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Strain wars 3: Differences in infectivity and pathogenicity between Delta and Omicron strains of SARS-CoV-2 can be explained by thermodynamic and kinetic parameters of binding and growth

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ABSTRACT

In this paper, for the first time, empirical formulas have been reported of the Delta and Omicron strains of SARS-CoV-2. The empirical formula of the Delta strain entire virion was found to be CH_{1.6383}O_{0.2844}N_{0.2294}P_{0.0064}S_{0.0042}, while its nucleocapsid has the formula CH_{1.5692}O_{0.3431}N_{0.3106}P_{0.0064}S_{0.0043}. The empirical formula of the Omicron strain entire virion was found to be CH_{1.6404}O_{0.2942}N_{0.2299}P_{0.0066}S_{0.0038}, while its nucleocapsid has the formula CH_{1.5734}O_{0.3442}N_{0.3123}P_{0.0064}S_{0.0033}. Based on the empirical formulas, standard thermodynamic properties of formation and growth have been calculated and reported for the Delta and Omicron strains. Moreover, standard thermodynamic properties of binding have been reported for Wild type (Hu-1), Alpha, Beta, Gamma, Delta and Omicron strains. For all the strains, binding phenomenological coefficients and antigen-receptor (SGP-ACE2) binding rates have been determined and compared, which are proportional to infectivity. The results show that the binding rate of the Omicron strain is between 1.5 and 2.5 times greater than that of the Delta strain. The Omicron strain is characterized by a greater infectivity, based on the epidemiological data available in the literature. The increased infectivity was explained in this paper using Gibbs energy of binding. However, no indications exist for decreased pathogenicity of the Omicron strain. Pathogenicity is proportional to infectivity. The results show that the Gibbs energy of binding is very similar for the Delta and Omicron strains. Thus, multiplication rate and pathogenicity are similar for the Delta and Omicron strains. The lower number of severe cases caused by the Omicron strain can be explained by increased number of immunized people. Immunization does not influence the possibility of occurrence of infection, but influences the rate of immune response, which is much more efficient in immunized people. This leads to prevention of more severe Omicron infection cases.

1. Introduction

SARS-CoV-2 was first isolated in late-2019, as the cause of COVID-19 disease. SARS-CoV-2 has shown a great tendency to mutate (Wang et al., 2021a; Callaway, 2020). Thus, during the last 2 years, a great number of strains appeared, some of them classified as variants of concern (VOC) (WHO, 2021a), which compete and suppress earlier strains (Popovic and Minceva, 2021a; Popovic and Popovic, 2022). Every new strain has caused a new wave of the pandemic, all over the world. The last two waves were caused by the Delta and Omicron strains. The last wave that began in December 2021 was caused by the Omicron strain and exhibited a great increase in the number of infections, but a lower number of severe cases [Abdullah et al., F. 2021]. A question is raised: is this a consequence of weakening (decrease in pathogenicity) of the Omicron strain or are there other reasons for this? To answer this question, viruses must be considered as open biothermodynamics systems (Popovic and Minceva, 2020a, M. 2020b; von Bertalanffy, 1950). Thus, it is necessary to chemically and thermodynamically characterize these two strains and compare their properties. The most important task is to find the binding rates of the Delta and Omicron strains to the host cell ACE2 receptor, as well as the virus multiplication rate inside the host cell. This became possible after publication of kinetic data that characterize the Delta and Omicron strains.

Infectivity of viruses is related to antigen-receptor binding rate, while pathogenicity is related to the capability of a virus to reproduce inside a host and damage host tissues. Virus infectivity is defined as the capacity of viruses to enter the host cell and exploit its resources to replicate and produce progeny infectious viral particles (Rodríguez-Lázaro et al., 2013). An artificial intelligence model was used to...
compare Omicron, Wild type and Delta infectivity (Chen et al., 2022). It was found that the Omicron strain may be over 10 times more contagious than the Wild type or about 2.8 times as infectious as the Delta variant (Chen et al., 2022). Moreover, the Omicron strain was found to be able to avoid immune response, up to 88% (Chen et al., 2022). Pathogenicity is the potential disease-causing capacity of pathogens. The measure of pathogenicity is virulence (Pirofski and Casadevall, 2012).

Organisms represent open thermodynamic systems with the property of growth (von Bertalanffy, 1950; von Stockar, 2013a; Popovic and Minceva, 2020a; Popovic, 2017). Thus, nonequilibrium thermodynamics needs to be used to analyze processes performed by organisms (Popovic, 2018; Popovic and Minceva, 2021c). Inside cells, viruses perform life processes. Two basic processes are important for the viral life cycle: binding and viral entrance into host cells, and viral multiplication inside host cells (Popovic and Minceva, 2021a; P. Gale, 2021, 2020, 2019, 2018; Riedel et al., 2019). Susceptibility and permissiveness are decisive factors for success of viral infections (Popovic and Minceva, 2021a). If at the same time, in the same place, two virus species or strains appear, they will compete for the host cell metabolic machinery and resources (Popovic and Minceva, 2021a). In that case, direct virus-host interactions occur, in parallel with indirect virus-virus-host interactions (Popovic and Minceva, 2021a). Interactions between viruses have their thermodynamic background (Lucia et al., 2021, 2020a, U. 2020b; Šimsek, 2021). Thermodynamic properties of the human host tissues have been reported in (Popovic and Minceva, 2020c). Various viral strains appear during mutations, replacement of nucleotides, leading to changes in information content of the mutated virus. Changes in information and entropy during self-assembly of open thermodynamic systems with the property of growth (to which viruses belong) have been reported in (Popovic, 2014; Skene, 2015; Hansen et al., 2012).

Thermodynamic properties of SARS-CoV-2 strains have been reported in (Popovic and Popovic, 2022). A decreasing trend has been reported in Gibbs energies of binding of SARS-CoV-2 strains through time (Popovic and Popovic, 2022). Mutation Y449S in the spike protein receptor-binding domain, which occurred with co-mutations Y449S and N501Y, was found to reduce infectivity compared to that of the Wild type, but can disrupt existing antibodies that neutralize the virus (Wang et al., 2021b). The property of infectivity is a complex phenomenon (Saragovi et al., 1999). There are several factors that result in the properties of infectivity and transmissibility. The first is thermodynamic Gibbs energy of binding and binding affinity (Gale, 2019, 2020, P. 2021; Popovic, 2022b). The second is kinetic – binding rate (Popovic, 2022b). The third is the infective reservoir size (HHS and CDC, 2012). The fourth is immune response (both quantitative and qualitative). The fifth is anti-epidemic measures (social distancing, wearing masks, lockdowns, isolation of infected, isolation of contacts etc.) (Hruda et al., 2021). All five factors need to be taken into account when discussing infectivity and transmissibility. The goal of this paper is to find what enabled the Omicron strain to dominate over the Delta and Wild type (Hu-1) strains. For this purpose, we will determine and compare the binding rates and multiplication rates of the Omicron, Delta and Wild type (Hu-1) strains. This can lead to a conclusion about whether the Omicron strain has, except for increasing its infectivity, decreased its pathogenicity. To achieve this, it is necessary to determine the elemental composition of the Delta and Omicron strains, their growth reactions, as well as thermodynamic properties of binding and growth. These properties include standard enthalpy of binding, standard entropy of binding, standard Gibbs energy of binding, binding phenomenological coefficient, binding rate, standard enthalpy of growth, standard entropy of growth and standard Gibbs energy of growth.

