Population Models-The Prohorov Metric Framework and Aggregate Data Inverse Problems

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- Consider approximation methods in estimation or inverse problems–quantity of interest is a probability distribution
- Assume we have parameter ($q \in Q$) dependent system with model responses $x(t, q)$ describing population of interest
- For data or observations, we are given a set of values $\{y_l\}$ for the expected values

$$\mathcal{E}[x_l(q)|P] = \int_Q x_l(q) dP(q)$$

for model $x_l(q) = x(t_l, q)$ wrt unknown probability distribution P describing distribution of parameters q over population

- Use data to choose from a given family $\mathcal{P}(Q)$ the distribution P^* that gives best fit of underlying model to data
- Formulate ordinary least squares (OLS) problem–not essential–could equally well use a WLS, MLE, etc., approach
- Seek to minimize

$$J(P) = \sum_l |\mathcal{E}[x_l(q)|P] - y_l|^2$$

  over $P \in \mathcal{P}(Q)$
- Even for simple dynamics for x_l is an infinite dimensional optimization problem–need approximations that lead to computationally tractable schemes
- That is, it is useful to formulate methods to yield finite dimensional sets $\mathcal{P}^M(Q)$ over which to minimize $J(P)$
- Of course, we wish to choose these methods so that "$\mathcal{P}^M(Q) \to \mathcal{P}(Q)$" in some sense

- In this case we shall use *Prohorov metric* [BBPP, Bi] of weak star convergence of measures to assure the desired approximation results

The data $\{y_l\}$ available (which, in general, will involve longitudinal or time evolution data) determines the nature of the problem.

- **Type I**: The most classical problem (which we shall refer to as a *Type I* problem) is one in which individual longitudinal data is available for each member in the population. In this case there is a wide statistical literature (in the context of hierarchical modeling, mixing distributions, mixed or random effects, mixture models, etc.)
  [BS, DGa1, DGa2, DG1, DG2, L1, L2, LL, Ma, SRM, S1, S2]
  which provides theory and methodology for estimating not only individual parameters but also population level parameters and allows one to investigate both intra-individual and inter-individual variability in the population and data.

- **Type II**: In what we shall refer to as *Type II* problems one has only *aggregate* or population level longitudinal data available. This is common in marine, insect, etc., *catch and release* experiments [BK] where one samples at different times from the same population but cannot be guaranteed of observing the same set of individuals at each sample time. This type of data is also typical in experiments where the organism or population member being studied is sacrificed in the process of making a single observation (e.g., certain physiologically based pharmacokinetic (PBPK) modeling [BPo, E, Po] and whole organism transport models [BK]). In this case one may still have dynamic (i.e., time course) models for individuals, but no individual data is available.

- **Type III:** Finally, the third class of problems which we shall refer to as *Type III* problems involves dynamics which depend explicitly on the probability distribution P itself. In this case one only has dynamics (*aggregate dynamics*) for the expected value

$$\bar{x}(t) = E[x(t, q, P)|P]$$

of the state variable. *No dynamics* are available for *individual trajectories* x(t, q) for a given $q \in Q$. Such problems arise in *viscoelasticity* and *electromagnetics* as well as biology (the HIV cellular models of Banks, Bortz and Holte [BBH]) see also [BBPP, BG1,BG2,G].

- While the approximations we discuss below are applicable to all three types of problems, we shall illustrate the computational results in the context of *size-structured marine populations (mosquitofish, shrimp)* and *Glioblastoma Multiforme (GBM)* where the inverse problems are of Type II.
- Finally, we note that in the problems considered here, one *can not sample directly from the probability distribution* being estimated and this again is somewhat different from the usual case treated in some of the statistical literature, e.g., see [Wahba1, Wahba2] and the references cited therein.

Example 1: The Growth Rate Distribution Model and Inverse Problem in Marine Populations

- Motivating application: estimation of growth rate distributions for size-structured mosquitofish and shrimp populations.
- Mosquitofish used in place of pesticides to control mosquito populations in rice fields–Marine biologists desire to correctly predict growth and decline of mosquitofish population–in order to determine the optimal densities of mosquitofish to use to control mosquito populations–a mathematical model that accurately describes the mosquitofish population would be beneficial in this application, as well as in other problems involving population dynamics and age/size-structured data.

- Based on data collected from rice fields, a reasonable mathematical model would have to predict two key features that are exhibited in the data: *dispersion* and *bifurcation* (i.e., a unimodal density becomes a bimodal density) of the population density over time [BBKW, BI, BFPZ].
- *Growth rate distribution (GRD) model*, developed in [BBKW] and [BI], captures both of these features in its solutions.
- Model is a modification of the *Sinko-Streifer model* (used for modeling age/size-structured populations) which takes into account that individuals have different characteristics or behaviors.

