Physicochemical properties of respiratory droplets and their role in COVID-19 pandemics: a critical review

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Key Words:
aerosol; COVID-19; evaporation; pandemic; respiratory droplet; virus

From the Contents

ABSTRACT

The ongoing coronavirus disease 2019 (COVID-19) pandemic is a serious challenge faced by the global community. Physical scientists can help medical workers and biomedical scientists, engineers, and practitioners, who are working on the front line, to slow down and eventually contain the spread of the COVID-19 virus. This review is focused on the physicochemical characteristics, including composition, aerodynamics, and drying behavior of respiratory droplets as a complex and multicomponent soft matter system, which are the main carrier of the virus for interpersonal transmission. The distribution and dynamics of virus particles within a droplet are also discussed. Understanding the characteristics of virus-laden respiratory droplets can lead to better design of personal protective equipment, frequently touched surfaces such as door knobs and touchscreens, and filtering equipment for indoor air circulation. Such an understanding also provides the scientific basis of public policy, including social distancing rules and public hygiene guidelines, implemented by governments around the world.

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic has been causing great loss of lives and negative impacts on the global economy. People across the world have been struggling to contain the spread of COVID-19.[1] The general public is guided to wear face masks and adopt social distancing and enhanced handwashing measures.[2] Doctors and healthcare workers are working on the front line to provide tests on possibly positive cases and take care of infected patients. Biomedical researchers are actively developing vaccines[3] and seeking anti-viral drugs for the treatment of COVID-19. Epidemiologists are collecting a large amount of data and constructing statistical models to predict the trend of the pandemic.[1, 4]

Researchers in physical sciences can and should make contributions to the ongoing combat against COVID-19.[5] In addition to the design of new personal protective equipment (PPE) with improved performance by optimizing materials and structures,[6] researchers in physical sciences can take part in revealing the transmission mechanisms of the virus. While the microscopic process of virus infection is a topic for molecular biology,[7] the transmission of a virus from person to person and the ultimate outbreak of a pandemic is an intrinsically interdisciplinary multi-scale problem that requires concerted efforts of researchers in different fields including physical sciences. Below we first provide an overview of the transmission pathways of respiratory tract viruses, the structure and composition of the COVID-19 virus particles and the virus-laden respiratory droplets, and then discuss research opportunities for physical scientists.

Overview of Transmission Pathways

It is well established that the transmission route of respiratory tract viruses including that causing COVID-19 begins with the release of respiratory droplets by an infected person through respiratory activities such as breathing, speaking,

coughing, and sneezing.[8, 9] These droplets are polydisperse with sizes ranging from about 1 µm to about 2 mm.[10-14] The size of a droplet plays an important role in determining its fate, as illustrated in **Figure 1**. (1) Large droplets (≥ 100 µm) fall to the ground or any open surface, such as the surfaces of door knobs, desks, handrails, and touchscreens, because of gravity. Viruses in these large droplets are transmitted to a healthy person if the person touches the surface contaminated by the droplets or the desiccated remains of the droplets.[15, 16] (2) Intermediate droplets (~10–100 µm) can defy gravity and be carried by an airflow. The droplets can then be inhaled by a healthy person, completing the droplet transmission of viruses. The reduction of droplet size resulting from the evaporation of water, which is the major liquid content of a respiratory droplet, further facilitates the droplet transmission.[17] (3) Small droplets (< 5 µm) can dry quickly. However, small droplets and droplet nuclei resulting from desiccation can be suspended in air for an extended period and form the so-called aerosol.[16, 18-21] Viruses in an aerosol can be transmitted to a healthy person through direct inhalation. This process can occur over a long distance (~5 m) from the source of droplets, in contrast to the short-range transmission caused by intermediate and large droplets, which typically takes place close (1 to 2 m) to the source.
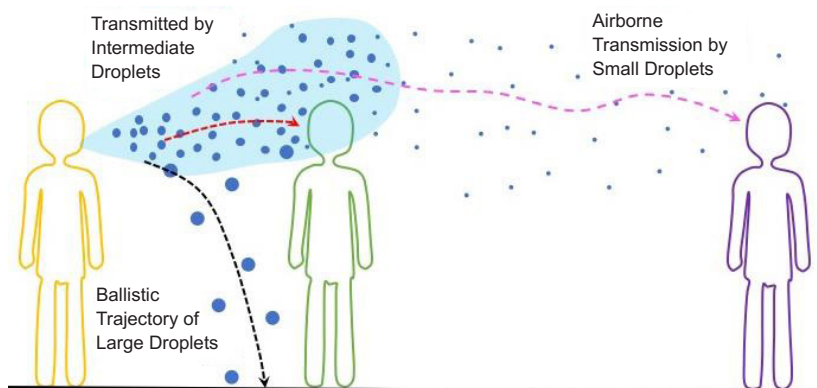

Figure 1. Schematic illustration of the different transmission routes of respiratory tract viruses via large (≥ 100 µm), intermediate (~10–100 µm), and small (< 5 µm) droplets.

