The Evolution of Virulence in Pathogens with Vertical and Horizontal Transmission

Fares Dhane, Sandrine Soeharjono & Kiri Stern
Department of Biology, Université de Montréal,
90 Vincent-d'Indy, Montréal (QC), H2V 2S9, Canada

ABSTRACT

We present an epidemiological model for the evolution of virulence displaying the trade-offs between vertical and horizontal transmission. The population dynamics between one host and 99 pathogen strains added individually every 1,000 timesteps in the presence of both mechanisms demonstrate that increased vertical transmission rates select for lower evolutionary stable levels of virulence. However, virulent vertically-transmitted pathogens can persist when they provide protection against even more virulent horizontally-transmitted strains. Furthermore, increasing horizontal transmission opportunities favour less virulent strains that are good at vertical transmission because of selection for greater host fitness. Finally, we present simulations allowing both transmission rates to evolve, and show that strains exhibiting high levels of vertical transmission can only be successful in contexts of low virulence.

Key words: Epidemiology, horizontal transmission, vertical transmission, pathogenicity, virulence.

INTRODUCTION

An essential part of parasitic transmission and the evolution of host-pathogen interactions is the mode of transmission. Vertical transmission is defined as the direct transfer of a parasite from one generation to the next during the birth of an offspring. On the other hand, horizontal transmission involves the transmission of parasites among related and non-related individuals alike, and can be passed on at any time in the hosts' life cycle (Ebert, 2013). Horizontal transmission can occur directly, such as through air-borne, food-borne or sexual infections, or indirectly through a vector (Chen *et al.*, 2006). It has been suggested that these different modes of transmission play a crucial role in determining the virulence of a pathogen (Clayton and Tompkins, 1994, Ewald, 1994), which reflects its ability to cause disease (Payne, 2017). The transmission process thus determines the spread and persistence of a given pathogen in a population, which is crucial to modeling population dynamics and designing proper disease control strategies.

In 1987, Ewald theorized that parasites using predominantly horizontal transmission methods would tend towards higher virulence, whereas those favouring vertical transmission would tend towards lower virulence. Additionally, an increase in host density would lead to an increase in the rate of contacts between infected and

non-infected hosts. However, it was observed that higher horizontal transmission opportunities actually select for a lower virulence equilibrium and shift towards greater vertical transmission in pathogens instead. This occurs because of the epidemiological feedback: higher contact rates between hosts allow for a greater number of equilibrium states to be attained, where high horizontal transmission isn't as effective (Lipstich *et al.*, 1995). This enables strains with lower basic reproductive ratios to possibly outcompete those with higher ones, thereby favouring vertical transmission instead.

We present an epidemiological model incorporating trade-offs between vertical and horizontal transmission, which allows us to observe the dynamics between 1 host population and 99 infected strains added individually every 1,000 time steps for a total of 99,000 iterations. This model gives the host population time to stabilize and adapt to the exposure to various pathogens between each transmission opportunity. Different simulations support the idea that vertical transmission is favoured over horizontal transmission in cases of decreased virulence, thus selecting for strains characteristized with low virulence. Furthermore, we find that as the number of opportunities for horizontal transmission increase, selection for strains with lower virulence also increases, given that infection is only allowed for one pathogenic strain at a time. Lastly, we present additional simulations in which each strain's properties may evolve through time, thus imitating further realistic conditions.

MATHEMATICAL MODEL FOR THE EVOLUTION OF VIRULENCE

We start by considering a model composed of one uninfected host population and two populations infected with either of two pathogenic strains. This model is a generalization of the single-strain model by Lipstich et al. (1995), and its dynamics are governed by the following equations :

$$\frac{dX}{dt} = (b_x X + e_1 Y_1 + e_2 Y_2)(1 - \frac{X+Y_1+Y_2}{K}) - u_x X - cX(\beta_1 Y_1 + \beta_2 Y_2) \quad (1)$$

$$\frac{dY_1}{dt} = b_1 Y_1 (1 - \frac{X+Y_1+Y_2}{K}) - u_1 Y_1 + c\beta_1 X Y_1 \quad (2)$$

$$\frac{dY_2}{dt} = b_2 Y_2 (1 - \frac{X+Y_1+Y_2}{K}) - u_2 Y_2 + c\beta_2 X Y_2 \quad (3)$$

Let X and Y_i be the number of uninfected hosts and number of hosts infected with pathogen strains i = 1, 2, respectively. Uninfected hosts have a maximal per capita birth rate b_x and a mortality rate u_x, resulting in a lifespan of $1/u_x$. Let e_i represent the per capita birth rate of uninfected hosts by hosts infected with strain i and b_i represent

the per capita birth rate of offsprings infected with strain i per unit time. Infected hosts die at the rate $u_i \geq u_x$. Let c be the rate of contact between hosts, representative of the opportunities for horizontal transmission and β_i be the horizontal transmission rate of strain i. Finally, let K represent the environment's carrying capacity.

