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AGGREGATE THERMODYNAMICS CONTROL INFECTIVITY IN HIV INFECTION DYNAMICS

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Abstract: **Following a persisting challenge of HIV, thermodynamic expressed drug primary mechanism of action β_1 that took account of the drug bioavailability and drug secondary mechanism of action β_2 parameters were introduced in a historical aggregate control parameter model which is later incorporated in an adopted basic viral dynamics model, an Ordinary Differential Equation (ODE) and the solution of the ensued model from numerical integration that utilized explicit Runge-Kutta method now the red series is simulated simultaneously alongside a solution from historical model from the drug absorbance efficiency now the green series for the infection time course using MATLAB™ function ode 23. Thermodynamic drug parameters introduced from day twenty to day three hundred achieved a higher value of $CD4^+$ T cell count that later converged to equilibrium in the first instance and in the second instance, drug parameters introduced from day twenty to day twenty five revealed a faster response by drugs with thermodynamic aggregate parameters even though it later settled to equilibrium with formulation having only the secondary parameter of absorbance as the efficiency. The solution showed dynamics as expected and are quite informative based on the fact that they both display infection time course that are in agreement with the literature. The solution dynamics changed to curative at the introduction of the thermodynamic drug parameters hence validating the model. They both changed from being progressive to regressive. $CD4^+$ T cell count got comprehensively improved while infected cell count and viral load dropped as expected. It is very worthy of note that expressed thermodynamic aggregate control dynamics picked up faster than only the absorbance model. The values of $CD4^+$ T cell count rose far above 90% (900) cells per µL ($cells\mu L^{-1}$) of the supply rate of the $CD4^+$ T cell count. The series red which is for thermodynamic aggregate control dynamics showed clearly that the combined efforts of both the drug primary and secondary mechanism of action acted faster. They both teamed up to resist the viral attack faster and earlier than that of drug secondary mechanism action alone.**

The result of this paper explains the fact that control infectivity in HIV dynamics can actually be expressed through combined Hamaker constants and absorbance parameters of the drugs in historical aggregate control infectivity model. The application of this study in pharmaceutical industries, in the area of drug design and in clinical studies cannot be overemphasized.

Keywords: **Human immunodeficiency virus, Interfacial energetics, Control Infectivity, Absorbance.**

1. INTRODUCTION

88. 4 million (71-3-112.8million) people have been infected with the HIV virus and about 42.3 million (35.7-51.1) million people have died of HIV since the beginning of the epidemic (WHO, 2024). Although the burden of the epidemic

continues to vary considerably between countries and regions an estimated 0.6% (0.6-0.7%) of adults aged 15-49 years worldwide are living with HIV. Again, 39.9 million (36.1-44.6) people were living with HIV at the end of 2023 (WHO, 2024). UNAIDS, (2013) documented that the solutions for the global increasing rate of Human Immunodeficiency Virus **(**HIV) infection are continuously being sought for, for its elimination.

The virus actually attaches its CD8+ cells on the wild CCR5 dendrites of the CD4+ T4 cells hence the mechanism of interaction between the virus and the surface of the lymphocyte continues to be of research interest. When the virus attaches itself to the surface of a given lymphocyte, an original area on the surface is destroyed while a new area is created. This change in surface area leads to change in surface energy of the surface. The nature of the cell changes if they penetrate the cell core. Determination of the energy associated with the creation of a new surface area is therefore necessary for the understanding of the mechanism of interaction. The energy of adhesion of the virus to the surface of the lymphocyte becomes of interest. Good, (1979) noted that the term surface energy is used because a change in the surface area of a solid cannot be accomplished without doing work against the elastic forces and plastic resistance of the solid.

