**Original Research Article**

**Bioenergetics perspective on any viral replication and clearance extrapolated to SARS–CoV–2–orchestrated pathophysiology**

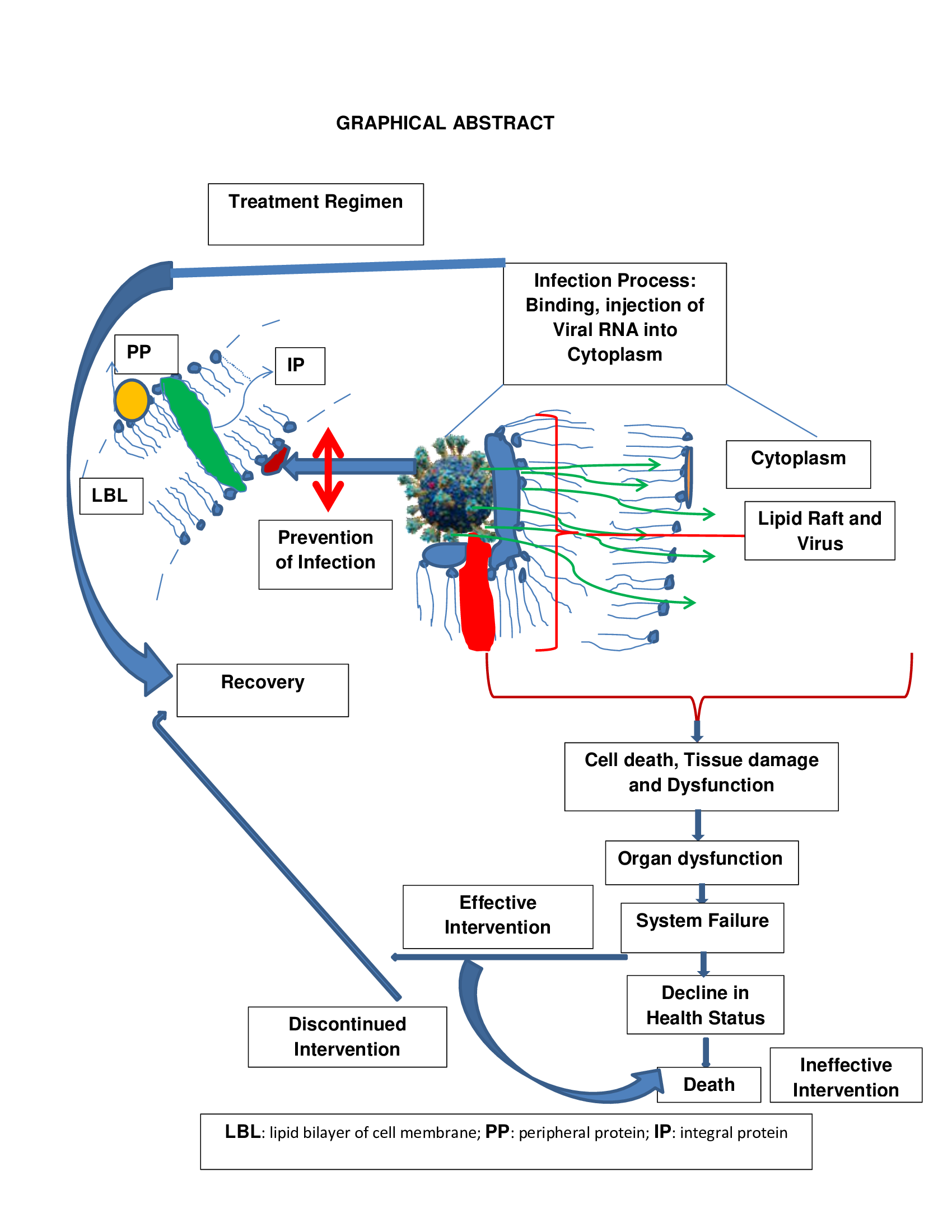
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ABSTRACT

