Pathogen evolution when transmission and virulence are stochastic

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Abstract Evolutionary processes are inherently stochastic, since we can never know with certainty exactly how many descendants an individual will leave, or what the phenotypes of those descendants will be. Despite this, models of pathogen evolution have nearly all been deterministic, treating values such as transmission and virulence as parameters that can be known ahead of time. We present a broadly applicable analytic approach for modeling pathogen evolution in which vital parameters such as transmission and virulence are treated as random variables, rather than as fixed values. Starting from a general stochastic model of evolution, we derive specific equations for the evolution of transmission and virulence, and then apply these to a particular special case; the SIR model of pathogen dynamics. We show that adding stochasticity introduces new directional components to pathogen evolution. In particular, two kinds of covariation between traits emerge as important: covariance across the population (what is usually measured), and covariance between random variables within an individual. We show that these different kinds of trait covariation can be of opposite sign and contribute to evolution in very different ways. In particular, probability covariation between random variables within an individual is sometimes a better way to capture evolutionarily important tradeoffs than is covariation across a population.

Keywords Pathogen evolution · Stochastic fitness · Virulence · Transmission · Directional stochastic effects

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1 Introduction

All organisms live in environments that are, to some degree, unpredictable, and this unpredictability influences both an individual's reproductive success and the phenotype of its offspring (through environmental effects on development). Fitness and offspring phenotype should therefore properly be treated as random variables – having probability distributions of possible values. This uncertainty is particularly pronounced for pathogens, which are subject to both stochastic uncertainty within a host (such as variation in the host's immune response), and in the host's environment.

Saying that transmission is stochastic simply means that when a pathogen infects a host, we can not predict with certainty how many subsequent hosts will be infected through transmission from the current host. Instead, we work with the probability distribution of possible transmission events. Similarly, saying that virulence is stochastic just means that we can not predict exactly how much harm a newly aquired pathogen will ultimately do to its host.

One well studied process that will create stochasticity in transmission rate is variation in interactions between susceptible and infected hosts. In many infectious disease models, the population is assumed to be large and evenly mixed, meaning that every individual contacts others at a fixed rate determined by their frequency (Keeling and Eames 2005). In reality, however, infected individuals often have limited and variable numbers of contacts with susceptible individuals (McCallum et al 2001). For example, some epidemiological studies have shown that during disease spreading, the population is heterogenous, with the most infectious individuals responsible for the majority of transmission events (Lloyd-Smith et al 2005; Ferrari et al 2004; Kilpatrick et al 2006; Paull et al 2012; Wolinska and King 2009). In particular Woolhouse et al (1997) identified an empirical relationship that in many disease systems, the most infectious 20% of individuals are responsible for 80% of the total infections. Stochastic variation in transmission thus appears to be a common feature of pathogen systems.

Another important component of pathogen fitness, virulence, is also likely to be stochastic, in part because of variation in the internal environment of the host – particularly the hosts immune system. For example, Brodin and Davis (2017) document striking variation of individual immune response in humans. This translates into variation in virulence rates for a particular pathogen, with virulence being relatively low in some hosts and high in others. Even within a host, variation in virulence could be a result of uncertainty in the ability of pathogens to evade the immune system and induce pathogenic effects.

Figure (1) shows the distribution of mortality rates as a function of time since infection (an estimator of $\frac{1}{v}$) for human immunodeficiency virus 1 (HIV1) [data from Mellors et al (1997)]. This data suggests both a high variance in virulence, and that the distribution of virulence values is asymmetrical. Similar variation has been seen in other studies, with the further observation that the pattern of variation may itself be influenced by external environmental variables

that the hosts experience. For example, in an experimental study of the *Daphia magna* infection by the bacterial parasite *Pasturia ramosa*, it was shown that changing environmental factors, such as nutrient availability or temperature, can alter the variance in both virulence and transmission, as well as the covariance between them (Vale et al 2011; Little et al 2013; Mitchell et al 2005). We thus seek a way to incorporate stochasticity in both transmission and virulence into models of pathogen evolution.

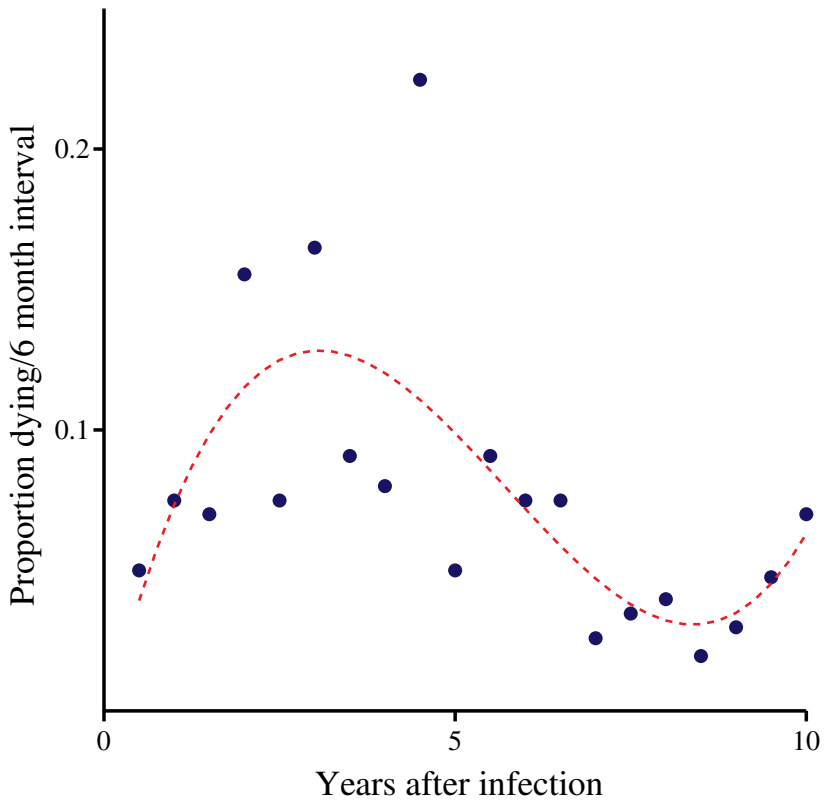

Fig. 1: The figure shows the distribution of mortality/year(virulence) during 10 consecutive years after infection with HIV1. The red fitted third-degree polynomial shows the positive skewness of data and so the high variance in virulence. The data are taken from Mellors et al (1997), that conducted the cohort study of patients after infection with HIV1 and free of clinical acquired immunodeficiency syndrome(AIDS).

In a stochastic evolutionary model, we treat both the number of offspring that each individual will produce and the phenotype of those offspring, as random variables – having distributions of possible values. The expected change in mean phenotype over one generation is then given by the stochastic Price equation (Rice 2008):

$$\widehat{\Delta\overline{\phi}} = [\![\widehat{\phi^o}, \widehat{\Omega}]\!] + \overline{\langle\!\langle \phi^o, \Omega \rangle\!\rangle} + \overline{\delta} \tag{1}$$

Table 1: Symbols and Notation

Symbol	Meaning
$\overline{X}$	Average value of X across its frequency distribution
$\widehat{A}$ or $E(A)$	Expected value of random variable A
A^*	Difference between random variable A and its expectation $\widehat{A}$ (i.e., $A-\widehat{A}$)
$[\![^2X]\!]$	Variance in the value of X, across its frequency distribution
$[\![^jX]\!]$	jth central moment of the frequency distribution of X
$\langle\!\langle^jA\rangle\!\rangle$	jth central moment of the probability distribution of random variable A
$[\![X,Y]\!]$	Frequency covariance of X and Y
$\langle\!\langle A,B\rangle\!\rangle$	Probability covariance of random variables A and B
w	Absolute fitness (number of descendants after one generation)
Ω	Relative fitness ($\Omega=\frac{w}{\overline{w}}$), conditional on $\overline{w}\neq 0$
ϕ	Phenotype of an individual
ϕ^o	Average phenotype of an individual's offspring
δ	$\phi^o-\phi$
θ	Birth rate of susceptible hosts
d	Death rate of the host in the absence of infection (Background Mortality)
c	The rate that infected groups become immune to further infections (Recovery Rate)
β_i	The rate at which susceptible hosts become infected by individuals in i^{th} infected group (transmission rate)
ν_i	The induced death rate of the individuals in i^{th} infected group by the pathogens (virulence rate)

