1 Bistable host-pathogen interaction explains varied infection outcomes

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10 **ABSTRACT:** Death or survival are the two outcomes of an infection. The development of an
11 infection depends on multiple interplaying factors, including the temporal dynamic of host
12 nutrition, immune response and pathogen proliferation, but how these factors collectively
13 determine the outcome of an infection is less understood. To understand the underlying principle
14 of infection, here, we took a systems approach by developing a simple mathematical model to
15 understand multi-factored host-pathogen interaction. We find that nonlinear interactions feedback
16 between host and pathogens resulting in two distinct trajectories of disease progression. We show
17 that disease progression, measured by the pathogen load, responds in a bistable manner, by either
18 proliferating or eventually being eliminated. We identified key processes accounting for bistability,
19 including host's resource assimilation, immune response and intrinsic noise. In addition, resource
20 availability, immunity, and pathogen load at the onset of infection are also critical in determining
21 the bistability. We then highlight, by discussing in the light of previous theoretical and
22 experimental work, how our framework provides testable theories for host-pathogen interaction
23 inside the host.

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28 INTRODUCTION

29 Infected hosts either die or survive. The progression of an infection and its symptoms depend on
 30 various factors that have been qualitatively examined in numerous ecological immunology studies [1-5].
 31 For example, manipulating nutrition and resource availability mediates host resistance and tolerance to
 32 pathogen infection, and thereby determines the course of infection [3,6-8]. Hosts consuming protein-
 33 rich diet resist bacterial infection more efficiently and survive better than hosts on a protein-deprived
 34 diet [9,10]. The protein-rich diet enhances the production of immune effectors such as antibodies [11]
 35 and antimicrobial peptides [5]. Carbohydrate-rich food by contrast can reduce the host's ability to
 36 eradicate pathogens but may result in hosts harboring more pathogens before the onset of symptoms [5],
 37 but see [13]. Experiments on diet-restriction, diet choice and metabolic shift during infection have also
 38 highlighted the significant role of resource and nutrition in host immunity [6,14-17]. In addition, the
 39 genetic background of both host and pathogen can affect the outcome of infections even within the
 40 same or closely related species [18]. For instance, hosts with varied and diversified expression of
 41 antimicrobial peptides differ in their ability in either resisting or tolerating pathogens [19-21].

42

43 To disentangle the contribution of multiple factors on the outcome of infection, a common approach is
 44 to analyze experimental studies that apply a full-factorial design by general linear models. However,
 45 such analyses have been criticized as they are limited to linear treatment-response hypotheses, single
 46 time point sampling, and their difficulties in inferring causality [22-24]. Within-host pathogen
 47 dynamics tend to be nonlinear, which means response variables do not proportionately change with
 48 explanatory factors or time [25,26]. For example, the progression of malaria infections in mice revealed
 49 damped oscillations of both pathogen load and blood immune cell count [27]. In other words, both the
 50 pathogen population and host's health fluctuate during the course of an infection. Measuring multiple
 51 response variables of the same host at different time points during infection clearly revealed such
 52 temporal dynamics [34]. Another important form of non-linearity is bistability, for which the pathogen
 53 load and host health are eventually attracted to two "steady states" corresponding to the death and
 54 survival of the host, respectively [25]. Empirical data, combined with mathematical analyses, revealed
 55 that the progression of infection and health dynamics in a number of hosts show this pattern [25,28-30].
 56 However, in lab experiments, such within-host temporal dynamics can be masked in small animal
 57 models that cannot be sampled more than once, for instance when sampling is destructive. Pooled
 58 sampling, by sacrificing enough individuals at each time point, still revealed bistability in pathogen

load in *Drosophila melanogaster* [31]. In experiments with a defined inoculum, pathogens firstly propagate, then either reach the carrying capacity of the host, or decrease to very low level. This divergence beginning at some time point can be shown with time series data [31].

