

# Theoretical Appendix for “Spatial evolutionary epidemiology of spreading epidemics”

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## 1 General model

In this document, we present the derivation of the dynamics of the mean virulence  $\bar{\alpha}_I$  given in the main text (equation (5) and (8)), which is valid for a wide range of epidemiological models with horizontally transmitted parasites and single infections.

### 1.1 Epidemiological dynamics

Using the fact that  $q_{i/S}p_S = p_{iS}$  (Matsuda et al., 1992), the dynamics of the total density of infected hosts,  $p_I = \sum_i p_i$ , is

$$\frac{dp_I}{dt} = \sum_i \beta_i p_{iS} - \sum_i (d + \alpha_i) p_i - \mu \sum_i p_i + \mu \sum_i \sum_j m_{ji} p_j \quad (\text{S1})$$

With the definitions of the frequencies  $f_i$  and  $f_{iS}$ , we can rewrite the latter equation in terms of the mean virulence and transmission rates. We obtain

$$\frac{dp_I}{dt} = \left( \sum_i \beta_i f_{iS} \right) p_{IS} - \sum_i (d + \alpha_i) f_i p_I - \mu p_I + \mu \sum_i \sum_j m_{ji} f_j p_I \quad (\text{S2})$$

The mutation terms drop out, because  $\sum_i m_{ji} = 1$  and  $\sum_j f_j = 1$ . We are left with

$$\frac{dp_I}{dt} = \bar{\beta}_{IS} q_{S/I} p_I - (d + \bar{\alpha}_I) p_I \quad (\text{S3})$$

### 1.2 Dynamics of global mean traits

Noting  $r_i = \beta_i q_{S/i} - (d + \alpha_i)$  and  $\bar{r}_I = \bar{\beta}_{IS} q_{S/I} - (d + \bar{\alpha}_I)$ , the dynamics of  $f_i = p_i/p_I$  can be written as

$$\frac{df_i}{dt} = (r_i - \bar{r}_I) f_i - \mu f_i + \mu \sum_j m_{ji} f_j \quad (\text{S4})$$

We can use this equation to derive the dynamics of the mean trait  $\bar{x}_I = \sum_i x_i f_i$  for any trait  $x$ , as follows

$$\begin{aligned} \frac{d\bar{x}_I}{dt} &= \sum_i x_i \frac{df_i}{dt} = \sum_i x_i (r_i - \bar{r}_I) f_i - \mu \sum_i x_i f_i + \mu \sum_i x_i \sum_j m_{ji} f_j \\ &= \sum_i x_i r_i f_i - \bar{x}_I \bar{r}_I - \mu \bar{x}_I + \mu \bar{x}_I^m \\ &= \text{Cov}_I(x_i, r_i) - \mu(\bar{x}_I - \bar{x}_I^m) \end{aligned} \quad (\text{S5})$$

The covariance in the last equation will depend on terms like

$$\text{Cov}_I(x_i, \alpha_i) = \sum_i x_i \alpha_i f_i - \bar{x}_I \bar{\alpha}_I := \sigma_I^{x\alpha}$$

where  $\sigma_I^{xy}$  is the (global) covariance between traits  $x$  and  $y$ , and

$$\begin{aligned} \text{Cov}_I(x_i, \beta_i q_{S/i}) &= \sum_i x_i \beta_i q_{S/i} f_i - \bar{x}_I \sum_i \beta_i q_{S/i} f_i \\ &= \left( \sum_i x_i \beta_i f_{iS} - \bar{x}_I \bar{\beta}_{IS} \right) q_{S/I} \\ &= \left[ \sigma_{IS}^{x\beta} + \bar{\beta}_{IS} (\bar{x}_{IS} - \bar{x}_I) \right] q_{S/I} \end{aligned}$$

where

$$\sigma_{IS}^{xy} = \sum_i x_i y_i f_{iS} - \bar{x}_{IS} \bar{y}_{IS}$$

is the (local) covariance between traits  $x$  and  $y$ , measured among IS pairs.

This gives us the following equation for the dynamics of  $\bar{\alpha}_I$

$$\frac{d\bar{\alpha}_I}{dt} = \left[ q_{S/I} \sigma_{IS}^{\alpha\beta} - \sigma_I^{\alpha\alpha} \right] + \bar{\beta}_{IS} q_{S/I} (\bar{\alpha}_{IS} - \bar{\alpha}_I) - \mu (\bar{\alpha}_I - \bar{\alpha}_I^m) \quad (\text{S6})$$

## 2 No host demography: SIS model

We first consider the limit of large host fecundity. In this limit, a site can only be occupied by either a susceptible or an infected host. This greatly simplifies the analysis. Our aim is to derive the dynamics of local mean traits,  $\bar{\alpha}_{IS}$  and  $\bar{\alpha}_{II}$ , and of spatial differentiation  $\bar{\alpha}_{IS} - \bar{\alpha}_I$ .

**Dynamics of  $\bar{\alpha}_{IS}$**  From the definition of the local mean,

$$\bar{x}_{IS} = \sum_i x_i f_{iS},$$

we obtain

$$\frac{d\bar{x}_{IS}}{dt} = \sum_i x_i \frac{df_{iS}}{dt} = \text{Cov}_{IS}(x_i, r_{iS}) - \mu (\bar{x}_{IS} - \bar{x}_{IS}^m) \quad (\text{S7})$$

where  $\text{Cov}_{IS}$  denotes the covariance over all infected hosts with a susceptible host in their neighbourhood and  $r_{iS}$  is the per-capita growth rate of  $iS$  pairs (in the absence of mutations). We have

$$\frac{dp_{iS}}{dt} = \sum_j (d + \alpha_j) p_{ij} + \beta_i \bar{\phi}_{i/SS} p_{SS} - p_{iS} \left[ d + \alpha_i + \phi \beta_i + \bar{\phi} \sum_j \beta_j q_{j/Si} \right] - \mu p_{iS} + \mu \sum_j m_{ji} p_{jS} \quad (\text{S8})$$

which yields

$$r_{iS} = \sum_j (d + \alpha_j) \frac{p_{ij}}{p_{iS}} + \beta_i \bar{\phi}_{i/SS} - \left[ d + \alpha_i + \phi \beta_i + \bar{\phi} \sum_j \beta_j q_{j/Si} \right]$$

Similarly, the density of pairs  $IS$  is

$$\frac{dp_{IS}}{dt} = (d + \bar{\alpha}_{II}) p_{II} + \bar{\beta}_{ISS} \bar{\phi}_{I/SS} p_{SS} - p_{IS} \left[ d + \bar{\alpha}_{IS} + \phi \bar{\beta}_{IS} + \bar{\phi} \bar{\beta}_{IS} q_{I/SI} \right] \quad (\text{S9})$$

To compute the covariance in equation (S7), we need to compute several covariances. First, we have covariances of the type

$$\begin{aligned} \text{Cov}_{IS}(x_i, y_i q_{S/i}) &= \sum_i x_i y_i q_{S/i} f_{iS} - \bar{x}_{IS} \sum_i y_i q_{S/i} f_{iS} \\ &= \left( \sum_i x_i y_i f_{iSS} - \bar{x}_{IS} \bar{y}_{ISS} \right) q_{S/SI} \\ &= (\sigma_{ISS}^{xy} + \bar{y}_{ISS} (\bar{x}_{ISS} - \bar{x}_{IS})) q_{S/SI} \end{aligned}$$

Second, we have covariances of the form

$$\begin{aligned}\text{Cov}_{IS}(x_i, \sum_j (d + y_j) \frac{p_{ij}}{p_{iS}}) &= \left( \sum_i \sum_j x_i (d + y_j) f_{ij} - \bar{x}_{IS} \sum_i \sum_j (d + y_j) f_{ij} \right) \frac{q_{I/I}}{q_{S/I}} \\ &= \left( \sum_i \sum_j x_i y_j f_{ij} - \bar{y}_{II} \bar{x}_{IS} \right) \frac{q_{I/I}}{q_{S/I}} + d(\bar{x}_{II} - \bar{x}_{IS}) \frac{q_{I/I}}{q_{S/I}}\end{aligned}$$

Note the difference between  $\sum_i \sum_j x_i y_j f_{ij} - \bar{x}_{II} \bar{y}_{II}$ , which measures the correlation between traits  $x$  and  $y$  in different neighbours, and  $\sum_i \sum_j x_i y_i f_{ij} - \bar{x}_{II} \bar{y}_{II}$ , which measures the correlation between traits  $x$  and  $y$  in individuals that have at least one neighbour.

