SARS-CoV-2 Infection—Of Music and Mechanics of Its Spikes! A Perspective

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ABSTRACT: The COVID-19 pandemic has been inflicted upon humanity by the SARS-CoV-2 virus, the latest insidious incarnation of the coronaviruses group. While in its wake intense scientific research has produced breakthrough vaccines and cures, there still exists an immediate need to further understand the origin, mechanobiology and biochemistry, and destiny of this virus so that future pandemics arising from similar coronaviruses may be contained more effectively. In this Perspective, we discuss the various evidential findings of virus propagation and connect them to respective underpinning cellular biomechanical states leading to corresponding manifestations of the viral activity. We further propose avenues to tackle the virus, including from a “musical” vantage point, and contain its relentless strides that are currently afflicting the global populace.

KEYWORDS: SARS-CoV-2, COVID-19, vaccines, mechanobiology, spikes, music, D614G, disulfide, ACE2, GSH, GSSG, endocytosis, dorian, lipid rafts, Egmont, Remdesivir, Cobicistat, Ritonavir, Lopinavir, Darunavir, peptide, piezoelectricity, hydrogen bonds

The aesthetically beautiful virus SARS-CoV-2 has wreaked untold misery on the human population since it raised its ugly head in late 2019. Indeed, the ubiquitous image of the virus (Figure 1) has been imprinted forever in the collective human consciousness! The popular depiction of the almost symmetric structure of the SARS-CoV-2 virus consists of a spherical interior on the surface on which are displayed reasonably uniformly distributed spikes. The spherical core and envelope protein of the SARS-CoV-2 virus has been suggested to be practically resistant to mutations,1 with mutations being mainly restricted to its spikes, i.e., the crowns that stick out of the sphere-like structure. A genomic epidemiology report estimated approximately 1 mutation per 1000 bases for the SARS-CoV-2 virus, i.e., a mutation propensity lower than that of the common influenza virus that averages 2 mutations per 1000 bases and HIV with an average of 4 mutations per 1000 bases. Also, among the three coronaviruses, viz. SARS-CoV-2, SARS-CoV, and NL63, that utilize angiotensin converting enzyme 2 (ACE2) as the host receptor, the mutation rate of SARS-CoV-2 has been estimated to be very low in comparison to the other two.3,4 However, more recent research has suggested that a specific mutation, D614G, in its spikes changes the mechanical stability and the density of the spikes, making it easier for such a mutated SARS-CoV-2 variant to infect the host cells.5−8 These revealing facts suggest that the mechanics of SARS-CoV-2’s spikes will be a major determinant of the efficacy of vaccines and drugs developed in response to this virus. As well, mechanobiology, driven by molecular chemistry, of the host’s cell membrane should play an equally important role in the susceptibility/efficacy for infection of this virus. Consequently, any study that sheds light on the mechanics and the ensuing mechanobiology involving the spikes of SARS-CoV-2 and the host organism’s cell membranes should be of prime importance and should be highly encouraged.

The spikes of SARS-CoV-2 are known to attach to the ACE2 sites of cellular membranes and deliver its genetic signature in the form of RNA that eventually leads to its replication and overtaking of the host organism.9,10 ACE2,11,12 in general, is a zinc metallopeptidase that has been implicated in regulating heart function, hypertension, and diabetes; however, it has also been discovered surprisingly to serve as the cellular entry point for the severe acute respiratory syndrome (SARS) virus, in

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Thus, from a basic molecular structure/chemistry point of view, a disruption of the SARS-CoV-2 spike protein’s folded three-dimensional structure should hamper its ability to attach to the specific binding sites of ACE2. Alternatively, a modification of the ACE2 binding sites’ structure should also facilitate the prevention of the virus docking to/at such entities. In this regard, recently, it was hypothesized that there is a tight coupling between cell mechanics, the activity of chromatin remodeling enzymes and NF-kB induced gene expression programs during SARS-CoV-2 propagation. It was further postulated that coronaviruses can potentially take advantage of the altered mechanical state of cells in aging hosts for their replication and propagation, hence, older persons being more susceptible to the virus.

