Estimating intratumoral heterogeneity from spatiotemporal data

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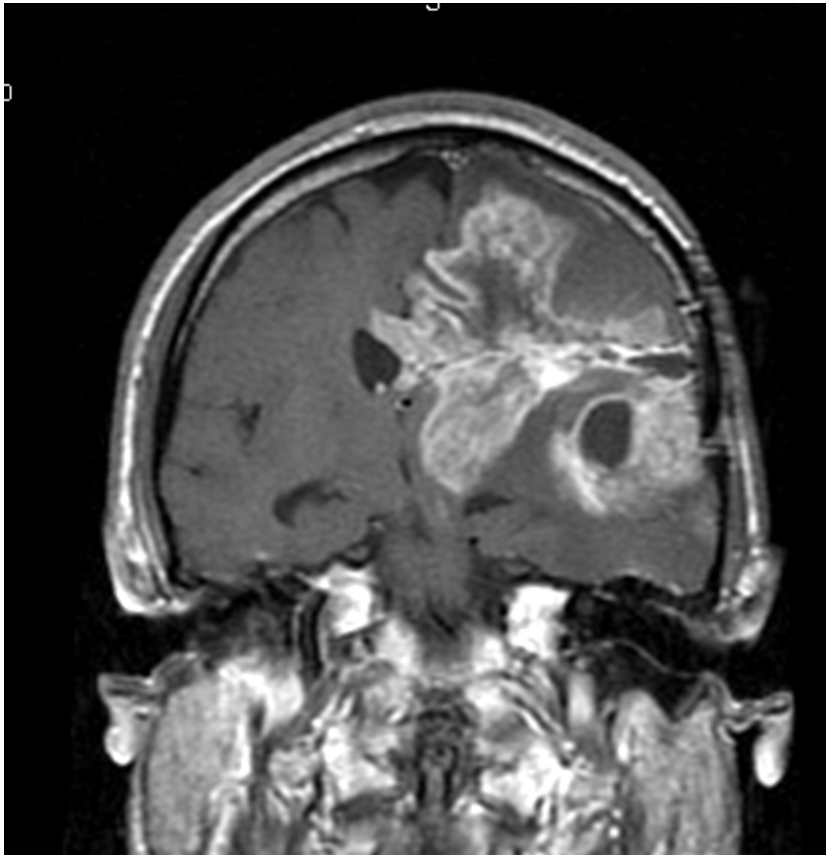
Glioblastoma Multiforme (GBM)

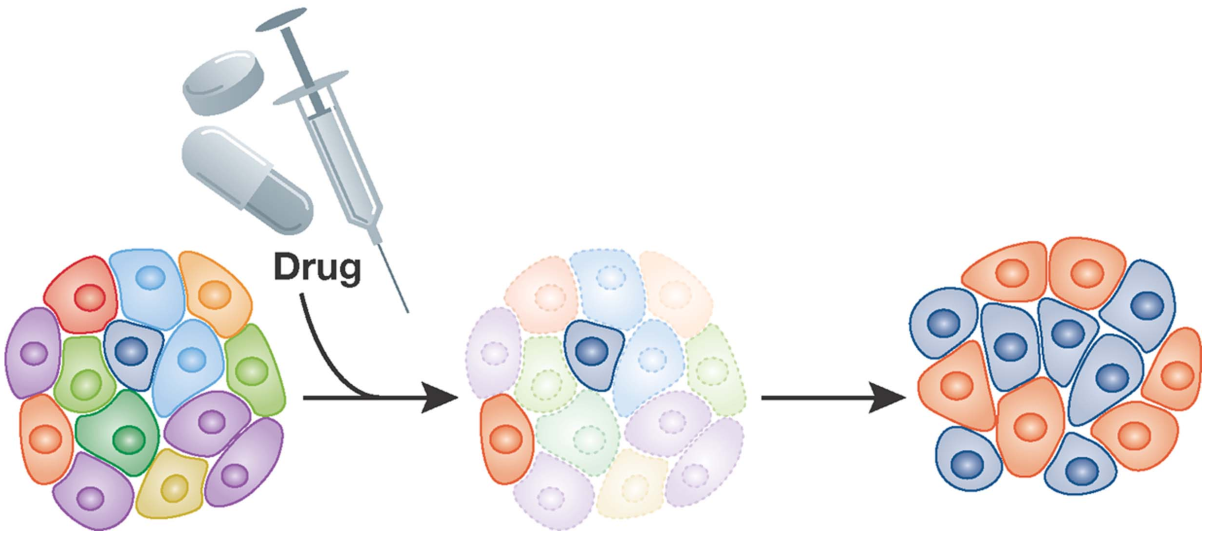


Sagittal cross-section of human brain with GBM

GBM is a deadly primary brain tumor characterized by:

- Phenotypic heterogeneity
- Low survivability
- Low response to treatment

Importance of heterogeneity

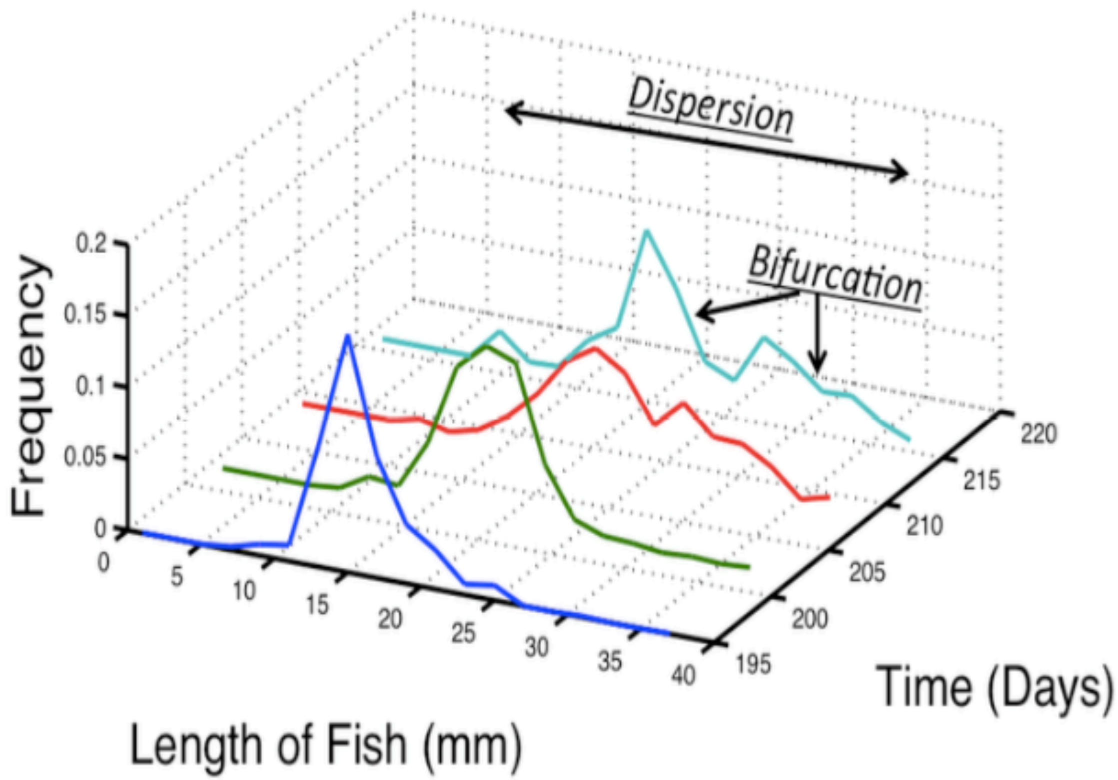


Source: Saunders, Nicholas A., et al. "Role of intratumoural heterogeneity in cancer drug resistance: molecular and clinical perspectives." *EMBO molecular medicine* 4.8 (2012): 675-684.

Incorporating heterogeneity in GBM Models

- Agent-based models
- Spatial models
- We can separate the tumor cell population into subpopulations:
  - `Go or grow’ in glioma growth
  - Androgen-dependent and androgen-independent cells in prostate cancer
  - Radio-sensitive and radio-resistant cells for treatment strategies
  - Oxidative-Phosphorylated cells and glycolitic cells

Random Differential Equations



Source: Banks, H. T. & Davis, J. L. A comparison of approximation methods for the estimation of probability distributions on parameters. *Appl. Numer. Math.* **57,** 753–777, (2007).

Dispersion and bifurcation features are not accounted for when using static parameters

Random Differential Equations

Consider the diffusion ($\boldsymbol{D}$) and growth ($\boldsymbol{\rho}$) as random variables defined on a compact set $\Omega = \Omega_{\boldsymbol{D}} \times \Omega_{\boldsymbol{\rho}}$

Model

$$\frac{\partial u(t,x,\boldsymbol{D},\boldsymbol{\rho})}{dt} = \nabla \cdot \left(\boldsymbol{D} \nabla u(t,x,\boldsymbol{D},\boldsymbol{\rho})\right) + \boldsymbol{\rho} u(t,x,\boldsymbol{D},\boldsymbol{\rho})(1 - u(t,x,\boldsymbol{D},\boldsymbol{\rho}))$$

Observation

$$u(t,x) = \mathbb{E}[u(t,x,\cdot,\cdot), P]$$

$$= \int_{\Omega} u(t,x,\boldsymbol{D},\boldsymbol{\rho}) dP(\boldsymbol{D},\boldsymbol{\rho})$$

Prohorov Metric Framework (PMF)

Idea: Using data, determine the approximate distributions of $\boldsymbol{D}$ and $\boldsymbol{\rho}$, *without any underlying assumptions about the pdf/cdf*

$$\hat{P} = \underset{P^M(\Omega)}{\operatorname{argmin}} \sum_{i,j} \left(\text{data}(t_j, x_i) - \int_{\Omega} u(t_j, x_i, \boldsymbol{D}, \boldsymbol{\rho}) dP(\boldsymbol{D}, \boldsymbol{\rho}) \right)^2$$

