HelmholtzZentrum münchen
German Research Center for Environmental Health

Approximate Bayesian Computation for Stochastic Single-Cell Time-Lapse Data Using Multivariate Test Statistics

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Institute of Computational Biology
Research Group Data-Driven Computational Modeling

Nantes, 16/09/15

Introduction

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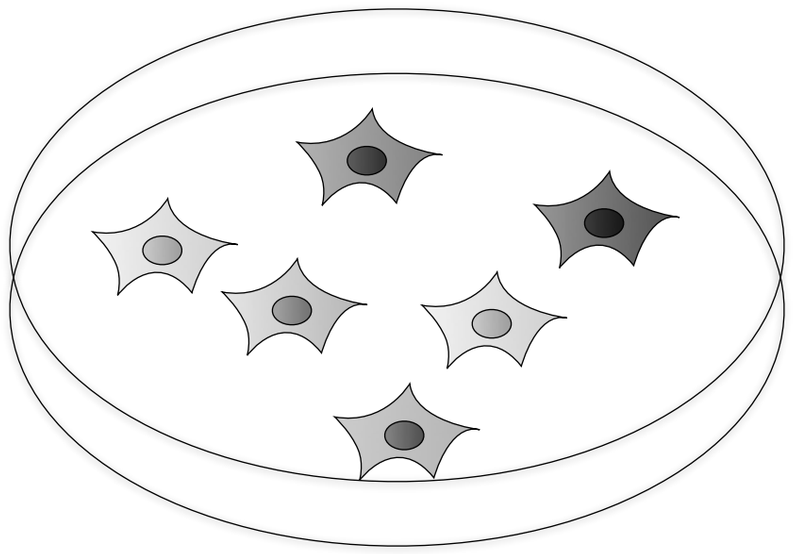
- Gene expression is known to be affected by different sources of variability[1]



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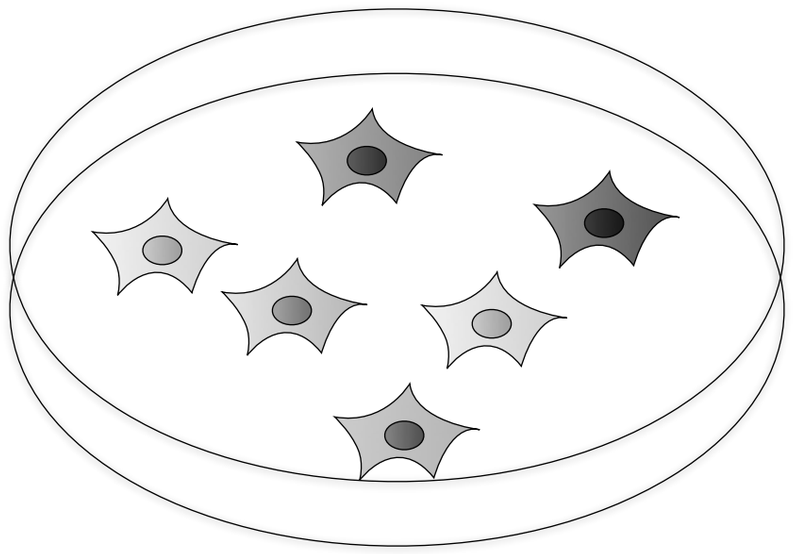

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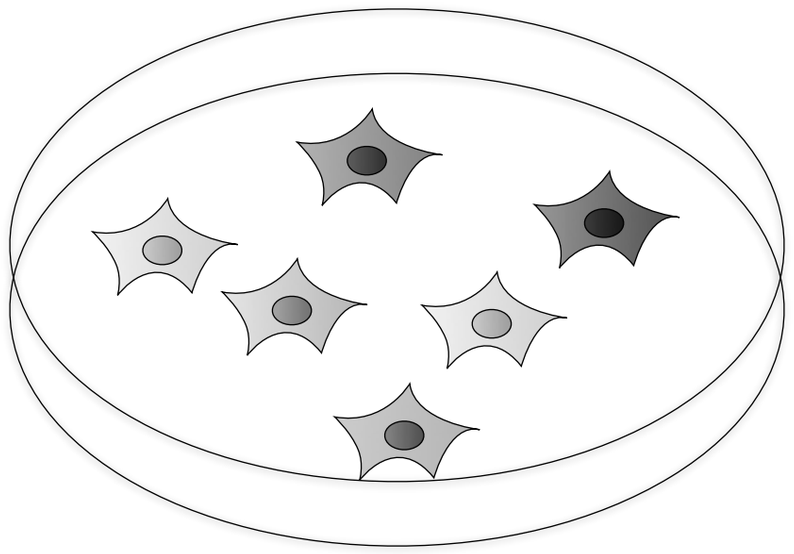
- Single-cell data for analysis of variability required



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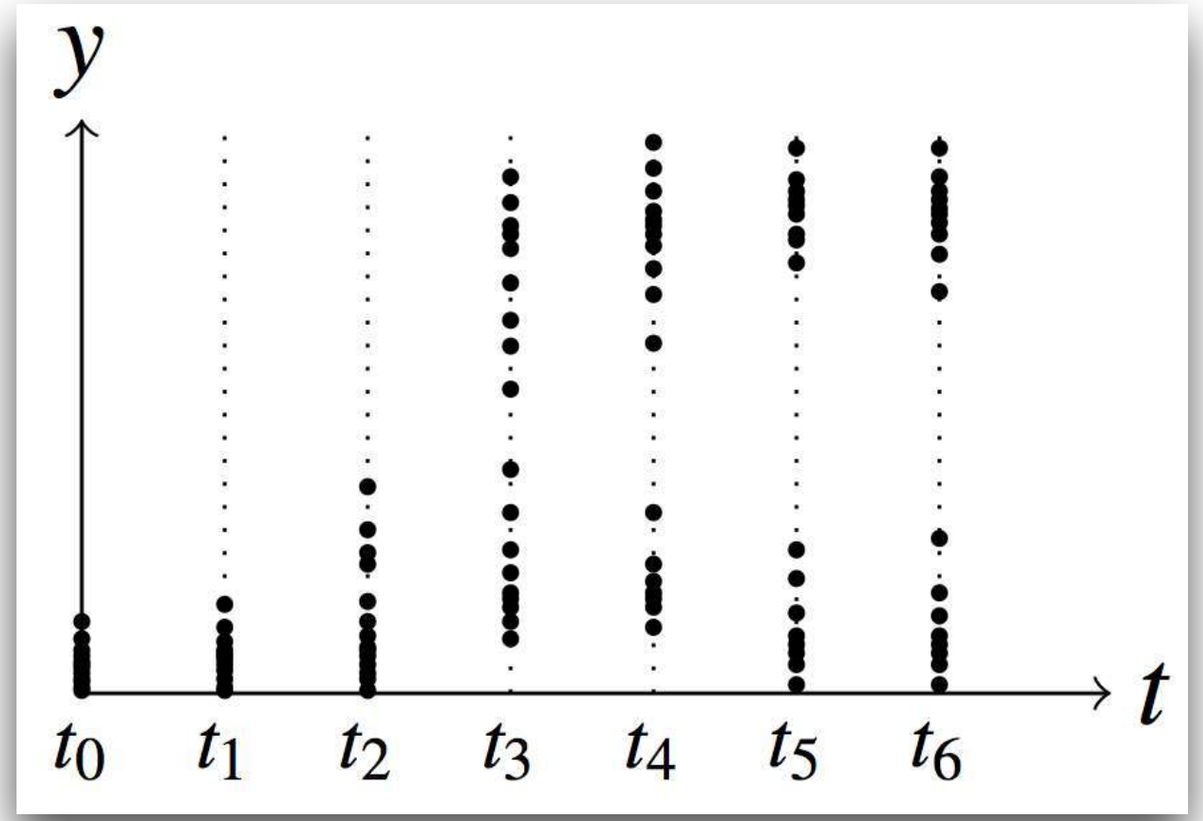

Single-cell snapshot data

Hasenauer, PhD thesis (2013)

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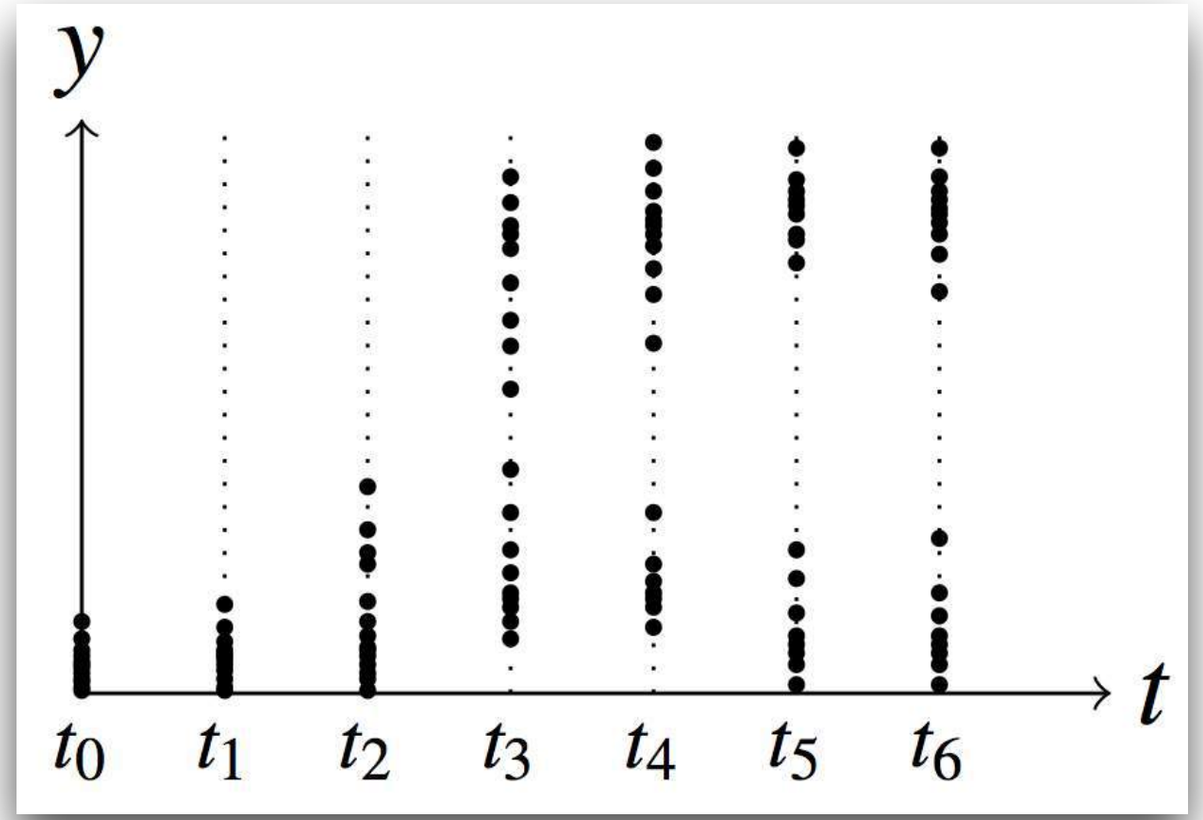

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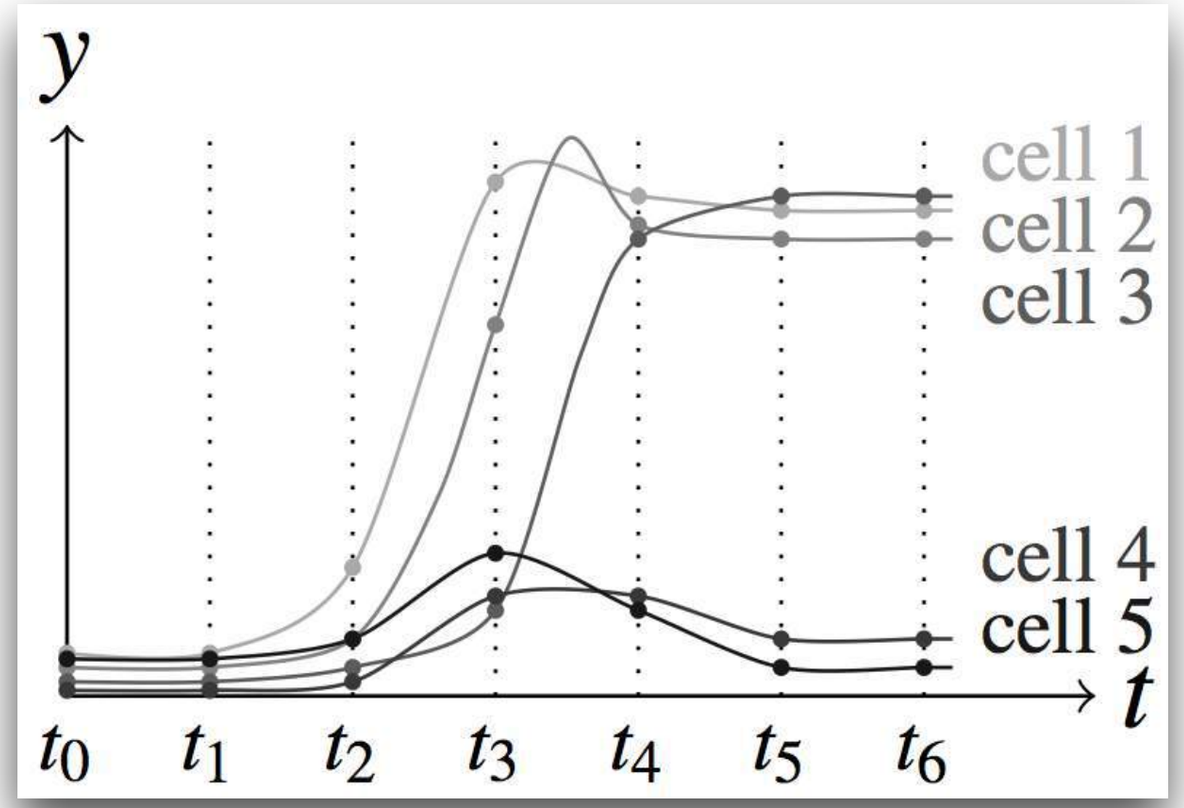

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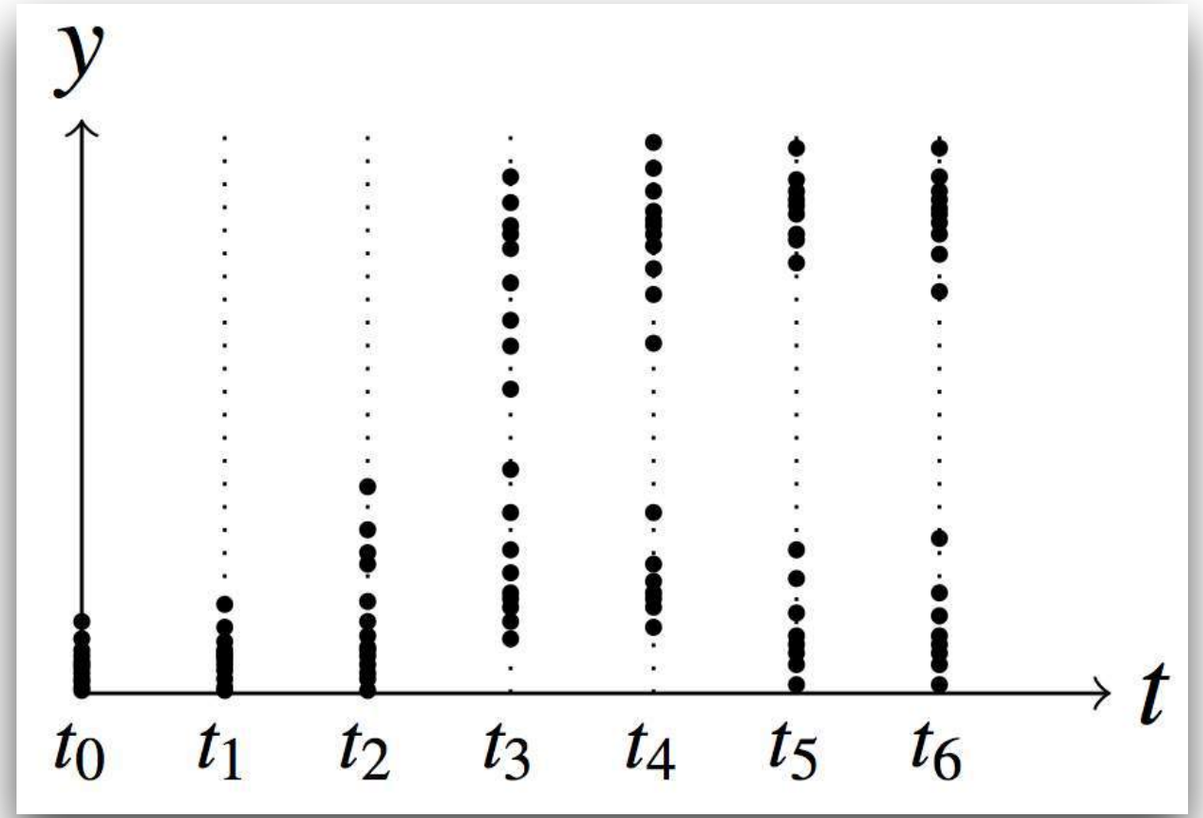

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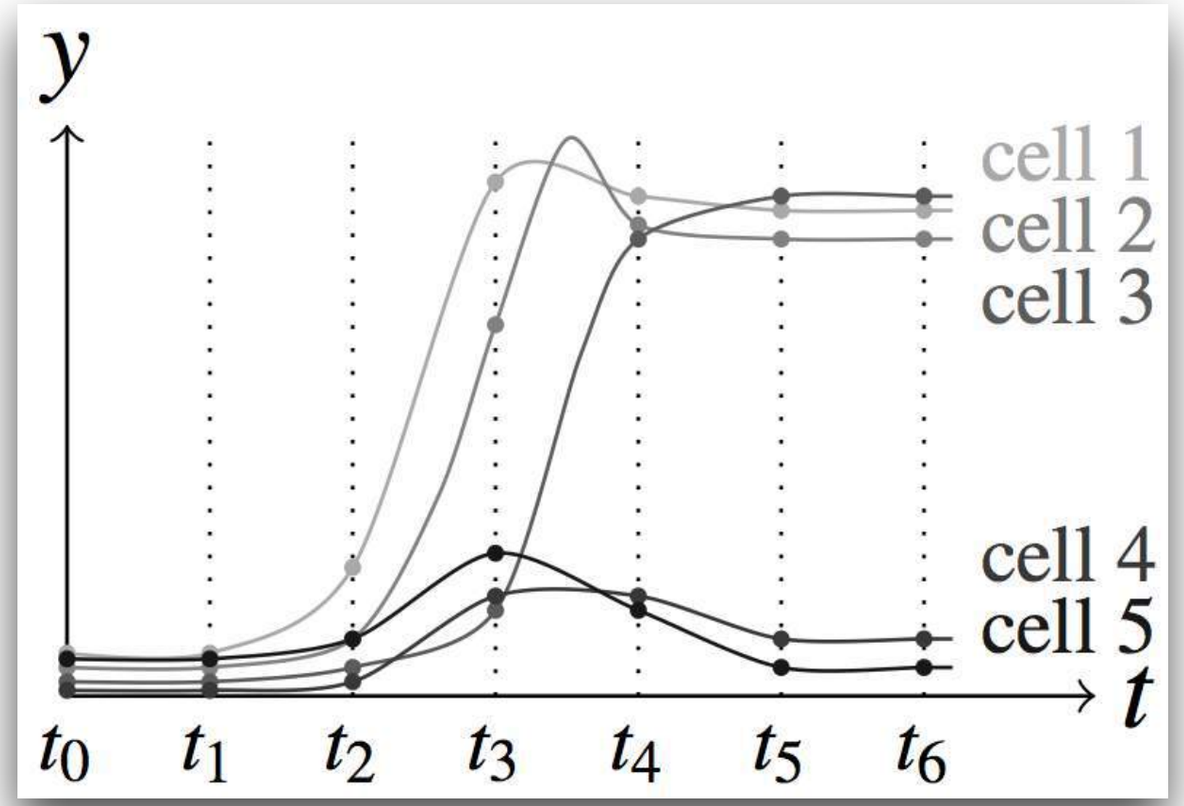

Single-cell time-lapse data

Single-cell time-lapse data provide information about temporal cross-correlation

Hasenauer, PhD thesis (2013)

Parameter inference for single-cell time-lapse data

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Derive model M with parameters θ and fit it to data D by e.g. maximizing the likelihood function or sampling from the posterior distribution p(θ|D)

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- θ: Parameters of process e.g. kinetic parameters, initial conditions, …

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- ABC circumvents calculation of likelihood by comparing observed and simulated data set

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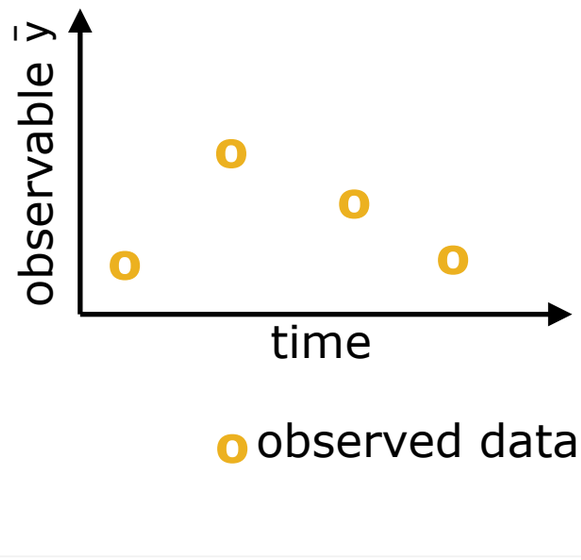

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Figure modified from Toni et al., Bioinformatics (2010)

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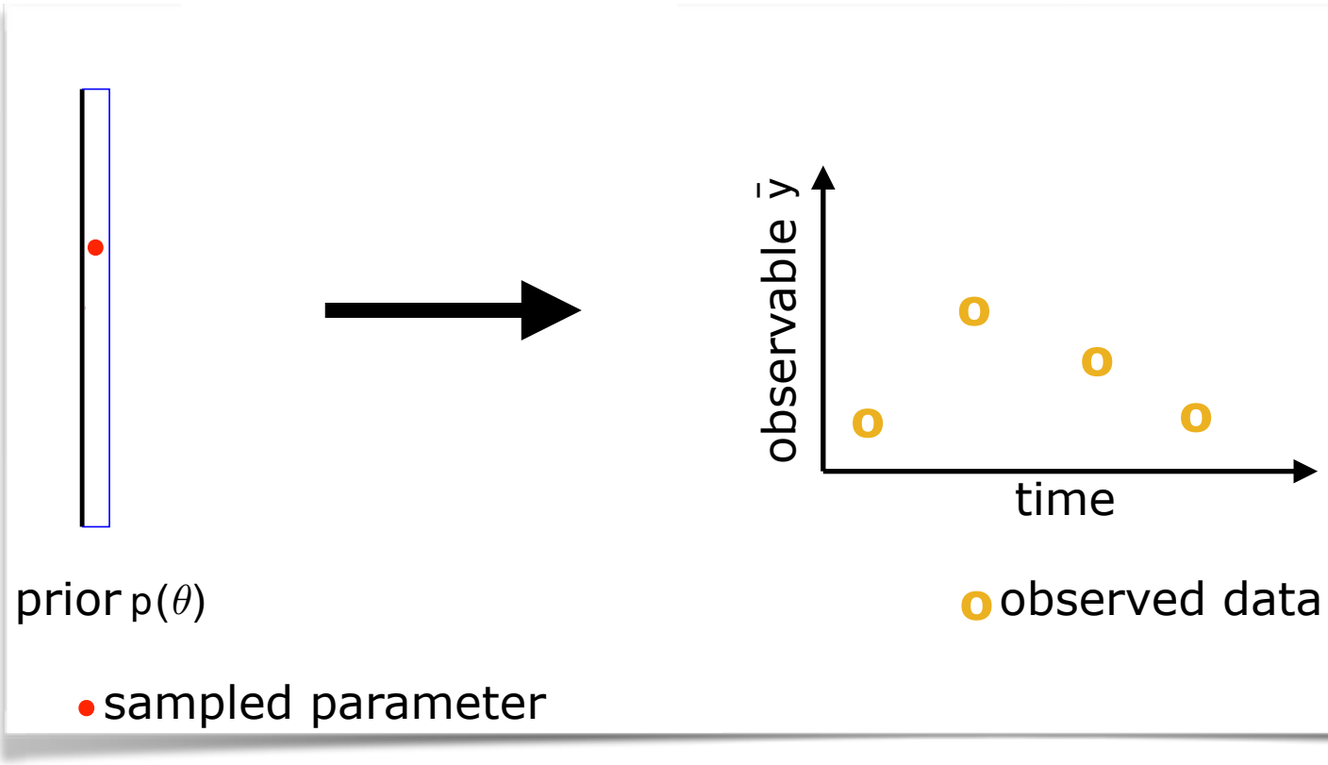

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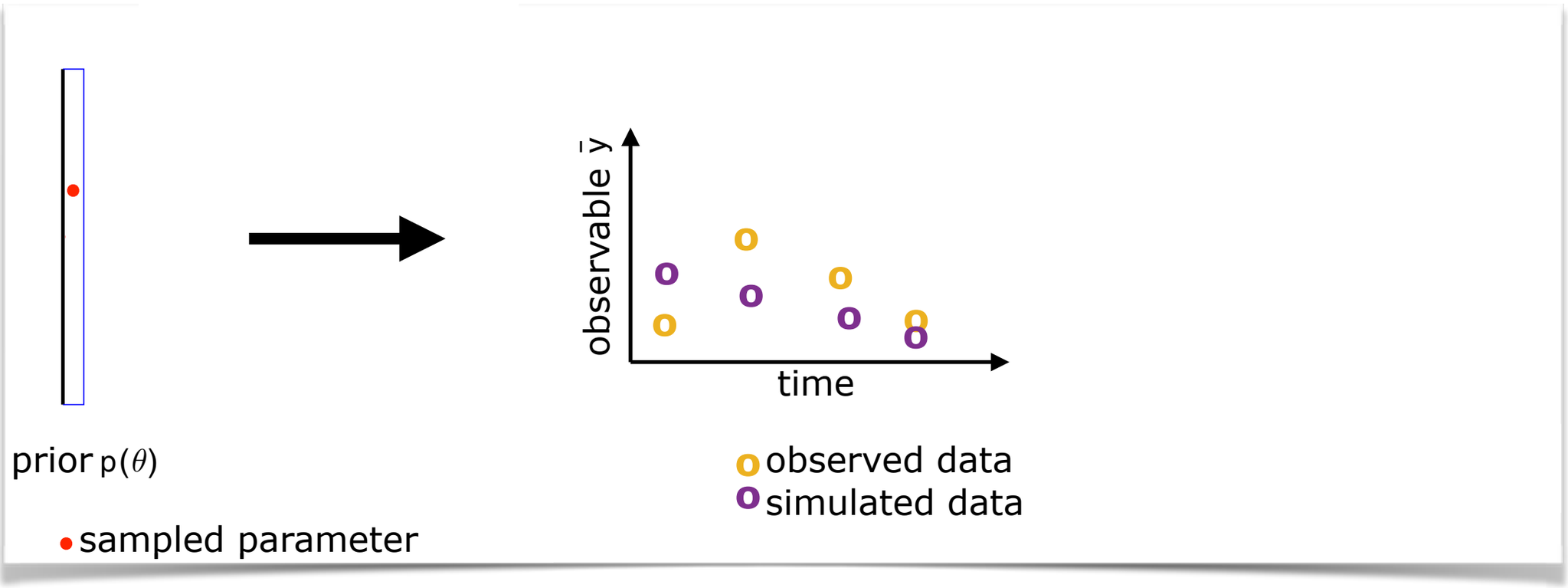

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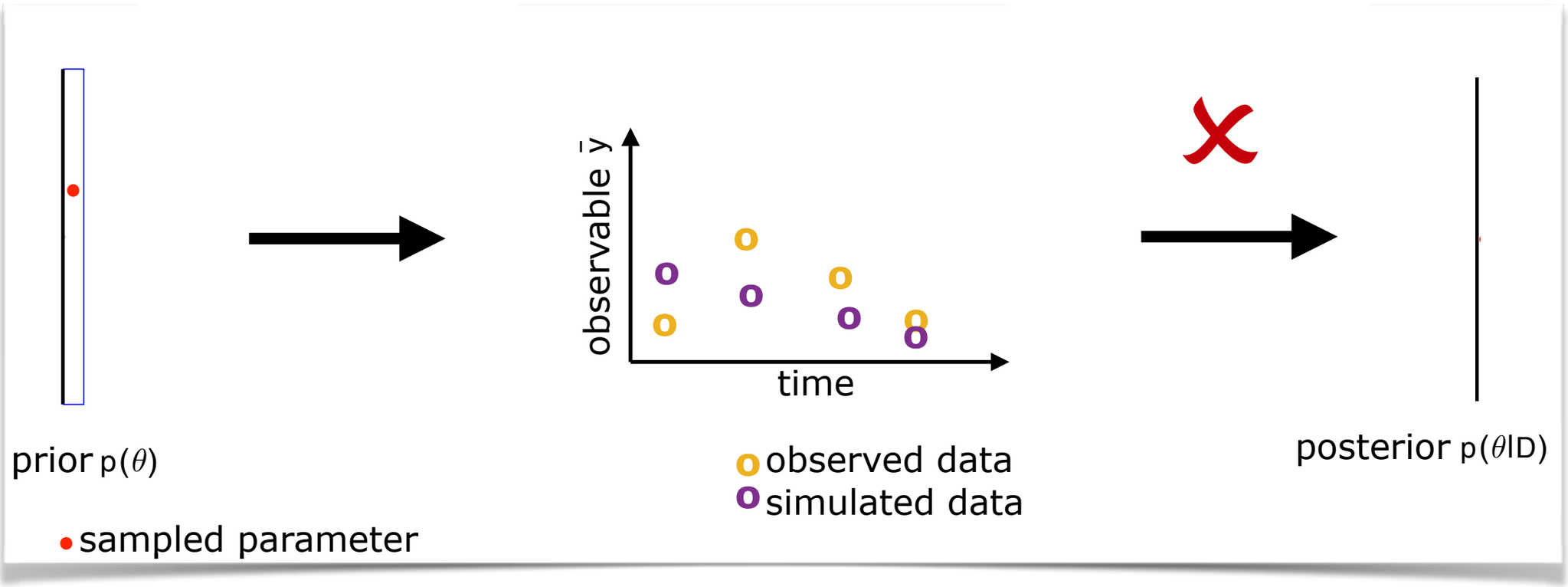

