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Dynamics of viral infections: incorporating both the intracellular and extracellular levels

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Abstract

To date, most models of viral infections have focused exclusively on modeling either the intracellular level or the extracellular level. To more realistically model these infections, we propose incorporating both levels of information into the description. One way of performing this task in a deterministic setting is to derive cell population balances from the equation of continuity. We apply such a balance to obtain a two-level model of a viral infection. We then use numerical simulation to demonstrate both cell culture and in vivo responses given a variety of experimental conditions. We compare these responses to those obtained from applying other commonly used models. The results demonstrate that, in contrast to commonly used models, the cell population balance provides a more intuitive and flexible modeling framework for incorporating both the intracellular and extracellular events occurring during viral infections. This improved capability to represent the trends in the biological measurements of interest offers a more systematic and quantitative understanding of how viral infections propagate and how to best control this propagation.
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1. Introduction

Viral infections present one of the most potent threats to human survival and well-being. The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that in 2002, 42 million people were living with HIV/AIDS, 5 million people were newly infected with HIV, and 3.1 million people died due to AIDS related illnesses. The World Health Organization estimates that of the 170 million people currently suffering from hepatitis C, roughly 1 million will develop cancer of the liver during the next 10 years. In the United States alone, researchers estimate that the 500 million cases of the common cold contracted annually cost $40 billion in health care costs and lost productivity (Fendrick, Monto, Nightengale, & Sarnes, 2003). Hence there is a vital humanitarian and eco-

nomic interest in systematically understanding how viral infections progress and how this progression can be controlled. Accordingly, researchers have invested significant amounts of time and money towards determining the roles that individual components such as the genome or proteins play in viral infections. As of yet, however, there exists no comprehensive picture that quantitatively incorporates and integrates data on viral infections from multiple levels.

Traditionally, mathematical models for viral infections have focused solely on events occurring in either the intracellular or extracellular level. At the intracellular level, kinetic models have been applied to examine the dynamics of how viruses harness host cells to replicate more virus (Arkin, Ross, & McAdams, 1998; Eigen, Biebricher, Gebinoga, & Gardiner, 1991; Endy, Kong, & Yin, 1997; Knijnenburg & Kreischer, 1983), and how drugs targeting specific virus components affect this replication (Endy & Yin, 2000; Reddy & Yin, 1999). These models, however, consider only one

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Nomenclature

A	derivative weight matrix for orthogonal collocation
B	birth rate of cells
c	small constant
D	death rate of cells
E_j	extracellular production rate
e_j	extracellular viral component
$f(t, z)\,\mathrm{d}z$	concentration of infected cells
$f(t, \tau_j)$	infected cell concentration evaluated at the point τ_j
i_j	intracellular viral component
K_j	equilibrium constant for the segregated, structured model
k_j	reaction rate constant for the segregated, structured model
$\bar{k}_j$	reaction rate constant for the unsegregated, structured model
$\hat{k}_j$	reaction rate constant for the purely extracellular model
$L_j(\tau)$	Lagrange interpolation polynomial of degree n for orthogonal collocation
$\log_{10}$	base ten logarithm
q_j	quadrature weight for orthogonal collocation
R_j	intracellular production rate
s_k	measurement predicted by the model
t	time
u_j	second-order input for extracellular component j
$\bar{u}_j$	input for extracellular component j
V	arbitrary, fixed control volume spanning a space in z
$\boldsymbol{v}_y$	vector specifying the y-component velocity of cells flowing through the volume V
$\boldsymbol{v}_z$	vector specifying the velocity of cells flowing through the volume V
$\boldsymbol{x}$	external characteristics
$\boldsymbol{y}$	internal characteristics
y_k	experimental measurement
$\boldsymbol{z}$	internal and external characteristics

Greek letters

β	parameter for the second-order input function
δ	Dirac delta function
ε_j	reaction rate for reaction j
τ	infected cell age
τ_d	age of the oldest infected cell permitted by the model
τ_u	natural period of the second-order input function
ζ	damping coefficient of the second-order input function

Subscripts

gen	genomic viral nucleic acid
I_1, I_2	viral enzyme inhibitors
inf	infected host cell
str	viral structural protein
tem	template viral nucleic acid
unc	uninfected host cell
V_1, V_2	viral enzymes
vir	extracellular virus

Table 1
Types of cell population models (Bailey & Ollis, 1986)

	Unstructured	Structured
Unsegregated	*Most idealized case*: cell population treated as one-component solute	Multicomponent average cell description
Segregated	Single component, heterogeneous individual cells	Multicomponent description of cell-to-cell heterogeneity, *actual case*!

infection cycle, whereas infections commonly consist of numerous infection cycles. At the extracellular level, researchers have considered how drug therapies affect the dynamics of populations of viruses (Bonhoeffer, May, Shaw, & Nowak, 1997; Herz, Bonhoeffer, Anderson, May, & Nowak, 1996; Nowak & May, 2000; Perelson, 2002; Wodarz & Nowak, 2002). These models, though, neglect the fact that these drugs target specific intracellular viral components. To better understand the interplay of intracellular and extracellular events, a different modeling framework is necessary. We propose that cell population balances offer one such framework.

Mathematical models for cell population dynamics may be effectively grouped by two distinctive features: whether or not the model has structure, and whether or not the model has segregations (Bailey & Ollis, 1986). If a model has structure, then multiple intracellular components affect the dynamics of the cell population. If a model has segregations, then some cellular characteristic can be employed to distinguish among different cells in a population. Table 1 summarizes the different combinations of models arising from these features. In this context, current extracellular models are equivalent to unstructured, unsegregated models because the cells in each population (uninfected cells and infected cells) are assumed indistinguishable from each other. In contrast, the cell population balance proposed in this paper is a structured, segregated model since it differentiates among infected cells and includes a multicomponent description of each infected cell at an intracellular level.

In this paper, we first outline the basics of deriving and solving population balance models for viral infections. Next, we construct a population balance model for a generic viral