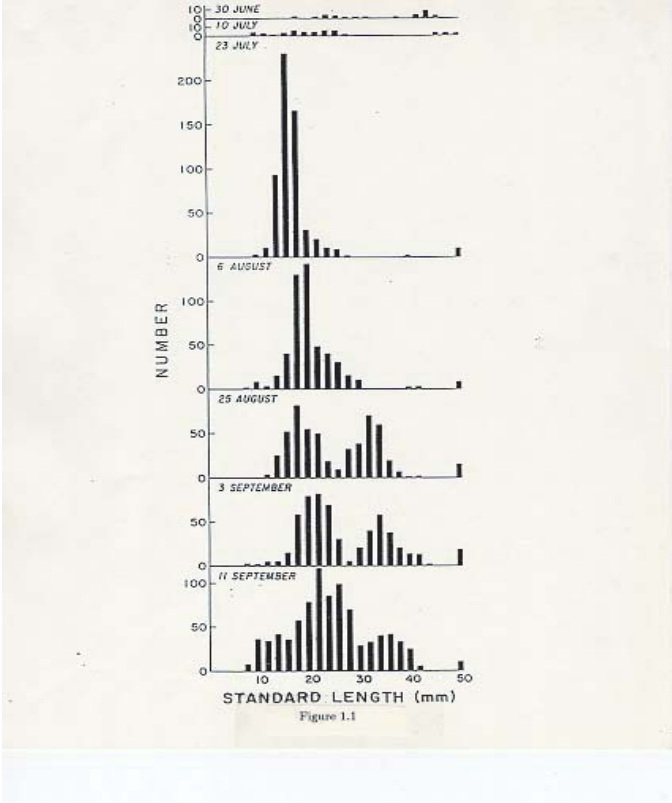


Figure:

Mosquitofish data.

- *Sinko-Streifer model (SS)* for size-structured mosquitofish populations given by

$$\begin{aligned} \frac{\partial v}{\partial t} + \frac{\partial}{\partial x}(gv) &= -\mu v, \quad x_0 < x < x_1, \quad t > 0 \qquad (1) \\ v(0,x) &= \Phi(x) \\ g(t,x_0)v(t,x_0) &= \int_{x_0}^{x_1} K(t,\xi)v(t,\xi)\partial\xi \\ g(t,x_1) &= 0. \end{aligned}$$

Here $v(t,x)$ represents size (given in numbers per unit length) or population density, where t represents time and x represents length of mosquitofish–growth rate of individual mosquitofish given by $g(t,x)$, where

$$\frac{dx}{dt} = g(t,x) \qquad (2)$$

for each individual (all mqf of given size have same growth rate)

- In SS $\mu(t,x)$ represents *mortality rate* of mosquitofish–function $\Phi(x)$ represents initial size density of the population, while K represents the *fecundity kernel.* The boundary condition at $x = x_0$ is *recruitment*, or *birth rate*, while the boundary condition at $x = x_1 = x_{max}$ ensures the maximum size of the mosquitofish is x_1. The SS model cannot be used as is to model the mosquitofish population because it *does not predict dispersion or bifurcation* of the population in time under biologically reasonable assumptions [BBKW, BI].

- By modifying the SS model so that the individual growth rates of the mosquitofish *vary across the population* (instead of being the same for all individuals in the population), one obtains a model, known as the *growth rate distribution (GRD) model*–does in fact exhibit both dispersal in time and development of a bimodal density from a unimodal density (see [BI, BFPZ]).
- In (GRD) model, population density $u(t, x; P)$, discussed in [BBKW] and developed in [BI], is actually given by

$$u(t, x; P) = \int_G v(t, x; g) dP(g). \tag{3}$$

- G is collection of admissible growth rates, P is probability measure on G, and $v(t, x; g)$ is solution of (SS) with g– model assumes pop. made up of *collections of subpopulations* –individuals in same subpopulation have same growth rate

- Based on work in [BI], solutions to GRD model exhibit both dispersion and bifurcation of the population density in time. Here assume that the *admissible growth rates* g have the form

$$g(x; b, \gamma) = b(\gamma - x)$$

for $x_0 \leq x \leq \gamma$ and zero otherwise, where b is the *intrinsic growth rate* of the mosquitofish and $\gamma = x_1$ is the maximum size. This choice based on work in [BBKW], where idea of other properties related to the growth rates varying among the mosquitofish is discussed.

