

Mathematical model of a cytokine storm

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Abstract

Cytokine storm is a life-threatening inflammatory response that is characterized by hyperactivation of the immune system, and which can be caused by various therapies, autoimmune conditions, or pathogens, such as respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease COVID-19. While initial causes of cytokine storms can vary, late-stage clinical manifestations of cytokine storm converge and often overlap, and therefore a better understanding of how normal immune response turns pathological is warranted. Here we propose a theoretical framework, where cytokine storm phenomenology is captured using a conceptual mathematical model, where cytokines can both activate and regulate the immune system. We simulate normal immune response to infection, and through variation of system parameters identify conditions where, within the frameworks of this model, cytokine storm can arise. We demonstrate that cytokine storm is a transitional regime, and identify three main factors that must converge to result in storm-like dynamics, two of which represent individual-specific characteristics, thereby providing a possible explanation for why some people develop CRS, while others may not. We also discuss possible ecological insights into cytokine-immune interactions and provide mathematical analysis for the underlying regimes. We conclude with a discussion of how results of this analysis can be used in future research.

Keywords: cytokine release syndrome; CRS, cytokine storm, mathematical model, IFN-gamma; IL-6; second touch hypotheses

32 Introduction

33 Cytokine storm, a life-threatening inflammatory response involving elevated levels of cytokines
34 and hyper activation of the immune system, has recently gained particular note as one of the
35 causes of morbidity and mortality from coronavirus disease COVID-19 (1). It has previously
36 been observed in a variety of other circumstances, including graft vs host disease (2) and other
37 viral infections, such as SARS (3); cytokine storms have also been implicated as one of the key
38 culprits in the severity of the 1918 Spanish flu pandemic (4). Additionally, cytokine storms have
39 been observed as a side effect of certain anti-cancer therapeutic interventions, such as chimeric
40 antigen receptor, of CAR-T cell therapy (5) and bispecific T cell engagers, also known as BiTEs
41 (6). One of the most notable therapy-induced instances of cytokine storm was the case of a
42 Phase I clinical trial of monoclonal antibody TGN1412, which resulted in severe damage to the
43 health of six volunteers that participated in the trial despite very accurately chosen initial doses
44 that were administered to them (7); numerous additional reports of the details of the case can
45 be found in the literature.

46 Cytokine storms are most often characterized by severe lung infections, which can lead
47 to respiratory distress, multi-organ failure, sepsis and in some cases, death (5,8,9).
48 Mechanistically, cytokine storms are mitigated by cytokines, which are molecules involved in
49 supporting and regulating the immune response. Cytokine interactions form complex networks,
50 geared towards mounting fast and efficient immune response against pathogens while also
51 preventing excessive damage to normal tissues. If these interactions become destabilized,
52 cytokine storms, or hypercytokinemia, may occur, where immune response causes greater
53 collateral harm than benefit. Some prominent cytokines that are elevated during cytokine storms
54 include interferon (IFN)-gamma, tumor necrosis factor (TNF)-alpha, as well as interleukins (IL)-
55 6,8 and 10 (1,3,5,8,9). More generally, cytokine storms appear to reflect a scenario when the
56 response to a pathogen, or an immune stimulatory agent, rather than a pathogen itself, results
57 in pathology, and this is the mechanism that we wish to explore in greater detail.

58 Notably, while they are often used interchangeably, there exists a distinction between
59 the terms “cytokine storm” and “cytokine release syndrome” (CRS). Cytokine storm typically
60 refers to an acute reaction, while CRS typically refers to a more delayed response. There exists
61 a discussion about qualitative differences between the two responses, how they are triggered
62 and how they proceed (5), although it appears that the final qualitative dynamics are very similar
63 between the two. Henceforth we will be using the term cytokine storm; however, we believe that
64 the proposed model can be used for better understanding of CRS as well.

65 Several mathematical models have been developed to try to create and formalize a
66 framework for better mechanistic understanding of cytokine storm dynamics. Waito et al. (10)
67 proposed a mathematical model of cytokine storm, where they grouped cytokines into 7
68 categories based on their pro- and anti-inflammatory properties. They use the model,
69 parameterized with mouse data, to describe the mutual influence of cytokine groups on each
70 other during a cytokine storm. Yiu et al. (11) developed a large scale eighteen-order
71 mathematical model to analyze the data from the TGN1412 clinical trial, using principal
72 component analysis to reveal functional cytokine clusters that were specific to this case.
73 Hopkins et al. (12) created a model of 9 major cytokines affecting the outcome of CAR-T cell
74 based therapy. A smaller more conceptual model was proposed by Baker et al. (13), where a
75 two-dimensional system of equations captured interactions between pro- and anti-inflammatory
76 cytokines, displaying large regions of bi-stability and oscillations reminiscent of immune
77 behavior in rheumatoid arthritis; the model was later extended by other authors, such as by
78 Zhang et al. (14).

79 Here we propose a conceptual mathematical model that is aimed to capture general
80 phenomenology of transition from norm to storm rather than the intricate details of cytokine
81 biology and interactions. We use the model to identify within a theoretical framework what
82 factors may be critical to result in this transition. The model is coupled with a model of viral
83 infection to initiate the immune-cytokine dynamics, which can be substituted with a different sub-
84 model depending on the question, since, according to (8), although the initial drivers leading to
85 cytokine storm dynamics may differ, late-stage clinical manifestations of cytokine storm
86 converge and often overlap, and therefore we expect the proposed modeling framework to be
87 translatable for different causes.

88 Through our analysis, we identify key processes that within this framework can result in
89 storm-like behavior. We demonstrate existence of a sequence of regimes as one transitions
90 from normal to storm-like behavior, that is parameter dependent. We show the impact of both
91 intrinsic individual-specific characteristics and infection-specific characteristics that need to
92 converge in order to result in a cytokine storm. We analyze the immune-cytokine dynamics from
93 an ecological point of view, showing that their interactions can shift from stabilizing predator-
94 prey like dynamics to mutually augmenting mutualistic relationship, and show how these shifts
95 are reflected in normal vs pathological dynamical behaviors. Finally, we show that the proposed
96 model predicts existence of “long-haulers”, patients with chronic persistent infections, which
97 have been observed in COVID-19, and that it predicts infection-induced autoimmunity. We

98 conclude with a discussion of next steps and potential experiments to be designed to test
99 predictions generated by this model to potentially identify patients that may be at a higher risk of
100 developing a cytokine storm.

101

102 **Model Description**

103 The proposed model consists of two subsystems: immune-cytokine subsystem (primary), and
104 an SIV (susceptible-infected-virus) sub-system (secondary) that serves to provide sufficient
105 perturbation to the immune-cytokine system to initiate an immune response.

106 Even before running simulations, we would expect to see the following types of responses:

- 107 1) Normal response: after external perturbation to the immune system subsides (infection is
108 cleared), immune-cytokine populations return to pre-infection equilibrium.
- 109 2) CRS: even though external perturbation to the immune system has subsided (infection
110 has been cleared), immune cells and cytokines continue affecting each other even in the
111 absence of external stimulus.

112 Notably, the goal of this work is to describe a mathematical model that can capture and
113 reproduce these behaviors, and to analyze conditions for when one or the other type of behavior
114 will occur.