2. Methods

2.1. Data sources

Dissociation constants for the SARS-CoV-2 Omicron strain have been
reported by Wu et al. (L. 2022), Han et al. (P. 2022), Zhang et al. (2021) and Khan et al. (2022). Wu et al. (L. 2022) found the affinity (binding) constant to be 0.37 \times 10^3 \text{ M}^{-1}, at 37 \degree C, using the non-competitive ELISA approach (Beatty et al., 1987). This corresponds to a dissociation constant of 2.7 \times 10^{-7} \text{ M}. Han et al. (2022) measured the dissociation constant to be 3.14 \times 10^{-8} \text{ M}, at 25 \degree C, using surface plasmon resonance (Rusnati et al., 2015). Zbang et al. (2021) reported the dissociation constant of 8.85 \times 10^{-9} \text{ M}, using surface plasmon resonance (Rusnati et al., 2015). Khan et al. (2022) found the dissociation constant to be 3.14 \times 10^{-8} \text{ M}, at 25 \degree C, using molecular docking simulations. Since the later two references (Zhang et al., 2022; Khan et al., 2022) reported no temperature, the analysis was made using the data from the first two references (L. Wu et al., 2022; Han et al., P. 2022). The considered binding constants of the Omicron strain are given in Table 1.

Dissociation constants for Hu-1 (Wild type), Alpha, Beta, Gamma, Delta and GD/1/2019-RBD strains were reported by Han et al. (P. 2022). The data were collected using surface plasmon resonance at 25 \degree C and are given in Table 2. The association rate constants, \(k_{on}\) and dissociation rate constants, \(k_{off}\) for all the analyzed strains were generously provided by Mr. Linjie Li and Dr. Jianxun Qi from the Institute of Microbiology of the Chinese Academy of Sciences. They were collected on the research resulting in the publication (Han et al., P. 2022). The \(k_{on}\) and \(k_{off}\) data were collected using surface plasmon resonance at 25 \degree C and can be found in Table 2.

Genetic and protein sequences of the Delta and Omicron strains were taken from the NCBI database (National Center for Biotechnology Information, 2022a). The data for the Omicron strain can be found with the following codes: genome (OL869974.1), nucleocapsid phosphoprotein (UGY75362.1), membrane glycoprotein (UFO69282.1), spike glycoprotein (UGY75354.1). The data for the Delta strain can be found with the following codes: genome (OM471068.1), nucleocapsid phosphoprotein (UIO52968.1), membrane glycoprotein (QUX81285.1), spike glycoprotein (GenBank: UKA47839.1). The protein copy numbers were taken from (Neuman and Buchmeier, 2011, 2006). The virion size was taken from (Neuman and Buchmeier, 2016).

### 2.2. Binding reaction and rate constants

The SARS-CoV-2 virus enters the host cell, in a process where the viral spike glycoprotein (SGP) binds to the host cell ACE2 receptor. Antigen-receptor binding can be described by the chemical reaction

\[
A + R \rightarrow AR
\]

(1)

Where \(A\) is the free virus antigen (SGP), \(R\) the host cell receptor (ACE2) and \(AR\) the antigen-receptor complex. Antigen-receptor binding is a reversible chemical process, consisting of a forward and a backward part. In the forward part the antigen and receptor bind to form the antigen-receptor complex, in a second order reaction. The concentrations of the free antigen, \([A]\), and free receptor, \([R]\), determine the rate of the forward reaction, \(r_{on}\), which is described by the law of mass action

\[
r_{on} = k_{on}[A][R]
\]

(2)

### Table 1

| \(T \) ( \degree C) | \(K_0 \) (M) | Reference | \(\Delta H \) (k/mol) | \(\Delta S \) (J/mol K) | \(\Delta G \) (kJ/mol) |
|-----------------|----------|----------|----------------|----------------|----------------|
| 37              | 2.7E-07  | L. Wu et al., 2022 | -143.5          | -336.8          | -39.9          |
| 25              | 3.14E-08 | Han et al., 2022  | -132.6          | -301.0          | -42.8          |

Where \(K_0\) is the forward rate constant, also known as the on-rate or association rate constant (Du et al., 2016). On the other hand, in the backward reaction, the antigen-receptor complex dissociates into the free antigen and receptor. The rate of the backward reaction, \(r_{off}\), depends only on the concentration of the antigen-receptor complex, \([AR]\), and follows first order kinetics

\[
r_{off} = k_{off}[AR]
\]

(3)

where \(k_{off}\) is the first order rate constant for dissociation of the antigen-receptor complex, also known as the off-rate constant (Du et al., 2016). Therefore, the overall binding rate, \(r_B\), is the difference of the forward and backward rates.

\[
r_B = r_{on} - r_{off}
\]

(4)

The overall binding rate, \(r_B\), becomes zero at equilibrium, implying that the equilibrium forward, \(r_{on}^{eq}\), and backward, \(r_{off}^{eq}\), rates are equal (Demirel, 2014).

\[
r_{on}^{eq} = r_{off}^{eq}
\]

(5)

This represents the kinetic perspective on antigen-receptor binding. A similar complementary perspective is given by nonequilibrium thermodynamics.

### 2.3. Thermodynamics of virus binding

Binding of the spike protein to the host cell receptor represents a chemical reaction, similar to protein-ligand binding (Du et al., 2016). The rate of the antigen-receptor binding reaction, \(r_B\), is related to Gibbs energy of binding, \(\Delta G\), by the phenomenological equation

\[
r_B = \frac{K_0}{T} \frac{\Delta G}{25} - 40.06\times10^{-7}mol\cdot\text{s}^{-1}
\]