In order to cause a new infection, viruses need to get into the body of a healthy person. Touching infectious virus-laden droplets or droplet nuclei deposited on an open surface followed by touching face immediately brings the viruses in contact with eyes, nose, and mouth. Droplets or droplet nuclei inhaled by a person can continue to travel inside the respiratory tract.[22] Larger ones are deposited in the upper respiratory tract, such as the nasal cavity and throat. Smaller droplets can reach the lower respiratory tract, travel through the hierarchy of the human lung structure, and eventually arrive at the alveoli. During this process, water may condense onto the inhaled droplets, enlarging them and facilitating their deposition on the surface of the human air pathway. No matter how and where the viruses are deposited, the viruses in the new host go through the mucus layer and subsequently penetrate the mucous membranes to enter healthy cells and multiply themselves.[23, 24] The new viruses generated then infect nearby healthy cells, migrate to other parts of the body, and ultimately lead to various symptoms.

Brief Description of Coronavirus Particles

A coronavirus particle possesses a core-shell structure,[7] as shown in **Figure 2**. At the core, there is a single-strand RNA enclosed by nucleocapsid proteins, which adopts the conformation of a tightly packed coil. The core is enveloped by a lipid bilayer membrane decorated with various proteins, including the "corona" formed by spike proteins. The diameter of a coronavirus particle can vary from about 60 nm to about 140 nm, with a typical value about 100 nm. After a virus particle enters a host cell, it releases its genetic materials, which then exploit the machinery of the host cell to make components needed to form new virus particles through a biological self-assembly process. To maintain infectivity, the lipid layer of a virus particle must remain intact through the entire transmission process before it invades a host cell. The lipid layer may be compromised by chemical sanitization using alcohol or through physical processes such as heating and desiccation, thus deactivating the virus. Therefore, a deeper understanding is needed on how the structure and activity of a virus particle are affected by the physical processes occurring during the transmission of respiratory droplets.

Composition of Respiratory Droplets

A respiratory droplet is a complex, multicomponent soft matter system, as shown in **Figure 3**. It is overly simplified by treating a respiratory droplet exhaled by an infectious patient as an aqueous solution of virus particles. Instead, various nonaqueous components are present in the droplet.[5, 25-28] Some representative nonaqueous components are listed and described in **Table 1**. The mass fraction of the nonaqueous components in a respiratory droplet is typically a few percent, but far exceeds that of the virus particles. The presence of these

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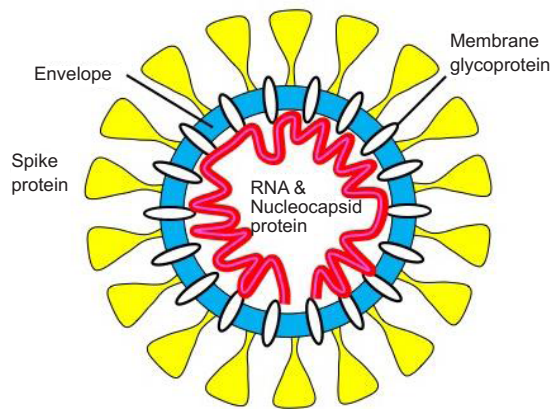
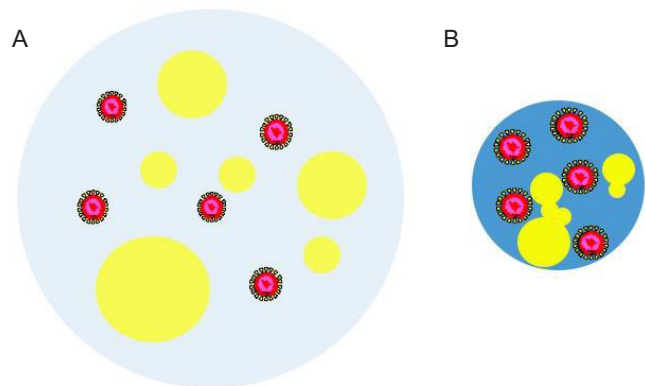**Figure 2.** Structure of a coronavirus particle.

