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INVERSE PROBLEMS FOR NONLINEAR DELAY SYSTEMS*

H. T. BANKS†, KERI REHM†, AND KARYN SUTTON†

Abstract. We consider inverse or parameter estimation problems for general nonlinear nonautonomous dynamical systems with delays. The parameters may be from a Euclidean set as usual, may be time dependent coefficients or may be probability distributions across a population as arise in aggregate data problems. Theoretical convergence results for finite dimensional approximations to the systems are given. Several examples are used to illustrate the ideas and computational results that demonstrate efficacy of the approximations are presented.

Key words. Nonlinear delay systems, inverse problems, uncertainty, computational methods.

AMS subject classifications. 34C55, 34K06, 34K28, 34K29, 34G20, 93C10.

1. Introduction. Delay differential equations have been a topic of much interest in the mathematical research literature for more than 50 years. Contributions range from classical applications and theoretical and computational methodologies [Ba79, Ba82, BBu1, BBu2, BKap, BellCook, Cushing, Diekmann, Driver, Gorecki, JKH1, JKH2, JKH3, Kap82, KapSal87, KapSal89, KapSch, Kuang, Minorsky, Webb, Wright] to modern applications in biology [BBJ, BBH, MSNP, NMiP, NMuP, NP]. In this paper we return to a topic that has become increasingly relevant in current research: a theoretical and computational approach for inverse problems involving nonlinear delay systems. One approach that is by now classical dates back to the 1970's [Ba79, BBu1, BBu2, BKap]. In this approach one approximates solutions to the infinite dimensional state systems such as (1) below by first converting them to an abstract evolution equation in a functional analytic state space setting. One can approximate solutions in finite dimensional subspaces spanned by pre-chosen basis elements (e.g., piece-wise linear or cubic splines) in a Galerkin approach which is equivalent to a finite element approximation framework (as is classically used for partial differential equations). One is then able to numerically calculate the generalized Fourier coefficients of approximate solutions relative to the splines, and with these coefficients, recover an approximation to the solutions of delay systems (1).

Here we turn to the mathematical aspects of these nonlinear FDE systems and present an outline of the necessary mathematical and numerical analysis foundations. Thus we provide an extension (to treat time dependent coefficients and general parameters including probability measures) of arguments for approximation and convergence in inverse problems found in [Ba82].

For nonlinear delay systems such as those discussed here, approximation in the context of a linear semigroup framework as presented [BBu1, BBu2, BKap] is not direct. However one can use the ideas of that theory as a basis for a wide class of nonlinear delay system approximations. Details in this direction can be found in the early work [Ba79, Kap82] which is a direct extension of the results of [BBu1, BBu2, BKap] to nonlinear delay systems. The new theoretical results presented here are extensions of these earlier ideas to general nonlinear, nonautonomous delay systems; specifically we extend the ideas of [Ba82] to treat nonlinear systems with time dependent coefficients

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†Center for Research in Scientific Computation & Center for Quantitative Sciences in Biomedicine, North Carolina State University, Raleigh, NC 27695-8212, USA ({htbanks; klrehm; klsutton}@ncsu.edu).

and/or parameters that may be probabilistic in nature (i.e., probability distributions as treated in [BBoIP, BBPP]). Several current application areas are used to illustrate the theory with examples.

We consider general systems of the form

$$\dot{z}(t) = f(t, z(t), z_t, z(t-\tau_1), \ldots, z(t-\tau_m), q) + f_2(t), \quad 0 \le t \le T, \quad z_0 = \phi \tag{1}$$

where $f = f(t, \eta, \psi, y_1, \ldots, y_m, q) : [0,T] \times X \times \mathbb{R}^{nm} \times \mathcal{Q} \to \mathbb{R}^n$. Here $X = \mathbb{R}^n \times L_2(-r, 0; \mathbb{R}^n)$, $0 < \tau_1 < \ldots < \tau_m = r$, z_t denotes the usual function $z_t(\theta) = z(t+\theta)$, $-r \le \theta \le 0$, and $\phi \in H^1(-r, 0)$. Here the admissible parameter set $\mathcal{Q}$ is a subset of a metric space (possibly infinite dimensional – i.e., some set of functions).

Associated with this system is an ordinary least squares [BDSS, BT] cost functional to be minimized. That is, we consider the problem of minimizing over $q \in \mathcal{Q}$ the ordinary least squares output functional

$$J(q, d) = \sum_{i=1}^{K} | Cz(t_i; q) - d_i |^2 , \tag{2}$$

where C is an observation operator and $\{d_i\}$ is a given data set.

As we shall see below, one can rewrite (1) as

$$\begin{aligned} \dot{x}(t) &= \mathcal{A}(t, q)x(t) + f(t) \\ x(0) &= x_0 , \end{aligned} \tag{3}$$

for states $x(t) = (z(t), z_t)$ in an abstract space X. One can then develop theoretical and computational methodologies to treat finite dimensional approximations in spaces X^N and $\mathcal{Q}^M$. These ideas are the focus of our presentation below.

2. Inverse or parameter estimation problems.

2.1. Approximation and convergence. For more details on general inverse problem methodology in the context of abstract distributed systems, the reader may consult [BK, BSW]. The book [BK] contains a general treatment of inverse problems for partial differential equations in a functional analytic setting. Here we treat nonlinear delay systems with a general family of probabilistic parameters.

The minimization in general abstract parameter estimation problems for (3) involves an infinite dimensional state space X and an infinite dimensional admissible parameter set $\mathcal{Q}$ (generally of functions or even probability distributions). To obtain computationally tractable methods, we thus consider Galerkin type approximations. Let X^N be a sequence of finite dimensional subspaces of X, and $\mathcal{Q}^M$ be a sequence of finite dimensional sets approximating the parameter set $\mathcal{Q}$. We denote by P^N the orthogonal projections of X onto X^N. Then a family of approximating estimation problems with finite dimensional state spaces and parameter sets can be formulated by seeking $q \in \mathcal{Q}^M$ which minimizes

$$J^N(q, d) = \sum_{i=1}^{K} | Cx^N(t_i; q) - d_i |^2, \tag{4}$$

where $x^N(t; q) \in X^N$ is the solution to a finite dimensional approximation of (3)) given by

$$\begin{aligned} \dot{x}^N(t) &= \mathcal{A}^N(t, q)x^N(t) + P^N f(t) \\ x^N(0) &= P^N x_0. \end{aligned} \tag{5}$$

For the parameter sets $\mathcal{Q}$ and $\mathcal{Q}^M$, and state spaces X^N, we make the following hypotheses.

(A1M) The sets $\mathcal{Q}$ and $\mathcal{Q}^M$ lie in a metric space $\tilde{\mathcal{Q}}$ with metric d. It is assumed that $\mathcal{Q}$ and $\mathcal{Q}^M$ are compact in this metric and there is a mapping $i^M : \mathcal{Q} \to \mathcal{Q}^M$ so that $\mathcal{Q}^M = i^M(\mathcal{Q})$. Furthermore, for each $q \in \mathcal{Q}$, $i^M(q) \to q$ in $\tilde{\mathcal{Q}}$ with the convergence uniform in $q \in \mathcal{Q}$.

(A2N) The finite dimensional subspaces X^N satisfy the approximation: For each $x \in X, |x - P^N x|_X \to 0$ as $N \to \infty$.

Solving the approximate estimation problems involving (4),(5), we obtain a sequence of parameter estimates $\{\bar{q}^{N,M}\}$. It is of paramount importance to establish conditions under which $\{\bar{q}^{N,M}\}$ (or some subsequence) converges to a solution for the original infinite dimensional estimation problem involving (2),(3). Toward this goal we have the following results.

THEOREM 1. *To obtain convergence of at least a subsequence of $\{\bar{q}^{N,M}\}$ to a solution $\bar{q}$ of minimizing* (4) *subject to* (5)*, it suffices, under assumption (A1M), to argue that for arbitrary sequences $\{q^{N,M}\}$ in $\mathcal{Q}^M$ with $q^{N,M} \to q$ in $\mathcal{Q}$, we have*

$$x^N(t; q^{N,M}) \to x(t; q). \tag{6}$$

Proof. Under the assumptions (A1M), let $\{\bar{q}^{N,M}\}$ be solutions minimizing (4) subject to the finite dimensional system (5) and let $\hat{q}^{N,M} \in \mathcal{Q}$ be such that $i^M(\hat{q}^{N,M}) = \bar{q}^{N,M}$. From the compactness of $\mathcal{Q}$, we may select subsequences, again denoted by $\{\hat{q}^{N,M}\}$ and $\{\bar{q}^{N,M}\}$, so that $\hat{q}^{N,M} \to \bar{q} \in \mathcal{Q}$ and $\bar{q}^{N,M} \to \bar{q}$ (the latter follows from the last statement of (A1M)). The optimality of $\{\bar{q}^{N,M}\}$ guarantees that for every $q \in \mathcal{Q}$

$$J^N(\bar{q}^{N,M}, d) \le J^N(i^M(q), d). \tag{7}$$

Using (6), the last statement of (A1M) and taking the limit as $N, M \to \infty$ in the inequality (7), we obtain $J(\bar{q}, d) \le J(q, d)$ for every $q \in \mathcal{Q}$, or that $\bar{q}$ is a solution of the problem for (2),(3). We observe that under uniqueness assumptions on the problems (a situation that we hasten to add is not often realized in practice), one can actually guarantee convergence of the entire sequence $\{\bar{q}^{N,M}\}$ in place of subsequential convergence to solutions.

We note that the essential aspects in the arguments given above involve compactness assumptions on the sets $\mathcal{Q}^M$ and $\mathcal{Q}$. Such compactness ideas play a fundamental role in other theoretical and computational aspects of these problems. For example, one can formulate distinct concepts of *problem stability* and *method stability* as in [BK] involving some type of continuous dependence of solutions on the observations z, and use conditions similar to those of (6) and (A1M), with compactness again playing a critical role, to guarantee stability. We illustrate with a simple form of *method stability* (other stronger forms are also amenable to this approach–see [BK]).