(6)

where \(K_0\) is the binding phenomenological coefficient and \(T\) is temperature (Demirel, 2014; Popovic and Mincheva, 2021a). Since all the analyzed strains of SARS-CoV-2 infect the same host, the temperature is the same for all the strains. However, every strain has its own \(K_0\) and \(\Delta G\). Thus, \(r_B\) of the Delta and Omicron strains depends on their \(K_0\) and \(\Delta G\) values. The \(\Delta G\) values vary between viruses, depending on mutations (and chemical change) in their SGP. The binding

| Strain | \(k_{on} \) (M\(^{-1}\)s\(^{-1}\)) | \(k_{off} \) (s\(^{-1}\)) | \(K_0 \) (M) | \(K_A \) (mol\(^2\)/dm\(^3\)) | \(K_B \) (M\(^{-1}\)) | \(\Delta G^0 \) (kJ/mol) |
|--------|----------------|----------------|----------|----------------|----------------|----------------|
| Wild type | 1.07E+05 | 2.67E-03 | 2.46E-03 | 5.51E+01 | 4.06E-07 | -43.43 |
| Alpha | 7.87E+04 | 4.26E-04 | 5.40E-09 | 8.91E-08 | 1.85E-08 | -47.19 |
| Beta | 9.26E+04 | 1.27E-03 | 1.38E-08 | 2.69E-08 | 7.22E-07 | -44.85 |
| Gamma | 7.76E+04 | 8.52E-04 | 1.10E-08 | 1.79E-08 | 9.08E-07 | -45.42 |
| Delta | 7.40E+04 | 1.88E-03 | 2.51E-08 | 3.89E-08 | 3.99E-07 | -43.38 |
| Omicron | 8.68E+04 | 2.61E-03 | 3.14E-08 | 5.72E-08 | 3.18E-07 | -42.82 |
| GD/1/2019-RBD | 1.07E+05 | 1.98E-03 | 1.91E-08 | 4.27E-08 | 5.24E-07 | -44.06 |

Table 2: Thermodynamic and kinetic data for binding of SARS-CoV-2 strains to the ACE2 receptor. The association rate constant, \(k_{on}\), and dissociation rate constant, \(k_{off}\), data were generously provided by Linjie Li and Jianxun Qi from the Institute of Microbiology of the Chinese Academy of Sciences. The dissociation equilibrium constant, \(K_0\), data was taken from (Han et al., P. 2022). Based on these values, the binding phenomenological coefficient, \(k_{off}\), binding equilibrium constant, \(K_0\), and standard Gibbs energy of binding, \(\Delta G^0\), have been calculated, as described in the Methods section. All the data is at 25 \degree C.
phenomenological coefficient depends on binding kinetic parameters. For chemical reactions the binding phenomenological coefficient is proportional the equilibrium forward reaction rate, \( r_{on} \), divided by the universal gas constant \( R_g \) (Demirel, 2014).

\[
L_B = \frac{r_{on}}{R_g} \quad \text{(7)}
\]

Combining Eqs. (7) and (2) gives

\[
L_B = \frac{k_{on}K_B[A^\text{tot}]^{1/n}}{R_g} \quad \text{(8)}
\]

The dissociation equilibrium constant is given by the equation (Du et al., 2016)

\[
K_D = \frac{[A]^n[R]^m}{[AR]^o} \quad \text{(9)}
\]

Combining Eqs. (7) and (8) results in

\[
L_B = \frac{k_{on}K_B[A^\text{tot}]^{1/n}}{R_g} \quad \text{(10)}
\]

The \( k_{on} \), \( k_{off} \), and \( K_D \) values for the analyzed strains are shown in Tables 1 and 2.

Since the reported \( K_D \) values are very small, the equilibrium is shifted towards antigen-receptor binding. Thus, most virus particles in the body will be bound to host cells, implying that the equilibrium antigen-receptor complex concentration is approximately equal to the total virion concentration in the organism \( [AR]^o \approx [V]^o \). Thus, Eq. (10) becomes

\[
L_B = \frac{k_{on}K_B[V]^o}{R_g} \quad \text{(11)}
\]

The value of \([V]^o\) was reported by Sender et al. (R., 2021), to be \( 1 \times 10^7 \) RNA copies per gram of tissue. It seems reasonable to assume that one RNA copy corresponds to one virion. In that case, the concentration of virions is \( 1 \times 10^{14} \) per gram of tissue. The density of tissues is \( 1050 \) g/dm³ (ITIS Foundation, R. 2021). Thus, the concentration of virions is \( 1.74 \times 10^{14} \) M.

2.4. Standard thermodynamic properties of binding

The dissociation process is the opposite of binding, meaning that dissociation equilibrium constants are reciprocal of binding equilibrium constants (Du et al., 2016). Thus, dissociation equilibrium constants were used to calculate binding equilibrium constants, \( K_B \), using the equation (Du et al., 2016)

\[
K_B = \frac{1}{K_D} \quad \text{(12)}
\]

The binding constants were used to find standard Gibbs energy of binding, \( \Delta G^\circ \), using the equation (Du et al., 2016)

\[
\Delta G^\circ = -R_T \ln K_B \quad \text{(13)}
\]

Temperature dependence of the binding constant was used to find standard enthalpy of binding, \( \Delta H^\circ \), using the Van ‘t Hoff equation (Atkins and de Paula, 2014, 2011)

\[
\frac{d}{dT} \ln K_B = \frac{\Delta H^0}{R_T} \quad \text{(14)}
\]

The calculated standard enthalpies of binding, \( \Delta H^\circ \), were combined with standard Gibbs energies of binding, \( \Delta G^\circ \), to find standard entropies of binding, \( \Delta S^\circ \), using the equation (Atkins and de Paula, 2014, 2011)

\[
\Delta G = \Delta H - T \Delta S \quad \text{(15)}
\]

2.5. Virus binding rate

Virus binding rates have been determined in three ways: kinetic, linear and exponential. The kinetic method uses the law of mass action. The overall binding rate is the difference of the forward and backward reaction rate and is given by Eq. (4). The forward and backward reaction rates are found by multiplying the appropriate reaction rate constants with concentrations of the reactants, using Eqs. (2) and (3), respectively. The rate constants, \( k_{on} \) and \( k_{off} \), were taken from Table 2.

The linear method uses linear nonequilibrium thermodynamics. Linear nonequilibrium thermodynamics states that the rate of a process is a linear function of its driving-force, to which it is related by the linear phenomenological Eq. (6). Thus, the linear method determines binding rate through Eq. (6), using binding phenomenological coefficients and standard Gibbs energies of binding from Table 2. Standard Gibbs energies of binding, \( \Delta G^\circ \), are converted into Gibbs energies of binding, \( \Delta G \), using the equation (Atkins and de Paula, 2011, 2014)

\[
\Delta G = \Delta G^\circ + R_T \ln Q \quad \text{(16)}
\]

where \( Q \) is the quotient of reaction (1) defined as

\[
Q = \frac{[A^\circ]^n[R^\circ]^m}{[AR]^o} \quad \text{(17)}
\]

The exponential method uses a more general nonequilibrium thermodynamic equation, which is valid outside the linear region. In general, chemical reaction rate is proportional to the exponent of the driving force, according to the equation (Demirel, 2014)

\[
r_B = r_{on}(1 - e^{-\Delta G^\circ/k_B T}) \quad \text{(18)}
\]

This equation reduces into phenomenological Eq. (6) in case of small values of Gibbs energy (since then the exponent can be approximated as \( e^x \approx 1 + x \), where \( x = \Delta G^\circ/R_T T \) and \( r_{on}/R_T = L_B \) (Demirel, 2014). The \( r_{on} \) values were calculated using \( k_{on} \) data from Table 2.

