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A Multiscale and Comparative Model for Receptor Binding of 2019

Novel Coronavirus and the Implication of its Life Cycle in Host Cells

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1   **ABSTRACT**

2   The respiratory syndrome caused by a new type of coronavirus has been emerging from

3   China and caused more than 1000 death globally since December 2019. This new virus,

4   called 2019 novel coronavirus (2019-nCoV) uses the same receptor called Angiotensin-

5   converting enzyme 2 (ACE2) to attack humans as the coronavirus that caused the severe

6   acute respiratory syndrome (SARS) seventeen years ago. Both viruses recognize ACE2

7   through the spike proteins (S-protein) on their surfaces. It was found that the S-protein

8   from the SARS coronavirus (SARS-CoV) bind stronger to ACE2 than 2019-nCoV.

9   However, function of a bio-system is often under kinetic, rather than thermodynamic,

10 control. To address this issue, we constructed a structural model for complex formed

11 between ACE2 and the S-protein from 2019-nCoV, so that the rate of their association

12 can be estimated and compared with the binding of S-protein from SARS-CoV by a

13 multiscale simulation method. Our simulation results suggest that the association of new

14 virus to the receptor is slower than SARS, which is consistent with the experimental data

15 obtained very recently. We further integrated this difference of association rate between

16 virus and receptor into a mathematical model which describes the life cycle of virus in

17 host cells and its interplay with the innate immune system. Interestingly, we found that

18 the slower association between virus and receptor can result in longer incubation period,

19 while still maintaining a relatively higher level of viral concentration in human body. Our

20 computational study therefore provides, from the molecular level, one possible

21 explanation that the new disease by far spread much faster than SARS.

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1 Introduction

The coronavirus disease 2019 (COVID-19) has emerged at the end of year 2019 from Wuhan, a city in China, as a new infectious disease [1, 2]. It has been found that the disease is caused by a new member of coronavirus family, 2019-nCoV [3, 4]. Like others in the same virus family, such as the coronavirus causing SARS [5, 6], 2019-nCoV is a single and positive-stranded RNA virus enveloped by lipid bilayer. The virus can capture and enter host cells in human through targeting specific receptors on their surface. Upon entry, the viral genome is released through membrane fusion. The released RNA genome of the virus is then replicated and translated into various types of viral proteins. The replicated RNA genome and synthesized viral proteins are finally assembled together into new viruses, before they escape and attack other cells [7, 8]. As a result, the infections of 2019-nCoV normally come with the similar symptoms as SARS, including fever, respiratory difficulty and pneumonia [9, 10]. Different from SARS, however, the new COVID-19 seems to have longer incubation period and thus is more contagious [11]. The disease has caused more than 70,000 confirmed cases with at least 1000 death globally, according to the data from the World Health Organization (WHO) on February 16th 2020. Therefore, the development of vaccine or therapeutic treatment for this ongoing public health crisis is highly demanding [12, 13].

Almost all the coronaviruses recognize their host cells through spike (S) proteins [14, 15]. S-protein is a glycoprotein expressed on the surface of viral envelop as homo-trimers [16]. Each S-protein further consists of two subunits. The S1 subunit includes a region called receptor-binding domain (RBD) which is used to target receptors in host cells, while the S2 subunit regulates the membrane fusion between virus and host cells [17]. These roles of S protein suggest that it could be a key target for vaccine and therapeutics developed to neutralize virus infection by blocking their invasion [18]. Moreover, it has been confirmed in a recent report that the new virus 2019-nCoV uses the same cell entry receptor ACE2 as SARS coronavirus [19]. The atomic structures of complex between human ACE2 and the RBD regions from S-protein of SARS-CoV have been obtained by x-ray crystallography [17]. It was also shown that the sequence of S-protein from SARS-CoV shares more than 70% identity with the S-protein from 2019-

1   nCoV [6]. Therefore, it is reasonable to hypothesize that the new coronavirus uses the

2   similar binding interface with ACE2 as SARS to enter host cells of human. The obvious

3   follow-up questions are: whether the 30% variations in sequences between S-protein of

4   2019-nCoV and SARS can cause any difference in their binding to ACE2? Moreover,

5   does this difference lead into any functional impacts on the life cycles of these viruses in

6   host cells?