115 *Viral subsystem*

116 In order to describe the impact of a viral infection on the immune system, we adapt an SIV
117 model described in (15). We consider the dynamics of the following 3 variables: susceptible
118 cells $S(t)$, infected cells $I(t)$ and viral particles $V(t)$. We assume that the population of susceptible
119 cells $S(t)$ undergoes normal turnover described by $S_{in} - k_S S(t)$, and can be infected by the
120 virus at a rate b , creating infected cells $I(t)$. Infected cells can die at a rate k_I or can be cleared
121 by immune cells $x(t)$ at a rate γ . Viral particles $V(t)$ are produced by the infected cells $I(t)$ at a
122 rate v_{in} and get cleared at a rate k_v . These mechanisms are described by system (1)

$$\begin{aligned} \frac{dS}{dt} &= S_{in} - k_s S(t) - \beta V(t) S(t) \\ \frac{dI(t)}{dt} &= \beta V(t) S(t) - k_I I(t) - \gamma x(t) I(t) \\ \frac{dV(t)}{dt} &= v_{in} I(t) - k_V V(t) \end{aligned} \quad (1)$$

123
124 This proposed model is of course highly simplified and primarily serves the purpose of
125 introducing a dynamic perturbation to the immune-cytokine subsystem; as such, it will not be
126 fully analyzed. It is used here instead of a simple mechanical perturbation to the immune-
127 cytokine subsystem to allow us to describe a variety of situations, such as chronic infection. It
128 can be modified and adapted to different questions as needed.

129

130 *Immune-cytokine subsystem*

131 The following system of equations aims to capture the qualitative aspects of the dynamical
132 relationship between immune cells $x(t)$, and two types of cytokines $y(t)$ and $z(t)$ that can regulate
133 immune activity and that appear to act synergistically in hyperactive immune response (16).

134 First, we describe the dynamics of $y(t)$, which are involved in direct regulation of T cells;
135 these can be interpreted as TNF-alpha or IFN-gamma. We also describe the dynamics of $z(t)$,
136 which can stimulate production of $y(t)$ and thus indirectly regulate immune cells $x(t)$; these
137 species can be interpreted as interleukins, such as IL-6.

138 We assume that cytokines $y(t)$ have a normal turnover rate and thus maintain an
139 infection-free baseline level $y^* = \frac{y_{in}}{k_2}$. We assume that interleukins $z(t)$ are produced in
140 response to interactions between immune cells $x(t)$ and cytokines $y(t)$, and are cleared at a
141 natural rate a_2 . Finally, the dynamics of immune cells $x(t)$ is described as follows: we assume
142 that immune cells have a normal turnover rate to maintain a normal infection-free level x^* .
143 Immune cell population can additionally increase in response to infection, as captured by the
144 term $\gamma x(t) I(t)$. Finally, we assume that there exists a threshold m , beyond which immune cells
145 receive an additional growth boost; we interpret the existence of threshold m to be with in
146 accordance with the second touch hypothesis (17), where antigen-experienced T cells require a
147 “second touch” by the necessary antigen to achieve full immune activation, resulting in part in a

148 delay between antigen encounter and immune cell expansion. The duration of additional
 149 immune cell expansion is regulated by cytokines $y(t)$ as follows: we assume that there exists a
 150 range of concentrations of $y(t)$ that acts as immune stimulatory, and a concentration that can
 151 become immune inhibitory. We assume that the immune cells have an additional positive
 152 growth term when concentration of cytokines is between $y_1 < y(t) < y_2$, thereby capturing in a
 153 phenomenological way the dual regulatory and inhibitory property of cytokines on the immune
 154 system.

155 The resulting system then takes the following form:

$$\begin{aligned}
 \underbrace{\frac{dx(t)}{dt}}_{\text{immune cells}} &= \underbrace{x_{in} - k_1 x(t)}_{\text{normal turnover}} + \underbrace{\gamma_1 x(t) I(t)}_{\text{inflow from infection}} + \underbrace{b_1 \frac{x(t)}{c_1 + x(t)} (m - x(t)) (y_1 - y(t)) (y(t) - y_2)}_{\substack{\text{immune cells } x \text{ undergo expansion when above threshold } m; \\ \text{upper bound for growth is regulated by cytokines}}} \\
 \underbrace{\frac{dy(t)}{dt}}_{\substack{\text{cytokines} \\ \text{(i.e., IFN-g/} \\ \text{TNF-a)}}} &= \underbrace{y_{in} - k_2 y(t)}_{\text{normal turnover}} + \underbrace{b_2 z(t)}_{\substack{\text{immune cells} \\ \text{stimulate cytokines}}} \\
 \underbrace{\frac{dz(t)}{dt}}_{\substack{\text{interleukins} \\ \text{(i.e., IL-6,8,10)}}} &= a_1 y(t) \frac{x(t)}{c_2 + x(t)} - a_2 z(t)
 \end{aligned} \tag{2}$$

157 Schematic representation of this model structure is given in Figure 1A. Notably, disease-free
 158 equilibrium has to satisfy $x^* < m$, which is necessary to capture antigen-induced immune cell
 159 expansion.

160

161 Next, we assume that compared to the dynamics of the immune cells $x(t)$, the y - z
 162 subsystem reaches a quasi-steady state before it can affect immune cells $x(t)$.

163 Therefore, taking $\frac{dz(t)}{dt} = 0$ leads to interleukins $z(t)$ reaching a quasi-steady state

164 $z^* = \frac{a_1 y(t) x(t)}{a_2 c_2 + x(t)}$. Substituting this expression into System (2), we get the following 2-

165 dimensional system of equations, describing interactions between immune cells and cytokines:

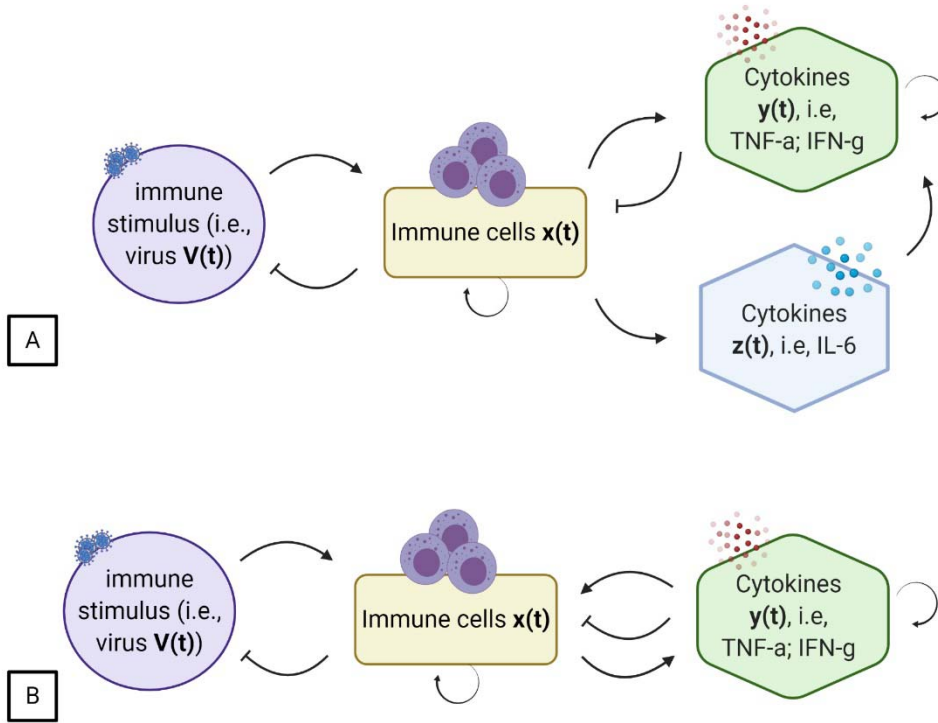
$$\begin{aligned}
 \frac{dx(t)}{dt} &= \underbrace{x_{in}}_{\text{immune}} - \underbrace{k_1 x(t)}_{\text{normal turnover}} + \underbrace{\gamma_1 x(t) I(t)}_{\text{inflow from infection}} + b_1 \underbrace{\frac{x(t)}{c_1 + x(t)} (x(t) - m) (y_1 - y(t)) (y(t) - y_2)}_{\substack{\text{immune cells } x \text{ grow additionally when above threshold } m; \\ \text{upper bound is regulated by cytokines}}} \\
 \frac{dy(t)}{dt} &= \underbrace{y_{in}}_{\text{cytokines}} - \underbrace{k_2 y(t)}_{\text{normal turnover}} + \underbrace{b_2 z^*(t)}_{\substack{\text{immune cells} \\ \text{stimulate cytokines}}} = \underbrace{y_{in}}_{\text{normal turnover}} - \underbrace{k_2 y(t)}_{\text{normal turnover}} + b_2 \underbrace{\frac{a_1 y(t) x(t)}{a_2 c_2 + x(t)}}_{\substack{\text{immune cells} \\ \text{stimulate cytokines}}}
 \end{aligned} \tag{3}$$

