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SURFACE THERMODYNAMICS OF ACTUAL INFECTIVITY RANGE IN HIV DYNAMICS

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Abstract: **Wide variability in both infection and response to therapy by individuals suffering from HIV and the associated resistance to antiretroviral drugs all relating to wide range of infectivity has been a problem. This article is a study of the surface thermodynamics of actual infectivity range in HIV dynamics. The methodology firstly involved incorporating an expressed thermodynamic transcriptional infectivity model representing the lower value of the infectivity range in an adopted basic viral model, an ordinary differential equation (ODE) and solving the ensued HIV model with a view to validating the infectivity model with the dynamics of the HIV model at transcriptional bifurcation. Secondly, adopted basic HIV model incorporated with formulated thermodynamic infectivity model was also solved in ninety different simulations to ascertain the infectivity value that generates dynamics that aligns with the reality of the literature vis a vis the upper value of the infectivity range. These established both the lower and upper values of the infectivity range of HIV infection. The solution approach involved numerical integration of ensued (ODE) model using MATLAB™ function ode 23 that also makes use of an explicit Runge-Kutta method. As expected, a less than unit value of the Transcriptional Bifurcation Infectivity of $1 * 10^{-4}$ $(mL/copies/d)$ was obtained, indicating the presence of attractive van der Waals forces between HIV particles and the lymphocytes particles within an infected blood sample. In principle, a greater than one (1) value would have meant repulsion or no interaction. From the ninety simulations, a concise actual thermodynamic infectivity range of $1 * 10^{-4}\left(mL/_{copies.d}\right)$ to $3 * 10^{-3}\left(mL/_{copies.d}\right)$ which is within historical range of $5.0 \text{ x } 10^{-10} \leq \beta \leq 1\left(mL/_{copies.d}\right)$, a proper subset of that of literature was established. The established actual thermodynamic infectivity range is validated fully by the entire historical range of $5.0 \text{ x } 10^{-10} \leq \beta \leq 1$ $(mL/copies/d)$. Following expectations, findings show a concise range and that thermodynamic concepts can validly be used to quantify infectivity parameter range. Thus, to overcome wide variability in response to therapy by individuals, it is recommended for pharmaceutical industries to be applied in the area of drug design and drug dosing and in pharmacognosy for drug optimization for complete and efficient infectivity depletion.**

Keywords: **Human immunodeficiency virus, Interfacial energetics, Infectivity, Genetics.**

1. INTRODUCTION

Several viral diseases are common in humans, wild and domestic animals or crop plants. Some common human diseases such as cold, influenza, chickenpox and cold sores are caused by viruses. Currently, twenty one families of viruses known to cause diseases in humans, including human immunodeficiency virus (HIV), Hepatitis, Herpes Simplex, Measles, etc., have continued to plague humans (Lai, 2014). Virus can be defined as a small agent that is only able to replicate itself inside the living cells of an organism (Lai, 2014). Viruses multiply by using the host cell's synthesizing machinery to cause the synthesis of viral building blocks, which then self-assemble into new viruses that are released into the environment. They are not susceptible to the action of antibodies (Khanal and Shrestha, 2013). When a virus enters a cell and completes its normal replication cycle, the host cell may undergo lysis due to a physical internal pressure exerted by

multiplying virus or immune response. During the course of virus replication, many cytotoxic viral components as well as by-products of viral replication accumulate in the cell (Klatt, 2015). Cell lysis and cytotoxic components cause death of the cell (Lai, 2014). If enough cells die, the whole organism will start to suffer the effects. Some viruses can cause lifelong or chronic infections where viruses continue to replicate in the body despite the host's defence mechanisms. The mechanisms by which viruses cause diseases in an organism depend largely on the viral species (Smith, 1972). Viruses can usually cause damage in the host via cell lysis, production of toxic substances and cell transformation (Doitsh and Greene, 2016).

Mathematical modeling of viral dynamics, and hence HIV dynamics, provides understanding of the underlying mechanisms that influence the spread of the disease and, in the process, it suggests control strategies. The phenomenon of disease modeling can be easily accomplished through mathematical framework (Geetha, and Balamuralitharan, 2018). The idea that HIV is a dynamic disease encompassing a number of different time scales running from hours to months and even years is reinforced by the results of studies that revealed the lifetime of infected cells, which relatively produce copies of the virus and the high replication rate of HIV in the body (Khanal and Shrestha, 2013). Ronsard *et al* in (Santoro and Perno, 2013), noted that a rate-limiting factor in the management of HIV infections, is the plethora of genetic variations in infectivity leading to failure of clinical trials. Virus infectivity in HIV infection is observed to vary (Ganusov, Neher and Perelson 2012). Following the wide range of variability in infection and response, about ten billion new viral particles of HIV can be generated daily, in chronic cases (Omenyi, 2005).

WHO, (2023) asserted that people living with HIV as at the end of 2022 stood at average of 39.0 million people with an estimated 0.7% (0.6-0.8%) of adults in their prime aged 15-49 years. The burden of the epidemic has continued to vary considerably between regions and countries. As of December 2012, an estimated 9.7 million people in low- and middle-income countries were receiving antiretroviral therapy, an increase of 1.6 million over 2011, (UNAIDS, 2013). It no longer should be considered as just one of the numerous public health problems but an issue that is on par with climate change and extreme poverty. AIDS is also a complex set of problems-requiring a combination of solutions, (Piot, 2005). Again at the end of 2018 and due to gaps in HIV services, 770 000 people out of approximately 37.9 million people living with HIV died from HIV related causes with 1.7 million people newly infected, (WHO, 2019). HIV, as one of the most intensively studied viral infections, now has massive drug development efforts starting soon after identification of the virus with twenty seven (27) different antiretroviral drugs capable of halting viral replication and preventing transmission and progression to AIDS but still without a cure (Hill *et al*., 2018). Primarily the goals of such an effective therapy regimen are stated as: "maximal and durable suppression of the viral load, restoration and/or preservation of immunologic function, improvement of quality of life, and reduction of HIV related morbidity and mortality" (Jeffry, 2006; US Department of Health and Human Services, 2005).