In Equation 1, ϕ^o denotes the mean phenotype of an individual's offspring (or of that individual in the future), and Ω denotes relative fitness – individual fitness divided by mean population fitness (see Table 1). $[\![\widehat{\phi^o},\widehat{\Omega}]\!]$ is the covariance, across the population, between expected offspring phenotype and expected relative fitness; We refer to this as the frequency covariance, since it involves the frequencies of individuals in the population. Because we are now treating ϕ^o and Ω as random variables, however, each individual has a probability distribution of possible values of offspring phenotype and relative fitness. These values can thus covary within an individual, producing a probability covariance that we denote $\langle\!\langle\phi^o,\Omega\rangle\!\rangle$. To illustrate the difference between these two kinds of covariance: Saying that $[\![\widehat{\phi^o},\widehat{\Omega}]\!]$ is positive for a population means that individuals within the population that have large values of $\widehat{\phi^o}$ also tend to have large values of $\widehat{\Omega}$. By contrast, saying that $\langle\!\langle\phi^o,\Omega\rangle\!\rangle$ is positive for an individual means that if an individual's value of ϕ^o ends up being larger than its expected value ($\widehat{\phi^o}$), then its value of Ω is also likely to be larger than its expected value ($\widehat{\Omega}$). The distinction between probability and frequency operations is critical in modeling stochastic processes in populations. The term δ captures processes, such as mutation, that change phenotype during the process of reproduction.

Equation (1) applies to any phenotype. It assumes only that the population is closed, meaning that there is no immigration or emigration. For the case of pathogen evolution, we will consider two phenotypic traits, transmission (β) and virulence (ν).

Note that this approach to introducing stochasticity is different from that used in stochastic differential equations (SDE). In SDE, one makes the main variable stochastic by assigning a variation to it using a Wiener process, while other variables are kept deterministic (Allen 2007). For example, a SDE model for the evolution of virulence might treat transmission and overall fitness as fixed values, while assigning random normally distributed noise to v. By contrast, our approach treats virulence, transmission, and fitness as random variables, which can have any distributions of values and can covary with one another. We will show that stochastic covariation between these values is biologically realistic and can significantly influence evolution.

2 Results

2.1 The General Case

Fitness enters into Equation (1) in the form of $\Omega = \frac{w}{\overline{w}}$, or relative fitness. In order to study selection, we need to write our equations in terms of individual fitness, w. This is easy in deterministic models – since $\frac{1}{\overline{w}}$ is a constant that we can factor out – but is challenging in stochastic models, in which both w and $\overline{w}$ are random variables that are correlated with one another. The solution is to approximate $\Omega_i = \dfrac{w_i}{\overline{w}}$ using a Taylor expansion (Rice 2008, 2009) (see Methods and Supplementary Materials). Using this approach, we can rewrite the stochastic Price equation (1) as:

$$\widehat{\Delta\overline{\phi}} = \frac{1}{\widehat{\overline{w}}}[\![\widehat{\phi^o},\widehat{w}]\!] + \frac{1}{\widehat{\overline{w}}}\overline{\langle\!\langle \phi^o, w\rangle\!\rangle} - \frac{1}{\widehat{\overline{w}}^2}[\![\widehat{\phi^o},\langle\!\langle w,\overline{w}\rangle\!\rangle]\!] - \frac{1}{\widehat{\overline{w}}^2}\overline{\langle\!\langle \phi^o,(w-\widehat{w})(\overline{w}-\widehat{\overline{w}})\rangle\!\rangle} - \frac{1}{\widehat{\overline{w}}^2}[\![\widehat{w},\langle\!\langle \phi^o,\overline{w}\rangle\!\rangle]\!] - \frac{1}{\widehat{\overline{w}}^2}\widehat{\overline{w}}\overline{\langle\!\langle \phi^o,\overline{w}\rangle\!\rangle} + O(\frac{1}{\widehat{\overline{w}}^3}) \tag{2}$$

Equation (2) is the general equation of change in the expected mean phenotype when descendant phenotype, and parent fitness are random variables. Often, the "descendants" are assumed to be offspring, but ϕ^o can also measure an individual's phenotype at a later time, or the phenotype of descendants after many generations. To apply this equation to transmission and virulence of pathogens, we consider a pathogen that has just infected a host, and interpret ϕ^o as the phenotype after that pathogen strain has grown within the host to the point at which it can be transmitted or kill the host.

We assume that there are n pathogen strains, and define β_i as the number of other hosts that will be directly infected by the descendants of strain i ($i = 1,...,n$), and ν_i as the probability that strain i kills its host before transmission. Both β and ν are random variables, since the exact transmission rate or time until death of the host can not be specified exactly beforehand. Substituting β and ν for ϕ^o in Equation (2), we obtain the following equations for the evolution of transmission and virulence:

$$\begin{aligned}\widehat{\Delta\overline{\beta}} \approx \frac{1}{\widehat{\overline{w}}}[\![\widehat{\beta},\widehat{w}]\!] + \frac{1}{\widehat{\overline{w}}}\overline{\langle\!\langle \beta, w\rangle\!\rangle} - \frac{1}{n\widehat{\overline{w}}^2}[\![\widehat{\beta},\langle\!\langle {}^2w\rangle\!\rangle]\!] - \frac{1}{n\widehat{\overline{w}}^2}\sum_{i\neq j}[\![\widehat{\beta}_i,\langle\!\langle w_i,w_j\rangle\!\rangle]\!] - \frac{1}{n\widehat{\overline{w}}^2}\overline{\langle\!\langle \beta,(w-\widehat{w})^2\rangle\!\rangle} - \frac{1}{n\widehat{\overline{w}}^2}\sum_{i\neq j}\overline{\langle\!\langle \beta_i,(w_i-\widehat{w}_i)(w_j-\widehat{w}_j)\rangle\!\rangle} \\ - \frac{1}{\widehat{\overline{w}}^2}[\![\widehat{w},\langle\!\langle \beta,\overline{w}\rangle\!\rangle]\!] - \frac{1}{\widehat{\overline{w}}}\overline{\langle\!\langle \beta,\overline{w}\rangle\!\rangle}\end{aligned} \tag{3}$$

$$\begin{aligned}\widehat{\Delta\overline{\nu}} \approx \frac{1}{\widehat{\overline{w}}}[\![\widehat{\nu},\widehat{w}]\!] + \frac{1}{\widehat{\overline{w}}}\overline{\langle\!\langle \nu, w\rangle\!\rangle} - \frac{1}{n\widehat{\overline{w}}^2}[\![\widehat{\nu},\langle\!\langle {}^2w\rangle\!\rangle]\!] - \frac{1}{n\widehat{\overline{w}}^2}\sum_{i\neq j}[\![\widehat{\nu}_i,\langle\!\langle w_i,w_j\rangle\!\rangle]\!] - \frac{1}{n\widehat{\overline{w}}^2}\overline{\langle\!\langle \nu,(w-\widehat{w})^2\rangle\!\rangle} - \frac{1}{n\widehat{\overline{w}}^2}\sum_{i\neq j}\overline{\langle\!\langle \nu_i,(w_i-\widehat{w}_i)(w_j-\widehat{w}_j)\rangle\!\rangle} \\ - \frac{1}{\widehat{\overline{w}}^2}[\![\widehat{w},\langle\!\langle \nu,\overline{w}\rangle\!\rangle]\!] - \frac{1}{\widehat{\overline{w}}}\overline{\langle\!\langle \nu,\overline{w}\rangle\!\rangle}\end{aligned} \tag{4}$$

Detailed derivations are presented in Methods and in the Supplementary Material.

