

# Supplementary Online Material for “Evolution of class-structured populations in periodic environments”

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Note: Unless they have an “S” prefix, all references are to equations or figures in the main text.

## S.1 Scenario 1: Curse of the Pharaoh

Figure S.1a shows that fluctuations in the production of susceptible hosts (top panel) cause fluctuations in the quantity and quality of classes  $A$  and  $B$  (middle and bottom panels). By averaging over these fast fluctuations, it is possible to track the frequency  $f_m(t)$  of the mutant. Figure S.1b shows that our reproductive-value-weighted selection gradient ( $\mathcal{S}$ , equation (9); dashed line) gives a very accurate prediction for the dynamics of the mutant frequency  $f_m(t)$  (grey) on the slow time scale (top panel). When one zooms in, we recover the fast fluctuations of the instantaneous selection gradient  $\mathcal{S}(t)$  (bottom panel). Note that the direction of selection is well predicted by the sign of  $\mathcal{S}(t)$ .

For the life cycle of Scenario 1, we can use equation (10) to derive the following dynamics of class frequencies:

$$\frac{df^A}{dt} = \beta^B S(t) f^B(t) - (d^A + \alpha^A) f^A(t) - r_w f^A(t) \quad (\text{S.1a})$$

$$\frac{df^B}{dt} = \beta^A f^A(t) - d^B f^B(t) - r_w f^B(t) \quad (\text{S.1b})$$

together with the dynamical equation for  $S(t)$ . There is no analytical solution in the general case, but numerical integration allows us to investigate the dynamics of the class frequencies. Note that the frequency of free-living pathogens (class  $B$ ) will always tend to lag behind the class  $A$  of infected hosts because these free-living pathogens are produced from class  $A$ .

In the absence of fluctuations ( $\zeta = 0$ ), the system reaches an equilibrium, which can be calculated by setting  $df^k/dt$  and  $r_w$  to zero. We thus obtain

$$\frac{f_{\text{cst}}^A}{f_{\text{cst}}^B} = \frac{d^B}{\beta^A} \quad \text{and} \quad S_{\text{cst}} = \frac{d^A + \alpha^A d^B}{\beta^B \beta^A}. \quad (\text{S.2})$$

In the presence of fluctuations ( $\zeta > 0$ ), an explicit expression of  $f^A(t)$  on the periodic attractor is beyond our reach, but, because

$$\left\langle \frac{d \ln(f^k)}{dt} \right\rangle = \langle r_w \rangle = 0,$$

we can show that

$$\left\langle \frac{f^A}{f^B} \right\rangle = \frac{d^B}{\beta^A} \quad \text{and} \quad \left\langle \frac{S f^B}{f^A} \right\rangle = \frac{d^A + \alpha^A}{\beta^B}. \quad (\text{S.3})$$

Hence, the ratio of class frequencies,  $f^A(t)/f^B(t)$ , fluctuates around an average value  $d^B/\beta^A$ , which corresponds to the ratio of class frequencies in the absence of fluctuations. In particular, this implies that, when  $d^B \rightarrow 0$  (i.e. when propagules live very long),  $f^A(t) \rightarrow 0$ . However, this information cannot be used to further simplify the selection gradient (17).

In contrast, the dynamics of reproductive values yield a very useful expression for the average of the ratio of individual reproductive values,  $v^B(t)/v^A(t)$ , on the periodic attractor. From equation (12) we obtain

$$\begin{aligned} \frac{dv^A}{dt} &= -\beta^A v^B(t) + (d^A + \alpha^A)v^A(t) + r_w v^A(t) \\ \frac{dv^B}{dt} &= -\beta^B S(t)v^A(t) + d^B v^B(t) + r_w v^B(t) \end{aligned}$$

and, using the fact that  $\langle d \ln(v^k)/dt \rangle = 0$  on the periodic attractor, we obtain

$$\left\langle \frac{v^B}{v^A} \right\rangle = \frac{d + \alpha^A}{\beta^A} \quad \text{and} \quad \left\langle \frac{v^A S}{v^B} \right\rangle = \frac{d^B}{\beta^B}. \quad (\text{S.4})$$

It is straightforward to check that the right-hand sides correspond to the equilibrium values in the absence of fluctuations.

