HIV/AIDS - A PREMER FOR MATHEMATICAL MODELING

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Preface

The aim of this Primer is to present an introduction to mathematical modeling of the attack of the virus HIV (Human Immunodeficiency Virus) on the human immune system which is the cause of the dreaded disease AIDS (acquired immuno deficiency syndrome). It is primarily intended for an audience of those who have knowledge of some basic tools of mathematics, namely, calculus, differential equations and matrix algebra. A sketchy supporting account of the biological and clinical processes, including the terminology used is given. The study of the infectious disease HIV/AIDS is multifaceted including basic and clinical sciences, epidemiology and public health, and social sciences. The intention of modeling is two fold. Firstly, the models should be a meaningful description yielding to numerical experiments (in the process replace a plethora of experiments, thus saving in costs and time). Secondly and most importantly, the modeling should have the goal of providing insight into the biological process itself. To develop new and sophisticated models, one needs to be familiar with the basics of language, mathematical, biological and clinical. In this Primer, we attempt to do the same, so as to give an optimized introduction to enable particularly a mathematician a clinician or a biologist to reach a research level and to be able to formulate and incorporate real life situations into the models. This Primer though fully self contained is only a first step to the development and analyses of the models. The hope is that mathematical models do to biological research what tissue research has done for animal and human research..

Introduction

The role of mathematical models concerning biological systems is far from being clear or being satisfactory. Whether a mathematical approach has contributed to a critical insight to the biological process itself is a debatable point. One can have the following extreme view as to what can be eventually accomplished. The question is really whether the development and behavior of living orgasms can ever be fully explained. As an example, the life process is essentially the development of a fertilized cell, as the result of information imparted by DNA. Transmission of this information which is the controlling factor in the life process is believed to be not entirely to

consist of chemical and physical processes. The description of the living system thus transcends the chemical and physical laws which govern even the atomic constituents. This seems to imply that in the 'final analysis that logic is not sufficient to explain life. Of course, we are at an "infinite' distance from the stage of such a 'final' analysis. This confirms our daily experience that in a contest between life and logic, life always wins!

The consequences of the human immunodeficiency virus invading the human immune system and the eventual path to its destruction is a complex one with many gaps in the knowledge of the biological process. The human immune system is mainly represented by the CD cells which are HIV specific and get infected by the virus. The mathematical modeling comprises of developing first order nonlinear equations expressing growth rates for various populations including those of the virus, infected and uninfected CD cells and concentrations of therapeutic drugs in the human body. Modeling allows us to introduce new components as well as simulation of the models and their solutions under a plethora of experimental situations. For example, the planning of intermittent therapy (as to drug doses, periods of intermittence etc.) become mere computer simulations and avoid intense real life experimental settings. The results of simulations lead to lesser clinical experiments as well as give valuable information of the biological processes. The rate at which CD cells can recover its population in an intermittent therapy provides valuable information when healthy HIV specific CD cells with drugs are used for therapy. The role of drugs is primarily to kill the virus, although it retards the proliferation of healthy cells.

It is essential to have an elementary working knowledge of the languages of relevant biology
As well as the framework of the processes involved including the bonding of HIC with CD cells, progression of AIDS with and without drug therapy (intermittent and continuous). A brief account of clinical and experimental aspects are also given. An account of modeling research so far with results and references gives a bird's eye view of the state of the research. An example of modeling where an insight into the biological process under therapy is valuable is described.

Some examples where mathematical modeling of biological processes can contribute to knowledge are (a) cholesterol accumulation in arteries (blood flow through and past porous media) where it is extraordinarily difficult to prescribe the conditions on boundaries that 'separate' arterial wall,, the cholesterol porous media and the blood flow (b) the pericardium enclosing the heart , the role of the pericardium inside the body is not clear (c) role of drugs on healthy cells and incorporation of this in modeling the disease.

3. Biological terms and the processes.

AIDS: Acquired Immuno Deficiency Syndrome where the natural immune system is Compromised

Antigen:

Antiretroviral:

Bone marrow:

B Cells and T Cells: The most abundant lymphocytes are termed B cells and T cells. B cells are produced in Bone marrow and mature there while the precursors of T cells are produced in the Bone marrow and mature in the (T) thymus. The surface of each T cell has thousands of identical T cell receptors (TCRs). One type of two types T cells (alpha/beta T cell) binds to an antigen presenting cell (APC). For each type antigen there are specific T cells.