Third, we have covariances of the form

$$\begin{aligned}\text{Cov}_{IS}(x_i, \sum_j y_j q_{j/Si}) &= \left( \sum_i \sum_j x_i y_j q_{j/Si} f_{iS} - \bar{x}_{IS} \sum_i \sum_j y_j q_{j/Si} f_{iS} \right) \\ &= \left( \sum_i \sum_j x_i y_j f_{jSi} - \bar{x}_{IS} \sum_i \sum_j y_j f_{jSi} \right) q_{I/SI} \\ &= \left( \sum_i \sum_j x_i y_j f_{jSi} - \bar{x}_{IS} \bar{y}_{ISI} \right) q_{I/SI}\end{aligned}$$

Using these formulae, we find for the mean virulence

$$\begin{aligned}\frac{d\bar{\alpha}_{IS}}{dt} &= -\sigma_{IS}^{\alpha\alpha} - \phi\sigma_{IS}^{\alpha\beta} + \bar{\phi}q_{S/SI}[\sigma_{ISS}^{\alpha\beta} + \bar{\beta}_{ISS}(\bar{\alpha}_{ISS} - \bar{\alpha}_{IS})] \\ &\quad + \frac{q_{I/I}}{q_{S/I}} \left( \sum_i \sum_j \alpha_i \alpha_j f_{ij} - \bar{\alpha}_{II} \bar{\alpha}_{IS} + (\bar{x}_{II} - \bar{x}_{IS}) \right) - \bar{\phi} \left( \sum_i \sum_j \alpha_i \beta_j f_{jSi} - \bar{\alpha}_{IS} \bar{\beta}_{ISI} \right) q_{I/SI} \\ &\quad - \mu(\bar{\alpha}_{IS} - \bar{\alpha}_{IS}^m)\end{aligned}\tag{S10}$$

We can rewrite equation (S10) in terms of the following covariances

$$\begin{aligned}\rho_{II}^{\alpha\alpha} &= \sum_i \sum_j \alpha_i \alpha_j f_{ij} - \bar{\alpha}_{II}^2 \\ \rho_{ISI}^{\alpha\beta} &= \sum_i \sum_j \alpha_i \beta_j f_{iSj} - \bar{\alpha}_{ISI} \bar{\beta}_{ISI}\end{aligned}$$

which have the following interpretations.  $\rho_{II}^{\alpha\alpha}$  measures the covariance between traits sampled in two *distinct* neighbouring infected hosts. Similarly,  $\rho_{ISI}^{\alpha\beta}$  measures the covariance between traits sampled in two *distinct* infected hosts separated by a susceptible host. In the main text, we consider the scaled version of these covariance coefficients, which are  $\rho = \rho_{II}^{\alpha\alpha} / \sigma_I^{\alpha\alpha}$  and  $\rho_S = \rho_{ISI}^{\alpha\beta} / \sigma_{IS}^{\alpha\beta}$  and have a straightforward interpretation in terms of relatedness coefficients. (In a neutral population, these coefficients are connected with the coefficients  $r$  and  $r_o$  introduced by Lion (2009) and Lion & Gandon (2009).)

Putting everything together, this gives us

$$\begin{aligned}\frac{d\bar{\alpha}_{IS}}{dt} &= -\sigma_{IS}^{\alpha\alpha} - \phi\sigma_{IS}^{\alpha\beta} + \bar{\phi}q_{S/SI}[\sigma_{ISS}^{\alpha\beta} + \bar{\beta}_{ISS}(\bar{\alpha}_{ISS} - \bar{\alpha}_{IS})] \\ &\quad + \frac{q_{I/I}}{q_{S/I}} (\rho_{II}^{\alpha\alpha} + (d + \bar{\alpha}_{II})(\bar{\alpha}_{II} - \bar{\alpha}_{IS})) - \bar{\phi} (\rho_{ISI}^{\alpha\beta} + \bar{\beta}_{ISI}(\bar{\alpha}_{ISI} - \bar{\alpha}_{IS})) q_{I/SI} \\ &\quad - \mu(\bar{\alpha}_{IS} - \bar{\alpha}_{IS}^m)\end{aligned}$$

Finally, we use the fact that  $\bar{\alpha}_I = q_{S/I}\bar{\alpha}_{IS} + q_{I/I}\bar{\alpha}_{II}$  and  $\bar{\alpha}_{IS} = q_{S/II}\bar{\alpha}_{ISS} + q_{I/II}\bar{\alpha}_{ISI}$  to simplify the equation as follows

$$\begin{aligned} \frac{d\bar{\alpha}_{IS}}{dt} = & \left[ \bar{\phi}q_{S/II}\sigma_{ISS}^{\alpha\beta} - \phi\sigma_{IS}^{\alpha\beta} - \bar{\phi}q_{I/II}\rho_{ISI}^{\alpha\beta} \right] - \left[ \sigma_{IS}^{\alpha\alpha} - \rho_{II}^{\alpha\alpha} \frac{q_{I/I}}{q_{S/I}} \right] \\ & - (\bar{\alpha}_{IS} - \bar{\alpha}_I) \frac{\bar{\alpha}_{II}}{q_{S/I}} + \bar{\phi}q_{S/II}(\bar{\beta}_{ISS} + \bar{\beta}_{ISI})(\bar{\alpha}_{ISS} - \bar{\alpha}_{IS}) + \mu(\bar{\alpha}_{IS} - \bar{\alpha}_{IS}^m) \end{aligned} \quad (\text{S11})$$

A similar expression can be written for  $\bar{\beta}_{IS}$ .

**Dynamics of  $\bar{\alpha}_{IS} - \bar{\alpha}_I$**  The dynamics of the difference between local and global mean virulence is easily obtained from equations (S19) and (S6). Rearranging the terms, we obtain

$$\begin{aligned} \frac{d(\bar{\alpha}_{IS} - \bar{\alpha}_I)}{dt} = & \sigma_{IS}^{\alpha\beta} \left[ \bar{\phi}q_{S/II} \frac{\sigma_{ISS}^{\alpha\beta}}{\sigma_{IS}^{\alpha\beta}} - q_{S/I} - (\phi + \bar{\phi}q_{I/II}\rho_S) \right] \\ & - \sigma_I^{\alpha\alpha} \left[ \frac{\sigma_{IS}^{\alpha\alpha}}{\sigma_I^{\alpha\alpha}} - 1 - \frac{q_{I/I}}{q_{S/I}} \rho \right] \\ & - (\bar{\alpha}_{IS} - \bar{\alpha}_I) \left( \bar{\beta}_{IS}q_{S/I} + \frac{d + \bar{\alpha}_{II}}{q_{S/I}} \right) \\ & + \bar{\phi}q_{S/II}(\bar{\beta}_{ISS} + \bar{\beta}_{ISI})(\bar{\alpha}_{ISS} - \bar{\alpha}_{IS}) \\ & - \mu \frac{N}{N-1} (\bar{\alpha}_{IS} - \bar{\alpha}_I) \end{aligned} \quad (\text{S12})$$

where the notations  $\rho = \rho_{II}^{\alpha\alpha}/\sigma_I^{\alpha\alpha}$  and  $\rho_S = \rho_{ISI}^{\alpha\beta}/\sigma_{IS}^{\alpha\beta}$  have been introduced. The last line of equation (S12) is obtained by simplifying the expression for the mutation bias under the assumption that  $\mu_{ij} = 1/(N-1)$  for  $i \neq j$  and 0 otherwise. We then have

$$\bar{\alpha}_I^m = \sum_i \sum_{j \neq i} \frac{1}{N-1} \alpha_i f_j = \sum_i \frac{\alpha_i}{N-1} - \frac{\bar{\alpha}_I}{N-1} \quad (\text{S13})$$

$$\bar{\alpha}_{IS}^m = \sum_i \frac{\alpha_i}{N-1} - \frac{\bar{\alpha}_{IS}}{N-1} \quad (\text{S14})$$

and as a result, the difference in mutation bias simplified to  $-\mu[(\bar{\alpha}_{IS} - \bar{\alpha}_{IS}^m) - (\bar{\alpha}_I - \bar{\alpha}_I^m)] = -\mu(N/(N-1))[\bar{\alpha}_{IS} - \bar{\alpha}_I]$ .

The equation for  $\bar{\alpha}_{IS} - \bar{\alpha}_I$  depends on  $\bar{\alpha}_{II}$ , which is the mean virulence among hosts with an infected neighbour. Because  $\bar{\alpha}_I = \bar{\alpha}_{IS}q_{S/I} + \bar{\alpha}_{II}q_{I/I}$ , we can express  $\bar{\alpha}_{II}$  in terms of  $\bar{\alpha}_{IS}$  and  $\bar{\alpha}_I$  only. However, we now provide the derivation for the dynamics of  $\bar{\alpha}_{II}$  as a proof of principle.

**Dynamics of  $\bar{\alpha}_{II}$**  Equation (S12) depends on the mean virulence of parasites in  $II$  pairs,  $\bar{\alpha}_{II}$ . To obtain the dynamics of  $\bar{\alpha}_{II}$ , we need the dynamics of  $p_{ij}$ , which are different for  $i = j$  and  $i \neq j$ .

$$j \neq i \quad \frac{dp_{ij}}{dt} = \bar{\phi}\beta_i q_{i/Sj} p_{Sj} + \bar{\phi}\beta_j q_{j/Si} p_{Si} - (d + \alpha_i)p_{ij} - (d + \alpha_j)p_{ij} \quad (\text{S15})$$

$$j = i \quad \frac{dp_{ii}}{dt} = 2(\phi + \bar{\phi}q_{i/Si})p_{iS} - 2(d + \alpha_i)p_{ii} \quad (\text{S16})$$

The difference comes from the extra reproduction term for a pair  $ii$  due to the infection event within a focal pair  $Si$ . In the derivation of the dynamics of  $\bar{\alpha}_{II}$  we need to carefully distinguish between these two cases. Using the fact that

$$\frac{d\bar{\alpha}_{II}}{dt} = \sum_i \left( \alpha_i r_{ii} f_{ii} + \sum_{j \neq i} \alpha_i r_{ij} f_{ij} \right) - \bar{\alpha}_{II} r_{II}$$

and that

$$\frac{dp_{II}}{dt} = 2(\phi\bar{\beta}_{IS} + \bar{\phi}\bar{\beta}_{ISI}q_{I/SI})p_{IS} - 2(d + \bar{\alpha}_{II})p_{II} \quad (\text{S17})$$

