The Continuous Model for the Transmission of HIV

Term Project for ACMS 383
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§ Abstract

This project discusses a simple continuous model for HIV infection, using ordinary differential equations. A mathematical model is motivated from the HIV infection in South Korea in which the interaction of the epidemic is likely to be minimized. An epidemic modeling technique, well-known as *SIR* model, is used for formulating the HIV infection as a system of differential equations. Hence the populations of three distinct classes - the susceptibles, the infectives, and the AIDS, are considered in the model. The exact solutions of the model cannot be found, nor do numerical simulations fail to be presented. Nevertheless, this project attempts to analyze the problem by linearization of nonlinear system and nondimensionalization, and to predict the behavior of the HIV infection.

§ Problem Description

▪ HIV Infection & AIDS

In the last 20 years, the apparition of HIV (Humane Immunodeficiency Virus) and the increasing incidence of AIDS (Acquired Immune Deficiency Syndrome) have been the most serious threat to the word's health problem. Once a person is infected with HIV, it is said that the person is seropositive to HIV and he or she is defined as "infectious". After a certain unknown latent period, some of infected people develop into AIDS whereas some remain seropositive. Similar to other STDs (Sexually Transmitted Diseases), AIDS have some key characteristics which are different than other epidemics. Firstly, the HIV infection is mainly restricted to a sexual active population. Secondly, the HIV has a relatively long incubation time until an infectious individual exhibits overt symptoms. Thirdly, the fact that there is little numerical information available leads to the lack of present knowledge about the transmission dynamics. These characteristics are crucial when we try to create a mathematical model for the HIV infection. In these days, the study of the transmission of HIV has arisen most in the epidemics and many other related fields, and now we will tackle a simple model for the HIV infection within a particular population group, using a system of ordinary differential equations.

▪ Scientific Questions

For the HIV infection model, we might ask a vast variety questions about the behavior of the infection. You might be interested in the biological process of antibodies to HIV, or the prediction of the latent period of HIV, or even the estimation, from the current AIDS patients, of the infectious population at a certain time. In this discussion, we are particularly interested in the interacting behavior of the population groups which are exposed to the threat of HIV. The list of the questions we're about to discuss is the followings:

- How can the transmission of HIV within a certain community be modeled with mathematical equations?
- Does AIDS ever slow down or remain unchanged in terms of the number of the population?

- What environmental conditions make the behavior of the infection change?
- How well does the model reflect a real problem, and what does it predict for the epidemic?

Here, we need to keep in mind that, when we try to answer the questions above, we might encounter some limitations resulted from mathematical difficulties and the lack of knowledge about the dynamics of the HIV infection.

§ Case Simplification and Assumptions

Recall the first key characteristic of the HIV infection. The infection is mainly restricted to a sexual active community. Therefore, we assume that the transmission of HIV occurs mostly within a high-risk population group, such as the prostitutes and the homosexual community. This assumption suits even better for a country with its conservative-sexual-culture. Besides, AIDS patients, who are at the end-stage of the HIV infection, are strictly isolated from sexual activities; therefore, they no longer affect the transmission of HIV. To simplify a real problem, we assume,

- A particular population, which is reasonably restricted, is at high-risk to HIV by sexual contact only. There are no vertical infection, no infection by blood transfusion or injection-drug use.
- The population is uniformly mixed, so the probability of acquiring HIV equally exists to every single individual within the community.
- Once infectious individuals are classified into AIDS patients, they are no longer engaged in the infection.
- There are no subtractions of the population except for disease-induced death.

At this point, in justification of these assumptions, it's not a bad idea to glance over the real data (see **Supplement Data #1**). These assumptions are made in order for a mathematical model to demonstrate a real problem as simply as possible.

§ Formulated Mathematical Model

For the HIV infection modeling, we will consider a group of infected, therefore infectious, individuals is introduced into a larger susceptible population. Besides, the infected individuals develop themselves into a group of AIDS patients, the end-stage of the infection. The population of each group will change respect to time while the infection progresses. Therefore, we will think of the change of the population as a mass balance idea,

rate of change in population = '**population growth**' – '**population loss**'.