Figure 3. Schematic illustration of a virus-laden respiratory droplet after being released by an infected person (A) and after the loss of some water content through evaporation (B). The water part of the droplet is colored light blue in A while blue in B. Yellow "bubbles" of various sizes indicate the nonaqueous components such as salt, proteins, and surfactants. The virus particles are drawn as core-shell structures with the core colored in red.

Table 1. List of representative nonaqueous components in a respiratory droplet

Nonaqueous components	Brief description
Salt and lactate	Soluble, present as charged ions
Cholesterol	Insoluble, non-polar (except for the hydroxyl group at one end)
Proteins and enzymes	Amphiphilic, net charge depends on the sequence of amino acids and pH
Lung surfactants	Amphiphilic mixture of phospholipids and proteins
Cell debris	Organic waste from epithelial and immune system cells
Bacteria	Most bacterial cell walls carry negative charges
Viruses	pH-dependent surface charges

nonaqueous components has a strong influence on the drying behavior of the droplet in an airflow and on various surfaces, as well as the viability and transmissibility of the viruses contained in the droplet.

Evaporation of Respiratory Droplets

Water evaporation is a basic physical process during the person-to-person transmission of virus-laden respiratory droplets. As illustrated in **Figure 3**, water evaporation directly affects the size of a droplet and thereby the probabilities of it being carried by an airflow, falling on an open surface, and depositing on the surface of a respiratory tract.[22, 29, 30] Moreover, evaporation affects the composition and structure

of the droplet and hence the microenvironment of the viruses within.[31-33] Virus particles only occupy a small fraction of the droplet. The infectivity of the virus is directly affected by the pH and salt concentration,[34-36] which are changed by the loss of water during evaporation.

Trajectories of Respiratory Droplets

The person-to-person transmission of virus-laden droplets involves their trajectories in an airflow. A droplet trajectory is affected by multiple factors including the droplet size, the initial velocity of the droplet at the source, gravity, and the drag force experienced by the droplet in the airflow.[30, 37, 38] Turbulent flow with the irregular and chaotic movement of

gas molecules is ubiquitous in respiratory activities as well as in aerodynamics.[39-42] Turbulence affects both the initial conditions of the droplets generated by respiratory activities and their trajectories afterward in the airflow. It can greatly extend the range traveled by a droplet. The stochastic nature of turbulent flow gives rise to the murky and sometimes inconsistent size criteria for dividing the droplets into small, intermediate, and large categories and associating droplet size to different transmission mechanisms. Additionally, because of the stochasticity of the droplet trajectories, the 2-m or 6-feet social distancing is an empirical measure that allows the majority but not all large droplets to fall out of an airflow. Further studies of the role of turbulence can help optimize the barriers in PPE for droplets of various sizes and improve the rules guiding social distancing. It can also help design effective equipment and procedures to filter potentially contaminated air for indoor air circulation.

Suggestion for Future Research
Physicochemical characterization of respiratory droplets

To understand the role of respiratory droplets in transmitting the COVID-19 virus (and many other respiratory viruses), it is crucial to have reliable methods to characterize respiratory droplets at various stages after they are released into air. Many physical attributes need to be measured for a droplet, such as size, drying rate, composition, internal pressure, pH value, internal distribution and structure of nonvolatile substances including virus particles, and diffusivity in air. These attributes largely determine the fate of a droplet and thus the transmission pathway.

Various characterization methods,[43, 44] such as fluorescent microscopy and spectroscopy, surface tensiometry, X-ray and neutron scattering, cryo-transmission electron microscope, and atomic force microscope, can be used to measure the physicochemical attributes of respiratory droplets. For example, droplet size and its distribution may be measured by droplet deposition analysis and light scattering method.[45] The attributes of a droplet are strongly correlated and the correlations can be used to deduce certain attributes from others. For example, a charged droplet can be placed in an electric field and its size can be deduced by measuring the mobility of the droplet. Droplet velocity in air can also be measured with an aerodynamic particle sizer that utilizes laser beams separated by a small distance to measure the time needed by a droplet to travel that distance.[45] The measured velocity can then be used to deduce the aerodynamic diameter of the droplet. The diffusivity of a droplet in air is determined by its size, air viscosity, and temperature. The variation of droplet size over time can be used to deduce its drying rate, which in turn is affected by the distribution of surfactant molecules in the droplet. Such a distribution sets the surface tension of a droplet, which together with the droplet size determines the internal pressure of the droplet through the Young-Laplace equation. As the size and composition of a droplet change with time, its pH value varies accordingly. The measurement of the structure and distribution of nonvolatile substances in droplets is more