Prohorov Metric Framework Theory

Theorem
There exists a (not necessarily unique) minimizer $\hat{P}$ (Banks, Hu, Thompson, 2015)

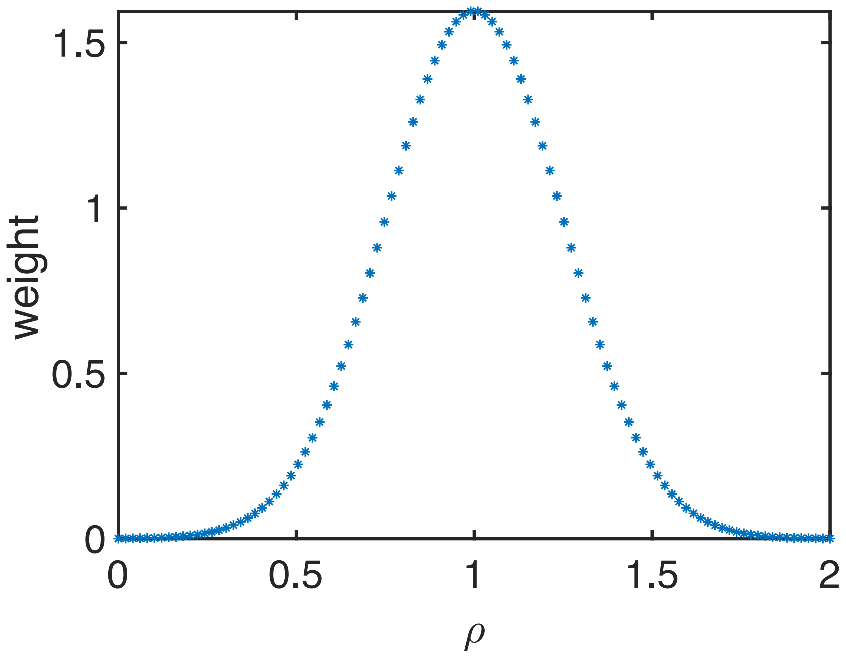
$$\hat{P} = \underset{P \in P^M(\Omega)}{\text{argmin}} \sum_{i,j} \left(\text{data}(t_j, x_i) - \int_\Omega u(t_j, x_i, \boldsymbol{D}, \boldsymbol{\rho}) dP(\boldsymbol{D}, \boldsymbol{\rho}) \right)^2$$

1. Since $\Omega = \Omega_{\boldsymbol{D}} \times \Omega_{\boldsymbol{\rho}}$ is a compact set, $P(\Omega)$ is a compact metric space
2. The minimizer is continuous in P

$\Longrightarrow$ There exists a (not necessarily unique) minimizer

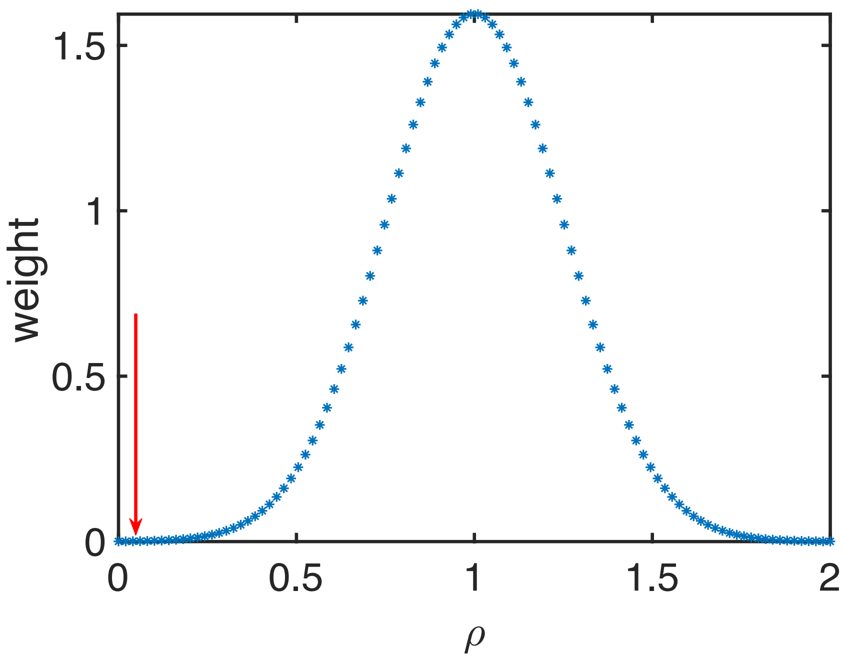
Creating Synthetic Data

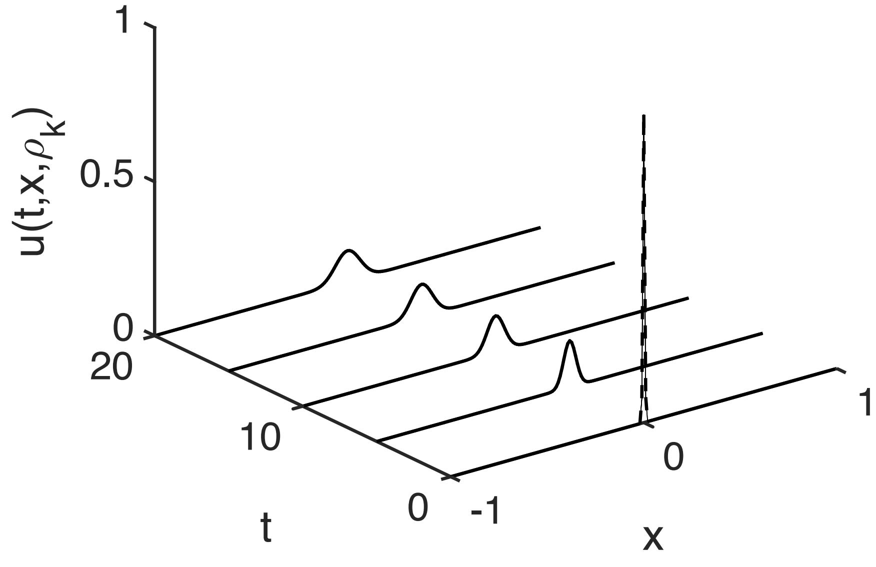
We finely mesh over the parameter $\boldsymbol{\rho} \in [0,2]$ and create our desired pdf



Creating Synthetic Data

$$\frac{\partial u(t,x,\rho_k)}{dt} = \nabla \cdot \left(D\nabla u(t,x,\rho_k)\right) + \rho_k u(t,x,\rho_k)\left(1 - u(t,x,\rho_k)\right)$$





Creating Synthetic Data

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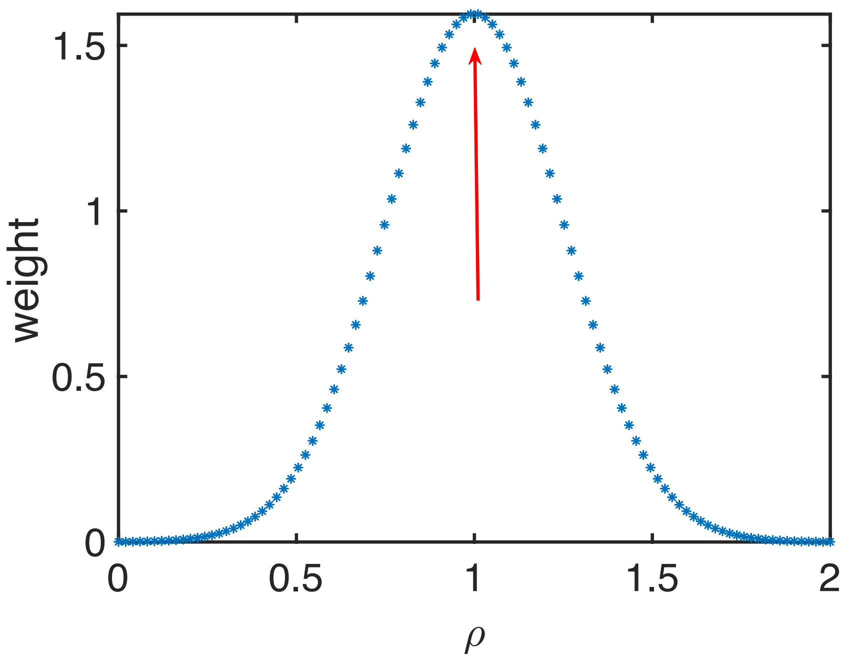