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| Kinetic and thermodynamic parameters for viral replication and depletion were given less attention in the literature. The activation energies of viral replication, clearance, and cell death were higher at earlier than later times. The values of dimensionless equilibrium constant () for viral replication (0.000045-0.003681) in Nef-positive HSC-F cells were greater than for Nef-negative HSC-F cells (0.000003-0.000353); those for viral depletion were generally higher (0.000004-0.004539). The magnitude of values diminished with time. The free energies (s) of replication and depletion in the cells were greater for negative (20.50-32.990 kJ/mol) than for positive cells (14.450-25.810 kJ/mol); the activation energies () of replication (116.7-135.1 kJ/mol) and cell death (125.5-137.8 kJ/mol) for negative cells were greater than those (117.8-129.2 kJ/mol & 119.5-130.9 kJ/mol, respectively) for positive cells. The free energies of activation () of viral replication and cell death were 103.35 and 105.08 kJ/mol, respectively, and 102.30 and 104.99 kJ/mol, respectively, for positive and negative cells, respectively; the value of ‘ of viral depletion was 105.234 kJ/mol. The for virus depletion and replication, was calculated using data reported for Nef—positive and —negative HSC—F cells in the literature. Extrapolating the result in this study to SARS-CoV-2, calls for weakly evaluation of therapeutic interventions. Since dimensionless equilibrium constant values of viral replication, depletion, and concomitant cell death are higher earlier than latter, it is diagnostically and therapeutically wise to adopt early interventions. These should lower the dimensionless equilibrium constant values and heighten the free energy and activation energy of viral replication and cell death with appropriate medications. The same parameters for viral depletion or clearance are expected to be heightened, more feasible with lower energy barriers. Future studies, *in vivo* and *in vitro*, calls for weekly evaluation possibly at different temperatures. |

***Keywords:***Nef HSC-F Cells; SARS-CoV-2; unitless equilibrium constant; Gibbs free energy of replication; Eyring model of Gibbs free energy of activation; Copeland model of activation energy; first-order rate constant.

**PIC 1. GRAPHICAL ABSTRACT**

**1.0 INTRODUCTION**

The quantitative characteristics of virus multiplication, depletion, and cell death have been studied in vitro (Iwami *et al*., 2012). In order to create time courses that follow the dynamics of viruses and target cells in experiments, it is necessary to investigate the quantitative aspects of virus reproduction. Iwami *et al*. (2012) cited the literature to support the necessity of breaking down and quantifying the kinetics of virus infection, which may involve numerical simulation of the experimental data, mathematical modeling, and mathematical analysis. Several characteristics that underlie the kinetics of virus infection, such as the burst size and the fundamental reproductive number, can be approximated by mathematically modeling the entire time courses (Iwami *et al*., 2012). The basis for this investigation is the observed studies on the decline in viral clearance half-life (Horby *et al*., 2021; Weinreich *et al*., 2021; Jayk *et al*., 2022; Watson *et al*., 2022; & Wongnak *et al*., 2024). This study discusses the Copeland model of activation energy of viral replication, depletion (clearance), and cell death, as well as Gibbs free energy. It implies that models addressing the critical issue of the thermodynamics of viral replication and concurrent death of susceptible cells must be developed. Weekly studies on the decline in viral clearance half-life are therefore, necessary.

Despite the advantages of inflammatory responses, a viral infection-induced storm of inflammation can result in diabetes, autoimmune disorders, cancer, cardiovascular disease, and other conditions. These are partially the result of tissue damage, malfunction, and cell death. The result is a decrease in health, system failure, organ dysfunction, and eventually death. In fact, any disease that impairs respiratory system function also dangerously jeopardizes the body's supply of metabolites and fuel molecules for regular bodily functions. Either an ineffective or stopped intervention is to blame for these results. Pharmaceutical and non-pharmaceutical treatments that are used in the early stages of an intervention can stop an infection from spreading. A successful intervention can stop the infection from spreading further.

Thermodynamic and activation energy questions, which could therefore highlight the energetics perspective on any viral replication and clearance extrapolated to SARS–CoV–2-orchestrated pathophysiology, cannot be avoided by the development and enhancement of drugs that require ongoing research. Since the energetics of viral replication and clearance receive less attention, the aim of this project is to demonstrate why medication and vaccine development, viral replication, clearance, and cell death all require an energetics background. The objectives of this study are as follows: Investigate derived equations in the literature for the calculation of dimensionless equilibrium constants for the biosynthesis of metabolic intermediates relevant to the biosynthesis of cholesterol, transcription factors, etc., as well as for viral replication, clearance, and cell death; calculate free and activation energies related to binding in general, viral replication, clearance, and cell death; and explain how thermodynamics (free energies) and activation energy can motivate the manufacturing and enhancement of drugs in general.