The identification of the actual mechanisms of virus/blood interactions parameters within the existing mathematical models has not been easy. A very serious problem in the mathematical modelling is the unavailability of experimental data on HIV/blood interactions. The impetus to unravel interfacial energetics and genetics in HIV discordant couples is rooted on the following successes in HIV through thermodynamics. Ani, (2015) through the study of interfacial energetics been established that the lymphocyte is the target of the virus. Ilo, Omenyi, and Dim, (2021a) had applied thermodynamics in the dynamics of HIV. Ilo, Omenyi and Ani, (2021b) had quantified drug primary mechanism of action through thermodynamics Hamaker concept. Ilo, (2022) through thermodynamics spectrophotometry gave an insight control infectivity in HIV dynamics. Ilo, (2024a) had developed a validated model through concepts of thermodynamics implementation to unravel the mystery of transcriptional bifurcation in HIV dynamics. And finally, Ilo, (2024b) had also established HIV adhesion driven infectivity through electrostatics interaction mechanism. In this paper HIV aggregate control infectivity are explored through interfacial energetics to ascertain its workability preference in the control and elimination of HIV.

2. PREVIOUS WORK/LITERATURE SURVEY

Viral Dynamics

In HIV infection, healthy cells are infected by the virus at a rate that is proportional to the product of their population size and the amount of free virus particles with a constant that is an indication of the effectiveness of the infection process (Bonhoeffer, May, Shaw, and Nowak, 1997; Hill, Rosenbloom, Nowark, & Siliciano, 2018). A stage without which the HIV life cycle would be cut short in the virus life cycle (replication cycle) is the first stage, the binding (attachment) stage. The viral particle is attracted to a cell (lymphocyte) with the appropriate CD4 receptor molecules where it attaches (binds) and by fusion to a susceptible cell membrane or by endocytosis (an energy using up process) and then enters the cell during entry to the body. These reasonings enabled researchers, notably Bonhoeffer, *et al.*, (1997), to propose a basic model of viral dynamics as:

$$\begin{aligned} \dot{x} &= \lambda - dx - \beta xv, \\ \dot{y} &= \beta xv - ay, \\ \dot{v} &= ky - uv. \end{aligned} \qquad (1)$$

Where x is susceptible cells, y is infected cells, v is virus particle, λ is rate of production of susceptible cells, d is death rate of susceptible cells, β is infectivity (interaction parameter), a is death rate of infected cells, k is rate of virus production and u is clearance rate of virus particles.

Three (3) main stages, namely the acute HIV infection (primary infection), asymptomatic and the advanced – aids as clearly shown in a typical HIV infection course Fig. 1 have been identified in HIV infection dynamics.

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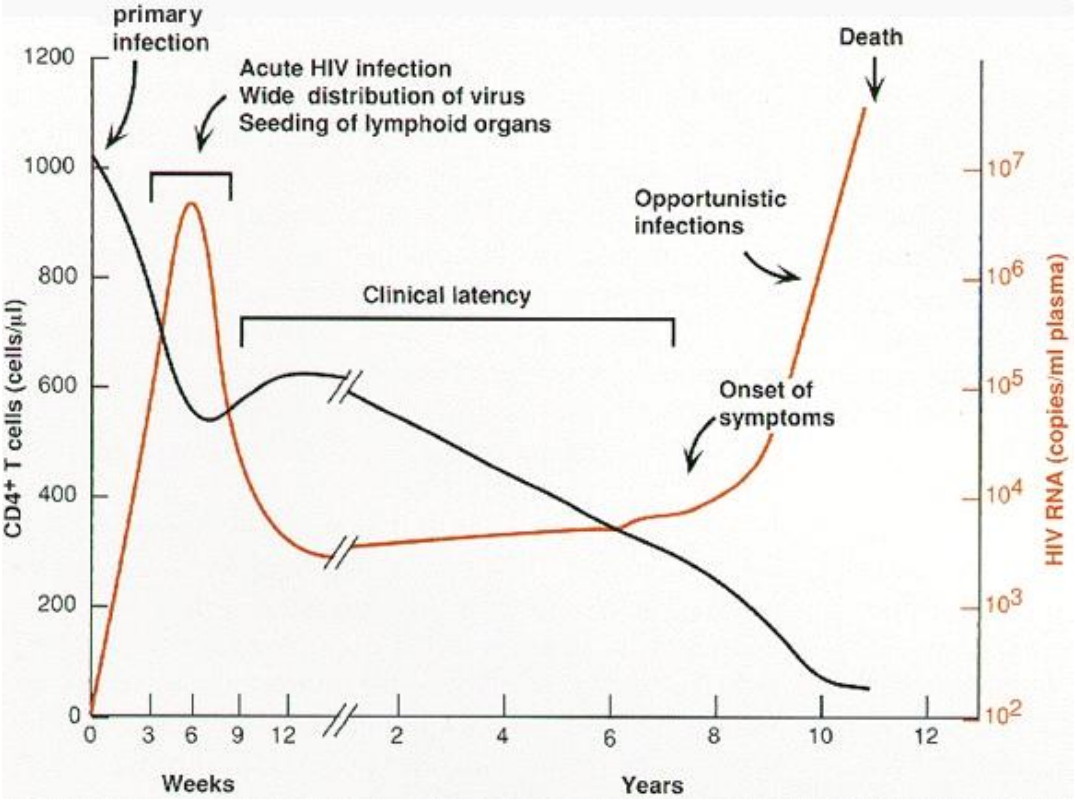