We then have

$$\begin{aligned} \frac{d\bar{\alpha}_{II}}{dt} &= \sum_i \left( \alpha_i \left[ 2\beta_i(\phi + \bar{\phi}q_{i/Si})\frac{p_{iS}}{p_{ii}} - 2(d + \alpha_i) \right] f_{ii} + \sum_{j \neq i} \alpha_i \left[ \bar{\phi}(\beta_i + \beta_j)q_{j/Si}\frac{p_{Si}}{p_{ij}} - (d + \alpha_i) - (d + \alpha_j) \right] f_{ij} \right) \\ &\quad - \bar{\alpha}_{II} \left( 2(\phi\bar{\beta}_{IS} + \bar{\phi}\bar{\beta}_{ISI}q_{I/SI})\frac{q_{S/I}}{q_{I/I}} - 2(d + \bar{\alpha}_{II}) \right) \\ &= - \left( \sum_i \alpha_i^2 \left( f_{ii} + \sum_{j \neq i} f_{ij} \right) - \bar{\alpha}_{II}^2 \right) - \left( \sum_i \sum_j \alpha_i \alpha_j f_{ij} - \bar{\alpha}_{II}^2 \right) \\ &\quad + 2\phi \left( \sigma_{IS}^{\alpha\beta} + \bar{\beta}_{IS}(\bar{\alpha}_{IS} - \bar{\alpha}_{II}) \right) \frac{q_{S/I}}{q_{I/I}} \\ &\quad + \bar{\phi}q_{I/SI} \frac{q_{S/I}}{q_{I/I}} \left( \sum_i \alpha_i \beta_i \left( f_{iSi} + \sum_{j \neq i} f_{iSj} \right) - \bar{\alpha}_{II}\bar{\beta}_{ISI} \right) + \bar{\phi}q_{I/SI} \frac{q_{S/I}}{q_{I/I}} \left( \sum_i \sum_j \alpha_i \beta_j f_{iSj} - \bar{\alpha}_{II}\bar{\beta}_{ISI} \right) \end{aligned}$$

which gives us finally

$$\frac{d\bar{\alpha}_{II}}{dt} = - [\sigma_{II}^{\alpha\alpha} + \rho_{II}^{\alpha\alpha}] + 2\phi \left( \sigma_{IS}^{\alpha\beta} + \bar{\beta}_{IS}(\bar{\alpha}_{IS} - \bar{\alpha}_{II}) \right) \frac{q_{S/I}}{q_{I/I}} + \bar{\phi}q_{I/SI} \frac{q_{S/I}}{q_{I/I}} \left( \sigma_{ISI}^{\alpha\beta} + \rho_{ISI}^{\alpha\beta} + 2\bar{\beta}_{ISI}(\bar{\alpha}_{ISI} - \bar{\alpha}_{II}) \right)$$

### 3 Host demography: oSI model

We now relax the assumption that host fecundity is very large. Then, we need to consider that a given site may be either empty or occupied.

#### 3.1 Dynamics of $\bar{\alpha}_{IS} - \bar{\alpha}_I$

As before, our aim is to write the dynamics of  $\bar{\alpha}_{IS} - \bar{\alpha}_I$ . We start with the dynamics of  $iS$  pairs in the oSI model (dropping the mutation terms for simplicity):

$$\frac{dp_{iS}}{dt} = b\bar{\phi}q_{S/oI}p_{oi} + \beta_i\bar{\phi}q_{i/SS}p_{SS} - \left[ 2d + \alpha_i + \phi\beta_i + \sum_j \beta_j\bar{\phi}q_{j/Si} \right] p_{iS} \quad (\text{S18})$$

The difference with the dynamics in the SIS model is the first term,  $b\bar{\phi}q_{S/oI}p_{oi}$ , which is replaced with  $\sum_j(d + \alpha_j)p_{ij}$  in the SIS model, and the  $2d$  term between brackets from the now explicit mortality of susceptible hosts. As a result, the change in mean local density  $\bar{\alpha}_{IS}$  is simply:

$$\begin{aligned} \frac{d\bar{\alpha}_{IS}}{dt} &= \left[ \bar{\phi}q_{S/SI}\sigma_{ISS}^{\alpha\beta} - \phi\sigma_{IS}^{\alpha\beta} - \bar{\phi}q_{I/SI}\rho_{ISI}^{\alpha\beta} \right] - \sigma_{IS}^{\alpha\alpha} \\ &\quad + \bar{\phi}bq_{S/oI} \frac{q_{o/I}}{q_{S/I}} (\bar{\alpha}_{IoS} - \bar{\alpha}_{IS}) \\ &\quad + \text{terms in } \bar{\alpha}_{ISx} - \bar{\alpha}_{IS} \text{ and mutation bias} \end{aligned} \quad (\text{S19})$$

and for the spatial differentiation  $\bar{\alpha}_{IS} - \bar{\alpha}_I$ :

$$\begin{aligned} \frac{d}{dt}(\bar{\alpha}_{IS} - \bar{\alpha}_I) &= \left[ \bar{\phi}q_{S/SI}\sigma_{ISS}^{\alpha\beta} - q_{S/I}\sigma_{IS}^{\alpha\beta} - \phi\sigma_{IS}^{\alpha\beta} - \bar{\phi}q_{I/SI}\rho_{ISI}^{\alpha\beta} \right] - (\sigma_{IS}^{\alpha\alpha} - \sigma_I^{\alpha\alpha}) \\ &\quad + \bar{\phi}bq_{S/oI} \frac{q_{o/I}}{q_{S/I}} (\bar{\alpha}_{IoS} - \bar{\alpha}_{IS}) \\ &\quad - \bar{\beta}_{IS}q_{S/I}(\bar{\alpha}_{IS} - \bar{\alpha}_I) \\ &\quad + \text{terms in } \bar{\alpha}_{ISx} - \bar{\alpha}_{IS} \text{ and mutation bias} \end{aligned} \quad (\text{S20})$$

The dynamics of  $\bar{\alpha}_{IS} - \bar{\alpha}_I$  thus depend upon the dynamics of  $\bar{\alpha}_{IoS} - \bar{\alpha}_{IS}$ . In the following, we will assume that  $\bar{\alpha}_{IoS}$  is close to  $\bar{\alpha}_{Io}$ , so that we need only track the dynamics of  $\bar{\alpha}_{Io} - \bar{\alpha}_I$ . Writing  $\bar{\alpha}_{IoS} - \bar{\alpha}_{IS} \approx \bar{\alpha}_{Io} - \bar{\alpha}_{IS} = (\bar{\alpha}_{Io} - \bar{\alpha}_I) - (\bar{\alpha}_{IS} - \bar{\alpha}_I)$ , and neglecting the terms in  $\bar{\alpha}_{ISx} - \bar{\alpha}_{IS}$ , we obtain

$$\begin{aligned} \frac{d}{dt}(\bar{\alpha}_{IS} - \bar{\alpha}_I) = & - \left[ \bar{\beta}_{IS} q_{S/I} + \bar{\phi} b q_{S/oI} \frac{q_{o/I}}{q_{S/I}} \right] (\bar{\alpha}_{IS} - \bar{\alpha}_I) \\ & + \bar{\phi} b q_{S/oI} \frac{q_{o/I}}{q_{S/I}} (\bar{\alpha}_{Io} - \bar{\alpha}_I) \\ & + \left[ \bar{\phi} q_{S/IS} \sigma_{ISS}^{\alpha\beta} - q_{S/I} \sigma_{IS}^{\alpha\beta} - \phi \sigma_{IS}^{\alpha\beta} - \bar{\phi} q_{I/SI} \rho_{ISI}^{\alpha\beta} \right] - (\sigma_{IS}^{\alpha\alpha} - \sigma_I^{\alpha\alpha}) \\ & + \text{mutation bias} \end{aligned} \quad (\text{S21})$$

### 3.2 Dynamics of $\bar{\alpha}_{Io} - \bar{\alpha}_I$

We proceed as above and start with the dynamics of  $p_{io}$ . We have

$$\frac{dp_{io}}{dt} = dp_{iS} + \sum_j (d + \alpha_j) p_{ij} + \beta_i \bar{\phi} q_{i/So} p_{oS} - \left[ d + \alpha_i + \bar{\phi} b q_{S/oI} \right] p_{io} \quad (\text{S22})$$

The first term contributes

$$\text{Cov}_{Io} \left( \alpha_i, d \frac{p_{iS}}{p_{io}} \right) = d \frac{q_{S/I}}{q_{o/I}} (\bar{\alpha}_{IS} - \bar{\alpha}_{Io})$$

The second term contributes

$$\text{Cov}_{Io} \left( \alpha_i, \sum_j (d + \alpha_j) \frac{p_{ij}}{p_{io}} \right) = \frac{q_{I/I}}{q_{o/I}} \left( \sum_i \sum_j \alpha_i (d + \alpha_j) f_{ij} - (d + \bar{\alpha}_{II}) \bar{\alpha}_{Io} \right) = \frac{q_{I/I}}{q_{o/I}} [\rho_{II}^{\alpha\alpha} + (d + \bar{\alpha}_{II})(\bar{\alpha}_{II} - \bar{\alpha}_{Io})]$$

