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THERMODYNAMICS AND SARS-COV-2: NEUROLOGICAL EFFECTS IN POST-COVID 19 SYNDROME

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ABSTRACT. There is increasing evidence that infection with SARS-CoV-2 can cause a spectrum of neurological symptoms. In this paper, we develop a theoretical concept underlying such neurological COVID-19 consequences by employing a non-equilibrium thermodynamic approach that allows linking the neuronal electric potential with a virus-induced pH variation. Our theoretical findings support further experimental work on therapeutically correcting electrolyte imbalances, such as Na^+ and K^+, to attenuate the neurological effects of SARS-CoV-2.

1. Introduction

Infection with the new severe acute respiratory syndrome coronavirus 2, *i.e.*, SARS-CoV-2, can lead to a variety of clinical symptoms ranging from respiratory and circulatory effects to neurological ones; some of these symptoms require immediate therapeutic intervention to try to stabilize vulnerable patients, while others are feared to potentially cause long term morbidity in some (Gu *et al.* 2020).

In this theoretical paper, we focus our analysis on the neurological consequences of SARS-CoV-2. Since the virus has seldom been found in the cerebrospinal fluid of the patients, the damage caused by the anti-virus immune response-mediated damage seems to be the culprit (Solomon 2021). Severe neurological manifestations, albeit rare by comparison, run the gamut from Guillain-Barre (demyelinating polyneuritis) syndrome, and ischemic stroke (Berlit *et al.* 2020; Kandimalla *et al.* 2020) to encephalitis (Ellul *et al.* 2020) while milder symptoms include temporary memory loss, altered mental state or 'brain fog' as well as olfactory and gustatory dysfunctions (Agyeman *et al.* 2020). In fact, partial or complete loss of smell, dysosmia or anosmia, as well as dysgeusia (loss of taste) are common symptoms during a SARS-CoV-2 infection, even in the absence of any other symptoms (Kanberg *et al.* 2020; Matschke *et al.* 2020; Paniz-Mondolfi *et al.* 2020; Meinhardt *et al.* 2021; Solomon 2021); as to the loss of smell, the virus seems to infect the olfactory epithelium, rather than the sensory neurons themselves (Kanberg *et al.* 2020; Matschke *et al.* 2020; Paniz-Mondolfi *et al.* 2020; Meinhardt *et al.* 2021). This notwithstanding, in autopsy studies of patients dying of COVID viral RNA transcripts were

found in brain tissue and viral proteins in the endothelial cells within the olfactory bulb (Song *et al.* 2021); in another study, inflammatory changes appear particularly extensive in the brainstem in proximity to cranial nerve origins (Matschke *et al.* 2020).

At present, the lasting consequences of this neuro-invasion are not fully understood, neither is the optimal therapeutic strategy as, for instance, targeting an over-active immune response with corticosteroids would be potentially dangerous in the presence of virus (Marshall 2020). In this paper, we therefore develop a non-equilibrium thermodynamic analysis of this mechanism, in order to suggest a possible new viewpoint that may hold promise for designing future therapies.

2. Materials and methods

Protein phosphorylation is a fundamental biochemical mechanism regulating cell functions, due to its ability to activate and deactivate some enzymes and receptors (Strong 2002; Rudolph *et al.* 2006). In this context the relation with kinases is of particular interest because kinases are related to cellular transduction signalling (Ardito *et al.* 2017).

Ions actively cross the cell membrane against its electrochemical potential by deriving the required energy from the hydrolysis of ATP, where the H^+-ATPase plays a fundamental role; this is related to the movement of positive charges into the cell, by generating large membrane voltage (inside negative and outside positive) and a pH gradient (Stevens and Forgac 1997; Tuszynski and Kurzynski 2003; Nakanishi-Matsui *et al.* 2010):

$$\mathrm{ATP} + \mathrm{H_2O} \rightarrow \mathrm{ADP} + \mathrm{P} \tag{1}$$

$$\mathrm{H}^+_{out} \rightarrow \mathrm{H}^+_{in} \tag{2}$$

with a subsequent variation of the pH because (Ashrafuzzaman and Tuszynski 2013):

$$\Delta\mathrm{pH} = \frac{F}{2.3RT}\left(\Delta\phi_m - \Delta G_{\mathrm{H}^+}\right) \tag{3}$$

where G depicts the Gibbs potential. The phosphorylation potential, $\Delta\bar{g}_p$ [kJ mol^{-1}], is well known and described by the following equation (Grabe *et al.* 2000; Tuszynski and Kurzynski 2003; Lucia *et al.* 2014; Lucia 2015a,b; Lucia *et al.* 2016; Lucia and Grisolia 2017; Lucia *et al.* 2017; Lucia and Grisolia 2018a,b; Lucia *et al.* 2018):

$$\Delta\bar{g}_p = -nF\Delta\phi \tag{4}$$

where n is the number of moles of ions per ATP synthesized, $F = 96.485 \times 10^3$ A s mol^{-1} is the Faraday constant, and $\Delta\phi$ stands for the membrane potential.