Therefore, a theoretical and practical framework of host-pathogen interactions and feedbacks could provide an understanding of the within-host infection dynamics [28,32,33]. By including the concept of within-host resource competition in host-pathogens dynamics, researchers have built models that capture the distribution of host resources in an infection [32,34]. Possible feedbacks between resource, host immunity, and pathogens are likely to be the vital factors affecting the dynamics. To gain a quantitative understanding of within-host dynamic of infection, we extend the within-host resource-centric framework to host-pathogen interactions and their feedbacks. Our framework integrates the type of infection, and the regulation of the pathogen load inside the host via host resources. Our model recapitulates that host fitness is reduced when the pathogen load is high, i.e. causing sickness behaviors or changing food consumption. The host immune system is activated by pathogen invasion, and immediately targets and finally can eliminate the pathogens, mediated by metabolic adjustment. Most importantly, the energetic and resource costs of the dynamics are balanced by the host's ingestion and metabolism. Thus, we expect a tipping point in the dynamics that differentiates the sustainability and collapse of the system, which also determines the survival or death of the host. In order to explain the phenomenon, we build a simple mathematical model that involves three major components in infection: resource assimilation of host, immune response of host and within-host dynamics of the pathogen. We propose that a feedback loop among those three components governs the progression and consequence of disease and infection and can yield a bistable outcome.

MATERIAL AND METHODS

A model of resource flow within the host

Here, we build a model based on the flow of within-host energetics/resources (thereafter resources) to understand infection dynamics. This view is motivated by several recent empirical studies [6,35-37]. For the host to maintain its energy and resource balance during infection, we assume that host's intrinsic resources are drained in three ways: basic metabolism, immune response, and pathogen

88 replication. Upon infection, host switches metabolism to distribute the energy and resources to combat
89 pathogens [16] (Fig. 1).

90

91 In our model, hosts convert the ingested food, C , at an arbitrary rate, α , into instantaneously usable
92 resources, R (see also Table S1 for all parameter definitions). The assimilation rate under infection is
93 reduced by ϕ , which represents the virulence of pathogens: host assimilation under infection is
94 $\alpha(1 - \phi)$. We include this term of host assimilation under infection by assuming that bacterial
95 endotoxins can block host metabolic functions, and hence host resource conversion and assimilation.
96 Host resources, R , are used at rate δ_R for maintaining metabolism, and at rate λ for immune defense.
97 The host immune defense includes the production of immune effectors I , such as antimicrobial peptides
98 and white blood cells, that use up resources. With the above assumptions, the rate of resource change
99 can be written as

$$\frac{dR}{dt} = \alpha C(1 - \phi) - \delta_R R - \lambda I R. \quad (1)$$

100 Once infected with pathogens, the host immune system responds to the infection by allocating
101 resources to produce immune effectors I . The absolute quantity of immune factors scales to the
102 pathogen density. We link the production rate of immune factors, β , to resource R and pathogen load P ,
103 by $\beta R P I$. At the same time, immune effectors are also removed by decay, for example they are
104 metabolized, with rate δ_I . The rate of immune effector change is described as:

$$\frac{dI}{dt} = \beta \lambda R P I - \delta_I I. \quad (2)$$

105 We first consider pathogen growth to be resource independent, but dependent on the carrying capacity
106 inside the host. A more comprehensive interaction between host and pathogen will be discussed later.
107 The rate of pathogen growth is described by the following relation,

$$\frac{dP}{dt} = \gamma P \left(1 - \frac{P}{\Omega}\right) - \delta_P I P, \quad (3)$$

108 where γ is the arbitrary growth rate of pathogens, which is limited by the carrying capacity of the host
109 Ω (if not by the availability of host resources). Pathogens are removed by the immune effectors with
110 rate δ_P and the natural death of pathogen can be neglected.

111

112 The types of feedback interactions between pathogen and host

113 The assimilation and distribution of host resource are also constrained by the feedback of pathogens.
 114 Different pathogens may consume host resource to different extend. Some pathogens consume
 115 considerable amounts of host resources, such as parasitic wasps and bacteria in some insect hosts
 116 [15,17], or *Plasmodium* and gastrointestinal helminths in vertebrates [38]. Apart from eliciting immune
 117 responses, the propagation of pathogen and/or pathogen-related toxins can undermine the resource in-
 118 take or assimilation of the host, such as reducing foraging and slowing down metabolism, which
 119 subsequently will result in host death. Here we focus on host exploitation by pathogens consuming host
 120 resources or directly producing pathogenic factors to harm the host, we categorize the interactions
 121 between host and pathogen into three types: a pathogen consumes host resources and disrupt the host's
 122 metabolic functions (A), a pathogen only consumes host resources (B), and a pathogen disrupts the
 123 host's metabolic functions without consuming many resources (C).