167 Schematic representation of this reduced system is shown in Figure 1B.

168 Final system of equations becomes

$$\begin{aligned}
 \frac{dS}{dt} &= S_{in} - k_s S(t) - \beta V(t) S(t) \\
 \frac{dI(t)}{dt} &= \beta V(t) S(t) - k_I I(t) - \gamma x(t) I(t) \\
 \frac{dV(t)}{dt} &= v_{in} I(t) - k_V V(t) \\
 \frac{dx(t)}{dt} &= x_{in} - k_1 x(t) + \gamma_1 x(t) I(t) + b_1 \frac{x(t)}{c_1 + x(t)} (x(t) - m) (y_1 - y(t)) (y(t) - y_2) \\
 \frac{dy(t)}{dt} &= y_{in} - k_2 y(t) + b_2 \frac{a_1 y(t) x(t)}{a_2 c_2 + x(t)}
 \end{aligned} \tag{4}$$

170



171

172 **Figure 1.** Schematic representation of immune-cytokine interactions subject to perturbation by
 173 infection. (A) Full system as described by Equations (1) and (2). (B) Mechanisms described by
 174 System (4).

175

176

177 The final System (4) captures the following set of key mechanisms:

- 178 1) Viral subsystem serves to provide a stimulus to the immune system that has the
 179 potential to trigger cytokine storm in the immune-cytokine subsystem x - y .
 180 2) Immune cells $x(t)$ undergo additional expansion only after threshold m is crossed.
 181 3) Once the threshold m is crossed, cytokines regulate the degree of immune cell
 182 expansion as determined by the values of parameters y_1 and y_2 .

183

184 Simulations are conducted as follows. The system is allowed to reach a steady state before
 185 infection is introduced at time $t=500$ (value chosen arbitrarily to ensure sufficient time for the
 186 model to reach a steady state). After the infection is introduced, we observe the resulting
 187 trajectories of immune cells $x(t)$ and cytokines $y(t)$, as well as the impact of the immune system
 188 on the infection.

189 Due to the phenomenological nature of the proposed model, parameter values were chosen
 190 arbitrarily in order to capture qualitatively different behaviors; furthermore, since the model is not
 191 fit to specific data, units are chosen to be generic units of volume and time that can be specified
 192 when necessary for the purposes of a specific data set. A summary of default parameter values
 193 used in the simulations is given in Table 1.

194

195 **Table 1.** Parameters used in System (4). Parameter values were chosen arbitrarily to allow to
 196 capture qualitatively different behaviors. Parameters a_1 and a_2 are taken as 1.

<i>Parameter</i>	<i>Description</i>	<i>Value</i>	<i>Units</i>
$S(0)$	Initial size of population of susceptible cells	1	vol.
$I(0)$	Initial size of population of infected cells	0	vol.
$V(0)$	Initial size of population of virus particles	0	vol.
$x(0)$	Initial size of population of immune cells	0.07	vol.
$y(0)$	Initial size of population of cytokines	0.18	vol.
S_{in}	Production rate of susceptible cells, $S(0) \times k_s$	0.01	vol./time
k_s	Normal decay rate of susceptible cells	0.01	1/time
k_I	Normal decay rate of infected cells	0.01	1/time
γ	Rate of elimination of infected cells by immune cells	0.5	1/vol/time
v_{in}	Rate of viral replication in infected cells	0.1	1/time
k_v	Natural virus decay rate	0.1	1/time
β	Rate at which virus infects susceptible cells	0.1	1/vol./time
x_{in}	Normal production of immune cells, $x(0) \times k_1$	7e-4	vol./time
k_1	Normal decay rate of immune cells	0.01	1/time
γ_1	Conversion of immune cell kill of infected cells into immune cell proliferation	0.05	1/vol/time
m	Threshold of activation of additional immune cell proliferation (second touch)	0.1	vol.
y_{in}	Cytokine production rate, $y(0) \times k_2$	0.018	vol./time
y_1	Cytokine-mediated threshold of immune cell expansion	1	vol.
y_2	Cytokine-mediated threshold of immune cell regulation	3	vol.
b_1	Rate of additional immune cell expansion as mitigated by cytokines	1	1/(time*vol. ³)
b_2	Rate of cytokine stimulation by immune cells	1	1/time
k_2	Normal cytokine decay rate	0.1	1/time
c_1	Population size that results in half-maximal growth of $x(t)$ in response to cytokine stimulation	1	vol.
c_2	Population size that results in half-maximal increase in production of cytokines in response to stimulation by immune cells	1	vol.

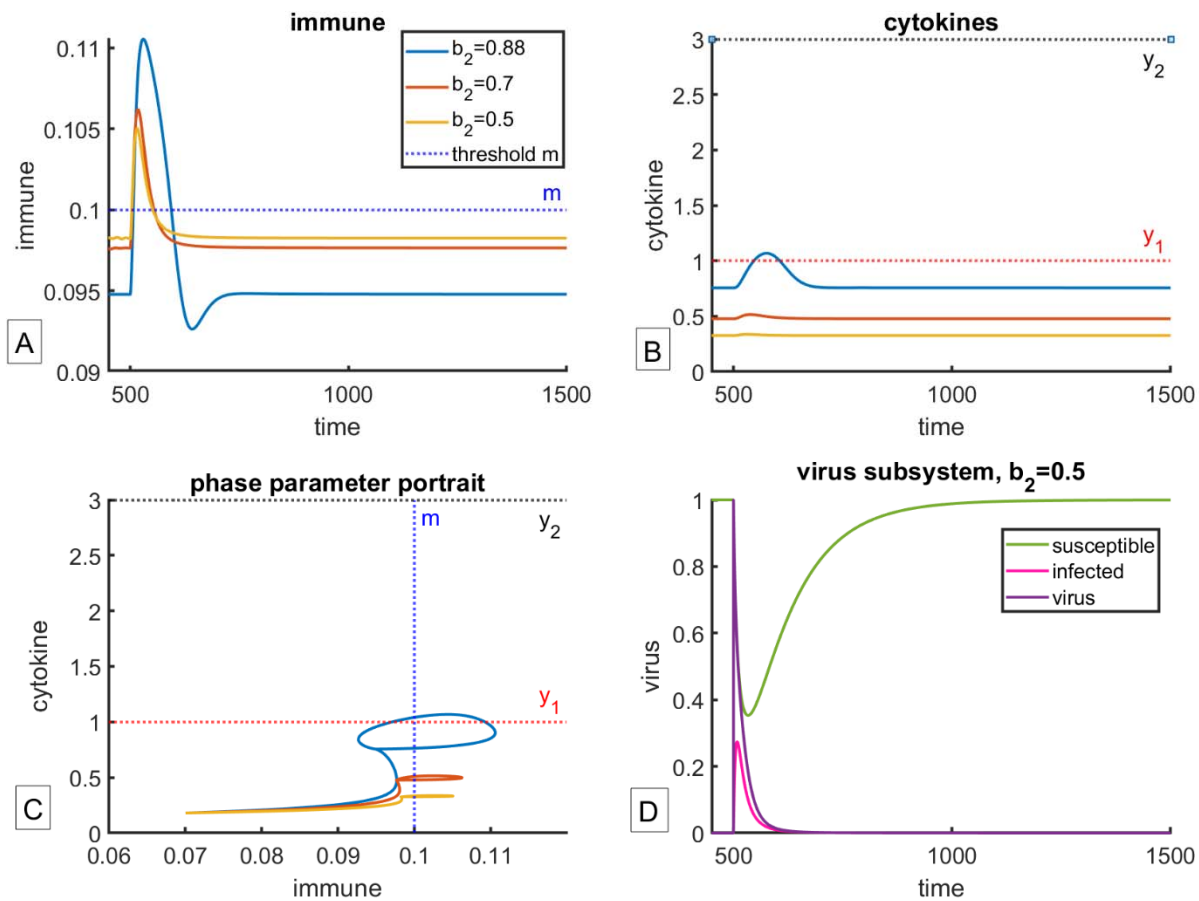
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198 **Results**

