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Sensitivity of dynamical systems to Banach space parameters ☆

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Abstract

We consider general nonlinear dynamical systems in a Banach space with dependence on parameters in a second Banach space. An abstract theoretical framework for sensitivity equations is developed. An application to measure dependent delay differential systems arising in a class of HIV models is presented.
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1. Introduction

The qualitative and quantitative investigation of parameter dependent systems is ubiquitous in science and engineering. The wide spread desire to treat uncertainty leads to the need to treat distributions of parameters in diverse applications ranging from classical physiologically based pharmacokinetics (PBPK) models [6,23,38] to social networks (e.g., the diffusion of ideas in populations [17]) to random effects and mixing distributions in statistical modeling [24,30–32].

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A powerful tool for the investigation of parameter dependency is the *sensitivity matrix*. Equations for the sensitivity of a system with respect to vector parameters are used in optimization and inverse problems (least squares, maximum likelihood, standard errors in statistics-[25]), model discrimination/model selection (dispersion matrix, Fisher information matrix-[20]), as well as applications in biology [18], mechanics [1,28], and control theory [42]. The large literature includes a number of books devoted to both elementary and advanced aspects of sensitivity [22, 26–28,36,42].

With the recently growing interest in incorporating uncertainty into models and systems, the need to employ dynamics with probabilistic structures has received increased emphasis. In particular, systems with probability measures embedded in the dynamics (problems involving *aggregate dynamics* as discussed in [6]) have become important in applications in biology [3,5,6], electromagnetics [7] and hysteretic [10,11,19,29,33] and polymeric [12,13,15] materials. These systems have the form

$$\dot{x}(t) = \mathcal{F}\big(t, x(t), P\big),$$

where P is a probability distribution or measure. In fact such systems are not new and arise in *relaxed* or *chattering* control problems [34,35,37,39–41] wherein the controls are probability measures. Indeed, such systems date back to the seminal work of L.C. Young on *generalized curves* in the calculus of variations [43,44].

In [3], Banks and Bortz consider systems which depend on parameterized probability measures $P = P(\nu, \sigma^2)$ and develop a framework for sensitivities with respect to the mean ν and variance σ^2 in the context of delay differential systems for HIV. Here we present a theory treating general Banach space parameters which include a general class of probability densities. The example we discuss entails a nonparametric density version of the HIV example treated in [3].

Specifically, we study the sensitivity equation of the ordinary differential equation

$$\begin{aligned} &\dot{x}(t) = f\big(t, x(t), \mu\big), \quad t \geqslant t_0, \\ &x(t_0) = x_0, \end{aligned} \tag{1}$$

where $f : \mathbb{R}_+ \times X \times \mathcal{M} \to X$ and X and $\mathcal{M}$ are complex Banach spaces. We wish to show for the parameter μ in a Banach space $\mathcal{M}$, the *Frechet* derivative of the solution x with respect to μ, $\frac{\partial}{\partial \mu} x(t, t_0, x_0, \mu) = y(t)$, exists and satisfies the equation

$$\begin{aligned} &\dot{y}(t) = f_x\big(t, x(t, t_0, x_0, \mu), \mu\big) y(t) + f_\mu\big(t, x(t, t_0, x_0, \mu), \mu\big), \quad t \geqslant t_0, \\ &y(t_0) = 0. \end{aligned} \tag{2}$$

Here we define the notation that is used throughout this paper. Let X and $\mathcal{M}$ be two complex Banach spaces and for $x \in X$, $\mu \in \mathcal{M}$, we denote by $|x|$, $|\mu|$, the norm of x and the norm of μ, respectively. The space of bounded linear operators from X onto Y is denoted by $B(X, Y)$. We let $C[A, B]$ represent the class of continuous functions from set A into set B. For a function $f : \mathbb{R}_+ \times X \times \mathcal{M} \to X$, the *Frechet* derivatives with respect to x and μ, if they exist, are represented by $f_x(t, x, \mu)$ and $f_\mu(t, x, \mu)$ and belong to $B(X, X)$ and $B(\mathcal{M}, X)$, respectively.

2. Theory

Consider the abstract differential equation (1) where $f : \mathbb{R}_+ \times X \times \mathcal{M} \to X$ is a continuous mapping; it is clear that for $t \geqslant t_0$, a solution $x(t, t_0, x_0, \mu)$ of (1) satisfies the integral equation

$$x(t, t_0, x_0, \mu) = x_0 + \int_{t_0}^{t} f\big(s, x(s, t_0, x_0, \mu), \mu\big)\, ds, \quad t \geqslant t_0. \tag{3}$$

In order to study the sensitivity of solutions of (1), one first must establish that the solution of (1) exists and is unique. The proofs follow from standard differential equation arguments (e.g., see [21]) using *successive approximations*. Therefore, we define the *successive approximations* for system (1) to be the functions, $x^0, x^1, \ldots,$ given recursively by

$$\begin{aligned} &x^0(t, t_0, x_0, \mu) = x_0, \\ &x^{k+1}(t, t_0, x_0, \mu) = x_0 + \int_{t_0}^{t} f\big(s, x^k(s, t_0, x_0, \mu), \mu\big)\, ds, \quad t \geqslant t_0, \end{aligned} \tag{4}$$

for $k = 0, 1, 2, \ldots.$

Lemma 1 *(Existence and Uniqueness of Solutions). Let $f : \mathbb{R}_+ \times X \times \mathcal{M} \to X$ be continuous and*

$$\big|f(t, x_1, \mu) - f(t, x_2, \mu)\big| \leqslant C|x_1 - x_2| \tag{5}$$

for some constant $C > 0$. Then the successive approximations x^k converge uniformly for $t \in [t_0, T]$ to a unique solution x of (1) such that $x(t_0, t_0, x_0, \mu) = x_0$.

Proof. Since the arguments are quite standard, we only outline the steps. For a given interval $I = [t_0, T]$ where $t \in I$, define

$$\Lambda^k(t, t_0, x_0, \mu) = \big|x^{k+1}(t, t_0, x_0, \mu) - x^k(t, t_0, x_0, \mu)\big|.$$

Then one can use induction to establish for constants M and C

$$\Lambda^k(t, t_0, x_0, \mu) \leqslant \frac{MC^k(t - t_0)^{k+1}}{(k+1)!}. \tag{6}$$

It follows that the partial sum

$$x^n(t, t_0, x_0, \mu) = x_0 + \sum_{k=0}^{n-1} \big(x^{k+1}(t, t_0, x_0, \mu) - x^k(t, t_0, x_0, \mu)\big)$$

converges uniformly to a continuous function x on $[t_0, T]$. If one then passes to the limit in Eq. (4), one obtains that x must satisfy Eq. (3).

