t)$ is the probability of going from state x at time t to state x' at time t' through a path with maximum state $x^* + N$
- $f^{(N)}$ is the same, except the maximum state cannot exceed $x^* + N$ (but does not have to reach it)

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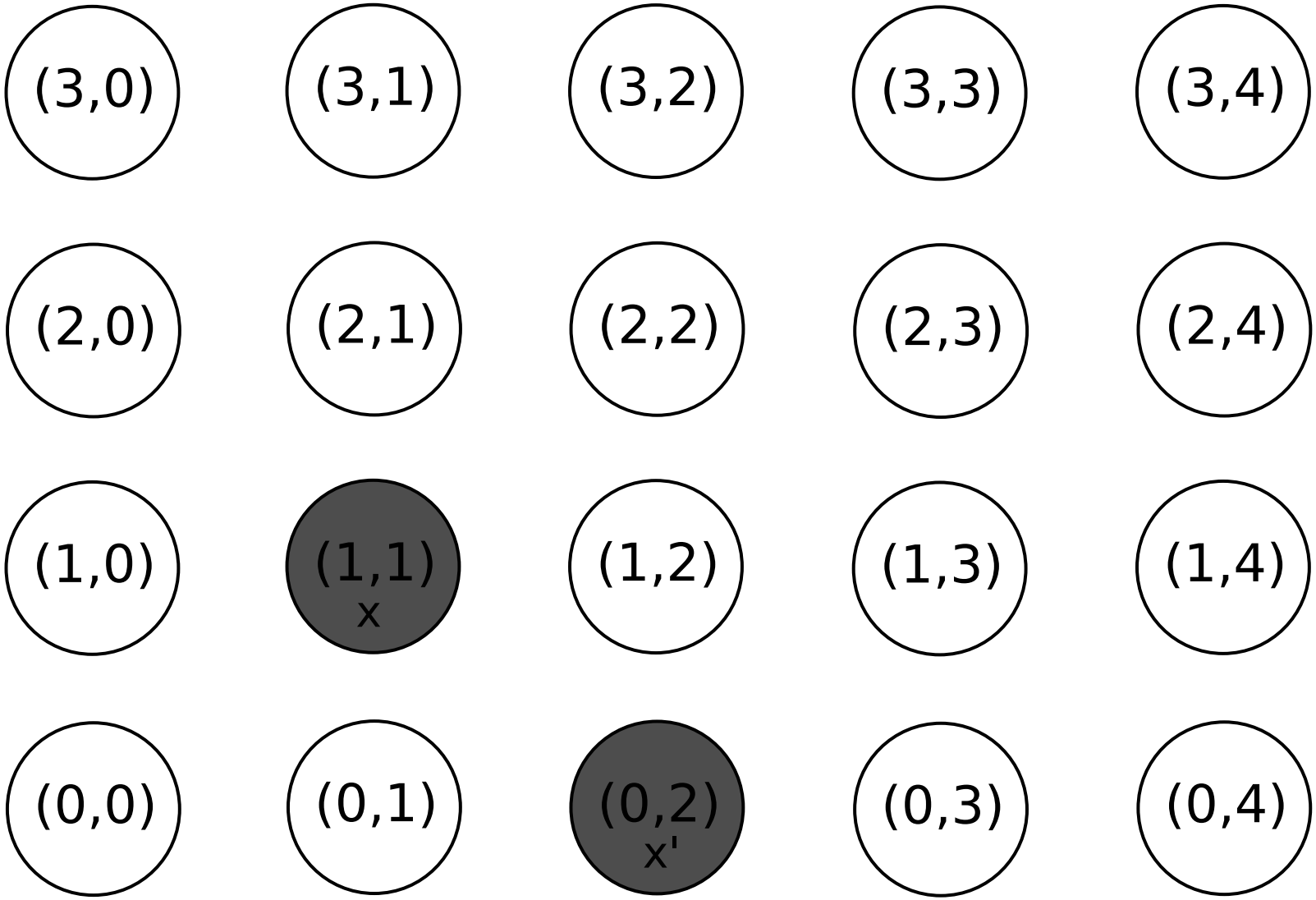
Any finite number of terms can be computed — Can the infinite sum be computed or estimated?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x
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(0,1)
(0,2)
x'