199 *Dynamical regimes*

200 Initial numerical analysis is performed through variation of parameter b_2 , which represents the
201 impact of immune cells on cytokine production; all other parameters were fixed at values
202 defined in Table 1 unless indicated otherwise.

203 *Norm*



204

205 **Figure 2.** Normal immune response to infection. Infection is introduced at time $t=500$; parameter
206 b_2 is increased from 0.5 to 0.7 to 0.88. All other parameters are held constant at values reported
207 in Table 1. (A) Dynamics of immune cells $x(t)$. (B) Dynamics of cytokines $y(t)$. (C) Phase
208 parameter-portrait of the x - y subsystem. (D) Dynamics of the virus subsystem for $b_2=0.5$; curves
209 are qualitatively similar for other values of parameter b_2 . After the infection is introduced, the
210 number of susceptible cells decreases, and the number of infected cells increases. This results
211 in increase in immune cells $x(t)$ as population size surpasses threshold m , followed by increase
212 in cytokines $y(t)$. After the infection is cleared, immune cells and cytokines return to pre-infection
213 equilibrium.

214

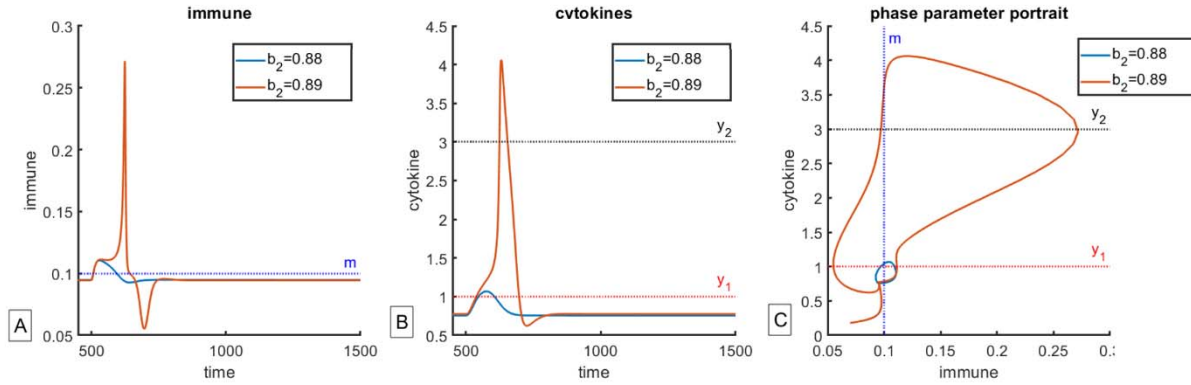
215 In the first set of simulations we observe expected dynamical behaviors for a normal immune
216 response. Infection at time $t=500$ is assumed to be sufficiently immunogenic to cause increase
217 in the size of the population of immune cells $x(t)$ for them to surpass threshold m , which now
218 leads to additional immune cell expansion (Figure 2A). As a result, the number of cytokines $y(t)$
219 increases as well (Figure 2B). Even though for $b_2=0.88$, the concentration of $y(t)$ surpasses
220 threshold y_1 , it is not sufficient to initiate additional immune proliferation, and the system quickly
221 returns to equilibrium. The phase-parameter portrait of immune-cytokine interactions is shown in
222 Figure 2C. The immune response is sufficient to clear the infection, as can be seen in Figure
223 2D.

224 Notably, there exists an inverse relationship between baseline levels of immune cells $x(t)$
225 and cytokines $y(t)$, with lower baseline levels of immune cells corresponding to higher baseline
226 levels of cytokines. While mathematically, this relationship is clearly affected by changes in
227 parameter b_2 , it may also be capturing age-related changes in immune-cytokine balance, with
228 the number of immune cells declining with age, coupled with increased levels of inflammatory
229 cytokines (18). This hypothesis is supported by the observation that older people may be more
230 susceptible to cytokine storms, at least in case of COVID-19 (19).

231

232 *Storm*

233 As we increase the value of parameter b_2 , we observe a qualitative change in system behavior,
234 where immune cells and cytokines start amplifying each other, as can be seen in Figure 3
235 (unless indicated otherwise, in all of the cases shown, the immune system is capable of clearing
236 the virus, and thus the panel with the viral subsystem is not shown). As one can see in Figure
237 3A, for $b_2=0.89$, infection-induced perturbation to the immune system causes a dramatic spike in
238 immune cell population size, leading to subsequent spike in the population of cytokines (Figure
239 3B), behavior which we interpret as cytokine storm. The phase parameter portrait of the x - y
240 interactions is shown in Figure 3C. While the population eventually returns to equilibrium, it
241 should be noted that after the spike, the model predicts a dip in immune population size before it
242 equilibrates; this prediction remains to be confirmed against experimental observations.



243

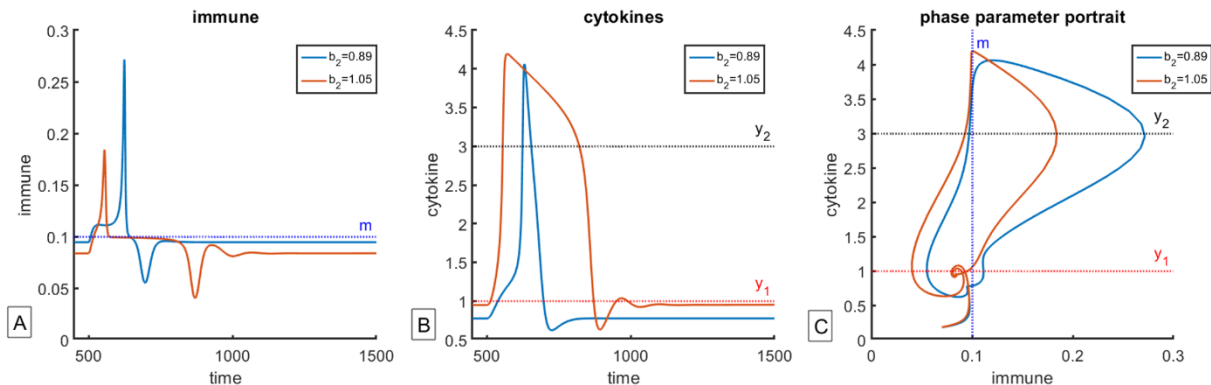
244 **Figure 3.** Normal vs storm-like response to infection. As parameter b_2 increases from 0.88
 245 0.89, qualitative change in behavior is observed, as immune cells $x(t)$ and cytokines $y(t)$ start
 246 augmenting each other's behavior. Infection is introduced at time $t=500$; parameter b_2 is
 247 increased from 0.88 to 0.89. All other parameters are held constant at values reported in Table
 248 1. (A) Dynamics of immune cells $x(t)$. (B) Dynamics of cytokines $y(t)$. (C) Phase parameter-
 249 portrait of the x - y subsystem. Dynamics of the virus subsystem is not reported as it is
 250 qualitatively similar to one reported in Figure 2D.