For each strain to invade and persist in the population, the basic reproductive rate of the parasite must be greater than 1 and satisfy the following conditions:

$$R_0 = H_0 + V_0 > 1 \quad (4)$$

$$H_0 = \frac{c\,\beta_i\,K}{u_i}\left(\frac{1-u_x}{b_x}\right) \quad (5)$$

$$V_0 = \frac{b_i\,u_x}{b_x\,u_i} \quad (6)$$

Where H_o represents the number of new horizontally-acquired cases from a single infected host in a population of uninfected hosts before the primary host dies and V_o represents the number of new vertically-acquired cases by the same host introduced into the uninfected population at equilibrium.

Generalizing this two-pathogen model to i strains allows for the study of more complex dynamics, such as in this epidemiological model.

JUSTIFICATION OF PARAMETERS

The initial number of uninfected and infected hosts with strain 1 are of X_o= 10 and $Y_{1,o}$ = 1, respectively. The carrying capacity K has a value of 80. It was determined by setting the infected host populations to zero and letting the uninfected host population stabilize without the impact of any factors. For the host population, its birth rate b_x is held constant at 1.0, while its mortality rate u_x is held constant at 0.2.

The values for variables c, b_i, e_i and u_i vary between strains and figures in order to compare their different impacts on the epidemiological evolutionary trajectories. The horizontal transmission rate and virulence of each strain are respectively constrained by the following equations:

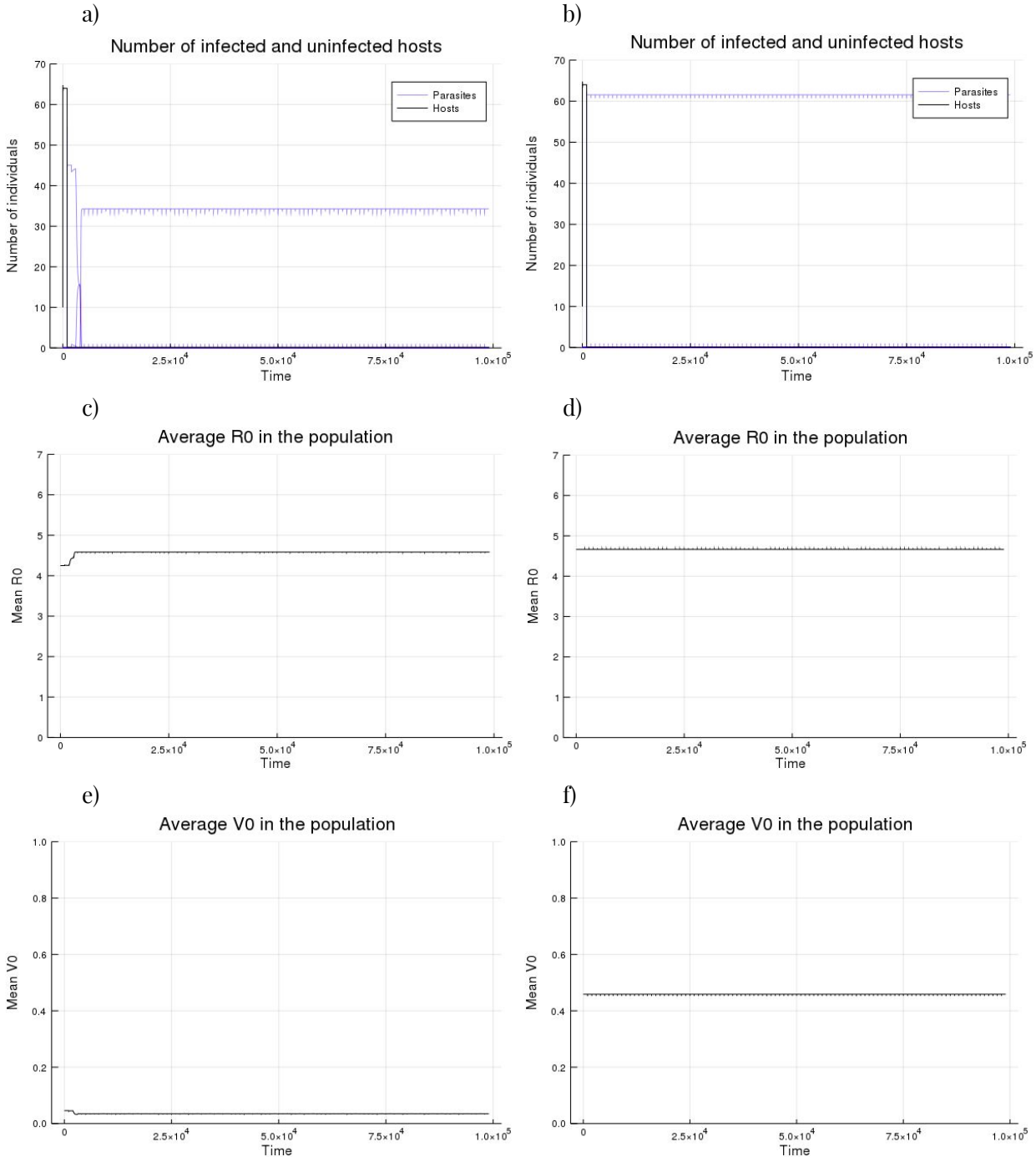
$$\beta_i = \frac{3\,(u_i - u_x)}{u_i - u_x + 1} \quad (7)$$