- Under assumption of varying intrinsic growth rates and maximum sizes, assume that b and γ are *random variables* taking values in the compact sets B and Γ, respectively. A reasonable assumption is that both are *bounded closed intervals*.

- Thus we take

$$G = \{g(\cdot; b, \gamma) | b \in B, \gamma \in \Gamma\}$$

so that G is also compact in, for example, $C[x_0, X]$ where $X = \max(\Gamma)$. Then $\mathcal{P}(G)$ is compact in the Prohorov metric and we are in framework outlined above. In illustrative examples, choose a growth rate parameterized by the intrinsic growth rate b with $\gamma = 1$, leading to a one parameter family of varying growth rates g among the individuals in the population. We also assume here that $\mu = 0$ and $K = 0$ in order to focus on only the distribution of growth rates; however, distributions could just as well be placed on μ and K.

- Next, introduce two different approaches that can be used in inverse problem for estimation of distribution of growth rates of the mosquitofish

- *First approach*, which has been discussed and used in [BI] and [BFPZ], involves the use of *delta distibutions*. We assume that probability distributions $\mathcal{P}^M$ placed on growth rates are *discrete* corresponding to a collection G^M with the form $G^M = \{g_k\}_{k=1}^M$ where $g_k(x) = b_k(1-x)$, for $k = 1, \ldots, M$. Here the $\{b_k\}$ are a *discretization* of B. For each subpopulation with growth rate g_k, there is a corresponding probability p_k that an individual is in subpopulation k. The population density $u(t, x; P)$ in (3) is then approximated by

$$u(t, x; \{p_k\}) = \sum_k v(t, x; g_k) p_k,$$

where $v(t, x; g_k)$ is the subpopulation density from (SS) with growth rate g_k. We denote this delta function approximation method as DEL(M), where M is number of elements used in this approximation.

- While it has been shown that DEL(M) provides a reasonable approximation to (3), a better approach might involve techniques that will provide a smoother approximation of (3) in the case of continuous probability distributions on the growth rates. Thus, as a *second approach*, we chose to use an approximation scheme based on piecewise linear splines. Here we have assumed that P is a continuous probability distribution on the intrinsic growth rates. We approximate the density $P' = \frac{dP}{db} = p(b)$ using piecewise linear splines, which leads to the following approximation for $u(t, x; P)$ in (3):

$$u(t, x; \{a_k\}) = \sum_k a_k \int_B v(t, x; g) l_k(b) db,$$

where $g(x; b) = b(1 - x)$, $p_k(b) = a_k l_k(b)$ is the probability density for an individual in subpopulation k and l_k represents the piecewise linear spline functions.

- This spline based approximation method is denoted by SPL(M,N), where M is the number of basis elements used to approximate the growth rate probability distribution and N is the number of quadrature nodes used to approximate the integral in the formula above. One can use the composite trapezoidal rule for the approximation of these integrals [QSS].

- One can use the approximation methods DEL(M) and SPL(M,N) in the inverse problem for the estimation of the growth rate distributions. The least squares inverse problem to be solved is

$$\begin{aligned} \min_{P\in\mathcal{P}^M(G)} J(P) &= \sum_{i,j} |u(t_i,x_j;P)-\hat{u}_{ij}|^2 \qquad (4)\\ &= \sum_{i,j} (u(t_i,x_j;P))^2 - 2u(t_i,x_j;P)\hat{u}_{ij} + (\hat{u}_{ij})^2, \end{aligned}$$

where $\{\hat{u}_{ij}\}$ is the data and $\mathcal{P}^M(G)$ is the finite dimensional approximation to $\mathcal{P}(G)$. When using DEL(M), the finite dimensional approximation $\mathcal{P}^M(G)$ to the probability measure space $\mathcal{P}(G)$ is given by

$$\mathcal{P}^M(G) = \left\{ P\in\mathcal{P}(G)|\ P' = \sum_k p_k\delta_{g_k},\ \sum_k p_k = 1 \right\},$$

where δ_{g_k} is the delta function with an atom at g_k. However, when using SPL(M,N), the finite dimensional approximation $\mathcal{P}^M(G)$ is given by

$$\mathcal{P}^M(G) = \left\{ P \in \mathcal{P}(G) |\ P' = \sum_k a_k l_k(b),\ \sum_k a_k \int_B l_k(b) db = 1 \right\}.$$