The third term contributes

$$\text{Cov}_{Io} \left( \alpha_i, \beta_i \bar{\phi} \frac{p_{iSo}}{p_{io}} \right) = \bar{\phi} q_{o/SI} \frac{q_{S/I}}{q_{o/I}} \left( \sum_i \alpha_i \beta_i f_{iSo} - \bar{\alpha}_{Io} \bar{\beta}_{ISo} \right) = \bar{\phi} q_{o/SI} \frac{q_{S/I}}{q_{o/I}} \left( \sigma_{ISo}^{\alpha\beta} + \bar{\beta}_{ISo} (\bar{\alpha}_{ISo} - \bar{\alpha}_{Io}) \right)$$

The fourth term contributes a  $-\sigma_{Io}^{\alpha\alpha}$  term, minus

$$\text{Cov}_{Io} (\alpha_i, b \bar{\phi} q_{S/oI}) = \bar{\phi} b q_{S/oI} (\bar{\alpha}_{IoS} - \bar{\alpha}_{Io})$$

Putting everything together, we obtain

$$\begin{aligned} \frac{d\bar{\alpha}_{Io}}{dt} = & d \frac{q_{S/I}}{q_{o/I}} (\bar{\alpha}_{IS} - \bar{\alpha}_{Io}) \\ & + \frac{q_{I/I}}{q_{o/I}} [\rho_{II}^{\alpha\alpha} + (d + \bar{\alpha}_{II})(\bar{\alpha}_{II} - \bar{\alpha}_{Io})] \\ & + \bar{\phi} q_{o/SI} \frac{q_{S/I}}{q_{o/I}} \left( \sigma_{ISo}^{\alpha\beta} + \bar{\beta}_{ISo} (\bar{\alpha}_{ISo} - \bar{\alpha}_{Io}) \right) \\ & - \sigma_{Io}^{\alpha\alpha} - \bar{\phi} b q_{S/oI} (\bar{\alpha}_{IoS} - \bar{\alpha}_{Io}) \end{aligned} \quad (\text{S23})$$

Using  $\bar{\alpha}_I = q_{S/I} \bar{\alpha}_{IS} + q_{I/I} \bar{\alpha}_{II} + q_{o/I} \bar{\alpha}_{Io}$ , we rewrite this as

$$\begin{aligned} \frac{d\bar{\alpha}_{Io}}{dt} = & d \frac{q_{S/I}}{q_{o/I}} (\bar{\alpha}_{IS} - \bar{\alpha}_I) - d \frac{q_{S/I}}{q_{o/I}} (\bar{\alpha}_{Io} - \bar{\alpha}_I) \\ & + \frac{q_{I/I}}{q_{o/I}} [\rho_{II}^{\alpha\alpha} - (d + \bar{\alpha}_{II})(\bar{\alpha}_{Io} - \bar{\alpha}_I)] \\ & - \frac{d + \bar{\alpha}_{II}}{q_{o/I}} [q_{S/I} (\bar{\alpha}_{IS} - \bar{\alpha}_I) + q_{o/I} (\bar{\alpha}_{Io} - \bar{\alpha}_I)] \\ & + \bar{\phi} q_{o/SI} \frac{q_{S/I}}{q_{o/I}} \left( \sigma_{ISo}^{\alpha\beta} + \bar{\beta}_{ISo} (\bar{\alpha}_{ISo} - \bar{\alpha}_{Io}) \right) \\ & - \sigma_{Io}^{\alpha\alpha} - \bar{\phi} b q_{S/oI} (\bar{\alpha}_{IoS} - \bar{\alpha}_{Io}) \end{aligned} \quad (\text{S24})$$

We thus obtain finally for the dynamics of  $\bar{\alpha}_{Io} - \bar{\alpha}_I$

$$\begin{aligned} \frac{d}{dt}(\bar{\alpha}_{Io} - \bar{\alpha}_I) &= \left[ d \frac{q_{S/I}}{q_{o/I}} - (d + \bar{\alpha}_{II}) \frac{q_{S/I}}{q_{o/I}} - \bar{\beta}_{IS} q_{S/I} + \bar{\beta}_{ISo} \bar{\phi} q_{o/SI} \frac{q_{S/I}}{q_{o/I}} \right] (\bar{\alpha}_{IS} - \bar{\alpha}_I) \\ &\quad - \left[ d \frac{q_{S/I}}{q_{o/I}} + (d + \bar{\alpha}_{II}) \frac{q_{o/I} + q_{I/I}}{q_{o/I}} + \bar{\beta}_{ISo} \bar{\phi} q_{o/SI} \frac{q_{S/I}}{q_{o/I}} \right] (\bar{\alpha}_{Io} - \bar{\alpha}_I) \\ &\quad + \frac{q_{I/I}}{q_{o/I}} \rho_{II}^{\alpha\alpha} + \bar{\phi} q_{o/SI} \frac{q_{S/I}}{q_{o/I}} \sigma_{ISo}^{\alpha\beta} - q_{S/I} \sigma_{IS}^{\alpha\beta} - (\sigma_{Io}^{\alpha\alpha} - \sigma_I^{\alpha\alpha}) \end{aligned} \quad (\text{S25})$$

(Note that we have dropped the mutation bias term for simplicity.)

In contrast with the SIS model (large fecundity), the relatedness coefficient  $\rho = \rho_{II}^{\alpha\alpha} / \sigma_I^{\alpha\alpha}$  appears in the equation for  $\bar{\alpha}_{Io} - \bar{\alpha}_I$ , and not that for  $\bar{\alpha}_{IS} - \bar{\alpha}_I$ . This can be understood by remarking that a mortality event now changes an II pair into an Io pair, and not into an IS pair.

## 4 Weak selection limit

Our aim in this section is to recover the expression of the selection gradient derived in Lion & Boots (2010) from our formalism.

### 4.1 No host demography: SIS model

In order to do so, we write the virulence of each strain as a deviation from the mean. That is, we write the virulence of strain  $i$  as

$$\alpha_i = \bar{\alpha}_I + \varepsilon \delta_i \quad (\text{S26})$$

Because  $\sum \alpha_i f_i = \bar{\alpha}_I$ , a useful corollary is

$$\sum_i f_i \delta_i = 0 \quad (\text{S27})$$

Then, for a trade-off function  $g$  between transmission and virulence, we have

$$\beta_i = g(\alpha_i) = g(\bar{\alpha}_I) + \varepsilon \delta_i g'(\bar{\alpha}_I) + \frac{1}{2} \varepsilon^2 \delta_i^2 g''(\bar{\alpha}_I) + O(\varepsilon^3) \quad (\text{S28})$$

We will use equations (S26) and (S28) to derive weak selection (small  $\varepsilon$ ) approximations of global and local moments. We will show that, provided  $\varepsilon$  is small enough, the mean traits change on a slow time scale compared to the epidemiological variables (e.g. the densities  $p_i, q_{S/i} \dots$ ). Indeed, the epidemiological dynamics are of order  $\varepsilon^0$  while the dynamics of the mean traits are scaled by the population variance and are thus of order  $\varepsilon^2$ .

#### 4.1.1 Global moments

We first note that the global variance in virulence is of second order in  $\varepsilon$ . We have the following exact result, which follows from equation (S26) and the definition of variance:

$$\sigma_I^{\alpha\alpha} = \varepsilon^2 \sum_i \delta_i^2 f_i \quad (\text{S29})$$

The global mean transmission,  $\bar{\beta}_I$ , can be obtained by summing equation (S28) over the distribution  $f_i$ . We then obtain

$$\bar{\beta}_I = g(\bar{\alpha}_I) + \frac{1}{2} g''(\bar{\alpha}_I) \sigma_I^{\alpha\alpha} + O(\varepsilon^3) \quad (\text{S30})$$

For the covariance between traits, we have

$$\begin{aligned}
\sigma_I^{\alpha\beta} &= \sum_i \alpha_i \beta_i f_i - \bar{\alpha}_I \bar{\beta}_I \\
&= \sum_i (\bar{\alpha}_I + \varepsilon \delta_i) \left( g(\bar{\alpha}_I) + \varepsilon \delta_i g'(\bar{\alpha}_I) + \frac{1}{2} \varepsilon^2 \delta_i^2 g''(\bar{\alpha}_I) \right) f_i - \bar{\alpha}_I \bar{\beta}_I + O(\varepsilon^3) \\
&= \bar{\alpha}_I \left( g(\bar{\alpha}_I) + \frac{1}{2} g''(\bar{\alpha}_I) \sigma_I^{\alpha\alpha} \right) - \bar{\alpha}_I \bar{\beta}_I + \varepsilon^2 g'(\bar{\alpha}_I) \sum_i \delta_i^2 f_i + O(\varepsilon^3) \\
\boxed{\sigma_I^{\alpha\beta} = g'(\bar{\alpha}_I) \sigma_I^{\alpha\alpha} + O(\varepsilon^3)} & \tag{S31}
\end{aligned}$$

#### 4.1.2 Local densities

Writing  $q_{S/i}$  as a function of the  $N$  variables  $\boldsymbol{\alpha} = (\alpha_1, \dots, \alpha_N)$ , we can Taylor-expand  $q_{S/i}(\boldsymbol{\alpha})$  as follows

$$q_{S/i}(\boldsymbol{\alpha}) = q_{S/i}(\bar{\boldsymbol{\alpha}}) + \varepsilon \sum_j \delta_j \left. \frac{\partial q_{S/i}}{\partial \alpha_j} \right|_{\boldsymbol{\alpha}=\bar{\boldsymbol{\alpha}}} + O(\varepsilon^2), \tag{S32}$$

where  $\boldsymbol{\alpha}$  is the vector collecting all virulence values, and  $\bar{\boldsymbol{\alpha}}$  is the vector  $\bar{\alpha}_I \mathbf{1}$ .

