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Review

Biothermodynamics of Viruses from Absolute Zero (1950) To – Virothermodynamics (2022)

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Abstract: Biothermodynamics of viruses is among the youngest, but rapidly developing scientific disciplines. During the COVID-19 pandemic, it has closely followed the results published by molecular biologists. Empirical formulas were published for 50 viruses and thermodynamic properties for multiple viruses and virus variants, including all variants of concern of SARS-CoV-2, SARS-CoV, MERS-COV, Ebola virus, Vaccinia and Monkeypox virus. A review of development of biothermodynamics of viruses during the last several decades and intense development during the last 3 years has been described in this paper.

Keywords: Thermodynamics; Calorimetry; Entropy; Enthalpy; Gibbs energy; Virus-host interaction; SARS-CoV-2; COVID-19; Ebola virus

1. Introduction

1.1. From Thermodynamics to biothermodynamics

There is a common opinion among many that thermodynamics is a scientific discipline related to machines, engines and devices, being related mostly to efficiency of energy transformation and utilization. Indeed, Lazarus Carnot [1786, 1803] and his son Sadi Carnot [1824] have through their brilliant research imposed such a perception into public during over two centuries [Müller, 2010]. In that way, classical thermodynamics began its development. It is less widely known that, simultaneously with classical thermodynamics, appeared biothermodynamics. Lavoisier and Laplace [Lavoisier and marquis de Laplace, 1783; Lavoisier and DeLaplace, 1994] developed the first calorimeter and one of the first samples for calorimetry was an organism - live mouse. Thus, simultaneously with classical thermodynamics, biothermodynamics started its development.

Often, the same researchers worked in the field of classical thermodynamics and biothermodynamics. Indeed, Boltzmann [1974], one of the founders of statistical thermodynamics, has written about change in entropy in living organisms. Clausius [1867, 1870, 1976] has laid the theoretical foundations of classical thermodynamics, with the goal of analysis of machines. However, von Bertalanffy [1950] has suggested the theory of open systems in biology. Schrödinger in his famous book "What is Life?" discussed the thermodynamic background of life processes [Schrödinger, 1944]. Morowitz [1992, 1968, 1955] has discussed potential controversies related to self-assembly in organisms and emergence of life, and the second law of thermodynamics.

Growth is one of the main characteristics of organisms. The answer to the question of what represents the driving force for growth of organisms was given by von Stockar [von Stockar and Liu, 1999; von Stockar, 2013a, 2013b; von Stockar et al., 2006; Patiño et al., 2007]. It seems that biothermodynamics has, even though it is less widely known than classical thermodynamics, has been equally long in the scientific arena and has given impressive results. Hansen analyzed whether an extended thermodynamic framework can be used to analyze processes in organisms that involve information, such as biological evolution [Hansen et al., 2021, 2018, 2009]. Application of thermodynamics to biological

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evolution was also discussed by Skene [2015]. Battley has made a great contribution towards applying the quantitative thermodynamic approach to living organisms and life processes [Battley, 2013, 1999a, 1999b, 1998, 1997, 1992]. Quantifying thermodynamic properties of organisms has also been contributed by Roels [Roels, 1983; von Stockar and Liu, 1999], and Sandler [Sandler and Orbey, 1991; Sandler, 2017]. Barros has applied thermodynamics to study growth of microorganisms in soil ecosystems [Barros, 2021; Barros et al., 2020, 2016]. Maskow has applied calorimetry and thermodynamic analysis to study growth of microorganisms in bioreactors [Maskow, 2013; Maskow and Harms, 2006] and ecosystems [Maskow et al., 2010a; Maskow and Paufler, 2015], as well as viruses in host cells [Maskow et al., 2010b]. Gushoeng et al. [2003] have also applied calorimetric methods to study multiplication of bacteriophages inside host cells.

1.2. Biothermodynamics intersects with biochemistry

Thermodynamic characterization of life processes has been a subject of interest for many researchers. Von Stockar et al. [2013, 2006] applied thermodynamics to quantitatively analyze thermodynamic feasibility of complex metabolic pathways, like glycolysis. Thermodynamic analysis has been used to find accurate Gibbs energy values with activity coefficient corrections, for important biological reactions, including Hexokinase reaction [Meurer et al., 2016], Glucose-6-phosphatase reaction and ATP hydrolysis [Meurer et al., 2017], 3-phosphoglycerate kinase reaction [Wangler et al., 2018], Triosephosphate isomerase reaction [Greinert et al., 2020a], Enolase reaction [Greinert et al., 2020b], and Glyceraldehyde 3-phosphate dehydrogenase reaction [Greinert et al., 2020c]. Also, thermodynamic analysis has been made of cellulose hydrolysis by microorganisms into aqueous glucose solution [Popovic et al., 2019]. Niebel et al. [2019] found that cellular metabolism is governed by an upper limit in Gibbs energy dissipation, using metabolomics. Ould-Moulaye et al. [1999] found Gibbs energy changes for the reactions in glycolysis and Krebbs cycle. Kümmel et al. [2006] discuss applications of thermodynamics in metabolic network models.

The importance of thermodynamic considerations in life sciences are clearly seen from the Gibbs energy being used to define catabolic and anabolic processes [Berg et al., 2002]. Annamalai used the quantitative thermodynamic approach to study the metabolic processes [Annamalai, 2021; Annamalai and Miller, 2017] and aging of organisms [Annamalai and Nanda, 2017; Annamalai and Silva, 2012; Silva and Annamalai, 2009, 2008, 2006]. Hayflick was among the first who related a thermodynamic property (entropy) to the aging process, in a series of papers [Hayflick, 2016, 2010, 2007a, 2007b, 2003, 2001, 1998, 1985].

1.3. From Biothermodynamics to virothermodynamics

Viruses are the most numerous organisms: there are more viruses than stars in the Universe [Wu, 2020]. There are 9,110 named species listed by the International Committee on Taxonomy of Viruses (ICTV) [Dance, 2021]. Until 2019, despite the wide variety of viruses, they have been the subject of research of microbiology, virology, biology and medicine. However, inside host cells, viruses represent growing open chemical and thermodynamic systems [Popovic, 2022j, 2018a, 2018b, 2017]. Until 2019, elemental composition was known only for the poliovirus [Wimmer, 2006; Molla et al., 1991]. This is a consequence of the fact that analytical laboratories rarely have biosafety levels required for work with most viruses, as well as the fact that viruses are difficult to isolate in sufficient amount and purity [Popovic, 2022a]. Until recently, viruses were not a subject of thermodynamic research. Thermodynamic properties of virus particles and nucleocapsids were unknown.

With the appearance of COVID-19 pandemic, various scientific disciplines attempted to give in the shortest time possible their contribution to the fight against the pandemic. Molecular biology has played an important role, with the reading of genetic sequences of SARS-CoV-2. Thermodynamics has joined the fight and in 2020, thermodynamic properties have been published for multiple viruses [Popovic and Minceva, 2020a]. An analysis was made of virus-host

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interactions in the cytoplasm (virus multiplication) [Popovic and Minceva, 2020a]. The first empirical formula and thermodynamic properties of the Hu-1 variant of SARS-CoV-2, as well as SARS-CoV and MERS-CoV, were published in 2020 [Popovic and Minceva, 2020b]. In 2020, in parallel with the COVID-19 pandemic, an epidemic caused by the rhinovirus occurred, while the influenza epidemic has not occurred that year. An explanation of coinfection by rhinovirus and SARS-CoV-2, and interference between influenza and SARS-CoV-2 has been published in [Popovic, 2021a]. SARS-CoV-2 belongs to the group of RNA viruses, which exhibit a great tendency to mutate [Duffy, 2018]. Thus, during 2.5 years of the pandemic, the virus has mutated several dozen times [Callaway, 2020; Barton et al., 2021; Wang et al., 2021]. The mutants have suppressed the older variants and caused new waves of the pandemic. Elemental composition and thermodynamic properties of SARS-CoV-2 variants from Hu-1 to Omicron BA.2.75 have been published in [Popovic and Popovic, 2022; Popovic, 2022b, 2022c, 2022d, 2022e, 2022f; Şimşek et al., 2021; Degueldre, 2021; Popovic and Minceva, 2020b]. Biothermodynamic characterization of viruses was continued on Monkeypox, Vaccinia and Ebola viruses [Popovic, 2022g, 2022h].

Infectivity and pathogenicity are terms mostly used in microbiology, biology and medicine. These terms have their physical basis and driving forces in biothermodynamics. The basis of infectivity of viruses is susceptibility and permissiveness (binding affinity and multiplication rate, respectively). Antigen-receptor binding represents a chemical reaction, similar to protein-ligand interactions [Du et al., 2016]. The driving force for antigen-receptor binding is Gibbs energy of binding [Popovic and Popovic, 2022; Popovic, 2022c, 2022f; Gale, 2021, 2020, 2019, 2018]. Thus, biothermodynamic consideration and determination of Gibbs energy of binding is very important for infection spreading [Lucia et al., 2020a, 2020b]. More negative Gibbs energy of binding of new variants has given an advantage during entry of a new strain over older ones, which has led to faster spreading of the virus and shorter incubation period. Gibbs energies of binding and binding affinities of viruses have been reported in the literature for various viruses [Casasnovas and Springer, 1995; Gale, 2021, 2020, 2019, 2018; Popovic and Popovic, 2022; Popovic, 2022b, 2022b, 2022c, 2022d, 2022e, 2022f, 2022h].

To explore the interaction between a virus and its human host, it was necessary to find thermodynamic properties for host organisms. Thermodynamic properties have been reported for human tissues [Popovic and Minceva, 2020c; Popovic, 2022h]. Thermodynamic properties of plant host organisms have been reported in [Popovic and Minceva, 2021b]. Phage-bacteria interactions are often used as a model in research of virus-host interactions. Thus, thermodynamic properties have been determined for a large number of bacteria [Popovic, 2019; Popovic et al., 2021; Duboc et al., 1999; Wang et al., 1976; Battley et al., 1997] and bacteriophages [Guosheng et al., 2003; Maskow et al., 2010b; Popovic and Minceva, 2020a].