124

125 In type A interactions the pathogen consumes host resources at rate ϵ . In addition, the pathogen disrupts
 126 host metabolism by reducing the assimilation of resource R , and the inhibition function ϕ is dependent
 127 on the pathogens; $\phi = P/(P + \theta_{P \rightarrow R})$, where P is pathogen load and $\theta_{P \rightarrow R}$ is the half-saturation
 128 threshold of the pathogen that impairs the flow of resources inside the host. Experiments show that the
 129 immune response to pathogen infection dose does not increase proportionately with the pathogen load
 130 [35]. We model the immune response with respect to pathogen load by $\beta P^\kappa / (P^\kappa + \theta_{P \rightarrow I}^\kappa)$. κ is a Hill
 131 coefficient, and $\theta_{P \rightarrow I}$ is the half saturation threshold of pathogen to elicit an immune response. Immune
 132 effectors, such as antimicrobial peptides, kill pathogens in a nonlinear fashion [45]. The death rate of
 133 pathogens has the form $\delta_P I^\eta / (\theta_{I \rightarrow P}^\eta + I^\eta)$. η is also a Hill coefficient, and $\theta_{I \rightarrow P}$ is the half saturation
 134 threshold of immune effectors to kill pathogens. Moreover, we assume that pathogen growth depends
 135 on the availability of resources as pathogens consume considerable resources. Modifying equation 1,
 136 equation 2 and equation 3 in the light of these assumptions, we obtain the full model of type A
 137 interaction with following dynamics:

$$\begin{aligned}\frac{dR}{dt} &= \alpha C \left(1 - \frac{P}{P + \Theta_{P \rightarrow R}}\right) - \delta_R R - \lambda IR - \epsilon PR, \\ \frac{dI}{dt} &= \frac{\beta \lambda R I P^\kappa}{P^\kappa + \Theta_{P \rightarrow I}^\kappa} - \delta_I I, \\ \frac{dP}{dt} &= \gamma \epsilon R P \left(1 - \frac{P}{\Omega}\right) - \frac{\delta_P P I^\eta}{\Theta_{I \rightarrow P}^\eta + I^\eta}.\end{aligned}\tag{4}$$

138

139 In Type B interaction, the host resource intake, C , and assimilation rate, α , are assumed independent of
140 pathogen load as the pathogen causes little or no harm to the host metabolic functions. Pathogens
141 consume resources from the host, and pathogen growth is thus resource dependent. Immune response
142 and pathogens elimination also follow a Hill Function. For those pathogens that fall into this category,
143 the host pathogen interaction can be captured by (also see Fig.1 and Fig. S3):

$$\begin{aligned}\frac{dR}{dt} &= \alpha C - \delta_R R - \lambda IR - \epsilon PR, \\ \frac{dI}{dt} &= \frac{\beta \lambda R I P^\kappa}{P^\kappa + \Theta_{P \rightarrow I}^\kappa} - \delta_I I, \\ \frac{dP}{dt} &= \gamma \epsilon R P \left(1 - \frac{P}{\Omega}\right) - \frac{\delta_P P I^\eta}{\Theta_{I \rightarrow P}^\eta + I^\eta}.\end{aligned}\tag{5}$$

144

145 In Type C interaction, the pathogen sabotages host metabolic functions, but consumes little resources
146 from the host. The growth of pathogen is therefore independent of host resources. With similar
147 assumptions as above regarding immune responses and pathogen elimination, we use the following
148 equations to capture the interaction:

$$\begin{aligned}\frac{dR}{dt} &= \alpha C \left(1 - \frac{P}{P + \Theta_{P \rightarrow R}}\right) - \delta_R R - \lambda IR, \\ \frac{dI}{dt} &= \frac{\beta \lambda R I P^\kappa}{P^\kappa + \Theta_{P \rightarrow I}^\kappa} - \delta_I I, \\ \frac{dP}{dt} &= \gamma P \left(1 - \frac{P}{\Omega}\right) - \frac{\delta_P P I^\eta}{\Theta_{I \rightarrow P}^\eta + I^\eta}.\end{aligned}\tag{6}$$

149

150 Consequently, if the host rapidly eliminates the pathogen or keeps the pathogen under threshold level
151 and is symptom free, it will eventually survive, as long as basal metabolism does not exceed

consumption and assimilation efficiency. Occasionally, the host could also maintain very high pathogen load while showing no or rather mild symptoms of infection which usually indicates high “tolerance” of the host. If pathogens are less resource costly, keeping large numbers of pathogens inside the body requires the host having an efficient turn-over of food into within host resources to clear toxic substance and repair host damage generated by pathogens. Thus, it is crucial for a host to balance the cost of maintaining high metabolic activity and reducing the damage of pathogen.