**2.0 EXPERIMENTAL**

Bits of information and data in the literature were explored for the evaluation of the equations from which dimensionless equilibrium constant values for viral replication, depletion, and cell death were generated; those values were explored for the computation thermodynamic and Copeland model-based activation energies. The relevant equations are shown in method section.

**2.1 Methods**

**2.1.1 The dimensionless equilibrium constant for infectivity, viral replication, and cell death**

, (1)

The symbols, *Nv*, *NLR*, *kv*, *kLR*, and τ stand for number density of the virus, number density of lipid raft (there may be more than one lipid raft per cell membrane or cell); it is also used as the number density of the cells, first-order rate constant of viral replication, first-order rate constant for cell death, and duration of events-the replication of virus and death of cells; *LR* and *v* denote lipid raft and virus respectively.

**2.1.2 The free energy component for infectivity**

, (2)

The Eyring version of activation energy that is Gibbs free energy of activation is given as:

(3)

where *k*+1 represents either *kv* or *kLR*.

**2.1.3 Copeland's (2002) model equation for activation energy**

, (4)

**3.0 RESULTS AND DISCUSSION**

**3.1 The thermodynamics of viral replication and concurrent death of susceptible cells**

The thermodynamics of viral replication in terms of higher number of copies per day, viral depletion and cell death are herein given attention. However, the velocity of the production of viral RNA copies (the number of copies per day) may not be the same as the rate constant for viral RNA production. This comment is analogous to the velocity of hydrolysis as opposed to the first-order constant for the same action. Different days present different rates of production of viral RNA copies. This is shown in the literature (Iwami *et al*., 2012). However, it is not very certain the authors meant rate constant. Besides, they stated the unit of the rate constant for infection (β) as (RNA/ml day) −1. The reciprocal of it is RNA copies/ ml. day, even if the value of β was 8.61 e. (−11). This implies that the value should be stated as 8.61 e. (−11) (RNA/ml · day)−1. This seeming ambiguity is unlike the units of viral production rate and death rate of susceptible cells, which are, respectively, 3.24 e. (4) RNA copies/day and 1.75/day. Nonetheless, it is uncertain whether the different susceptible cells possess the same rate of death. In other to address this challenge, graphical approaches were explored for the determination of death rate constants rather than velocities. Since viral particles replicate in a host cell, the death of cells that follows are contemporary events: The fact that the host genetic material is hijacked is synonymous to cell death. Figures 1 and 2 present the plots showing death rate constant () 1.1609 and 1.1241/day for Nef-negative HSC-F Cells and Nef-positive HSC-F Cells respectively. These values are, however, less than 1.75 /day (Iwami *et al*., 2012), which seemed to be arbitrarily chosen (although it was reported as an estimate) for, perhaps, convenience's sake. This research sees it differently because the cells are different *ab initio*.

**Figure 1: Death rate constant of Nef-negative HSC-F Cells (Nef-neg-HSC-F-Cells)**

**by a plot of In(*Nc*(*τ*=0)/*Nc*(τ=*i*)) versus the time, τ in days where *i* is any time ≪ ∞.** Enabling data are from Iwami *et al.*(2012).

**Figure 2: Death rate constant of Nef-positive HSC-F Cells (Nef-pos-HSC-F-cells)**

**by a plot of In(*Nc*(τ=0)/*Nc*(τ=*i*)) versus the time, τ in days where *i* is any time ≪ ∞.** Reference is as stated earlier.

There was a need to also determine graphically the rate constant for viral replication. Figures 3 and 4 show that, the rate constants for the replication of the virus are 2.5192 and 2.1957/day for Nef-negative HSC-F Cells and Nef-positive HSC-F Cells respectively.

**Figure 3: Rate constant for the replication of virus applied to Nef-NEGATIVE HSC-F CELLS (Nef-neg-HSC-F-Cells).** The original data are as in previous reference.

**Figure 4: Rate constant for the replication of virus applied to   
Nef-POSITIVE HSC-F CELLS (Nef-pos-HSC-F-Cells).** The original data are as in previous reference.

As illustrated in Figure 5, the first-order rate constant must be graphically established in order to calculate the activation energy for the virus's depletion based on Copeland's model. The negative natural log of the ratio of the original number of the virus at zero time to the viral number or density as time tends to infinity is plotted against time in days, just as it was previously.