The second virus-host interaction is in the cytoplasm. In the paper [Popovic and Minceva, 2020a, 2020b] a biothermodynamic mechanism was suggested for virus hijacking of host cell metabolism. The permissiveness represents the ability of a virus to multiply inside the host [Hou et al., 2017]. Multiplication of a virus represents a chemical reaction of polymerization of nucleotides into nucleic acids, and amino acids into structural and functional proteins of the virus [Popovic, 2022h]. The driving force for these reactions is Gibbs energy of biosynthesis [Popovic, 2022i]. After their biosynthesis, the virus components undergo self-assembly into the new virus particle [Buzón et al., 2020; Garmann et al., 2019]. During biosynthesis and self-assembly viruses change their thermodynamic properties [Popovic, 2014a, 2014b]. Thus, the virus life cycle represents a biological, chemical and thermodynamic process that should be analyzed using nonequilibrium thermodynamic apparatus [Popovic and Minceva, 2021c].

The aim of this review paper is to summarize the intense development in the field of biothermodynamics of viruses during the last few decades and try to predict directions of future development of the youngest scientific discipline – virothermodynamics.

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2. Methods and Results

This section discusses the methodologies used in biothermodynamics of viruses and the results they provide. First, the experimental techniques are discussed, followed by theoretical approaches.

2.1. Experimental approaches in biothermodynamics of viruses

Binding affinities of virus antigens to host cell receptors (susceptibility) have been measured using surface plasmon resonance [Rusnati et al., 2015; Han et al., 2022] and non-competitive ELISA approach [Beatty et al., 1987; Wu et al., 2022]. Surface plasmon resonance (SPR) gives kinetic and thermodynamic data on antigen-receptor binding, including association rate constant, k_{on}, dissociation rate constant, k_{off}, and dissociation equilibrium constant, K_D [Rusnati et al., 2015; Han et al., 2022]. SPR is a label free optical technique that measures biomolecular interactions in real time, by detecting reflected light from a prism-gold film interface [Rusnati et al., 2015]. The non-competitive ELISA approach measures thermodynamic properties of antigen-receptor binding [Beatty et al., 1987; Wu et al., 2022]. It represents a simple, rapid, and reliable method for measuring dissociation equilibrium constants, K_D [Beatty et al., 1987; Wu et al., 2022]. The experimental results can be used to calculate other important parameters of antigen-receptor binding, including binding equilibrium constants, K_B, standard Gibbs energies of binding, $\Delta_B G^0$, binding phenomenological coefficients, L_B, and binding rates, r_B [Popovic, 2022c, 2022f].

Calorimetry has been used to study viruses, including differential scanning calorimetry (DSC), isothermal titration calorimetry (ITC) and reaction calorimetry. Differential scanning calorimetry (DSC) measures the difference in heat absorption rates between sample and reference during gradual heating, revealing various thermal effects such as phase transitions or protein unfolding [Privalov, 2012; Sarge et al., 2014]. DSC has been used since the 1970s in research on viruses, including measurements of energetics of virus capsid self-assembly and denaturation [Krell et al., 2005; Yang et al., 2017], virus particle structure [Bauer et al., 2015, 2013], thermal stability [Yang et al., 2017; Makarov et al., 2013; Virudachalam et al., 1985a, 1985b], virus identification [Krell et al., 2005], virus denaturation [Toinon et al., 2015 ; Brouillette et al., 1982], entry into host cell [Banerjee et al., 2010; Nebel et al., 1995], capsid self-assembly [Sturtevant et al., 1981; Stauffer, 1970] and vaccine development [Deschuyteneer et al., 2010; Wang et al., 2015].

While DSC performs measurements by changing temperature, isothermal titration calorimetry (ITC) measures heat released or absorbed when as a reagent is titrated into a solution at constant temperature [Privalov, 2012; Sarge et al., 2014]. ITC was also applied to study a wide range of phenomena related to viruses, such as virus adsorption and disassembly [Yu et al., 2015], influence on metabolism and cell cycle [Javorsky et al., 2022; Prins et al., 2010], apoptosis inhibition [Anasir et al., 2017; Aladag et al., 2014], virus structure and entry into host cells [Liu et al., 2014], nucleocapsid self-assembly [Maassen et al., 2019], inactivation [Yang et al., 2020; Kawahara et al., 2018], immune response evasion [Gao et al., 2021], antiviral therapy development [Zhou et al., 2022; Noble et al., 2016; Sharma et al., 2016 Byrn et al., 2015], vaccine development [Vorobieva et al., 2014] etc. Finally, reaction calorimetry or isothermal microcalorimetry measures heat released or absorbed during a chemical reaction, usually at constant temperature (without titration like in ITC) [Privalov, 2012; Sarge et al., 2014]. Reaction calorimetry has been applied to study virus multiplication inside host cells [Sigg et al., 2022; Tkhilaishvili et al., 2018a; Guosheng et al., 2003; Morais et al., 2014], phage action against bacterial biofilms [Tkhilaishvili et al., 2020a, 2020b, 2018a, 2018b, 2018c; Wang et al., 2020a, 2020b], phage-bacteria interactions [Fanaei Pirlar et al., 2022; Wang et al., 2020c], phage transition from lytic into lysogenic cycles [Maskow et al., 2010b], antiviral therapy [Shadrick et al., 2013; Tkhilaishvili, 2022; Gelman et al., 2021], and influence on marine ecosystem metabolism [Djamali et al., 2012].

2.2. Theoretical approaches in biothermodynamics of viruses

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Thermodynamic properties of viruses can be calculated using biothermodynamic methodology. Thermodynamic properties of virus biosynthesis can be found from virus elemental composition in three steps:

(1) empirical formula
(2) thermodynamic properties of live matter
(3) thermodynamic properties of biosynthesis

The first step is to find empirical formulas of virus live matter. This can be done using the atom counting method [Popovic, 2022a], which gives elemental composition of viruses using widely available data on genetic sequences [Sayers et al., 2022; NCBI, 2022; Khare et al., 2021; Elbe and Buckland-Merrett, 2017; Shu and McCauley, 2017], protein sequences [Sayers et al., 2022; NCBI, 2022; UniProt Consortium, 2021] and virus morphology [Popovic, 2022a]. The second step is to calculate thermodynamic properties of virus live matter, using predictive biothermodynamic models [Popovic, 2022a]. Elemental composition of virus live matter can be used to find its thermodynamic properties using the Patel-Erickson equation [Patel and Erickson, 1981; Battley, 1998; Popovic, 2022c, 2019], Battley equation [Battley, 1999; Popovic, 2022c, 2019] and Hurst-Harrison equation [Hurst and Harrison, 1992; Ozilgen and Sorgüven, 2017]. The third step is to use elemental composition of live matter to construct biosynthesis reactions for the viruses [Popovic, 2022c; Popovic and Minceva, 2020a]. The biosynthesis reactions are combined with thermodynamic properties of live matter to find thermodynamic properties of growth [Popovic, 2022c; Popovic and Minceva, 2020a].

Phenomenological equations are an important tool, relating thermodynamic and kinetic properties of processes [Demirel, 2014; Balmer, 2010; von Stockar, 2013a]. Phenomenological equations are intuitive and simple to apply, stating that the rate of a process is proportional to its thermodynamic driving force - Gibbs energy [Demirel, 2014; Balmer, 2010]. A phenomenological equation for a chemical process has the general form [Demirel, 2014; Balmer, 2010]

$$r = -\frac{L}{T}\Delta G \quad (1)$$

where r is the rate of a chemical process, T temperature, while ΔG is Gibbs energy change of the process. L is a constant known as phenomenological coefficient and is specific for each process. Phenomenological equations can be applied to both antigen-receptor binding and virus multiplication inside host cells [Popovic, 2022c, 2022f]. In case of antigen-receptor binding, the binding phenomenological equation relates binding rate, r_B, and Gibbs energy of binding, $\Delta_B G$:

$$r_B = -\frac{L_B}{T}\Delta_B G \quad (2)$$

where L_B is the binding phenomenological coefficient [Popovic, 2022c, 2022f, 2022k].

Similarly, growth phenomenological equation relates the rate of biosynthesis of virus components, r_{bs}, to Gibbs energy of biosynthesis, $\Delta_{bs}G$:

$$r_{bs} = -\frac{L_{bs}}{T}\Delta_{bs} G \quad (3)$$

where L_{bs} is the biosynthesis phenomenological coefficient [Popovic, 2022h, 2022c, 2022k]. Phenomenological equations have also been applied to analyze growth of bacteria [von Stockar, 2013; Demirel, 2014].

3. Discussion

The path from thermodynamics to biothermodynamics was very short. The researchers who laid the foundations of classical thermodynamics were also the first to apply them to living organisms [Lavoisier and marquis de Laplace, 1783]. The road from biothermodynamics to biothermodynamics of viruses, virothermodynamics, has been much longer. It lasted 150 years. In that period, the basis was laid for experimental measurements on virus samples, as well as the methodology for theoretical analysis. Thus, the opportunities for virus research offered by

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biothermodynamics are great. However, the limiting factor for research represents the problem of providing biological samples of sufficient size and adequate purity, high sample prices, as well as finding laboratories with required biosafety level and personnel ready to work on biothermodynamics [Popovic, 2022a]. Having in mind that the discipline is really young, biothermodynamics courses are rarely offered at universities in Europe, even though it seems that students are showing interest for this discipline. In this early period of development of biothermodynamics of viruses, of particular importance are results of molecular biology, which have made widely available the data on sequences of nucleic acids and proteins, as well as the work of virologists who made available data on virus morphology.

