Biothermodynamics of Viruses

Subjects: Virology

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Biothermodynamics of viruses is among the youngest but most rapidly developing scientific disciplines. During the COVID-19 pandemic, it 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.
Biothermodynamics of viruses has suggested a physicochemical mechanism of how viruses can hijack host cell metabolism.

thermodynamics calorimetry entropy enthalpy

1. From Thermodynamics to Biothermodynamics

There is a common opinion that thermodynamics is a scientific discipline related to machines, engines and devices, dealing mostly with efficiency of energy transformation and utilization. Indeed, Lazarus Carnot [1][2] and his son Sadi Carnot [3] have, through their brilliant research, imposed such a perception into the public for over two centuries [4]. In this way, classical thermodynamics began its development. It is less widely known that, simultaneously with classical thermodynamics, appeared biothermodynamics. Lavoisier and Laplace [5][6] developed the first calorimeter and one of the first samples for calorimetry was an organism—a live guinea pig. Thus, simultaneously with classical thermodynamics, biothermodynamics started its development.

Often, the same researchers worked in the field of classical thermodynamics and biothermodynamics. Indeed, Boltzmann [7], one of the founders of statistical thermodynamics, has written about change in entropy in living organisms. Clausius [8][9][10] has laid the theoretical foundations of classical thermodynamics, with the goal of analyzing machines. However, von Bertalanffy [11] has suggested the theory of open systems in biology. Schrödinger in his famous book “What is Life?” discussed the thermodynamic background of life processes [12]. Morowitz [13][14][15] 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 the growth of organisms was given by von Stockar [16][17][18][19][20]. It seems that biothermodynamics, even though it is less widely known than classical thermodynamics, has existed in the scientific arena for as long, 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 [21][22][23]. Application of thermodynamics to biological evolution was also discussed by Skene [24]. Battley has made a great contribution

towards applying the quantitative thermodynamic approach to living organisms and life processes [25][26][27][28][29][30]. Roels [16][31], and Sandler [32][33] have also contributed to quantifying the thermodynamic properties of organisms. Barros has applied thermodynamics to study the growth of microorganisms in soil ecosystems [34][35][36]. Maskow has applied calorimetry and thermodynamic analysis to study the growth of microorganisms in bioreactors [37][38] and ecosystems [39][40], as well as viruses in host cells [41]. Guosheng et al. [42] have also applied calorimetric methods to study the multiplication of bacteriophages inside host cells.

2. Biothermodynamics Intersects with Biochemistry

Thermodynamic characterization of life processes has been a subject of interest for many researchers. Von Stockar et al. [19][43] applied thermodynamics to quantitatively analyze thermodynamic feasibility of complex metabolic pathways, such as glycolysis. Thermodynamic analysis has been used to find accurate Gibbs energy values with activity coefficient corrections for important biological reactions, including Hexokinase reaction [44], Glucose-6-phosphatase reaction and ATP hydrolysis [45], 3-phosphoglycerate kinase reaction [46], Triosephosphate isomerase reaction [47], Enolase reaction [48], and Glyceraldehyde 3-phosphate dehydrogenase reaction [49]. Additionally, thermodynamic analysis was made of cellulose hydrolysis by microorganisms in the aqueous glucose solution [50]. Niebel et al. [51] found that the cellular metabolism is governed by an upper limit in Gibbs energy dissipation, using metabolomics. Ould-Moulaye et al. [52] found Gibbs energy changes for the reactions in glycolysis and Krebbs cycle. Kümmel et al. [53] discuss applications of thermodynamics in metabolic network models.

The importance of thermodynamic considerations in life sciences is clearly seen from the Gibbs energy being used to define catabolic and anabolic processes [54]. Annamalai used the quantitative thermodynamic approach to study the metabolic processes [55][56] and the aging of organisms [57][58][59][60][61]. Hayflick was among the first who related a thermodynamic property (entropy) to the aging process in a series of papers [62][63][64][65][66][67][68][69].

3. From Biothermodynamics to Virothermodynamics

Viruses are the most abundant organisms: there could be more viruses than stars in the universe [70]. There are 9,110 named species listed by the International Committee on Taxonomy of Viruses (ICTV) [71]. 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 [72][73][74][75]. Until 2019, elemental composition was known only for the poliovirus [76][77]. 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 amounts and purity [78]. Until recently, viruses were not a subject of thermodynamic research. The thermodynamic properties of virus particles and nucleocapsids were unknown.