Then, the terms for the population growth and loss can be defined by the interaction of each population group in the infection. To mathematically translate, we will introduce a system of ordinary differential equations. Let's declare variables before creating ODEs.

- **Variables vs. Parameters**

N - total population of a community	K - recruitment rate to a population
S - susceptible class	α - infective rate
I - infectious (infected) class	β - conversion rate (from infection to AIDS)
A - AIDS patients class	δ - disease-induced death rate

The number of each population changes in time, so it can be expressed as a function of time, and the total population, $N(t)$, consists of three sub-classes, $S(t)$, $I(t)$, and $A(t)$. First, let's consider the rate of change in the susceptible class, $S(t)$, which represents all individuals having sexual activity, who are exposed to HIV. Since there is a population growth at a rate, K, new incomers will immediately belong to the susceptible class, $S(t)$. Then, these individuals may be infected by sexual contact with an individual in the infectious class, $I(t)$. Note that the infection occurs at a rate proportional to the number of the infectives and the susceptibles; that is αSI, where an universal parameter, α, represents all infective factors according to our assumptions. Thus, once individuals are infected, there will be the subtraction of population at the rate, αSI, from $S(t)$. Along with the population growth at the rate, K, we finally have the equation, $dS/dt = K - \alpha SI$. Simultaneously, the infection will also invoke addition to $I(t)$ at the same rate, αSI. In the same manner, the development of infected individuals, $I(t)$, into AIDS at a certain rate will result the subtraction of population from $I(t)$ and the addition of population to the AIDS patients, $A(t)$ Let β be the conversion rate from the infection to AIDS, then the subtraction and the addition from $I(t)$ to $A(t)$ can be expressed as βI. Finally, AIDS patients die out at a rate δ, which is the diseases-induced death rate. As a result, a simple model can be formed as a system of deferential equations,

$$\frac{dS}{dt} = K - \alpha SI$$
$$\frac{dI}{dt} = \alpha SI - \beta I \qquad \textbf{[1]}$$
$$\frac{dA}{dt} = \beta I - \delta A \ .$$

Note that the system of the differential equations is a nonlinear 3-dimensional system. Also, note that the first equation is an inhomogeneous since it has a recruitment rate K per unit time to the susceptible class; as a result, the total population, $N(t) = S(t) + I(t) + A(t)$, is not constant . The K term is much like a "*forcing term*" which often arises from an external force in a physical application. The reason that we need to mention the K term will be explained later when we analyze the system.

§ Analysis of the Mathematical Model

Unfortunately, we cannot explicitly solve the system of the differential equation, [1]. Instead, we can import an analytic approach to study the behavior of the infection. In the system, [1], dS/dt and dI/dt

are independent on AIDS patients, *A*. In other words, AIDS patients no longer affect the primary infection, so we will consider *dS*/*dt* and *dI*/*dt* only. Then, we have an equivalent 2-dimensional system for our model,

$$\frac{dS}{dt} = K - \alpha SI$$
$$\frac{dI}{dt} = \alpha SI - \beta I \ . \qquad \textbf{[2]}$$

Primarily, we're interested in equilibria, if any, at which both *S* and *I* do not change; that is, neither increasing nor decreasing. For that, we need to find S^* and I^* such that both $dS/dt = 0$ and $dI/dI = 0$. To do that, we will look at the intersection of the nullclines of *S* and *I*.

