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Review

Brief history of thermodynamic research on microorganisms

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Abstract: Pathogen-host interaction (virus-host, bacteria-host and fungi-host) is analyzed from the perspective of biothermodynamics. A mechanistic model of pathogen-host interactions, which was earlier applied to virus-host interactions, was applied for the first time to bacteria-host and fungi-host interactions. Through a mechanistic model suggested in this research, it is possible to explain the phenomenon of tropism of microorganisms to develop infections in certain tissues. Gibbs energy of biosynthesis represents the driving force for growth of bacteria inside host organisms. A growing bacterial colony represents a thermodynamic system, while the host organism is its surroundings. The permissiveness coefficient determines the possibility of growth of bacteria in an appropriate environment (tissue).

Keywords: Viruses; Escherichia coli; Klebsiella aerogenes; Candida utilis; Gibbs energy of biosynthesis; Biosynthesis reaction; Enthalpy; Entropy; Pathogen-host interaction

1. Introduction

Microorganisms have surrounded us and interacted with plants, animals and humans, causing diseases [Burkovski, 2022; Altermann and Kazmierczak, 2003; Cavalier-Smith, 2006; Schopf, 2006]. Microorganisms have surrounded us for a long time. A closer encounter with microorganisms has started during the early 18th century [van Leeuwenhoek, 1700; Lane, 2015; Payne, 1970].

The first thermodynamic research on living organisms, which represent hosts for microorganisms, has been made by Lavoisier and Laplace [Lavoisier and marquis de Laplace, 1783; Lavoisier and DeLaplace, 1994]. The germ theory of disease has been proved by Pasteur [Bordenave, 2003]. Robert Koch has showed in 1886 that microorganisms (bacteria) cause diseases [Nobel Prize, 2023]. Ivanovsky in 1892 and Beijerinck in 1898 have described and discovered the tobacco mosaic virus [Zaitlin, 1998; Beijerinck, 1898].

By the early 20th century, science has identified subcellular and cellular microorganisms, as causes of diseases in humans, animals and plants. Diseases appear as a consequence of interactions of microorganisms with host organisms. However, chemical and biothermodynamic backgrounds of interactions of microorganisms with multicellular host organisms have not been elucidated in full for the next 100 years, even though assumptions existed for this.

Clausius has founded thermodynamics, with desire to achieve better energy utilization by machines [Clausius, 1867, 1870, 1976]. Clausius has set the philosophical framework and developed the mathematical tools for research on energetics of processes performed in nature. Von Bertalanffy has made thermodynamics closer to biology, through the theory of open systems in biology [von Bertalanffy, 1950, 1971]. Boltzmann was the first to apply the entropy concept in analysis of organisms [Boltzmann, 1974]. This work was extended by Schrödinger, who made the first physical definition of live based on entropy [Schrödinger, 1944].

Morowitz made a great contribution to application of thermodynamics in life sciences, including explanation of biological order and complexity [Morowitz, 1955, 1968,

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1995; Morowitz et al., 2000, 1988], as well as the emergence of life [Morowitz, 1992]. Prigogine has developed nonequilibrium thermodynamics, which found many applications in characterization of microorganisms and multicellular organisms [Prigogine, 1977, 1947; Prigogine and Wiamme, 1946; Glansdorff and Prigogine, 1971; Popovic, 2018; Demirel, 2014]. Moreover, nonequilibrium thermodynamics has been used in research on interactions of microorganisms with multicellular organisms and other microorganisms [Prigogine, 1977, 1947; Prigogine and Wiamme, 1946; Glansdorff and Prigogine, 1971; Popovic, 2018; Demirel, 2014]. Von Stockar found that the physical driving force for growth and metabolism of microorganisms is Gibbs energy [von Stockar, 2013a, 2013b; von Stockar and Liu, 1999; von Stockar et al., 2013, 2008, 2006; von Stockar and Marrison, 1993; Patiño et al., 2007]. Thermodynamics has been applied to study various metabolic processes [Greinert et al., 2020a, 2020b, 2020c; Meurer et al., 2017, 2016; Wangler et al., 2018; Niebel et al., 2019; Popovic et al., 2019; Du et al., 2018a, 2018b; Smeaton et al., 2018; Alazmi et al., 2019; Barros, 2021; Nagai et al., 2018]. Hansen et al. [2021, 2018, 2009] and Skene [2015] worked on relating the laws of thermodynamics and theory of evolution. Changes in entropy and information during growth and biosynthesis in organisms has been discussed in [Popovic, 2014a, 2014b].

Virions consist of genetic material (DNA or RNA) that encodes the information for the primary structure of proteins and a capsid that consists of viral structural proteins. Some viruses possess an envelope that consists of lipids. Thus, virions consist of a certain amount of substance, clearly separated from the virus’s environment [Popovic, 2022b, 2022c, 2022d]. Thus, viruses represent thermodynamic systems [Popovic, 2022b, 2022c, 2022d]. Viruses perform biological processes of replication, transcription, translation, self-assembly, mutation etc. These processes have their chemical and thermodynamic background. Replication, transcription and translation represent chemical reactions of polymerization of monomers (nucleotides or amino acids) into polymers (nucleic acids or proteins) [Lee et al., 2020; Pinheiro et al., 2008; Dodd et al., 2020; Johansson and Dixon, 2013]. The driving force for reactions of polymerization is Gibbs energy of biosynthesis [Popovic, 2022a; Demirel, 2014]. This is why Gibbs energy determines biosynthesis rate, according to the phenomenological equation [Popovic, 2023c, 2023d; von Stockar, 2013a; Demirel, 2014].

Biosynthesis rate is a chemical term, which is related to the biological term of multiplication rate [Popovic and Minceva, 2020a]. Hypothetically, the thermodynamic driving force has a supreme position over information content. The proof for this is the fact that viroids represent circular RNA molecules that do not contain any information, but are still able to hijack the cellular metabolic machinery and perform replication driven by Gibbs energy of biosynthesis [Popovic, 2022a]. Moreover, parts of RNA of viroids serve as antigens that viroids use to enter host cells [Venkataraman et al., 2021]. Thus, viroids possess no information for biosynthesis of proteins. However, led by Gibbs energy of biosynthesis of nucleic acid, they are able to perform all processes as viruses, except for self-assembly.

From the perspective of biology and medicine, microorganisms represent causes of various diseases that appear as a consequence of interaction with host organisms. From the perspective of chemistry, these interactions represent chemical reactions, driven by Gibbs energy. From the perspective of thermodynamics, they represent processes that change the state of systems, related to changes in thermodynamic properties of enthalpy, entropy, Gibbs energy etc. Microorganisms represent open thermodynamic systems performing growth and accumulation of substances [Popovic, 2019]. State parameters of microorganisms as thermodynamic systems have been calculated [Battley, 1999a, 1992; Şimşek et al., 2021; Popovic, 2019; Popovic and Minceva, 2020a] and determined experimentally [Battley, 1999b, 1998; Battley et al., 1997; Popovic et al., 2021; Wimmer, 2006; Molla et al., 1991].

Mutations represent a process described in biology, during which there is spontaneous replacement of nucleotides with other nucleotides. This changes the information content in the nucleic acid. As a consequence of changed information in the nucleic acid, there

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are changes in proteins during the process of translation. Every nucleotide has its empirical formula. Replacement of one or more nucleotides with another (which is the basis of mutation) leads to change in empirical formula of the thermodynamic system (bacteria or virus). Empirical formulas of viruses have been reported in the literature [Degueldre, 2021; Şimşek et al., 2021; Popovic, 2023b, 2023c, 2023d].

Thermodynamics has been applied to study various aspects of SARS-CoV-2. This includes the empirical formula and energy content of SARS-CoV-2 particles [Şimşek et al., 2021; Degueldre, 2021; Popovic, 2022a], energy cost of infection for the host organism [Yilmaz et al., 2020; Özilgen and Yilmaz, 2021], interaction with host cells [Lucia et al., 2021, 2020a; Popovic, 2022a], epidemiology [Lucia et al., 2020b; Kaniadakis et al., 2020], impact on society [Nadi and Özilgen, 2021]. The importance of thermodynamics for research on interactions between SARS-CoV-2 and the human organism, and its application in design of medicines has been discussed [Head et al., 2022].

Mutations that appeared during 3 years on SARS-CoV-2, from the Hu-1 to XBB.1.5 variant, have been reported in the literature [Degueldre, 2021; Şimşek et al., 2021; Popovic, 2023b, 2023c, 2023d, 2022b, 2022c, 2022d, 2022e, 2022f, 2022g, 2022h; Popovic and Popovic, 2022; Popovic and Minceva, 2021a, 2020b]. Chemical and thermodynamic properties of various viruses can be found in the literature [Popovic, 2022i, 2022j, 2022k, 2023e]. Moreover, phage-bacteria interactions have been characterized through the thermodynamic approach and calorimetry [Maskow et al., 2010; Guosheng et al., 2003; Tkhilaishvili et al., 2020a, 2020b, 2018a, 2018b, 2018c; Tkhilaishvili, 2022; Wang et al., 2020a, 2020b; Sigg et al., 2022; Popovic, 2023f].

