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Breaking news: Empirical formulas, molar masses, biosynthesis reactions and thermodynamic properties of virus particles – Biosynthesis and binding of Omicron JN.1 variant of SARS-CoV-2

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Abstract: Breaking news are usually disturbing. Natural disasters, wars, epidemics, *etc*., are reported as breaking news. This paper reports a decreased danger of spreading of epidemics caused by the JN.1 variant, since analyses indicate that infectivity of the new variant is decreased compared to most earlier variants, which is confirmed by the number of cases (7500 daily in USA). Moreover, JN.1, despite the great number of mutations, has not been able to achieve the values of Gibbs energy change of biosynthesis (and thus virus multiplication rate) of the Hu-1 wild type. The research shows that infectivity and pathogenicity of the JN.1 variant has not reached worrying size, which means that there is no reason to expect the epidemiologic situation getting worse.

Keywords: biothermodynamics; Gibbs energy; immune evasion; infectivity; pathogenicity; virus time evolution.

INTRODUCTION

The year 2019 was at an end. On the social networks, several doctors from Wuhan warned about the appearance of a large number of infected people. Later, the new disease was named COVID-19. Breaking news in the media have alarmed the general public long before governments and health authorities reacted in most countries. After that, an overreaction occurred, with the enforcement of a lockdown, which was in some cases extreme. Fortunately, the scientific community reacted in a much more rational way. Very soon, it was discovered that the cause of the future pandemic is a virus from the *Coronaviridae* family, named SARS-CoV-2 Hu-1 variant. Molecular biologists have very soon reported the nucleic

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acid sequences[1] and the protein sequences.[2] The virus morphology was known from before.[3]

SARS-CoV-2 belongs to RNA viruses.[4] RNA viruses exhibit a significant tendency towards mutation.[5] From 2019 to 2024, SARS-CoV-2 has mutated several dozen times.[6] The new variants of SARS-CoV-2 have suppressed the older variants and caused pandemic waves.[7] All the mutations of SARS-CoV-2 have been described and its genetic sequence, as well as the protein sequences of all the variants, have been reported.[8] As of January 4, 2024, during the COVID--19 pandemic, over 773 million cases have been reported with almost 7 million deaths.[9]

Except for researchers in the fields of molecular biology, virology, clinical medicine and immunology, the research was joined by scientists from the fields of biothermodynamics, chemistry, biochemistry and biophysics. Before 2019, it was known that a virus can be analysed as a chemical system[10] and processes that viruses perform as chemical reactions.[11] The empirical formula was known only for the poliovirus.[10]

Antigen–receptor binding is a process very similar to the protein ligand interactions.[12,13] Furthermore, the process of virus multiplication consists of polymerization of nucleotides into viral nucleic acids[14,15] and amino acids into viral proteins,[16] as well as self-assembly processes.[17] The Gibbs energy change is a measure of a driving force for these processes/reactions.[18,19]

The empirical formulas of SARS-CoV-2 variants have been reported in the literature.[20,21] The empirical formulas of viruses can be calculated with the atom counting method, based on their genetic sequences, protein sequences and morphology.[22,23] The results obtained with the atom counting method are in good agreement with experimental results.[22,23]

Based on the empirical formulas, it is possible to apply the Patel–Erickson model (Thornton's rule)[24,25] and Battley model[26] to calculate thermodynamic properties – enthalpy, entropy and Gibbs energy changes, including the driving force for chemical reactions involving viruses.[27–31] Thermodynamic properties of biosynthesis, including Gibbs energy change of biosynthesis – the driving force of virus multiplication, has been reported for major variants of SARS-CoV--2.[20,32] The biothermodynamic approach was also applied to study multiplication of the Ebola virus,[28] Mpox virus,[29] West Nile virus,[30] Rotavirus,[55] *etc*.

The virus–host interaction begins at the cell membrane with antigen–receptor binding, which allows a virus to enter its host cell.[13,33] The driving force of the antigen–receptor binding is related to Gibbs energy change of binding.[27,34–36] Moreover, the thermodynamic approach has also been applied to study the antigen–receptor binding of arboviruses,[35] HIV,[35] Ebola virus,[28] SARS-CoV,[13] *etc*.

Knowing the thermodynamic properties of virus particles and processes that comprise the viral life cycle is very important.[37] Based on the known thermos-

dynamic properties, it is possible to draw conclusions about the pathogenesis of viral infections[13,38,39] and epidemiology.[40]

During the COVID-19 pandemic, the appearance of new variants has often caused panic, first of all due to fear of change in infectivity and pathogenicity of the virus. The goal of this paper is to perform chemical and thermodynamic characterization of the new Omicron JN.1 variant, which has been spreading during December 2023 and January 2024, mostly in USA and Europe. Moreover, another goal is to predict the potential changes in the infectivity and the pathogenicity of the JN.1 variant, before the epidemiologic data arrive, in the moment when the epidemic wave reaches its maximum.