To establish uniqueness of the solution, one uses Gronwall's inequality and (5) in the usual manner to bound the difference in any two possible solutions by zero. Details are given in [14]. □

Lemma 2 *(Continuous Dependence of Solutions on Parameters). Let $f \in C[\mathbb{R}_+ \times X \times \mathcal{M}, X]$ and for $\mu = \mu_0$, let $x(t, t_0, x_0, \mu_0)$ be a solution of*

$$\dot{x} = f(t, x, \mu_0), \quad x(t_0) = x_0, \tag{7}$$

existing on $[t_0, T]$. *Assume further that*

$$\lim_{\mu\to\mu_0} f(t,x,\mu) = f(t,x,\mu_0), \tag{8}$$

uniformly in (t,x) *and for* $(t,x_1,\mu), (t,x_2,\mu) \in \mathbb{R}_+ \times X \times \mathcal{M}$,

$$\bigl|f(t,x_1,\mu) - f(t,x_2,\mu)\bigr| \leqslant C|x_1 - x_2| \tag{9}$$

for some constant $C > 0$. *Then the differential system*

$$\dot{x} = f(t,x,\mu), \quad x(t_0) = x_0, \tag{10}$$

has a unique solution $x(t,t_0,x_0,\mu)$ *satisfying*

$$\lim_{\mu\to\mu_0} x(t,t_0,x_0,\mu) = x(t,t_0,x_0,\mu_0), \quad t \in [t_0,T]. \tag{11}$$

Proof. On any interval $[t_0,T]$, the existence and uniqueness of the solution is provided in Lemma 1. We first wish to show continuous dependence of solutions on μ. Let $t \in [t_0,T]$ and define, $z(t,\mu,\mu_0) = x(t,t_0,x_0,\mu) - x(t,t_0,x_0,\mu_0)$, we have

$$\begin{aligned}
\bigl|z(t,\mu,\mu_0)\bigr| &= \bigl|x(t,t_0,x_0,\mu) - x(t,t_0,x_0,\mu_0)\bigr| \\
&\leqslant \int_{t_0}^{t} \bigl|f\bigl(s,x(s,t_0,x_0,\mu),\mu\bigr) - f\bigl(s,x(s,t_0,x_0,\mu_0),\mu_0\bigr)\bigr|\,ds \\
&= \int_{t_0}^{t} \bigl|f\bigl(s,x(s,t_0,x_0,\mu),\mu\bigr) - f\bigl(s,x(s,t_0,x_0,\mu_0),\mu\bigr) \\
&\quad + f\bigl(s,x(s,t_0,x_0,\mu_0),\mu\bigr) - f\bigl(s,x(s,t_0,x_0,\mu_0),\mu_0\bigr)\bigr|\,ds \\
&\leqslant \int_{t_0}^{t} \bigl\{\bigl|f\bigl(s,x(s,t_0,x_0,\mu),\mu\bigr) - f\bigl(s,x(s,t_0,x_0,\mu_0),\mu\bigr)\bigr| \\
&\quad + \bigl|f\bigl(s,x(s,t_0,x_0,\mu_0),\mu\bigr) - f\bigl(s,x(s,t_0,x_0,\mu_0),\mu_0\bigr)\bigr|\bigr\}\,ds \\
&\leqslant \int_{t_0}^{t} C\bigl|x(s,t_0,x_0,\mu) - x(s,t_0,x_0,\mu_0)\bigr|\,ds \\
&\quad + \int_{t_0}^{t} \bigl|f\bigl(s,x(s,t_0,x_0,\mu_0),\mu\bigr) - f\bigl(s,x(s,t_0,x_0,\mu_0),\mu_0\bigr)\bigr|\,ds.
\end{aligned}$$

Let us define $g(s,\mu)$ by

$$g(s,\mu) = \bigl|f\bigl(s,x(s,t_0,x_0,\mu_0),\mu\bigr) - f\bigl(s,x(s,t_0,x_0,\mu_0),\mu_0\bigr)\bigr|$$

and note that $g(s,\mu) \to 0$ uniformly in s as $\mu \to \mu_0$ from the assumption on f in Eq. (8). It follows

$$\bigl|z(t,\mu,\mu_0)\bigr| \leqslant \int_{t_0}^{T} g(s,\mu)\,ds + \int_{t_0}^{t} C\bigl|x(s,t_0,x_0,\mu) - x(s,t_0,x_0,\mu_0)\bigr|\,ds. \tag{12}$$

When we apply Gronwall's inequality and take the limit as $\mu \to \mu_0$ on both sides of (12), we obtain

$$\lim_{\mu\to\mu_0} \bigl|z(t,\mu,\mu_0)\bigr| \leqslant \lim_{\mu\to\mu_0} \left(\int_{t_0}^{T} g(s,\mu)\,ds\right) e^{C(t-t_0)} = 0$$

and thus

$$\lim_{\mu\to\mu_0} x(t,t_0,x_0,\mu) = x(t,t_0,x_0,\mu_0).$$

This completes the proof. □

Lemma 3 *(Mean Value Theorem). Let $f \in C[\mathbb{R}_+ \times X \times \mathcal{M}, X]$ and*

(i) *If $f_x(t,x,\mu)$ exits and is continuous for $x \in X$, then for $x_1, x_2 \in X$, $\mu \in \mathcal{M}$, $t \geqslant 0$,*

$$f(t,x_1,\mu) - f(t,x_2,\mu) = \int_0^1 f_x\bigl(t, sx_1 + (1-s)x_2, \mu\bigr)(x_1 - x_2)\,ds.$$

(ii) *If $f_\mu(t,x,\mu)$ exists and is continuous for $\mu \in \mathcal{M}$, then for $\mu_1, \mu_2 \in \mathcal{M}$, $x \in X$, $t \geqslant 0$,*

$$f(t,x,\mu_1) - f(t,x,\mu_2) = \int_0^1 f_\mu\bigl(t, x, s\mu_1 + (1-s)\mu_2\bigr)(\mu_1 - \mu_2)\,ds.$$

Proof. First we consider (i). Let

$$G(s) = f\bigl(t, sx_1 + (1-s)x_2, \mu\bigr), \quad 0 < s \leqslant 1,$$

and using the chain rule of *Frechet* derivatives, we have

$$G'(s) = f_x\bigl(t, sx_1 + (1-s)x_2, \mu\bigr)(x_1 - x_2).$$

Note that $G(s)$ is well defined since X is a convex space. Integrating $G'(s)$ for $s \in (0,1]$, we obtain $G(1) - G(0)$ which is equivalent to $f(t,x_1,\mu) - f(t,x_2,\mu)$ and hence we have (i).