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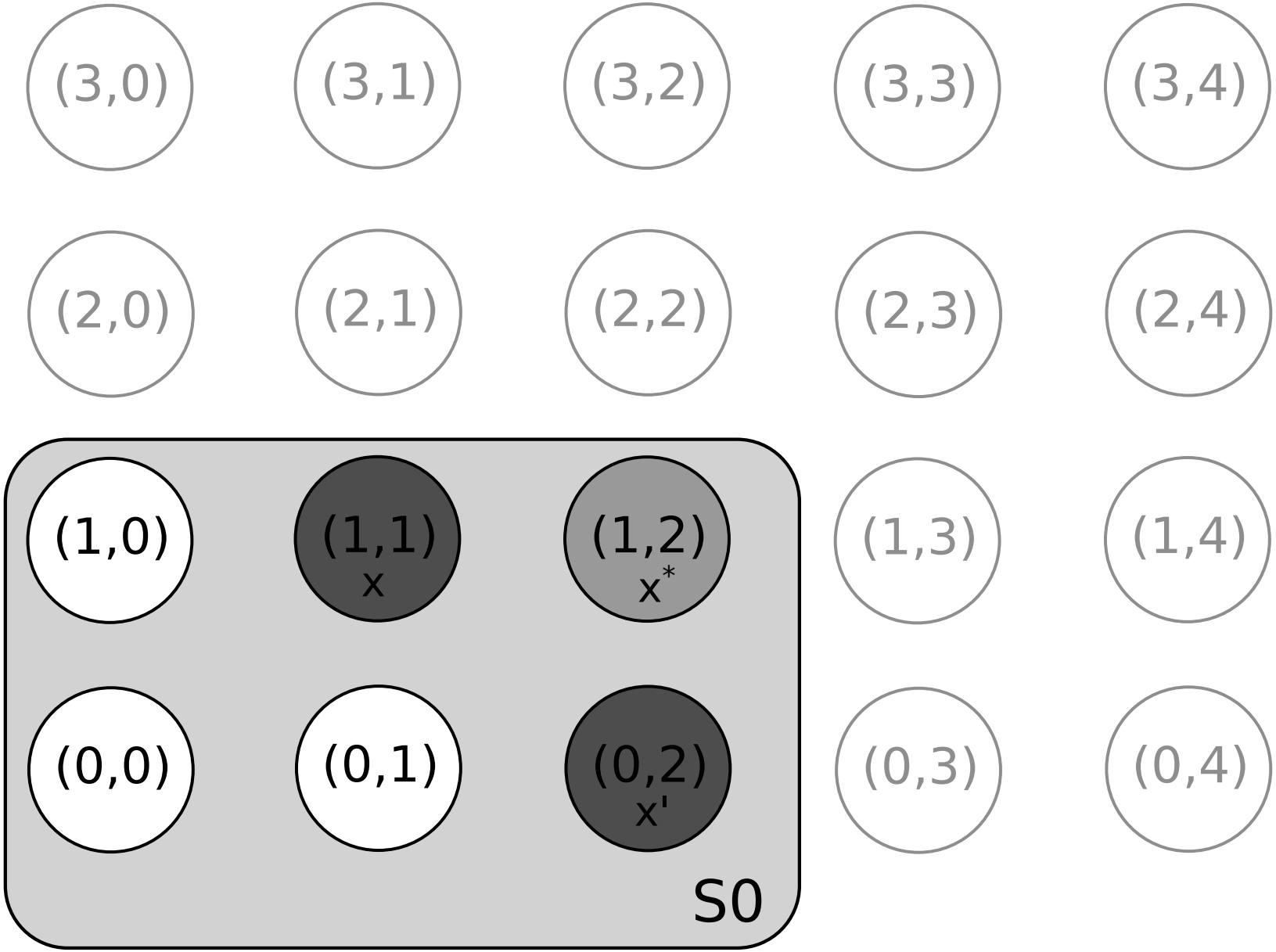
(0,4)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(1,0)
(1,1)
x
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x*
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(1,4)
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x'
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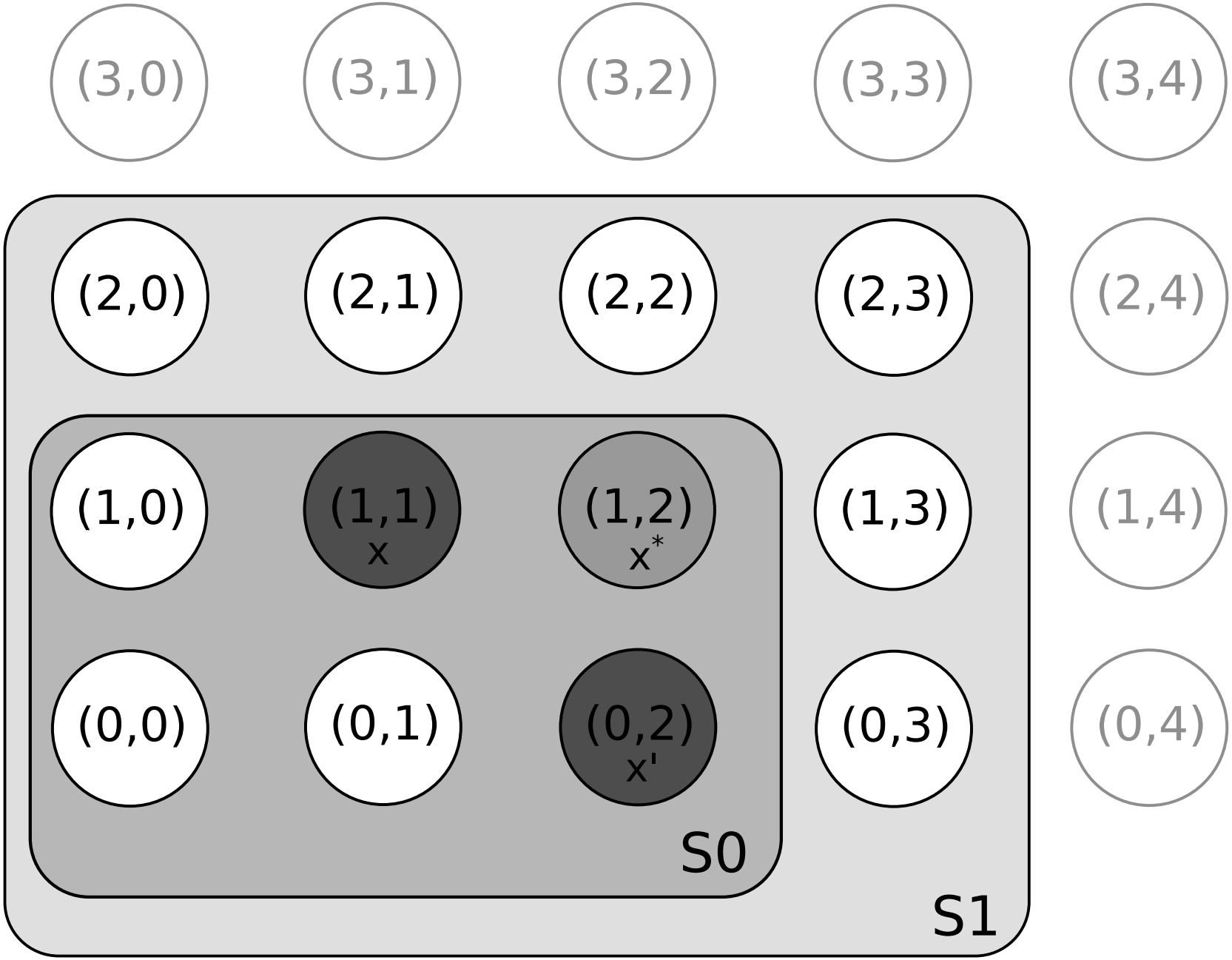
S0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x*
(1,3)
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x'
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(0,4)
S0
S1

