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A CRITICAL REVIEW ON HEAT AND MASS TRANSFER MODELLING OF VIRAL INFECTION AND VIRION EVOLUTION
The case of SARS-CoV2

by

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Is it possible to characterize the SARS-CoV-2 viral infection by analysing the viral hijacking of cellular metabolism for its reproduction and multiplication? Gibbs free energy appears to be the critical factor of successful virus infection. A virus always has a more negative Gibbs free energy of growth than its host. Hence, the synthesis of viral components is thermodynamically favourable. On the other side, it could be essential to better thermodynamically understand how S1 and S2 spike protein interacts with the ACE2 receptors and the cell membrane more efficiently than the usual nutrients, which are intercepted. Gibbs energy gives a static model, which does not include the time arrow of viral evolution. A better comprehension of this evolutional path could require an accurate analysis of entropy generation or exergy disruption of binding, replication, and multiplication.

Keywords: *virus, cells, thermodynamics, Gibbs energy, entropy, exergy, entropy generation, exergy disruption*

Introduction

In March 2021, during the preliminary research activity toward a heat and mass transfer model of the COVID-19 infection mechanism, Michele Trancossi was infected and symptomatic. This event was fundamental for accelerating this preliminary work toward a better comprehension of virus variants and infection, reproduction, and spread mechanisms. This paper presents a critical bibliographic analysis on both the traditional and an open system evolutionary thermodynamic approach to stimulate an effective discussion on the two complementary approaches and their possible integration to better answer the need for evolving infections.

According to a traditional equilibrium thermodynamic model, Popovic and Minceva [1] have proposed an excellent bio-thermodynamic analysis of MERS-CoV, SARS-CoV, and SARS-CoV-2. Popovic and Minceva [2] have also produced an excellent thermodynamic insight into viral infections and describe the lytic cycle hijack of cell metabolism in terms of low Gibbs energy. They [3] determine enthalpy, entropy, and Gibbs free energy of 32 microorganism species. Popovic and Minceva [4] have also estimated the enthalpies of formation,

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the molar entropies, the Gibbs energies of formation, and the molar heat capacities at 25 °C and 37 °C for the human soft tissues. The results show that Gibbs energy of formation, except for adipose tissues, is low compared to the constituent elements. In addition, they determine the average constant pressure heat capacity of hydrated human body soft tissues, and the results agree with other data in the literature.

This preliminary research considers the previous described results and discusses the possibility of evolving the heat and mass transfer research on COVID-19, which has been preliminarily envisaged by Trancossi *et al*. [4]. In particular, it is necessary to define the instrument for an adequate analysis of two different bio-thermodynamic processes:

– The virus bonding and ingestion based on Van der Waals attraction between spike proteins S1 and ACE receptors [5, 6] and the fusion with membrane, which is driven by the spike protein S2 [7, 8].
– The viral hijacking mechanism and subsequent replication and reproduction [9] favoured by a negative difference between the standard Gibbs energy of growth [10, 11] of virus nucleocapsids and one of the common biochemical transformations inside the host cell.

Gibbs energy of growth seems to be the driving force of many biochemical processes. For example, Popovic and Minceva [1] have remarked that the nucleocapsids of Coronavirus have more negative Gibbs energies of formation than the host cell components. Besides, they show that the ratio of Gibbs energies of formation is always greater than unity. Hence, they [2] explain that the virus can hijack the host cell's metabolism because a more negative Gibbs energy of formation favours a biochemical process against the possible competing ones.