METHODS

Data sources

The genetic sequence of the Omicron JN.1 variant of SARS-CoV-2 was taken from GISAID, the global data science initiative.[41] It is labelled hCoV-19/Canada/ON-KHS-09219--v1/2023 and can be found under the accession number EPI_ISL_18615181. It was isolated on December 4, 2023, in the Canadian province Ontario. Thus, the findings of this study are based on the metadata associated with one sequence available on GISAID up to January 9, 2024, and accessible at https://doi.org/10.55876/gis8.240109xh (please see the Supplementary material for more details).

The protein sequences were taken from the NCBI database.[42] The sequence of the nucleocapsid phosphoprotein of SARS-CoV-2 was obtained under the accession number QIK50455.1. The sequence of the membrane protein of SARS-CoV-2 was obtained under the accession number QHR63293.1. The sequence of the spike glycoprotein of SARS-CoV-2 was obtained under the accession number QHR63290.2. The number of protein copies in the virus particle was taken from Neuman *et al.*[3] In a SARS-CoV-2 particle, there are 2368 copies of the nucleocapsid phosphoprotein, 1184 copies of the membrane protein and 222 copies of the spike glycoprotein.[3]

The dissociation equilibrium constant, K_d, of the Omicron JN.1 variant of SARS-CoV-2 was taken from.[43] It was measured by surface plasmon resonance at room temperature.[43]

Atom counting method

The empirical formulas, chemical formulas and macromolecular composition of the Omicron JN.1 variant of SARS-CoV-2 were obtained with the atom counting method, as described in the previous paper.[22] The atom counting method is a computational method for the calculation of empirical formulas of macromolecules and macromolecular assemblies, including virus particles.[22] The input of the program are genetic sequences, protein sequences and morphology.[22]

Patel–Erickson model

The Patel–Erickson model[24,25] was used to find the enthalpy of live matter (virus particle, nucleocapsid and nucleic acid). The Patel–Erickson model gives enthalpy of live matter based on its empirical formula.[24,25] First, from the empirical formula, the degree of reduction, E, is calculated:

$$E = 4n_C + n_H - 2n_O - 0n_N + 5n_P + 6n_S \quad (1)$$

where n_C, n_H, n_O, n_N, n_P and n_S are numbers of C, H, O, N, P and S atoms in the empirical formula, respectively.[24,25] Then, the degree of reduction is used to find the standard enthalpy change of combustion, $\Delta_C H^\ominus$, of live matter:[24,25]

$$\Delta_C H^\ominus(\text{bio}) = -111.14 \text{ kJ mol}^{-1} \times E \quad (2)$$

After that, $\Delta_C H^\ominus$ is used to find standard enthalpy change of formation, $\Delta_f H^o$, of live matter, with Hess's law:[25]

$$\Delta_f H^\ominus(\text{bio}) = n_C \Delta_f H^\ominus(CO_2) + (n_H/2)\Delta_f H^\ominus(H_2O) + (n_P/4)\Delta_f H^\ominus(P_4O_{10}) + \\ + n_S \Delta_f H^\ominus(SO_3) - \Delta_C H^\ominus \quad (3)$$

Battley model

The Battley model[26] was used to find the entropy of live matter (virus particles, nucleocapsids and nucleic acids). The Battley model gives entropy of live matter based on its empirical formula.[26] Standard molar entropy, $S_m^\ominus$, of live matter is obtained from the equation:

$$S_m^\ominus(\text{bio}) = 0.187 \Sigma_J (S_m^\ominus(J)/a_J) n_J \quad (4)$$

where $S_m^\ominus(J)$ is standard molar entropy of element J in its standard state elemental (pure) form, a_J number of atoms of element J in its standard state elemental form, and n_J is the number of atoms of element J in the empirical formula of live matter.[26] The standard entropy change of formation, $\Delta_f S^\ominus$, can be found as:[26]

$$\Delta_f S^\ominus(\text{bio}) = -0.813 \Sigma_J (S_m^\ominus(J)/a_J) n_J \quad (5)$$

The standard Gibbs energy change of formation, $\Delta_f G^\ominus$, of live matter is found from $\Delta_f H^\ominus$ and $\Delta_f S^\ominus$:

$$\Delta_f G^\ominus(\text{bio}) = \Delta_f H^\ominus(\text{bio}) - T\Delta_f S^\ominus(\text{bio}) \quad (6)$$

where T is temperature.[44]

Stoichiometry of biosynthesis reactions

Based on empirical formulas, the biosynthesis reactions were formulated with stoichiometry. The biosynthesis reactions are macrochemical equations that explain the conversion of nutrients into new live matter in metabolism[18] The general biosynthesis reaction of viruses has the form:[20,32,45]

$$(\text{Amino acid}) + CH_2O + O_2 + HPO_4^{2-} + HCO_3^- \rightarrow (\text{Bio}) + SO_4^{2-} + H_2O + H_2CO_3 \quad (7)$$