Russian Roulette Truncation

- We want to estimate the value of

$$f = \sum_{n=0}^{\infty} f_n$$

where the f_n's are computable.

Russian Roulette Truncation

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$$f = \sum_{n=0}^{\infty} f_n$$

  where the f_n's are computable.
- Choose a single term f_k with probability p_k; estimate $\hat{f} = \frac{f_k}{p_k}$
- $\hat{f}$ is unbiased... but its variance can be high.

Russian Roulette Truncation

- We want to estimate the value of

$$f = \sum_{n=0}^{\infty} f_n$$

  where the f_n's are computable.
- Truncate the sum randomly: stop at term k with probability q_k.
- Form $\hat{f}$ as a partial sum of the $f_n, n = 1, \ldots, k$, rescaled appropriately.

$$\hat{f} = \sum_{n=0}^{k} \frac{f_n}{\prod_{j=0}^{k-1} (1 - q_j)}$$

Russian Roulette

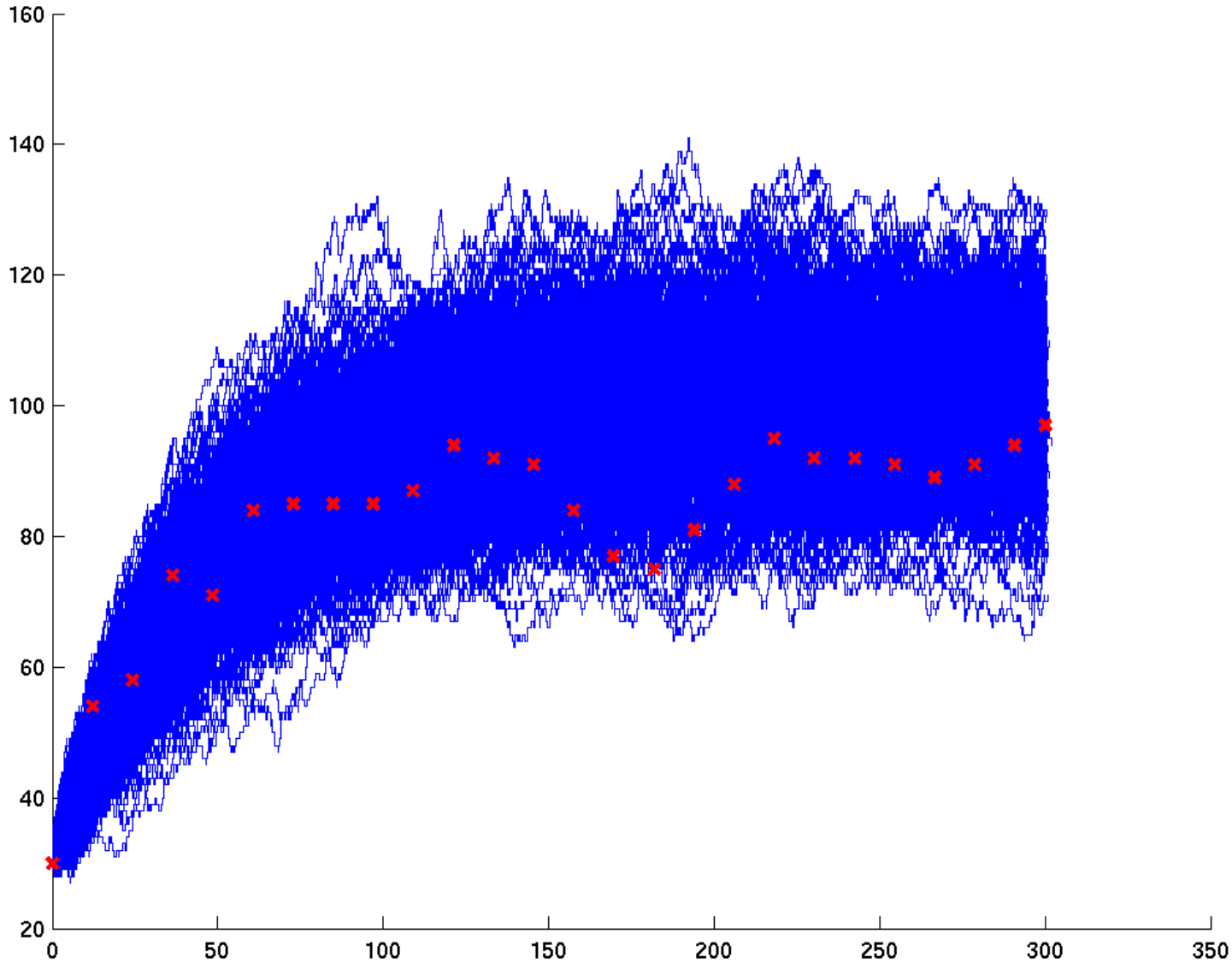
$\hat{f} \leftarrow f_0$
$i \leftarrow 1$
$p \leftarrow 1$
loop
    Choose to stop with probability q_i
    if stopping **then**
        return $\hat{f}$
    else
        $p \leftarrow p \cdot (1 - q_i)$
        $\hat{f} \leftarrow \hat{f} + \frac{f_i}{p}$
        $i \leftarrow i + 1$
    end if
end loop

Russian Roulette

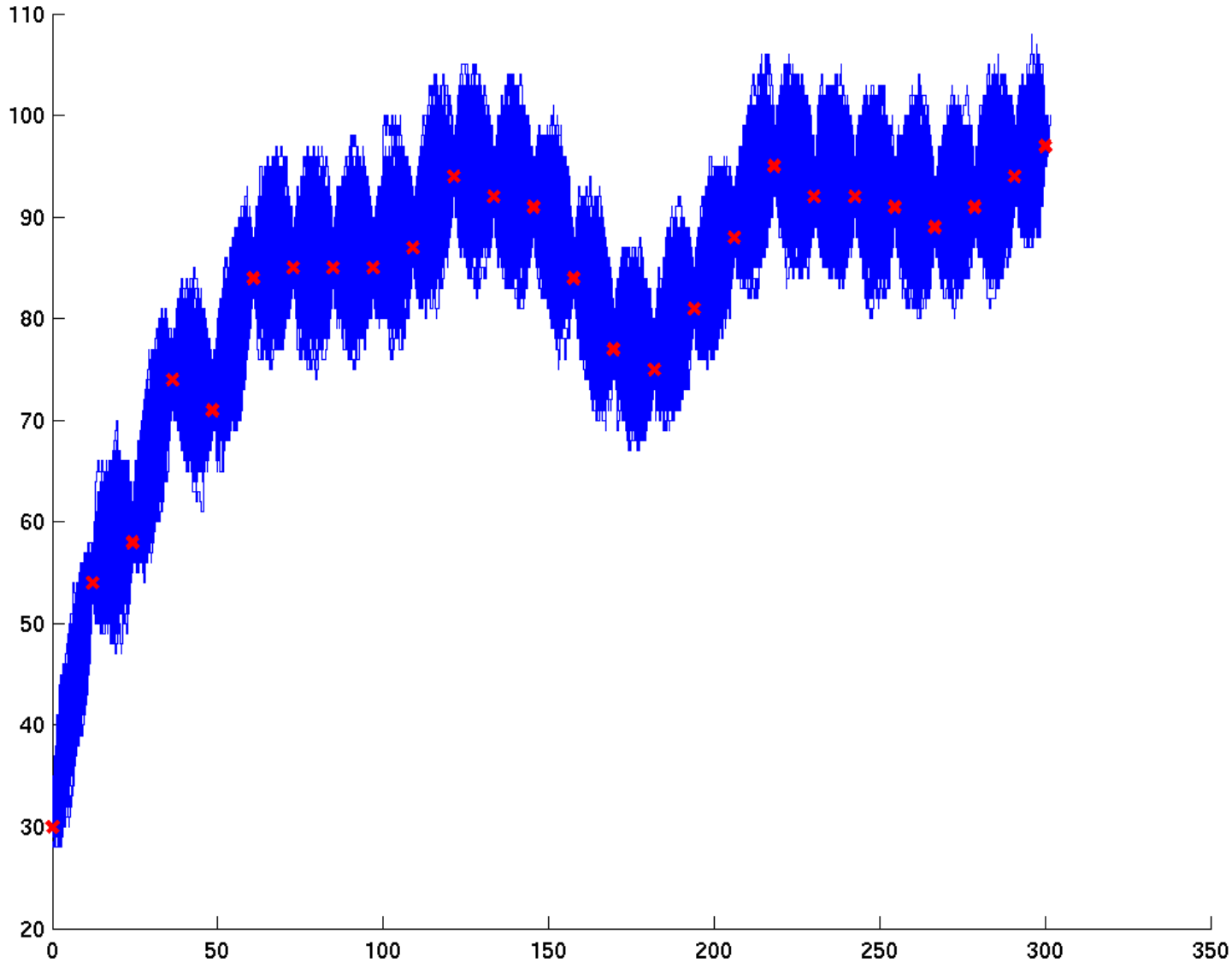
$$\hat{f} = \sum_{n=0}^{k} \frac{f_n}{\prod_{j=0}^{k-1}(1-q_j)}$$

- In our case, f is a probability that we wish to approximate.
- Using $\hat{f}$ instead of f leads to an error; however $\hat{f}$ is unbiased: $E[\hat{f}] = f$.
- $\hat{f}$ is also guaranteed to be positive.
- Pseudo-marginal algorithms can use this and still draw samples from the correct distribution.
- We have developed both Metropolis-Hastings and Gibbs-like sampling algorithms based on this approach[5].

[5] *Unbiased Bayesian Inference for Population Markov Jump Processes via Random Truncations.* A.Georgoulas, J.Hillston and D.Sanguinetti, to appear in Stats & Comp.



