Infection, inflammation, and intervention: mechanistic modelling of epithelial cells in COVID-19

Supplementary Information

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S1 Parameter sensitivity

Upon understanding the criteria for which healthy and infectious steady-states can be achieved in the MVSIC model, it is natural to ask what differences in a patient's underlying physiology result in different qualitative responses to viral infection. For instance, if a person's immune cells are slower to recruit pro-inflammatory mediators to the infected epithelial cells, will this result in a mild or severe case of inflammation later? To understand what, if any, qualitative features change when altering a certain parameter grouping, we perform a sensitivity analysis of the parameters appearing in the MVSIC model.

One method of performing a sensitivity analysis is to determine which parameters in a model have the greatest influence on a particular model output. With an output selected, we can then determine the extent to which uncertainty in model parameters contributes to the variability of model outputs [1]. Various types of sensitivity analyses can be utilised [2]; we consider the extended Fourier amplitude sensitivity analysis (eFAST), which is a method based on variance decomposition techniques (c.f. [3, 4]). Input parameters are varied resulting in a variation in model output, where the variation is quantified using the metric $s^2 = \sum_{i=1}^{N}(y_i - \bar{y})^2/(N-1)$, where N is the total number of model simulations, y_i the ith model output, and $\bar{y}$ the sample mean. The algorithm partitions the output variance, determining what proportion of the variance can be attributed to the variation of each parameter. Partitioning of variance works by varying each parameter at a particular frequency using a sinusoidal function. Fourier analysis is used to measure the strength of each parameter's frequency in the model output, which provides a quantification of the model's sensitivity to the parameter. The total number of model simulations N, is given by $N = N_S \times N_R \times k$, where N_s is the total number of samples per search curve, k the number of varied parameters, and N_R the resampling size. In this study we use $N_S = 257$, $N_R = 4$, and $k = 16$. As parameters are varied simultaneously over a pre-defined parameter space, this method is a global sensitivity analysis. In our analysis, the parameter space relates to five times smaller and five times larger than the Mild/Healthy state parameters shown in Table 2, thereby incorporating all three qualitative states previously discussed.

Various outputs of the MVSIC model can be chosen, depending on what variable and feature is considered the most important. For instance, we can determine which parameters affect the minimum value of S, denoted as $S_{\min}$, as this key quantity is strongly linked to the presence or absence of a hyperinflammatory state. Another suitable model output is a quantity linked to the fluctuating levels of pro-inflammatory cytokines, since disruptions in the immune system from large fluctuations will cause additional strain on the immune response. By defining

$$C_T = \frac{1}{T}\int_0^T \left|\frac{\mathrm{d}C}{\mathrm{d}t}\right| \,\mathrm{d}t, \tag{S1}$$

we obtain a suitable metric for describing the average fluctuations in cytokine levels over the interval $0 \leq t \leq T$. A final metric that we will consider is related to the difference in maximum and minimum cytokine levels after a certain amount of time has passed (e.g. $t > 20$); we denote this metric with $\Delta C_{t>20}$. This metric is also associated with fluctuating cytokine levels, but does not penalise stable co-existence equilibria (such as in the asymptomatic state) as severely.

The eFAST analysis outputs both first-order and total-order sensitivity indices between 0 and 1, representing the fraction of model output variance accounted for by the input variation of a given parameter. The first-order sensitivity index of a parameter evaluates the fractional contribution of a single parameter on the output variance, while the total-order index also takes into account the interaction between the parameter in consideration and other model parameters. In Figure S1, we observe the relative sensitivity of the MVSIC model parameters with the three aforementioned model outputs. Parameters with a total-order sensitivity index less than or equal to that of the dummy parameter, shown in the right column of Figure S1, should be considered not significantly