We might say that an *approximation method,* such as that formulated above involving $\mathcal{Q}^M, X^N$ and (4)-(5), is *stable* if

$$dist(\tilde{q}^{N,M}(d^k), \tilde{q}(d^*)) \to 0$$

as $N, M, k \to \infty$ for any $d^k \to d^*$ (in this case in the appropriate Euclidean space), where $\tilde{q}(z)$ denotes the set of all solutions of the problem for (2)-(3) and $\tilde{q}^{N,M}(d)$

denotes the set of all solutions of the problem for (4)-(5). Here "dist" represents the usual distance set function. Under (6) and (A1M), one can use arguments very similar to those sketched above to establish that one has this method stability. If the sets $\mathcal{Q}^M$ are not defined through a mapping i^M as supposed above, one can still obtain this method stability if one replaces the last statement of (A1M) by the assumptions:

(i) If $\{q^M\}$ is *any* sequence with $q^M \in \mathcal{Q}^M$, then there exist q^* in $\mathcal{Q}$ and subsequence $\{q^{M_k}\}$ with $q^{M_k} \to q^*$ in the $\tilde{\mathcal{Q}}$ topology.

(ii) For *any* $q \in \mathcal{Q}$, there exists a sequence $\{q^M\}$ with $q^M \in \mathcal{Q}^M$ such that $q^M \to q$ in $\tilde{\mathcal{Q}}$.

Similar ideas may be employed to discuss the question of *problem stability* for the problem of minimizing (2) over $\mathcal{Q}$ (i.e., the original problem) and again compactness of the admissible parameter set plays a critical role.

Compactness of parameter sets also plays an important role in computational considerations. In certain problems, the formulation outlined above (involving $\mathcal{Q}^M = i^M(\mathcal{Q})$) results in a computational framework wherein the $\mathcal{Q}^M$ and $\mathcal{Q}$ all lie in some uniform set possessing compactness properties. The compactness criteria can then be reduced to uniform constraints on the derivatives of the admissible parameter functions. There are numerical examples (for example, see [BI86]) which demonstrate that imposition of these constraints is necessary (and sufficient) for convergence of the resulting algorithms. (This offers a possible explanation for some of the numerical failures [YY] of such methods reported in the engineering literature.)

The sets (spaces) $\mathcal{Q}$ and $\mathcal{Q}^M$ in the inverse problem framework above are an important component in any problem formulation and may involve constant vector parameters, time or spatially dependent functions or even probability measures. In many widely encountered problems the set of admissible parameters $\mathcal{Q}$ may consist of simply some compact subset of finite dimensional Euclidean space. In this case one does not need the additional family of sets $\mathcal{Q}^M$ in the above theory (i.e., the above formulation and theory holds with $\mathcal{Q}^M = \mathcal{Q}$ for all M). However in an increasing number of applications (for example in the three examples outlined below) the parameters sought are functions of time or space. Then one often uses approximation families to construct the family $\mathcal{Q}^M$. For example, in Example 1 below, some of the parameters to be estimated are time dependent coefficients in ordinary differential equation dynamical systems. In this case one might choose some set of functions $\mathcal{Q}$ on a time interval $[0, T]$ and then choose piecewise linear splines for the approximating families $\mathcal{Q}^M$ (see [BBJ] for details) and use spline approximation properties (e.g., see [BK]) to argue that the conditions of **(A1M)** hold.

Problems with uncertainty in parameters (or parameters representing some distribution across a population in the case of aggregate data [BBi, BBH, BBPP, BD, BDTR, BDEHADB, BDEHAD, BFPZ, BG1, BG2, BPi, BPo]) pose even more interesting and challenging possibilities. Several choices may arise for an underlying finite dimensional Euclidean set Q: (i) Q is a compact subset of $\mathbb{R}^p$; (ii) $Q = [-r, 0]$ is a set of possible delay times τ in some dynamical process. In these cases a frequent choice is

$$\mathcal{Q} = \mathcal{P}(Q) = \{P : Q \to \mathbb{R}^1 \ : \ P \text{ is a probability distribution on } Q\},$$

i.e., $\mathcal{Q}$ is the set of all probability distributions on Q. To investigate theoretical, computational and approximation issues for these problems, it is necessary to put a topology on the space of probability measures: a natural choice for $\mathcal{P}(Q)$ is the Prohorov metric ρ topology (see [Bi, Hu, P]). Convergence in this metric $\rho(P_k, P) \to 0$

is equivalent to $\int_Q g dP_k(q) \to \int_Q g dP(q)$ for all bounded, continuous $g : Q \to \mathbb{R}^1$. Thus if we view $\mathcal{P}(Q)$ as a subset of the topological dual of the bounded continuous functions on Q, i.e., $\mathcal{P}(Q) \subset C_B(Q)^*$, convergence in the Prohorov metric is equivalent to weak* convergence and the weak* topology is metrizable with the Prohorov metric. Then one must construct families $\mathcal{Q}^M = \mathcal{P}^M(Q)$ to approximate the distributions $\mathcal{Q} = \mathcal{P}(Q)$ in the Prohorov metric.

To pursue this, 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 so that the conditions **(AIM)** can be satisfied. This can be done in the context of a framework one based on the *Prohorov metric* [BBPP, BBi] of weak* convergence of measures.

A general theoretical framework is given in [BBPP] with specific results on the approximations we use here given in [BBi, BPi]. Briefly, ideas for the underlying theory are as follows:

1. One argues *continuity of* $P \to J(P)$ on $\mathcal{Q} = \mathcal{P}(Q)$ with the Prohorov metric ρ;
2. If Q is compact then $\mathcal{Q} = \mathcal{P}(Q)$ is a *complete metric space*, indeed *compact*, when taken with Prohorov metric;
3. Approximation families $\mathcal{Q}^M = \mathcal{P}^M(Q)$ are chosen so that elements $P^M \in \mathcal{P}^M(Q)$ can be found to approximate elements $P \in \mathcal{P}(Q)$ in Prohorov metric;
4. *Well-posedness* (existence, continuous dependence of estimates on data, etc.) is obtained along with *feasible computational methods.*

The desired results can be developed using several approximation theories that have been recently developed and used in the context of problems other than those with delay systems. The first, developed in [BBi] and based on Dirac delta measures, is summarized in the following theorem.

THEOREM 2. *Let Q be a complete, separable metric space, $\mathcal{B}$ the class of all Borel subsets of Q and $\mathcal{P}(Q)$ the space of probability measures on $(Q, \mathcal{B})$. Let $Q_0 = \{q_j\}_{j=1}^{\infty}$ be a countable, dense subset of Q. Then the set of $P \in \mathcal{P}(Q)$ such that P has finite support in Q_0 and rational masses is dense in $\mathcal{P}(Q)$ in the ρ metric. That is,*

$$\mathcal{P}_0(Q) \equiv \{P \in \mathcal{P}(Q) : P = \sum_{j=1}^{k} p_j \Delta_{q_j}, k \in \mathcal{N}^+, q_j \in Q_0,\ p_j \text{ rational}, \sum_{j=1}^{k} p_j = 1\}$$

is dense in $\mathcal{P}(Q)$ taken with the ρ metric, where Δ_{q_j} is the Dirac measure with atom at q_j.

It is rather easy to use the ideas and results associated with this theorem to develop computationally efficient schemes. Given $Q_d = \bigcup_{M=1}^{\infty} Q_M$ with $Q_M = \{q_j^M\}_{j=1}^M$ (a "partition" of Q) chosen so that Q_d is dense in Q, define

$$\mathcal{Q}^M = \mathcal{P}^M(Q) = \{P \in \mathcal{P}(Q) : P = \sum_{j=1}^{M} p_j \Delta_{q_j^M}, q_j^M \in Q_M,\ p_j \text{ rational}, \sum_{j=1}^{M} p_j = 1\}.$$

Then we find

(i) $\mathcal{Q}^M = \mathcal{P}^M(Q)$ is a compact subset of $\mathcal{Q} = \mathcal{P}(Q)$ in the ρ metric,

(ii) $\mathcal{P}^M(Q) \subset \mathcal{P}^{M+1}(Q)$ whenever Q_{M+1} is a refinement of Q_M,

(iii) "$\mathcal{P}^M(Q) \to \mathcal{P}(Q)$" in the ρ topology; that is, for M sufficiently large, elements in $\mathcal{P}(Q)$ can be approximated in the ρ metric by elements of $\mathcal{P}^M$.

A second class of approximations was developed and used in [BPi] for problems where one assumes that the probability distributions to be approximated possess densities in L^2. These involves approximation with piecewise linear splines at the level of the densities.

THEOREM 3. *Let $\mathcal{F}$ be a weakly compact subset of $L^2(Q)$, Q compact and let $\mathcal{P}_{\mathcal{F}}(Q) \equiv \{P \in \mathcal{P}(Q) : P' = p,\ p \in \mathcal{F}\}$. Then $\mathcal{Q} = \mathcal{P}_{\mathcal{F}}(Q)$ is compact in $\tilde{\mathcal{Q}} = \mathcal{P}(Q)$ in the ρ metric. Moreover, if we define $\{\ell_j^M\}$ to be the linear splines on Q corresponding to the partition Q_M, where $\bigcup_M Q_M$ is dense in Q, define*

$$\mathcal{P}^M \equiv \{p^M : p^M = \sum_j b_j^M \ell_j^M, b_j^M \ \textit{rational}\ \}$$

and if

$$\mathcal{Q}^M = \mathcal{P}_{\mathcal{F}^M} \equiv \{P_M \in \mathcal{P}(Q) : P_M = \int p^M,\ p^M \in \mathcal{P}^M\},$$

we have $\bigcup_M \mathcal{P}_{\mathcal{F}^M}$ is dense in $\mathcal{Q} = \mathcal{P}_{\mathcal{F}}(Q)$ taken with the ρ metric.

A study comparing the relative strengths and weaknesses of these two classes of approximation schemes in the context of inverse problems is given in [BD].