Until 2019, the empirical formula was known only for the poliovirus [Wimmer, 2006; Molla et al., 1991]. During the last 3 years, the atom counting method has been developed for calculating empirical formulas of microorganisms [Popovic, 2022m]. Empirical formulas of SARS-CoV-2 virus particles have been reported by [Degueldre, 2021; Şimşek et al., 2021; Popovic, 2023b, 2023c, 2023d, 2022c, 2022d, 2022f, 2022h; Popovic and Minceva, 2020b]. Thermodynamic properties of human host tissues have been reported in the literature [Xu et al., 2022; Popovic, 2022i; Popovic and Minceva, 2020c]. In that way, conditions were formed for research on virus-host interactions from the perspective of thermodynamics. Models were developed for hijacking of host cell metabolism [Popovic and Minceva, 2020a] and for thermodynamic consequences of virus mutations [Popovic, 2023b, 2022f]. Thermodynamic background of virus-host interactions is available in the literature [Casasnovas and Springer, 1995; Gale, 2022, 2020, 2019, 2018; Mahmoudabadi et al., 2020; Ceres and Zlotnick, 2002; Katen and Zlotnick, 2009; Tzlil et al., 2004].

Interactions at the membrane (antigen-receptor binding) influences infectivity [Popovic, 2022a]. A virus characterized by a more negative Gibbs energy of binding exhibits greater infectivity [Popovic, 2022a]. A more negative Gibbs energy of biosynthesis of viruses leaves consequences on virus multiplication rate and damage to host cells (pathogenicity) [Popovic, 2022a].

The goal of this paper is to shed more light onto microorganism-host interactions from the perspective of biothermodynamics and to relate the biological phenomena with their thermodynamic driving forces and mechanisms that make them possible.

2. Materials and Methods

2.1. Data sources

Elemental composition of human tissues, in the form of empirical formulas, was obtained from [Popovic and Minceva, 2020c]. The information on empirical formulas of live matter of different human tissues is given in Table 1. Thermodynamic properties of human tissues were taken from [Popovic and Minceva, 2020c] and are given in Table 2.

Data on elemental composition of microorganism live matter, in the form of empirical formulas, was taken from [Popovic, 2019]. They are shown in Table 3. Thermodynamic properties of microorganism live matter were taken from [Popovic, 2019] and are given in Table 4.

2.2. Biosynthesis reactions

Biosynthesis reactions are macrochemical equations that summarize conversion of nutrients into new live matter [von Stockar, 2013b; Battley, 1999b, 1998; Popovic, 2022a]. The reactants in biosynthesis reactions are nutrients. Every nutrient contributes one or more elements to the formation of new live matter [Riedel et al., 2019]. A general biosynthesis reaction for microorganisms and their host tissues has the form

$$\begin{aligned}&\text{(Amino acid)} + CH_2O + O_2 + HPO_4^{2-} + H_2O + HCO_3^{-} + Na^{+} + K^{+} + Mg^{2+} + \\ &\qquad Ca^{2+} + Cl^{-} \rightarrow \text{(Bio)} + SO_4^{2} + H_2O + H_2CO_3\end{aligned} \tag{1}$$

where (amino acid) represents a mixture of amino acids with the empirical formula $CH_{1.798}O_{0.4831}N_{0.2247}S_{0.022472}$, CH_2O carbohydrates, and (Bio) represents the empirical formula of live matter [Popovic, 2022a, 2022c, 2022h]. Amino acids represent a source of energy, carbon, nitrogen and sulfur [Popovic, 2022a, 2022c, 2022h]. CH_2O are an additional source of carbon and energy [Popovic, 2022a, 2022c, 2022h]. O_2 is the electron acceptor, which takes excess electrons when carbon from nutrients is oxidized into the oxidation state in live matter [Popovic, 2022a, 2022c, 2022h]. HPO_4^{2-} is the source of phosphorus [Popovic, 2022a, 2022c, 2022h]. The ions Na^{+}, K^{+}, Mg^{2+}, Ca^{2+} and Cl^{-} are the sources of sodium, potassium, magnesium, calcium and chlorine, respectively [Popovic, 2022a, 2022c, 2022h]. On the product side, the main product is new live matter (Bio). Additional metabolic products are SO_4^{2} which takes excess sulfur that is not incorporate into live matter [Popovic, 2022a, 2022c, 2022h]. HCO_3^{-} and H_2CO_3 form a bicarbonate buffer that takes excess hydrogen ions produced during biosynthesis, but also take excess carbon that is not incorporated into new live matter [Popovic, 2022a, 2022c, 2022h].

2.3. Thermodynamic properties of biosynthesis

Biosynthesis stoichiometry can be used to find thermodynamic properties of biosynthesis, through Hess's law. Biosynthesis reactions are chemical equations and have characteristic thermodynamic properties, which include standard enthalpy of biosynthesis, $\Delta_{bs}H^0$, standard entropy of biosynthesis, $\Delta_{bs}S^0$, and standard Gibbs energy of biosynthesis, $\Delta_{bs}G^0$. These can be found using the Hess's law

$$\Delta_{bs}H^0 = \sum_{products} \nu\, \Delta_f H^0 - \sum_{reactants} \nu\, \Delta_f H^0 \tag{2}$$

$$\Delta_{bs}S^0 = \sum_{products} \nu\, S_m^o - \sum_{reactants} \nu\, S_m^o \tag{3}$$

$$\Delta_{bs}G^0 = \sum_{products} \nu\, \Delta_f G^0 - \sum_{reactants} \nu\, \Delta_f G^0 \tag{4}$$

where $\Delta_f H^0$ is standard enthalpy of formation, S^0_m standard molar entropy, $\Delta_f G^0$ standard Gibbs energy of formation, and ν stoichiometric coefficient [Atkins and de Paula, 2011, 2014].

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Table 1: Empirical formulas of live matter of human tissues. The general empirical formula of live matter for human tissues has the form $C_{nC}H_{nH}O_{nO}N_{nN}P_{nP}S_{nS}Na_{nNa}K_{nK}Mg_{nMg}Ca_{nCa}Cl_{nCl}$. Data taken from [Popovic and Minceva, 2020c].

Name	**Live matter composition**										
	n_C	n_H	n_O	n_N	n_P	n_S	n_{Na}	n_K	n_{Mg}	n_{Ca}	n_{Cl}
Human body 1 (average)	1	1.7296	0.2591	0.1112	0.0134	0.0030	0.0027	0.0031	0.0000	0.0173	0.0018
Human body 2 (average)	1	1.7131	0.2674	0.0965	0.0189	0.0033	0.0033	0.0027	0.0006	0.0187	0.0020
Adipose tissue 1	1	1.8005	0.1218	0.0216	0.0000	0.0007	0.0010	0.0000	0.0000	0.0000	0.0007
Adipose tissue 2	1	1.8024	0.1124	0.0100	0.0000	0.0006	0.0009	0.0000	0.0000	0.0000	0.0006
Adipose tissue 3	1	1.8083	0.1066	0.0025	0.0000	0.0006	0.0008	0.0000	0.0000	0.0000	0.0005
Adrenal gland	1	1.7391	0.1627	0.0785	0.0014	0.0026	0.0000	0.0011	0.0000	0.0000	0.0024
Aorta	1	1.5313	0.2917	0.2450	0.0106	0.0076	0.0071	0.0021	0.0000	0.0082	0.0000
Blood-erythrocytes	1	1.4984	0.3047	0.2663	0.0020	0.0059	0.0000	0.0049	0.0000	0.0000	0.0036
Blood-plasma	1	1.7117	0.2767	0.2301	0.0000	0.0091	0.0382	0.0000	0.0000	0.0000	0.0331
Blood-whole	1	1.5408	0.2919	0.2572	0.0035	0.0068	0.0047	0.0056	0.0000	0.0000	0.0092
Brain-grey matter	1	1.9096	0.2590	0.1625	0.0122	0.0079	0.0110	0.0097	0.0000	0.0000	0.0107
Brain-white matter	1	1.8361	0.2017	0.1105	0.0080	0.0039	0.0054	0.0048	0.0000	0.0000	0.0052
Connective tissue	1	1.5480	0.3087	0.2568	0.0000	0.0109	0.0151	0.0000	0.0000	0.0000	0.0049
Eye lens	1	1.5143	0.2934	0.2507	0.0020	0.0058	0.0027	0.0000	0.0000	0.0000	0.0017
Gallblader - wall	1	1.6101	0.2757	0.2013	0.0055	0.0079	0.0037	0.0087	0.0000	0.0000	0.0024
Gastrointestinal tract - oesophagus	1	1.7041	0.2256	0.1640	0.0034	0.0033	0.0045	0.0027	0.0000	0.0000	0.0059
Gastrointestinal tract - small intestine (wall)	1	1.6480	0.2310	0.1789	0.0028	0.0054	0.0038	0.0044	0.0000	0.0000	0.0024
Gastrointestinal tract - stomach	1	1.6419	0.2140	0.1519	0.0044	0.0043	0.0030	0.0053	0.0000	0.0000	0.0039
Heart 1	1	1.6861	0.2340	0.1789	0.0056	0.0054	0.0038	0.0066	0.0000	0.0000	0.0049
Heart 2	1	1.6327	0.2689	0.2248	0.0075	0.0073	0.0051	0.0089	0.0000	0.0000	0.0066
Heart 3	1	1.6415	0.2689	0.2268	0.0032	0.0062	0.0043	0.0051	0.0000	0.0000	0.0084
Kidney 1	1	1.6151	0.2452	0.1949	0.0059	0.0057	0.0079	0.0047	0.0000	0.0023	0.0051