In the introduction section, it was mentioned that viruses represent the most numerous living organisms. Moreover, there is nearly 10 000 different virus species. However, during the last few years, empirical formulas have been determined for less than 50 species, while thermodynamic properties are known for less than 70 species. Various virus species (and variants) are characterized by specific empirical formulas. For example, the Hu-1 variant (wild type) of SARS CoV-2 is characterized by its specific empirical formula $CH_{1.6390}O_{0.2851}N_{0.2301}P_{0.0065}S_{0.0038}$ [Popovic and Minceva, 2020b; Popovic, 2022f]. The empirical formula of the Ebola virus is $CH_{1.569}O_{0.3281}N_{0.2786}P_{0.00173}S_{0.00258}$ [Popovic, 2022f]. This difference in empirical formulas can be used for identification of various virus species and their variants, using single particle inductively coupled plasma mass spectroscopy analysis (SP-ICP-MS) [Degueldre, 2021] or the atom counting method [Popovic, 2022a]. Moreover, each variant of SARS-CoV-2 is characterized by its own empirical formula [Popovic, 2022b, 2022c, 2022d, 2022e, Popovic and Minceva, 2020b].

Panta rhei. World is moving and changing. The natural driving forces are hidden in the objective world and the human body. What were the physicochemical forces that drives life? Organisms perform biological and chemical processes. The driving force of all chemical processes in animate and inanimate matter represents Gibbs energy [Atkins and de Paula, 2011, 2014; Balmer, 2011; Demirel, 2014, von Stockar, 2013a]. This is why Gibbs energy represents the driving force for interactions of organisms with their environment [von Stockar, 2013a, 2013b; von Stockar and Liu, 1999; Liu et al., 2007; Patiño et al., 2007].

Viruses represent obligate intracellular parasites [Gelderblom, 1996]. This is why the environment of viruses during their life cycle is animate matter – host cell. Thus, the virus interacts with its host cell at the membrane, by binding to specific receptors on host cell surface and entry into host cells, as well as inside the cell in the cytoplasm, performing replication, transcription, translation, self-assembly and maturation. After maturation, new virions leave the cell, leading to its damage. All these phenomena represent chemical reactions or physical processes. Antigen-receptor binding represents a chemical reaction similar to protein ligand interactions [Popovic, 2022f, Du et al., 2016]. Transcription represents the process of transmission of information that in its basis represents polymerization of nucleotides into RNA [Pinheiro et al., 2008]. Translation represents a process of conversion of information from the RNA code into a protein code, based on a polymerization reaction of amino acids [Lee et al., 2020]. Both these process, as well as replication of nucleic acids [Dodd et al., 2020; Johansson and Dixon, 2013] are driven by Gibbs energy of biosynthesis. Biosynthesis reaction of structural and functional proteins of cells and biosynthesis of virus components are competitive. According to equations (1) and (3), reaction rate depends on Gibbs energy of biosynthesis. During competition, the reaction that occurs faster has an advantage. This is the way in which a virus hijacks the host cell's metabolism. In order to predict the outcome of this interaction, it is necessary to know thermodynamic properties (Gibbs energy, entropy and enthalpy) of both the virus and its host cell.

The permissiveness coefficient represents the ratio of rates of biosynthesis of virus components and host cell components. A permissiveness coefficient greater than 1 indicates the advantage in synthesis of virus components, leading to a successful viral life cycle inside the host. The permissiveness coefficient, P, is given by the equation

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$$P = \frac{r_{bs}(virus)}{r_{bs}(host)} = \frac{\Delta_{bs}G^0(virus)}{\Delta_{bs}G^0(host)} \quad (4)$$

where r_{bs} represents biosynthesis rate, while $\Delta_{bs}G^0$ is standard Gibbs energy of biosynthesis [Popovic, 2022h]. By comparing permissiveness coefficients for two different viruses (or virus variants) for the same host tissue, it is possible to conclude whether during simultaneous contact with both viruses by the same host, there will be coinfection or interference. This practical application can be of use to epidemiologists and infectologists, since it is not rare for two viruses to appear in the same population at the same time and in the same place. If permissiveness coefficients of two viruses are similar for the same tissue, then the probabilities of virus multiplication will be similar. Such was the case with SARS-CoV-2 and rhinovirus [Popovic and Minceva, 2021a]. This resulted in simultaneous occurrence of COVID-19 pandemic and an epidemic caused by the rhinovirus. Also, a similar observation was made with epidemics caused by influenza and parainfluenza viruses. On the other hand, if there is a significant difference in permissiveness coefficients between two potential causes of epidemics, then one epidemic will suppress the other. This happened in the winters 2020/21 and 2021/22, when the influenza epidemics did not occur during the COVID-19 pandemic [Popovic and Minceva, 2021a].

It is obvious that biothermodynamics of viruses is able to offer a wide variety of important information, useful first of all to virologists, microbiologists, biologists, epidemiologists and infectologists. Knowing thermodynamic properties and mechanistic models that are developed in biothermodynamics can shed more light on basic processes from the domains of biophysics and chemistry, which represent the basis for biological phenomena. The immune response (humoral) implies antigen-antibody reaction. The antigen-antibody reaction is similar to protein-ligand interactions. Thus, driving force for antigen-antibody interaction is Gibbs energy of this interaction. Cellular immune response is related to mobilization of immune cells and thus increase in their number. This results in growth. Growth, like with other cells, represents a biological and biothermodynamic phenomenon, driven by Gibbs energy of growth. Thus it is necessary to know thermodynamic properties of immune cells. After an extensive search of the literature, the author could not find data on thermodynamic properties of lymphocytes, leukocytes and macrophages. Infection is a complex biological process, which except for the infective agent (microorganism) involves a host cell/tissue and immune cells. To reveal the thermodynamic basis of infections in full, it is necessary to know all 3 elements (thermodynamic properties of microorganisms, immune system and host cells). Biothermodynamics is a young discipline and obviously faces many challenges and a great work that needs to be done. The effort on the development of biothermodynamics seems justified, since it can greatly help explanation of pathogeneses of many diseases that occur as a result of microorganism-host interactions.

Time evolution of viruses can be followed through change in Gibbs energies of binding and biosynthesis [Popovic, 2022k]. Viruses exhibit a tendency to mutate. RNA viruses exhibit a greater tendency to mutate than DNA viruses [Duffy, 2018]. Mutations lead to change in information contained in the virus nucleic acid, but also change in empirical formula of the virus and its thermodynamic properties. During time and acquisition of new mutations, it is possible to follow changes in thermodynamic properties of viruses. A tendency was observed in the temporal evolution of viruses towards more negative Gibbs energy of binding [Popovic, 2022k]. This can be related to the prediction of the theory of evolution, that viruses should become more and more adapted to their host with time [Popovic, 2022k].

4. Conclusion

Biothermodynamics of viruses is among the youngest scientific disciplines. However, appearance of new viruses, their rapid mutation, which can lead to epidemics and pandemics with a great number of cases and casualties, have given an impulse for the very rapid development of biothermodynamics of viruses. Knowing biothermodynamic

properties can give useful information to epidemiologists and infectologists about the mechanism of virus-host interaction and virus-virus competition. Knowing empirical formulas of viruses is significant because it allows fast and accurate identification of known viruses or detection of new viruses or variants. Moreover, phenomenological equations, which belong to nonequilbrium thermodynamics, have proven themselves an important tool for analysis of rates of antigen-receptor binding and rate of virus multiplication inside host cells. The permissiveness coefficient could be useful during estimation of the degree of damage to host tissues, caused by multiplication of viruses, as well as assessment of the outcome of virus-virus competition during simultaneous presence of two viruses or virus variants in the same time and the same place.

References:

Aladag, A., Hoffmann, S., Stoldt, M., Bösing, C., Willbold, D., & Schwarten, M. (2014). Hepatitis C virus NS5A is able to competitively displace c-Myc from the Bin1 SH3 domain in vitro. *Journal of peptide science : an official publication of the European Peptide Society*, *20*(5), 334–340. https://doi.org/10.1002/psc.2618

Annamalai, K. (2021). Oxygen Deficient (OD) Combustion and Metabolism: Allometric Laws of Organs and Kleiber's Law from OD Metabolism? *Systems*, *9*(3), 54. MDPI AG. Retrieved from http://dx.doi.org/10.3390/systems9030054

Annamalai, K., & Nanda, A. (2017). Biological Aging and Life Span Based on Entropy Stress via Organ and Mitochondrial Metabolic Loading. *Entropy*, *19*(10), 566. MDPI AG. Retrieved from http://dx.doi.org/10.3390/e19100566

Annamalai, K., & Miller, J. A. (2017). Link between O2 Deficient Metabolism in Organs and Group Combustion in Engineering. In *Proceedings of the 10th US National Combustion Meeting, College Park, MD, USA* (pp. 23-26).

Annamalai, K., & Silva, C. (2012). Entropy Stress and Scaling of Vital Organs over Life Span Based on Allometric Laws. *Entropy*, *14*(12), 2550–2577. MDPI AG. Retrieved from http://dx.doi.org/10.3390/e14122550

Anasir, M. I., Caria, S., Skinner, M. A., & Kvansakul, M. (2017). Structural basis of apoptosis inhibition by the fowlpox virus protein FPV039. *The Journal of biological chemistry*, *292*(22), 9010–9021. https://doi.org/10.1074/jbc.M116.768879

Atkins, P. W., & de Paula, J. (2011). *Physical Chemistry for the Life Sciences (2nd edition)*, W. H. Freeman and Company. ISBN-13: 978-1429231145

Atkins, P.W. & de Paula, J. (2014). *Physical Chemistry: Thermodynamics, Structure, and Change, 10th Edition*. New York: W. H. Freeman and Company. ISBN-13: 978-1429290197

Balmer, R.T. (2010). *Modern Engineering Thermodynamics*, Cambridge, MA: Academic Press. https://doi.org/10.1016/C2009-0-20199-1

Banerjee, M., Speir, J. A., Kwan, M. H., Huang, R., Aryanpur, P. P., Bothner, B., & Johnson, J. E. (2010). Structure and function of a genetically engineered mimic of a nonenveloped virus entry intermediate. *Journal of virology*, *84*(9), 4737–4746. https://doi.org/10.1128/JVI.02670-09

Barros, N. (2021). Thermodynamics of Soil Microbial Metabolism: Applications and Functions. *Applied Sciences*, *11*(11), 4962. MDPI AG. Retrieved from http://dx.doi.org/10.3390/app11114962

