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A deterministic model for homologous antibody dependant enhancement on influenza infection

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ABSTRACT

Antibody dependant enhancement refers that viral infectivity was unexpectedly enhanced at low antibody concentration compared to when antibodies were absent, such as Dengue, Zika and influenza virus. To mathematically describe switch from enhancement to neutralisation with increase of antibody concentration, one hyperbolic tangent variant is used as switching function in existed models. However, switching function with hyperbolic tangent contains four parameters, and does not always increase with antibody concentration. To address this problem, we proposed a monotonically increasing Logistical function variant as switching function, which only contains position parameter and magnitude parameter. Analysing influenza viral titre estimated from 21 focus reduction assay (FRA) datasets from neutralisation group (viral titre lower than negative control on all serial dilutions) and 20 FRA dataset from enhancement group (viral titre higher than negative control on high serial dilution), switching function with Logistic function performs better than existed model independent of both groups and exhibited different behaviour/character; specifically, magnitude parameter estimated from enhancement group is lower, but position parameter estimated from enhancement group is higher. A lower magnitude parameter refers that enhancement group more rapidly switches from enhancement to neutralisation with increase of antibody concentration, and a higher position parameter indicates that enhancement group provides a larger antibody concentration interval corresponding to enhancement. Integrating estimated neutralisation kinetics with viral replication, we demonstrated that antibody-induced bistable influenza kinetics exist independent of both groups. However, comparing with neutralisation group, enhancement group provides higher threshold value of antibody concentration corresponding to influenza infectivity. This explains the observed phenomenon that antibody dependent enhancement enhances susceptibility, severity, and mortality to influenza infection. On population level, antibody dependant enhancement can promote H1N1 and H3N2 influenza virus cooperate to sustain long-term circulation on human populations according to antigenic seniority theory.

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1. Introduction

Influenza virus, a major human health concern, is responsible for estimated 290,000–650,000 deaths annually (Krammer et al., 2018). Influenza virus is an enveloped, segmented, negative-sense ribonucleic acid (RNA) virus that belongs to Orthomyxoviridae family (Nayak et al., 2013). Two surface glycoproteins on influenza virus are hemagglutinin (HA) and neuraminidase (NA) targeted by both cell-mediated immunity and antibody-mediated immunity (Krammer et al., 2018). Adaptive immunity against influenza virus consists of both cell-mediated immunity to lyse infected epithelial cells and antibody-mediated immunity to neutralise free influenza virus (Baumgarth et al., 2013; Krammer, 2019; Turner et al., 2013).

Antibody responses mainly target two surface glycoproteins HA and NA to neutralise free influenza virus by blocking virus entering susceptible cells, hampering virus uncoating to releasing genome segment and preventing virus releasing from infected cells (Krammer, 2019). However, antibody-dependent enhancement (ADE) associated with influenza virus was first reported for rabbit IgG monoclonal antibodies (anti-HA) promoting H1N1 virus amplification on P388D1 cells through an Fcγ receptor dependent pathway (Ochiai et al., 1992; Tamura et al., 1991). Neutralising antibody binding to the globular head and non-neutralising antibody binding to the base of the head domain destabilise the stem domain on HA (H3N2 virus) were found to exhibit antibody dependant enhancement on epithelial cells (Winarski et al., 2019). Contrary to previous research, Khurana et al. (2014) demonstrated that swine heterologous anti-HA2 antibodies induced by whole inactivated H1N2 vaccine binds close to the fusion peptide and promotes virus membrane fusion, thereby enhancing H1N1pdm09 infection on Madin-Darby canine kidney (MDCK) cells (Khurana et al., 2013). Moreover, homologous antisera against H3N2 influenza virus enhanced virus infectivity on MDCK cells (epithelial cell) (Xu, 2022).

Antibody dependent enhancement promotes viral infectivity by helping viruses to enter cells (known as extrinsic ADE) and assists viral replication by inhibiting cellular innate antiviral responses (known as intrinsic ADE) (Taylor et al., 2015). Mathematical modelling attempts are majorly used to understand extrinsic ADE, particularly for dengue virus and Zika virus. Gujarati and Ambika (2014) first proposed mathematical model $S_T(A) = \frac{\tanh\,(C1(A-A_{max}))}{1+e^{-C_2(A-A_{min})}}$, to describe switch between enhancement and neutralisation with increasing antibody concentration (Gujarati et al., 2014), where A represents antibody concentration. This model intends to understand potentially fatal secondary infections due to different serotype dengue infection. Biao Tang al et used same model to describe the impact of ADE on disease severity of Zika virus and dengue virus sequential and co-infection (Tang et al., 2020). However, mathematical model $S_T(A) = \frac{\tanh\,(C1(A-A_{max}))}{1+e^{-C_2(A-A_{min})}}$ have four parameters and does not always increase with antibody concentration (show in Fig. 1C).

To better delineate switch from enhancement to neutralisation with increase of antibody, we propose a monotonically increasing Logistic function variant with position parameter and magnitude parameter as switching function. Comparing sum of squared error (SSE), Akaike information criterion (AIC) and modified AIC, we found that switching function with Logistic function performs better than that with hyperbolic tangent. Integrating neutralisation kinetics with influenza replication, antibody always leads to bistable influenza kinetics independent of enhancement or neutralisation group. Comparing with neutralisation group, enhancement group provides a higher threshold of antibody concentration corresponding to influenza infectivity. On population level, antibody dependant enhancement can promote H1N1 and H3N2 influenza virus cooperate to sustain long-term circulation on human populations according to antigenic seniority theory.