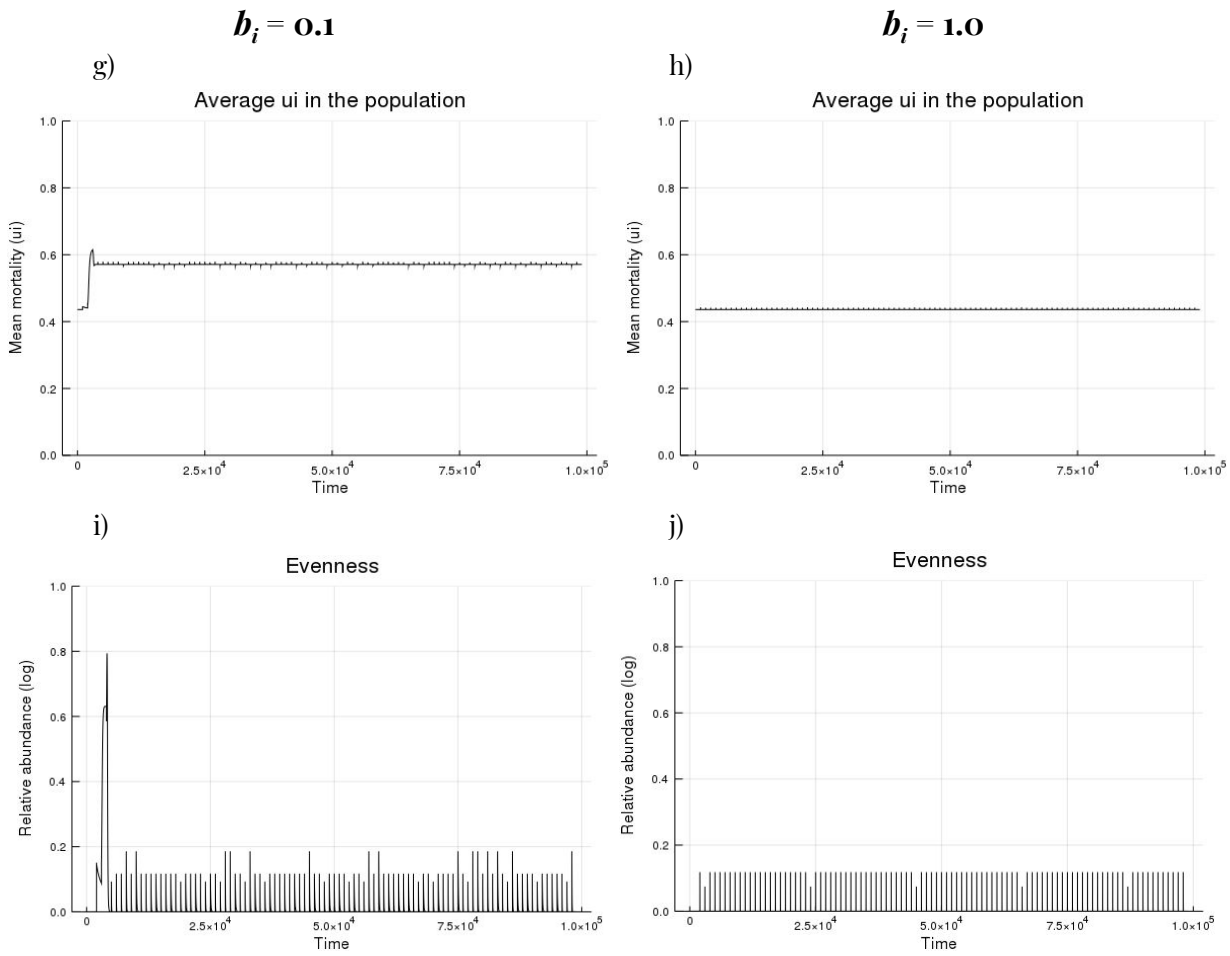
$$Virulence = 1 - \frac{(b_i + e_i)\,u_x}{b_x\,u_i} \quad (8)$$