Barros, N., Fernandez, I., Byrne, K. A., Jovani-Sancho, A. J., Ros-Mangriñan, E., & Hansen, L. D. (2020). Thermodynamics of soil organic matter decomposition in semi-natural oak (Quercus) woodland in southwest Ireland. *Oikos*, *129*(11), 1632-1644. https://doi.org/10.1111/oik.07261

Barros, N., Hansen, L. D., Piñeiro, V., Pérez-Cruzado, C., Villanueva, M., Proupín, J., & Rodríguez-Añón, J. A. (2016). Factors influencing the calorespirometric ratios of soil microbial metabolism. *Soil Biology and Biochemistry*, *92*, 221-229. https://doi.org/10.1016/j.soilbio.2015.10.007

Barton, M. I., MacGowan, S. A., Kutuzov, M. A., Dushek, O., Barton, G. J., & van der Merwe, P. A. (2021). Effects of common mutations in the SARS-CoV-2 Spike RBD and its ligand, the human ACE2 receptor on binding affinity and kinetics. eLife, 10, e70658. https://doi.org/10.7554/eLife.70658

Battley E. H. (2013). A theoretical study of the thermodynamics of microbial growth using Saccharomyces cerevisiae and a different free energy equation. *The Quarterly review of biology*, *88*(2), 69–96. https://doi.org/10.1086/670529

Battley, E.H. (1999a). An empirical method for estimating the entropy of formation and the absolute entropy of dried microbial biomass for use in studies on the thermodynamics of microbial growth. *Thermochimica Acta*, 326(1-2), 7-15. https://doi.org/10.1016/S0040-6031(98)00584-X

Battley, E.H. (1999b). The thermodynamics of microbial growth. In: *Handbook of Thermal Analysis and Calorimetry*, vol. 4: *From Macromolecules to Man*; *E.B. Kemp, ed.*, Amsterdam: Elsevier, 219-235. https://doi.org/10.1016/S1573-4374(99)80008-9

Battley, E.H. (1998). The development of direct and indirect methods for the study of the thermodynamics of microbial growth. *Thermochimica Acta*, 309 (1-2), 17-37. https://doi.org/10.1016/S0040-6031(97)00357-2

Battley, E.H., Putnam, R.L. and Boerio-Goates, J. (1997). Heat capacity measurements from 10 to 300 K and derived thermodynamic functions of lyophilized cells of Saccharomyces cerevisiae including the absolute entropy and the entropy of formation at 298.15 K. *Thermochimica Acta*, 298(1-2). 37-46. https://doi.org/10.1016/S0040-6031(97)00108-1

Battley, E.H. (1992). On the enthalpy of formation of Escherichia coli K-12 cells, *Biotechnology and Bioengineering*, 39, 5-12. https://doi.org/10.1002/bit.260390103

Bauer, D. W., Li, D., Huffman, J., Homa, F. L., Wilson, K., Leavitt, J. C., Casjens, S. R., Baines, J., & Evilevitch, A. (2015). Exploring the Balance between DNA Pressure and Capsid Stability in Herpesviruses and Phages. *Journal of virology*, *89*(18), 9288–9298. https://doi.org/10.1128/JVI.01172-15

Bauer, D. W., Huffman, J. B., Homa, F. L., & Evilevitch, A. (2013). Herpes virus genome, the pressure is on. *Journal of the American Chemical Society*, *135*(30), 11216–11221. https://doi.org/10.1021/ja404008r

Beatty, J. D., Beatty, B. G., & Vlahos, W. G. (1987). Measurement of monoclonal antibody affinity by non-competitive enzyme immunoassay. *Journal of immunological methods*, *100*(1-2), 173–179. https://doi.org/10.1016/0022-1759(87)90187-6

Berg, J.M., Tymoczko, J.L. and Stryer, L. (2002). Biochemistry, 5th ed. New York: W H Freeman.

Boltzmann, L. (1974). The second law of thermodynamics. In: *Theoretical physics and philosophical problems*, McGuinnes, B., ed., Boston, MA: D. Riedel Publishing Company, LLC. ISBN 978-90-277-0250-0 (translation of the original version published in 1886)

Brouillette, C. G., Compans, R. W., Brandts, J. F., & Segrest, J. P. (1982). Structural domains of vesicular stomatitis virus. A study by differential scanning calorimetry, thermal gel analysis, and thermal electron microscopy. *The Journal of biological chemistry*, *257*(1), 12–15. PMID: 6273421

Buzón, P., Maity, S., & Roos, W. H. (2020). Physical virology: From virus self-assembly to particle mechanics. *Wiley interdisciplinary reviews. Nanomedicine and nanobiotechnology*, *12*(4), e1613. https://doi.org/10.1002/wnan.1613

Byrn, R. A., Jones, S. M., Bennett, H. B., Bral, C., Clark, M. P., Jacobs, M. D., Kwong, A. D., Ledeboer, M. W., Leeman, J. R., McNeil, C. F., Murcko, M. A., Nezami, A., Perola, E., Rijnbrand, R., Saxena, K., Tsai, A. W., Zhou, Y., & Charifson, P. S. (2015). Preclinical activity of VX-787, a first-in-class, orally bioavailable inhibitor of the influenza

virus polymerase PB2 subunit. *Antimicrobial agents and chemotherapy*, *59*(3), 1569–1582. https://doi.org/10.1128/AAC.04623-14

Callaway E. (2020). The coronavirus is mutating - does it matter?. *Nature*, *585*(7824), 174–177. https://doi.org/10.1038/d41586-020-02544-6

Carnot, L. (1786). *Essai sur les machines en général*. Dijon, France : De l'imprimerie de Defay. (English translation: "Essay on machines in general") ISBN-13: 978-1147666625

Carnot, L. (1803). *Principes fondamentaux de l'équilibre et du movement*. Paris, France: De l'imprimerie de Crapelet. (English translation: "Fundamental principles of equilibrium and movement") ISBN: 2016170190

Carnot, S. (1824). *Réflexions sur la puissance motrice du feu et sur les machines propres à développer cette puissance*. Paris, France: Bachelier. (English translation: "Reflections on the motive power of fire and on machines fitted to develop that power") ISBN-13: 978-0486446417

Casasnovas, J.M. and Springer, T.A. (1995). Kinetics and thermodynamics of virus binding to receptor: Studies with rhinovirus, intercellular adhesion molecule-1 (ICAM-1), and surface plasmon resonance. *Journal of Biological Chemistry*, 270(22), 13216-13224. https://www.doi.org/10.1074/jbc.270.22.13216

Clausius, R. (1867). The Mechanical Theory of Heat – with its Applications to the Steam Engine and to Physical Properties of Bodies, London: John van Voorst.

Clausius, R. (1870). On a Mechanical Theorem Applicable to Heat, Philosophical Magazine Series 4, 40 (1870), 265, p. 122

Clausius, R. (1976). On different forms of the fundamental equations of the mechanical theory of heat and their convenience for application, In: *The Second Law of Thermodynamics*; J. Kestin, ed., Stroudsburg, PA: Dowen, Hutchingson and Ross, Inc. ISBN-13: 978-0470989449

Dance A. (2021). Beyond coronavirus: the virus discoveries transforming biology. *Nature*, *595*(7865), 22–25. https://doi.org/10.1038/d41586-021-01749-7

Degueldre, C. (2021). Single virus inductively coupled plasma mass spectroscopy analysis: A comprehensive study. *Talanta*, *228*, 122211. https://doi.org/10.1016/j.talanta.2021.122211

Demirel, Y. (2014). *Nonequilibrium Thermodynamics: Transport and Rate Processes in Physical, Chemical and Biological Systems, 3rd ed*. Amsterdam: Elsevier. ISBN: 9780444595812

Deschuyteneer, M., Elouahabi, A., Plainchamp, D., Plisnier, M., Soete, D., Corazza, Y., Lockman, L., Giannini, S., & Deschamps, M. (2010). Molecular and structural characterization of the L1 virus-like particles that are used as vaccine antigens in Cervarix™, the AS04-adjuvanted HPV-16 and -18 cervical cancer vaccine. *Human vaccines*, *6*(5), 407–419. https://doi.org/10.4161/hv.6.5.11023

Djamali, E., Nulton, J. D., Turner, P. J., Rohwer, F., & Salamon, P. (2012). Heat output by marine microbial and viral communities. *Journal of Non-Equilibrium Thermodynamics*, *37*(3), 291-313. https://doi.org/10.1515/jnetdy-2011-0235

Dodd, T., Botto, M., Paul, F. et al. (2020). Polymerization and editing modes of a high-fidelity DNA polymerase are linked by a well-defined path. *Nat Commun* 11, 5379. https://doi.org/10.1038/s41467-020-19165-2

Du, X., Li, Y., Xia, Y. L., Ai, S. M., Liang, J., Sang, P., ... & Liu, S. Q. (2016). Insights into protein–ligand interactions: mechanisms, models, and methods. *International journal of molecular sciences*, *17*(2), 144. https://doi.org/10.3390/ijms17020144

Duboc, P., Marison, I., & Von Stockar, U. (1999). Quantitative calorimetry and biochemical engineering. In: *Handbook of Thermal Analysis and Calorimetry*, vol. 4: *From Macromolecules to Man*; *E.B. Kemp, ed.*, Amsterdam: Elsevier, 267-365. https://doi.org/10.1016/S1573-4374(99)80009-0

Duffy S. (2018). Why are RNA virus mutation rates so damn high?. *PLoS biology*, *16*(8), e3000003. https://doi.org/10.1371/journal.pbio.3000003

Elbe, S., & Buckland-Merrett, G. (2017). Data, disease and diplomacy: GISAID's innovative contribution to global health. *Global challenges (Hoboken, NJ)*, *1*(1), 33–46. https://doi.org/10.1002/gch2.1018

Fanaei Pirlar, R., Wagemans, J., Ponce Benavente, L., Lavigne, R., Trampuz, A., & Gonzalez Moreno, M. (2022). Novel Bacteriophage Specific against Staphylococcus epidermidis and with Antibiofilm Activity. *Viruses*, *14*(6), 1340. MDPI AG. Retrieved from http://dx.doi.org/10.3390/v14061340