7   Comparing with the time-consuming and labor-expensive experimental studies,

8   computational modeling serves as an ideal alternative approach to carry out fast tests on

9   biological systems under the conditions that are currently inaccessible in the laboratory

10   [20-26]. Therefore, here we developed a multiscale computational strategy to compare

11   the process of recognition between the SARS-CoV and host cells with the interactions

12   between the new coronavirus and host cells. A mesoscale model is used to simulate the

13   process in which the coronaviruses are captured by ACE2 receptors on cell surface. We

14   further constructed a structural model for complex formed between ACE2 and RBD of

15   2019-nCoV S-protein, so that the rate of their association can be estimated by a coarse-

16   grained Monte-Carlo simulation and further compared with the binding of S-protein from

17   SARS-CoV. Our simulation indicates that association of the new virus to the receptor is

18   slower than SARS, which is consistent with the experimental data obtained very recently.

19   We integrated this difference of association rate between virus and receptor into a simple

20   mathematical model which describes the life cycle of virus in host cells and its interplay

21   with the innate immune system. Interestingly, we found that the slower association

22   between virus and receptor can result in longer incubation period, while still maintaining

23   a relatively higher level of viral concentration in human body. Our computational study

24   therefore explains, from the molecular level, why the new COVID-19 disease is by far

25   more contagious than SARS. In summary, this multiscale model serves as a useful

26   addition to current understanding for the spread of coronaviruses and related infectious

27   agents.

28   **Results and Discussions**

29   A rigid-body (RB) based model is first constructed to simulate the kinetic process

30   about how viruses are captured by the cell surface receptors on plasma membrane. In

1   brief, within a three-dimensional simulation box, the plasma membrane is represented by

2   a flat surface below the extracellular region. The area of the square is 1 μm^2, while the

3   height of the simulation box is 500 nm. A number of ACE2 receptors (200) are initially

4   placed on the membrane surface (pink in **Figure 1a**). They are represented by rigid

5   bodies of cylinders and their binding sites are located on top of the cylinders (red dots in

6   **Figure 1a**). The height of each cylinder is 10nm and its radius is 5nm. On the other hand,

7   space above the plasma membrane represents the extracellular region. A number of

8   coronaviruses are located in this area (golden in **Figure 1a**). Each virus is simplified as a

9   spherical rigid body with a given radius (40nm). Trimeric S-proteins are uniformly

10 distributed on the spherical surface of each virus (green dots in **Figure 1a**). Each S-

11 protein can interact with an ACE2 receptor on plasma membrane. After any S-protein on

12 one virus forms an encounter complex with a receptor, we assume that the host cell is

13 captured by the virus. The dissociation between the virus and the receptor is not

14 considered in the system, because we also assume that, after the association between S-

15 protein and ACE2, the virus can enter the cell through membrane fusion. Following the

16 initial random configuration, the diffusion of receptors and viruses, as well as their

17 association, were simulated by a diffusion-reaction algorithm until the system reached

18 equilibrium. The detail process of the simulation is specified in the **Methods**.

19   Before the rigid-body simulation, in order to provide a more realistic estimation

20 on the binding between ACE2 and different coronaviruses, we specifically compared the

21 S-protein from 2019-nCoV with the S-protein from SARS. We applied our previously

22 developed residue-based kinetic Monte-Carlo (KMC) method to simulate the associate

23 processes of these two systems. In detail, the atomic coordinates of the complex between

24 human ACE2 and the RBD domain from the S-protein of SARS are taken from the PDB

25 id 2AJF [17]. In parallel, the structural model of the complex between human ACE2 and

26 the RBD domain from the S-protein of 2019-nCoV was computationally constructed,

27 following the procedure described in the **Methods**. The structural comparison of these

28 two protein complexes is shown in **Figure 1b**. For both systems, 500 trajectories based

29 on their complex structures were generated by the KMC simulation which algorithm is

30 specified in the **Methods**. In the initial conformation of each trajectory, S-protein and

31 receptor were separated and placed with a random position relative to each other in which

1   the distance between their binding interfaces is fallen within a given cutoff value d_c of 20

2   Å. At the end of each trajectory, receptor and viral protein either form an encounter

3   complex through their binding interface observed in the complex structure, or diffuse

4   away from each other. Based on the simulation results collected from all the 500

5   trajectories, we counted how many times an encounter complex can be formed by the end

6   of the simulation time, which gives the probability of association. As a result, the

7   comparison of calculated probabilities of association for both systems is plotted in **Figure**

8   **2a**.

