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Time delay systems with distribution dependent dynamics☆

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Abstract

General delay dynamical systems in which uncertainty is present in the form of probability measure dependent dynamics are considered. Several motivating examples arising in biology are discussed. A functional analytic framework for investigating well-posedness (existence, uniqueness and continuous dependence of solutions), inverse problems, sensitivity analysis and approximations of the measures for computational purposes is surveyed.

Keywords: Inverse dynamics problem; Probability distribution function; Sensitivity analysis; Biomedical systems

1. Introduction

The purpose of this presentation is to survey recent as well as forthcoming results in our research efforts on models with delays and hysteresis where probabilistic uncertainty is present in a significant way. While we focus our motivation here on examples arising in biological applications (Banks & Bihari, 2001; Banks, Bortz, & Holte, 2003; Banks, Bortz, Pinter, & Potter, 2003; Banks & Bortz, 2005a,b; Banks & Davis, 2006; Banks & Pinter, 2005; Banks, Bokil et al., 2006; Banks & Nguyen, 2006; Banks, Dediu, & Nguyen, 2006), similar systems arise in other applications as diverse as materials (Banks, Hood, & Medhin, submitted for publication; Banks, Kurdila, & Webb, 1997a,b; Banks, Medhin, & Pinter, 2004; Banks, Medhin, & Pinter, 2007; Banks, Medhin, & Pinter, submitted for publication; Banks & Pinter, 2005), electromagnetics (Banks & Gibson, 2005; Banks & Gibson, 2006), physics, communication networks, etc. As is explained here, there are a wide class of models related to cellular level population dynamics that lead to systems of the form:

$$\dot{x}(t) = \int_{-r}^{0} x(t+\theta)\,\mathrm{d}P(\theta) + f(t, x(t)) \tag{1}$$

where P is a generally unknown probability measure that must be estimated from aggregate or population level (as opposed to individual level) observations or data. The probability measure P (which we shall also refer to as a probability distribution when no confusion results) may be discrete, absolutely continuous (continuous) or a combination of both. In addition to the obvious inverse problems, there are fundamental questions related to modeling of uncertainty, well-posedness, sensitivity, estimation and approximation. The primary goal of this note is to outline a theoretical and computational framework to treat these problems.

2. Example from cellular pathways: HIV infection

Our first example is typical of delay systems that arise in biochemical pathways and cellular level kinetics of drug metabolism as well as other synthesis models. In Banks et al. (2003) and Banks and Bortz (2005a) the authors study a model for progression of Human Immunodeficiency Virus (HIV) at the cellular level. The model involves compartments T, A, C, and V for *in vitro* blood level counts in mice of target (CD4 +) cells, acutely infected cells, chronically infected cells and active viral particles, respectively. Free virus V infects target cells T,

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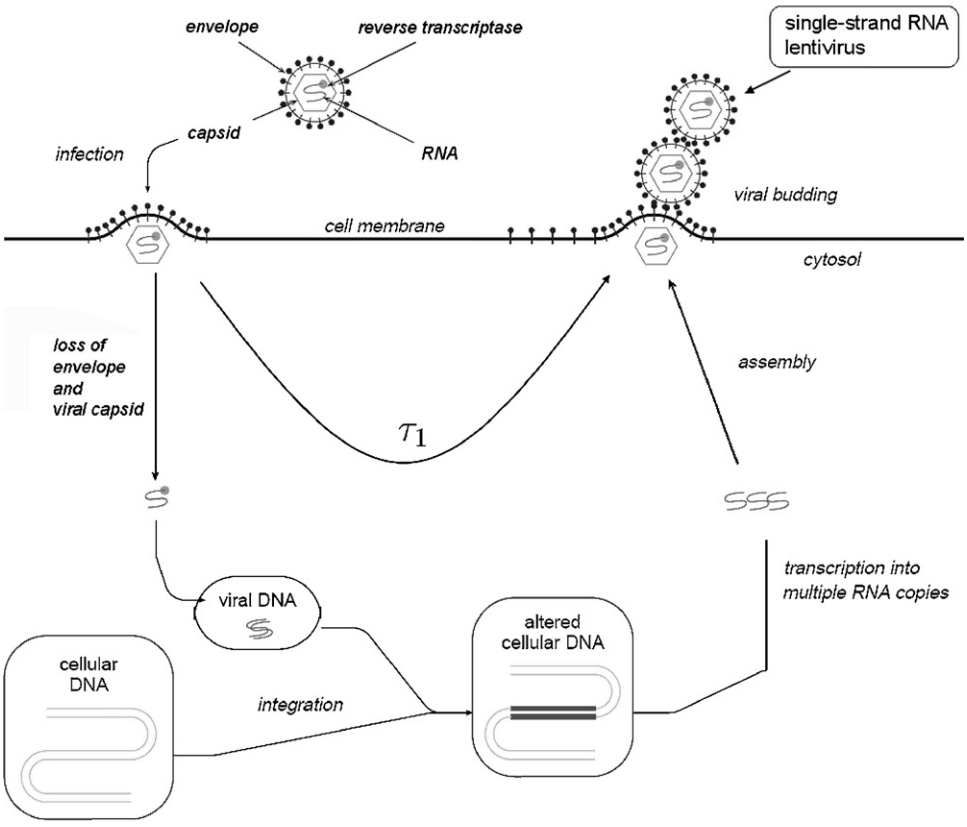

Fig. 1. HIV infection pathway in acutely infected cells.

transforming them into acutely infected cells A which at some time later become chronically infected cells C. The basic pathway for infection and production of virus for acutely infected cells is schematically depicted in Fig. 1. For models in which the individual kinetics for loss of envelope and capsid, integration, transcription, and assembly are not detailed, it is necessary (see Banks et al., 2003) to include a delay τ_1 from the time of infection of a target cell T until it first produces free virus V. There is also some delay τ_2 before an acutely infected cell A becomes a chronically infected cell C.

Here we outline a brief derivation from first principles (with assumptions based on the biology) that supports a mathematical model in which the delays are treated as probabilistically distributed across the population of cells found in a typical *in vitro* culture.

First consider the delay between initial acute infection and the cell becoming what is termed a chronically infected cell characterized by differences in cell dynamics (see Banks et al., 2003). It is biologically unrealistic (and unacceptable in the modeling to biologists) to expect an entire population of cells to simultaneously change infection characteristics precisely $\tau_2(\tau_2 > 0)$ hours after initial viral infection. Therefore, one might 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 probability distribution $\bar{P}_2$ (which is not assumed to necessarily possess a density $\bar{p}_2$—it could have point masses). 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, the rate of change in this subpopulation of cells is governed by

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

where

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

is the total number of CD4+ cells (infected and uninfected). The expected value of the population of chronic cells is given by integrating with respect to the distribution $\bar{P}_2$, over all possible delay values, obtaining

$$C(t) = \mathcal{E}_2[C(t;\tau)] = \int_0^\infty C(t;\tau)\,\mathrm{d}\bar{P}_2(\tau). \tag{2}$$

Here the parameters r_v, δ_C, δ and γ are appropriate rate parameters (for details, see Banks et al., 2003). Therefore, the rate of change in the total population of chronic cells is governed by

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

$$C(0) = C_0,$$