Gale P. (2021). Using thermodynamic equilibrium models to predict the effect of antiviral agents on infectivity: Theoretical application to SARS-CoV-2 and other viruses. Microbial risk analysis, 100198. Advance online publication. https://doi.org/10.1016/j.mran.2021.100198

Gale P. (2020). How virus size and attachment parameters affect the temperature sensitivity of virus binding to host cells: Predictions of a thermodynamic model for arboviruses and HIV. *Microbial risk analysis*, *15*, 100104. https://doi.org/10.1016/j.mran.2020.100104

Gale P. (2019). Towards a thermodynamic mechanistic model for the effect of temperature on arthropod vector competence for transmission of arboviruses. *Microbial risk analysis*, *12*, 27–43. https://doi.org/10.1016/j.mran.2019.03.001

Gale P. (2018). Using thermodynamic parameters to calibrate a mechanistic dose-response for infection of a host by a virus. *Microbial risk analysis*, *8*, 1–13. https://doi.org/10.1016/j.mran.2018.01.002

Gao, X., Zhu, K., Qin, B., Olieric, V., Wang, M., & Cui, S. (2021). Crystal structure of SARS-CoV-2 Orf9b in complex with human TOM70 suggests unusual virus-host interactions. *Nature communications*, *12*(1), 2843. https://doi.org/10.1038/s41467-021-23118-8

Garmann, R. F., Goldfain, A. M., & Manoharan, V. N. (2019). Measurements of the self-assembly kinetics of individual viral capsids around their RNA genome. *Proceedings of the National Academy of Sciences of the United States of America*, *116*(45), 22485–22490. https://doi.org/10.1073/pnas.1909223116

Gelderblom, H. R. (1996). Structure and Classification of Viruses. In S. Baron (Ed.), *Medical Microbiology*. (4th ed.). University of Texas Medical Branch at Galveston. PMID: 21413309

Gelman, D., Yerushalmy, O., Alkalay-Oren, S., Rakov, C., Ben-Porat, S., Khalifa, L., Adler, K., Abdalrhman, M., Coppenhagen-Glazer, S., Aslam, S., Schooley, R. T., Nir-Paz, R., & Hazan, R. (2021). Clinical Phage Microbiology: a suggested framework and recommendations for the in-vitro matching steps of phage therapy. *The Lancet. Microbe*, *2*(10), e555–e563. https://doi.org/10.1016/S2666-5247(21)00127-0

Greinert, T., Baumhove, K., Sadowski, G. and Held, C. (2020a). Standard Gibbs energy of metabolic reactions: IV. Triosephosphate isomerase reaction. *Biophysical Chemistry*, 258, 106330. https://doi.org/10.1016/j.bpc.2020.106330

Greinert, T., Vogel, K., Seifert, A.I., Siewert, R., Andreeva, I.V., Verevkin, S.P., Maskow, T., Sadowski, G. and Held, C. (2020b). Standard Gibbs energy of metabolic reactions: V. Enolase reaction, *Biochimica et Biophysica Acta (BBA) - Proteins and Proteomics*, 1868(4), 140365. https://doi.org/10.1016/j.bbapap.2020.140365

Greinert, T., Vogel, K., Mühlenweg, J. K., Sadowski, G., Maskow, T., & Held, C. (2020c). Standard Gibbs energy of metabolic reactions: VI. Glyceraldehyde 3-phosphate dehydrogenase reaction. *Fluid Phase Equilibria*, *517*, 112597. https://doi.org/10.1016/j.fluid.2020.112597

Guosheng, L., Yi, L., Xiangdong, C., Peng, L., Ping, S., & Songsheng, Q. (2003). Study on interaction between T4 phage and Escherichia coli B by microcalorimetric method. *Journal of virological methods*, *112*(1-2), 137–143. https://doi.org/10.1016/s0166-0934(03)00214-3

Han, P., Li, L., Liu, S., Wang, Q., Zhang, D., Xu, Z., Han, P., Li, X., Peng, Q., Su, C., Huang, B., Li, D., Zhang, R., Tian, M., Fu, L., Gao, Y., Zhao, X., Liu, K., Qi, J., Gao, G. F., … Wang, P. (2022). Receptor binding and complex structures of human ACE2 to spike RBD from omicron and delta SARS-CoV-2. *Cell*, S0092-8674(22)00001-0. Advance online publication. https://doi.org/10.1016/j.cell.2022.01.001

Hansen, L. D., Tolley, H. D., & Woodfield, B. F. (2021). Transformation of matter in living organisms during growth and evolution. *Biophysical Chemistry*, *271*, 106550. https://doi.org/10.1016/j.bpc.2021.106550

Hansen, L. D., Popovic, M., Tolley, H. D., & Woodfield, B. F. (2018). Laws of evolution parallel the laws of thermodynamics. *The Journal of Chemical Thermodynamics*, *124*, 141-148. https://doi.org/10.1016/j.jct.2018.05.005

Hansen, L. D., Criddle, R. S., & Battley, E. H. (2009). Biological calorimetry and the thermodynamics of the origination and evolution of life. *Pure and Applied Chemistry*, *81*(10), 1843-1855. https://doi.org/10.1351/PAC-CON-08-09-09

Hayflick, L. (2016). Unlike the Stochastic Events That Determine Ageing, Sex Determines Longevity. In: Rattan, S., Hayflick, L. (eds) Cellular Ageing and Replicative Senescence. Healthy Ageing and Longevity. Springer, Cham. https://doi.org/10.1007/978-3-319-26239-0_17

Hayflick, L. (2010). Unlike ageing, longevity is sexually transmitted. *Médecine & Longévité*, *2*(3), 114-128. https://doi.org/10.1016/j.mlong.2010.07.004

Hayflick, L. (2007a). Entropy explains aging, genetic determinism explains longevity, and undefined terminology explains misunderstanding both. *PLoS genetics*, *3*(12), e220. https://doi.org/10.1371/journal.pgen.0030220

Hayflick L. (2007b). Biological aging is no longer an unsolved problem. *Annals of the New York Academy of Sciences*, *1100*, 1–13. https://doi.org/10.1196/annals.1395.001

Hayflick, L. (2003). Modulating aging, longevity determination and the diseases of old age. *Modulating Aging and Longevity*, *5*, 1.

Hayflick, L. (2001). The Quest for Immortality: Science at the Frontiers of Aging. *Radiation Research*, *156*(3), 334-336. https://doi.org/10.1667/0033-7587(2001)156[0334:]2.0.CO;2

Hayflick L. (1998). How and why we age. *Experimental gerontology*, *33*(7-8), 639–653. https://doi.org/10.1016/s0531-5565(98)00023-0

Hayflick, L. (1985). Theories of biological aging. *Experimental gerontology*, *20*(3-4), 145-159. https://doi.org/10.1016/0531-5565(85)90032-4

Hou, W., Armstrong, N., Obwolo, L. A., Thomas, M., Pang, X., Jones, K. S., & Tang, Q. (2017). Determination of the Cell Permissiveness Spectrum, Mode of RNA Replication, and RNA-Protein Interaction of Zika Virus. *BMC infectious diseases*, *17*(1), 239. https://doi.org/10.1186/s12879-017-2338-4

Hurst, J.E. and Harrison, B.K. (1992). Estimation of liquid and solid heat capacities using a modified Kopp's rule. *Chemical Engineering Communications*, 112(1), 21–30. https://doi.org/10.1080/00986449208935989

Javorsky, A., Maddumage, J. C., Mackie, E., Soares da Costa, T. P., Humbert, P. O., & Kvansakul, M. (2022). Structural insight into the Scribble PDZ domains interaction with the oncogenic Human T-cell lymphotrophic virus-1 (HTLV-1) Tax1 PBM. *The FEBS journal*, 10.1111/febs.16607. Advance online publication. https://doi.org/10.1111/febs.16607

Johansson, E., & Dixon, N. (2013). Replicative DNA polymerases. *Cold Spring Harbor perspectives in biology*, *5*(6), a012799. https://doi.org/10.1101/cshperspect.a012799

Kawahara, T., Akiba, I., Sakou, M., Sakaguchi, T., & Taniguchi, H. (2018). Inactivation of human and avian influenza viruses by potassium oleate of natural soap component through exothermic interaction. *PloS one*, *13*(9), e0204908. https://doi.org/10.1371/journal.pone.0204908

Khare, S., Gurry, C., Freitas, L., Schultz, M. B., Bach, G., Diallo, A., Akite, N., Ho, J., Lee, R. T., Yeo, W., Curation Team, G. C., & Maurer-Stroh, S. (2021). GISAID's Role in Pandemic Response. *China CDC weekly*, *3*(49), 1049–1051. https://doi.org/10.46234/ccdcw2021.255

Krell, T., Manin, C., Nicolaï, M. C., Pierre-Justin, C., Bérard, Y., Brass, O., Gérentes, L., Leung-Tack, P., & Chevalier, M. (2005). Characterization of different strains of poliovirus and influenza virus by differential scanning calorimetry. *Biotechnology and applied biochemistry*, *41*(Pt 3), 241–246. https://doi.org/10.1042/BA20040113

Kümmel, A., Panke, S., & Heinemann, M. (2006). Systematic assignment of thermodynamic constraints in metabolic network models. *BMC bioinformatics*, *7*, 512. https://doi.org/10.1186/1471-2105-7-512

Lavoisier, AL, & marquis de Laplace, PS (1783). *Mémoire sur la chaleur: Lû à'Académie royale des sciences, le 28 Juin 1783*. Paris, France: De l'Imprimerie royale. (English translation: "Memoir on Heat Read to the Royal Academy of Sciences, 28 June 1783")

Lavoisier, A. L., & DeLaplace, P. S. (1994). Memoir on heat read to the royal academy of sciences, 28 june 1783. *Obesity research*, *2*(2), 189-202. https://doi.org/10.1002/j.1550-8528.1994.tb00646.x (Modern translation in English)

Lee, J., Schwarz, K. J., Kim, D. S., Moore, J. S., & Jewett, M. C. (2020). Ribosome-mediated polymerization of long chain carbon and cyclic amino acids into peptides in vitro. *Nature communications*, *11*(1), 4304. https://doi.org/10.1038/s41467-020-18001-x