251

252 *Storms of different magnitude*

253 As we further increase the value of parameter b_2 , we observe that the magnitude of the
 254 predicted cytokine storm changes, as does its duration (Figure 4). Moreover, increase in the
 255 value of parameter b_2 , which represents the magnitude of cytokine stimulation by the immune
 256 cells, results in less severe storms, as can be clearly seen through both the maximal size
 257 reached by population of immune cells (Figure 4A), and the size of the characteristic storm-like
 258 loop as seen on the phase parameter portrait in Figure 4C.

259



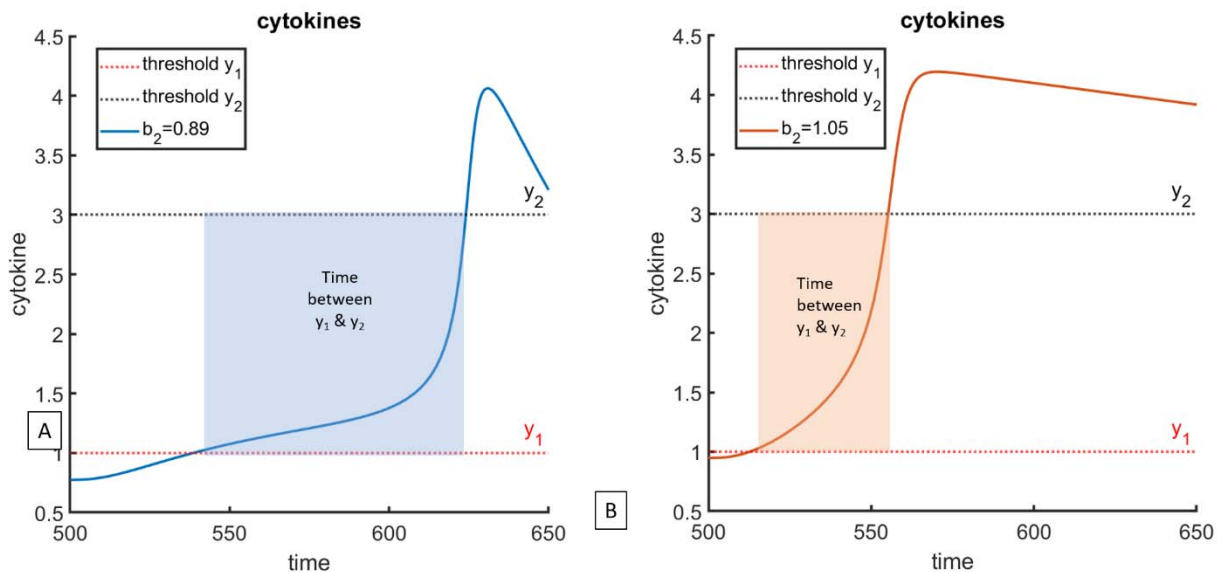
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261 **Figure 4.** Storms of varying magnitude. As the value of parameter b_2 increases from 0.89 to
 262 1.05, one can observe storm-like behavior, but the magnitude of the predicted storm is different
 263 depending on the value of b_2 . Infection is introduced at time $t=500$. All other parameters are held
 264 constant at values reported in Table 1. (A) Dynamics of immune cells $x(t)$. (B) Dynamics of
 265 cytokines $y(t)$. (C) Phase parameter-portrait of the x - y subsystem. Dynamics of the virus
 266 subsystem is not reported as it is qualitatively similar to one reported in Figure 2D.

267

268

269 The explanation for this observation lies in timing, and specifically, the amount of time that the
 270 population of cytokines $y(t)$ spends between thresholds y_1 and y_2 (Figure 5). Larger b_2 results in
 271 increased production of cytokines $y(t)$, and so they reach the inhibitory concentration faster than
 272 for smaller values of b_2 , resulting in a shorter and less severe storm-like behavior.



273

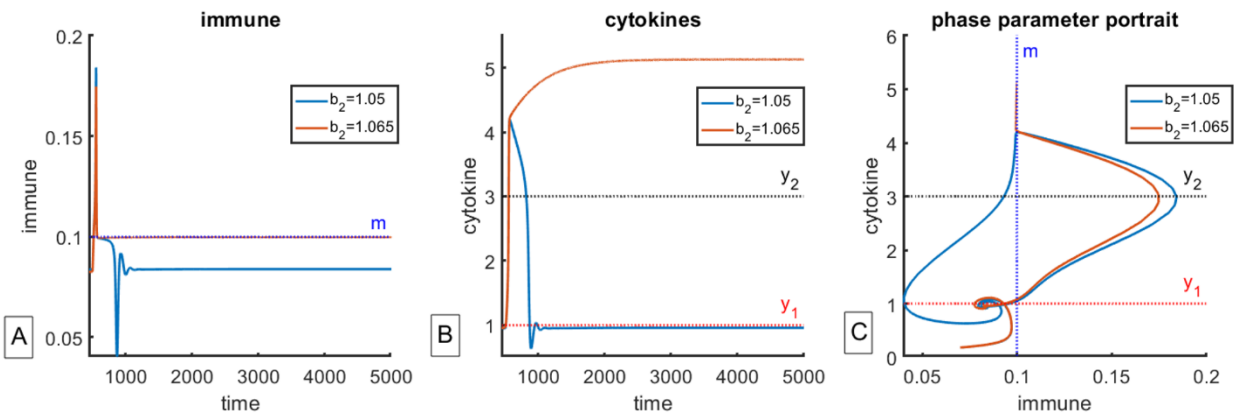
274 **Figure 5.** Timing as the key to variations in storm magnitude. (A) Time between thresholds y_1
 275 and y_2 for $b_2=0.89$. (B) Time between thresholds y_1 and y_2 for $b_2=1.05$. Since b_2 represents
 276 stimulation of cytokines by the immune cells, larger values of b_2 result in faster time between
 277 thresholds y_1 and y_2 , resulting in a storm of a smaller magnitude.

278

279 *New norm*

280 Finally, as we further increase the value of parameter b_2 , we observe the population reaching a
 281 new equilibrium, with population of immune cells $x(t)$ equilibrating at the threshold m , which is
 282 higher than pre-disease baseline; in this case, cytokines equilibrate above threshold y_2 (Figure

283 6). We propose that this behavior can be interpreted as infection-induced autoimmunity, a
 284 phenomenon that has been previously reported in the literature (20).



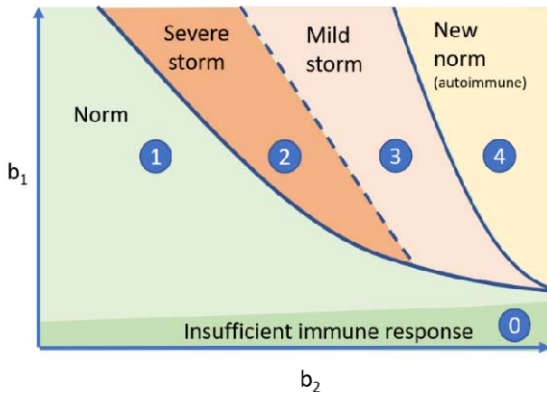
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286 **Figure 6.** New norm. As the value of parameter b_2 increases from 1.05 to 1.065, one can
 287 observe shift towards a new equilibrium, where immune cells $x(t)$ equilibrate at threshold m , and
 288 cytokines $y(t)$ equilibrate above threshold y_2 . Infection is introduced at time $t=500$. All other
 289 parameters are held constant at values reported in Table 1. (A) Dynamics of immune cells $x(t)$.
 290 (B) Dynamics of cytokines $y(t)$. (C) Phase parameter-portrait of the x - y subsystem. Dynamics of
 291 the virus subsystem is not reported as it is qualitatively similar to one reported in Figure 2D.