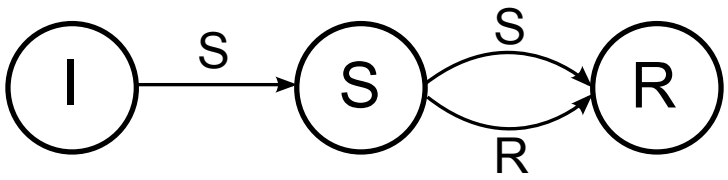
SSA samples



Posterior samples

Outline

Example model



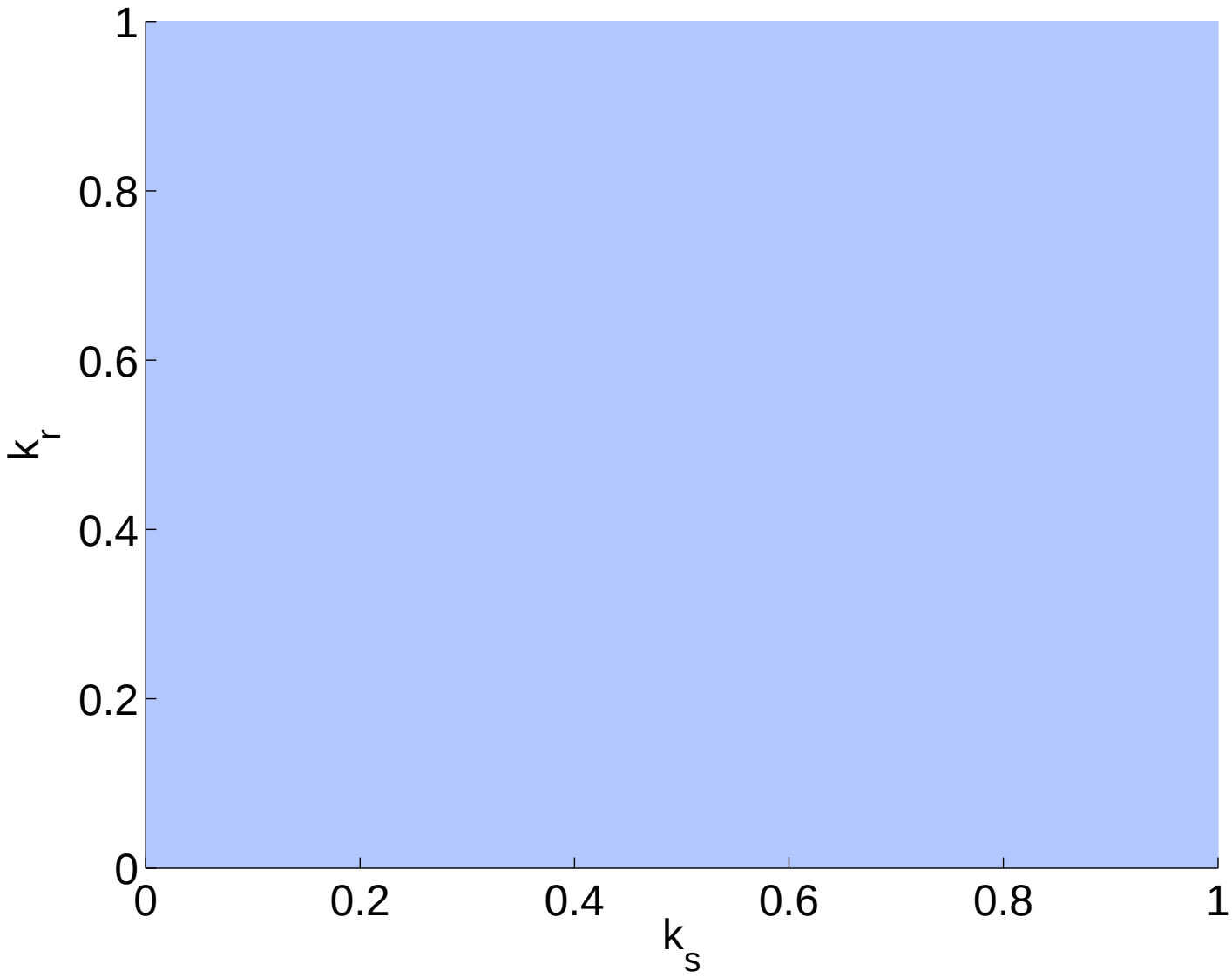

```
k_s = Uniform(0,1);
k_r = Uniform(0,1);

kineticLawOf spread : k_s * I * S;
kineticLawOf stop1 : k_r * S * S;
kineticLawOf stop2 : k_r * S * R;

I = (spread,1) ↓ ;
S = (spread,1) ↑ + (stop1,1) ↓ + (stop2,1) ↓ ;
R = (stop1,1) ↑ + (stop2,1) ↑ ;

I[10] ⋈* S[5] ⋈* R[0]

observe('trace')
infer('ABC') //Approximate Bayesian Computation
```

Results

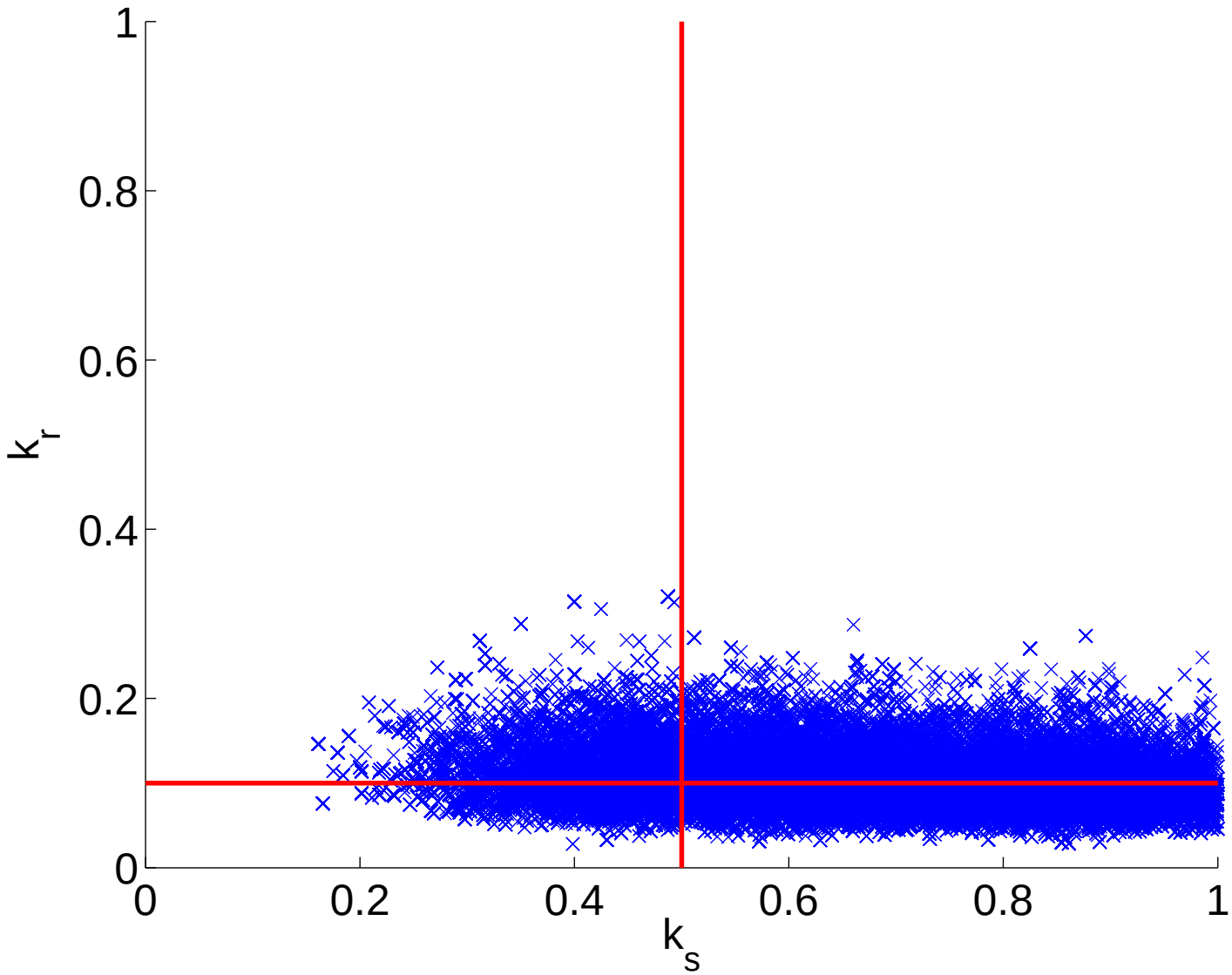
Tested on the rumour-spreading example, giving the two parameters uniform priors.