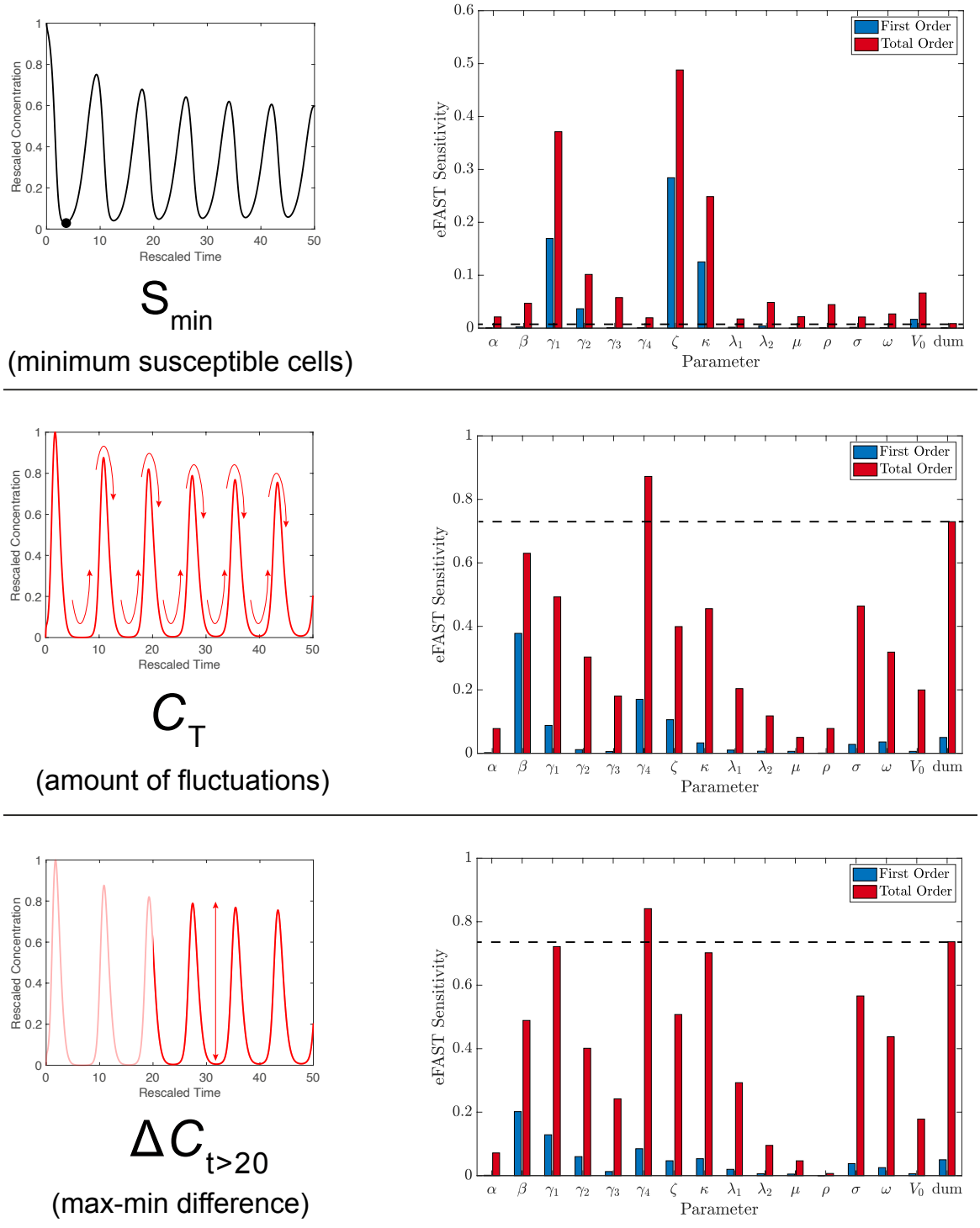

Figure S1: **Sensitivity of MVSIC model parameters on various outputs.** Model parameters that alter a particular output more are larger in eFAST sensitivity magnitude. Parameters whose total-order sensitivity values are below the dummy parameter (black dashed line) are considered to be insignificant. Three model outputs are shown: (top) the minimum value of S, denoted as $S_{\min}$; (middle) the cumulative amount of pro-inflammatory mediator fluctuations, denoted as C_T and defined in (S1); (bottom) the difference in maximum and minimum pro-inflammatory mediator levels for $t > 20$, denoted as $\Delta C_{t>20}$.

different from zero.