CD Cells: Most of the T cells belong to CD4 or CD8 , the distinction being in having a particular glycoprotein it has on its surface, which also determines what types of cells it can bind to CD8+ T cells bind epitopes of class I (histocompatibility molecules) of the antigen, while CD4+ cells bind the epitopes of class II

CD8+ T Cells: These are cytotoxic T lymphocytes (CTLs) and they destroy the antigen cell to

which they have bound. The role of these cells generally to monitor all cells of the body , ready to destroy the invading virus with class I molecules.

CD4+ T cells: These cells are necessary for both cell mediate immunity (CD4+Tcells bind to APCs and they release lymphokines that attract other cells to the area resulting in inflammation. This acumulation helps in the fight against the virus) and antibody mediated immunity (these CD4+cells are called helper T cells bind to antigen presented by B cells resulting in development of plasma cells which secrete antibodies against the virus. HIV binds to CD4 molecules and infect CD4+ cells. As the disease progresses, the number of CD4+T cells declines to lower than normal levels of 1000microliters. Cd8+ cells destroys inected CD4+ cells.

Clonal expansion:

DNA:

Epitope:

HIV : Human immuno deficiency virus which may lead to the disease AIDS

Inhibitors:

Lymphocytes: These are small white blood cells and they bear the major responsibility for carrying out the activities of the immune system. These are one of ffive white blood cells or leukocytes

Pathogen: Invasive foreign infectious microbial organisms such as bacteria, fungi or virus usually harmful to human body.

Pathogenesis:

Peptide:

Receptors:

Reverse Transcriptase (RT):

Substrate

Thymus: It is a temporary organ developed in the fetus, attaining its largest size at the time of puberty, when it ceases to grow and gradually dwindles. It is situated partly in the thorax

Virus:

Processes: When the body is attacked by an infectious virus, the virus invades certain cells and subverts the metabolism of the cell to make more virus. In due course, these newly formed virus articles leave the cell and attack new uninfected cells. Once inside the cell the virus is safe form the CD cells. Only during transit from the cell, the CD cells can attack them. In early stages, the infected cells display some virus proteins on the cell surface when the CD cells can destroy the virus. We discuss the growth of the populations as functions of time of the virus (V(t)), uninfected CD4+ cells (T (t)), infected CD4+T cells (T (t))

Appendix 1. History of HIV/AIDS
(Main Source: http://www.avert.org)

It is well known that the sole cause of the disease AIDS is a result of HIV infection, although some very few cases are known where HIV does not lead to AIDS. The enormity of the problem and with no clear signals as to the wane or satisfactory drug treatments of the disease, it is important to know the history of the development and proliferation of the world population. Drug therapy allows for control (though not elimination) of the progression of the disease, thus prolonging life under HIV and also by providing some improvements in the quality of life for many.

It is not known where or how HIV/AIDS originated and there are many theories, substantiated or otherwise. It is surmised that by 1986, more than 100,000 have been affected and till then there was no clear awareness or any preventive actions existed. The disease has been mainly a gay disease with recorded origins in California. There has been (even now) considerable controversy about transmission of AIDS. It is now accepted that bodily fluids (including blood transfusions) , and the birthing process are major forms of transmission. It took some time to establish that women and children are immune. The word AIDS was first used in 1981. Aids may have also developed independently in many countries at the same time. It was termed gay plague in U.K. with all the stigmas which made it a disease for concealment. Even by the end of 1984, there had been known 7000 cases and about 4000 deaths. AIDS spread as rapidly in heterosexuals as in homosexuals. Around 1986, tests fo aids were developed and at that time the drug AZT (azidothymidin) showed that it slowed the attack of HIV. AZT was first synthesized in 1964, which had then proved ineffective as a cancer drug. In1987, AZT became the first antiretrovial drug for treatment of AIDS. The World health Organization estimated that 5 to 10 million people were affected with HIV worldwide, with up to 3 million developing AIDS in the next five years. In 1990, it was shown that AZT could slow progression to AIDS in HIV positive individuals with no symptoms. A second drug ddl (dideoxyinosine) wae developed particularly for those patients with AZT intolerance.