In that context, an understanding of the molecular structure of the active ACE2 sites in the cell membrane and cytoskeleton as a function of a person’s age should be illuminating. It has been well-established that, as we age, such cellular constructs undergo cumulative “oxidative stresses” caused by reactive oxygen species (ROS) such as free radicals, peroxides, lipid peroxides, and heavy metals. The management of such oxidative stresses experienced by our bodies is undertaken by a finely regulated interaction of the ROS with the tripeptide glutathione. Humans and other animals can naturally produce glutathione. Glutathione exists in reduced (GSH) and oxidized (GSSG) states. The ratio of reduced glutathione to oxidized glutathione within cells is a measure of cellular oxidative stress where an increased GSSG-to-GSH ratio is indicative of greater oxidative stress. In healthy cells and tissue, more than 90% of the total glutathione pool is in the reduced form (GSH), with the remainder being in the disulfide form (GSSG). The thiol/disulfide balance during aging suggests that there is a decrease in plasma glutathione and cysteinylglycine with a concomitant increase in the oxidized forms of thiols. Since individuals with preexisting conditions such as high blood pressure, diabetes, lung diseases, etc. have undergone greater oxidative stresses, their GSSG-to-GSH ratio and consequently the amount of disulfide bonds in their cellular constructs will be high, especially near and at sites such as ACE2. It is also known that the thiol to disulfide conversion can be modulated by mechanical stress in addition to oxidative stress. For example, protein disulfide isomerases, a group of enzymes responsible for effects including thrombosis, nitric oxide internalization, and virus internalization has been seen to be an upstream organizer of cytoskeletal mechainoadaptation in vascular smooth muscle cells. Microthromboemboilis is known to be one of the manifestations during the COVID-19 pathogenesis. The above commentary on the state of the disulfide versus thiol entities in cell membranes and cytoskeletons is particularly relevant with regard to SARS-CoV-2 infection and propagation since the spike proteins of SARS-CoV-2 are known to contain up to 13 different disulfide units that are distributed broadly in about four regions in the spike. A recent study proposed that the age-dependent decline of low molecular weight thiol/disulfide ratio of the extracellular fluids could play a role in promoting the protein–protein interaction of the spike proteins of SARS-CoV-2 and the host cells in the airways. Another recent molecular modeling study reported that the binding affinity of the SARS-CoV-2 spikes to the ACE2 sites was significantly impaired when all of the disulfide bonds of both ACE2 and SARS-CoV-2 spike proteins were reduced to thiols groups. The study also found that the impact on the binding affinity was less severe when the disulfide bonds of only one of the binding partners were reduced to thiols. This suggests that disulfides in ACE2 provide “binding” or “docking” sites for disulfides and/or thiols in SARS-CoV-2. Hence, any targeted disruption of such sites can be hypothesized to alleviate COVID-19 infection of cells. Such disruptive forces could include mechanical forces as suggested above seen during the modification of behavior of protein disulfide isomerase. Specifically, it would be interesting to see how such mechanical forces/stresses affect the fine balance of the thiol/disulfide equilibrium. Generally, in this context, one of us has modeled the response of the viscoelastic properties of tau proteins and its impact on the microstructure of the axonal cytoskeleton during an axonal stretch injury such as traumatic brain injury (TBI). Above a critical strain rate, the microtubules in the axons were found to undergo mechanical breaking with rearrangement of the various bonds in the protein’s folded structure. Separately, during a TBI scenario, the occurrence of intracellular protein cross-linking has been attributed to intrachain disulfide formation, leading eventually to cell death. While, understandably, such extreme conditions of mechanical strains may not be experienced during a virus infection scenario, the collective strain instances that a person experiences in one’s lifetime should accumulate as a function of age and individual-specific, literal mechanically stressful exposures and would affect the integrity of the fine structures of cellular membranes. In fact, with regard to TBI, the effect of such mechanical strain has been found in females to be elevated compared to that in males, especially in the microtubules, with the female axons being consistently smaller with fewer microtubules than male axons. In contrast, interestingly, it has been also seen that with regard to the propagation of SARS-CoV-2 and other similar viruses that females are less susceptible than males due to the presence of an extra X chromosome. However, this appears reasonable as the ACE2 gene lays on X chromosomes, thus allowing females to be potentially heterozygous and
differently assorted compared to males who are hemizygous. In fact, several genes involved in inflammation have been located to reside on the X chromosome, which also contains a high number of immune-related genes responsible for innate and adaptive immune response to infection.25,26 The presence of the extra X chromosome and its impact on the propensity for strain-induced modification/mechanotransduction of COVID-19 infection in females versus males will indeed be an interesting aspect to explore in future work.