The movement of the ions can be analysed by introducing the Onsager general phenomenological relationships as they pertain to both the electrochemical potential and the heat flux (Callen 1960; Yourgrau *et al.* 1982; Goupil 2011; Lucia and Grisolia 2020a,d,f):

$$\begin{cases} \mathbf{J}_e = -L_{11}\dfrac{\nabla\mu_e}{T} - L_{12}\dfrac{\nabla T}{T^2} \\ \\ \mathbf{J}_Q = -L_{21}\dfrac{\nabla\mu_e}{T} - L_{22}\dfrac{\nabla T}{T^2} \end{cases} \tag{5}$$

where $\mathbf{J}_e$ is the current density [A m^{-2}], $\mathbf{J}_Q$ denotes the heat flux [W m^{-2}], $\mu_e = \mu + ze\phi$ is the electrochemical potential [J mol^{-1}], with μ the chemical potential [J mol^{-1}], ze the electric charge [A s mol^{-1}], and ϕ the membrane potential [V], respectively; T is the living cell temperature and L_{ij} represent the phenomenological coefficients, such that (Katchalsky and Currant 1965) $L_{12}(\mathbf{B}) = L_{21}(-\mathbf{B})$ (Onsager-Casimir relation, Degroot and Mazur 1962), and $L_{11} \geq 0$ and $L_{22} \geq 0$, and $L_{11}L_{22} - L_{12}L_{21} > 0$ (Katchalsky and Currant 1965). The result consists of a model of the life cycle based on two related processes (Lucia and Grisolia 2020a,d):

- a continuous energy generation (metabolism), due to ion fluxes: The ion and metabolite fluxes can be described by imposing $\mathbf{J}_e \neq \mathbf{0}$ and $\mathbf{J}_Q = \mathbf{0}$;
- a continuous heat flux from the cell to its microenvironment: The heat exchange towards the environment can be described by imposing $\mathbf{J}_e = \mathbf{0}$ and $\mathbf{J}_Q \neq \mathbf{0}$.

In this way, we can split the life cycle into two thermodynamic processes, as it is usually done in irreversible thermodynamics for any complex process (Callen 1960). Now, if ion and metabolite fluxes occur, $\mathbf{J}_e \neq \mathbf{0}$ and $\mathbf{J}_Q = \mathbf{0}$, it follows (Callen 1960; Yourgrau *et al.* 1982; Lucia and Grisolia 2020a):

$$\frac{d\mu_e}{dT} = -\frac{L_{21}}{L_{11}}\frac{1}{T} \tag{6}$$

with a related heat flux (Callen 1960; Yourgrau *et al.* 1982):

$$\frac{du}{dt} = -\nabla\cdot\mathbf{J}_Q \tag{7}$$

where u is the internal energy density [W m^{-3}]. Living cells exchange heat power towards their environment by convection, and so, we can write (Lucia and Grisolia 2020h)

$$\frac{du}{dt}\,dV = \delta\dot{Q} = -\alpha\,(T - T_0)\,dA \tag{8}$$

where $\alpha \approx 0.023 Re^{0.8} Pr^{0.35}\lambda/\langle R\rangle$ is the coefficient of convection, A the area of the external surface of the cell membrane, V is the cell volume, T depicts the mean temperature of the external surface of the cell's membrane, and T_0 is the temperature of the cell environment. So, considering Eqs. (7) and (8), and the Divergence Theorem (Apostol 1969), the heat flux can be written as:

$$J_Q = \alpha\,(T - T_0) \tag{9}$$

and the related power flux yields:

$$\dot{Q} = \int_A \mathbf{J}_Q\cdot\hat{\mathbf{n}}\,dA = \alpha\,(T - T_0)A \tag{10}$$