FIGURE 1

Here we compare the evolutionary trajectories with the variable b_i held constant at the values of 0.1 and 1.0 for every pathogenic strain in their respective column. Since e_i directly depends on it through the equation $e_i = b_x - b_i$, each strain also possesses the value of 0.9 and 0.0, respectively.

b_i = 0.1 **b_i = 1.0**





Evolutionary dynamics of 99 infected strains introduced every 1000 generations for two vertical transmission values, b_i = 0.1 (left column) and b_i = 1.0 (right column) are simulated. As shown, (a,b) demonstrate the number of uninfected and infected hosts with each strain; (c,d) display the mean R_o in the population; (e,f) display the average of all new infections acquired vertically; (g,h) display the average mortality in the population; (i,j) display the evenness of the total population. The simulations show that higher vertical transmission selects for lower mortality and horizontal transmission, whereas R_o seems to stay fairly constant. Constant parameters: c = 4.0, b_x = 1.0, u_x = 0.2, $e_i = b_x - b_i$. Each infected strain possesses a random value of $u_i \in [u_x, 1]$ which in turn determines its value of β_i according to equation (7), as aforementioned in the text.

FIGURE 2

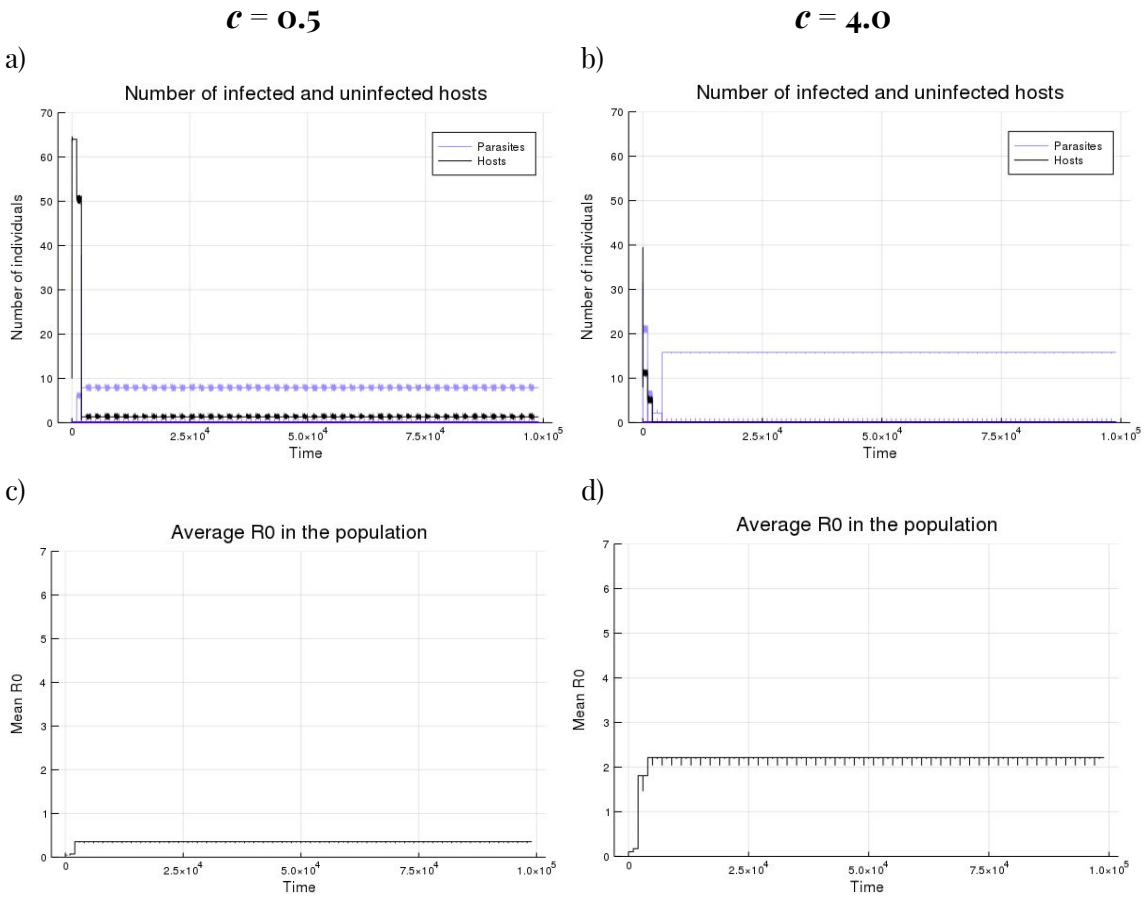
Here we present the evolutionary trajectories with additional variables r_1, r_2 and r_3. Their values are randomly chosen from a uniform distribution over [0,1]. They respectively designate the total virulence of the strain, the fraction of virulence attributable to fecundity loss, and the fraction of offspring of infected hosts which are infected. The resulting constraints on the simulations' parameters are the following:

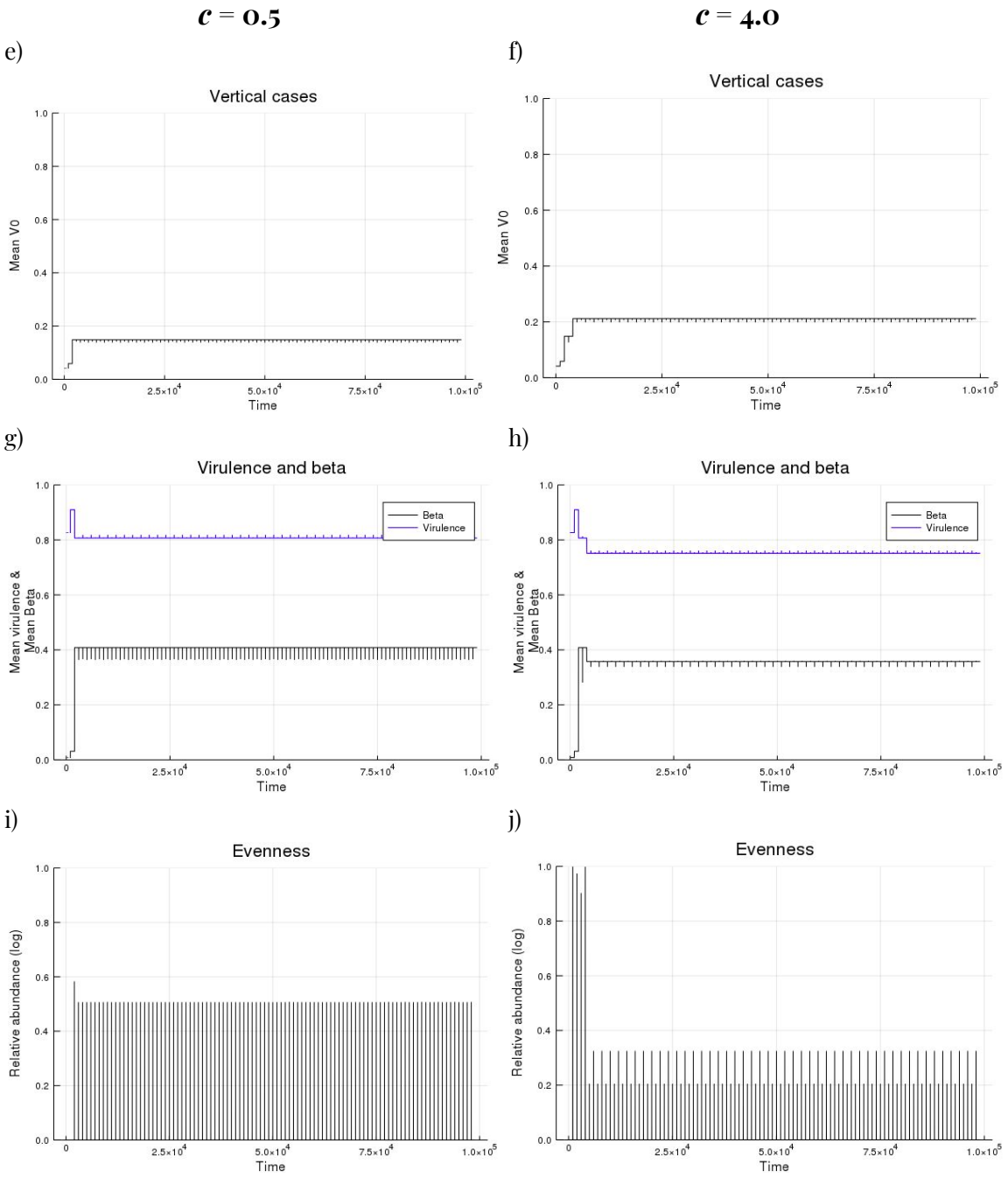
$$e_i = b_x (1 - r_3)(1 - r_1 r_2) \tag{9}$$