For the total local density  $q_{S/I}(\boldsymbol{\alpha})$ , we have a similar expression

$$q_{S/I}(\boldsymbol{\alpha}) = q_{S/I}(\bar{\boldsymbol{\alpha}}) + \varepsilon \sum_j \delta_j \left. \frac{\partial q_{S/I}}{\partial \alpha_j} \right|_{\boldsymbol{\alpha}=\bar{\boldsymbol{\alpha}}} + O(\varepsilon^2) \tag{S33}$$

Let us consider first what happens in a neutral model. If we start from a spatial configuration where mutations are uniformly distributed in space, we can assume  $q_{S/i}(\bar{\boldsymbol{\alpha}}) = q_{S/I}(\bar{\boldsymbol{\alpha}})$ . As a result, we have

$$\frac{q_{S/i}}{q_{S/I}} = 1 + \varepsilon \frac{1}{q_{S/I}} \sum_j \delta_j \left. \frac{\partial (q_{S/i} - q_{S/I})}{\partial \alpha_j} \right|_{\boldsymbol{\alpha}=\bar{\boldsymbol{\alpha}}} + O(\varepsilon^2) \tag{S34}$$

#### 4.1.3 Local moments

Next, we consider the difference between local and global mean virulence,  $\bar{\alpha}_{IS} - \bar{\alpha}_I$ . We have

$$\begin{aligned}
\bar{\alpha}_{IS} - \bar{\alpha}_I &= \sum_i \alpha_i f_{iS} - \bar{\alpha}_I \\
&= \varepsilon \sum_i \delta_i f_i \frac{q_{S/i}}{q_{S/I}} \\
\boxed{\bar{\alpha}_{IS} - \bar{\alpha}_I = \varepsilon^2 \sum_i \sum_j \delta_i \delta_j f_i \frac{1}{q_{S/I}} \left. \frac{\partial (q_{S/i} - q_{S/I})}{\partial \alpha_j} \right|_{\boldsymbol{\alpha}=\bar{\boldsymbol{\alpha}}} + O(\varepsilon^3)} & \tag{S35}
\end{aligned}$$

For the sake of simplicity, we shall note  $\Delta q$  the double sum in the above expression. We thus write

$$\boxed{\bar{\alpha}_{IS} = \bar{\alpha}_I + \varepsilon^2 \Delta q + O(\varepsilon^3)}. \tag{S36}$$

Hence, the difference between local and global mean virulence is  $O(\varepsilon^2)$  and as a result, the scaled difference  $D = (\bar{\alpha}_{IS} - \bar{\alpha}_I) / \sigma_I^{\alpha\alpha}$  is  $O(1)$ .

We can use this result to make further progress. We first look at the local variance,  $\sigma_{IS}^{\alpha\alpha}$ . We have, using equation (S36),

$$\bar{\alpha}_{IS}^2 = \bar{\alpha}_I^2 + 2\varepsilon^2 \bar{\alpha}_I \Delta q + O(\varepsilon^4) \tag{S37}$$

$$\sum_i \alpha_i^2 f_{iS} = \bar{\alpha}_I^2 + 2\varepsilon^2 \bar{\alpha}_I \Delta q + \varepsilon^2 \sum_i \delta_i^2 f_i + O(\varepsilon^3) \tag{S38}$$



which yields

$$\boxed{\sigma_{IS}^{\alpha\alpha} = \sigma_I^{\alpha\alpha} + O(\varepsilon^3)} \quad (\text{S39})$$

Second, the local mean transmission can be expanded as

$$\bar{\beta}_{IS} = g(\bar{\alpha}_{IS}) + \frac{1}{2}g''(\bar{\alpha}_{IS})\sigma_{IS}^{\alpha\alpha} + O(\varepsilon^3) \quad (\text{S40})$$

This can be simplified as

$$\boxed{\bar{\beta}_{IS} = g(\bar{\alpha}_I) + \frac{1}{2}g''(\bar{\alpha}_I)\sigma_I^{\alpha\alpha} + O(\varepsilon^3)}. \quad (\text{S41})$$

Finally, we can write the local covariance  $\sigma_{IS}^{\alpha\beta}$  as

$$\boxed{\sigma_{IS}^{\alpha\beta} = g'(\bar{\alpha}_I)\sigma_I^{\alpha\alpha} + O(\varepsilon^3)}. \quad (\text{S42})$$

#### 4.1.4 Third-order moments

We proceed as previously for the third-order moments. We have

$$\sigma_{ISS}^{\alpha\alpha} = \sigma_I^{\alpha\alpha} + O(\varepsilon^3) \quad (\text{S43})$$

$$\sigma_{ISS}^{\alpha\beta} = g'(\bar{\alpha}_{ISS})\sigma_{IS}^{\alpha\alpha} + O(\varepsilon^3) = g'(\bar{\alpha}_I)\sigma_I^{\alpha\alpha} + O(\varepsilon^3) \quad (\text{S44})$$

$$T \equiv \frac{\bar{\alpha}_{ISS} - \bar{\alpha}_{IS}}{\sigma_I^{\alpha\alpha}} = O(1) \quad (\text{S45})$$

#### 4.1.5 Separation of time scales

**Dynamics of densities** Putting everything together, we can write the dynamics of  $p_i$  as

$$\frac{dp_i}{dt} = \left[ \bar{\beta}_{IS}q_{S/I} - (d + \bar{\alpha}_I) \right] p_i + O(\varepsilon) \quad (\text{S46})$$

which shows that the dynamics of the  $p_i$ 's are  $O(1)$ . Similarly, the dynamics of the  $q_{S/i}$ 's are  $O(1)$ .

**Dynamics of frequencies** The dynamics of the frequencies  $f_i$  are given by

$$\frac{df_i}{dt} = (r_i - r_I)f_i \quad (\text{S47})$$

In a neutral model, we necessarily have  $r_i = \bar{r}_I$  to ensure that we do not have any frequency change. Hence, in a model under selection, we have

$$\frac{df_i}{dt} = \varepsilon \sum_j \delta_j \left. \frac{\partial(r_i - \bar{r}_I)}{\partial\alpha_j} \right|_{\alpha=\bar{\alpha}} + O(\varepsilon^2) \quad (\text{S48})$$

The dynamics of strain frequencies are therefore  $O(\varepsilon)$ .

**Dynamics of mean traits** Finally, the dynamics of global mean virulence can be written as

$$\frac{d\bar{\alpha}_I}{dt} = \sigma_I^{\alpha\alpha} \left[ q_{S/I} \frac{\sigma_{IS}^{\alpha\beta}}{\sigma_I^{\alpha\alpha}} - 1 + \bar{\beta}_{IS}q_{S/I}D \right] \quad (\text{S49})$$

Note that all the terms between brackets are  $O(1)$ . As a result, the dynamics of the mean virulence is  $O(\varepsilon^2)$ .

**Separation of time scales 1** This demonstrates that strain densities are fast variables compared to the mean trait. As a result, we can assume that they reach an equilibrium on a fast time scale while the mean virulence remains constant.

**Dynamics of the variance** The global variance changes as follows:

$$\frac{d\sigma_I^{\alpha\alpha}}{dt} = \varepsilon^2 \sum_i \delta_i^2 \frac{df_i}{dt}. \quad (\text{S50})$$

Hence, because  $df_i/dt$  is  $O(\varepsilon)$ , the dynamics of variance is  $O(\varepsilon^3)$ .

**Dynamics of the scaled difference in mean traits,  $D$**  Finally, we can write the dynamics of  $D$  as

$$\frac{dD}{dt} = \frac{1}{\sigma_I^{\alpha\alpha}} \frac{d(\bar{\alpha}_{IS} - \bar{\alpha}_I)}{dt} - \frac{D}{\sigma_I^{\alpha\alpha}} \frac{d\sigma_I^{\alpha\alpha}}{dt} \quad (\text{S51})$$

The second term depends on the dynamics of the variance, and is  $O(\varepsilon)$ . Using equation (S12) and the results above, we can show that

$$\frac{dD}{dt} = g'(\bar{\alpha}_I) \left[ \bar{\phi} q_{S/IS} - q_{S/I} - \phi - \bar{\phi} q_{I/IS} \rho_S \right] + \frac{q_{I/I}}{q_{S/I}} \rho - D \left[ \bar{\beta}_I q_{S/I} + \frac{\bar{\alpha}_I}{q_{S/I}} \right] + 2\bar{\phi} q_{S/IS} \bar{\beta}_I T + O(\varepsilon). \quad (\text{S52})$$

This shows that the dynamics of  $D$  is  $O(1)$ . As a result, we can treat  $D$  as a fast variable and use a quasi-equilibrium assumption.

**Separation of time scales 2** The scaled difference between local and global mean virulences,  $D$ , is a fast variable compared to the mean virulence.

#### 4.1.6 Quasi-equilibrium assumption

Because of the separation of time scale 2, we can assume that the variable  $D$  reaches a quasi-equilibrium value  $\hat{D}$  on a fast time scale compared to the mean virulence. Solving equation (S52) for  $\hat{D}$  and plugging the result into equation (S49) gives us the approximate dynamics of the mean virulence under this quasi-equilibrium assumption.