2. Preliminary background

Reference (Xu, 2022) used Focus Reduction Assay (FRA) to propose that homologous ferret H3N2 antisera/antibody enhances influenza infectivity on epithelial cells, where the FRA assay is designed to detect and measure neutralising antibodies by its ability to block influenza virus entry and replication. Homologous antibody dependent enhancement on epithelial cells refers that an antibody concentration-dependent pattern based on the surface receptor promotes the virus-antibody complex to enter MDCK cells. Specifically, at low antibody concentration, a large proportion of free virus entered cells through sialic acid pathway, while a small proportion of influenza virus bound to antibody entered through the surface receptor (shown in Fig. 1A). For influenza virus, dengue virus and Zika virus, mathematical model describes antibody dependent enhancement consisting of two main components (shown in Fig. 1B), including switching function and interaction term. Switching function describes antibody dependent enhancement on low antibody concentrations and antibody dependant neutralisation on high antibody concentrations. Switching function indicates antibody dependent enhancement if its value is negative; switching function indicates antibody dependent neutralisation if its value is positive. Interaction term describes magnitude of antibody dependent enhancement or antibody dependant neutralisation with antibody concentration and viral titre (shown in Fig. 1B). Reference (Gujarati et al., 2014) and (Tang et al., 2020) propose switching function $S_T(A) = \frac{\tanh\,(C1(A-A_{max}))}{1+e^{-C_2(A-A_{min})}}$ using hyperbolic tangent variant. However, typical curve of switching function $S_T(A) = \frac{\tanh\,(C1(A-A_{max}))}{1+e^{-C_2(A-A_{min})}}$ deceases and increases with increase of

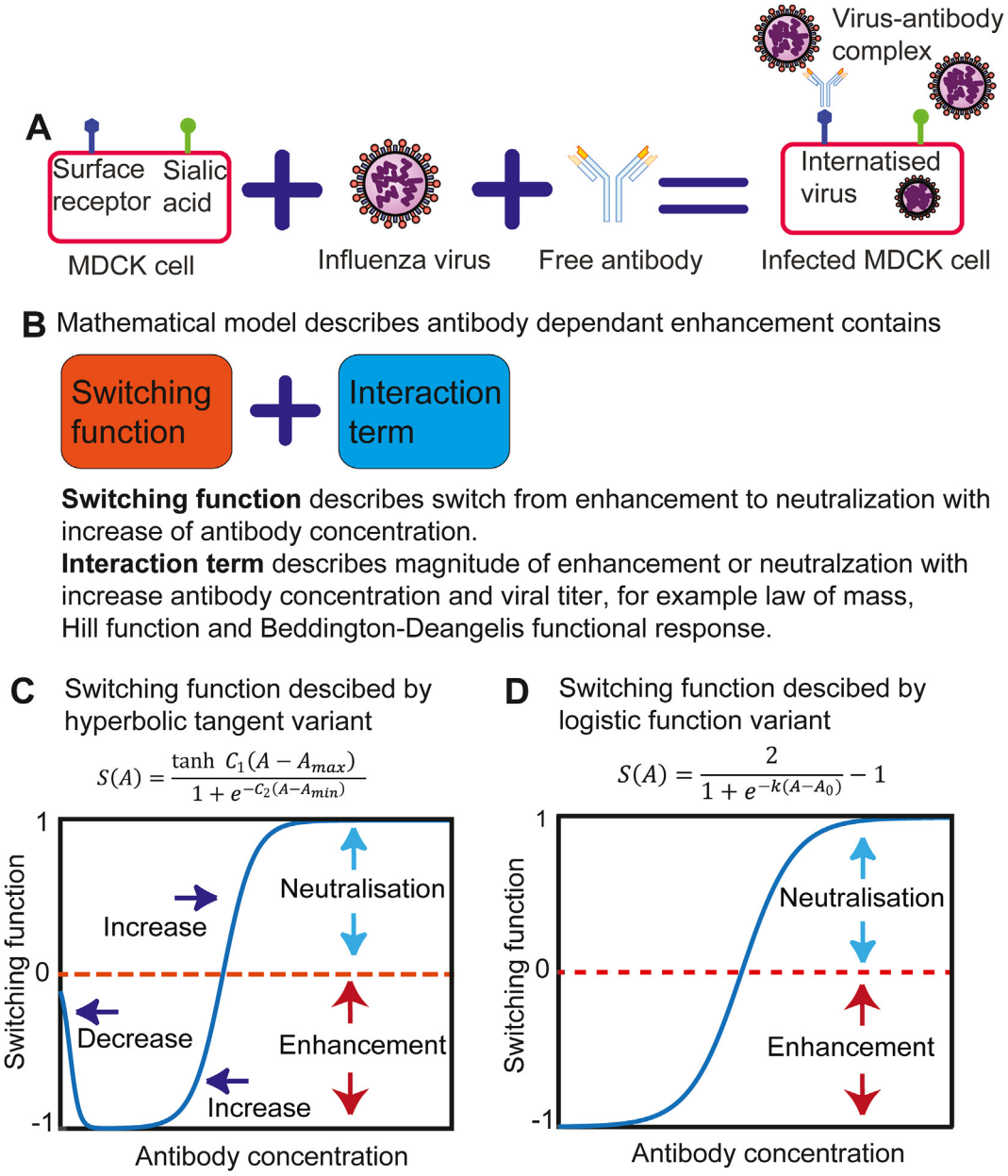

Fig. 1. Mathematical models describing antibody dependent enhancement on MDCK cells. **(A)** In the presence of low antibody concentration, the virus-antibody complex enters MDCK cells through the surface receptor, while free virus can enter MDCK cells through the sialic acid pathway. **(B)** Schematic diagram of mechanical model describing antibody dependant enhancement and antibody dependant neutralisation. Mechanical model consists of two parts, including switching function and interaction term. Switching function describes switch from antibody dependant enhancement on low antibody concentrations to antibody dependant neutralisation on high antibody concentration. Interaction term describe magnitude of enhancement and neutralisation with antibody concentration. **(C)** Typical curve of switching function described by hyperbolic tangent variant. **(D)** Typical curve of switching function described by Logistic function variant.

antibody concentrations (shown in Fig. 1C), which is not biologically feasible. Here, we used Logistic function variant as switching function $S_L(A) = \frac{2}{1+e^{-k(A-x_0)}} - 1$. Typical curve of switching function $S_L(A) = \frac{2}{1+e^{-k(A-x_0)}} - 1$ always increases with antibody concentrations (shown in Fig. 1D); $S_L(A)$ converges to -1 (enhancement) when A converges to 0, and $S_L(A)$ converges to 1 (neutralisation) when A converges to $+\infty$. Moreover, switching function $S_L(A) = \frac{2}{1+e^{-k(A-x_0)}} - 1$ provide two less than parameters to be fitted. Here, we expected that switching function $S_L(A) = \frac{2}{1+e^{-k(A-x_0)}} - 1$ is a better candidate to describe antibody dependent enhancement.