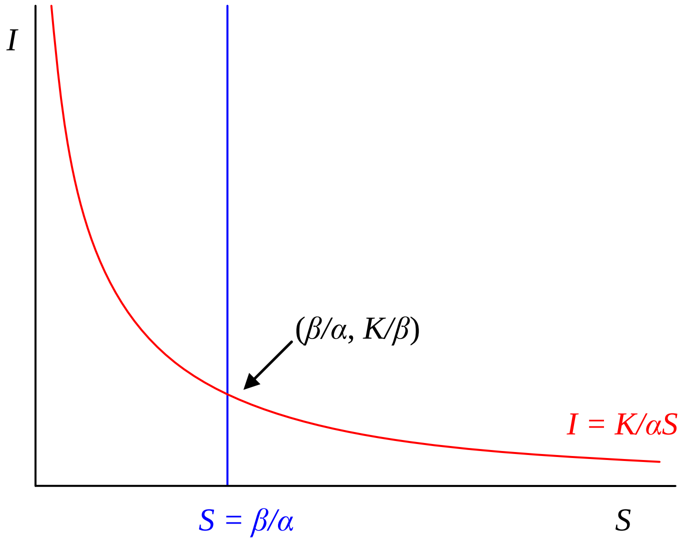


Figure 1. *S* and *I* nullclines in the 1st quadrant

We have one equilibrium $E(S^*, I^*) = (\beta/\alpha, K/\beta)$ in the first quadrant. Thus, when $S^* = \beta/\alpha$ and $I^* = K/\beta$, the infection results a condition in which there is no change in the population of the susceptible class and the infected class. However, this is not quite enough information to predict the behavior of the infection. We need to know whether the equilibrium is stable or unstable. Since the system is nonlinear, we need to linearize the system at the equilibrium $E(S^*, I^*)$ to determine its stability by taking the *Jacobian* matrix, which is defined as,

$$J(S^*, I^*) = \begin{pmatrix} \frac{\partial f}{\partial S} & \frac{\partial f}{\partial I} \\ \frac{\partial g}{\partial S} & \frac{\partial g}{\partial I} \end{pmatrix} \Bigg|_{(S^*, I^*)} \qquad \text{where,} \qquad \frac{dS}{dt} = f(S, I), \quad \frac{dI}{dt} = g(S, I) \ .$$

Then, the linearization of the system at the equilibrium *E* can be calculated as,

$$J\left(\frac{\beta}{\alpha}, \frac{K}{\beta}\right) = \begin{pmatrix} \dfrac{-\alpha K}{\beta} & \beta \\ \dfrac{\alpha K}{\beta} & 0 \end{pmatrix}.$$

By looking at the eigenvalues of this matrix, we can determine the stability of the original nonlinear system at the equilibrium. This implies the original nonlinear system would behave like the linearized system at the equilibrium. The eigenvalues of the *Jacobian*, *λ*, are calculated as,

$$\lambda = \frac{\dfrac{-\alpha K}{\beta} \pm \sqrt{\left(\dfrac{-\alpha K}{\beta}\right)^2 - 4\alpha K}}{2} .$$

Since the eigenvalues, *λ*, are determined by the parameters, we need to break down into two cases to determine the stability of the equilibrium.

- **When** $\dfrac{\alpha K}{\beta^2} \geq 4$ **[3]**

The eigenvalues, *λ*, have two negative real parts since we know,

$$\frac{\alpha K}{\beta} > \sqrt{\left(\frac{-\alpha K}{\beta}\right)^2 - 4\alpha K} > 0 .$$

Hence the system forms a nodal sink at the equilibrium. That implies the system have the behavior of exponential decay at the equilibrium, *E*(*S**, *I**) = (*β/α*, *K/β*), which is asymptotically stable. Thus, every solution of the system will approach to the stable equilibrium point, *S** = *β/α* and *I** = *K/β*, as time *t* goes to infinity.

- **When** $\dfrac{\alpha K}{\beta^2} < 4$ **[4]**

The eigenvalues, *λ*, have complex parts along with a negative real part, $-\dfrac{\alpha K}{\beta}$. Hence the system forms a spiral sink at the equilibrium. That means the system have a certain form of oscillation behavior at equilibrium, *E*(*S**, *I**) = (*β/α*, *K/β*), while its solutions still move to stable direction. In other words, the system behaves in a damped oscillatory manner with a certain period determined by the parameters. Given the model parameters, the period of the oscillation plays a role for us to predict the further behavior of the infection.
Interestingly, in either case, we can observe a stable equilibrium point, *S** = *β/α* and *I** = *K/β*, where the infection would have a steady state. Now, an interesting question comes out. The parametric

conditions with inequality, [3] and [4], come purely from the mathematical analysis. In fact, though, we don't have clear intuition about how they are related to the behavior of the epidemic. Keeping this in mind, we will reconsider the system of the differential equations, [2], which originally gives us a general picture of the epidemic interaction. If we nondimensionalize the system,

$$\frac{dS}{dt} = K - \alpha SI$$
$$\frac{dI}{dt} = \alpha SI - \beta I \ ,$$

with the characteristic scales, $c_S = \frac{\beta}{\alpha}$ for the susceptible class S, $c_I = \frac{\beta}{\alpha}$ for the infected class I, and $c_T = \frac{1}{\beta}$ for time t, we end up with a nondimensionalized system of the differential equations as the following.