In 1993, AIDS became the leading cause o death among Americans between the ages of 25 and 44. AZT also reduced by two thirds the risk of transmission of HIV from infected mothers to their babies during birth. In 1999, researchers in Alabama found that the Simian virus the chimpanzees carried in Africa was almost identical to HIV virus which lead to a conclusion that the origin of HIV was due to apes. Although it is not a common occurrence, HIV seems to have crossed species from apes to humans. The cross over seems to have happened simultaneously in different

continents viz.,U.S. and Africa. Major sources of transmission of HIV have been (a) sex with one partner with the virus (b) use of infected needles (c)mother to child (d) transfusion of blood.

By the end of 1999, it was estimated 33 million will have HIV/AIDS.

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HIV/AIDS, A PRIMER FOR MATHEMATICAL MODELING

CONTENTS

PREFACE

The aim is to present an introduction to mathematical modeling the disease HIV/AIDS. It is intended primarily for an audience of those who have knowledge of basic tools of mathematics. namely, differential equations, matrix algebra. A comprehensive account of basic knowledge and terminology of associated biological and clinical purposes. A good mathematical model not only reflects to biological process, but it should also enable one to fit an understanding of the processes. A mathematical model could replace a large number of experiments by its ability to vary the various parameters at hill. This account is meant to be self sufficient for a mathematician to appreciate and develop models which are flexible to include new clinical and experimental information. It is hoped that mathematical modeling replaces a variety of experiments, human and otherwise, an example of which is given. It is also hoped that this primer leads to development of models.

1. Introduction

The consequence of the human immunodeficiency virus (HIV) invading the human immune system and its eventual destruction is a complex one in its biological processes. We human immune system is represented mainly by the CD cells manufactured in the bone marrow. Some CD cells are HIV specific and get infected with HIV. The mathematical modeling comprises of developing systems of first order 19 differential equations expressing growth rates for various populations including those of the virus, infected CD cells, manufactured CD cells, concentration of drugs in the human body.

It is essential to have at least an elementary knowledge of the language of biology and the framework of to processes including of HIV into CD cells, progolrian of AIDS with and without drug therapy (intervikent or continuous). A brief account of clinical and experimental aspects are also given. Modeling research so far into results and references are also given. An example of modeling where some insight into the biological process is described.

2. History of AIDS

(Source: http://www.avert.org)

It is not known where or how AIDS originated, although there are many unsubstantiated theses. It is summered this by 1886 more then 100,000 persons may have been infected as there was no clear awareness or any prevented actions. The disease has been mainly a gay disease with recorded origins in california. There was considerable controversy about transmission of AIDS. It is now accepted that bodily fluids and giving birth are major known forms of transmission. Woman and children are not immune. The word AIDS was first used in 1981. AIDS also seem to have occurred in a number of different countries. It was also termed in U.K. as gay plaque. By the end of 1984 there had been over 7000 AIDS cases and about 4000 deaths. AIDS spread as rapidly in heterosexuals as homosexuals. Around 1986, lists for AIDS were developed and at that times the drug AZT (azidothymidine) showed that it should the attacks of the HIV. AZT was first synthesized in 1964, which proved ineffective as an anti cancer drug. In 1987, AZT was the first antinetroviral drug treatment of AIDS. The World Health Organization estimated 5 to 10 million people were infected with HIV Worldwide, with up to 3 million developing AIDS in next five years. In 1990 it was shown that AZT could slow progression to AIDS in HIV positive individuals with no symptoms at all. A second drug ddl (dideo xyinomine) was developed particularly for those patients with AZT in tolerance.

In 1993, AIDS had becomes to leading causing death among americans between the ages of 25 to 44. AZT also reduced by this trends to risk of transmission of HIV from infected motions to their bodies.
In 1999, researchers in Alabama found this to similar virus to chimpanzees carried in Africa was absent identical to HIV which made some conclude that the origin of HIV was due to apes. Although not common, HIV seems to have cloned species from apes to human. This crossover seems to have happened simultaneous in this different continents named, U.S. and Africa.
Major sources of transmission of HIV in the modern world are (a) sex with one partner with HIV (b) sex of infected needles (c) motion to child (d) transfusion of infected blood. By the end of 1999, it was estimated 33 million people have HIV/AIDS.

Since explicit analytic solution of the solutions (7.1), (7.2) under initial conditions are not feasible, are with discuss the nature of the solutions (stability of the solutions) around critical points and use approximation methods (finite difference, etc.) to derive approximate values for the variables. We sat below some of the processes in analyzing the system (7.1), (7.2).