3. Mathematics models describing neutralisation kinetics with and without enhancement

Reference (Xu, 2022) categorized FRA datasets in two groups, including enhancement group and neutralisation group. Specifically, the majority showed antibody enhances influenza infectivity at low antibody concentrations, but suppresses influenza infectivity on high antibody concentrations, which is referred as enhancement group (shown in Fig. 2A); minority of FRA datasets exhibited that antibody suppress influenza infectivity at any antibody concentrations, which is referred as neutralisation group herein. In the following analysis, model workflow outlines the results (shown in Fig. 2B).

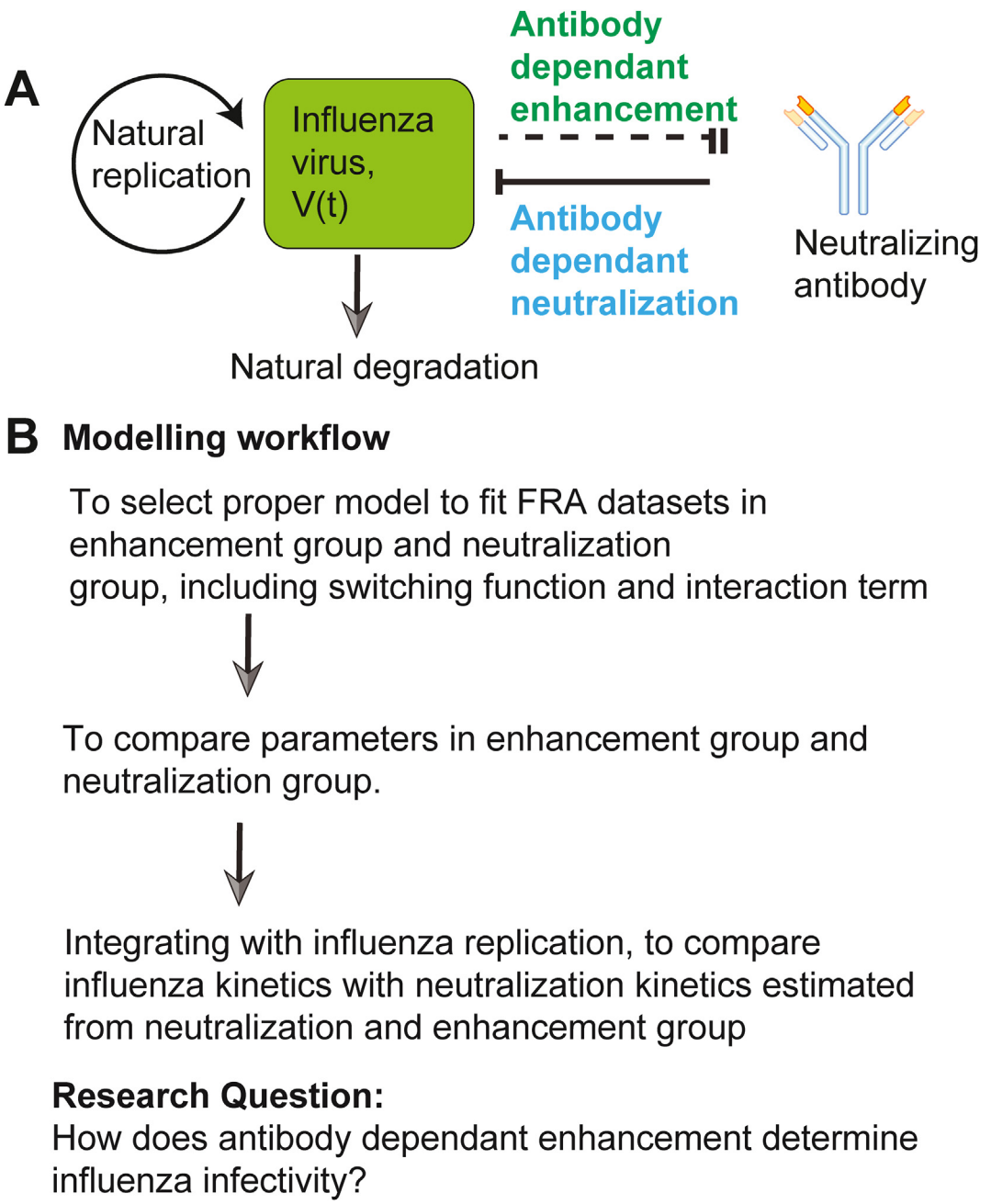

Fig. 2. A Mechanistic mathematical model of influenza kinetics in presence of antibody dependant enhancement. **(A)** Proposed mathematical models describe influenza kinetics with antibody dependant enhancement. Influenza virus kinetics follows limited growth with natural replication and natural degradation. Neutralising antibody enhances influenza infectivity on low antibody concentrations, but suppresses influenza infectivity on high antibody concentrations. **(B)** The model workflow outlines the results.