We find

$$\hat{D} = \frac{1}{\bar{\beta}_I q_{S/I} + \frac{\bar{\alpha}_I}{q_{S/I}}} \left( g'(\bar{\alpha}_I) \left[ \bar{\phi} q_{S/IS} - q_{S/I} - \phi - \bar{\phi} q_{I/IS} \rho_S \right] + \frac{q_{I/I}}{q_{S/I}} \rho + 2\bar{\phi} q_{S/IS} \bar{\beta}_I T \right) \quad (\text{S53})$$

Three additional steps are needed to recover the selection gradient of Lion & Boots (2010).

First, we need to assume that the epidemiological dynamics are at equilibrium. This directly flows from Separation of time scales 1, because the epidemiological densities are fast variables. Hence, we have  $\bar{r}_I \approx 0$ , which yields

$$\bar{\beta}_I q_{S/IS} = d + \bar{\alpha}_I \approx \bar{\beta}_I q_{S/I} \quad (\text{to zeroth order in } \varepsilon). \quad (\text{S54})$$

In addition, using  $dp_{IS}/dt = 0$  and  $dp_{II}/dt = 0$  (see equations (S9) and (S17)), we also have at equilibrium

$$\bar{\beta}_{ISS} \bar{\phi} q_{S/IS} = (d + \bar{\alpha}_{IS}) \quad (\text{S55})$$

which can be rewritten to zeroth order in  $\varepsilon$  as

$$\bar{\phi}q_{S/II} = \frac{d + \bar{\alpha}_I}{\bar{\beta}_I} = q_{S/II} \quad (\text{S56})$$

Second, we will neglect the third-order difference  $T$ . This amounts to the classical moment closure approximation called ‘‘pair approximation’’, which is generally accurate on random networks (Matsuda et al., 1992; van Baalen, 2000). The pair approximation was used in Lion & Boots (2010) to close the system.

Third, we only need the equilibrium neutral values of the relatedness coefficients  $\rho$  and  $\rho_S$  in equation (S53), because we only need to retain the  $O(1)$  component of these relatedness coefficients and because  $\rho$  and  $\rho_S$  are defined as scaled covariances which can also be treated as fast variables. When  $N = 2$ , it is straightforward to show that  $\rho$  and  $\rho_S$  take the form of relatedness coefficients previously introduced in the literature. Specifically, with a resident ( $R$ ) and a mutant ( $M$ ) strains, we have

$$\rho = \frac{f_{MM} - f_M^2}{f_M - f_M^2}, \quad (\text{S57})$$

which measures relatedness between two parasites infecting neighbouring hosts, and

$$\rho_S = \frac{f_{MSM} - f_M^2}{f_M - f_M^2} \quad (\text{S58})$$

which measures relatedness between two parasites infecting the two infected hosts in a ISI configuration. These two measures of relatedness have been introduced in Lion & Gandon (2009). In the two-strain case, we further have at equilibrium in the neutral model (Lion, 2010)

$$q_{I/II}\rho = \phi + \bar{\phi}q_{I/II}\rho_S. \quad (\text{S59})$$

We will use this relationship in the following.

#### 4.1.7 From the change in mean trait to the selection gradient

Using the expression for  $\hat{D}$  above and the relationships  $T = 0$ ,  $\bar{\phi}q_{S/II} = q_{S/II}$  and  $q_{I/II}\rho = \phi + \bar{\phi}q_{I/II}\rho_S$ , we finally obtain the following expression for the change in mean virulence:

$$\frac{d\bar{\alpha}_I}{dt} = \sigma_I^{\alpha\alpha} \left( 1 - \frac{q_{I/II}\rho}{1 + q_{S/II}} \right) \left[ g'(\bar{\alpha}_I)q_{S/II} - 1 \right] + O(\varepsilon^3) \quad (\text{S60})$$

where  $q_{S/II} = (d + \bar{\alpha}_I)/\bar{\beta}_I$  at equilibrium.

The term between square brackets shows that evolutionary endpoints are given by a marginal value theorem,

$$\frac{d\beta(\alpha)}{d\alpha} = \frac{\beta}{d + \alpha}, \quad (\text{S61})$$

yielding the same result as in the corresponding non-spatial model, while the term between curved brackets shows spatial structure slows down the evolutionary dynamics through the relatedness term  $\rho$ . The invasion analysis route to this result is discussed in detail in Lion, [in press](#).

## 4.2 Host demography: oSI model

We now derive the weak selection approximation of the dynamics of  $\bar{\alpha}_I$  in the oSI model. Noting

$$\mathbf{X} = \begin{pmatrix} \frac{\bar{\alpha}_{IS} - \bar{\alpha}_I}{\sigma_I^{\alpha\alpha}} \\ \frac{\bar{\alpha}_{Io} - \bar{\alpha}_I}{\sigma_I^{\alpha\alpha}} \end{pmatrix}$$

we have the following system of equations

$$\frac{d\mathbf{X}}{dt} = \mathbf{A}\mathbf{X} - \mathbf{C} \quad (\text{S62})$$

where

$$\mathbf{A} = \begin{pmatrix} -[\bar{\beta}_{IS}q_{S/I} + b\bar{\phi}q_{S/oI} \frac{q_{o/I}}{q_{S/I}}] & b\bar{\phi}q_{S/oI} \frac{q_{o/I}}{q_{S/I}} \\ d \frac{q_{S/I}}{q_{o/I}} - (d + \bar{\alpha}_{II}) \frac{q_{S/I}}{q_{o/I}} - \bar{\beta}_{IS}q_{S/I} + \bar{\beta}_{ISo}\bar{\phi}q_{o/SI} \frac{q_{S/I}}{q_{o/I}} & -[d \frac{q_{S/I}}{q_{o/I}} + (d + \bar{\alpha}_{II}) \frac{q_{o/I} + q_{I/I}}{q_{o/I}} + \bar{\beta}_{ISo}\bar{\phi}q_{o/SI} \frac{q_{S/I}}{q_{o/I}}] \end{pmatrix} \quad (\text{S63})$$

and

$$\mathbf{C} = \begin{pmatrix} -\frac{\sigma_{IS}^{\alpha\beta}}{\sigma_I^{\alpha\alpha}} \left[ \bar{\phi}q_{S/SI} \frac{\sigma_{IS}^{\alpha\beta}}{\sigma_{IS}^{\alpha\beta}} - q_{S/I} - (\phi + \bar{\phi}q_{I/SI}\rho_S) \right] + \frac{(\sigma_{IS}^{\alpha\alpha} - \sigma_I^{\alpha\alpha})}{\sigma_I^{\alpha\alpha}} \\ -\frac{q_{I/I}}{q_{o/I}}\rho - \bar{\phi}q_{o/SI} \frac{q_{S/I}}{q_{o/I}} \frac{\sigma_{IS}^{\alpha\beta}}{\sigma_I^{\alpha\alpha}} + q_{S/I} \frac{\sigma_{IS}^{\alpha\beta}}{\sigma_I^{\alpha\alpha}} + \frac{(\sigma_{Io}^{\alpha\alpha} - \sigma_I^{\alpha\alpha})}{\sigma_I^{\alpha\alpha}} \end{pmatrix}$$

The quasi-equilibrium solution of  $\mathbf{X}$  is obtained by setting (S62) to zero, where we only need to retain the  $O(1)$  terms of  $\mathbf{A}$  and  $\mathbf{C}$ . Using Cramer's rule to solve the system, we obtain for  $D_S = (\bar{\alpha}_{IS} - \bar{\alpha}_I)/\sigma_I^{\alpha\alpha}$ :

$$\hat{D}_S = \frac{1}{\det \mathbf{A}} \begin{vmatrix} -\frac{\sigma_{IS}^{\alpha\beta}}{\sigma_I^{\alpha\alpha}} \left[ \bar{\phi}q_{S/SI} \frac{\sigma_{IS}^{\alpha\beta}}{\sigma_{IS}^{\alpha\beta}} - q_{S/I} - (\phi + \bar{\phi}q_{I/SI}\rho_S) \right] + \frac{(\sigma_{IS}^{\alpha\alpha} - \sigma_I^{\alpha\alpha})}{\sigma_I^{\alpha\alpha}} & b\bar{\phi}q_{S/oI} \frac{q_{o/I}}{q_{S/I}} \\ -\frac{q_{I/I}}{q_{o/I}}\rho - \bar{\phi}q_{o/SI} \frac{q_{S/I}}{q_{o/I}} \frac{\sigma_{IS}^{\alpha\beta}}{\sigma_I^{\alpha\alpha}} + q_{S/I} \frac{\sigma_{IS}^{\alpha\beta}}{\sigma_I^{\alpha\alpha}} + \frac{(\sigma_{Io}^{\alpha\alpha} - \sigma_I^{\alpha\alpha})}{\sigma_I^{\alpha\alpha}} & -[d \frac{q_{S/I}}{q_{o/I}} + (d + \bar{\alpha}_{II}) \frac{q_{o/I} + q_{I/I}}{q_{o/I}} + \bar{\beta}_{ISo}\bar{\phi}q_{o/SI} \frac{q_{S/I}}{q_{o/I}}] \end{vmatrix}$$