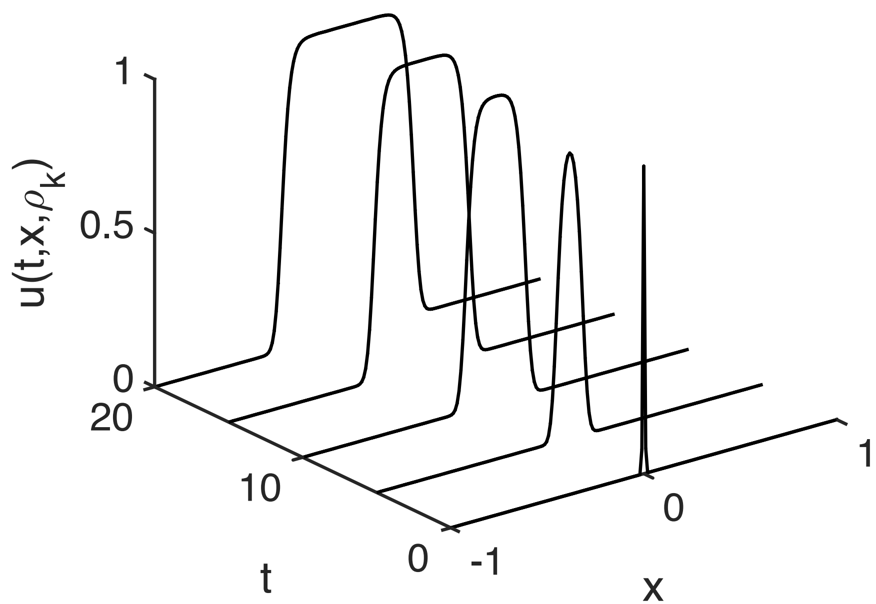

Creating Synthetic Data

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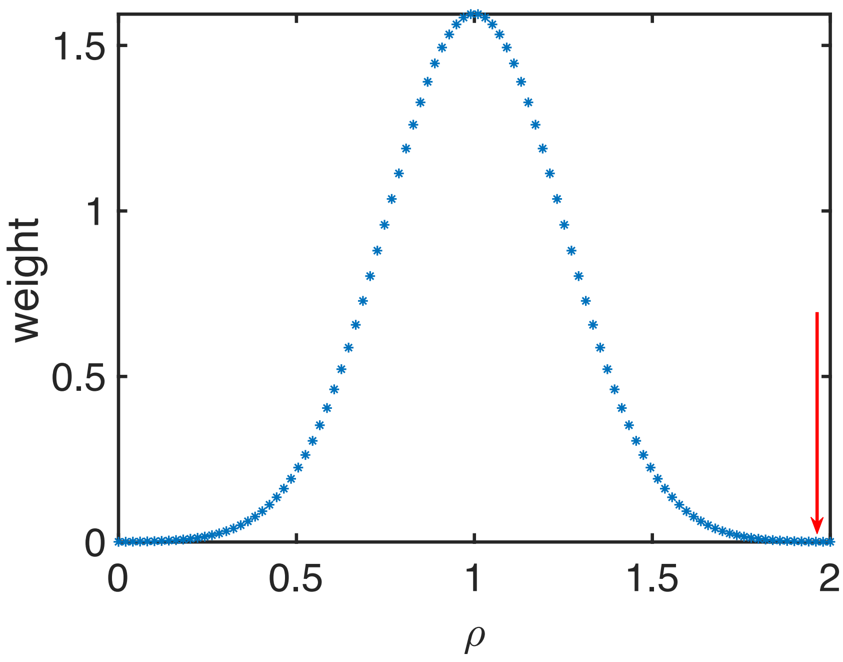
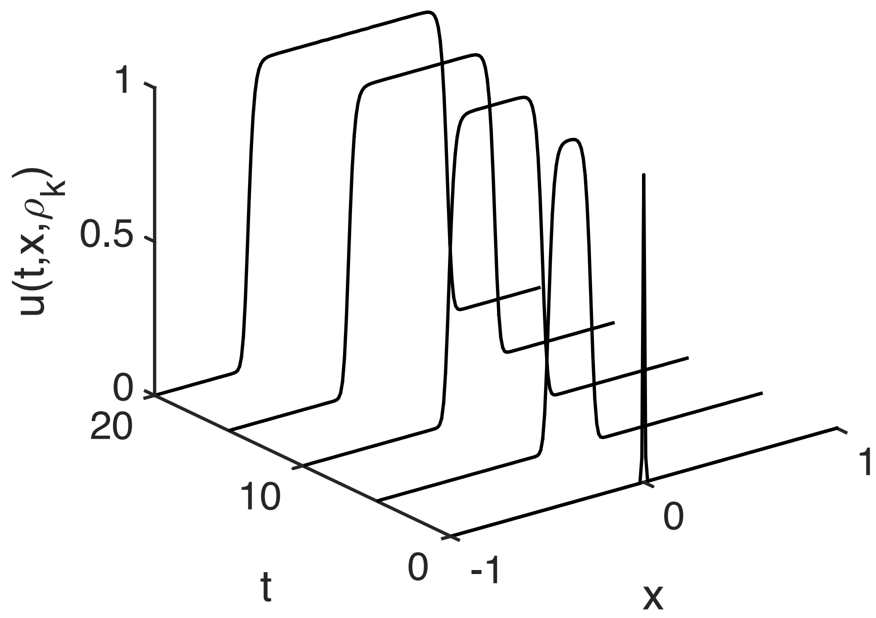
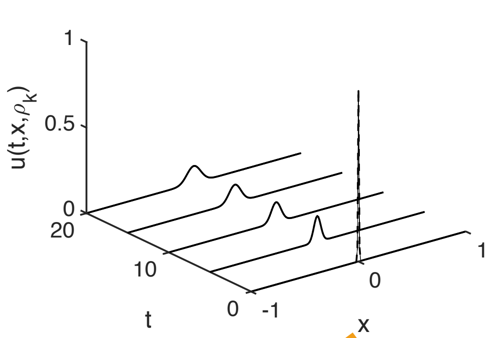
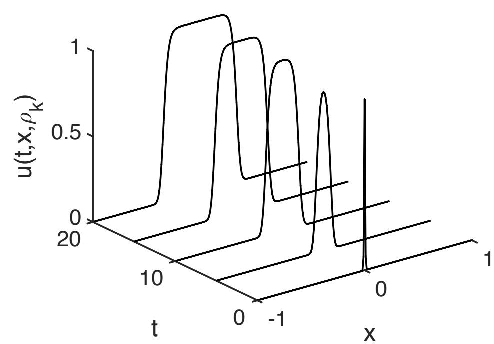
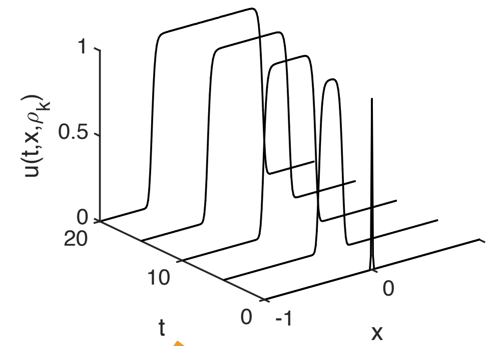




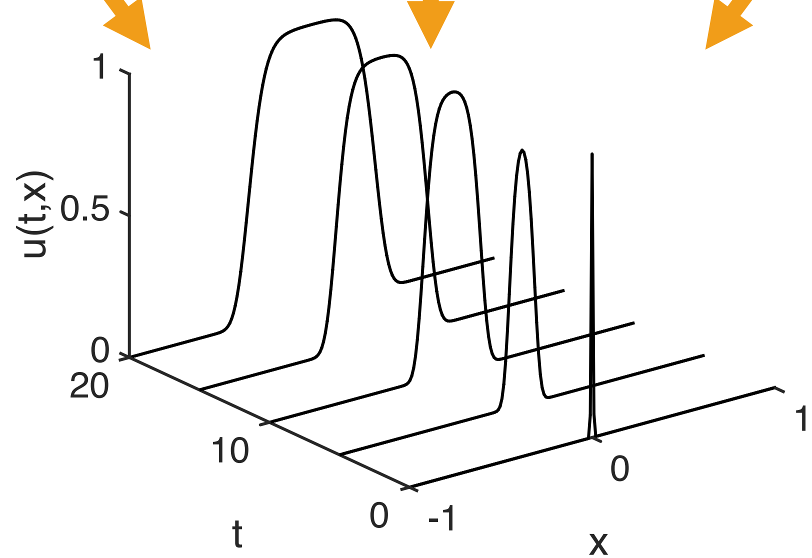
Creating Synthetic Data





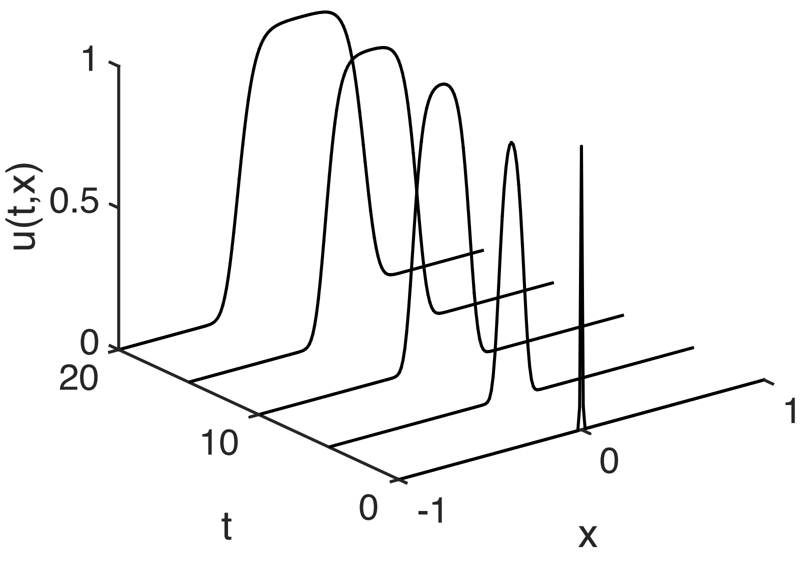


$$u(t,x) = \sum_{k=1}^{N} u(t,x,\rho_k)\omega_k$$

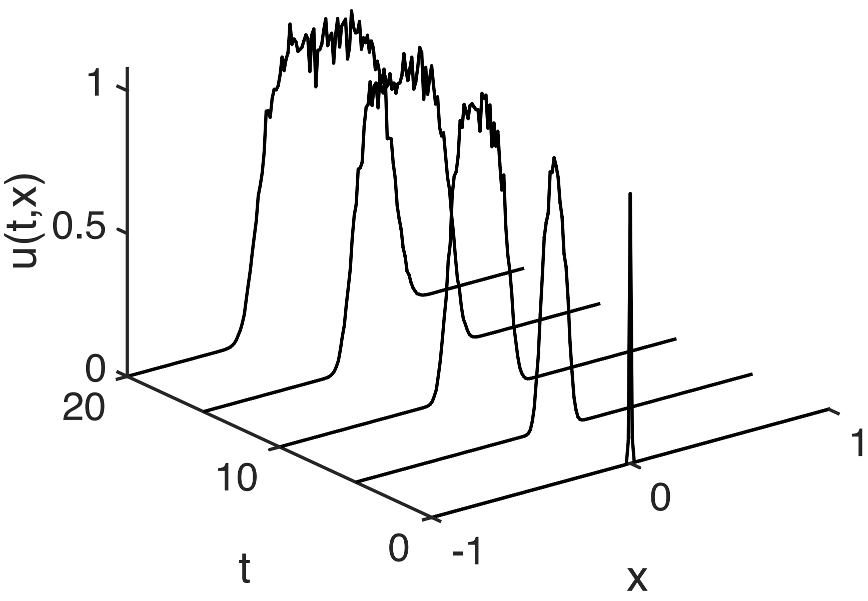


Creating Synthetic Data

$$\text{data}\left(t_j, x_i\right) = \text{sim}\left(t_j, x_i\right) + \varepsilon\,\text{sim}\left(t_j, x_i\right)$$
$$\varepsilon \sim 0.05N(0,1)$$



sim



data

Performing the Inverse Problem: Delta Functions

Assume there are M nodes equispaced over $\Omega_{\boldsymbol{\rho}}$ such that $\boldsymbol{\rho}^M = \{\Delta_{\rho_k}, k = 1, \dots, M\}$

$$\hat{P} = \underset{P^M(\Omega)}{\operatorname{argmin}} \sum_{i,j} \left[\text{data}(t_j, x_i) - \left(\sum_{k=1}^{M} u(t_j, x_i, D, \rho_k) \omega_k \right) \right]^2$$

where $\omega_k \geq 0$ represent a discrete probability density function. Thus, we require