Here, we propose four models (System 1–4) to FRA datasets to estimate virus neutralisation kinetics for enhancement and neutralisation group. First, we adapted System 1 used from Reference (Gujarati et al., 2014) and Reference (Tang et al., 2020) (System 1, *Method*); switching function is $S_T(A) = \frac{\tanh\,(C1(A-A_{max}))}{1+e^{-C_2(A-A_{min})}}$ (hyperbolic tangent variant, Fig. 1C), and interaction term is $\frac{\phi A(t)V(t)}{1+\eta A(t)+\gamma V(t)}$ modelled by Beddington-Deangelis functional term (Cantrell et al., 2001). Secondly, System 2 combined switching function $S_L(A) = \frac{2}{1+e^{-k(A-A_0)}} - 1$ with interaction term $\frac{\alpha A(t)V(t)}{1+\eta A(t)+\gamma V(t)}$ modelled by Beddington-Deangelis functional response (System 2, *Method*) (Cantrell et al., 2001). Thirdly, System 3 combined switching function $S_L(A) = \frac{L}{1+e^{-k(A-A_0)}} - A$ with interaction term $\frac{\alpha A(t)V(t)}{1+\eta A(t)}$ modelled by Hill function (System 3, *Method*). Finally, System 4 combined switching function $S_L(A) = \frac{2}{1+e^{-k(A-A_0)}} - 1$ with interaction term $\alpha A(t)V(t)$ modelled by law of mass action (System 4, *Method*).

4. Virus neutralisation kinetics for neutralisation group and enhancement group exhibits different behaviours

Virus neutralisation kinetics were quantified for seasonal influenza A/H3N2 viruses against homologous antisera using focus reduction assay (FRA), allowing the estimation of viral titre before and during virus-antibody incubation (see *Methods*). We selected 41 FRA datasets (21 from neutralisation group and 20 from enhancement group).

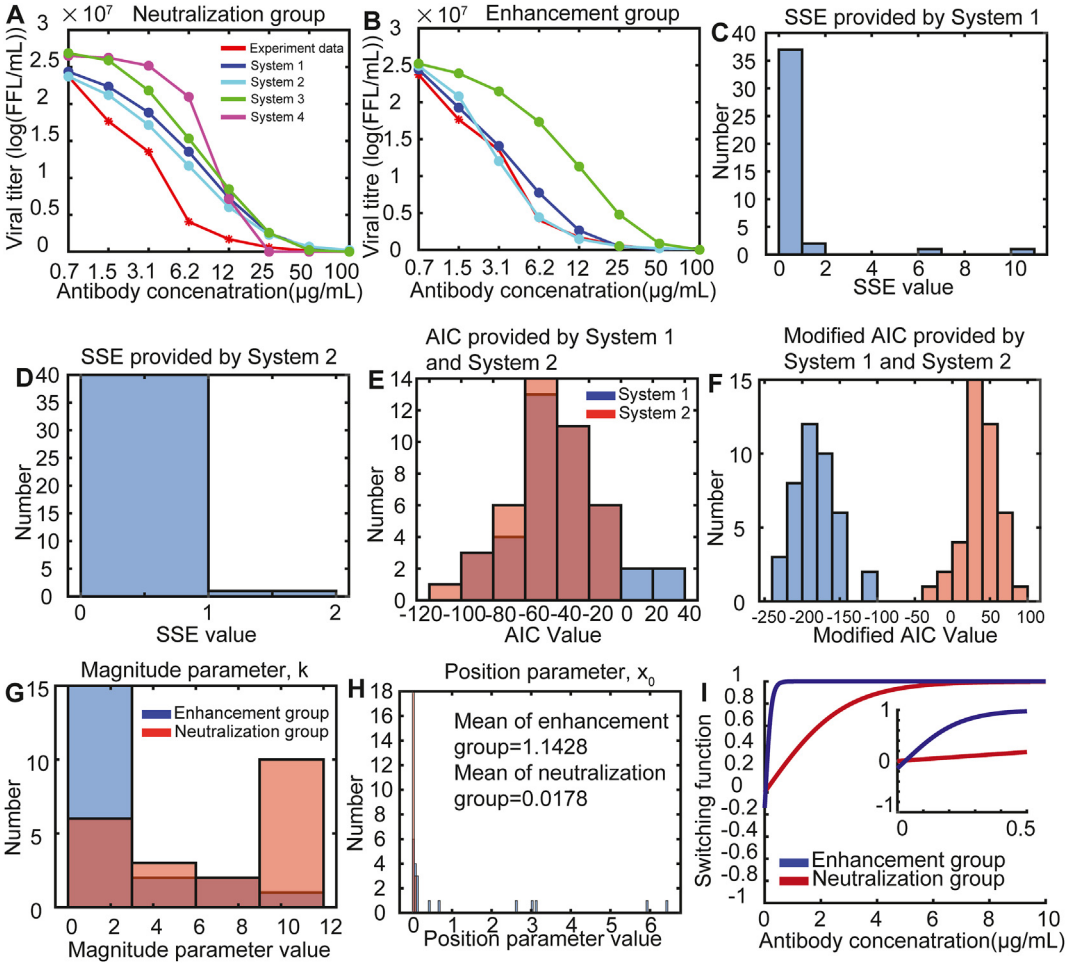

Fig. 3. Quantitative relationship between virus titre and antibody concentration established through Focus Reduction Assays. (A) Enhancement group and **(B)** neutralisation group in Focus Reduction Assays and fitted with four proposed model. Purple, green, red and blue lines and circles represent experiment data and estimated value provided by System 1, System 2, System 3 and System 4. Note in Panel **(B)**, estimated values provided by System 3 and System 4 overlap, and purple circles and curve cannot be seen. **(C)** Histogram of SSE provided by System 1. **(D)** Histogram of SSE provided by System 2. **(E)** Histogram of AIC provided by System 1 and System 2. **(F)** Histogram of modified AIC provided by System 1 and System 2. **(G)** Histogram of magnitude parameter *k* estimated from enhancement group and neutralisation group. **(H)** Histogram of position parameter x_0 estimated from enhancement group and neutralisation group. **(I)** Switching function with respect to antibody concentration and switching parameters estimated from enhancement and neutralisation groups.