Under weak selection, we can rewrite this as

$$\hat{D}_S = \frac{1}{\det \mathbf{A}} \begin{vmatrix} -\frac{d\beta}{d\alpha} \left[ \bar{\phi}q_{S/SI} - q_{S/I} - (\phi + \bar{\phi}q_{I/SI}\rho_S) \right] & b\bar{\phi}q_{S/oI} \frac{q_{o/I}}{q_{S/I}} \\ -\frac{q_{I/I}}{q_{o/I}}\rho - \bar{\phi}q_{o/SI} \frac{q_{S/I}}{q_{o/I}} \frac{d\beta}{d\alpha} + q_{S/I} \frac{d\beta}{d\alpha} & -[d \frac{q_{S/I}}{q_{o/I}} + (d + \bar{\alpha}_I) \frac{q_{o/I} + q_{I/I}}{q_{o/I}} + \bar{\beta}_I \bar{\phi}q_{o/SI} \frac{q_{S/I}}{q_{o/I}}] \end{vmatrix}$$

and we can also use the relationship  $\phi + \bar{\phi}q_{I/SI}\rho_S = q_{I/I}\rho$  at equilibrium, so we get:

$$\hat{D}_S = \frac{1}{\det \mathbf{A}} \begin{vmatrix} -\frac{d\beta}{d\alpha} \left[ \bar{\phi}q_{S/SI} - q_{S/I} - q_{I/I}\rho \right] & b\bar{\phi}q_{S/oI} \frac{q_{o/I}}{q_{S/I}} \\ -\frac{q_{I/I}}{q_{o/I}}\rho - \bar{\phi}q_{o/SI} \frac{q_{S/I}}{q_{o/I}} \frac{d\beta}{d\alpha} + q_{S/I} \frac{d\beta}{d\alpha} & -d \frac{q_{S/I}}{q_{o/I}} - (d + \alpha) \frac{q_{o/I} + q_{I/I}}{q_{o/I}} - \beta \bar{\phi}q_{o/SI} \frac{q_{S/I}}{q_{o/I}} \end{vmatrix}$$

Note however that we don't have  $\bar{\phi}q_{S/SI} = q_{S/I}$  at equilibrium in the oSI model.

Some further simplifications follow from the following equations for the densities of pairs:

$$\frac{dp_{oI}}{dt} = -p_{oI}(d + \alpha + b\bar{\phi}q_{S/oI}) + dp_{SI} + (d + \alpha)p_{II} + p_{oS}(\bar{\phi}\beta q_{I/So}) \quad (\text{S64})$$

Setting this to zero, we find

$$\beta \bar{\phi}q_{o/SI}q_{S/I} + dq_{S/I} + (d + \alpha)q_{I/I} = q_{o/I}(d + \alpha + b\bar{\phi}q_{S/oI})$$

Thus, the bottom-right element of the determinant in the expression for  $\hat{D}_S$  can be written as  $-(2(d + \alpha) + b\bar{\phi}q_{S/oI})$  and we have

$$\hat{D}_S = \frac{1}{\det \mathbf{A}} \begin{vmatrix} -\frac{d\beta}{d\alpha} \left[ \bar{\phi}q_{S/SI} - q_{S/I} - q_{I/I}\rho \right] & b\bar{\phi}q_{S/oI} \frac{q_{o/I}}{q_{S/I}} \\ -\frac{q_{I/I}}{q_{o/I}}\rho - \bar{\phi}q_{o/SI} \frac{q_{S/I}}{q_{o/I}} \frac{d\beta}{d\alpha} + q_{S/I} \frac{d\beta}{d\alpha} & -2(d + \alpha) - b\bar{\phi}q_{S/oI} \end{vmatrix}$$

Calculating the determinant, the numerator of  $\hat{D}_S$  can be written as the following sum:

$$b\bar{\phi}q_{S/oI} \left\{ \frac{d\beta}{d\alpha} \left[ \bar{\phi}q_{S/SI} - q_{S/I} - q_{I/I}\rho \right] + \frac{q_{I/I}}{q_{S/I}}\rho + \frac{d\beta}{d\alpha}(\bar{\phi}q_{o/SI} - q_{o/I}) \right\} \\ + 2(d + \alpha) \frac{d\beta}{d\alpha} \left[ \bar{\phi}q_{S/SI} - q_{S/I} - q_{I/I}\rho \right]$$

Now we can tidy this things up a bit by noting that

$$\begin{aligned} \bar{\phi}q_{o/SI} - q_{o/I} &= \bar{\phi}(1 - q_{S/SI} - q_{I/SI}) - (1 - q_{S/I} - q_{I/I}) \\ &= -(\bar{\phi}q_{S/SI} - q_{S/I}) - (\phi + \bar{\phi}q_{I/SI} - q_{I/I}) \\ &= -(\bar{\phi}q_{S/SI} - q_{S/I}) \end{aligned}$$

(the last equality follows from setting  $dp_{II}/dt = 0$  and is only valid at equilibrium). This gives us for the numerator:

$$b\bar{\phi}q_{S/oI} \left\{ \frac{d\beta}{d\alpha} [-q_{I/I}\rho] + \frac{q_{I/I}}{q_{S/I}}\rho \right\} + 2(d+\alpha)\frac{d\beta}{d\alpha} [\bar{\phi}q_{S/SI} - q_{S/I} - q_{I/I}\rho]$$

and therefore the numerator of  $\hat{D}_S$  can be written as

$$-Z \left[ \frac{d\beta}{d\alpha} q_{S/I} (q_{I/I}\rho + u(q_{I/I}\rho - \bar{\phi}q_{S/SI} + q_{S/I})) - q_{I/I}\rho \right]$$

where

$$Z = \frac{b\bar{\phi}q_{S/oI}}{q_{S/I}} \quad \text{and} \quad u = \frac{2(d+\alpha)}{\bar{\phi}bq_{S/oI}}$$

With some further work, we can rewrite  $u$  to obtain the expression in Lion & Boots (2010). We have

$$\frac{dp_{IS}}{dt} = p_{oI}b\bar{\phi}q_{S/oI} + p_{SS}\beta\bar{\phi}q_{I/SS} - p_{IS}(2d+\alpha+\phi\beta+\bar{\phi}\beta q_{I/SI})$$

Setting this to zero yields

$$\begin{aligned} b\bar{\phi}q_{S/oI} &= \frac{q_{S/I}}{q_{o/I}} [2d+\alpha+\beta(\phi+\bar{\phi}q_{I/SI}) - \beta\bar{\phi}q_{S/SI}] \\ &= \frac{q_{S/I}}{q_{o/I}} [2d+\alpha+\beta q_{I/I} - \beta\bar{\phi}q_{S/SI}] \quad (\text{from } dp_{II}/dt = 0) \end{aligned}$$

We then obtain, using  $q_{S/I} = (d+\alpha)/\beta$ :

$$u = \frac{2\beta q_{o/I}}{2d+\alpha+\beta q_{I/I} - \beta\bar{\phi}q_{S/SI}}$$

which, using again  $q_{S/I} = (d+\alpha)/\beta$ , can be rewritten as the eqn after eqn (6) in Lion & Boots (2010):

$$u = \frac{2\beta q_{o/I}}{1 + \frac{d}{\beta} - q_{o/I} - \beta\bar{\phi}q_{S/SI}}$$

To compute the denominator of  $\hat{D}_S$ , we start from the neutral value of  $\mathbf{A}$ , which is

$$\mathbf{A} = \begin{pmatrix} -(\beta q_{S/I} + b\bar{\phi}q_{S/oI}\frac{q_{o/I}}{q_{S/I}}) & b\bar{\phi}q_{S/oI}\frac{q_{o/I}}{q_{S/I}} \\ (d - (d+\alpha) - \beta q_{S/I} + \beta\bar{\phi}q_{o/SI})\frac{q_{S/I}}{q_{o/I}} & -\left(d\frac{q_{S/I}}{q_{o/I}} + (d+\alpha)\frac{(q_{o/I}+q_{I/I})}{q_{o/I}} + \beta\bar{\phi}q_{o/SI}\frac{q_{S/I}}{q_{o/I}}\right) \end{pmatrix}$$

Setting equation (S64) to zero, we can simplify this as

$$\mathbf{A} = Z \begin{pmatrix} -(\beta q_{S/I} + b\bar{\phi}q_{S/oI}\frac{q_{o/I}}{q_{S/I}}) & q_{o/I} \\ b\bar{\phi}q_{S/oI} - (d+\alpha)\frac{q_{I/I}+q_{S/I}}{q_{o/I}} & -(u+1)q_{S/I} \end{pmatrix}$$

which yields

$$\begin{aligned} \det \mathbf{A} &= Z \left[ (u+1)q_{S/I} \left( \beta q_{S/I} + b\bar{\phi}q_{S/oI}\frac{q_{o/I}}{q_{S/I}} \right) - b\bar{\phi}q_{S/oI}q_{o/I} + (d+\alpha)(q_{I/I} + q_{S/I}) \right] \\ &= Z \left[ (u+1)\beta q_{S/I}^2 + ub\bar{\phi}q_{S/oI}q_{o/I} + (d+\alpha)(q_{I/I} + q_{S/I}) \right] \end{aligned}$$

Using the fact that  $b\bar{\phi}q_{S/oI} = 2(d+\alpha)/u$  and  $\beta q_{S/I} = (d+\alpha)$ , we obtain finally

$$\det \mathbf{A} = Z\beta q_{S/I} \left[ 2q_{o/I} + (u+2)q_{S/I} + q_{I/I} \right]. \quad (\text{S65})$$

We thus have

$$\hat{D}_S = - \frac{\left[ \frac{d\beta}{d\alpha} q_{S/I} \left( q_{I/I} \rho + u(q_{I/I} \rho - \bar{\phi} q_{S/SI} + q_{S/I}) \right) - q_{I/I} \rho \right]}{\beta q_{S/I} \left[ 2q_{o/I} + (u+2)q_{S/I} + q_{I/I} \right]}. \quad (\text{S66})$$

Plugging this into equation (S49), we obtain

$$\frac{d\bar{\alpha}_I}{dt} = \sigma_I^{\alpha\alpha} \left( 1 - \frac{q_{I/I} \rho}{\kappa} \right) \left[ \frac{d\beta}{d\alpha} q_{S/I} (1 - \omega X) - 1 \right] \quad (\text{S67})$$

where

$$\begin{aligned} \kappa &= 2q_{o/I} + (u+2)q_{S/I} + q_{I/I} = 1 + q_{S/I} + q_{o/I} + uq_{S/I} \\ \omega &= \frac{u}{\kappa - q_{I/I} \rho} \\ X &= q_{I/I} \rho - \bar{\phi} q_{S/SI} + q_{S/I}. \end{aligned}$$

We thus recover equation (17) in the main text, and also the result of Lion & Boots (2010).