The proof of (ii) is very similar to the proof of (i) and hence we omit it. □

Theorem 1. *Suppose the function $f(t,x,\mu)$ of (1) has a continuous Frechet derivative $f_x(t,x,\mu)$ with respect to x and $f_\mu(t,x,\mu)$ with respect to μ with*

$$\bigl|f_x(t,x,\mu)\bigr| \leqslant M_0 \quad \textit{and} \quad \bigl|f_\mu(t,x,\mu)\bigr| \leqslant M_1$$

for some constant $M_0 > 0$ and $M_1 > 0$. Then the Frechet derivative $y(t) = \frac{\partial}{\partial\mu} x(t,t_0,x_0,\mu)$ exists with $y(t)$ in $B(\mathcal{M}, X)$ and satisfying the equation

$$\begin{aligned} &\dot{y}(t) = f_x\bigl(t, x(t,t_0,x_0,\mu), \mu\bigr) y(t) + f_\mu\bigl(t, x(t,t_0,x_0,\mu), \mu\bigr), \quad t \geqslant t_0, \\ &y(t_0) = 0. \end{aligned} \tag{13}$$

Proof. Since $f_x \in C[\mathbb{R}_+ \times X \times \mathcal{M}, B(X,X)]$, $f_\mu \in C[\mathbb{R}_+ \times X \times \mathcal{M}, B(\mathcal{M}, X)]$, applying Lemma 1, we find that the differential system (13) has a unique solution which we denote by

$y(t)$. For a fixed $\mu \in \mathcal{M}$, $\mu + h \in \mathcal{M}$, and $t \in [t_0, T]$, we let $m(t, \mu, h) = x(t, t_0, x_0, \mu + h) - x(t, t_0, x_0, \mu)$. Then

$$m(t, \mu, h) = \int_{t_0}^{t} \bigl\{ f\bigl(s, x(s, t_0, x_0, \mu + h), \mu + h\bigr) - f\bigl(s, x(s, t_0, x_0, \mu), \mu\bigr) \bigr\}\, ds.$$

From the *Frechet* differentiability of f with respect to $x \in X$ and $\mu \in \mathcal{M}$, we have

$$\begin{aligned}
&f\bigl(t, x(t, t_0, x_0, \mu + h), \mu + h\bigr) - f\bigl(t, x(t, t_0, x_0, \mu), \mu\bigr) \\
&\quad = f\bigl(t, x(t, t_0, x_0, \mu + h), \mu + h\bigr) - f\bigl(t, x(t, t_0, x_0, \mu + h), \mu\bigr) \\
&\qquad + f\bigl(t, x(t, t_0, x_0, \mu + h), \mu\bigr) - f\bigl(t, x(t, t_0, x_0, \mu), \mu\bigr) \\
&\quad = f_\mu\bigl(t, x(t, t_0, x_0, \mu + h), \mu\bigr)(\mu + h - \mu) + w_1(h) \\
&\qquad + f_x\bigl(t, x(t, t_0, x_0, \mu), \mu\bigr)\bigl[x(t, t_0, x_0, \mu + h) - x(t, t_0, x_0, \mu)\bigr] + w_2\bigl(m(t, \mu, h)\bigr),
\end{aligned}$$

where

$$\frac{|w_1(h)|}{|h|} \to 0 \quad \text{and} \quad \frac{|w_2(m(t, \mu, h))|}{|m(t, \mu, h)|} \to 0$$

as $|h|$, $|m(t, \mu, h)| \to 0$, respectively. Consequently, we define $g_1(t, h)$ and $g_2(t, h)$ by

$$g_1(t, h) = \frac{|w_1(h)|}{|h|}, \tag{14}$$

$$g_2(t, h) = \frac{|w_2(m(t, \mu, h))|}{|m(t, \mu, h)|}, \tag{15}$$

and hence $g_1(t, h)$ and $g_2(t, h) \to 0$ uniformly in t as $|h| \to 0$.

Now for $y(t)$ satisfying system (13), we consider

$$\begin{aligned}
\frac{|m(t, \mu, h) - y(t)h|}{|h|} &= \frac{1}{|h|} \Biggl| \int_{t_0}^{t} \bigl\{ f_\mu\bigl(s, x(s, t_0, x_0, \mu + h), \mu\bigr)h + w_1(h) \\
&\quad + f_x\bigl(s, x(s, t_0, x_0, \mu), \mu\bigr)\bigl[m(s, \mu, h)\bigr] + w_2\bigl(m(s, \mu, h)\bigr) \\
&\quad - f_x\bigl(s, x(s, t_0, x_0, \mu), \mu\bigr)y(s)h - f_\mu\bigl(s, x(s, t_0, x_0, \mu), \mu\bigr)h \bigr\}\, ds \Biggr| \\
&\leqslant \int_{t_0}^{t} \frac{|f_\mu(s, x(s, t_0, x_0, \mu + h), \mu) - f_\mu(s, x(s, t_0, x_0, \mu), \mu)|\,|h|}{|h|}\, ds \\
&\quad + \int_{t_0}^{t} \bigl| f_x\bigl(s, x(s, t_0, x_0, \mu), \mu\bigr) \bigr| \frac{|m(s, \mu, h) - y(s)h|}{|h|}\, ds \\
&\quad + \int_{t_0}^{t} \frac{|w_2(m(s, \mu, h))|}{|h|}\, ds + \int_{t_0}^{t} \frac{|w_1(h)|}{|h|}\, ds.
\end{aligned}$$