When using the $S_{\min}$ model output, we see that the parameters associated with the existence of the infectious steady-state, characterised by the inequality shown in (S8), are the most significant parameters. This is to be expected: parameter regimes in the healthy/mild qualitative states are less likely to experience a steep drop in $S(t)$. Furthermore, we note that the parameters α, γ_3, and λ_1 are insignificant parameters with respect to the $S_{\min}$ output, as they have the same total-order sensitivity magnitude as the dummy parameter.

As the model parameters κ and γ_4 can be effectively modified by the absence or presence of the intervention parameters ϵ and ϕ, we conclude that the intervention strategies associated with reducing viral transmission and pro-inflammatory cytokine levels are indeed significant and plausible in this model. Naturally, the intervention parameter grouping associated with reducing viral transmission, $\kappa(1-\epsilon)$, is one of the most significant parameter groupings present in the model, as the presence of viral loads are the catalyst for a potential hyperinflammatory state. However, it should be also noted that the intervention parameter grouping associated with reducing pro-inflammatory cytokine levels, $\gamma_4(1+\phi)$, is as significant of a parameter grouping as the initial viral load, V_0, in the $S_{\min}$ output. In other words, altering the initial viral load in the MVSIC model has about the same amount of influence as altering the pro-inflammatory cytokine clearance rate via intervention.

S2 Derivation of unique infectious steady-state

As discussed in Section 2.3, the infectious steady-state $(S^*, I^*, V^*, M^*, C^*)$ of the MVSIC model has strictly positive components and satisfies the following system of nonlinear equations:

$$\kappa(1-\epsilon)[1-\kappa(1-\epsilon)V^*][\zeta-\gamma_1(\lambda_1 M^*+1)] = \gamma_1\gamma_2(\lambda_1 M^*+1)(\lambda_2 M^*+1), \tag{S2}$$

$$C^* = M^* - \frac{\rho V^*[1-\kappa(1-\epsilon)V^*]}{\gamma_3(\alpha+V^*)}, \tag{S3}$$

$$\gamma_4(1+\phi)C^* - \mu M^*\left(\frac{V^{*m}}{\omega^m+V^{*m}}\right) = [1-\kappa(1-\epsilon)V^*]\left[1+\frac{\sigma\kappa(1-\epsilon)V^*}{\gamma_1(\lambda_1 M^*+1)}\right]\left(\frac{V^{*n}}{\beta^n+V^{*n}}\right). \tag{S4}$$

We can solve (S2) for M^* and determine that

$$M^*(V^*) = \mathcal{A}(V^*)\left[\sqrt{1+\mathcal{B}(V^*)}-1\right], \tag{S5}$$

where

$$\mathcal{A}(V^*) = \frac{1}{2\lambda_1\lambda_2}\left[\lambda_1+\lambda_2+\frac{\lambda_1\kappa(1-\epsilon)[1-\kappa(1-\epsilon)V^*]}{\gamma_2}\right], \tag{S6}$$

$$\mathcal{B}(V^*) = \frac{(\zeta-\gamma_1)\kappa(1-\epsilon)[1-\kappa(1-\epsilon)V^*]-\gamma_1\gamma_2}{\gamma_1\gamma_2\lambda_1\lambda_2\mathcal{A}(V^*)^2}. \tag{S7}$$

To ensure that $M^* > 0$, the infectious steady-state can only exist when $\mathcal{B}(V^*) > 0$ for any $V^* > 0$, implying that

$$\gamma_1 < \frac{\zeta\kappa(1-\epsilon)}{\gamma_2+\kappa(1-\epsilon)}. \tag{S8}$$

To determine what value of V^* corresponds to the infectious steady-state, we substitute (S2), (S3) and (S5) into (S4) and obtain

$$M^*\left[\gamma_4(1+\phi)-\mu\left(\frac{V^{*m}}{\omega^m+V^{*m}}\right)\right] = [1-\kappa(1-\epsilon)V^*]\left[\left(1+\frac{\sigma\kappa(1-\epsilon)V^*}{\gamma_1(\lambda_1 M^*+1)}\right)\left(\frac{V^{*n}}{\beta^n+V^{*n}}\right)+\frac{\rho\gamma_4(1+\phi)V^*}{\gamma_3(\alpha+V^*)}\right]. \tag{S9}$$