- Approximate Bayesian Computation
- Returns posterior as a set of points (samples)
- Observations: time-series (single simulation)

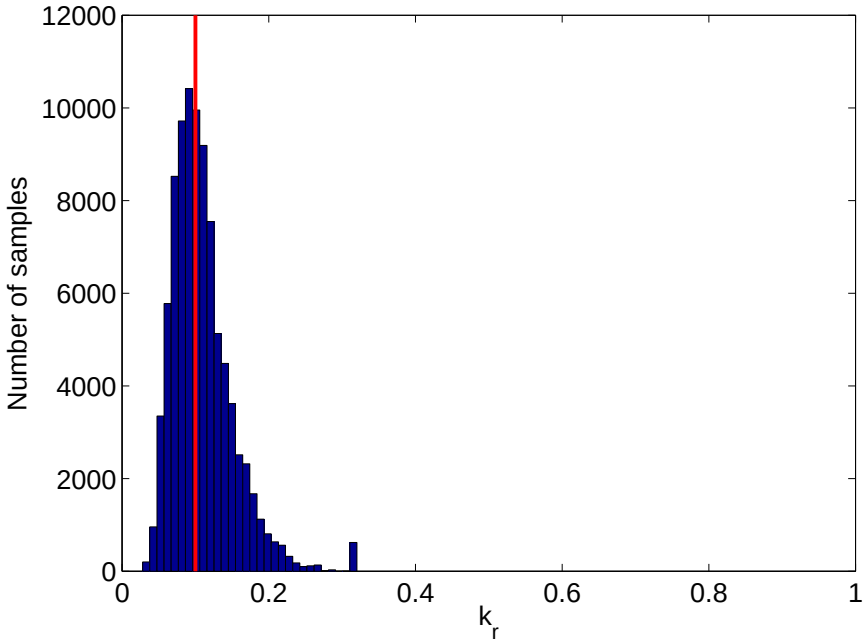
Results: ABC

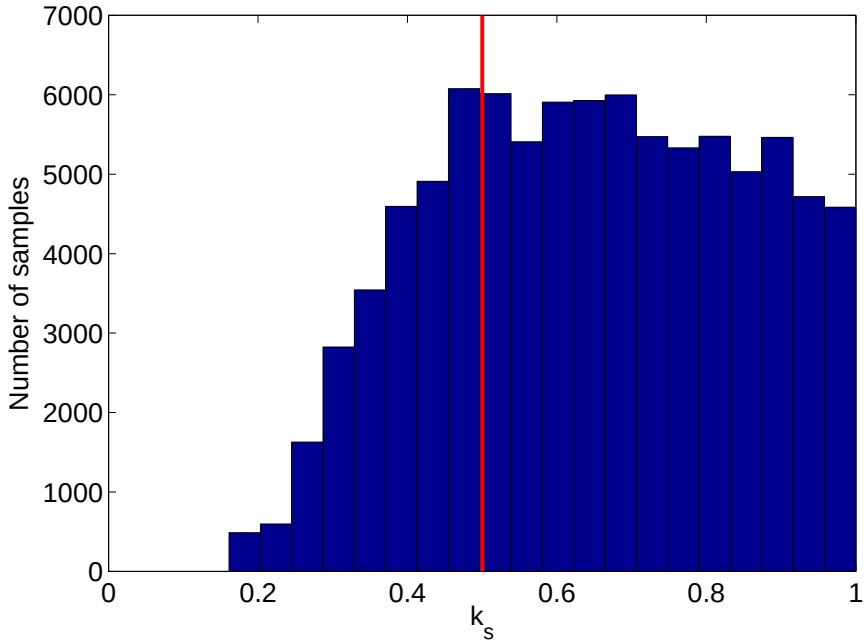


Results: ABC



Results: ABC


12000
10000
8000
6000
4000
2000
0
Number of samples
0
0.2
0.4
0.6
0.8
1
k_r


7000
6000
5000
4000
3000
2000
1000
0
Number of samples
0
0.2
0.4
0.6
0.8
1
k_s

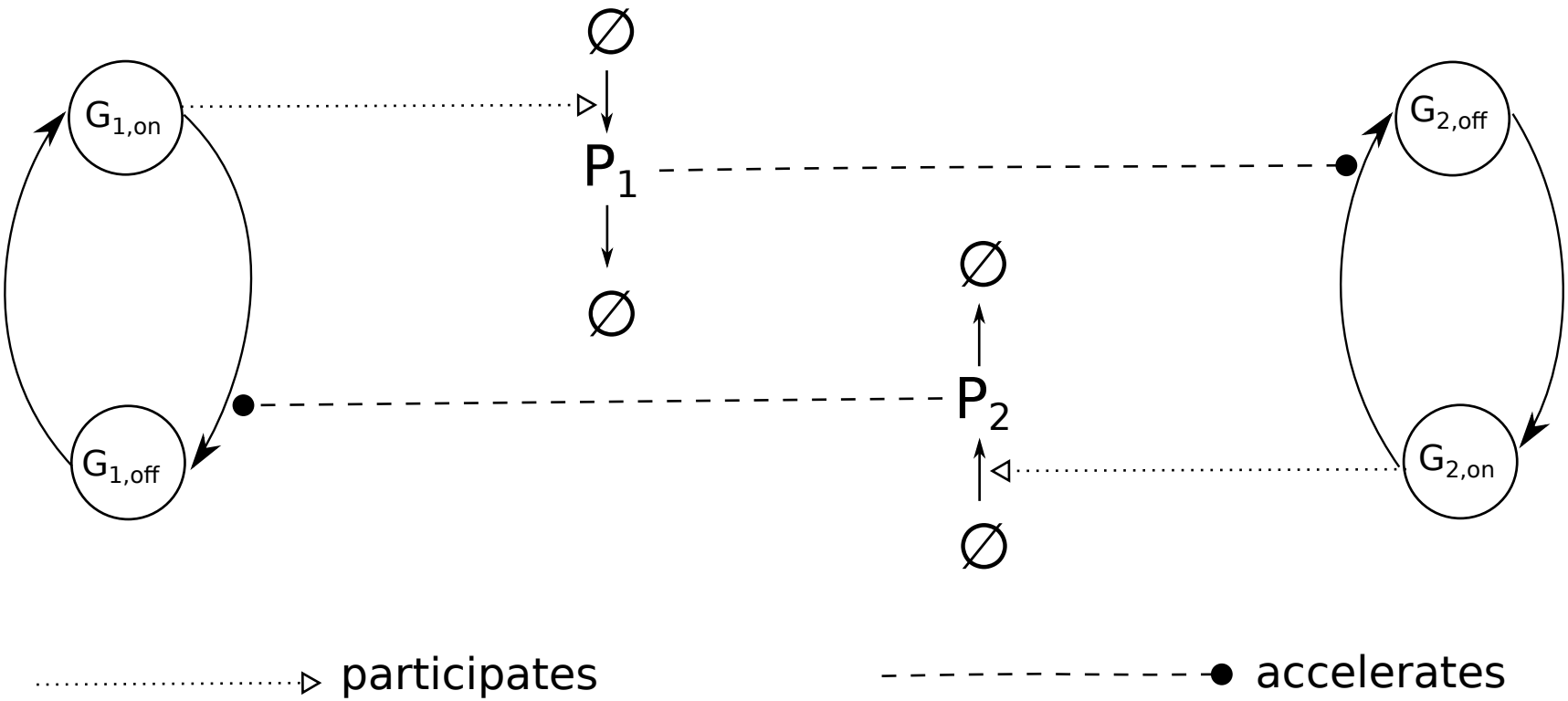
Genetic Toggle Switch

- Two mutually-repressing genes: promoters (unobserved) and their protein products
- Bistable behaviour: switching induced by environmental changes
- Synthesised in *E. coli*[6]
- Stochastic variant[7] where switching is induced by noise

[6] Gardner, Cantor & Collins, *Construction of a genetic toggle switch in Escherichia coli*, Nature, 2000

[7] Tian & Burrage, *Stochastic models for regulatory networks of the genetic toggle switch*, PNAS, 2006