Thus we have that compactness of admissible parameter sets play a fundamental role in a number of aspects, both theoretical and computational, in parameter estimation problems. This compactness may be assumed (and imposed) explicitly as we have outlined here, or it may be included implicitly in the problem formulation through *Tikhonov regularization* as discussed for example by Kravaris and Seinfeld [KS], Vogel [Vog] and widely by many others. In the regularization approach one restricts consideration to a subset $\mathcal{Q}_1$ of parameters which has compact embedding in $\mathcal{Q}$ and modifies the least-squares criterion to include a term which insures that minimizing sequences will be $\mathcal{Q}_1$ bounded and hence compact in the original parameter set $\mathcal{Q}$.

After this short digression on general inverse problem concepts, we return to the convergence (6).

2.2. State approximation and convergence for nonlinear systems. We consider the general system

$$\dot{z}(t) = f(t, z(t), z_t, z(t-\tau_1), \ldots, z(t-\tau_m), q) + f_2(t), \quad 0 \le t \le T, \quad z_0 = \phi \tag{8}$$

where $f = f(t, \eta, \psi, y_1, \ldots, y_m, q) : [0,T] \times X \times \mathbb{R}^{nm} \times \mathcal{Q} \to \mathbb{R}^n$. Here $X = \mathbb{R}^n \times L_2(-r, 0; \mathbb{R}^n)$, $0 < \tau_1 < \ldots < \tau_m = r$, z_t denotes the function $z_t(\theta) = z(t+\theta)$, $-r \le \theta \le 0$, and $\phi \in H^1(-r, 0)$. We shall make use of the following hypotheses throughout our presentation.

(H1) The function f satisfies a global Lipschitz condition:

$$\begin{aligned} |f(t, \eta, \psi, y_1, \ldots, y_m, q) \ - \ & f(t, \xi, \tilde{\psi}, w_1, \ldots, w_m, q)| \le \\ & K\left(|\eta - \xi| + |\psi - \tilde{\psi}| + \textstyle\sum_{i=1}^m |y_i - w_i|\right) \end{aligned}$$

for some fixed constant K and all $(\eta, \psi, y_1, \ldots, y_m)$, $(\xi, \tilde{\psi}, w_1, \ldots, w_m)$ in $X \times \mathbb{R}^{nm}$ uniformly in t and in $q \in \mathcal{Q}$.

(H2) The function $f(\cdot, \cdot\cdot, q) : [0,T] \times X \times \mathbb{R}^{nm} \to \mathbb{R}^n$ is differentiable for each q.

(H3) The function $q \to f(\cdot, \cdot\cdot, q)$ is continuous on $\mathcal{Q}$.

REMARK 1. If we define the function $F : [0,T] \times \mathbb{R}^n \times C(-r,0;\mathbb{R}^n) \times \mathcal{Q} \subset [0,T] \times X \times \mathcal{Q} \to \mathbb{R}^n$ given by

$$F(t,x,q) = F(t,\eta,\psi,q) = f(t,\eta,\psi,\psi(-\tau_1),\ldots,\psi(-\tau_m),q) \tag{9}$$

we observe that even though f satisfies (H1), F will not satisfy a continuity hypothesis on its domain in the X norm.

We define the nonlinear operator $\mathcal{A}(t;q) : \mathcal{D}(\mathcal{A}) \subset X \to X$ by

$$\mathcal{D}(\mathcal{A}) \equiv \{(\psi(0),\psi) \mid \psi \in H^1(-r,0)\}$$

$$\mathcal{A}(t;q)(\psi(0),\psi) \equiv (F(t,\psi(0),\psi,q), D\psi)$$

where here $D\psi = \psi'$. Note that $\mathcal{D}(\mathcal{A})$ is independent of t and q. We then may write the system (8) in abstract form

$$\begin{array}{rcl} \dot{x}\,(t) & = & \mathcal{A}(t;q)x(t) + (f_2(t),0) \\ x\,(0) & = & \zeta = (\phi(0),\phi)\,, \end{array} \tag{10}$$

for states $x(t) = (z(t), z_t)$ in the abstract space X.

THEOREM 4. *Assume that (H1) holds and let $x(t;\phi,f_2) = (z(t;\phi,f_2), z_t(\phi,f_2))$, where z is the solution of (8) corresponding to $\phi \in H^1$, $f_2 \in L_2$. Then for $\zeta = (\phi(0),\phi)$, $x(t;\phi,f_2)$ is the unique solution on $[0,T]$ of*

$$x(t;q) = \zeta + \int_0^t [\mathcal{A}(\sigma;q)x(\sigma;q) + (f_2(\sigma),0)]d\sigma. \tag{11}$$

Furthermore, $f_2 \to x(t;\phi,f_2)$ is weakly sequentially continuous from L_2 (weak) to X (strong).

These results can be established (we do not do so here) in one of several routine ways: fixed point theorem arguments [JKH4] or Picard iteration arguments. Either of these approaches can be used to establish existence, uniqueness and continuous dependence of solution of (11). For existence, uniqueness and continuous dependence of solution of (8), we note that our condition (H1) is a global version of the local hypothesis of Kappel and Schappacher in [KapSch], so that their results also yield immediately the desired result for (8) in the autonomous case.

The uniqueness of solutions to (11) follows in the usual manner once we establish that $\mathcal{A}$ satisfies a dissipative inequality. We do this in a space X_g that is topologically equivalent to X. Renorm X by the weighting function g defined on $[-r,0)$, where $g(\xi) = j$ for $\xi \in [-\tau_{m-j+1}, -\tau_{m-j})$, $j = 1,2,\ldots,m$ (we define $\tau_0 = 0$). Define the Hilbert space $X_g \equiv \mathbb{R}^n \times L_2(-r,0;g;\mathbb{R}^n)$ to be the elements of X with this new inner product

$$< (\eta,\phi),(\zeta,\psi) >_{X_g} = < \eta,\zeta >_{\mathbb{R}^n} + \int_{-r}^0 \phi(\xi)\psi(\xi)g(\xi)d\xi. \tag{12}$$

This gives rise to an equivalent topology to that of X as long as $g(\xi) > 0$ for all $\xi \in [-r, 0)$ (see [BBu2, p. 186], [BKap, Webb] for more details). Then the nonlinear operator $\mathcal{A}(t;q)$ is dissipative if for some $\kappa > 0$ we have

$$\langle \mathcal{A}(t;q)x - \mathcal{A}(t;q)w, x - w\rangle_{X_g} \leq \kappa \langle x - w, x - w\rangle_{X_g} \tag{13}$$

for all $x, w \in \mathcal{D}(\mathcal{A})$ and all t and $q \in \mathcal{Q}$. This can be used to immediately argue uniqueness of solutions. We outline the arguments to establish the fundamental inequality (13). We have for $x = (\phi(0), \phi), w = (\psi(0), \psi)$

$$\begin{aligned}
< \mathcal{A}(t;q)x - \mathcal{A}(t;q)w, x - w >_{X_g} &= < F(t, \phi(0), \phi) - F(t, \psi(0), \psi), \phi(0) - \psi(0) >_{\mathbb{R}^n} \\
&\quad + < D\phi - D\psi, \phi - \psi >_{L_2(-r,0;g;\mathbb{R}^n)} \\
&= < F(t, \phi(0), \phi) - F(t, \psi(0), \psi), \phi(0) - \psi(0) >_{\mathbb{R}^n} \\
&\quad + \int_{-r}^{0} D(\phi(\xi) - \psi(\xi))(\phi(\xi) - \psi(\xi))g(\xi)d\xi \\
&= < F(t, \phi(0), \phi) - F(t, \psi(0), \psi), \phi(0) - \psi(0) >_{\mathbb{R}^n} \\
&\quad + \sum_{j=1}^{m} \int_{-\tau_{m-j+1}}^{-\tau_{m-j}} D(\phi(\xi) - \psi(\xi))(\phi(\xi) - \psi(\xi))g(\xi)d\xi.
\end{aligned} \tag{14}$$

Consider the last term and denote $\Delta_{m-j} = (\phi - \psi)(\tau_{m-j}) = \phi(-\tau_{m-j}) - \psi(-\tau_{m-j})$ for $j = 0, 1, \ldots, m$. Then for $\Delta(\xi) = \phi(\xi) - \psi(\xi)$ we have

$$\begin{aligned}
&\sum_{j=1}^{m} \int_{-\tau_{m-j+1}}^{-\tau_{m-j}} D(\Delta(\xi))\Delta(\xi)g(\xi)d\xi \\
&\quad = \sum_{j=1}^{m} \frac{1}{2} j\Delta(\xi)^2 |_{\xi=-\tau_{m-j+1}}^{\xi=-\tau_{m-j}} \\
&\quad = \sum_{j=1}^{m} \left(\frac{j}{2}|\Delta_{m-j}|^2 - \frac{j}{2}|\Delta_{m-j+1}|^2 \right) \\
&\quad = \frac{1}{2}\sum_{j=1}^{m} j|\Delta_{m-j}|^2 - \frac{1}{2}\sum_{k=0}^{m-1}(k+1)|\Delta_{m-k}|^2 \quad (\text{ for } k = j-1) \\
&\quad = \frac{1}{2}m|\Delta_0|^2 + \frac{1}{2}\sum_{j=1}^{m-1} j|\Delta_{m-j}|^2 - \frac{1}{2}\sum_{k=1}^{m-1}(k+1)|\Delta_{m-k}|^2 - \frac{1}{2}|\Delta_m|^2 \\
&\quad = \frac{1}{2}m|\Delta_0|^2 - \frac{1}{2}\sum_{j=1}^{m-1}|\Delta_{m-j}|^2 - \frac{1}{2}|\Delta_m|^2 \\
&\quad = \frac{1}{2}m|\Delta_0|^2 - \frac{1}{2}\sum_{j=0}^{m-1}|\Delta_{m-j}|^2 = \frac{m+1}{2}|\Delta_0|^2 - \frac{1}{2}\sum_{j=0}^{m}|\Delta_{m-j}|^2.
\end{aligned}$$