This result suggests that it may be useful to rewrite equation (17) to reveal the selection gradient in a constant environment. We thus write:

$$\mathcal{S}(t) = c^A(t) \left( \frac{v^B(t)}{v^A(t)} \frac{d\beta^A}{dz} - \frac{d\alpha^A}{dz} \right) \quad (\text{S.5})$$

where  $c^A(t) = v^A(t)f^A(t)$  is the class reproductive value at time  $t$  (Taylor, 1990; Rousset, 2004; Lion, 2018). Averaging over the period then gives equation (20) in the main text:

$$\mathcal{S} = \langle c^A \rangle \mathcal{S}_{\text{cst}} + \frac{d\beta^A}{dz} \text{Cov} \left( c^A(t), \frac{v^B(t)}{v^A(t)} \right). \quad (\text{S.6})$$

In the absence of fluctuations, or when the covariance is zero, the ESS is predicted from  $\mathcal{S}_{\text{cst}} = 0$ , which takes the form of a simple marginal value theorem:

$$\frac{d\beta^A}{dz} = \frac{\beta^A}{d + \alpha^A}.$$

In other words, the ESS maximises the ratio  $\beta^A/(d + \alpha^A)$ . Any departure from this prediction is caused by a non-zero covariance between  $c^A(t)$  and  $\frac{v^B(t)}{v^A(t)}$ . We can develop this covariance and use (S.4) to express this covariance as a function of the reproductive outputs through class  $A$  ( $v^A(t)f^A(t)$ ) and through class  $B$  ( $v^B f^A(t)$ ). We obtain:

$$\text{Cov} \left( c^A(t), \frac{v^B(t)}{v^A(t)} \right) = \langle v^B f^A \rangle - \langle v^A f^A \rangle \left\langle \frac{v^B}{v^A} \right\rangle = \langle v^B f^A \rangle - \langle v^A f^A \rangle \frac{d^A + \alpha^A}{\beta^A} \quad (\text{S.7})$$

so that the sign of this covariance tells us whether the ratio of the average reproductive outputs is greater or smaller than the average of the ratio of reproductive outputs. In other words, the covariance is positive if

$$\frac{\langle v^B f^A \rangle}{\langle v^A f^A \rangle} > \left\langle \frac{v^B}{v^A} \right\rangle = \frac{d^A + \alpha^A}{\beta^A}$$

and negative otherwise.

As a final remark on this model, we note that, as in earlier studies (Bonhoeffer et al., 1996; Day & Gandon, 2006), we have neglected the decrease in propagule density due to the infection of new hosts. This effect can be captured by adding a  $-\beta^B S(t)I^B(t)$  term to the dynamics of  $I^B$ , but this has no qualitative impact on our results.

## S.2 Scenario 2: host preference

Figure S.2a shows that, with our choice of periodic fluctuations in  $\nu(t)$  (top panel), the system alternates between periods of high densities of susceptible  $A$  hosts and intermediate densities of susceptible  $B$  hosts (middle panel). When one host is present, the other is either absent or present at low densities. The resulting dynamics of reproductive values (bottom panel) show that the qualities of  $A$  and  $B$  hosts fluctuate over time, but that  $B$  hosts are always more valuable than  $A$  hosts. However, some degree of preference for  $A$  hosts ( $z > 0$ ) may evolve because the densities of susceptible hosts are not equal. This can be shown both for constant and periodic environments.

In the constant case, it is easy to show that, in the resident population at equilibrium

$$\frac{v_{\text{cst}}^A}{v_{\text{cst}}^B} = \frac{R^A}{R^B}$$

where  $R^k = \beta^k / (d + \alpha^k)$  is the basic reproductive ratio in a fully susceptible populations with only  $k$  hosts present. Thus at the ESS the following condition must be satisfied:

$$R^A S_{\text{cst}}^A = R^B S_{\text{cst}}^B$$

which can be numerically solved to yield an intermediate ES value  $z_{\text{eq}}^*$ .

In the periodic case, the selection gradient vanishes when

$$\langle v^A S^A \rangle = \langle v^B S^B \rangle.$$

To see how periodic fluctuations can affect the ES preference strategy, we now fix the resident trait at  $z_w = z_{\text{eq}}^*$ , and track the frequency of a mutant with a slightly increased preference for  $A$  hosts ( $z_m = z_w + 0.001$ ). In the absence of fluctuations, this mutant should be counter-selected. In figure S.2b, we show that the dynamics of the mutant frequency in the full eco-evolutionary model (solid grey line) is very well predicted, on the slow time scale, by equation (8) with  $\mathcal{S} = \beta(\langle v^A S^A \rangle - \langle v^B S^B \rangle)$  (dashed line), as expected from our general mathematical analysis. Biologically, this means that, although at all times pathogens in  $B$  hosts have a higher individual reproductive value than pathogens in  $A$  hosts (figure S.2a, bottom panel), a mutant with increased preference for  $A$  hosts can still be favoured if the fluctuations in the densities of susceptible hosts tilt the balance in the right direction. In the main text, we show that the deviation from the ESS in the constant environment,  $z_{\text{eq}}^*$ , becomes larger as the period,  $T$ , increases.