2.6. Elemental composition and growth reactions

Elemental composition of virus particles has been determined using the atom counting method (Popovic, 2022a). The atom counting method calculates the number of atoms of each element in a virus particle, based on its genetic sequence, protein sequences, protein copy numbers and virus size (Popovic, 2022a). The atom counting method was applied, using a custom-made computer program. More details on the atom counting method can be found in (Popovic, 2022a).

The genetic and protein sequences for the Delta strain were complete and were used as they were reported (National Center for Biotechnology Information, 2022a). However, for the Omicron strain, there were several gaps of unknown nucleotides and amino acids in the nucleic acid and protein sequences, respectively (National Center for Biotechnology Information, 2022a). In the Omicron strain genome (NCBI ID: OLB869974.1), there were three gaps, 3 unknown nucleotides starting at position 11,107, 16 unknown nucleotides starting at 22,526 and 8 unknown nucleotides starting at 28,165. In the nucleocapsid phosphoprotein of the Omicron strain (NCBI ID: UG175362.1), there was a 3 amino acid long gap starting at position 31. In the spike glycoprotein of the Omicron strain (NCBI ID: UGY75354.1), there was a 6 amino acid gap starting at position 382. The gaps were filled, using the corresponding genetic and protein sequences of the Delta strain. The corresponding sequences of the Omicron and Delta strain were first aligned using the Needleman-Wunsch algorithm (Needleman and Wunsch, 1970), implemented using NCBI BLAST (National Center for Biotechnology Information, 2022b). Since the sequences of the Delta and Omicron strains matched completely around the areas of the gaps, the gaps in the Omicron sequences were filled using the corresponding parts of the Delta sequences, obtained using alignment.

Elemental composition of virus particles was used to construct
growth reactions for the analyzed SARS-CoV-2 strains. Growth reactions are macrochemical equations that quantify growth of organisms, describing conversion of nutrients into new live matter and other metabolic products (von Stockar, 2013a, 2013b; Battley, 1998, 2013b). Growth reactions have been used to study a wide range of organisms, including bacteria (Battley, 2019), fungi (Battley, 2013, 1998), algae (Wang et al., 2017), plants (Popovic and Minecva, 2021b) and viruses (Popovic and Minecva, 2020a, M. 2020b, 2021a). Growth reactions for the analyzed viruses have the general form (Popovic and Minecva, 2020a, M. 2020b, 2021a):

\[(\text{Amino acid}) + O_2 + HPO_4^{2-} + HCO_3^- \rightarrow (\text{Bio}) + SO_4^{2-} + H_2O + H_2CO_3\]  

(19)

Amino acids represent the carbon and energy source, and the nitrogen source (Popovic and Minecva, 2020a, M. 2020b; von Stockar, 2013b). Oxygen is the electron acceptor (Popovic and Minecva, 2020a, M. 2020b; von Stockar, 2013b). The hydrogenophosphate ion is the phosphorus source, while the hydrogen carbonate ion is a part of the bicarbonate buffer that takes the produced \(H^+\) ions (Popovic and Minecva, 2020a, M. 2020b; von Stockar, 2013b). The sulfate ion takes excess sulfur, while \(H_2CO_3\) takes oxidized carbon and excess \(H^+\) ions, as a part of the bicarbonate buffer (Popovic and Minecva, 2020a, M. 2020b; von Stockar, 2013b). The stoichiometric coefficients of the growth reactions for the three analyzed strains of SARS-CoV-2 can be found in Table S.

2.7. Thermodynamic properties of virus live matter and growth

Elemental composition of virus live matter was used to find standard thermodynamic properties of the analyzed SARS-CoV-2 strains. Standard enthalpy of formation of virus live matter was calculated using the Patet-Erickson equation, also known as Thornton’s rule. Elemental composition of live matter can be used to find the number of electrons transferred to oxygen during its complete combustion, \(E\), using the equation:

\[E = 4n_{C} + n_{H2} - 2n_{O} - 0 n_{S} + 5n_{P} + 6n_{S}\]  

(20)

where \(n_{C}\), \(n_{H2}\), \(n_{O}\), \(n_{S}\) and \(n_{P}\) represent the number of carbon, hydrogen, oxygen, nitrogen, phosphorus and sulfur atoms in the empirical formula of live matter, respectively (Battley, 1998, 1992; Popovic, 2019). The number of electrons \(E\) can be used to calculate standard enthalpy of combustion of live matter, \(\Delta H^f(bio)\), using the Patet-Erickson equation (Patel and Erickson, 1981; Battley, 1998, 1992; Popovic, 2019):

\[\Delta H^f(bio) = -111.14 \frac{kJ}{C\text{mol}} E\]  

(21)

\[\Delta H^r(bio)\] is the enthalpy change of the combustion reaction of live matter:

\[C_{nc}H_{na}O_{nb}N_{nb}P_{na} = n_{C} CO_2 + \frac{1}{2} n_{H2} O_2 + \frac{1}{2} n_{S} S_2 + \frac{1}{2} n_{P} P_2O_{4n} + n_{S} SO_3\]  

(22)

Thus, Hess’s law can be used to convert standard enthalpy of combustion of live matter, \(\Delta H^r(bio)\), into standard enthalpy of formation of live matter, \(\Delta H^f(bio)\) (Atkins and de Paula, 2011, 2014):

\[\Delta H^f(bio) = n_{C} \Delta H^f(CO_2) + \frac{n_{H}}{2} \Delta H^f(H_2O) + n_{P} \Delta H^f(P_2O_{4n})\] 

\[+ n_{S} \Delta H^f(SO_3) - \Delta H^f(bio)\]  

(23)

A similar procedure can be used to find standard molar entropy of virus live matter, using the Battley equation. The Battley equation relates elemental composition of live matter to its standard molar entropy, \(S^0_{m(bio)}\):

\[S^0_{m(bio)} = 0.187 \sum_{j} \frac{v_{j}^b J}{a_{j}}\]  

(24)

where \(S^0_{m(bio)}\) is standard molar entropy of element \(j\), \(a_{j}\) number of atoms of element \(J\) in its standard state form and \(n_{J}\) is the number of atoms of element \(J\) in the empirical formula of the virus (Battley, 1999; Popovic, 2019). The Battley equation can be modified to give standard entropy of formation of live matter, \(\Delta S^f(bio)\). This is done by replacing the coefficient \(-0.187\) with \(-0.813\) (Battley, 1999):

\[\Delta S^f(bio) = -0.813 \sum_{j} \frac{v_{j}^b J}{a_{j}}\]  

(25)

Finally, \(\Delta S^f(bio)\) can be combined with \(\Delta H^f(bio)\), to find standard Gibbs energy of formation of live matter, \(\Delta G^f(bio)\), using the equation (Battley, 1998; Popovic, 2019):

\[\Delta G^f(bio) = \Delta H^f(bio) - T \Delta S^f(bio)\]  

(26)

Standard thermodynamic properties of virus live matter can be combined with growth reactions, to find standard thermodynamic properties of growth. Standard thermodynamic properties of growth are thermodynamic property changes accompanying growth reactions. They include: standard enthalpy of growth, \(\Delta H^g\), standard entropy of growth, \(\Delta S^g\), and standard Gibbs energy of growth, \(\Delta G^g\). These properties can be found using the Hess’s law:

\[\Delta G^g = \sum_{\text{products}} \nu \cdot \Delta H^f - \sum_{\text{reactants}} \nu \cdot \Delta H^f\]  

(27)

\[\Delta S^g = \sum_{\text{products}} \nu \cdot S^o_{u} - \sum_{\text{reactants}} \nu \cdot S^o_{u}\]  

(28)

\[\Delta G^g = \sum_{\text{products}} \nu \cdot \Delta G^f - \sum_{\text{reactants}} \nu \cdot \Delta G^f\]  

(29)

where \(\nu\) represents a stoichiometric coefficient (Atkins and de Paula, 2011, 2014). Standard Gibbs energy of growth, \(\Delta G^g\), is of particular importance, since it represents the driving force of growth and is related to growth rate.