Furthermore, considering Eq. (5), together with the second hypothesis of our modelling ($\mathbf{J}_e = \mathbf{0}$, $\mathbf{J}_Q \neq \mathbf{0}$), it follows (Lucia and Grisolia 2020a):

$$\frac{d\mu_e}{d\ell} = \frac{T J_Q}{\left(L_{22}\frac{L_{11}}{L_{12}} - L_{21}\right)} = -\frac{\alpha T (T - T_0)}{\left(L_{22}\frac{L_{11}}{L_{12}} - L_{21}\right)} \tag{11}$$

where ℓ is the length of a cell membrane and $|\nabla\mu_e| \approx d\mu_e/d\ell$. This relation is the link between the cell membrane's electric potential and the temperature of the cell itself. Eqs. (9) and (11) allow us to obtain:

$$J_Q = \alpha (T - T_0) = -\frac{1}{T}\left(L_{22}\frac{L_{11}}{L_{12}} - L_{21}\right)\frac{d\mu_e}{d\ell} \tag{12}$$

where

$$\left(L_{22} - L_{21}\frac{L_{12}}{L_{11}}\right) = K_J T^2 \tag{13}$$

with K_J being the Thomson coefficient. Consequently, it follows:

$$\frac{\partial \mu_e}{\partial \ell} = \frac{\partial \mu_e}{\partial T}\frac{\alpha}{K_J}\left(T_{surf} - T_0\right) \tag{14}$$

from which, taking into account that $\mu_e = \mu + ze\phi$, becomes:

$$\frac{\partial \mu}{\partial \ell} = -ze\frac{d\phi}{d\ell} + \frac{\partial \mu_e}{\partial T}\frac{\alpha}{K_J}\left(T_{surf} - T_0\right) \tag{15}$$

Now, considering Eq. (3) we can obtain:

$$\frac{\partial \mu_e}{\partial T} = \frac{K_J}{\alpha}\frac{F + ze}{T_{surf} - T_0}\frac{d\phi}{d\ell} - \frac{K_J}{\alpha}\frac{2.3RT_0}{T_{surf} - T_0}\frac{d\mathrm{pH}}{d\ell} \tag{16}$$

which links the electrochemical potential to the pH.

In order to understand the effect of SARS-CoV-2 on the brain, we use a simple model of information coding, introduced previously in our thermodynamic analysis of Alzheimer's disease (Lucia *et al.* 2020b). Specifically, a brain cell requires a Na^+-inflow, and a countering flow of K^+-outflow to develop the functionality of processing signals (Bustamante *et al.* 2004). During this function, the consumption of one molecule of ATP (adenosine triphosphate) requires that the membrane pump extrudes 3 Na^+-ions and imports 1 K^+-ion. At the stationary state, a neuron maintains its pump current:

$$I_p = \frac{\Delta\phi_{Na^+} - \Delta\phi_m}{R_{Na^+}} + \frac{\Delta\phi_{K^+} - \Delta\phi_m}{R_{K^+}} \tag{17}$$

where R_i ($i = [Na^+]$ or $[K^+]$) stands for the electric resistance of the ion considered during its current flux through the membrane, and $\Delta\phi_m$ is the membrane electric potential variation, $\Delta\phi_{Na^+}$ is the electric potential variation due to the Na^+-flux (Goldman 1943; Attwell and Laughlin 2001; Ashrafuzzaman and Tuszynski 2013):

$$\Delta\phi_{\mathrm{Na}^+} = -\frac{RT}{F}\ln\left(\frac{[\mathrm{Na}^+]_f}{[\mathrm{Na}^+]_i}\right) \tag{18}$$

$\Delta\phi_{\mathrm{K}^+}$ is the electric potential variation due to the K^+-flux (Goldman 1943; Attwell and Laughlin 2001; Ashrafuzzaman and Tuszynski 2013):

$$\Delta\phi_{\mathrm{K}^+} = -\frac{RT}{F}\ln\left(\frac{[\mathrm{K}^+]_f}{[\mathrm{K}^+]_i}\right) \tag{19}$$

where $R = 8314$ J mol^{-1} K^{-1} denotes the constant of the ideal gasses, $F = 96,485$ C mol^{-1} is the Faraday constant, f and i means final and initial respectively, and they are referred to the initial and finale state of the neuronal signalling process, and T is the temperature, and

$$R_{in} = \frac{1}{\dfrac{1}{R_{\mathrm{Na}^+}} + \dfrac{1}{R_{\mathrm{K}^+}}} \tag{20}$$

under the biochemical constraint:

$$\frac{d[\mathrm{Na}^+]}{dt} = -\frac{d[\mathrm{K}^+]}{dt} \tag{21}$$

where [A] is the concentration of the A-ion ($\mathrm{Na}^+/\mathrm{K}^+$). In order to maintain a normal membrane potential of around (Attwell and Laughlin 2001) -70 mV a neuron ($R_{in} =$ 200 MΩ of input resistance) requires an influx of around 1.02×10^9 Na^+-K^+ ions s^{-1} ($\Delta\phi_{Na^+} = -50$ mV and $\Delta\phi_{K^+} = -100$ mV) which necessitates 3.42×10^8 hydrolysed ATP molecules s^{-1} (Attwell and Laughlin 2001), consumed at a rate of I_p/F: it generates a pump current I_p of 1.63×10^{-10} A. Next, considering Eqs. (21), (18) and (19) it follows that (19) becomes:

$$\begin{aligned}
\frac{\partial\mu_{e,\mathrm{Na}^+}}{\partial T} &= -\frac{K_J R T_0}{F\alpha}\frac{F+ze}{T_{surf}-T_0}\frac{1}{[\mathrm{Na}^+]}\frac{d[\mathrm{Na}^+]}{d\ell} - \frac{K_J}{\alpha}\frac{2.3RT_0}{T_{surf}-T_0}\frac{d\mathrm{pH}}{d\ell}\\
\frac{\partial\mu_{e,\mathrm{K}^+}}{\partial T} &= -\frac{K_J R T_0}{F\alpha}\frac{F+ze}{T_{surf}-T_0}\frac{1}{[\mathrm{K}^+]}\frac{d[\mathrm{K}^+]}{d\ell} - \frac{K_J}{\alpha}\frac{2.3RT_0}{T_{surf}-T_0}\frac{d\mathrm{pH}}{d\ell}
\end{aligned} \tag{22}$$

which points out that, in order to maintain a normal chemical potential the cell, or neuron in this case, must actively change its concentration of ions if a change in the pH occurs as a result of the viral infection.

As a consequence of the previous steps, a density entropy rate due to irreversibility (dissipation function, Yourgrau *et al.* 1982) is generated (Lucia and Grisolia 2017):

$$\sigma = -\frac{1}{T_0}\sum_{i=1}^{N}\mathbf{J}_i\cdot\nabla\mu_i \geq 0 \tag{23}$$

where T_0 represents the environmental temperature, $\sum_{i=1}^{N} \mu_i \mathbf{J}_i$ is the contribution of the inflows and outflows, and μ denotes the chemical potential. So, using the previous relations we obtain:

$$\begin{aligned}\sigma \approx & -\frac{RJ_{\mathrm{Na}^+}(ze)_{\mathrm{Na}^+}}{F\ell}\ln\left(\frac{[\mathrm{Na}^+]_f}{[\mathrm{Na}^+]_i}\right)+\frac{J_{\mathrm{Na}^+}}{T_0}\frac{\partial\mu_{e,\mathrm{Na}^+}}{\partial T}\frac{\alpha}{K_J}\left(T_{surf}-T_0\right)+ \\ & -\frac{RJ_{\mathrm{K}^+}(ze)_{\mathrm{K}^+}}{F\ell}\ln\left(\frac{[\mathrm{K}^+]_f}{[\mathrm{K}^+]_i}\right)+\frac{J_{\mathrm{K}^+}}{T_0}\frac{\partial\mu_{e,\mathrm{K}^+}}{\partial T}\frac{\alpha}{K_J}\left(T_{surf}-T_0\right)\end{aligned} \tag{24}$$

Starting from this last equation, and considering the previous condition of non-negative entropy density (Katchalsky and Currant 1965), we arrive at the following condition:

$$\begin{aligned}\frac{RJ_{\mathrm{Na}^+}(ze)_{\mathrm{Na}^+}}{F\ell}\ln\left(\frac{[\mathrm{Na}^+]_f}{[\mathrm{Na}^+]_i}\right)-\frac{J_{\mathrm{Na}^+}}{T_0}\frac{\partial\mu_{e,\mathrm{Na}^+}}{\partial T}\frac{\alpha}{K_J}\left(T_{surf}-T_0\right)\leq \\ -\frac{RJ_{\mathrm{K}^+}(ze)_{\mathrm{K}^+}}{F\ell}\ln\left(\frac{[\mathrm{K}^+]_f}{[\mathrm{K}^+]_i}\right)+\frac{J_{\mathrm{K}^+}}{T_0}\frac{\partial\mu_{e,\mathrm{K}^+}}{\partial T}\frac{\alpha}{K_J}\left(T_{surf}-T_0\right)\end{aligned} \tag{25}$$

which suggests that to maintain stability of the neuronal cell system the effect of sodium fluxes is less pronounced than that of potassium.

3. Results

Our conjecture yielded Eqs. (3), (15) and (17). These equations highlight the link between the neuronal signalling process and the neurons' membrane transport. Specifically, Eq. (3) states that a change in pH determines a related variation in membrane potential and in proton flux, related to Gibbs energy and chemical potential (Eq. (15)). As such, a variation in the neuronal ion current pump occurs, with the consequence of modifying the membrane potential related to Na^+ and K^+. In turn, this change determines a modulation in the concentrations of these chemical species with a symmetry breaking in the stationary condition for the neurons. Consequently, the signalling process changes which may offer an explanation for the neurological consequences of infection with SARS-CoV-2. Indeed, we proved (Lucia *et al.* 2020c) that SARS-CoV-2 leads to changes in pH-homeostasis due to modifications of H^+-fluxes. Taken together, this suggests that a promising therapeutic strategy would seek to control the neurons' membrane potential through manipulation of the ions responsible for it.