Next we want to show

$$\frac{|w_2(m(t,\mu,h))|}{|h|} \leqslant K\frac{|w_2(m(t,\mu,h))|}{|m(t,\mu,h)|}$$

for some constant $K > 0$. Hence, we want to look at

$$\begin{aligned}\bigl|m(t,\mu,h)\bigr| &= \left|\int_{t_0}^{t}\bigl\{f_\mu\bigl(s,x(s,t_0,x_0,\mu+h),\mu\bigr)h + w_1(h)\right.\\ &\quad\left. + f_x\bigl(s,x(s,t_0,x_0,\mu),\mu\bigr)\bigl[m(s,\mu,h)\bigr] + w_2\bigl(m(s,\mu,h)\bigr)\bigr\}\,ds\right|\\ &\leqslant \int_{t_0}^{t}\bigl\{\bigl|f_\mu\bigl(s,x(s,t_0,x_0,\mu+h),\mu\bigr)\bigr||h| + \bigl|w_1(h)\bigr|\\ &\quad + \bigl|f_x\bigl(s,x(s,t_0,x_0,\mu),\mu\bigr)\bigr|\bigl|m(s,\mu,h)\bigr| + \bigl|w_2\bigl(m(s,\mu,h)\bigr)\bigr|\bigr\}\,ds.\end{aligned}$$

From Eqs. (14) and (15), we obtain

$$\bigl|w_1(h)\bigr| = g_1(t,h)|h|, \qquad \bigl|w_2\bigl(m(t,\mu,h)\bigr)\bigr| = g_2(t,h)\bigl|m(t,\mu,h)\bigr|.$$

Furthermore, with the assumptions that $|f_x| \leqslant M_0$, $|f_\mu| \leqslant M_1$, the function $|m(t,\mu,h)|$ is bounded by

$$\begin{aligned}&\int_{t_0}^{t}\bigl\{M_1|h| + g_1(s,h)|h| + M_0\bigl|m(s,\mu,h)\bigr| + g_2(s,h)\bigl|m(s,\mu,h)\bigr|\bigr\}\,ds\\ &\quad\leqslant \int_{t_0}^{T} M_1|h| + g_1(s,h)|h|\,ds + \int_{t_0}^{t}\bigl(M_0 + g_2(s,h)\bigr)\bigl|m(s,\mu,h)\bigr|\,ds.\end{aligned}$$

Again, applying Gronwall's inequality, we obtain

$$\bigl|m(t,\mu,h)\bigr| \leqslant K|h|,$$

where $K = (\int_{t_0}^{T}\{M_1 + g_1(s,h)\}\,ds)e^{\int_{t_0}^{T} M_0 + g_2(s,h)\,ds}$ where $g_1(s,h)$ and $g_2(s,h)$ converge to 0 uniformly in s as $|h| \to 0$. It follows

$$\frac{|w_2(m(t,\mu,h))|}{|h|} \leqslant K\frac{|w_2(m(t,\mu,h))|}{|m(t,\mu,h)|}.$$

Hence,

$$\begin{aligned}\frac{|m(t,\mu,h) - y(t)h|}{|h|} &\leqslant \int_{t_0}^{t}\frac{|f_\mu(s,x(s,t_0,x_0,\mu+h),\mu) - f_\mu(s,x(s,t_0,x_0,\mu),\mu)|\,|h|}{|h|}\,ds\\ &\quad + \int_{t_0}^{t} M_0\frac{|m(s,\mu,h) - y(s)h|}{|h|}\,ds\end{aligned}$$

$$+\int_{t_0}^{t} K\frac{|w_2(m(s,\mu,h))|}{|m(s,\mu,h)|}\,ds+\int_{t_0}^{t}\frac{|w_1(h)|}{|h|}\,ds.$$

Since $x(t,t_0,x_0,\mu)$ is continuously dependent on μ from Lemma 2, we have

$$\lim_{|h|\to 0}\big|f_\mu\big(t,x(t,t_0,x_0,\mu+h),\mu\big)-f_\mu\big(t,x(t,t_0,x_0,\mu),\mu\big)\big|=0,$$

which implies

$$\big|f_\mu\big(t,x(t,t_0,x_0,\mu+h),\mu\big)-f_\mu\big(t,x(t,t_0,x_0,\mu),\mu\big)\big|\leqslant g_3(t,h),$$

where $g_3(t,h)\to 0$ as $|h|\to 0$. In addition, we apply the inequalities in Eqs. (14) and (15), and thus obtain

$$\begin{aligned}\frac{|m(t,\mu,h)-y(t)h|}{|h|}&\leqslant\int_{t_0}^{t} M_0\frac{|m(s,\mu,h)-y(s)h|}{|h|}\,ds\\&\quad+\int_{t_0}^{T}\big\{g_1(s,h)+Kg_2(s,h)+g_3(s,h)\big\}\,ds.\end{aligned}\tag{16}$$

Hence, using Gronwall's inequality and taking the limit of (16) as $|h|\to 0$, we have

$$\begin{aligned}&\lim_{|h|\to 0}\frac{|m(t,\mu,h)-y(t)h|}{|h|}\\&\quad\leqslant\lim_{|h|\to 0}\left\{\int_{t_0}^{T}\big\{g_1(s,h)+Kg_2(s,h)+g_3(s,h)\big\}\,ds\right\}e^{M_0(t-t_0)}=0,\end{aligned}\tag{17}$$

which completes the proof. □

Remark. Although in this manuscript we consider, for ease in exposition, a strong assumption of global Lipschitz on f, we can also readily establish similar results for the case of weaker assumptions involving local Lipschitz conditions on f plus domination of f by an affine function. Details of this approach can be found in [2, Lemma 2.1]. Many systems of interest in applications (including the example of [4,5] described below) satisfy these weaker assumptions.

3. A special case

In this section, we consider a special case of Eq. (1) where the parameter of interest is an element in a convex subset of $\mathcal{M}$. This allows us to extend the results given in [3] to provide sensitivity equations for probability density dependent systems. First, we define $p\in\mathcal{M}=L^2(Q)$ and $x\in X$ where $Q=[-r,0]$ and $X=\mathbb{R}^4\times L^2(-r,0;\mathbb{R}^4)$. Then for $x(t)=(v(t),v_t)$ we consider a system (1) with the right side of the form

$$f\big(t,x(t),p\big)=F\big(t,v(t)\big)+\int_Q v(t+\tau)p(\tau)\,d\tau,\tag{18}$$

where v_t denotes the function $\tau\to v(t+\tau)$, $\tau\in[-r,0]$. For each $x=(\eta,\phi)\in X$ we define $g(x,p)=\int_Q\phi(t+\tau)p(\tau)\,d\tau$. Then $g(x,p)$ is *Frechet* differentiable on $\mathcal{M}=L^2(Q)$ and we have $g'(\hat{x},\hat{p})p = g(\hat{x},p)$. Due to our particular interest, we restrict the parameter space to the sets of probability density functions in $L^2(Q)$ and define

$$\mathcal{M}_c = \left\{ p \in L^2(Q) \mid p \geqslant 0 \text{ and } \int_Q p(\tau)\,d\tau = 1 \right\}.$$