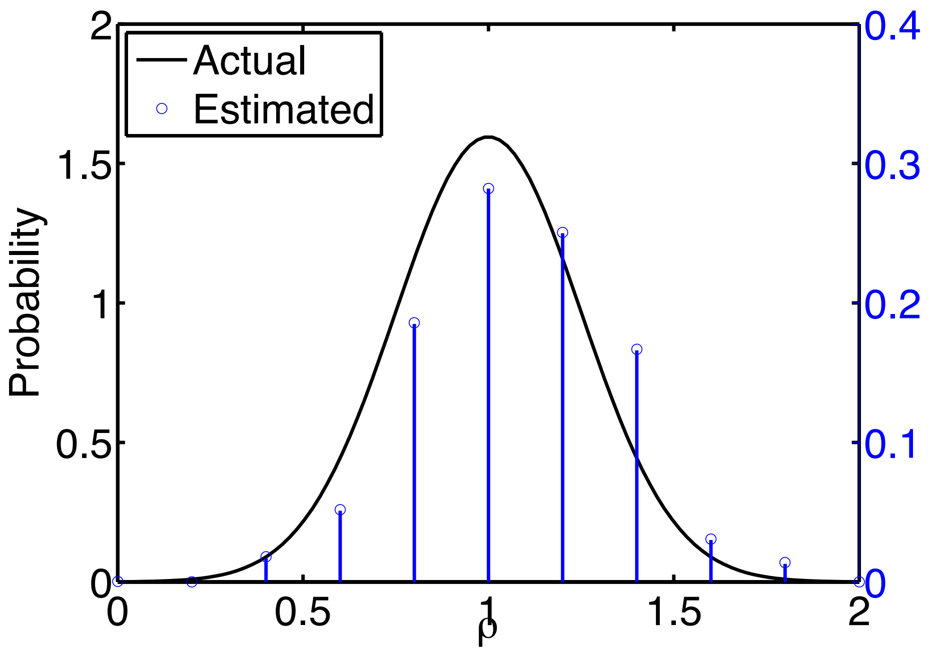
$$\sum_{k=1}^{M} \omega_k = 1$$

Performing the Inverse Problem: Delta Functions

$$\hat{P} = \underset{P^M(\Omega)}{\operatorname{argmin}} \sum_{i,j} \left[\text{data}(t_j, x_i) - \left(\sum_{k=1}^{M} u(t_j, x_i, D, \rho_k) \omega_k \right) \right]^2$$

Example: we have M=11 nodes, equispaced over [0,2] and we precompute $u(t, x, D, \rho_k)$

We are solving for the ω_k, the discrete weights



Performing the Inverse Problem: Spline Functions

Assume M nodes equispaced over $\Omega_{\boldsymbol{\rho}}$ such that $\boldsymbol{\rho}^M = \{s_k(\boldsymbol{\rho}), k = 1, \ldots, M\}$, where s_k are hat functions

$$\hat{P} = \underset{P^M(\Omega)}{\operatorname{argmin}} \sum_{i,j} \left[\text{data}(t_j, x_i) - \left(\sum_{k=1}^{M} a_k \int_{\Omega_\rho} u(t_j, x_i, D, \boldsymbol{\rho}) s_k(\boldsymbol{\rho}) d\boldsymbol{\rho} \right) \right]^2$$

where $p_k = a_k s_k(\boldsymbol{\rho}) \geq 0$ represent a probability density function. Thus, we require

$$\sum_{k=1}^{M} a_k \int_{\Omega_\rho} s_k(\boldsymbol{\rho}) d\boldsymbol{\rho} = 1$$

Performing the Inverse Problem: Spline Functions

$$\hat{P} = \underset{P^M(\Omega)}{\operatorname{argmin}} \sum_{i,j} \left[\text{data}(t_j, x_i) - \left(\sum_{k=1}^{M} a_k \int_{\Omega_\rho} u(t_j, x_i, D, \boldsymbol{\rho}) s_k(\boldsymbol{\rho}) d\boldsymbol{\rho} \right) \right]^2$$

Example: we have M=11 nodes, equispaced over [0,2]

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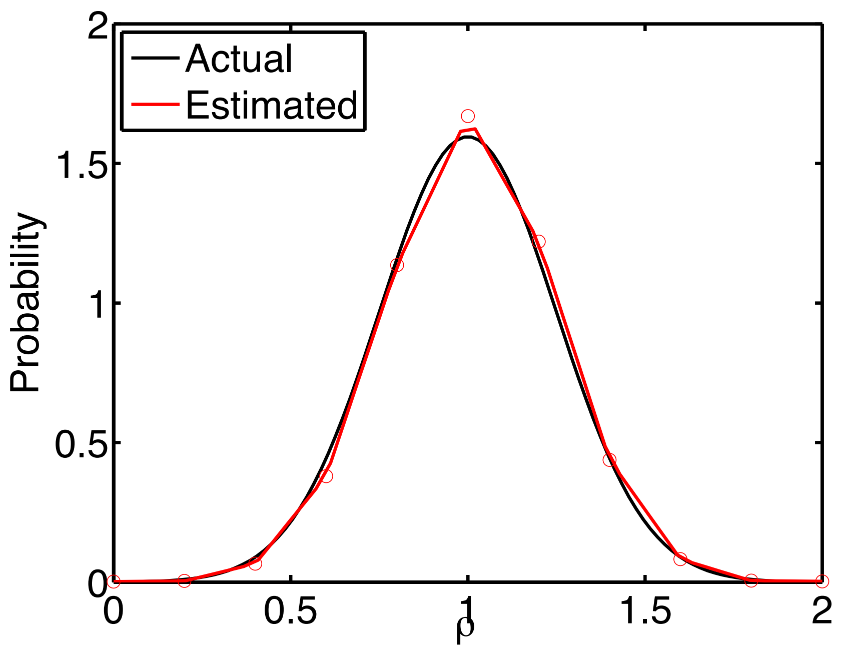
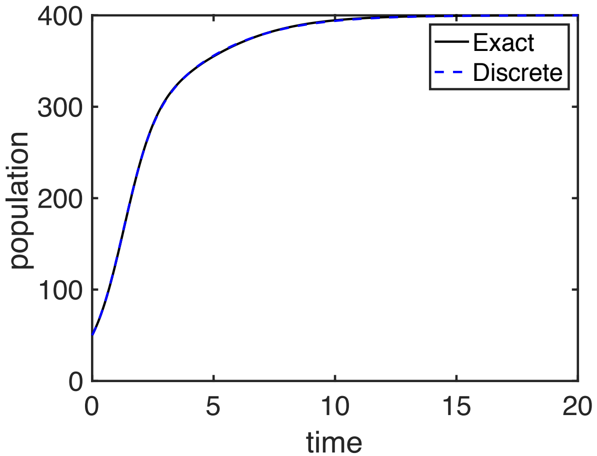
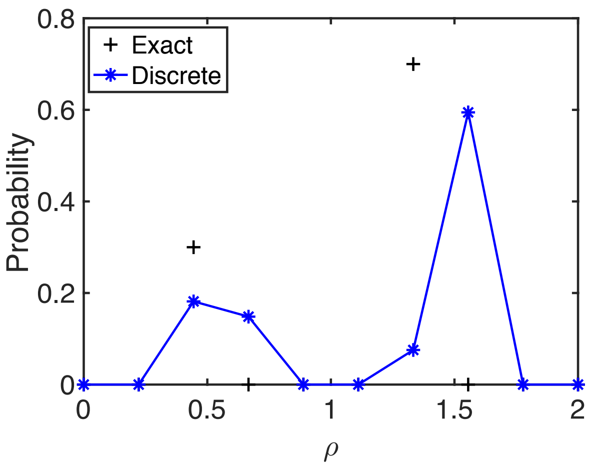


How to choose M: the optimal number of nodes?