The first terms on the right-hand side of the Equation (3) $\left(\frac{1}{\widehat{\overline{w}}}[\![\widehat{\beta},\widehat{w}]\!]\right)$ and Equation (4) $\left(\frac{1}{\widehat{\overline{w}}}[\![\widehat{v},\widehat{w}]\!]\right)$ contain the frequency covariances between the expected absolute fitness of a pathogen strain and its expected transmission and virulence. This is the same as the covariance term in the original, deterministic, Price equation (Price 1970).

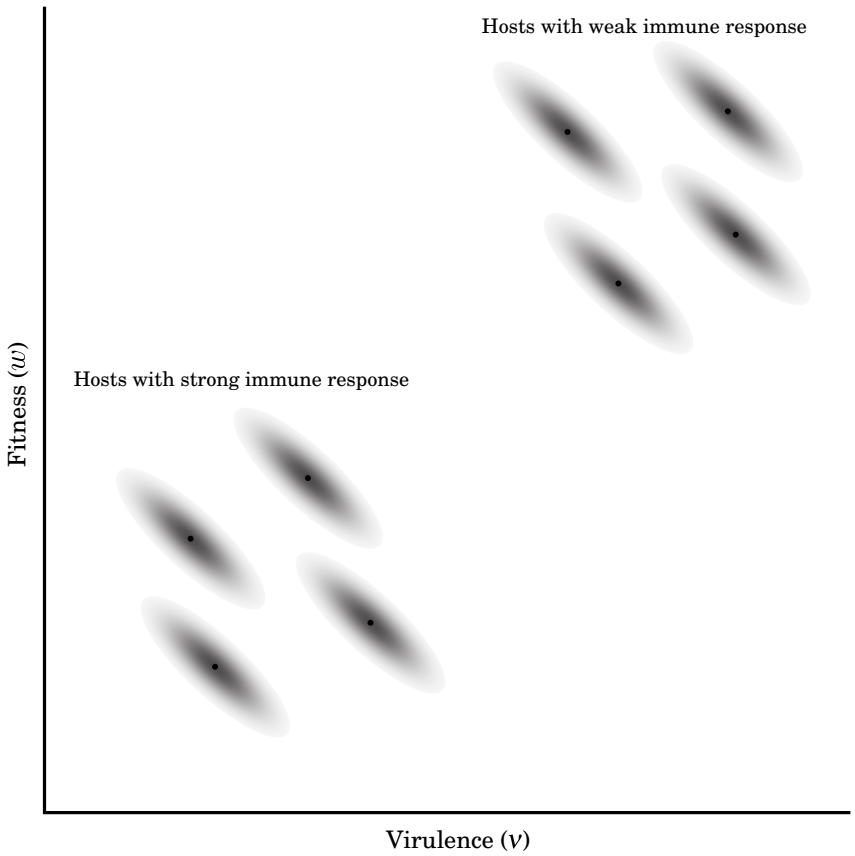

Fig. 2: A hypothetical case of eight different pathogen strains, in eight hosts, for which $[\![\widehat{v},\widehat{w}]\!] > 0$, but $\langle\!\langle v_i, w_i \rangle\!\rangle < 0$ for each strain (so $\overline{\langle\!\langle v_i, w_i \rangle\!\rangle} < 0$). Each solid black dot represents the expected values of virulence ($\widehat{v}$) and fitness ($\widehat{w}$) for one strain. The shaded distributions surrounding each solid black dot indicate the probability distribution of virulence and fitness for that strain. Pathogen strains on the lower left corner show low expected virulence and low expected fitness since they happen to be in hosts with strong immune responses. The strains on the upper right corner of the figure are in hosts with weak immune systems, leading to high expected virulence but also higher fitness of the pathogen. Within any one host, the pathogen has a greater chance of transmission if it does minimal harm to its host; leading to the negative probability covariance between fitness and virulence for each strain.

In the deterministic models such as (Day and Gandon 2006, 2007), the frequency covariance is the only term capturing the relationship between the fitness and phenotype. When phenotype and fitness are stochastic, however, two new kinds of terms appear, corresponding to evolutionary processes that are invisible to deterministic models.

First: when fitness and phenotype are random variables, they can covary for a single individual. This is captured by the second terms of the Equation (3), $\left(\frac{1}{\widehat{\overline{w}}}\overline{\langle\!\langle \beta, w \rangle\!\rangle}\right)$ and Equation (4) $\left(\frac{1}{\widehat{\overline{w}}}\overline{\langle\!\langle \nu, w \rangle\!\rangle}\right)$. These terms contain the probability covariances between the absolute fitness of the pathogen strain with its transmission and virulence, averaged over the entire population.

To illustrate the difference between the frequency covariance, $[\![\widehat{\nu}, \widehat{w}]\!]$, and the probability covariance, $\langle\!\langle \nu, w \rangle\!\rangle$, Figure (2) shows a hypothetical case in which they have different signs. We consider a population of hosts that vary in immune resistance; with some having a strong immune response and some a weak response. Those pathogens that infect hosts with a strong response will tend to have both low expected fitness ($\widehat{w}$) and low expected virulence ($\widehat{\nu}$), while those infecting hosts with weak immune response will have higher values of both $\widehat{w}$ and $\widehat{\nu}$ (black dots in the figure). We thus have a positive frequency covariance between expected fitness and expected virulence ($[\![\widehat{\nu}, \widehat{w}]\!] > 0$). Considering any one pathogen within a particular host, however, the pathogen is likely to have higher fitness if it does not kill the host quickly. There is thus a negative probability covariance between fitness and virulence ($\langle\!\langle w, \nu \rangle\!\rangle < 0$) for each individual pathogen.

The terms discussed above result from probability covariation between fitness and descendant phenotype. The second class of evolutionary phenomena that appears when we make fitness stochastic – directional stochastic effects – result from covariation between individual fitness (w) and mean population fitness ($\overline{w}$) (written as $\langle\!\langle w, \overline{w} \rangle\!\rangle$ in the third term on the righthand side of Equation (16).

Figure (3A) illustrates the basic mechanism of directional stochastic effects. If all else is held equal, the magnitude of evolutionary change is inversely proportional to mean population fitness. This is a general property of evolutionary models, manifest in the fact that population genetic models for change in allele frequency, and quantitative genetic models for change in mean phenotype, always contain a $\frac{1}{\overline{w}}$ term (unless it is assumed that $\overline{w} = 1$). Figure (3A) shows a hypothetical case for a population of two individuals that have the same expected fitness, but different variances. In the example, there is an equal probability that mean phenotype will increase or decrease. when $\overline{\phi}$ increases, though, the absolute magnitude of change is greater than when it decreases ($\frac{1}{2}$ *vs.* $-\frac{1}{6}$). The reason for this discrepancy is that $\overline{\phi}$ increases when $\overline{w}$ is low, and decreases when $\overline{w}$ is large.