9   The figure shows that probability of association between ACE2 and the S-protein

10 from 2019-nCoV is remarkably lower than the probability of association between ACE2

11 and the S-protein from SARS. Specifically, among the 500 simulation trajectories of

12 SARS system, we found that 8 of them successfully formed encounter complexes, while

13 among the 500 simulation trajectories of 2019-nCoV system, only 2 of them successfully

14 formed encounter complexes. This result suggests that the association of the S-protein

15 from SARS to the receptor is about four times faster than the association of the S-protein

16 from 2019-nCoV. The different of association rate from our simulation, interestingly, is

17 confirmed by the experimental data that was measured very recently by Dr. McLellan's

18 lab [27]. Using surface plasma resonance (SPR), they showed that the association rate k_a

19 of binding between 2019-nCoV RBD domain and ACE2 equals $1.36 \times 10^5 M^{-1} s^{-1}$, while the

20 rate between SARS RBD domain and ACE2 equals $3.62 \times 10^5 M^{-1} s^{-1}$. Therefore, the

21 experimental evidence indicated that the association of the S-protein from SARS to the

22 receptor is about three times faster than the association of the S-protein from 2019-nCoV,

23 which is quantitatively consistent with our simulation results.

24   We then fed the information derived from the structure-based simulations into the

25 rigid-body model. Two specific simulation systems were compared. A relatively fast rate

26 of association between receptors and S-proteins on viral surfaces was adopted in the first

27 system to represent the binding process of SARS, while a relatively slow rate of

28 association between receptors and S-proteins on viral surfaces was adopted in the second

29 system to represent the binding process of 2019-nCoV. All the other parameters such as

30 diffusion constants and concentrations in both systems remain the same. As a result, the

1   total numbers of viruses that were captured by host cells are plotted in **Figure 2b** as a

2   function of simulation time. Without surprise, the figure shows that although almost all

3   viruses were attached to the cell surfaces by the end of both simulations, the kinetic

4   process in the SARS system is much faster than the 2019-nCoV system, which is resulted

5   from the difference in the association rate between receptors and their corresponding S-

6   proteins. This leads into the fact that during the early stage of simulations, more SARS

7   viruses attach to host cells than 2019-nCoV. For instance, when the simulations in both

8   systems reached the first 10^5 nanoseconds, there have already been more than 40 SARS

9   viruses attached to the cell surfaces. In contrast, there were less than 20 viruses attached

10   to the cell surfaces within the same amount of time in the 2019-nCoV system.

11   Considering that the function of a bio-system is often under kinetic, rather than

12   thermodynamic, control [28, 29], we suggest that this time-dependent behavior is

13   biologically more relevant. In reality, not all the viruses have the opportunity to find their

14   target receptors on host cells. Many of them will be recognized and removed by our

15   innate immune system. Therefore, the capability of how fast a specific type of

16   coronavirus can target its receptors is especially critical to the process of its invasion, as

17   well as the follow-up stages in its life cycle.

18   In order to further explore the impacts of our rigid-body simulation results on the

19   rest process of virus infection after they invade into host cells, we proposed a

20   mathematical model to delineate a simplified version of viral life cycle including its

21   replication and packaging in host cells, the inflammatory signaling pathways due to the

22   detection of foreign pathogens, and the follow-up inflammatory responses which lead to

23   the apoptosis of infected cells and the removal of viruses by the recruitment of immune

24   cells. The model can be summarized by the diagram shown in **Figure 3**. Specifically,

25   coronavirus [V] can turn healthy cells [H] into infected cell [In] by binding to the

26   receptors ACE2 on their surfaces. The RNA genome [m] is then released from bound

27   virus [Vb], and then translated into different viral proteins. These proteins and replicated

28   RNA are further packaged together as [P] in cytoplasm and finally escape from infected

29   cells. On the other side, in order to avoid viral spread, our innate immune system triggers