With the appearance of the COVID-19 pandemic, various scientific disciplines attempted to contribute, in the shortest time possible, 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 [79]. An analysis was made of virus–host interactions in the cytoplasm (virus multiplication) [79]. 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 [80]. In 2020, in parallel with the COVID-19 pandemic, an epidemic caused by the rhinovirus occurred, while the influenza epidemic did not occur that year. An explanation of coinfection by rhinovirus and SARS-CoV-2, and interference between influenza and SARS-CoV-2 has been published in [81]. SARS-CoV-2 belongs to the group of RNA viruses, which exhibit a great tendency to mutate [82]. Thus, during the 2.5 years of the pandemic, the virus has mutated several times [83][84][85][86]. The mutants suppressed the older variants and caused new waves of infection during the pandemic. The elemental composition and thermodynamic properties of SARS-CoV-2 variants from Hu-1 to Omicron BA.2.75 have been published in [80][86][87][88][89][90][91][92][93]. The biothermodynamic characterization of viruses was continued for Monkeypox, Vaccinia and Ebola viruses [94][95].

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 the 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 [96]. The driving force for antigen–receptor binding is the Gibbs energy of binding [86][88][91][97][98][99][100][101]. Thus, biothermodynamic consideration and determination of Gibbs energy of binding is very important for infection spreading [102][103]. More negative Gibbs energy of binding of new variants gave an advantage to new strains during entry over older ones, which 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 [86][87][88][89][90][91][95][97][98][99][100][101][104].

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 [95][105] since virus–human interactions have been of particular importance. Thermodynamic properties of plant host organisms are reported in [106]. Phage–bacteria interactions are often used as a model in the research of virus–host interactions. Thus, thermodynamic properties have been determined for a large number of bacteria [29][107][108][109][110] and bacteriophages [41][42][79].

The second virus–host interaction is in the cytoplasm. In papers [79][80], 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 [111]. The 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 [95]. The driving force for these reactions is the Gibbs energy of biosynthesis [112]. After their biosynthesis, the virus components undergo self-assembly into a new virus particle [113][114]. During biosynthesis and self-assembly, viruses change their thermodynamic properties [115][116]. Thus, the virus life cycle represents a biological, chemical and thermodynamic process that should be analyzed using a nonequilibrium thermodynamic apparatus [117].

Viruses represent the smallest organisms, but also belong to the most contagious and deadly microorganisms. They spread very rapidly, often causing epidemics and pandemics, which result in large numbers of casualties. Furthermore, there are very few antiviral medicines. Thus, the fight against epidemics and pandemics is directed towards epidemiological measures and the application of vaccines. However, vaccine production, especially in the case of new viruses, requires a lot of time and resources. For example, the vaccines against SARS-CoV-2 were awaited for a year. The ability of some viruses to develop mutations fast leads to the need for new vaccines. Some of the available novel vaccines have proved themselves effective for the Hu-1, Alpha, Beta, Gamma and Delta variants. However, these vaccines are much less effective for the newer Omicron variants due to their ability to evade the immune response. This has imposed a need for the production of polyvalent vaccines, which also takes time and long-term testing. Knowing the thermodynamic properties of the host and virus, as well as the application of a mechanistic model of interactions on the cell membrane and in the cytoplasm, could, in the future, contribute to designing new vaccines and antiviral medicines. Moreover, such knowledge could aid in finding places and methods for vaccine application. For example, every human tissue is characterized by a specific value of Gibbs energy of biosynthesis of its building blocks. On the other hand, every virus variant is characterized with its own specific Gibbs energy of biosynthesis. The ratio of these two values is the permissiveness coefficient, which is different for various virus–host cell pairs. The result of this is that some viruses can be synthetized in one type of cell, while in others their multiplication is significantly slower. By choosing a tissue for vaccine application where virus growth is slower, it is possible to give enough time to the immune system to respond to a low virus concentration. Such a vaccine would be attenuated (live), capable of inducing an immune response but, due to the low permissiveness coefficient, unable to cause a disease in a more severe clinical form. The attenuation process of a vaccine based on biothermodynamic properties would not be performed through a long passage that requires great resources and time, but through choosing a place of application where the virus can multiply very slowly. Thus, one of the potential applications of biothermodynamics in virology would be in vaccinology. Such a vaccine would not be based on empirical data but on engineering, using biothermodynamic tools, which would help to significantly save time and resources in the design and production of vaccines.

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