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Kidney 2	1	1.6364	0.2581	0.2184	0.0073	0.0071	0.0099	0.0058	0.0000	0.0028	0.0064
Kidney 3	1	1.6891	0.2593	0.1484	0.0075	0.0077	0.0067	0.0059	0.0000	0.0000	0.0043
Liver 1	1	1.6480	0.2904	0.1851	0.0084	0.0081	0.0075	0.0066	0.0000	0.0000	0.0049
Liver 2	1	1.6079	0.3277	0.2246	0.0092	0.0089	0.0083	0.0073	0.0000	0.0000	0.0054
Liver 3	1	1.5863	0.2866	0.2462	0.0077	0.0111	0.0103	0.0061	0.0000	0.0000	0.0101
Lung - parenchyma	1	1.6268	0.2836	0.2532	0.0074	0.0107	0.0100	0.0059	0.0000	0.0000	0.0097
Mammary gland 1	1	1.7549	0.1585	0.0775	0.0012	0.0023	0.0016	0.0000	0.0000	0.0000	0.0010
Mammary gland 2	1	1.6091	0.2502	0.2008	0.0025	0.0047	0.0033	0.0000	0.0000	0.0000	0.0021
Mammary gland 3	1	1.6184	0.2580	0.1805	0.0045	0.0066	0.0031	0.0072	0.0000	0.0000	0.0020
Muscle - sceletal 1	1	1.6390	0.2695	0.2039	0.0054	0.0079	0.0037	0.0086	0.0000	0.0000	0.0024
Muscle - sceletal 2	1	1.5606	0.3106	0.2297	0.0069	0.0100	0.0047	0.0110	0.0000	0.0000	0.0030
Muscle - sceletal 3	1	1.6659	0.2583	0.2213	0.0083	0.0081	0.0112	0.0066	0.0000	0.0000	0.0073
Ovary	1	1.7316	0.1885	0.1116	0.0046	0.0022	0.0062	0.0036	0.0000	0.0000	0.0040
Pancreas	1	1.6663	0.2830	0.2409	0.0044	0.0084	0.0117	0.0069	0.0000	0.0000	0.0000
Prostate	1	1.7527	0.1561	0.0704	0.0009	0.0018	0.0000	0.0015	0.0000	0.0000	0.0016
Skeleton - red marrow	1	1.8135	0.1107	0.0093	0.0000	0.0006	0.0008	0.0000	0.0000	0.0000	0.0005
Skeleton - yellow marrow	1	1.8135	0.1107	0.0093	0.0000	0.0006	0.0008	0.0000	0.0000	0.0000	0.0005
Skin 1	1	1.6631	0.2195	0.1578	0.0016	0.0045	0.0042	0.0012	0.0000	0.0000	0.0041
Skin 2	1	1.6032	0.2376	0.1765	0.0019	0.0037	0.0051	0.0015	0.0000	0.0000	0.0050
Skin 3	1	1.5756	0.2571	0.2008	0.0025	0.0047	0.0066	0.0019	0.0000	0.0000	0.0064
Spleen	1	1.6405	0.2753	0.2428	0.0103	0.0066	0.0046	0.0082	0.0000	0.0000	0.0060
Testis	1	1.6986	0.2342	0.1732	0.0039	0.0076	0.0106	0.0062	0.0000	0.0000	0.0068
Thyroid	1	1.6913	0.3035	0.1729	0.0033	0.0031	0.0088	0.0026	0.0000	0.0000	0.0057
Urinary bladder - wall	1	1.6101	0.2757	0.2013	0.0055	0.0079	0.0037	0.0087	0.0000	0.0000	0.0024

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Table 2: Thermodynamic properties of live matter of human tissues. This table shows standard enthalpies of formation, $\Delta_f H^0$, standard molar entropies, $S^0{}_m$, and standard Gibbs energies of formation, $\Delta_f G^0$. Data taken from [Popovic and Minceva, 2020c].

Name	**$\Delta_f H^0$ (kJ/C-mol)**	**$S^0{}_m$ (J/C-mol K)**	**$\Delta_f G^0$ (kJ/C-mol)**
Human body 1 (average)	-75.75	29.48	-37.54
Human body 2 (average)	-81.14	29.26	-43.21
Adipose tissue 1	-33.36	25.78	0.06
Adipose tissue 2	-31.32	25.41	1.62
Adipose tissue 3	-30.19	25.24	2.52
Adrenal gland	-40.53	26.90	-5.66
Aorta	-69.48	30.01	-30.58
Blood-erythrocytes	-65.03	30.14	-25.95
Blood-plasma	-75.88	32.48	-33.77
Blood-whole	-66.01	30.45	-26.54
Brain-grey matter	-73.32	32.83	-30.76
Brain-white matter	-55.50	29.61	-17.11
Connective tissue	-67.79	30.78	-27.89
Eye lens	-61.97	29.76	-23.39
Gallblader – wall	-63.06	29.88	-24.33
Gastrointestinal tract – oesophagus	-55.44	29.36	-17.38
Gastrointestinal tract - small intestine (wall)	-53.75	29.00	-16.16
Gastrointestinal tract – stomach	-50.63	28.15	-14.14
Heart 1	-56.99	29.62	-18.59
Heart 2	-63.88	30.56	-24.27
Heart 3	-63.78	30.66	-24.04
Kidney 1	-59.18	29.29	-21.21
Kidney 2	-63.82	30.31	-24.53
Kidney 3	-62.85	29.63	-24.44
Liver 1	-68.92	30.42	-29.49
Liver 2	-76.24	31.39	-35.55
Liver 3	-66.50	30.83	-26.53
Lung – parenchyma	-66.99	31.37	-26.32
Mammary gland 1	-40.07	26.96	-5.12
Mammary gland 2	-55.95	29.21	-18.08
Mammary gland 3	-59.12	29.22	-21.24
Muscle - sceletal 1	-62.58	30.16	-23.50
Muscle - sceletal 2	-69.68	30.52	-30.12
Muscle - sceletal 3	-63.52	30.76	-23.65
Ovary	-48.80	28.04	-12.46
Pancreas	-67.09	31.41	-26.37
Prostate	-39.80	26.78	-5.09

Skeleton - red marrow	-31.29	25.50	1.77
Skeleton - yellow marrow	-31.29	25.50	1.77
Skin 1	-51.46	28.57	-14.43
Skin 2	-54.25	28.55	-17.25
Skin 3	-58.17	29.08	-20.48
Spleen	-65.95	31.09	-25.65
Testis	-58.18	29.78	-19.59
Thyroid	-73.20	30.90	-33.14
Urinary bladder – wall	-63.06	29.88	-24.33

Table 3: Empirical formulas of microorganism live matter. The general empirical formula of microorganism live matter is $C_{nC}H_{nH}O_{nO}N_{nN}$. Data taken from [Popovic, 2019].

Name	C	H	O	N
Bacteria (general)	1	1.666	0.270	0.200
Escherichia coli	1	1.770	0.490	0.240
Klebsiella aerogenes	1	1.750	0.430	0.220
Candida utilis	1	1.830	0.540	0.100

Table 4: Thermodynamic properties of formation of microorganism live matter. This table shows standard enthalpies of formation, $\Delta_f H^0$, standard molar entropies, S^0_m, and standard Gibbs energies of formation, $\Delta_f G^0$. Data taken from [Popovic, 2019].