2.8. Growth rate and driving force

Growth rate of microorganisms, \(r_g\), is proportional to their Gibbs energy of growth, \(\Delta G^g\), according to the phenomenological equation:

\[r_g = \frac{L_g}{T} \Delta G^g\]  

(30)

where \(L_g\) is the growth phenomenological coefficient (different than the binding phenomenological coefficient) Westerhoff et al., 1982; Hellingwerf et al., 1982; von Stockar, 2013a; Demirel, 2014; Popovic and Minecva, 2020a, M. 2020b, 2021a). Notice that Eqs. (6) and (30) have the same form, but apply to two different reactions. Both Eqs. (6) and (30) belong to the family of phenomenological equations (Demirel, 2014). However, they apply for different processes, namely binding and multiplication, respectively. Eq. (6) gives the rate of the antigen-receptor binding reaction (1). On the other hand, Eq. (30) applies to Eq. (19), giving growth (multiplication) rate.

3. Results

Standard thermodynamic parameters of antigen-receptor binding have been calculated for the Omicron strain, using Eqs. (12) through (15). The results include standard enthalpy of binding, \(\Delta H^s\), standard entropy of binding, \(\Delta S^s\), and standard Gibbs energy of binding, \(\Delta G^s\), at 25°C and 37°C. They are presented in Table 1. Standard Gibbs energies of binding are negative at both temperatures, implying a spontaneous
process. This is in accordance with the observation that the Omicron strain binds to the ACE2 receptor. Standard enthalpies of binding are negative at both temperatures. Standard entropies of binding are also negative at both temperatures, implying that the binding process is driven by enthalpy.

Table 2 shows binding phenomenological coefficients, \( L_\beta \), binding equilibrium constants, \( K_\beta \), and standard Gibbs energy of binding, \( \Delta_\text{GR} \), for the Hu-1 (Wild type), Alpha, Beta, Gamma, Delta, Omicron and GD/1/2019-RBD strains of SARS-CoV-2. All the data in Table 2 are at 25 °C. Standard Gibbs energies of binding of all the analyzed strains are negative. The binding phenomenological coefficients are on the same order of magnitude for all the analyzed strains, but their values differ. The same trend can be observed for the binding equilibrium constants.

Table 3 shows binding phenomenological coefficients and standard Gibbs energies of binding of the analyzed SARS-CoV-2 strains. The Omicron strain has a less negative standard Gibbs energy of binding (\(-42.82\) kJ/mol), but a greater value of the binding phenomenological coefficient (\(3.89 \times 10^{18}\) mol\(^2\) K / J s dm\(^3\)). The Delta strain has a more negative Gibbs energy of binding (\(-43.38\) kJ/mol), but also lower binding phenomenological coefficient (\(3.89 \times 10^{18}\) mol\(^2\) K / J s dm\(^3\)). This observation about \( L_\beta \) and \( \Delta_\text{GR} \) applies to the other strains in Fig. 1.

For example, the Wild type is characterized by the least negative standard Gibbs energy of binding, but the most negative binding phenomenological coefficient. The Alpha strain has the most negative standard Gibbs energy of binding, but the least negative binding phenomenological coefficient. It seems obvious that it is not enough to observe just the standard Gibbs energy of binding or binding affinity to determine the binding rate. Binding rates for the analyzed SARS-CoV-2 strains have been calculated for the first time and are given in Table 3.

Empirical formulas of Delta and Omicron SARS-CoV-2 strains have been calculated and are given in Table 4. The empirical formula of the Delta strain entire virion was found to be \( \text{CH}_1.6385\text{O}_0.2844\text{N}_0.2299\text{P}_0.0060\text{S}_0.0042 \), while its nucleocapsid has the formula \( \text{CH}_1.5692\text{O}_0.3431\text{N}_0.3106\text{P}_0.0060\text{S}_0.0043 \). The empirical formula of the Omicron strain entire virion was found to be \( \text{CH}_1.6406\text{O}_0.2842\text{N}_0.2299\text{P}_0.0064\text{S}_0.0038 \), while its nucleocapsid has the formula \( \text{CH}_1.5734\text{O}_0.3442\text{N}_0.3122\text{P}_0.0060\text{S}_0.0033 \). It is interesting to compare these formulas to that of the Wild type (Hu-1) strain. The empirical...
formula of the Wild type entire virion was found to be CH$_{1,639}$O$_{608}$N$_{238}$P$_{10}$O$_{500}$S$_{0,003}$, while its nucleocapsid has the formula CH$_{1,570}$O$_{452}$N$_{332}$P$_{10}$O$_{500}$S$_{0,003}$ (M. Popovic and Minceva, 2020b). Differences can be seen, which appeared due to mutations.

Based on the elemental composition of virus nucleocapsids, growth reactions were formulated. Growth reactions for the Wild type, Delta and Omicron SARS-CoV-2 strains can be found in Table 5. They are necessary for calculating thermodynamic properties of growth of the virus strains. Based on elemental composition, standard thermodynamic properties of live matter of Delta and Omicron SARS-CoV-2 strains have been calculated. They can be found in Table 6. These were combined with growth reactions to find standard thermodynamic properties of growth, given in Table 7. For the Delta strain, standard enthalpy of growth was found to be $-227$ kJ/mol, standard entropy of growth is $-37$ J/C-mol K, while the standard Gibbs energy of growth was found to be $-217$ kJ/mol. For the Omicron strain, standard enthalpy of growth was found to be $-232$ kJ/mol, standard entropy of growth is $-37$ J/C-mol K, while the standard Gibbs energy of growth was found to be $-221$ kJ/mol. These properties can be compared to those of the Wild type (Hu-1) strain. For the Wild type, standard enthalpy of growth is $-233$ kJ/mol, standard entropy of growth is $-38$ J/C-mol K, while the standard Gibbs energy of growth is $-222$ kJ/mol (M. Popovic and Minceva, 2020b).

4. Discussion

The discussion will be divided into two parts. The first part is about chemical and thermodynamic characterization of antigen-receptor binding of SARS-CoV-2 strains. In the second part, thermodynamic characterization of growth (multiplication) of SARS-CoV-2 strains will be made. Finally, the consequences of differences in thermodynamic properties between the strains will be considered on infectivity and pathogenicity of SARS-CoV-2 strains.