challenging and typically requires collection of exhaled droplets followed by chemical analysis through various spectrometric methods. A broad spectrum of characterization tools, such as those from colloidal science[43] and physical chemistry,[46] can be harnessed to measure the physicochemical properties of respiratory droplets and the results can be combined to yield a complete picture of their dynamics and structural evolution in an airflow, which will provide valuable insight into their capability of transmitting the COVID-19 virus.

Evaporation of droplets in airflows

The evaporation of droplets is driven by the difference between the partial vapor pressure at the droplet surface and the ambient vapor pressure. Both the rate of evaporation and the ultimate droplet size after evaporation are affected by the relative humidity (RH) and temperature of the ambient environment.[40, 47] The dependence of droplet evaporation on ambient conditions is the key to understanding the seasonality and variation by geographic regions of the outbreak of respiratory virus diseases. Evidence has shown that an outbreak is more likely to peak in winter and in regions with cold and dry climates.[48] Inside the respiratory tract, RH and temperature affect the evaporation of an inhaled droplet and the inverse process of water condensation onto the droplet,[22, 49] thus influencing its probability of depositing onto the surface of the respiratory airway.

Evaporation of a liquid droplet at quiescent conditions has been studied both experimentally and theoretically. However, evaporation of droplets in a laminar or turbulent airflow, both of which occur along the transmission path of viruses (**Figure 4**), need to be systematically studied. For experiments, an airflow mimicking that along the trajectories of droplets at various conditions needs to be introduced around the suspended liquid droplets. For theoretical research, an airflow may be incorporated as the boundary conditions for the droplet undergoing evaporation. A theoretical study of evaporation in turbulent flow would be more challenging than that in laminar flow, as the theoretical description of turbulent flow relies on an appropriate turbulence model and thus is more complex. Nevertheless, the study including a turbulent airflow is significant given the ubiquity of turbulence along the droplet trajectory. Investigating the physics of evaporation in an airflow, in particular, the dependence of the evaporation rate and droplet size on RH and temperature, is critical to the efforts of reducing virus transmission by controlling indoor conditions, such as in the setting of passenger airplanes.

Evaporation of droplets on surfaces

A liquid droplet deposited on a superhydrophobic surface has been used in the experimental study of droplet evaporation.[50] An extensive study of droplet evaporation on various open surfaces is much needed. Evaporation reduces water from the droplet and affects the time during which the viruses remain infectious on the surface, as the infectivity of the viruses relies on a certain amount of water. Apart from the airflow surrounding the droplet, the rate of evaporation depends on the interaction between the droplet and the surface (wetting

behavior) and also the structural features of the surface (**Figure 5**). Elucidating the drying behavior of the deposited droplets may shed light on the origin of the varying virus lifetime on different surfaces.[6] It has been shown that the virus lifetime is shorter on rough and porous surfaces, such as the surfaces of textiles and paper, compared with that on smooth and less permeable surfaces, such as the surfaces of stainless steel, glass, and plastics.[16, 51] One conjecture is that larger surface roughness enhances the rate of evaporation and the surface porosity provides a pathway for water adsorption, both accelerating

the desiccation of the droplet and hence shortening the virus lifetime. Thorough experimental and theoretical research is needed to evaluate the conjecture. A recent study also showed that the charge state of a surface also strongly affects the deactivation time of the virus in the deposited droplet.[6] Understanding the relation between virus lifetime and droplet evaporation on a surface can guide the improvement of the surfaces of PPE as well as the design of a self-sanitizing surface, including those that can slowly release anti-viral chemicals to disinfect the viruses in the deposited droplets.
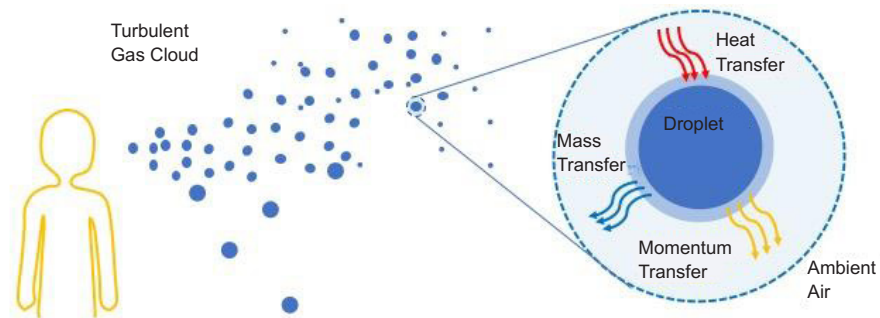