Returning to (14), we have

$$
\begin{aligned}
&< \mathcal{A}(t;q)x - \mathcal{A}(t;q)w, x - w >_{X_g} \\
&\qquad \le | < F(t,\phi(0),\phi) - F(t,\psi(0),\psi), \phi(0) - \psi(0) >_{\mathbb{R}^n} | \\
&\qquad\quad + \frac{m+1}{2}|\Delta_0|^2 - \frac{1}{2}\sum_{j=0}^{m}|\Delta_{m-j}|^2 \\
&\qquad \le K\left(|\Delta_0| + |\Delta| + \sum_{i=1}^{m}|\Delta_i|\right)|\Delta_0| \\
&\qquad\quad + \frac{m+1}{2}|\Delta_0|^2 - \frac{1}{2}\sum_{j=0}^{m}|\Delta_{m-j}|^2 \\
&\qquad \le K|\Delta_0|^2 + \frac{K^2}{2}|\Delta|^2 + \frac{1}{2}|\Delta_0|^2 + \frac{1}{2}\sum_{i=1}^{m}|\Delta_i|^2 + \frac{mK^2}{2}|\Delta_0|^2 \\
&\qquad\quad + \frac{m+1}{2}|\Delta_0|^2 - \frac{1}{2}\sum_{j=0}^{m}|\Delta_{m-j}|^2 \\
&\qquad \le \left(K + \frac{mK^2}{2} + \frac{m+1}{2}\right)|\Delta_0|^2 + \frac{K^2}{2}|\Delta|^2_{L_2} \\
&\qquad \le \left(K + \frac{mK^2}{2} + \frac{m+1}{2}\right)|\Delta|^2_X \\
&\qquad \le \kappa|x-w|^2_X \\
&\qquad \le \kappa|x-w|^2_{X_g},
\end{aligned}
$$

using the definition of the inner product. Therefore choosing

$$\kappa = K + \frac{mK^2}{2} + \frac{m+1}{2},$$

we have that $\mathcal{A}(t;q)$ is dissipative in X_g, uniformly in t and q .

Turning next to the approximation of (8) through approximation of (11), we let X^N be the spline subspaces of X discussed in detail in [BKap]. We briefly outline the results for the piecewise linear subspaces X_1^N (see Section 4 of [BKap]) given by

$$X_1^N = \{(\phi(0),\phi) \mid \quad \phi \text{ is a continuous first-order spline function with knots at } t_j^N = -jr/N, j = 0,1,\ldots,N\}.$$

A careful study of the arguments behind our presentation reveals that the approximation results given here hold for general spline approximations. For example, if one were to treat cubic spline approximations (X_3^N of [BKap]), one would use the appropriate approximation analogues of Theorem 2.5 of [Schultz] and Theorem 21 of [SchuVarg] (e.g., see Theorem 4.5 of [Schultz]). Hereafter, when we write X^N, the reader should understand that we mean X_1^N of [BKap].

Let $P^N = P_g^N$ be the orthogonal projection (in $\langle\ ,\ \rangle_g \equiv \langle\ ,\ \rangle_{X_g}$) of X onto X^N so that as we have already discussed it immediately follows that $P^N x \to x$ for all $x \in X$. Similar to the approach in [BKap] as extended in [Ba82], for arbitrary $\{q^N\}$ with $q^N \to q$ we define the approximating operator

$$\mathcal{A}^N(t) = P^N \mathcal{A}(t;q^N)P^N$$

and consider the approximating equations in X^N given by

$$x^N(t) = P^N\zeta + \int_0^t [\mathcal{A}^N(\sigma)x^N(\sigma) + P^N(f_2(\sigma), 0)]d\sigma \tag{15}$$

which, because X^N is finite-dimensional, are equivalent to

$$\dot{x}^N(t) = \mathcal{A}^N(t)x^N(t) + P^N(f_2(t), 0), \quad x^N(0) = P^N\zeta. \tag{16}$$

Note that $x^N(t) = x^N(t; q^N)$. From (13) and the definition of $\mathcal{A}^N$ in terms of the self-adjoint projections P^N, we have at once that under (H1) the sequence $\{\mathcal{A}^N\}$ satisfies on X a uniform dissipative inequality

$$\langle \mathcal{A}^N(t)x - \mathcal{A}^N(t)w, x - w\rangle_g \leq \kappa\langle x - w, x - w\rangle_g. \tag{17}$$

Uniqueness of solutions of (15) then follows immediately from this inequality. Upon recognition that (16) is equivalent to a nonlinear ordinary differential equation in Euclidean space with the right-hand side satisfying a global Lipschitz condition, one can easily argue existence of solutions for (16) and hence for (15) on any finite interval $[0, T]$. Our main result to be discussed here, which ensures that solutions of (16) converge to those of (8), can now be stated.

THEOREM 5. *Assume (H1), (H2), (H3) and $q^N \to q$ in $\mathcal{Q}$. Let $\zeta = (\phi(0), \phi)$, $\phi \in H^1$ and $f_2 \in L_2(0, T)$ be given, with x^N and x the corresponding solutions on $[0, T]$ of (16) and (8), respectively. Then $x^N(t) \to x(t) = (z(t; \phi, f_2), z_t(\phi, f_2))$, as $N \to \infty$, uniformly in t on $[0, T]$.*

REMARK 2. One can actually obtain slightly stronger results than those given in Theorem 5. One can consider solutions of (8) and (16) corresponding to initial data $(z(0), z_0) = (\eta, \phi) = \zeta$ with $\eta \in \mathbb{R}^n$, $\phi \in L_2$ (i.e., $\zeta \in X$) and argue that the results of Theorem 5 hold also in this case.

To indicate briefly our arguments for Theorem 5, we consider for given initial data ζ and perturbation f_2 the corresponding solutions x and x^N of (11) and (15). Define $\Delta^N(t) \equiv x^N(t) - x(t)$ and $F_2(t) = (f_2(t), 0)$, we obtain immediately that

$$\Delta^N(t) = (P^N - I)\zeta + \int_0^t \left[\mathcal{A}^N(\sigma)x^N(\sigma) - \mathcal{A}(\sigma)x(\sigma) + (P^N - I)F_2(\sigma)\right] d\sigma. \tag{18}$$

We next use a rather standard technique for analysis of differential equations (see [Barbu]), the foundations of which we state as a lemma since we shall refer to it again.

LEMMA 3. *If X is a Hilbert space and $x : [a, b] \to X$ is given by*

$$x(t) = x(a) + \int_a^t y(\sigma)d\sigma,$$

then

$$|x(t)|^2 = |x(a)|^2 + 2\int_0^t \langle x(\sigma), y(\sigma)\rangle d\sigma.$$

This lemma is essentially a restatement of the well-known result [Barbu, p. 100] that in a Hilbert space

$$\frac{d}{dt}\left(\frac{1}{2}|x(t)|^2\right) = \langle \dot{x}(t), x(t)\rangle.$$

Applying Lemma 3 to (18), we obtain

$$\begin{aligned}
|\Delta^N(t)|^2 &= |(P^N - I)\zeta|^2 \\
&\quad +2\int_0^t \langle \mathcal{A}^N(\sigma)x^N(\sigma) - \mathcal{A}(\sigma)x(\sigma) + (P^N - I)F_2(\sigma), \Delta^N(\sigma)\rangle d\sigma \\
&= |(P^N - I)\zeta|^2 + 2\int_0^t \langle \mathcal{A}^N(\sigma)x^N(\sigma) - \mathcal{A}^N(\sigma)x(\sigma), \Delta^N(\sigma)\rangle d\sigma \\
&\quad +2\int_0^t \langle (\mathcal{A}^N(\sigma) - \mathcal{A}(\sigma))x(\sigma) + (P^N - I)F_2(\sigma), \Delta^N(\sigma)\rangle d\sigma.
\end{aligned}$$

If we use (17) on the first integral term in this last expression, we then have

$$\begin{aligned}
|\Delta^N(t)|^2 &\leq |(P^N - I)\zeta|^2 + 2\int_0^t \omega|\Delta^N(\sigma)|^2 d\sigma \\
&\quad +2\int_0^t \langle (\mathcal{A}^N(\sigma) - \mathcal{A}(\sigma))x(\sigma) + (P^N - I)F_2(\sigma), \Delta^N(\sigma)\rangle d\sigma \\
&\leq |(P^N - I)\zeta|^2 + 2\int_0^t \omega|\Delta^N(\sigma)|^2 d\sigma \\
&\quad +2\int_0^t [\tfrac{1}{2}|(\mathcal{A}^N(\sigma) - \mathcal{A}(\sigma))x(\sigma)|^2 + \tfrac{1}{2}|\Delta^N(\sigma)|^2 \\
&\quad +\tfrac{1}{2}\left|(P^N - I)F_2(\sigma)\right|^2 + \tfrac{1}{2}\left|\Delta^N(\sigma)\right|^2] d\sigma \\
&= \left|(P^N - I)\zeta\right|^2 + \int_0^t \left|(\mathcal{A}^N(\sigma) - \mathcal{A}(\sigma))x(\sigma)\right|^2 d\sigma + \int_0^t \left|(P^N - I)F_2(\sigma)\right|^2 d\sigma \\
&\quad +2(\omega + 1)\int_0^t |\Delta^N(\sigma)|^2 d\sigma.
\end{aligned}$$

An application of Gronwall's inequality to this then yields the estimate

$$|\Delta^N(t)|^2 \leq [\epsilon_1(N) + \epsilon_2(N) + \epsilon_3(N)] \exp\left(2(\omega + 1)t\right), \tag{19}$$

where

$$\epsilon_1(N) = |(P^N - I)\zeta|^2,$$

$$\epsilon_2(N) = \int_0^T \left|(\mathcal{A}^N(\sigma) - \mathcal{A}(\sigma))x(\sigma)\right|^2 d\sigma,$$

$$\epsilon_3(N) = \int_0^T \left|(P^N - I)F_2(\sigma)\right|^2 d\sigma.$$

Since $P^N \to I$ strongly in X and the convergence $|(P^N - I)F_2(\sigma)| \to 0$ in ϵ_3 is dominated, to prove Theorem 5 it suffices to argue that $\epsilon_2(N) \to 0$ as $N \to \infty$. To that end, we state the following sequence of lemmas.