Since $\mathcal{M}_c$ is a convex subset of $\mathcal{M} = L^2(Q)$, we may differentiate g with respect to p using the directional derivative for $p, q \in \mathcal{M}_c$. We find that g is differentiable with respect to p in the direction of $(q - p)$ with

$$g'(\hat{x},p)(q-p) = g(\hat{x},q-p). \tag{19}$$

Obviously, Eq. (19) implies the directional derivative of g is the *Frechet* derivative on $\mathcal{M}$ restricted to $q - p$ where $p, q \in \mathcal{M}_c$. It follows that for Eq. (1) with the right side defined in (18) for $p \in \mathcal{M}_c$, the corresponding sensitivity function satisfies the sensitivity Eq. (13) of Section 2.

4. Approximations and numerical results

To apply the theoretical results of Section 2 to a specific system of interest, we derive and approximate the sensitivity equation of an HIV model that has the structure of the special case presented in Section 3. We consider an HIV model of distributed delay differential equations derived and investigated by Banks et al., in [4,5]

$$\begin{aligned}
\dot{V}(t) &= -cV(t) + n_C C(t) - \alpha V(t)T(t) + \eta_A \int_{-r}^{0} A(t+\tau)p_1(\tau)\,d\tau,\\
\dot{A}(t) &= (r_v - \delta_A)A(t) - \delta Y(t)A(t) + \alpha V(t)T(t) - \gamma \int_{-r}^{0} A(t+\tau)p_2(\tau)\,d\tau,\\
\dot{C}(t) &= (r_v - \delta_C)C(t) - \delta Y(t)C(t) + \gamma \int_{-r}^{0} A(t+\tau)p_2(\tau)\,d\tau,\\
\dot{T}(t) &= (r_u - \delta_u)T(t) - \delta Y(t)T(t) - \alpha V(t)T(t) + S, \quad \text{for } t \geqslant 0,
\end{aligned} \tag{20}$$

where $Y(t) = A(t) + C(t) + T(t)$. All the parameters and compartments are defined and described in Tables 1 and 2. Here p_1 and p_2 are probability density functions for the time delay τ_1 and τ_2, respectively, where $\tau_1 < 0$ represents the time delay between acute infection and viral production and $\tau_2 < 0$ denotes the delay between acute infectivity and chronic infectivity such that $-r < \tau_1 + \tau_2 < 0$. We employ $v = [V, A, C, T]^T$ and $x(t) = (v(t), v_t) \in X = \mathbb{R}^4 \times L^2(-r,0;\mathbb{R}^4)$. We let the parameter space $\mathcal{M} = L^2(-r,0) \times L^2(-r,0)$ and $\mathcal{M}_c = \{(p_1,p_2) \in \mathcal{M} \mid p_1,\ p_2 \geqslant 0 \text{ and } \int_{-r}^{0} p_1(\tau)\,d\tau = \int_{-r}^{0} p_2(\tau)\,d\tau = 1\}$. Then the HIV system (20) can be rewritten as an abstract Cauchy problem

$$\begin{aligned}
\dot{x}(t) &= \mathcal{A}x(t) + f_2(t), \quad t \geqslant 0,\\
x(0) &= x_0,
\end{aligned} \tag{21}$$

where $r > 0$ is finite, $f_2(t) = ([0,0,0,S]^T, 0) \in X$, and $x_0 = (\eta,\phi) \in X$. Here $\mathcal{A}$ is a nonlinear operator such that $\mathcal{A} : \mathcal{D}(\mathcal{A}) \subset X \to X$ and $\mathcal{A}(\eta,\phi) = (L(\eta,\phi) + f_1(\eta), \frac{d}{d\tau}\phi)$ where $\mathcal{D}(\mathcal{A}) = \{(\eta,\phi) \in X \mid \phi \in H^1(-r,0;\mathbb{R}^4) \text{ and } \eta = \phi(0)\}$. Furthermore, for $(\eta,\phi) \in \mathbb{R}^4 \times L^2(-r,0;\mathbb{R}^4)$,

Table 1
Definition and values of in vitro model parameters

Parameters	Values	Description
c	0.12	infectious viral clearance rate
n_A	0.1194	infectious viral production rate for acutely infected cells
n_C	1.6644×10^{-6}	infectious viral production rate for chronically infected cells
γ	8.7625×10^{-4}	rate at which acutely infected cells become chronically infected
r_v	0.035	birth-rate for virus infected cells
r_u	0.035	birth-rate for uninfected cells
δ_A	0.0775	death-rate for acutely infected cells
δ_C	0.0257	death-rate for chronically infected cells
δ_u	0.0160	death-rate for uninfected cells
δ	5.4495×10^{-13}	density dependent overall cell death-rate
α	1.3359×10^{-6}	probability of infection
S	0.0	constant rate of target cell replacement

Table 2
Definition of in vitro model compartments

Notations	Description
V	infectious viral population
A	acutely infected cells
C	chronically infected cells
T	uninfected or target cells
Y	total cell population (infected and uninfected)

$$L(\eta,\phi) = \begin{bmatrix} -c & 0 & n_C & 0 \\ 0 & r_v-\delta_A & 0 & 0 \\ 0 & 0 & r_v-\delta_C & 0 \\ 0 & 0 & 0 & r_u-\delta_u \end{bmatrix}\eta + n_A[\delta_{(1,2)}]_{(4,4)}\int_{-r}^{0}\phi(\tau)p_1(\tau)\,d\tau$$

$$+\gamma\big([\delta_{(3,2)}]_{(4,4)} - [\delta_{(2,2)}]_{(4,4)}\big)\int_{-r}^{0}\phi(\tau)p_2(\tau)\,d\tau,$$

$$f_1(\eta) = \begin{bmatrix} -\alpha\eta_1\eta_4 \\ -\delta(\sum_{i=2}^4 \eta_i)\eta_2 + \alpha\eta_1\eta_4 \\ -\delta(\sum_{i=2}^4 \eta_i)\eta_3 \\ -\delta(\sum_{i=2}^4 \eta_i)\eta_4 - \alpha\eta_1\eta_4 \end{bmatrix},$$

where $[\delta_{(i,j)}]_{(4,4)}$ is a 4×4 matrix with a one in the (i,j)th component and zeros everywhere else. In [4,5] the mass action product nonlinearities in f_1 are replaced by saturating nonlinear functions—see the definition of $\bar{f}_1$ in [4,5]. The resulting model then satisfies the required conditions of the theory in Section 2.