Liu, T., Sae-Ueng, U., Li, D., Lander, G. C., Zuo, X., Jönsson, B., Rau, D., Shefer, I., & Evilevitch, A. (2014). Solid-to-fluid-like DNA transition in viruses facilitates infection. *Proceedings of the National Academy of Sciences of the United States of America*, *111*(41), 14675–14680. https://doi.org/10.1073/pnas.1321637111

Liu, J. S., Vojinović, V., Patino, R., Maskow, T., & von Stockar, U. (2007). A comparison of various Gibbs energy dissipation correlations for predicting microbial growth yields. *Thermochimica Acta*, *458*(1-2), 38-46. https://doi.org/10.1016/j.tca.2007.01.016

Lucia, U., Grisolia, G., & Deisboeck, T. S. (2021). Thermodynamics and SARS-CoV-2: neurological effects in post-Covid 19 syndrome. *Atti della Accademia Peloritana dei Pericolanti*, 99(2), A3. https://doi.org/10.1478/AAPP.992A3

Lucia, U., Grisolia, G., & Deisboeck, T. S. (2020a). Seebeck-like effect in SARS-CoV-2 bio-thermodynamics. *Atti della Accademia Peloritana dei Pericolanti-Classe di Scienze Fisiche, Matematiche e Naturali*, *98*(2), 6. https://doi.org/10.1478/AAPP.982A6

Lucia, U., Deisboeck, T. S., & Grisolia, G. (2020b). Entropy-based pandemics forecasting. *Frontiers in Physics*, *8*, 274. https://doi.org/10.3389/fphy.2020.00274Mahmoudabadi, G., Milo, R. and Phillips, R. (2017). Energetic cost of building a virus. *PNAS*, 114(22), E4324-E4333. https://doi.org/10.1073/pnas.1701670114

Maassen, S. J., Huskens, J., & Cornelissen, J. (2019). Elucidating the Thermodynamic Driving Forces of Polyanion-Templated Virus-like Particle Assembly. *The journal of physical chemistry. B*, *123*(46), 9733–9741. https://doi.org/10.1021/acs.jpcb.9b06258

Makarov, V. V., Skurat, E. V., Semenyuk, P. I., Abashkin, D. A., Kalinina, N. O., Arutyunyan, A. M., Solovyev, A. G., & Dobrov, E. N. (2013). Structural lability of Barley stripe mosaic virus virions. *PloS one*, *8*(4), e60942. https://doi.org/10.1371/journal.pone.0060942

Maskow, T., & Paufler, S. (2015). What does calorimetry and thermodynamics of living cells tell us?. *Methods*, *76*, 3-10. https://doi.org/10.1016/j.ymeth.2014.10.035

Maskow, T. (2013). Miniaturization of calorimetry: Strengths and weaknesses for bioprocess monitoring. In: *Biothermodynamics: the role of thermodynamics in Biochemical Engineering*, von Stockar, U., ed., Lausanne: EPFL Press, pp. 423-442.

Maskow, T., Kemp, R., Buchholz, F., Schubert, T., Kiesel, B., & Harms, H. (2010a). What heat is telling us about microbial conversions in nature and technology: from chip- to megacalorimetry. *Microbial biotechnology*, *3*(3), 269–284. https://doi.org/10.1111/j.1751-7915.2009.00121.x

Maskow, T., Kiesel, B., Schubert, T., Yong, Z., Harms, H., & Yao, J. (2010b). Calorimetric real time monitoring of lambda prophage induction. *Journal of virological methods*, *168*(1-2), 126–132. https://doi.org/10.1016/j.jviromet.2010.05.002

Maskow, T., & Harms, H. (2006). Real time insights into bioprocesses using calorimetry: state of the art and potential. *Engineering in Life Sciences*, *6*(3), 266-277. https://doi.org/10.1002/elsc.200520123

Meurer, F., Bobrownik, M., Sadowski, G. and Held, C. (2016). Standard Gibbs energy of metabolic reactions: I. Hexokinase reaction, *Biochemistry*, 55(40), 5665-5674. https://doi.org/10.1021/acs.biochem.6b00471

Meurer, F., Do, H.T., Sadowski, G. and Held, C. (2017). Standard Gibbs energy of metabolic reactions: II. Glucose-6-phosphatase reaction and ATP hydrolysis. *Biophysical Chemistry*, 223, 30-38. https://doi.org/10.1016/j.bpc.2017.02.005

Molla, A., Paul, A. V., & Wimmer, E. (1991). Cell-free, de novo synthesis of poliovirus. *Science (New York, N.Y.)*, *254*(5038), 1647–1651. https://doi.org/10.1126/science.1661029

Morais, F.M., Buchholz, F., Hartmann, T. *et al.* (2014). Chip-calorimetric monitoring of biofilm eradication with bacteriophages reveals an unexpected infection-related heat profile. *J Therm Anal Calorim* **115**, 2203–2210. https://doi.org/10.1007/s10973-013-3494-4

Morowitz, H.J. (1992). *Beginnings of Cellular Life: Metabolism Recapitulates Biogenesis*. New Haven, CT: Yale University Press. ISBN-13: 978-0300102109

Morowitz, H.J. (1968). *Energy Flow in Biology: Biological Organization as a Problem in Thermal Physics*. New York: Academic Press. https://lccn.loc.gov/67031041

Morowitz, H.J. (1955). Some order-disorder considerations in living systems. Bulletin of Mathematical Biophysics, 17, 81–86. https://doi.org/10.1007/BF02477985

Müller, I. (2010). *A History of Thermodynamics: The Doctrine of Energy and Entropy*. Berlin: Springer. ISBN-13: 978-3642079641

NCBI (2022). NCBI database [online] National Center for Biotechnology Information, Available at: https://www.ncbi.nlm.nih.gov/ (Accessed on November 5, 2022)

Nebel, S., Bartoldus, I., & Stegmann, T. (1995). Calorimetric detection of influenza virus induced membrane fusion. *Biochemistry*, *34*(17), 5705–5711. https://doi.org/10.1021/bi00017a001

Niebel, B., Leupold, S., & Heinemann, M. (2019). An upper limit on Gibbs energy dissipation governs cellular metabolism. *Nature metabolism*, *1*(1), 125–132. https://doi.org/10.1038/s42255-018-0006-7

Noble, C. G., Lim, S. P., Arora, R., Yokokawa, F., Nilar, S., Seh, C. C., Wright, S. K., Benson, T. E., Smith, P. W., & Shi, P. Y. (2016). A Conserved Pocket in the Dengue Virus Polymerase Identified through Fragment-based Screening. *The Journal of biological chemistry*, *291*(16), 8541–8548. https://doi.org/10.1074/jbc.M115.710731

Ould-Moulaye, C. B., Dussap, C. G., & Gros, J. B. (1999). Estimation of Gibbs energy changes of central metabolism reactions. *Biotechnology techniques*, *13*(3), 187-193. https://doi.org/10.1023/A:1008962302957

Ozilgen, M. and Sorgüven, E. (2017). *Biothermodynamics: Principles and Applications.* Boca Raton: CRC Press. https://doi.org/10.1201/9781315374147

Patiño, R., Janssen, M., & von Stockar, U. (2007). A study of the growth for the microalga Chlorella vulgaris by photo-bio-calorimetry and other on-line and off-line techniques. *Biotechnology and bioengineering*, *96*(4), 757–767. https://doi.org/10.1002/bit.21182

Pinheiro, A. V., Baptista, P., & Lima, J. C. (2008). Light activation of transcription: photocaging of nucleotides for control over RNA polymerization. *Nucleic acids research*, *36*(14), e90. https://doi.org/10.1093/nar/gkn415

Popovic, M. and Popovic, M. (2022). Strain Wars: Competitive interactions between SARS-CoV-2 strains are explained by Gibbs energy of antigen-receptor binding. *Microbial Risk Analysis*. https://doi.org/10.1016/j.mran.2022.100202

Popovic M. (2022a). Atom counting method for determining elemental composition of viruses and its applications in biothermodynamics and environmental science. *Computational biology and chemistry*, *96*, 107621. https://doi.org/10.1016/j.compbiolchem.2022.107621

Popovic, M. (2022b). Strain wars 2: Binding constants, enthalpies, entropies, Gibbs energies and rates of binding of SARS-CoV-2 variants. *Virology*, 570, 35-44. https://doi.org/10.1016/j.virol.2022.03.008

Popovic M. (2022c). Strain wars 3: Differences in infectivity and pathogenicity between Delta and Omicron strains of SARS-CoV-2 can be explained by thermodynamic and kinetic parameters of binding and growth. *Microbial risk analysis*, 100217. Advance online publication. https://doi.org/10.1016/j.mran.2022.100217

Popovic, M. (2022d). Strain Wars 4 - Darwinian evolution through Gibbs' glasses: Gibbs energies of binding and growth explain evolution of SARS-CoV-2 from Hu-1 to BA.2. *Virology*. https://doi.org/10.1016/j.virol.2022.08.009

Popovic, M. (2022e). Strain Wars 5: Gibbs energies of binding of BA.1 through BA.4 variants of SARS-CoV-2. *Microbial Risk Analysis*. https://doi.org/10.1016/j.mran.2022.100231

Popovic, M. (2022f). Omicron BA.2.75 Subvariant of SARS-CoV-2 Is Expected to Have the Greatest Infectivity Compared with the Competing BA.2 and BA.5, Due to Most Negative Gibbs Energy of Binding. *BioTech*, 11(4), 45. MDPI AG. Retrieved from http://dx.doi.org/10.3390/biotech11040045

Popovic, M. (2022g). Formulas for death and life: Chemical composition and biothermodynamic properties of Monkeypox (MPV, MPXV, HMPXV) and Vaccinia (VACV) viruses. *Thermal Science*, 26(6A). https://doi.org/10.2298/TSCI220524142P

Popovic, M. (2022h). Why doesn't Ebola virus cause pandemics like SARS-CoV-2? *Microbial Risk Analysis*, 100236. https://doi.org/10.1016/j.mran.2022.100236

Popovic, M. (2022i). Omicron BA.2.75 Sublineage Follows the Expectations of the Evolution Theory: Less Negative Gibbs Energy of Biosynthesis Indicates Decreased Pathogenicity. Preprints 2022, 2022100386 (https://doi.org/10.20944/preprints202210.0386.v1).