30   inflammatory signaling pathways in the infected cells [30]. For instance, the viral RNAs

31   can be detected by RIG-I-like receptors (RLRs) [31]. The RNA binding of RLRs

1   receptors initiates the signaling cascade by interacting with the mitochondrial antiviral-

2   signaling (MAVS) protein [32]. The aggregation of MAVS on the surface of

3   mitochondria will trigger the NF-κB signaling pathway that turns on gene expression of

4   specific cytokines [S] to stimulate the inflammatory responses [33, 34]. The inflammation

5   of host organism leads to the apoptosis of infected cells and the removal of virus by

6   recruited immune cells such as microphages. In summary, the change of concentration for

7   each variable in above system can be described by following set of ordinary differential

8   equations (ODE).

9
$$\frac{d[H]}{dt} = r_H - \frac{k_b[H][V]}{S_V + [V]} \tag{1}$$

10
$$\frac{d[Vb]}{dt} = \frac{k_b[H][V]}{S_H + [H]} - k_r[Vb] \tag{2}$$

11
$$\frac{d[m]}{dt} = k_r[Vb] - k_p[m] \tag{3}$$

12
$$\frac{d[P]}{dt} = k_p[m] - k_a[P] \tag{4}$$

13
$$\frac{d[S]}{dt} = \frac{s_s[m]}{[m] + K_m} - d_s[S] \tag{5}$$

14
$$\frac{d[In]}{dt} = \frac{k_b[H][V]}{S_V + [V]} - \frac{d_I[In][S]}{[In] + K_I} \tag{6}$$

15
$$\frac{d[V]}{dt} = k_a[P] - \frac{k_b[H][V]}{S_H + [H]} - \frac{d_v[V][S]}{K_V + [V]} \tag{7}$$

16   Equation (1) describes the change of the healthy cells as a function of time in the

17   system. The parameters r_H, k_b, and S_V in the equation represent cell generating rate, the

18   rate and saturation coefficient of virus binding, respectively. Equations (2) to (4) indicate

19   the entry, replication and packaging of virus in host cells, in which the parameters k_r, k_p,

20   and k_a represent rates of viral protein translation, assembly and releasing. Equation (5)

1   describes the stimulation of inflammatory signaling by viral RNA. The parameters s_S, K_m,

2   and d_S in the equation represent the maximal activation rate, the saturation coefficient and

3   the rate of degradation of inflammatory signals. Equation (6) gives how infected cells

4   change in the system, while the parameters in the equation d_I, and K_I indicate the rate and

5   saturation coefficient of cell apoptosis that is stimulated by inflammatory signals. Finally,

6   equation (7) suggests that the variation of total virus in the system depends on the release

7   of newly packaged virus from infected cells, the binding of free virus to the healthy cells,

8   and the immune response triggered by inflammatory signals. The parameters d_V and K_V in

9   the equation give the maximal rate and saturation coefficient immune cells used to kill

10   virus. Altogether, we solved above ODEs numerically by a stochastic simulation

11   algorithm. The brief introduction of the simulation algorithm will be specified in the

12   **Methods**.

13   Given predefined weights for all the simulation parameters and the initial values

14   for each element, the dynamics of the system is evolved as a function of time. The

15   simulation results of the mathematical model are summarized in **Figure 4**. As shown by

16   the red curve in **Figure 4a**, the change of free virus in the system can be divided into

17   three stages. It first decreases from its initial value. After reaching the minimal level, the

18   number of virus then bounces back in the second phase until it drops again and finally

19   vanishes at the end of the third phase. Relative to the free virus, the number of virus

20   captured by host cells equals 0 at the beginning of the simulation. It increases in the first

21   stage and diminishes in the second, as shown by the blue curve in the figure. In the third

22   phase, very few viruses bound to host cells are detected in the system. Corresponding to

23   the change of virus, the number of healthy cells is plotted as the black curve. The curve

24   shows that the level of healthy cells reduces from the beginning and rises only after all

25   free viruses are removed from the systems. Based on these kinetic profiles, the dynamics

26   of the system can thus be interpreted as follows. In the first stage of simulation, free

27   viruses invade into the healthy cells by binding to the receptors on their surface. We

28   suggest that this stage corresponds to the incubation period. In the second stage, new

29   viruses are assembled in and released from the infected cells. At the same moment, the

30   viral genomes left in the infected cells stimulate the immune response. As a result, the

31   total amount of virus is gradually lowered in the third phase, indicating that these viruses

1   are cleared up by the innate immune system. After the removal of all viruses, the healthy

2   cells in the system grow again, representing the recovery of the patient.