The nutrients for biosynthesis of virus live matter include: amino acids with the empirical formula $CH_{1.798}O_{0.4831}N_{0.2247}S_{0.022472}$ (source of energy, carbon, nitrogen and sulphur), carbohydrates with the empirical formula CH_2O (additional carbon and energy source), O_2 (electron acceptor), HPO_4^{2-} (source of phosphorus).[20,32,45] The main products of biosynthesis are new live matter (bio) with the empirical formula $C_{nC}H_{nH}O_{nO}N_{nN}P_{nP}S_{nS}$, SO_4^{2-} (excess sulphur removal) and H_2CO_3 (oxidized carbon removal).[20,32,45] Moreover, H^+ produced during biosynthesis are absorbed by the bicarbonate buffer made of HCO_3^- and H_2CO_3.[20,32,45]

Thermodynamic properties of biosynthesis

The thermodynamic properties of biosynthesis were calculated with Hess's law.[44] They were calculated by the application of Hess's law to the biosynthesis reactions and thermosdynamic properties of live matter. Thermodynamic properties of biosynthesis include the standard enthalpy of biosynthesis, $\Delta_{bs}H^\ominus$, the standard entropy of biosynthesis, $\Delta_{bs}S^\ominus$, and the standard Gibbs energy of biosynthesis, $\Delta_{bs}G^\ominus$.[18] They were found with the equations:

$$\Delta_{bs}H^{\ominus} = \Sigma_{Products}\nu\Delta_f H^{\ominus} - \Sigma_{Reactants}\nu\Delta_f H^{\ominus} \quad (8)$$

$$\Delta_{bs}S^{\ominus} = \Sigma_{Products}\nu S_m^{\ominus} - \Sigma_{Reactants}\nu S_m^{\ominus} \quad (9)$$

$$\Delta_{bs}G^{\ominus} = \Sigma_{Products}\nu\Delta_f G^{\ominus} - \Sigma_{Reactants}\nu\Delta_f G^{\ominus} \quad (10)$$

where ν represents a stoichiometric coefficient.[18,20,25,32,45]

Antigen–receptor binding

The interaction of a virus with its host cell begins at the host cell membrane.[46] There, the virus antigen binds to the host cell receptor.[46] The antigen–receptor binding is a chemical process similar to protein ligand binding.[12,34] The antigen–receptor binding can be represented with the chemical reaction:

$$(An) + (Re) \rightleftarrows (An–Re) \quad (11)$$

where (An) is the free virus antigen, (Re) free host receptor and (An–Re) the antigen–receptor complex.[12,34] The dissociation equilibrium constant, K_d, is given by the equation:

$$K_d = \frac{[An][Re]}{[An-Re]} \quad (12)$$

where [An] is the concentration of the free virus antigen, [Re] the concentration of the free host receptor and [An–Re] the concentration of the antigen–receptor complex.[12,34] From K_d, the binding equilibrium constant, K_B, can be determined:[12,34]

$$K_B = \frac{1}{K_d} = \frac{[An-Re]}{[An][Re]} \quad (13)$$

Based on K_B, it is possible to calculate standard Gibbs energy change of binding, $\Delta_B G^{\ominus}$:[12,34]

$$\Delta_B G^{\ominus} = -RT\ln K_B \quad (14)$$

RESULTS AND DISCUSSION

Table I gives the empirical formulas of the virus particle, nucleocapsid and nucleic acid of the Omicron JN.1 variant of SARS-CoV-2, which were determined for the first time in this research. Table II gives chemical formulas of the entire virus particle, nucleocapsid and nucleic acid of the Omicron JN.1 variant of SARS-CoV-2. Table III gives the macromolecular composition of the virus particle, nucleocapsid and nucleic acid of the Omicron JN.1 variant. Table IV presents the thermodynamic properties of live matter of the virus particle, nucleocapsid and nucleic acid of the Omicron JN.1 variant of SARS-CoV-2. Table V gives the biosynthesis stoichiometries of the virus particle, nucleocapsid and nucleic acid of the Omicron JN.1 variant. Table VI presents the thermodynamic properties of biosynthesis of the virus particle, nucleocapsid and nucleic acid of the Omicron JN.1 variant of SARS-CoV-2. Table VII shows the thermodynamic properties of antigen-receptor binding of the Omicron JN.1 variant of SARS-CoV-2.