Because any individual's fitness is a component of mean population fitness, the probability covariance between w and $\overline{w}$ can be broken up into two components; one involving the variance in an individual's fitness, and the other involving the probability covariance between that individual and others in the population. For the ith pathogen strain, we can write:

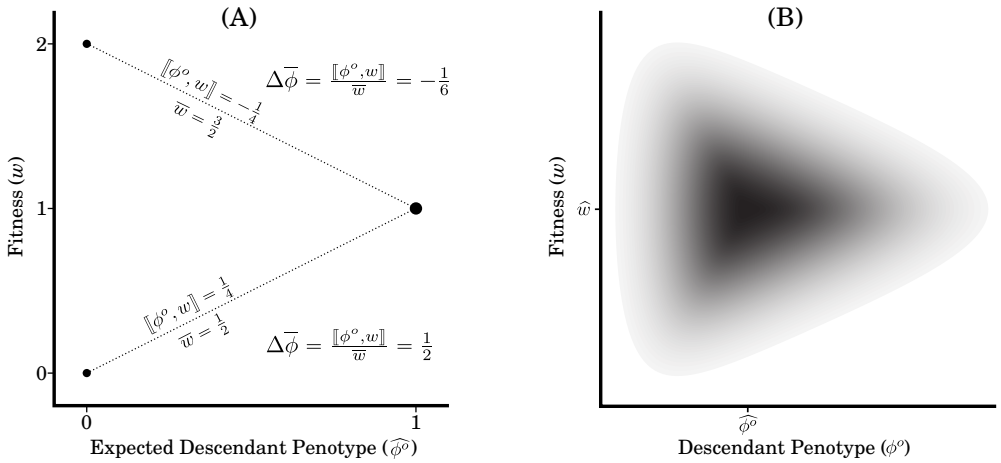

Fig. 3: Directional Stochastic Effects. (A) A population of two sets of individuals with different offspring phenotypic values, 0 and 1, having different fitness distributions. When those with $\widehat{\phi^o} = 0$ have two offspring each, $\overline{\phi}$ declines by $-\frac{1}{6}$, when they have 2 offspring each, $\overline{\phi}$ increases by $\frac{1}{2}$; for a total expected change of $+\frac{1}{6}$. Though the strength of selection (captured by $[\![\phi^o, w]\!]$) is the same, and in opposite directions, the change in $\overline{\phi}$ is different in the two cases because $\overline{w}$ is different. (B) Joint fitness and offspring phenotype distribution for an individual in which $\langle\!\langle \phi^o, (w - \widehat{w})^2 \rangle\!\rangle$ is nonzero. This probability distribution of w and ϕ^o within an individual leads to the same evolutionary effect as does the frequency distribution across individuals shown in (A).

$$\langle\!\langle w_i, \overline{w} \rangle\!\rangle = \frac{\langle\!\langle {}^2 w_i \rangle\!\rangle}{n} + \frac{1}{n} \sum_{j \neq i} \langle\!\langle w_i, w_j \rangle\!\rangle \tag{5}$$

This is the origin of the 3rd and 4th terms in Equations (3) and (4).

The third terms in the Equations (3) and (4), $-[\![\widehat{\beta}, \langle\!\langle {}^2 w \rangle\!\rangle]\!]$ and $-[\![\widehat{\nu}, \langle\!\langle {}^2 w \rangle\!\rangle]\!]$, are negative, meaning that they act to pull the population towards phenotypes that have minimum variance in fitness ($\langle\!\langle {}^2 w \rangle\!\rangle$). Thus, if $[\![\widehat{\nu}, \langle\!\langle {}^2 w \rangle\!\rangle]\!] > 0$ – meaning that expected virulence covaries positively with variance in fitness – then this directional stochastic effect will tend to reduce the expected change in virulence. Note that this effect is distinct from selection proper, which is captured by the $\frac{1}{\widehat{\overline{w}}}[\![\widehat{\nu}, \widehat{w}]\!]$ term. As a result, it is possible for a particular strain of the pathogen to have a lower expected fitness, but to nonetheless be expected to increase, if it also has a much lower variance in fitness than do other strains. The magnitude of directional stochastic effects is greatest when either the number of pathogen strains (n) or the expected pathogen growth rate ($\widehat{\overline{w}}$) is small. We thus expect these effects to be most important at times of low pathogen diversity – such as when a pathogen is introduced into a new host population – or when the pathogen population within a host is declining – such as when it is under attack by the host's immune system. (Note that the directional stochastic effects are different from drift. Drift is nondirectional, in the sense that the expected frequency change of the phenotype due to the drift alone is zero).

Intuitively, the reason that there is a directional stochastic effect acting to reduce variance in fitness is that a strain with high variance (high $\langle\!\langle {}^2 w \rangle\!\rangle$) contributes disproportionately to the variance in mean population fitness, $\langle\!\langle {}^2 \overline{w} \rangle\!\rangle$. As a result, when that strain with a high value of ϕ and high $\langle\!\langle {}^2 w \rangle\!\rangle$ happens to have a particularly high fitness, $\overline{w}$ also tends to be high – reducing the magnitude of increase. In contrast, when that strain has a lower value of w, then $\overline{w}$ also tends to be low – leading to a large decline in $\overline{\phi}$. This is the case for the individual with $\phi = 0$ in Figure 3A.

Equation (5) shows that there is another way in which an individual's fitness can covary with mean fitness – if it covaries with the fitness of others. This is the source of the fourth terms in Equations (3) and (4) ($-\frac{1}{n\widehat{\overline{w}}^2}\sum_{i\neq j}[\![\widehat{\beta}_i, \langle\!\langle w_i, w_j \rangle\!\rangle]\!]$ and $-\frac{1}{n\widehat{\overline{w}}^2}\sum_{i\neq j}[\![\widehat{v}_i, \langle\!\langle w_i, w_j \rangle\!\rangle]\!]$). These terms capture how covariance between the fitness of different pathogen strains can affect the evolution of transmission and virulence. An example of a case in which we might expect $[\![\widehat{v}_i, \langle\!\langle w_i, w_{j\neq i} \rangle\!\rangle]\!] < 0$ is a case in which there are multiple strains competing within the host, such that the most virulent strain is the best competitor (so that other strains tend to do poorly when it does well). This would make the fourth term on the righthand side of Equation (4) positive; contributing to an increase in mean virulence.

The third and fourth terms in Equations (3) and (4), discussed above, appear whenever fitness is a random variable. If descendant phenotype is also a random variable, as we are assuming here, then we also encounter terms containing the probability covariance between phenotype and mean population fitness ($-\frac{1}{\widehat{\overline{w}}^2}[\![\widehat{w}, \langle\!\langle \beta, \overline{w} \rangle\!\rangle]\!]$ and $-\frac{1}{\widehat{\overline{w}}^2}[\![\widehat{w}, \langle\!\langle v, \overline{w} \rangle\!\rangle]\!]$ in our example). The interpretation of these is similar to that of the cases containing $\langle\!\langle w, \overline{w} \rangle\!\rangle$, except here it is a probability covariance between phenotype and mean fitness that influences the magnitude of change when it is associated with the expected fitness of individuals.

The fifth terms of the Equations (3) and (4), $-\frac{1}{n\widehat{\overline{w}}^2}\overline{\langle\!\langle \beta, (w-\widehat{w})^2 \rangle\!\rangle}$ and $-\frac{1}{n\widehat{\overline{w}}^2}\overline{\langle\!\langle v, (w-\widehat{w})^2 \rangle\!\rangle}$ involve an association between a stochastic phenotype and uncertainty in fitness. (They are thus the stochastic phenotype analogues of the third terms). Figure (3B) shows a case in which $\langle\!\langle \phi^o, (w-\widehat{w})^2 \rangle\!\rangle$ is nonzero. Note that the expected value of $(w-\widehat{w})^2$ is just the probability variance in fitness. Saying that $\langle\!\langle \beta, (w-\widehat{w})^2 \rangle\!\rangle < 0$ is equivalent to saying that, for a particular pathogen strain: when that strain has higher than expected transmission (β), it also has lower uncertainty in fitness.