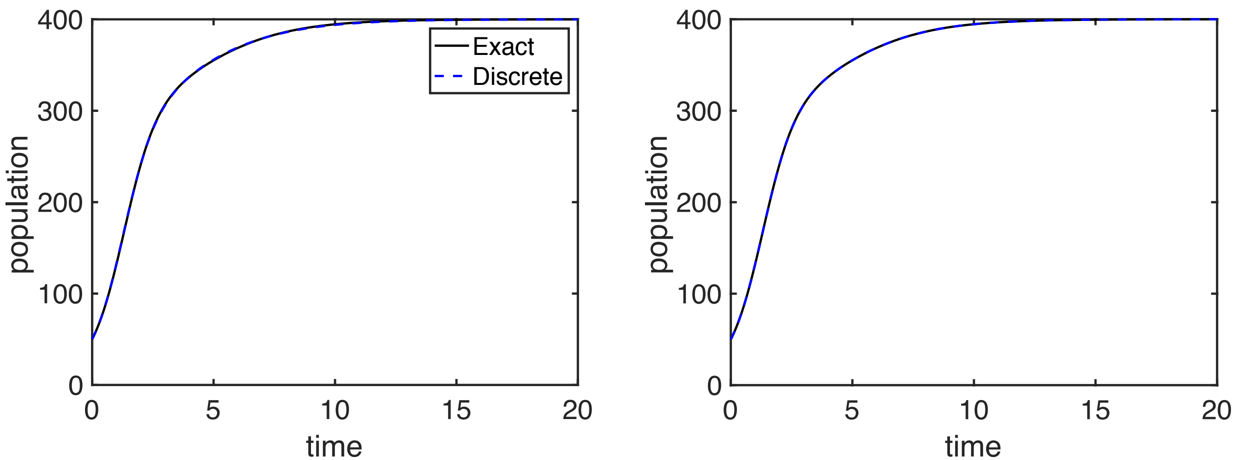


RSS = 875.8139

Increasing M: the number of nodes



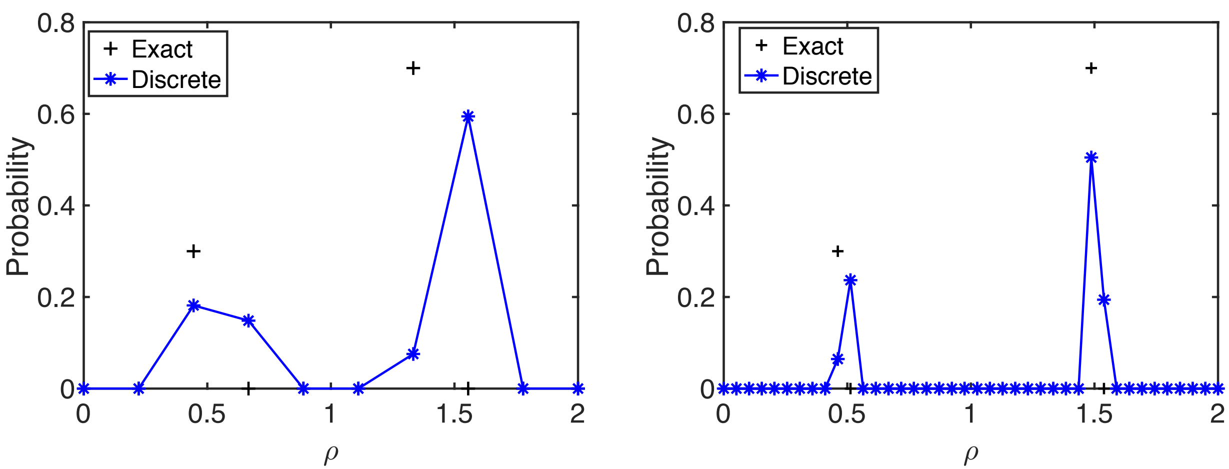
How to choose M: the optimal number of nodes?



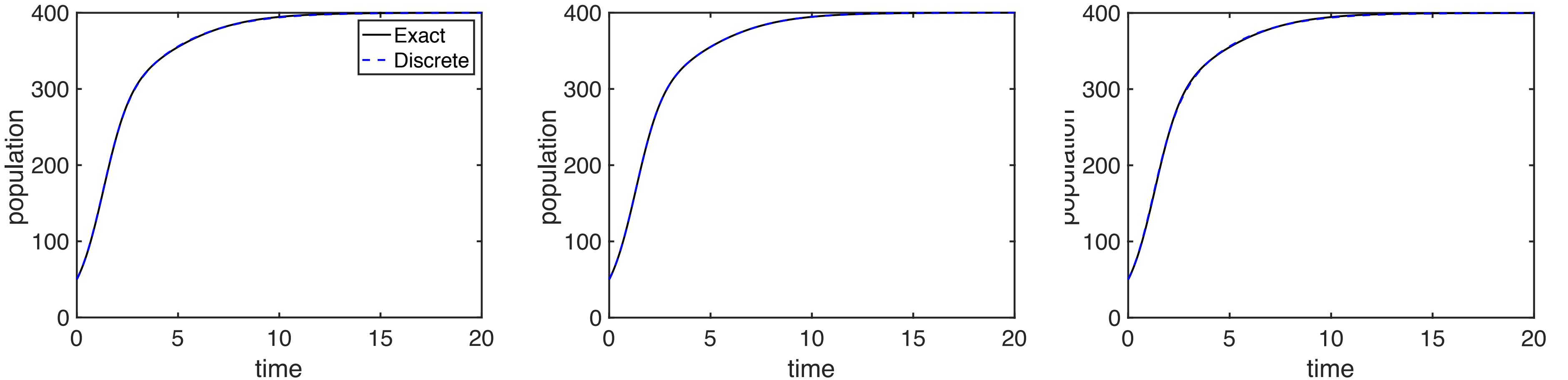
RSS = 875.8139

RSS = 3.6191

Increasing M: the number of nodes

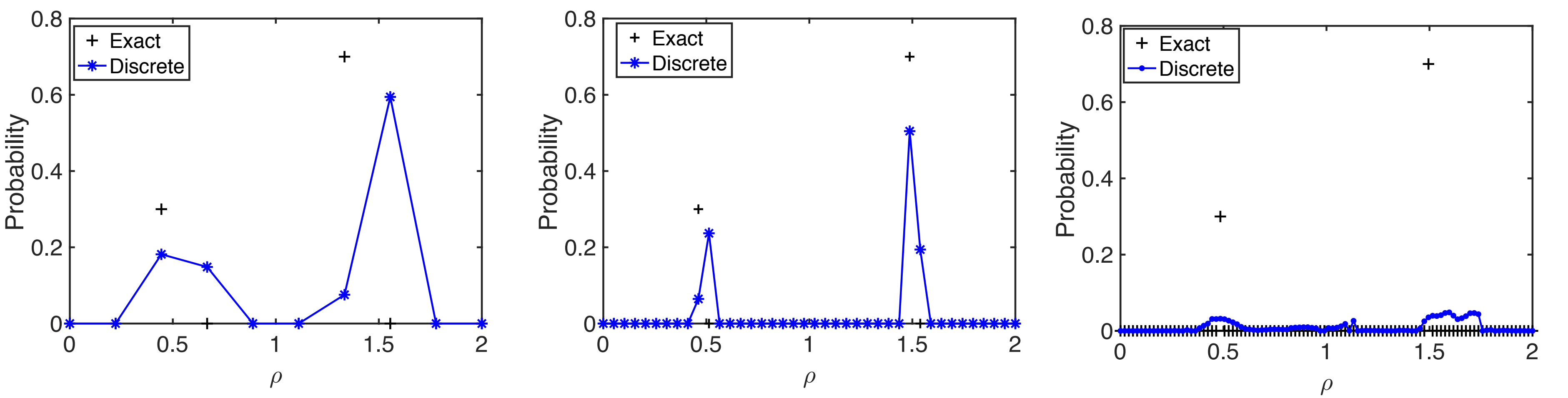


How to choose M: the optimal number of nodes?



RSS = 875.8139 RSS = 3.6191 2.5656e+03

Increasing M: the number of nodes



How to choose M: the optimal number of nodes?

Akaike Information Criteria (AIC) as a model comparison test in the context of least-squares

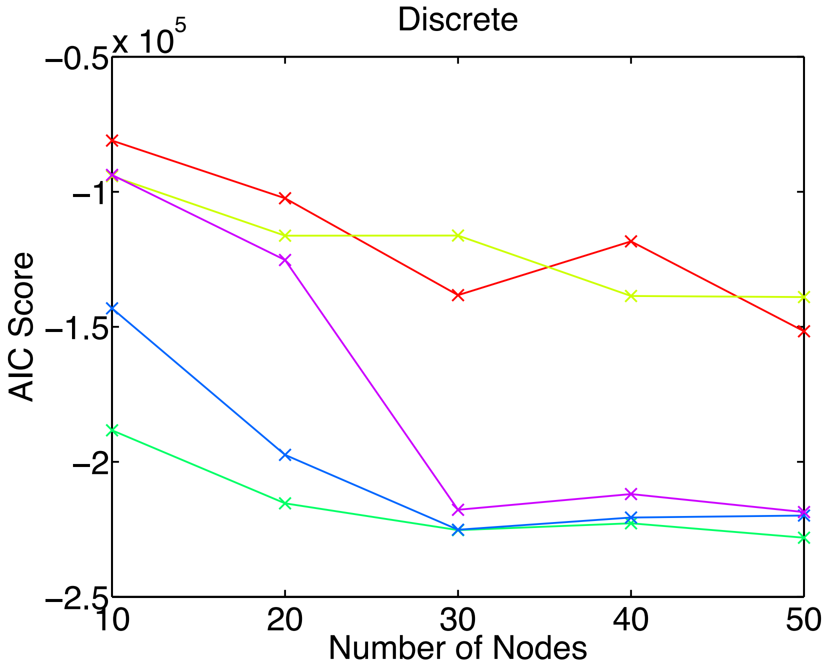
$$AIC = N \ln\left(\frac{\mathrm{RSS}}{N}\right) + N(1 - \ln(2\pi)) + 2(M + 1)$$