Genetic Toggle Switch



Toggle switch model: species

```
G1 = activ1 ↑ + deact1 ↓ + expr1 ⊕;
G2 = activ2 ↑ + deact2 ↓ + expr2 ⊕;

P1 = expr1 ↑ + degr1 ↓ + deact2 ⊕ ;
P2 = expr2 ↑ + degr2 ↓ + deact1 ⊕

G1[1] <*> G2[0] <*> P1[20] <*> P2[0]

observe(toggle_obs);
infer(rouletteGibbs);
```

```
θ_1 = Gamma(3,5); //etc...

kineticLawOf expr1 : θ_1 * G1;
kineticLawOf expr2 : θ_2 * G2;
kineticLawOf degr1 : θ_3 * P1;
kineticLawOf degr2 : θ_4 * P2;

kineticLawOf activ1 : θ_5 * (1 - G1);
kineticLawOf activ2 : θ_6 * (1 - G2);
kineticLawOf deact1 : θ_7 * exp(r * P2) * G1;
kineticLawOf deact2 : θ_8 * exp(r * P1) * G2;

G1 = activ1 ↑ + deact1 ↓ + expr1 ⊕;
G2 = activ2 ↑ + deact2 ↓ + expr2 ⊕;
P1 = expr1 ↑ + degr1 ↓ + deact2 ⊕ ;
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G1[1] <*> G2[0] <*> P1[20] <*> P2[0]

observe(toggle_obs);
infer(rouletteGibbs);
```
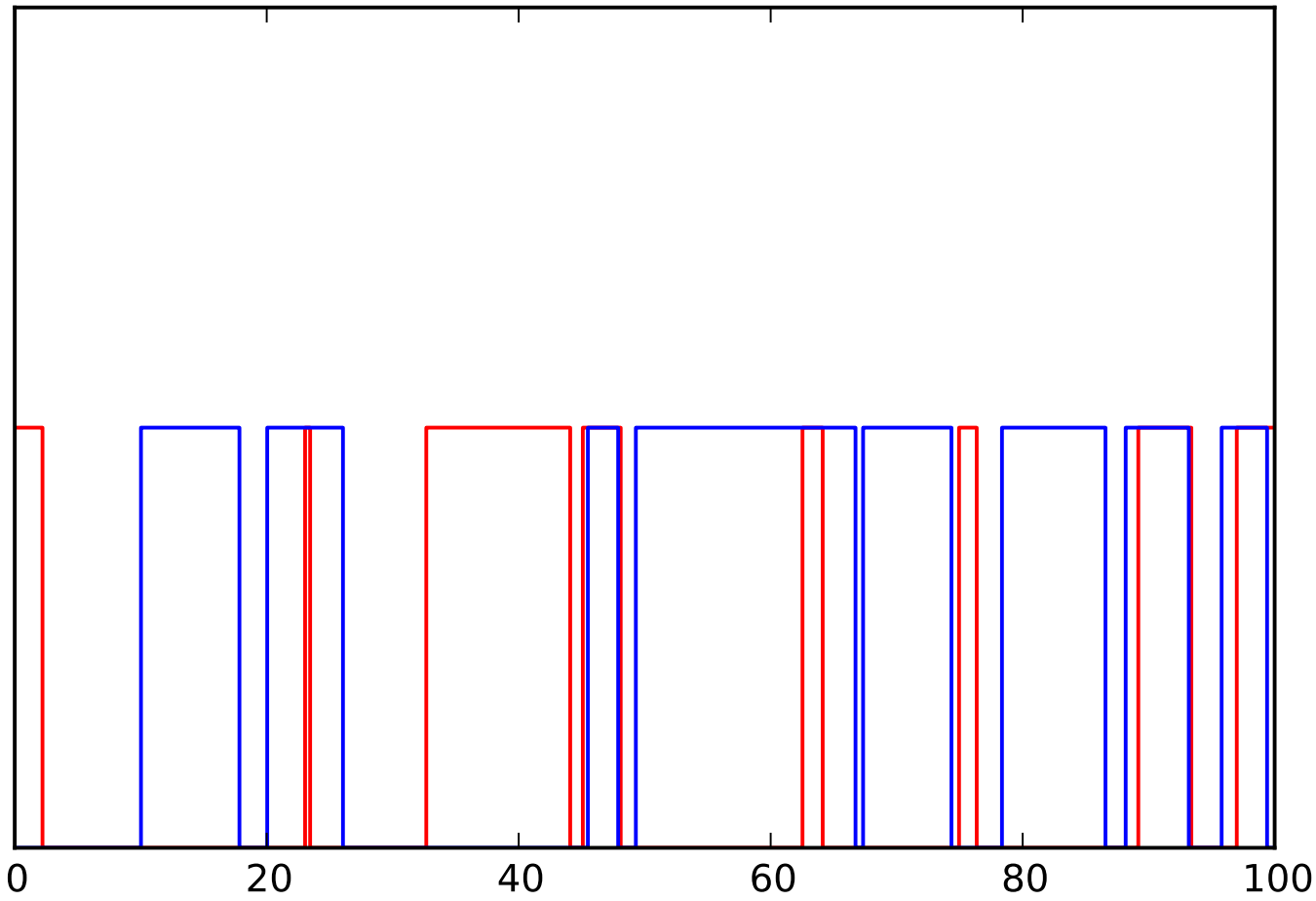
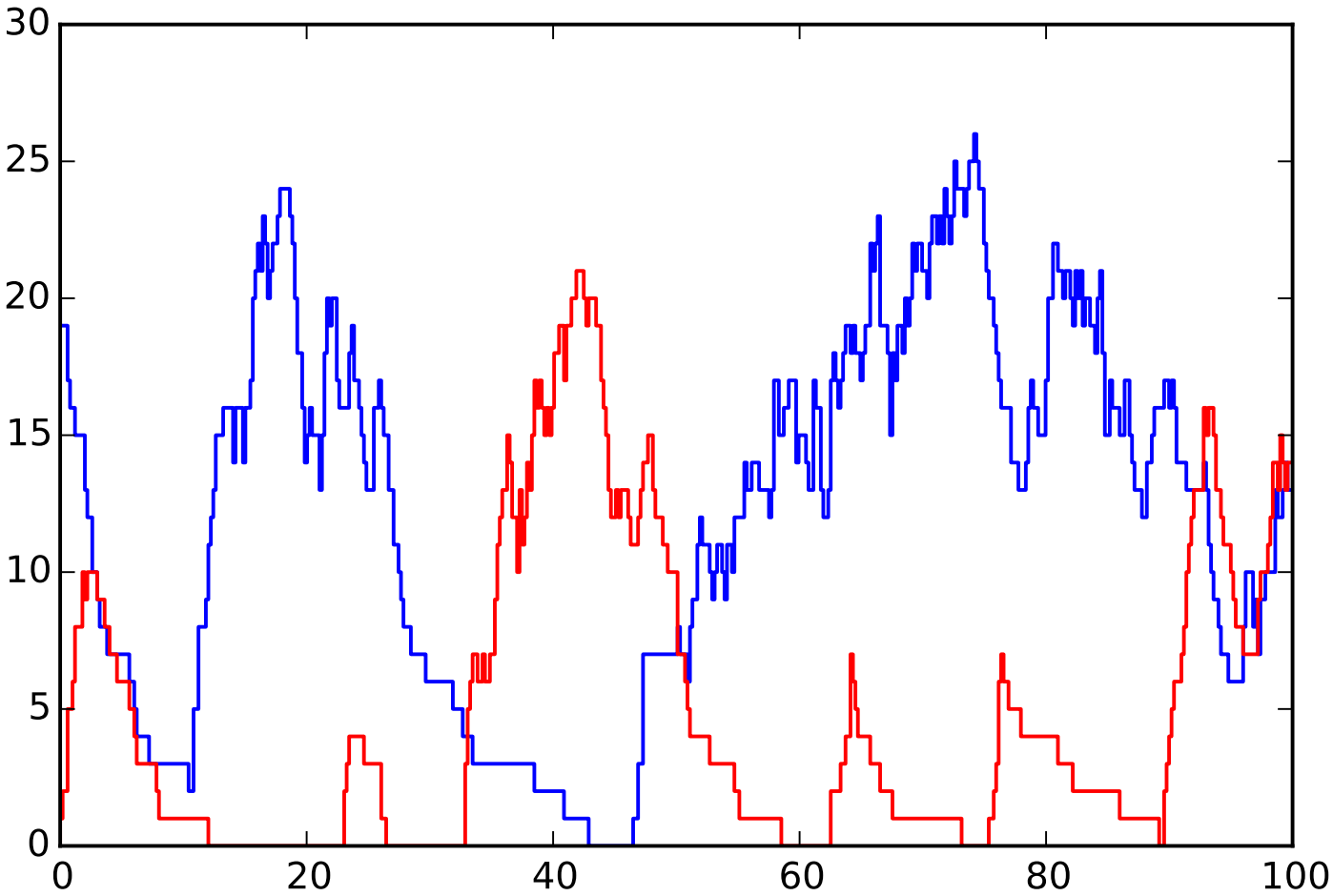