The present work presents a critical review focusing on the possibilities toward describing Covid-19 infection employing with an unsteady virus's finite system thermodynamics and irreversibility [12, 13] model. Biochemical and biological systems are finite open living systems and require to be modelled by irreversible thermodynamic processes. The virus infection process (bonding, ingestion, replication, multiplication, and spread) is presented to account for irreversibility effects. The viral mutations and insurgence of novel variants hold a second fundamental direction for irreversibility analysis and the arrow of time imprinted on one-way (irreversible) phenomena according to the Second law of thermodynamics [14, 15]. Virus and cell interactions deal with the arrow of time and the evolution of thermodynamic phenomena. The evolution timeline assumes fundamental importance since the birth of modern biology [16] and thermodynamics [17]. Any biological phenomenon is intrinsically evolutionistic. Therefore, it may take advantage of new models, which overcome the limits of traditional thermodynamic models based on discrete semi-static models based on successive equilibrium conditions [18]. The thermodynamic evolution can be described in macroscopic terms of physical and biological transformations. It underpins the holistic models of the evolution in complex systems. It relates to the configurations assumed by a system and the phenomenon of design:

– The mechanisms of the interactions between the virus and the infected cells.
– The evolution thermodynamics of the successful virus variants, which gain easier access to the human cells.

Hence, according to Lorente and Bejan [19], the comprehension of the changes in the configuration of the virus and the time arrow toward the necessary increasing easiness of flows in Nature could predict possible evolutional paths and forecast the potential effect of mutations. Thus, the evolution of a virus plays a role toward a higher capability to respond to future risks and support faster development of more efficient vaccines and definition of preventive measures and cares for limiting or blocking the flow of virus mutations and limiting the infection.

Methods

Virus composition

Knight [20], Masters [21] describe the four main components of viruses: nucleic acids, proteins, lipids, and non-nucleic acid carbohydrates. They have well-defined elemental composition and allow determining the elemental composition of virions by the atom counting method. In the virion, the total number of atoms of the element *J* is the sum of contributions from four classes of molecules:

$$N_{J,\text{virus}} = N_{J,\text{NA}} + N_{J,\text{prot}} + N_{J,\text{lip}} + N_{J,\text{CH}} \tag{1}$$

The suffix NA represents the nucleic acid, prot – the proteins, lip – the lipids, and CH – the non-nucleic acid carbohydrates. The virus's chemical formula has the form:

$$\mathrm{C}_{n_\mathrm{C}}\mathrm{H}_{n_\mathrm{H}}\mathrm{O}_{n_\mathrm{O}}\mathrm{N}_{n_\mathrm{N}}\mathrm{P}_{n_\mathrm{P}}\mathrm{S}_{n_\mathrm{S}}$$

The same method is adopted for the different components of the virion. In particular, the nucleic acid composition is estimated from the NCBI database [22] and has the formulation:

$$\mathrm{C}_{n_{\mathrm{C,NA}}}\mathrm{H}_{n_{\mathrm{H,NA}}}\mathrm{O}_{n_{\mathrm{O,NA}}}\mathrm{N}_{n_{\mathrm{N,NA}}}\mathrm{S}_{n_{\mathrm{S,NA}}}$$

in which $n_{J,\text{NA}}$ is the number of the molecule *J* in the nucleic acid. The viral proteins sequences are accessible from the UniProt database [23] and the NCBI database [22]. Four different proteins constitute coronaviruses: nucleoproteins (PN), membrane proteins (PM), envelope proteins (PE), spike proteins (PS), and structural proteins in the nucleocapsid [24]. The typical formula of the considered proteins is:

$$\mathrm{C}_{n_{\mathrm{C,PR}}}\mathrm{H}_{n_{\mathrm{H,PR}}}\mathrm{O}_{n_{\mathrm{O,PR}}}\mathrm{N}_{n_{\mathrm{N,PR}}}\mathrm{S}_{n_{\mathrm{S,PR}}}$$

where $n_{J,\text{PR}}$ is the number of the atoms of the element *J* in a protein molecule.