Name	$\Delta_f H^0$ (kJ/C-mol)	S^0_m (J/C-mol K)	$\Delta_f G^0$ (kJ/C-mol)
Bacteria (general)	-61.90	30.15	-22.82
Escherichia coli	-114.11	36.36	-66.98
Klebsiella aerogenes	-100.14	34.60	-55.28
Candida utilis	-127.13	35.54	-81.06

3. Results

3.1. Biosynthesis reactions and thermodynamic properties of human tissues

Based on empirical formulas from Table 1, biosynthesis reactions were formulated for different human tissues. In a biosynthesis reaction every nutrient contributes one or more elements to the formation of new live matter. The biosynthesis reactions for human tissues are given in Table 5. The biosynthesis reaction for the entire human organism has the form

$$0.4949\ CH_{1.798}O_{0.4831}N_{0.2247}S_{0.022472} + 0.7193\ CH_2O + 0.0134\ HPO_4^{2-} + 0.0281\ HCO_3^- + 0.0027\ Na^+ + 0.0031\ K^+ + 0.0173\ Ca^{2+} + 0.0018\ Cl^- \rightarrow CH_{1.7296}O_{0.2591}N_{0.1112}P_{0.0134}S_{0.0030}Na_{0.0027}K_{0.0031}Ca_{0.0173}Cl_{0.0018} + 0.0081\ SO_4^2 + 0.0778\ H_2O + 0.2423\ H_2CO_3 \quad (5)$$

where the empirical formula $CH_{1.798}O_{0.4831}N_{0.2247}S_{0.022472}$ represents a mixture of amino acids [Popovic, 2022a], CH_2O carbohydrates [Popovic, 2022a], while $CH_{1.7296}O_{0.2591}N_{0.1112}P_{0.0134}S_{0.0030}Na_{0.0027}K_{0.0031}Ca_{0.0173}Cl_{0.0018}$ is the empirical formula of the human organism from Table 1.

Biosynthesis reactions have also been formulated for various tissues. For example, the biosynthesis reaction for erythrocytes is

$$1.1849\ CH_{1.798}O_{0.4831}N_{0.2247}S_{0.022472} + 0.2372\ O_2 + 0.0020\ HPO_4^{2-} + 0.0386\ HCO_3^- + 0.0049\ K^+ + 0.0036\ Cl^- \rightarrow CH_{1.4984}O_{0.3047}N_{0.2663}P_{0.0020}S_{0.0059}K_{0.0049}Cl_{0.0036} + 0.0207\ SO_4^2 + 0.1127\ H_2O + 0.2236\ H_2CO_3 \quad (6)$$

where $CH_{1.4984}O_{0.3047}N_{0.2663}P_{0.0020}S_{0.0059}K_{0.0049}Cl_{0.0036}$ is the empirical formula of erythrocytes (Table 1).

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Table 5: Biosynthesis reactions of human tissues. The general biosynthesis reaction has the form: (Amino acid) + CH_2O + O_2 + HPO_4^{2-} + H_2O + HCO_3^- + Na^+ + K^+ + Mg^{2+} + Ca^{2+} + Cl^- → (Bio) + SO_4^{2} + H_2O + H_2CO_3, where (Amino acids) represents a mixture of amino acids with the empirical formula $CH_{1.798}O_{0.4831}N_{0.2247}S_{0.022472}$ and (Bio) represents the empirical formula of live matter from Table 1.

Name	Reactants											→	Products			
	Amino acid	CH_2O	O_2	HPO_4^{2-}	H_2O	HCO_3^-	Na^+	K^+	Mg^{2+}	Ca^{2+}	Cl^-		Bio	SO_4^{2-}	H_2O	H_2CO_3
Human body 1 (average)	0.4949	0.7193	0.0000	0.0134	0.0000	0.0281	0.0027	0.0031	0.0000	0.0173	0.0018	→	1	0.0081	0.0778	0.2423
Human body 2 (average)	0.4293	0.8007	0.0000	0.0189	0.0000	0.0175	0.0033	0.0027	0.0006	0.0187	0.0020	→	1	0.0064	0.1008	0.2475
Adipose tissue 1	0.0960	1.2713	0.0000	0.0000	0.0000	0.0032	0.0010	0.0000	0.0000	0.0000	0.0007	→	1	0.0014	0.0884	0.3704
Adipose tissue 2	0.0447	1.3400	0.0000	0.0000	0.0000	0.0011	0.0009	0.0000	0.0000	0.0000	0.0006	→	1	0.0004	0.0937	0.3857
Adipose tissue 3	0.0245	1.3715	0.0000	0.0000	0.0000	0.0092	0.0008	0.0000	0.0000	0.0000	0.0005	→	1	0.0000	0.0888	0.4052
Adrenal gland	0.3493	0.9250	0.0000	0.0014	0.0000	0.0064	0.0000	0.0011	0.0000	0.0000	0.0024	→	1	0.0052	0.0926	0.2808
Aorta	1.0902	0.0000	0.0856	0.0106	0.0000	0.0381	0.0071	0.0021	0.0000	0.0082	0.0000	→	1	0.0169	0.1103	0.1284
Blood-erythrocytes	1.1849	0.0000	0.2372	0.0020	0.0000	0.0386	0.0000	0.0049	0.0000	0.0000	0.0036	→	1	0.0207	0.1127	0.2236
Blood-plasma	1.0238	0.0335	0.0000	0.0000	0.0000	0.0329	0.0382	0.0000	0.0000	0.0000	0.0331	→	1	0.0139	0.0242	0.0902
Blood-whole	1.1448	0.0000	0.1672	0.0035	0.0000	0.0319	0.0047	0.0056	0.0000	0.0000	0.0092	→	1	0.0189	0.0997	0.1766
Brain-grey matter	0.7230	0.4799	0.0000	0.0122	0.0229	0.0022	0.0110	0.0097	0.0000	0.0000	0.0107	→	1	0.0084	0.0000	0.2051
Brain-white matter	0.4917	0.7647	0.0000	0.0080	0.0000	0.0033	0.0054	0.0048	0.0000	0.0000	0.0052	→	1	0.0072	0.0346	0.2597
Connective tissue	1.1429	0.0000	0.1675	0.0000	0.0000	0.0399	0.0151	0.0000	0.0000	0.0000	0.0049	→	1	0.0148	0.0905	0.1828
Eye lens	1.1154	0.0000	0.1416	0.0020	0.0000	0.0356	0.0027	0.0000	0.0000	0.0000	0.0017	→	1	0.0193	0.1133	0.1510
Gallblader - wall	0.8957	0.1737	0.0000	0.0055	0.0000	0.0235	0.0037	0.0087	0.0000	0.0000	0.0024	→	1	0.0122	0.0954	0.0929
Gastrointestinal tract - oesophagus	0.7300	0.4163	0.0000	0.0034	0.0000	0.0209	0.0045	0.0027	0.0000	0.0000	0.0059	→	1	0.0131	0.0654	0.1672
Gastrointestinal tract - small intestine (wall)	0.7961	0.3211	0.0000	0.0028	0.0000	0.0252	0.0038	0.0044	0.0000	0.0000	0.0024	→	1	0.0125	0.0843	0.1423
Gastrointestinal tract - stomach	0.6760	0.4773	0.0000	0.0044	0.0000	0.0173	0.0030	0.0053	0.0000	0.0000	0.0039	→	1	0.0109	0.1042	0.1706
Heart 1	0.7961	0.3325	0.0000	0.0056	0.0000	0.0194	0.0038	0.0066	0.0000	0.0000	0.0049	→	1	0.0125	0.0695	0.1480