Figure 2.1: (b) Approximate Time-Course of HIV Infection. (Pantaleo, Graziosi and Fauci, 1993)

When infection is not yet established, normal $CD4^+$ T cell counts range from five hundred (500) to one thousand six hundred (1600) cells per cubic micro litre, on the average (1000) cells per cubic micro litre and drops to less than hundred (500) cells per μL (cells mm^{-3}) if infection is fully established.

Control Infectivity Parameter

The interaction between the virus *v* and the lymphocyte *x* is clearly given as *xv* and the appropriate infectivity parameter is β. When there is therapy (control), infectivity can be reduced with application of drugs. Two approaches are evident. The first is a function of the efficiency of drugs and the infectivity clearly shown in equation (2).

$$\beta_c = \beta_0(1 - \eta) \qquad (2)$$

η is drug (response) efficiency.

The second approach due to (Costanza *et al.* cited in Rivadeneira, *et al.*, 2014) is a control aggregate parameter which is a function drug amount gave control interaction parameter β_C, under therapy as

$$\beta_C = (\beta_0 - \beta_1 u - \beta_2 u^2) \qquad (3)$$

It is an empirical approximation for pharmacodynamic (concerned with the effects of drugs and the mechanisms of their action, that is, how a drug works) and pharmacokinetic (study of effects of the body on the actions of a drug, basically the time course of drug absorption) equations used to relate the real dose with its efficiency. The first term of the equation (3) is the disease mechanism of action term (infectivity) that is, virus mechanism of action term commonly known as disease interaction term, the second term is the drug primary (dominant) mechanism of action term while the third term is the drug secondary mechanism of action term with β_2 being identified as a function of β_1. β_0 is actual disease mechanism of action (infectivity), β_1 drug primary mechanism of action parameter and has value greater than one, β_2 is drug secondary mechanism of action parameter and has maximum value of one, u represent drug amount.

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Hamaker coefficient in HIV drugs.

Achebe, (2010), had expressed that for HAART to be active, equation (4) holds. Omenyi, S. N. (2005) had also explained the repulsive ability negative Hamaker coefficient in sufaces of biological interest. Also, Ani, (2015) established that absorbance parameters of drugs are functions of the drugs interfacial energetics parameters, that is the Hamaker parameters of the drug.

$$A_{PLS} = A_{PS} + A_{LL} - A_{PL} - A_{SL} < 0 \qquad (4)$$

Bioavailability

Pharmacokinetic studies of antiretroviral drugs are often conducted in healthy adults and the results are interpolated to HIV/AIDS patients. HIV/AIDS have been known to cause morphological and physiological changes capable of altering the pharmacokinetics of antiretroviral drugs. Mukonzo, et al (2011), in their research on bioavailability of Efavirenz observed that HIV/AIDS patients were found to have 30% lower relative bioavailability than healthy subjects. They concluded their research that HIV/AIDS disease is associated with reduced bioavailability of efavirenz.