4. Discussion and conclusions

In patients COVID-19 is characterized by a wide variety of symptoms, some of them neurological with at times very significant morbidity (Marshall 2020). To shed more light onto this, we have developed our non-equilibrium thermodynamics approach that focuses on the effect of SARS-CoV-2-induced pH variation on the ion and thermal fluxes across the cell membrane. As emphasized in Eqs. (16) and (22), this 'pH-ion flux' link can potentially

support the development of new therapeutic strategies to combat SARS-CoV-2's neuronal effects.

Electrolyte imbalances are common in Covid-19 patients, including hypokalemia which has been found to be an independent predictor of the requirement for mechanical ventilation (Moreno-Pérez *et al.* 2020) and which may predispose to cardiac complications and necessitate potassium supplement therapy (Chen *et al.* 2020), and hypocalcemia (Zhou *et al.* 2020) which can lead to muscle twitches and tremors. Furthermore, hyponatremia *i.e.*, a serum sodium [Na^+] level of below 135 mmol L^{-1}, can cause serious central nervous system symptoms ranging from headaches, lethargy, and cramps to seizures, coma, and respiratory arrest (Giuliani and Peri 2014). Interestingly, hyponatremia has indeed been noted as an early sign in Covid-19 infections (Gheorghe *et al.* 2021). Clinical management of this common, multifactorial sodium imbalance in Covid-19 patients depends on the exact etiology and therefore can involve electrolyte replacement therapy in patients suffering from hyponatremia primarily due to fluid losses or infusion of hypertonic saline in cases of insufficient antidiuretic hormone secretion, seen as a consequence of the systemic inflammation triggered by the virus (Gheorghe *et al.* 2021). It is intriguing in this context that a recent article, available so far only as preprint, describes in vitro experiments where hypertonic saline (1.5% NaCl) inhibits SARS-Cov-2 replication completely, presumed to be achieved by cell plasma membrane depolarization and intracellular energy deprivation (Machado *et al.* 2020). If these experimental findings can be confirmed, our theoretical conjecture supports advancing this concept from in vitro to in vivo studies, in an effort to gain insights if hypertonic saline could help mitigate SARS-CoV-2 effects on the central nervous system. Finally, in light of these very recent experimental findings on sodium, Eq. (25) may deserve attention as it indicates that the impact of correcting potassium levels may be even more pronounced. Still, it must be noted that in clinics addressing electrolyte imbalances is highly non-trivial and extensive, experimental work would be required to properly assess risk vs. benefit of serum adjustments of Na^+ and/or K^+.

In summary, our thermodynamics approach conceptualizes that SARS-CoV-2-induced pH fluctuations trigger ion-flux changes across the neuron cell membrane which in turn alters signalling throughout the system. Cautiously extrapolated, this may explain some of the neurological symptoms seen in COVID patients and it supports further research in therapeutically addressing electrolyte imbalances.

Authors' contributions

Conceptualization, U.L and T.S.D.; methodology, U.L., G.G. and T.S.D.; software, G.G.; validation, U.L., T.S.D. and G.G.; formal analysis, U.L.; investigation, G.G.; resources, U.L.; data curation, G.G.; writing-original draft preparation, U.L., G.G. and T.S.D.; writing—review and editing, U.L., G.G. and T.S.D.; visualization, G.G.; supervision, U.L., T.S.D.; project administration, U.L.; funding acquisition, U.L. All authors have read and agreed to the published version of the manuscript.

References

Agyeman, A. A., Chin, K. L., Landersdorfer, C. B., Liew, D., and Ofori-Asenso, R. (2020). "Smell and Taste Dysfunction in Patients With COVID-19: A Systematic Reviewand Meta-analysis". *Mayo Clinic Proceedings* **95**, 1621–1631. DOI: 10.1016/j.mayocp.2020.05.030.

Apostol, T. M. (1969). *Calculus. Multi-Variable Calculus and Linear Algebra with Applications to Differential Equations and Probability*. Vol. 2. Hoboken: Wiley.

Ardito, F., Giuliani, M., Perrone, D., Troiano, G., and Muzio, L. L. (2017). "The crucial role of protein phosphorylation in cell signaling and its use as targeted therapy". *International Journal of Molecular Medicine* **40**, 271–280. DOI: 10.3892/ijmm.2017.3036.

Ashrafuzzaman, M. and Tuszynski, J. A. (2013). *Membrane Biophysics*. Berlin: Springer. DOI: 10.1007/978-3-642-16105-6.

Attwell, D. and Laughlin, S. B. (2001). "An energy budget for signaling in the grey matter of the brain". *Journal of Cerebral Blood Flow and Metabolism* **21**, 1133–1145. DOI: 10.1097/00004647-200110000-00001.

Berlit, P., Bösel, J., Gahn, G., Isenmann, S., Meuth, S. G., Nolte, C. H., Pawlitzki, M., Rosenow, F., Schoser, B., Thomalla, G., and Hummel, T. (2020). ""Neurological manifestations of COVID-19" - guideline of the German society of neurology". *Neurological Research and Practice* **2**, 51. DOI: 10.1186/s42466-020-00097-7.

Bustamante, C., Chemla, Y. R., Forde, N. R., and Izhaky, D. (2004). "Mechanical processes in biochemistry". *Annual Review of Biochemistry* **73**, 705–748. DOI: 10.1146/annurev.biochem.72.121801.161542.

Callen, H. B. (1960). *Thermodynamics*. New York: Wiley.

Chen, D., Li, X., Song, Q., Hu, C., Su, F., Dai, J., Ye, Y., Huang, J., and Zhang, X. (2020). "Assessment of Hypokalemia and Clinical Characteristics in Patients With Coronavirus Disease 2019 in Wenzhou, China". *JAMA Network Open* **3**(6), e2011122–e2011122. DOI: 10.1001/jamanetworkopen.2020.11122.

Degroot, S. R. and Mazur, P. (1962). *Non-Equilibrium Thermodynamics*. Amsterdam: North-Holland Publishing Company.

Ellul, M. A., Benjamin, L., Singh, B., Lant, S., Michael, B. D., Easton, A., Kneen, R., Defres, S., Sejvar, J., and Solomon, T. (2020). "Neurological associations of COVID-19". *The Lancet Neurology*, 767–783. DOI: 10.1016/S1474-4422(20)30221-0.

Gheorghe, G., Ilie, M., Bungau, S., Stoian, A. M. P., Bacalbasa, N., and Diaconu, C. C. (2021). "Is There a Relationship between COVID-19 and Hyponatremia?" *Medicina* **57**, 55. DOI: 10.3390/medicina57010055.

Giuliani, C. and Peri, A. (2014). "Effects of Hyponatremia on the Brain". *Journal of Clinical Medicine* **3**, 1163–1177. DOI: 10.3390/jcm3041163.

Goldman, D. E. (1943). "Potential impedance, and rectification in membranes". *Journal of General Physiology* **27**, 37–60. DOI: 10.1085/jgp.27.1.37.

Goupil, C. (2011). "Thermodynamics of Thermoelectricity". In: *Thermodynamics*. Ed. by T. Mizutani. Shanghai: IntechOpen. DOI: 10.5772/12988.

Grabe, M., Wang, H., and Oster, G. (2000). "The mechanochemistry of V-ATPase proton pumps". *Biophysical Journal* **78**, 2798–2813. DOI: 10.1016/S0006-3495(00)76823-8.

Gu, J., Han, B., and Wang, J. (2020). "COVID-19: Gastrointestinal Manifestations and Potential Fecal–Oral Transmission". *Gastroenterology* **158**(6), 1518–1519. DOI: 10.1053/j.gastro.2020.02.054.

Kanberg, N., Ashton, N. J., Andersson, L.-M., Yilmaz, A., Lindh, M., Nilsson, S., Price, R. W., Blennow, K., Zetterberg, H., and Gisslén, M. (2020). "Neurochemical evidence of astrocytic and

neuronal injury commonly found in COVID-19". *Neurology* **95**, e1754-e1759. DOI: 10.1212/WNL.0000000000010111.

Kandimalla, R., John, A., Abburi, C., Vallamkondu, J., and Reddy, P. H. (2020). "Current Status of Multiple Drug Molecules, and Vaccines: An Update in SARS-CoV-2 Therapeutics". *Molecular Neurobiology* **57**, 4106–4116. DOI: 10.1007/s12035-020-02022-0.

Katchalsky, A. and Currant, P. F. (1965). *Nonequilibrium Thermodynamics in Biophysics*. Boston: Harvard University Press.

Lucia, U. (2015a). "Bioengineering thermodynamics of biological cells". *Theoretical Biology and Medical Modelling* **12**, 29. DOI: 10.1186/s12976-015-0024-z.

Lucia, U. (2015b). "Bioengineering thermodynamics: An engineering science for thermodynamics of biosystems". *International Journal of Thermodynamics* **18**, 254–265. DOI: 10.5541/ijot.5000131605.

Lucia, U. and Grisolia, G. (2017). "Second law efficiency for living cells". *Frontiers in Bioscience, Scholar* **9**, 270–275. DOI: 10.2741/s487.

Lucia, U. and Grisolia, G. (2018a). "Constructal law and ion transfer in normal and cancer cells". *Proceedings of the Romanian Academy Series A* **19**, 213–218. URL: https://acad.ro/sectii2002/proceedings/doc2018-1s/continut/213-218.pdf.

Lucia, U. and Grisolia, G. (2018b). "Cyanobacteria and microalgae: Thermoeconomic considerations in biofuel production". *Energies* **11**, 156. DOI: 10.3390/en11010156.

Lucia, U. and Grisolia, G. (2020a). "How Life Works — A Continuous Seebeck-Peltier Transition in Cell Membrane?" *Entropy* **22**, 960. DOI: 10.3390/e22090960.

Lucia, U. and Grisolia, G. (2020d). "Non-equilibrium thermodynamic approach to Ca^{2+}-fluxes in cancer". *Applied Sciences* **10**, 6737. DOI: 10.3390/app10196737.

Lucia, U. and Grisolia, G. (2020f). "Thermal physics and glaucoma: From thermodynamic to biophysical considerations to design future therapies". *Applied Sciences* **10**, 7071. DOI: 10.3390/app10207071.

Lucia, U. and Grisolia, G. (2020h). "Thermal Resonance and Cell Behavior". *Entropy* **22**, 774. DOI: 10.3390/e22070774.

Lucia, U., Grisolia, G., and Astori, M. R. (2017). "Constructal law analysis of Cl^- transport in eyes aqueous humor". *Scientific Reports* **7**, 6856. DOI: 10.1038/s41598-017-07357-8.

Lucia, U., Grisolia, G., and Deisboek, T. S. (2020b). "Alzheimer's Disease: A Thermodynamic Perspective". *Applied Sciences* **10**, 7562. DOI: 10.3390/app10217562.

Lucia, U., Grisolia, G., Dolcino, D., Astori, M. R., Massa, E., and Ponzetto, A. (2016). "Constructal approach to bio-engineering: The ocular anterior chamber temperature". *Scientific Reports* **6**, 31099. DOI: 10.1038/srep31099.

Lucia, U., Grisolia, G., Ponzetto, A., and Deisboeck, T. S. (2018). "Thermodynamic considerations on the role of heat and mass transfer in biochemical causes of carcinogenesis". *Physica A* **490**, 1164–1170. DOI: 10.1016/j.physa.2017.08.075.

Lucia, U., Ponzetto, A., and Deisboeck, T. S. (2014). "A thermo-physical analysis of the proton pump vacuolar-ATPase: The constructal approach". *Scientific Reports* **4**, 1. DOI: 10.1038/srep06763.

Lucia, U., Grisolia, G., and Deisboeck, T. S. (2020c). "Seebeck-like effect in SARS-CoV-2 biothermodynamics". *Atti della Accademia Peloritana dei Pericolanti. Classe di Scienze Fisiche, Matematiche e Naturali* **98**(2), A6. DOI: 10.1478/AAPP.982A6.

Machado, R. R. G., Glaser, T., Araujo, D. B., Petiz, L. L., Oliveira, D. B. L., Durigon, G. S., Leal, A. L., Pinho, J. R. R., Ferreira, L. C. S., Ulrich, H., Durigon, E. L., and Guzzo, C. R. (2020). "Hypertonic saline solution inhibits SARS-CoV-2 in vitro assay". *bioRxiv*. DOI: 10.1101/2020.08.04.235549. eprint: https://www.biorxiv.org/content/10.1101/2020.08.04.235549v2.full.pdf.

Marshall, M. (2020). "How COVID-19 can damage the brain". *Nature* **585**, 342–343. DOI: 10.1038/d41586-020-02599-5.

Matschke, J., Lütgehetmann, M., Hagel, C., Sperhake, J. P., Schröder, A. S., Edler, C., Mushumba, H., Fitzek, A., Allweiss, L., Dandri, M., Dottermusch, M., Heinemann, A., Pfefferle, S., Schwabenland, M., Magruder, D. S., Bonn, S., Prinz, M., Gerloff, C., Püschel, K., Krasemann, S., Aepfelbacher, M., and Glatzel, M. (2020). "Neuropathology of patients with COVID-19 in Germany: a post-mortem case series". *The Lancet Neurology* **19**, 919–929. DOI: /10.1016/S1474-4422(20)30308-2.