Lipids are located in the viral envelope, and their composition resembles one of the host cell membranes. Cooper [25] assumes that the composition of the viral envelope human cell membranes: 45% cholesterol, 17% phosphatidylcholine, 17% sphingomyelin, 16% phosphatidylethanolamine, 6% phosphatidylserine, and 2% glycolipids (mole fractions). The number of lipid molecules can be determined by accounting for the free volume between envelope proteins. The typical composition is assumed to be $CH_3(CH_2)_nCOOH$, where *n* is an even number ranging from 2 to 28. The number of lipid constituent *X*, *c(X)*, was determined by multiplying C_{lip} with the mole fraction of that lipid, *x(X)*:

$$c(X) = x(X)C_{\text{lip}} \tag{2}$$

The number element *J* atoms in all lipids, $N_{J,\text{lip}}$, was determined:

$$N_{J.\text{lip}} = \sum\nolimits_X n_{J,X}C_X \tag{3}$$

where $n_{J,X}$ is the number of atoms of element *J* in a single molecule of the lipid *X*.

Non-nucleic acid carbohydrates are a fundamental part of the viral envelope, being glycolipids and glycoproteins. Glycolipids are represented by stearoyl-glucose, $C_{24}H_{46}O_7$, the glucose residue, which belongs to non-nucleic acid carbohydrates. Oligosaccharide composition has been assumed to be equal to Orthomyxoviridae. For each spike protein molecule, 14000 Dalton of oligosaccharides was added, composed of mannose and 2 N-acetylglucosamine residues in a ratio of 5:2 [4].

The molar mass of any constitutive substance Y can be determined and is measured in Dalton:

$$M_Y = \sum_J n_{J,Y} m_J \tag{4}$$

where $n_{J,Y}$ is the number of atoms of element J in the specific organic substance Y and m_J is the atomic mass of the element J. The molar mass m_Y can be calculated:

$$m_Y = \sum_J \left(\frac{n_{J,Y}}{N_A} \right) m_J \tag{5}$$

where N_A is Avogadro's number.

Traditional thermodynamic models

The outstanding work by Popovich and Minceva [1-4] move in the frame of traditional thermodynamics of closed systems. Chemical or physical processes occurring within a closed system produce an amount of entropy S, which is greater than zero in natural or irreversible phenomena and equal to zero in ideal or reversible processes [26]. Thus, in a closed system, the spontaneous processes are irreversible and lead to the following general expression of the Second law of thermodynamics:

$$\mathrm{d}S \geq 0 \tag{6}$$

If the considered system is divided into an arbitrary number of subsystems, the entropy production can be expressed by the entropy production in any of the considered subsystems:

$$\mathrm{d}S_i = \sum_J \mathrm{d}S_{i,J} \geq 0 \tag{7}$$

Hence not to violate the requirement by eq. (6), entropy generation by every macroscopic subsystem J must separately be greater than or equal to zero:

$$\mathrm{d}S_{i,J} \geq 0 \tag{8}$$

It is evident that the subsystems are identified by an entropic criterion [27]: *the entropy increases in one subsystem cannot be reduced by being absorbed and consumed by any other subsystem even if close in space such as separate elements of a single volume maybe.*

Hence, entropy production and absorption occur within a single volume. This principle is evident for metabolic systems [28], for which it is possible to evaluate $\mathrm{d}S_i$ for spontaneous processes quantitatively. Systems undergoing spontaneous changes are not at equilibrium. Otherwise, in a classical thermodynamic approach, any system is modelled in terms of states of local equilibrium, in which the Gibbs equation allow expressing local entropy:

$$\mathrm{d}S = \frac{1}{T}\mathrm{d}U + \frac{P}{T}\mathrm{d}V - \sum_J \frac{a_J}{T}\mathrm{d}n_J \tag{9}$$

where T [K] is the thermodynamic temperature, $\mathrm{d}U$ – the energy exchange between the system and the surrounding environment, which is assumed positive when the system receives energy, $\mathrm{d}V$ – the volume change of the system during bio-thermodynamic processes, a_J – the chemical potential of any substance J, and $\mathrm{d}n_J$, – the change in the number of molecules per unit volume of any substance J. The Gibbs equation requires that the system is at equilibrium [29]. This assumption is restrictive because it requires assuming a local equilibrium condition that is not necessarily reached in a real system.