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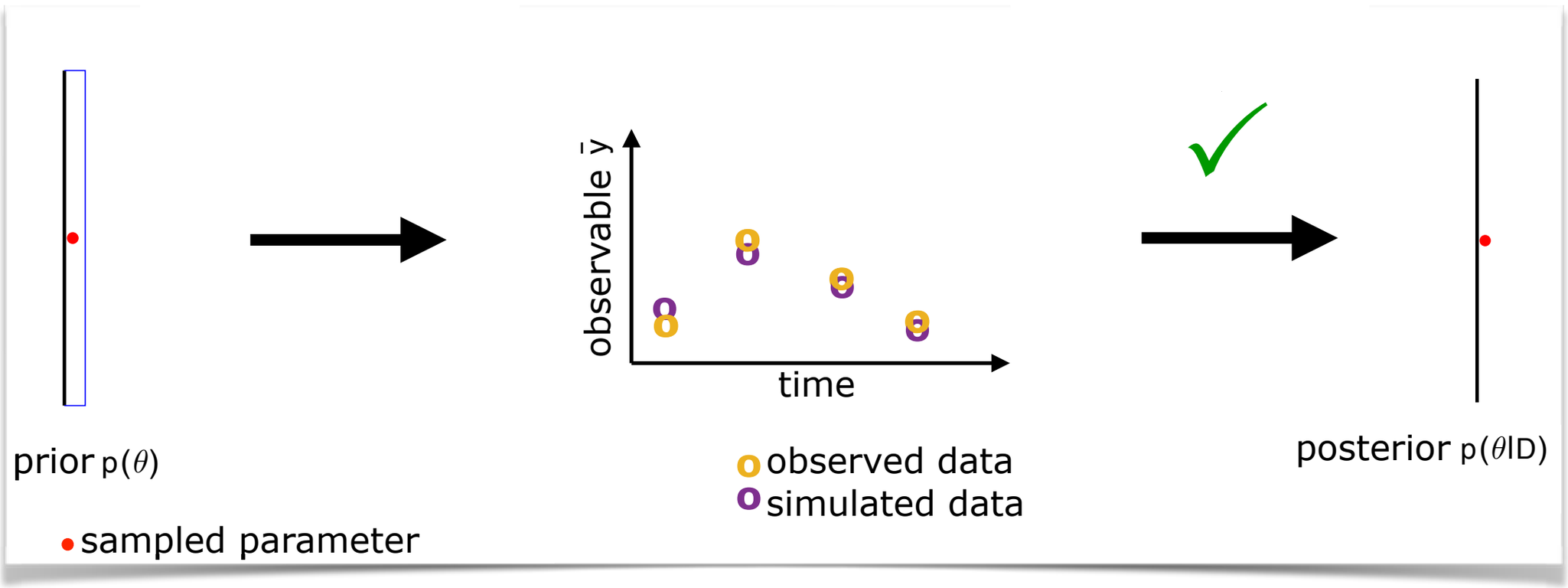

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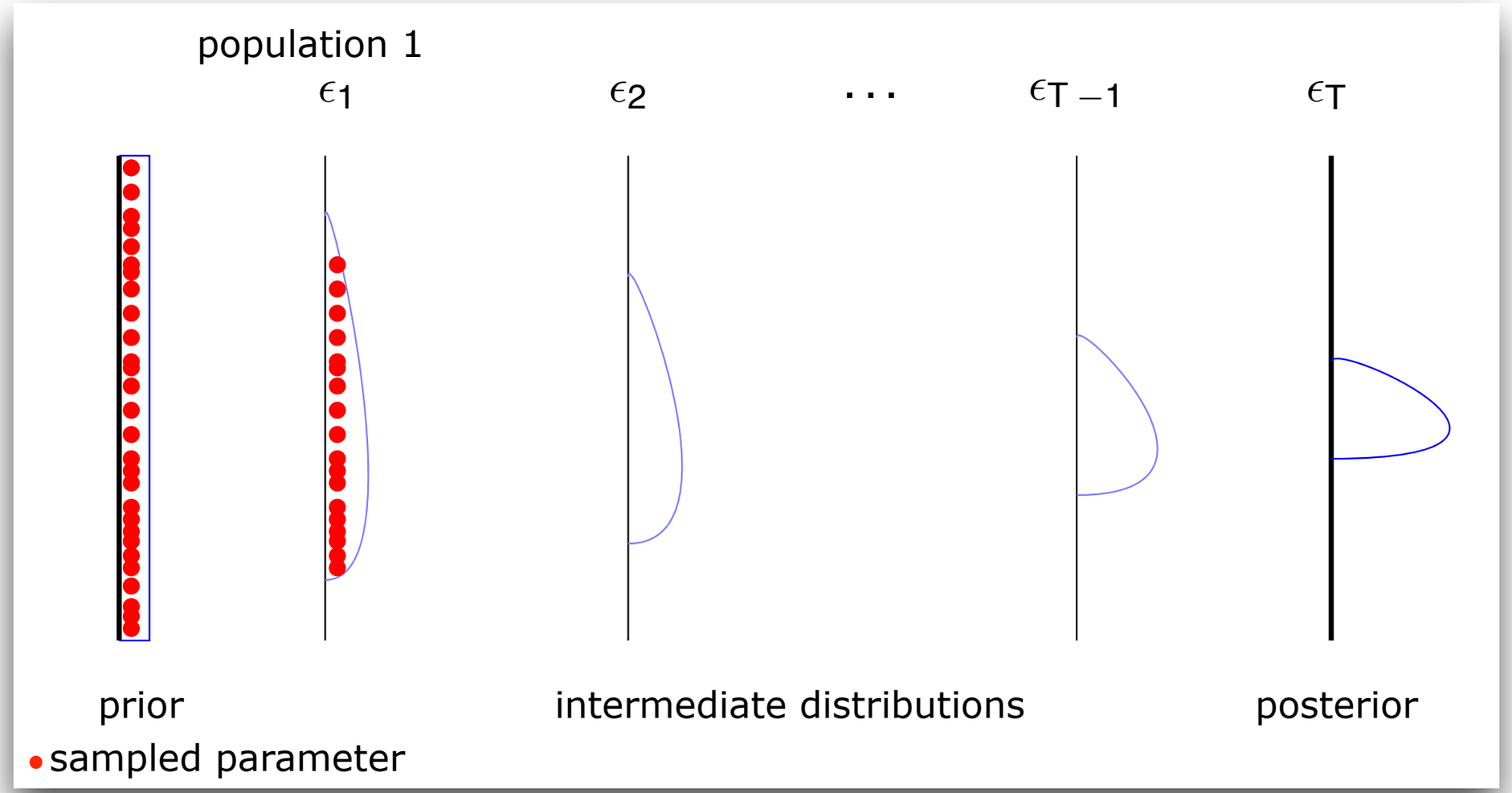

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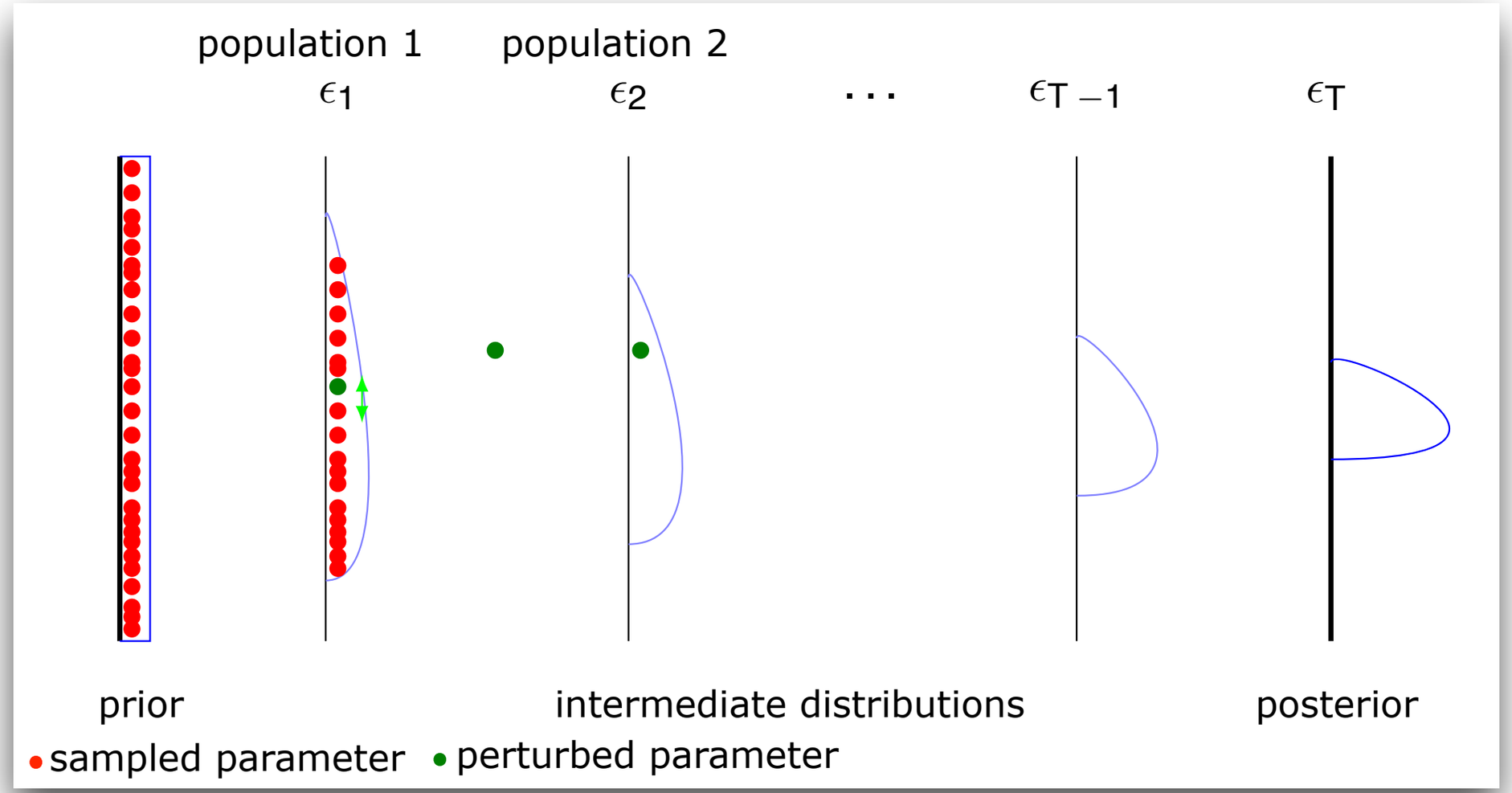

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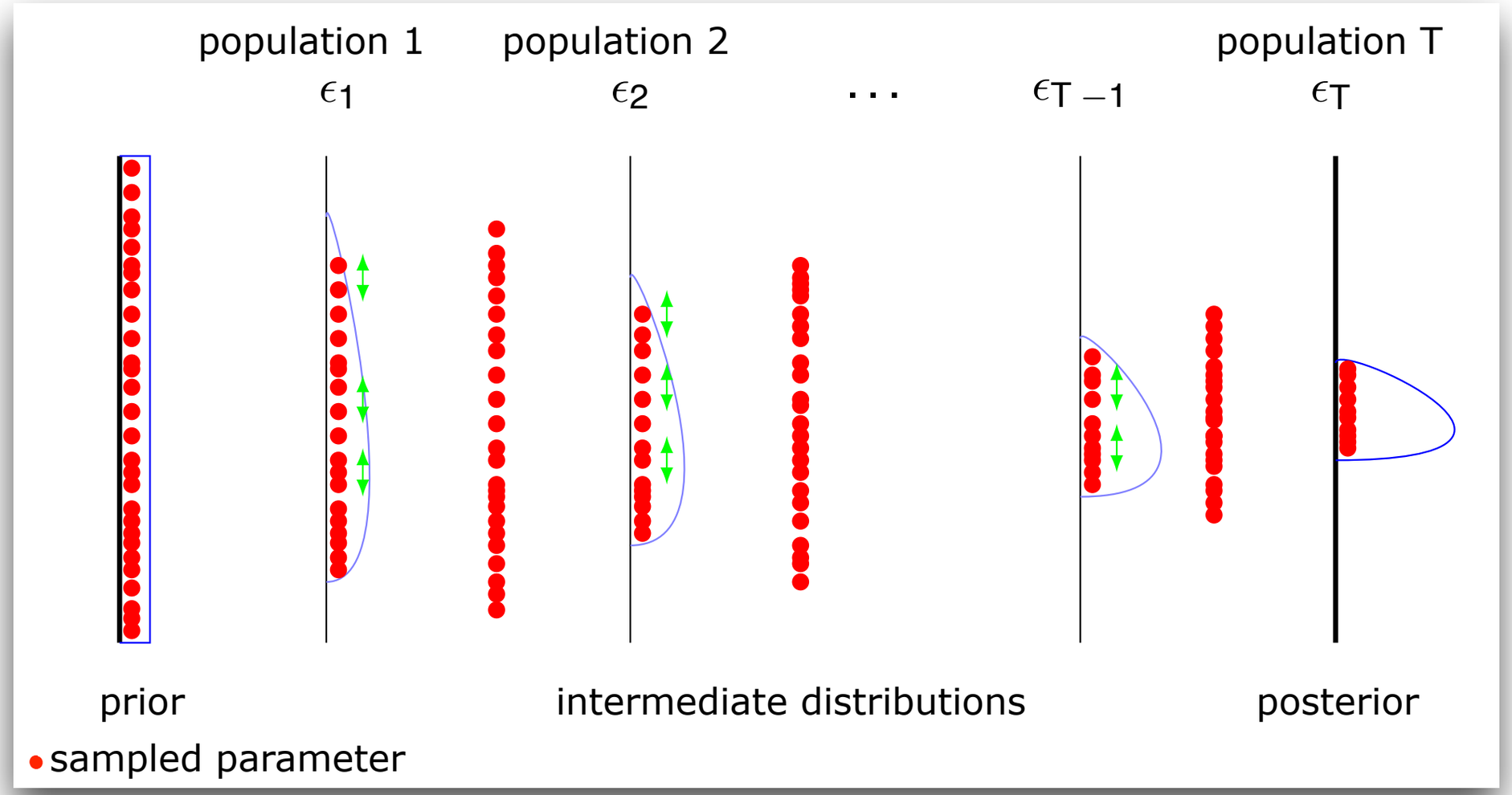

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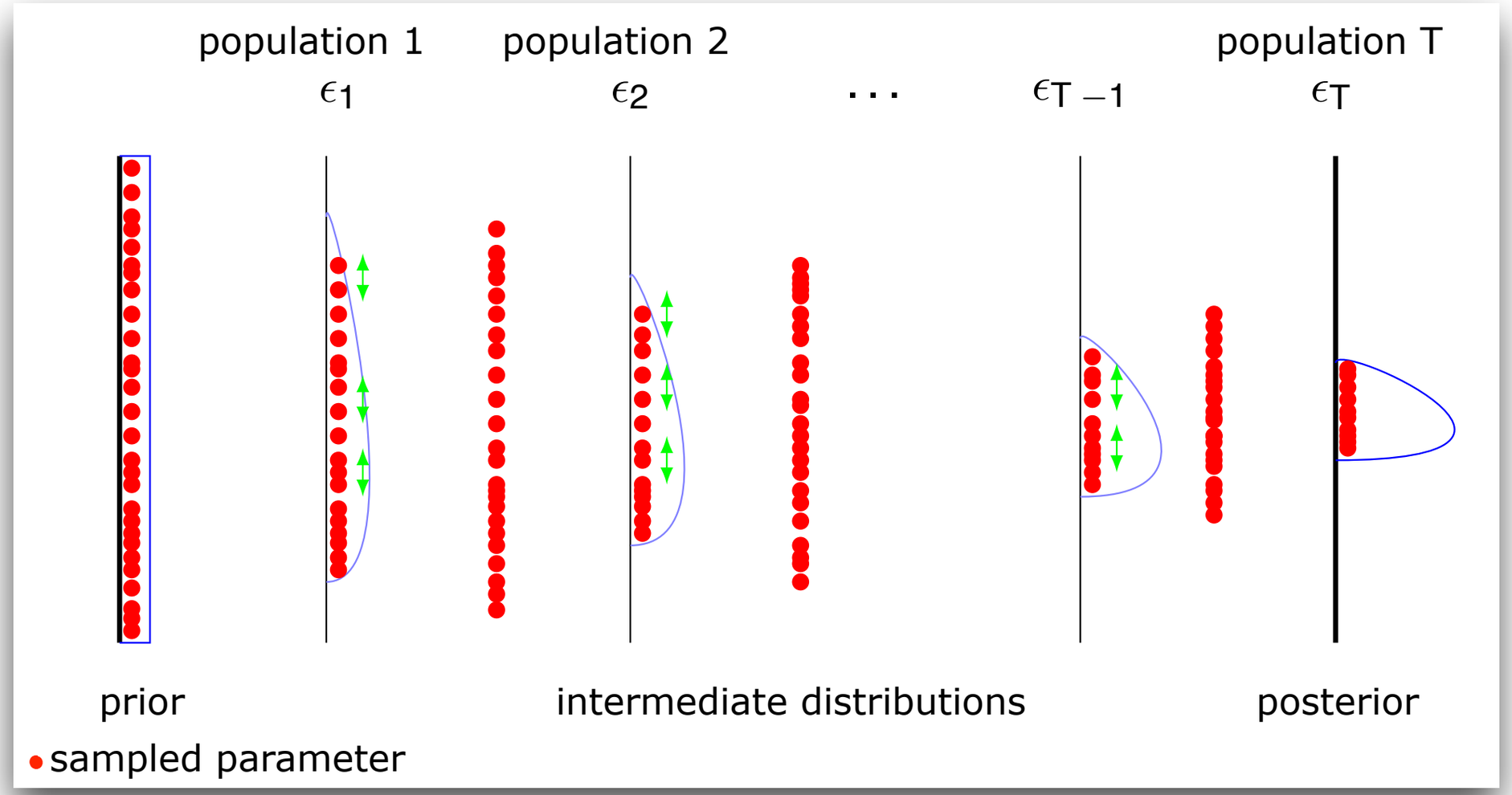

Accept parameter samples with decreasing tolerance

Figure modified from Toni et al., Bioinformatics (2010)

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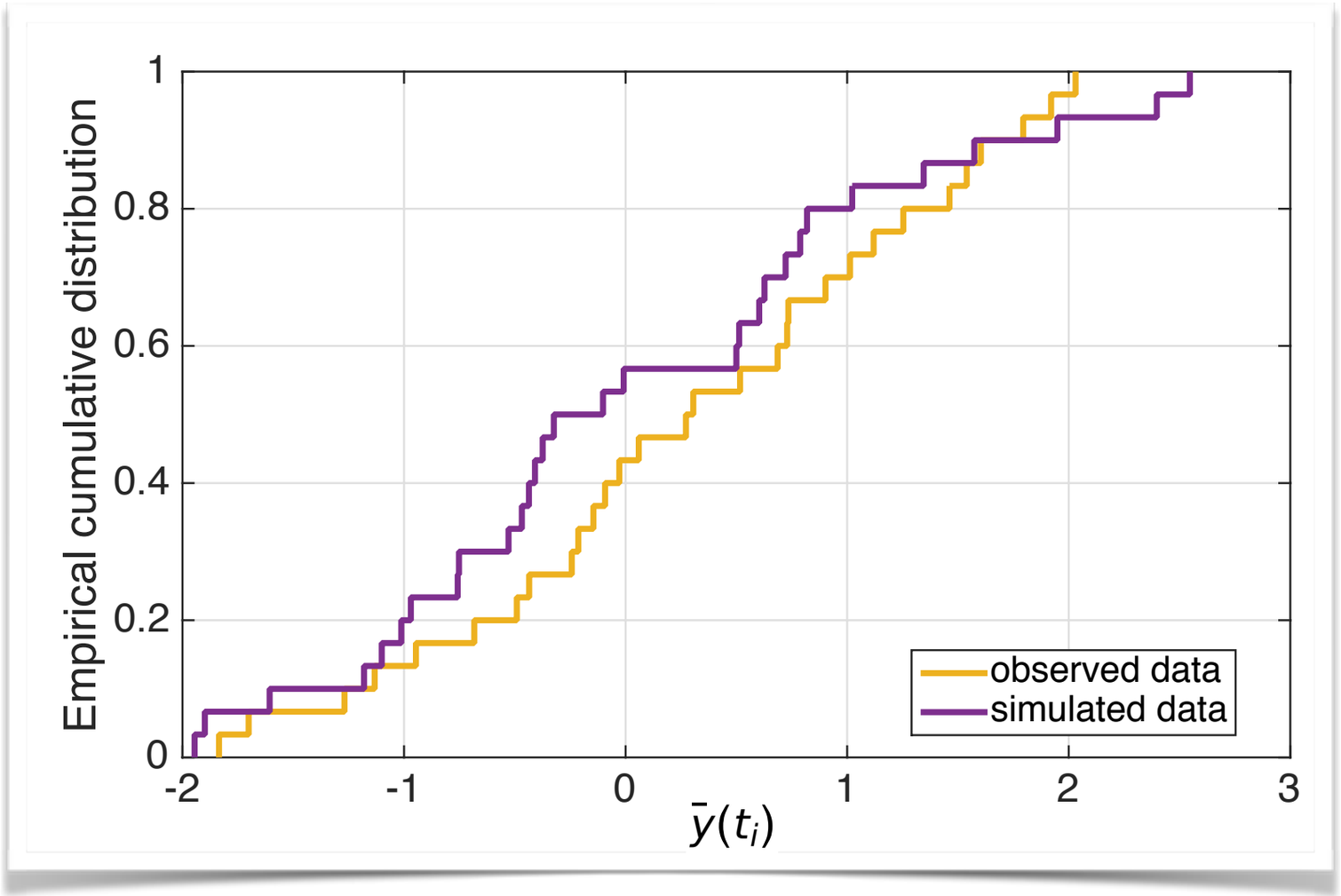

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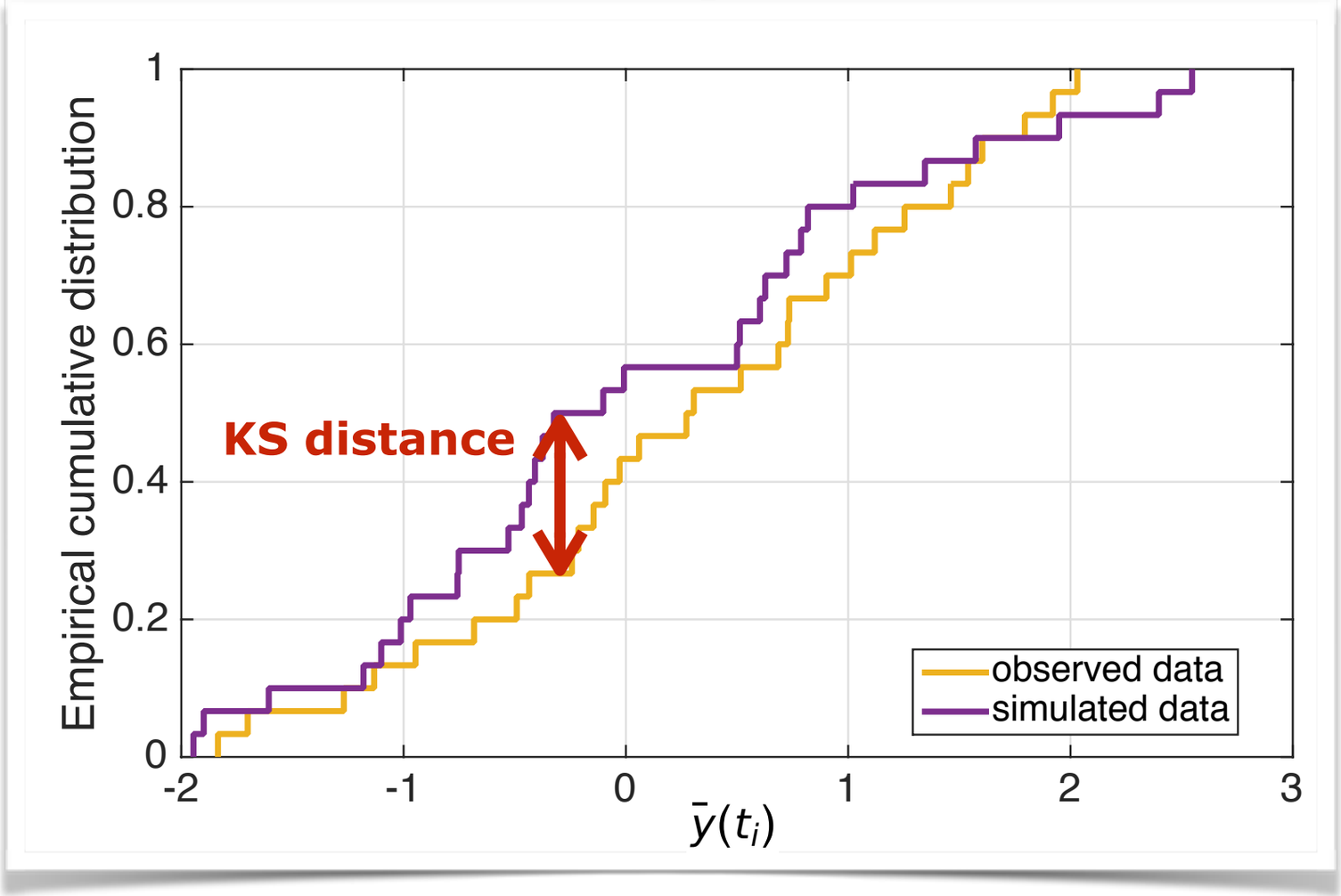

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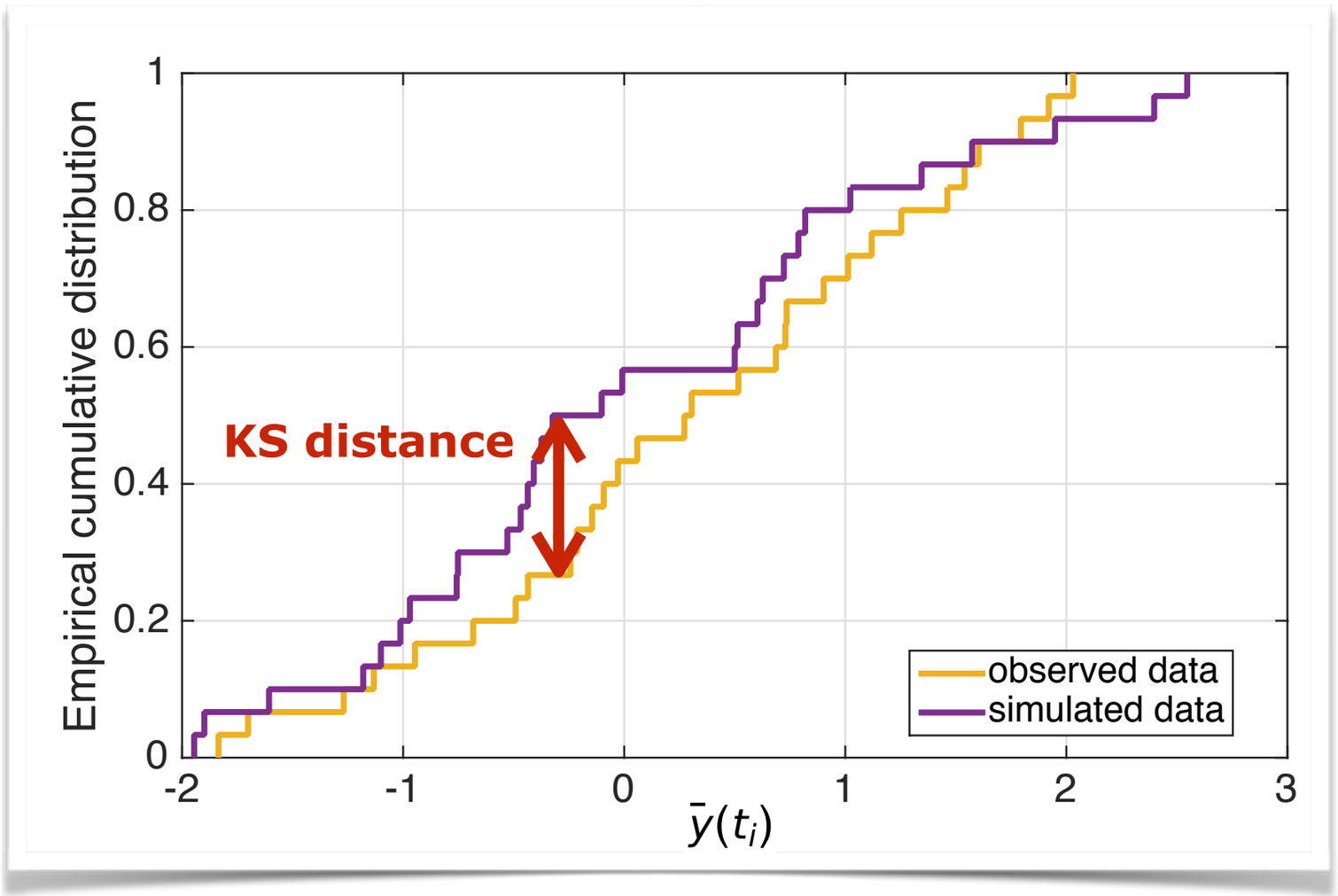

Accept parameters that produce a low KS distance

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ABC SMC with multivariate test statistics