LEMMA 4. *Assume (H1), (H3) and let* $\mathcal{X} \equiv \{x = (\phi(0), \phi) \mid \phi \in H^2\}$. *Then for each* t, $\mathcal{A}^N(t)x \to \mathcal{A}(t)x$ *as* $N \to \infty$ *for each* $x \in \mathcal{X}$.

LEMMA 5. *For fixed* $q \in \mathcal{Q}$, *let* $\mathcal{C}_q \equiv \{(\zeta, f_2) \in \mathcal{D}(\mathcal{A}) \times L_2(0,T) \mid \phi \in H^2, f_2 \in H^1,$ *with* $\dot{\phi}(0) = F(0, \zeta, q) + f_2(0)$ *where* $\zeta = (\phi(0), \phi)\}$. *Assume that (H1), (H2) hold. Then for* $(\zeta, f_2) \in \mathcal{C}_q$ *the corresponding solution* $\sigma \to x(\sigma) = (z(\sigma), z_\sigma)$ *of* (11) *(*z *is the solution of* (8)*) satisfies* $x(\sigma) \in \mathcal{X}$ *for each* $\sigma \in (0, T]$.

LEMMA 6. *Assume (H1), (H2), (H3) and let* $(\zeta, f_2) \in \mathcal{C}_q$ *with* x^N *and* x *the corresponding solutions of* (15) *and* (11). *Then* $x^N(t) \to x(t)$ *uniformly in* t *on* $[0, T]$.

LEMMA 7. *Assume (H1). Then the solutions of* (11) *and* (15) *depend continuously (in the* $X \times L_2$ *topology) on* $(\zeta, f_2) \in \mathcal{D}(\mathcal{A}) \times L_2$, *uniformly in* t *on* $[0, T]$.

LEMMA 8. *For each* $q \in \mathcal{Q}$, *the set* $\mathcal{C}_q$ *defined in Lemma 5 is dense in* $\mathcal{D}(\mathcal{A}) \times L_2 \subset X \times L_2$.

We obtain the convergence of Theorem 5 by combining Lemmas 6, 7 and 8. The proof of Lemma 7 employs Lemma 3 along with Gronwall's inequality in much the same way as above in deriving (19) from (18). We note that Lemma 5 requires hypothesis (H2) in order to obtain enough smoothness of solutions x of (11) so that $x(\sigma) \in \mathcal{X}$ for each σ, which then permits the convergence arguments of Lemma 6.

In developing the estimates to establish Lemma 6 (which, by our above remarks, requires only that we argue $\epsilon_2(N) \to 0$), we use heavily the standard spline estimates found in [Schultz] and [SchuVarg]. Lemmas 4 and 5 yield that $\mathcal{A}^N(\sigma)x(\sigma) \to \mathcal{A}(\sigma)x(\sigma)$ for each σ so that to prove Lemma 6 one only need show that this convergence is dominated, thereby guaranteeing $\epsilon_2(N) \to 0$. In making the arguments for Lemma 6, one obtains at the same time error estimates on the convergence in Theorem 5. For example, one readily finds the following: for $\phi \in H^2$, f satisfying (H1), (H2), $\dot{\phi}(0) = F(\phi(0), \phi)$ and $f_2 \equiv 0$, the convergence $x^N(t) \to x(t)$ is $O(1/N)$. For higher-order splines and higher-order convergence estimates (e.g., cubic splines with convergence $O(1/N^3)$), one of course needs additional smoothness (beyond (H2)) on f.

The convergence given in Theorem 5 yields state approximation techniques for nonlinear FDE systems based on the spline methods developed in [BKap]. These results can be applied directly to control and identification problems, the latter of which are discussed in [Ba82].

REMARK 9. Results for special classes of the systems above can actually be obtained from the arguments for nonautonomous nonlinear delay systems in [Ba79]. In that approach, one requires all discrete delays to appear in the linear part of the system dynamics while continuous delays may appear in the nonlinear part. One then writes the system dynamics as an autonomous linear part plus a nonlinear perturbation. The linear part generates a linear semigroup as in [BBu1, BBu2, BKap]. One then uses the linear semigroup in a variation of parameters implicit representation of the solution to the nonlinear system. Mathematical tools used then are Picard iterates for existence, and the Trotter-Kato theorem [BBu1, BBu2, BKap] (for the linear semigroup) plus a Gronwall inequality. An alternative (and more general) approach given in [Ba82] eschews use of the Trotter-Kato theorem in treating general nonautonomous nonlinear delay systems which allows discrete delays in the nonlinear

components of the system. As we have seen, the main mathematical tools are dissipative properties of the general nonlinear operator $\mathcal{A}(t)$ representing the system and direct approximation $\mathcal{A}^N(t) \to \mathcal{A}(t)$ (no Trotter-Kato!) along with a Gronwall inequality. Finally, a nonlinear semigroup (with dissipative generators) approach along with a corresponding nonlinear Trotter-Kato convergence result are given by Kappel in [Kap82]. With these results one can treat directly general autonomous nonlinear delay systems in the spirit of a linear semigroup approach [Pa].

3. Examples. We present three examples from diverse applications to illustrate use of the above theoretical and computational framework. The first two applications have been discussed in detail in other presentations and hence we give only brief summaries. However, the third example is particularly novel, representing current efforts in an area where dynamical mathematical modeling is virtually nonexistent in the research literature. Thus we illustrate the above theory in a little more detail for this application and present some specific new and preliminary findings.

3.1. Example 1: Insect/Insecticide models. We describe here a nonautonomous delay system arising in insect/insecticide investigations [BBDS2, BBJ]. Mathematical models that are suitable for field data with mixed populations should consider reproductive effects and should also account for multiple generations, containing neonates (juveniles) and adults and their interconnectedness. This suggests the need at the minimum for a coupled system of equations describing two separate age classes. Additionally, due to individual differences within the insect population, it is biologically unrealistic to assume that all neonate aphids born on the same day reach the adult age class at the same time. In fact, the age at which the insects reach adulthood varies from as few as five to as many as seven days. Hence one must include a term in any model to account for this variability, leading one to develop a coupled differential equation model including distributed delays for the insect population dynamics. We consider the delay between birth and adulthood for neonate pea aphids and present a mathematical model that treats this delay as a random variable.

Let $a(t)$ and $n(t)$ denote the number of adults and neonates, respectively, in the population at time t. We lump the mortality due to insecticide into one time varying parameter $p_a(t)$ for the adults, $p_n(t)$ for the neonates, and denote by $d_a(t)$ and $d_n(t)$ the background or natural mortalities for adults and neonates, respectively. We let $b(t)$ be the time varying rate at which neonates are born into the population.

We suppose that there is a time delay for maturation of a neonate to adult life stage. We further assume that this time delay varies across the insect population according to a probability distribution $P(\tau)$ for $\tau \in [-T_n, 0]$ with corresponding density $k(\tau) = \frac{dP(\tau)}{d\tau}$. Here we tacitly assume an upper bound on T_n for the maturation period of neonates into adults. Thus, we have that $k(\tau)$, $\tau < 0$, is the probability per unit time that a neonate who has been in the population $-\tau$ time units becomes an adult. Then the rate at which such neonates become adults is $n(t+\tau)k(\tau)$. Summing over all such τ's, we obtain that the rate at which neonates become adults is $\int_{-T_n}^{0} n(t+\tau)k(\tau)d\tau$. Using the biological knowledge that the maturation process varies between five and seven days (i.e., k vanishes outside $[-7, -5]$), we obtain the

functional differential equation (FDE) system

$$
\begin{array}{rcl}
\frac{da}{dt}(t) & = & \int_{-7}^{-5} n(t+\tau)k(\tau)d\tau - (d_a(t)+p_a(t))\,a(t) \\
\frac{dn}{dt}(t) & = & b(t)a(t) - (d_n(t)+p_n(t))\,n(t) - \int_{-7}^{-5} n(t+\tau)k(\tau)d\tau \\
a(\theta) & = & \Phi(\theta), \quad n(\theta)=\Psi(\theta), \quad \theta\in[-7,0) \\
a(0) & = & a^0, \qquad n(0)=n^0,
\end{array} \tag{20}
$$

where k is now a probability density kernel which we have assumed has the property $k(\tau) \geq 0$ for $\tau \in [-7,-5]$ and $k(\tau)=0$ for $\tau \in (-\infty,-7)\cup(-5,0]$.

In this problem the parameters to be estimated are time dependent coefficients $d_a(t), p_a(t), b(t), d_n(t), p_n(t)$ as well as the probability density maturation kernels $k(\tau)$.

In summary, the authors of [BBJ] present a time delay differential equation model with time dependent parameters as well as probability density maturation kernels that might be used to investigate mixed neonate/adult multi-generational populations. The formulation includes these models as special cases of a class of abstract differential equations with function space parameters (including probability densities) which are readily approximated by finite element systems (the spaces $\mathcal{Q}^M$ are piecewise linear splines for time varying coefficients as well as density kernels). The inverse problems are formulated in the context of both ordinary and generalized least squares frameworks, and computations are carried out (including an uncertainty analysis with confidence intervals via asymptotic error analysis involving approximate sampling distributions) with simulated noisy data to demonstrate both efficiency and efficacy of the methodologies.

3.2. Example 2: HIV infection dynamics. We next consider classes of nonlinear functional or delay differential equation models which arise in attempts to describe temporal delays in HIV pathogenesis. These models, first developed in [BBH] consider incorporation of variability (i.e., general probability distributions) for these delays into systems that cannot readily be reduced to a finite number of coupled ordinary differential equations (as is done in the method of stages). In [BBH], the authors introduced several classes of nonlinear models (including discrete and distributed delays), and presented discussions of theoretical and computational approaches. The models were validated with *in vitro* experimental data [RWE] in successful inverse problem efforts. This was supported by statistical significance tests for the importance of including delays in the dynamics.

