**Introduction**

The infection of the Human Immunodeficiency Virus (HIV) is produced by two types of virus: The HIV-1, which is pandemic, and has been intensively studied, while HIV-2 is endemic to Africa and less investigated. The main clinical difference between HIV-1 and HIV-2 is the duration of the clinical latency period: 8 years for HIV-1 and 10 years or more for HIV-2. Resemblances in the mechanisms of infection make possible using models for HIV-1 for understanding HIV-2 infection.

The main objective of this research is to develop a mathematical model for HIV-2 that addresses viral reservoirs within individuals, based on information about HIV-1 dynamics.

The current research grant from CCS for modeling the control of HIV-2 viral infection by engineered-therapeutic viruses (without reservoir) has successfully finished the first phase, consisting of modeling the HIV-1 infection, and the therapeutic treatment. This allows working on the second and last phase: HIV-2 infection and treatment (without reservoir). Our results are being presented in a poster and were submitted to be presented at an HIV meeting of experimentalists and theorists; a manuscript is in preparation (see list of activities below). The skills and expertise gained can be extremely useful to extend our current research program by including viral reservoirs in the study.

It has been demonstrated that **latently infected CD4 cells are not targeted by current anti-HIV therapies and immune response, thus acting as long-lived reservoirs for HIV and hindering its eradication** (Swiggard et. al 2005 and references therein). Other drawbacks of current therapies include: tendency to increase resistance of HIV to therapies, high cost and toxicity. An alternative therapy using genetically engineered virus (EV) has been recently proposed. Engineered viruses attach to and kill already infected cells. Lab studies showed significant decreases in viral load in human (Schnell et al 1997) and simian cells (Okuma et. al 2005). These are the first steps towards a working therapy for humans. **We hypothesize that cellular reservoirs are targeted by engineered viruses, thus opening the opportunity to overcome the main obstacle for successful eradication of HIV infection.**

Following the same strategy used in the current research project, the proposed research will start by modeling HIV-1 with reservoir, taking advantage of available information. Once the model performs satisfactorily, it will be easier to use this knowledge to model HIV-2.
The results of this research will include the conditions under which the therapeutic infection is most likely to be successful. This information is useful for clinicians and experimentalists as criteria for the optimal design of the therapeutic virus. Other results include the expected reduction of the reservoir and recovery of CD4 cells relative to the model without treatment, the best timing of treatment introduction, and how persistent the therapeutic infection is when the reservoir is depleted.

**Methodology**

The mathematical model is based on Revilla and Garcia-Ramos (2003), and includes four interacting populations: CD4 host cells (uninfected [resting and activated], single-infected [resting and activated] and double-infected [resting and activated]), effector CD8 cells (immune response), HIV and engineered viruses. The graphical representation of the model is in figure 1. The structure of the corresponding set of differential equations can be straightforwardly obtained, while the parameters and functional relationships may change, in order to improve the performance of the model.

**Figure 1. A.** The model consists of four interacting dynamics: The host cell cycle: the HIV-1 infection, the immune response and the therapeutic infection. 1) **Host cell cycle:** Resting CD4 cells ($x'$) are produced at a constant rate $\lambda$, and die at rate $d_1x'$. In the presence of HIV-1 ($v$), they are transformed into an activated state ($x$) at rate $pxv$. Activated cells $x$ proliferate at rate $pvx$, return to resting state at rate $rx$, and die at rate $d_2x$. 2) **HIV infection:** a) Pathogenic virus $v$ infects activated cells $x$, producing single-infected cells ($y$) at rate $\beta xv$, that release HIV-1 virus. Single-infected cells die at rate $ay$, produce viral particles at rate $ky$ and HIV-1 virus are removed at rate $uv$. b) Resting cells are infected at rate $s_1vx'$. 3) **Reservoir:** Two pathways are possible: i) single-infected cells return to latent-infected state ($y'$) at rate $ry$, ii) resting CD4 cells ($x'$) are infected at rate $s_1vx'$. Latent-infected cells are reactivated at rate $mvy'$, and die at rate $d_3y'$. 3) **Therapeutic infection:** Recombinant virus ($w$) infects a) single-infected activated cells

\[
\begin{align*}
\dot{x}' &= \lambda + rx - mx'v - s_1x'v - d_1x' \\
\dot{y}' &= s_1x'v + ry - my'y'v - s_2y'w - d_3y' \\
\dot{z}' &= s_2y'w - mz'v + rz - d_4z' \\
\dot{v} &= ky - uv \\
\dot{l} &= gxyzl - hl \\
\dot{x} &= mx'v - rx + pxv - \beta xv - d_2x \\
\dot{y} &= my'y'v - ry + \beta xv - ay - ily \\
\dot{z} &= mz'v - rz + ayw - ilz - bz \\
\dot{w} &= qz - cw
\end{align*}
\]
(y), producing superinfected cells (z) at rate $\alpha yw$. Double infected cells produce recombinant virus at rate $cz$ and die at rate $bz$. Recombinant viruses are removed at rate $qz$. b) Single-infected reservoir cells ($y'$) are superinfected ($z'$) at rate $s_2yw$, reactivated at rate $mz'v$, return to resting state at rate $rz$ and die at rate $dz'$. 4) **Immune response:** Activated CD8 cells ($l$) remove two types of infected cells at rates $ily$, (single) and $i'ly$ (double); proliferate at rate $gxl$, and die at rate $hl$.  