**Figure 5: First-order rate constant for the depletion of the virus**

Drug design and associated research, field tests, and evaluation cannot be completed without consideration for thermodynamic and activation energy characterization being a basis for reevaluation and redesign so as to effectively halt viral replication and upscale viral clearance with new, improved medications. The researchers in question whose results deserve such characterization are as follows: Efforts are focused on ways to reduce the viral clearance half-life since it improves resistance to the pathophysiologic effects of SARS-CoV-2 infection that results in COVID-19. This necessitated long-term research, typically spanning two or more years. The median viral clearance half-lives, for example, decreased from an average of 16.5 in 2021 to 9.2 in 2023, a relative decrease of 44% in individuals not taking antiviral medication, according to estimations spanning seven days (Wongnak *et al*., 2024).

When patients were given ritonavir-boosted nirmatrelvir, the median viral clearance half-life decreased by 26%, from 6.4 hours in 2022 to 4.8 hours in 2023 (Wongnak *et al*., 2024). However, to calculate clearance rate constants as demonstrated in this study, these investigations must be conducted in various places at weekly intervals on a monthly basis in order to offer clearance rates on a daily basis. These findings suggest that, untreated infected persons harbored higher copies of viral particles even if there is an incidence of depletion due, perhaps, to host cell limited defense capability, whereas the treated patients had their viral particles degraded or depleted at the highest amount leading to lower median viral clearance half-life.

The pharmacometric assessment of potential antiviral medications created and manufactured to combat SARS-CoV-2 requires comparing the viral clearance and its rate in trial findings. In clinical studies, the time to viral clearance as measured by serial qPCR (quantitative polymerase chain reaction is a laboratory technique used to amplify and quantify specific DNA sequences in real-time) of nasopharyngeal swab samples is considered a credible biomarker of viral response; nevertheless, model-based estimations of the rate of viral clearance are required to compare data from different methodologies (Watson *et al*., 2022). Following an investigation of prospectively collected viral clearance profiles from 280 infection cases, it was demonstrated that a mixed-effects single exponential decay model provides a reliable pharmacodynamics summary of viral clearance (Watson *et al*., 2022). As stated earlier, these outcomes are subject to thermodynamic feasibility and activation energy studies so as to garner bits of information as to how best to enhance clearance through drug design improvement. But, first, there is a need to determine the dimensionless equilibrium constants, which, with free and activation energy data, can be extrapolated to the SARS-CoV-2 scenario.

The values of the dimensionless equilibrium constant, *Keq(δ)*, for viral replication and cell death for Nef-positive HSC-F and Nef-negative HSC-F cells exposed to the virus are shown in Tables 1 and 2, respectively. While the values of *Keq(δ)* for Nef-positive HSC-F are greater than those for Nef-negative HSC-F cells, both kinds of cells showed decreasing magnitude of the *Keq(δ)* values with time. This has therapeutic significance, as will be discussed shortly. Nonetheless, the immediate concern is that viral replication and cell death are more thermodynamically feasible for Nef-positive HSC-F than Nef-negative HSC-F cells.

In other words, Nef-positive HSC-F cells (Table 3) had higher virus pathogenicity than Nef-negative HSC-F cells (Table 4). Generally speaking, the processes have low feasibility or spontaneity since the free energy of viral multiplication and cell death are positive values. Taking advantage of this circumstance by creating medications that can encourage the decrease of *Keq(δ)* values not only at the micro-anatomical level, *i.e.*, the cellular and viral levels, but also at the enabling biochemical (metabolic) level is the proper preventive measure as opposed to a reactive one.

**Table 1: Dimensionless equilibrium constant, for viral replication and cell (Nef-positive HSC-F) dysfunction and death with time (τ)**

**τ** 5 6 7 8 9

**(days)**

**/e. (−3)** 3**.**6871.138 0.383 0.139 0.045

**Table 2: Dimensionless equilibrium constant, for viral replication and cell (Nef-negative HSC-F) dysfunction and death with time (τ).**

**τ** 1 2 3 4 5

**(days)**

**/e. (−3)** 0.3530.107 0.031 0.009 0.003

**Table 3: Dimensionless equilibrium constant, for viral depletion and cell (Nef-positive HSC-F) dysfunction and death with time (τ).**

**τ** 5 6 7 8 9

**(days)**

**/e. (−3)** 4.5391.226 0.393 0.013 0.004

The activation energies for viral replication are greater for Nef-negative HSC-F than for Nef-positive HSC-F cells; the converse is the case for cell death (Tables 4 and 5).