Model analysis and simulation

Using the models described above, we analyzed how the different parameter settings determine the final infection outcome within a host. We solve the equations numerically with sets of parameters and initial conditions (table S1). To examine the bistable infection outcomes of host individuals, we simulated dynamics of infection in individuals with four varied initial conditions ($R = 10^0$, $I = 10^0$, $P = 10^{4.99}$; $R = 10^0$, $K = 10^0$, $P = 10^0$; $R = 10^6$, $K = 10^6$, $P = 10^{4.99}$; $R = 10^6$, $K = 10^6$, $P = 10^0$).

To explore the criticality and sensitivity of the interaction, we numerically solved the system until the steady states are reached. The steady states are identified when the difference of solutions between two time points are less than 10^{-5} . We then record the pathogen load at the end of each simulation and analyzed the bistability across simulations. To broadly explore how the initial settings of resource level, immunity and pathogen load affect the infection outcomes, we set an orthogonal combination of three initial conditions ranging from 10^0 to 10^5 . We then identified two infection trajectories by monitoring the pathogen load. If the pathogen load reaches the host’s carrying capacity, the trajectory is classed as “death”, otherwise as “survival”.

To investigate how intrinsic noise affect the dynamics of infection, we ran simulations by adding a noise term to each of the states in the deterministic model. For each simulation we drew one random number from a normal distribution with mean 0 and variance of σ^2 . We ran 500 simulations for each noise level, and explored noise levels between values of 10^{-5} to 10^{-2} . We repeated these sets of simulations for each of the three initial parameter settings, resource assimilation, immune response, and pathogen load.

In order to simulate the bimodal distribution of pathogen load in experiments, we ran simulations by drawing the parameter value of resource assimilation from a uniform distribution $\alpha \sim U[1500, 1700]$,

and the parameter value of immune response from a logarithmic uniform distribution $\lambda \sim 10^U[2, 5]$. Such draws were conducted for 5000 samples. We then recorded the pathogen load at different time points in each replicate. All the calculations and simulations are implemented in R 3.6.0.

RESULTS

Bistable infection outcomes

We modeled the in-host infection dynamic of simple interactions among three components: the flow of within-host resources, immune response, and pathogen load (Fig. 1a). Our analysis showed that the interactions of these three components collectively determines the outcome of the infection. In particular, disease progression falls into two different trajectories: (a) pathogen load increases to the maximum and (b) a decline of pathogen load to some controlled level that resembles a chronic infection (Fig. 1b, Fig. 1c). This pattern reveals a typical pattern of bistability. Resource supply, immune activation, and pathogen load, follow two distinct trajectories which determine death or survival of the host (Fig. S1, Fig. S2).

Our analysis also showed that host resource assimilation and the strength of the immune response are two important contributors for the bistable pattern of an infection (Fig. 1d, Fig. 1e). If the rate of resource assimilation and immune response is lower than the threshold level, the pathogen population will grow to high titres that can lead to the death of the host. If the rate of resource assimilation and immune response is at intermediate levels, the pathogen either propagates or is controlled. If the rate of resource assimilation and immune response is above threshold levels, the pathogen will always be controlled (Fig. 1d, Fig. 1e).

Different pathogens manipulate hosts in different ways by controlling the regulatory relations among host resource assimilation, host immune response, and pathogen virulence. Our analysis further revealed that the ways how different pathogens manipulate hosts does not qualitatively change the bistable outcome of the host pathogen interaction (Fig. S3).

210 **Initial levels of resource, immunity and pathogen load before infection determine the infection** 211 **trajectory**

212 Immune challenge and environmental stress can alter reservoirs of host resources and levels of host
213 immunity prior to infection. One would also expect that immune challenged hosts having a higher level
214 of basic immunity are likely to survive another infection. We investigated whether changes or
215 variations in initial host immunity and resource reservoir conditions together with pathogen load would
216 impact the outcome of infection. By fixing the rates of resource assimilation and immune reaction, we
217 find that the dynamics of infection are sensitive to the initial conditions of level of immunity, the
218 availability of resources, and pathogen load before infection (Fig. 2a, Fig 2b). Sampling across a wide
219 range of the three initial parameters—immune response, pathogen load and host resources—in our
220 model, we found that increased initial immunity increased host survival, higher initial pathogen load
221 increased host mortality, however, the initial resource reservoir did not affect survival probabilities(Fig
222 2c). We assessed combined effects of initial parameter settings and thereby revealed that small
223 differences in quantity of the combinations can result in distinct infection trajectories (Fig. S4) in
224 certain ranges.