## 5 Effect of the number of neighbours

In this section, we investigate the effect of the number of neighbours on the dynamics. We compare three two-dimensional lattices : a square lattice with a Von Neumann neighbourhood ( $n = 4$ ), a triangular lattice ( $n = 6$ , used for the simulations in the main text) and a square lattice with a Moore neighbourhood ( $n = 8$ ). Figure S1 shows that, when  $n$  increases, the dynamics of the spatial epidemics get closer to those observed under global dispersal. This is expected because both an increase in the number of contacts and an increased dispersal tend to decrease spatial structure. Also, as the number of neighbours increases, fluctuations between different runs of the same process are reduced, yielding smoother curves.

We also provide additional figures (third row) showing the effect of three components of equation (9) in the main text: the transmission differential,  $\bar{\phi} q_{S/SI} \sigma_{IS}^{\alpha\beta} - q_{S/I} \sigma_{IS}^{\alpha\beta}$  (in black), the negative effect of the virulence cost,  $\sigma_{IS}^{\alpha\alpha} - \sigma_I^{\alpha\alpha}$  (in dotted black), and the net effect of genetic structure on the dynamics of spatial differentiation, as measured by  $-\sigma_{IS}^{\alpha\beta} (\phi + \bar{\phi} q_{I/SI} \rho_S) + \sigma_I^{\alpha\alpha} q_{I/I} \rho / q_{S/I}$  (in grey). These figures show that both the transmission differential and genetic structure have a positive effect on spatial differentiation.

Finally, the figures on the fourth row show the dynamics of measures of genetic structure. Rather than directly plotting the dynamics of the relatedness coefficients  $\rho$  and  $\rho_S$ , we show instead the dynamics of the quantities  $\phi + \bar{\phi} q_{I/SI} \rho_S$  (in black) and  $q_{I/I} \rho$  (in grey). The main reason for choosing these quantities comes from earlier work (Lion, 2009). At neutral equilibrium and low mutation in the SIS model, we know that these two quantities must be equal. The lower panel of figure S1 shows that, in our simulations, the two quantities are generally distinct (this is due to the deviation from neutrality). Interestingly, however, they appear to converge to the same value at the tip-off point where the mutant goes from being selected for to being counter-selected. This is also the point where the effect of genetic structure on the build-up of spatial differentiation is the strongest (see figures on the third panel of figure S1).

Another observation is that, as  $n$  increases, the curves are shifted towards lower values. It is important to note, however, that simply increasing the number of neighbours from 4 to 8 is not sufficient to get rid of the effect of relatedness and kin competition. We would need to take the limit  $n \rightarrow \infty$  which is equivalent to the global dispersal scenario we investigate in the mean text. Under global dispersal, both  $\rho$  and  $\rho_S$  quickly converge to zero (results not shown).

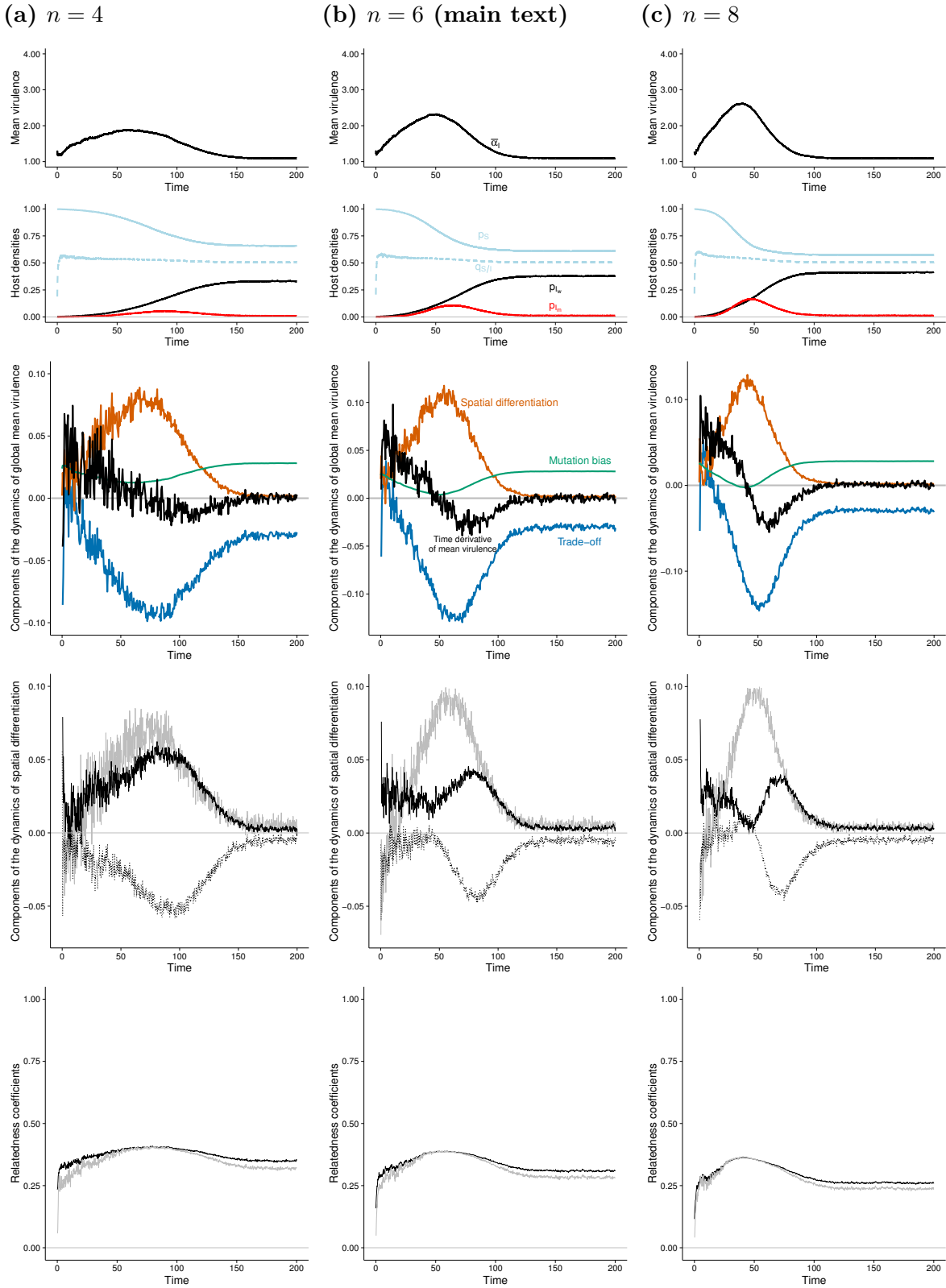


Figure S1: Effect of the number of neighbours on the evolutionary dynamics. From top to bottom panel: dynamics of global mean virulence, dynamics of host densities, dynamics of the components of eqn (8) in the main text, dynamics of some components of eqn(9) in the main text, dynamics of measures of genetic structure. See the text for more detailed description of the figures.

## 6 Snapshot of mean epi-evolutionary dynamics for global dispersal

We present here for reference the equivalent of figure 5 in the main text for global dispersal.

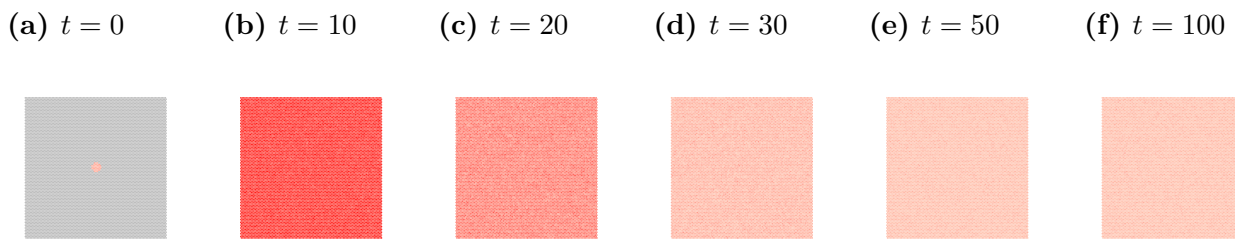


Figure S2: Snapshots of the lattice at different time points. Each snapshot represents the average of 100 runs for the same scenario as in Figure 2b. For each time point, each site is coloured in grey if the host is uninfected in all runs, or in red if it has been infected in at least one run. The mean virulence among runs where the focal site is occupied by an infected individual is shown, and colour-coded using various shades of red (higher levels of red indicate higher virulence).

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