**Table 4: Gibbs free energy (Δ*G*) and** Copeland **model of activation energy of viral replication, and cell (Nef-positive HSC-F) dysfunction and death with time (τ).**

**τ** 5 6 7 8 9

**(days)**

**Δ*G*)/*e*. (4)** 1.4451.748 2.029 2.290 2.581

**(J/mol.)**

***Ea*(vr)/e.(5)** 1.178 1.208 1.236 1.262 1.292

**(J/mol.)**

***Ea*(cd)/e.(5)** 1.195 1.226 1.254 1.280 1.309

**(J/mol.)**

The lower case alphabet, ‘*e’* stands for exponent.The temperature was 310.15 k. Eyring free energy of activation () = 103.348 kJ/mol. (for viral replication, vr); 105.075 kJ/mol. (for cell death, cd); vr and cd stand for viral replication and cell death respectively.

**Table 5: Gibbs free energy (Δ*G*) and** Copeland **model of activation energy of viral replication, and cell (Nef-negative HSC-F) dysfunction and death with time (τ).**

**τ** 1 2 3 4 5

**(days)**

**Δ*G*)/*e*. (4)** 2.0502.358 2.677 2.996 3.279

**(J/mol.)**

***Ea*(vr)/e.(5)** 1.167 1.259 1.291 1.323 1.351

***Ea*(cd)/e.(5)** 1.255 1.286 1.318 1.350 1.378

**(J/mol)**

Eyring free energy of activation () = 102.299 kJ/mol. (for viral replication, vr); 104.992 kJ/mol. (for cell death, cd).

For convenience, thermodynamic concerns have also been discussed in relation to viral depletion and cell death limited to Nef-positive HSC-F. The first are the values, which once more displayed a decreasing tendency over time (Table 3). Both viral replication's and viral depletion's free energy declined over time. Activation energies follow the same pattern (Table 6). The activation energies based on Copeland's model and free energy of activation for viral depletion (Table 6) are noteworthy because they are higher than those for viral replication in Nef-positive HSC-F (Table 4).

**Table 6: Gibbs free energy (Δ*G*) and** Copeland **model of activation energy of viral depletion, and cell (Nef-positive HSC-F) dysfunction and death with time (τ).**

**τ** 5 6 7 8 9

**(days)**

**Δ*G*)/*e*. (4)** 1.3911.729 2.022 2.901 3.205

**(J/mol.)**

***Ea*(vd)/e.(5)** 1.191 1.225 1.255 1.332 1.373

***Ea*(cd)/e.(5)** 1.190 1.224 1.253 1.341 1.371

**(J/mol)**

Eyring free energy of activation () = 105.234 kJ/mol. (for viral replication, vd); 105.075 kJ/mol. (for cell death, cd); vd stands for viral depletion.

As previously opined (Udema, 2025a), a power law governs the plot of against time (τ) in earlier days (Figure 6). Therefore, it is important that the medical team respond sooner rather than later in order to prevent the catastrophe that plagued the previous outbreak as a result of the authorities' complacency. This is in line with the empirically supported view that higher drug efficacy and earlier treatment initiation are associated with better outcomes: 74% of target cells remained uninfected after the course of infection—when treatment was initiated 1 day after symptom onset and antiviral effectiveness was 90 % (84). It is also in line with the observation that patients who were given ritonavir-boosted nirmatrelvir had a median viral clearance half-life that decreased by 26%, from 6.4 hours in 2022 to 4.8 hours in 2023 (Wongnak *et al*., 2024).

Despite the researchers' reservations (Watson *et al*., 2022; Horby *et al*., 2021), the concern for a proven case of median viral clearance half-life reduction is now out of the question only if early intervention is undertaken in cases of initial infection to achieve a high rate of viral clearance. Given that immunopathology takes over after about a week of sickness, early intervention with antiviral medication delivery to infected individuals or patients has the ability to reduce viral multiplication (Weinreich *et al*., 2021, Jayk *et al*., 2022 & Horby *et al*., 2021). This kind of outcome calls for the design of drugs that can increase the activation energy for viral replication.