It is known that from pathogenesis of HIV infection that retroviruses are unable to replicate outside of living host cells and do not contain deoxyribonucleic acid (DNA). The pathogenesis of HIV infection is a function of the virus life cycle, host cellular environment, and quantity of viruses in the infected individual. In the virus life cycle (replication cycle) the most crucial stage is the first stage, the binding (attachment) stage. It is a stage without which the HIV life cycle would be cut short. Now at entry to the body, 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. Fusion of the viral and host membranes is a critical step during infection by membrane enclosed viruses like HIV and influenza. The probability of infection is a function of both the number of infective HIV virions in the body fluid which contacts the host as well as the number of cells available at the site of contact that have appropriate CD4 receptors (Klatt, 2015: Sundquist and Kraussilich, 2012). This probability could only be attained as a result of the unavoidable contact between the virion and the lymphocyte. These 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.

As a problem, wide range of variability in infection and response to therapy by individual HIV and the associated resistance to antiretroviral drugs relating to infectivity have persisted. Transient rebounds of plasma viremia have also continued to be a problem under the use Highly Active Antiretroviral Therapy (HAART). Following the wide range of variability in infection and response, about ten billion new viral particles of HIV can be generated daily, in chronic cases (Omenyi, 2005).

With the objectives of quantifying the requisite thermodynamic bifurcation infectivity representing the lower limit and simulating the infection dynamics from the solution of the adopted thermodynamic model for upper limit of the thermodynamic infectivity range, within historical (literature) infectivity range, actual thermodynamic infectivity range is established the from simulations based on realities from literature and validated based also on the historical exposition.

In HIV/blood interactions, HIV is usually modelled as a particle. This model follows from the balance between electrostatic repulsion – van der Waals attraction mechanism. This approach which involved experimental and theoretical analyses has yielded some good results. However, in the studies on mathematical modelling reported so far, little or no effort was put into the understanding of the promoters of the virus binding effects on the lymphocytes. Interfacial energetics have been applied in the understanding of the binding mechanism and the quantification of the binding energy. It becomes necessary therefore that thermodynamic interfacial energetics principles should be introduced in these mathematical models. Incorporation of this principle into the viral dynamics forms the thrust of this work.

2. PREVIOUS WORK/LITERATURE SURVEY

Biological systems, Genetics and Thermodynamics

Abel and Trevors, (2005); Abel and Trevors, (2006); Abel and Trevors, (2007) observed that life is not possible without functional genetic instructions (FGI) and that living organisms are alive because FGI maintains stable ordered (low entropy) states. In other words, living organisms are programmed by FGI through cellular communication pathways, to grow and reproduce by maintaining a variety of hemistable, ordered structures (low entropy). They are programmed by functional genetic instructions (FGIs), which flow through a biochemical communication pathway involving DNA – RNA- proteins, to instruct cells how to assemble into living organisms achieved by absorption of energy. All known life forms depend on having the correct FGIs maintained in their cells. Again, life at the molecular level is instructed to grow and reproduce while in organisms, thermodynamic governed FGI controls gene expression, thus maintaining the low entropy, homeostatic state necessary for organisms to survive and reproduce. This is possible because of the correct FGI and the amount of energy (metabolism) invested is less than the return and as such, the entropy of the organism decreases to allow reproduction, while the entropy of the environment increases.

Construction of first cells, and all subsequent species, were governed by the most fundamental of all laws—the laws of thermodynamics (Trevors and Saier, 2011). The laws of thermodynamics govern energy transformations and mass distributions. The transformation of energy and matter in living organisms occurs when FGIs are passed on to the offspring of the species. Remarkably, at molecular level, the biosphere among other things is an immense biochemical gene factory containing enormous amounts of genetic instructions operating under the laws of thermodynamics.

FGIs can resist some attacks by viruses, chemicals and physical agents such as UV light, but when the attack is successful, the genome can be damaged beyond repair and as a consequence, if the FGI is permanently damaged, it is difficult to halt progression of the disease and death of the organism (Trevors and Saier, 2011). Ilo, (2022) observed that pathogenic agents and genomes are in a kind of thermodynamic onslaught and counter onslaught. Species have the correct amount of FGI to wage the challenge against entropy and if the organism is damaged or injured or the FGI are damaged by a virus, bacteriophage, mutagen, radiation, chemicals heat and cold, the challenge can be lost. If the damage passes a certain threshold and repair is not possible, the outcome is usually death of the organism. As natural selection is brutal and painful, it was asserted that the strict relationship between the most fundamental of all laws, thermodynamics, and FGI in organisms, emerges as central to knowledge and understanding of organisms, evolution and diseases (Trevors and Saier, 2011).

Mass action term and the infectivity parameter in viral dynamics

Lymphocytes can bind to cells that have surface antigens in immunology; collaboration between specific antigen-recognizing and antigen-binding cells is often required for the initiation of immune responses, (Bell, 1978; Greaves *et. al*.,1974). In multicellular organisms, the social behaviour of cell is affected significantly by contacts with other cells or with biological substrata such as collagen (Bell, 1978). Adhesion of such specificity as to suggest mediation by specific receptor molecules on the cells, there are some definite information about the receptors that are involved in the contacts.

The parameters in mass action term of both uncontrolled and controlled HIV dynamics have been identified to progress and regress infection respectively. Infection and treatment (infection depletion or control) are felt on the mass action term of every viral dynamic. Note that infectivity is the characteristics of a disease agent or parasite that embodies capability of entering or adhering to cell, surviving in, colonizing it and multiplying or replicating in a susceptible host or simply put, is the ability of pathogen to establish an infection by overcoming host reconnaissance. Several lines of evidence observe that leucocyte adhesion molecules promote HIV-1 mediated cell fusion and syncytium formation for HIV infectivity (Berman and Nakamura, 1994; Ilo, Omenyi and Dim, 2021a). Liao, Roos and Hildreth, (2000); Ilo, Omenyi and Ani, (2021b) observes that adhesion molecules can have profound effects on virus infectivity and its resistance to neutralisation by antiviral antibodies.