3   We further incorporated the results derived from the rigid-body simulations into

4   the mathematical model to compare the viral life cycle in SARS and COVID-19. The

5   rigid-body simulation suggests that SARS-CoV binds to receptor ACE2 faster than 19-

6   nCoV, given the same amount of time. Therefore, we applied the mathematical model to

7   two comparative systems. A relatively fast viral binding rate k_b was adopted in the first

8   system to represent the binding process of SARS, while a relatively slow rate was

9   adopted in the second to represent the binding process of 2019-nCoV. All the other

10   parameters such as diffusion constants and concentrations in both systems remain the

11   same. As a result, the kinetic profiles indicating the changes of free virus level along with

12   the simulation time in these two systems are shown in **Figure 4b**. The figure suggests

13   that the first stage in the simulation of 2019-nCoV (red curve) is longer than the

14   simulation of SARS (black curve). This is consistent with the clinical observation that the

15   incubation period of COVID-19 could be as long as 14 days, while the incubation period

16   is normally from 2 to 7 days. More interestingly, we found that the level of free virus at

17   the end of the first period in the simulation of 2019-nCoV is relatively higher than the

18   corresponding level of free virus in the simulation of SARS. Considering that a patient

19   can contain a higher level of new coronavirus during his or her incubation period which

20   is also longer than SARS, our simulation gives the insights about why COVID-19 is more

21   contagious and spread faster than SARS [11]. Finally, when both simulations came to

22   their third phases, we found that the total amount of virus of SARS is higher than 2019-

23   nCoV. This gives possible explanation about why the symptoms in most COVID-19

24   patients are relatively mild and not as severe as the symptoms in SARS patients [35].

25   In summary, it is important to point out that the life cycles of different

26   coronaviruses can also be caused by many other factors such as the difference in the

27   assembling pathways of these viruses. Additionally, the infectious response of each

28   individual is also a case-dependent issue, relying on the expression levels of ACE2

29   receptors and the heterogeneity of immune response in different patients. Nevertheless,

30   our multiscale computational model highlights the potential role of binding kinetics

1   between human receptor and S-proteins from different coronavirus in, and provided the

2   possible mechanism from the molecular level to their impacts on, regulating the

3   dynamics of the entire viral life cycle.

4   **Conclusions**

5   The recent outbreak of COVID-19 has drawn substantial attention especially after

6   it spread to more than thirty countries and became a Public Health Emergency of

7   International Concern (PHEIC) [2, 36, 37]. The disease is caused by a new type of

8   positive-stranded RNA virus, known as 2019-nCoV. Similar as the coronavirus that leads

9   to SARS, it has been confirmed that the S-protein in 2019-nCoV also mediates its

10   recognition with the human receptor ACE2. However, the differences of receptor binding

11   in these two virus systems and their underlying implications are not well understood. It

12   has been found that the kinetic aspect of binding between biomolecules in many

13   biological systems is usually more important to their functions. Here, using

14   computational structural prediction and coarse-grained simulations, we first have

15   compared the association rate of binding between ACE2 and the S-protein from SARS-

16   CoV with binding between ACE2 and the S-protein from 2019-nCoV. Consistent with

17   the experimental data obtained very recently, we found association of the new virus to the

18   receptor is slower than SARS. We further interrogate the impact of this result on the

19   difference in viral life cycle between SARS and COVID-19. By incorporating the

20   information derived from coarse-grained simulations into a mathematical model, we

21   found that the slower association between 2019-nCoV and ACE2 can result in longer

22   incubation period, while still maintaining a relatively higher level of viral concentration

23   in human body. This multiscale modeling framework, therefore, can offer one possible

24   molecular mechanism to explain why this new infectious disease spreads much faster

25   than SARS.