With regard to COVID-19 infection, one of us recently expounded on the molecular vibrations of the spike protein in the SARS-CoV-2 virus and the specific vibrational signature or “musical structure” that is inherent in such an ensemble of proteins.27 Specifically, the musical representation of the spikes of SARS-CoV-2, based on the molecularly visualized version (Figure 2) of its Protein Data Bank (PDB) ID 6ves structure, was demonstrated to produce a complex musical arrangement, featuring an array of melodies interwoven and reflecting the complex hierarchical folded geometry. The differences in tones were related to the vibrational symphony that occurs during distinct physiological event, i.e., infection, propagation versus replication. A similar approach has also been utilized to represent the moment of infection, as realized in a piano composition.27 This piece is the musical reflection of infection (Figure 3), the moment during which the virus interacts with the cell, a microscope into the details of molecular motions of attachment and release. Additionally, such vibrational and associated mechanical events should also be able to produce specific electronic rearrangements at defined regions in the 3D ensembles of proteins. For example, viruses, amino acids, and proteins have been known to produce noncentrosymmetric organizations, leading to piezoelectricity upon mechanical strain due to an enhancement in the collective dipole moments.28 One of us recently reported on such a system possessing an enhanced collective dipole moment due to the specific placement of distinct (i.e., β) peptide bonds within cyclic amino acid rings in an ensemble peptide nanotubular structure.29 Mechanical transformations/defor mations of such protein structures as a function of temperature, pH, and ion concentrations can also produce appreciable local electronic perturbations which could reasonably alter the folded structure of a similar functional protein in action.

From the preceding, the nature and extent of hydrogen bonding (i.e., intra- versus interchain H-bonding) in these proteins can also be expected to have an important impact on the activity of the virus including that caused by nanoconfinement.30−32 Generally, this particular phenomenon is very common in most reversible protein/polymeric systems with physiological functions such as in the muscle actin/myosin proteins wherein the inclusion or exclusion of water, contained in cellular intrafluid, during a mechanical activity such as the stretching or relaxation of such proteins causes a reversible change in the intra- to interchain H-bonding in such systems.33 Such reversibility ensures that the structure of the system is not permanently altered; however, it is altered enough to facilitate the necessary physiological function. In a similar way, the efficacy of SARS-CoV-2 propagation will depend on the maintenance of its precisely folded structure and, particularly, that of its spikes. Any perturbations to such finely balanced hydrogen-bonded structure can be expected to lead to a loss in efficacy of propagation causing it to be ineffective. Recently, a similar effect caused by known peptide pharmaceuticals such as Cobicistat, Ritonavir, Lopinavir, and Darunavir, all peptide-like, small molecules, on the hydrogen-bonded structure of the SARS-CoV-2 virus has been reported. These small peptide-like molecules, being hydrophilic and owing to their amide bond containing backbone, were able to have the necessary flexibility to fit optimally inside the binding site of the SARS-CoV-2 spikes in the PDB structure 6YF2F and bind to the spike residues forming hydrogen bonds and a salt bridge with Gln-192, Glu-166, His-166, and His-41 residues, thereby altering the spikes’ 3D-folded structure, leading to disruption of its activity.34 In a recent report, a dynamic optimization AI-based platform was utilized to explore the drug−dose parameter space to identify drug−drug interactions to rank optimal drug−dosage combinations from a diverse set of 12 drugs that are currently being explored in various clinical trials to combat the SARS-CoV-2 virus.35

Figure 2. Molecular visualization of the SARS-CoV-2 virus’ spike protein, depicting the structure of the three folded, interwoven protein chains.

Figure 3. Visualization of the SARS-CoV-2 virus’ spike protein (outer left part) interacting with the ACE2 receptor in complex with a membrane protein that it chaperones (B0AT1) (right part).
Remdesivir in combination with peptide-like drugs Ritonavir and Lopinavir as an optimal regimen against COVID-19, once again pointing to the efficacy of peptide-like structures to disrupt SARS-CoV-2 activity. Furthermore, an increase in acidity at the local environment of ACE2 binding sites can also be expected to facilitate the conversion of disulfide to thiois near such site. Such increased acidity should also be able to disrupt the hydrogen-bonded folded structure of SARS-CoV-2 spike proteins. Consequently, any drug capable of selectively enhancing local acidity around ACE2 sites should be able to affect the mechanism of the virus binding. Also, any mechanical stress that impact the hydrogen-bonded folded structures of SARS-CoV-2’s spikes can be expected to disrupt its infection ability.