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Heart 2	1.0003	0.0540	0.0000	0.0075	0.0000	0.0228	0.0051	0.0089	0.0000	0.0000	0.0066	→	1	0.0152	0.0749	0.0771
Heart 3	1.0092	0.0366	0.0000	0.0032	0.0000	0.0276	0.0043	0.0051	0.0000	0.0000	0.0084	→	1	0.0165	0.0650	0.0733
Kidney 1	0.8672	0.2233	0.0000	0.0059	0.0000	0.0279	0.0079	0.0047	0.0000	0.0023	0.0051	→	1	0.0138	0.0938	0.1184
Kidney 2	0.9720	0.0968	0.0000	0.0073	0.0000	0.0298	0.0099	0.0058	0.0000	0.0028	0.0064	→	1	0.0148	0.0722	0.0986
Kidney 3	0.6604	0.4955	0.0000	0.0075	0.0000	0.0077	0.0067	0.0059	0.0000	0.0000	0.0043	→	1	0.0072	0.0885	0.1636
Liver 1	0.8236	0.2692	0.0000	0.0084	0.0000	0.0134	0.0075	0.0066	0.0000	0.0000	0.0049	→	1	0.0104	0.0902	0.1061
Liver 2	0.9994	0.0248	0.0000	0.0092	0.0000	0.0188	0.0083	0.0073	0.0000	0.0000	0.0054	→	1	0.0135	0.0902	0.0430
Liver 3	1.0956	0.0000	0.0791	0.0077	0.0000	0.0180	0.0103	0.0061	0.0000	0.0000	0.0101	→	1	0.0135	0.0909	0.1136
Lung - parenchyma	1.1266	0.0000	0.1070	0.0074	0.0000	0.0206	0.0100	0.0059	0.0000	0.0000	0.0097	→	1	0.0146	0.0661	0.1472
Mammary gland 1	0.3448	0.9363	0.0000	0.0012	0.0000	0.0092	0.0016	0.0000	0.0000	0.0000	0.0010	→	1	0.0055	0.0837	0.2903
Mammary gland 2	0.8936	0.1782	0.0000	0.0025	0.0000	0.0269	0.0033	0.0000	0.0000	0.0000	0.0021	→	1	0.0153	0.0929	0.0987
Mammary gland 3	0.8033	0.2958	0.0000	0.0045	0.0000	0.0222	0.0031	0.0072	0.0000	0.0000	0.0020	→	1	0.0115	0.1008	0.1213
Muscle - sceletal 1	0.9073	0.1696	0.0000	0.0054	0.0000	0.0241	0.0037	0.0086	0.0000	0.0000	0.0024	→	1	0.0125	0.0794	0.1010
Muscle - sceletal 2	1.0221	0.0000	0.0073	0.0069	0.0000	0.0246	0.0047	0.0110	0.0000	0.0000	0.0030	→	1	0.0129	0.1075	0.0467
Muscle - sceletal 3	0.9847	0.0898	0.0000	0.0083	0.0000	0.0220	0.0112	0.0066	0.0000	0.0000	0.0073	→	1	0.0141	0.0606	0.0966
Ovary	0.4967	0.7324	0.0000	0.0046	0.0000	0.0145	0.0062	0.0036	0.0000	0.0000	0.0040	→	1	0.0089	0.0790	0.2437
Pancreas	1.0719	0.0000	0.0330	0.0044	0.0000	0.0413	0.0117	0.0069	0.0000	0.0000	0.0000	→	1	0.0157	0.0400	0.1131
Prostate	0.3134	0.9749	0.0000	0.0009	0.0000	0.0084	0.0000	0.0015	0.0000	0.0000	0.0016	→	1	0.0052	0.0882	0.2967
Skeleton - red marrow	0.0415	1.3475	0.0000	0.0000	0.0000	0.0010	0.0008	0.0000	0.0000	0.0000	0.0005	→	1	0.0004	0.0886	0.3899
Skeleton - yellow marrow	0.0415	1.3475	0.0000	0.0000	0.0000	0.0010	0.0008	0.0000	0.0000	0.0000	0.0005	→	1	0.0004	0.0886	0.3899
Skin 1	0.7021	0.4433	0.0000	0.0016	0.0000	0.0208	0.0042	0.0012	0.0000	0.0000	0.0041	→	1	0.0113	0.0878	0.1662
Skin 2	0.7856	0.3149	0.0000	0.0019	0.0000	0.0258	0.0051	0.0015	0.0000	0.0000	0.0050	→	1	0.0140	0.1070	0.1264
Skin 3	0.8936	0.1666	0.0000	0.0025	0.0000	0.0279	0.0066	0.0019	0.0000	0.0000	0.0064	→	1	0.0153	0.1091	0.0881
Spleen	1.0806	0.0000	0.0447	0.0103	0.0000	0.0215	0.0046	0.0082	0.0000	0.0000	0.0060	→	1	0.0177	0.0649	0.1021
Testis	0.7709	0.3692	0.0000	0.0039	0.0000	0.0216	0.0106	0.0062	0.0000	0.0000	0.0068	→	1	0.0098	0.0639	0.1616
Thyroid	0.7696	0.3258	0.0000	0.0033	0.0000	0.0274	0.0088	0.0026	0.0000	0.0000	0.0057	→	1	0.0141	0.0644	0.1228
Urinary bladder - wall	0.8957	0.1737	0.0000	0.0055	0.0000	0.0235	0.0037	0.0087	0.0000	0.0000	0.0024	→	1	0.0122	0.0954	0.0929

The biosynthesis reaction for the blood plasma is

$$1.0238\ CH_{1.798}O_{0.4831}N_{0.2247}S_{0.022472} + 0.0335\ CH_2O + 0.0329\ HCO_3^- + 0.0382\ Na^+ + 0.0331\ Cl^- \rightarrow CH_{1.7117}O_{0.2767}N_{0.2301}S_{0.0091}Na_{0.0382}Cl_{0.0331} + 0.0139\ SO_4^2 + 0.0242\ H_2O + 0.0902\ H_2CO_3 \quad (7)$$

where $CH_{1.7117}O_{0.2767}N_{0.2301}S_{0.0091}Na_{0.0382}Cl_{0.0331}$ is the empirical formula of the blood plasma (Table 1).

The biosynthesis reaction for the eye lens tissue is

$$1.1154\ CH_{1.798}O_{0.4831}N_{0.2247}S_{0.022472} + 0.1416\ O_2 + 0.0020\ HPO_4^{2-} + 0.0356\ HCO_3^- + 0.0027\ Na^+ + 0.0017\ Cl^- \rightarrow CH_{1.5143}O_{0.2934}N_{0.2507}P_{0.0020}S_{0.0058}Na_{0.0027}Cl_{0.0017} + 0.0193\ SO_4^2 + 0.1133\ H_2O + 0.1510\ H_2CO_3 \quad (8)$$

where $CH_{1.5143}O_{0.2934}N_{0.2507}P_{0.0020}S_{0.0058}Na_{0.0027}Cl_{0.0017}$ is the empirical formula of the eye lens tissue (Table 1).

The biosynthesis reaction of the small intestine tissue, constituting a part of the gastrointestinal tract, is

$$0.7961\ CH_{1.798}O_{0.4831}N_{0.2247}S_{0.022472} + 0.3211\ CH_2O + 0.0028\ HPO_4^{2-} + 0.0252\ HCO_3^- + 0.0038\ Na^+ + 0.0044\ K^+ + 0.0024\ Cl^- \rightarrow CH_{1.6480}O_{0.2310}N_{0.1789}P_{0.0028}S_{0.0054}Na_{0.0038}K_{0.0044}Cl_{0.0024} + 0.0125\ SO_4^2 + 0.0843\ H_2O + 0.1423\ H_2CO_3 \quad (9)$$

where $CH_{1.6480}O_{0.2310}N_{0.1789}P_{0.0028}S_{0.0054}Na_{0.0038}K_{0.0044}Cl_{0.0024}$ is the empirical formula of the small intestine tissue (Table 1).

The biosynthesis reaction for the skin tissue is

$$0.7021\ CH_{1.798}O_{0.4831}N_{0.2247}S_{0.022472} + 0.4433\ CH_2O + 0.0016\ HPO_4^{2-} + 0.0208\ HCO_3^- + 0.0042\ Na^+ + 0.0012\ K^+ + 0.0041\ Cl^- \rightarrow CH_{1.6631}O_{0.2195}N_{0.1578}P_{0.0016}S_{0.0045}Na_{0.0042}K_{0.0012}Cl_{0.0041} + 0.0113\ SO_4^2 + 0.0878\ H_2O + 0.1662\ H_2CO_3 \quad (10)$$

where $CH_{1.6631}O_{0.2195}N_{0.1578}P_{0.0016}S_{0.0045}Na_{0.0042}K_{0.0012}Cl_{0.0041}$ is the empirical formula of the skin tissue (Table 1).

The biosynthesis reaction for the urinary bladder wall tissue is

$$0.8957\ CH_{1.798}O_{0.4831}N_{0.2247}S_{0.022472} + 0.1737\ CH_2O + 0.0055\ HPO_4^{2-} + 0.0235\ HCO_3^- + 0.0037\ Na^+ + 0.0087\ K^+ + 0.0024\ Cl^- \rightarrow CH_{1.6101}O_{0.2757}N_{0.2013}P_{0.0055}S_{0.0079}Na_{0.0037}K_{0.0087}Cl_{0.0024} + 0.0122\ SO_4^2 + 0.0954\ H_2O + 0.0929\ H_2CO_3 \quad (11)$$

where $CH_{1.6101}O_{0.2757}N_{0.2013}P_{0.0055}S_{0.0079}Na_{0.0037}K_{0.0087}Cl_{0.0024}$ is the empirical formula of the urinary bladder wall tissue (Table 1).

Table 6: Thermodynamic properties of biosynthesis of human tissues. This table shows standard enthalpies of biosynthesis, $\Delta_{bs}H^0$, standard entropies of biosynthesis, $\Delta_{bs}S^0$, and standard Gibbs energies of biosynthesis, $\Delta_{bs}G^0$.