A similar interpretation applies to the terms $-\left(\frac{1}{n\widehat{\overline{w}}^2}\sum_{i\neq j}\overline{\langle\!\langle \beta_i, (w_i-\widehat{w}_i)(w_j-\widehat{w}_j) \rangle\!\rangle}\right)$ and $-\left(\frac{1}{n\widehat{\overline{w}}^2}\sum_{i\neq j}\overline{\langle\!\langle v_i, (w_i-\widehat{w}_i)(w_j-\widehat{w}_j) \rangle\!\rangle}\right)$. Here, it is an association between stochastic phenotype and the similarity in fitness between different individuals (or strains) that influences evolution.

Finally, the terms $-\frac{1}{\widehat{\overline{w}}}\overline{\langle\!\langle \beta, \overline{w} \rangle\!\rangle}$ and $-\frac{1}{\widehat{\overline{w}}}\overline{\langle\!\langle v, \overline{w} \rangle\!\rangle}$ capture the direct correlation between stochastic phenotype and mean population fitness, averaged over the entire population. As in the examples above, these terms are negative because high values of $\overline{w}$ reduce the magnitude of evolutionary change, so the magnitude of change in a trait is reduced when that trait covaries with $\overline{w}$.

Equations (3) and (4) involve relationships between transmission (or virulence) and fitness. Of course, the fitness of a pathogen is a function of both its transmission and its virulence, as well as other factors. If we know, for a particular pathogen, how fitness is related to β and ν, we can substitute that function into Equations (3) and (4) to derive a specific model for that pathogen. In the next section, we do this for the widely studied SIR model of pathogen dynamics.

2.2 Special Case: The SIR Model

The SIR model is a compartmental epedemiological model in which we follow the dynamics of three different categories of hosts: those that are uninfected but susceptible to the pathogen (S), those that are infected (I), and those that have recovered from infection (R). For pathogen strain i, the continuous time SIR model is:

$$\begin{aligned} \dot{S} &= \theta - dS - S\sum_{i=1}^{n}\beta_i I_i \\ \dot{I}_i &= \beta_i S I_i - dI_i - \nu_i I_i - cI_i, \quad i = 1..n \\ \dot{R} &= \sum_{i=1}^{n} cI_i - dR \end{aligned} \tag{6}$$

In Equations (6), I_i represents the density of individuals infected by the ith strain of the pathogen, β is transmission rate, ν is virulence (the degree to which the infection increases the death rate of infected hosts), d is the background death rate (in the absence of infection), and c is the "clearance" rate (the rate at which infected hosts eliminate the infection, such as through immune response). A dot over a variable indicates a time derivative. (See Table 1.)

Day and Gandon (2006, 2007) developed a way to apply the deterministic Price equation to the evolution of pathogens that follow SIR dynamics. They assume that a host can harbor, at most, a single pathogen strain at any given time. In this case, the fitness of pathogen strain i is equal to the per capita growth rate of infected hosts, I_i, that carry strain i. Using Equations (6), we can write the fitness of pathogen strain i as a function of transmission (β) and virulence (ν):

$$w_i = \frac{\dot{I}_i}{I_i} = S\beta_i - \nu_i - d_i - c_i \tag{7}$$

Note that using a different epidemiological model would give us a different equation for the absolute fitness.

We consider a pathogen that has just infected a host, and treat descendant phenotype (ϕ^o in the general equation) as the value of β or ν when that pathogen's descendants are transmitted to another host. We thus essentially treat β and ν as having heritabilities of 1. By contrast, d and c are properties of the host, and are thus environmental variables from

the perspective of the pathogen. We will include them because they may interact with β and ν to influence pathogen evolution, but we assume that d and c are not heritable by the pathogen.

We introduce stochasticity by treating the parameters β, ν, d, and c in Equation (7) as random variables. For simplicity, and consistent with the assumption that a host can harbor only one strain at a time, we will assume that different strains are stochastically independent of one another - meaning that the fourth and sixth terms of Equations (3) and (4) are zero.

Substituting Equation (7) into Equations (3) and (4) and rearranging the terms extensively, yields the following equation for the vector of expected changes in mean transmission, and virulence, natural mortality, and clearance rate over one generation (see Supplementary Materials):

$$\begin{bmatrix} \widehat{\Delta\overline{\beta}} \\ \widehat{\Delta\overline{\nu}} \\ \widehat{\Delta\overline{d}} \\ \widehat{\Delta\overline{c}} \end{bmatrix} = G^{[2]} \cdot \overrightarrow{\kappa} + 2g^{[2]} \cdot \overrightarrow{\kappa} + G^{[3]} \cdot \sigma_G^{[2]} + g^{[3]} \cdot \sigma_G^{[2]} + H^{[3]} \cdot \sigma_H^{[2]} \tag{8}$$

The terms on the righthand side of Equation (8) are written in terms of vectors, matrices, and tensors of degree 3. Below, we discuss the biological meaning of each term in turn.

The first term on the right-hand side of the Equation (8) contains a matrix, $G^{[2]}$, and a vector, $\overrightarrow{\kappa}$, defined as:

$$G^{[2]} = \begin{pmatrix} [\![^2\widehat{\beta}]\!] & [\![\widehat{\beta},\widehat{\nu}]\!] & [\![\widehat{\beta},\widehat{d}]\!] & [\![\widehat{\beta},\widehat{c}]\!] \\ [\![\widehat{\nu},\widehat{\beta}]\!] & [\![^2\widehat{\nu}]\!] & [\![\widehat{\nu},\widehat{d}]\!] & [\![\widehat{\nu},\widehat{c}]\!] \\ [\![\widehat{d},\widehat{\beta}]\!] & [\![\widehat{d},\widehat{\nu}]\!] & [\![^2\widehat{d}]\!] & [\![\widehat{d},\widehat{c}]\!] \\ [\![\widehat{c},\widehat{\beta}]\!] & [\![\widehat{c},\widehat{\nu}]\!] & [\![\widehat{c},\widehat{d}]\!] & [\![^2\widehat{c}]\!] \end{pmatrix}, \quad \overrightarrow{\kappa} = \frac{1}{\widehat{\overline{w}}} \begin{pmatrix} S \\ -1 \\ -1 \\ -1 \end{pmatrix} \tag{9}$$

$G^{[2]}$, the matrix of frequency covariances between our traits, is analogous to the standard G matrix in quantitative genetics. It is multiplied by the fitness gradient, $\overrightarrow{\kappa}$, which shows the direction of maximum increase in fitness (Lande 1976; Lande and Arnold 1983). The matrix $G^{[2]}$ will appear in any model with parameters β, ν, d, and c. The specific form of $\overrightarrow{\kappa}$ given in Equation (9), however, is specific to the SIR model (Equations 6) – a different model would yield a different $\overrightarrow{\kappa}$.

For the case of the *SIR* model, the form of $\overrightarrow{\kappa}$ shown in Equation (9) shows that selection always favors increasing the average transmission with a strength of $\frac{S}{\widehat{\overline{w}}}$ (where S is the density of uninfected but susceptible hosts), while decreasing the average virulence, background mortality, and recover rate, with a strength of $(-\frac{1}{\widehat{\overline{w}}})$. How this selection influences

evolution is of course also influenced by $G^{[2]}$. A positive covariance between β and ν will tend to reduce the degree to which transmission can increase and the degree which virulence can decrease.

Note that the expected change in mean transmission, $\widehat{\Delta\overline{\beta}}$, contains the terms $-[\![\widehat{\beta},\widehat{d}]\!]$ and $-[\![\widehat{\beta},\widehat{c}]\!]$. This illustrates the importance of including the "environmental" factors d and c in our analysis.

In the absence of mutation, $G^{[2]} \cdot \overrightarrow{\kappa}$ is the only term that would appear in a deterministic model, and is equivalent to the selection term in the models of Day and Gandon (2006, 2007). All of the other terms in Equation (8) contain variances and covariances of random variables; and are thus invisible to deterministic models.