Popovic, M. (2022j). Biothermodynamic Key Opens the Door of Life Sciences: Bridging the Gap between Biology and Thermodynamics. *Preprints*, 2022100326. https://doi.org/10.20944/preprints202210.0326.v1

Popovic, M. (2022k). Beyond COVID-19: Do biothermodynamic properties allow predicting the future evolution of SARS-CoV-2 variants?. *Microbial risk analysis*, *22*, 100232. https://doi.org/10.1016/j.mran.2022.100232

Popovic, M., Stenning, G., Göttlein, A., & Minceva, M. (2021). Elemental composition, heat capacity from 2 to 300 K and derived thermodynamic functions of 5 microorganism species. *Journal of biotechnology*, *331*, 99–107. https://doi.org/10.1016/j.jbiotec.2021.03.006

Popovic, M., & Minceva, M. (2021a). Coinfection and Interference Phenomena Are the Results of Multiple Thermodynamic Competitive Interactions. *Microorganisms*, *9*(10), 2060. https://doi.org/10.3390/microorganisms9102060

Popovic, M., & Minceva, M. (2021b). Standard Thermodynamic Properties, Biosynthesis Rates, and the Driving Force of Growth of Five Agricultural Plants. *Frontiers in plant science*, *12*, 671868. https://doi.org/10.3389/fpls.2021.671868

Popovic M. & Minceva, M. (2021c). Comment on: "A critical review on heat and mass transfer modelling of viral infection and virion evolution: The case of SARS-CoV2". *Thermal Science*. http://dx.doi.org/10.2298/TSCI211021329P

Popovic, M., & Minceva, M. (2020a). A thermodynamic insight into viral infections: do viruses in a lytic cycle hijack cell metabolism due to their low Gibbs energy?. *Heliyon*, *6*(5), e03933. https://doi.org/10.1016/j.heliyon.2020.e03933

Popovic, M., & Minceva, M. (2020b). Thermodynamic insight into viral infections 2: empirical formulas, molecular compositions and thermodynamic properties of SARS, MERS and SARS-CoV-2 (COVID-19) viruses. *Heliyon*, 6(9), e04943. https://dx.doi.org/10.1016%2Fj.heliyon.2020.e04943

Popovic, M. E., & Minceva, M. (2020c). Thermodynamic properties of human tissues. *Thermal Science*, *24*(6 Part B), 4115-4133. https://doi.org/10.2298/TSCI200109151P

Popovic, M., Woodfield, B. F., & Hansen, L. D. (2019). Thermodynamics of hydrolysis of cellulose to glucose from 0 to 100 C: cellulosic biofuel applications and climate change implications. *The Journal of Chemical Thermodynamics*, *128*, 244-250. https://doi.org/10.1016/j.jct.2018.08.006

Popovic, M. (2018a). Living organisms from Prigogine's perspective: an opportunity to introduce students to biological entropy balance. *Journal of Biological Education*, *52*(3), 294-300. https://doi.org/10.1080/00219266.2017.1357649

Popovic, M. (2018b). Research in entropy wonterland: A review of the entropy concept. *Thermal Science*, 22(2), 1163-1178. http://dx.doi.org/10.2298/TSCI180115012P

Popovic, M. (2017). Researchers in an Entropy Wonderland: A Review of the Entropy Concept, *arXiv:*1711.07326 [physics.chem-ph] https://doi.org/10.48550/arXiv.1711.07326

Popovic, M. (2014a). Comparative study of entropy and information change in closed and open thermodynamic systems. *Thermochimica Acta*, 598, 77-81. https://doi.org/10.1016/j.tca.2014.11.002

Popovic, M. (2014b). Entropy change of open thermodynamic systems in self-organizing processes. *Thermal Science*, 18(4), 1425-1432. https://doi.org/10.2298/TSCI140424065P

Prins, K. C., Binning, J. M., Shabman, R. S., Leung, D. W., Amarasinghe, G. K., & Basler, C. F. (2010). Basic residues within the ebolavirus VP35 protein are required for its viral polymerase cofactor function. *Journal of virology*, *84*(20), 10581–10591. https://doi.org/10.1128/JVI.00925-10

Privalov, P. L. (2012). *Microcalorimetry of macromolecules: the physical basis of biological structures*. Hoboken, NJ: John Wiley & Sons. ISBN: 978-1-118-10451-4

Roels, J.A. (1983). *Energetics and Kinetics in Biotechnology*, Amsterdam: Elsevier.

Rusnati, M., Chiodelli, P., Bugatti, A., & Urbinati, C. (2015). Bridging the past and the future of virology: surface plasmon resonance as a powerful tool to investigate virus/host interactions. *Critical reviews in microbiology*, *41*(2), 238–260. https://doi.org/10.3109/1040841X.2013.826177

Sandler, S. I., & Orbey, H. (1991). On the thermodynamics of microbial growth processes. *Biotechnology and bioengineering*, 38(7), 697–718. https://doi.org/10.1002/bit.260380704

Sandler, S.I. (2017). Chemical, Biochemical, and Engineering Thermodynamics, 5th ed. Hoboken, NJ: Wiley. ISBN: 978-1-119-32128-6

Sarge, S. M., Höhne, G. W., & Hemminger, W. (2014). *Calorimetry: fundamentals, instrumentation and applications*. Hoboken, NJ: John Wiley & Sons. ISBN: 978-3-527-32761-4

Sayers, E. W., Bolton, E. E., Brister, J. R., Canese, K., Chan, J., Comeau, D. C., Connor, R., Funk, K., Kelly, C., Kim, S., Madej, T., Marchler-Bauer, A., Lanczycki, C., Lathrop, S., Lu, Z., Thibaud-Nissen, F., Murphy, T., Phan, L., Skripchenko, Y., Tse, T., … Sherry, S. T. (2022). Database resources of the national center for biotechnology information. *Nucleic acids research*, *50*(D1), D20–D26. https://doi.org/10.1093/nar/gkab1112

Schrödinger, E. (1944). *What is life? The physical aspect of the living cell,* Cambridge: Cambridge university press. ISBN: 0-521-42708-8

Sharma, R., Fatma, B., Saha, A., Bajpai, S., Sistla, S., Dash, P. K., Parida, M., Kumar, P., & Tomar, S. (2016). Inhibition of chikungunya virus by picolinate that targets viral capsid protein. *Virology*, *498*, 265–276. https://doi.org/10.1016/j.virol.2016.08.029

Shu, Y., & McCauley, J. (2017). GISAID: Global initiative on sharing all influenza data - from vision to reality. *Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin*, *22*(13), 30494. https://doi.org/10.2807/1560-7917.ES.2017.22.13.30494

Silva, C. A., & Annamalai, K. (2009). Entropy generation and human aging: lifespan entropy and effect of diet composition and caloric restriction diets. *Journal of Thermodynamics*, 186723. https://doi.org/10.1155/2009/186723

Silva, C., & Annamalai, K. (2008). Entropy Generation and Human Aging: Lifespan Entropy and Effect of Physical Activity Level. *Entropy*, *10*(2), 100–123. MDPI AG. Retrieved from http://dx.doi.org/10.3390/entropy-e10020100

Silva, C., & Annamalai, K. (2006). 1st Law, Metabolism; 2nd Law and Entropy Generaion: Secret to Longevity in Lifespan?. In *9th AIAA/ASME Joint Thermophysics and Heat Transfer Conference* (p. 2940). https://doi.org/10.2514/6.2006-2940

Şimşek, B., Özilgen, M., & Utku, F. Ş. (2021). How much energy is stored in SARS-CoV-2 and its structural elements?. *Energy Storage*, e298. https://doi.org/10.1002/est2.298

Skene, K.R. (2015). Life's a Gas: A Thermodynamic Theory of Biological Evolution. *Entropy*, 17(8), 5522-5548. https://doi.org/10.3390/e17085522

Shadrick, W. R., Mukherjee, S., Hanson, A. M., Sweeney, N. L., & Frick, D. N. (2013). Aurintricarboxylic acid modulates the affinity of hepatitis C virus NS3 helicase for both nucleic acid and ATP. *Biochemistry*, *52*(36), 6151–6159. https://doi.org/10.1021/bi4006495

Sigg, A. P., Mariotti, M., Grütter, A. E., Lafranca, T., Leitner, L., Bonkat, G., & Braissant, O. (2022). A Method to Determine the Efficacy of a Commercial Phage Preparation against Uropathogens in Urine and Artificial Urine Determined by Isothermal Microcalorimetry. *Microorganisms*, *10*(5), 845. MDPI AG. Retrieved from http://dx.doi.org/10.3390/microorganisms10050845

Stauffer, H., Srinivasan, S., & Lauffer, M. A. (1970). Calorimetric studies on polymerization-depolymerization of tobacco mosaic virus protein. *Biochemistry*, *9*(2), 193–200. https://doi.org/10.1021/bi00804a001

Sturtevant, J. M., Velicelebi, G., Jaenicke, R., & Lauffer, M. A. (1981). Scanning calorimetric investigation of the polymerization of the coat protein of tobacco mosaic virus. *Biochemistry*, *20*(13), 3792–3800. https://doi.org/10.1021/bi00516a019

Tkhilaishvili, T., Wang, L., Tavanti, A., Trampuz, A., & Di Luca, M. (2020a). Antibacterial Efficacy of Two Commercially Available Bacteriophage Formulations, Staphylococcal Bacteriophage and PYO Bacteriophage, Against Methicillin-Resistant *Staphylococcus aureus*: Prevention and Eradication of Biofilm Formation and Control of a Systemic Infection of *Galleria mellonella* Larvae. *Frontiers in microbiology*, *11*, 110. https://doi.org/10.3389/fmicb.2020.00110