We consider here the sensitivity of the system (20) with respect to p_1. Similar ideas and calculations can be pursued for sensitivity with respect to p_2 or to the pair $(p_1,p_2)\in\mathcal{M}_c$. For $y=[\frac{\partial V}{\partial p_1},\frac{\partial A}{\partial p_1},\frac{\partial C}{\partial p_1},\frac{\partial T}{\partial p_1}]^T$, we find that the sensitivity equation of the HIV system (20) with respect to p_1 is the solution of

$$\dot{y}(t,x,p_1) = J_v\big(v(t)\big)y(t,x,p_1) + g_1(t,v_t,p_1), \quad t\geqslant 0,$$
$$y(0)=0, \tag{22}$$

where $x(t)=(v(t),v_t)$,

$$J_v=\begin{bmatrix} -c-\alpha T & 0 & n_C & -\alpha V \\ \alpha T & r_v-\delta_A-\delta(2A+C+T) & -\delta A & -\delta A+\alpha V \\ 0 & -\delta C & r_v-\delta_C-\delta(A+2C+T) & -\delta C \\ -\alpha T & -\delta T & -\delta T & r_u-\delta_u-\delta(A+C+2T)-\alpha V \end{bmatrix}$$

and

$$g_1(t,v_t,p_1)=\begin{bmatrix} n_A\int_{-r}^{0} A(t+\tau)p_1(\tau)\,d\tau \\ 0 \\ 0 \\ 0 \end{bmatrix}.$$

In order to solve the sensitivity equation, we obviously need the solution x of system (21). Since we cannot compute the exact solution x of (21), we approximate x by x^N using the linear spline approximation scheme for delay differential equations developed by Banks and Kappel in [8]. We employ $\{X^N,\ P^N,\ \mathcal{A}^N\}$ to be the approximating scheme where X^N is the spline subspace of X, P^N is the orthogonal projection of X onto X^N, and $\mathcal{A}^N$ is the approximating operator of $\mathcal{A}$ such that $\mathcal{A}^N=P^N\mathcal{A}P^N$. Thus, the approximation to system (21) is described by

$$\begin{aligned} &\dot{x}^N(t)=\mathcal{A}^N x^N(t)+P^N f_2(t), \quad t\geqslant 0,\\ &x^N(0)=P^N x_0. \end{aligned} \tag{23}$$

As shown in [5,8], the approximating scheme, $\{X^N,\ P^N,\ \mathcal{A}^N\}$, yields solutions such that $x^N(t)\to x(t)$ uniformly in t on a finite interval, as $N\to\infty$ and fixed $(p_1,\ p_2)\in\mathcal{M}_c$. In order to apply the linear spline approximation scheme, we fix the basis for a subspace X_1^N of X^N to be the piece-wise linear splines. Before we construct the splines, we partition $[-r,0]$ by $t_i^N=-i(r/N)$ for $i=0,1,\dots,N$ and then define the splines $\hat{\beta}^N=(\beta^N(0),\beta^N)$, where $\beta^N=(e_0^N,e_1^N,\dots,e_N^N)\otimes I_n$. Here I_n denotes the $n\times n$ matrix and the piecewise linear e_i^N's are defined by

$$e_i^N(t_j^N)=\delta_{ij} \quad \text{for } i,j=0,1,\dots,N.$$

When we restrict $\mathcal{A}^N$ to X_1^N, we have a matrix representation of $\mathcal{A}^N$, which we denote as A_1^N. Furthermore, we define $w^N(t)$ and $F^N(t)$ to be $x^N(t)=\hat{\beta}^N w^N(t)$ and $P^N f_2(t)=\hat{\beta}^N F^N(t)$, respectively. It follows that solving for $x^N(t)$ in system (23) is equivalent to solving for $w^N(t)$ in the nonlinear ordinary differential equation

$$\begin{aligned} &\dot{w}^N(t)=A_1^N w^N(t)+F^N(t), \quad t\geqslant 0,\\ &w^N(0)=w_0^N, \end{aligned} \tag{24}$$

where $\hat{\beta}^N w_0^N=P^N x_0$. When w^N are thus obtained, Theorem 3.2 in [8] combined with the results from [2] guarantees that the product $\hat{\beta}^N w^N$ converge uniformly in t on a finite interval to x^N, the solution of system (23). We have only briefly summarized the linear spline approximation scheme here; for more details on the proof of the results and how to compute A_1^N, $P^N x_0$, and $P^N f_2$, see [5,8].

When we apply the linear spline approximation scheme to our HIV system, we establish a $4(N+1)$-dimensional nonlinear ordinary differential equation system. The solution of the constructed system, w^N, is for the generalized Fourier coefficients when we expand the solution x in terms of $(N+1)$ piecewise linear spline basis elements. For our simulations, we consider $x_0=(v(0),v(\tau))$ where

