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**RESPONSE TO COMMENT ON:
A CRITICAL REVIEW ON HEAT AND MASS TRANSFER MODELLING
OF VIRAL INFECTION AND VIRION EVOLUTION
THE CASE OF SARS-COV2**

by

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The paper contains a response to the comment by Popovich and Mincheva, focusing on the different meanings of the analysis according to the First and the Second law of thermodynamics and their complementary and never alternative nature.

Introduction

“Doubt is clearly a value in science. It is important to doubt and that the doubt is not a fearful thing, but a thing of great value.” Richard P. Feynman

The authors [1] are grateful to Dr. Popović and Prof. Mincheva for the appreciated comments [2]. First, the paper must be premised to follow a former interdisciplinary preliminary study [3]. This response is expected to clarify and exhaustively respond to the key issues indicated. Therefore, as it will be demonstrated, the intention of the critique analysis by authors is not to judge an appreciable activity but only to foresee how this milestone could extend or improve toward a vision that could embrace both the First and the Second law of thermodynamics.

Preliminary consideration on atom counting method and similar ones adopted previously

The authors are sorry to have not been aware of a former paper [4] cited by Popović and Mincheva. Indeed, they have deduced the atom counting method from a previous paper [5], in which the method has been enunciated and described: “... *elemental composition was calculated based on their structures taken from UniProt and NCBI (mode details in Supplementary Information 1 and 2), by counting the total number of atoms of each element in their genetic material and protein capsid.*”

Therefore, the authors have independently derived their activity from Popović and Mincheva [5], which ultimately defines the atom counting methods as a precious instrument

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for calculating Gibbs free energy. In addition, a similar method has been used by Szargut [6] and Morris and Syargut [7] for estimating the chemical exergy of molecular compounds. Therefore, the claim does not appear motivated.

Methodological considerations

Thermodynamic is a unique scientific corpus [8, 9] based on universal laws, which do not depend on the specific problem and have no disciplinary boundaries except thermodynamic itself. Hence, the natures of Gibbs free energy and exergy (or entropy generation) are complementary and not alternative.

Cells, viruses, and their subsystems are finite open thermodynamic systems with a finite lifetime [10, 11]. They are subject to the First and Second law of thermodynamics. The discussed paper [1] is only an attempt toward a positive discussion toward increasing the amount of available information from the Second law of thermodynamics. The only objective is to analyse the delivered information and intrinsic limits [12] of both the First law analysis (Gibbs free energy) and the Second law analysis (exergy or entropy generation).

Discussion on the physical meaning of Gibbs free energy and exergy

The sentences that Popović and Mincheva have evidenced and criticized do not refer to their outstanding analysis according to the First law of thermodynamics. They do not affect the positive evaluation of their work and its importance in determining the potential of infection (the probability of the chemical reaction between spike protein and ACE receptors). They aim only to evidence the different levels of information, the limits, and approximations of different methods, which produce analysis according to different laws of thermodynamics. The expected result is a better comprehension of how they can jointly describe physical, chemical, and biochemical processes and jointly increase the amount of achievable information. It does not mean to express any criticism to a well-stated method such as the one derived from the Phenomenological Law [13], which is a fundamental instrument for describing experimental activities.

To better understand the problem, the clash between Duhem [14] and Gouy [15] on the priority of discovering available energy can be cited. Today, it is easy to understand that they were both right. However, they referred to different physical magnitudes. Duhem [14] has considered the Gibbs free energy ($u-TS$) and Gouy [15] the exergy ($u-TOS$). This example aims to clarify the goals better: an open debate on complementary approaches, discussing their limits, analysing the delivered information, understanding possible correlations, and identifying possible collaborative paths.

The paper [1] must be intended in the constructive sense of the Kantian critique [16] through extending the results according to the First law with complementary ones according to the Second law. Therefore, this response moves in this direction. Finally, it will present some preliminary integration of the results according to the First law with complementary ones according to the Second law according to Szargut *et al.* [17].

Materials and methods

Traditional thermodynamic system and balances

Bejan [18] states that the most general systems are unsteady. The instantaneous inventories of mass, energy, and entropy can be defined from work transfer rate, heat transfer rates from the temperature reservoirs, and mass-flow rates, through the inlets and outlets. The thermodynamic model is necessarily and fully defined through both the First law:

$$\frac{dE}{dt} = \sum_{i=0}^n \dot{Q}_i - \dot{W} + \sum_{in} \dot{m}h - \sum_{out} \dot{m}h = \dot{Q}_0 + \sum_{i=1}^n \dot{Q}_i - \dot{W} + \sum_{in} \dot{m}h - \sum_{out} \dot{m}h \quad (1)$$

and the Second law of thermodynamics:

$$\dot{S}_{gen} = \frac{dS}{dt} = \sum_{i=0}^n \frac{\dot{Q}_i}{T_i} - \sum_{in} \dot{m}s + \sum_{out} \dot{m}s = \frac{\dot{Q}_0}{T_0} + \sum_{i=1}^n \frac{\dot{Q}_i}{T_i} - \sum_{in} \dot{m}s + \sum_{out} \dot{m}s \geq 0 \quad (2)$$

where h is the sum of specific enthalpy, kinetic energy, and potential energy of a particular stream at the boundary. Equation (2) is the total entropy generation rate, \dot{S}_{gen} , which must satisfy the Second law inequality. Therefore, decreasing the total entropy generation rate is advantageous. It can be accomplished by varying one or more quantities along the system boundary.

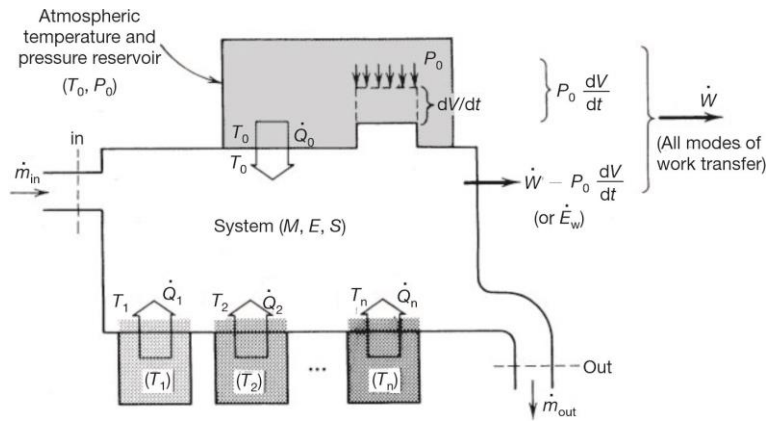


Figure 1. Schematic representation of typical thermodynamic systems [40].

If the environmental heat transfer has been selected to be the floating variable which changes as \dot{S}_{gen} varies, it can be eliminated between eqs. (1) and (2) determining the irreversibility:

$$T_0 \dot{S}_{gen} = \dot{W} + \frac{dE}{dt} - \sum_{i=1}^n \dot{Q}_i \left(1 - \frac{T_0}{T_i} \right) - \sum_{in} \dot{m}(h - T_0 s) + \sum_{out} \dot{m}(h - T_0 s) \quad (3)$$

Gibbs free energy

Gibbs free energy [19] has been originally defined as: “the greatest amount of mechanical work which can be obtained from a given quantity of a certain substance in a given initial state, without increasing its total volume or allowing heat to pass to or from external bodies, except such as at the close of the processes are left in their initial condition.”

It can be expressed as:

$$G = H + T \Delta S = U + PV - TS \quad (4)$$

Being evaluated at T, P of the system in equilibrium with the environment, a static magnitude applies to an unsteady system describing a particular state. Gibbs energy requires that the system is in equilibrium with the surrounding environment.

The general equation of ΔG of a biochemical reaction at constant pH is given by the sum of Gibbs free energy of formation of the products minus the Gibbs energy of the reactants so that:

$$\Delta G^o = \sum_{\text{products}} \Delta G_f^o - \sum_{\text{reactants}} \Delta G_f^o \quad (5)$$

and becomes in the case of biochemical reactions:

$$\Delta G = \sum_{j=1}^{\text{products}} \eta_j [\Delta_f G^0 + RT \ln(C_j)] - \sum_{i=1}^{\text{reactants}} \eta_i [\Delta_f G^0 + RT \ln(C_i)] \quad (6)$$

where η is the stoichiometric coefficient, R – the gas constant, T – the temperature of the system, C – the intracellular metabolite concentration, and $\Delta_f G_0$ – the standard Gibbs free energy of formation of the metabolite at the environmental pH, I , and T . It is fundamental to understand if a chemical reaction is spontaneous [20] and may occur without external actions. In particular, a reaction is spontaneous when it produces a negative variation of G and non-spontaneous when the change of G is positive.

Therefore, Gibbs energy change is the maximum work produced by a substance or a set of substances before and after a chemical transformation or a transformation step. It is time-independent and does not deliver information about the path and the evolution over time of the transformation. The same result has been evidenced by Fasman [21] and Dimian *et al.* [22]. Therefore, it does not deliver any information about the path, reaction mechanism, and chemical or biochemical reaction rate. It delivers information only about the initial and final state of a reaction or a step of a process. Therefore, it is evident that the change of Gibbs free energy is only the differential between two works that can be obtained in equilibrium conditions. Even if a process is unsteady, Gibbs free energy estimation requires setting even artificially a virtual equilibrium point because it has no physical sense outside the equilibrium, as seen above.

Extension of the use of Gibbs free energy to unsteady phenomena

Under precise hypotheses and limits, Demirel *et al.* [22], Demirel and Sandler [23], and Demirel [24] extends Gibbs free energy even to unsteady phenomena. According to Onsager [25, 26], Demirel states that elementary volumes can determine a local thermodynamic state at individual points of the system that is not in equilibrium. If they are small enough, the elementary volumes allow treating the substance in them as homogeneous. If they are large enough to include a sufficient number of molecules, they apply the phenomenological laws. Therefore, the local state defines a state of microscopic reversibility:

- the symmetry of all mechanical equations of motion of individual particles with respect to time and
- if two alternative paths exist for a simple reversible reaction and one of these paths is preferred for the backward reaction, the same path must also be preferred for the forward reaction.

As stated by Onsager and Machlup [27], microscopic reversibility allows assuming Onsager's reciprocal relations to be valid. A direct consequence is the reversibility of molecular behaviour, which allows considering a kind of symmetry related to the transport processes and how they couple each other.

If the thermodynamic system is not in equilibrium, local states in local thermodynamic equilibrium may exist. Consequently, the extensive thermodynamic variables are functions of position and time. In addition, the thermodynamic functions can be determined at every point for substances in equilibrium. For example, temperature and pressure are defined by $T = (\partial U / \partial S) V$, $P = -(\partial U / \partial V) S$. Inside the aforementioned hypotheses, the classical-thermodynamic functions are assumed to be valid, including Gibbs free energy and Gibbs-

Duhem equation in a system with multiple species. In the case of mixtures of mono-atomic gasses, Prigogine has expanded the molecular distribution function in an infinite series around the equilibrium molecular distribution function, f_0 :

$$f = f_0 + f_1 + f_2 + \dots \quad (7)$$

Equation (7) is valid for both equilibrium and non-equilibrium systems. In particular, non-equilibrium systems are characterized by an equilibrium distribution function of $f_0 + f_1$, which describes a non-equilibrium system sufficiently close to equilibrium [24]. It is necessary to observe that the analysis by Prigogine can be applied only to mixtures of mono-atomic gases and may depend on the Chapman-Enskog model [28, 29]. The validity domain of the local thermodynamic equilibrium [30, 31] is not generally known from a microscopic perspective. It applies to a stationary system, in which the thermodynamic quantities at an arbitrary point are not dependent on time. It is valid when the gradients of intensive thermodynamic functions are small, and their local values vary slowly with respect to the local state of the system. It does not apply to unsteady systems such as turbulent and shockwave phenomena. Any change in an intensive parameter is comparable to the molecular mean free path, and energy dissipation rapidly damps large deviations from the equilibrium. Experimental activities are necessary to determine the range of validity of the local thermodynamic equilibrium for a specific system.

Demirel [24] observes that near equilibrium, linear non-equilibrium thermodynamics correlate forces and flows linearly. This approach is an alternative to conventional thermodynamics, which risks ignoring the local fluctuation of the physical properties in macroscopic systems. The introduction of internal degrees of freedom allows describing a large class of irreversible processes and scales such as biochemical ones. Therefore, a probabilistic approach allows formulating the First and Second law of thermodynamics along single fluctuation trajectories, and consistent kinetics valid beyond the linear region can be imposed. Furthermore, the degrees of freedom define the state of the system. Any change of state due to the driving forces or to the fluctuations defines the system's trajectory along which the thermodynamic quantities (work, heat, *etc.*) are distributed. In addition, the Crooks fluctuation theorem [32] allows comparing the probability distributions for the work spent in the actual process with the time-reversed one. It states that the probability of violating the Second law of thermodynamics becomes exponentially small as time or system size increases and allows accounting for the fluctuations.

Exergy

The concept of exergy was implicit in Carnot's demonstration of perpetual motion's impossibility [33]. Furthermore, this concept was implicit in Gibbs' [19] *availability function*, which represents the *freely available work*. Later the concept of exergy was exhaustively defined by Rant [34]. Sciubba and Wall [35] have given the following general definition: *the maximum theoretical useful work obtained if a system S is brought into thermodynamic equilibrium with the environment by means of processes in which the S interacts only with this environment*. In addition, Kotas [36] has provided the following of chemical exergy: *the maximum work obtainable when a given system is brought from the environmental state (p_0, T_0, z) to the standard dead state (p_0, T_0, z_0).*

Exergy [37] formulation is similar to the one of Gibbs free energy [38]:

$$B = [h(T, p) - h(T_0, p_0)] - T_0 [s(T, p) - s(T_0, p_0)] \quad (8)$$

The exergy concept can be understood by assuming an ideal Carnot engine between the system and its reference environment. Unfortunately, such an engine cannot exist in the real world. Therefore, it allows measuring the ideal and most efficient thermodynamic interaction between the system and its surroundings [39]. In the case of chemical exergy, the ideal Carnot engine works between the reference environment and the dead state. It is then evident that exergy does not describe the system in equilibrium with the environment (Gibbs free energy) but the maximum amount of work extracted from a system going in equilibrium with its environment, reaching the maximum entropy.

Equations of a living cell according to the First and Second law

If a control volume coincident with a cell is assumed, and its metabolic processes can be described by the energy and exergy balances can be expressed by reformulating eqs. (1) and (2):

$$Q = H_{\text{reac}} - H_{\text{prod}} - W \quad (9)$$

$$B_{\text{dest}} = B_{\text{reac}} - B_{\text{prod}} - Q \left(1 - \frac{T_0}{T_b} \right) - W \quad (10)$$

where H_{reac} is the enthalpy of the reactants, H_{prod} – the enthalpy of the products, B_{reac} – the exergy content of the reactants, B_{prod} – the exergy content of the products, Q – the heat released, W – the performed work, T_0 – the environment/reference temperature, and T_b – the body temperature.

How to correlate Gibbs energy and exergy

Gibbs free energy and exergy can be directly correlated, as stated by Szargut *et al.* [40]. However, standard chemical exergy calculation requires assuming a standard environmental condition (temperature, pressure, standard concentration of the substances in the natural environment).

The standard chemical exergy of any chemical compound can be calculated through the exergy balance of a reversible formation reaction:

$$B_{\text{chem}} = \Delta G_f + \sum_e n_e b_{\text{chem},e} \quad (11)$$

where ΔG_f is the Gibbs energy of formation, n_e – the amount of molecules or kmol of the element e , and $b_{\text{chem},e}$ – the standard chemical exergy of the element e .

Results

According to the method stated by Trancossi *et al.* [1] and the further considerations expressed here to explain the aim of the expressed considerations, the model has been even if still partially implemented in MATLAB, and the following results have been achieved. First, the chemical exergy of the compound is the energy necessary to form the compound. According to Szargut *et al.* [40], it is calculated by the stoichiometric sum of the chemical elements plus the variation in Gibbs free energy of the element formation at 298.15 K and 101325 Pa.

If organic compounds considered, the formulation by Szargut *et al.* [40] has also been corrected according to Borgert and Moura [41]. They have determined the exergy of the compounds related to the metabolic cycle, taking into account the compounds' concentration

in the environment, ionic dissociations, metal compounds formation, ionic forces, and electric potential. In order to provide a preliminary sample, the authors have calculated the magnitudes related to the cycle of glucose, tab. 1.

Table 1. Two different estimations of chemical exergy in the cycle of glucose according to the original formulation by Szargut [40] and corrected values by Borgert and Moura [42] which account the effect of the concentration of the different compounds

Compound	Elements exergy [kJmol ⁻¹]	Gibbs energy of formation [kJmol ⁻¹]	Chemical exergy [40] [kJmol ⁻¹]	Entropy (B/T0) [kJK ⁻¹ mol ⁻¹]	Chemical exergy [42] [kJmol ⁻¹]
G	3890	-384.4	3505.6	12.16589	3492.4
G6P	4639.3	-1270.6	3368.7	11.69079	3347.2
F6P	4639.3	-1267.8	3371.5	11.7005	3346.8
FDP	5388.7	-2149.4	3239.3	11.24171	3194.8
P	1590.9	-338.4	1252.5	4.346694	1232.9
P pH8	1590.9	-320.4	1270.5	4.409162	1250.9
OA	1887	-690.7	1196.3	4.151657	1173.5
C	3065.6	-908.6	2157	7.485685	2107.5
KG	2533.4	-588.9	1944.5	6.748221	1921.6
S	2121.1	-487.6	1633.5	5.668922	1579.8
F	1885	-498.7	1386.3	4.811036	1320.3
M	2123.1	-637.3	1485.8	5.156342	1448.7
ADP	7263.6	-1364.2	5899.4	20.47336	5810.9
ATP	8131	-225.9	7905.1	27.43398	5784.0
PiH	987.4	-1047.4	-60	-0.20822	-128.7
ADP pH8	7263.6	-1291.8	5971.8	20.72462	5883.4
ATP pH8	8131	-2153.3	5977.7	20.7451	5856.6
PiH pH8	987.4	-1040.6	-53.2	-0.18463	-121.9
NAD	13673.8	1112.9	14786.7	51.31598	14768.1
NADH	13791.9	1178.5	14970.4	51.9535	14946.0
NAD pH8	13673.8	1268.8	14942.6	51.85702	14923.9
NADH pH8	13791.9	1340.4	15132.3	52.51536	15107.9
FAD	16728.3	1510.4	18238.7	63.29585	18215.9
FADH ₂	16964.4	1569.2	18533.6	64.31928	18505.0
H	118.1	0	118.1	0.409856	118.1
H ₂	118.1	0	118.1	0.409856	118.1
O ₂	4	0	4	0.013882	4.0
H ₂ O	9.5	0	9.5	0.032969	9.5
C	15.9	0	15.9	0.05518	19.9
CO ₂	19.9	0	19.9	0.069061	3492.4

The calculation shows that a compound with the same chemical formulation can assume different values. Comparing the results of exergy obtained for glucose with the ones calculated for α-D-Galactose and Sorbose by Wall [42], it appears evident the critical influence on the values of exergy of the molecule structure. Therefore, further analysis on the best coupling of atom counting methods and molecular structure is necessary.

Therefore, it is evident that exergy formulation could perform the analysis according to the Second law with much lower computation requirements than entropy analysis [43, 44].

Conclusions

“Everything we know is only some kind of approximation because we know that we do not know all the laws yet. Therefore, things must be learned only to be unlearned again or, more likely, to be corrected.” Richard P. Feynman

The present response clearly shows the intentions of the preliminary study by Trancossi *et al.* [1]. It does not criticize the appreciable work according to the First law of thermodynamics by Popović and Mincheva. It aims only to discuss the possibility of extending the delivered information with the analysis according to the Second law. In particular, it can be remarked that the analyses according to the First and the Second law of thermodynamics are never alternative. They are only different and complementary ways to comprehend physical and chemical problems better, giving different information on the system and its evolution. The availability of multiple complementary information, even if any of them with precise limits is only an enrichment of scientific knowledge.

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Generally the last paragraph of the paper is the place to acknowledge people (dedications), places, and financing (you may state grant numbers and sponsors here).

Nomenclature

B_{reac}	– exergy content of the reactants	S	– entropy
B_{prod}	– exergy content of the products	\dot{S}	– entropy generation rate
$b_{\text{chem},e}$	– standard chemical exergy of the element e	s	– specific entropy
E	– energy	T	– temperature
G	– Gibbs free energy	T_0	– environment/reference temperature
H	– total enthalpy	T_b	– body temperature
H_{reac}	– enthalpy of the reactants	t	– time
H_{prod}	– enthalpy of the products	U	– total internal energy
h	– enthalpy	V	– volume
\dot{m}	– mass-flow	W	– work
n_e	– amount of molecules of the element e	\dot{W}	– power
P	– pressure	<i>Greek symbols</i>	
\dot{Q}	– heat flow	ΔG_f	– Gibbs energy of formation
		η_i	– stoichiometric coefficient

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