Previous incidences of viral epidemics such as SARS and MERS have impelled biophysicists to explore the physical aspects of mechanisms of viral entry into the host cells. Specific interactions of a dynamic nature such as receptor-mediated membrane adhesion, believed to be the first step of viral endocytosis, have been explained from an energetics perspective. The viral contact with the host cell initiates at a nucleation site on the host membrane where the ACE2 receptor concentration per unit membrane surface area is sufficiently high to permit an increased chance of S (spike) protein ligand—ACE2 receptor binding. Once the viral spike protein binding has been initiated, a temporal progression of the membrane adhesion during endocytosis needs energy to be expended by the virus—cellular substrate system. An initial, entropy-maximizing receptor distribution on the host cell membrane is disturbed by free energy perturbations during the binding process leading to a dynamic redistribution of the receptors on the host cell membrane. Such a redistribution, in conjunction with the binding of previously free receptors, results in a reduced receptor configurational entropy, with an associated free energy cost. The elastic flexural and tensile energy is additionally required for the bending and stretching of the host cell membrane to conform to the shape of the approaching extraneous viral particle and receive it for inclusion. Many epithelial cells, the targets of the SARS-CoV-2 in the upper respiratory and alveolar system, feature a fuzzy extracellular protein matrix of the glycocalyx, which may need to be navigated through to permit a receptor—ligand binding, further escalating the energy expenditure. Additional weaker components such as an energy hill associated with van der Waals forces might play minor roles in the energy landscape of the virus—cellular substrate systems, as well. The driving force for the system, which “pays” for the energy costs, arises from the reduction in internal energy after each ligand—receptor bonding is realized. The competition between these energy components reveals a parametric regime over which viral endocytosis becomes thermodynamically favorable. Shenoy and Freund established that the ratio of ligand to receptor density plays a significant role in establishing the temporal growth and stability of the adhesion front. Gao et al. were able to numerically evaluate the optimal shape and optimal ligand density for the spherical virus to capture the chemomechanical coupling between membrane elasticity, receptor protein diffusion kinetics, and ligand binding. Assuming a hyperelastic behavior for the bilipid layer, the model predicts that the active receptors localize with lipid rafts and can further enhance raft formation. A receptor-rich microdomain over a lipid raft might exceed the threshold receptor density requirement according to classical nucleation theory and in proximity of viral ligands might serve as ideal nucleation sites. However, unlike the colocalization of HCoV-229E receptors CD13 with lipid rafts, the colocalization of ACE2 receptors with lipid rafts is not an established phenomenon. Yet it is known from in vitro experiments that lipid rafts play a salient, though not clearly understood, role in the viral entry process. In mechanistic studies exploring how SARS-CoV-2 invades host cells, infection by the virus was found to be cholesterol-rich lipid-raft-dependent. Cholesterol depletion studies of cell membranes with methyl-β-cyclodextrin was found to result in reduction of the virus infection. Hence, a better understanding of various viral endocytic mechanisms adhered by the SARS-CoV-2 virus and its associated mechanobiology is being sought urgently, and biophysical models present a promising method of analyzing their associated mechanobiological principles.

As discussed previously, the mutation D614G in the spikes of SARS-CoV-2—likely that of other variants—is seen to change the mechanical features of the spikes, and hence a SARS-CoV-2 virus ensemble carrying such a mutation is seen to have a greater density of spikes and, consequently, a greater propensity for infection. This makes one wonder about the mechanobiology of the D614G mutation and its effect on the infection ability! Specifically, what aspect of the D614G mutation, or those of other variants (i.e., the sequence of base pairing, etc., and perhaps other internal H-bonding, disulfide bonds, etc.) is it that changes its mechanical integrity and how the mechanisms of interaction with the cell receptor proceeds. Also, once it mechanically changes the structure of the spike, and especially the way it moves, vibrates, and hence interacts with other soft matter, what effect does such fortification of the structure have on the spikes’ ability to infect, i.e., to attach to ACE2 sites? Does such fortified spikes display external disulfide bonds in an “optimal configuration” to interact with similar disulfide bonds on the ACE2 sites?
Appropriate mechanobiological investigations should be able to shed light on such phenomena, building on evidence from earlier work that vibrational and mechanical features are important for the self-organization of biomaterials such as elastin.