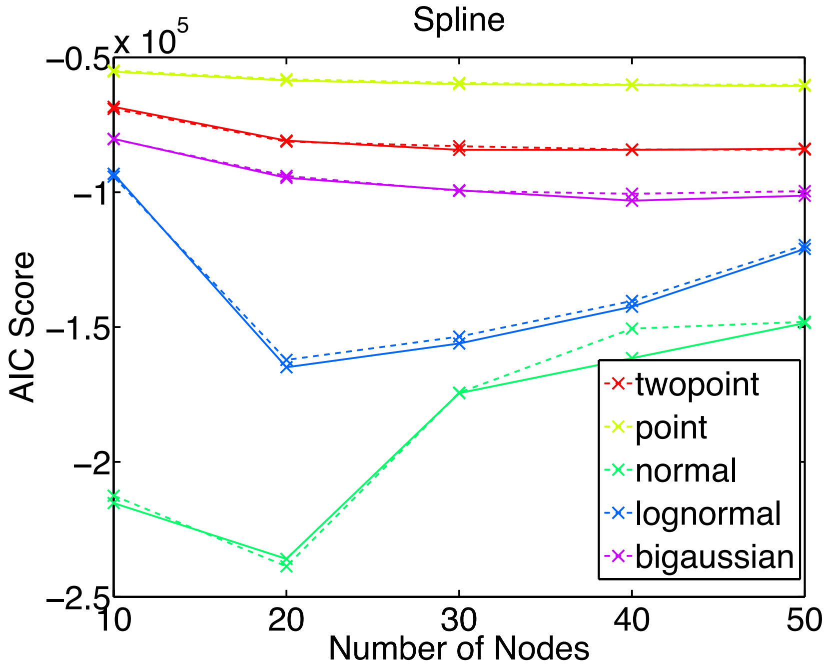
N: number of data points

RSS: error between data and solution $u(t, x)$

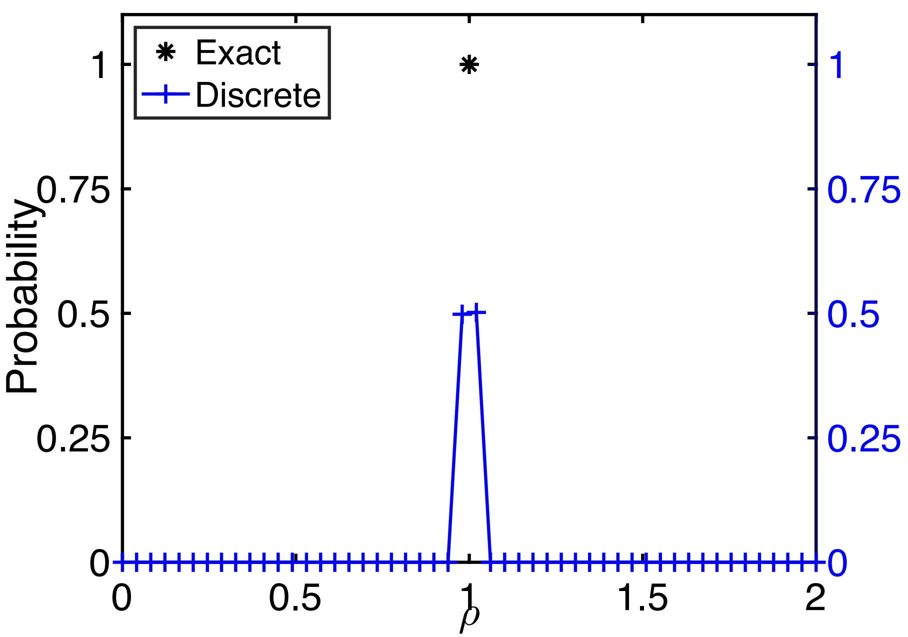
M: number of parameters being fit (our M nodes)

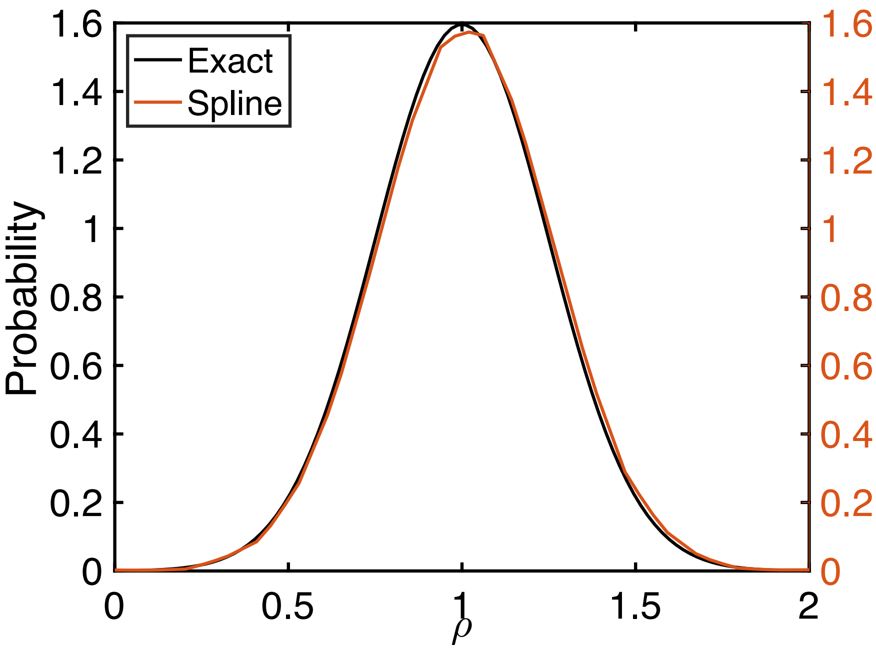
How to choose M: the optimal number of nodes?





Representative Results: finding $\boldsymbol{\rho}$





Performing the Inverse Problem: Delta Functions

Assume there are M_ρ nodes equispaced over $\boldsymbol{\Omega_\rho}$ such that $\boldsymbol{\rho}^M = \{\Delta_{\rho_k}, k = 1, \dots, M_\rho\}$ and that there are M_D nodes equispaced over $\boldsymbol{\Omega_D}$ such that $\boldsymbol{D}^M = \{\Delta_{D_l}, l = 1, \dots, M_D\}$

$$\hat{P} = \underset{P^M(\Omega)}{\operatorname{argmin}} \sum_{i,j} \left[\text{data}(t_j, x_i) - \left(\sum_{l=1}^{M_D} \sum_{k=1}^{M_\rho} u(t_j, x_i, D_l, \rho_k) \omega_k \omega_l \right) \right]^2$$

where $\omega_k, \omega_l \geq 0$ represent a discrete probability density function. Thus, we require

$$\sum_{k=1}^{M_\rho} \omega_k = 1 \qquad \sum_{l=1}^{M_D} \omega_l = 1$$

Performing the Inverse Problem: Spline Functions

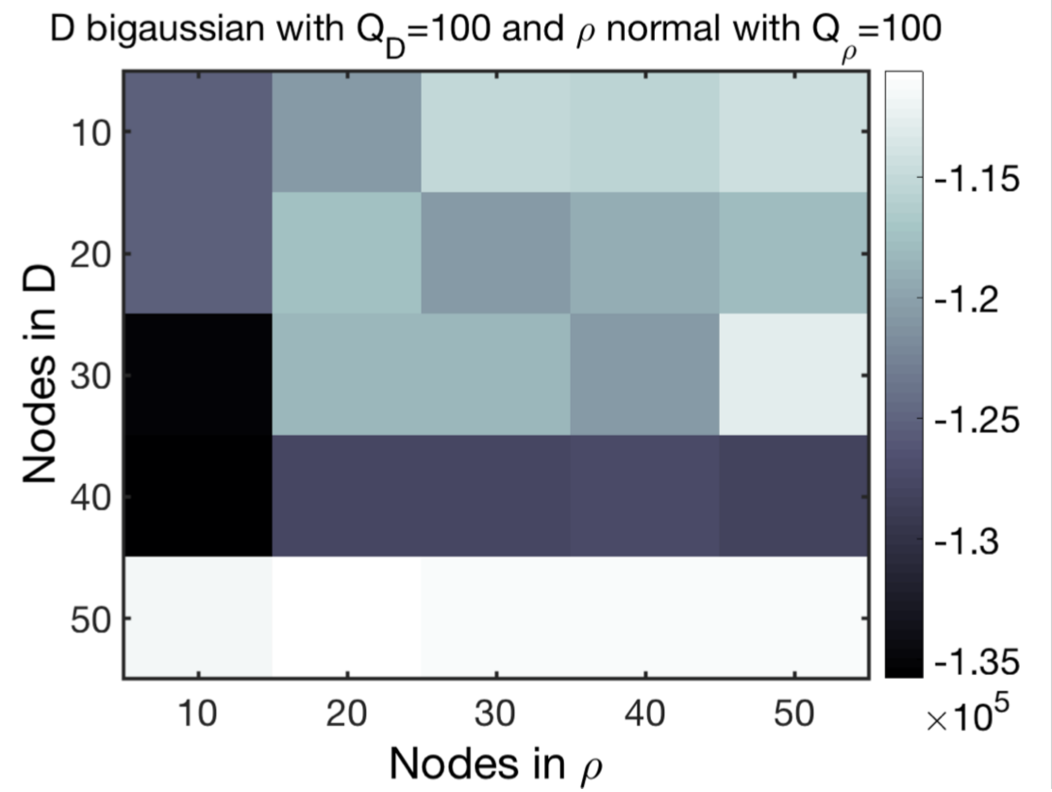
Assume M_ρ nodes equispaced over $\Omega_{\boldsymbol{\rho}}$ such that $\boldsymbol{\rho}^{M_\rho} = \{s_k(\boldsymbol{\rho}), k = 1, \dots, M_\rho\}$, and M_D nodes equispaced over $\Omega_{\boldsymbol{D}}$ such that $\boldsymbol{D}^{M_D} = \{s_l(\boldsymbol{D}), l = 1, \dots, M_D\}$, where s_k, s_l are hat functions

$$\hat{P} = \underset{P^M(\Omega)}{\operatorname{argmin}} \sum_{i,j} \left[\mathrm{data}(t_j, x_i) - \sum_{l=1}^{M_D} a_l \int_{\Omega_{\boldsymbol{D}}} \left(\sum_{k=1}^{M_\rho} b_k \int_{\Omega_\rho} u(t_j, x_i, \boldsymbol{D}, \boldsymbol{\rho}) s_l(\boldsymbol{D}) d\boldsymbol{D} \right) s_k(\boldsymbol{\rho}) d\boldsymbol{\rho} \right]^2$$

where $p_k = b_k s_k(\boldsymbol{\rho}) \geq 0$, $p_l = a_l s_l(\boldsymbol{D}) \geq 0$ represent probability density functions.