- Furthermore, we note that this least squares inverse problem (4) becomes a quadratic programming problem [BI, BFPZ]. Letting $\mathbf{p}$ be the vector that contains $p_k, 1 \le k \le M$, when using DEL(M) or $a_k, 1 \le k \le M$, when using SPL(M,N), we let $\mathbf{A}$ be the matrix with entries given by

$$A_{km} = \sum_{i,j} v(t_i, x_j; g_k) v(t_i, x_j; g_m),$$

$\mathbf{b}$ the vector with entries given by

$$b_k = -\sum_{i,j} \hat{u}_{ij} v(t_i, x_j; g_k),$$

and

$$c = \sum_{i,j} (\hat{u}_{ij})^2,$$

where $1 \leq k, m \leq M$. In the place of (4), we now minimize

$$F(\mathbf{p}) \equiv \mathbf{p}^T \mathbf{A}\mathbf{p} + 2\mathbf{p}^T \mathbf{b} + c \tag{5}$$

over $\mathcal{P}^M(G)$. We note when using DEL(M) we also had to include the constraint

$$\sum_k p_k = 1,$$

while when using SPL(M,N) we had to include the constraint

$$\sum_k a_k \int_B l_k(b) db = 1.$$

However, in both cases, we were able to include these constraints along with non-negativity constraints on the $\{p_k\}$ and $\{a_k\}$ in the programming of these two inverse problems.

Example 2: Glioblastoma Multiforme (GBM)

- Glioblastoma Multiforme (GBM) is a deadly primary brain tumor
- GBM is characterized by both high proliferation and diffusivity
- Mean Survival time with treatment is less than 15 months after detection
- Begins avascularaly, so early stages can be modeled by spheroids
- Symptoms include
  - hemorrhaging
  - nausea
  - vomiting
  - headaches
  - memory loss
  - seizures

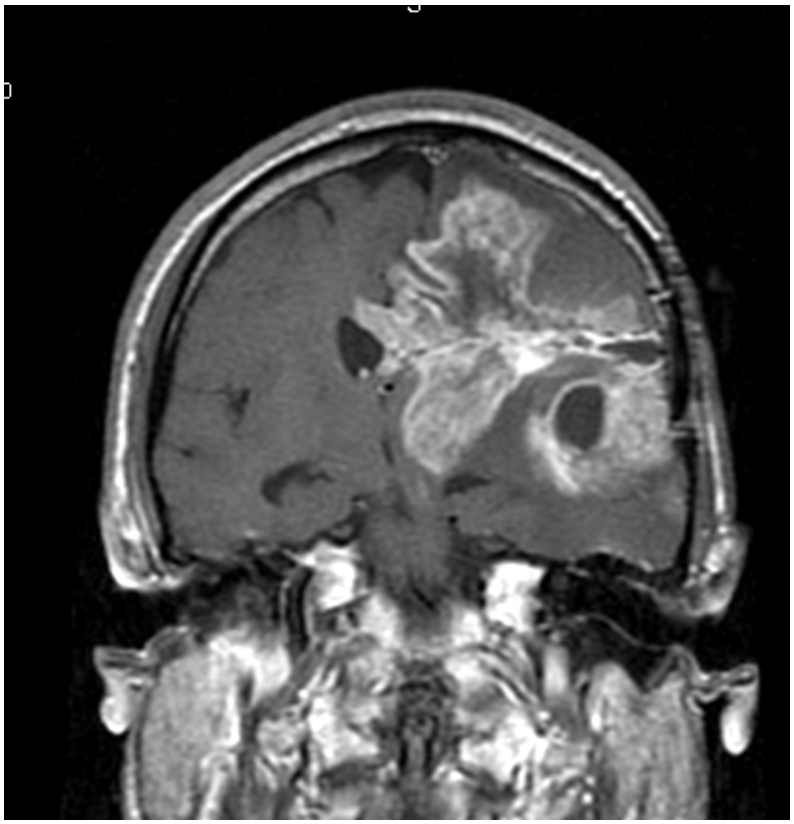
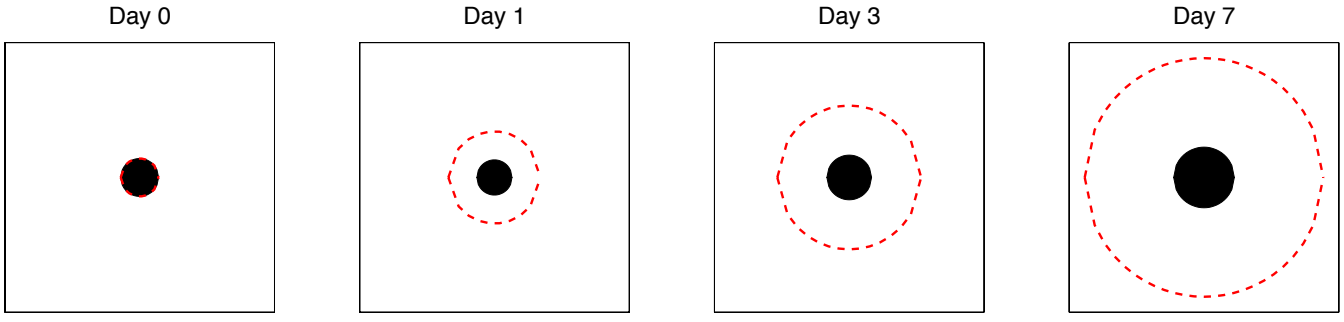