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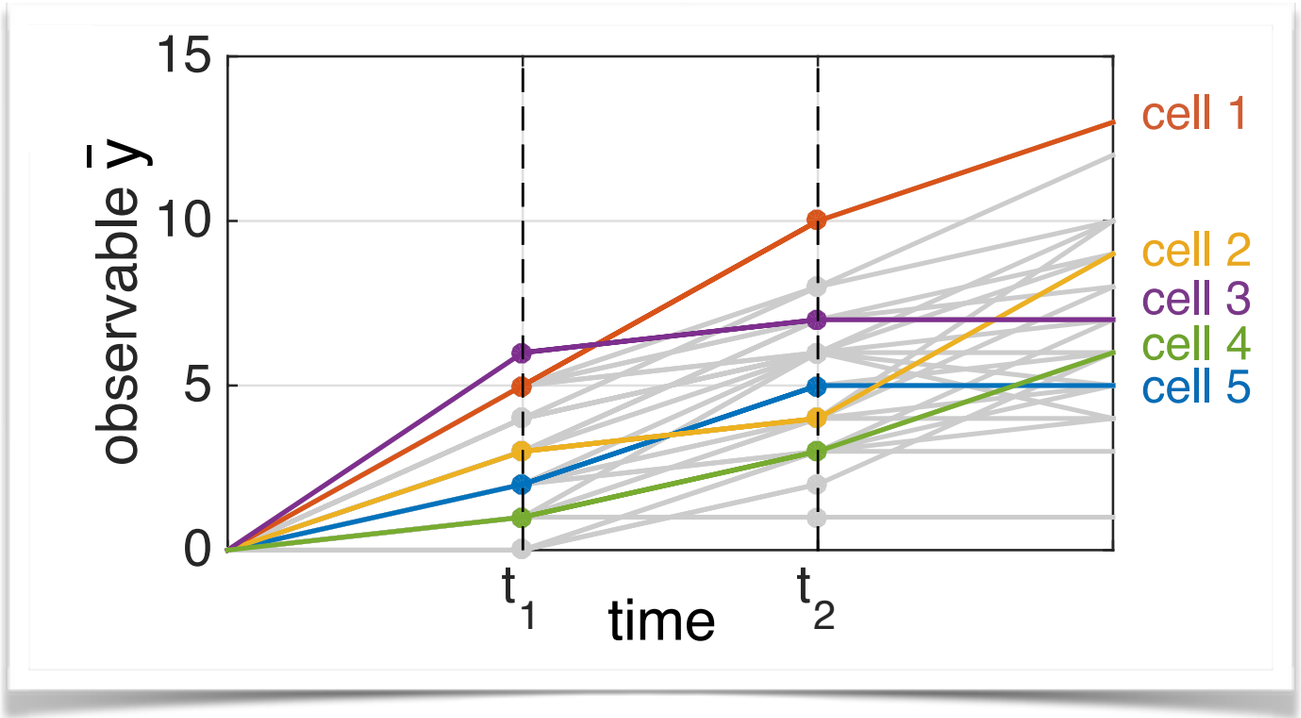

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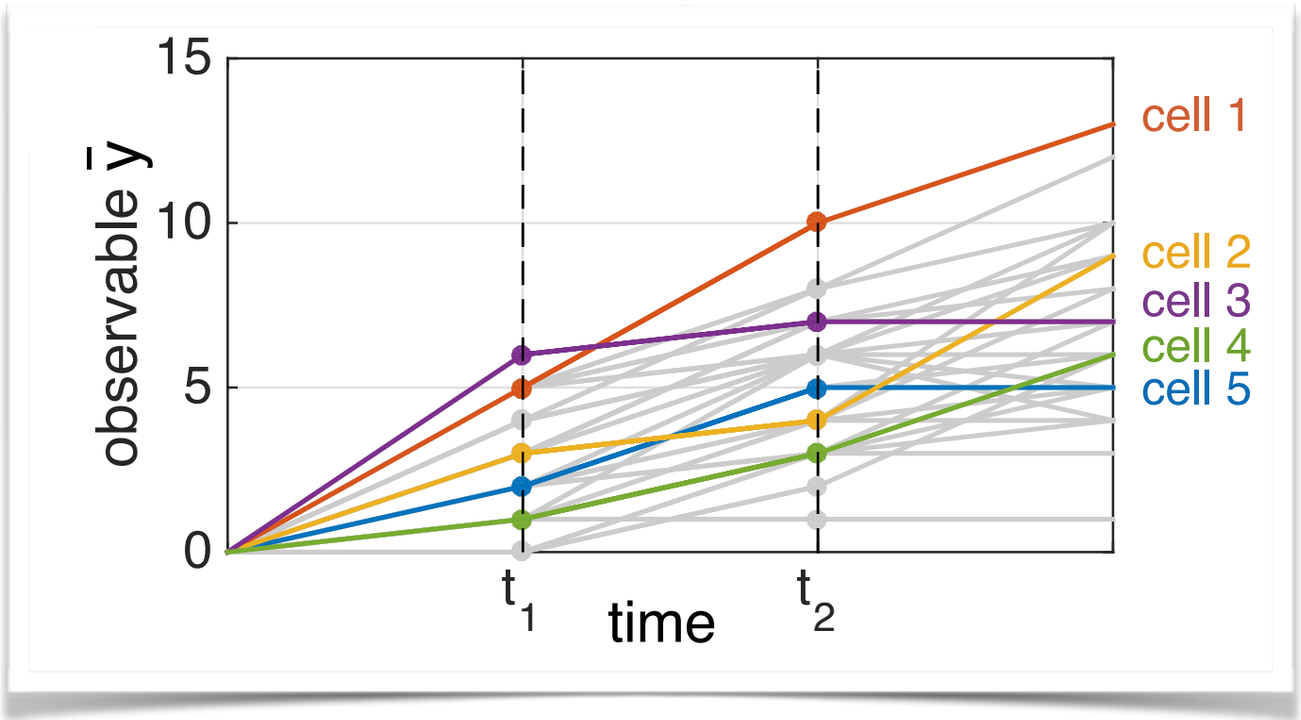

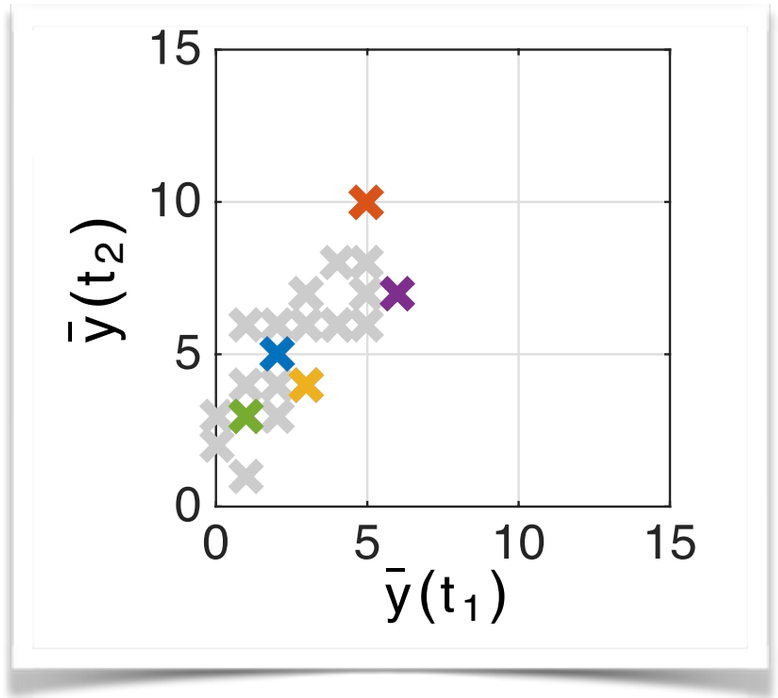

single-cell trajectory
measurement
two-dimensional representation of the trajectory

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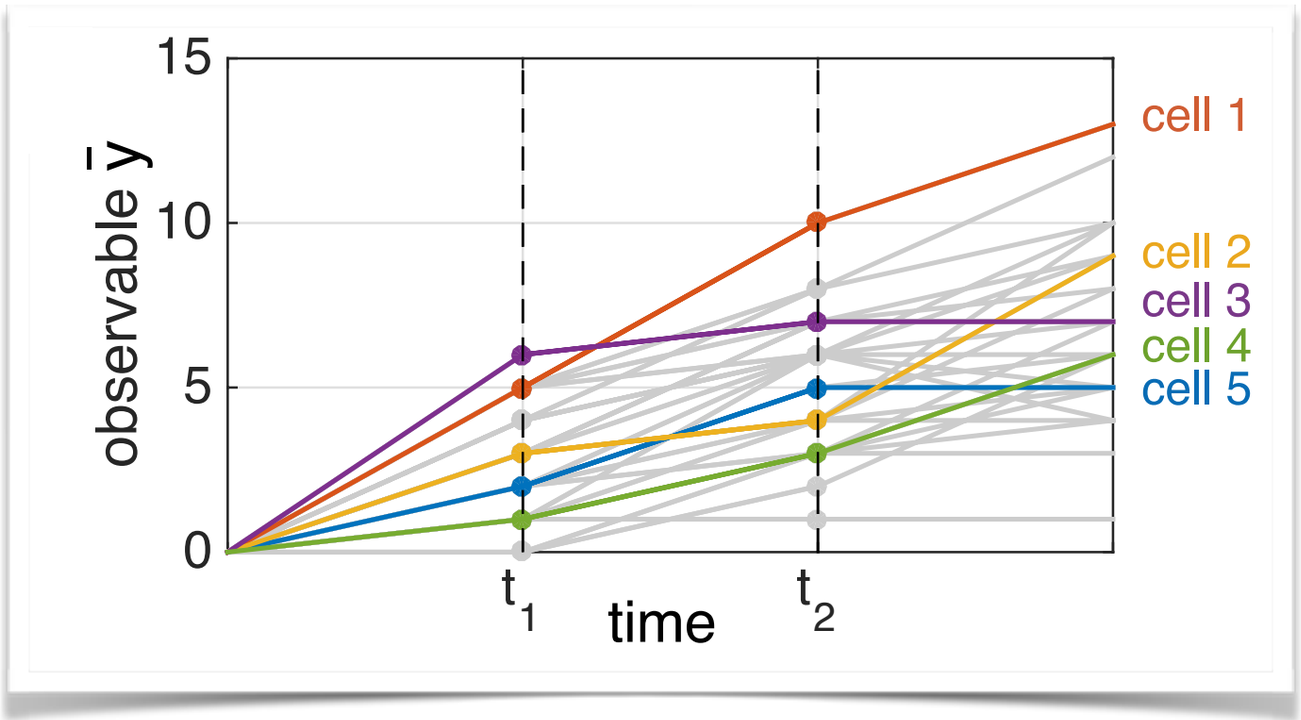

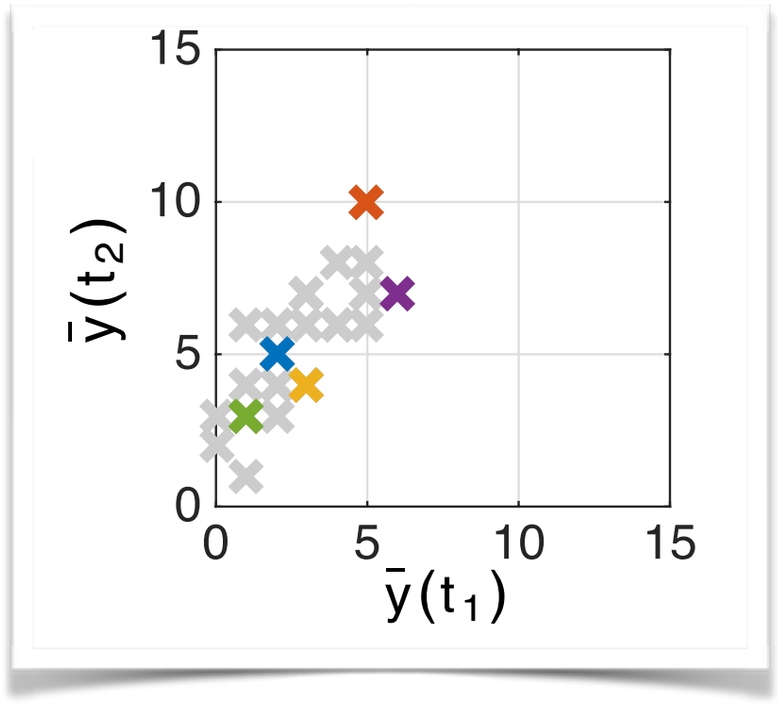

single-cell trajectory
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Use multivariate statistics on the distribution of single-cell trajectories in the rejection step of ABC SMC

Cross-match test

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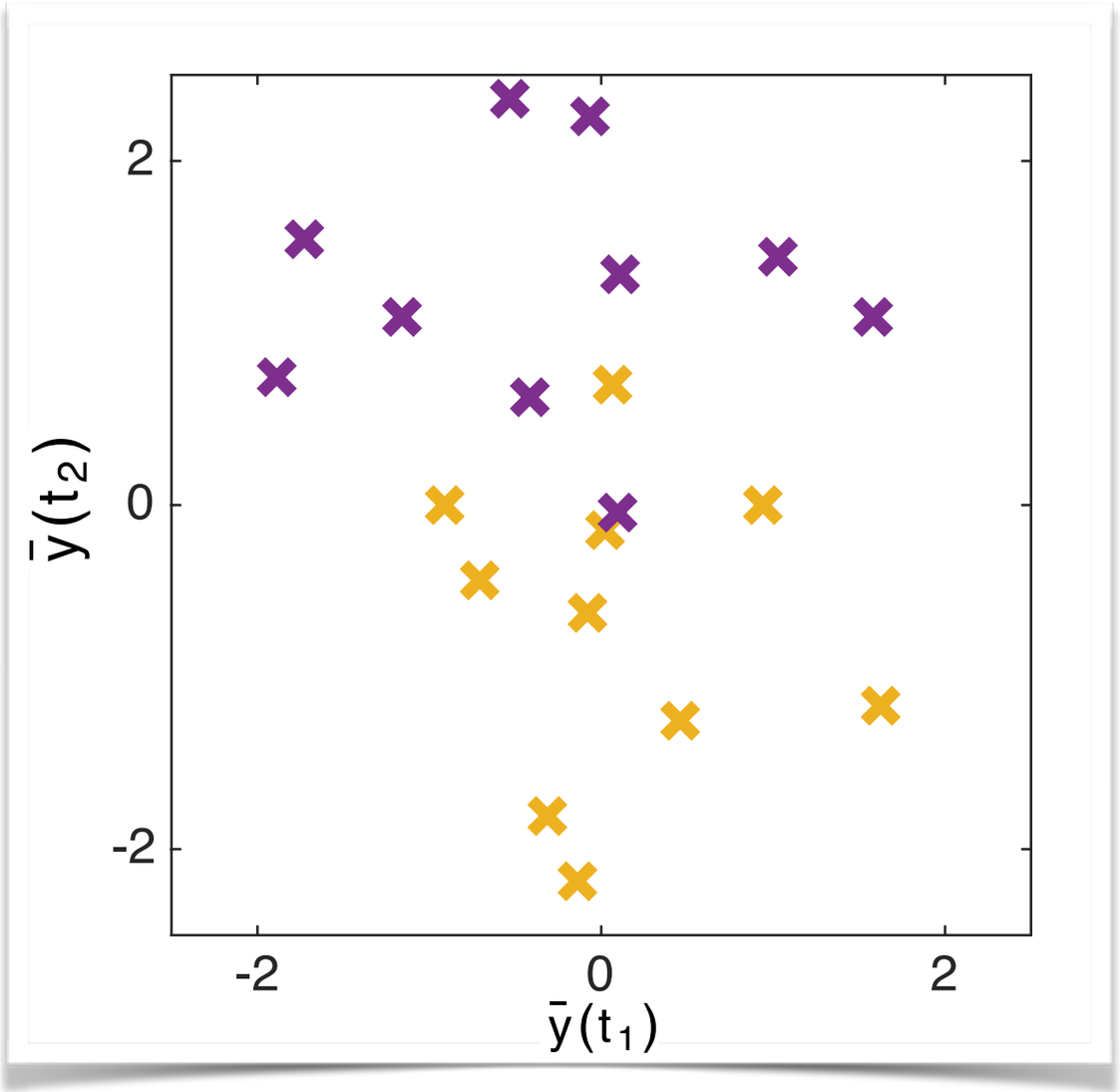

observed samples
simulated samples

Rosenbaum, Journal of the Royal Statistical Society (2005)

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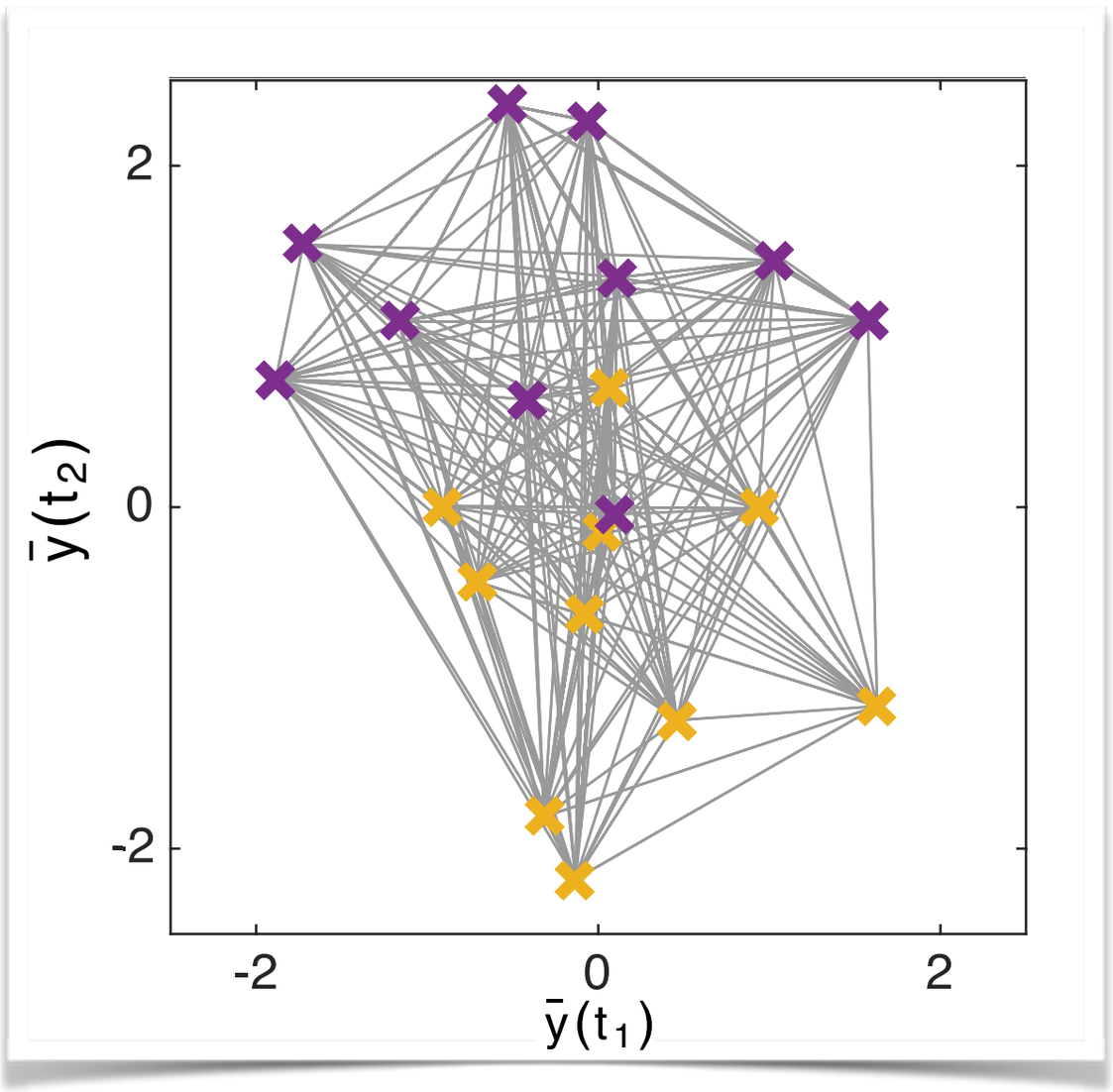

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Perform a minimum weight non-bipartite matching on a complete graph

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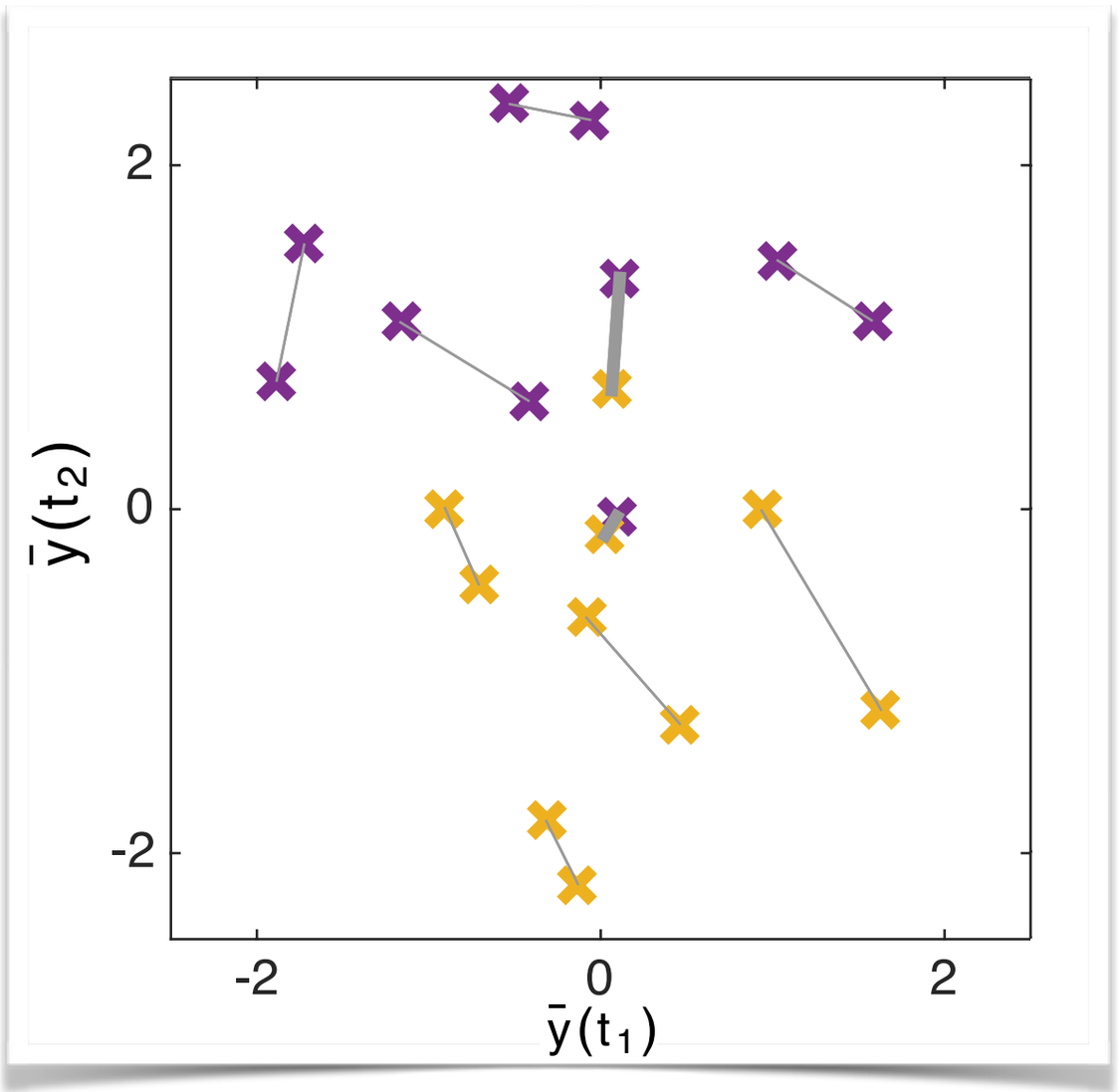

observed samples
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no cross-match
cross-matches

Perform a minimum weight non-bipartite matching on a complete graph

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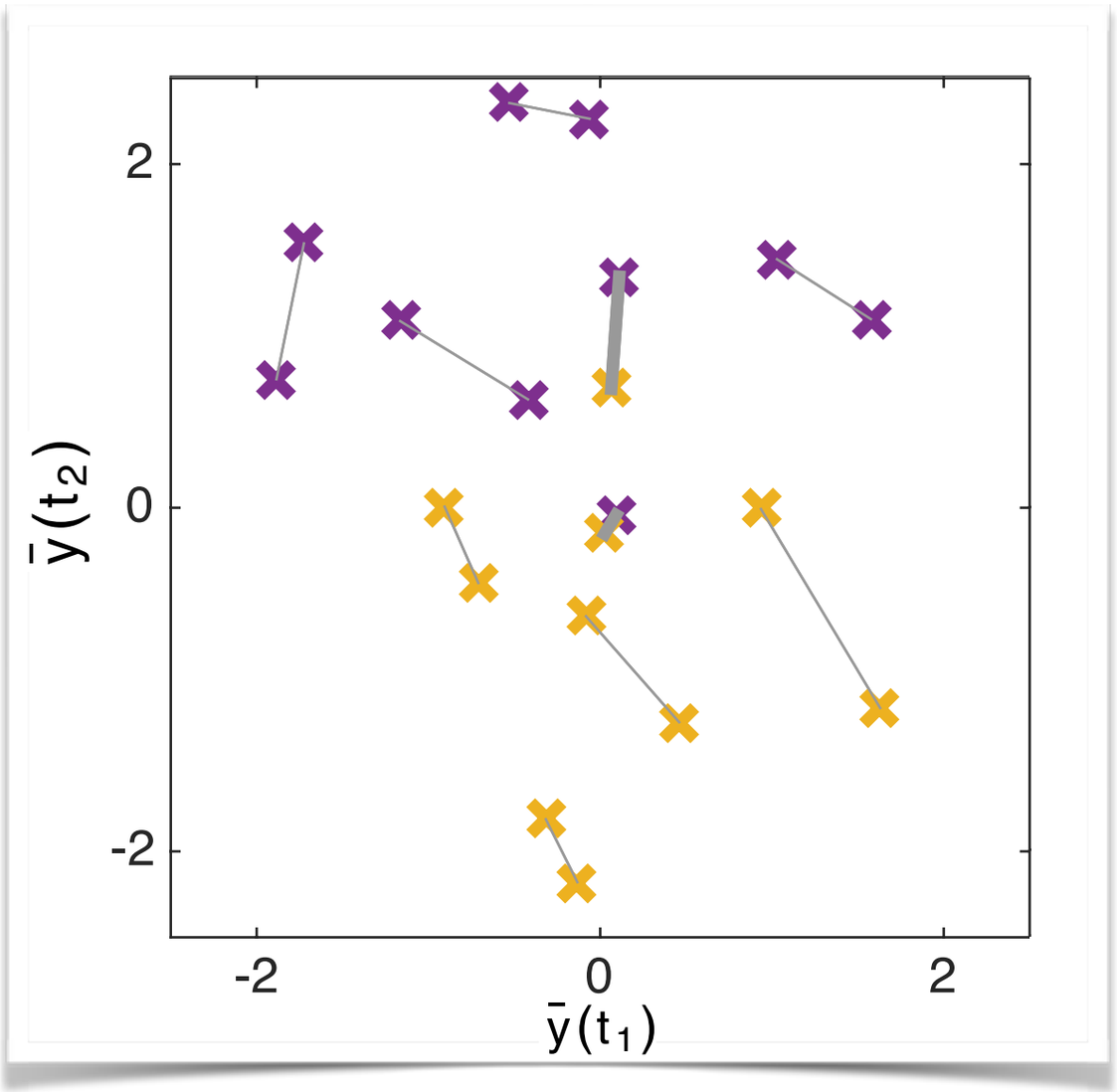