For alternative biochemical reactions, which may occur inside a biochemical system, the Gibbs free energy of formation and growth acts as a thermodynamic potential. It measures the *useful* or process-initiating work obtainable from an isothermal, isobaric thermodynamic system [30, 31]. Hence the Gibbs free energy can be defined as the maximum amount of non-expansion work that can be extracted from a closed system. The Gibbs free energy reaches a maximum only in an ideal reversible process and is given by:

$$G = H - TS \tag{10}$$

Every system evolves toward achieving a minimum of free energy at standard temperature and pressure. Thus, if entropy and heat increase with respect to the ideal equilibrium condition, Gibbs free energy reduces. The change in Gibbs free energy, ΔG, allows understanding the spontaneity of a reaction in well-defined equilibrium conditions [32]:

$$\Delta G = \Delta H - T\Delta S \tag{11}$$

Three cases can be considered: $\Delta G < 0$: if the reaction is spontaneous and proceeds as written; $\Delta G = 0$: if the reaction is at equilibrium; $\Delta G > 0$: if the spontaneous direction of the reaction is the reverse one. The eq. (11) shows that an increase in entropy produces a decrease in ΔG. Typical samples are the spontaneous decomposition of large molecules into smaller ones and the rearrangement of molecules [33], which usually increases the disorder of molecules around (*i.e*., the hydrophobic effect, which drives the folding process of the proteins).

A generic chemical reaction $aA \leftrightarrow bB$ is considered, where a and b are the stochiometric integers and A and B molecules. At pH = 7, the change in Gibbs free energy ΔG is given by:

$$\Delta G = \Delta G^{\circ'} + \mathrm{R}T \ln \frac{[B]^b}{[A]^a} \tag{12}$$

A more complex multiple substrate reactions $aA + cC \leftrightarrow bB + dD$ leads to the following expression of the change in Gibbs free energy:

$$\Delta G = \Delta G^{\circ'} + \mathrm{R}T \ln \frac{[C]^c [D]^d}{[A]^a [B]^b} \tag{13}$$

In eqs. (12) and (13), $\Delta G°$ is the change in Standard Gibbs Free energy, which means the change in energy that occurs when products and reactants are at standard conditions in an environment with pH = 7. Hence, standard Gibbs free energy is a constant for a given reaction and is expressed by:

$$\Delta G = \Delta G^{\circ'} + \mathrm{R}T \ln \frac{\text{products}}{\text{reactants}} \tag{14}$$

The fundamental limit of using Standard Gibbs Free energy as a means of thermodynamic analysis relates to the fact that chemical reactions must occur in local isothermal conditions [34]. Being $\Delta G°'$ a constant for a given reaction, ΔG is mainly influenced by a logarithmic function of the ratio between products and reactants [35]. At standard conditions, where any substance is 1 mole, the RTln*(*products/reactants*)* term is zero. Hence, $\Delta G°'$ indicates the direction of the reaction. If $\Delta G°'$ is negative, the reaction is energetically favourable. If $\Delta G°'$ is positive, the reaction is unfavourable.

When the ratio of products/reactants is changed, the natural logarithm term changes consequently. If it increases, the value of ΔG increases indicating a less favourable reaction. If the value of ΔG decreases, the biochemical process becomes more convenient. These results satisfy Le Chatelier's principle [36]: a system responds to stress by acting to alleviate it. In a closed system, ΔG for a reaction will always move to a value of equilibrium, whatever is the starting positive or negative value [37].

Free energy of electrical nature may be available inside biochemical processes and is generated by electrical potential. For example, the proton exchange across the membrane of mitochondria and chloroplasts generates Coulombic energy. This energy allows synthesizing the adenosine triphosphate. A similar process occurs in the transmission of nervous signals by the differential distribution of sodium and potassium. The same phenomenon moves some molecules in secondary active transport processes across membranes. For example, protons H^+ differential is the driving phenomena of lactose transport. In any case, it must be remarked that the described approach describes the thermodynamics of open and living systems within a classical equilibrium thermodynamic vision. Hence, it may present some consequent limits and a lack of realism. In particular, the traditional equilibrium thermodynamic approach shows a low capability to describe time-dependent phenomena because it requires the hypothesis of local equilibrium and does not consider the evolution of the phenomena in terms of time.