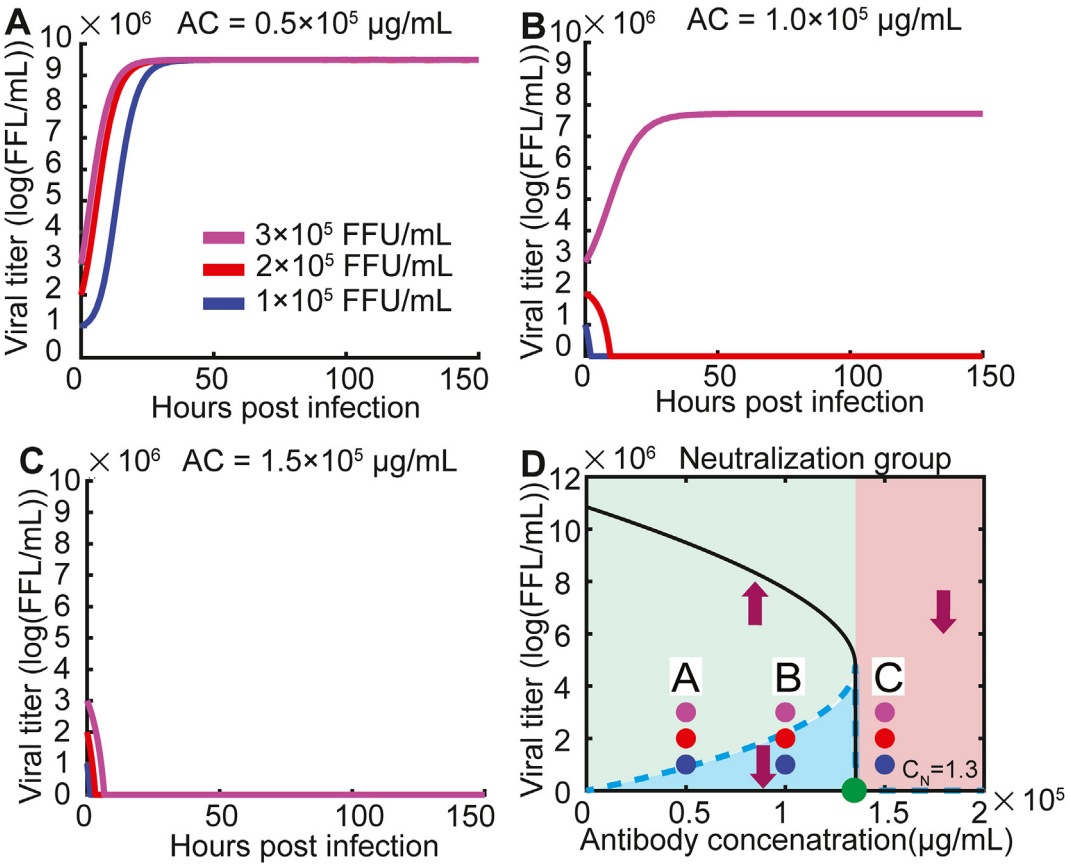

Fig. 4. Simulated kinetics of influenza kinetics with different combinations of inoculum size and antibody concentration with low antibody consumption (Neutralisation group). **(A)** and **(B)** when antibody concentration was between 0 and C_N, virus was not affected if viral inoculum was above the dashed cyan curve and was inhibited if viral inoculum was below the dashed cyan curve. **(C)** Virus with any inoculum size was inhibited when antibody concentration was greater than C_N. Bifurcation diagram **(D)** showing viral titre as a function of antibody concentration. Threshold value is located on $C_N = 1.3 \times 10^5$ FFU/mL (green solid cycle). Viral inoculum threshold increases with increase of antibody concentration (cyan dashed curve). The maximal capacity of viral titre decreases with increases of antibody concentration (black solid curve). Purple arrows represent any viral inoculum size. In Panel (D), A represents AC $= 0.5 \times 10^5$ μg/mL, B represents AC $= 1 \times 10^5$ μg/mL, C represents AC $= 1.5 \times 10^5$μg/mL, and AC refers to antibody concentration. Blue, red and purple curve and circles represent viral kinetics with viral inoculum 1×10^6, 2×10^6, and 3×10^6 FFU/mL in (A–D).

First, we found System 1 and System 2 can fit 41 FRA dataset independent of enhancement group or neutralisation group, but System 3 and System 4 cannot (shown in Fig. 3A–D, Fig. S1 and Tables S1–4, Supplementary material). Then, comparing sum of squared error (SSE) and Akaike information criterion (AIC), System 2 provides 23 lower SSE and lower 33 AIC than System 1 does (shown in Fig. 3C–E, and Tables S1–2, Supplementary material); System 1 always provides lower modified AIC (Fig. 3F), which grants for future research.

Next, two parameters in switching function, magnitude parameter k and position parameter A_0, also exhibit significant difference in neutralisation and enhancement group. First, magnitude parameter k estimated from enhancement group follows unimodal distribution and its peak majorly ranges from 0 to 2. On the other hand, magnitude parameter k estimated from enhancement group follows bimodal distribution, and its minor peak range from 0 to 2, and major peak range from 9 to 10 (shown in Fig. 3G). However, position parameter A_0 estimated from neutralisation group is lower than that estimated from enhancement group, because mean of position parameter A_0 estimated from enhancement group and neutralisation group are 1.1428 and 0.0178 (p-value = 0.0141, shown in Fig. 3H). Finally, switching function of enhancement or neutralisation group converges to 1 with increase of antibody concentration. Comparing with neutralisation group, switching function of enhancement group increases more rapidly with increase of antibody concentration (shown in Fig. 3I). Switching function in both groups has antibody concentration interval corresponding to enhancement, but that in enhancement group provides a large antibody concentration interval (shown in Fig. 3I).