Experiment

- Simulated observations
- Gamma priors on all parameters (required by algorithm)
- Goal: learn posterior of 8 parameters
- 5000 samples taken using the Gibbs-like random truncation algorithm

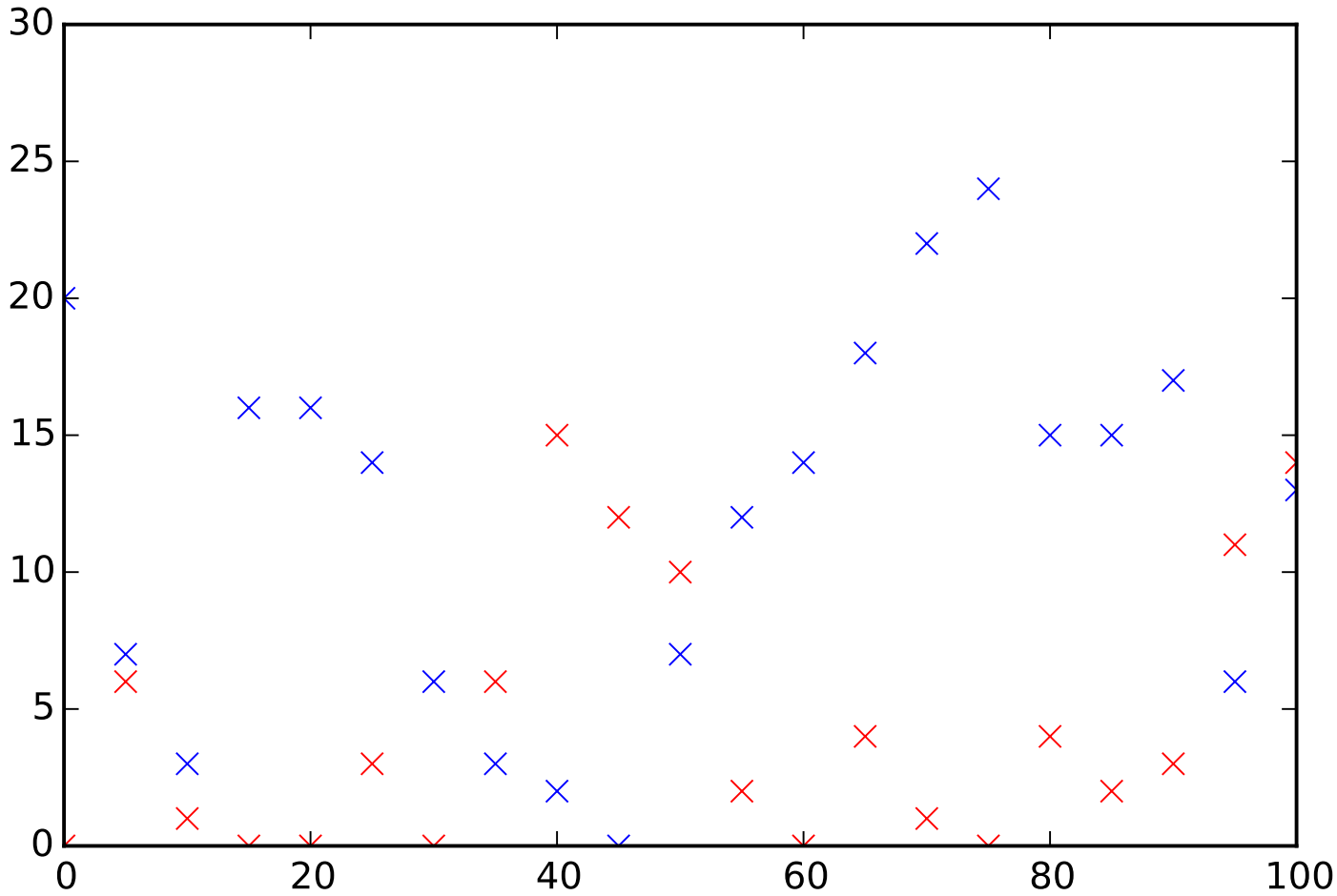
Promoters



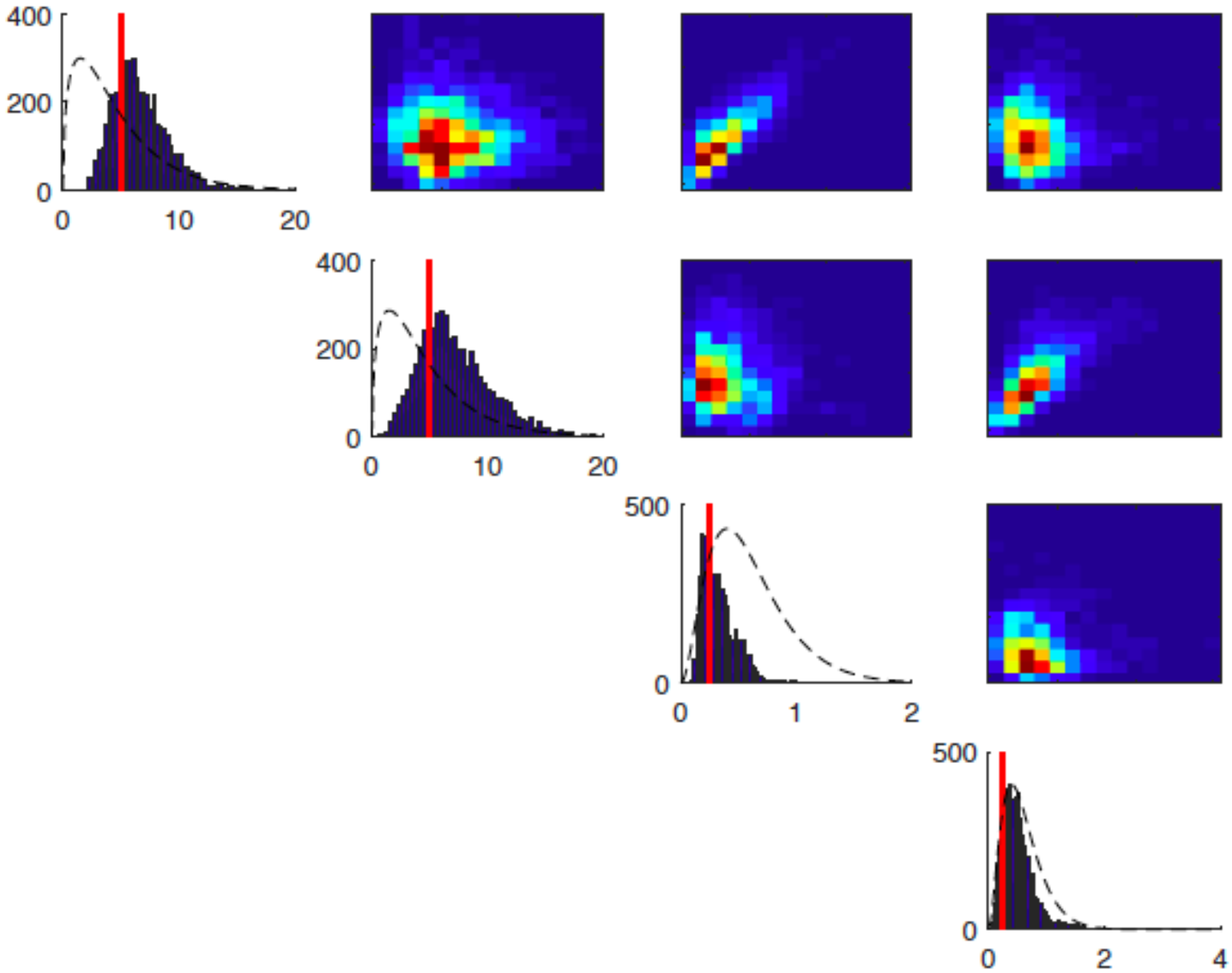
Proteins



Observations used

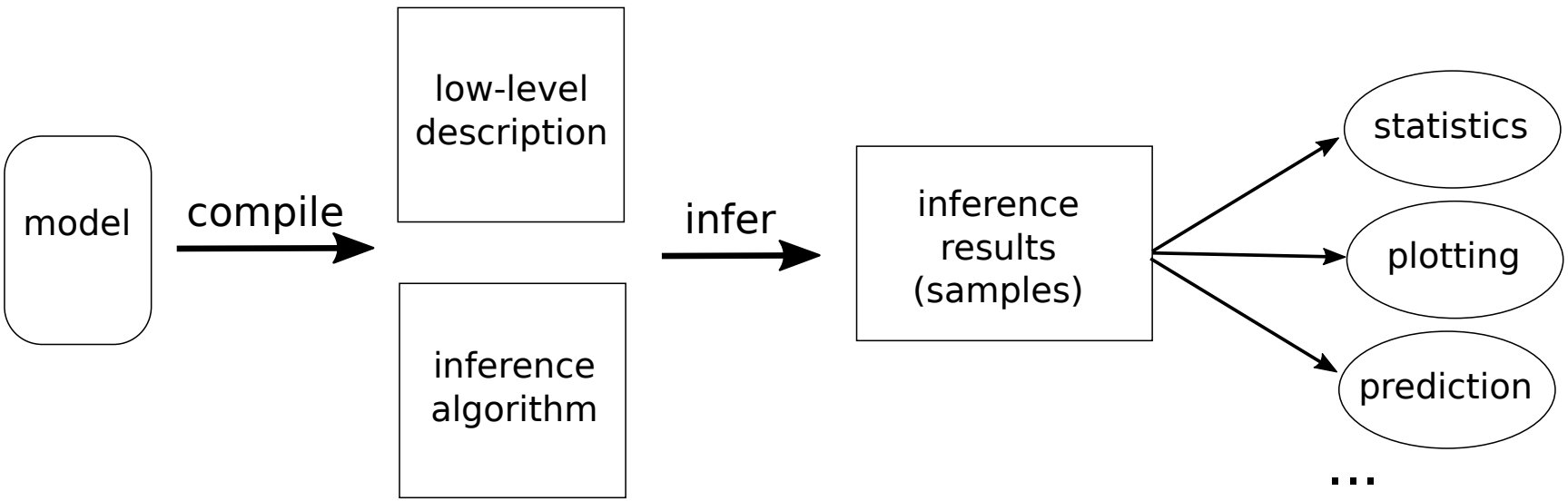


Results



Outline

Workflow


model
compile
low-level
description
inference
algorithm
infer
inference
results
(samples)
statistics
plotting
prediction
...

Summary

- ProPPA is a process algebra that incorporates uncertainty and observations directly in the model, influenced by probabilistic programming.
- Syntax remains similar to Bio-PEPA.
- Semantics defined in terms of an extension of Constraint Markov Chains.
- Observations can be either time-series or logical properties.
- Parameter inference based on random truncations (Russian Roulette) offers new possibilities for inference.

Thanks

- Anastasis Georgoulas

- Guido Sanguinetti