The underlying biology is discussed in some detail in [BBH] to which we refer interested readers. Viruses are obligate intra-cellular parasites with a multitude of pathways for infecting and reproducing within their target hosts. The Human Immunodeficiency Virus (HIV) is a lentivirus that is the etiological agent for the slow, progressive, and fatal Acquired Immunodeficiency Syndrome (AIDS) for which there is currently no known cure.

For HIV, the core of the virus is composed of single-stranded viral RNA and protein components. As depicted in Figure 1, when an HIV virion comes into contact with an uninfected CD4 target cell, the viral envelope glycoproteins fuse to the cell's lipid bilayer at a CD4 receptor site and the viral core is injected into the cell. Once inside, the protein components enable transcription and integration of the viral RNA into viral DNA and then incorporation into the cellular DNA (provirus). With its altered cellular DNA, the cell produces capsids and protein envelopes and transcribes multiple copies of viral RNA. The cell assembles a virion by then encasing the newly produced viral RNA in a capsid followed by a protein envelope. The new HIV virion

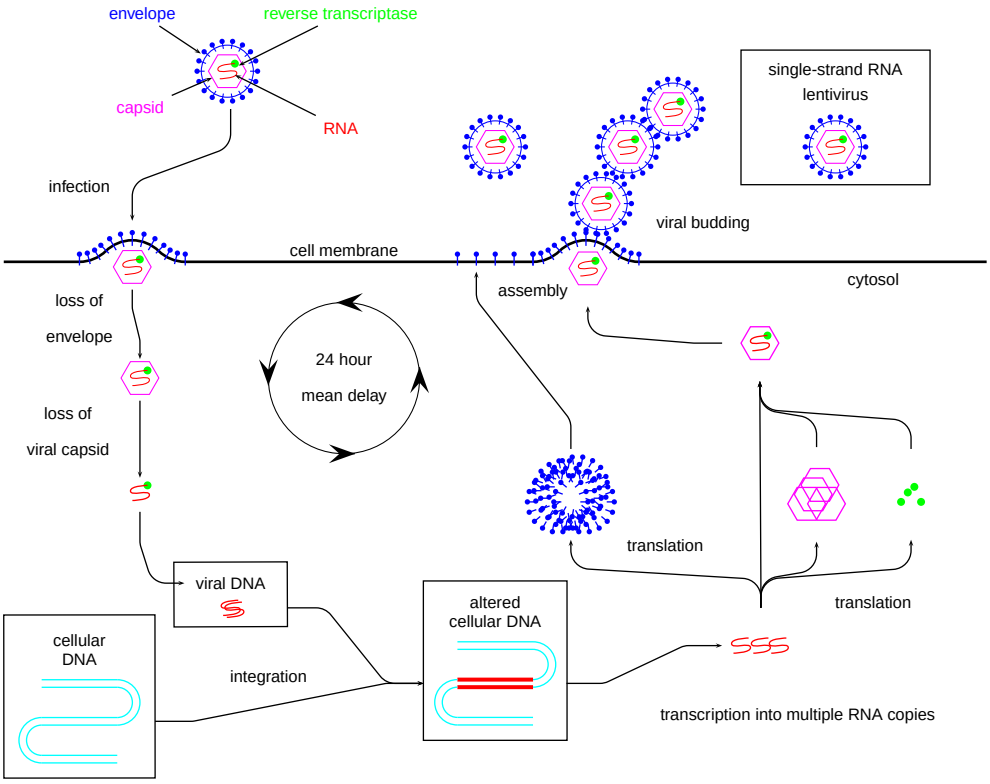

FIG. 1. *HIV Infection Pathway*

pushes out through the cell membrane budding off in chains of virions (though sometimes single virions do float away into the plasma). The time from viral infection to viral production (sometimes called the *eclipse phase*) is not instantaneous, and (as indicated in the figure) it is estimated that the first viral release occurs approximately 24 hours after the initial infection.

Within the HIV modeling community, there has been considerable debate on the proper compartment definitions in models. The multi-compartment model introduced and employed in [BBH] describes pathways from the moment a virion contacts the appropriate receptor site as the beginning of *acute infection*. If the acutely infected cell survives through its first viral release, roughly 3 hours later the physiological characteristics of the cell change and it is subsequently classified as a *chronically infected* cell. Note that in the chronic stage, it is possible for the cells to continue to divide (albeit at a much slower rate than acutely infected or non-infected cells) and to produce virions.

In the course of developing the models, one employs a delay to mathematically represent the temporal lag between the initial viral infection and the first release of new virions. We concentrate on the mathematical modeling of viral dynamics, focusing in particular on the mathematical aspects and biological nature of the delays in primary infection. The models are extensions of previous modeling work on HIV infection dynamics for *in vitro* laboratory experiments from the (continuous) delay differential equations developed in [BGHKNS], which in turn were based on a discrete dynamical

Notation	*Description*
c	Infectious viral clearance rate
n_A	Infectious viral production rate for acutely infected cells
n_C	Infectious viral production rate for chronically infected cells
γ	Rate at which acutely infected cells become chronically infected
r_v	Birth-rate for virally infected cells
r_u	Birth-rate for uninfected cells
δ_A	Death-rate for acutely infected cells
δ_C	Death-rate for chronically infected cells
δ_u	Death-rate for uninfected cells
δ	Density dependent overall cell death-rate
p	Rate of infection
S	Constant rate of target cell replacement

TABLE 1
in vitro *model parameters*

system from [HE]. Our primary interest here is to present the functional differential equations required when treating cellular level data containing significant variability as a specific example to which the theory developed in this paper is applicable. In this example, a major part of the efforts involved estimation of parameters that are probability densities.

A central focus of the modeling efforts have been on attempting to obtain reasonable mathematical representations of these delays. The problem of how to mathematically represent these phenomena is decidedly nontrivial and includes issues such as how to account for intra-individual variability (e.g., intercellular variability arising within a single infected individual or laboratory assay) and/or inter-individual variability arising between individual subjects or data from multiple assays. These issues are highly significant and dealing with the levels of variability and the resulting mathematical ramifications is of primary interest.

The basic model involving delays has the form

$$
\begin{aligned}
\dot{V}(t) &= -cV(t) + n_A A(t-\tau_1) + n_C C(t) - pV(t)T(t) \\
\dot{A}(t) &= (r_v - \delta_A - \delta X(t))A(t) - \gamma A(t-\tau_1-\tau_2) + pV(t)T(t) \\
\dot{C}(t) &= (r_v - \delta_C - \delta X(t))C(t) + \gamma A(t-\tau_1-\tau_2) \\
\dot{T}(t) &= (r_u - \delta_u - \delta X(t) - pV(t))T(t) + S \ ,
\end{aligned} \tag{21}
$$

where the state variables are given by V =infectious viral population, A=acutely infected cells, C=chronically infected cells, T=uninfected or target cells, $X = A + C + T$=total cell population (infected and uninfected), and the parameters are given in Table 1. In this model, it is assumed that the delays τ_1, τ_2 are fixed for each cell, and that one can precisely describe the capacity of each member of the population (of infected cells) to produce virions as a function of time. More precisely, exactly τ_1 units of time after a cell becomes infected, it begins producing virus. Exactly τ_2 units of time later, that same cell then becomes chronically infected (assuming it lives to this stage).

From a biological viewpoint, it is unlikely that all cells have precisely the same

delay times in their production characteristics or conversion to a chronically infected stage. To accommodate some variability expected in such biological populations, let the delay in the first equation in (21) be modeled by treating the delay time τ between acute infection and viral production as a probabilistic quantity (i.e., a random variable) with distribution $P_1(\tau)$ so that the first equation in (21) is replaced by (see the appendix of [BBH] for a more detailed discussion of the foundations underlying such an equation)

$$\dot{V}(t) = -cV(t) + n_A \int_{-\infty}^{0} A(t+\tau) dP_1(\tau) + n_C C(t) - p(V(t), T(t)) \,. \tag{22}$$

The function $p(V,T)$, where $x \mapsto p(x)$, $x = (V,T)$, is globally Lipschitz as hypothesized in (H1) in Section 2 above. For the efforts here and in [BBH], the function p is assumed to be locally bilinear, i.e., $p(V,T) = pVT$ before saturation and constant or linear thereafter (see [BBH]).

Likewise, let the delay between acute infectivity and chronic infectivity (with distribution $P_2(\tau)$) be represented in altered forms of the second and third equations of (21) by

$$\dot{A}(t) = (r_v - \delta_A - \delta X(t))A(t) - \gamma \int_{-\infty}^{0} A(t+\tau) dP_2(\tau) + pV(t)T(t) \tag{23}$$

$$\dot{C}(t) = (r_v - \delta_C - \delta X(t))C(t) + \gamma \int_{-\infty}^{0} A(t+\tau) dP_2(\tau) \,. \tag{24}$$

The resulting model becomes the special case

$$\begin{array}{rcl} \dot{V}(t) &=& -cV(t) + n_A \int_{-\infty}^{0} A(t+\tau) k_1(\tau) d\tau + n_C C(t) - pV(t)T(t) \\ \dot{A}(t) &=& (r_v - \delta_A - \delta X(t))A(t) - \gamma \int_{-\infty}^{0} A(t+\tau) k_2(\tau) d\tau + pV(t)T(t) \\ \dot{C}(t) &=& (r_v - \delta_C - \delta X(t))C(t) + \gamma \int_{-\infty}^{0} A(t+\tau) k_2(\tau) d\tau \\ \dot{T}(t) &=& (r_u - \delta_u - \delta X(t) - pV(t))T(t) + S \,, \end{array} \tag{25}$$

whenever P_1, P_2 possess probability densities k_1, k_2 respectively. In the discussions in [BBH], all numerical simulations for each of the systems of functional differential equations given above were performed using the methods described in Section 2 with piecewise linear splines for the states. There it was found, not surprisingly, the presence of nonzero delays has a dramatic effect upon the simulations. Issues related to the exact nature of τ and whether or not it should be modeled as a fixed value for every cell or distributed across the cell populations and how this distribution can be represented, as well as further evidence of the statistical significance of the presence of the delays are the focus of discussions in [BBH].