26   **Methods**

27   *Construct the structural models for the complexes between receptors and viral S-proteins*

28   The atomic structures of complex between ACE receptor and different viral S-

29   proteins are needed for the simulations of their association. The structural models of these

1 protein complexes were prepared as follows. The complex structure between human

2 ACE2 and the RBD domain from the S-protein of SARS was determined by the x-ray

3 crystallography experiment (PDB id 2AJF) [17]. On the other hand, the structural model

4 of the complex between human ACE2 and the RBD domain from the S-protein of 2019-

5 nCoV was constructed by computational modeling. In detail, the atomic structure of

6 2019-nCoV S-protein RBD domain was first predicted by I-TASSER [38] based on the

7 newly released sequence of 2019-nCoV [39]. In parallel, the backbone model of the

8 complex between human ACE2 and the RBD domain from 2019-nCoV S-protein was

9 generated using the template-based structure prediction tool COTH [40, 41]. We then

10 superimposed the predicted atomic coordinates of 2019-nCoV S-protein RBD domain

11 onto its relative backbone position in the complex model, and also aligned the atomic

12 coordinates of human ACE2 from the crystal structure onto the relative backbone

13 position in the complex model. As a result, the structural comparison of these two protein

14 complexes is plotted in **Figure 1b**.

15 *Estimate the association between ACE2 and S-protein by kinetic Monte-Carlo simulation*

16   A previously developed kinetic Monte-Carlo algorithm [42] was used to simulate

17 the association between S-protein and ACE2. A coarse-grained model of protein

18 structures is used. Each residue in a protein is represented by its Cα atom and the

19 representative center of its side-chain. The simulation starts from an initial conformation,

20 in which two proteins in the complex are separated and placed randomly. Following the

21 initial conformation, each protein diffuses randomly within one simulation step. A

22 physics-based scoring function containing electrostatic interaction and hydrophobic effect

23 is used to guide the diffusions of proteins during simulations. Based on the calculated

24 energy, Metropolis criterion is applied to determine if the corresponding diffusional

25 movements can be accepted or not. The simulation trajectory will be terminated if an

26 encounter complex is successfully formed through the corresponding interface observed

27 in the constructed model of native protein complexes. Otherwise, above simulation

28 procedure will be repeated until it reached the maximal time duration. This method was

29 applied to study the association between ACE2 and both S-proteins from the two virus

30 systems. For each system, 500 trajectories are carried out. Each trajectory starts from a

1   relatively different initial conformation, but the initial distances between the binding

2   interfaces of S-proteins and receptors in all trajectories are below 20Å. The probabilities

3   of association were then derived and compared based on counting how many encounter

4   complexes formed among these trajectories in the two systems.

5   *Model the cellular attachment of coronavirus by rigid-body diffusion-reaction algorithm*

6   As described in the **Results**, a rigid-body (RB) based model is constructed to

7   simulate the binding between coronaviruses and cell surface receptors ACE2 on plasma

8   membrane. Given the model representation and a randomly-generated initial

9   configuration (**Figure 2a**), the dynamics of the system is evolved by following a

10   diffusion-reaction algorithm [43-45]. Viruses or receptors are selected by random order

11   for stochastic diffusion within each simulation time step. A virus is free to diffusion

12   throughout the simulation box, while diffusions of membrane-bound receptors are

13   confined to the plasma membrane. Periodic boundary conditions along both x and y

14   directions are applied. Moreover, viruses are not allowed to move below the plasma

15   membrane. If any virus moves beyond the top of the simulation box, it will be bounced

16   back. The amplitude and probability of translational and rotational movements for viruses

17   and receptors are determined by its corresponding diffusion constant. Association

18   between viruses and receptors are followed after diffusions. Association is triggered if the

19   distance between any S-protein in a virus and the binding site of a receptor is below a

20   predetermined cutoff value. The probability to trigger the association is determined by

21   the association rate, which was estimated by the kinetic Monte-Carlo method described in

22   the previous section. Assuming that viruses can enter the cell through membrane fusion

23   after they associate with ACE2, the dissociation between the virus and the receptor is not

24   considered in the system. Finally, as above diffusion-reaction process iterates in both

25   Cartesian and compositional spaces, the system will finally reach equilibrium.

26   *Solve the ordinary differential equations of viral life cycle by stochastic simulations*

27   We use the stochastic simulation algorithm (SSA) developed by Gillespie to

28   model the processes of biochemical reactions from equation (1) to equation (7) [46]. The

29   algorithm starts from the initiation of time and populations of each species in the

1   simulation system. Within each simulation step, the rates for all reactions are re-estimated

2   by the given parameters and updated population of corresponding species. One of these

3   reactions is then randomly selected based on the calculation of their relative weights.