Figure 4. Schematic illustration of the evaporation of a respiratory droplet in a turbulent airflow.
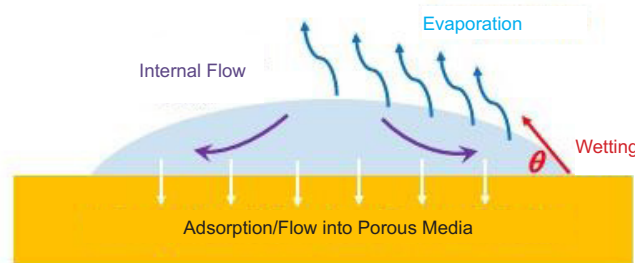

Figure 5. Schematic illustration of the evaporation of a droplet on the surface of a porous material.

Evaporation of complex fluid droplets

Respiratory droplets are composed of a complex fluid containing multiple components. A surrogate model of the droplet[50] has been used to study the water evaporation rate and the size and internal structure of the droplet nuclei after evaporation (**Figure 6**). The model droplet contains water and three other components including NaCl, mucin, and 1,2-dihexadecanoyl-sn-glycero-3-phosphocholine, which is one of the most abundant lung surfactants. Morphological changes including liquid-liquid phase separations and the crystallization of salts and surfactants during evaporation are revealed by optical and fluorescence microscopies. Since the Laplace pressure depends on the droplet size, the pressure inside the droplet thus varies as the droplet undergoes evaporation and changes its size. The changes of the internal pressure and structure inside a droplet may potentially deform and damage the virus particles, specifically the lipid membranes. Future work is needed to reveal the effects of morphological changes on the integrity and thus the infectivity of the virus particles. It has also been shown that the presence of surfactants retards the evaporation process and inhibits the rehydration of non-volatile components in a dry droplet.[50] Presumably, the presence of surfactants is

related to the reduction of surface tension. However, during evaporation the surfactants can accumulate at the surface of the droplet and form a skin layer, thus slowing down the drying process. This is another topic for future research. Ongoing and future experiments also call for a systematic study of the evaporation of a complex fluid droplet on the theoretical side.

Future experimental and theoretical studies should include the evaporation of a complex fluid droplet in a more realistic scenario with an airflow. Identifying the effects of different environmental factors on evaporation and thereby the virus infectivity may help engineer the composition of respiratory droplets at the source, such as using specialized chewing gum and inhalable surfactants, for the containment of virus transmission.

Distribution of viruses in a droplet

A respiratory droplet of an infected person typically contains multiple virus particles. The infectivity of the viruses is possibly related to the distribution of these particles in the droplet. One conjecture is that a cluster of virus particles would increase the effectiveness of the infection of healthy human cells. At quiescent conditions, the viruses may be uniformly