$$v(0)=\left[0,1.5\times 10^6,0,1.35\times 10^6\right]^T,$$

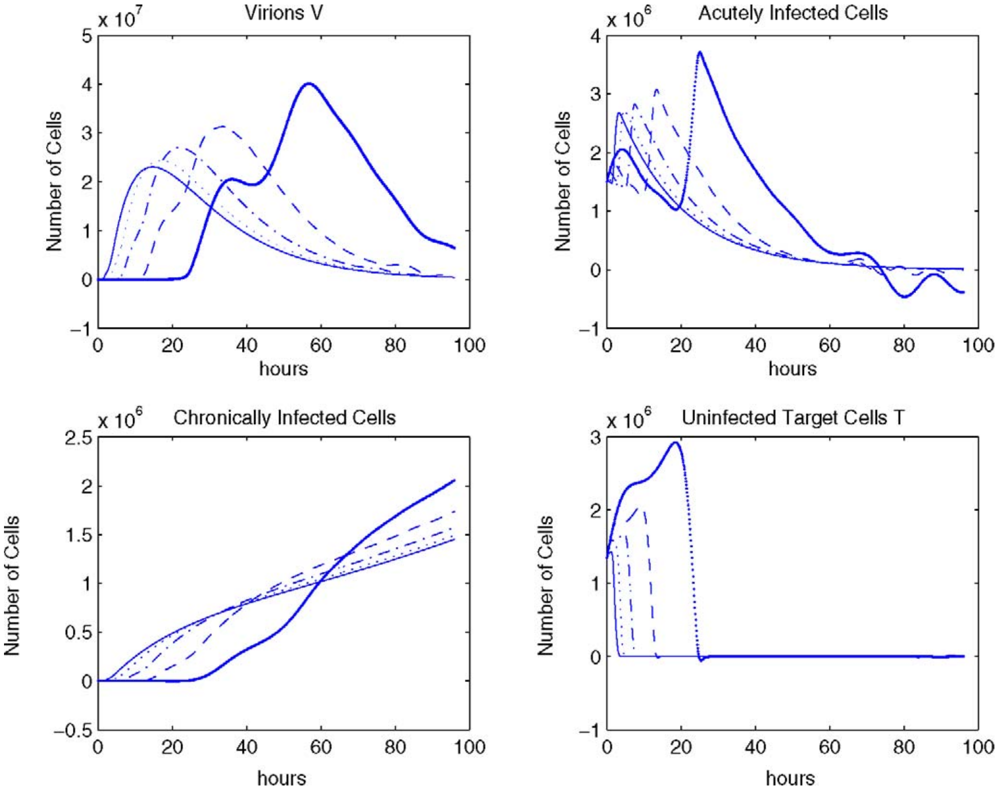

Fig. 1. Simulations of v^N where the thick solid line corresponds to $N = 16$, - - - represents $N32$, -.-.-. represents $N = 64$, ... represents $N = 128$, and the thin solid line is for $N = 256$.

and $v(\tau) = 0$ for $\tau \in [-r, 0)$. The values of the parameters we use are listed in Table 1. The functions p_1 and p_2 are modified Gaussian probability density functions with means $\tau_1 = -22.8$ and $\tau_2 = -26$, respectively, each with variance 1. Due to the nature of our problem where we only consider p_1 and p_2 for $\tau \in [-r, 0]$, we actually use normalized truncated Gaussian density functions in our computations. That is, we have

$$p_i(\tau) = \frac{1}{\sigma\sqrt{(2\pi)}} e^{-\frac{(\tau-\tau_i)^2}{2\sigma^2}} \quad \text{for } i = 1, 2, \tag{25}$$

where $\tau_1 = -22.8$, $\tau_2 = -26$, and $\sigma = 1$. Further, we normalize the p_i so that $\int_{-r}^{0} p_i(\tau)\,d\tau = 1$; i.e., we divide p_i by d where $d = \int_{-r}^{0} p_i(\tau)\,d\tau$. Applying the Banks–Kappel linear spline approximation scheme and the corresponding theoretical arguments to the system described above with fixed p_1 and p_2, one can obtain that $v^N = [V^N, A^N, C^N, T^N]^T$ converges as $N \to \infty$. This convergence is illustrated computationally in Fig. 1 for the fixed p_1 and p_2 given above. We note that these solutions require quadratures on the integral terms involving the p_1 and p_2. We used the Runge–Kutta method in MATLAB's ODE23 for solution of our approximate ordinary differential equations (24) and (26) below.

Since we only have x^N, the approximations of x, we must approximate the solutions of the sensitivity Eq. (22). Moreover, it is of interest to further approximate the densities p_1 in the func-

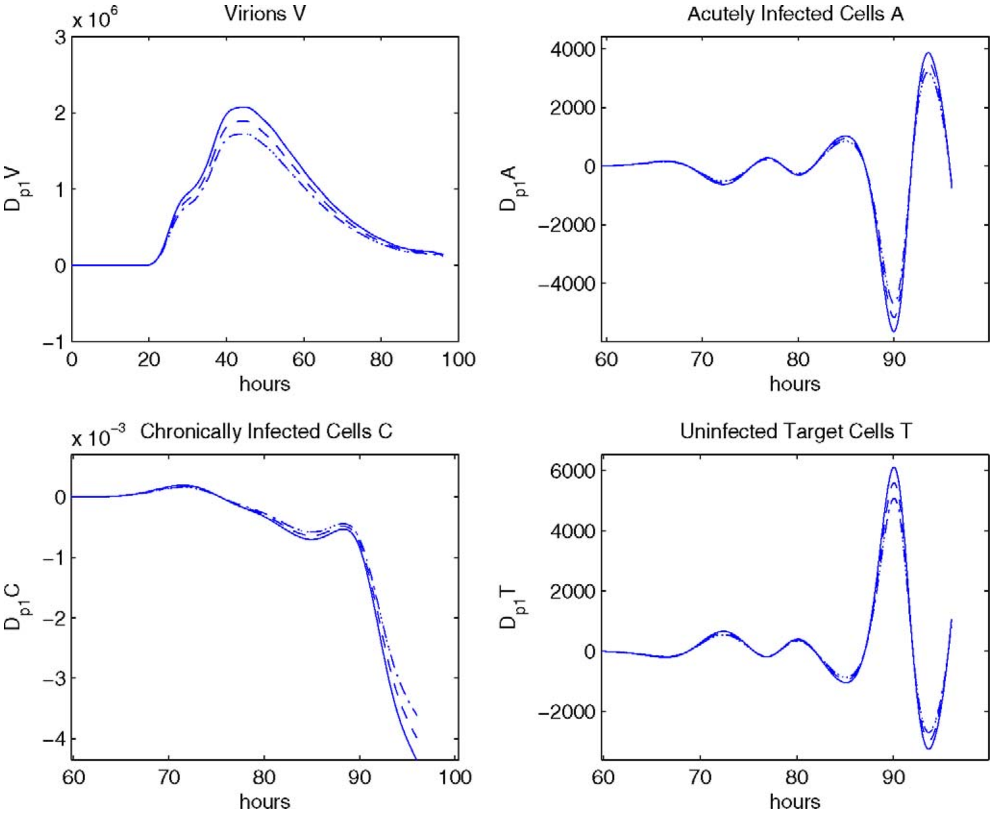

Fig. 2. Simulations of $y^{N,M}$ for a fixed $N = 32$, where ..... represents $M = 50$, -.-.-. represents $M = 100$, - - - corresponds to $M = 200$, and the solid line represents $M = 400$.