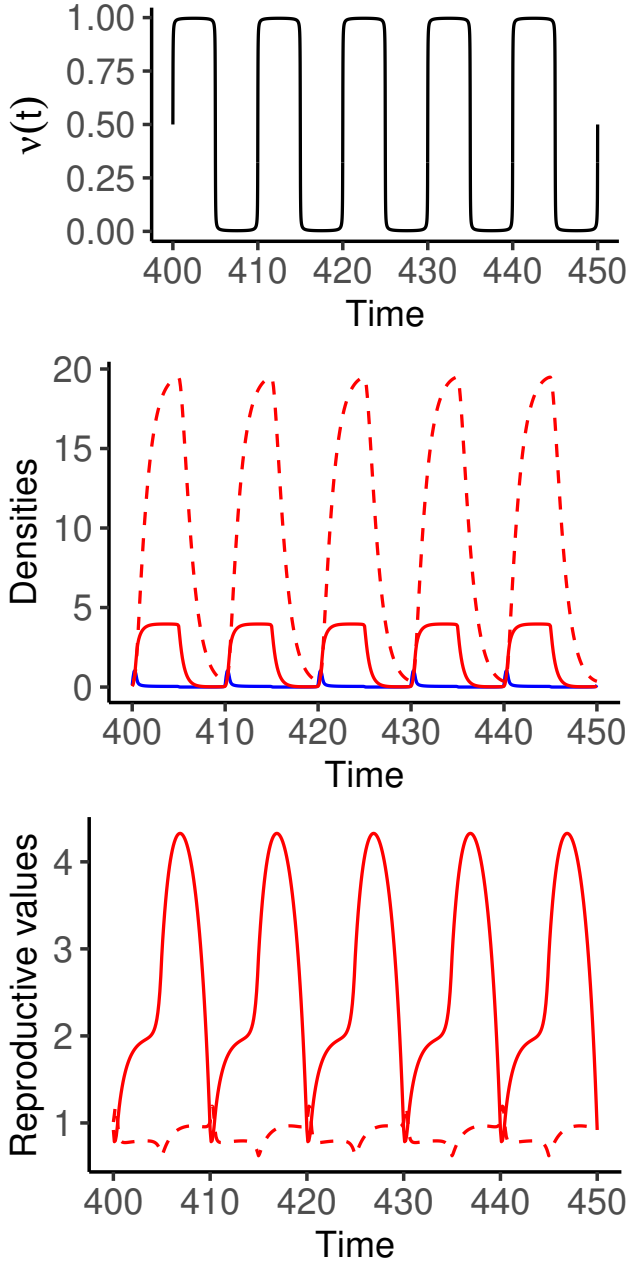
In the limit of large periods, for a function  $\nu$  that approaches a step function with minimum 0, maximum 1 and mean  $1/2$ , it is possible to obtain an analytical expression of the ESS. We note that, for large periods, the system approximately behaves as an alternance of single-class equilibria. When only  $A$  hosts are present, we have  $S^B = 0$ ,  $v^A = 1$  and  $S^A = S_e^A = 1/(p^A R^A)$ , where  $S_e^A$  is the equilibrium solution for a population with only  $A$  hosts. When only  $B$  hosts are present, we have  $S^A = 0$ ,  $v^B = 1$  and  $S^B = S_e^B = 1/(p^B R^B)$ , where  $S_e^B$  is the equilibrium solution for a population with only  $B$  hosts. Thus, we have  $\mathcal{S} = \beta \langle D \rangle$  where  $\langle D \rangle = \langle v^A S^A \rangle - \langle v^B S^B \rangle = (1/2)(S_e^A - S_e^B) = (1/2)[1/(p^A R^A) - 1/(p^B R^B)]$ , so that, for  $p^A = z = 1 - p^B$ , the solution of  $\mathcal{S} = 0$  is given by

$$z^* = \frac{R^B}{R^A + R^B} = \frac{d + \alpha^A}{2d + \alpha^A + \alpha^B}.$$

which is the upper limit in figure 5c.

Note that the simulations are performed without any cost of preference, so that the singularity is actually degenerate (i.e. the second isocline of the PIP is vertical near the ESS). However, adding a