In May 2023, WHO has declared the end of the COVID-19 pandemic.[47] Unfortunately, SARS-CoV-2 has not understood that the pandemic is finished, probably because it obeys the laws of biology, chemistry and physics, and not the

laws of WHO. SARS-CoV-2 Omicron variant has continued its path as time goes by, acquiring new mutations. Thus, in summer, autumn and winter, several new variants have appeared, which were analysed in the literature.[21,32] The laws of biology, chemistry and physics have a supremacy over all other laws, while the fight for survival is the most fundamental law of all living organisms. The newest variant Omicron JN.1 began the development of its epidemic wave in the United States (5000 to 15000 new cases daily) and Europe (3000 to 5000 new cases daily), during the last several weeks. The epidemic wave from December 2023 and January 2024 is of much lower intensity than the pandemic waves caused by the Hu-1, Delta and earlier Omicron variants.[9] The appearance of JN.1, like those of previous variants have caused panic in the general population and the media. The scientific community has reacted very soon, reporting the nucleic acid sequence of the new variant (GISAID ID: EPI_ISL_18615181).[41] The published data represent an excellent basis for the further research, but do not inform enough about the changed infectivity, the pathogenicity and the immune evasion. To obtain a quantitative picture of potential changes, it is necessary to have quantitative data, based on which it is possible to assess the changes in infectivity, the pathogenicity and the potential immune evasion.

TABLE I. Empirical formulas and molar masses of empirical formulas of the virus particle, nucleocapsid and nucleic acid of Omicron JN.1 variant of SARS-CoV-2. Empirical formulas have the general form $C_{nC}H_{nH}O_{nO}N_{nN}P_{nP}S_{nS}$, where *n*C, *n*H, *n*O, *n*N, *n*P and *n*S are numbers of C, H, O, N, P and S atoms in the empirical formula, respectively

Name	C	H	O	N	P	S	*Mr* / g C-mol^{-1}
Virus particle	1	1.6390	0.2841	0.2300	0.006439	0.003765	21.75
Nucleocapsid	1	1.5710	0.3431	0.3124	0.006004	0.003349	23.75
Nucleic acid	1	1.2299	0.7397	0.3863	0.105318	0.000000	33.76

TABLE II. Chemical formulas and molar masses of entire virus particle, nucleocapsid and nucleic acid of Omicron JN.1 variant of SARS-CoV-2. Chemical formulas have the general form $C_{mC}H_{mH}O_{mO}N_{mN}P_{mP}S_{mS}$, where *m*C, *m*H, *m*O, *m*N, *m*P and *m*S are numbers of C, H, O, N, P and S atoms in the chemical formula, respectively

Name	C	H	O	N	P	S	*Mr*(tot) / MDa
Virus particle	1.01E+07	1.66E+07	2.87E+06	2.32E+06	6.51E+04	3.80E+04	219.7
Nucleocapsid	4.95E+06	7.78E+06	1.70E+06	1.55E+06	2.97E+04	1.66E+04	117.6
Nucleic acid	2.82E+05	3.47E+05	2.09E+05	1.09E+05	2.97E+04	0.00E+00	9.5

TABLE III. Macromolecular composition of the virus particle, nucleocapsid and nucleic acid of Omicron JN.1 variant of SARS-CoV-2. Contents of all macromolecular constituents are expressed as mass fractions in %

Name	RNA	DNA	Proteins	Lipids	Carbohydrates
Virus particle	4.3	0.0	77.0	17.2	1.5
Nucleocapsid	8.1	0.0	91.9	0.0	0.0
Nucleic acid	100.0	0.0	0.0	0.0	0.0

TABLE IV. Thermodynamic properties of live matter of virus particles, nucleocapsids and nucleic acid of Omicron JN.1 variant of SARS-CoV-2

Name	$\Delta_f H^{\ominus}$ / kJ C-mol^{-1}	$S_m^{\ominus}$ / J C-mol^{-1} K^{-1}	$\Delta_f G^{\ominus}$ / kJ C-mol^{-1}
Virus particle	–64.43	30.70	–24.63
Nucleocapsid	–75.40	32.47	–33.31
Nucleic acid	–173.12	37.98	–123.90

TABLE V. Biosynthesis stoichiometry of the virus particle, nucleocapsid and nucleic acid of Omicron JN.1 variant of SARS-CoV-2. The general biosynthesis reaction has the form: (Amino acid) + CH_2O + O_2 + HPO_4^{2-} + HCO_3^- → (Bio) + SO_4^{2-} + H_2O + HCO_3^- + H_2CO_3. (Amino acid) denotes the empirical formula of amino acids and (Bio) denotes the empirical formula of live matter

Name	Reactants					→	Products				
	Amino acid	CH_2O	O_2	HPO_4^{2-}	HCO_3^-		Bio	SO_4^{2-}	H_2O	HCO_3^-	H_2CO_3
Virus particle	1.0236	0.0105	0.0000	0.0064	0.0256	→	1	0.0192	0.0674	0.0000	0.0597
Nucleocapsid	1.3903	0.0000	0.4925	0.0060	0.0438	→	1	0.0279	0.0550	0.0000	0.4341
Nucleic acid	1.7190	0.0000	1.0650	0.1053	0.0000	→	1	0.0386	0.3306	0.1334	0.5856

TABLE VI. Thermodynamic properties of biosynthesis of virus particles, nucleocapsids and nucleic acids of Omicron JN.1 variant of SARS-CoV-2