tionals g_1 with finite-dimensional parameterized densities p_1^M. (This type of approach is useful in inverse problems when one must estimate the densities.) In this case, we desire convergence of solutions $y^{N,M}$, the solution of (22) with approximations x^N and p_1^M in place of x and p_1, to y. To illustrate with an example, we define $p_1^M(\tau) = \sum_{i=1}^M a_i^M l_i^M(\tau)$, such that $p_1^M \to p_1$, where the l_i^M's are the usual piecewise linear splines (see for example [9]). We enforce the probability density constraints $p_1^M \geqslant 0$ and $\int_{-r}^0 \sum_{i=1}^M a_i^M l_i^M(\tau)\,d\tau = 1$. It is obvious that when $x^N \to x$ and $p_1^M \to p_1$, we have $J_v(v^N) \to J_v(v)$ and $g_1(t, v_t^N, p_1^M) \to g_1(t, v_t, p_1)$ as $N, M \to \infty$. Therefore, the sensitivity function y can be approximated by the solution of

$$\begin{aligned} &\dot{y}^{N,M}(t) = J_v\big(v^N(t)\big)y^{N,M}(t) + g_1^{N,M}(t), \quad t \geqslant 0, \\ &y^{N,M}(0) = 0, \end{aligned} \tag{26}$$

where

$$g_1^{N,M}(t) = \begin{bmatrix} n_A \int_{-r}^0 A^N(t+\tau) p_1^M(\tau)\,d\tau \\ 0 \\ 0 \\ 0 \end{bmatrix}.$$

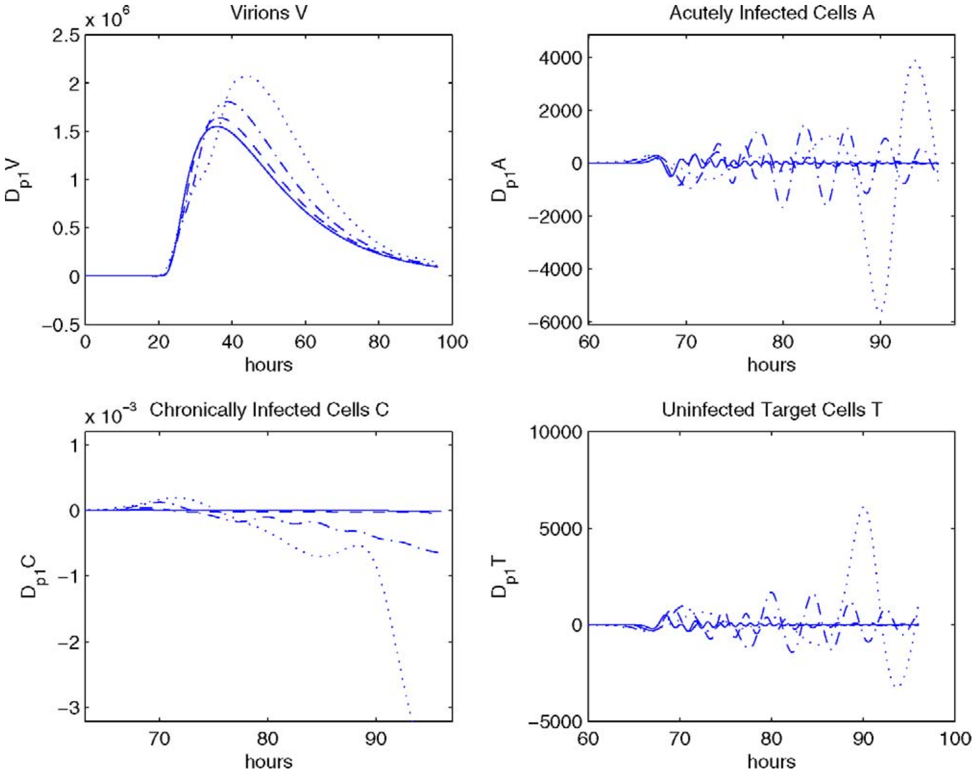

Fig. 3. Simulations of $y^{N,M}$ for a fixed $M = 256$, where ..... represents $N = 32$, -.-.-. represents $N = 64$, - - - corresponds to $N = 128$, and the solid line is for $N = 256$.

Using standard arguments with the convergence $x^N \to x$, $p_1^M \to p_1$, one can readily establish that $y^{N,M} \to y$ as $N, M \to \infty$. Similar convergence arguments can be made for the solutions $x^{N,M}$ of the system (23) with the p_i's approximated by p_i^M's. We note that this is precisely the type of convergence results required to establish *method stability* in inverse problems (see [9,16]).

To illustrate our statement on convergence of $y^{N,M}$, we first fix $N = 32$ and solve Eq. (26) for different values of M. As graphed in Fig. 2, we have $y^{N,M}$ converges for a fixed $N = 32$ as $M \to \infty$. Next we fix $M = 256$ and solve Eq. (26) for different values of N. We depict the solution $y^{N,M}$ for $M = 256$ and different values of N in Fig. 3 where it is evident that $y^{N,M}$ converges for $M = 256$ and $N \to \infty$.

5. Concluding remarks

In this paper we have given a general theoretical sensitivity framework for abstract systems in a Banach space with dynamics that depend on vector (Banach) space parameters. We then show that this includes a sensitivity theory for systems that depend on probability densities wherein a natural space for the parameters is $\mathcal{M} = L^2$. We also demonstrated how one could treat theoretically and computationally examples with distributed delays in the context of this framework. The example we presented illustrates the connection between the efforts here and those in [3] where parameterized distributions are considered. In some sense, one can consider our present efforts as an infinite-dimensional extension of standard sensitivity theories for finite-dimensional vector parameters.

Our current theory readily accommodates measures that are absolutely continuous with respect to Lebesgue measure (i.e., measures with a probability density). An important generalization of our efforts would allow treatment of measures with an absolutely continuous component and a saltus component of the form

$$P(\tau)=\sum_{i=1}^{k} p_i \Delta_{\tau_i}(\tau)+\int_{-r}^{\tau} p(\xi)\,d\xi$$

or

$$dP(\tau)=\sum_{i=1}^{k} p_i \delta_{\tau_i}(\tau)\,d\tau+p(\tau)\,d\tau,$$

where Δ_τ is the Dirac measure with atom or mass at τ. We are currently pursuing such a theory in which the parameter space is no longer a Banach space, but rather a metric space that is based on a combination of the Prohorov metric topology (see [6]) and the L^2 topology (or possibly the *weak* L^2 topology for compatibility with the Prohorov metric-see [15]).

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