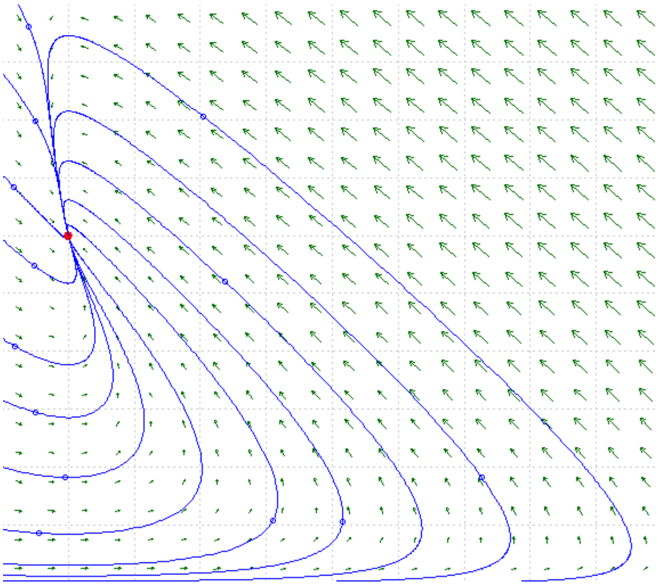
$$\frac{d\tilde{S}}{d\tilde{t}} = \frac{\alpha K}{\beta^2} - \tilde{S}\tilde{I}$$
$$\frac{d\tilde{I}}{d\tilde{t}} = \tilde{I}(\tilde{S} - 1)$$

where, $\frac{\alpha K}{\beta^2}$ is a free parameter, μ .

Now, we can easily notice that the free parameter, μ, in the nondimensionalized system is same as the one shown up in the parametric conditions, [3] and [4]. That means the overall behavior of the epidemic can be observed by changing the free parameter, $\mu = \frac{\alpha K}{\beta^2}$ with the nondimesionalized equations.

If we simply look at the nondimensionalized epidemic model, the free parameter, μ, can be interpreted as recruitment to the population of a HIV-high-risk community, N; of course, the recruitment then immediately belongs to the susceptible class, S, as the infection is in progress. This phenomenon is analogous to the fact that the original system, [2], has the K term, which represents new immigrants to the susceptible class per unit time. Note that, in the dimensionless system, the dimension of K, $[K] = \frac{P}{T}$, where $[S] = [I] = P$ and $[t] = T$. Recall the "*forcing term*" that we mentioned earlier. It becomes now clearer that the K term acts like a "*forcing term*" which makes the behavior of the infection change. In fact, it is more accurate to say the free parameter, $\mu = \frac{\alpha K}{\beta^2}$, determines the behavior of the overall epidemic. The below figures* visually present the different behavior of the infection at the equilibrium.

* All figures are magnified for clearer view of differences.