Figure: Sagittal cross-section of human brain with GBM

A Biological Introduction

- In 2007, Stein et. al performed cell line experiments on most common mutation of Epidermal Growth Factor Receptor gene (U87ΔEGFR) and wild-type EGFR (U87WT)
- This proved there are distinct behavioral differences between 'migrating' cells and 'proliferating cells'
- Concluded that migrating and proliferating cells must be modeled separately using equation

$$\frac{\partial u_i(r,t)}{\partial t} = \underbrace{D\nabla^2 u_i}_{\text{diffusion}} + \underbrace{g u_i\left(1 - \frac{u_i}{u_{\max}}\right)}_{\text{logistic growth}} - \underbrace{v_i \nabla_r \cdot u_i}_{\text{taxis}} + \underbrace{s\delta(r - R(t))}_{\text{shed cells from core}}$$



We propose to describe GBM cell phenotypic heterogeneity by using parameter distributions for the parameters ρ and D. The random differential equation governing diffusion and growth is:

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

We assume that the parameters $\boldsymbol{D}$ and $\boldsymbol{\rho}$ are random variables defined on a compact set $\Omega = \Omega_{\boldsymbol{D}} \times \Omega_{\boldsymbol{\rho}}$. The distribution of the parameters is given by $P(\boldsymbol{D},\boldsymbol{\rho})$, and $v(t,x)$ represents the aggregate population observable (which is defined as the expectation over subpopulations $c(t,x,\boldsymbol{D},\boldsymbol{\rho})$:

$$v(t,x) = \mathbb{E}\left[c(t,x,\cdot,\cdot),P\right] = \int_{\Omega} c(t,x,\boldsymbol{D},\boldsymbol{\rho}) dP(\boldsymbol{D},\boldsymbol{\rho})$$

The random differential equation is sufficiently flexible to model the classic reaction-diffusion equation (assuming a point distribution of $\boldsymbol{D}$ and $\boldsymbol{\rho}$) and a "go or grow" type equation (assuming, for example, a bi-gaussian distribution of $\boldsymbol{D}$ and $\boldsymbol{\rho}$).

Two different methods for approximating the probability measure $P(\boldsymbol{D}, \boldsymbol{\rho})$ are using either delta functions or spline functions. Although using spline functions are known to yield more accurate convergence in the probability density function (PDF) and cumulative distribution function (CDF), delta functions are able to better approximate CDFs that have discontinuous derivatives. Therefore, we illustrate use of both approximations, since we do not wish to make any assumptions about, or restrictions on, the CDF.

Suppose that the aggregate spatiotemporal data we want to model is given by v_{ji}, representing the data at time j and spatial location i, where $j = 1, .., N_t$ and $i = 1, ..., N_x$. Then, we estimate:

$$\hat{P} = \underset{P^M(\Omega)}{\operatorname{argmin}} \sum_{j,i=1}^{N_t,N_x} (v_{ji} - v(t_j, x_i; P))^2$$

where M represents the number of elements used in the approximation (explained in the sections below).

This becomes:

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

where c is the numerical solution. Previous experimental data [Stein2007] suggests that it is not unreasonable to assume that data can be collected radially at spatial increments of 40 microns, daily. This is the basis for describing the data in the form of v_{ji}. Two methods are used to approximate the probability measure P: a discrete approximation based on delta functions, and a continuous approximation using spline basis functions.

