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## Moment equations in spatial evolutionary ecology

Sébastien Lion

Centre d'Écologie Fonctionnelle et Évolutive (CEFE), UMR 5175 CNRS – Université de Montpellier – Université Paul-Valéry Montpellier – EPHE, 1919, route de Mende, 34293 Montpellier Cedex 5, France

## HIGHLIGHTS

- I review the toolkit of moment equations for spatial evolutionary models.
- I first show how to derive spatial moment equations from first principles.
- The selection gradient depends on measures of genetic and demographic structure.
- I discuss the connection with inclusive fitness theory.

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## ABSTRACT

How should we model evolution in spatially structured populations? Here, I review an evolutionary ecology approach based on the technique of spatial moment equations. I first provide a mathematical underpinning to the derivation of equations for the densities of various spatial configurations in network-based models. I then show how this spatial ecological framework can be coupled with an adaptive dynamics approach to compute the invasion fitness of a rare mutant in a resident population at equilibrium. Under the additional assumption that mutations have small phenotypic effects, I show that the selection gradient can be expressed as a function of neutral measures of genetic and demographic structure. I discuss the connections between this approach and inclusive fitness theory, as well as the applicability and limits of this technique. My main message is that spatial moment equations can be used as a means to obtain compact qualitative arguments about the evolution of life-history traits for a variety of life cycles.

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## 1. Introduction

Classical evolutionary models usually rely on the assumption that the population is well-mixed, thus neglecting the role of spatial structuring in the evolutionary process. In recent years, a growing number of studies have addressed this shortcoming by investigating evolution in spatially or socially structured populations (for reviews, see [Rousset, 2004](#); [Lion and van Baalen, 2008](#)).

Over the years, a wide range of techniques have been introduced to tackle this important question ([Tilman and Kareiva, 1997](#); [Dieckmann et al., 2000](#); [Rousset, 2004](#)). Individual-based (or agent-based) simulations are a natural framework in which to explore the role of local interactions or limited dispersal on the evolution of a trait, and still form the backbone of virtually all studies in spatial evolutionary ecology. Pure simulation studies, however, usually have some downsides. First, it may be easy to get lost into unnecessary details of the biological process, thereby

increasing the difficulty of picking up the biological signal from the simulation noise. Second, the danger is great of interpreting the outcome of simulations using appealing verbal arguments instead of either testing one's hypotheses using simulation experiments, or providing an analytical underpinning to the results.

Although analytical models of spatial evolutionary dynamics are notoriously difficult to handle, a fair number of successful approaches have been introduced in the field over the years. Three main analytical frameworks exist to this date: metapopulation models with large local population sizes ([Metz and Gyllenberg, 2001](#); [Jansen and Vitalis, 2007](#)); models of deme-structured populations with finite and constant local populations (see [Rousset, 2004](#); [Rousset and Ronce, 2004](#); [Lehmann et al., 2006](#) for extensions to populations with fluctuating demography); and spatial moment equations ([Matsuda et al., 1992](#); [Bolker and Pacala, 1997](#); [Van Baalen and Rand, 1998](#); [Rand, 1999](#); [Law and Dieckmann, 2000](#); [Lion and van Baalen, 2008](#)).

The aim of spatial moment equations is to derive equations for the dynamics of spatial moments. This approach can be applied to discrete space (stochastic processes on networks, [Matsuda et al., 1992](#); [Rand, 1999](#); [Van Baalen, 2000](#)) or to continuous space (spatial point

E-mail address: [sebastien.lion@cefe.cnrs.fr](mailto:sebastien.lion@cefe.cnrs.fr)<http://dx.doi.org/10.1016/j.jtbi.2015.10.014>

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processes, Bolker and Pacala, 1997, 1999; Law and Dieckmann, 2000). In discrete space, one will typically track the densities of sites in a given state (densities of singlets), the densities of pairs of sites, the densities of triplets of sites, and so on. In continuous space, equations for the global densities of different types, along with the dynamics of spatial correlations between two or more types, are needed. Both frameworks have their respective merits and limitations, but, to my knowledge, only a very restricted number of studies have modelled evolutionary dynamics in continuous space (see e.g. North et al., 2011; Barraquand and Murrell, 2012a,b). I will therefore focus my review on discrete-space models and briefly outline the most salient similarities of continuous-space models in Box 1.