Thermodynamics and evolution

According to Bejan [38] the total entropy change *dS* in an elemental open living system (a single cell) may be expressed as the sum of two terms [39]:

$$\mathrm{d}S = \mathrm{d}S_e + \mathrm{d}S_i \tag{15}$$

where $\mathrm{d}S_i$ is the entropy change due to physical or chemical changes within the considered system supposed to be closed (it may be only zero or positive) and $\mathrm{d}S_e$ – the entropy change which is due to the exchange of energy and matter across the boundaries of the systems with the surrounding environment (it may assume any sign for the considered system). According to the eq. (15), the total entropy change in a biological system depends on both the internal transformations as they happen in a closed system and the entropy exchanges with the exterior environment. This model allows describing a biological living system's lifetime as the sum of incremental periods during which incremental changes occur. The thermodynamic model can be improved by assuming nonequilibrium thermodynamic assumptions. Lucia [39] describes living cells as adaptive thermodynamic engines converting matter and energy from one form to another [40] through both transport processes across the external membrane and internal metabolic and chemical reactions [30, 31]. Matter and energy are the properties of any system with respect to a reference state and change over time because of heat and mass transfer processes and internal biochemical reactions [41, 42]. Living cells transform the matter that enters the cell through multiple processes, including replication, transcription, and translation. The disruption of chemical bonds, hydrolysis, and electromagnetic gradients transform energy into valuable mechanical work, waste matter, and heat dispersed into the environment [34, 36, 43, 44] and constitute a measurable footprint and available set of information. According to its time arrow, the heat exchanges and thermodynamic transformations could be analysed in terms of entropy generation and living organisms' development [45]. This field is defined as bioengineering thermodynamics and relates to energy and matter flow and conversions in living organisms. It requires the analysis according to both the first and the Second law of

thermodynamics. It allows assessing both the conservation of energy and the Second law of thermodynamics. Besides, it allows understanding how entropy increases because of the interactions between biological systems and the environment.

Toward an unsteady model of viral infections

The present notes are not expected to produce numerical results but only a methodological discussion, but only a review with the aim of facilitating a more comprehensive cooperation between medicine, engineering, physics, biology, and chemistry in a common methodological framework, which may allow avoiding losing by duplicating the respective activities under different disciplines which may not produce data which are suitable to be reused by other fields.

Cells as the unit of living matter

A cell is the smallest living organism [46]. It is a limited open thermodynamic system [47]. It is enclosed by a functional plasma membrane, a selective barrier that allows the nutrients to enter and the waste products expelled. The cell is highly organized and subdivided into many specialized subsystems (organelles) in the interior, each surrounded by a separate membrane [48, 49]. About 70% of a cell weight is constituted by water, and most intracellular reactions occur in an aqueous environment.

The organelles are surrounded by an aqueous solution (cytoplasm), which fill most of the volume of the cell and contains the cytosol, an organized framework by fibrous molecules (cytoskeleton) that allow the cells to keep their shape and to modify it and enable organelles to move within the cell. The cytosol contains the necessary molecules involved in cellular biosynthesis, making large biological molecules from small ones. The significant organelles are the nucleus, which keeps the genetic information necessary for life, growth, and reproduction; the mitochondria, which allow the energy transactions required for cell survival; the lysosomes, which digest unwanted materials within the cell; endoplasmic reticulum and the Golgi apparatus, which synthesize necessary molecules and then process, sort, and direct them to the specific locations where they are necessary.