(a) Fast variables



(b) Slow variable

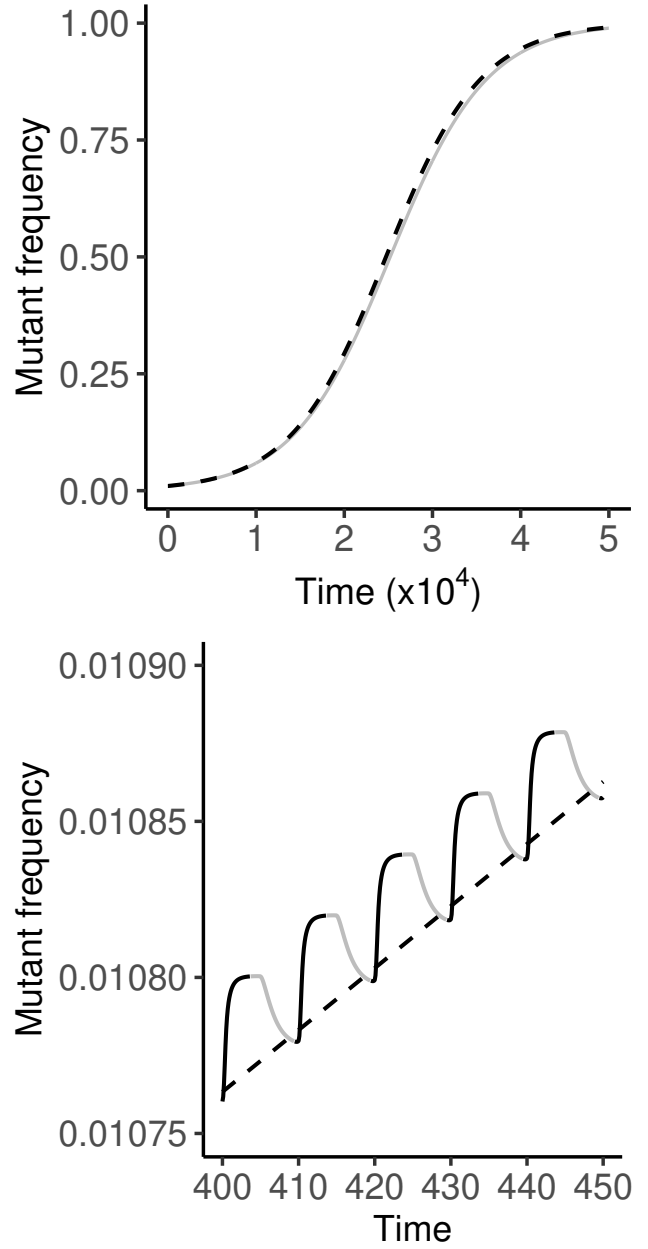


Figure S.1: **Scenario 1: The Curse of Pharaoh.** (a) Ecological dynamics on the fast time scale. Top: periodic probability of production of susceptible hosts,  $\nu(t)$ . Middle: dynamics of host densities (blue: susceptible hosts, red: infected hosts (solid line:  $A$  class, dashed line:  $B$  class (propagules))). Bottom: dynamics of individual reproductive values for pathogens in  $A$  (solid) and  $B$  (dashed) hosts. (b) Slow-time dynamics of the frequency of a mutant  $f_m(t)$  (grey) compared to the prediction using the average selection gradient (dashed line). The lower panel is a zoom showing the oscillations of the mutant frequency on the fast time scale. The direction of selection is well predicted by the sign of the instantaneous selection gradient  $\mathcal{S}(t)$  (black: positive, grey: negative). Parameters:  $\nu(t) = 0.5(1 + (2/\pi) \arctan(\sin(2\pi t/T)/0.01))$ ,  $b = 8$ ,  $d = d^A = d^B = 1$ ,  $\beta^A(z) = \beta_0 z/(1+z)$ ,  $\beta^B = \beta_0 = 10$ ,  $\alpha^A(z) = z$ ,  $z_w = 1$ ,  $z_m = z_w + 0.005$ ,  $T = 10$ . The value of  $z_w$  is the ESS value in a constant environment with  $\nu = 0.5$ .

small constant cost  $c = 1.5(z - 1/2)^2$  to the death rates of infected hosts in both classes is enough to make the singularity evolutionarily stable. This only adds a small negative term to the selection gradient that is independent of fluctuations, and has no qualitative impact on our results.

### S.3 Scenario 3: imperfect vaccines

As for scenario 2, figure S.3 shows the dynamics on both the fast, ecological time scale and the slow, evolutionary time scale for a given set of parameter values (chosen such that the trait is at the ESS value in the absence of fluctuations). Again, figure S.3b shows that the averaged selection gradient using reproductive values accurately predicts the dynamics of the mutant frequency  $f_m(t)$ .

The dynamics of the individual reproductive values are given by the system:

$$\frac{dv^A}{dt} = \beta^A(v^A p^A S^A + v^B p^B S^B) - (d + \alpha^A + r_w)v^A, \quad (\text{S.8})$$

$$\frac{dv^B}{dt} = \beta^B(v^A p^A S^A + v^B p^B S^B) - (d + \alpha^B + r_w)v^B. \quad (\text{S.9})$$

Because on the periodic attractor, we have

$$\left\langle \frac{d \ln(v^k)}{dt} \right\rangle = 0 \quad \text{and} \quad \langle r_w \rangle = 0,$$

it follows that

$$\left\langle \frac{v^A p^A S^A + v^B p^B S^B}{v^k} \right\rangle = \frac{d + \alpha^k}{\beta^k} = \frac{1}{R^k}. \quad (\text{S.10})$$

In figure S.4 (bottom panel), we show that the mean of the ratio  $\omega^k = (v^A p^A S^A + v^B p^B S^B)/v^k$  is indeed equal to  $1/R^k$ . Furthermore, as the period becomes large,  $\omega^k$  is nearly always equal to  $1/R^k$  except for brief deviations when the environment changes. On the other hand, the middle panel shows that the mean of the reproductive values  $\langle v^k \rangle$  are close to their values in a constant environment  $v_{eq}^k$  for short periods, but as the period increases, so does the difference between  $\langle v^k \rangle$  and  $v_{eq}^k$ .