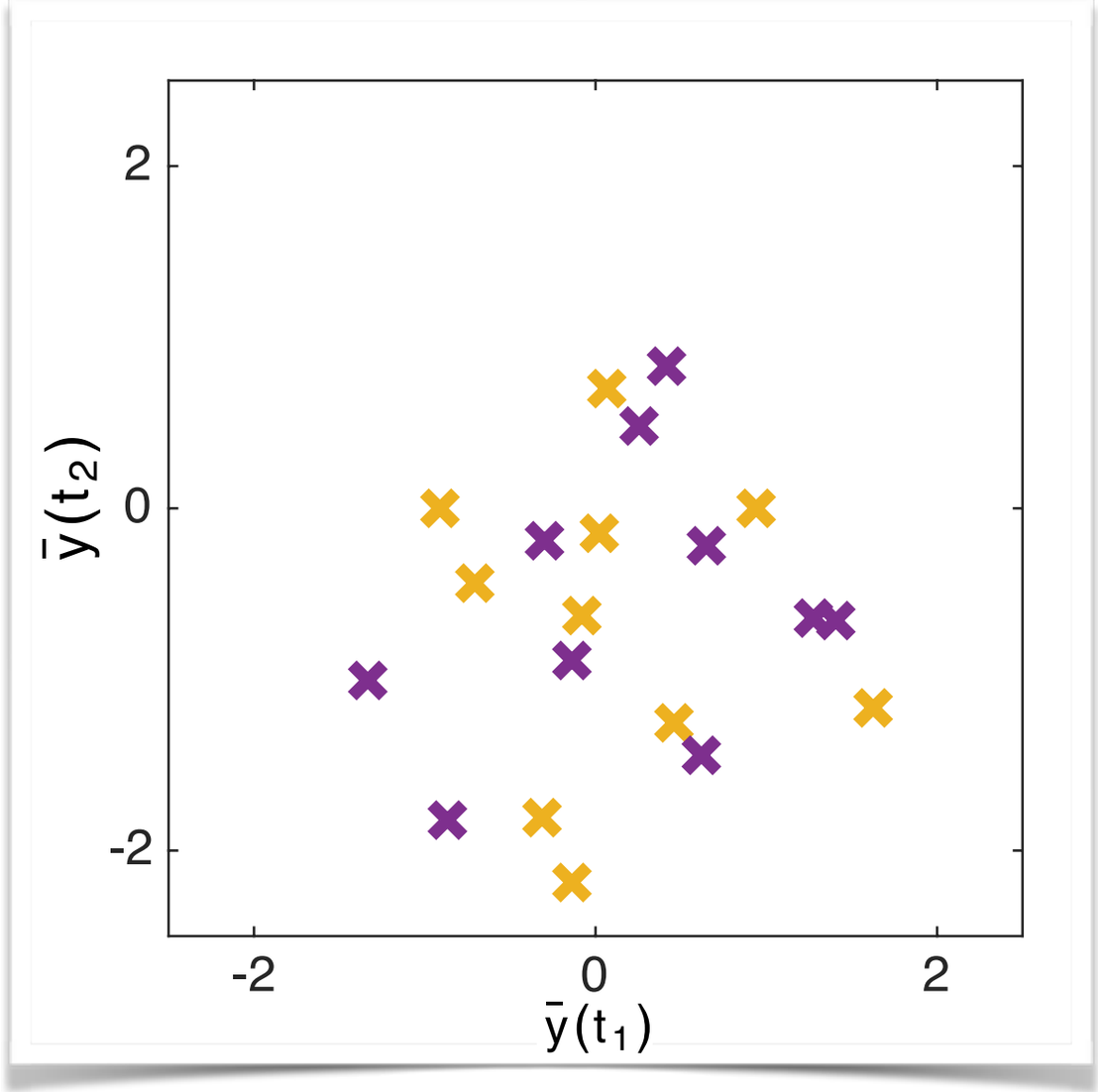

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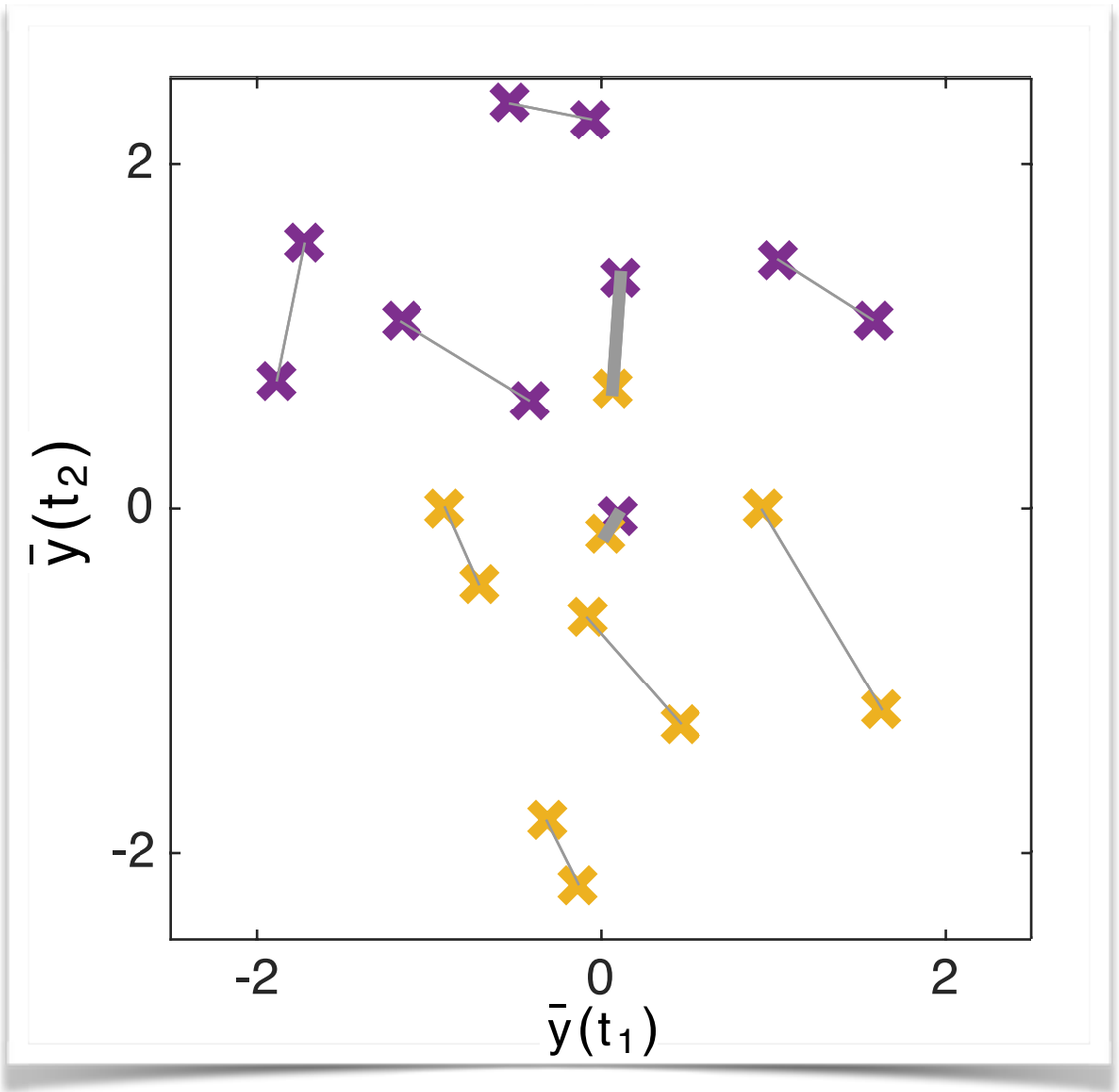

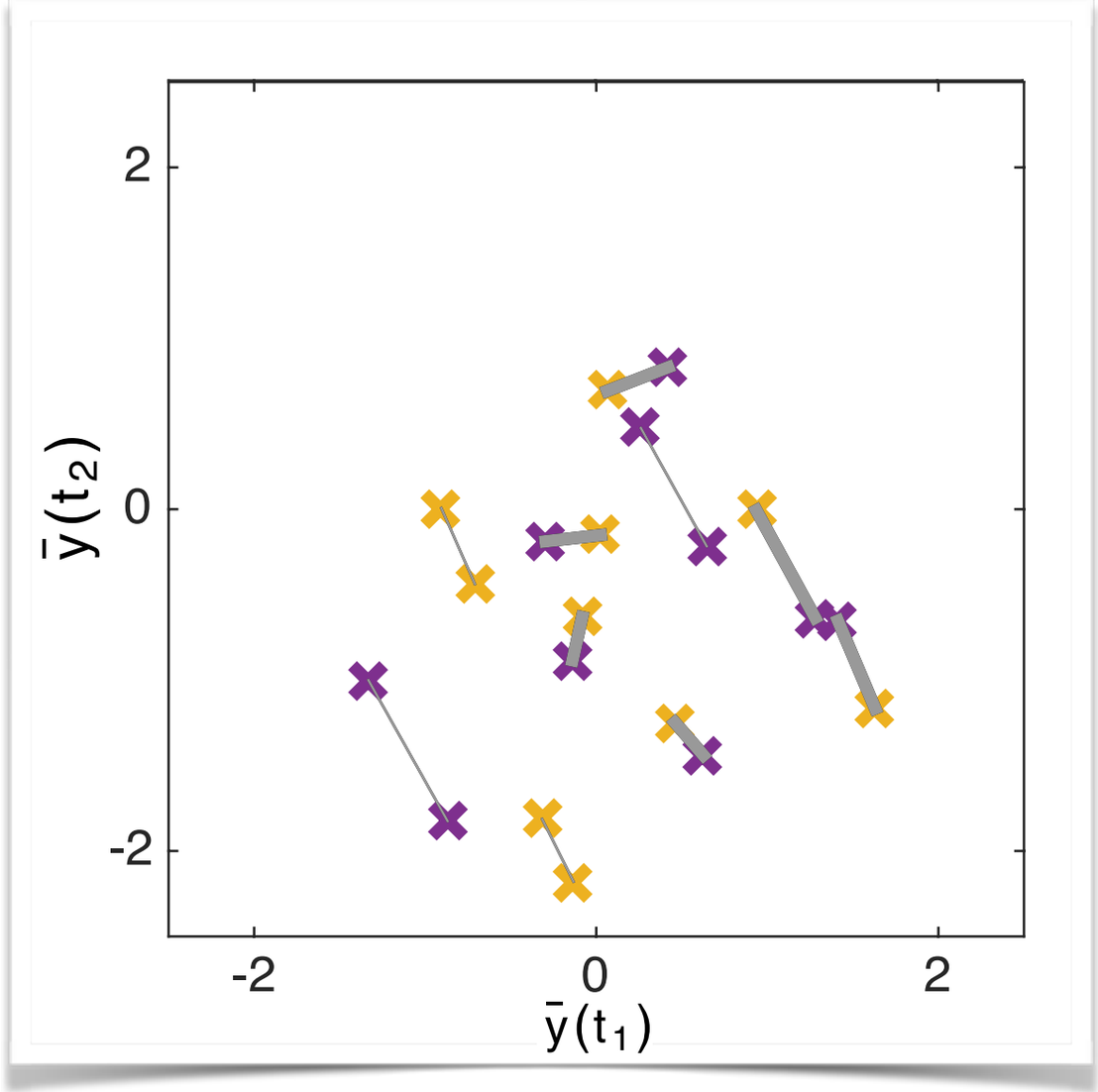

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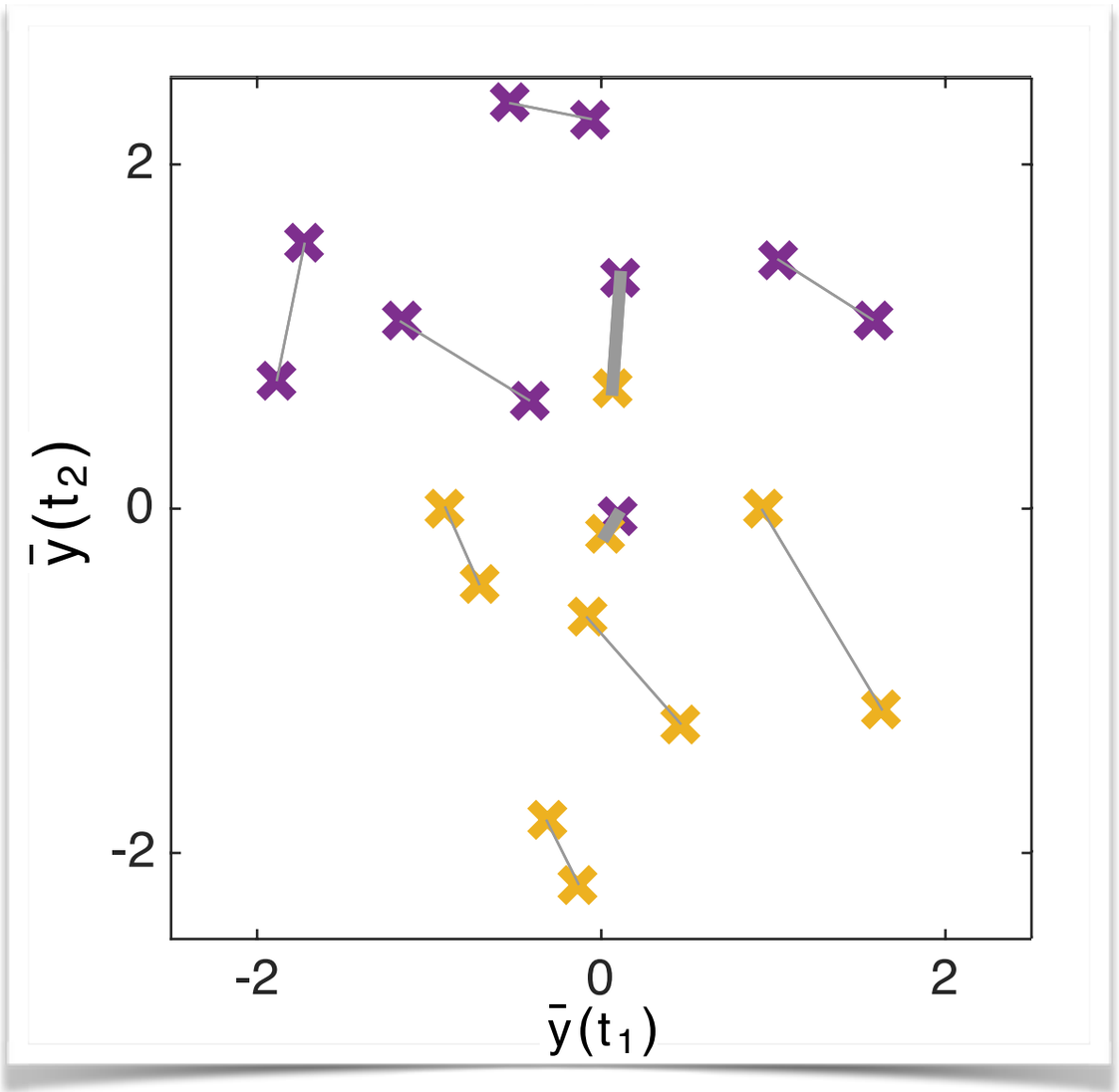

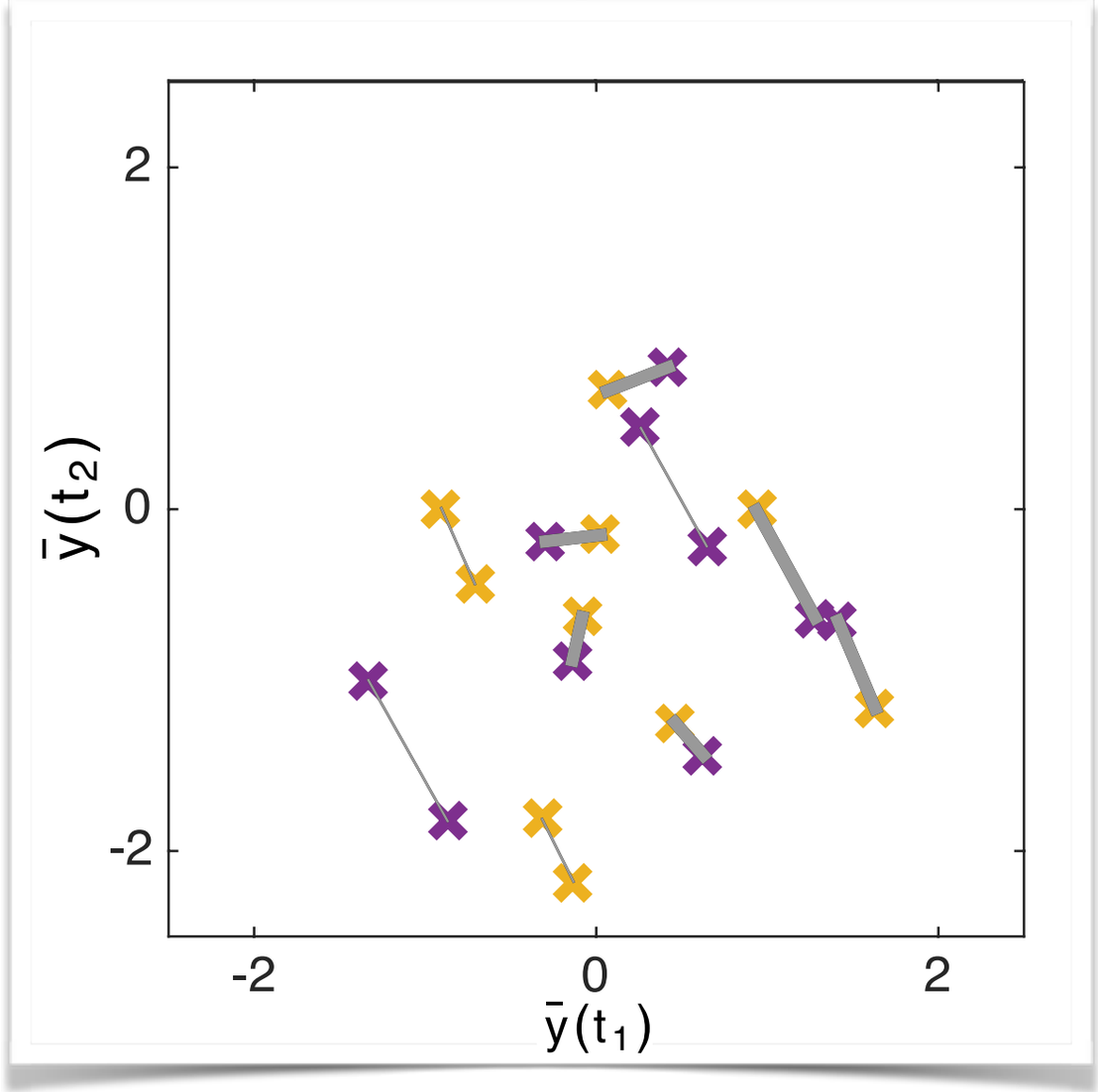

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Accept parameters that produce more cross-matches

Rosenbaum, Journal of the Royal Statistical Society (2005)

Maximum Mean Discrepancy (MMD)

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$$\text{MMD} = \left(\frac{1}{n^2} \sum_{i \neq j}^{n} k(\mathbf{x}_i, \mathbf{x}_j) + \frac{1}{m^2} \sum_{i \neq j}^{m} k(\mathbf{y}_i, \mathbf{y}_j) - \frac{2}{nm} \sum_{i,j=1}^{n,m} k(\mathbf{x}_i, \mathbf{y}_j) \right)^{\frac{1}{2}}$$

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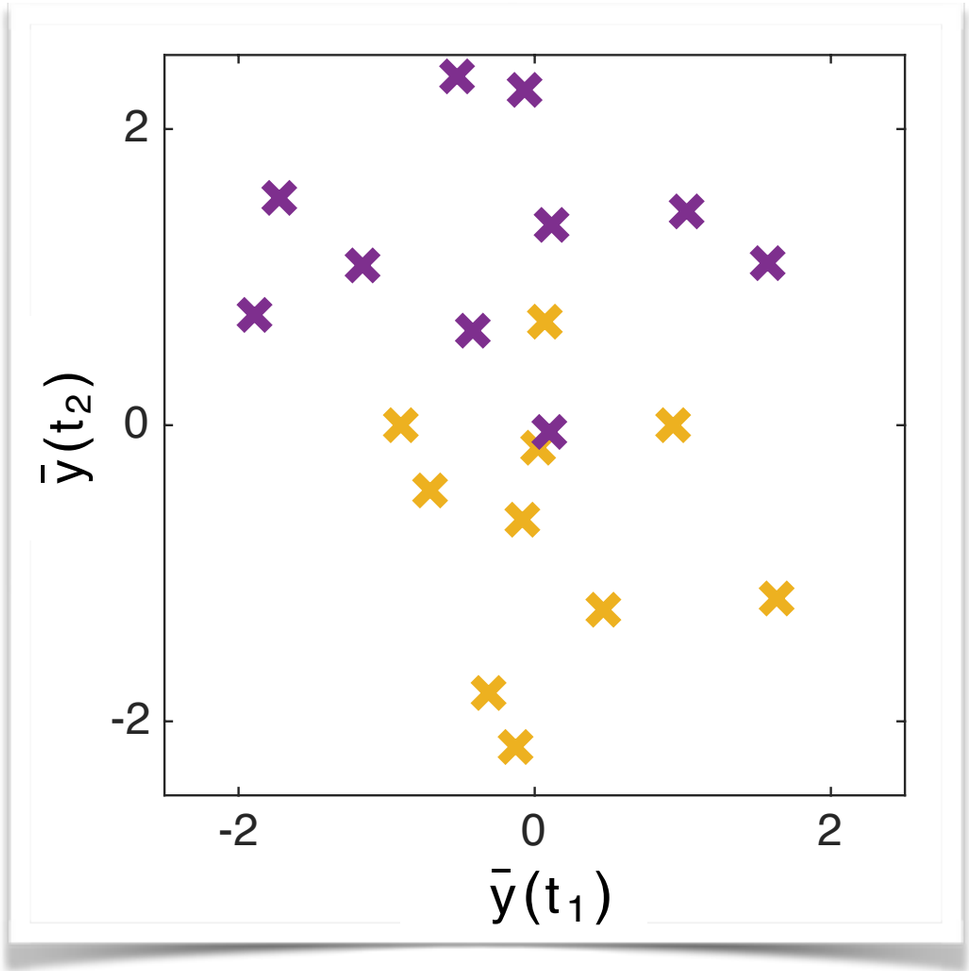

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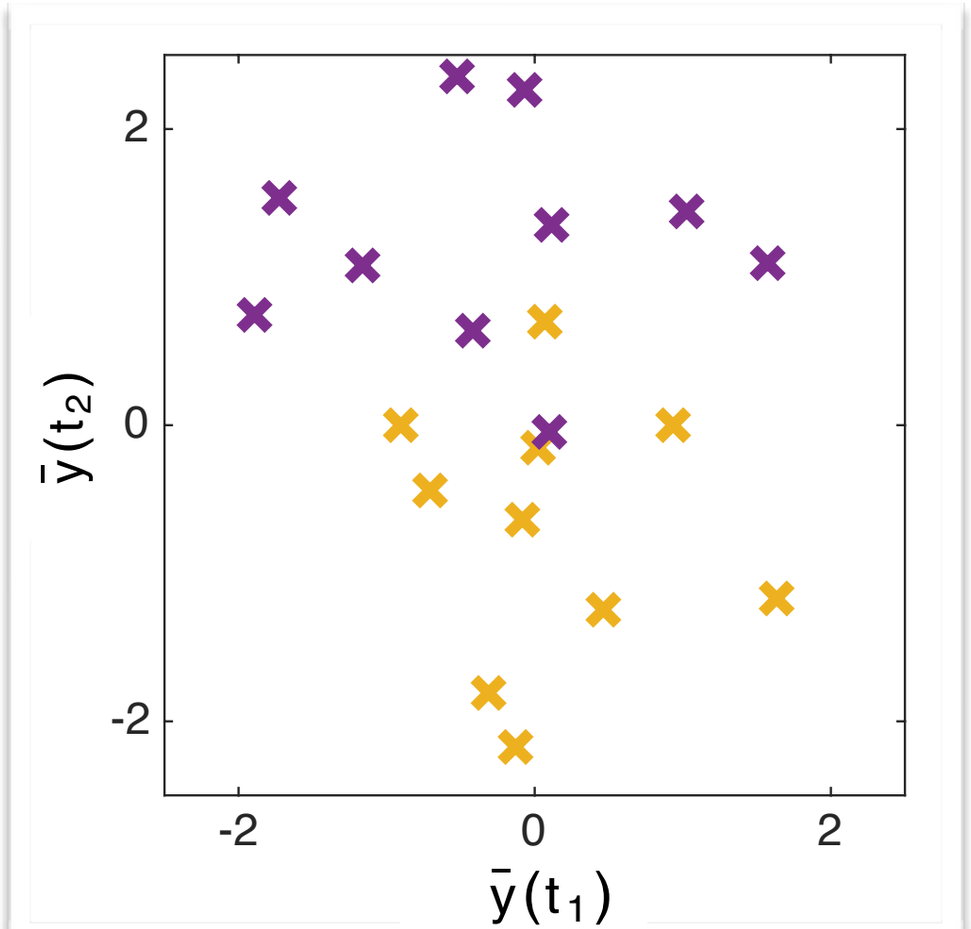

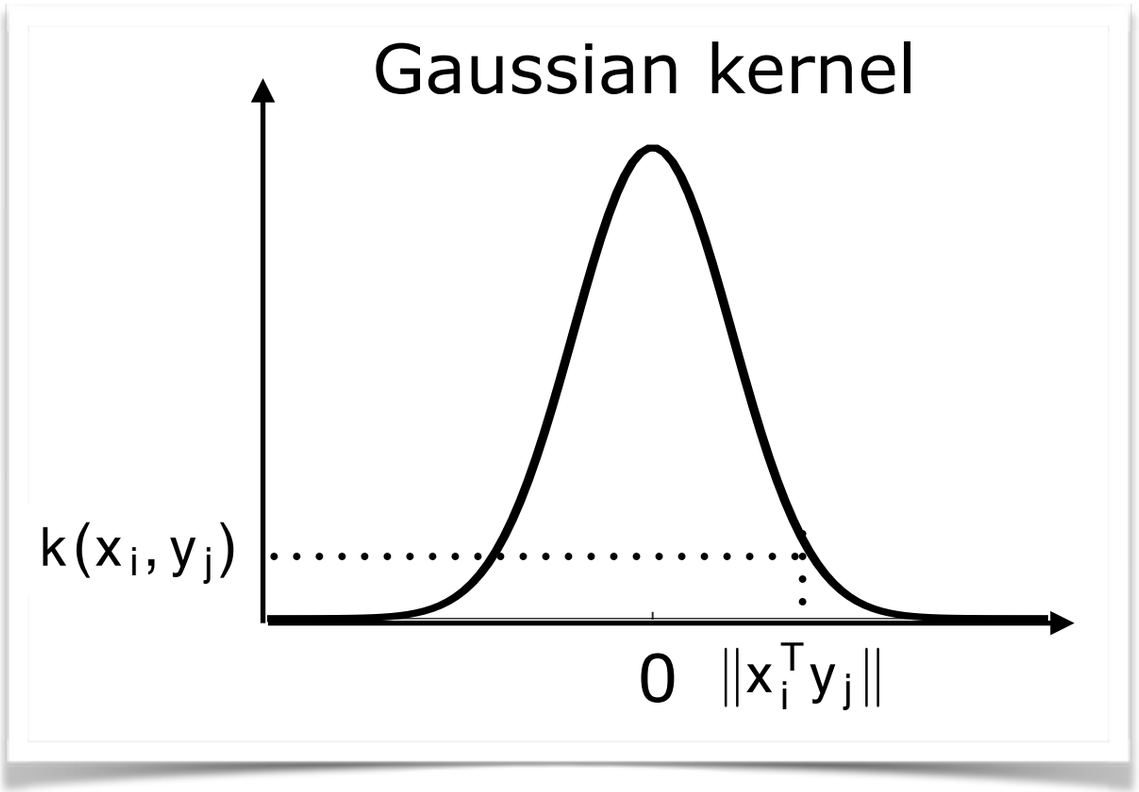

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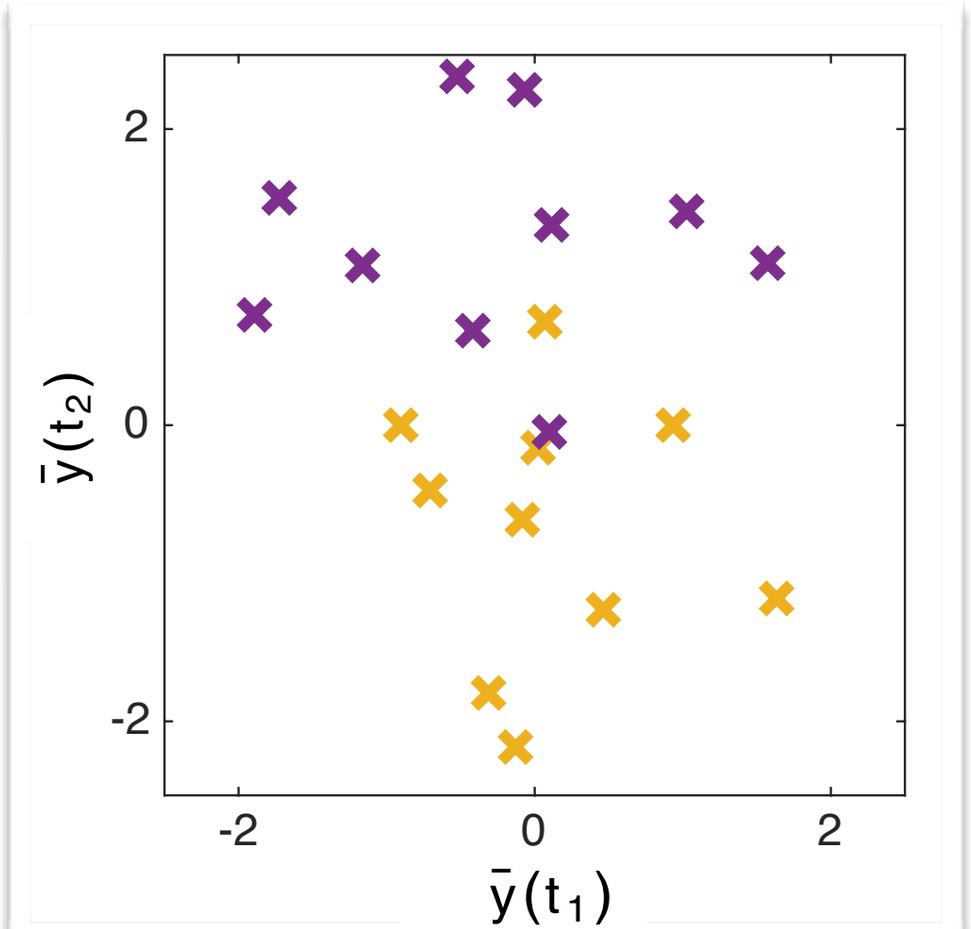

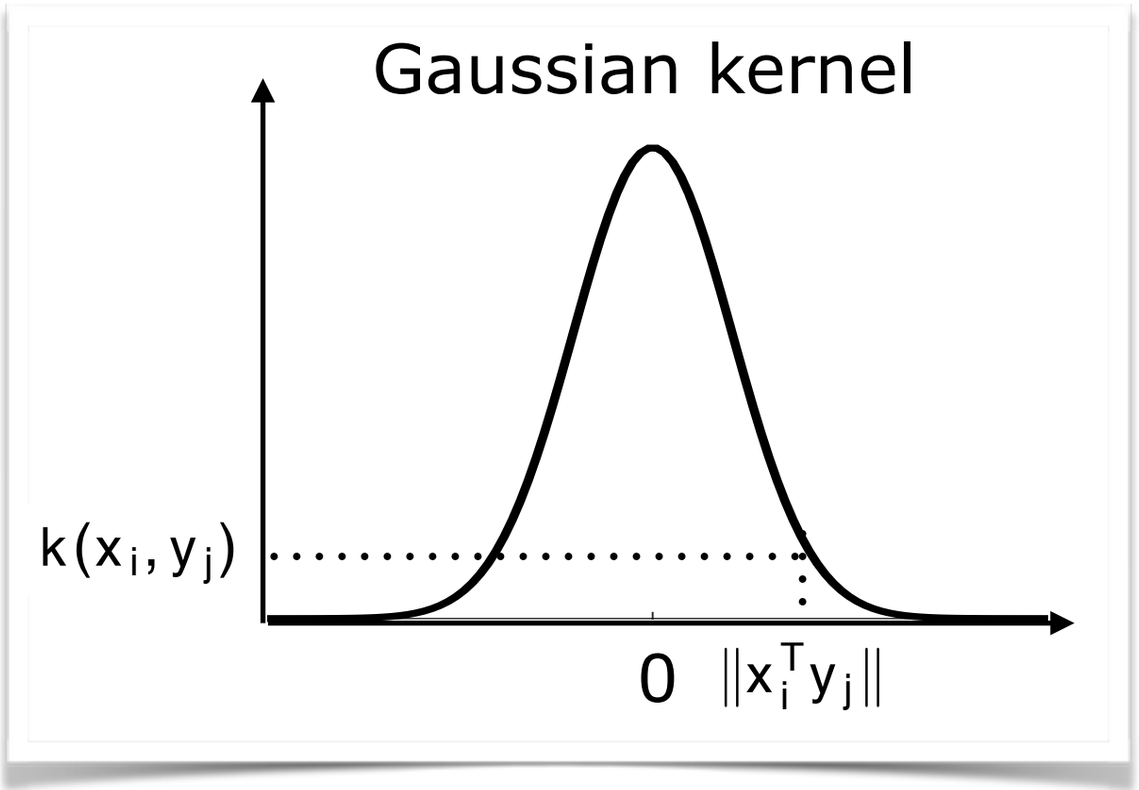

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- simulated samples $y_1, \ldots, y_m$