distributed across the droplet or aggregated to form clusters, as illustrated in **Figure 7**. Factors affecting the distribution of the virus particles inside a droplet may include the concentration of viruses, the interactions between viruses and other components of the droplet, such as proteins and surfactants, and the interactions among viruses themselves as well. Besides, if liquid-liquid phase separation occurs in the droplet, the viruses may be preferentially distributed in certain parts of the resulting internal structure. In experiments, the distribution of virus particles may be studied using fluorescence microscopy where a suitable fluorophore is used to label the virus particles and pinpoint their locations in the droplet.[50] In theory, the thermodynamics framework (e.g., the Flory-Huggins theory) developed for the phase behavior of synthetic nanoparticles in a matrix of synthetic polymers[52] may provide hints for a new theoretical description. On the modeling side, particle-based approaches such molecular dynamics simulations may be used to reveal how the virus particle distribution is affected by the presence of other components in the droplet and how this distribution evolves as the droplets undergoes evaporation.
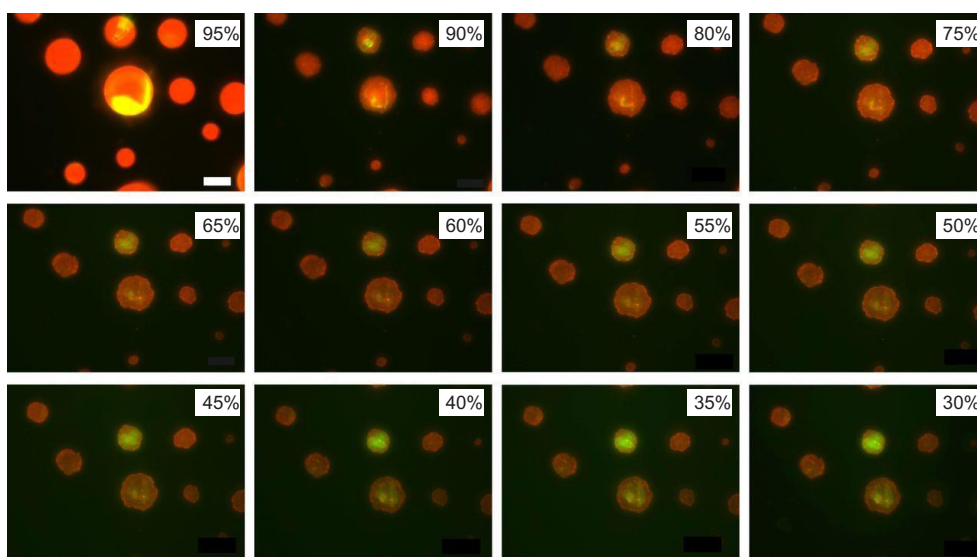

Figure 6. Fluorescence images of model droplets exposed to decreasing relative humidity. A droplet contains water, NaCl, mucin (red), and DDPC (green). DDPC: 1,2-dihexadecanoyl-sn-glycero-3-phosphocholine. Reprinted with permission from Vejerano and Marr.[50] Copyright (2018) The Royal Society.
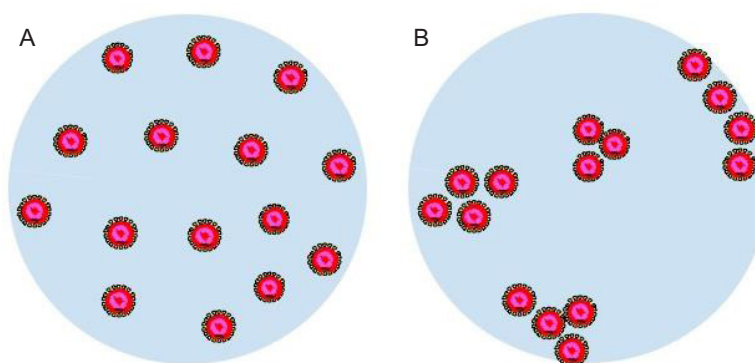

Figure 7. Schematic illustration of a respiratory droplet with uniformly distributed virus particles (A) and aggregated clusters of virus particles (B). The virus particles are drawn as core-shell structures with the core colored in red.

At conditions out of equilibrium, in particular, during the evaporation of droplets in an airflow, the distribution of virus particles may be altered compared to that at quiescence. Morphological changes of the droplet itself induced by liquid-liquid phase separation and crystallization of certain components may directly change the distribution of virus particles. Internal flows of water molecules induced during evaporation may re-distribute the virus particles as well, as shown in **Figure 8**. One intriguing question is whether the virus particles tend to aggregate at the edge of a deposited droplet (**Figure 8A**), similar to the "coffee ring" effect[53] for a puddle of particle-laden liquid after drying, or accumulate at the droplet-air interface (**Figure 8B**),[54] or form stratified structures during evaporation as observed in drying colloidal suspensions and colloid/polymer mixtures.[55-57] The aggregation of virus particles on the droplet-air interface may facilitate the transport of the viruses after they are taken into the body of a healthy person. Experimentally, fluorescence microscopy may be used to track the evolution of the virus particle distribution at controlled evaporation conditions. Theoretically, the physics

underlying the "coffee ring" effect and the stratification process (i.e., the physics of particle motion under various gradients) may be invoked to study the conjectured flow-induced redistribution of viruses.