Convergence and Consistency Theory

The Prohorov metric is the weak* convergence of measures when the space of probability measures $P(\Omega)$ is imbedded in the dual $C^*(\Omega)$ of space of bounded continuous functions on Ω. We discuss briefly convergence, consistency theory, assuming only estimating $\boldsymbol{D}$ as a distribution, (we note theory extends to two parameters). We assume a family of permissible probability functions for our diffusion and growth rates on $P(\Omega)$. We attempt to perform the estimation in a least-squares framework

$$\hat{P} = \underset{P \in P(\Omega)}{\operatorname{argmin}} J_N(\vec{v}, P) = \underset{P \in P(\Omega)}{\operatorname{argmin}} \sum_{j,i} (v_{ji} - v(t_j, x_i; P))^2 \qquad (6)$$

to obtain a best fit for a nominal or "true" parameter P_0. To illustrate, let $\Omega = \Omega_{\boldsymbol{D}}$ be the continuum of values on $[0, D_{\max}]$. Hence family of probability functions $P(\Omega)$ is a compact metric space in the Prohorov metric. Minimizer function is continuous in P; there exists a (not necessarily unique) minimizer $\hat{P}$.

Existence of the Estimator

One can prove the existence [BanksThompson2015] of P_N and $\hat{P}_N$ as measurable functions mapping a subset of $\mathbb{R}^N$ (that is, the data $\vec{v} \in \mathbb{R}^N$ where $N = (N_t, N_x)$) into the space of probability measures on Ω. We remark that the statement of the existence thm concerns the estimate $\hat{P}_N$ obtained from the data realizations $\vec{v} \in \mathbb{R}^N$. This is sufficient to establish the existence of the estimator P_N as a measureable function as well, since the random vector $\vec{V}$ is by definition a measurable function from a probability triple into $\mathbb{R}^N$, and the composition of measurable functions is measurable.

Theorem

Define the function $J_N : \mathbb{R}^N \times \mathcal{P}(\Omega) \to \mathbb{R}$ *according to Equation* (6). *Assume* (Ω, d) *is separable and compact and take the space of probability measures* $\mathcal{P}(\Omega)$ *with the Prohorov metric* ρ. *Assume further that* $J_N(\cdot, P)$ *is a measurable function from* $\mathbb{R}^N \to \mathbb{R}$ *for each* $P \in \mathcal{P}(\Omega)$, *and that* $J_N(\vec{v}, \cdot) : \mathcal{P}(\Omega) \to \mathbb{R}$ *is continuous for each* $\vec{v} \in \mathbb{R}^N$. *Then there exists a measurable function* $\hat{P}_N : \mathbb{R}^N \to \mathcal{P}(\Omega)$ *such that*

$$J(\vec{v}, \hat{P}_N(\vec{v})) = \inf_{P \in \mathcal{P}(\Theta)} J(\vec{v}, P).$$

In order to approximate this minimizer, we replace the infinite dimensional optimization problem by a sequence of finite-dimensional optimization problems with Dirac distributions. Thus, we set $\Omega^M = \{\Delta_{D_k}, k = 1, .., M\}$, where M represents the number of nodes, or elements, used in the approximation. Our family of approximating probability functions becomes

$$P^M(\Omega^M) = \left\{ P^M = \sum_{k=1}^{M} w_k \Delta_{D_k} | w_k \geq 0 \text{ and } \sum_{k=1}^{M} w_k = 1 \right\},$$

where Δ_{D_k} represent the Dirac delta functions at the point D_k and w_k are the weights and/or probabilities. Again it has been previously proven [Banks2012FA,BHT2014] that there exists a minimizer for the discrete approximation problem

$$\hat{P}^M = \underset{P \in P^M(\Omega^M)}{\text{argmin}} \sum_{j,i=1}^{N_t,N_x} (v_{ji} - v(t_j, x_i; P))^2.$$

There are a number of questions that arise immediately in the class of problems we have defined. Perhaps the most obvious are questions of convergence (what happens as $M \to \infty$ in the Dirac or spline approximations?) and consistency (what happens as $N = (N_t, N_x) \to \infty$?) These questions have been successfully investigated both theoretically ([BHT2014,BPin,BanksThompson2015] and the references therein) and computationally [BD2007,BDTR] and the references. A further issue involves the partial differential equation approximations $c_{\tilde{N}}$ to the solution c. Again, the necessary convergence issues have been successfully addressed in [BHT2014,BK1989]. In summary we can assert that the approximations $\hat{P}^M_{N,\tilde{N}}$ converge to a true distribution P_0 as the number of elements used in the approximations increase (i.e., $M, N, \tilde{N} \to \infty$).

Consistency of the Estimator

(A1) For any fixed $N = N_t \times N_x$, the error random variables $\{\mathcal{E}_j\}_{j=1}^{N}$ are independent and identically distributed, defined on some probability triple $(\Theta, \Sigma_\Theta, P_\Theta)$.