Reduction of viral load, which is likely when antiviral drugs are administered in a timely manner, has been given credibility with the administration of casirivimab and imdevimab (REGN-CoV-2) (Weinreich, *et al*., 2021), and recently, the ribonucleoside analogue molnupiravir (J[ayk,](https://journals.asm.org/doi/10.1128/aac.00192-22#core-collateral-B6) *et al*., 2022 & Fischer *et al*., 2022) and the main protease inhibitor nirmatrelvir (Hammond *et al*., 2022).

It has been observed that the removal of plasma membrane cholesterol (by treatment with methyl-β-cyclodextrin) reduced the levels of ACE2 and the furin protease in lipid rafts, thereby reducing SARS-CoV-2 infection; on the other hand, loading cells with cholesterol *via* treatment with apolipoprotein (Apo) E and serum increased the trafficking of ACE2 and the furin protease to lipid rafts, resulting in increased SARS-CoV-2 infection. This suggests that plasma membrane cholesterol is required for proper trafficking and localization of receptors that facilitate SARS-CoV-2 infection (Kluck *et al*., 2021 & Wang *et al*., 2023).

**Figure 6:** **A plot of the dimensionless (unit less) equilibrium constant (*Keq*(δ)) for viral replication and cell death versus time.** The values of *kLR*(rate constant for cell death) and *kv* (rate constant for viral replication) are 1.1241 /day and 1.0567 /day respectively for Nef-Positive HSC-F Cells (Figures 3 and 6 respectively): Periods between 5 to 9 days were adopted. The day of detectable life Nef-Positive HSC-F Cells (a number = 15392) was on the 3rd day; the maximum number of cell was at the 5th day while the initial viral load was 150096 at zero time; the decreasing trend in the number of cells began from the 5th to the 8th day as reported by Iwami *et al*. (2012). The variation of *Keq*(δ) with time (τ) in days obeys the power law.

Proteins known as transcription factors play a part in determining gene expression by attaching to particular DNA sequences and so regulating gene transcription. Since transcription factors are proteins, they can undergo post-translational modifications including phosphorylation, glycosylation, acetylation, and methylation, if needed, as well as any other mechanism involved in the biosynthesis of any protein. Particularly important in this context are cofactors, coenzymes, and enzymes; in fact, inhibiting some or all of the enzymes and increasing their Michaelis-Menten constants (s) can reduce their specificity constant. This can therefore result in a greater Gibbs free energy of activation for viral particle multiplication, which generally reduces the process' thermodynamic viability. This situation can prevent the viral number density in the cells from increasing further.

Higher specificity constants, low s, and larger dimensionless equilibrium constants can all be caused by high affinity for the virus's binding domains. Energy barriers can be lowered and thermodynamic feasibility increased by drugs that can eliminate virus particles (depletion or clearance at lowered median half-life). There is a suggestion that the ability of SARS-CoV-2 to interact with lipids is as a result of the viral genetic material content of lipid-enveloped RNA. Studies in the past have, according to Cure & Cure (2021), shown that total cholesterol, high-density lipoprotein, and low-density lipoprotein (LDL) levels are lower in patients with severe novel coronavirus disease (COVID-19) compared to patients with non-severe COVID-19. However, there is a need for caution in that it is not known if cholesterol exists freely in the plasma. It is equally important to recall that viral replication occurs in the cytoplasm, where it has been observed that lowering cholesterol with statin therapy can reduce viral replication (Cure & Cure, 2021). Yet, what seems to be a contradiction is the observation that low lipid levels increase mortality and disease severity in COVID-19 ([Zenellu](https://lipidworld.biomedcentral.com/articles/10.1186/s12944-021-01607-5" \l "ref-CR11" \t "_blank) *et al*., 2021). Then, this scenario should call for higher lipid concentration in the cytoplasm in order to hinder viral replication, even if it has also been posited that cholesterol plays a vital role in the assembly, replication, and infectivity of SARS-CoV-2 viral RNA (Kharma & Garg, 2021).

The whole situation suggests that cholesterol, in particular, plays a crucial role in the virus's pathogenicity and life cycle. However, its impact on the virus's activity can be viewed as having two sides: in some circumstances, it promotes viral entry and reproduction within the cell, while in other circumstances, it prevents viral replication. When, exactly, is the question?