292

293 *Sequence of dynamical regimes*

294 Next, we wanted to capture the impact on system dynamics of variation of parameter b_1 , which
 295 represents the rate at which cytokines $y(t)$ stimulate immune system $x(t)$; all other parameters
 296 were held constant at values given in Table 1. The result is shown in Figure 7, which reveals a
 297 sequence of dynamical regimes, where cytokine storm is a transient regime that can become
 298 realized when several conditions are met. Specifically, we have shown that for low b_1 , the
 299 immune response is insufficient to clear the infection (region 0), regardless of the value of b_2 .
 300 Once the value of b_1 is sufficiently large, we can observe that increasing b_2 leads first to normal
 301 response (region 1), after which the immune system quickly returns to pre-disease equilibrium.
 302 As we increase b_2 , we observe storm-like behavior, with smaller b_2 predicting more severe
 303 storms due to longer time spent between thresholds y_1 and y_2 (region 2). Further increase in b_2
 304 leads to less severe storms because of shorter time spent between y_1 and y_2 (region 3). Finally,
 305 further increase of b_2 results in what we term a “new norm”, or infection-induced autoimmunity
 306 (region 4).



307

308 **Figure 7.** Sequence of regimes predicted by the model, subject to variation of parameters b_1
 309 and b_2 , where cytokine storm is revealed to be a transient regime.

310

311 *Conditions corresponding to storm-like behavior*

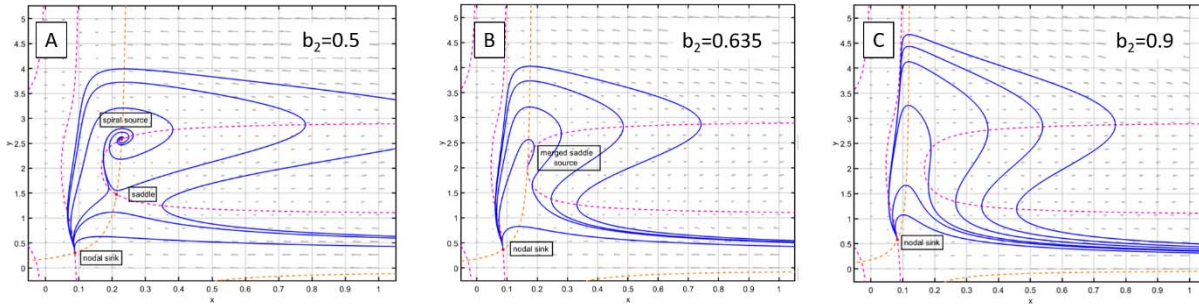
312 Additional insights into observed behaviors can be obtained from analysis of isoclines and the
 313 change in their relative positions depending on values of parameters within the relevant
 314 parameter space; parameter values are held at values reported in Table 2 unless indicated
 315 otherwise. Recall that we are only considering the case when stable disease-free equilibrium is
 316 such that $x^* < m$, and additional immune cell expansion only occurs after this threshold is passed
 317 as a result of perturbation, either from infection or any other cause.

318 Isoclines for System (3) are given by

$$\begin{aligned}
 319 \quad Is_1 : y &= \frac{1}{2} \left(y_1 + y_2 - \frac{\sqrt{b_1 x (x-m) \left(4(1+x)(x_{in} - k_1 x) - b_1 (m-x)x (y_1 - y_2)^2 \right)}}{b_1 (m-x)x} \right), \\
 Is_2 : y &= \frac{1}{2} \left(y_1 + y_2 + \frac{\sqrt{b_1 x (x-m) \left(4(1+x)(x_{in} - k_1 x) - b_1 (m-x)x (y_1 - y_2)^2 \right)}}{b_1 (m-x)x} \right), \quad (5) \\
 Is_3 : y &= \frac{(1+x)y_{in}}{k_2 - b_2 x + k_2 x}.
 \end{aligned}$$

320 Depending on parameter values, isoclines can have between one and three points of
 321 intersection. As one can see in Figure 8, there always exists one stable equilibrium, a nodal
 322 sink, which corresponds to infection-free immune-cytokine balance. Additionally, there can exist
 323 two more equilibrium points, a spiral source and a saddle point, which exist for small values of

324 b_2 (Figure 8A); as b_2 increases, the source and the saddle merge (Figure 8B) and eventually
 325 disappear (Figure 8C), resulting in existence only of the nodal sink.



326

327 **Figure 8.** Isocline analysis of immune-cytokine subsystem (3). (A) For smaller b_2 , there can
 328 exist 3 equilibrium points, one stable node, one spiral source and a saddle point. (B) As the
 329 value of b_2 increases, saddle and source merge into a single point. (C) As b_2 increases further,
 330 only one equilibrium point remains. We observe that storm-like dynamics occurs only when
 331 there exists a single equilibrium point.

332

333 In this system, we observed that storm-like dynamics occur only when there exists only one
 334 equilibrium point (Figure 8C).

335

336 Ecological perspective

337 To further our understanding of this system, we analyze it from the perspective of community
 338 modules, which are frequently used in ecological systems (21). Consider partial derivatives of
 339 immune-cytokine subsystem (3):

340

$$\begin{pmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{pmatrix}, \quad \text{where}$$

$$a_{11} = \gamma_1 I(t) - k_1 + b_1(y - y_1)(y - y_2) \left(1 - \frac{1+m}{(1+x)^2}\right)$$

$$a_{12} = \frac{b_1(m-x)x(2y - y_1 - y_2)}{1+x}$$

$$a_{21} = \frac{a_1 b_2}{a_2} \left(\frac{y}{(1+x)^2}\right)$$

$$a_{22} = \frac{a_1 b_2}{a_2} \frac{x}{(1+x)} - k_2$$

341 Recall from (21) that if a_{21} is > 0 , depending on the sign of a_{12} , the relationship between the two
 342 variables can be either mutualistic if $a_{21}>0$, or predator-prey if $a_{12}<0$. In a mutualistic system,
 343 $\begin{pmatrix} a_{11} & + \\ + & a_{22} \end{pmatrix}$, populations amplify each other, while in a predator-prey type system, $\begin{pmatrix} a_{11} & - \\ + & a_{22} \end{pmatrix}$,
 344 the two interacting populations regulate each other. Within the context of the proposed immune-
 345 cytokine System (3), one can classify observed dynamical regimes depending on the sign of a_{12}
 346 as follows.

347 The two populations are in a mutualistic relationship when $x < m, y > \frac{y_1 + y_2}{2}$ or when
 348 $x > m, y < \frac{y_1 + y_2}{2}$; in this case, immune cells $x(t)$ and cytokines $y(t)$ amplify each other, which
 349 corresponds to regions of accelerated immune and cytokine population size increase as
 350 observed in Figure 9. The two populations are in a predator-prey type relationship if
 351 $x < m, y < \frac{y_1 + y_2}{2}$ or $x > m, y > \frac{y_1 + y_2}{2}$; in this case cytokines act as regulators and
 352 “dampeners” of immune response. Notably, if $a_{12}=0$, then the two populations are in a
 353 commensal relationship, where cytokines $y(t)$ benefit from the interactions but cause neither
 354 increase nor decrease to the immune population size. This occurs when $x = m$ or $y = \frac{y_1 + y_2}{2}$, a
 355 behavior we observe in the “new norm” region of Figure 7.