225

226 **Intrinsic noise fosters bistability**

227 We next examined whether intrinsic noise leads to bistable infection outcomes. First, we fixed the
228 deterministic system at a state that pathogen will not be cleared. Then, we introduced a noise term
229 either into resource assimilation, immune reaction, or pathogen growth. We found that when the noise
230 level is low, the system will maintain the previously set state, in which the infection is acute and the
231 pathogen will not be cleared. As the noise level increase, the system either falls into the controlled state,
232 in which pathogen will be kept at low abundance and the host suffers chronic infection, or into the
233 uncontrolled state, in which the pathogen will grow and the host suffers acute infection. In addition, our
234 results show that noise in resource assimilation, immune response, and pathogen growth all contribute
235 to bistability in the infection outcomes at the critical level (Fig. 3).

236

237 **Bistability leads to variations in pooled time-series data**

238 In Fig. 4 we simulated the progression of infection and *in-silico* sampled the bacterial load at different
239 time points in host individuals. In the pooled data, bacterial load diversified after initial infection,

reached considerably variable bacteria load at some intermediate time points during progression, before finally converging to a bimodal distribution. Variations in bacterial load create differences with several orders of magnitude. We then explored two different parameters settings: a) fixed initial conditions with varied rates of resource assimilation and immune response, and b) varied initial condition with fixed rates of resource assimilation and immune response. In both cases, the pathogen load in hosts sampled at different time points first followed the same pattern, a unimodal distribution, followed by a bifurcation, i.e. splitting into a bimodal distribution (Fig 4).

DISCUSSION

In this study, we modeled a feedback in host resource assimilation, host immune response and pathogen performance. These parameters interacted and generated bistable infections that lead to either survival or death of the host. In particular, the bistability of our model depends on the rates of immune response and metabolism as it is highly sensitive to the rate parameters, α and β . This may be the result of collective effects of the underlying molecular mechanisms, for example, spontaneous gene up-regulation during infection could shift hosts to the survival trajectory [16]. In addition, immune responses, such as the expression of antimicrobial peptides, tend to show correlated spatial and temporal patterns during infection [16]. Moreover, a recent study investigating a densely sampled time-series of whole genome transcriptomics in *Drosophila* found that genes in the same “functional clusters” displayed correlated expression patterns during the course of infection [40]. Also, pathogens can manipulate the host response by reducing the resource assimilation of the host, a reduction in food intake and compromised metabolism [17,35,41]. Reduced resource assimilation subsequently lowers host condition and decreases the ability to maintain homeostasis and to clear infections. This is partially due to toxic factors released by pathogens. Pathogens producing no toxic factors, but directly competing for resources with the host, may also compromise host condition and can result in the same bistable outcome (Fig S3). In line with previous theoretical studies that highlight resource availability for fighting and tolerating pathogens [17,35,41], our simple model captures the feedbacks among immunity, pathogens, and host resources and explains the survival and death of host in an infection. We highlight that the feedbacks among host resource, pathogen load, and the ability to maintain immunity are potentially key mechanisms to determine the infection outcome.

Our model found that bistability of host-pathogen interactions is very sensitive to initial conditions. For example the baseline of immunity and resources, are critical for determining the bistable infection outcome. Variations of baseline immunity, resource, and pathogen load can be the result of differential food supply or prior pathogen exposure. Changes in baseline immunity are commonly observed in studies on “memory effects” of invertebrate immune systems [42,43]. Although our model, together with published experimental work, finds that higher levels of baseline immunity lead to better infection outcomes, there is still large uncertainty and variation at the individual level. Slight differences in the combination of initial conditions (immunity, resource, and pathogen load) will lead to distinct trajectories of life and death (Fig. 2 A, 2B). It is known that most immune challenges up-regulate cellular and humoral immunity, but it probably changes levels of other physiological aspects such as carbohydrate and amino acids resources, before the whole system reverts to homeostasis [44]. To observe the divergent infection outcomes, we propose that future experiments could be designed to monitor a variety of related physiological states with reasonable time-resolution, which would also require large sample sizes [31,40,44].