The demarch of spatial moment equations is very similar to the use of moment equations in quantitative genetics, in which one seeks to derive equations for the dynamics of the mean, variance, and higher-order moments of the distribution of the evolving trait. As in quantitative genetics, one is ultimately faced with an infinite system of equations that needs to be closed using an appropriate moment closure approximation. In quantitative genetics, the distribution of the trait is often assumed to be Gaussian (Lande, 1976; Lande and Arnold, 1983; Abrams, 2001; Day and Proulx, 2004). Thus, only the mean and variance of the distribution are needed. In spatial models, alternative moment closure approximations, such as the pair approximation, have been developed for both discrete-space and continuous-space models (Matsuda et al., 1992; Sato et al., 1994; Bolker and Pacala, 1999; Rand, 1999; Dieckmann and Law, 2000; Van Baalen, 2000; Ellner, 2001; Murrell et al., 2004).

The purpose of this paper is to provide a methods-minded review of the use of moment equations in spatial evolutionary ecology. My main motivation is to dissipate the confusion about the inner workings of the method and make it more palatable to the average (theoretical) biologist. Currently, the use of spatial moment equations is hampered by several obstacles. First, different authors use different approaches and notations. Second, the link to biological concepts such as inclusive fitness theory is still not well understood. Third, the popularisation of the technique under the misleading label “pair approximation” has been instrumental in spreading the misconception that the method may only be applied to interactions between pairs of individuals, or is inherently flawed because it necessarily ignores larger-scale spatial patterns. Lastly, new technical developments of the approach have usually been introduced in the literature as new biological questions were investigated, so that, overall, progress in this area has been brought forward by a fruitful wave of pluralism, but largely outside a well-defined and consistent theoretical framework.

Throughout this review, I will use a running example of a simple SIS epidemiological model (also known as the contact process in the mathematical literature, Harris, 1974; Liggett, 1985; Neuhauser, 1992). This review consists of two parts that are largely independent of one another. Readers familiar with the derivation of spatial moment equations should feel free to directly jump to the second part. In the first part, I focus on ecological dynamics and show how deterministic moment equations can be derived from first principles, using a microscopic description of the stochastic process. I first unfold the general machinery, then apply the result to the SIS epidemiological model (or contact process). In the second part, I show how spatial moment equations can be coupled with an adaptive dynamics evolutionary framework to derive analytical approximations for the direction of selection in terms of local measures of genetic and demographic structure. The approach is general, but for the sake of simplicity, I mostly discuss the application to the SIS model. The result for the SIS model is particularly simple, both mathematically and biologically, but further extensions and complications are reviewed in the discussion.

## 2. Ecological dynamics

Spatial moment equations may be thought of as deterministic approximations of a stochastic individual-based process in space. Mathematically, this stochastic process is a Markov process and the moment equations give the expected dynamics of various spatial configurations, which can be derived from the generator of this Markov process (Liggett, 1985; Champagnat and Méléard, 2007; Ovaskainen et al., 2014). The general theory goes beyond the discrete-space approach I review here and has been developed for general processes in continuous space (Ovaskainen et al., 2014), at the cost of greater mathematical complexity (see Box 1 for a rapid overview).

### 2.1. Space

Let us consider a network of  $N$  sites. Each site can be in one of  $M$  states. The set of all possible states is  $\Omega$ , which, for simplicity, will be considered a subset of  $\mathbb{Z}$  (i.e. each state is represented by an integer). The state of site  $i$  is  $\sigma_i \in \Omega$  and the state of the network is represented by the vector  $\sigma = (\sigma_i)$ . The connectivity of the network is encapsulated in an  $N \times N$  symmetric matrix  $(J_{ij})$  where  $J_{ij}$  is 1 if there is a connection between sites  $i$  and  $j$ , and 0 otherwise. No site is connected to itself ( $J_{ii} = 0$ ). For simplicity, I shall assume that  $\mathbf{J}$  is constant over time (i.e., I focus on static networks).