3. METHODOLOGY

Thermodynamic expressed drug primary mechanism of action β_1 that took account of the drug bioavailability and drug secondary mechanism of action β_2 parameters are introduced in an aggregate control parameter model which was later incorporated in an adopted basic viral dynamics model, an Ordinary Differential Equation (ODE) and the solution of the ensued model from numerical integration that utilized explicit Runge-Kutta method now the red series is simulated simultaneously alongside a solution from historical model from the drug efficiency now the green series for the infection time course using MATLAB™ function ode 23. Drug parameters were introduced from day twenty to day three hundred to show convergence to high value of $CD4^+$ T cell count for a particular drug in the first instance, figure 2 and in the second instance figure 3, drug parameters were introduced from day twenty to day twenty five to show that actually formulation with aggregate drug parameters acts and picks faster even though it will still settle to equilibrium with formulation having only the efficiency parameter. The solution showed dynamics as expected.

HIV dynamics thermodynamics control model

Equation (5) is a thermodynamic control model based on efficiency of drug. It serves as a validation for the proposed thermodynamic aggregate control model of equation (6). Since data for both primary and secondary mechanism of action are obtained for a particular drug, the solutions of equations (5) and (6) are plotted to both validate the expressed aggregate model and probably showcase that though the aggregate model dynamics lately converge to the efficiency model dynamics, it picks faster showcasing its advantage.

$$\frac{dx_\eta}{dt} = \lambda - dx_\eta - \beta_0 x_\eta v_\eta + \beta_0 \left(\frac{\tilde{a}_{bd} - \tilde{a}_b}{\tilde{a}_d - \tilde{a}_b}\right) x_\eta v_\eta,$$

$$\frac{dy_\eta}{dt} = \beta_0 x_\eta v_\eta - \beta_0 \left(\frac{\tilde{a}_{bd} - \tilde{a}_b}{\tilde{a}_d - \tilde{a}_b}\right) x_\eta v_\eta - a y_\eta,$$

$$\frac{dv_\eta}{dt} = k y_\eta - u v_\eta. \qquad (5)$$

Incorporating the thermodynamically expressed aggregate control infectivity parameter from (Ilo, 2022) in the adopted model equation (3), the ensued model (6) is incorporated in (1) to have (7) and utilised in the simultaneous simulation with (5).

$$\beta_C = \left(\beta_\infty - (0.3)\left(\frac{(A_{PL} + A_{SL})}{(A_{PS} + A_{LL})}\right)\omega - (0.3)\beta_{2T}\omega^2\right) \qquad (6)$$

$$\frac{dx_\omega}{dt} = \lambda - dx_\omega - \left(\beta_\infty - (0.3)\left(\frac{(A_{PL} + A_{SL})}{(A_{PS} + A_{LL})}\right)\omega - (0.3)\beta_{2T}\omega^2\right) x_\omega v_\omega,$$

$$\frac{dy_\omega}{dt} = \left(\beta_\infty - (0.3)\left(\frac{(A_{PL} + A_{SL})}{(A_{PS} + A_{LL})}\right)\omega - (0.3)\beta_{2T}\omega^2\right) x_\omega v_\omega - a y_\omega,$$

$$\frac{dv_\omega}{dt} = k y_\omega - u v_\omega. \qquad (7)$$

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Where A_{PS} is hamaker constant for both particles of virus (p) and lymphocyte (s), A_{LL} is hamaker constant for serum (plasma) (L), A_{PL} is hamaker constant for both particles of virus (p) and serum (L), A_{SL} is hamaker constant for both particles of lymphocyte (s) and serum (L), $\tilde{a}_d$ is peak absorbance for drug film only, $\tilde{a}_b$ is peak absorbance for blood component only, $\tilde{a}_{bd}$ is peak absorbance for drug film coated given blood component and ω is amount of drug.