Accept parameters that produce a small MMD

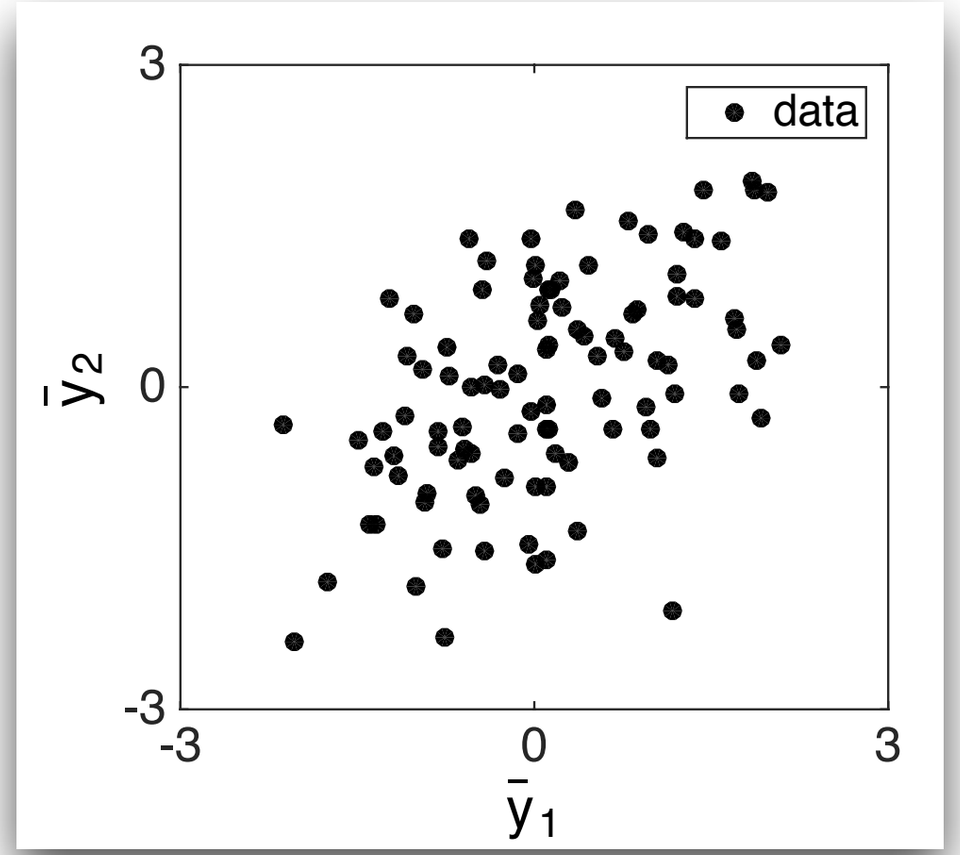
Borgwardt et al., Bioinformatics (2006)

Example: Bivariate Normal Distribution

Example: Bivariate Normal Distribution

Data: 100 samples of a bivariate normal distribution $\bar{y} \sim N(\mu, \Sigma)$

with $\mu = \begin{pmatrix} 0 \\ 0 \end{pmatrix}$ and $\Sigma = \begin{pmatrix} \theta_1 & \theta_2 \\ \theta_2 & \theta_1 \end{pmatrix}$



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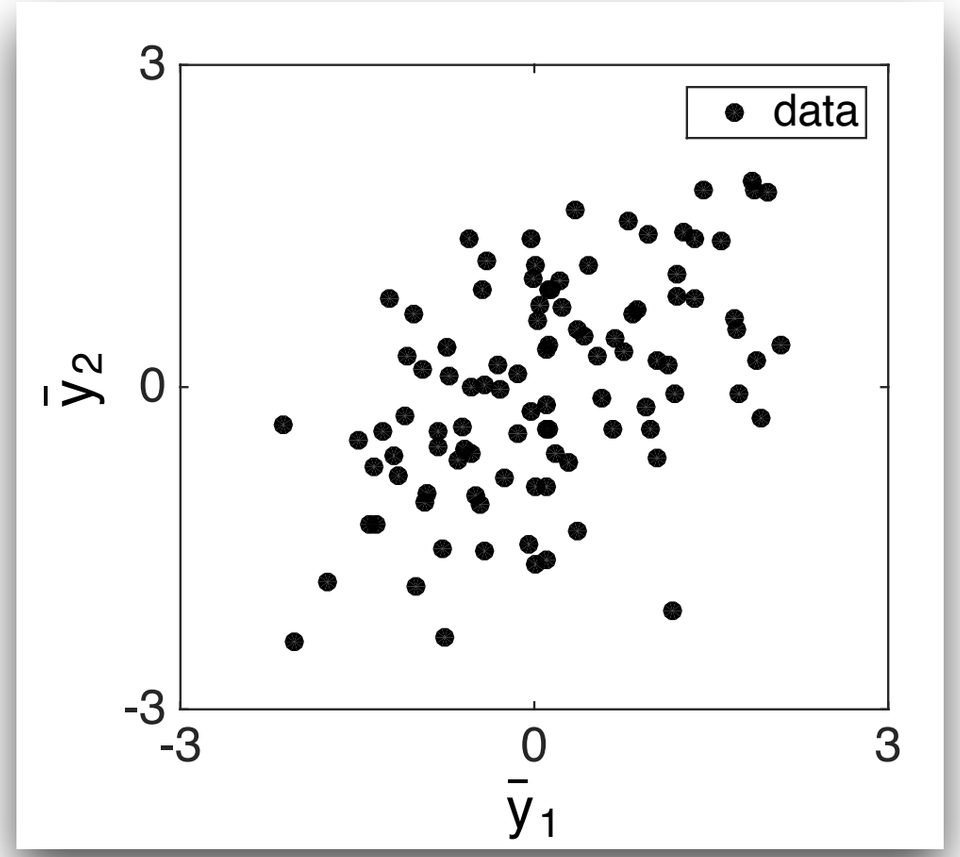

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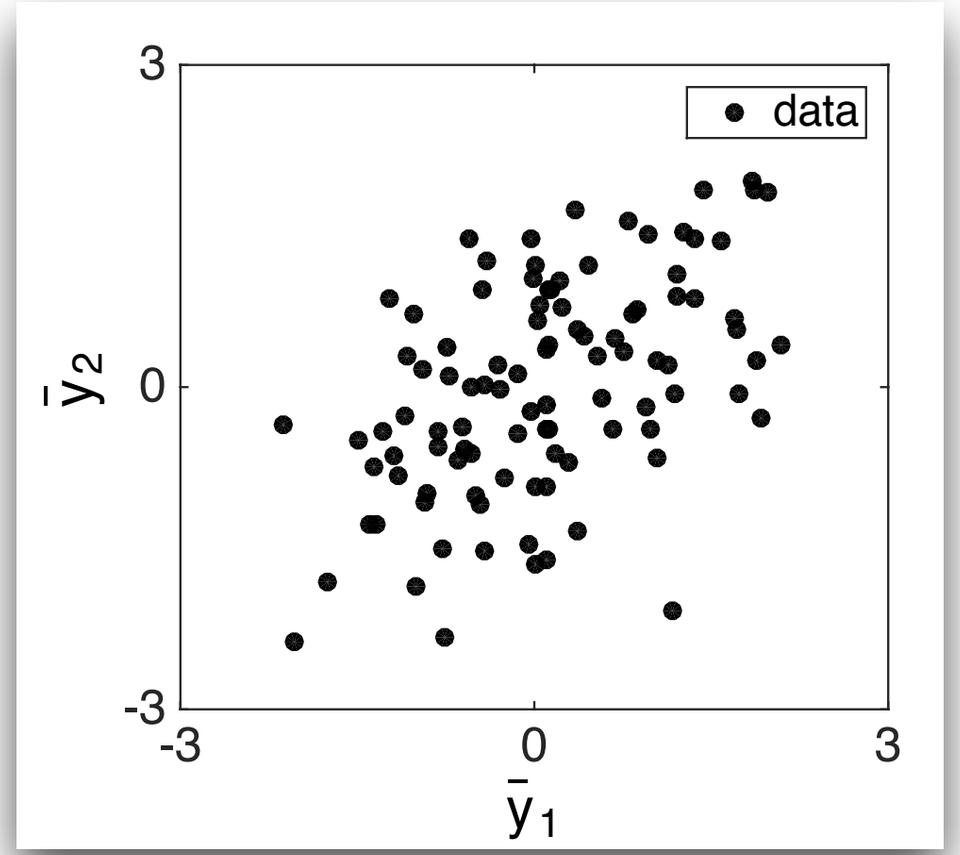
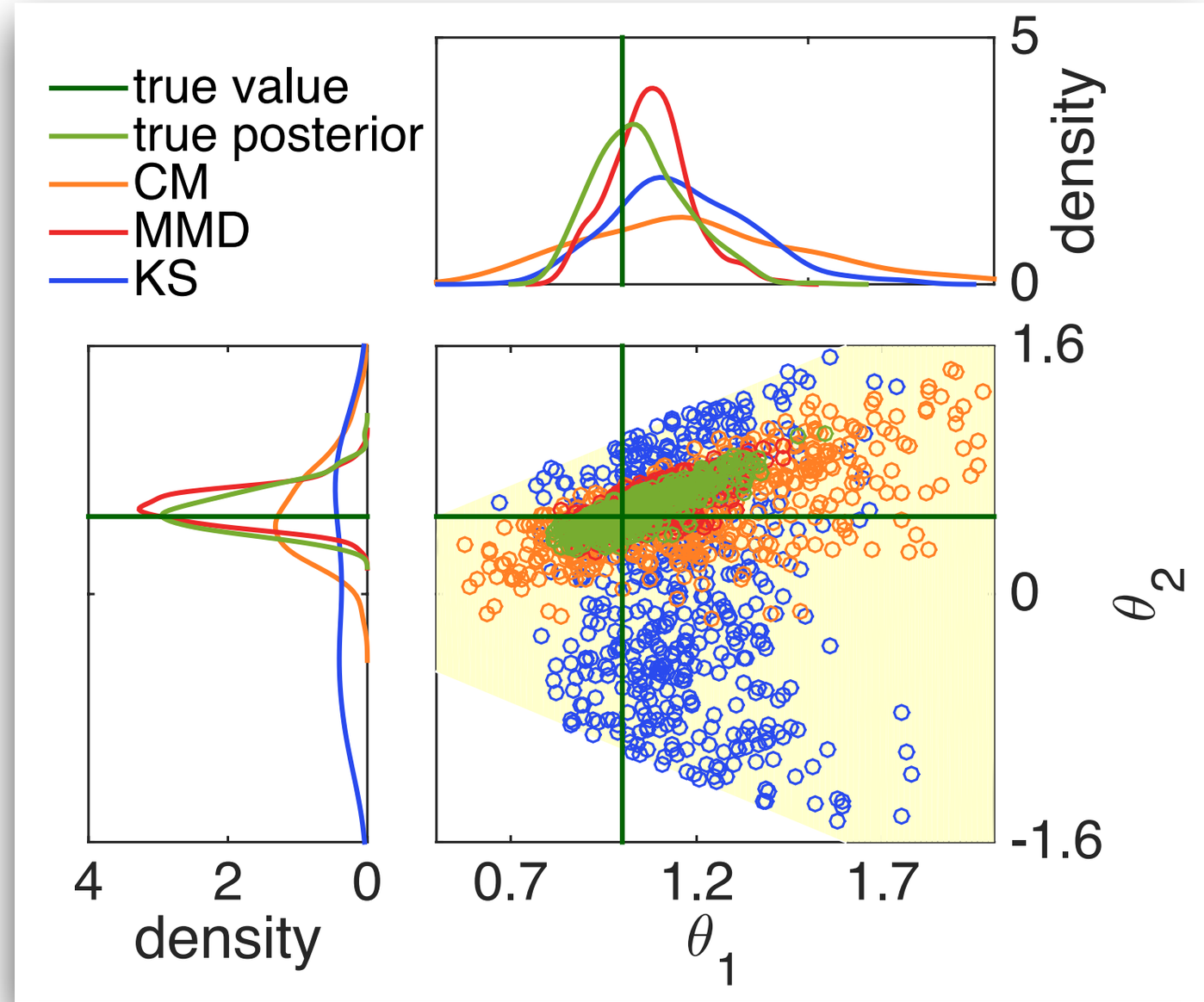


Compare ABC SMC with cross-match test (CM), maximum mean discrepancy (MMD), and maximal Kolmogorov-Smirnov distance (KS)

Posterior approximations

Posterior approximations



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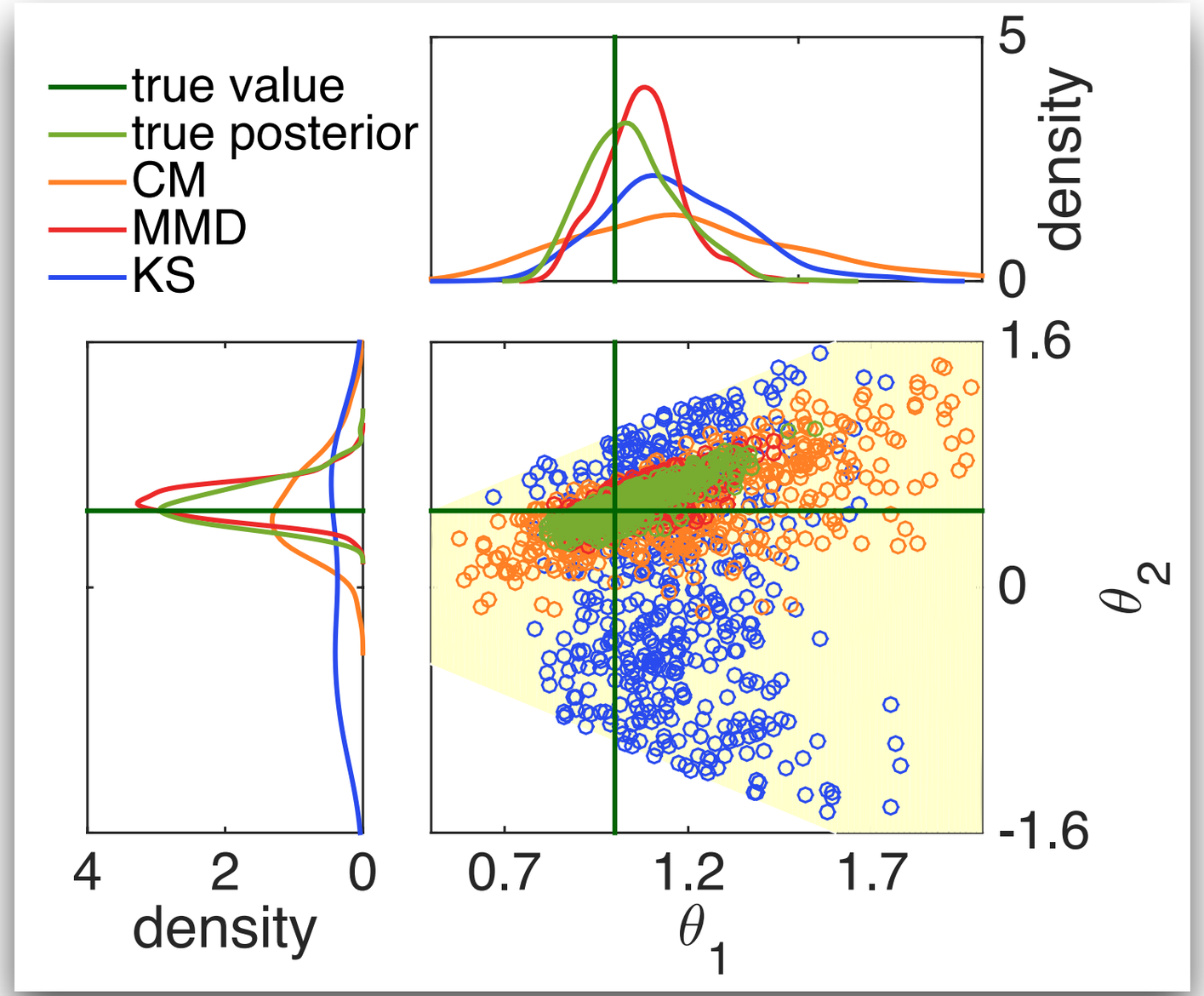
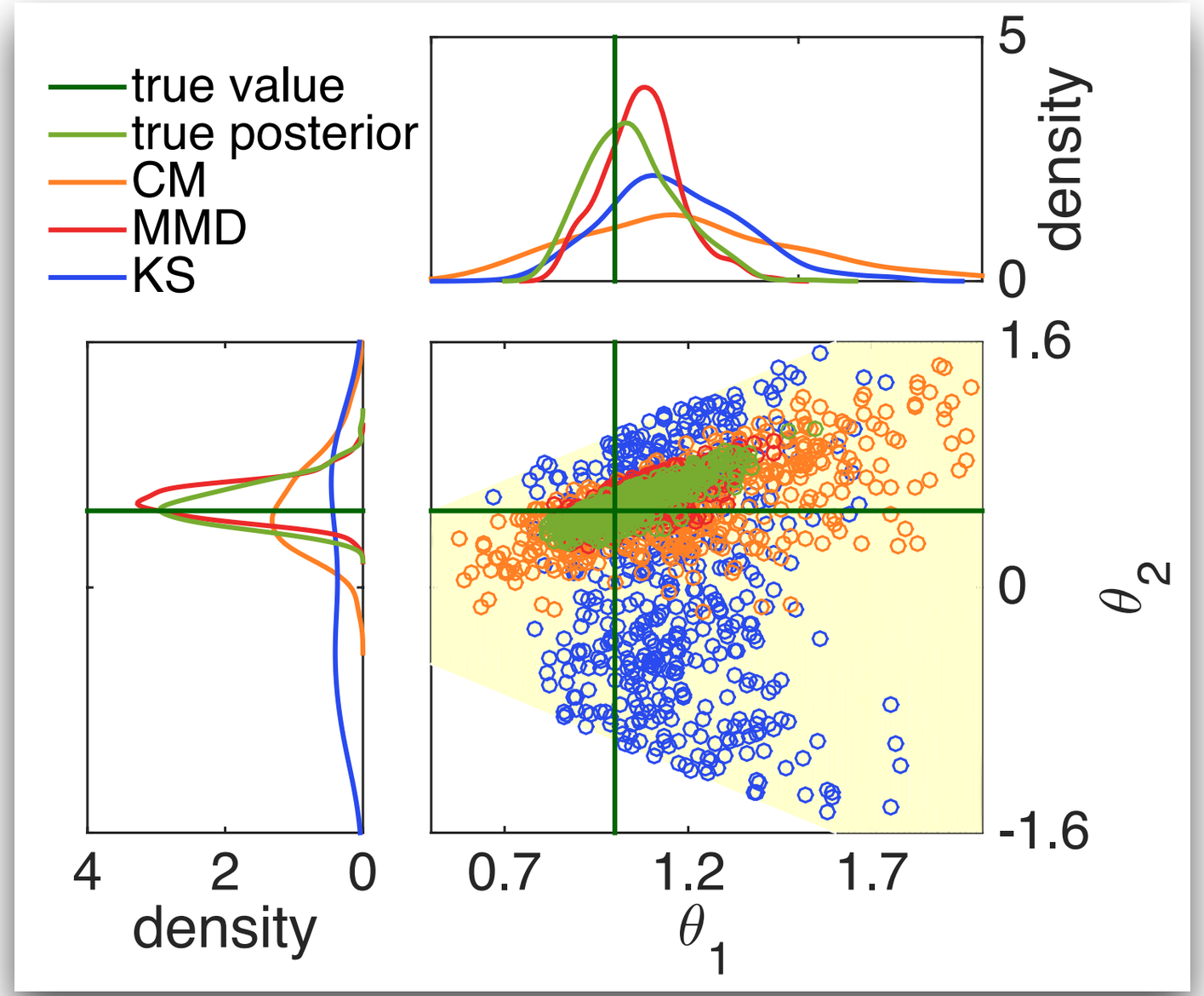


- For KS only θ_1 is identifiable

Posterior approximations



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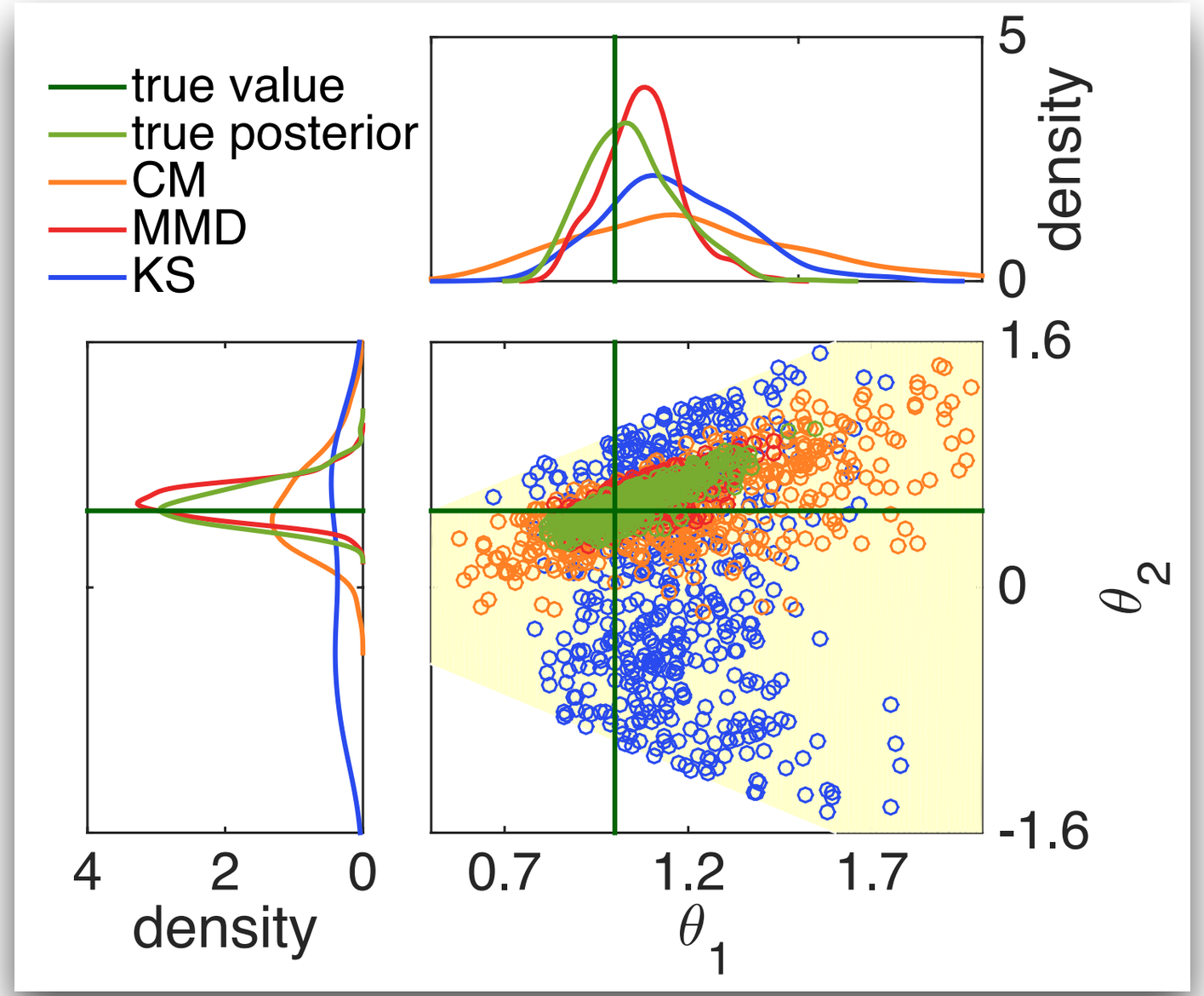
Posterior approximations



- For KS only θ_1 is identifiable
- CM gives a wider posterior approximation
- Only MMD gives a reasonable posterior approximation

Artificial single-cell time-lapse data

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- One stage model of gene expression with mRNA synthesis rate λ and degradation rate γ

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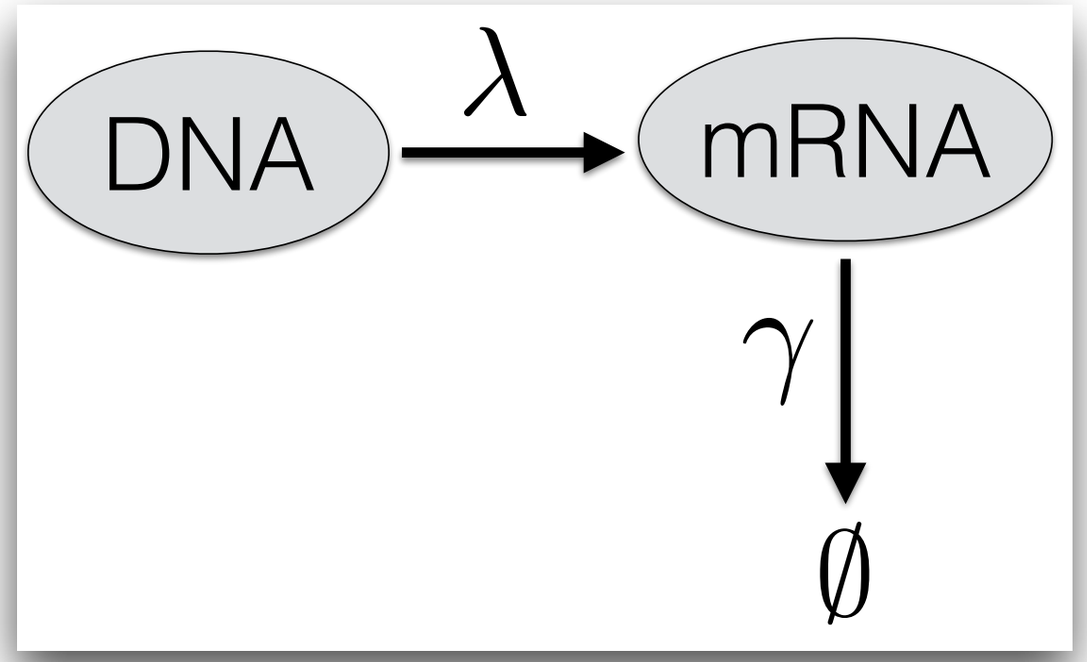
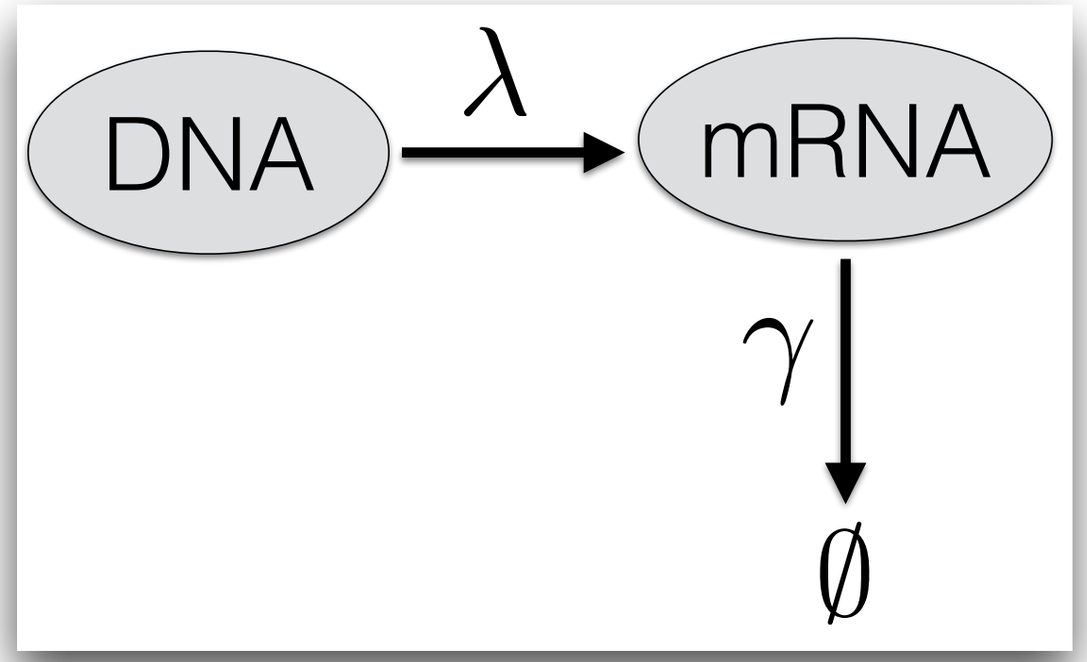


Artificial single-cell time-lapse data

- One stage model of gene expression with mRNA synthesis rate λ and degradation rate γ
- Comparison of ABC SMC with multivariate statistics (MMD) and univariate statistics (KS)