284

Our model also finds that pathogen load sampled from different host individuals at different time points varies substantially, a finding commonly observed in experiments [15,27,31,35,45-49]. We reason that this variation could result from the bistable characteristics. In large animal models, for example following *Plasmodium* infection in individual mice revealed distinct damped oscillating pattern of pathogen load within the host [27,50]. However, for smaller model hosts such as *Drosophila*, continuously monitoring pathogens dynamics in the same individuals is largely constrained. To circumvent these constraints, researchers sampled pooled times series data from different individuals at the same time point [31,45]. This causes large variations in pathogen distribution even in precisely controlled experimental conditions. Sampling pathogen loads with finer time-resolution revealed bifurcating pathogen loads and their consequence of bistable outcome. Our model seeks to explain this phenomenon. We suggest that the nonlinear characteristics of the host-pathogens interaction might be sufficient to generate these bistable outcomes. Individual hosts could progress along different infection trajectories, for which pathogen load varies at single time points. We further examined the stochastic nature within the host and found that small internal perturbations of immune responses and resource metabolism could drive the infection from the one steady state to another.

300

301 We also investigated how different type of pathogens influence the patterns of infection. Pathogens,
302 such as viruses, may cause severe harm to hosts, but consume little resources of hosts [51];
303 alternatively, they may cause little direct harm to the host, but consume large amount of resources of
304 hosts, for example in the case of helminth [52]. We separately implemented these distinct pathogens in
305 our model. Our results showed that the bistable nature of the infection dynamics does not qualitatively
306 change for different pathogens in our models.

307

308 In our model, solutions of states co-determined the trajectories of infection outcomes and recovered the
309 diagram of disease trajectories. Relating the change of pathogen load to the host's health is crucial to
310 understand the disease progression and provides insight into understanding concepts such as tolerance
311 vs. resistance. Researchers have shown a correlation between host health and pathogen load in time-
312 series data [25,30]. These correlations shape different trajectories on the "phase plane" that differentiate
313 survival and death of hosts. This is consistent with the idea that infection outcomes in various
314 circumstance are bistable. Moreover, correlating pathogen load with many other physiological and
315 immunological states essentially generate similar patterns. In short, many infection-related
316 physiological states together shape the nonlinearity of the in-host infection dynamics. Our model can
317 provide a mechanistic explanation for the distinct infection trajectories of the death-survival diagram
318 [25,30](see also Fig S4).

319

320 We revealed the nonlinear interaction between host and pathogen, in which disease progression
321 followed two distinct trajectories which lead to death and survival of hosts. The catastrophic shift in
322 some critical parameters determines the death and survival of the host. Thus, it is crucial to identify
323 these critical conditions in which a catastrophic shift will happen. This includes tracking pathogen load,
324 host immunity, and nutrition level in real time. Treating infectious disease is to probe the non-linearly
325 dynamical system, and trying to delay the catastrophic shift by manipulating particular parameters.
326 Besides directly killing pathogens, these strategies also include using drugs to neutralize the toxic
327 substance secreted by the pathogens, which could substantially reduce the damage to the host and
328 increase host tolerance. Moreover, metabolic dysfunction, caused by infection, will drastically reduce
329 the host's ability to maintain homeostasis during infection. Extra supplement of energy may eventually
330 help overcoming the infection. These properties that emerge from a non-linear system should be taken
331 into consideration when developing a more comprehensive approach to treat infections.

332 **Note.** At the final stage of writing this manuscript, a related work was brought to our attention: Stephen
 333 P. Ellner, Nicolas Buchon, Tobias Dörr, Brian P. Lazzaro. Host-pathogen Immune Feedbacks Can
 334 Explain Widely Divergent Outcomes from Similar Infections. bioRxiv. doi:
 335 <https://doi.org/10.1101/2021.01.08.425954>