**B.** Set of differential equations for the full system using dot notation ($\dot{c} \equiv dc/dt$). Units are counts of cells (virus) mm$^{-3}$ day$^{-1}$.

Analytical solutions for the equilibrium points of the system of ordinary differential equations will be obtained using symbolic mathematics software. Due to the complexity of the system, information on the stability of equilibria will be obtained from numerical simulations using specialized routines for stiff systems (oscillations in cell and viral densities are expected). Analytical expressions can be used to compute the efficiency of the therapy, as well as the criteria for successful therapeutic infection. Transient and asymptotic behavior should fit qualitatively the clinical data on the progression of the infection, and in that sense, they are as important as the equilibria.

The model will be parameterized using published estimates. For those parameters that are not found, a wide parameter space will be searched by evaluating the equilibria and transient behavior. When this fails to provide good results, the functional relationships between state variables will be changed, and the parameter space searched again.

**References**


Research plan
Previous experience indicates that the best strategy is to work on HIV-1 dynamics in a first phase, and compare the results with published results. A second phase is then to use acquired knowledge to model HIV-2. For both virus types, preliminary simulations are required to get a first approximation of the relative flexibility of alternative functional relationships among compartments of the model. This saves time on the parameter space search by focusing in one or two alternative models. Analytical expressions of equilibrium points will be computed after preliminary numerical simulations. Literature search will continue at all times, to ensure the model incorporates updated information. Finally, we allow time for the preparation of manuscripts.

Timetable

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Expected products
Results will be published in peer-reviewed journals: From the ongoing research, a manuscript on the mathematical modeling of control of HIV-1 infection using engineered viruses is in preparation (without reservoir), and its counterpart on HIV-2 is in progress. For the model with reservoir, two articles, dealing with each type of virus are projected. Other ways to communicate our results include scientific meetings.

List of current support
Active grants
1. There are two grants currently active by Garcia-Ramos and P. Crowley, one from NSF and the other by NIH. Only the NIH grant (NIH 5 R03 AI 06468-02, Evaluating Control of HIV Infection by Engineered Virus) is directly related to the present proposal. This NIH grant is modeling, HIV-1 and considers additional objectives beyond the present proposal. This grant ends in April, 2006. Both
studies complement each other, allowing important comparisons in the dynamics of these infections in the future. This grant covers part of my salary.

2. Center for Computational Sciences, project title: Modeling the control of HIV-2 viral infection by Engineered-therapeutic viruses. Dates: July 2005-June 2006. This grant covers the rest of my salary.

Amount of support
This project requires $18.6 K plus benefits to cover nominee’s salary for 8 months. This was estimated assuming an annual basic salary (without benefits) of $28 K.

List of activities involving our CCS grant
Curriculum Vitae

Derik Castillo-Guajardo, Ph.D.
Theoretical Ecologist

Phone: 859 257 5306
Electronic address: dcast2@uky.edu
Current position: Postdoctoral Scholar at the Department of Biology, University of Kentucky, under Dr. Gisela Garcia-Ramos and Dr. Philip H. Crowley, modeling a therapy for HIV.

Studies


August 2000 Autumn School in Mathematical Biology, held in the Center for Investigations in Mathematics (CIMAT), Guanajuato, Mexico.


Summer 1996 Cornell-Sacnas Mathematical Sciences Summer Institute. Cornell University, EUA.


Academic activities

Oct 2003 Oral presentation at the XXXVI National Congress of the Mexican Mathematical Society: “Coevolution of virulence and resistance”

Nov 2002 Invited lecture at ALAB 2002, meeting of the Latin American Society for Biomathematics, at CIMAT: "Coevolution of virulence and resistance using frequency-dependent fitness functions"

Feb 2001 Oral presentation at BIOMAT II. Biomathematics meeting sponsored by the Metropolitan Technological University of Santiago de Chile: “How do we go from evolution to coevolution using quantitative characters?”
June 2000 Poster "The effect of refuges in the ecology of a two-parasitoid, one-host system". Meeting: "Theory and Mathematics in Biology and Medicine" sponsored by The Society for Mathematical Biology and the European Society for Mathematical Biology, at Vrije Universiteit, Amsterdam, The Netherlands. I was sponsored by The Landahl Travel Awards

Teaching experience


Publications


Equihua-Zamora, M; Castillo-Guajardo, D; Villegas, R, and Alducin, G. A simple method for evaluating flight altitude in migratory, predatory birds. Submitted to IBIS.


Working experience
Aug 2005 to date. Postdoctoral Scholar in University of Kentucky’s Department of Biology. Project: Modeling HIV-2 therapy using engineered virus. Funding from Center for Computational Sciences and NIH grant to Drs. G. Garcia-Ramos and P.H. Crowley.