For convenience, I define the indicator variable  $a_i$  as

$$a_i(\sigma) = \begin{cases} 1 & \text{if site } i \text{ is in state } a \\ 0 & \text{otherwise} \end{cases}$$

and the vector-valued function  $\mathbf{a}(\sigma)$  that returns the vector  $(a_i(\sigma))$ .

### 2.2. Spatial observables

The vector  $\sigma$  contains all the information on the network at a given time. The objective of spatial moment equations is to track the dynamics of a small number of well-chosen functions of  $\sigma$  (observables) instead of the full dynamics of  $\sigma$ .

For instance, one can calculate the number of sites in state  $a$ , which is (dropping the dependency on  $\sigma$  for convenience)

$$[a] = \sum_{i=1}^N a_i = \mathbf{a}^T \mathbf{1},$$

where  $\mathbf{1}$  is the  $N \times 1$  vector containing only ones. This corresponds to moments of the first order of the spatial distribution of individuals. Obviously, we need more information to characterise this distribution. We can take one further step and compute the number of pairs of sites in state  $ab$ , which is

$$[a : b] = \sum_{i=1}^N \sum_{j=1}^N J_{ij} a_j b_i = \mathbf{a}^T \mathbf{J} \mathbf{b}.$$

The notation “:” indicates that the indicator functions  $a$  and  $b$  are to be evaluated on pairs of sites. Note that, because the matrix  $\mathbf{J}$  is symmetric, we have  $[a : b] = [b : a]$ . Similarly, the number of triplets, quadruplets, and increasingly more complicated configurations of sites can be computed as functions of  $\sigma$  and of the connectivity matrix  $\mathbf{J}$ .

Another quantity that will turn out to be useful is the average number of  $a$  neighbours of a  $b$  site, which is defined as

$$[a | b] = \frac{[a : b]}{[b]}.$$

This is related to the notion of local density that is typically used in the literature to analyse models on regular networks (see Section 2.6).

## Box 1–Moment equations in continuous space: an overview.

In contrast with reaction–diffusion equations, moment-based ecological models in continuous space represent populations as a finite configuration of (marked) discrete points in the real plane (Bolker and Pacala, 1997; Bolker, 1999; Bolker and Pacala, 1999; Dieckmann and Law, 2000; Law and Dieckmann, 2000; Murrell et al., 2004; Champagnat and Méléard, 2007; Ovaskainen et al., 2014). As in the discrete-space case, one is interested in how the state of the population (the configuration) changes as a result of various events. However, this task is mathematically challenging in continuous space because the space of such configurations is infinite and we need to consider a measure-valued Markov process (Champagnat and Méléard, 2007; Ovaskainen et al., 2014). The generator of this Markov process allows us to derive equations for the time evolution of various observables, as in the discrete case.

For the SIS model in continuous space, one may for instance track the total densities of hosts infected by the resident ( $\bar{I}$ ) and mutant ( $\bar{I}'$ ) parasite respectively. We have (Bolker, 1999)

$$\frac{d\bar{I}}{dt} = \beta(\bar{S}\bar{I} + \bar{c}_{SI}) - \gamma\bar{I}, \quad (a)$$

$$\frac{d\bar{I}'}{dt} = \beta'(\bar{S}\bar{I}' + \bar{c}_{S'I'}) - \gamma'\bar{I}', \quad (b)$$

where  $\bar{S}$  is the total density of susceptible hosts, and

$$\bar{c}_{Sx} = 2 \int_0^\infty U(r)c_{Sx}(r) dr$$

is the average covariance between susceptible hosts and infected hosts of a given type, weighted by the infection kernel  $U(r)$  describing the probability that a parasite propagule lands at distance  $r$  from a focal individual.

Eq. (b) allows us to derive the following expression for the invasion fitness:

$$\lambda' = \beta' \left( \bar{S} + \frac{\bar{c}_{S'I'}}{\bar{I}'} \right) - \gamma' \quad (c)$$

The term between brackets is the continuous-space analogous of  $q_{S'/I'}$  in Eq. (9). The main difference is that the average covariance is a centred moment and therefore the effect of space is expressed as a deviation from the non-spatial density  $\bar{S}$ . However, the biological interpretations are similar.