Biological systems are open and highly optimized thermodynamic systems [50-53]. As a result, they have the highest possible efficiency in both ensuring a selective transport of energy and mass across their boundaries and converting the maximum energy from one to another form in the least time. Cells appear a thermodynamic paradox [54, 55]. On one side, they evolve the matter, which feeds them towards maximum disorder. On the other side, they maintain the highest possible degree of organization in space and time spontaneously. This result is obtained by a complex set of metabolic reactions, chemical reactions, and transport processes. Consequently, biological systems are non-equilibrium open systems that realize irreversible physical and biochemical processes with the ability of exchanging matter and energy with the surrounding environment and converting energy from one form to another. Different phenomena occur simultaneously. They may couple generating new effects, as, for example, the transport of a substrate against the direction imposed by the electrochemical potential gradient, known as active transport.

Entropy and evolving living organisms

Entropy is a state function. Therefore, entropy characterizes the thermodynamic state of a closed system and the related irreversibility. Entropy allows understanding the efficiency of the physical, biological, and chemical processes and the associated dissipations,

which can always be analysed through the Second law of thermodynamics [56, 57]. This analysis accounts for Prigogine's results on dissipative structures [58-60] and entropy in unsteady systems [61] and the thermodynamic model of evolution as stated by Bejan [62, 63]. Natural and living systems are open systems that exchange heat and mass and interact with the environment. This set of interactions with the environment assumes a fundamental role in the thermodynamic analysis of available and living systems. Lucia [50] claims that observing the cell environment is much easier than observing the living cell itself. Besides, Lucia [50] presents a model of living cells, which have the following characteristics:

– cells are finite and open irreversible real linear or non-linear systems,
– any process which happens in the cell has a finite duration τ;
– it is impossible to understand what happens in each instant in the range $[0,\tau]$,
– initial state, inputs and outputs, and the final results after time τ are well-known, and
– the balance equations consider the balance of fluxes of energy and mass in terms of the different species, which flows, including molecules, elements, ions, and electrons.

The aforementioned model does not necessarily require considering the system's instantaneous equilibrium but the overall equilibrium during the different phases of the process. The cells spontaneously exchange heat with the surrounding environment. The heat exchanges relate to biochemical and biophysical processes and assume a fundamental role in cell infection. Viruses and cells are complex systems with interacting processes that are difficult to be understood in terms of individual contributions.

The First law of thermodynamics could express irreversibility:

$$\mathrm{d}E_{\mathrm{in}} = \mathrm{d}W + \mathrm{d}Q + \mathrm{d}E_{\mathrm{irr}} \tag{16}$$

On the other side, both cells and viruses do not fulfil the limits of classic thermodynamics. They are finite open systems with a finite lifetime, and most of the related processes and the efficiency of those processes relate to a precise timeline. In particular, viruses are not living systems outside a living cell and become parasitic living systems when they enter inside a cell.

Entropy is a function of state. It characterizes the thermodynamic state of the system. The related irreversibility and entropy generation allow understanding the system evolution and how far the system is from the state attained by reversible transformations [60]:

$$S_g = \frac{\mathrm{d}S}{\mathrm{d}t} \tag{17}$$

Entropy generation is always positive ($S_g \geq 0$), and the systems evolve to decrease the free energy in the least time [64-66]. Hence, entropy generation describes complex irreversible systems because:

– it describes the system without requiring any unreal local equilibrium hypothesis,
– it introduces the lifetime of both a process and the related and constituent sub-processes,
– it considers a timeframe greater than or equal to the lifetime of the whole process or sub-process, and
– it allows studying the complete process during its development and considers a fully developed process that provides a larger amount of information on process results.

The proposed analysis focuses on observing the flow in terms of entropy and heat, and mass transfer. Natural and living systems are open systems that exchange heat and mass and interact with the environment. This set of interactions with the environment assumes a fundamental role in the thermodynamic analysis of open and living systems [67]. The Second

law of thermodynamics provides entropy balance for intrinsic (or internal) and external states in a biochemical system. Generally, a system with an irreversible process can be expressed by estimating how entropy changes over time:

$$\frac{\mathrm{d}S}{\mathrm{d}t} = \frac{\mathrm{d}S_e}{\mathrm{d}t} + \frac{\mathrm{d}S_i}{\mathrm{d}t} \tag{18}$$

where the subscripts *e* refers to external entropy flux and *I* to internal entropy generation.