(A2) For $\vec{\mathcal{E}} = (\mathcal{E}_1, \ldots, \mathcal{E}_N)$, $E[\vec{\mathcal{E}}] = 0$ and $Cov[\vec{\mathcal{E}}] = \sigma^2 I_N$, where I_N is the $N \times N$ identity matrix.

(A3) (Ω, d) is a separable, compact metric space; the space $\mathcal{P}(\Omega)$ is taken with the Prohorov metric ρ.

(A4) For all j, $1 \leq j \leq N_t$, i, $1 \leq i \leq N_x$, $(t_j, x_i) \in \tilde{T}$ for some compact space $\tilde{T}$.

(A5) The model function $v \in C(\mathcal{P}(\Omega), C(\tilde{T}))$.

(A6) There exists a measure μ on $\tilde{T}$ such that for all $g \in C(\tilde{T})$

$$\frac{1}{N} \sum_{j,i=1} g(t_j, x_i) \equiv \int_{\tilde{T}} g(t,x) d\mu_N(t,x) \to \int_{\tilde{T}} g(t,x) d\mu(t,x)$$

(A7) The functional $J_0(P) = \int_{\tilde{T}} (v(t,x;P_0) - v(t,x;P))^2 \, d\mu(t,x)$ is uniquely minimized at $P_0 \in \mathcal{P}(\Omega)$.

Theorem

Under assumptions (A1)-(A7), the estimators $P_N \xrightarrow{w^*} P_0$ *as* $N \to \infty$ *with probability 1. That is,*

$$P_\Omega\left(\left\{\theta \middle| P_N(\vec{V})(\theta) \to P_0\right\}\right) = 1.$$

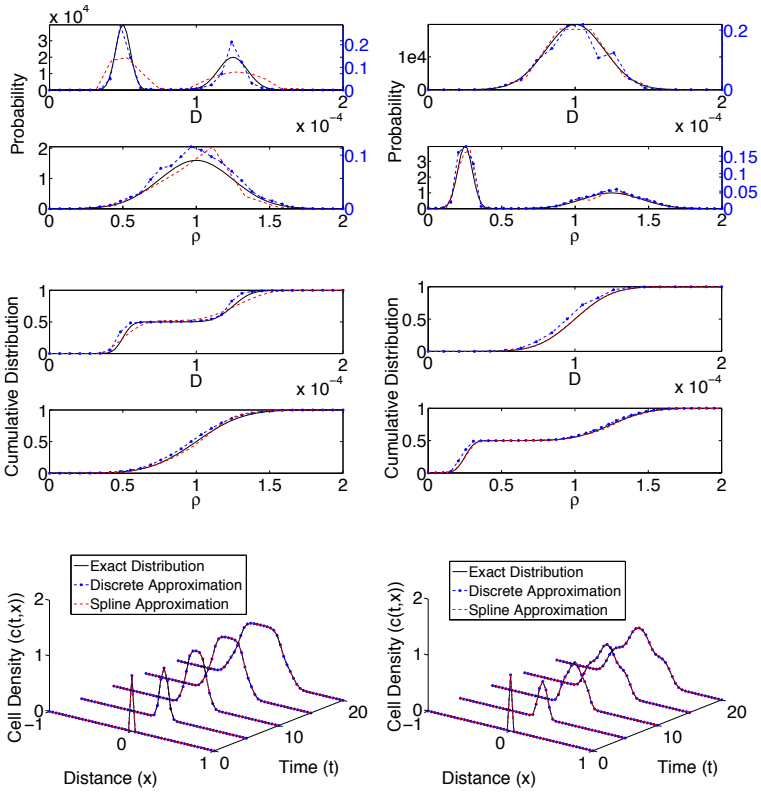


Figure: Fits (no noise) using the optimal number of nodes ($\boldsymbol{\rho}$ bigaussian; $\boldsymbol{D}$ normally distributed) (left); $\boldsymbol{D}$ bigaussian, $\boldsymbol{\rho}$ normally distributed (right). Top panels: pdf comparisons for actual distribution (black), spline approximation (red), discrete approximation (blue). Middle panel: cdf comparisons. Bottom panel: solutions of RDE.