To proceed from (c), one may derive equations for the dynamics of spatial covariances  $c_{SI}(r)$ ,  $c_{I'I'}(r)$ ,  $c_{I'I}(r)$ . These spatial covariances describe the demographic and genetic structuring of the parasite population. Estimates for relatedness at different distances could in principle be obtained from the dynamics of these covariances (see Robledo-Arnuncio and Rousset, 2010 for another approach). As in the discrete case, the equations for the spatial covariances will depend on higher-order spatial moments and moment closure approximations can be used to reduce the dimensionality of the system (Dieckmann and Law, 2000; Murrell et al., 2004). Under weak selection, quasi-equilibrium approximations could also be used to make analytical progress by treating  $\bar{c}_{S'I'}/\bar{I}'$  as a fast variable, as the local densities  $q_{x/I'}$  in the discrete-space models. Although it appears that the additional mathematical complexity has so far limited the use of moment-based continuous-space models in evolutionary ecology, recent studies (e.g. North et al., 2011; Barraquand and Murrell 2012a, b) pave the way for a fruitful development of these techniques.

## 2.3. Events and dynamics

The state of the network will change according to various biological events. Depending on the life cycle, different events may

be considered, such as birth, death, infection, migration, and so on. Here, I will provide a general representation of the stochastic process in terms of creation and destruction events. For simplicity, I will only consider events that may change the state of only one site. This excludes in particular predation, migration (an event in which an individual moves to an empty site) but allows for dispersal (an event in which the offspring of a reproducing adult individual can disperse to an empty site). However, it is straightforward to extend the theory to pair events, at the expense of more notational clutter (see e.g. Rand, 1999; Van Baalen, 2000).

If the state of site  $i$  changes from  $a$  to  $b$ , the indicator variable  $a_i$  changes from 1 to 0, and  $b_i$  changes from 0 to 1. Accordingly, the state of the whole network changes from  $\sigma$  to  $\sigma + (b-a)\mathbf{e}_i$ , where  $\mathbf{e}_i$  is an  $N \times 1$  unit vector which has zeros everywhere except on the  $i$ th entry. The probability that such a transition occurs is

$$P(\sigma(t+\delta t) = \sigma(t) + (b-a)\mathbf{e}_i | \sigma(t)) = r_i^{a \rightarrow b}(\sigma)\delta t + O(\delta t^2),$$

where  $r_i^{a \rightarrow b}(\sigma)$  is the transition rate at site  $i$ .

Mathematically, those assumptions define a continuous-time Markov jump process  $\sigma_t$  on the (finite) state space  $\mathcal{S} = \Omega^N$ . The behaviour of the process is encapsulated by its infinitesimal generator (Liggett, 1985; Konno, 1997), which is defined for all bounded measurable functions on  $\mathcal{S}$  by

$$\mathcal{L}f(\sigma) = \sum_{i=1}^N \sum_{a,b \in \Omega} r_i^{a \rightarrow b}(\sigma) [f(\sigma + (b-a)\mathbf{e}_i) - f(\sigma)] \quad (1)$$

The summation is made over all possible transitions that can change the state of the network at site  $i$ . The generator thus measures the total change in the observable  $f$ , weighted by the rates at which each transition occurs.

The link between the dynamics of observables and the generator is through the backward Kolmogorov equation (Konno, 1997)

$$\frac{d\mathbb{E}_0[f(\sigma)]}{dt} = \mathbb{E}_0[\mathcal{L}f(\sigma)] \quad (2)$$

Here, the expectation of an observable  $f$  represents the ensemble mean, i.e., the expectation of  $f$  over all realisations of the process, conditional on the initial configuration of the system,  $\sigma_0$ . Later on, I shall drop the 0 subscript for the sake of simplicity. Given an initial configuration of the system, this allows us to compute the expected dynamics of all observables  $f(\sigma)$  of the system.