In the limit of large periods,  $c^A(t)$  converges towards  $\nu(t)$ . This can be seen by noting that, for large periods, the model essentially behaves as a succession of single-class equilibria. Half the time, only  $A$  hosts are present, so that  $c^A = 1$ . The rest of the time, there are only  $B$  hosts and  $c^A = 0$ . Hence the mean value of the class reproductive value converges towards  $1/2$ , and the selection gradient simplifies to  $\langle \mathcal{S} \rangle = (\mathcal{S}^A + \mathcal{S}^B)/2$ . With a trade-off  $\alpha^A = z$ ,  $\alpha^B = (1 - r_a)z$  and  $\beta^B = \beta^A = \beta_0 z / (1 + z)$ , the ES virulence for large periods has the very simple expression:

$$z^* = \frac{1}{\sqrt{1 - r_a/2}}$$

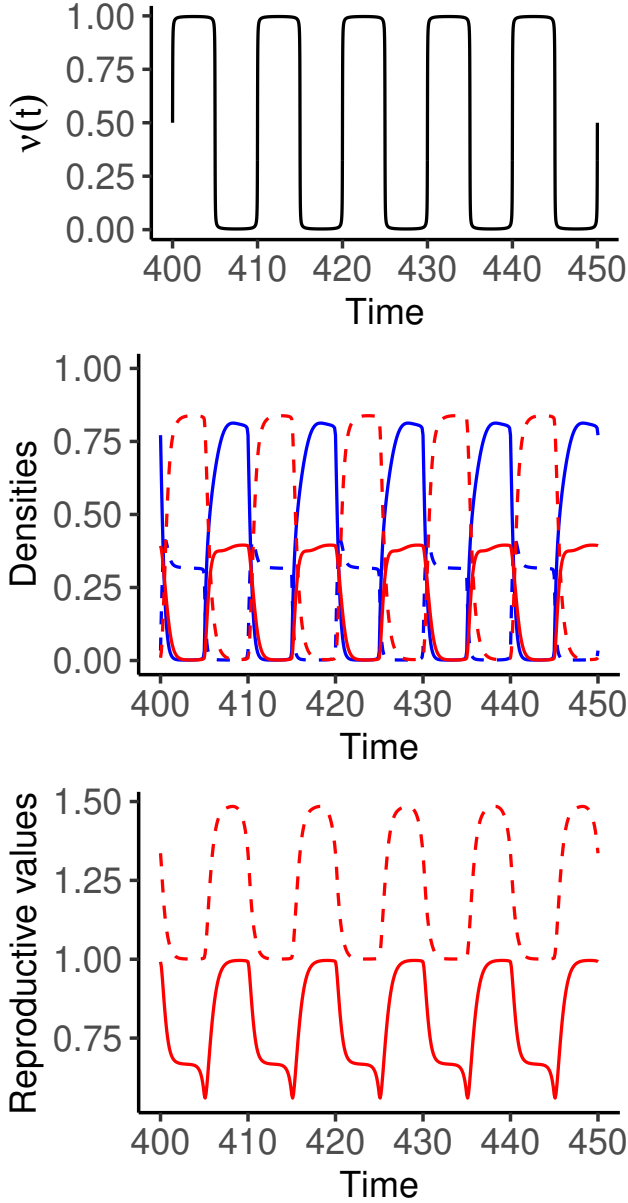
(see also Walter & Lion (2021) for a slightly more general result).

Finally, we note that the dynamics of the individual reproductive values can be used to show that, for a vaccine that linearly reduces transmission (i.e.  $r_a = 0$  and  $r_b > 0$ ), we have

$$\frac{d \left[ (1 - r_b)v^A - v^B \right]}{dt} = 0$$

which means that, although the reproductive values fluctuate due to the dynamics of the host densities, their ratio  $v^A(t)/v^B(t)$  remains constant and equal to  $1/(1 - r_b)$  at all times. This can be confirmed numerically (results not shown).