4.1. Antigen-receptor binding and infectivity

SARS-CoV-2 had appeared in late 2019 and has until now caused a pandemic with 498 million reported cases and 6.2 million casualties (WHO, 2022a; Worldometer, 2022). This great number of cases and casualties was caused by several waves of the pandemic, by different strains of SARS-CoV-2. Thus, SARS-CoV-2 has during the last two years caused a great number of deaths (Abdullah et al., F. 2021). This led to a decrease in pressure on hospitals and lower number of death cases (Abdullah et al., F. 2021). A question is raised of whether the increase in infectivity is accompanied by a decrease in pathogenicity? If yes, how can this phenomenon be explained? The connection between infectivity, pathogenicity, and mutations in Delta and Omicron SARS-CoV-2 strains has been discussed by (Han et al., P. 2022). However, the exact reason has not yet been determined.

Both Delta and Omicron strains use the same receptor, ACE2, for entering their host cells (Han et al., P. 2022; I. Wu et al., 2022). The host cells are the same, since both strains attack the same tissues that possess ACE2 receptors (e.g., primary infection in the upper respiratory system, secondary infection in the lower respiratory system etc.) (Liu et al., 2021). However, the Delta strain causes pulmonary infections much more often than the Omicron strain, even though both strains use the same receptor (Abdullah et al., F. 2021).

The incubation period for infections caused by the Omicron strain is shorter (3 days), compared to the incubation period of the Delta strain (4 days) and Hu-1 strain (5 or more days) (Jansen et al., 2021). Thus, the

| Table 5 | Stoichiometric coefficients for the growth reactions of Wild type, Delta and Omicron SARS-CoV-2 strains. The coefficients in the table correspond to the general growth reaction (Amino acid) + O$_2$ + HPO$_4^{2-}$ + HCO$_3^-$ → (Bio) + SO$_4^{2-}$ + H$_2$O + H$_2$CO$_3$. The product (Bio) denotes virus live matter (new virions), described by the empirical formula from Table 4. The growth reactions are for virus nucleocapsids, which are synthesized by hijacking the host cell metabolic machinery [Popovic and Minceva, 2020a]. |
|---------|---------------------------------------------------------------|
| | Strain | Reactants | Amino acid | O$_2$ | HPO$_4^{2-}$ | HCO$_3^-$ | Products | Bio | SO$_4^{2-}$ | H$_2$O | H$_2$CO$_3$ |
| Wild type (Hu-1) | 1.3905 | 0.4937 | 0.0060 | 0.0437 | → | 1 | 0.0279 | 0.0551 | 0.4342 |
| Delta (B.1.617.2) | 1.3820 | 0.4811 | 0.0060 | 0.0415 | → | 1 | 0.0268 | 0.0579 | 0.4235 |
| Omicron (B.1.1.529) | 1.3892 | 0.4910 | 0.0060 | 0.0438 | → | 1 | 0.0279 | 0.0539 | 0.4330 |

| Table 6 | Standard thermodynamic properties of formation of nucleocapsids of SARS-CoV-2 Wild type, Delta and Omicron strains. The properties include standard enthalpy of formation, $\Delta H^0_{\text{bio}}$, standard molar entropy, $S^0_{\text{bio}}$, and standard Gibbs energy of formation, $\Delta G^0_{\text{bio}}$. The data for the Wild type (Hu-1) strain was taken from [Popovic and Minceva, 2020b]. |
|---------|---------------------------------------------------------------|
| | Strain | $\Delta H^0_{\text{bio}}$ (kJ/C-mol) | $S^0_{\text{bio}}$ (J/C-mol K) | $\Delta G^0_{\text{bio}}$ (kJ/C-mol) |
| Wild type (Hu-1) | $-76$ | $33$ | $-34$ |
| Delta (B.1.617.2) | $-75$ | $32$ | $-33$ |
| Omicron (B.1.1.529) | $-77$ | $33$ | $-34$ |

| Table 7 | Standard thermodynamic properties of growth of Wild type, Delta and Omicron strains of SARS-CoV-2 nucleocapsids. The properties include standard enthalpy of growth, $\Delta H^0$, standard entropy of growth, $\Delta S^0$, and standard Gibbs energy of growth, $\Delta G^0$. The data for the Wild type (Hu-1) strain was taken from [Popovic and Minceva, 2020b]. |
|---------|---------------------------------------------------------------|
| | Strain | $\Delta H^0$ (kJ/C-mol) | $\Delta S^0$ (J/C-mol K) | $\Delta G^0$ (kJ/C-mol) |
| Wild type (Hu-1) | $-233$ | $-38$ | $-222$ |
| Delta (B.1.617.2) | $-227$ | $-37$ | $-217$ |
| Omicron (B.1.1.529) | $-222$ | $-37$ | $-221$ |
rate of entry of the virus into host cells during primary infections with the Omicron strain should be greater. On the other hand, the Omicron strain attacks lower respiratory pathways less often than the Delta strain (Abdullah et al., F. 2021). This means that the infectivity of the Omicron strain is certainly greater than that of the Delta strain. Infectivity is related to susceptibility (Hu et al., S. 2021), while permissiveness is related to pathogenicity (Manjarrez-Zavala et al., 2013). However, a question remains open: is there a difference in pathogenicity between the Delta and Omicron strains?

Binding strength of SARS-CoV-2 strains to host cell receptors has been a subject of intense research (Han et al., P. 2022; L. Wu et al., 2022; Chen et al., 2022; Wang et al., 2021b; P. Gale, 2021; M.I. Barton et al., 2021; Augusto et al., 2021; Laffebet et al., 2021). Omicron, Delta, and Wild type SARS-CoV-2 RBDS were found to have similar binding strength to the ACE2 receptor, according some reports (Han et al., P. 2022). However, the Omicron RBD has also been reported to show a weaker binding affinity than the Delta variant, to human ACE2, by other researchers (L. Wu et al., 2022). The binding affinity of the Omicron strain is lower than that of the Delta strain. However, the incubation period is shorter and rate of spreading is greater for the Omicron strain. Thus, the rate of entry of the Omicron strain into the host cell is expected to be greater than that of the Delta strain, despite its weaker binding affinity. This means that properties other than the binding affinity influence the entry rate into host cells. SARS-CoV-2 infections were found to have a thermodynamic physiological basis (Head et al., 2022). Gibbs energy of binding of the Omicron strain (B.1.1.529) is \( \Delta G^B = -42.8 \) kJ/mol, while its binding constant is \( K_B = 3.18 \times 10^{-7} \) M \(^{-1} \) (Table 2). On the other hand, the Delta strain is characterized by \( \Delta G^B = -49.50 \) kJ/mol and \( K_B = 2.17 \times 10^{-6} \) M \(^{-1} \) (Popovic and Popovic, 2022). The data indicate that the more negative Gibbs energy should make binding of the Delta strain more spontaneous. However, from these data, no conclusions can be drawn on entry rate of Omicron and Delta strains into host cells. This is a consequence of the fact that the virus entry rate into host cells depends, not only on binding affinity and Gibbs energy, but also on the binding phenomenological coefficient, according to Eq. (6). Binding phenomenological coefficients of various SARS-CoV-2 strains have been reported in Table 2.