$$b_i = b_x r_3 (1 - r_1 r_2) \tag{10}$$

$$\alpha = 1 - V_0 \tag{11}$$

$$\beta_i = \frac{r_1 - (\alpha\, b_i)}{b_x} \tag{12}$$

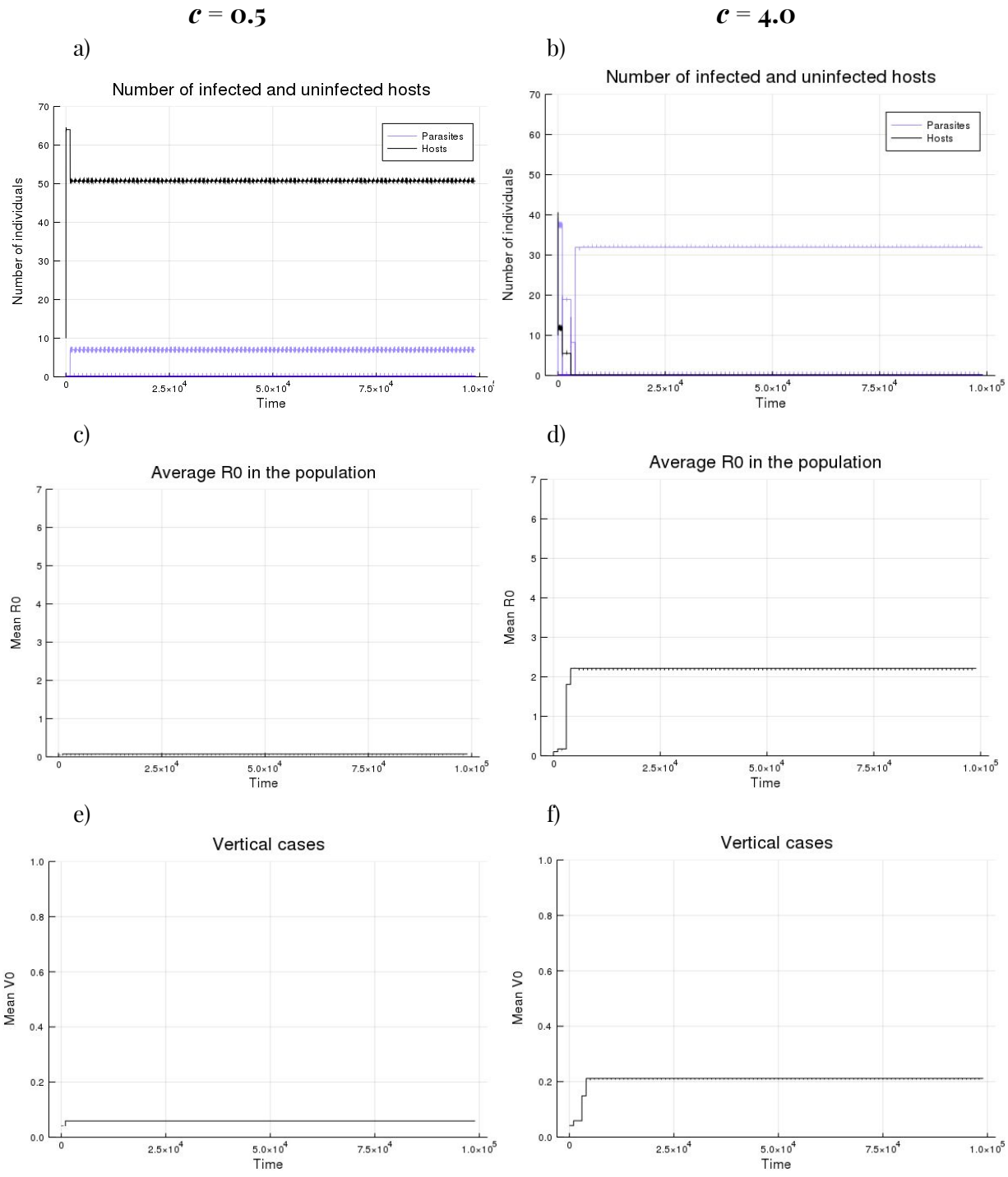


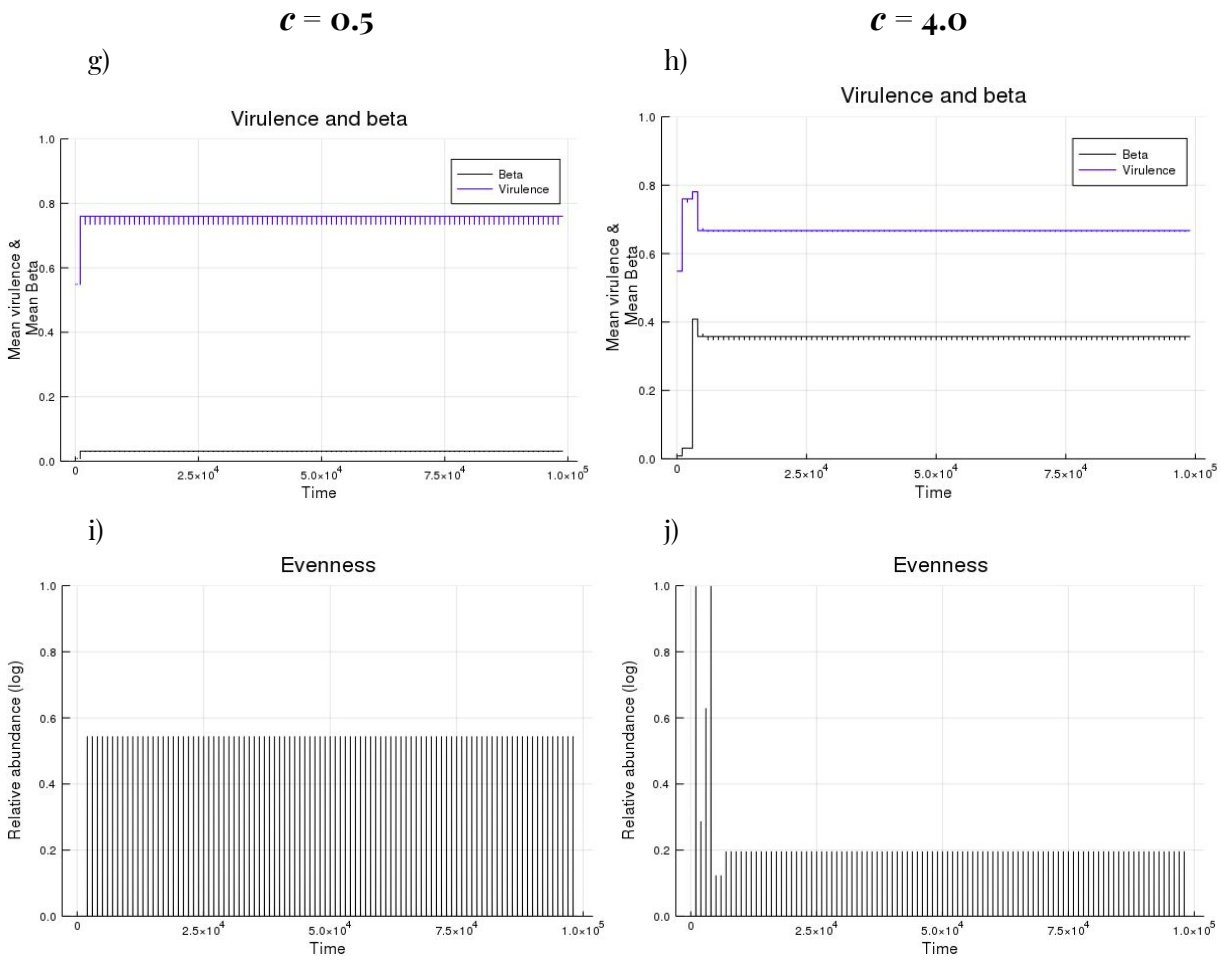


Evolutionary dynamics of 99 infected strains introduced every 1000 generations for two horizontal transmission opportunity values, c = 0.5 (left column) and c = 4.0 (right column). The parameters are identical to those in Figure 2 but with values of e_i, h_i and β_i constrained through equations (9), (10) and (12) by parameters r_1, r_2 and r_3 each chosen randomly from a uniform distribution over [0,1]. As shown, (a,b) demonstrate the number of uninfected and infected hosts with each strain; (c,d) display the mean R_o in the population; (e,f) display the average of all new infections acquired vertically; (g,h) display the average virulence and horizontal transmissibility β_i; (i,j) display the evenness of the total population. The simulations show that a higher rate of contacts between hosts, c, selects for lower virulence at equilibrium and higher vertical transmission rates. Constant parameters: b_x = 1.0 and u_x = 0.2. Each infected strain possesses a random value of $u_i \in [u_x, 1]$.

FIGURE 3

Here we show the evolutionary trajectories where both vertical and horizontal transmission parameters can vary with a constraint. All parameters are identical to those in Figure 2, with the exception of r_3 restricted by the range [0, r_1] such that the fraction of infected offspring from infected hosts may not exceed the total virulence.





Evolutionary dynamics of 99 infected strains introduced every 1000 generations for two values of horizontal transmission opportunity values, c = 0.5 (left column) and c = 4.0 (right column). All parameters are identical to those in Figure 2 but with a constraint r_3 value chosen randomly from a uniform distribution over [0, r_1]. As shown, (a,b) demonstrate the number of uninfected and infected hosts with each strain; (c,d) display the mean R_o in the population; (e,f) display the average of all new infections acquired vertically; (g,h) display the average virulence and horizontal transmissibility β_i; (i,j) display the evenness of the total population. Similar to Figure 2, the simulations above show that a higher rate of contacts between hosts c selects for lower virulence and higher vertical transmission rates. However, higher levels of virulence may evolve and an increase in vertical transmission results in little fitness benefit.

DISCUSSION

Parameter Constraints

In Figure 1, we simulate the evolutionary trajectories for two different values of vertical transmission, b_i = 0.1 and 1.0, which are held constant for all strains. This scenario represents a case of imperfect vertical transmission such that there is no net loss of fertility due to infection. In other words, virulence (i.e. the loss of fitness of the host) depends solely on mortality through equation (8); we thus neglect the decrease in fitness from the reduction of the number of uninfected offspring.