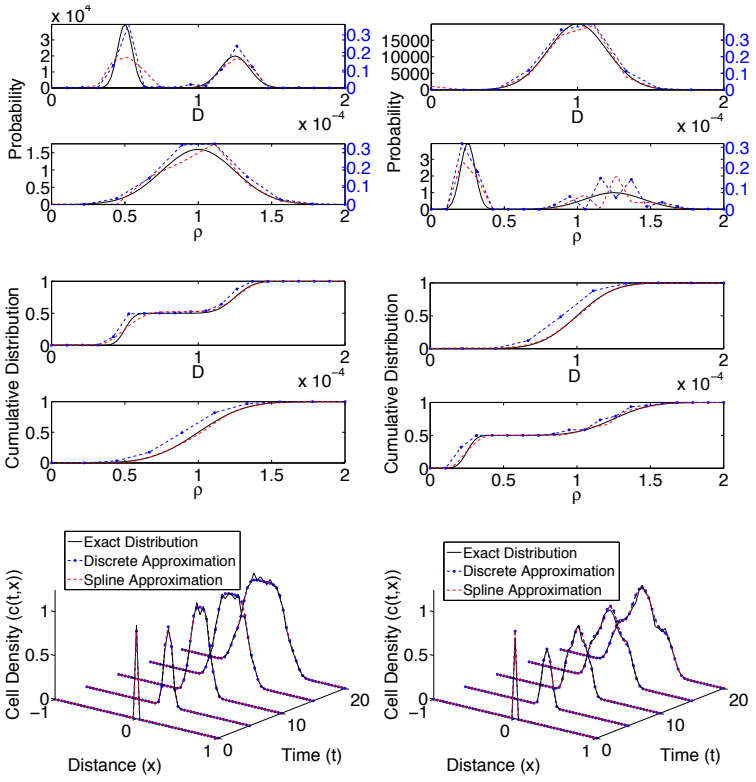


Figure: Fits using the optimal number of nodes $\boldsymbol{D}$ bigaussian and $\boldsymbol{\rho}$ normally distributed (left) and case where $\boldsymbol{\rho}$ bigaussian and $\boldsymbol{D}$ normally distributed (right) for solutions which have added noise. Top panels: pdf comparisons for actual solution, the spline approximation and the discrete approximation. In middle: the cdfs. Bottom: the solutions of RDE.

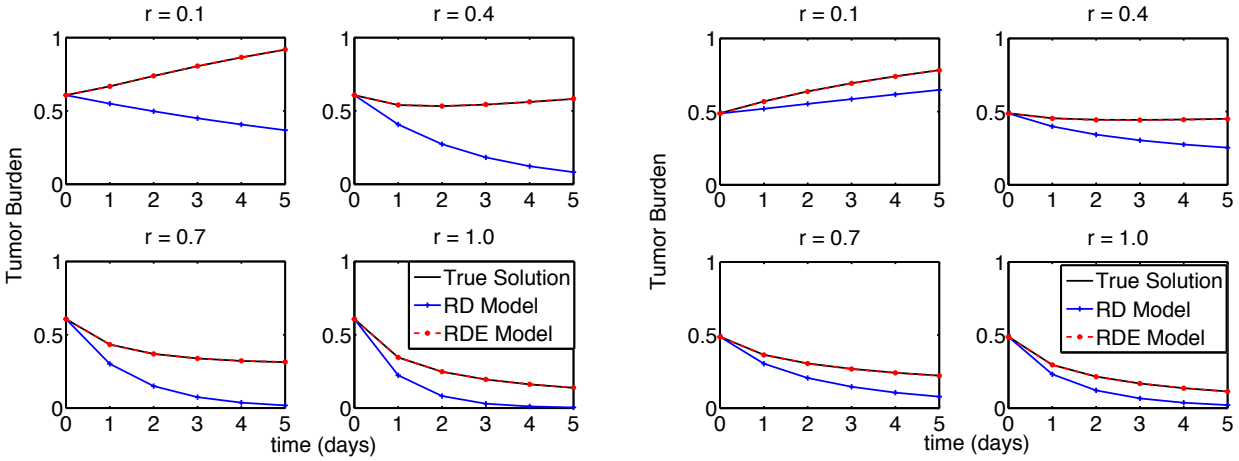


Figure: Simulations of log-kill chemotherapy treatment for the case where $\boldsymbol{D}$ is bigaussian and $\boldsymbol{\rho}$ is normal (left) and the case where $\boldsymbol{D}$ is normally distributed and $\boldsymbol{\rho}$ is bigaussian for varying values of r (right). The reaction-diffusion equation, shown in blue solid line with pluses, vastly overestimates the efficacy of chemotherapy treatment. The RDE model (red dashes) with parameter distributions estimated from noisy data almost exactly match the true solution.

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