Another possible explanation exists for the shorter incubation period and faster spreading of the Omicron strain. It is related to potential faster multiplication of the Omicron strain, which would result in a greater virus reservoir. The Omicron strain has 45 mutations (Wie et al., C. 2021), of which 32 are on the SGP (Song and Masaki, 2021). This means that the remaining 13 mutations are located at regions other than SGP. Mutations in these regions could have an influence on Gibbs energy of growth, causing a change in virus multiplication rate (Popovic and Minceva, 2020a; U. 2020b). This hypothesis implies greater multiplication rate of the Omicron strain, which would cause greater damage on the attacked host tissues, accompanied by greater number of severe cases and casualties. However, epidemiological and clinical observations do not support this hypothesis (Abdullah et al., F. 2021). Thus, there are some indications that Omicron strain enters the host faster, but multiplies slower. This slower multiplication could appear as the result of mutation occurred in non-SGP region of virus nucleic acid.

It has been already mentioned that infectivity is a complex process, influenced by several variables. Except for thermodynamic properties (change in enthalpy, entropy, standard Gibbs energy of binding, standard Gibbs energy of growth and binding constant), infectivity is influenced by kinetic properties (binding rate, \( k_m \) and \( k_p \)). Moreover, the quantity and quality of immune response cannot be neglected either. The infective reservoir size also influences infectivity. The infective reservoir size is a variable quantity. For example, in the moment of appearance of a new strain, its infective reservoir is relatively small compared to the reservoir of the dominant strain. If thermodynamic, kinetic and immunological factors are favorable for the new strain, then it will through competition increase the number of people infected with the new strain, suppressing the earlier variants. This can be interpreted as appearance of interference (Popovic and Minceva, 2021a).

During analysis of mechanisms of infection by various virus strains, one should have in mind that the competition is between two or no more than three strains simultaneously. For example, currently in Germany, three strains are circulating: Delta, Omicron and BA.2. The strains characterized by lower infectivity will be suppressed, due to competition.

Table 2 gives two parameters important for analysis of the phenomenon of infectivity. Standard Gibbs energy of binding, \( \Delta G^B \), and binding phenomenological coefficient, \( L_p \), change differently in various strains. Change in Gibbs energy in one strain can be compensated by change in binding phenomenological coefficient (Fig. 1), according to Eq. (6). Table 3 gives antigen-receptor binding rates. A comparison can be made of binding rates of the Omicron and Delta strains, which are currently dominant. The binding rate of the Omicron strain is between 1.5 and 2.5 times greater than that of the Delta strain (Table 3). This is in good agreement with the results found in the literature (Chen et al., 2022).

Evolution of SARS-CoV-2 through mutations from Wild type to Delta strain has been described, from the thermodynamic perspective, in (Popovic and Popovic, 2022). Standard Gibbs energy of binding was found to be an important parameter in evolution of new virus strains (Popovic and Popovic, 2022). However, standard Gibbs energy of binding is not the only parameter that influences infectivity. According to the results of this research, if we consider only Gibbs energy of binding, then the order is:

\[ \text{Alpha} < \text{Gamma} < \text{Beta} < \text{Wildtype} < \text{Delta} < \text{Omicron} \]

This order does not explain the existence of Alpha, Gamma and Beta variants from the perspective of natural selection. However, as was mentioned, except for Gibbs energy of binding, other properties need to be taken into account when analyzing the infectivity order. For example, one should have in mind the changes in phenomenological coefficients and binding rates (Tables 2 and 3).

Fig. 2 shows an increase in binding rate, during evolution of SARS-CoV-2 from Wild type to the Omicron strain. The trend of increase in binding rate is ascending, starting from Wild type to Omicron. If we use binding rate to assess infectivity, then the Fig. 2 shows the expected increase in antigen-receptor binding rate. The reason for this is that binding rate includes, except for change in Gibbs energy, change in binding phenomenological coefficient. A complete perspective should be available in the future, when other parameters become available required to evaluate infectivity of virus strains. For example, if Omicron has an 88% ability to avoid immune response (Chen et al., 2022), then certainly this quality contributes to the infectivity of the Omicron strain. This is in good agreement with the results of Barton et al. (M.I. 2021).

The rate of antigen-receptor binding for the Delta strain has been determined using three methods: kinetic, linear and exponential, as described in the Methods section. The results of the three methods are given in Table 3. For the Delta strain, the kinetic method gave a binding rate of 276.7 \( \times 10^{20} \) M/s, the linear method gave 308.3 \( \times 10^{20} \) M/s, while the exponential method gave 322.7 \( \times 10^{20} \) M/s. The results obtained through the three methods are on the same order of magnitude.

For the Omicron strain, the kinetic method gave a binding rate of 683.2 \( \times 10^{20} \) M/s, the linear method gave 453.3 \( \times 10^{20} \) M/s, while the exponential method gave 474.5 \( \times 10^{20} \) M/s. Again, the three methods gave similar results. The binding rate for the Omicron strain is between 1.5 and 2.5 times greater than that of the Delta strain. This means that the Omicron strain enters the host cell faster and has an advantage in the competition for resources with the Delta strain. This also means that the incubation period in infections with the Omicron strain is shorter. This is in agreement with the clinical observations (Jansen et al., 2021). Moreover, greater binding rate of the Omicron strain leads to interference and suppression of the “slower” Delta strain. This is supported by the fact that in a very short period the Omicron strain suppressed the Delta strain in London and rest of the UK, representing 76 to 90% of new COVID-19 cases (WHO, 2021b). Thus, the greater binding rate of the
Omicron strain to host cells gives it a better access to the multiplication machinery and other resources (i.e. nucleotides, amino acids etc.) during competition, enabling the domination of the Omicron strain and suppression of the Delta strain.

On the other hand, standard Gibbs energy of binding of the Delta strain is \(-43.38\) kJ/mol (Table 2), while that of the Omicron strain is \(-42.82\) kJ/mol (Table 2). Thus, according to Eq. (6), rate of Delta strain binding would have been greater, if only Gibbs energy were the determining factor. More negative Gibbs energy should lead to faster binding of the Delta strain to host cells, shorter incubation period and faster propagation of the Delta strain. However, this is not the case. These facts clearly show that it is not possible to make conclusions on propagation rate and incubation period, based only on Gibbs energy, but it is also required to know the kinetic aspect, through the binding phenomenological coefficient. Knowing both standard Gibbs energy of binding and binding phenomenological coefficient can give information on antigen-receptor binding rate and virus entry into host cells.