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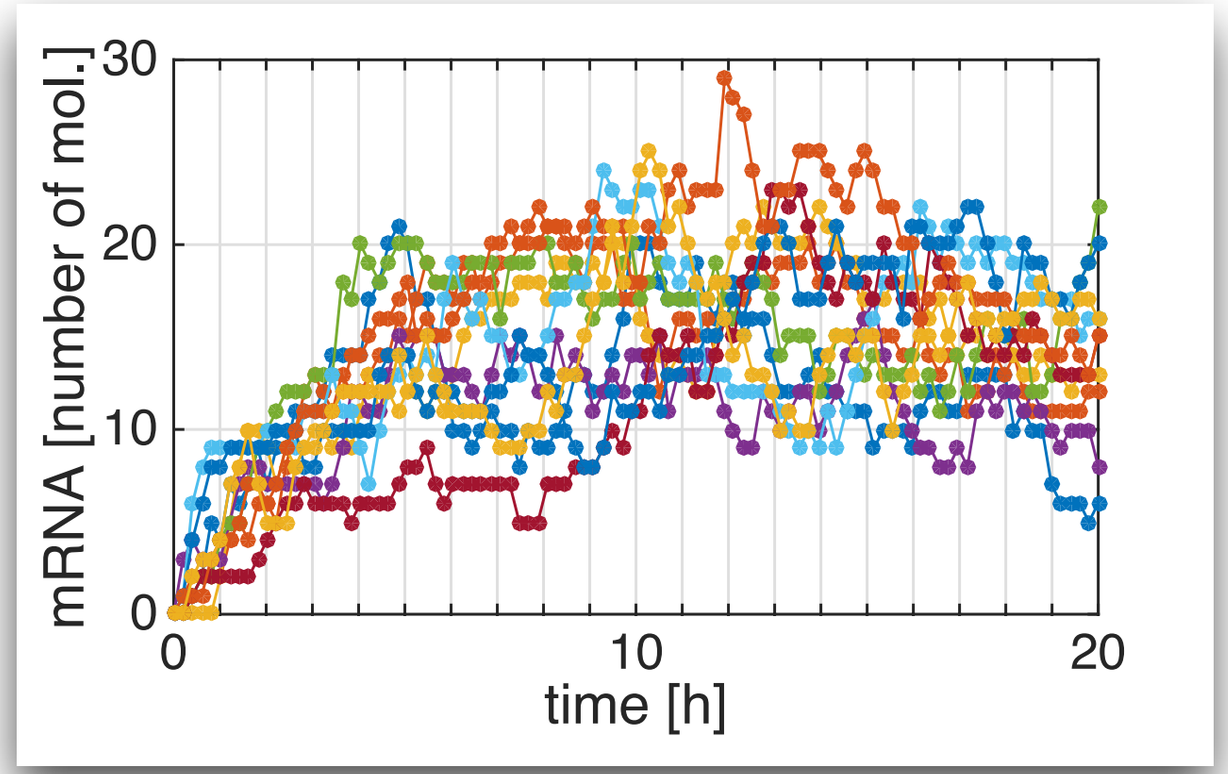
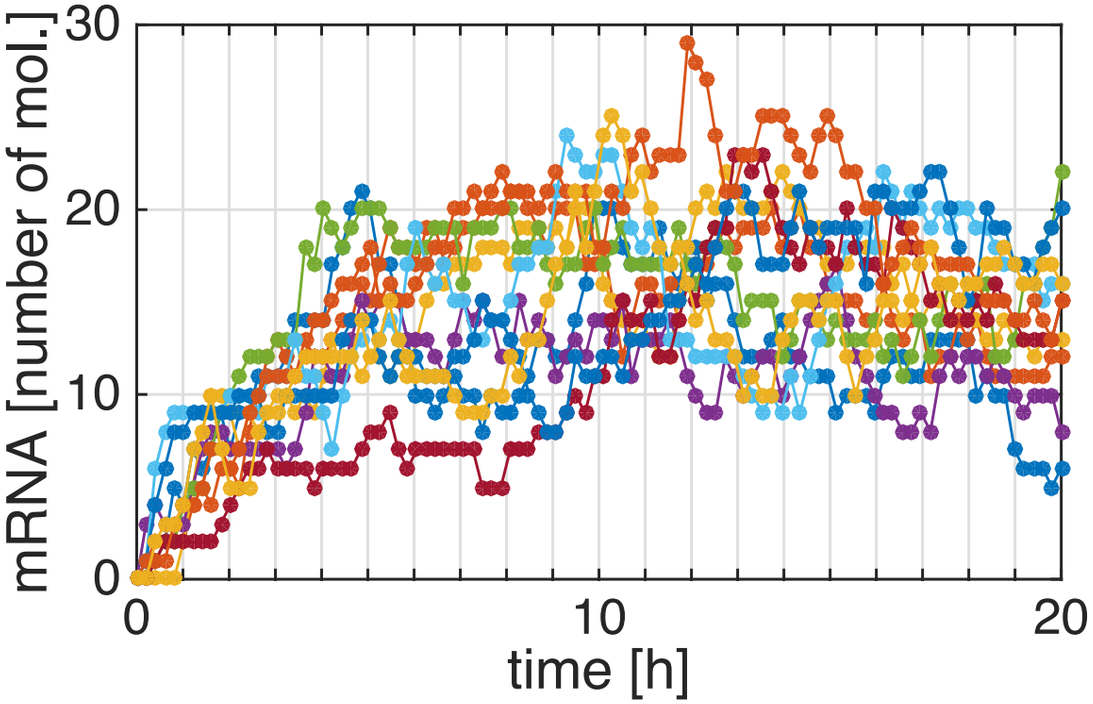


Non-equilibrium time-series

Artificial single-cell time-lapse data



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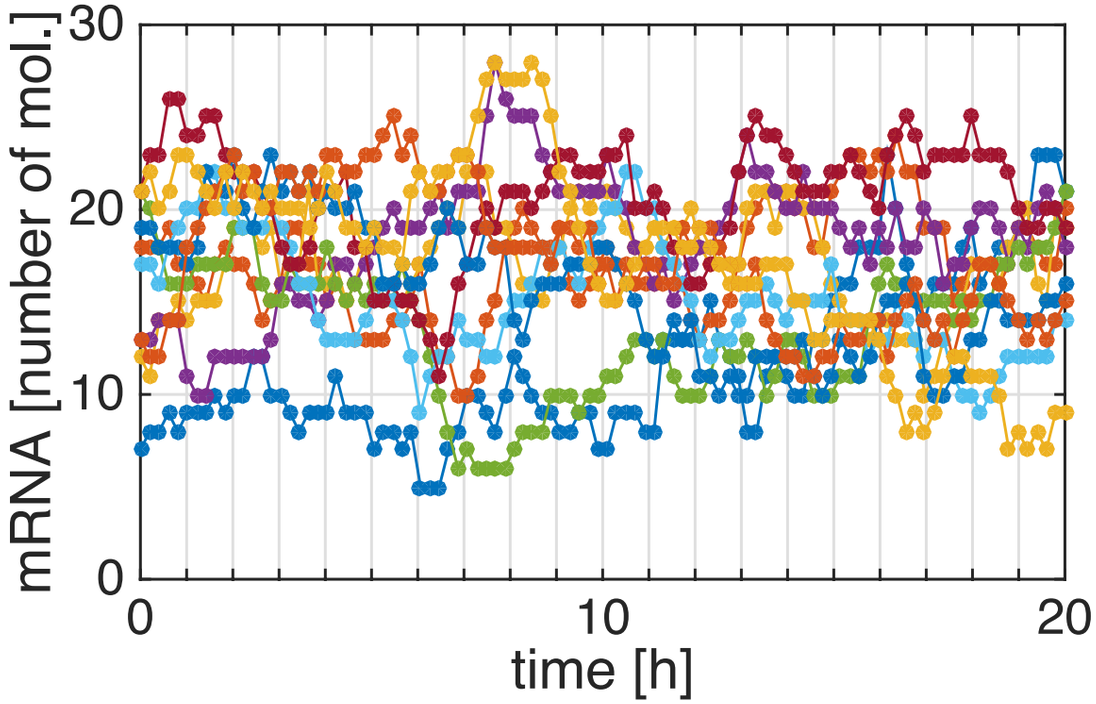
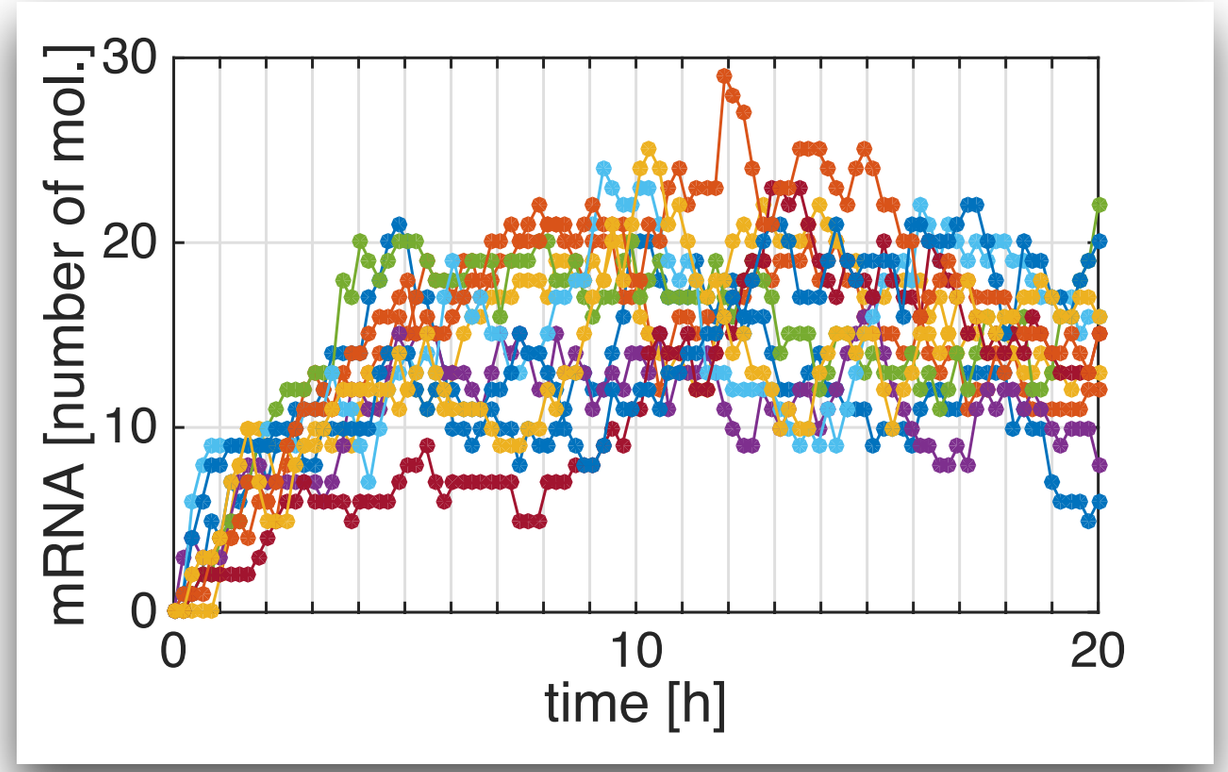


Equilibrium time-series

Artificial single-cell time-lapse data



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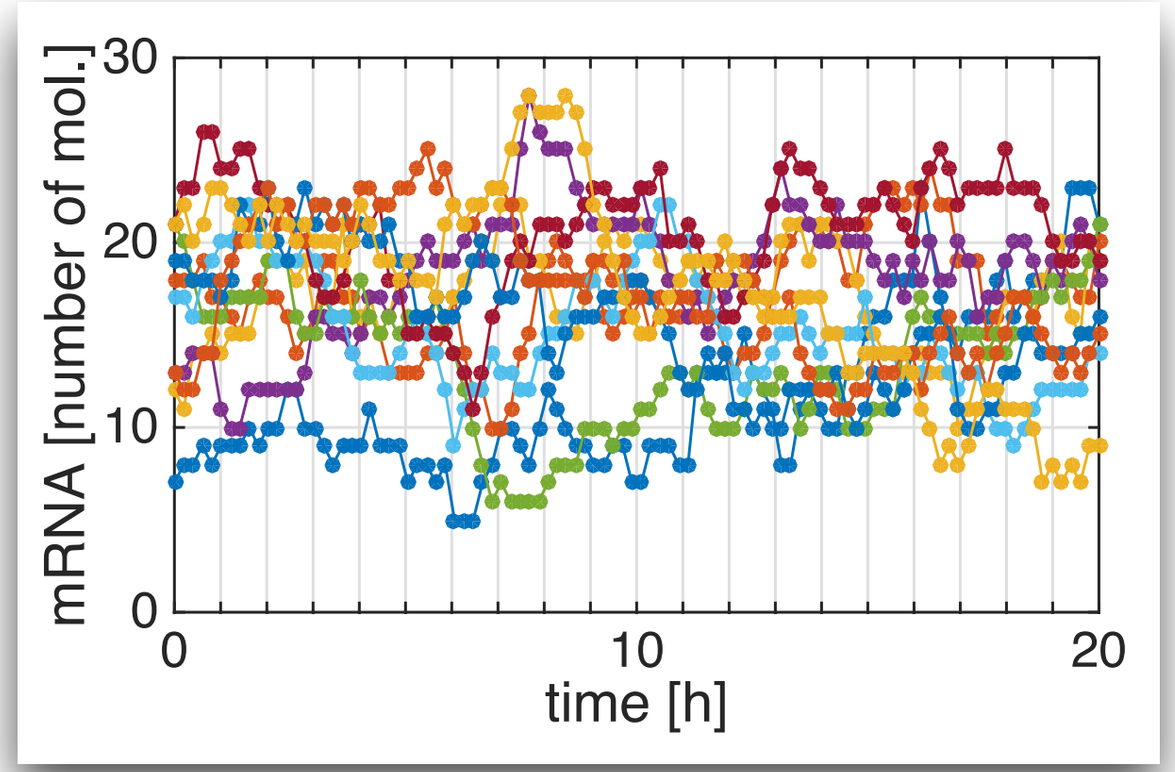

Equilibrium time-series

- Generate time-series using the Stochastic Simulation Algorithm [1]

1 Gillespie, Annual Review of Physical Chemistry (2007)

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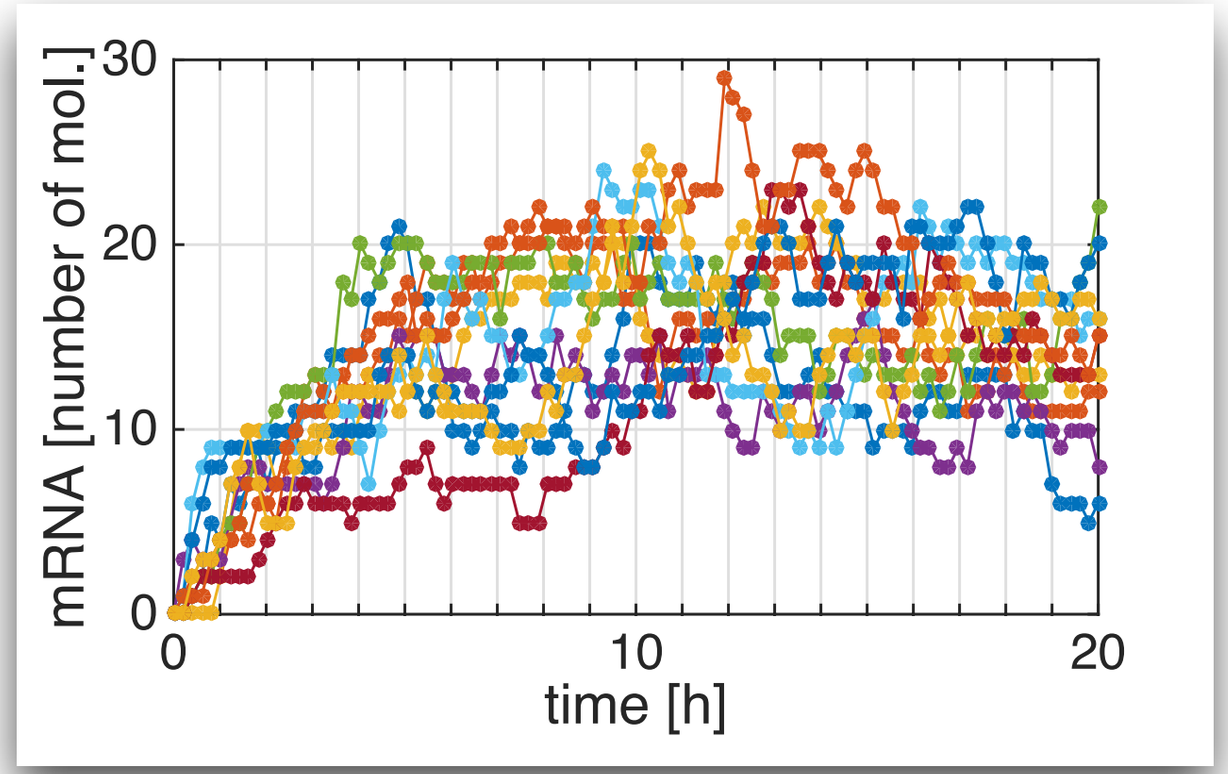

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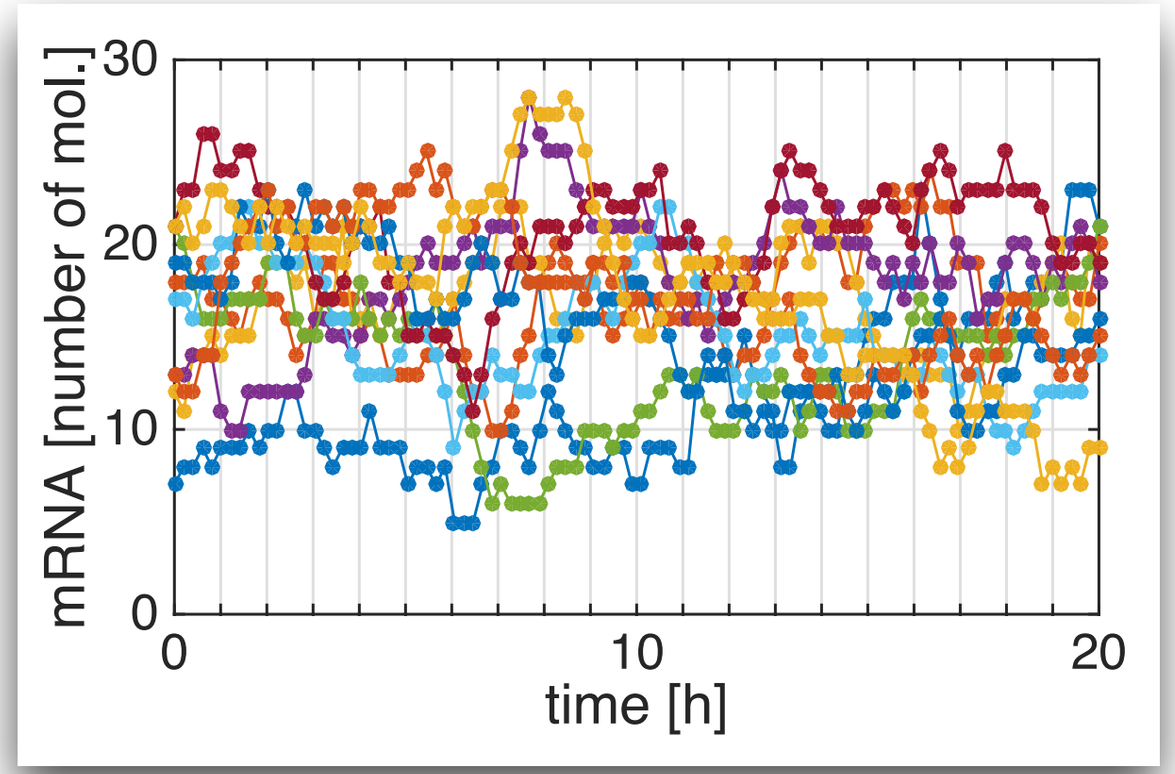


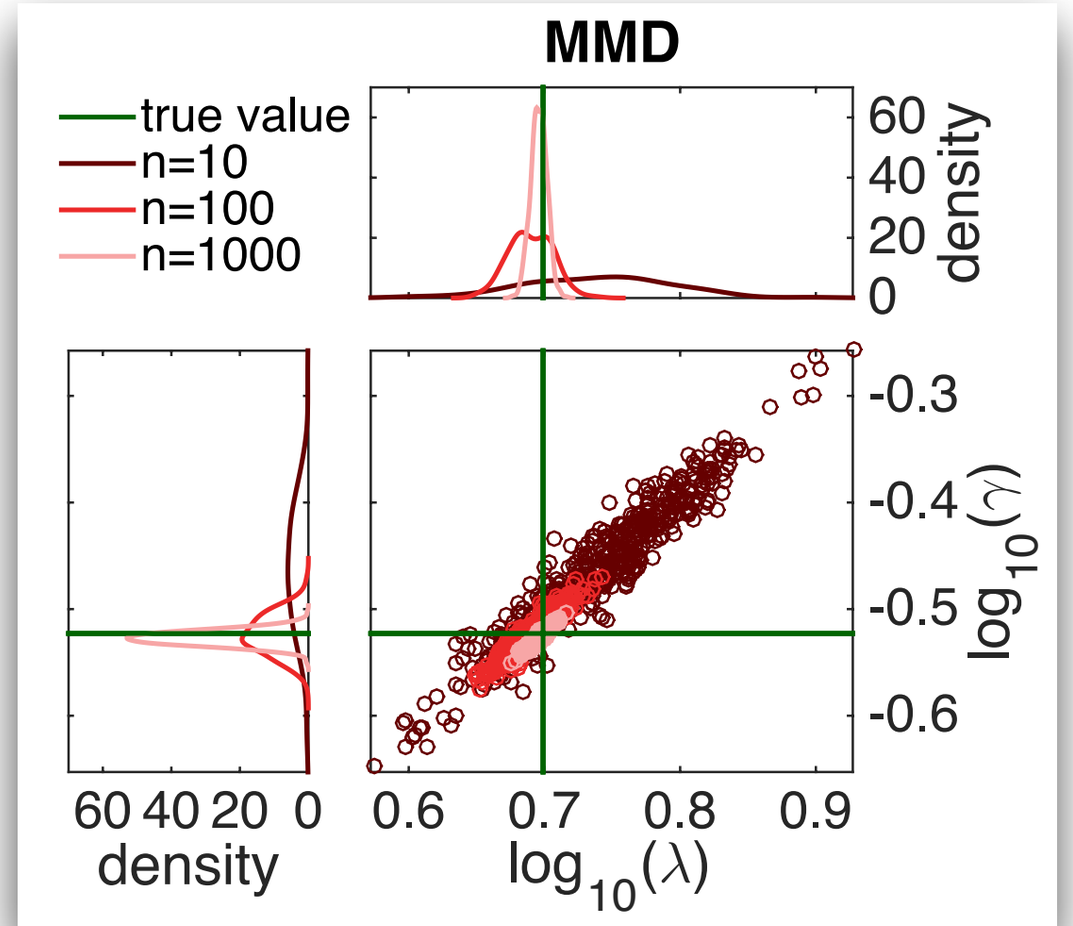
Equilibrium time-series

- Generate time-series using the Stochastic Simulation Algorithm [1]
- Consider 10, 100, 1000 cells and equilibrium and non equilibrium time-series

1 Gillespie, Annual Review of Physical Chemistry (2007)

Posterior approximations for non-equilibrium time-series

Posterior approximations for non-equilibrium time-series



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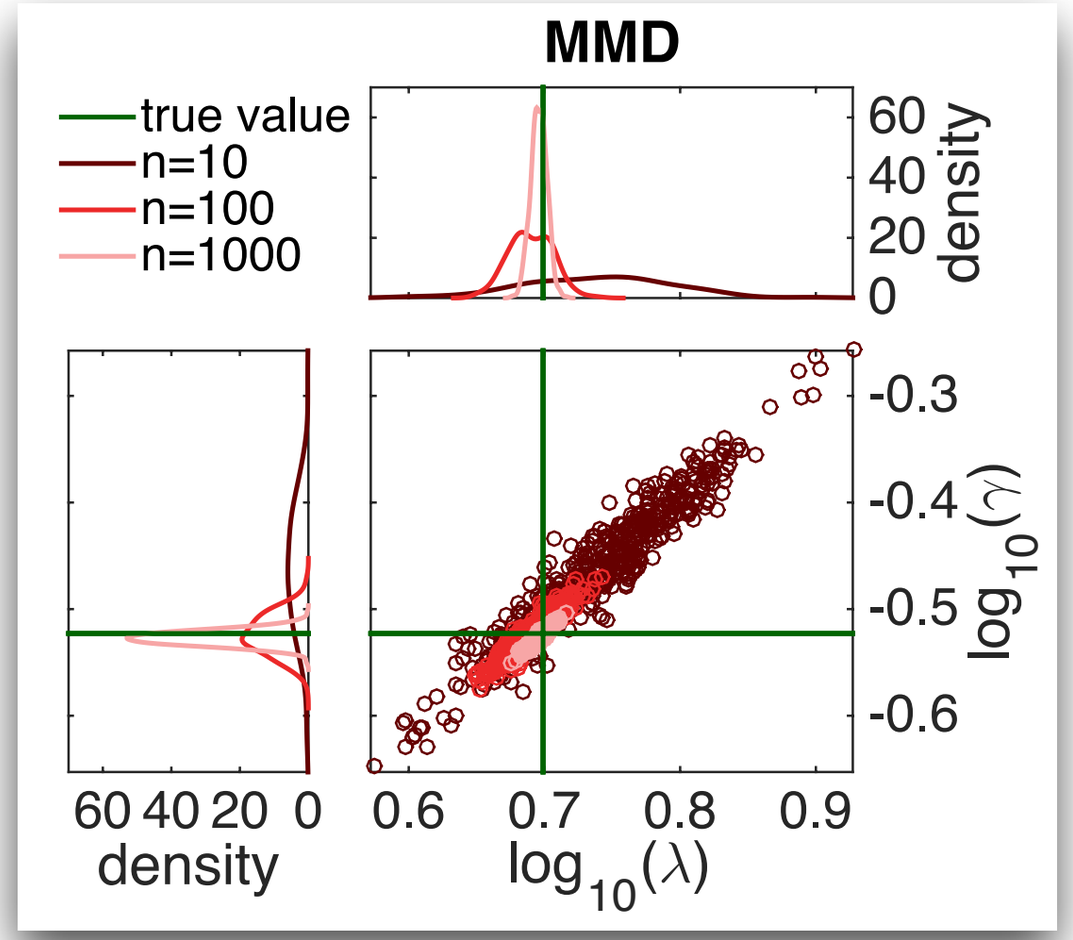