Expanding further on the preceding nanomechanical analysis of the structure and motions of atoms and molecules at multiple scales, the sonified versions of the coronavirus spike protein of SARS-CoV-2 was realized in the dorian mode with its pleasing note. In a way, this perhaps is a metaphor for the nature of the virus to deceive the host and exploit it for its own manipulation. From an energetic point of view, such pleasantness would suggest a perfect matching between various significant vibrational frequencies and energies of the SARS-CoV-2’s spike proteins and the ACE2 binding sites, suggesting that the sonified version of the ACE2 binding sites should perhaps also resonate in a similar dorian mode. This is not at all surprising in light of Hati et al.’s finding of the presence of compatible disulfide bonds in both the spikes of SARS-CoV-2 and the cytoskeletal ACE2 sites. Logically, the subsequent entry and replication by the virus should then be expected to produce disharmony in notes, i.e., overpowering counterpoints, between that of the invader and the rest of the physiological cellular machinery that is being attacked. We also suggested that one possible engineering task to stopping the virus was by creating protein molecule, through counterpoint composition, that binds specifically to the virus spike, thereby shutting down the pathway of infection. This would be akin to a scenario where the disharmonious note, or frequency, is introduced to the virus via a vaccine or a pharmaceutical drug prior to the susceptible cells being lulled by the “pleasant notes” of the virus to their eventual extinction. From a musical vantage point, one could think of those countercounters to be such as in the final “victory symphony” contained in the brilliant coda of Beethoven’s Egmont Overture where the valiant Count Egmont’s death scene is so magnificently captured! However, in a wonderful twist to the ending of the valiant and tragic fate of Egmont in the Overture named after him, in the current scenario, the allegory would not be that of a few sacrificial ACE2 Count Egmonts laying down their lives against the invading SARS-CoV-2 marauders, rather valiant and clever ACE2 Count Egmonts ultimately prevailing in the fight against such insidious invaders! Furthermore, it would be illuminating to analyze how the fortified and dense disposition of spikes contained in mutated spikes of various variants affect the “resulting music”, building on the concept of transmodal exchange of information via categorization

Additionally, with regard to airborne transmission of SARS-CoV-2 virus, it has been suggested that the virus tends to be deactivated in humid and hot conditions. In this regard, a detailed study of the interaction and effects of humidity (water) and temperature (resulting from rapid motion of water, gases, and other particulates in air) and pH (acidity) in the environment with folded structures of spike proteins of SARS-CoV-2 will provide a distinct understanding of the stability of such structures in the environment and its transmission rate. In line with our sonification study, one has to then explore and arrive at the various collective notes and symphonies that are produced by these elements and what their effects are on the music of SARS-CoV-2. Are these counterpoints produced and exerted by the various elements overpowering enough of SARS-CoV-2’s innate “musical signature” or, more generally, its vibrational feature that may influence how spike proteins bind and interact with cell receptors? Also, what optimum combination of such elements would produce such a destructive counter point on the SARS-CoV-2’s melody? This then also brings us to the effect that external sound, i.e., a purposeful excitation of various gas molecules can have on the viscoelastic property and stability of SARS-CoV-2, i.e., on the mechanobiology of this virus. Considering the virus as a material, not merely a biochemical structure, could the magnitude of such an exerted force, i.e., sound signal, cause enough rotational, vibrational, and possibly some piezoelectricity-induced perturbations to the structure of the SARS-CoV-2 virus and its spikes so as to permanently damage them? In simpler words, can sound destabilize the SARS-CoV-2 virus? Can we use specific frequencies of sound to destroy specific amino acids in SARS-CoV-2 virus and ultimately destabilize/destroy it? Perhaps using a carefully crafted and lethal sound dose such as a hypersonic boom of an aircraft? While it may not be music to our ears in the literal sense (figuratively, it certainly isn’t!), it may wreak untold misery on the virus. Defensibly, one’s melody is another’s misery!

Finally, since the writing of this Perspective several other new mutations of SARS-CoV-2, such as Delta (B.1.617.2) and Omicron (B.1.1.529), have appeared and caused further indescribable misery on humanity. While the morphological features especially of their spike proteins vary reasonably from the D614G mutation, the underpinning mechanobiology and other transmissivity sciences remain quite similar. In fact, such sciences are also commonly shared among many transmissive respiratory viruses. As there will certainly be other future endemic and pandemic viral attacks on humanity, the several questions and hypotheses that we have posited here are worthy of further investigations as they are and would be generally valid in the present and future viral attack scenarios. More importantly, our suggestions encompass the totality of environmental survivability, transmissibility, and infectivity of such viruses and also the health, gender, and age of the person who is being infected. Understandably, in this Perspective, although we have not addressed the long hauler COVID-19 effects that some persons who have been infected with the virus suffer, it is possible that some of the mechanobiological changes that we discussed above upon SARS-CoV-2 viral infection are irreversible or at a minimum are reversible at a long time scale. This, perhaps, leads to manifestations of such long hauler syndromes. It is also likely that such irreversible events occur at organs with most oxidative stress damages such as heart, lungs, etc. It would be very instructive and useful to study such effects so that these remnant effects of COVID-19 can also be addressed in the future. It is our hope that such a concerted and focused addressing of these aspects may be useful to lead to more effective breakthroughs in the fight against pandemics such as COVID-19 and its long-term effects and, in the first place, may also prevent the transition of these viruses from an endemic to a pandemic state.

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