$$\sum_{k=1}^{M_\rho} b_k \int_{\Omega_{\boldsymbol{\rho}}} s_k(\boldsymbol{\rho}) d\boldsymbol{\rho} = 1 \qquad \sum_{l=1}^{M_D} a_l \int_{\Omega_{\boldsymbol{D}}} s_l(\boldsymbol{D}) d\boldsymbol{D} = 1$$

Selection of M



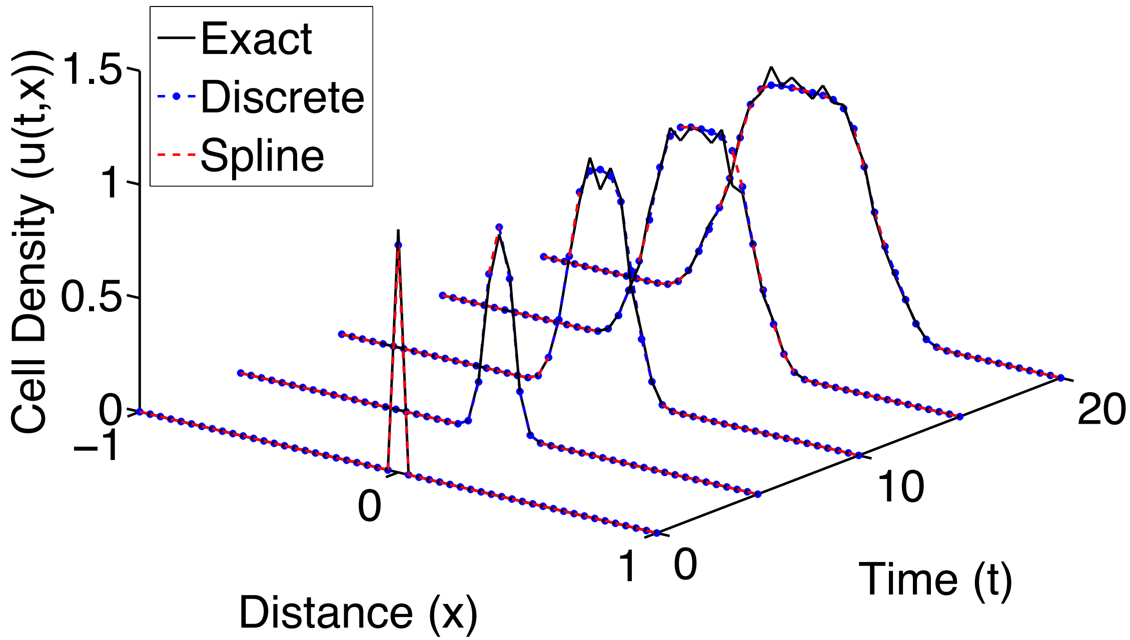
Representative Results

$\boldsymbol{\rho}$ normally distributed and $\boldsymbol{D}$ bigaussian

Goal: Recover parameter distributions

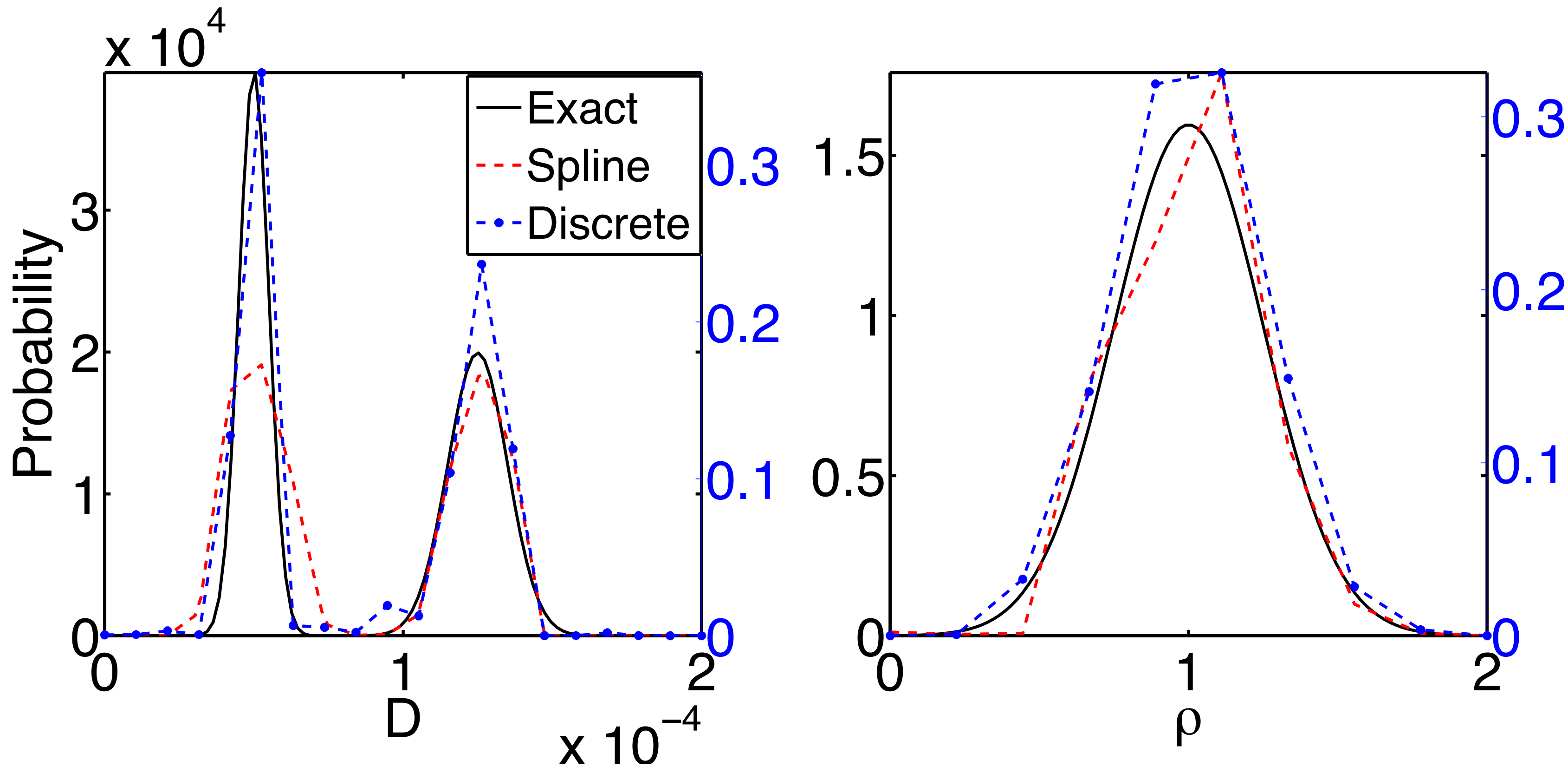
$$\text{data}(t_j, x_i) = \text{sim}(t_j, x_i) + \varepsilon \text{sim}(t_j, x_i)$$

$$\varepsilon \sim 0.05 N(0,1)$$



Rutter, Banks and Flores. Estimating Intratumoral Heterogeneity from Spatiotemporal Data. *Under review*

Resulting pdf Estimates



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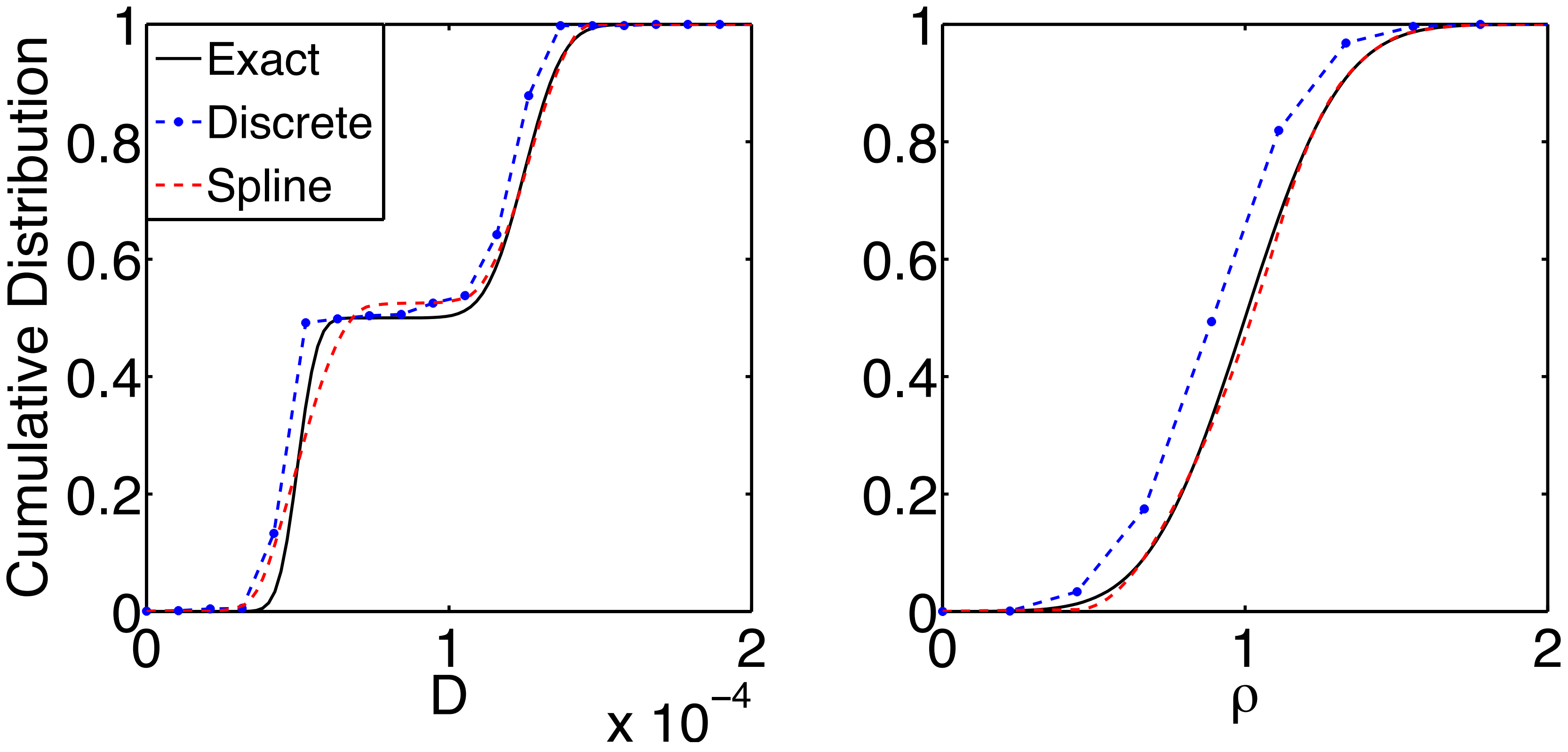
Resulting cdf Estimates