The second term on the right-hand side of the Equation (8) also contains the fitness gradient, $\overrightarrow{\kappa}$, but here it is multiplied by a different matrix, $g^{[2]}$, defined as:

$$g^{[2]} = \begin{pmatrix} \overline{\langle\!\langle {}^2\beta \rangle\!\rangle} & \overline{\langle\!\langle \beta,\nu \rangle\!\rangle} & \overline{\langle\!\langle \beta,d \rangle\!\rangle} & \overline{\langle\!\langle \beta,c \rangle\!\rangle} \\ \overline{\langle\!\langle \nu,\beta \rangle\!\rangle} & \overline{\langle\!\langle {}^2\nu \rangle\!\rangle} & \overline{\langle\!\langle \nu,d \rangle\!\rangle} & \overline{\langle\!\langle \nu,c \rangle\!\rangle} \\ \overline{\langle\!\langle d,\beta \rangle\!\rangle} & \overline{\langle\!\langle d,\nu \rangle\!\rangle} & \overline{\langle\!\langle {}^2d \rangle\!\rangle} & \overline{\langle\!\langle d,c \rangle\!\rangle} \\ \overline{\langle\!\langle c,\beta \rangle\!\rangle} & \overline{\langle\!\langle c,\nu \rangle\!\rangle} & \overline{\langle\!\langle c,d \rangle\!\rangle} & \overline{\langle\!\langle {}^2c \rangle\!\rangle} \end{pmatrix} \tag{10}$$

Since β, ν, d, and c are random variables, each has distribution of possible values for any one pathogen strain; they can therefore covary for a single pathogen. The matrix $g^{[2]}$ contains the frequency means, across all pathogen strains, of these probability variances and covariances.

The probability covariance between transmission and virulence can be positive or negative, depending on the biology of pathogen and host. For example, if the process of transmission requires harming the initial host, we would expect a positive probability covariance between virulence and transmission. Such is the case with amoebic dysentery, caused by the unicellular protozoan *Entamoeba histolytica*. In this case, the pathogen gets out of the host by inducing diarrhea (Harries 1982), which can cause dehydration and be lethal if not treated. Increasing transmission of amoebic dysentery is thus likely to accompany increasing virulence (Powell et al 1966). By contrast, we expect a negative probability covariance between transmission and virulence in cases in which transmission of pathogens relies on a reasonably healthy host. Sexually transmitted diseases such as HIV infection should thus show a negative value of $\overline{\langle\!\langle \beta,\nu \rangle\!\rangle}$.

Equations (8) and (10) show that the expected change in mean transmission, $\widehat{\Delta\overline{\beta}}$, contains the term $-\overline{\langle\!\langle \beta,\nu \rangle\!\rangle}$. The expected change in mean virulence, $\widehat{\Delta\overline{\nu}}$, contains the term $S \cdot \overline{\langle\!\langle \beta,\nu \rangle\!\rangle}$. Thus a positive probability covariance between β and ν would inhibit the evolution of increased transmission and amplify the evolution of increased virulence. A negative value of $\overline{\langle\!\langle \beta,\nu \rangle\!\rangle}$ would have the opposite effect; amplifying the effects of selection for increased transmission while reducing the evolution of increased virulence.

The third term on the right-hand side of the Equation (8), $G^{[3]}\sigma_G^{[2]}$, is the inner product of a third order tensor, $G^{[3]}$, and a second order tensor, the matrix $\sigma_G^{[2]}$. These can be written as follows (where $\phi_1^o = \beta$, $\phi_2^o = \nu$, $\phi_3^o = d$, $\phi_4^o = c$):

$$G_{ijk}^{[3]} = [\![\widehat{\phi_i^o}, \langle\!\langle \phi_j^o, \phi_k^o \rangle\!\rangle]\!] \quad \sigma_G^{[2]} = \frac{1}{n\widehat{\overline{w}}^2} \begin{pmatrix} -S^2 & S & S & S \\ S & -1 & -1 & -1 \\ S & -1 & -2 & -1 \\ S & -1 & -1 & -2 \end{pmatrix} \tag{11}$$

$G^{[3]}$ is a three dimensional array, with element (i, j, k) defined by Equation (11) (see Supplementary Materials for a visual schematic diagram of $G^{[3]}$). The term $G^{[3]}\sigma_G^{[2]}$ captures directional stochastic effects, as discussed in the previous section. The elements of $G^{[3]}$ are components of the $[\![\widehat{\phi^o}, \langle\!\langle w, \overline{w} \rangle\!\rangle]\!]$ term from Equation (2). Taken together, the combined elements of $G^{[3]}\sigma_G^{[2]}$ push the population towards phenotypes that minimize the variance in individual fitness and the covariance between the fitness values of different individuals.

Note that the only positive terms in $\sigma_G^{[2]}$ are terms that multiply elements of $G^{[3]}$ that contain $\langle\!\langle \beta, \nu \rangle\!\rangle$, $\langle\!\langle \beta, d \rangle\!\rangle$, or $\langle\!\langle \beta, c \rangle\!\rangle$. This means that either β or ν will tend to increase if it has a positive frequency covariance with $\langle\!\langle \beta, \nu \rangle\!\rangle$, $\langle\!\langle \beta, \nu \rangle\!\rangle$, or $\langle\!\langle \beta, \nu \rangle\!\rangle$. The reason is that ν, d, and c all contribute negatively to fitness while β contributes positively.

The fourth and the fifth terms of the Equation (8), $g^{[3]} \cdot \sigma_G^{[2]}$ and $H^{[3]} \cdot \sigma_H^{[2]}$, are made up of the following terms:

$$g_{ijk}^{[3]} = \overline{\langle\!\langle \phi_i^o, \phi_j^o \phi_k^o \rangle\!\rangle} \tag{12}$$

$$H_{ijk}^{[3]} = [\![\langle\!\langle \phi_i^o, \phi_j^o \rangle\!\rangle, \widehat{\phi_k^o}]\!] \quad \sigma_H^{[2]} = \frac{1}{n\widehat{\overline{w}}^2} \begin{pmatrix} S^2 & -S & -S & -S \\ -S & 1 & 1 & 1 \\ -S & 1 & 1 & 1 \\ -S & 1 & 1 & 1 \end{pmatrix} \tag{13}$$

Though complicated, these terms all derive from the covariance between individual phenotypes and mean population fitness.

3 Discussion

Uncertainty in both fitness and offspring phenotype can influence pathogen evolution in a variety of ways. This is clear from the fact that in the general equations for evolution of transmission and virulence, Equations (3) and (4), all of the terms after the first one, in each equation, contain probability operations and would thus not appear in a deterministic

model. Though the equations contain many stochastic terms, the stochastic components of directional evolution discussed in this paper all fall into two general categories: Probability covariances between traits, and directional stochastic effects.

Probability covariances between traits arise whenever the traits that influence fitness are random variables – meaning that they have a distribution of possible values. This is definitely the case for transmission and virulence of a pathogen since, when a pathogen infects a host, we can not say with certainty how long the host will survive or how many others it will infect.

The concept of a probability covariance between transmission and virulence is relevant to one of the central issues in the study of pathogen evolution: the idea that there are "tradeoffs" between transmission and virulence that constrain the evolution of both traits. Anderson and May (1982) assumed a positive association between transmission and virulence. Subsequently, other authors have considered different tradeoff scenarios corresponding to different biological properties of pathogens and hosts (Alizon et al 2009; Leggett et al 2017).

The kinds of tradeoffs described by these authors are more accurately captured by the probability covariance between β and v ($\langle\!\langle \beta, v \rangle\!\rangle$) than by the frequency covariance between their expected values. The frequency covariance ($[\![\widehat{\beta}, \widehat{v}]\!]$) is influenced by the current distribution of pathogen strains and available hosts (Figure 2), whereas the probability covariance captures tradeoffs resulting from the basic biology of pathogen and host.