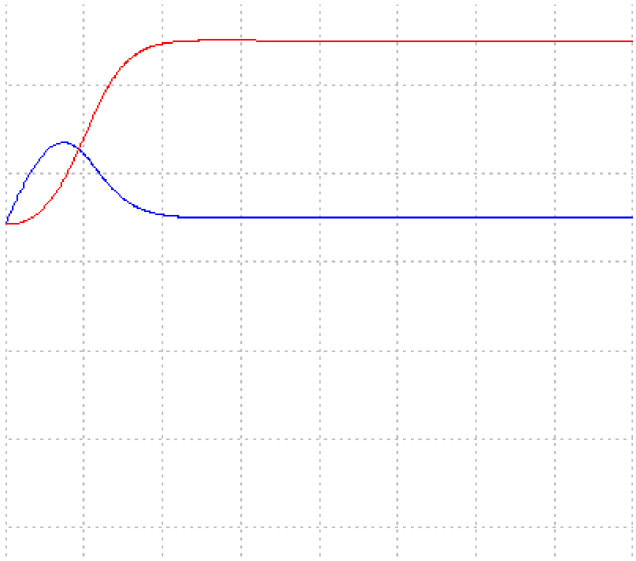
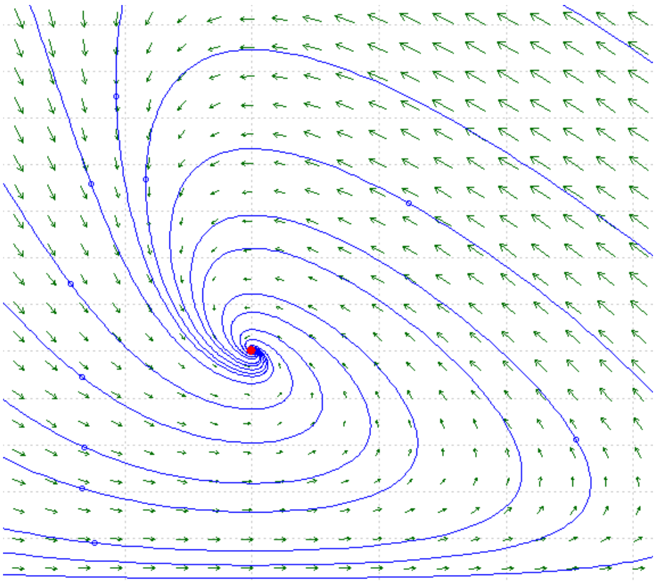


Figure 2. When $\mu \geq 4$, the solutions in the phase-plane move to the nodal sink equilibrium, E(S*, I*) = (β/α, K/β)

Figure 3. . When $\mu \geq 4$, S (blue) and I (red) approach to a steady state of the infection as $t \to \infty$.



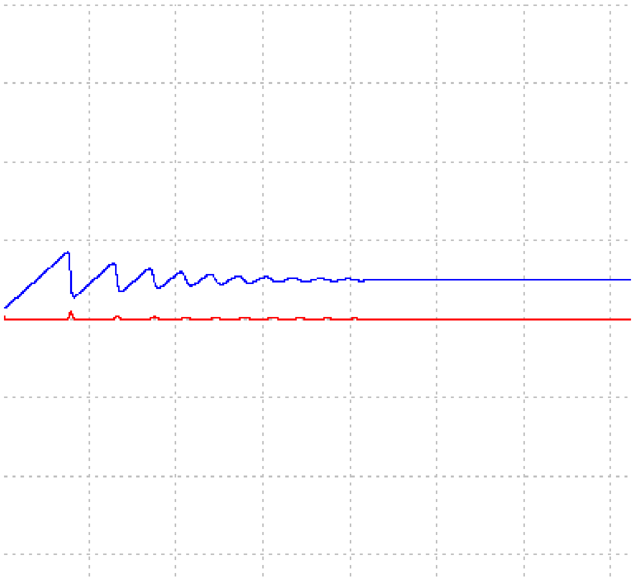


Figure 4. When $\mu < 4$, the solutions in the phase-plane move to the spiral sink equilibrium, E(S*, I*) = (β/α, K/β)

Figure 5. When $\mu < 4$, S (blue) and I (red) approach to a steady state, in oscillation manner, as $t \to \infty$.

The general behavior of the epidemic as shown in the figures is predicted under the initial condition of the epidemic, starting close enough to the equilibrium point, and as time goes to infinity. However, what happens the very beginning of the epidemic? The question might be a more realistic concern especially for the short history of HIV infection reflected on the real data (see **Supplement Data #1**). Consider the second differential equation of the system,

$$\frac{dI}{dt} = \alpha SI - \beta I \ .$$

At the very beginning of the epidemic, the populations of the infected class and the AIDS patients are almost negligible compared to the susceptible class. Therefore, $N = S + I + A$, becomes $N \approx S$. Besides, the relatively long incubation time of HIV leads to the insignificance of the term $-\beta I$ which represent the conversion from the infecteves to the AIDS. Ignorance of HIV with the "there-is-no-AIDS-in-our-country" attitude could also cause $-\beta I \approx 0$ during that particular time span. Now, according to these assumptions, we have an equivalent differential equation,