Hill, *et al* (2018) observed that the dynamics of HIV are intricately connected to the population dynamics of lymphocytes. This is because lymphocytes act as prey and predators of the virus. Bonhoeffer, *et al* (1997) on their own said that measurement of changes in plasma virus during therapy should ideally be completed by quantification of infected cells in the tissue containing most of the virus population (the lymph system for HIV and the liver for HBV). Infected cells abundance in those tissues before and at therapy should provide a more direct turnover rate assessment. This abundance may provide estimate of further parameters of virus dynamics like the rate of infection of new cells β, and the rate of virus production from infected cells k, they further stated. From immunology of HIV infection target cells are assumed to be infected by free virus according to a simple mass action infection term βxv. In the same way, because of mass action reaction term, each infected T cell is also assumed to produce N viral particles over their lifespan. Conclusively therefore, infection of target cells by free virus and production of viral particles by infected T cells are made possible by the infectivity parameter β in the simple mass action (infection) term.

Various researchers have come up with various infectivity values. This wide range of historical HIV infectivity values as recorded by Ilo, (2022) were used in the formulation of HAART. This value is within the range of $5.0 \times 10^{-10} \leq \beta \leq 1$ $\left({}^{mL}/_{copies.d}\right)$. This range were all obtained through mathematical approach and fitting of data. Out of all, no thermodynamic approach was used to obtain the range hence the need for this work.

Viral dynamics models in HIV/blood interaction

Using the basic model in its unique labelling of terms, Bonhoeffer *et al*., (1997) in line with HIV immunology gave equation (1)

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

They also maintained that the basic reproduction number R_0 defined as average number of newly infected cells produced from any one infected cell if most cells are uninfected $(x = {}^{\lambda}/_{d})$ is expressed as

$$R_0 = \frac{\lambda\beta k}{dau} \qquad (2)$$

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 probability of infection, termed by various researchers as adhesion coefficient, mass action parameter, probability of infection, infection rate, infection rate constant, a is death rate of infected cells, k is rate of virus production and u is clearance rate of virus particles.

At transcriptional bifurcation, $R_0 = 1$, therefore equation (3) is obtained thus,

$$\frac{\lambda\beta k}{dau} = 1 \qquad (3)$$

HIV dynamics and immune response compromise

Fig. 1, 2, 3 & 4 shows a typical HIV infection course. It has three (3) main stages, namely the acute HIV infection (Primary infection), asymptomatic and the advanced – AIDS. Immediately after exposure to HIV, what follows is a period of rapid viral replication. A range of 80 to 90 percent of persons with primary HIV infection develop an acute syndrome characterized by flu-like symptoms of malaria, pharyngitis and sometimes rash. Seroconversion occurs following primary infection. When one develops antibodies to HIV, he seroconverts from antibody-negative to antibody-positive. Antibodies to the virus may develop from as little as one week to several months or more after infection with HIV. As clearly seen in fig 3 & 4, one should test positive on antibody test after antibodies to HIV appear in the blood, (ATIS, 2002). Secondly as the name implies this stage means without symptoms. This period of infection is also known as the clinical latency period. One with HIV infection does not exhibit any evidence of disease or any clinically noticeable ill effects, even though HIV is continuously infecting new cells and actively replicating. During the asymptomatic period, HIV is active within lymphoid organs where large amounts of virus become trapped in the follicular dendritic cell network, (ATIS, 2002). Thirdly and finally, most severe stage is here and it is synonymous with AIDS. The virus eventually gets out of control and the remaining immune cells are destroyed after a normally long period. It could be identified by documentation of an AIDS-defining condition or by $CD4^+$ T cell count below 200 cells per µL (mm^{-3}) (<14% of lymphocytes) (Nettleman and David, 2021). Here, patients become vulnerable to opportunistic infections because immune system is badly damaged.

One can battle AIDS without treatment for about three years. Life expectancy drops to about a year with someone who has dangerous opportunistic infection.

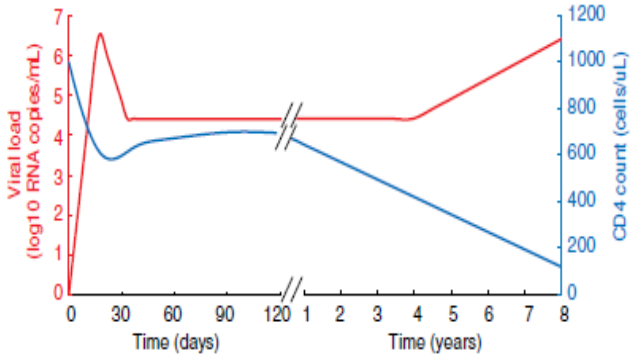

Figure 1: Approximate Time-Course with CD4 Count and Viral Load Estimates (Hill et al, 2018)

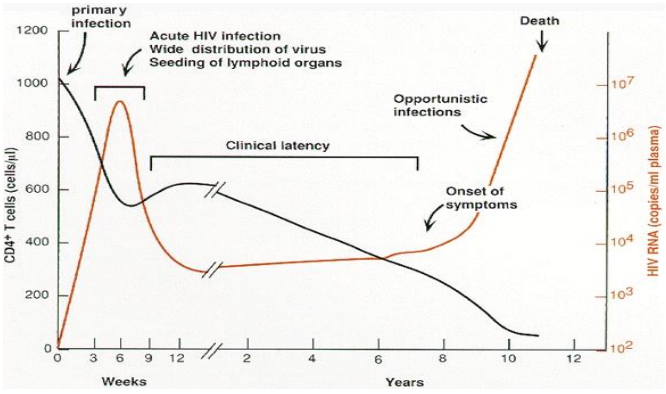

Figure 2: Approximate Time-Course of HIV Infection. (Pantaleo, Graziosi and Fauci, 1993)

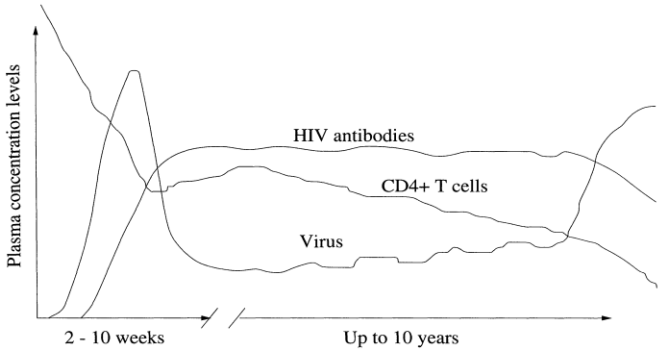

Figure 3: Approximate Time-Course of HIV Infection, (Witten and Perelson, 2004; Perelson and Nelson, 1999).