4. RESULTS AND DISCUSSIONS

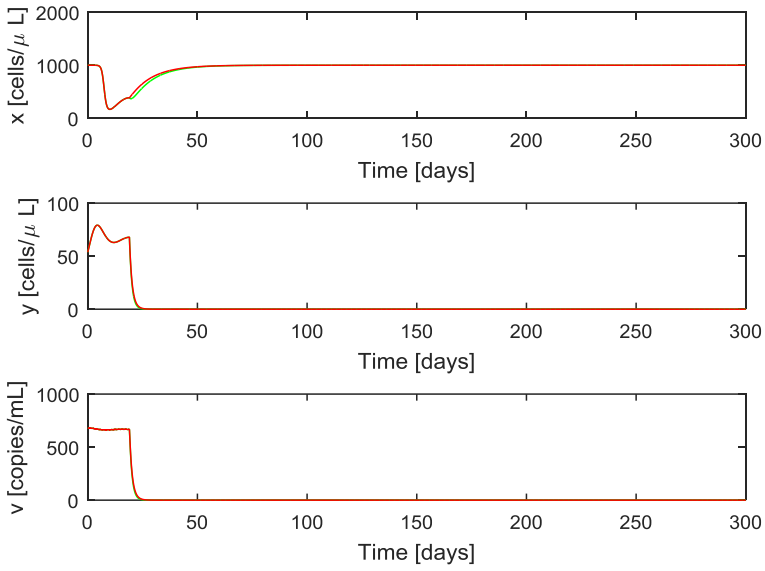

Fig 2 Simulation with thermodynamics aggregate control dynamics model to equilibrium.

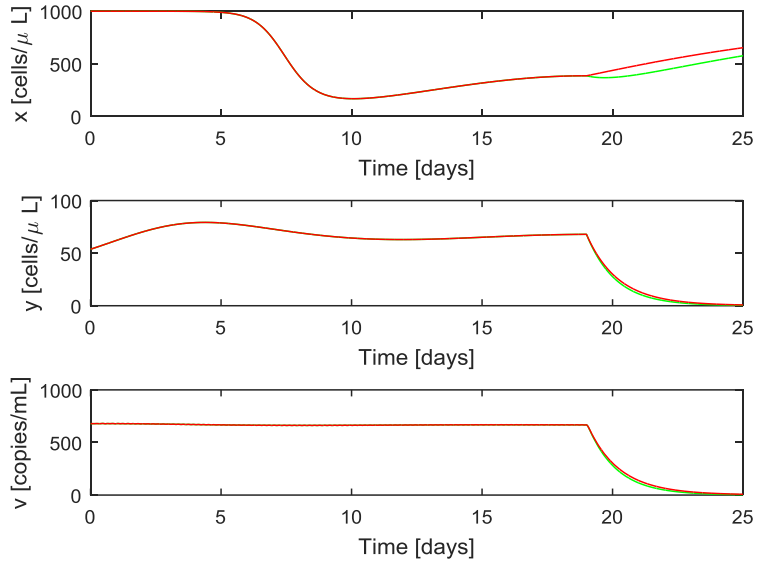

Fig 2; Simulation with thermodynamics aggregate control dynamics model to pick up.

Figures 2 and 3 are quite informative based on the fact that they both display infection time course that are in agreement with the literature. Figure 2 and 3 show actually the historical drug parameters were capable of changing the disease dynamics hence validating the model. They both changed from being progressive to regressive. $CD4^+$ T cell count got comprehensively improved while infected cell count and viral load dropped as expected. It is very worthy of note that expressed thermodynamic aggregate control dynamics picks up faster than only the absorbance model. The values of $CD4^+$

T cell count rose far above 90% (900) cells per μL ($cells\mu L^{-1}$) of the supply rate of the $CD4^+$ T cell count. The series red which is for thermodynamic aggregate control dynamics shows clearly the combined efforts of both the drug primary and secondary mechanism of action. They both teamed up to resist the viral attack faster and earlier than that of drug secondary mechanism action alone.

The result of this paper explains the fact that control infectivity in HIV dynamics can actually be expressed through Hamaker constants and absorbance parameters of the drugs. The application of this study in pharmaceutical industries, in the area of drug design and in clinical studies cannot be overemphasized.

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