5. Antibody-induced bistable influenza kinetics exist independent on neutralisation group or enhancement group

Combining virus neutralisation kinetics (estimated from neutralisation group or enhancement group) with influenza replication (Xu, 2022), we have influenza kinetics in presence of antibody (System 6, *Methods*). Using bifurcation diagram and

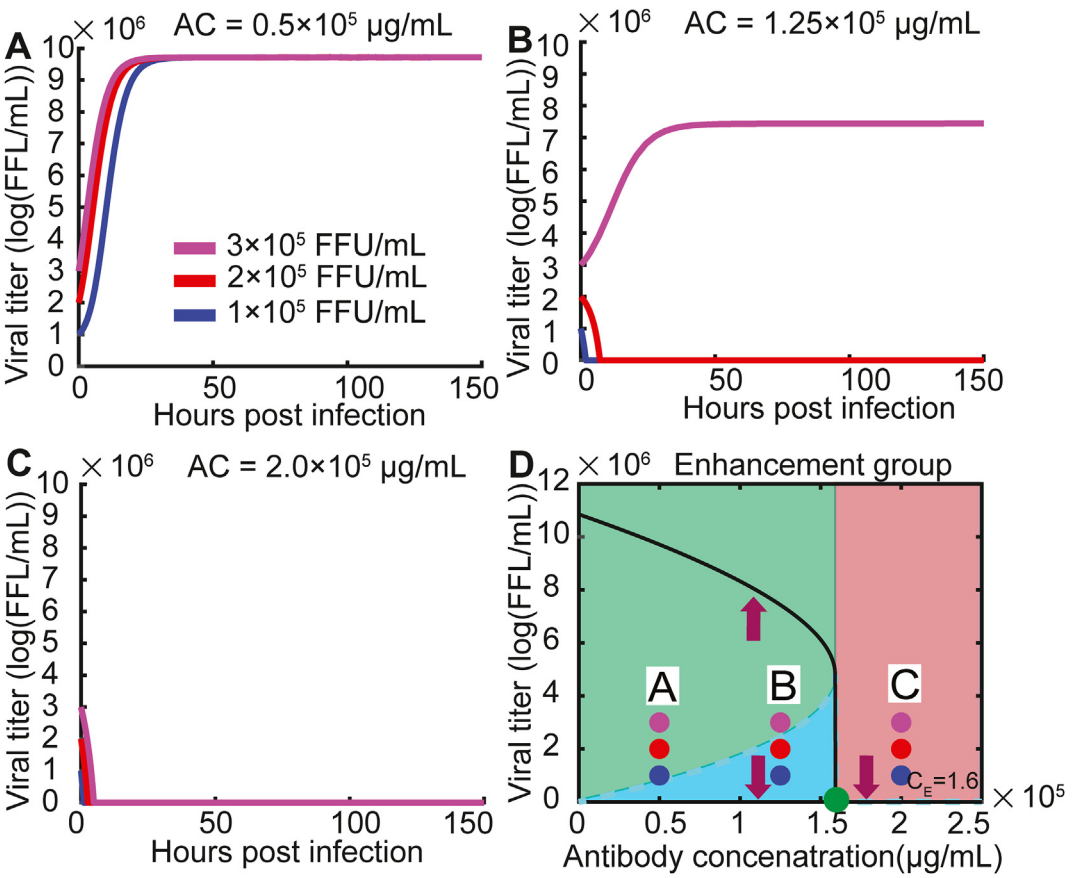

Fig. 5. Simulated kinetics of influenza kinetics with different combinations of inoculum size and antibody concentration (Enhancement group). (A) and **(B)** when antibody concentration was between 0 and C_E, virus was not affected if viral inoculum was above the dashed cyan curve and was inhibited if viral inoculum was below the dashed cyan curve. **(C)** Virus with any inoculum size was inhibited when antibody concentration was greater than C_N. Bifurcation diagram **(D)** showing viral titre as a function of antibody concentration. Threshold values is located on $C_E = 1.6 \times 10^5$ FFU/mL (green solid cycle). Viral inoculum threshold increases with increase of antibody concentration (cyan dashed curve). The maximal capacity of viral titre decreases with increases of antibody concentration (black solid curve). Purple arrows represent any viral inoculum size. In Panel (D), A represents AC = 0.5×10^5 μg/mL, B represents AC = 1×10^5 μg/mL, C represents AC = 1.5×10^5μg/mL, and AC refers to antibody concentration. Blue, red and purple curve and circles represent viral kinetics with viral inoculum 1×10^6, 2×10^6, and 3×10^6 FFU/mL in (A–D).

numerical simulation, we demonstrated that antibodies induced bistable influenza kinetics exists independent of neutralisation group or enhancement group (shown in Figs. 4 and 5). Bistability refers that for a given antibody concentration, large viral inoculum sizes remain infectious and small viral inoculum sizes are inhibited. Moreover, comparing with enhancement group, neutralisation group provide a lower threshold value corresponding to influenza infectivity (shown in Figs. 4D and 5D); this explained the enhanced susceptibility, severity, and mortality on patients (Gagnon et al., 2018; Shanks et al., 2012).

First, we used neutralisation group as an example. In simulations of influenza replication kinetics with virus neutralisation kinetics (estimated from neutralisation group) estimated from neutralisation group, there existed of one threshold C_N that divided the antibody concentration interval into two regimes, and the threshold value $C_N = 1.3 \times 10^5$ μg/mL (shown in Fig. 4D). For this figure, the neutralisation parameters are row thirty-nine of Table S2. At different antibody concentration intervals, viral kinetics exhibited different dynamics. Virus kinetics exhibited bistability at the antibody concentration interval between 0 and C_N, where small viral inoculums were inhibited, and large viral inoculums established infection at the same antibody concentration (shown in Fig. 4B). The viral inoculum threshold (above which the virus is not affected) increased with increase of antibody concentration (the red dashed curve in Fig. 4D). For example, at low antibody concentration A = 0.5×10^5 μg/mL, virus inoculum sizes 1×10^6 FFU/mL, 2×10^6 FFU/mL and 1×10^6 FFU/mL all maintain infectivity (shown in Fig. 4A and D), whereas at high antibody concentration A = 1×10^5 μg/mL, only high inoculum sizes 1×10^6 FFU/mL maintain infectivity (shown in Fig. 4B and D). At antibody concentrations higher than the threshold C_N, the virus was inhibited independent of inoculum size (shown in Fig. 4C and D). Antibody concentration is approximated to be constant over 150 h incubation (shown in Fig. S2).