The variables V and C in the above model are actually expected values. To explain this, we first consider the delay between initial acute infection and initial chronic infection of a cell. It is biologically unrealistic to expect an entire population of cells to simultaneously change infection characteristics $\bar{\mu}_2 = \tau_1 + \tau_2$ ($\bar{\mu}_2 > 0$) hours after initial viral infection. Therefore, suppose that the delay between initial acute infection and chronic infection varies across the cell population (thus mathematically characterizing the intercellular variability) according to a probabilistic distribution $\bar{P}_2$ with density $\bar{k}_2$. We denote by $C(t;\tau)$ the subpopulation consisting of chronically infected cells that either maintained their acute infection characteristics for τ time units or are the progeny of those same cells. In other words, for some $\tau > 0$, there

exists a subpopulation $C(t;\tau)$ of the chronically infected cells which either spent τ hours as acutely infected cells (before converting to chronically infected cells) or are descendants of cells that spent exactly τ hours as acutely infected cells. Thus, as derived carefully in [BBH] one has

$$C(t) = \mathcal{E}_2[C(t;\tau)] = \int_0^\infty C(t;\tau)\bar{k}_2(\tau)d\tau\,, \tag{26}$$

where

$$\dot{C}(t;\tau) = (r_v - \delta_C - \delta X(t))\, C(t;\tau) + \gamma A(t-\tau)\,,$$

with

$$X(t) = A(t) + C(t) + T(t).$$

Integration of this equation over the distribution $\bar{P}_2$, over all possible delays, yields the equation for C, the expected value of the population of chronic cells, given by

$$\begin{aligned} \dot{C}(t) &= \mathcal{E}_2[\dot{C}(t;\tau)] \\ &= (r_v - \delta_C - \delta X(t))\, C(t) + \gamma \textstyle\int_0^\infty A(t-\tau)\,\bar{k}_2(\tau)\,d\tau \\ C(0) &= C_0\,, \end{aligned} \tag{27}$$

where C_0 is the initial condition for the total chronically infected cell population. A simple change of variables in the integral term as described below results in the third equation of (25).

A similar argument can be made for the delay between viral infection and viral production for the acutely infected cells $A(t)$. One supposes that the delay between infection and production (for acutely infected cells $A(t)$) varies across the population with probability distribution $\bar{P}_1$ and corresponding density $\bar{k}_1$ and partitions the expected total viral population V into those virions V_A produced by acutely infected cells and those virions V_C produced by chronically infected cells. We then denote by $V_A(t;\tau)$ the subpopulation of virus which are produced by an acutely infected cell τ hours after being infected. Thus, the rate of change in this subgroup of virions is governed by

$$\dot{V}_A(t;\tau) = -cV_A(t;\tau) + n_A A(t-\tau) - pV_A(t;\tau)T(t)\,.$$

To obtain the (expected) number of virus at time t that have been produced by acutely infected cells, we must integrate over the distribution $\bar{P}_1$, over all possible delays

$$V_A(t) = \mathcal{E}_1[V_A(t;\tau)] = \int_0^\infty V_A(t;\tau)\bar{k}_1(\tau)d\tau\,,$$

which yields the governing equation for this larger subpopulation of virions

$$\begin{aligned} \dot{V}_A(t) &= \mathcal{E}_1[\dot{V}_A(t;\tau)] \\ &= -cV_A(t) + n_A \int_0^\infty A(t-\tau)\bar{k}_1(\tau)d\tau - pV_A(t)T(t)\,. \end{aligned}$$

To account for the chronically infected cells as a source of virions, we denote V_C as the subpopulation of virions produced by chronically infected cells. Thus the equation describing the rate of change in the size of this subpopulation is

$$\dot{V}_C(t) = -cV_C(t) + n_C C(t) - pV_C(t)T(t)\,,$$

where the expected value C of the total population of chronically infected cells is defined in (26). Therefore, the governing equations for the total population of virus are described by

$$\begin{aligned}\dot{V}(t) &= \mathcal{E}_1[\dot{V}_A(t;\tau) + \dot{V}_C(t)] \\ &= -c(V_A(t) + V_C(t)) + n_A \int_0^\infty A(t-\tau)\bar{k}_1(\tau)d\tau + n_C C(t) \\ &\quad -p(V_A(t) + V_C(t))T(t) \\ &= -cV(t) + n_A \int_0^\infty A(t-\tau)\bar{k}_1(\tau)d\tau + n_C C(t) - pV(t)T(t) \\ V(0) &= V_0\,,\end{aligned}$$

where V_0 is the initial condition for the total virions population.

If one assumes that the A and T subclasses have no subpopulation structures, and are therefore governed by

$$\begin{aligned}\dot{A}(t) &= (r_v - \delta_A - \delta X(t))\,A(t) - \gamma \int_0^\infty A(t-\tau)\,\bar{k}_2(\tau)\,d\tau \\ &\quad +pV(t)\,T(t) \\ A(0) &= A_0 \\ \dot{T}(t) &= (r_u - \delta_u - \delta X(t) - pV(t))\,T(t) + S \\ T(0) &= T_0\,,\end{aligned}$$

with initial conditions A_0 and T_0, we are subsequently led to the model equations (25) by making the change of variables $k_i(\xi) = \bar{k}_i(-\xi)$ so that the densities are now defined on $(-\infty, 0)$ instead of $(0, \infty)$.

In summary, the theoretical and approximation methodology of Section 2 provide a sound foundation for inverse problem investigations such as those of [BBH]. Among the important findings for the models developed are: (i) an excellent fit to *in vitro* experimental data; (ii) a rigorous model comparison statistical analysis to support importance of delays (statistical significance in improving fits-to-data) in the models; (iii) analysis to show that the models with discrete delays yield essentially similar dynamic responses to those from models with continuous delays. This last finding is important biologically since it is highly unlikely that all cells in a population can respond with fixed uniform delays.

3.3. Example 3: The drinking behavior control system (DBCS). Researchers studying alcohol abuse and addiction have collected vast amounts of information on substance use, participant's willingness to change behavior, and participant's success in a particular treatment. Many hypotheses have been formulated concerning possible (difficult-to-measure) factors that control a patient's motivations and behavior, such as the relative importance of drinking in their lives, commitment to reducing their alcohol consumption, and recognition of reasons to not use a substance, to name a few. However, the relative contributions of these possible mechanisms for behavior change are unclear. The interplay among these factors as they change over time is a natural, albeit difficult, question to address via dynamical mathematical models. In order to better understand these ideas in a quantitative context and to identify underlying mechanisms governing drinking behavior in problem drinkers during therapy, we have, in joint efforts [BRSDHKM] with a team of psychologists at Columbia University, attempted to model behavior control systems informed by a dataset, Project MOTION. We present here an initial model developed in these collaborations.

Further details on Project MOTION and the data collected can be found in [BRSDHKM]. Briefly, approximately 90 participants were assigned to one of three therapy-based treatment groups. In addition to attending the four therapy sessions over an eight week period, patients were directed to call an interactive voice recording (IVR) system and answer a survey of 41 questions every day during the evening for eight weeks. Our modeling efforts focused on the data from the IVR surveys since there are numerous longitudinal time points, which we anticipated would be more informative of the underlying dynamic processes.

The 41 questions of the IVR are divided into topical groups in the survey form. Each group has its own scale by which a participants' numerical responses are interpreted. Since it is prohibitive to construct an initial model from so many variables, we averaged responses from similar categories which led to *conceptual variables*. Among the conceptual variables we considered based on the IVR data were stressful events, pleasant events, pressure to drink, current mood, perceived stress, desire to drink, commitment to not drink for the next 24 hours, confidence and commitment to reduce drinking for the next 24 hours, guilt concerning drinking behavior, and alcohol consumption. The models were then developed based on these variables. During the formulation of these models based on the longitudinal data, we determined that delays and cumulative effects are important and should be included in order to accurately reflect the dynamic changes in a person's behavior.

In one of our preliminary models, we focused on three state variables: desire to drink or Desire, denoted as $D(t)$; the extent to which the subject feels their drinking over the recent past was excessive, referred to in short as Guilt, $G(t)$; and alcoholic beverage consumption rate or Alcohol, $A(t)$. The alcohol consumption function $A(t)$ describes the rate at which the participant is consuming alcoholic beverages and has units of drinks/time. In contrast the other two state variables are unit-less, measuring the extent to which a subject agrees with a statement on the intensity of their feelings on a particular subject. One preliminary simplified model had the form

$$
\begin{aligned}
\frac{d}{dt}A(t) &= -a_{12}\left(\int_{-r}^{0} G(t+s)\kappa_1(s)ds\right)^2 + a_{13}\chi_{\{D>0\}}D(t)\\
\frac{d}{dt}G(t) &= a_{21}\left(A(t-\tau_1) - A_G^*\right)\\
\frac{d}{dt}D(t) &= -a_{32}\left[exp\left(\frac{1}{G_{D1}^*}\int_{-r}^{0} G(t+s)\kappa_2(s)ds\right) - G_{D2}^*\right],
\end{aligned}
\tag{28}
$$

where $\kappa_1(s) = \frac{x+2}{2}$, $\kappa_2(s) = \frac{(x+2)^3}{4}$, and $r = 2$, indicating that behavior over the past two days has an impact on current behavior. We included an indicator function $\chi_{(D>0)}$ to reflect that only when a person desires alcohol does his/her drinking behavior change. Additionally, we enforced the conditions $A(t) \geq 0$ and $G(t) \geq 0$, where for all variables a value of 0 indicates a neutral value (the scaled variables had values in the range $[-2, 2]$). For example $D(t) = 0$ indicates neither a desire nor a dislike for alcohol, and $G(t) = 0$ indicates that a person feels no particular feelings of guilt or virtue.

Interestingly, it appeared that one patient's drinking pattern could be reasonably described when considering just two variables: the alcohol consumption rate $A(t)$, and the guilt $G(t)$. A key observation was that the individual's drinking was driven by an innate reward/desire mechanism. This mechanism is the ingrained desire for drinking that separates problem drinkers from those who drink casually (or less). It is

known that animals and human beings in particular yearn for something representing a reward, with the specific reward varying among individuals. Examples include food for some people, smoking for others, etc. In addition, it is known that individuals learn to turn this desire off when the reward is unavailable or they have decided they cannot indulge. So in addition to being a mechanism for desire it can also have the effect of controlling or limiting one's intake of alcohol.