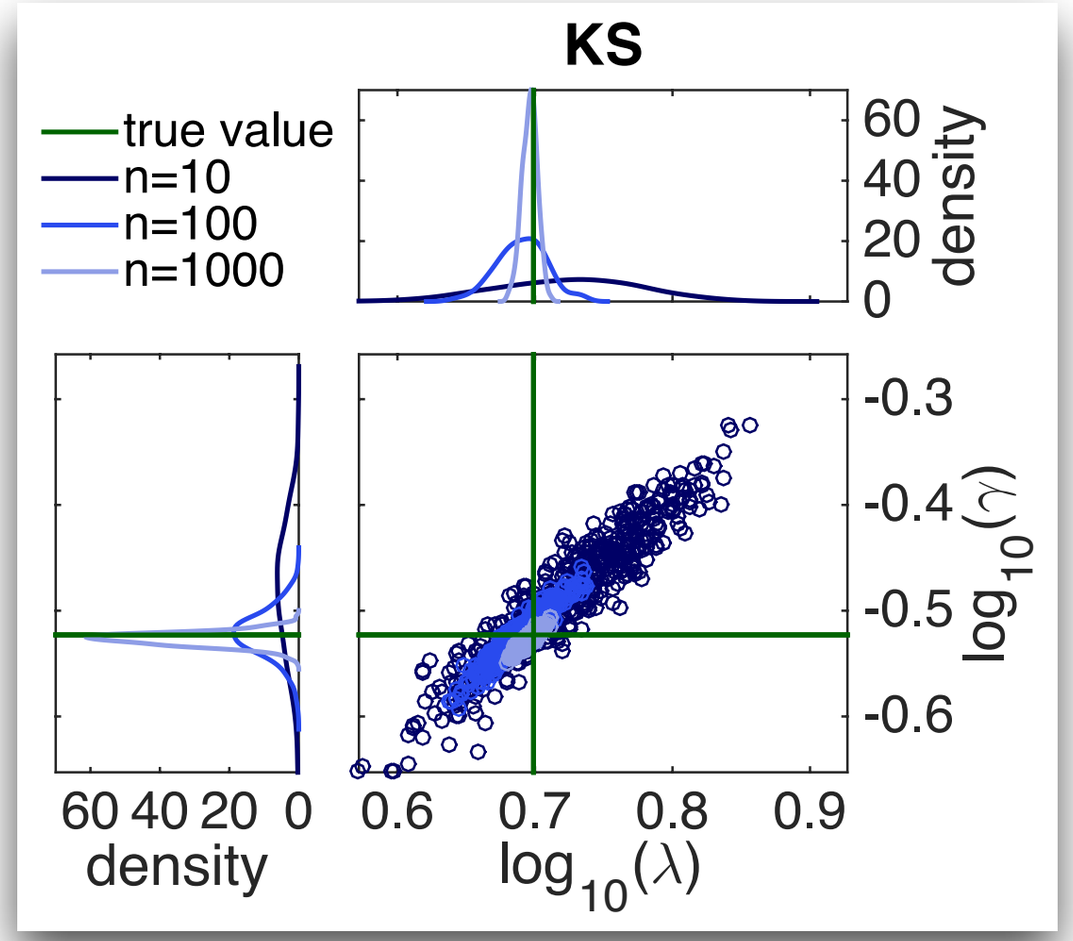

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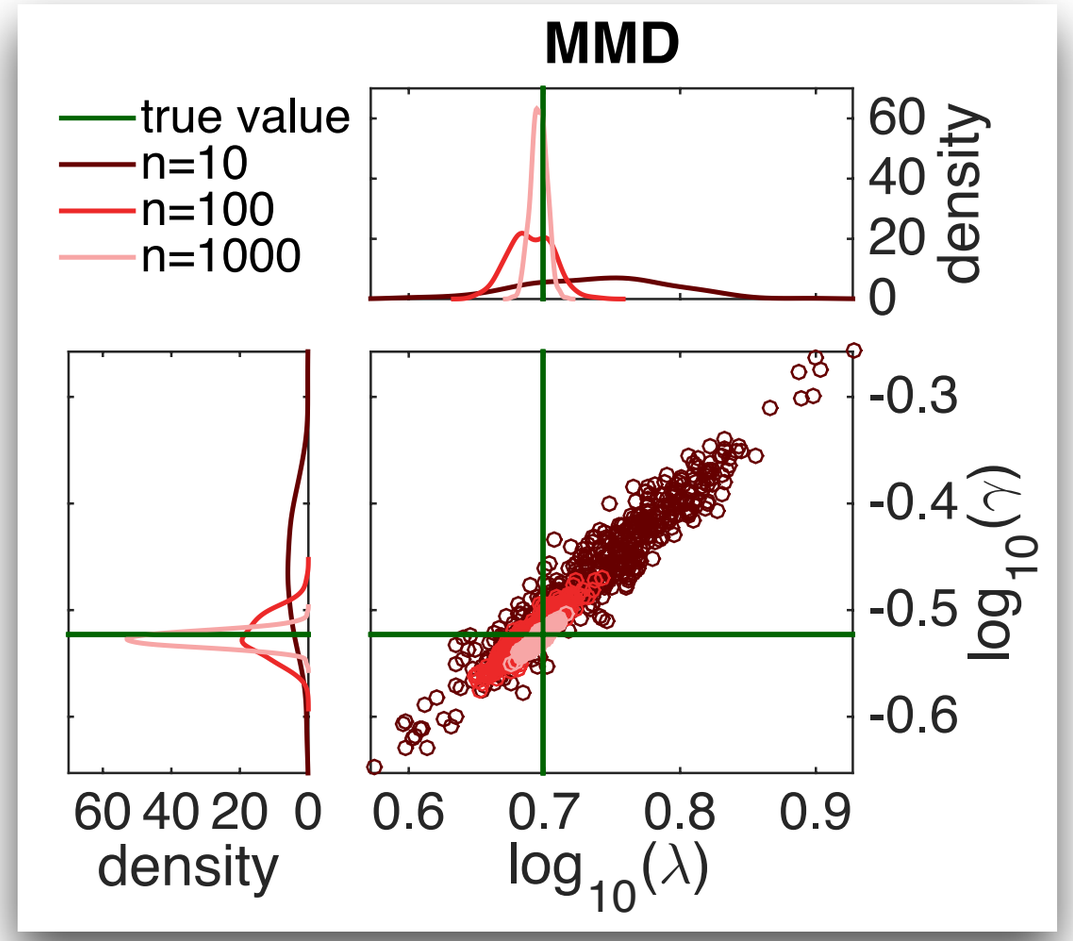
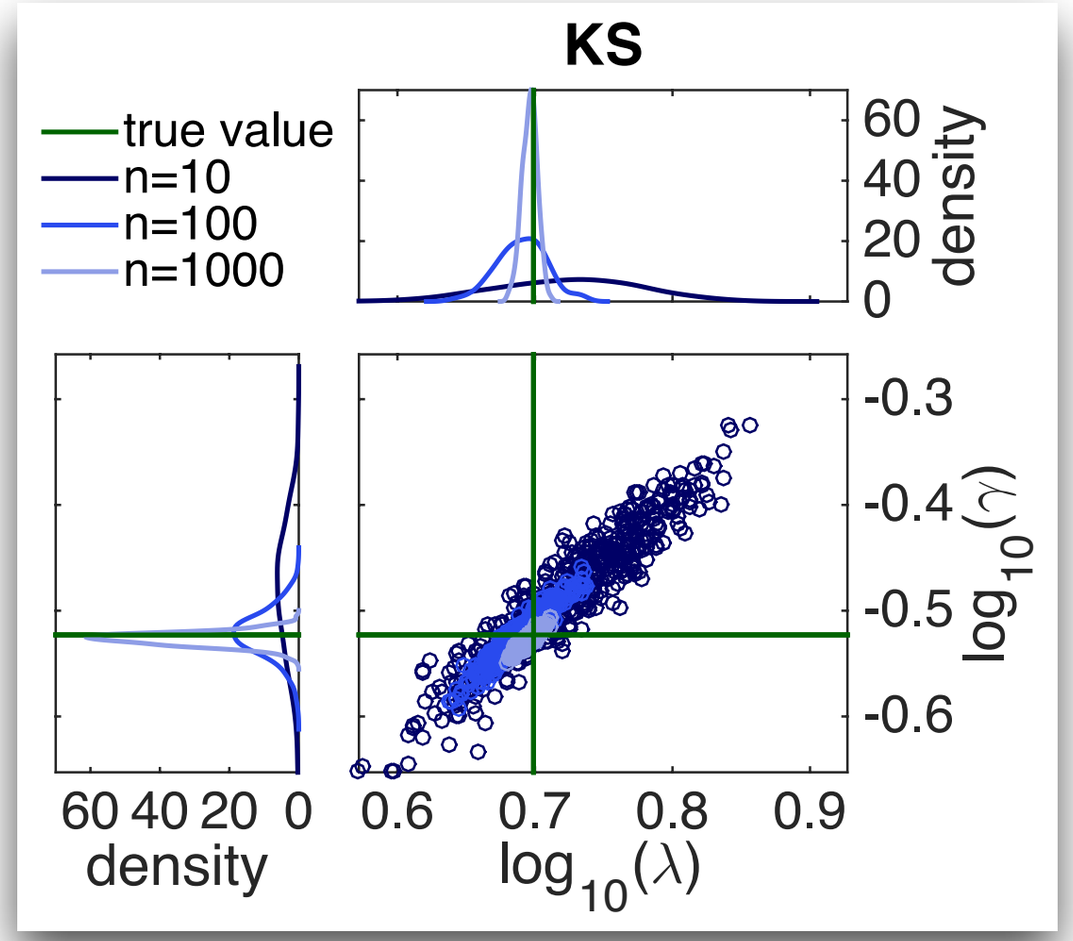
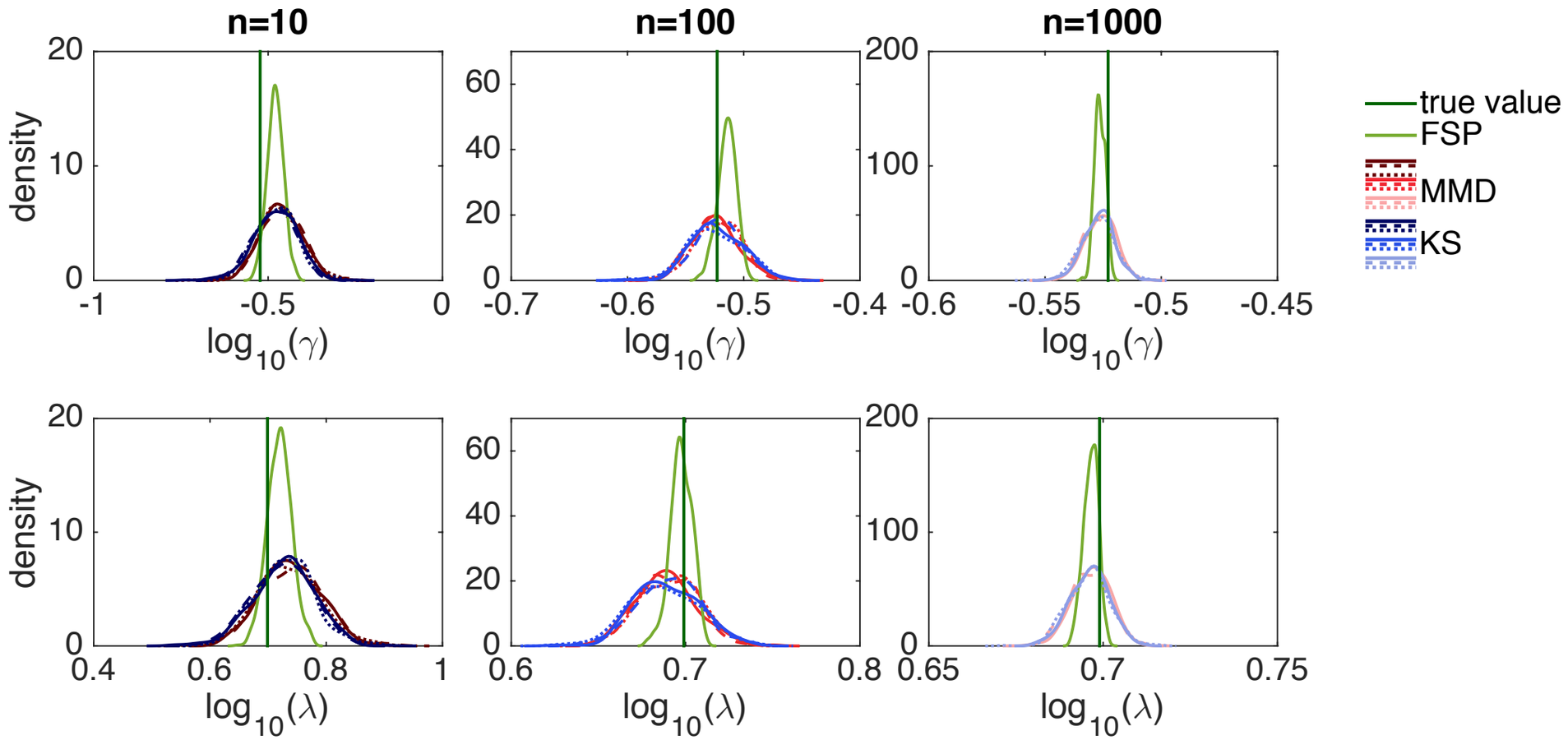




MMD and KS perform similar

Posterior approximations for non-equilibrium time-series



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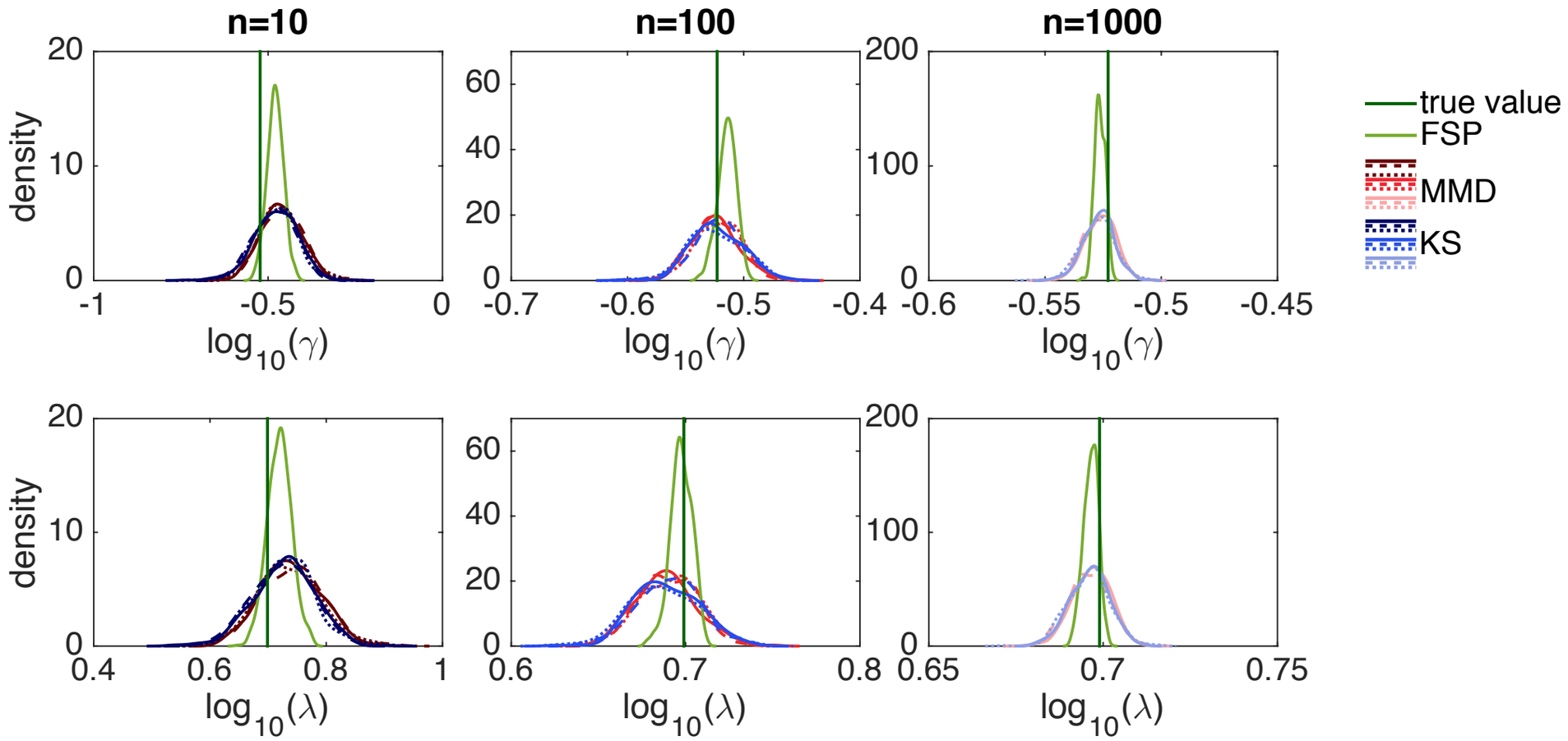

- Comparison of posterior approximation with Finite State Projection (FSP)[1]

1 Munsky et al., J. Chem. Phys. (2006)

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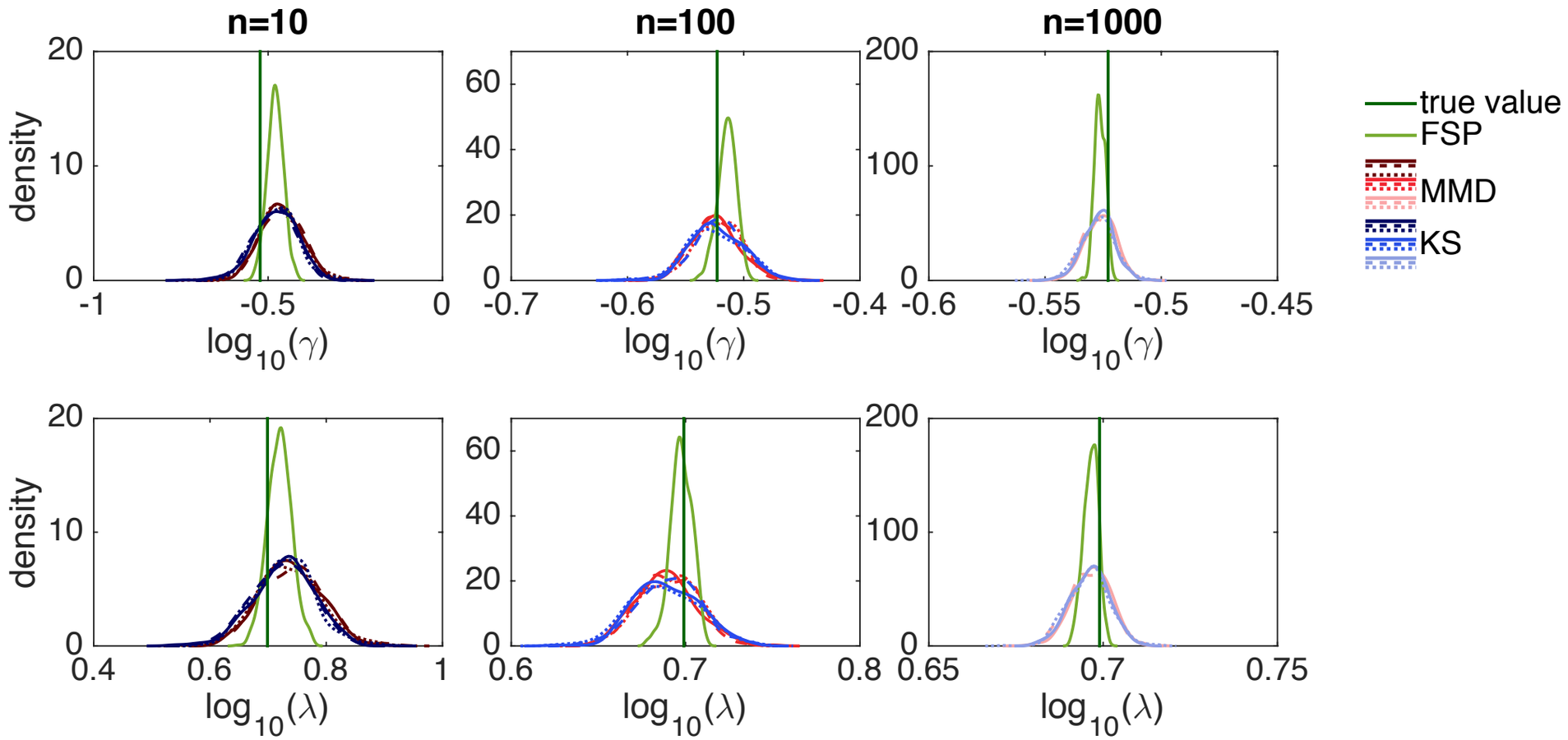

- Comparison of posterior approximation with Finite State Projection (FSP)[1]
- FSP gives narrower posterior approximations compared to MMD and KS

1 Munsky et al., J. Chem. Phys. (2006)

Posterior approximations for equilibrium time-series

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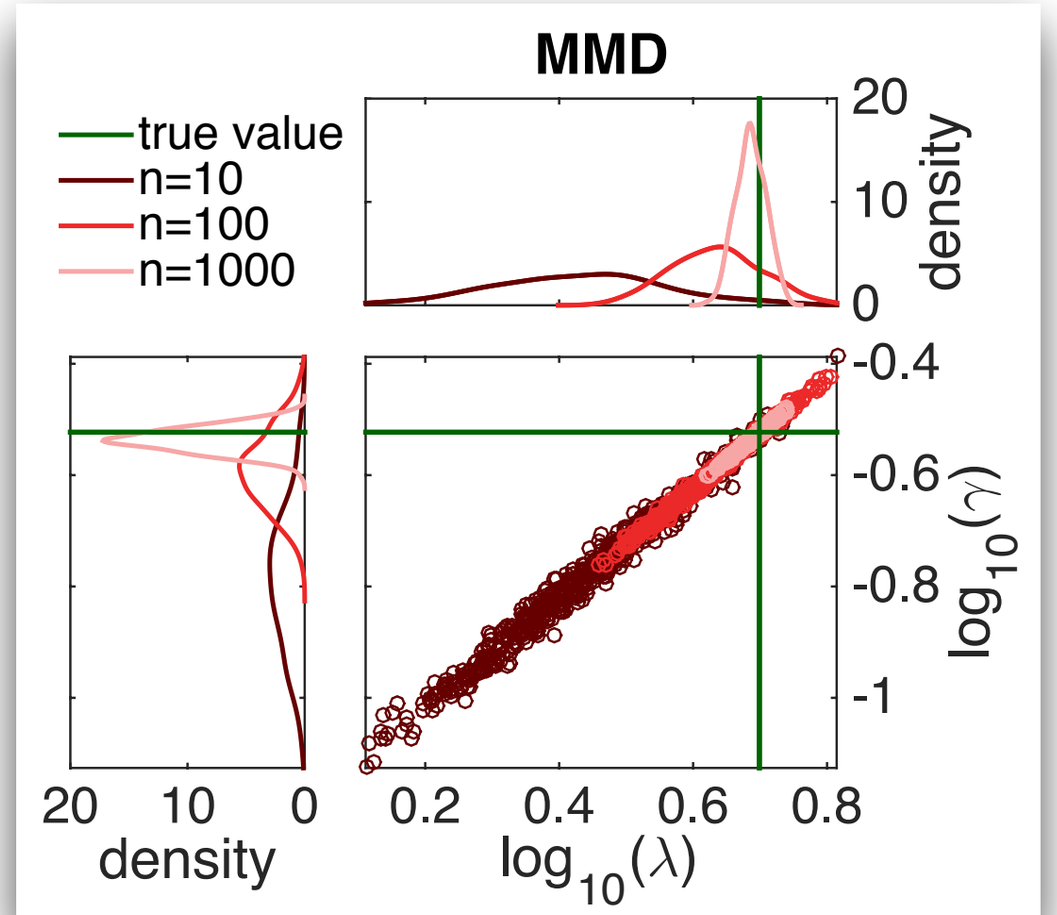

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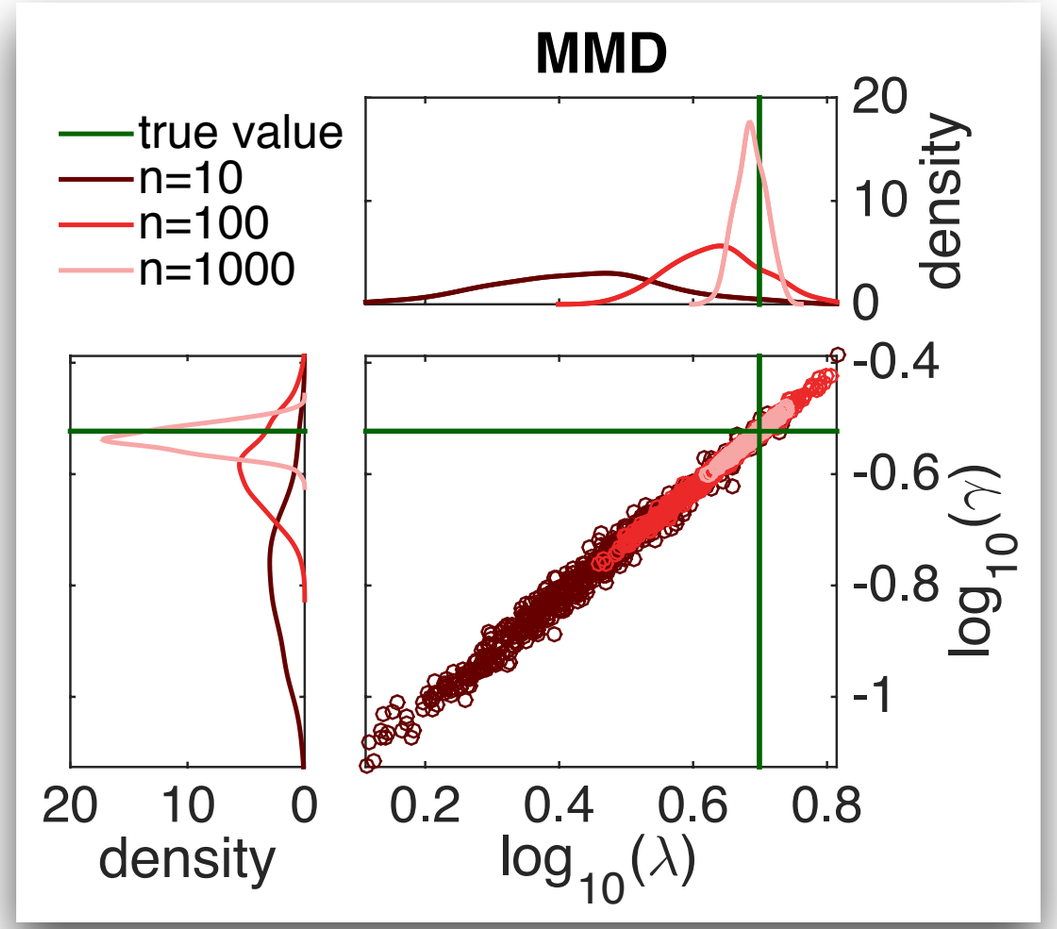

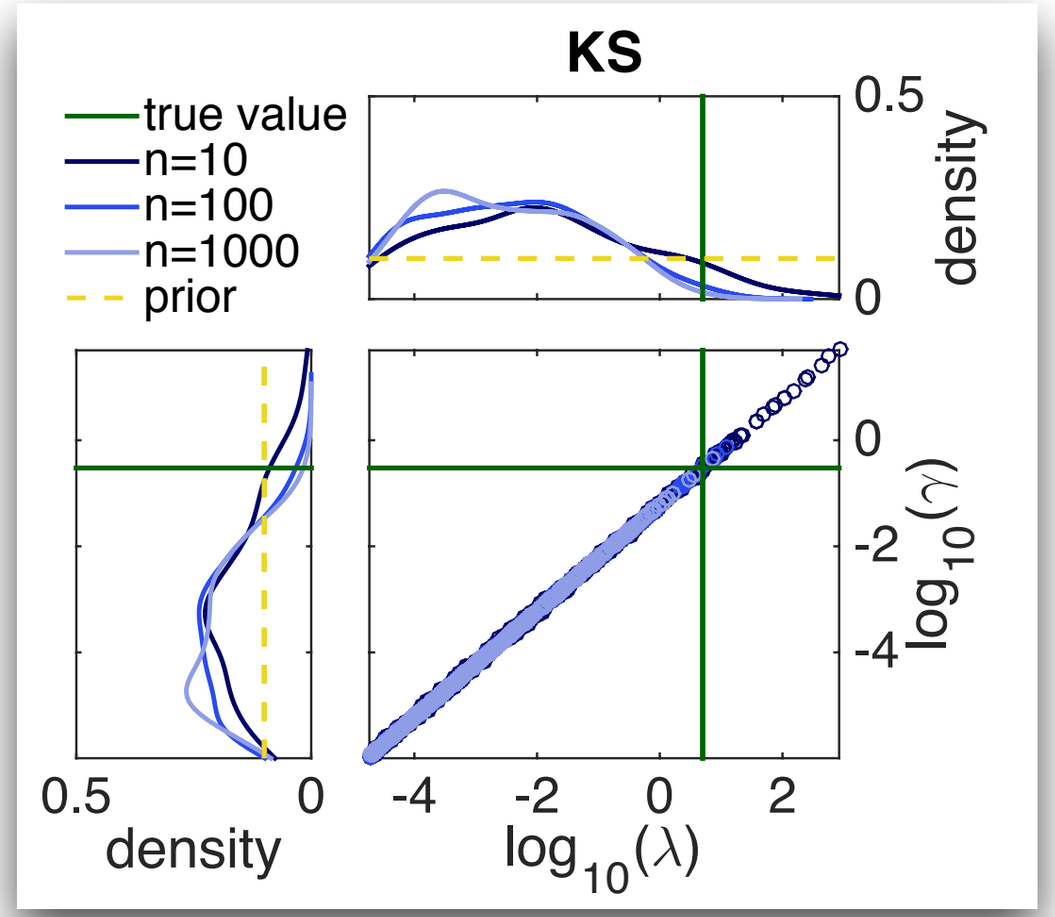

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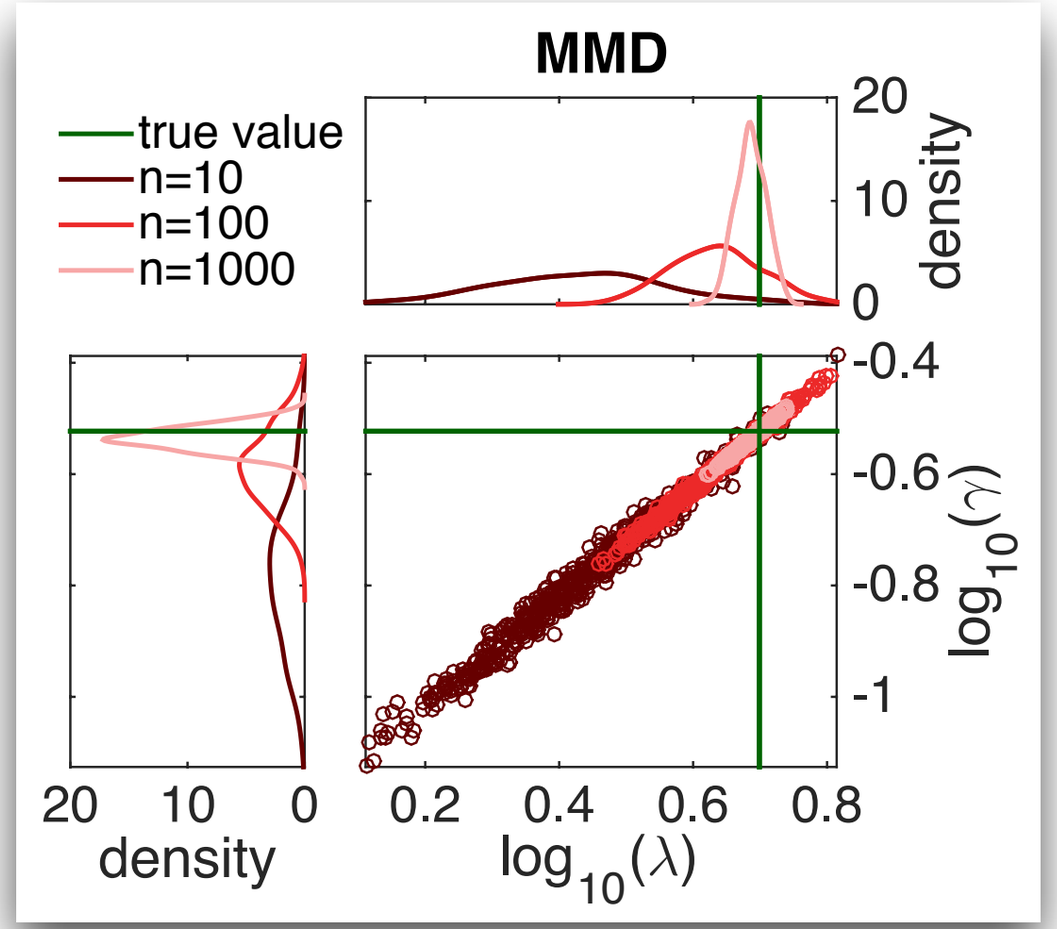