Measuring the probability covariance between β and v would, ideally, involve using replicate clones of both pathogen and host, to minimize variation due to genetic differences. We know of no experimental studies have specifically done this. But some studies using the *Daphnia magna-Pasturia ramosa* system have provided data from which $\overline{\langle\!\langle \beta, v \rangle\!\rangle}$ can be estimated. Vale et al (2011) estimated the covariance between transmission potential and virulence for bacteria in different clones of Daphnia. Similarly, Little et al (2013) estimated the variance in transmission potential in different temperatures and at different food levels. One interesting conclusion from these studies is that the value of $\langle\!\langle \beta, v \rangle\!\rangle$ can change sign as a result of environmental changes.

Specifically, Vale et al (2011) found that the covariance between β and v was negative when hosts were given ample resources, but became positive when hosts were severely nutrient stressed. Thus, physiological stress on the host can lead to the evolution of increased virulence of the pathogen.

The second way in which stochasticity can influence directional evolution is through what Rice (2008) called directional stochastic effects. These result from the fact that the same strength of selection (the relation between expected fitness and phenotype, measured either as a covariance or a regression) will produce different magnitudes of evolutionary change depending on the mean population fitness ($\overline{w}$), which is itself a random variable. The third through eighth terms in Equations (3) and (4) are all related to this kind of evolutionary process.

The simplest directional stochastic effect favors phenotypes that have relatively low variance in fitness (corresponding to the $-\frac{1}{n\widehat{\overline{w}}^2}[\![\phi,\langle\!\langle^2 w\rangle\!\rangle]\!]$ term in Equations (3) and (4); note that this is not the same as having high geometric mean fitness (Rice 2008). Pathogen fitness involves both evading the host's immune system – which is likely to exhibit stochastic variation both within and between hosts (Papalexi and Satija 2017; Duneau et al 2017) – and transmission from one host to another, which is likely to add further stochasticity. It is thus likely to be very unpredictable. A trait that reduces this uncertainty, even at the expense of reducing expected fitness, could thus spread – especially when the number of pathogen strains is small (small n in Equations (3) and (4)) or the population of pathogens is declining (small $\widehat{\overline{w}}$).

Another way in which a trait can increase due to directional stochastic effects is through a negative probability covariance between the fitness of individuals possessing it and other individuals in the population. (Terms containing $[\![\phi_i,\langle\!\langle w_i,w_j\rangle\!\rangle]\!]$ in Equations (3) and (4)). For pathogens, this effect would favor a strain that deals differently with the host's immune system than do other strains, even if it does no better on average. This effect would thus be a diversifying force with regard to how pathogens interact with their hosts.

Making our evolutionary models stochastic by allowing traits such as transmission and virulence to be random variables substantially increases the complexity of our results. Upon examination, however, the new terms that appear all correspond to real biological phenomena that would be missed by a purely deterministic analysis.

4 Methods

The relative fitness of an individual, $\Omega=\frac{w}{\overline{w}}$ conditional on $\overline{w}\neq 0$, is a ratio of correlated random variables. In order to evaluate its expected value or its probability covariance with other random variables, we need to expand it in such a way that all random variables are in the numerator. Following Rice (2009), we define $w_i^*=w_i-\widehat{w_i}$, and expand Ω_i as:

$$\Omega_i=\frac{w_i}{\overline{w}}=\frac{w_i}{\widehat{\overline{w}}+\overline{w}^*}=\frac{w_i}{\widehat{\overline{w}}}\left(1+\frac{\overline{w}^*}{\widehat{\overline{w}}}\right)^{-1}=\frac{\widehat{w}_i}{\widehat{\overline{w}}}\left(1+\sum_{j=1}^{\infty}(-1)^j\frac{(\overline{w}^*)^j}{(\widehat{\overline{w}})^j}\right) \tag{14}$$

We now find the expected value, $\widehat{\Omega}$ as Rice (2009):

$$\widehat{\Omega}_i=E\left(\frac{w_i}{\overline{w}}|\overline{w}\neq 0\right)=\frac{\widehat{w}_i}{\widehat{\overline{w}}}+\sum_{j=1}^{\infty}(-1)^j\frac{\widehat{w}_i\langle\!\langle^j\overline{w}\rangle\!\rangle+\langle\!\langle w_i,^j\overline{w}\rangle\!\rangle}{(\widehat{\overline{w}})^{j+1}} \tag{15}$$

For a population of size N, the jth order terms in these series tend to scale as $\frac{1}{N}$, so we approximate $\widehat{\Omega}_i$ by setting $j=1$. This yields:

$$\Omega_i\approx\frac{w_i}{\widehat{\overline{w}}}-\frac{(\overline{w}-\widehat{\overline{w}})w_i}{\widehat{\overline{w}}^2}\qquad\widehat{\Omega}_i\approx\frac{\widehat{w}_i}{\widehat{\overline{w}}}-\frac{\langle\!\langle w_i,\overline{w}\rangle\!\rangle}{(\widehat{\overline{w}})^2} \tag{16}$$

Using Equation (16), we write $[\![\widehat{\phi^o}, \widehat{\Omega}]\!]$ from Equation (1) as follow:

$$[\![\widehat{\phi^o}, \widehat{\Omega}]\!] \approx \frac{1}{\widehat{\overline{w}}}[\![\widehat{\phi^o}, \widehat{w}]\!] - \frac{1}{\widehat{\overline{w}}^2}[\![\widehat{\phi^o}, \langle\!\langle w, \overline{w}\rangle\!\rangle]\!] \tag{17}$$

we also use Equation (16) and obtain:

$$\overline{\langle\!\langle \phi^o, \Omega\rangle\!\rangle} \approx \frac{1}{\widehat{\overline{w}}}\overline{\langle\!\langle \phi^o, w\rangle\!\rangle} - \frac{1}{\widehat{\overline{w}}^2}\overline{\langle\!\langle \phi^o, (\overline{w} - \widehat{\overline{w}})w\rangle\!\rangle} \tag{18}$$

The second term of the Equation (18) can be manipulated as follow:

$$\frac{1}{\widehat{\overline{w}}^2}\overline{\langle\!\langle \phi^o, (\overline{w} - \widehat{\overline{w}})w\rangle\!\rangle} = \frac{1}{\widehat{\overline{w}}^2}\overline{\langle\!\langle \phi^o, (w - \widehat{w})(\overline{w} - \widehat{\overline{w}})\rangle\!\rangle} + \frac{1}{\widehat{\overline{w}}^2}\overline{\langle\!\langle \phi^o, \widehat{w}(\overline{w} - \widehat{\overline{w}})\rangle\!\rangle} \tag{19}$$

Recall the formula $\overline{ab} = [\![a, b]\!] + \overline{a}\overline{b}$ which bar indicates the average over all individuals in population. Therefore, the second term on the right-hand side of the Equation (19), can be expanded as follows:

$$\overline{\langle\!\langle \phi^o, \widehat{w}(\overline{w} - \widehat{\overline{w}})\rangle\!\rangle} = \overline{\widehat{w}\langle\!\langle \phi^o, \overline{w}\rangle\!\rangle} - \overline{\widehat{w}\langle\!\langle \phi^o, \widehat{\overline{w}}\rangle\!\rangle} = \overline{\widehat{w}\langle\!\langle \phi^o, \overline{w}\rangle\!\rangle} = [\![\widehat{w}, \langle\!\langle \phi^o, \overline{w}\rangle\!\rangle]\!] + \widehat{\overline{w}}_i\overline{\langle\!\langle \phi^o, \overline{w}\rangle\!\rangle} \tag{20}$$

Therefore, we obtain:

$$\overline{\langle\!\langle \phi^o, \Omega\rangle\!\rangle} \approx \frac{1}{\widehat{\overline{w}}}\overline{\langle\!\langle \phi^o, w\rangle\!\rangle} - \frac{1}{\widehat{\overline{w}}^2}\overline{\langle\!\langle \phi^o, (w - \widehat{w})(\overline{w} - \widehat{\overline{w}})\rangle\!\rangle} - \frac{1}{\widehat{\overline{w}}^2}[\![\widehat{w}, \langle\!\langle \phi^o, \overline{w}\rangle\!\rangle]\!] - \frac{1}{\widehat{\overline{w}}^2}\widehat{\overline{w}}\overline{\langle\!\langle \phi^o, \overline{w}\rangle\!\rangle} \tag{21}$$

and substituting Equations (17) and (21) in Equation (1) yields Equation (2).