336
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468

469 Fig. 1 The bistability or hysteresis of host-pathogen interaction. (A) A schematic illustration of a
 470 minimal model which encapsulates within-host interactions of resources, immunity, and pathogens
 471 during the course of an infection. Solid arrows indicate positive interactions, while dashed arrows
 472 represent negative interactions. In such interaction with feedback loops, the pathogen population either
 473 propagates to the maximal carrying capacity of the host, or is reduced to a persistent low level
 474 dependent on resource assimilation, α (B), and immune response, β (C). Numerical simulations with
 475 varied initial values of P, R and I, show two distinct equilibria in terms of pathogen load across wide
 476 range of rate of resource assimilation (D) and Immune response (E). The four initial conditions are $R =$
 477 10^0 , $I = 10^0$, $P = 10^{4.99}$; $R = 10^0$, $K = 10^0$, $P = 10^0$; $R = 10^6$, $K = 10^6$, $P = 10^{4.99}$; $R =$
 478 10^6 , $K = 10^6$, $P = 10^0$.

479

480

481 Fig. 2 Small variations in initial conditions determine distinct infection outcomes. (A, B) With identical
 482 rate parameters, small differences in initial quantity of resource, immunity, and pathogen load will lead
 483 to different disease trajectories during infection. (C) The pooled distribution of trajectories of death and
 484 survival against initial parameter settings of immunity, resource, and pathogen. This suggests that a
 485 wide range of initial level of these “state” will cause bimodal distribution of death and survival as the
 486 consequence of an infection. The range of initial conditions for resource, immunity and pathogen are
 487 all from 10^0 to 10^5 .

Fig.3 Intrinsic stochasticity or noise results in bistable infection outcomes. Perturbation of the dynamics of infections changes the disease trajectories which resulted in bimodal distributions of pathogens. When the noise level is low, all cases of infection have only one equilibrium in which infection is acute and the pathogen load is high. As the noise increase, infection in some cases will be controlled, in which the pathogen load is maintained lowly. Moreover, intrinsic noise in resource (A), immunity (B) and pathogen growth (C) will all cause the same patterns of bimodal distribution.

499

500 Fig. 4 Bistability leads to variations in pooled time-series data. We numerically solve the model with
 501 varied immune response rates (A) and initial quantity of pathogens (B), in which the distributions of
 502 both parameters are following the uniform distribution $\alpha \sim U[1500, 1700]$ and logarithmic uniform
 503 distribution $\beta \sim 10^U[2, 5]$, respectively. Data sampled from different time points shows large variations
 504 with several orders of magnitude.

505

506 Fig. S1 The dynamics of immunity, pathogen load, and resource levels for different levels of immune
507 response (A). These patterns fall into two different trajectories (B).

508

509 Fig. S2 The dynamics of immunity, pathogen load and resources levels showed different patterns under
510 different levels of resource assimilation (A). These patterns fall into two different trajectories (B).

Fig. S3 Infections with different patterns of in-host interaction share the bistability with respect to resource assimilation and immune response.

514

515 Fig. S4 The infection trajectories are resembled by two-by-two correlation of resource level, immunity
516 and pathogen load, in which there are always two trajectories representing the consequences of the
517 infection. Red means host killed by pathogens; blue means host overcoming pathogens either killing
518 them all or survive with persistence of low pathogen load.

519 Table S1.

520 Variables and parameters used in the model. All the default values, if not specified elsewhere, are listed
521 below.

522

Variables/Parameters	Default values	Description
R	10^3	Total directly usable resource in host, such as carbohydrates and amino acids.
P	$10^{2.5}$	Pathogen load.
I	10^3	Overall immunity level, which includes blood cells related to immune function, immune peptides phenoloxidases and other related antipathogen enzymes.
Ω	10^5	Physiological and physical carrying capacity of pathogens in host.
$\Theta_{P \rightarrow R}$	10^4	Threshold values of pathogens for affecting resource assimilation.
$\Theta_{P \rightarrow I}$	10^2	Threshold values of pathogens for initiating immune response.
Θ_I	10^6	Threshold values of immunity for killing pathogens.
C	1	Total in-take food.
α	10^4	Rate of resource assimilation.
β	3000	Rate of immune response, for example, the rate of generating immune substance.
γ	1	Growth rate of pathogen.
δ_R	1	Rate of resources consumption by host.
δ_I	1	Clearing rate of immune substance.
δ_P	1	Clearing rate of pathogen.
ε	10^{-2}	Rate of resource consumption of pathogen.
λ	10^{-5}	Rate of resource consumption of immunity.
κ	1	Hill coefficient for pathogens.
η	2	Hill coefficient for immunity.

523