Next, for enhancement group, we found that observed antibody-induced bistable influenza kinetics still exist (shown Fig. 5A, B and 5C). However, threshold of antibody concentration corresponding influenza infectivity provided in

enhancement group $C_E = 1.6 \times 10^5$ μg/mL (shown in Fig. 5D) is higher than that provided by neutralisation group $C_N = 1.3 \times 10^5$ μg/mL. Antibody concentration is approximated to constant over 150 h incubation (shown in Fig. S3). For this figure, the neutralisation parameters are row six of Table S2.

6. Discussion

Dissecting the viral titre estimated from 41 FRA datasets (21 from neutralisation group and 20 from enhancement group), switching function with Logistic function performs better than that with hyperbolic tangent variant independent of neutralisation group or enhancement group. Switching function estimate from neutralisation group or enhancement group exhibited different outcomes; particularly, magnitude parameter estimated from enhancement group is lower, but position parameter estimated from enhancement group is higher. A lower magnitude parameter refers that enhancement group more rapidly switches from enhancement to neutralisation with increase of antibody concentration, and a higher position parameter indicates that enhancement group provides a larger antibody concentration interval corresponding to enhancement. Integrating neutralisation kinetics with influenza replication, antibody-induced bistable influenza kinetics independent on neutralisation group or enhancement group. However, comparing with neutralisation group, enhancement group provides higher threshold value of antibody concentration corresponding to influenza infectivity. This explains the observed phenomenon that on individual level, antibody dependant enhancement leads to enhanced susceptibility, severity, and mortality. On population level, combining with antigenic seniority, antibody dependant enhancement may promote H1N1 and H3N2 influenza virus cooperate to sustain long-term circulation.

Reference (Gujarati et al., 2014) and (Tang et al., 2020) used hyperbolic tangent variant as switching function. Here, we compared the combination of hyperbolic tangent variant and saturated model described by Beddington-Deangelis functional response (System 1), Logistic function variant and saturated model described by Beddington-Deangelis functional response (System 2), Logistic function variant and semi-saturated model described by Hill function (System 3), and Logistic function variant and linear model by law of mass action (System 4). Comparing SSE and AIC, we suggested that Logistic function used as switching function and Beddington-Deangelis functional response used as interaction term performs better. Admittedly, comparing modified AIC, hyperbolic function used as switching function and Beddington-Deangelis functional response used as interaction term performs better, because we used residual sum of squares to estimate parameters. In future research, it is worthwhile to perform FRA assay with several biological replicates and use maximum likelihood estimation to estimate parameters. Unexpectedly, switching function in both groups has a certain antibody concentration interval corresponding to enhancement, and enhancement group provides a larger antibody concentration interval corresponding to enhancement. Switching function in enhancement group rapidly increase and converges to 1 with increase of antibody concentration. This coincides with the observed phenomenon that antibody dependent enhancement occurs on low antibody concentration, and antibody dependant neutralisation occurs on high antibody concentration. System 1 (hyperbolic tangent variant and Beddington-Deangelis functional term) has eight parameters, and System 2 (Logistic function variant and saturated model) also has six parameters. This hints that switching function and interaction term work together to determine fitting outcomes.

Antigenic seniority, also known as HA imprinting, describes the phenomenon of having higher antibody titres to influenza variants encountered earlier in life relative to more recent encounters (Lessler et al., 2012). Moreover, the further the relatedness between test virus and reference virus (virus used to produce antisera) was, the more probable that enhancement occurred (Xu, 2022). In this manuscript, we propose that antibody dependent enhancement provide higher threshold value of antibody concentration corresponding to influenza infectivity. This implies that H1N1 and H3N2 influenza virus cooperate to sustain long-term circulation on human populations. Specifically, H1N1 virus infected human cohort first, H3N2 virus infected next and H3N2 virus infected human cohort infected human cohort on the third round. According to antigenic seniority, human cohort majorly produces antibody specific to H1N1 virus, which promote H3N2 virus replication and H3N2 worsen influenza infection; similarly, human cohort majorly produces antibody specific to H3N2 virus, which promote H1N1 virus replication and H1N1 worsen influenza infection. Due to this positive feedback loop, H1N1 and H3N2 influenza virus cooperate to maintain long-term circulation on human populations.

Using viral replication parameters from one experiment and virus neutralisation parameters from another experiment, the existence of antibody-induced bistable viral kinetics independent of enhancement group or neutralisation group has been predicted. To identify the bistable antibody interval for a specific test virus and reference virus (reference virus is used to produce antisera/antibody) pair and antibody concentration interval, further work is required to experimentally validate this prediction in a single experimental system.

7. Method

7.1. Mathematical model

To quantitatively understand the role of antibody concentration in switching between enhancement at low antibody concentration and neutralisation at high antibody concentration, we propose the following four systems to fit FRA assay data.