The endogenous cholesterol concentration is necessary for the first exposure and subsequent events, such as binding on the cell membrane; for the second period of time, cholesterol in the cytoplasm is also necessary for viral replication and the release of new viral particles through budding. These procedures might lower the amount of cholesterol in the cytoplasm and membrane. This appears to be corroborated by the finding that cholesterol functions as a conductor when SARS-CoV-2 enters cells by combining with ACE2, indicating that elevated cholesterol levels may make people more vulnerable to SARS-CoV-2 (Wang *et al*., 2021). Such bits of information about some biomolecules including cholesterol in particular calls for further thermodynamics and activation energy analysis in a manner that can influence improvements in medications.

**3.2 Further thermodynamics and activation energy issue**

The thermodynamics and activation energy of viral multiplication, clearance/depletion, and cell death may be summarized in this section in order to show how to effectively manage each process. Factors that influence the magnitudes of first-order rate constants for viral replication, depletion, and cell death have biophysical and biochemical roots. The biophysics is about the kinetics of monomers and metabolites relevant to the biosynthesis of lipids and proteins, including receptors, transcription factors, enzymes, *etc*. The biochemistry of the metabolic pathway is dually influenced by the kinetics of translational motion, activation energy, and thermodynamics. Some of the equations (Udema, 2025b) relevant to the reasons are, first:

**3.2.1 Kinetic equations other than Arrhenius equation or Copeland’s model**

, (5)

where , ,,,,, and are the instantaneous translational velocity before terminal velocity of the solute, Boltzmann constant, Kelvin temperature, translational diffusion coefficient, density of water, mass of water, and mass of the solute respectively. With a particular solute, equation (5) demonstrates that if temperature and are low and is large, can be low; if the aforementioned parameters are low and excessive, respectively, the opposite is true. A significant determinant that impacts, which influences, is the viscosity of the medium of transit. The frequency of collisions between the solute and its target is determined by kinetic factors, including this and the time (Eq. (6)) required to achieve a uniform dispersion of the diffusing solute, after which the mean square displacement is reached. This statement implies the activation energy, which depends on the kinetic energy.

, (6)

where,, and are the time taken to attain uniform distribution of the diffusing solute, hydrodynamic radius of the solute, and the coefficient of viscosity respectively.

, (7)

, (8)

where,, and are the molar concentrations of the substrate, enzyme-substrate complex, free enzyme and Michaelis-Menten constant respectively. If ligand and receptor is the case, the parameters can be replaced by,, and, respectively.

(9)

where is the dissociation constant.

**3.2.2 Graphical approach in the determination of**

, (10)

where and are respectively, the maximum velocity of catalysis in enzyme catalyzed reaction, intercept, and slope in a plot of *v* versus [*S*].

(11)

As Eqs (10) and (11) show, high and values cause low values of*.* Taking the role of cholesterol, as an example of a lipid, in the binding of any virus and its replication, as well as the role of transcription factors, one can clearly appreciate that the biosynthesis of these molecules can be controlled. It could be up - or down-regulation. The up-regulation would enhance viral binding to the cell membrane and replication, leading tohigher*,* lower*,* and higher values. The converse is trueifand are high. Thus, according to Eq. (7), there should be a significant buildup of acetyl-CoA, low levels of products, acetoacetyl-CoA, and CoA-SH. The whole situation translates into high feasibility and low activation energy for viral clearance but low thermodynamic feasibility *(+*Δ*G)* and high activation energy for viral reproduction. These result from a well-made drug that should be reproduced with consideration for activation energy factors and thermodynamics.

**4.0 CONCLUSION**

The energetics characterisation of the depletion, also known as the clearance of viral particles, includes the free energy and activation components. The dimensionless equilibrium constant for virus depletion, cellular malfunction, and death—the last of which is a sinequanon for fatality—was calculated using data reported for Nef—Positive HSC—F Cells in the literature. Extrapolating the result in this study to SARS-CoV-2 or any other deadly virus, calls for weakly evaluation of therapeutic interventions. Since dimensionless equilibrium constant values, free energies and activation energies of viral replication, depletion, and concomitant cell death are higher earlier than latter, it is diagnostically and therapeutically wise to adopt early interventions. These should lower the dimensionless equilibrium constant values and heighten the free energy and activation energy of viral replication and cell death with appropriate medications. The same parameters for viral depletion or clearance are expected to be lowered, more feasible with lower energy barriers. Future studies, in vivo and vitro, calls for weakly evaluation.

**DISCLAIMER (ARTIFICIAL INTELLIGENCE)**

The sole author hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, *etc*.) and text-to-image generators have been used during the writing or editing of this manuscript.

**COMPETING INTERESTS DISCLAIMER:**

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

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