Name	$\Delta_{bs}H^0$ (kJ/C-mol)	$\Delta_{bs}S^0$ (J/C-mol K)	$\Delta_{bs}G^0$ (kJ/C-mol)
Human body 1 (average)	-21.59	34.71	-31.37
Human body 2 (average)	-22.80	37.61	-33.44
Adipose tissue 1	-37.48	52.61	-51.88
Adipose tissue 2	-39.21	55.10	-54.28
Adipose tissue 3	-39.88	57.11	-55.78
Adrenal gland	-27.97	39.84	-38.93
Aorta	-42.41	1.08	-42.85
Blood-erythrocytes	-113.09	-15.73	-108.40
Blood-plasma	0.72	5.75	-0.96
Blood-whole	-79.52	-9.41	-76.74
Brain-grey matter	-13.05	23.99	-19.86
Brain-white matter	-22.50	34.45	-32.09
Connective tissue	-79.55	-9.14	-76.81
Eye lens	-69.40	-6.84	-67.37
Gallblader – wall	-6.45	12.02	-9.93
Gastrointestinal tract – oesophagus	-14.30	21.42	-20.30

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Gastrointestinal tract - small intestine (wall)	-11.68	18.34	-16.85
Gastrointestinal tract – stomach	-15.27	23.59	-21.87
Heart 1	-11.32	18.73	-16.64
Heart 2	-3.20	8.47	-5.76
Heart 3	-3.67	7.41	-5.88
Kidney 1	-8.30	15.13	-12.65
Kidney 2	-4.60	11.13	-7.91
Kidney 3	-14.14	23.06	-20.60
Liver 1	-8.04	14.62	-12.23
Liver 2	-1.40	5.41	-3.10
Liver 3	-37.09	-0.90	-36.91
Lung – parenchyma	-50.51	-2.80	-49.76
Mammary gland 1	-28.64	40.69	-39.84
Mammary gland 2	-8.61	12.87	-12.30
Mammary gland 3	-10.08	16.42	-14.73
Muscle - sceletal 1	-6.60	12.37	-10.18
Muscle - sceletal 2	-4.30	4.46	-5.71
Muscle - sceletal 3	-3.87	10.51	-7.01
Ovary	-22.26	33.11	-31.44
Pancreas	-18.09	4.71	-19.54
Prostate	-29.53	41.76	-41.01
Skeleton - red marrow	-39.47	55.48	-54.65
Skeleton - yellow marrow	-39.47	55.48	-54.65
Skin 1	-15.06	22.33	-21.29
Skin 2	-11.57	17.13	-16.38
Skin 3	-7.23	11.57	-10.54
Spleen	-22.74	3.10	-23.78
Testis	-11.39	19.96	-17.01
Thyroid	-11.19	15.52	-15.53
Urinary bladder – wall	-6.45	12.02	-9.93

The biosynthesis reactions were combined with thermodynamic properties of live matter of human tissues, from Table 2. This gave standard thermodynamic properties of biosynthesis of human tissues, which are given in Table 6. They include standard enthalpy of biosynthesis, $\Delta_{bs}H^0$, standard entropy of biosynthesis, $\Delta_{bs}S^0$, and standard Gibbs energy of biosynthesis, $\Delta_{bs}G^0$. For example, for the entire human organism, standard enthalpy of biosynthesis is -21.59 kJ/C-mol, standard entropy of biosynthesis is 34.71 J/C-mol K and standard Gibbs energy of biosynthesis is -31.37 kJ/C-mol. For erythrocytes, standard enthalpy of biosynthesis is -113.09 kJ/C-mol, standard entropy of biosynthesis is -15.73 J/C-mol K and standard Gibbs energy of biosynthesis is -108.40 kJ/C-mol. For blood plasma, standard enthalpy of biosynthesis is 0.72 kJ/C-mol, standard entropy of biosynthesis is 5.75 J/C-mol K and standard Gibbs energy of biosynthesis is -0.96 kJ/C-mol. For the eye lens tissue, standard enthalpy of biosynthesis is -69.40 kJ/C-mol, standard entropy of biosynthesis is -6.84 J/C-mol K and standard Gibbs energy of biosynthesis is -67.37 kJ/C-mol. For the small intestine wall tissue, standard enthalpy of biosynthesis is -11.68 kJ/C-mol,

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standard entropy of biosynthesis is 18.34 J/C-mol K and standard Gibbs energy of biosynthesis is -16.85 kJ/C-mol. For the skin tissue, standard enthalpy of biosynthesis is -15.06 kJ/C-mol, standard entropy of biosynthesis is 22.33 J/C-mol K and standard Gibbs energy of biosynthesis is -21.29 kJ/C-mol. For the urinary bladder wall tissue, standard enthalpy of biosynthesis is -6.45 kJ/C-mol, standard entropy of biosynthesis is 12.02 J/C-mol K and standard Gibbs energy of biosynthesis is -9.93 kJ/C-mol.

3.2. Biosynthesis reactions and thermodynamic properties of microorganisms

Based on empirical formulas in Table 3, biosynthesis reactions were formulated for microorganism live matter, which are presented in Table 7. For live matter of bacteria in general, biosynthesis of new live matter can be described through the macrochemical equation

$$0.8900\ CH_{1.798}O_{0.4831}N_{0.2247}S_{0.022472} + 0.1765\ CH_2O + 0.0400\ HCO_3^- \rightarrow CH_{1.666}O_{0.270}N_{0.200} + 0.0200\ SO_4^{2} + 0.0570\ H_2O + 0.1065\ H_2CO_3 \quad (12)$$

where the empirical formula $CH_{1.798}O_{0.4831}N_{0.2247}S_{0.022472}$ represents a mixture of amino acids [Popovic, 2022a], CH_2O carbohydrates [Popovic, 2022a], and $CH_{1.666}O_{0.270}N_{0.200}$ represents the empirical formula of bacterial live matter (Table 3).

Production of new live matter of *Escherichia coli* can be described by the biosynthesis reaction

$$1.0680\ CH_{1.798}O_{0.4831}N_{0.2247}S_{0.022472} + 0.1285\ O_2 + 0.0170\ H_2O + 0.0480\ HCO_3^- \rightarrow CH_{1.770}O_{0.490}N_{0.240} + 0.0240\ SO_4^{2} + 0.1160\ H_2CO_3 \quad (13)$$

where $CH_{1.770}O_{0.490}N_{0.240}$ is the empirical formula of *E. coli* live matter (Table 3).

The biosynthesis reaction for the bacterium *Klebsiella aerogenes* is

$$0.9790\ CH_{1.798}O_{0.4831}N_{0.2247}S_{0.022472} + 0.0210\ CH_2O + 0.0140\ O_2 + 0.0440\ HCO_3^- \rightarrow CH_{1.750}O_{0.430}N_{0.220} + 0.0220\ SO_4^{2} + 0.0040\ H_2O + 0.0440\ H_2CO_3 \quad (14)$$

where $CH_{1.750}O_{0.430}N_{0.220}$ is the empirical formula of the *K. aerogenes* live matter (Table 3).

The biosynthesis reaction for the fungus *Candida utilis* is

$$0.4450\ CH_{1.798}O_{0.4831}N_{0.2247}S_{0.022472} + 0.6350\ CH_2O + 0.0200\ HCO_3^- \rightarrow CH_{1.830}O_{0.540}N_{0.100} + 0.0100\ SO_4^{2} + 0.0300\ H_2O + 0.1000\ H_2CO_3 \quad (15)$$

where $CH_{1.830}O_{0.540}N_{0.100}$ is the empirical formula of live matter of *C. utilis* (Table 3).

Table 7: Biosynthesis stoichiometry of microorganisms. The general biosynthesis reaction for microorganism live matter has the form (Amino acid) + CH_2O + O_2 + H_2O + HCO_3^- → (Bio) + SO_4^{2} + H_2O + H_2CO_3, where (Amino acids) represents a mixture of amino acids with the empirical formula $CH_{1.798}O_{0.4831}N_{0.2247}S_{0.022472}$ and (Bio) represents the empirical formula of live matter from Table 3.