Meinhardt, J., Radke, J., Dittmayer, C., Franz, J., Thomas, C., Mothes, R., Laue, M., Schneider, J., Brünink, S., Greuel, S., Lehmann, M., Hassan, O., Aschman, T., Schumann, E., Chua, R. L., Conrad, C., Eils, R., Stenzel, W., Windgassen, M., Rößler, L., Goebel, H.-H., Gelderblom, H. R., Martin, H., Nitsche, A., Schulz-Schaeffer, W. J., Hakroush, S., Winkler, M. S., Tampe, B., Scheibe, F., Körtvélyessy, P., Reinhold, D., Siegmund, B., Kühl, A. A., Elezkurtaj, S., Horst, D., Oesterhelweg, L., Tsokos, M., Ingold-Heppner, B., Stadelmann, C., Drosten, C., Corman, V. M., Radbruch, H., and Heppner, F. L. (2021). "Olfactory transmucosal SARS-CoV-2 invasion as a port of central nervous system entry in individuals with COVID-19". *Nature Neuroscience* **24**, 168–175. DOI: 10.1038/s41593-020-00758-5.

Moreno-Pérez, O., Leon-Ramirez, J.-M., Fuertes-Kenneally, L., Andres, M. P. M., Garcia-Navarro, M., Ruiz-Torregrosa, P., Boix, V., Gil, J., and Merino, E. (2020). "Hypokalemia as a sensitive biomarker of disease severity and the requirement for invasive mechanical ventilation requirement in COVID-19 pneumonia: A case series of 306 Mediterranean patients". *International Journal of Infectious Diseases* **100**, 449–454. DOI: 10.1016/j.ijid.2020.09.033.

Nakanishi-Matsui, M., Sekiya, M., and Futai, R. K. N. M. (2010). "The mechanism of rotating proton pumping ATPases". *Biochimica et Biophysica Acta - Bioenergetics* **1797**, 1343–1352. DOI: 10.1016/j.bbabio.2010.02.014.

Paniz-Mondolfi, A., Bryce, C., Grimes, Z., Gordon, R. E., Reidy, J., Lednicky, J., Sordillo, E. M., and Fowkes, M. (2020). "Central nervous system involvement by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)". *Journal of Medical Virology* **92**, 699–702. DOI: 10.1002/jmv.25915.

Rudolph, M. G., Stanfield, R. L., and Wilson, I. A. (2006). "How TCRs bind MHCs, peptides, and coreceptors". *Annual Review of Immunology* **24**, 419–466. DOI: 10.1146/annurev.immunol.23.021704.115658.

Solomon, T. (2021). "Neurological infection with SARS-CoV-2 - the story so far". *Nature Reviews Neurology* **17**, 65–66. DOI: 10.1038/s41582-020-00453-w.

Song, E., Zhang, C., Israelow, B., Lu-Culligan, A., Prado, A. V., Skriabine, S., Lu, P., Weizman, O.-E., Liu, F., Dai, Y., Szigeti-Buck, K., Yasumoto, Y., Wang, G., Castaldi, C., Heltke, J., Ng, E., Wheeler, J., Alfajaro, M. M., Levavasseur, E., Fontes, B., Ravindra, N. G., Dijk, D. V., Mane, S., Gunel, M., Ring, A., Kazmi, S. A. J., Zhang, K., Wilen, C. B., Horvath, T. L., Plu, I., Haik, S., Thomas, J.-L., Louvi, A., Farhadian, S. F., Huttner, A., Seilhean, D., Renier, N., Bilguvar, K., and Iwasaki, A. (2021). "Neuroinvasion of SARS-CoV-2 in human and mouse brain". *Journal of Experimental Medicine* **218**, e20202135. DOI: 10.1084/jem.20202135.

Stevens, T. H. and Forgac, M. (1997). "Structure, function and regulation of the vacuolar (H^+)-ATPase". *Annual Review of Cell and Developmental Biology* **13**, 779–808. DOI: 10.1146/annurev.cellbio.13.1.779.

Strong, R. K. (2002). "Asymmetric ligand recognition by the activating natural killer cell receptor NKG2D, a symmetric homodimer". *Molecular Immunology* **38**, 1029–1037. DOI: 10.1016/s0161-5890(02)00032-9.

Tuszynski, J. A. and Kurzynski, M. (2003). *Introduction to Molecular Biophysics*. Boca Raton: CRC Press, pp. 383–392.

Yourgrau, W., Merwe, A. van der, and Raw, G. (1982). *Treatise on Irreversible and Statistical Thermophysics*. New York: Dover.

Zhou, X., Chen, D., Wang, L., Zhao, Y., Wei, L., Chen, Z., and Yang, B. (2020). "Low serum calcium: a new, important indicator of COVID-19 patients from mild/moderate to severe/critical". *Bioscience Reports* **40**, BSR20202690. DOI: 10.1042/BSR20202690.

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