## 2.4. Moment equations

The expected change in the number of sites in state  $a$ ,  $[a]$ , can be deduced from 1 by using  $f(\sigma) = \mathbf{a}(\sigma)^T \cdot \mathbf{1}$ , which gives

$$\frac{d\mathbb{E}[a]}{dt} = \sum_{b \in \Omega} \left( \mathbb{E} \left[ \sum_{i=1}^N r_i^{b \rightarrow a}(\sigma) \right] - \mathbb{E} \left[ \sum_{i=1}^N r_i^{a \rightarrow b}(\sigma) \right] \right) \quad (3)$$

or, with the shorthand  $\langle \mathbf{g} \rangle = \mathbb{E} \left[ \sum_{i=1}^N g_i(\sigma) \right]$ ,

$$\frac{d\langle a \rangle}{dt} = \sum_{b \in \Omega} \left[ \langle r^{b \rightarrow a} \rangle - \langle r^{a \rightarrow b} \rangle \right] \quad (4)$$

In other words, for each possible event, the transition rates need to be averaged over all sites and all realisations of the process. The expected density of sites in state  $a$  changes according to the balance between creation events (which occur from state  $a$  at average rate  $\langle r^{b \rightarrow a} \rangle$ ) and destruction events (which produce sites in state  $a$  at average rate  $\langle r^{a \rightarrow b} \rangle$ ). Note that the notation  $\langle \cdot \rangle$  is used to denote the ensemble mean of a spatial average, while  $[\cdot]$  refers to the spatial average in a single realisation of the process.

In a similar fashion, we can derive dynamics for the densities of adjacent pairs of sites (see Appendix A.2). The resulting equation for  $ab$  pairs takes a similar form as Eq. (4), but the transition rates need to be

averaged over all connected pairs. Hence, differential equations for the expected values of various spatial configurations (e.g. singlets, pairs, triplets) can be systematically derived from Eq. (2). The derivation can even be automated using symbolic computation software such as Mathematica. Minus van Baalen wrote a package for spatial moment equations in discrete space (<http://www.roseaie.lautre.net/minus/corrdyn/packages/index.html>), and Ben Bolker wrote a similar package for continuous space (<http://ms.mcmaster.ca/bolker/meqs/emonk/index.html>). For a related discussion of the derivation of moment equations in continuous space, see Ovaskainen et al. (2014).

### 2.5. Example: the spatial SIS model

As an application, I shall consider the spatial SIS epidemiological model. Each site is a host that can be either susceptible ( $S$ ) or infected ( $I$ ). Infection to a neighbouring susceptible host occurs at rate  $\beta$ , while recovery occurs at rate  $\gamma$ . Hence, we have  $\Omega = \{S, I\}$  (or  $\{0, 1\}$ ). As shown in Appendix A.3, the dynamics of the expected number of infected hosts can be written as

$$\frac{d\langle I \rangle}{dt} = \beta \langle S : I \rangle - \gamma \langle I \rangle \quad (5)$$

where  $\langle S : I \rangle$  is the expected number of  $SI$  pairs.

Note that up to now, I have made no additional assumption about the spatial structure. Eq. (5) is exact and valid for any connectivity matrix  $\mathbf{J}$  and any network size  $N$ . However, the dynamics of  $\langle I \rangle$  depends on the dynamics of  $\langle S : I \rangle$ , which will in turn depends on the dynamics of triplets of sites, and so on (Appendix A.3). Hence, spatial moment equations provide us with an unclosed system of equations. In the literature, much effort has been put in trying to find good-quality closure formulae to close the system at the order of pairs (Sato et al., 1994; Rand, 1999; Van Baalen, 2000; Dieckmann and Law, 2000; Murrell et al., 2004). This enterprise has proven to be difficult at best. However, whereas moment closure approximations are required for quantitative accuracy, the same is not necessarily true if one is only interested in qualitative predictions. In fact, in my experience, starting the analysis by closing the system is usually a bad idea, and it is best to keep the use of moment closure approximations as a last resort. I shall come back to this point later on, when I discuss the topic of relatedness. With this in mind, I think spatial moment equations can provide us with an easy way to add “space” to well-understood non-spatial models, even when a full analytical solution to the spatial problem is beyond our grasp.

### 2.6. Large regular networks

Up to now, I have made no assumption on the size of the network, but typically, the spatial moment equations derived above are used as deterministic approximations of the process on a large network. This boils down to an assumption of spatial ergodicity: in an infinite network, one expects the ensemble and spatial averages to be interchangeable. Thus, on a sufficiently large network, a given realisation of the stochastic process can be expected to fluctuate along a deterministic trajectory predicted by the ensemble mean. Henceforth, I shall assume that spatial ergodicity holds and replace all ensemble means  $\langle \cdot \rangle$  by their spatial counterparts  $[\cdot]$ .