Since $M^*(V^*)$ is monotone decreasing and positive, from (S5) we have that $V/[\lambda_1 M^*(V^*)+1]$ is monotone increasing. Consequently, we have that

$$\mathcal{F}(V) := \frac{M(V)\left[\gamma_4(1+\phi)-\mu\left(\frac{V^m}{\omega^m+V^m}\right)\right]}{\left(1+\frac{\sigma\kappa(1-\epsilon)V}{\gamma_1(\lambda_1 M(V)+1)}\right)\left(\frac{V^n}{\beta^n+V^n}\right)+\frac{\rho\gamma_4(1+\phi)V}{\gamma_3(\alpha+V)}} \tag{S10}$$

is always monotone decreasing. Since we require $\mathcal{F}(V^*) = S^* = 1-\kappa(1-\epsilon)V^* \geq 0$, we are only interested in values of V^* where both $M(V^*) \geq 0$ and $\gamma_4(1+\phi) \geq \mu\left(\frac{V^{*m}}{\omega^m+V^{*m}}\right)$. In other words, we only consider $V^* \in (0, V_{\max}]$, where

$$V_{\max} = \begin{cases} \min\left(\dfrac{1}{\kappa(1-\epsilon)} - \dfrac{\gamma_1\gamma_2}{\kappa^2(1-\epsilon)^2(\zeta-\gamma_1)},\ \omega\left[\dfrac{\gamma_4(1+\phi)}{\mu-\gamma_4(1+\phi)}\right]^{\frac{1}{m}}\right), & \mu > \gamma_4(1+\phi), \\ \dfrac{1}{\kappa(1-\epsilon)} - \dfrac{\gamma_1\gamma_2}{\kappa^2(1-\epsilon)^2(\zeta-\gamma_1)}, & \mu \leq \gamma_4(1+\phi). \end{cases} \tag{S11}$$

By construction, we note that when (S8) holds, $1-\kappa(1-\epsilon)V_{\max} > 0$. Therefore, the infectious steady-state exists for all values of $V^* > 0$ that satisfy

$$\mathcal{F}(V^*) = 1-\kappa(1-\epsilon)V^*, \qquad V^* \in (0, V_{\max}]. \tag{S12}$$

When $V^* \to 0^+, \mathcal{F}(V^*) \to +\infty$ and thus $\mathcal{F}(V^*) > 1-\kappa(1-\epsilon)V^*$ as $V^* \to 0^+$. When V^* attains its maximal feasible value, $V_{\max}$, this corresponds to $\mathcal{F}(V_{\max}) = 0$ and $\mathcal{F}(V_{\max}) < 1-\kappa(1-\epsilon)V_{\max}$ when (S8) holds. From the Intermediate Value Theorem, there must be at least one value $\hat{V} \in (0, V_{\max})$ such that $\mathcal{F}(\hat{V}) = 1-\kappa(1-\epsilon)\hat{V}$.

To show that this infectious steady-state is unique, we suppose instead that there are exactly two values $\tilde{V} \neq \hat{V}$, that satisfy (S12). Since $\mathcal{F}(V^*) \to +\infty$ as $V^* \to 0^+$, while $\mathcal{F}(V_{\max}) = 0$, this means that we must also have $\mathcal{F}'(\tilde{V}) = -\kappa(1-\epsilon)$. In other words, $\mathcal{F}'(\tilde{V})$ must also be tangential to $1-\kappa(1-\epsilon)\tilde{V}$ as well as satisfying (S12) . Furthermore, we have that

$$\frac{\mathcal{F}(\tilde{V})-1}{\tilde{V}} = \mathcal{F}'(\tilde{V}) = -\kappa(1-\epsilon), \tag{S13}$$

implying that for some $\tilde{V} \in (0, V_{\max})$,

$$\tilde{V}\mathcal{F}'(\tilde{V}) - \mathcal{F}(\tilde{V}) + 1 = 0. \tag{S14}$$

However, it can be shown, using symbolic evaluation software or equivalents, that $\tilde{V}\mathcal{F}'(\tilde{V}) - \mathcal{F}(\tilde{V}) + 1$ is strictly negative for $\tilde{V} \in [0, V_{\max}]$, which yields a contradiction. As any larger number of infectious steady-states would have to transition through the aforementioned 'two-solution' case in parameter space, we conclude that the infectious steady-state is therefore unique.

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