The model resulting from analysis of the data for this patient in such a context is given by

$$\begin{aligned} \frac{d}{dt}A(t) &= -a_{12}\chi_{\{G>G^*\}}(G(t)-G^*) + a_{13}h(t) \\ \frac{d}{dt}G(t) &= a_{21}\left[\int_{-r}^{0} A(t+s)ds - (1+c\chi_{\{W(t)\}})A^*\right] \end{aligned} \tag{29}$$

where the function $h(t)$ represents the subject's desire/reward mechanism, which increases going into the weekend (to turn it 'on'), and decreases coming out of the weekend (thereby turning it 'off'). This particular individual allowed himself to drink on the weekend as long as he refrains during the week, so $h(t)$ has the form

$$h(\hat{t}) = \begin{cases} 2(\hat{t}-1.5) & 1.5 \le \hat{t} < 2 \quad \text{(Friday a.m. through Friday p.m.)} \\ -2(\hat{t}-2.5) & 2 \le \hat{t} < 2.5 \quad \text{(Friday p.m. through Saturday a.m.)} \\ -2(\hat{t}-3.5) & 3.5 \le \hat{t} < 4 \quad \text{(Sunday a.m. through Sunday p.m.)} \\ 2(\hat{t}-4.5) & 4 \le \hat{t} < 4.5 \quad \text{(Sunday p.m. through Monday a.m.)} \\ 0 & \text{otherwise,} \end{cases}$$

where $\hat{t} = t \mod 7$.

The effect of 'guilt' decreases the individual's drinking rate only once it surpasses a certain 'threshold' level G^*. In contrast, the effect of alcohol, or specifically the number of drinks consumed in the recent past $\int_{-r}^{0} A(t+s)ds$ can decrease one's guilt if it is below a certain acceptable level, A^* during the week and $(1+c)A^*$ during the weekend (this is implemented through the week/weekend characteristic function $\chi_{\{W(t)\}}$). If it surpasses these levels which the individual has rationalized as acceptable, he feels that his drinking was excessive, with the extent of that feeling proportional to how much his recent drinking has surpassed those levels.

3.3.1. Simulated inverse problem. Not surprisingly, most of the parameters are unknown in the above delay model, and it is of great interest to be able to estimate them using longitudinal data. To investigate our ability to do so, we generated some data with various levels of added noise, representative of that in the IVR, on the drinks consumed over the past day $d_j^1 \approx f^1(t_j) \equiv \int_{-1}^{0} A(t_j+s)ds$ and the extent to which they felt that was excessive $d_j^2 \approx f^2(t_j) \equiv G(t_j)$. The generated data has been computed as

$$\begin{aligned} d_j^1 &= f^1(t_j) + \frac{k}{100}\text{mean}_j\{f^1(t_j)\}\mathcal{N}(0,1), \\ d_j^2 &= f^2(t_j) + \frac{k}{100}\text{mean}_j\{f^2(t_j)\}\mathcal{N}(0,1), \end{aligned}$$

where $j = 1, \ldots, K$, and $k = 1, 5$, or 10, corresponding to 1%, 5% or 10% error. Here $\mathcal{N}(0,1)$ is a standard Gaussian with mean zero and unity variance. All computations,

including the generation of data for use in the inverse problem, were done using piecewise linear splines with $N = 32$ to solve the delay system. The relevant timescale for the IVR data appears to be 'triweekly', as daily data exhibits too much variation so that the trends were not obvious, and too much information was lost if the daily responses were averaged over a week. We note that averaging is preferred to summing with these data, to lessen the impact of missing responses. Drinking behavior with most individuals is starkly different on the weekends as opposed to weekdays, so one of the time intervals of the triweekly time scale begins on Fri evening and lasts to the time of the call on Sun evening. The other two time intervals are Sun evening to Wed evening, and then Wed evening to Fri evening. A comparison of noise-less (0% error) data and that with 10% error is shown in Figure 2. Parameter values and initial conditions used to generate these data are given in Table 2.

a_{12}	0.15	A^*	1.5
a_{13}	16	r	1
a_{21}	0.8	$A(0)$	1
c	4.25	$G(0)$	-0.5

TABLE 2

Parameter values and initial conditions used to generate the data. Initially, $A(\phi) = 1$, $G(\phi) = -0.5$ *for* $\phi \in [-r, 0)$.

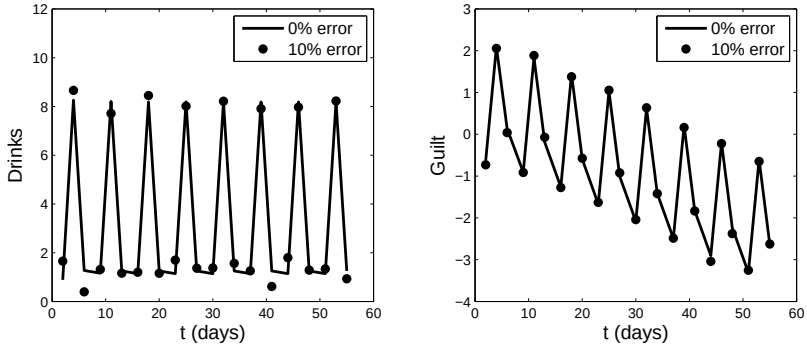

FIG. 2. *Generated data with 0% and 10% error. Contained in the left panel is the number of drinks over a day* $d_j^1 \approx \int_{-1}^{0} A(t_j + s)ds$ *and in the right is the guilt* $d_j^2 \approx G(t_j)$. *These are compared to the model solution (solid lines) with no noise.*

Specifically, we discuss here our ability to estimate parameters $\theta = (a_{13}, a_{21})^T$ and $\theta = (a_{13}, r)^T$ where r is the length of time that the drinking may influence the individual's 'guilt'. The period of time over which the individual may be reflecting to influence that response may not always be known.

Estimates $\hat{\theta}$ to parameters are obtained by minimizing the ordinary least squares functional

$$J(\theta) = \sum_{j=1}^{K} \left| d_j^1 - f^1(t_j; \theta) \right|^2 + \left| d_j^2 - f^2(t_j; \theta) \right|^2$$

over the feasible parameter set $\Theta \subset \mathbb{R}^2$.

Values of estimates for $\theta = (a_{13}, a_{21})^T$ with known cumulative effect $r = 1$, and for $\theta = (a_{13}, r)^T$ are contained in Table 3 for $1, 5$, and 10% noise, respectively. Since parameter estimates are relatively close to their 'true' values, or the values that were used to generate the data, it appears that we could reasonably expect to estimate these parameters from similar data. The fit to 10% noisy data is shown in Figure 3 when estimating the length of time interval r and parameter a_{13}. Fits when estimating either $\theta = (a_{13}, a_{21})^T$ or $\theta = (a_{13}, r)^T$ are comparable, as suggested by the RSS values.

The many influences behind drinking behavior are difficult to identify and relate in a quantitative manner. However, our initial modeling efforts have shown behavior similar to that seen in data from Project MOTION. Performing the inverse problem on simulated data from the models such as (28) and (29) is not a trivial task, but the above results and other computational results suggest that this will be feasible with appropriate data. Current investigations into the sensitivity of the model with respect to the parameters and discrete delays will provide information regarding which parameters are most influential on model behavior.

	a_{13}	a_{21}	RSS	a_{13}	r	RSS
True value	16	0.8		16	1	
Initial guess	14	1		14	1.2	
$\hat{\theta}^{(1)}$	15.999	0.8001	0.0397	15.9994	1.0001	0.03967
$\hat{\theta}^{(5)}$	16.011	0.79928	0.688	15.9942	1.00196	0.6746
$\hat{\theta}^{(10)}$	15.9880	0.80119	3.588	16.0043	1.0001	3.5865

TABLE 3

Parameter estimates $\hat{\theta} = (\hat{a}_{13}, \hat{a}_{21})^T$ on the left, and $\hat{\theta} = (\hat{a}_{13}, \hat{r})^T$ on the right and the residual sum of squares RSS from fitting generated data with 1, 5, and 10% error, respectively. The superscript in the symbol $\hat{\theta}$ indicates the level of error.

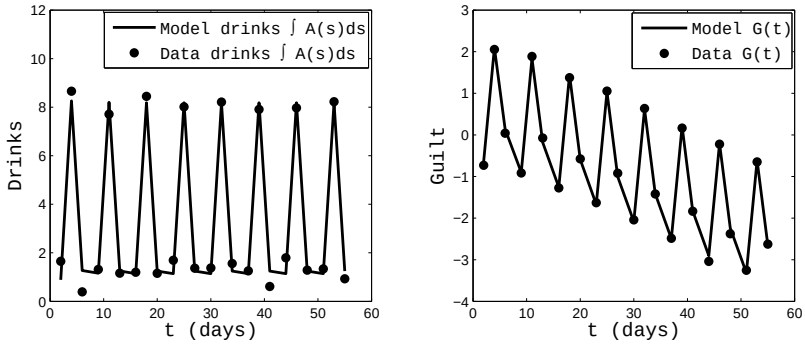

FIG. 3. *Best fit solutions when estimating $\hat{\theta}^{(10)} = (\hat{a}_{13}, \hat{r})^T$ compared to generated data with 10% error.*

4. Concluding remarks. In this paper we have presented new theoretical results for inverse problems involving general nonlinear nonautonomous delay systems with functional (time-dependent rate functions, probability distributions) parameters. An approximation framework that entails approximation of both the infinite dimensional dynamical state spaces and infinite dimensional parameter sets is given. This

provides a rigorous foundation for a wide class of problems arising in applications. We illustrate the ideas by brief discussions of examples from insect populations with time dependent maturation and death rate, cellular level HIV models with uncertainty in process delays, and models for changing behavior in response during alcohol therapy. We also demonstrate the efficacy of the approximation methods with computations for the behavioral models.

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