In the following two figures, we present simulations of the evolutionary dynamics with varying vertical and horizontal parameters under constraints through equations (9-12). In Figure 2, strains are permitted to have very low virulence and very high vertical transmission (through r_1, $r_3 \in [0,1]$). This state is typically seen in the evolution of avirulence. In Figure 3, high levels of vertical transmission are only permitted with high levels of virulence through the $r_3 \in [0,r_1]$ restriction. This is typically associated with pathogens that require sufficient replication within the host, usually resulting in the harming of the host.

Analysis of Results

As we can see in Figure 1, different parasitic strains persist due to coexistence and competitive exclusion, which varies in degree at every new generation. Contrary to the results observed in Lipstich *et al.* (1996), the average invasion and persistence condition R_0 fluctuates around 4.6 in both scenarios. This indicates a lesser importance on the horizontal transmission parameter, in the case where there is a higher vertical transmission rate; representing a situation in which the population is saturated with infected individuals by pathogens with vertical transmission and low virulence. Additionally, lower virulence results in lower mean mortality through equation (8) and as observed in graph (h). Graphs (i, j) describe the evenness of the total population, which is observed to stay the same in both situations. Because of the high reproductive rate ($R_0 > 1$), a small number of strains occupy the majority of the population.

In Figures 2 and 3, when comparing the two simulations with different transmission opportunities, selection for the type of transmission will depend on whether high vertical transmission is limited by virulence. When there is a competition between both transmission types, there will always be selection for the type that guarantees greater host fitness. And as seen in Ebert and Bull (2003), vertically- transmitted strains are less virulent than horizontally-transmitted ones. A horizontally-transmitted strain will always push the host to invest its energy in contact rather than reproduction, while vertical transmission ensures the opposite. A

less virulent strain using vertical transmission provides the host with greater fitness than a very virulent strain using horizontal transmission, which therefore guarantees its persistence in the population over time. This dynamic is reflected in the relationship between virulence and the type of transmission (Levin, 1996). However, in the case where high vertical transmission requires high virulence, horizontally-transmitted pathogens would prevail because of the low fitness benefits from vertical transmission.

Figure 2 shows the evolutionary trajectories where high vertical transmission is compatible with low virulence. Two different cases, with identical parameters except for the rate of contact between hosts, c = 0.5 and c = 4.0 in each respective column, are presented. As predicted, an increase in its value selects for less virulent strains exhibiting high vertical transmission rates. This can be explained by the fact that as the number of contacts between individuals increases, the number of available susceptible individuals decreases, leading to saturation. Also, the population evenness is directly correlated to the invasion and persistence condition. As R_0 increases above 1, a decrease in evenness is observed; the reproduction of only a few dominant strains increases the disparity between the number of individuals of the dominant strains and of the remaining ones. Whereas when R_0 is less than 1, species evenness is better distributed across all strains, since no single strain is able to dominate.

Figure 3 (a) describes an equilibrium in which the host population can persist without parasites. This can be explained through the limited vertical transmission (through the constraint $r_3 \in [0, r_1]$) and the low rate of horizontal transmission, which is directly correlated to the contact rate (c = 0.5). Equation (4) confirms this observation, whereby the invasion and persistence of a parasite can only occur when the sum of H_0 and V_0 is greater than 1. Selection thus favours parasites exhibiting relatively high virulence and employing horizontal transmission. As previously described, the fraction of infected offsprings from infected hosts, and thus vertical transmission, is limited by the total virulence of the strain. This constraint results in the mean V_0 barely attaining a vertical basic reproductive ratio of 0.2, thus demonstrating the limited fitness benefit conferred by vertical transmission. Horizontal transmission is, therefore, less virulent than vertical transmission. Results show that natural selection will always selected the less virulent strains, which explains the decrease in virulence shown in graphs (g,h). Finally, as in Figure 2, the invasion and persistence condition dictates population evenness.

CONCLUSION

Few models consider the evolution of virulence for parasites with mixed horizontal and vertical transmission. Here, we show that selection depends on whether high vertical transmission rates are constrained by low or high virulence. It is observed that selection favours vertically-transmitted strains, but only when vertical transmission is compatible with low virulence. On the other hand, situations where high vertical transmission rates are only possible with high virulence, horizontal transmission is favoured. Ultimately, selection will always favour the least virulent strain, regardless of the type of transmission.

These findings could suggest that efforts to reduce vertical transmission of pathogens could, unintentionally, shift selection towards mutants of increased virulence. It is possible that vertical transmission has evolutionarily placed a selection pressure on pathogens to evolve at relatively low levels of virulence, thereby allowing the mother-to-offspring chain of transmission to continue over several generations. However, in cases where the horizontal transmission rates are also low, reducing vertical transmission might be sufficient to eliminate a pathogen from a population by bringing its basic reproductive ratio below 1.

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