Name	$\Delta_{bs}H^{\ominus}$ / kJ C-mol^{-1}	$\Delta_{bs}S^{\ominus}$ / J C-mol^{-1} K^{-1}	$\Delta_{bs}G^{\ominus}$ / kJ C-mol^{-1}
Virus particle	–4.80	6.94	–6.94
Nucleocapsid	–232.88	–37.48	–221.74
Nucleic acid	–484.11	–98.20	–456.07

TABLE VII. Thermodynamic properties of antigen–receptor binding of Omicron JN.1 variant of SARS-CoV-2; the K_d value was taken from literature[43]

Virus	Variant	Interaction	K_d / M	K_B / M^{-1}	$\Delta_B G^{\ominus}$ / kJ mol^{-1}
SARS-CoV-2	Omicron JN.1	RBD with ACE2	1.45E–08	6.90E+07	–44.74

The infectivity of any virus or virus variant depends on its antigen–receptor binding affinity. In essence, the antigen receptor binding represents a purely chemical interaction similar to protein–ligand interactions. The driving force for this reaction is Gibbs energy change of binding.[34] This is why in the essence of affinity there is the value of Gibbs energy change of binding. The virus variant characterized by a more negative Gibbs energy change exhibits a greater affinity. Consequently, the increased affinity implies a greater infectivity, due to the greater rate of antigen–receptor binding and the faster entry rate of viruses into host cells. If in the same moment two virus variants appear in the same host, they compete for the receptors and the variant characterized by a more negative Gibbs energy change of binding will exclude the other variant or variants from the organism/population.[34,45]

The changes of Gibbs energy (change in thermodynamic properties) appear as a consequence of a change in chemical composition. The change in chemical

composition appears as a consequence of mutations. During mutations, there is the change in the sequence of nucleotides, which leads to the change in chemical composition. The empirical formula of the Hu-1 wild type is $CH_{1.6390}O_{0.2851}N_{0.2301}P_{0.0065}S_{0.0038}$,[48] while the empirical formula of the Omicron BA.1 variant is $CH_{1.6404}O_{0.2842}N_{0.2299}P_{0.0064}S_{0.0038}$,[48] which is different from that of JN.1 $CH_{1.6390}O_{0.2841}N_{0.2300}P_{0.006439}S_{0.003765}$ (Table I). The hydrogen content of the JN.1 variant is similar to that of the Hu-1 wild type, both of which are lower than that of the BA.1 variant. The oxygen content of the JN.1 variant is lower than those of Hu-1 and BA.1 variants. The nitrogen content of the JN.1 variant is between those of the Hu-1 and BA.1 variants. The phosphorus content of the JN.1 variant is similar to that of the BA.1 variant and lower than that of the Hu-1 variant. The sulphur content is similar for all three variants. Therefore, every variant of SARS-CoV-2 is characterized by a specific empirical formula, which can be used to identify the variant. This is in agreement with the result that the virus particles can be identified with single particle ICP-MS.[49]

Empirical formulas have been determined for other viruses: West Nile virus $CH_{1.7651}O_{0.2609}N_{0.1469}P_{0.019712}S_{0.003745}$[30] and Poxviruses $CH_{1.5876}O_{0.3008}N_{0.2538}P_{0.00223}S_{0.00554}$.[29] The empirical formula of JN.1 variant of SARS-CoV-2 is $CH_{1.6390}O_{0.2841}N_{0.2300}P_{0.006439}S_{0.003765}$ (Table I). The hydrogen content of the JN.1 variant is lower than that of the West Nile virus and higher than that of the Poxviruses. The oxygen content of the JN.1 variant is lower than that of poxviruses and higher than that of West Nile virus. The nitrogen content of the JN.1 variant is lower than that of Poxviruses and higher than that of the West Nile virus. The phosphorus content of the JN.1 variant is lower than that of West Nile virus and higher than that of Poxviruses. The sulphur content of the JN.1 variant is higher than those of the West Nile virus and Poxviruses. Therefore, every virus species is characterized by a specific empirical formula.

The chemical formula of the entire virus particle of the Omicron JN.1 variant of SARS-CoV-2 is $C_{1.01\times10^7}H_{1.66\times10^7}O_{2.87\times10^6}N_{2.32\times10^6}P_{6.51\times10^4}S_{3.80\times10^4}$, which has a molar mass of 219.7 MDa (Table II). The chemical formula of the West Nile virus is $C_{1.54\times10^6}H_{2.71\times10^6}O_{4.01\times10^5}N_{2.26\times10^5}P_{3.03\times10^4}S_{5.76\times10^3}$,[30] while that of the poliovirus is $C_{332652}H_{492388}O_{131196}N_{98245}P_{7501}S_{2340}$.[10] The virus particle of the JN.1 variant is composed of a much larger number of atoms than those of the West Nile virus and poliovirus. This is in agreement with the larger size of the SARS-CoV-2 virus particle $(90\ nm)^3$ than those of the West Nile virus (50 nm)[50] and poliovirus (30 nm).[51]