1. For switching function described by hyperbolic tangent variant and unsaturated interaction term modelled by Beddington-Deangelis functional term, the rate of change of viral titre and antibody concentration is given by

$$\begin{cases} \dfrac{dV(t)}{dt} = \dfrac{-\alpha A(t)V(t)}{1+\eta A(t)+\gamma V(t)} S_T(A) \\ \dfrac{dA}{dt} = -\dfrac{\phi A(t)V(t)}{1+\eta A(t)+\gamma V(t)} \\ S_T(A) = \dfrac{\tanh\left(C_1(A-A_{max})\right)}{1+e^{-C_2(A-A_{min})}} \end{cases}, \tag{1}$$

2. Switching function described by Logistic function variant and unsaturated interaction term modelled by Beddington-Deangelis functional response, the rate of change of viral titre and antibody concentration is given by

$$\begin{cases} \dfrac{dV(t)}{dt} = \dfrac{-\alpha A(t)V(t)}{1+\eta A(t)+\gamma V(t)} S_L(A) \\ \dfrac{dA}{dt} = \dfrac{-\phi A(t)V(t)}{1+\eta A(t)+\gamma V(t)} \\ S_L(A) = \dfrac{2}{1+e^{-k(A-A_0)}} - 1 \end{cases} \tag{2}$$

3. Switching function described by Logistic function variant and semi-saturated interaction term modelled by Hill function, the rate of change of viral titre and antibody concentration is given by

$$\begin{cases} \dfrac{dV(t)}{dt} = \dfrac{-\alpha A(t)V(t)}{1+\eta A(t)} S_L(A) \\ \dfrac{dA}{dt} = \dfrac{-\phi A(t)V(t)}{1+\eta A(t)} \\ S_L(A) = \dfrac{2}{1+e^{-k(A-A_0)}} - 1 \end{cases} \tag{3}$$

4. For switching function described by Logistic function variant and unsaturated interaction term modelled by law of mass action, the rate of change of viral titre and antibody concentration is given by

$$\begin{cases} \dfrac{dV(t)}{dt} = -\alpha A(t)V(t)S_L(A) \\ \dfrac{dA}{dt} = -\phi AV \\ S_L(A) = \dfrac{2}{1+e^{-k(A-A_0)}} - 1 \end{cases} \tag{4}$$

Interpretation of parameter goes as follows. $A(t)$ represents antibody concentration with respect to time t. α represents the virus neutralisation rate by antibody binding; ϕ represents antibody consumption rate by binding to virus; η controls the saturation in neutralisation rate as antibody concentration increases; γ controls the saturation in neutralisation rate as viral

titre increases. A_{max} represents threshold value between antibody dependant enhancement and antibody dependant neutralisation. A_{min} represents parameter for low influenza specific antibody presenting low level of antibody dependent enhancement. Parameters C_1 and C_2 control switching function $S_T(A)$ changes its value smoothly from 0 to -1 as antibody concentration A becomes greater than A_{min} and to $+1$ as antibody concentration A rises above A_{max}. Parameter k refers magnitude parameter and A_0 refers position parameter determining enhancement and neutralisation group.

Since, in the absence of neutralising antibody, influenza replication *in vitro* and *in vivo* is solely limited by the availability of susceptible cells (Xu, 2022), the change of influenza virus is described as the one-dimensional ODE model,

$$\frac{dV(t)}{dt} = \frac{\rho V(t)}{1+\beta V(t)} - \sigma V(t) \tag{5}$$

where $V(t)$ represent viral titre $V(t)$ represents viral titre with respect to time t. Parameter ρ represents replication rate of influenza virus; β controls natural saturation of viral replication at high viral titre ; σ represents degradation rate of influenza virus. Parameter values $\rho = 1.2308$ FFU/mL/hour, $\beta = 5.3831$ hour/FFU/mL and $\sigma = 0.7770$ FFU/mL/hour.

Combining System 2 and 5 leads to the rate of change of viral titre and antibody concentration,

$$\begin{cases} \dfrac{dV(t)}{dt} = \dfrac{\rho V(t)}{1+\beta V(t)} - \sigma V(t) - \dfrac{\alpha A(t) V(t)}{1+\eta A(t)+\gamma V(t)} S_L(A) \\ \dfrac{dA}{dt} = \dfrac{-\phi A(t) V(t)}{1+\eta A(t)+\gamma V(t)} \\ S_L(A) = \dfrac{L}{1+e^{-k(x-x_0)}} - A \end{cases} \tag{6}$$

7.2. Parameter estimation

For the estimation of virus neutralisation parameters, influenza virus within 1-h incubation using the formula is estimated as titre $=$ FN $\times$ 10^{DR} $\times$ SV FFU/mL, where FN represented the number of foci in each well, DR represented the dilution rate, SV represented the sample volume and FFU represented the focus formation unit. The sum of squared error (SSE) is $SSE_1 = \sum_{i=1}^{n} (log_{10}(T_A) - log_{10}\, F(T_A))^2$, where T_A is experiment viral titre concentration and estimated viral titre concentration over serial dilution.

Next, the AIC ($AIC = 2k + nln\left(\frac{RSS^2}{n}\right)$) and the modified AIC ($AICc = 2k + nln\left(\frac{RSS^2}{n}\right) + \frac{2k^2+2k}{n-k-1}$) for small sample sizes of unsaturated and saturated neutralisation models were calculated, where k is the number of parameters, n is the sample size, and RSS represents the residual sum of squares.

7.3. Focus reduction assay

To quantify the neutralisation kinetics of influenza viruses, focus reduction assays (FRA) for seasonal influenza A/H3N2 strains against homologous antisera were performed. The viral titre before and during virus-antibody incubation could be estimated. Serial dilutions of antisera were incubated for 1 h with diluted virus. A total of 100 μL of the virus-sera mixture was then applied to confluent MDCK cells and incubated for 18–20 h at 35 °C in 5% CO_2. The FRA was performed for each virus individually with antisera raised against a representative set of A/H3N2 viruses. The virus-sera mixture was added to confluent MDCK cell lines. Following overnight incubation, focus formation units (FFU) were quantified by immunostaining using an anti-nucleoprotein monoclonal antibody and subsequent detection using a horseradish peroxidase (HRP)-conjugated secondary antibody and TrueBlue substrate. The number of FFU per well was quantified from plate images using an Immunospot analyser and Biospot software.

CRediT authorship contribution statement

Shilian Xu: Writing – original draft, Software, Investigation, Conceptualization. **Jiaru Yang:** Writing – original draft, Data curation.

Declaration of competing interest

The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.idm.2024.07.003.

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