4.2. Multiplication inside the host cell and pathogenicity

In the section above, a mechanistic explanation of increased infectivity and faster transmission of the Omicron strain was presented. On the other hand, the Omicron strain has demonstrated a decrease in pathogenicity for lung tissue. The thermodynamic properties of various human tissues are available in the literature (Popovic and Minceva, 2020c). They are the same for infection of both Delta and Omicron strains. Thus, thermodynamic properties of lung tissue influence equally the permissiveness of Delta and Omicron strains. On the other hand, they do not influence the virus-virus interaction of the Delta and Omicron strains. Interaction between the Omicron and Delta strains, except for Gibbs energy of binding, depends on Gibbs energy of growth. Standard Gibbs energy of growth has been reported for the Wild type (Hu-1 strain) nucleocapsid to be \(-222.2\) kJ/C-mol (M. Popovic and Minceva, 2020b).

Using the atom counting method (Popovic, 2022a), elemental compositions have been determined for the Delta and Omicron strains of SARS-CoV-2. The elemental composition of the Wild type (Hu-1) strain has been taken from (M. Popovic and Minceva, 2020b). The elemental composition of the three strains can be found in Table 4. The empirical formula of the Delta strain nucleocapsid was found to be \(\text{CH}_{1.5692}\text{O}_{0.3431}\text{N}_{0.3106}\text{P}_{0.0060}\text{S}_{0.0043}\). The empirical formula of the Omicron strain nucleocapsid was found to be

\[ \text{CH}_{1.5692}\text{O}_{0.3431}\text{N}_{0.3106}\text{P}_{0.0060}\text{S}_{0.0043} \]
CH\textsubscript{1.5734}O\textsubscript{8.3442}N\textsubscript{3.312}P\textsubscript{0.0066}S\textsubscript{0.0032}. The empirical formula of the Wild type nucleocapsid is CH\textsubscript{1.5708}O\textsubscript{3.452}N\textsubscript{3.125}P\textsubscript{0.0066}S\textsubscript{0.0033} (M. Popovic and Minecva, 2020h). Similar results were reported by Degueldre (C. 2021) and Şimşek et al. (R. 2021). Elemental composition of the Wild type, Delta and Omicron strains are different. The differences originate from mutations. Mutations lead to change in genetic sequence and amino acid chains of proteins. Thus, a difference exists in the number and type of amino acids and nucleotides in biopolymers comprising different strains, resulting in differences in elemental composition.

Thermodynamic properties of formation of live matter of analyzed SARS-CoV-2 strains can be found in Table 6. Based on thermodynamic properties of formation and growth reactions (Table 5), thermodynamic properties of growth were calculated. The Wild type has the most negative Gibbs energy of growth (−222 kJ/C-mol), followed by the Omicron strain (−221 kJ/C-mol) and after it the Delta strain (−217 kJ/C-mol). The strain characterized by the most negative Gibbs energy of growth, the Wild type, should exhibit the greatest multiplication rate. The greatest growth (multiplication) rate should lead to greatest damage to host tissues and most severe clinical picture (Casadevall and Pirofski, 2000). Indeed, the Wild type has caused more severe clinical pictures than Omicron and Delta strains (WHO, 2022h). The calculated standard Gibbs energies of growth show that the Omicron strain should exhibit a greater multiplication rate than the Delta strain. In that case, damage to the host tissue caused by the Omicron strain should be greater than that caused by the Delta strain. This would lead to a more severe clinical picture. However, the last pandemic wave has been dominated by the Omicron strain and is characterized by less severe clinical pictures than the wave caused by the Delta strain. The explanation for this phenomenon seems to originate from increased number of vaccinated people. Even though all available vaccines were produced based on Hu-1 sequence, mass vaccination has led to excitation of immune system of the vaccinated people, which could have led to a more rapid immune response during infections and reinfections (for those who already had COVID-19 caused by an earlier strain) with the Omicron strain. In that case, Omicron infections could appear in both vaccinated and unvaccinated people. Having in mind the its greater entry rate, the Omicron strain has an advantage in causing primary infections. More severe clinical pictures and complications caused by Omicron are less common in vaccinated and recovered, due to excitation immune system. However, unvaccinated people and those who haven’t recovered from COVID-19 can have a more severe clinical picture, caused by Omicron. This is supported by the fact that the number of hospitalized vaccinated cases of Omicron strain is lower than that of unvaccinated cases (Veneti et al., 2022). Even though, no vaccine is available for the Omicron strain, it is obvious that vaccination with available vaccines is recommended, for avoiding more severe clinical pictures.

Primary infection with the Omicron strain, due to mutations, occurs in vaccinated, recovered and unvaccinated. After that, the immune system of vaccinated and recovered should in a short time period be able to produce antibodies that would prevent the Omicron strain from causing lung infections. In unvaccinated people, the Omicron strain multiplies at the same rate as in vaccinated, but an unexcited immune system is not able to produce antibodies in a short time period. This enables a secondary infection on lungs.

Fig. 2 shows rate of binding of various strains during the evolution of SARS-CoV-2. A trend can be observed (dotted line) of increase in binding rate. From clinical and epidemiological data, it is known that the Omicron strain transmits faster (Jansen et al., 2021). The epidemiological data can be explained by the increase in binding rate of the Omicron strain (Fig. 2). From Fig. 2a, it can be seen that the reason for faster transmission is the increased rate of antigen-receptor binding, which appeared due to acquired mutations. However, the binding phenomenological coefficient, even though it varies between strains, does not show great changes over prolonged time intervals. This can be seen from Fig. 2b.

5. Conclusions

Empirical formulas have been reported for the first time for the Delta and Omicron strains of SARS-CoV-2. They are different, due to mutations present in the two strains. Based on empirical formulas, growth reactions for the two strains have been formulated and reported. Moreover, standard thermodynamic properties of formation and growth have been reported for the two strains. These properties determine the virus multiplication rate inside the host cell.

On the other hand, the virus entry rate into host cells depends, not only on binding affinity and Gibbs energy, but also on the binding phenomenological coefficient. Thus, knowing the antigen-receptor binding rate and the rate of virus entry into host cells requires knowledge of standard Gibbs energy of binding and the binding phenomenological coefficient. Binding phenomenological coefficients have been determined for Wild type, Alpha, Beta, Gamma, Delta and Omicron strains of SARS-CoV-2. The rate of binding of SGP to the ACE2 receptor have been calculated using kinetic and nonequilibrium thermodynamic approaches. The calculated values are on the same order of magnitude. The entry rates of SARS-CoV-2 strains have been quantified by their binding rates. The greater binding rate of the Omicron strain indicates a greater infectivity.

Similar values of Gibbs energy of growth of the Delta and Omicron strains indicate that the multiplication rates of both strains are similar. The fact that the Omicron strain causes less severe clinical pictures can be explained by the phenomenon of immune system alertness. Therefore, mechanistic analysis of infectivity and pathogenicity requires knowledge of not only Gibbs energies of binding and growth, but also of the corresponding phenomenological coefficients.

CRediT authorship contribution statement

Marko Popovic: Conceptualization, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The author declares no conflict of interest.

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