4   Finally, populations for the corresponding species are updated. The simulation moves

5   forward to the next step by adding the system time with τ, in which τ is an exponential

6   random variable with the average value equals the reciprocal of the summation for all the

7   reactions. Above process is iterated so that the populations of each species in the system

8   evolve along the simulation time. The values of all parameters in the simulation were

9   chosen to be within the biologically meaningful range. The choice of these parameters

10   does not qualitatively affect the general dynamic patterns of the system.

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1 **Acknowledgement**

6

7 **Author Contributions**

8 Y.W. designed research; Z.S. and Y.W. performed research; Z.S. and Y.W. analyzed data;

9 Y.W. wrote the paper.

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11 **Declaration of Interests**

12 **Competing financial interests:** The authors declare no competing financial interests.

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1   **Figure Legends**

2   **Figure 1**: A mesoscopic model is constructed to simulate the kinetic process about how

3   viruses are captured by the cell surface receptors on plasma membrane **(a)**. The plasma

4   membrane is represented by a flat surface below the extracellular region, which contains

5   a number of ACE2 receptors (pink). The space above the plasma membrane represents

6   the extracellular region which contains a number of coronaviruses (golden). Each virus is

7   simplified as a spherical rigid body with trimeric S-proteins uniformly distributed on its

8   surface (green dots). Each S-protein monomer can interact with an ACE2 receptor on the

9   plasma membrane. The rate of their association was estimated by Monte-Carlo

10 simulations based on the structure models of complexes between ACE2 and RBD

11 domains from S-proteins of different coronavirus **(b)**. The proteins in the figure are coded

12 by different color index.

13 **Figure 2**: We used structure-based kinetic Monte-Carlo simulations to estimate the

14 association between ACE2 and S-proteins from SARS-CoV and 2019-nCoV. For each

15 system, 200 simulation trajectories were generated. Based on these trajectories, the

16 calculated probabilities of association are plotted in **(a)**. We found that the association

17 between ACE2 and SARS-CoV S-proteins (right column) is faster than the association

18 between ACE2 and 2019-nCoV S-protein (left column). We then fed the information into

19 the rigid-body-based simulations. The simulations show the total numbers of viruses that

20 were captured by host cells increased as a function of simulation time **(b)**. Moreover, we

21 found that during the early stage of simulations, more SARS-CoV (black curve) attach to

22 host cells than 2019-nCoV (red curve).

23 **Figure 3**: A mathematical model was proposed to delineate the simplified process of

24 viral life cycle, including its replication and packaging in host cells, the inflammatory

25 signaling pathways due to the detection of foreign pathogens, and the follow-up

26 inflammatory responses which lead to the apoptosis of infected cells and the removal of

27 viruses by the recruitment of immune cells. The meaning of each variable in the diagram

28 is specified on the right. The system can further be described by a set of ordinary

29 differential equations, as written from Equation (1) to Equation (7) in the main text.

1   **Figure 4**: Given predefined weights for all the rate parameters and the initial values for

2   each variable in the model, the dynamics of the system is evolved as a function of time by

3   solving the mathematical model numerically with a stochastic simulation algorithm. The

4   figure suggests that the dynamics of the system can be divided into three stages **(a)**. We

5   further applied the model to two comparative systems. A relatively fast viral binding rate

6   k_b was adopted in the first system to represent the binding process of SARS, while a

7   relatively slow rate was adopted in the second to represent the binding process of 2019-

8   nCoV. As shown in **(b)**, we found that the first stage in the simulation of 2019-nCoV (red

9   curve) is longer than the simulation of SARS (black curve), while the level of free virus

10   at the end of the first period in 2019-nCoV is relatively higher than the corresponding

11   level of free virus in SARS.

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Figure 4