Tkhilaishvili, T., Wang, L., Perka, C., Trampuz, A., & Gonzalez Moreno, M. (2020b). Using Bacteriophages as a Trojan Horse to the Killing of Dual-Species Biofilm Formed by *Pseudomonas aeruginosa* and Methicillin Resistant *Staphylococcus aureus*. *Frontiers in microbiology*, *11*, 695. https://doi.org/10.3389/fmicb.2020.00695

Tkhilaishvili, T., Di Luca, M., Abbandonato, G., Maiolo, E. M., Klatt, A. B., Reuter, M., Möncke-Buchner, E., & Trampuz, A. (2018a). Real-time assessment of bacteriophage T3-derived antimicrobial activity against planktonic and

biofilm-embedded Escherichia coli by isothermal microcalorimetry. *Research in microbiology*, *169*(9), 515–521. https://doi.org/10.1016/j.resmic.2018.05.010

Tkhilaishvili, T., Lombardi, L., Klatt, A. B., Trampuz, A., & Di Luca, M. (2018b). Bacteriophage Sb-1 enhances antibiotic activity against biofilm, degrades exopolysaccharide matrix and targets persisters of Staphylococcus aureus. *International journal of antimicrobial agents*, *52*(6), 842–853. https://doi.org/10.1016/j.ijantimicag.2018.09.006

Tkhilaishvili, T., Di Luca, M., & Trampuz, A. (2018c). SIMULTANEOUS AND SEQUENTIAL APPLICATIONS OF PHAGES AND CIPROFLOXACIN IN KILLING MIXED-SPECIES BIOFILM OF PSEUDOMONAS AERUGINOSA AND STAPHYLOCOCCUS AUREUS. In *Orthopaedic Proceedings* (Vol. 100, No. SUPP_17, pp. 65-65). The British Editorial Society of Bone & Joint Surgery.

Tkhilaishvili, T. (2022). *Bacteriophages as an alternative strategy in the treatment and prevention of implant-associated infections* (Doctoral dissertation). http://dx.doi.org/10.17169/refubium-32604

Toinon, A., Greco, F., Moreno, N., Claire Nicolai, M., Guinet-Morlot, F., Manin, C., & Ronzon, F. (2015). Study of rabies virus by Differential Scanning Calorimetry. *Biochemistry and biophysics reports*, *4*, 329–336. https://doi.org/10.1016/j.bbrep.2015.10.010

UniProt Consortium (2021). UniProt: the universal protein knowledgebase in 2021. *Nucleic acids research*, *49*(D1), D480–D489. https://doi.org/10.1093/nar/gkaa1100

Virudachalam, R., Harrington, M., & Markley, J. L. (1985a). Thermal stability of cowpea mosaic virus components: differential scanning calorimetry studies. *Virology*, *146*(1), 138–140. https://doi.org/10.1016/0042-6822(85)90060-1

Virudachalam, R., Low, P. S., Argos, P., & Markley, J. L. (1985b). Turnip yellow mosaic virus and its capsid have thermal stabilities with opposite pH dependence: studies by differential scanning calorimetry and 31P nuclear magnetic resonance spectroscopy. *Virology*, *146*(2), 213–220. https://doi.org/10.1016/0042-6822(85)90005-4

Von Bertalanffy, L. (1950). The theory of open systems in physics and biology. *Science*, 111(2872), 23-29. https://doi.org/10.1126/science.111.2872.23

Von Stockar, U. (2013a). Live cells as open non-equilibrium systems. In Urs von Stockar, ed., *Biothermodynamics: The Role of Thermodynamics in Biochemical Engineering*, Lausanne: EPFL Press, 475-534.

Von Stockar, U. (2013b). Biothermodynamics of live cells: energy dissipation and heat generation in cellular structures. In: *Biothermodynamics: the role of thermodynamics in Biochemical Engineering*, von Stockar, U., ed., Lausanne: EPFL Press, pp. 475-534.

Von Stockar, U., Maskow, T. and Vojinovic, V. (2013). Thermodynamic analysis of metabolic pathways. In: *Biothermodynamics: the role of thermodynamics in Biochemical Engineering*, von Stockar, U., ed., Lausanne: EPFL Press, pp. 581-604.

Von Stockar, U., Maskow, T., Liu, J., Marison, I. W., & Patino, R. (2006). Thermodynamics of microbial growth and metabolism: an analysis of the current situation. *Journal of Biotechnology*, *121*(4), 517-533. https://doi.org/10.1016/j.jbiotec.2005.08.012

von Stockar, U., & Liu, J. (1999). Does microbial life always feed on negative entropy? Thermodynamic analysis of microbial growth. *Biochimica et biophysica acta*, *1412*(3), 191–211. https://doi.org/10.1016/s0005-2728(99)00065-1

Vorobieva, N., Sanina, N., Vorontsov, V., Kostetsky, E., Mazeika, A., Tsybulsky, A., Kim, N., & Shnyrov, V. (2014). On the possibility of lipid-induced regulation of conformation and immunogenicity of influenza a virus H1/N1 hemagglutinin as antigen of TI-complexes. *Journal of molecular microbiology and biotechnology*, *24*(3), 202–209. https://doi.org/10.1159/000365053

Wang, R., Chen, J., Gao, K., Hozumi, Y., Yin, C., & Wei, G. W. (2021). Analysis of SARS-CoV-2 mutations in the United States suggests presence of four substrains and novel variants. *Communications biology*, *4*(1), 228. https://doi.org/10.1038/s42003-021-01754-6

Wang, L., Tkhilaishvili, T., & Trampuz, A. (2020a). Adjunctive Use of Phage Sb-1 in Antibiotics Enhances Inhibitory Biofilm Growth Activity versus Rifampin-Resistant Staphylococcus aureus Strains. *Antibiotics*, *9*(11), 749. MDPI AG. Retrieved from http://dx.doi.org/10.3390/antibiotics9110749

Wang, L., Tkhilaishvili, T., Trampuz, A., & Gonzalez Moreno, M. (2020b). Evaluation of Staphylococcal Bacteriophage Sb-1 as an Adjunctive Agent to Antibiotics Against Rifampin-Resistant *Staphylococcus aureus* Biofilms. *Frontiers in microbiology*, *11*, 602057. https://doi.org/10.3389/fmicb.2020.602057

Wang, L., Tkhilaishvili, T., Bernal Andres, B., Trampuz, A., & Gonzalez Moreno, M. (2020c). Bacteriophage-antibiotic combinations against ciprofloxacin/ceftriaxone-resistant Escherichia coli in vitro and in an experimental Galleria mellonella model. *International journal of antimicrobial agents*, *56*(6), 106200. https://doi.org/10.1016/j.ijantimicag.2020.106200

Wang, G., Wang, H. J., Zhou, H., Nian, Q. G., Song, Z., Deng, Y. Q., Wang, X., Zhu, S. Y., Li, X. F., Qin, C. F., & Tang, R. (2015). Hydrated silica exterior produced by biomimetic silicification confers viral vaccine heat-resistance. *ACS nano*, *9*(1), 799–808. https://doi.org/10.1021/nn5063276

Wang, H.Y., Mou, D.G., & Swartz, J.R. (1976). Thermodynamic evaluation of microbial growth. *Biotechnology and Bioengineering*, 18(12), 1811-1814. https://doi.org/10.1002/bit.260181214

Wangler, A., Schmidt, C., Sadowski, G. and Held, C. (2018). Standard Gibbs energy of metabolic reactions: III. The 3-phosphoglycerate kinase reaction. *ACS Omega*, 3(2), 1783-1790. https://doi.org/10.1021/acsomega.7b01704

Wimmer E. (2006). The test-tube synthesis of a chemical called poliovirus. The simple synthesis of a virus has far-reaching societal implications. *EMBO reports*, *7 Spec No*(Spec No), S3–S9. https://doi.org/10.1038/sj.embor.7400728

Wu, L., Zhou, L., Mo, M., Liu, T., Wu, C., Gong, C., Lu, K., Gong, L., Zhu, W., & Xu, Z. (2022). SARS-CoV-2 Omicron RBD shows weaker binding affinity than the currently dominant Delta variant to human ACE2. *Signal transduction and targeted therapy*, *7*(1), 8. https://doi.org/10.1038/s41392-021-00863-2

Wu, K.J. (2020). There are more viruses than stars in the universe. Why do only some infect us? *National Geographic Magazine*. Available at: https://www.nationalgeographic.com/science/article/factors-allow-viruses-infect-humans-coronavirus

Yang, Y., Song, Y., Lin, X., Li, S., Li, Z., Zhao, Q., Ma, G., Zhang, S., & Su, Z. (2020). Mechanism of bio-macromolecule denaturation on solid-liquid surface of ion-exchange chromatographic media - A case study for inactivated foot-and-mouth disease virus. *Journal of chromatography. B, Analytical technologies in the biomedical and life sciences*, *1142*, 122051. https://doi.org/10.1016/j.jchromb.2020.122051

Yang, Y., Zhao, Q., Li, Z., Sun, L., Ma, G., Zhang, S., & Su, Z. (2017). Stabilization study of inactivated foot and mouth disease virus vaccine by size-exclusion HPLC and differential scanning calorimetry. *Vaccine*, *35*(18), 2413–2419. https://doi.org/10.1016/j.vaccine.2017.03.037

Yu, M., Zhang, S., Zhang, Y., Yang, Y., Ma, G., & Su, Z. (2015). Microcalorimetric study of adsorption and disassembling of virus-like particles on anion exchange chromatography media. *Journal of chromatography. A*, *1388*, 195–206. https://doi.org/10.1016/j.chroma.2015.02.048

Zhou, J., Rong, X. L., Cao, X., Tang, Q., Liu, D., Jin, Y. H., Shi, X. X., Zhong, M., Zhao, Y., & Yang, Y. (2022). Assembly of Poly(ethylene glycol)ylated Oleanolic Acid on a Linear Polymer as a Pseudomucin for Influenza Virus Inhibition and Adsorption. *Biomacromolecules*, *23*(8), 3213–3221. https://doi.org/10.1021/acs.biomac.2c00314

 doi:10.20944/preprints202211.0112.v1