(a) Fast variables



(b) Slow variable

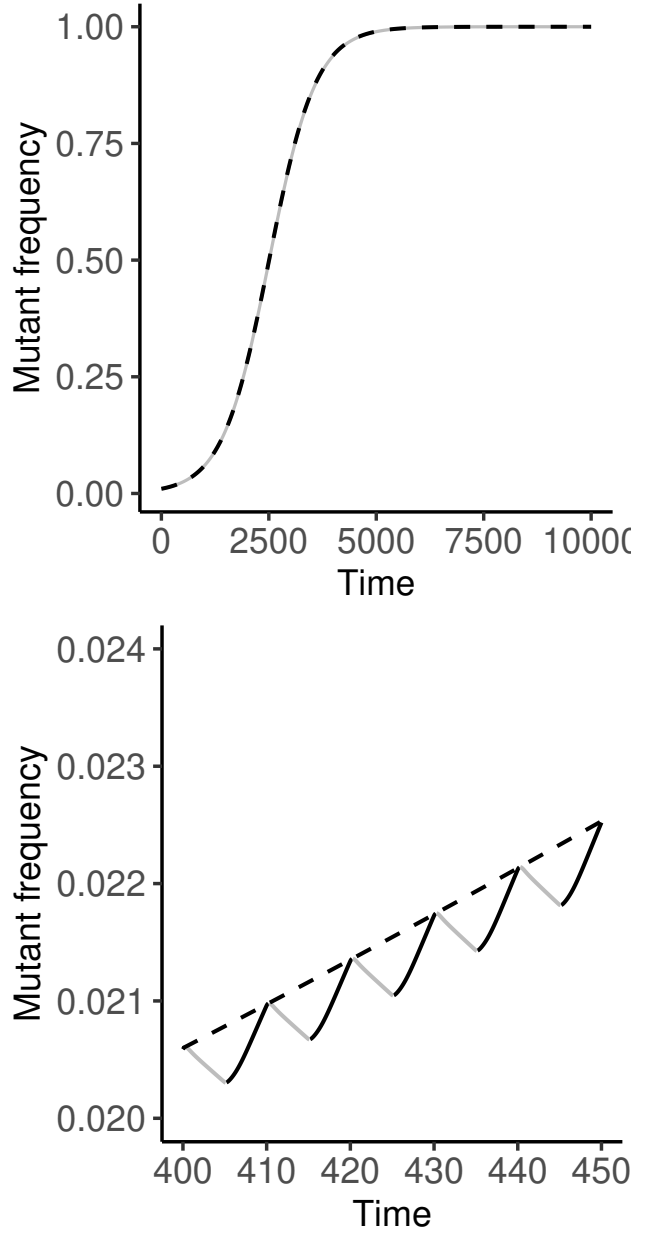


Figure S.2: **Scenario 2: host preference.** (a) Ecological dynamics on the fast time scale. Top: periodic probability of production of  $A$  susceptible hosts,  $\nu(t)$ . Middle: dynamics of host densities (blue: susceptible hosts, red: infected hosts, solid lines:  $A$  hosts, dashed lines:  $B$  hosts). Bottom: dynamics of individual reproductive values for pathogens in  $A$  (solid) and  $B$  (dashed) hosts. (b) Slow-time dynamics of the frequency of a mutant  $f_m(t)$  (grey) compared to the prediction using the average selection gradient (dashed line). The lower panel is a zoom showing the oscillations of the mutant frequency on the fast time scale. The direction of selection is well predicted by the sign of  $\nu^A(t)S^A(t) - \nu^B(t)S^B(t)$  (black: positive, grey: negative). Parameters:  $\nu(t) = 0.5(1 + (2/\pi) \arctan(\sin(2\pi t/T)/0.01))$ ,  $b = 2$ ,  $d^A = d^B = 1$ ,  $\beta^A = \beta^B = \beta = 10$ ,  $\alpha^A = 2$ ,  $\alpha^B = 1$ ,  $z_w = 0.368652$ ,  $z_m = z_w + 0.001$ ,  $T = 10$ . The value of  $z_w$  is the ESS value in a constant environment  $\nu = 0.5$ .