Dynamics of virus particles in a droplet

The motion of virus particles in a respiratory droplet, as illustrated in **Figure 9A**, is important to their distribution in the droplet and also the transport of the viruses to human cells after the inhalation of the droplet. While the biosynthesis of a virus particle is not a passive process, the motion of a virus particle in a droplet is passively agitated by thermal fluctuation. The complex fluid in a respiratory droplet exhibits dynamic viscoelasticity that provides the background for the passive motion of embedded virus particles. The coupling of the virus particles and the viscoelastic background gives rise to a random motion, the mobility of which is quantified by the diffusion coefficient. On the side of the virus particle, the coupling depends on its size and shape. Favorable attractions of the virus particle to certain components of the droplet act to slow down the diffusion. An attraction stronger than the thermal energy

may even bind a virus particle to nearby molecules and result in a combined motion. The mobility of virus particles can be measured by tracking them using fluorescence microscopy. A theoretical model for virus mobility may be developed based on recent theoretical research on the mobility of synthetical particles in a viscoelastic polymer matrix.[58-60]

The abovementioned study may be generalized to investigate the motion of virus particles in a mucus layer (**Figure 9B**), which is a protective fluid layer that covers the mucous membrane lining, eyes, nose, and lungs.[23] This layer is also a multi-component soft matter system exhibiting interesting viscoelastic properties. The virus mobility in this layer is critical to the interpenetration through the mucus layer for virus infection. While mucus is a complex fluid different from the materials making up a respiratory droplet, the same experimental and theoretical tools discussed previously may be used to conduct the research. A more general study of nanoscale objects in a complex viscoelastic liquid can also benefit the design of nanocarriers that can penetrate the respiratory liquid or mucus layer to deliver anti-viral chemicals.
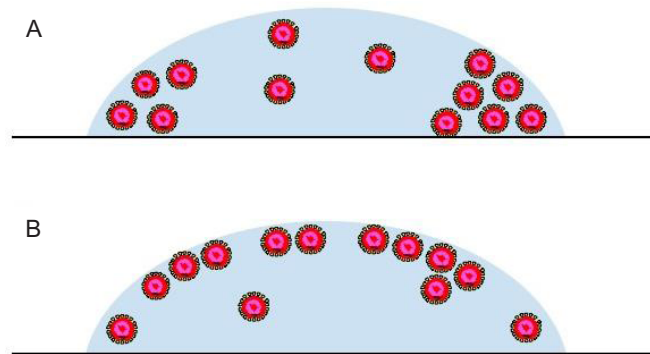

Figure 8. The distribution of virus particles in a droplet on a surface is conjectured to be affected by the evaporation dynamics and internal flow. The virus particles can possibly aggregate at the edge of the deposited droplet (A) or the droplet-air interface (B). The virus particles are drawn as core-shell structures with the core colored in red.
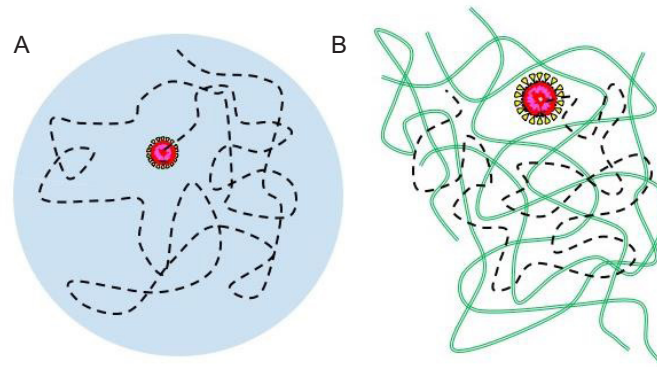

Figure 9. Schematic illustration of the trajectory (black dashed lines) of an individual virus particle in a respiratory droplet (A) and a mucus layer (green chains) (B). The virus particles are drawn as core-shell structures with the core colored in red.

Summary

As of the publication of this article, the COVID-19 pandemic is far from being contained. An important question to the researchers in physical sciences is: What non-medical, non-

clinical-care research can be performed to address the real-world challenge posed by the COVID-19 virus? In light of the imperative need, this article presents an overview of virus-laden respiratory droplets, which play a crucial role in

COVID-19 transmission, and further offers a list of suggestions for future research. The authors hope that this article would encourage physical scientists to navigate the literature, design new studies, inform policymakers, and educate the general public about the science of virus transmission.

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