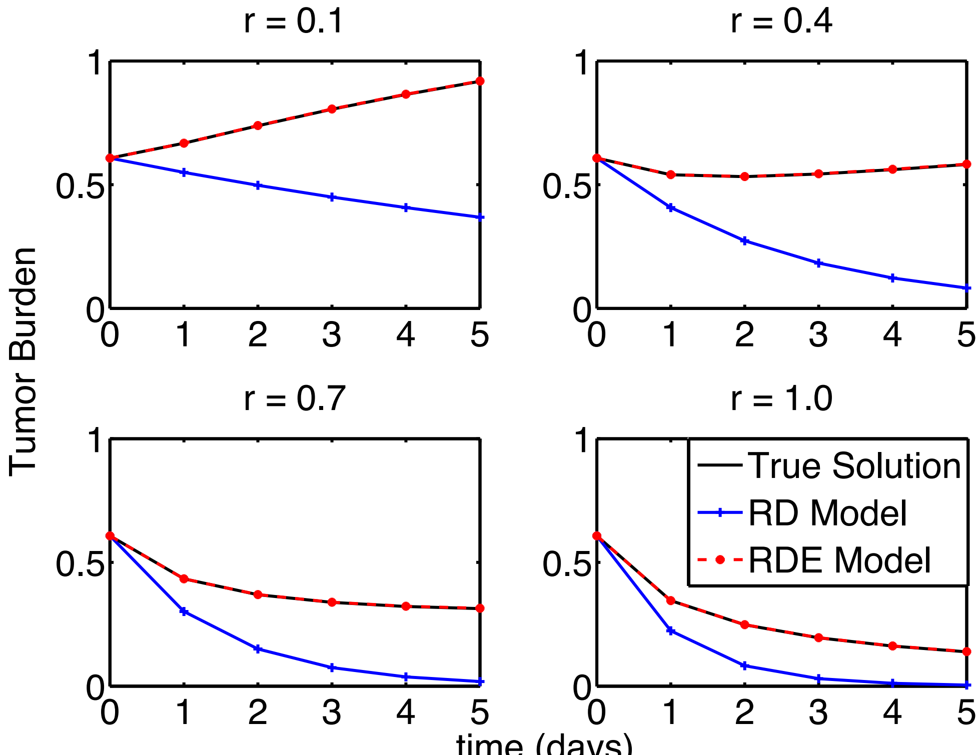


Rutter, Banks and Flores. Estimating Intratumoral Heterogeneity from Spatiotemporal Data. *Under review*

Treatment Prediction Assuming Heterogeneity

Assuming a log-kill hypothesis, we add the term:

$$-r\frac{\rho}{\bar{\rho}}u(t,x)$$

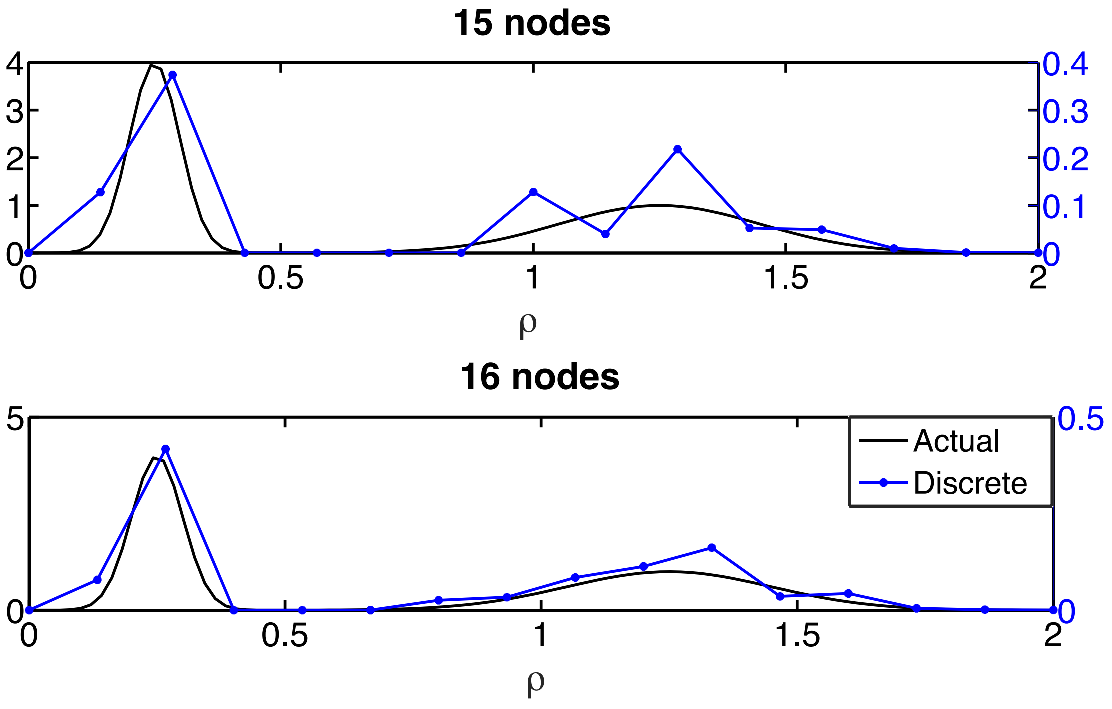


Conclusions

- We can recover parameter distributions from spatiotemporal data from a variety of pdfs
- Assuming cellular homogeneity may result in overestimating treatment efficacy
- However, there remain many questions to be answered…

Future Projects

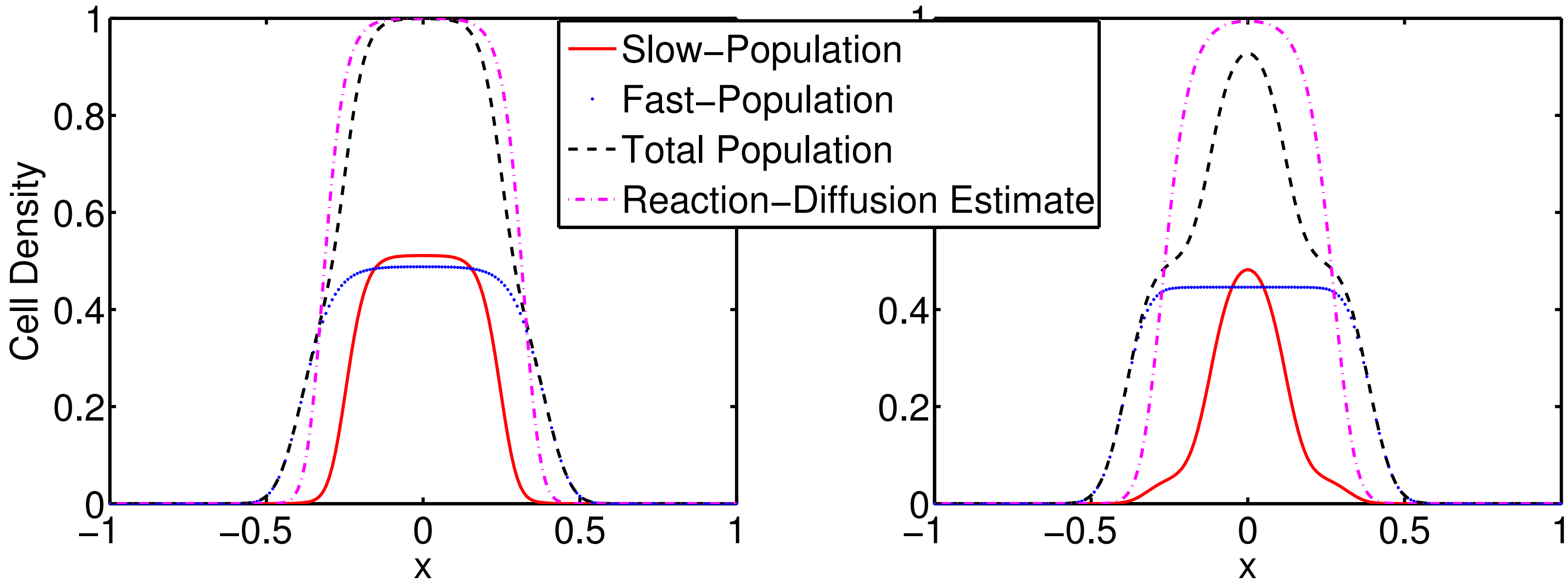
1. Adaptive meshing of nodes



Future Projects

2. Rewrite to consider carrying capacity on total population

$$\frac{\partial u(t,x,\rho_k)}{dt} = \nabla \cdot \left(D\nabla u(t,x,\rho_k)\right) + \rho_k u(t,x,\rho_k)\left(1 - \sum_{k=1}^{M} u(t,x,\rho_k)\right)$$



Future Projects

3. Uncertainty quantification/sensitivity analysis of resulting parameter distributions
4. How much data is needed to recover distributions?
5. Use the framework to model and estimate
   - Metabolic heterogeneity
   - Heterogeneity in therapy resistance
   - Androgen sensitivity in prostate cancer cells
6. Fit to *in vitro* or *in vivo* data
7. Extend framework to deal with 2D and 3D space

Thank you for your attention!

Questions?