Name	**Reactants**					→	**Products**			
	Amino acid	**CH_2O**	**O_2**	**H_2O**	**HCO_3^-**		**Bio**	**SO_4^{2-}**	**H_2O**	**H_2CO_3**
Bacteria (general)	0.8900	0.1765	0.0000	0.0000	0.0400	→	1	0.0200	0.0570	0.1065
Escherichia coli	1.0680	0.0000	0.1285	0.0170	0.0480	→	1	0.0240	0.0000	0.1160
Klebsiella aerogenes	0.9790	0.0210	0.0140	0.0000	0.0440	→	1	0.0220	0.0040	0.0440
Candida utilis	0.4450	0.6350	0.0000	0.0000	0.0200	→	1	0.0100	0.0300	0.1000

The microbial biosynthesis reactions were combined with thermodynamic properties of microbial live matter from Table 4. This gave thermodynamic properties of biosynthesis of microorganisms, which are given in Table 8. They include standard enthalpy of biosynthesis, $\Delta_{bs}H^0$, standard entropy of biosynthesis, $\Delta_{bs}S^0$, and standard Gibbs energy of biosynthesis, $\Delta_{bs}G^0$. For bacteria in general, standard enthalpy of biosynthesis is -10.35 kJ/C-mol, standard entropy of biosynthesis is 12.19 J/C-mol K and standard Gibbs energy of biosynthesis is -13.81 kJ/C-mol. For *E. coli*, standard enthalpy of biosynthesis is -64.34 kJ/C-mol, standard entropy of biosynthesis is -12.25 J/C-mol K and standard Gibbs energy of biosynthesis is -60.68 kJ/C-mol. For *Klebsiella aerogenes*, standard enthalpy of biosynthesis is -12.06 kJ/C-mol, standard entropy of biosynthesis is 0.28 J/C-mol K and standard Gibbs

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energy of biosynthesis is -12.13 kJ/C-mol. For *Candida utilis*, standard enthalpy of biosynthesis is -18.94 kJ/C-mol, standard entropy of biosynthesis is 16.11 J/C-mol K and standard Gibbs energy of biosynthesis is -23.11 kJ/C-mol.

Table 8: Thermodynamic properties of biosynthesis of microorganisms. This table shows standard enthalpies of biosynthesis, $\Delta_{bs}H^0$, standard entropies of biosynthesis, $\Delta_{bs}S^0$, and standard Gibbs energies of biosynthesis, $\Delta_{bs}G^0$.

Name	$\Delta_{bs}H^0$ (kJ/C-mol)	$\Delta_{bs}S^0$ (J/C-mol K)	$\Delta_{bs}G^0$ (kJ/C-mol)
Bacteria (general)	-10.35	12.19	-13.81
Escherichia coli	-64.34	-12.25	-60.68
Klebsiella aerogenes	-12.06	0.28	-12.13
Candida utilis	-18.94	16.11	-23.11

4. Discussion

Microbial population number of cellular [Casadevall and Pirofski, 2000] and subcellular [Domingo, 2020] microorganisms are extremely large, compared with those of their host species. Host organisms are surrounded with various virus species, which exhibit great specificity. Viruses can infect host organisms, but can also exist passively in the environment and wait for a new host.

Specificity of viruses is exhibited on antigen-receptor interactions that are performed on the cell membrane. The *conditio sine qua non* for successful virus-host interaction is presence of an appropriate antigen on the virus surface and an appropriate receptor on the host cell surface [Riedel et al., 2019]. Various viruses use various receptors for binding and entrance into the host cell [Maginnis, 2018]. For example, all SARS-CoV-2 variants use the ACE2 receptor [Shirbhate et al., 2021; Gawish et al., 2022]. Antigen-receptor interactions proceed through a mechanism similar to protein-ligand interactions [Du et al., 2016; Popovic and Popovic, 2022]. The driving force for antigen-receptor interactions is Gibbs energy of binding [Gale, 2022, 2020, 2019, 2018; Casasnovas and Springer, 1995; Popovic and Popovic, 2022; Popovic, 2022b]. The antigen-receptor binding reaction is competitive. If two virus species or variants use the same receptors, then they compete [Popovic and Minceva, 2021a]. For example, several dozen variants of SARS-CoV-2 use the same ACE2 receptor. During the COVID-19 pandemic, the phenomenon was noticed that multiple SARS-CoV-2 variants appeared in the same population at the same time in the same place. Competition between the variants for “soil” occurs. The result of competition was the suppression of the old variants with newer ones, which exhibited greater infectivity [Eales et al, 2022]. All variants of SARS-CoV-2 have been chemically and thermodynamically characterized [Popovic, 2023b, 2023c, 2023d, 2022b, 2022c, 2022d, 2022e, 2022f, 2022g, 2022h; Popovic and Popovic, 2022; Popovic and Minceva, 2021a, 2020b; Şimşek et al., 2021; Degueldre, 2021].

During the time evolution of the virus, through acquisition of mutations, changes occurred in the elemental composition, information content in the genome and spike glycoprotein, towards formation of a greater binding affinity for the receptor [Makowski et al, 2022]. An increase in binding affinity resulted in a greater antigen-receptor binding rate. This gave an advantage to the mutated variants to spread within the population. Some of the new variants caused pandemic waves. Some of the mutated variants have exhibited the ability of immune evasion [Gao et al., 2021; Cao et al., 2022a; Barton et al., 2021]. This phenomenon has exhibited an additional reason for the advantage of the new variants during the competition with older ones.

A virus represents an obligate intracellular parasite, which hijacks host cell metabolism [Summers, 2009; Thaker et al., 2019; Popovic and Minceva, 2020a; Proal and VanElzakker, 2021; Sumbria et al., 2021]. A virus performs biological processes of replication, transcription, translation and self-assembly. Replication, transcription and translation

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represent chemical processes of polymerization of nucleotides and amino acids into nucleic acids, and structural and functional proteins of the virus [Lee et al., 2020; Pinheiro et al., 2008; Dodd et al., 2020; Johansson and Dixon, 2013]. The driving force for replication, transcription and translation is Gibbs energy of biosynthesis [Demirel, 2014; Balmer, 2010; Popovic, 2022a]. Gibbs energy of biosynthesis for various viruses is available in the literature [Popovic, 2023b, 2023c, 2023d, 2022c, 2022d, 2022f, 2022h; Popovic and Minceva, 2021a, 2020b]. According to the phenomenological equation, biosynthesis rate depends on Gibbs energy of biosynthesis [Demirel, 2014; Balmer, 2010; von Stockar, 2013a; Popovic, 2022a].

Gibbs energy of biosynthesis is, according to the phenomenological equations, directly proportional to the rate of biosynthesis of building blocks [Popovic, 2023a, 2023b, 2023c, 2022h]. The newly synthetized virions lead to damage of host cells. Greater damage to host cells indicates greater pathogenicity. Through analysis of evolution of SARS-CoV-2 from Hu-1 to the new BA.5.2, BF.7 and XBB.1.5 variants, it was shown that Gibbs energy of biosynthesis of Hu-1 is the most negative, while the variants that appeared through various mutations exhibited a less negative Gibbs energy of biosynthesis that that of Hu-1. Thus, we can conclude that SARS-CoV-2 has evolved towards an increase in infectivity, accompanied by a slight decrease or maintenance of constant pathogenicity.

A virus consists of a nucleic acid, a capsid and sometimes an envelope. Thus, a virus is clearly bordered from its surroundings [Popovic and Minceva, 2020a]. A virion exchanges substances with its environment and performs metabolic processes by using the host cell’s machinery, in processes of replication, transcription and translation, accumulating matter during the multiplication process. Thus, the environment of the virus is the host cell, while the wider environment is the host organism. However, the virocell concept has been suggested [Forterre, 2011, 2013; Forterre and Krupovic, 2012; Howard-Varona et al., 2020; Rosenwasser et al., 2016]. According to the virocell concept, a virus and its host cell represent a system, while the surrounding is the tissue. This concept would require formulation of new mechanistic models and defining of state parameters of the thermodynamic system – virocell. Such a model seems to be less accurate, since the obtained Gibbs energy as the driving force for multiplication would not reflect only the multiplication of viruses, but also include biosynthesis of building blocks of the host cell. The building blocks of the host cell have their own Gibbs energy of biosynthesis, just like viruses have their own. Reactions of biosynthesis of viruses and those of host cell components are competitive. Due to a difference in Gibbs energies of biosynthesis of viruses and host cells, it is possible to explain the phenomenon of hijacking of host cell machinery. If we accept the virocell concept, then we would not be able to use the mechanistic model for hijacking of cell metabolic machinery.

It is obvious that mechanistic models of virus-host interactions on the membrane (antigen-receptor binding) and virus-host interactions in the cytoplasm can significantly contribute to better understanding of virus-host interactions and explain the phenomena like infectivity, pathogenicity, interference and coinfection [Gale, 2022, 2020, 2019, 2018; Lucia et al., 2021, 2020a, 2020b; Özilgen and Yilmaz, 2021, Yilmaz et al., 2020; Mahmoudabadi et al., 2017; Popovic, 2022a; Popovic and Minceva, 2021a].