The biosynthesis reaction of the virus particle of Omicron JN.1 variant is:

$$1.0236CH_{1.798}O_{0.4831}N_{0.2247}S_{0.022472} + 0.0105CH_2O +$$

$$0.0064HPO_4^{2-} + 0.0256HCO_3^- \rightarrow CH_{1.6390}O_{0.2841}N_{0.2300}P_{0.006439}S_{0.003765} +$$

$$0.0192SO_4^{2-} + 0.0674H_2O + 0.0597H_2CO_3 \quad (15)$$

where $CH_{1.798}O_{0.4831}N_{0.2247}S_{0.022472}$ is the empirical formula of amino acids and $CH_{1.6390}O_{0.2841}N_{0.2300}P_{0.006439}S_{0.003765}$ is the empirical formula of the JN.1 virus particle. The biosynthesis reaction of the nucleocapsid of Omicron JN.1 variant is

$$1.3903CH_{1.798}O_{0.4831}N_{0.2247}S_{0.022472} + 0.4925O_2 + 0.0060HPO_4^{2-} + 0.0438\ HCO_3^- \rightarrow CH_{1.5710}O_{0.3431}N_{0.3124}P_{0.006004}S_{0.003349} + 0.0279SO_4^{2-} + 0.0550H_2O + 0.4341H_2CO_3 \quad (16)$$

where $CH_{1.5710}O_{0.3431}N_{0.3124}P_{0.006004}S_{0.003349}$ is the empirical formula of the JN.1 nucleocapsid. The biosynthesis reaction of the nucleic acid of Omicron JN.1 variant is:

$$1.7190CH_{1.798}O_{0.4831}N_{0.2247}S_{0.022472} + 1.0650O_2 + 0.1053\ HPO_4^{2-} \rightarrow CH_{1.2299}O_{0.7397}N_{0.3863}P_{0.105318} + 0.0386\ SO_4^{2-} + 0.3306\ H_2O + 0.1334HCO_3^- + 0.5856\ H_2CO_3 \quad (17)$$

where $CH_{1.2299}O_{0.7397}N_{0.3863}P_{0.105318}$ is the empirical formula of the JN.1 nucleic acid.

Based on the empirical formulas, thermodynamic properties can be calculated, with the Patel–Erickson model[24,25] and Battley model.[26] The Gibbs energy change of biosynthesis of microorganisms represents the driving force for microorganism multiplication.[18,19,34,45] By multiplying inside host cells, a virus leads to its damage in several ways. One of them is the lytic cycle.[46] Less obvious, but still realistic way of damage of the host cells is competition for resources. Namely, a virus hijacks the host cell metabolic machinery, making it function for the virus multiplication completely, while the synthesis of host cell building blocks is inhibited. Thus, since the reparatory mechanisms become ineffective, with time there is damage of the host cell. According to the phenomenological equations, the reaction rate (in this case rate of virus multiplication) depends on the Gibbs energy change of biosynthesis. A greater multiplication rate leads to greater damage of the host cell. Thus, virus pathogenicity is greater if Gibbs energy change of biosynthesis of the virus is more negative.

It is obvious that the infectivity and the pathogenicity depend on thermodynamic properties – Gibbs energy change of binding and Gibbs energy change of biosynthesis, respectively. Furthermore, the binding of antibodies to virus antigens also represents a chemical reaction, similar to protein–ligand interactions.[12,34] Thus, the driving force for the antigen–antibody binding reaction is the Gibbs energy change of the antigen–antibody binding and the antigen–antibody binding rate, according to the phenomenological equations, depends on it. Therefore, two different molecules – antibody and receptor – bind to the same substrate – antigen – and the reactions are competitive. This means that the reaction char-

acterized with a more negative Gibbs energy change will have an advantage. Macroscopically, if the Gibbs energy change of the reaction of antigen–antibody binding is more negative than the Gibbs energy change of the antigen–receptor binding, then the virus will be inactivated and removed from the host organism and will not lead to the development of a disease. On the other hand, if the Gibbs energy change of antigen–receptor binding is more negative than the Gibbs energy change of the antigen–antibody binding, then there will be immune evasion.

In this research, Gibbs energy change of binding was determined for the first time for the Omicron JN.1 variant of SARS-CoV-2, which is given in Table VII. Gibbs energy changes of binding have been determined for other variants of SARS-CoV-2: Hu-1 wild type –43.43 kJ mol^{-1},[48] Delta B.1.617 variant –43.38 kJ mol^{-1},[48] and Omicron BA.2 variant –51.50 kJ mol^{-1}.[52] Gibbs energy changes of binding of different variants of SARS-CoV-2 during its time evolution are shown in Fig. 1. Please notice that the JN.1 variant originates from the Omicron variant and has appeared by acquisition of mutations with the goal to survive. Obviously, the JN.1 variant has evolved towards less negative Gibbs energy change (which is not a rule observed during evolution of SARS-CoV-2). Indeed, SARS-CoV-2 has exhibited a tendency to evolve towards increase in infectivity and maintenance of pathogenicity.[53] The evolution of the JN.1 variant towards less negative Gibbs energy change of binding could be a consequence of extensive immunization by natural means or by vaccines. The decrease in Gibbs energy change of binding is a result of changed virus antigen structure. Since the changed antigen structure of the virus is different than those of the previous