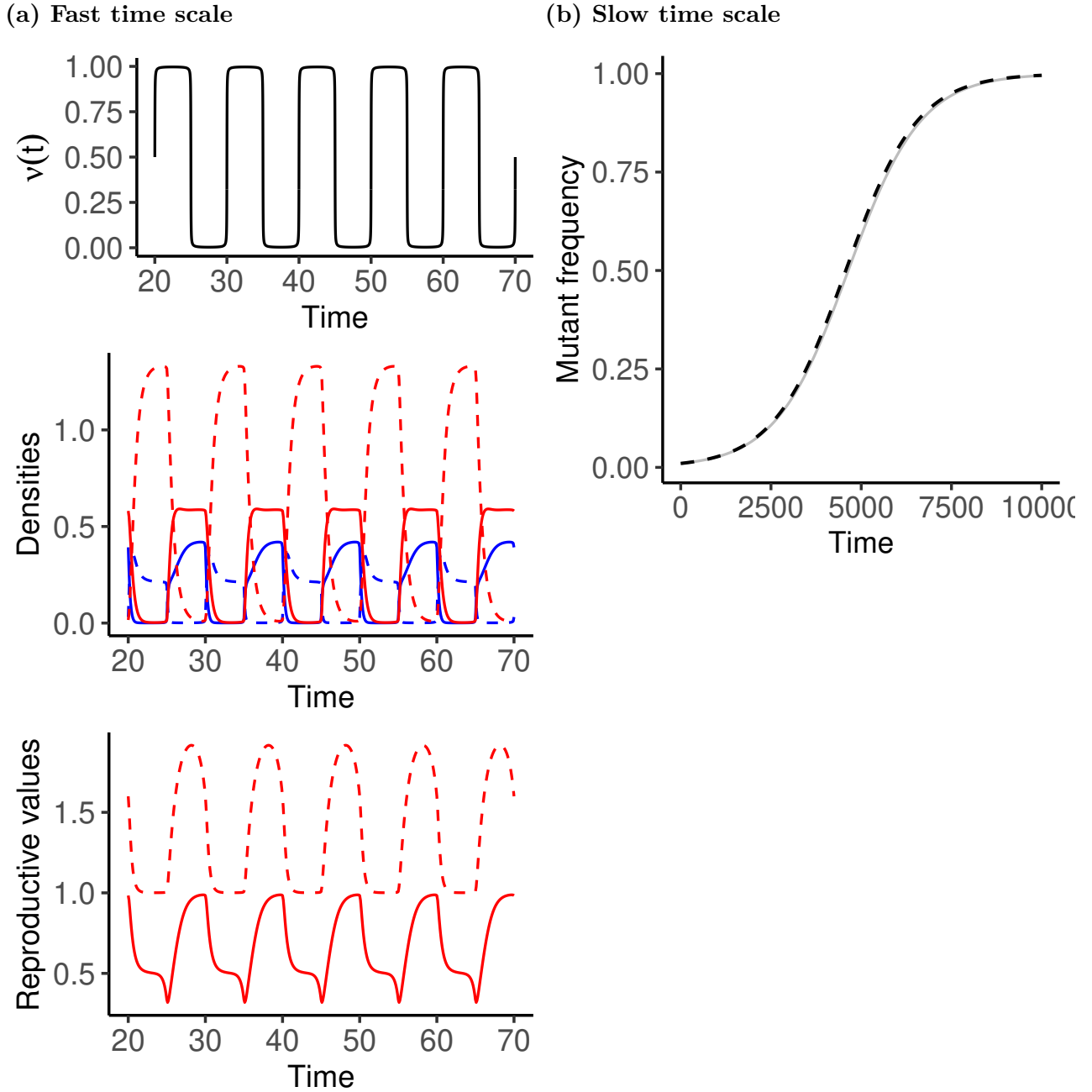


Figure S.3: **Scenario 3: imperfect vaccine and virulence.** (a) Ecological dynamics on the fast time scale. Top: periodic probability of production of  $A$  susceptible hosts,  $\nu(t)$ . Middle: dynamics of host densities (blue: susceptible hosts, red: infected hosts, solid lines:  $A$  hosts, dashed lines:  $B$  hosts). Bottom: dynamics of individual reproductive values for pathogens in  $A$  (solid) and  $B$  (dashed) hosts. (b) Slow-time dynamics of the frequency of a mutant  $f_m(t)$  (grey) compared to the prediction using the average selection gradient (dashed line). Parameters:  $\nu(t) = 0.5(1 + (2/\pi) \arctan(\sin(2\pi t/T)/0.01))$ ,  $b = 2$ ,  $d^A = d^B = 1$ ,  $\beta^A(z) = \beta^B(z) = \beta = 10z/(1+z)$ ,  $\alpha^A = z$ ,  $\alpha^B = (1 - r_a)z$ ,  $r_a = 0.8$ ,  $z_w = 1.667$ ,  $z_m = z_w - 0.01$ ,  $T = 10$ . The value of  $z_w$  is the ESS value in a constant environment  $\nu = 0.5$ .