I will also add another assumption and consider that each site is connected to exactly  $n$  other sites. This defines a regular network ( $\sum_{j=1}^N J_{ij} = n$  for all  $i$ ). Virtually all published models in evolutionary ecology using pair approximation have been formalised on regular networks (but see e.g. Rand, 1999; Eames and Keeling, 2002; Keeling and Eames, 2005; Leventhal et al., 2015), and most use the following concepts of global and local densities. For a given state  $a$ , the global density of sites in state  $a$  is defined as

the fraction of sites in that state,

$$p_a = \frac{[a]}{N}.$$

Similarly, among all  $N \times n$  pairs of sites on the network, the fraction of pairs in state  $ab$  is denoted  $p_{ab}$  and defined as the global density of  $ab$  pairs,

$$p_{ab} = \frac{[a : b]}{Nn}$$

Global densities for triplets of sites,  $p_{abc}$  can also be defined.

From global densities, one also defines the local densities of sites,  $q_{a/b}$  and  $q_{a/bc}$

$$q_{a/b} = \frac{p_{ab}}{p_b} = \frac{[a|b]}{n}$$

$$q_{a/bc} = \frac{p_{abc}}{p_{bc}} = \frac{[a|bc]}{n-1}$$

In words,  $q_{a/b}$  is the average proportion of  $a$  sites in the neighbourhood of a site in state  $b$ . Similarly,  $q_{a/bc}$  is the average proportion of  $a$  sites in the neighbourhood of a site in state  $b$  that is connected to a site in state  $c$ . The  $n-1$  in the definition of  $q_{a/bc}$  comes from the fact that there are  $Nn(n-1)$  triplets in total on a regular network, and will appear in the equations of pairs through the variables

$$\phi = \frac{1}{n}$$

$$\bar{\phi} = 1 - \phi = \frac{n-1}{n}$$

Equipped with these notations, Eq. (5) can be rewritten on a large regular network as

$$\frac{dp_I}{dt} = (\beta q_{S/I} - \gamma) p_I, \quad (6)$$

where, for simplicity, the transmission rate  $\beta$  as been rescaled as  $n\beta$  (in other words, it is now a per-capita rate and not a per-contact rate). The non-spatial counterpart of this equation is

$$\frac{dp_I}{dt} = (\beta p_S - \gamma) p_I \quad (7)$$

The only difference between the spatial and non-spatial equations is that the global density of susceptible hosts,  $p_S$ , is replaced by the local density,  $q_{S/I}$ . More generally, in a well-mixed population, local and global densities should converge to the same value ( $q_{a/b} \approx p_a$  and  $q_{a/bc} \approx p_a$ ). This corresponds to what is generally called the mean-field approximation in biology. The pair approximation goes one step further by positing  $q_{a/bc} \approx q_{a/b}$ . Thus, it takes into account some information about the neighbourhood of a focal site, but ignores the possibility of “loops” on the network, i.e. the fact that  $a$  and  $c$  may still be indirectly connected because of network clustering. Pair approximation therefore tends to perform reasonably well on random networks, but poorly on lattices or small-world networks with non-zero clustering coefficient, for which improved pair approximations have been developed (Sato et al., 1994; Rand, 1999; Van Baalen, 2000).

Finally, I note that, in the SIS model, the dynamics of the susceptible class is directly obtained from the dynamics of the infected class because of the conservation relationship  $p_S + p_I = 1$ . Similar conservation equations hold for local and pair densities (e.g.  $q_{S/I} + q_{I/I} = 1$ ). I refer the reader to Rand (1999) and Van Baalen (2000) for other treatments of the derivation of spatial moment equations on regular and irregular networks.



### 3. Evolutionary dynamics

The previous section has provided a stochastic underpinning to the derivation of spatial moment equations in ecology. In the limit of a large network size, these spatial moment equations provide a deterministic approximation of the underlying stochastic individual-based process. In principle, if we were to write down the equations for the dynamics of all moments of the spatial distribution, we would know everything about the dynamics of the system.