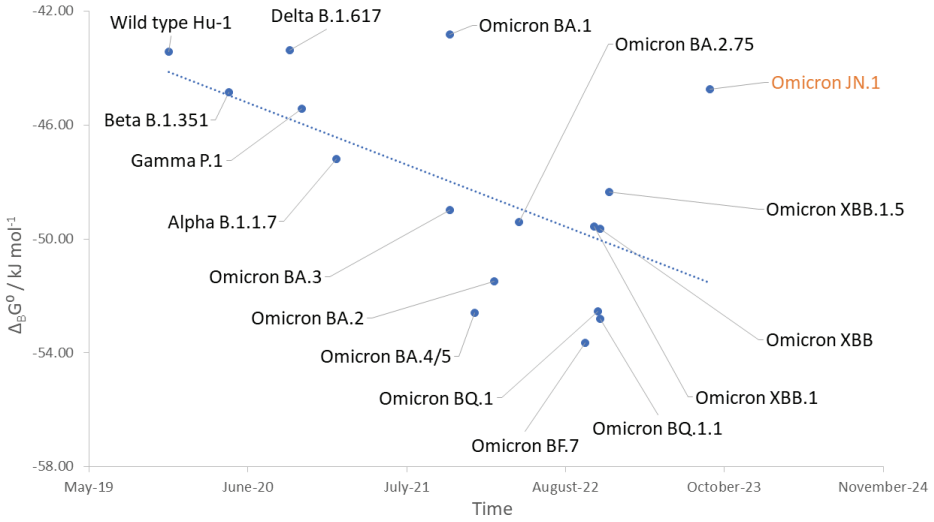

Fig. 1. Gibbs energy change of binding of different SARS-CoV-2 variants during the time evolution of the virus. $\Delta_B G^0$ represents standard Gibbs energy change of binding.

variants, it also binds with a lower affinity to highly specific host antibodies. The lower affinity of binding to antibodies provides immune evasion.

Development of vaccines based on virus variants in circulation is important in order to achieve greater specificity of the response antibodies to the virus and avoid antibody-dependent enhancement.[54] During the pandemic, SARS-CoV-2 developed a great number of mutations. These mutations allow some variants to avoid immune response. Thus, it is important for vaccines to follow the time evolution of SARS-CoV-2.

Infectivity does not depend only on the rate of entry of virus particles into host cells and immune response. The process of infection is much more complex and includes concentration of viruses at the site of entry into host organism (infective inoculum) expressed in number of infectious particles per mL. The concentration of infectious particles is much lower in an open space. This is why the possibility of infection in an open space is much lower. The lower the volume of a closed space, the greater the concentration and the possibility of infection. Furthermore, infectivity also depends on diffusion through nose mucosa and furin cleavage.[13] Due to complexity of the process of infection and the arguments in favour of a stronger immune response of the host organism, it seems that we can be optimistic regarding the epidemic spreading of SARS-CoV-2 variants, with the consciousness that the virus will continue to adapt during the evolution process in the future.

Pathogenicity of viruses depends on the degree of damage that a virus causes during infection. The degree of damage depends on the multiplication rate of the virus. The multiplication rate is, according to the phenomenological equations, dependent on the driving force of multiplication – Gibbs energy change of biosynthesis. Gibbs energy change of biosynthesis of the Omicron JN.1 variant is –221.74 kJ C-mol^{-1}. Gibbs energies changes of biosynthesis of different SARS--CoV-2 variants are given in Fig. 2. Gibbs energies change of biosynthesis of other SARS-CoV-2 variants are: Hu-1 wild type –222.2 kJ C-mol^{-1},[21] Omicron BA.2 –221.22 kJ C-mol^{-1},[52] Omicron XBB.1.5 Kraken –221.22 kJ C-mol^{-1},[34] Omicron XBB.1.16 Arcturus –221.19 kJ C-mol^{-1},[32] and Omicron EG.5 Eris –221.75 kJ C-mol^{-1}.[21] From this we can conclude that Gibbs energy change of biosynthesis has changed very little and that pathogenicity of SARS-CoV-2 variants has remained similar during evolution. This is in agreement with the predictions of theory of evolution, that organisms will evolve towards maintenance of the species. An increase in pathogenicity would lead to a greater number of lethal cases, which would as a consequence lead to lower possibility for the virus to survive.