The third and fourth terms of the Equation (2) can further expanded as:

$$\frac{1}{\widehat{\overline{w}}^2}[\![\widehat{\phi^o}, \langle\!\langle w, \overline{w}\rangle\!\rangle]\!] = [\![\widehat{\phi^o}, \langle\!\langle w_i, \frac{1}{n}\sum_{j=1}^{n} w_j\rangle\!\rangle]\!] = \frac{1}{n\widehat{\overline{w}}^2}[\![\widehat{\phi^o}, \langle\!\langle {}^2w\rangle\!\rangle]\!] + \frac{1}{n\widehat{\overline{w}}^2}\sum_{i\neq j}[\![\widehat{\phi_i^o}, \langle\!\langle w_i, w_j\rangle\!\rangle]\!] \tag{22}$$

$$\frac{1}{\widehat{\overline{w}}^2}\overline{\langle\!\langle \phi^o, (w - \widehat{w})(\overline{w} - \widehat{\overline{w}})\rangle\!\rangle} = \frac{1}{n\widehat{\overline{w}}^2}\overline{\langle\!\langle \phi^o, \sum_{j=1}^{n}(w_i - \widehat{w}_i)(w_j - \widehat{w}_j)\rangle\!\rangle} = \frac{1}{n\widehat{\overline{w}}^2}\overline{\langle\!\langle \phi^o, (w_i - \widehat{w}_i)^2\rangle\!\rangle} + \frac{1}{n\widehat{\overline{w}}^2}\sum_{j\neq i}\overline{\langle\!\langle \phi^o, (w_i - \widehat{w}_i)(w_j - \widehat{w}_j)\rangle\!\rangle} \tag{23}$$

and substituting these equations in Equation (2) and β and ν for offspring phenotype, results Equations (3) and (4).

From model (6), we derive the equation for fitness of pathogen strain i as:

$$w_i = S\beta_i - \nu_i - d_i - c_i \tag{24}$$

Note that in SIR model the pathogen strains are stochastically independent in fitness. By substituting Equation (24) in Equations (3) and (4) we derive Equation (8) (see Supplementary Materials). We present Equation (8) with the tensor notations. For the strain i, we define the random variables $\phi_1^o = \beta$, $\phi_2^o = \nu$, $\phi_3^o = d$, $\phi_4^o = c$. The covariance terms on the right-hand sides of Equations (8) can be grouped into 4×4 degree 2 and $4 \times 4 \times 4$ degree 3 tensors (note that a tensor of degree 2 is just a matrix). The elements of each tensor can be shown as follow:

$$G_{ij}^{[2]} = [\![\widehat{\phi_j^o}, \widehat{\phi_j^o}]\!], \quad g_{ij}^{[2]} = \overline{\langle\!\langle \phi_i^o, \phi_j^o \rangle\!\rangle}, \quad G_{ijk}^{[3]} = [\![\widehat{\phi_i^o}, \langle\!\langle \phi_j^o, \phi_k^o \rangle\!\rangle]\!], \quad g_{ijk}^{[3]} = \overline{\langle\!\langle \phi_i^o, \phi_j^o \phi_k^o \rangle\!\rangle}, \quad H_{ijk}^{[3]} = [\![\langle\!\langle \phi_i^o, \phi_j^o \rangle\!\rangle, \widehat{\phi_k^o}]\!] \tag{25}$$

where $i = 1...4, \quad j = 1...4, \quad k = 1...4$. Also we obtain:

$$\vec{\kappa} = \begin{pmatrix} \kappa_1 \\ \kappa_2 \\ \kappa_3 \\ \kappa_4 \end{pmatrix} = \frac{1}{\widehat{\overline{w}}} \begin{pmatrix} S \\ -1 \\ -1 \\ -1 \end{pmatrix} \tag{26}$$

$$\sigma_G^{[2]} = \begin{pmatrix} \sigma_{G_{11}}^{[2]} & \sigma_{G_{12}}^{[2]} & \sigma_{G_{13}}^{[2]} & \sigma_{G_{14}}^{[2]} \\ \sigma_{G_{21}}^{[2]} & \sigma_{G_{22}}^{[2]} & \sigma_{G_{23}}^{[2]} & \sigma_{G_{24}}^{[2]} \\ \sigma_{G_{31}}^{[2]} & \sigma_{G_{32}}^{[2]} & \sigma_{G_{33}}^{[2]} & \sigma_{G_{34}}^{[2]} \\ \sigma_{G_{41}}^{[2]} & \sigma_{G_{42}}^{[2]} & \sigma_{G_{43}}^{[2]} & \sigma_{G_{44}}^{[2]} \end{pmatrix} = \frac{1}{n\widehat{\overline{w}}^2} \begin{pmatrix} -S^2 & S & S & S \\ S & -1 & -1 & -1 \\ S & -1 & -2 & -1 \\ S & -1 & -1 & -2 \end{pmatrix} \tag{27}$$

$$\sigma_H^{[2]} = \begin{pmatrix} \sigma_{H_{11}}^{[2]} & \sigma_{H_{12}}^{[2]} & \sigma_{H_{13}}^{[2]} & \sigma_{H_{14}}^{[2]} \\ \sigma_{H_{21}}^{[2]} & \sigma_{H_{22}}^{[2]} & \sigma_{H_{23}}^{[2]} & \sigma_{H_{24}}^{[2]} \\ \sigma_{H_{31}}^{[2]} & \sigma_{H_{32}}^{[2]} & \sigma_{H_{33}}^{[2]} & \sigma_{H_{34}}^{[2]} \\ \sigma_{H_{41}}^{[2]} & \sigma_{H_{42}}^{[2]} & \sigma_{H_{43}}^{[2]} & \sigma_{H_{44}}^{[2]} \end{pmatrix} = \frac{1}{n\widehat{\overline{w}}^2} \begin{pmatrix} S^2 & -S & -S & -S \\ -S & 1 & 1 & 1 \\ -S & 1 & 1 & 1 \\ -S & 1 & 1 & 1 \end{pmatrix} \tag{28}$$

The tensor inner products on the right-hand side of equation (8) is 4 by 1 vector and can be written as follow:

$$G^{[2]}.\overrightarrow{\kappa} = \sum_{i=1}^{4}\sum_{j=1}^{4} G_{ij}^{[2]}\kappa_j \tag{29}$$

$$g^{[2]}.\overrightarrow{\kappa} = \sum_{i=1}^{4}\sum_{j=1}^{4} g_{ij}^{[2]}\kappa_j \tag{30}$$

$$G^{[3]}.\sigma_G^{[2]} = \sum_{i=1}^{4}\sum_{j=1}^{4}\sum_{k=1}^{4} G_{ijk}^{[3]}\sigma_{G_{kj}}^{[2]} \tag{31}$$

$$g^{[3]}.\sigma_G^{[2]} = \sum_{i=1}^{4}\sum_{j=1}^{4}\sum_{k=1}^{4} g_{ijk}^{[3]}\sigma_{G_{kj}}^{[2]} \tag{32}$$

$$H^{[3]}.\sigma_H^{[2]} = \sum_{i=1}^{4}\sum_{j=1}^{4}\sum_{k=1}^{4} H_{ijk}^{[3]}\sigma_{H_{kj}}^{[2]} \tag{33}$$

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