Adding evolution to a spatial ecological model requires us to add states to  $\Omega$  (one or more mutants), and possibly mutation events. But all this does not alter the generality of the above framework. Following an approach pioneered by Van Baalen and Rand (1998), I will now show that we can use the dynamics of spatial moments to compute the invasion fitness of a rare mutant and the selection gradient (Metz et al., 1992; Geritz et al., 1998). I will use the example of parasite evolution in the spatial SIS model to illustrate this approach.

#### 3.1. Invasion fitness: global densities

I now consider that hosts may be infected by two strains of parasites. Hosts infected by the resident parasite ( $I$ ) recover at rate  $\gamma$  and transmit the disease at rate  $\beta$ . Hosts infected by the mutant parasite ( $I'$ ) have epidemiological parameters  $\gamma'$  and  $\beta'$ . The dynamics of infected hosts is then

$$\begin{aligned}\frac{dp_I}{dt} &= (\beta q_{S/I} - \gamma)p_I = \lambda p_I \\ \frac{dp_{I'}}{dt} &= (\beta' q_{S/I'} - \gamma')p_{I'} = \lambda' p_{I'}\end{aligned}$$

From these equations, we can deduce the change in the frequency of mutant parasites,  $f = p_{I'}/(p_I + p_{I'})$ , which is

$$\frac{df}{dt} = f(1-f)(\lambda' - \lambda) \quad (8)$$

If the mutant is rare and the resident population is at equilibrium ( $\lambda = 0$ ), the invasion fitness (Metz et al., 1992; Geritz et al., 1998) is simply given by the per-capita growth rate

$$\lambda' = \beta' q_{S/I'} - \gamma'. \quad (9)$$

A rare mutant will invade the resident population at equilibrium if  $\lambda' > 0$ . Furthermore, at equilibrium, the condition  $\lambda = 0$  implies that

$$\hat{q}_{S/I} = \frac{\gamma}{\beta}. \quad (10)$$

In a resident population at equilibrium, the local density of susceptible hosts is simply given by the ratio of recovery and transmission rates. In a well-mixed population, an analogous relationship holds true for the global density of susceptible hosts in the population.

In contrast with well-mixed populations, however, mutant parasites will typically not experience the same density of susceptible hosts as resident parasites ( $q_{S/I'} \neq q_{S/I}$ ). This difference in the local amount of resources introduces an additional selective pressure in space. In the remainder of this section, I will show how analytical expressions for this new selective force can be derived from spatial moment equations.

#### 3.2. Invasion fitness: pairs

Pair dynamics provide an alternative derivation of the invasion fitness. Consider the vector  $\mathbf{p}$  that collects the densities of the pairs

$xI'$ , where  $x \in \Omega$ . Hence

$$\mathbf{p} = \begin{pmatrix} p_{SI'} \\ p_{II'} \\ p_{I'I'} \end{pmatrix} \quad (11)$$

From the pair dynamics, we can write the dynamics of  $\mathbf{p}$  in matrix form (Appendix A.4)

$$\frac{d\mathbf{p}}{dt} = \mathbf{A}(\mathbf{Q})\mathbf{p} \quad (12)$$

where the dependency on  $\mathbf{Q}$  indicates that the matrix  $\mathbf{A}$  depends on local densities  $q_{S/I}$ ,  $q_{I/I}$ ,  $q_{I'/I'}$  and also on some triple densities  $q_{S/SI'}$ ,  $q_{I'/SI'}$ , etc.

If the mutant is rare or selection is weak, it can be shown that the vector of local densities  $\mathbf{Q}$  reaches a quasi-equilibrium on a fast time scale. Then,  $\mathbf{A}$  can be approximated by a constant matrix  $\bar{\mathbf{A}}$ , and classical theory for class-structured populations (Taylor, 1990; Charlesworth, 1994; Caswell, 2001) allows us to compute the invasion fitness as the dominant eigenvalue of  $\bar{\mathbf{A}}$ .

#### 3.3. Separation of time scales: quasi-equilibrium assumption

Early on in the development of spatial moment equations, it has been noted that local densities tend to equilibrate on a fast time scale compared to global densities (Matsuda et al., 1992; