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PERSPECTIVES TO FIGHT VIRUSES. THE EXAMPLE OF SARS-CoV-2

Costas Demetzos [1,*#], Panagiotis Vlamos [2], Dimitrios Vlachakis [3,4,5,6,*]

[1] *School of Health Sciences, Department of Pharmacy, Laboratory of Pharmaceutical Technology, Section of Pharmaceutical Nanotechnology, Panepistimiopolis Zografou, National and Kapodistrian University of Athens, Greece.*
[2] *Department of Informatics, Ionian University, Corfu, Greece.*
[3] *Laboratory of Genetics, Department of Biotechnology, School of Applied Biology and Biotechnology, Agricultural University of Athens, 11855 Athens, Greece.*
[4] *University Research Institute of Maternal and Child Health & Precision Medicine, Medical School, National and Kapodistrian University of Athens, 11527 Athens, Greece.*
[5] *Division of Endocrinology and Metabolism, Center of Clinical, Experimental Surgery and Translational Re-search, Biomedical Research Foundation of the Academy of Athens, 11527 Athens, Greece.*
[6] *School of Informatics, Faculty of Natural & Mathematical Sciences, King's College London, WC2R 2LS, Bush House, Strand, London, U.K.*

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**Corresponding author: First author (senior) demetzos@pharm.uoa.gr, and third dimvl@aua.gr #Ordinary member of the European Academy of Sciences and Arts, Class IV, Natural Sciences*

ABSTRACT

Aim: Coronaviruses well studied in the past provide scientific tools and knowledge that is used for identifying the molecular basis of the new SARS-CoV-2. It belongs to complex systems and its evolution and mutations must be observed under the lens of the nonlinearity as it is far from the equilibrium conditions. The new properties that SARS-CoV-2 carries were incubated for a long time in microcosm refining its information content. Various animal species acted as transmitters of SARS-CoV-2 to human beings. In this perspective article, we argue that the infection ability of the new virus can correlate with its thermodynamic payload. Design: We suggest that by identifying the thermodynamic content and biophysical profile of the viruses' proteins using a mathematical framework of nonlinear complex systems, we can simulate its molecular origin and design weapons for fighting it. We suggest discovering for artificial 'decision-making' nano-platforms that can decrypt the 'crypted information code' of viruses that permit their mutation process taking place not randomly but based on the self-assembly process of its nucleotides following the micro and macro environmental conditions. Main outcomes: Our proposition is to design nanoplatforms (decision making nanocarriers) that can carry thermodynamic variables that could interrupt the mutations, virulence, and proliferation. This approach is innovative and is a challenge that should be checked in the future. This concept needs generous funding by governments for supporting intelligence and innovative research projects. Mainly, we need solidarity between nations to shield the health of societies.

KEYWORDS: Coronavirus; SARS-CoV-2; nanotechnology; nano thermodynamics; nano-platform; biophysics; complexity

1. INTRODUCTION

Coronaviruses belong to the family of coronaviridae and the first one described in human was in 1960s (https://www.cdc.gov/coronavirus/index.html). The family Coronaviridae is enveloped single-stranded RNA virus and this family is divided into four genera: α, β, γ and δ. The first two genera α and β infect mammals and humans, while genera γ and δ infect birds. SARS-CoV-2 is a new coronavirus of the β genus with a crown shaped surface and 60-140 nm diameter. Metagenomic data could be a direction to shield the world population from a future coronaviruses' strain human infection (Menachery, et al., 2015). SARS-CoV-2 contains four different proteins, S (spike protein) which can bind to the receptor of the host organism, and the M and E proteins which are responsible for the structural morphology of virus envelope and the N protein which involves in the assembly of the virus and its genome (RNA) (Yang & Wang, 2020). The structural integrity of SARS-CoV-2 depends on the appropriate sequence and conformational quality of its proteinic cargo to safely wrap its genetic content composed of 29,900 nucleotides of RNA. It is of interest to point out that the coronavirus's genome is bigger than the genome of most of the RNA viruses (The Economist, 2020). The recent published work by J. Shang et al., suggests that the new coronavirus SARS-CoV-2 receptor, is the same as SARS-CoV (ACE2). It is notable that an ACE2 binding-ridge in the new SARS CoV-2 Receptor Binding Domain (RBD) is in more compact conformation (Shang et al., 2020). This is an important finding because the thermodynamic and biophysical stabilization of the conformation could be correlated with the infectious effectiveness of the SARS-CoV-2. Moreover, in the same publication (Shang et al., 2020) the authors present the crystal structure of the SARS-CoV-2 Receptor-Binding Domain (RBD) in complex with the receptor ACE2. This is a finding that encourages efforts towards designing effective medicines and vaccines. The molecular basis that explains the entry of SARS-CoV-2 to the host cells, is achieved by using the so-called spike (S) protein. Moreover, by mapping the residue of the SARS-CoV-2 in comparison to that of SARS-CoV in the ACE2 binding ridge, there emerges a possible thermodynamic gap that should be determined (Shang et al., 2020). From our point of view, such findings should be correlated with the thermodynamic content of the SARS-CoV-2 receptor-binding domain (RBD) complex with the receptor ACE2 and needs thermodynamic and biophysical approaches (García-Iriepa, et al., 2020). The manuscript deals with the thermodynamic profile of the virus SARS-CoV2 and its thermodynamic content. It is obvious that the infection profile is not based only on the thermodynamics of the spike (S) protein. In our point of view, the overall thermodynamic content of the virus's proteins and not only of the spike (S) protein that involves into the proliferation and infection profile of virus, should be evaluated, and calculated using the already exist in silico tools, among others. We must notice that the paper deals with the thermodynamic total profile of virus which is a challenging scientific field and a radical proposition to identify the information content that permits mutations of SARS-CoV-2 and could help the design of new and innovative therapies.

Viruses are open systems that have internal machinery for their entropy production. Klaus Mainzer (Mainzer, 2007) states that 'These systems (i.e., open systems) maintain their structure by dissipation and consumption of energy and are called 'dissipative structures''.

When gradients are large enough, Gibbs free energy becomes available and organized structures emerge in a spontaneous manner, acting to reduce the gradient and dissipate the free energy. In addition to assembly, from a thermodynamic perspective, Popovic et al. demonstrated that the ratio (R) of standard Gibbs energies of growth (ΔrG^{o}) of the virus and the host cell directly affects the hijacking of host metabolic pathways as well as the nature of the viral life cycle (Popovic & Minceva, 2020). This ratio can be summarized as such:

$$R= r(virus)/r(host)=\Delta rG0(virus)/ \Delta rG0(host)$$

After viral entry, if R>1, synthesis of viral components is faster than that of host cell, ultimately leading to a lytic viral life cycle. If R<1 the virions will exit through budding. Differences in Gibbs energy of growth ratios account for a perceived "choice" between lytic and lysogenic cycles when attacking different cell types, as observed in human herpes virus (HHV). It must be noted that even if the condition of a lower virus Gibbs energy of growth is met, the absence of an appropriate receptor can hinder the virus from performing its cycle.

Next to the analog approach, the digital approach is also very close to the information theory (Brillouin, 1962). The entropy (thermodynamics) is related to the available possible states of a system and the level of organization demonstrated. The entropy / information balance of a bio-system such as SARS-CoV-2 is well correlated to its effectiveness and in our point of view should be examined. In the case of SARS-CoV-2

it is possible that its aggressiveness is due to different conformational properties and functionality of proteins, S, M, E and N. Such effects have been studied regarding the thermodynamic changes and biophysical behavior of phospholipidic artificial cell membranes with proteins and antiviral drugs by using Differential Scanning Calorimetry (DSC), SAXS and WAXS (Konstantinidi, et al., 2020). It is important to underline that the information content, thermodynamics, and biophysics, embrace the 'crypted code' and the silent functionality that HIV-1 needs for effective interactions (Binder, Barragan & Menger, 2003). The 'crypted code' is the thermodynamic based variables such as changes of enthalpy (ΔH), of entropy (ΔS), of Gibbs free energy (ΔG) etc. Our suggestion is to calculate through in-depth studies all the above variables using Artificial Intelligence (AI) for accurate calculations and develop artificial nanoplatforms that can carry such information.

Such behavior could be a guide on how an aggressive virus like HIV-1 infect human beings. It should be noted that the relationship between information theory and quantum mechanics is recognized as important and quantum theory is considered as a modern ally against contemporary infections (Konstantinidi, et al., 2020). It is also important to point out that the amount and the quality of information to be obtained from an experiment incorporating quantum mechanics approach, is related to the accuracy of the experimental set-up. The relationship between information and entropy, signals the level of the quality of the organization of the bio-system. In terms of "information entropy", Shannon's entropy measures the lack of information. When this information is "known", there is a reduction of information entropy with a parallel increase in thermodynamic entropy, since there is now predictability of behavior, e.g., mutation rates in biological organisms and viruses. During the system's operation, the decrease in the rate of entropy production provides the opportunity for information gain (Crevecoeur, 2019). In our case the genome of the SARS-CoV-2 is carrying information that is coded in a very elegant manner. Mutations that are normally occurred can be correlated with the effort to maintain for some period in a nonequilibrium state, reducing the entropy content and thus to increase its complexity, gain its survival. The hierarchy of the level of complexity through lyotropic transitions of its genome should enable the production of microstates that influence its macroscopic behavior. Such microstates can provide as an outcome a unique sequence of nucleotides giving rise to new mutations Such mechanisms along with autocatalysis that is used in biomolecular multiplicity, realizes an evolutionary process of biosystems and consequently of viruses. However, discrete configurations of a bio-system are related to the variable P, with the entropy S and information I, (Eq.1) and (Eq.2), respectively.

$$S = k_B \ln Po \quad \text{(Eq. 1)}$$

$$I = k_B \ln (Po/P1) \quad \text{(Eq. 2)}$$

Po is the number of equally probable possibilities; P1 is the number of equally probable possibilities when the Information (I) is given; k_B is the Boltzmann's constant (k_B=1.38064852 x 10^{-23} JK^{-1}) (Brillouin, 1962).

To develop an artificial 'decision-making nano-platform' we need to think of a digitalized performance of the nano-platform. Such digitalized approach could include a copy of the thermodynamic variables of a biological epitope (i.e., the complex of spike (S) protein of SARS-CoV-2, with the ACE2 receptor) and measurements regarding its thermodynamic content. By stabilizing such nanoplatforms they can affect and block the thermodynamic profile of the virus which is related to its virulence and interrupt its proliferation. Such nanoplatforms can be artificial based lipidic nanoparticles such as liposomes or liquid crystals and they can act as 'decision – making' nanocarriers. The 'decision -making nanoplatform' could be the 'lipid rafts' that are located on the surface of lipidic nanoparticles such as liposomes, liquid crystals etc. These 'lipid rafts' can carry the thermodynamic memories that are identified using the already existing tools or by designing new AI based innovative tools. The 'lipid rafts' that can be produced on the surface of artificial membranes as 'decision-making nanoplatforms' can be used for delivering thermodynamic information to interrupt the information flow and multimodal network of the virus and consequently its virulence and proliferation**.** The variables that nano-platforms can carry should be incorporated into the 'lipid rafts' that correspond to lipidic domains (thermodynamically metastable phases in a dynamic and non-linear process). For instance, HIV virus infect cells delivering its information content into the 'lipid rafts' of the healthy cells (Binder, Barragan & Menger, 2003). Such results can offer data that are used as input for the 'decision-making nano-platform'. This process will result in digitalized nano-platforms as apps for rapid and accurate detection of the information content of a biological epitope to detect the immunogenicity in society, as well as for developing nanotechnological platforms for therapeutic and monitoring purposes. Based on the findings dealing with the molecular basis of action and on the well-known way that virus infects human, SARS-like coronaviruses such as SARS-CoV-2,

could be characterized as 'digital hackers' incorporating ancient memories coming from the beginning of the universe, on how they can attack digital computerized machines, like DNA. Such 'digital hackers' are 'experienced and educated' regarding the natural evolution process, in a way that they recognize the biological machine language and the digital code of the mammalians. The human digital code that viruses attack for hacking is the 'crypted code' that is well wrapped into genome (Demetzos, 2016). Viruses composed of RNA replicate themselves based on their 'bulk information' content which is incorporated into their proteinic capsid. They are of high quality and well adapted 'digital machines' which are beyond the current scientific and computer science knowledge. Their 'digital machinery' content permits their mutation process taking place not randomly but based on the self-assembly process of its nucleotides, following the micro and macro environmental conditions. If there is a 'crypted code' that governs the mutation process, like an algorithm that awaits specific parameter values that come from environment changes and interactions with various components, then it would be possible that the mutations realized through self-assembly. By mapping such conditions which act as initiator we can recognize which is the most frequently distributor which promotes the effective mutations. Using a mathematical framework of nonlinear complex systems, we can combine and simulate its molecular origin along with the environmental condition to project its evolutionary process through effective mutations and to develop appropriate weapons for shielding people. To the best of our knowledge indeed, there are methods to measure thermodynamic parameters of e.g., the binding of viral proteins on receptors but not the tools that herein describe. Such tools would not copy the molecular, rather than the thermodynamic imprint of viral components. However, this could be favorable and assist the efforts to develop innovative nanoplatforms that can incorporate virus protein information related to its thermodynamic content.

The emerging concepts of Genomic Intelligence and Bio-Cybersecurity represent inspired efforts towards the unified processing of natural genomic information held within the four-letter, digital code of the genome. Using the work of Turing, Gödel and Post as a foundation, Markose describes the notion of a framework for genomic intelligence, where the genomic immune-cognitive, characterized by a sense of consistency, can detect the attack by a "hacker"/antigen with specific gene code and can ultimately produce a response (Markose, 2021).