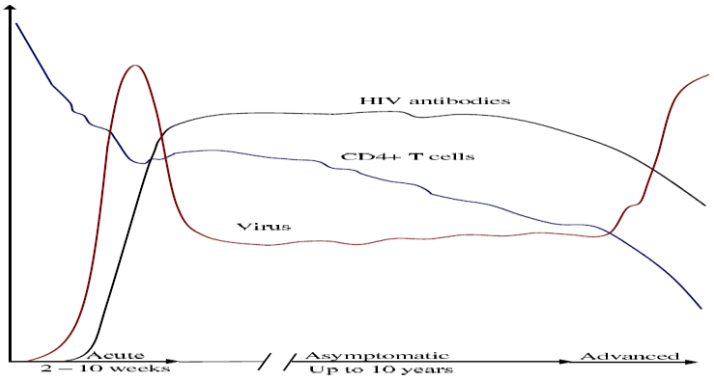

Figure 4: Approximate Time-Course of HIV Infection, (Jeffrey, 2006; Hunt, 2005).

Normal $CD4^+$ T cell counts range from five hundred (500) to one thousand six hundred (1600) cells per cubic micro liter hence from the figures above, it is evident that $CD4^+$ T cell counts drops to less than hundred (500) cells per μL (mm^{-3}) if infection is fully established.

Transcriptional bifurcation Infectivity

Recent technological advancements have enabled the profiling of a large number of genome-wide features in individual cells (Amezquita et al 2019). Again recently, attention has turned to modeling bifurcations where, part-way along such trajectories, cells undergo some fate decision and branch into two or more distinct cell types (Campbell and Yau 2017). For a bifurcation in genetic expression what is required is some genes that show differential expression between the branches and some that show concordant expression - lacking the former would give a non-branching trajectory and lacking the latter would give separate cell types. General transcription factors are proteins that help to position Pol II correctly on the promoter, the region of a gene where transcription is initiated, pull aside the two strands of DNA and then move Pol II into the elongation mode. Essentially, the key transcription levels include the recruitment and assembly of the entire transcription machinery, the initiation step, pause release and elongation phases, as well as termination of transcription. A promoter is a region of DNA where RNA polymerase binds to initiate transcription. A terminator is a sequence of DNA that causes RNA polymerase to terminate transcription. A transcription unit is the sequence between sites of initiation and termination by RNA polymerase; may include more than one gene.

Liu, et al (2023) asserted that the bifurcation theory can help study the parameter stability of dynamic nonlinear systems. Hidde, (2002) also asserted that studying gene regulatory networks can help understand genes' interactions and regulatory mechanisms as well as help realize the overall understanding of gene function, which is of great significance for the research on finding and identifying human pathogenic factors. Biological applications of bifurcation theory provide a framework for understanding the behaviour of biological networks modeled as dynamical systems. In the context of a biological system, bifurcation theory describes how small changes in an input parameter can cause a bifurcation or qualitative change in the behaviour of the system. The ability to make dramatic change in system output is often essential to organism function, and bifurcations are therefore ubiquitous in biological networks such as the switches of the cell cycle. Biological networks originate from evolution and therefore have less standardized components and potentially more complex interactions than networks designed by humans, such as electrical networks. At the cellular level, components of a network can include a large variety of proteins, many of which differ between organisms. Network interactions occur when one or more proteins affect the function of another through transcription, translation, translocation, phosphorylation, or other mechanisms. These interactions either activate or inhibit the action of the target protein in some way. While humans build networks with a concern for simplicity and order, biological networks acquire redundancy and complexity over the course of evolution. Therefore, it can be impossible to predict the quantitative behaviour of a biological network from knowledge of its organization. Similarly, it is impossible to describe its organization purely from its behaviour, though behaviour can indicate the presence of certain network motifs (a distinctive sequence on a protein DNA having a three-dimensional structure that allows binding interactions to occur).

Thermodynamic Viral Dynamics Model, Genetic resistance factor and variation of infectivity in HIV infection

Ilo, (2022), and Anacleto *et al.*, (2019) had established that infectivity is a function of resistance due to genetic factor ε and the strength of adhesion to the susceptible cell by the infectious agent (the infection driving factor) Ω.

$$\beta = \int(\varepsilon\Omega) \qquad (4)$$

In other words, the infection (fusion) of a HIV particle to a lymphocyte is enabled or driven by adhesion of HIV unto CD4 receptor. The implication is that disease progression which is susceptible to HIV is respectively inhibited by the resistance due to genetic factor. This means that infectivity at dynamic condition, which is the area of interest of this work, is a function of infection driving factor (adhesion coefficient) and genetic factor. Recall (Chazal, et. al., 2014) in the result of their work on loss of infectivity of HIV-1 particles which showed that infectivity rate at static condition is about 10 times the ideal situation and that blood in the circulatory system is in constant motion.

Ilo, (2022) had expressed that HIV infectivity as a multiple of resistance due to genetic factor ε and the disease driving factor Ω hence equation (5).

$$\beta = \varepsilon\left(\frac{\psi(\gamma_{PS})}{\gamma_{PL}+\gamma_{SL}}\right) \qquad (5)$$

Where terms in equation (5) could further be evaluated approximately as,

$$\gamma_{PS} \cong \sqrt{\gamma_P \gamma_S} \quad (6)$$

$$\gamma_{PL} \cong \sqrt{\gamma_P \gamma_L} \quad (7)$$

$$\gamma_{SL} \cong \sqrt{\gamma_S \gamma_L} \quad (8)$$

γ_P is the surface free energy of HIV (infected lymphocytes),

γ_S is the surface free energy of lymphocytes (uninfected lymphocytes),

γ_L is the surface free energy of serum (infected).

ψ being equal to 0.1 according to Chazal, *et al.* (2014).

Geometric mean value expression of equation (6) to equation (8) was applied to get the interfacial free energies γ_{PS}, γ_{PL} and γ_{SL}.

Ilo (2022) had incorporated thermodynamic expressed infectivity (adhesion coefficient) model that took care of interfacial energetics involved in HIV infectivity to obtain

$$\begin{aligned} \dot{x} &= \lambda - dx - \varepsilon\left(\frac{\psi(\gamma_{PS})}{\gamma_{PL}+\gamma_{SL}}\right)xv, \\ \dot{y} &= \varepsilon\left(\frac{\psi(\gamma_{PS})}{\gamma_{PL}+\gamma_{SL}}\right)xv - ay, \\ \dot{v} &= ky - uv. \end{aligned} \quad (9)$$

For the lower limit of the infectivity range which serves as the value below which the disease progression becomes curative, basic reproductive number R_0 is expressed as,

$$R_0 = \frac{\lambda\beta k}{dau} \quad (2)$$

But at transcriptional bifurcation (branching into distinct cell type), $R_0 = 1$, also Ilo, (2022) had expressed infectivity as $\beta = \varepsilon\left(\frac{\psi(\gamma_{PS})}{\gamma_{PL}+\gamma_{SL}}\right)$ consequently, the thermodynamic transcriptional bifurcation genetic resistance factor (genome) ε_{TB} equation (10) is expressed thus,

$$\varepsilon_{TB} = \frac{dau}{\lambda\left(\frac{\psi(\gamma_{PS})}{\gamma_{PL}+\gamma_{SL}}\right)k} \quad (10)$$

Therefore, thermodynamic transcriptional bifurcation infectivity β_{TB} which is the infectivity value below which all infectivity values are control infectivity is quantified using the value of ε_{TB} obtained from equation (10) as,

$$\beta_{TB} = \varepsilon_{TB}\left(\frac{\psi(\gamma_{PS})}{\gamma_{PL}+\gamma_{SL}}\right) \quad (11)$$

It served as the lower limit of thermodynamically determined infectivity range. The upper limit is determined from a careful analysis of the simulated infection dynamics bearing in mind the dynamics revealed as reality in the literature as actual where value of uninfected cell is not zero within few days.

Recent works on HIV eradication using thermodynamic Interfacial energetics

Ani, Achebe and Omenyi, (2013), through spectrophotometric measurements of absorbance data established that there is a decrease in the absorbance values of all the infected blood components (red blood cells, white blood cells and the plasma). This marks a major role of HIV on blood components and such could provide an insight to any approach to solving the problem.

Using spectrophotometry again, Ani, Ani and Chukwuneke, (2015a) showed that antiretroviral drugs have the effect of increasing the peak absorbance values of both the infected and uninfected components of blood which by implication increased the light absorption capacity of the blood cells, a revelation expected to yield good result in drug optimization and improvement.

In the Study of role of attractive van der Waals forces in the interactions between the antiretroviral drugs and blood components, Ani, Chime and Wadzani, (2016a) stated that mechanism of action of antiretroviral drugs on uninfected blood is made possible by attractive van der Waals forces. The positive sense of the absolute values for the combined Hamaker coefficient A_{131abs} for each of the five antiretroviral drugs interacting with uninfected blood samples given as D1=0.36760*10^{-21} Joule, D2=0.46337*10^{-21} Joule, D3=0.53021*10^{-21} Joule, D4=0.50971*10^{-21} Joule and D5=0.49599*10^{-21} Joule which is an indication of net positive van der Waals forces. This signifies attraction between the antiretroviral drugs and lymphocytes and gives impetus to study further the HIV challenge from the attractive van der Waals – repulsive electrostatic forces mechanism.

Ani, Omenyi and Achebe, (2015b) used absorbance data in MATLAB software tool to establish absolute values of combined Hamaker coefficients for each drug. The positive sense of the Hamaker coefficients for the virus interacting with blood samples not coated with the drugs indicated the vulnerability of the lymphocytes.

Ani, Omenyi and Achebe, (2015c); Ani, Wadzani, Ujam, Ejiofor, Mbonu (2016b) used absorbance data of the interacting systems obtained from a digital spectrometer in a MATLAB software tool to establish that absolute vales for the combined Hamaker coefficients, A_{132abs} obtained for each of the five drugs interacting with infected lymphocytes varied from a negative sense of -0.2481*10^{-21} Joule for drug 4 to -0.05845*10^{-21} Joule for drug 3, implying a net negative van der Waals forces which indicates a possible repulsion or blocking of the invading virus by the administered drug which is assumed to coat the lymphocyte, thereby possibly resulting to reduction of viral load and increase of CD4 counts.

After measuring the peak absorbance data for blood (infected with and without ARV and uninfected) and drug interaction, Ani, Omenyi and Achebe, (2015d) showed that antiretroviral drug has the effect of increasing the peak absorbance values of both the infected and uninfected blood components.

Ani, Omenyi and Achebe, (2015e) in their work observed that with absorbance data of ARV and uninfected blood, the surface properties of a blood component can be significantly changed and that some coating (which could prevent interaction) had really occurred on the surfaces of lymphocytes.

Furthermore, Ani, Omenyi and Nwigbo, (2015f), in their research which assert that their findings suggest a thermodynamic criterion for HIV-blood-drug interaction prediction, confirm the existence of some relationship between drug coating of surface of blood cell and the cell surface free energy by observing that the drug 1 which has highest coating effectiveness also has the highest surface free energy (47.5MJ/m^2).

Ani, (2015g) in his PhD work recorded successes in quantifying interfacial energies of HIV/blood interaction. To unravel the mystery of transcriptional bifurcation in HIV dynamics Ilo, (2024a) had developed a validated model through concepts of thermodynamics implementation. Ilo, (2024b) had also established HIV adhesion driven infectivity through electrostatics interaction mechanism.

3. METHODOLOGY

This study involves the determination of viral infectivity range in HIV-blood interactions. The methodology involved solving the proposed thermodynamic model by (Ilo, 2022) for condition of lower infectivity range as well as the upper infectivity range. The solution approach was implementation of the model in MATLAB™ function ode 23 that makes use of an explicit Runge-Kutta formula by numerical integration of the proposed viral dynamics. Historical experimental data for the simulation of the infection time course were those of HIV/blood interaction energetics obtained as published by (Ani, 2015 g) and Ani, *et al* (2015f). Primarily, the method comprises quantifying the thermodynamic expressed transcriptional bifurcation infectivity model and validating it from extensive simulations of solution of the thermodynamic expressed HIV dynamic model for expected infection dynamics infectivity range. All approaches in the method are just to establish range through solutions of the proposed HIV dynamics thermodynamic model via over ninety (90) simulations of the infection time courses of the associated genetic resistance. The thermodynamic actual infectivity range is obtained by determining the infection time course that is obtainable in reality based on the provisions by the literature for the upper range while for the lower range, the transcriptional bifurcation infectivity is validated from the simulation as a transitional value between disease progression and control. The established thermodynamic infectivity range is validated with the historical infectivity range as its proper sub set.

4. RESULTS AND DISCUSSIONS

Thermodynamic Transcriptional Bifurcation Infectivity Value

Thermodynamic Transcriptional Bifurcation Infectivity β_{TB} is found to be $1 * 10^{-4}$ $(mL/copies/d)$. This value shows clearly in the simulated dynamics a bifurcation dynamic where the disease dynamics changed progression to being curative and having a basic reproduction number of less than one.

Figures 5 to 16 below are results of infection dynamics simulations within thermodynamic infectivity range. The figures shows actual infection time course for uninfected cell $(x)\left({cells}/{\mu L}\right)$, infected cell $(y)\left({cells}/{\mu L}\right)$ and viral load $(v)\left({copies}/{mL}\right)$ time-course of uncontrolled infection dynamics that is simulated with thermodynamically quantified infectivity. They are situations that can be actually obtained in reality where the CD4 count is usually between greater than zero and less than five hundred cells per micro litre $500\left({cells}/{\mu L}\right)$. The uninfected cell count is usually a yardstick for the disease progression assessment. Figure 16 marks the range lower limit. It is the point or transitory stage at which all disease progression changes to curative while figure 5 shows the dynamics of disease progression in the upper limit where the uninfected count value as a yard stick of disease progression measure is expected in reality not to be approximately equal to zero.

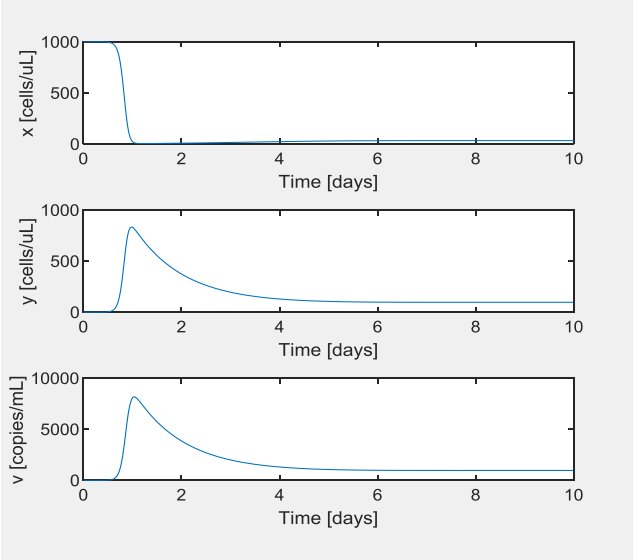

Figure 5: Simulation with Infectivity value of $3 * 10^{-3}\left({\mathbf{mL}}/{\mathbf{copies.d}}\right)$.

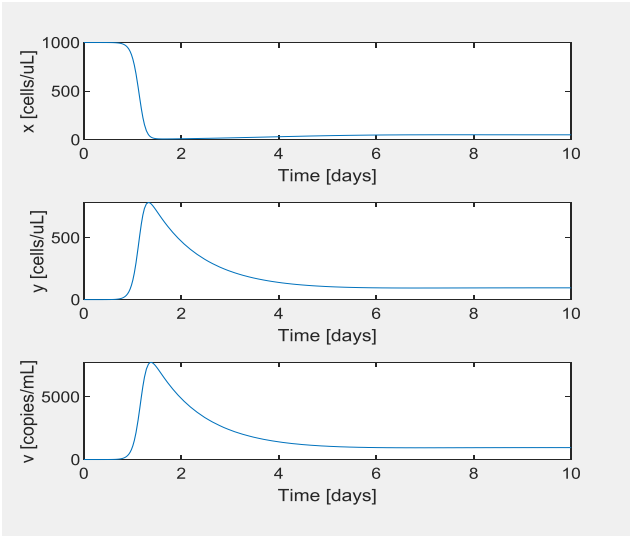

Figure 6: Simulation with Infectivity value of $2 * 10^{-3}\left({\mathbf{mL}}/{\mathbf{copies.d}}\right)$.

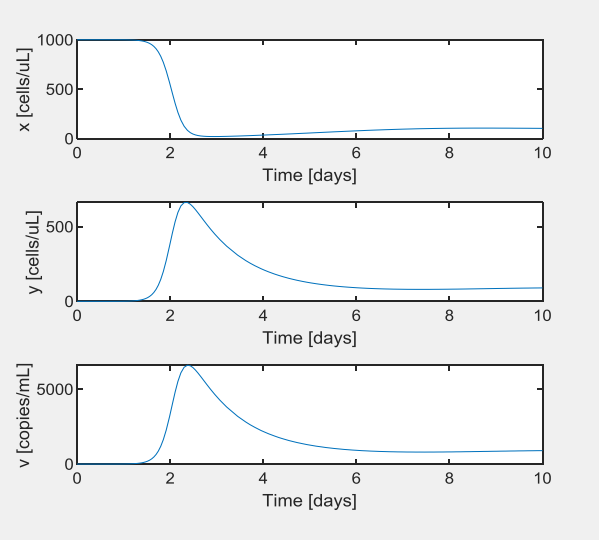

Figure 7: Simulation with Infectivity value of $1 * 10^{-3}$ $\left(mL/_{copies.d}\right)$.

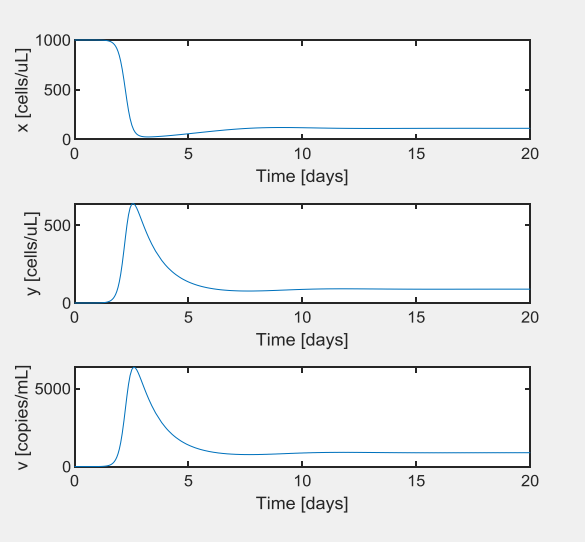

Figure 8: Simulation with Infectivity value of $9 * 10^{-4}$ $\left(mL/_{copies.d}\right)$.

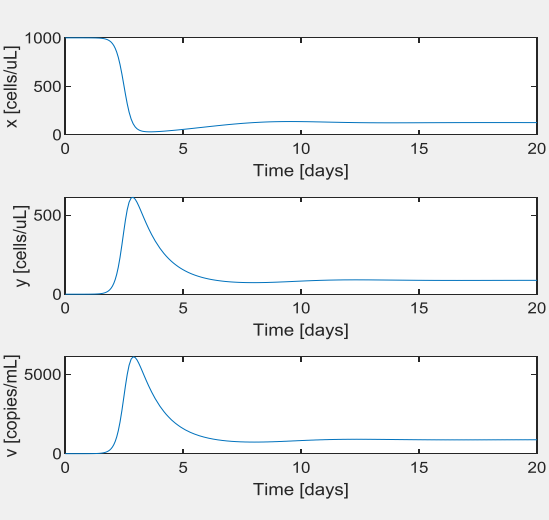

Figure 9: Simulation with Infectivity value of $8 * 10^{-4}$ $\left(mL/_{copies.d}\right)$.

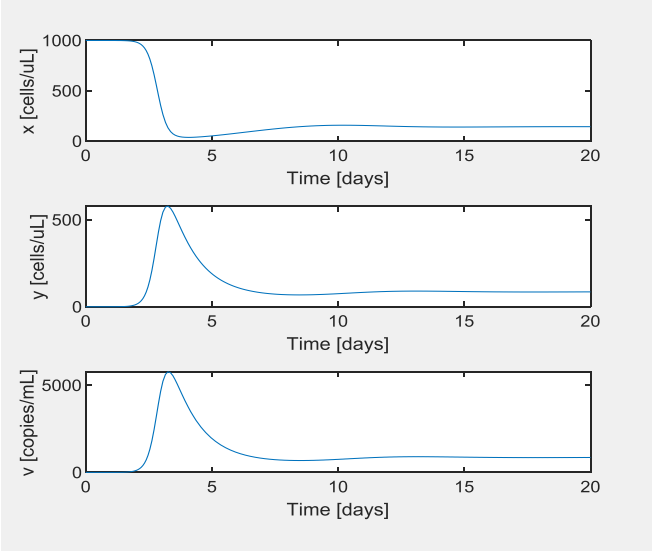

Figure 10: Simulation with Infectivity value of $7 * 10^{-4}$ $\left({}^{mL}/_{copies.d}\right)$.

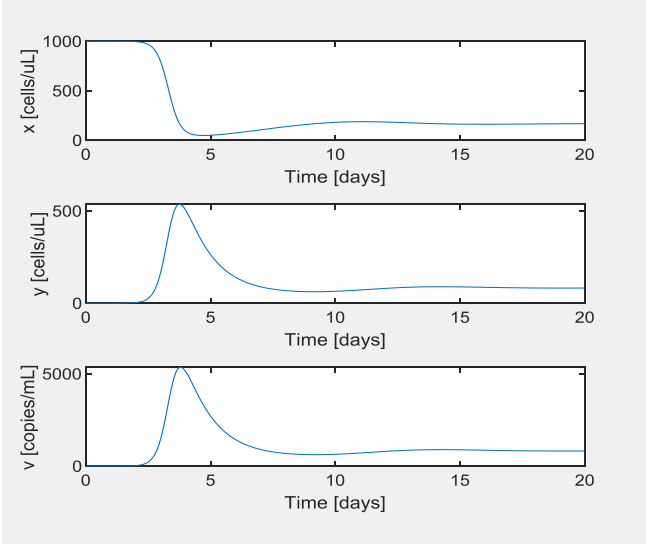

Figure 11: Simulation with Infectivity value of $6 * 10^{-4}$ $\left({}^{mL}/_{copies.d}\right)$.

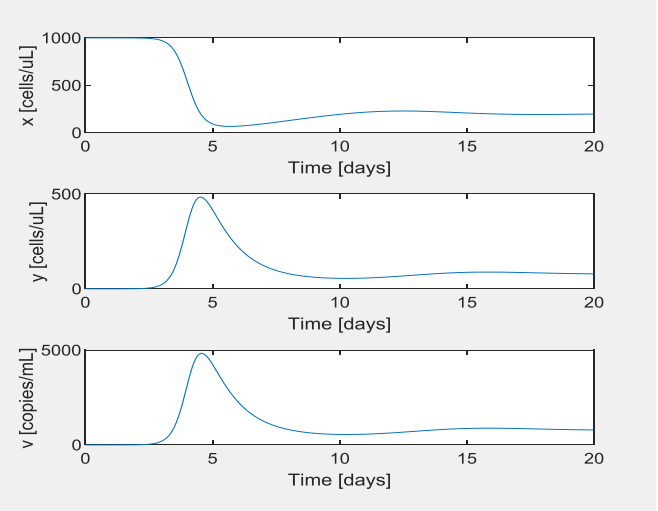

Figure 12: Simulation with Infectivity value of $5 * 10^{-4}$ $\left({}^{mL}/_{copies.d}\right)$.

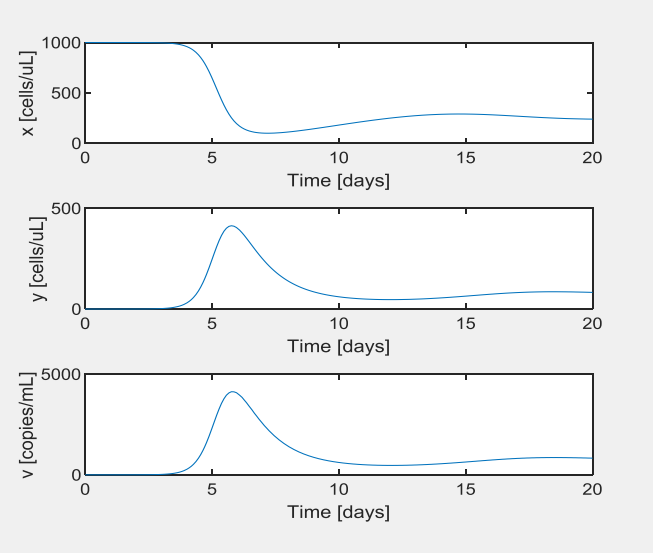

Figure 13: Simulation with Infectivity value of $4 * 10^{-4}$ $\left({}^{mL}/_{copies.d}\right)$.

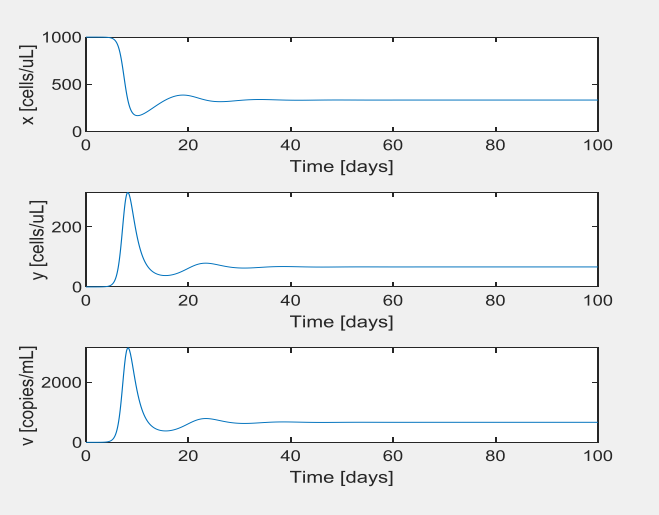

Figure 14: Simulation with Infectivity value of $3 * 10^{-4}$ $\left({}^{mL}/_{copies.d}\right)$.

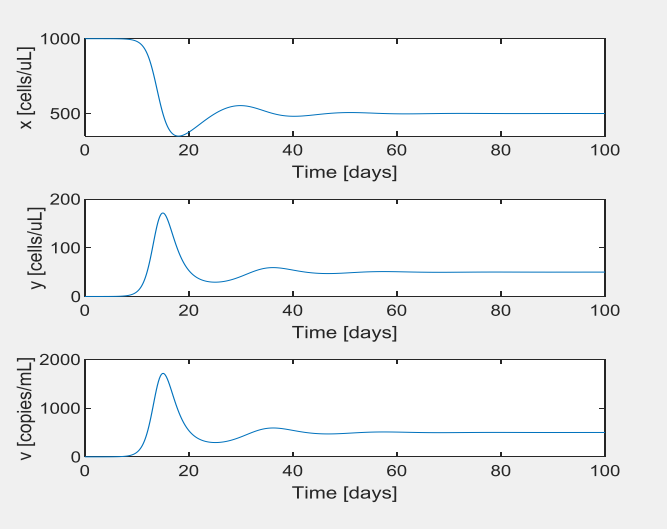

Figure 15: Simulation with Infectivity value of $2 * 10^{-4}$ $\left({}^{mL}/_{copies.d}\right)$.

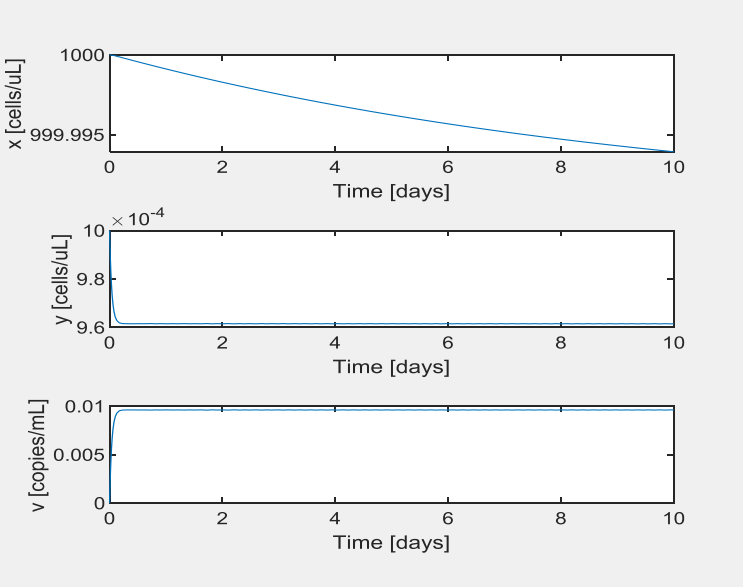

Figure 16: Simulation with Infectivity value of $1 * 10^{-4}\left({}^{mL}/_{copies.d}\right)$, Transcription Bifurcation Infectivity.

5. CONCLUSION AND RECOMMENDATIONS

Thermodynamic infectivity range of $1 * 10^{-4}\left({}^{mL}/_{copies.d}\right)$ to $3 * 10^{-3}\left({}^{mL}/_{copies.d}\right)$ is established as a proper sub set of historical HIV infectivity range. The result is established through interfacial free energy concept. With the thermodynamic expressed infectivity expression in the basic reproductive number expression, thermodynamic transcriptional bifurcation infectivity was found to be $1 * 10^{-4}$ $(mL/copies/d)$. This, informed by the literature for reality, led to the establishment of the thermodynamic infectivity range through several simulations with HIV thermodynamic model as $1 * 10^{-4}\left({}^{mL}/_{copies.d}\right)$ to $3 * 10^{-3}\left({}^{mL}/_{copies.d}\right)$. This conforms to the expectation of being within the historical infectivity range.

A very essential thermodynamic transcriptional bifurcation infectivity quantified is expected to play a very important role in the formulation of drug regimen for critical transition of HIV infectivity values from uncontrolled to a drug controlled one. Since a thermodynamic HIV infectivity range has been established, individuals' infectivity value with physical meaning should be determined by this novel thermodynamic approach to forestall any possible clinical failure that may arise as a result of infectivity variability. Additive material profiling from thermodynamics interfacial energetics is paramount in further studies.

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