$$\frac{dI}{dt} = \alpha NI \ .$$

By inspection, we can easily obtain the solution of the equation, $I = I_0 e^{\alpha Nt}$. Clearly, $\alpha > 0$ as long as the epidemic is in effect and $N > 0$ since it's a population. Therefore, no matter how small the parameters are, the infection will exponentially grow in the beginning of the epidemic. This is what's actually happening in the real world at least in last 20 years (see **Supplement Datat #2**).

§ Results

The endemic equilibrium $E(S^*, I^*) = (\beta/\alpha, K/\beta)$ is asymptotically stable. When $\mu \geq 4$, a relatively larger recruitment rate to the susceptible class, the epidemic slows down after some time. In this case, if a group of infected individuals is introduced to the susceptible class, the population of the susceptible class will approach to $S^* = \beta/\alpha$ while the population of the infected class approaches to $I^* = K/\beta$, as time increases. On the other hands, when $\mu < 4$, a relatively smaller recruitment rate to the susceptible class, the epidemic slows down with a certain period due to oscillation in terms of the model parameters while the population of S and I still approach to the same equilibrium point. However, in the very beginning of the epidemic, we could observe the infection obeying the exponential growth, $I = I_0 e^{\alpha Nt}$.

§ Improvements

We assume that all susceptible individuals have an equal probability to acquire HIV from infected individuals, which is not necessarily true in a real problem. Thus, an improvement can be made by accounting for the transmission probability which is embedded in the infective rate, α, for the model in this project. In addition, the model neglects the natural death, non-HIV-related subtraction from each population group. This should be counted on a more sophisticated model. Like all other epidemic, the most demanded work for the HIV infection model might be to estimate accurate parameters; not only do the parameters enable us to numerically simulate the epidemic, but they would also characterize social behavior especially for venereal diseases. Due to the lack of the precise numerical data for HIV infection and its relatively short history, it is known that estimating the model parameters is considerably difficult. Indeed, in our model, there is an unknown constant immigration rate to the susceptible class. In general, an in-depth study of the dynamics of HIV infection along with modeling technique is required for the improvement of the model. For additional information, a powerful technique, called “Backcalculation method”, is preferably used out there to estimate the susceptible population from the current HIV-infected population.

§ Conclusion

A simple continuous model can mirror a primary interaction of HIV infection, using a system of ODEs. The modeling is accomplished by formulating the rate of change of each population with their interactions. According to the results, by changing an environmental-control parameter, μ, the long-term behavior of HIV infection slightly changes until the infection reaches a steady state. Knowing the simplified model might be somewhat inappropriate for the dynamics of HIV infection, though, fundamental mathematical modeling techniques are accomplished in this project to conceptualize a physical phenomenon. Finally, analytic approaches are conveniently used to understand the factors governing the behavior of the model.

Reference

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Supplement Data #1

The continuous model for the HIV infection in this project is created based on the data, as of Sep. 2003, quoted from *National Institute of Health in South Korea* (http://www.nih.go.kr).

Year	Infected	Infected female	AIDS patients	Death	AIDS-induced death
85~'93	320	34	16	42	14
1994	90	11	11	13	9
1995	107	19	14	21	14
1996	105	12	22	33	25
1997	124	17	33	36	30
1998	129	18	35	46	37
1999	186	26	34	43	34
2000	219	25	32	52	32
2001	328	35	42	58	42
2002	399	34	88	76	58
2003	398	26	37	55	38
total	2405	257	364	475	333

Infection Routes		Infected	%
Sexual contact	Abroad Heterosexual	369	98.3
	Local Heterosexual	904	
	Homosexual	643	
Blood transfusion	Abroad	14	1.3
	Local	12	
Vertical Infection		5	0.4
Injection Drug Use		2	
Etc.		225	-
In progress of Epidemic Investigation		231	-
Total		2405	100

* percentage of 1949 individuals with known-infection-routes

Supplement Data #2

The graphs plot the data in the Supplement Datat #1.