The eq. (18) describes the total entropy change per unit time. It is the sum of the entropy exchanged with the environment and the entropy produced in the system per unit of time.

A living cell is constituted by multiple tiny organelles (sub-volumes) with high levels of specialization [66]. Being entropy an extensive quantity, the total internal entropy generation in a cell is the sum of the entropy generation by all the organelles *J*:

$$\frac{\mathrm{d}S_i}{\mathrm{d}t} = \sum\nolimits_J \frac{\mathrm{d}S_{i,J}}{\mathrm{d}t} \tag{19}$$

from which it results:

$$\frac{\mathrm{d}S}{\mathrm{d}t} = \frac{\mathrm{d}S_e}{\mathrm{d}t} + \sum\nolimits_J \left(\frac{\mathrm{d}S_i}{\mathrm{d}t} \right)_J \tag{20}$$

In each volume element, the entropy production is called the *local entropy generation*.

According to Mercer [68], the local entropy production can be broken down into different parts depending on their nature. This model has been formalized with a higher level of detail by Lucia and Grazzini [66]. Lucia [66] has analysed entropy as a quantification of the system's evolution toward increasingly more probable states. Hence, entropy generation is a means of understanding irreversibility concerning the causes that generate it [69]. The total entropy generation is given by:

$$\dot{S}_g = \dot{S}_{g,\mathrm{tf}} + \dot{S}_{g,\mathrm{dc}} + \dot{S}_{g,\mathrm{vg}} + \dot{S}_{g,\mathrm{cr}} + \dot{S}_{g,\mathrm{de}} \tag{21}$$

where $\dot{S}_{g,\mathrm{tf}}$ is the thermal flux driven by the temperature difference, $\dot{S}_{g,\mathrm{dc}}$ – the diffusion current driven by chemical potential gradients, $\dot{S}_{g,\mathrm{vg}}$ – the velocity gradient coupled with viscous stress, $\dot{S}_{g,\mathrm{cr}}$ – the chemical reaction rate driven by affinity, and $\dot{S}_{g,\mathrm{de}}$ – the energy dissipated because of work and interactions with the environment. Cells can be considered chemical engines, in which both specific ordered heat and mass exchanges and chemical reactions occur. Any process occurs in a particular timeframe with well-defined starting times $t_{0,k,}$ and durations Δt_k. Assuming that human organs are at rest and neglecting the possible interaction with the external environment, the entropy generation can be evaluated. If it is assumed that the ability of the cells to store energy and both the entropy generation related to viscous stress and external field are supposed null, the entropy generation reduces to:

$$S_g = S_{g,\mathrm{de}} + S_{g,\mathrm{cr}} \tag{22}$$

The potential chemical gradient, which primarily occurs in the cytoplasm, is:

$$\psi_k = \frac{\sum_J \rho_J \left(\mu_{J,\mathrm{os}} - \mu_{J,\mathrm{is}} \right)}{d_m} \tag{23}$$

where ρ_j is the concentration of the j^{th} specie, *os* means outside, and *is* means inside the cell. Hence, $S_{g,\text{dc}}$ can be expressed:

$$\dot{S}_{g,\text{de}} \approx \frac{\dot{x}_{\text{th}} V}{T} \frac{\sum_J \rho_J \left(\mu_{J,\text{os}} - \mu_{J,\text{is}}\right)}{d_m} \tau_{\text{dc}} \tag{24}$$

where τ_{dc} is the lifetime of this process, V and d_m are the volume and depth of the membrane, respectively, $\dot{x}_{\text{th}}$ – the thermal velocity, and T – the mean temperature of the membrane. Besides, the entropy generation $S_{g,cr}$ by the chemical reaction rate driven by reaction affinity is:

$$\dot{S}_{g,\text{cr}} \approx V\left(\sum_k N_k \frac{A_k}{T}\right)\tau_{\text{cr}} \tag{25}$$

where τ_{cr} is the lifetime of the chemical reaction process, N_k – the number per unit time and volume of the k^{th} chemical reaction, and A_k – the affinity, evaluated as the standard Gibbs' free energy variation. Hence, entropy generation can be expressed:

$$\dot{S}_g = \dot{S}_{g,\text{dc}} + \dot{S}_{g,\text{cr}} \approx \frac{\dot{x}_{\text{th}} V}{T} \frac{\sum_k \rho_i \left(\mu_{k,\text{os}} - \mu_{k,\text{is}}\right)}{d_m} \tau_{\text{dc}} + V\left(\sum_k N_k \frac{A_k}{T}\right)\tau_{\text{cr}} \tag{26}$$

The eq. (26) is difficult to be used in practice because of its complexity. Hence, a different strategy for modelling the living cells according to the Second law of thermodynamics can be envisaged [70]. If cells are assumed as black boxes, eventually divided into subsystems, the relative inflow and outflow balances can be easier quantified and described [71].

Discussion

Exergy is the maximum shaft work done by the composite system and a so possible entropic and exergetic biological systems analysis methods, with a particular interest in human cells and virions structures. It moves from the excellent work by Popovich and Mincheva [1, 2 ,4] and Popovich [3], who consider a traditional closed system model and discusses its possible extension toward non-equilibrium thermodynamics. The results and the method have been analysed. A possible evolution has been discussed toward a better comprehension of the evolution in both infection mechanisms and virions.

A preliminary discussion on the methods has been produced. It moves toward defining a common background for an evolutional unsteady thermodynamic assessment of both the virion and the infection. This activity allows discussing how a more detailed model that can describe and forecast virus attack, bonding, replication, and multiplication processes in the respiratory tract cell when attacked by a Coronavirus in particular by SARS-CoV-2. Besides, it aims to analyse the viral evolution toward better comprehension and a possible prediction of the viral evolution timeline in different climatic conditions. This activity fosters the definition of a common framework for extensive multidisciplinary cooperation. It could facilitate the related thermodynamic activity into the engineering and the applied physics sectors. It could also allow a more extensive interdisciplinary collaboration and recognizance of the results toward a faster solution of thermodynamics-related problems in the case of possible future pandemics. Besides, introducing an unsteady thermodynamics analysis and related methodological framework could better comprehend the virion evolution, infection prevention. It can also determine new intelligent, deployable, and easily adaptable vaccines, possible social prevention measures, and technologies, reducing and breaking the pandemic's diffusion.

Nomenclature

A – affinity, evaluated as the variation of the standard Gibbs' free energy [J]
a – chemical potential of any substance [Jmol^{-1}]
B – exergy [W]
d_m – thickness [m]
E – energy [J]
G – Gibbs free energy [J]
H – enthalpy [J]
N, n – number of molecules [–]
N_k – number per unit time and volume of the k^{th} chemical reaction
P – pressure [Pa]
Q – heat [J]
R – gas constant [JK^{-1}mol^{-1}]
S – entropy [JK^{-1}]
S_a, $\dot{S}$ - entropy generation [W]
T – thermodynamic temperature [K]
t – time [s]
U – energy exchange between the system and the surrounding environment [J]
V – volume [m^3]
W – work [J]
$\dot{x}$ – velocity, T is the mean temperature of the membrane

Greek symbols

ψ – potential chemical gradient [Jmol^{-1}]
μ_0 – chemical potential
τ – lifetime [s]
ρ_i – concentration of the ith specie

Subscripts

0 – reference state
CH – non-nucleic acid carbohydrates
cr – chemical reaction
e – exchange across the boundaries of the systems with the surrounding environment
i – related to within the considered system supposed to be closed
in – input
irr – irreversible
J – generic element
k – k^{th} chemical reaction
lip – lipids
NA – nucleic acid
prot – proteins
th – thermal

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