356 These results are summarized in Table 2 and visualized in Figure 9.

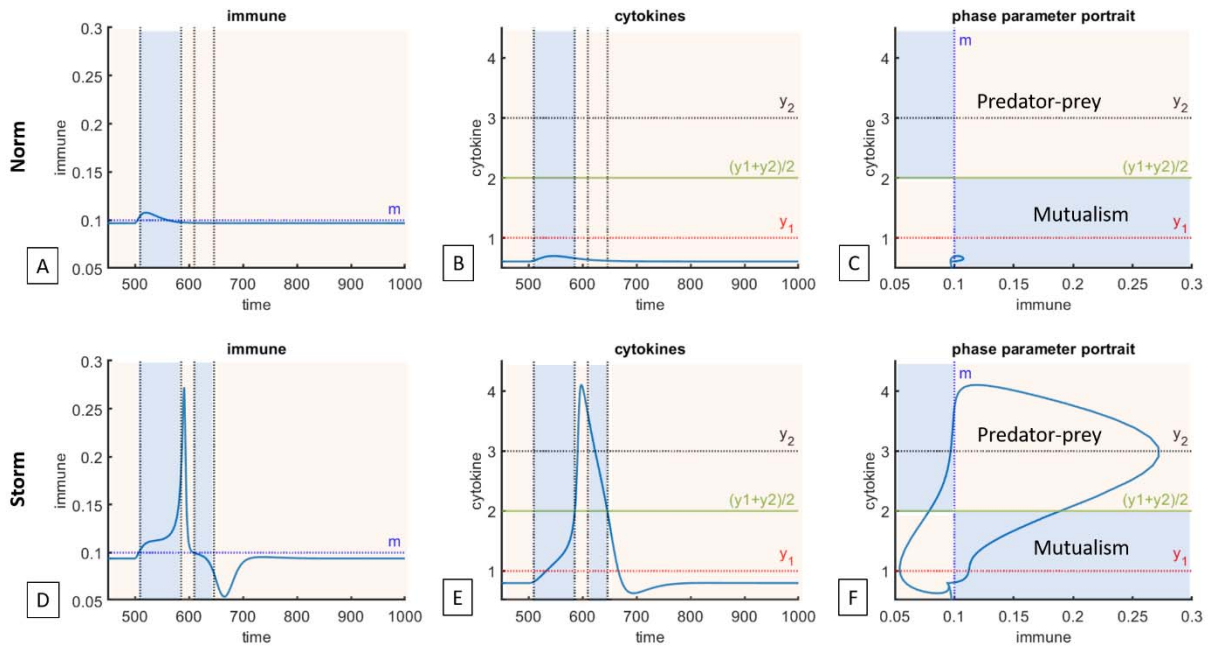
357

358 **Table 2.** Ecological relationships between immune cells $x(t)$ and cytokines $y(t)$.

Relationship	Commensalism	Mutualism	Predator-prey
Dynamics	cytokines $y(t)$ benefit from interaction but cause neither good nor harm	immune cells $x(t)$ and cytokines $y(t)$ amplify each other	Immune cells $x(t)$ and cytokines $y(t)$ regulate each other
Conditions	$x = m$ or $y = \frac{y_1 + y_2}{2}$	$x < m$ or $x > m$ $y > \frac{y_1 + y_2}{2}$ or $y < \frac{y_1 + y_2}{2}$	$x < m$ or $x > m$ $y < \frac{y_1 + y_2}{2}$ or $y > \frac{y_1 + y_2}{2}$

359

360 s



361

362 **Figure 9.** Application of ecological analysis to immune-cytokine trajectories for normal and
 363 storm-like responses. Boundaries for predator-prey vs mutualism interactions are given in Table
 364 2. Top panel: norm, $b_2=0.8$, other parameters reported in Table 1. Dashed lines correspond to
 365 conditions when switch from mutualism to predator-prey like behavior can occur. (A) Immune
 366 cells $x(t)$; (B) cytokines $y(t)$; (C): phase parameter portrait. Normal immune response involves a
 367 single transition from stabilizing predator-prey type interaction to mutually amplifying mutualist
 368 and back to stabilizing predator-prey. Bottom panel: cytokine storm, $b_2=0.9$. (D) immune cells
 369 $x(t)$, (E) cytokines $y(t)$, (F) phase-parameter portrait. In a cytokine storm, there exists an
 370 additional predator-prey to mutualism cycle compared to normal response.

371

372 Notably, this perspective could provide potential additional explanation for why timing matters in
 373 treatment administration: if a cytokine blocker results in reducing cytokine concentration such
 374 that the system moves into, or remains in a mutualistic regime, then it may instead amplify the
 375 severity of immune and cytokine production rather than reduce its impact.

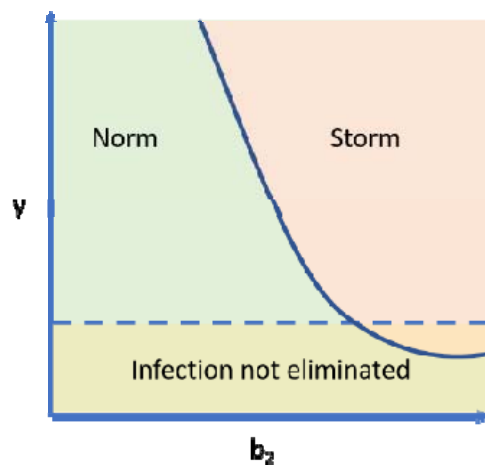
376

377 *Impact of parameter γ and the severity of infection*

378 Up to this point, we have identified the impact of the following parameters on occurrence of a
 379 cytokine storm: 1) parameters b_1 and b_2 , which represent the degree to which immune cells and
 380 cytokines stimulate each other's production, 2) parameter m , which represents a threshold for

381 additional immune cell expansion, and 3) parameters y_1 and y_2 , which determine a region of
382 cytokine-induced stimulation or inhibition of additional immune cell expansion.

383 Now we evaluate the impact of responsiveness of immune system to infected cells themselves
384 as measured through changes in the value of parameter γ . We fix the value of b_1 and vary
385 parameters b_2 and γ to evaluate whether the infection was cleared, and whether the immune-
386 cytokine response is normal or storm-like. As one can see in schematic Figure 10, the model
387 predicts that for large enough values of γ , the infection will be cleared without a cytokine storm;
388 it also confirms that increase in the value of b_2 can lead to storm-like behavior. Notably, the
389 model also predicts the possibility of a cytokine storm without infection clearance (figure not
390 shown, parameter values are $b_2=0.9$, $\gamma = 0.1$, $b_1=1$; other parameters are as reported in Table
391 1). In this case, the immune system is not efficient in clearing the infection (small γ) but the
392 cytokine-immune dynamics are triggered, resulting storm-like dynamics due to a combination of
393 individual-specific intrinsic factors summarized above.