Cellular microorganisms (bacteria, archaea, yeast) represent open thermodynamic systems with the property of growth [Popovic, 2019]. The driving force for growth of cellular microorganisms is Gibbs energy of biosynthesis [von Stockar, 2013a, 2013b]. Thermodynamic system can be a single microbial cell or microbial colony that appears due to multiplication of microorganisms through accumulation of matter taken from the environment [von Stockar, 2013a, 2013b]. The environment for a growing microbial colony, as a thermodynamic system, is the growth medium or tissue on which the microorganism is a parasite. Elemental composition and thermodynamic properties of live matter (enthalpy, entropy, Gibbs energy) have been reported in the literature for over 35 microorganism species [Popovic, 2019; Popovic et al., 2021; Calabrese et al., 2021]. These data have enabled a better understanding of microorganism-host interactions, through development of mechanistic models. Having in mind the universality of nature and the fact that similar models apply to viroids [Popovic, 2023a], viruses [Popovic, 2022a] and bacteria [Popovic, 2019; Calabrese et al., 2021], it can be expected that development of mechanistic models with the application of thermodynamic properties of biosynthesis, it is possible to shed more light on other parasite-host interactions.

The biothermodynamic background of virus-host cell interaction is available in the literature [Popovic and Minceva, 2020a]. Let us try to analyze the biothermodynamic background of bacteria-host tissue interaction in this paper. In Tables 1-4, data are given on chemical and thermodynamic properties of biosynthesis for human tissues. In Tables 5-8, chemical and thermodynamic properties are given for biosynthesis for microorganisms that interact with humans: bacteria in general, *Escherichia coli*, *Klebsiella aerogenes* and *Candida utilis*. The biothermodynamic mechanisms of pathogen-host interactions are universal and are based on fundamental laws of thermodynamics and kinetics. Biosynthesis reactions for host cell components and pathogens are competitive. The rate at which these reactions occur depends on Gibbs energy of biosynthesis, for both subcellular and cellular parasites. Both subcellular and cellular parasites represent thermodynamic systems, clearly separated from the environment, which exchange and accumulate substances taken from the environment. In that way, they achieve growth of the microorganism population.

To describe the biothermodynamic background of interactions between bacteria and human host tissues, we must compare Gibbs energies of biosynthesis of bacteria to Gibbs energies of biosynthesis of host cell building blocks. In that way, we will calculate the permissiveness coefficients for multiplication of bacteria in certain tissues. Gibbs energy of biosynthesis for the entire human organism is around -31.37 kJ/C-mol. Gibbs energy of biosynthesis of *Escherichia coli* is -60.68 kJ/C-mol. Since the rate of biosynthesis of building blocks depends on the driving force – Gibbs energy of biosynthesis, according to phenomenological equations, it is obvious that *Escherichia coli* can multiply in a human host. The permissiveness coefficient for *E. coli* is

$$P=\frac{\Delta_{bs}G(pathogen)}{\Delta_{bs}G(host)}=\frac{-60.68\frac{\text{kJ}}{\text{C-mol}}}{-31.37\frac{\text{kJ}}{\text{C-mol}}}=1.93 \tag{16}$$

where $\Delta_{bs}G$ is Gibbs energy of biosynthesis [Popovic, 2022a]. The permissiveness coefficient is greater than 1, which represents a thermodynamic confirmation of the observation that *E. coli* can be found in the human organism [Riedel et al., 2019]. Moreover, it is known that *E. coli* very often causes urinary infections. Gibbs energy of biosynthesis for the urinary bladder walls is -9.93 kJ/C-mol. The permissiveness coefficient is

$$P=\frac{\Delta_{bs}G(pathogen)}{\Delta_{bs}G(host)}=\frac{-60.68\frac{\text{kJ}}{\text{C-mol}}}{-9.93\frac{\text{kJ}}{\text{C-mol}}}=6.11 \tag{17}$$

It is obvious that the urinary pathways represent the predilected tissue for multiplication of *E. coli*, which is indicated by the greater permissiveness coefficient. However, Gibbs energy of biosynthesis for the eye lens is -67.37 kJ/C-mol. Thus, the permissiveness coefficient is

$$P=\frac{\Delta_{bs}G(pathogen)}{\Delta_{bs}G(host)}=\frac{-60.68\frac{\text{kJ}}{\text{C-mol}}}{-67.37\frac{\text{kJ}}{\text{C-mol}}}=0.90 \tag{18}$$

Since the permissiveness coefficient is lower than unity, the biosynthesis reaction for the eye lens live matter has an advantage and it can be expected that *E. coli* is not able to multiply on the eye lens. Furthermore, Gibbs energy of biosynthesis of erythrocytes is -108.40 kJ/C-mol. This means that the permissiveness coefficient is

$$P=\frac{\Delta_{bs}G(pathogen)}{\Delta_{bs}G(host)}=\frac{-60.68\frac{\text{kJ}}{\text{C-mol}}}{-108.40\frac{\text{kJ}}{\text{C-mol}}}=0.56 \tag{19}$$

The permissiveness coefficient for biosynthesis (multiplication of *E. coli*) is lower than 1. Thus, multiplication of *E. coli* on pure erythrocytes is difficult. On other tissues, multiplication of *E. coli* is possible, with different dynamics. The rate of multiplication depends on, according to the phenomenological equations, on Gibbs energy of biosynthesis

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$$r_{bs} = -\frac{L_{bs}}{T} \Delta_{bs} G \tag{20}$$

where r_{bs} is biosynthesis rate, T is temperature, L_{bs} the biosynthesis phenomenological coefficient. Since the environment is the same for both the microorganism and host cells, the L_{bs} coefficient is the same for both. Thus, the biosynthesis reactions for different tissues, which are characterized by approximately equal or less negative Gibbs energy, enable growth of *E. coli* on that tissue.

Gibbs energy of biosynthesis of *Klebsiella aerogenes* is -12.13 kJ/C-mol. The less negative Gibbs energy of biosynthesis of *Klebsiella* makes its biosynthesis reaction much slower than that of *E. coli*. Thus, infections with *Klebsiella* are much less frequent. This is in very good agreement with the observation that infections with *Klebsiella* are opportunistic infections [Ssekatawa et al., 2021]. The pathogen-host interaction of *Klebsiella* with human tissues can occur only under changes in chemical and thermodynamic properties of human tissues. This is the case under various pathological states (diseases) of human tissues, when their elemental composition and thermodynamic properties change. This could be an explanation for the opportunistic character of *Klebsiella*. However, Gibbs energy of biosynthesis of urinary bladder wall is -9.93 kJ/C-mol. This means that the permissiveness coefficient for *Klebsiella* in the urinary pathways is

$$P = \frac{\Delta_{bs}G(pathogen)}{\Delta_{bs}G(host)} = \frac{-12.13\frac{\text{kJ}}{\text{C-mol}}}{-9.93\frac{\text{kJ}}{\text{C-mol}}} = 1.22 \tag{21}$$

Moreover, if during catateterization *Klebsiella* enters the blood, it is able to multiply in the blood plasma. Gibbs energy of biosynthesis of the blood plasma is -0.96. This means that the permissiveness coefficient is

$$P = \frac{\Delta_{bs}G(pathogen)}{\Delta_{bs}G(host)} = \frac{-12.13\frac{\text{kJ}}{\text{C-mol}}}{-0.96\frac{\text{kJ}}{\text{C-mol}}} = 12.64 \tag{22}$$

The high permissiveness coefficient allows rapid multiplication of *K. aerogenes*, but only if it passes the barriers of other tissues, in which multiplication is much more difficult.

Candida utilis interacts with various human tissues in immunocompromised patients [Sreelekshmi et al., 2021]. The biothermodynamic background of this interactions can be explained in a similar way to that with bacteria-host and virus-host interactions. Gibbs energy of biosynthesis of *Candida utilis* is -23.11 kJ/C-mol. Very close values of Gibbs energy of biosynthesis are those of the urinary tract, gastrointestinal tract and skin. This makes infections of these organs the most likely. The fact that most other organs (Table 4) have a more negative Gibbs energy of biosynthesis, makes multiplication of *Candida* in these tissues difficult.

5. Conclusions

Biothermodynamics and mechanistic models have proved themselves as powerful tools in research on interactions of microorganisms with their hosts (e.g. virus-host interactions, bacteria-host interactions) and inanimate matter (e.g. bioreactors). Chemical and thermodynamic characterization of microorganisms (determination of empirical formula, enthalpy, entropy and Gibbs energy) has significantly contributed to shedding more light on virus-host interactions.

Until now, over 50 virus species and variants have been characterized: SARS, MERS, SARS-CoV-2 (from Hu-1 to BA.5.2, BF.7 and XBB.1.5), Ebola virus, Monkeypox, HIV-1, Herpes simplex, bacteriophages, viroids etc. It is important to continue the thermodynamic research on biothermodynamic background of various viruses and their interactions with their environment.

This paper reports biosynthesis reactions and thermodynamic properties of biosynthesis of the bacteria *E. coli* and *Klebsiella aerogenes*, and the fungus *Candida utilis*. Moreover, the biothermodynamic background of bacteria-host interaction and fungi-host interactions were analyzed. It was found that these interactions occur through the same model as the virus-host interactions.

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