To preserve somatic integrity and genetic identity, the immune system is called to set in place a "cyber security" system based on the constant of its genetic code. The immune system continuously overhauls its defensive tactics against these biotic "hackers" which plan to "highjack" gene codes of the target cells. The system orchestrates a response through engineering novel antibodies with precision, as well as by using the MHC receptors of its periphery to update the system's "index" from the basal healthy stage to the "meta record" with the hijacker's specific code after the attack.

The most dangerous effect of RNA viruses on human beings is their ability to effectively attack the human genome stealing information that is of high 'biological value'. According to the information theory by Shannon (Shannon, 1948) and to the entropic approaches, information is the statistically predominant direction of the organization process of the bio-system (i.e., coronavirus) based on the hierarchy of which bio-system is considered as necessary for survival (Shannon, 1948). Szilard argues that "additional information about a system can lead to decrease its entropy…" (Szilard, 1929). We can argue that information means coding and entropy means the amount of information described, and that they are related in the following way:

$$JK^{-1} = 10^{23} \text{ bits} \qquad \text{or} \qquad 1 \text{ bit} = 10^{-23} JK^{-1}$$

Based on findings that the structural morphological changes of SARS-CoV-2 in the ACE2-binding ridge caused by a four-residue motif (residues 482-485: Gly-Val-Glu-Gly) the more compact conformation of the complex, is well understood (Shang et al., 2020). This compact conformation can be correlated with the different information content of SARS-CoV-2 in comparison with that of SARS-CoV. In our point of view, this information gap between SARS-CoV and SARS-CoV-2 could be correlated with the different strength of infection, between these two strains. This concept would be helpful to design personalized therapies.

The practical applicability of the knowledge yielded by an information theory analysis on viral genomic data was demonstrated by Serrano-Solís et al. on another RNA virus, Influenza A virus (Serrano-Solís & José, 2013). Through determining the average information content for each genomic segment of various influenza A subtypes, it became possible for the researchers to estimate the oscillation of information during the course of the virus' evolution. A significant increase of the information level of segment 6 in Influenza A (H1N1)

subtype 2009, was predicted to have an effect on the efficacy of oseltamivir - a widely used anti-influenza drug targeting S6 - against that specific subtype. This example serves to show that the careful analysis of the evolutionary entropy of RNA viruses can have critical implications, from the host immune response to the spread or reemergence of a pandemic and the efficacy of antiviral drugs and vaccines.

The major problems to develop digitalized 'decision-making nano-platforms' are:

- Firstly, to understand in depth the complexity of microcosmos and the invisible dynamic phenomena that are characterized by uncertainty which embrace the evolution of the whole life.
- The second is that viruses can manage the information, based on non-equilibrium processes. Moreover, viruses are able to recognize and to hack ancient 'crypted codes' (Demetzos, 2016). Viruses can identify the complex natural phenomena and can easily decoding the mammalian and the human genome.

We should design artificial 'decision-making nano-platform' using computer and molecular dynamics to behave as the proteinic information content of a real virus.

1. FUTURE PERSPECTIVES

The future project against viruses attack in our point of view, needs deepest scientific investigation using a strong collaboration worldwide with experts in nanotechnology, in biology, in physics, in chemistry, in health sciences, in pharmacology, in molecular dynamics and in computer sciences. Moreover, biophysics, nano-thermodynamics, mathematics, nanotechnology, and topology should be included into the quiver of scientific community. Such collaborations would be more than crucial to establish digitalized therapies and monitoring approaches based on the decoding of the genome sequence and on the information content that is encoded into viruses proteinic capsid. By establishing such knowledge, we can easily map the next coronavirus generation shielding the world population from a new one virus attack

2. CONCLUSIONS

In conclusion, our strong belief is that: virus attacks on the level of information. We should be ready to manage and quickly decode virus's information and to develop as quickly as possible digital tools, protocols, and nano-platforms for therapeutic purposes to fight viruses. The governments and the nations should be sensitive and informed regarding such an 'information war'. As Klaus Mainzer (Mainzer, 2007) states 'It is amazing to recognize that Aristotle's idea of cyclic nature corresponds to periodic attractors or limit cycle solutions of corresponding differential equations. The cyclic nature of these systems allows them not only to develop stability but also to develop hierarchy of complex structures within themselves. A cycle of living systems as it was already described in antiquity becomes autocatalytic by virtue of an evolutionary feedback.' Finally, the solidarity between nations should be unambiguously considered as a priority, while the human values and human dignity should be protected.

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