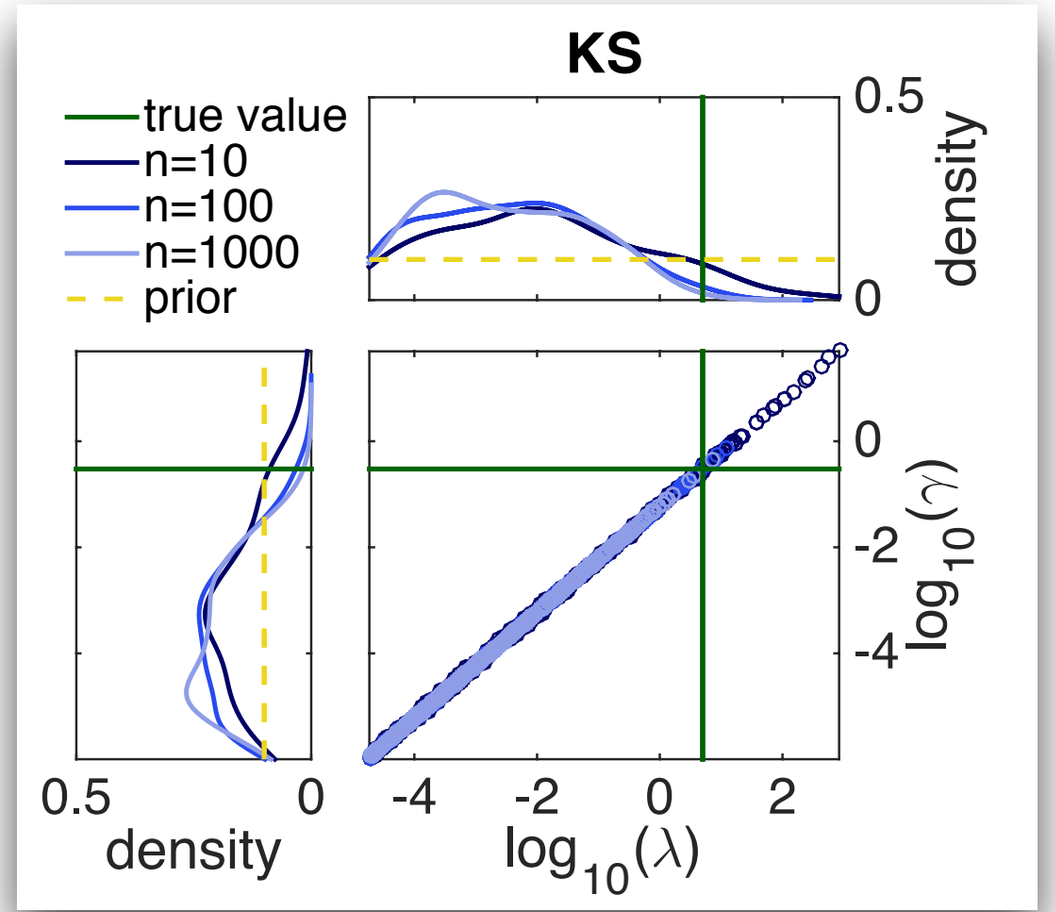

KS can only estimate ratio of parameters

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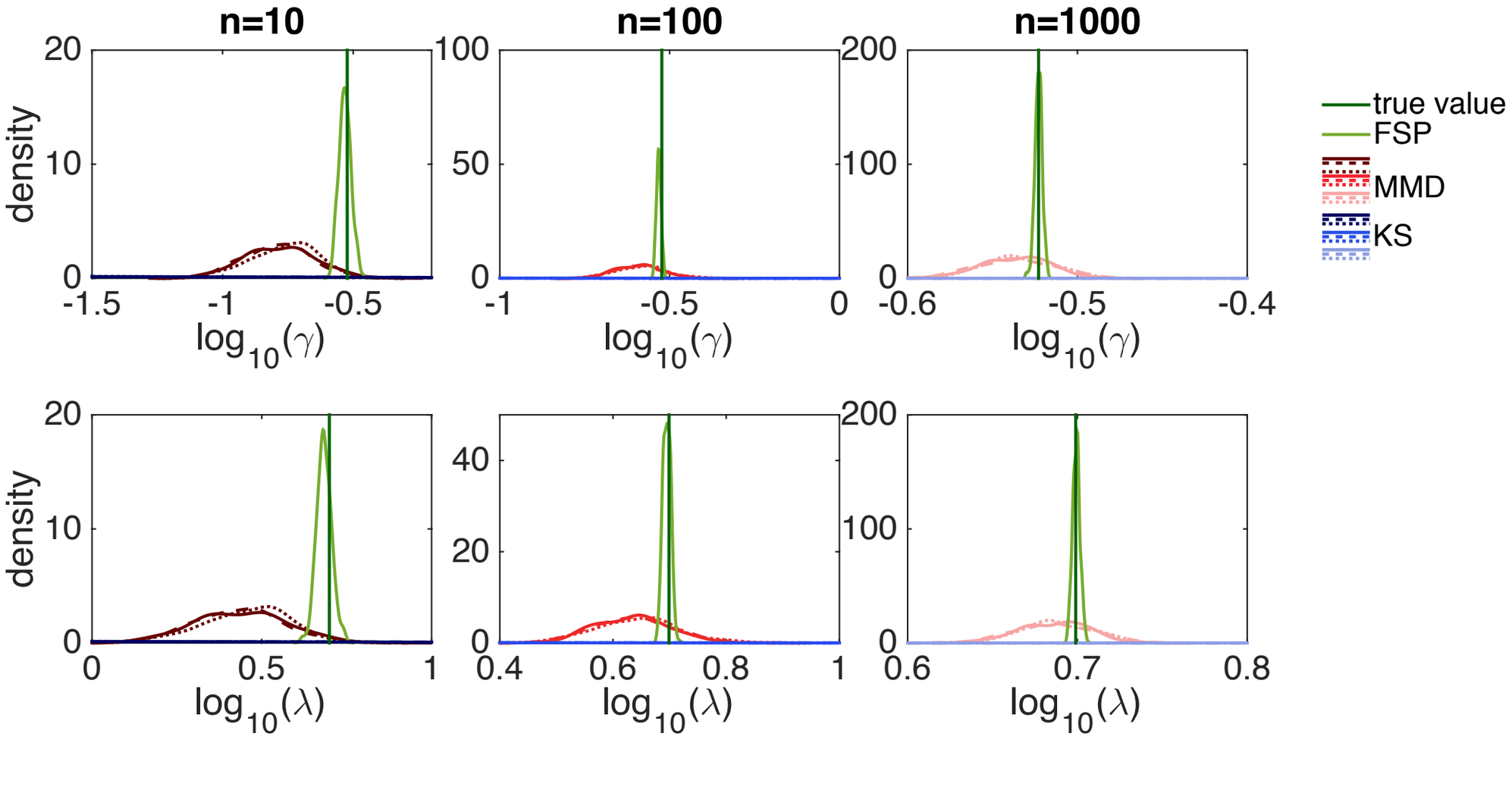

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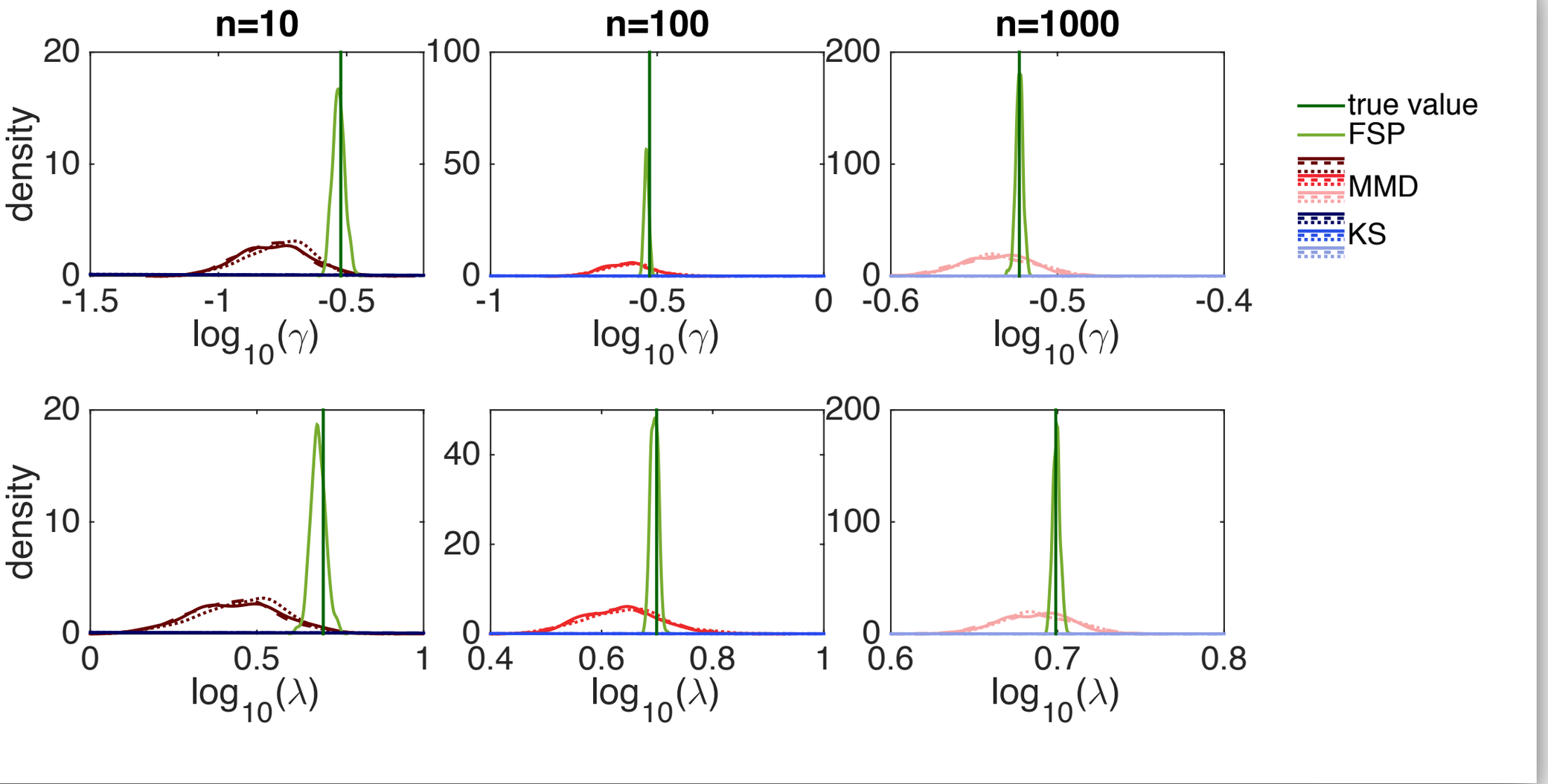
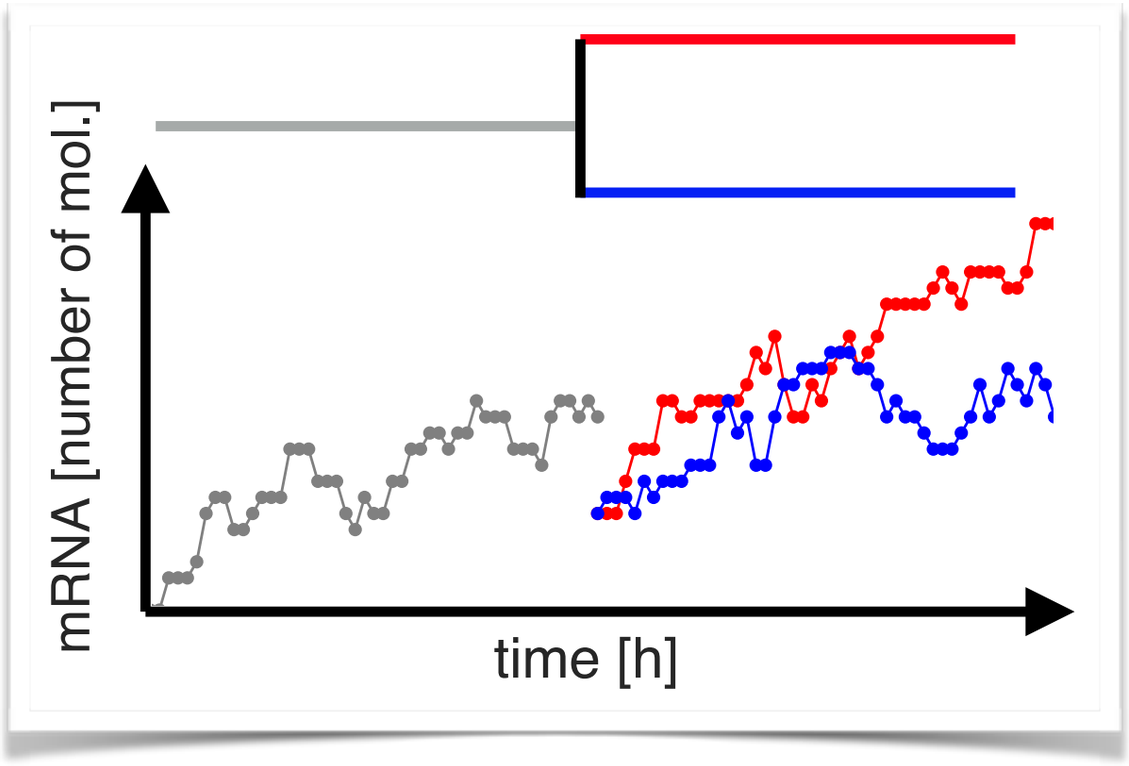


Bigger difference between FSP and MMD for equilibrium data

Tree-structured data

Tree-structured data

- Data often contain information about the ancestors of a cell[1]



1 Etzrodt et al., Cell Stem Cell (2014)

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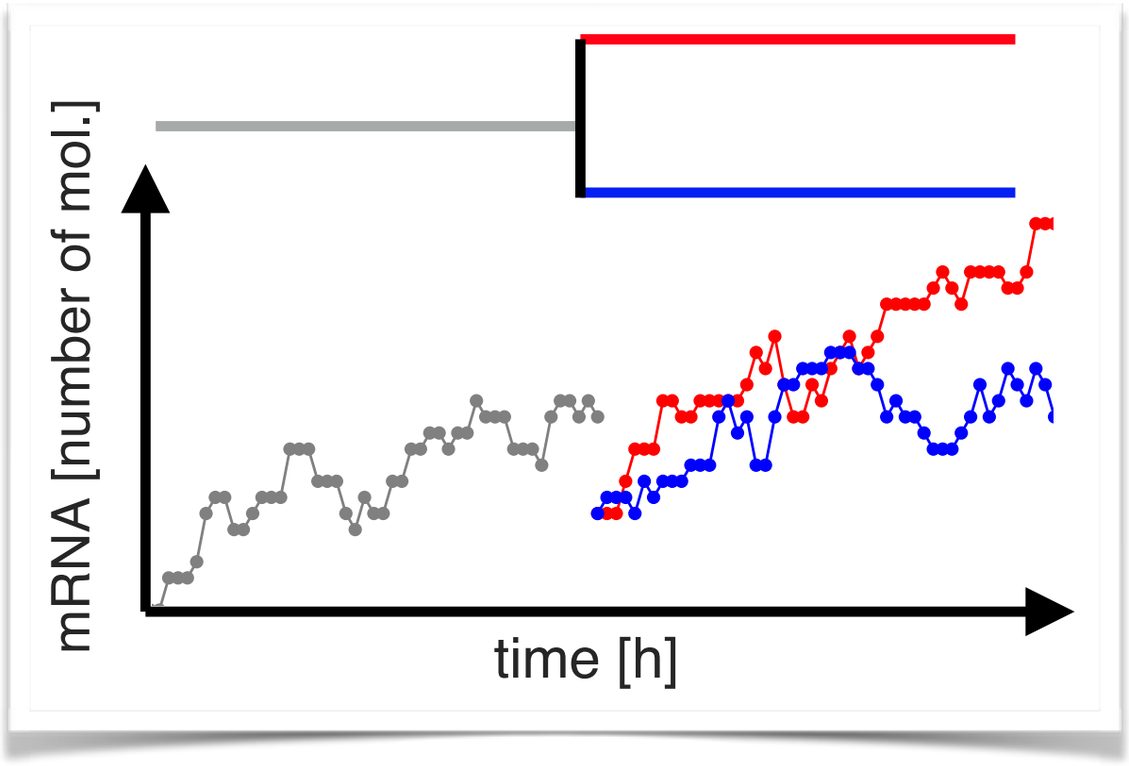

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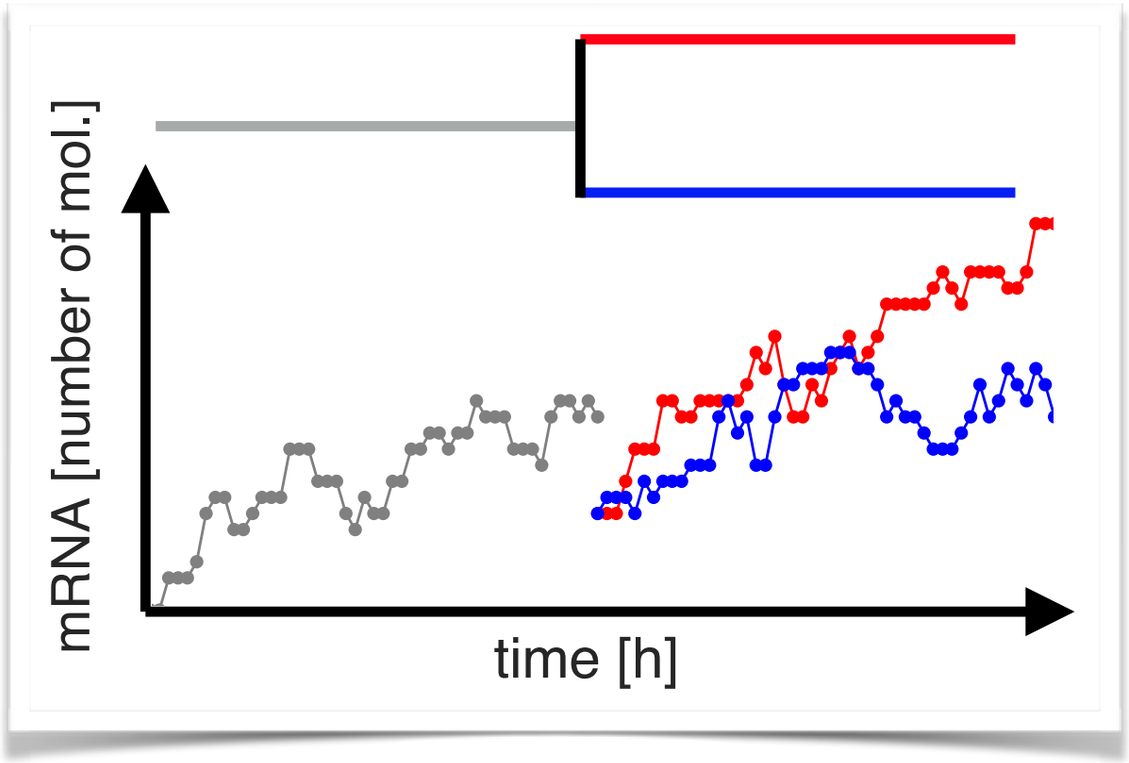

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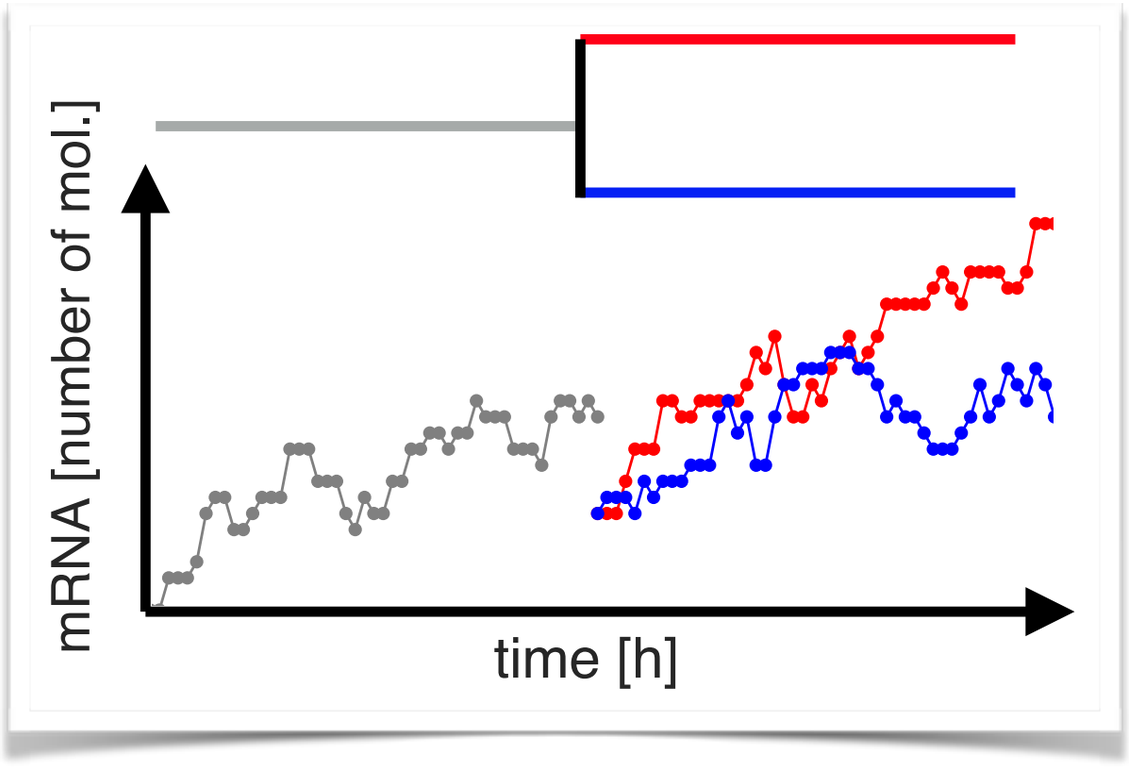
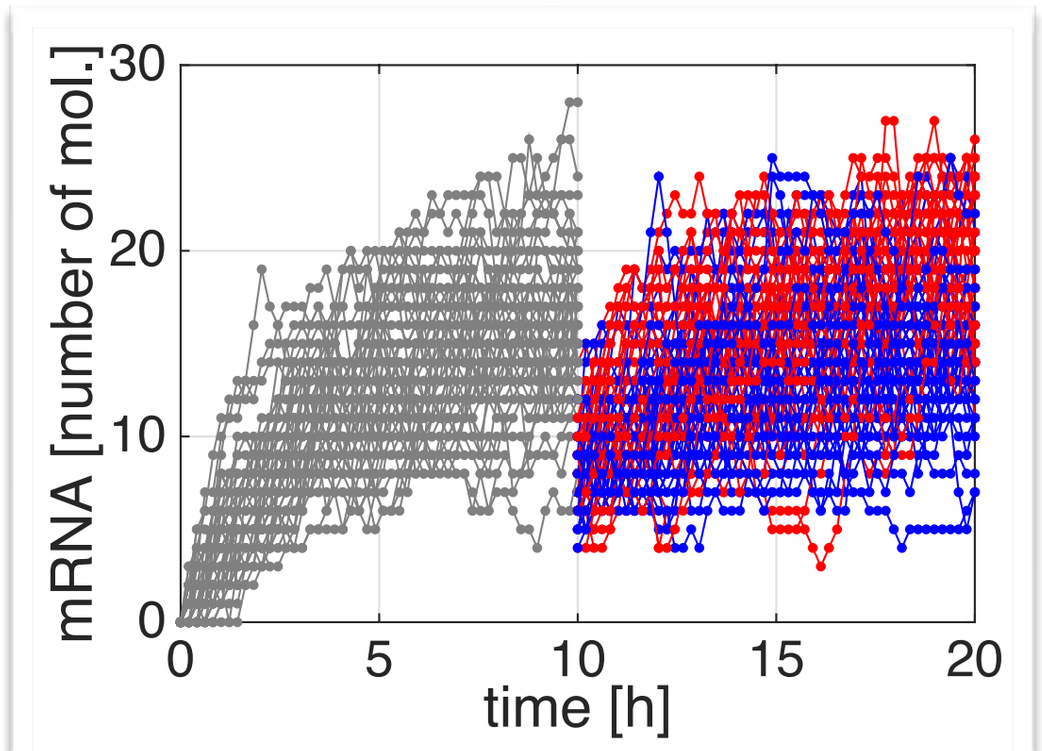
- Artificial data of 50 simple trees





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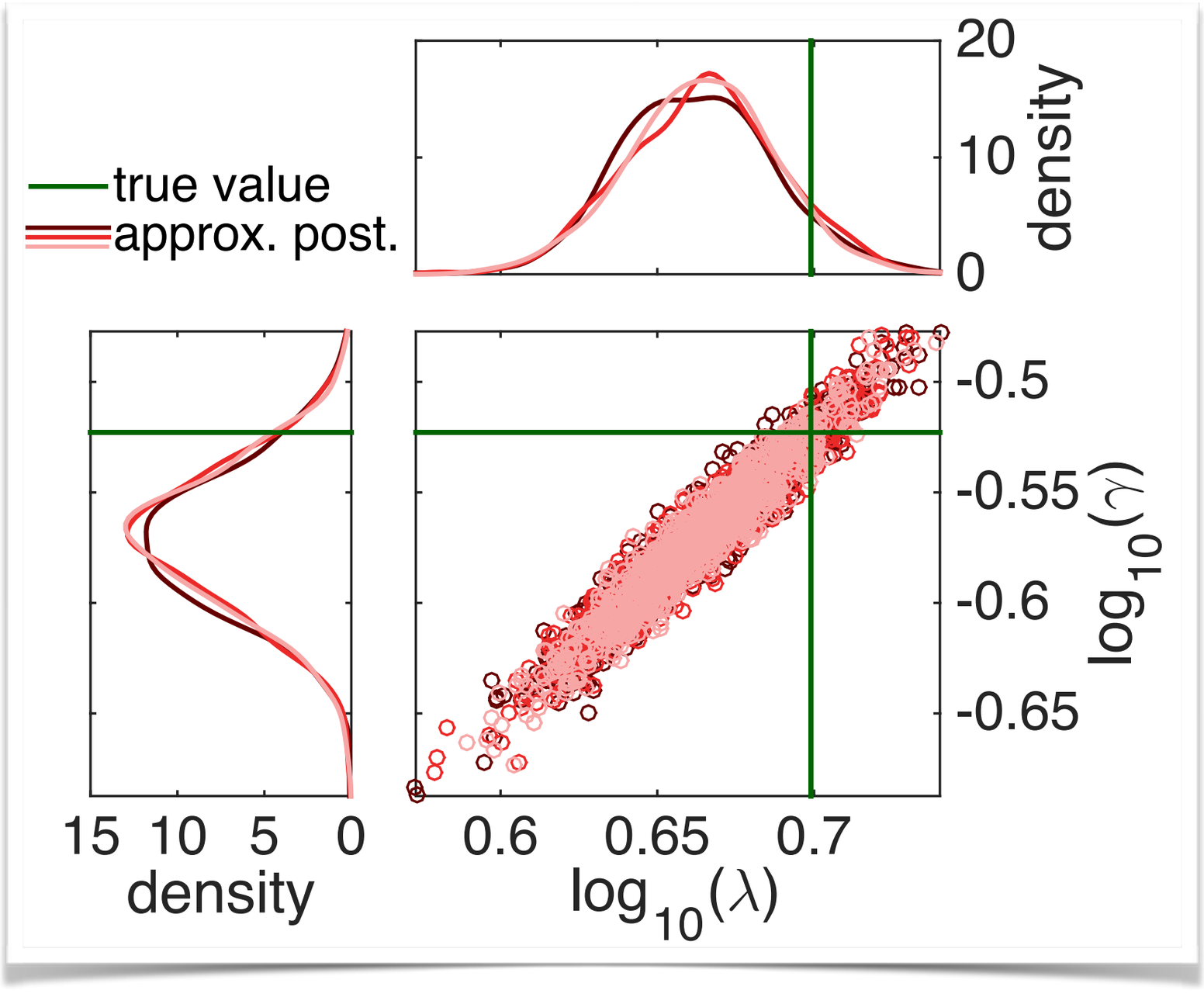

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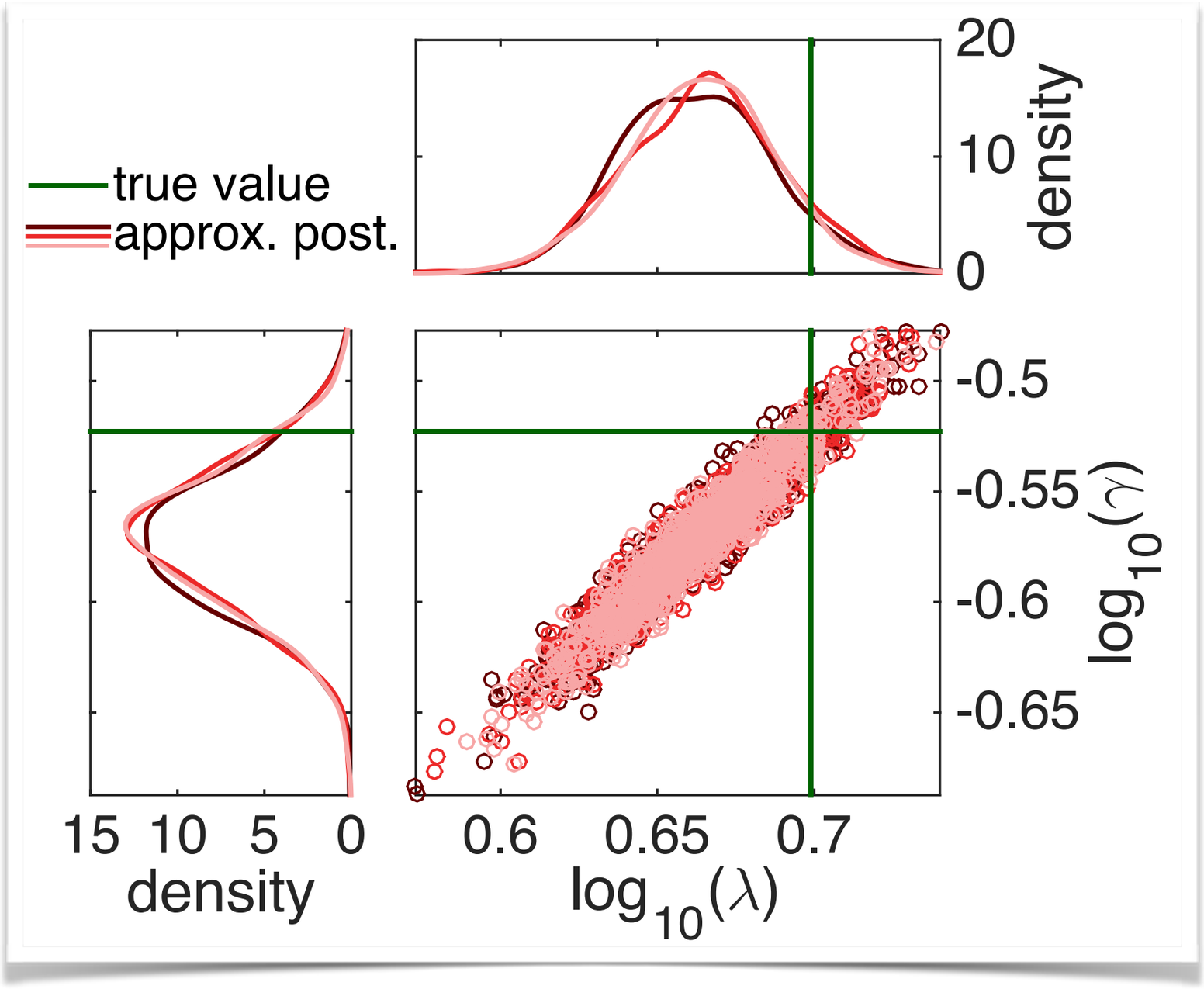

Use the method to exploit lineage information

Outlook

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- Evaluate information content of lineage information

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Flexible framework for the analysis of single-cell time-lapse data, which might help getting deeper insight into the cellular mechanisms and therefore advance e.g. stem cell research.

Acknowledgement

Jan Hasenauer
Carsten Marr
Fabian Theis
Dennis Rickert

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Data-Driven Computational Modelling

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