In the basis of all biological processes performed by viruses, including the life cycle, the infection and the damage to host cells, are physical and chemical processes. This is why mechanistic models are useful for the better understanding

of mechanisms through which biological, physical and chemical processes occur and indicate the ways in which we can influence the course of the pandemic. At the very beginning of the COVID-19 pandemic, there were many misleading information. It was not clear what are the paths of the transmission of COVID-19 infection. Due to this, use of gloves was introduced, even though the primary path of transmission is not fecal-oral, but respiratory. In some countries, money was replaced by contactless payment, even though the transmission by indirect contact is almost impossible. Moreover, the extensive lockdown was enforced in almost all countries, even though it is clear that in the respiratory infections maintenance of distance and avoidance of small closed spaces (*e.g.*, elevators, toilets) should be effective in the avoidance of infections like COVID-19, especially with the extensive application of face masks. In the moment when the mechanistic models were developed and in parallel epidemiological measures and especially vaccines, the fight against the pandemic became much more efficient. However, the damage to production and logistics that could have been avoided has already been made. Moreover, a lot of time was needed for the population to understand that the application of facial masks is a very effective method for the suppression of pandemic, since it decreases the size of infectious inoculum. However, first of all thanks to the scientific community, the number of new cases of COVID-19 has been significantly decreased and the end of the pandemic was declared.

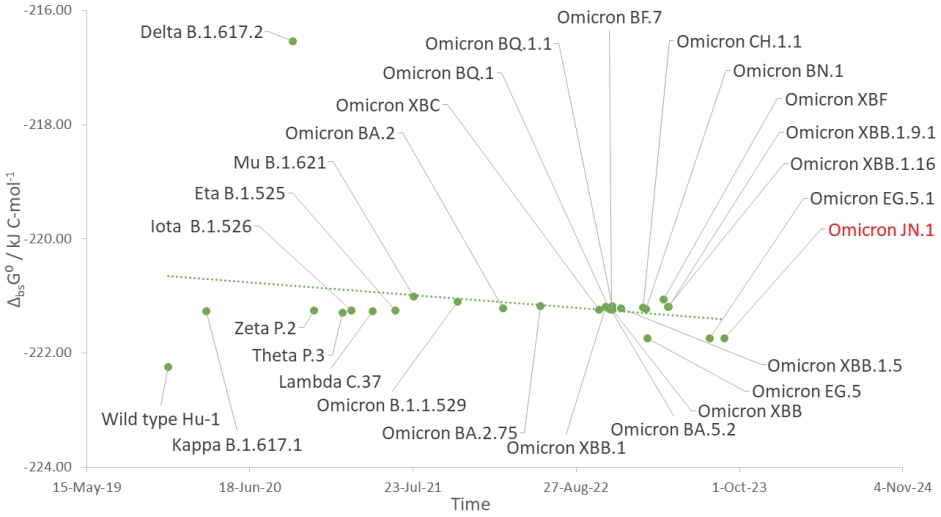

Fig. 2. Gibbs energies change of biosynthesis of different SARS-CoV-2 variants during the time evolution of the virus. $\Delta_{bs}G^0$ represents standard Gibbs energy change of biosynthesis.

CONCLUSIONS

The COVID-19 pandemic might be over. However, the new variants of SARS-CoV-2 are appearing quite frequently. Omicron JN.1 is the last in a sequence of variants. The mechanistic models allow the prediction that the Omicron JN.1 variant can cause a new epidemic wave, with a lower amplitude in the number of new infections (decreased infectivity) and a smaller number of casualties. The smaller number of casualties is a consequence of a smaller number of infected people with the unchanged pathogenicity of the Omicron JN.1 variant. This process is also contributed by the process of immunization. It seems that the need for the active immunization will be necessary for a long period. Moreover, the development of new vaccines will be needed, which will be based on some of the newer variants, due to the acquisition of a larger number of mutations in the new variants.

SUPPLEMENTARY MATERIAL

Additional data and information are available electronically at the pages of journal website: https://www.shd-pub.org.rs/index.php/JSCS/article/view/12786, or from the corresponding author on request.

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ИЗВОД

УДАРНЕ ВЕСТИ: ЕМПИРИЈСКЕ ФОРМУЛЕ, МОЛАРНЕ МАСЕ, РЕАКЦИЈЕ БИОСИНТЕЗЕ И ТЕРМОДИНАМИЧКЕ ОСОБИНЕ ВИРУСНИХ ЧЕСТИЦА: БИОСИНТЕЗЕ И ВЕЗИВАЊА OMICRON JN.1 ВАРИЈАНТЕ SARS-COV-2

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Ударне вести су обично узнемирујуће. О природним катастрофама, ратовима, епидемијама, итд. се извештава као о ударним вестима. У овом раду је приказано смањење опасности од ширења епидемија изазваних варијантом JN.1, јер анализе показују да је инфективност нове варијанте слабија у односу на већину ранијих варијанти, што потврђује и број случајева (7500 дневно у САД). Штавише, JN.1 упркос великом броју мутација није успео да постигне вредности промене Гибсове енергије биосинтезе (а самим тим и стопе размножавања вируса) дивљег типа Hu.1. Истраживање показује да инфективност и патогеност варијанте JN.1 није достигла забрињавајућу величину, што значи да нема разлога за очекивање погоршање епидемиолошке ситуације.

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