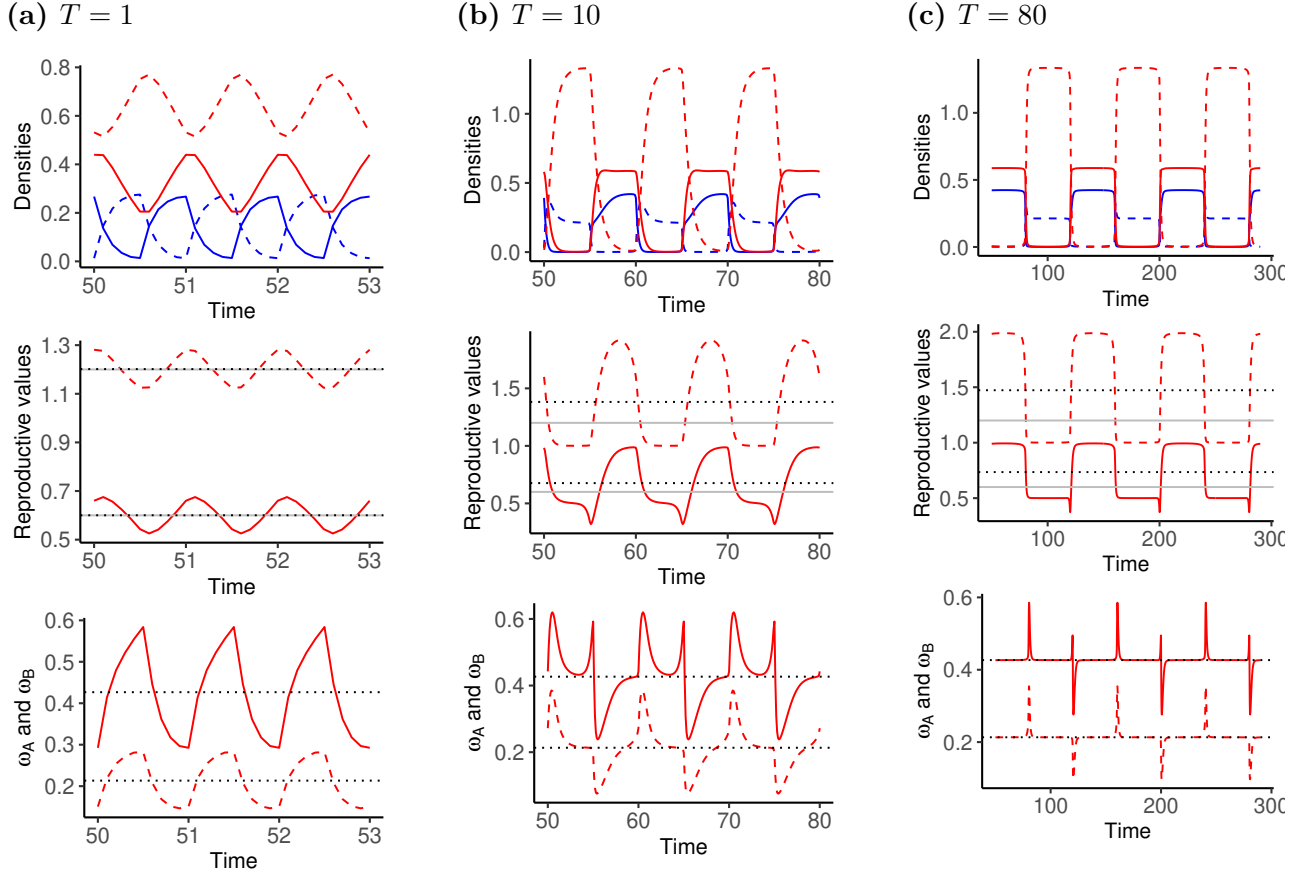


Figure S.4: **Scenario 3: imperfect vaccine and virulence.** (a) Ecological dynamics on the fast time scale for increasing periods. (a)  $T = 1$ . (b)  $T = 10$ . (c)  $T = 80$ . Top: dynamics of host densities (blue: susceptible hosts, red: infected hosts, solid lines:  $A$  hosts, dashed lines:  $B$  hosts). Middle: dynamics of individual reproductive values for pathogens in  $A$  (solid) and  $B$  (dashed) hosts. The gray and dotted lines indicate the equilibrium and mean values respectively. Bottom: dynamics of  $\omega^k = (v^A S^A + v^B S^B)/v^k$  compared to the mean value  $(d + \alpha^k)/\beta^k$ . Parameters:  $\nu(t) = 0.5(1 + (2/\pi) \arctan(\sin(2\pi t/T)/0.01))$ ,  $b = 2$ ,  $d^A = d^B = 1$ ,  $\beta^A(z) = \beta^B(z) = \beta = 10z/(1+z)$ ,  $\alpha^A = z$ ,  $\alpha^B = (1 - r_a)z$ ,  $r_a = 0.8$ ,  $z_w = 1.667$ . The value of  $z_w$  is the ESS value in a constant environment  $\nu = 0.5$ .



## References

- Bonhoeffer, S., R. E. Lenski & D. Ebert (1996). The curse of the Pharaoh: the evolution of virulence in pathogens with long living propagules. *Proc. R. Soc. B.* **263**(1371): 715–721.
- Day, T. & S. Gandon (2006). Insights from Price’s equation into evolutionary epidemiology. In: *Disease evolution: models, concepts and data analyses*. Ed. by Feng, Z., Dieckmann, U. & Levin, S. **71**. DIMACS Series in Discrete Mathematics and Theoretical Computer Science. American Mathematical Society, pp. 23–43.
- Lion, S. (2018). Class structure, demography and selection: reproductive-value weighting in non-equilibrium, polymorphic populations. *Am. Nat.* **191**(5): 620–637. DOI: <https://doi.org/10.1101/155879>.
- Rousset, F. (2004). Genetic structure and selection in subdivided populations. Princeton University Press, Princeton, NJ, USA.
- Taylor, P. D. (1990). Allele-frequency change in a class-structured population. *Am. Nat.* **135**(1): 95–106. DOI: [10.1086/285034](https://doi.org/10.1086/285034).
- Walter, A. & S. Lion (2021). Epidemiological and evolutionary consequences of periodicity in treatment coverage. *Proc. R. Soc. B.* **288**: 20203007. DOI: [10.1098/rspb.2020.3007](https://doi.org/10.1098/rspb.2020.3007).