394

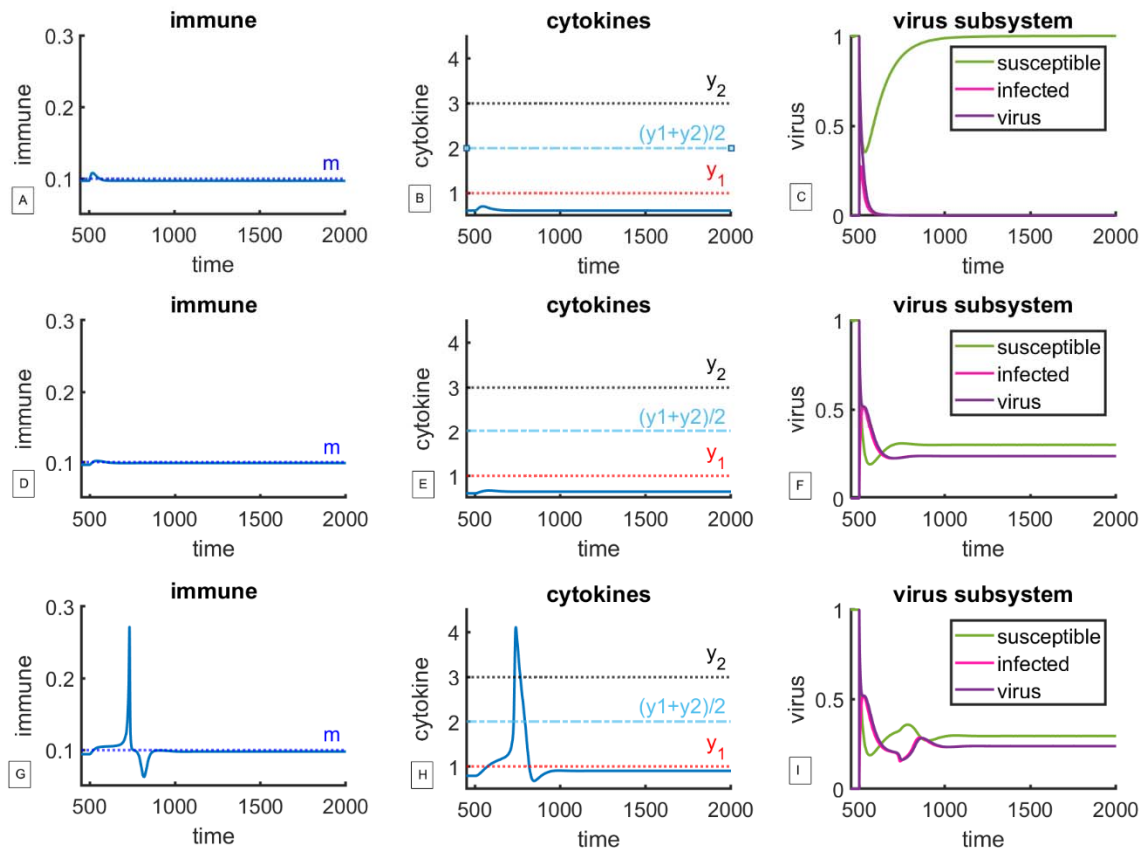
395 **Figure 10.** Impact of variation of immunogenicity parameter γ on immune response. It is possible
396 to observe both normal and storm-like response, with or without infection elimination.

397

398 *Chronic infection and the long-haulers*

399 Long-haulers are a subset of patients who develop chronic coronavirus disease (22–24). Within
400 the frameworks of the proposed model, this behavior is captured as stable non-trivial equilibrium
401 between all five variables of System (4), as can be seen in Figure 11. Notably, as predicted by
402 analysis done in Figure 10, this can occur with or without storm-like dynamics.

403



404

405 **Figure 11.** Model predicts possibility of chronic infection (long haulers) with and without cytokine
 406 storm. Top panel: normal immune response, $\gamma=0.5$, $b_2=0.8$, other parameters reported in Table
 407 1. (A) Immune cells $x(t)$, (B) cytokines $y(t)$, (C) viral subsystem. Infection is eliminated. Middle
 408 panel, normal immune response; $\gamma=0.1$, $b_2=0.8$. (D) immune cells $x(t)$, (E) cytokines $y(t)$, (F)
 409 virus subsystem. Even though immune-cytokine dynamics are normal, the efficiency of infection
 410 kill is too low, resulting in persistent infection, which can be interpreted as a “long hauler”.
 411 Bottom panel: $b_2=0.9$, $\gamma=0.1$. (G) immune cells $x(t)$, (H) cytokines $y(t)$, (I) viral subsystem. Even
 412 though immune-cytokine dynamics show cytokine storm, the efficiency of infection elimination is
 413 insufficient, suggesting that an individual can go through a cytokine storm and still not clear the
 414 infection. Note: in figures A, D and G, immune system equilibrates below threshold m , returning
 415 to its pre-disease baseline. The y-axis was scaled to enable comparison between the cases.

416

417 Discussion

418 Here we propose a conceptual mathematical model of immune-cytokine interactions capable of
 419 reproducing the qualitative behaviors that capture transition from normal immune response to a
 420 response that can be interpreted as cytokine storm. The goal of the model was not to describe a

421 particular data set or to incorporate great biological detail but to capture qualitative relationships
422 between the broad classes of immune cells and cytokines that are sufficient to reproduce these
423 dynamics, as well as to identify key parameters that may suggest whether an individual may be
424 susceptible to experiencing a cytokine storm. The proposed model was coupled with a SIV
425 model that describes immune response to a viral infection and which serves to trigger immune-
426 cytokine interactions. The viral subsystem serves as a source of perturbation and is not the
427 focus of the current discussion; it was chosen nevertheless to enable demonstration of various
428 dynamical regimes, such as chronic infection, and can be substituted by another model tailored
429 to the question of interest.

430 We show that there exists a parameter-dependent sequence of dynamical regimes
431 (Figure 7) that describe how immune cells and cytokines stimulate each other in response to
432 infection as the body tries to mount an appropriately strong immune response while also
433 avoiding excessive activation. Specifically, we show that as the value of parameter b_2 (extent of
434 cytokine stimulation by immune cells) increases, we see a transition from normal response
435 (Figures 2 and 3) to cytokine storm (Figure 4) to a regime that we interpret as infection-induced
436 autoimmunity (Figure 6). We also demonstrate that counterintuitively, lower b_2 predicts more
437 severe storm-like behavior due to longer time spent between cytokine-specific thresholds y_1 and
438 y_2 (Figure 5). If the framework proposed here is true, then susceptibility to a cytokine storm is
439 more likely to be an individual-specific characteristic that may or may not become realized
440 subject to a challenge to the immune system. The model also predicts the existence of so-called
441 long-haulers, patients harboring a chronic infection that may or may not be accompanied by
442 storm-like immune-cytokine dynamics (Figure 11).

443 The proposed immune-cytokine model is reduced to two equations, which allows for
444 additional analysis. Specifically, a 2-dimensional system was analyzed from the point of view of
445 ecological community modules, revealing conditions under which the immune cells and
446 cytokines were in a mutually amplifying mutualistic vs more stabilizing predator-prey type
447 relationship (Table 2). We were able to show the difference between normal and storm-like
448 behavior from the point of view of switching between the two types of ecological relationships
449 (Figure 9), where an additional mutualistic phase amplifies storm-like behavior.

450 Through our analysis, we demonstrate that within the frameworks of the proposed model,
451 cytokine storm is a transient regime that can become realized when the following individual and
452 infection- specific conditions are met:

- 453 1) when baseline level of immune cells is close to activation threshold m ,
454 2) when cytokines spend a lot of time between thresholds y_1 and y_2 , either because the two
455 thresholds are far apart, or when the value of parameter b_2 is small, and
456 3) when the infection is sufficiently immunogenic.

457 Even through here the perturbation to immune-cytokine equilibrium was achieved using a
458 viral subsystem, other model variations can be used in future work, including simulations of
459 impact of therapeutic agents that are known to have a high likelihood of cytokine storm reaction,
460 such as bispecific T cell engagers (BiTEs) or CAR-T cell therapies (5,6,25,26). Furthermore,
461 since two of the three identified factors that can result in a storm-like reaction to an
462 immunological challenge are individual-specific, it is likely that they can be leveraged during
463 patient selection process for such therapies if a sufficiently robust approach to estimating these
464 qualities can be found, such as genetic factors that may serve as predictive biomarkers (27). It
465 is our hope that the proposed model can help narrow down the list of possible culprits
466 responsible for cytokine storms and guide additional research into ways that it can be mitigated.

467

468

469

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473

474 **Conflicts of Interest**

475 IK is an employee of EMD Serono, US subsidiary of Merck KGaA. Views expressed in this
476 manuscript are author's personal views and do not necessarily represent the views of EMD
477 Serono.

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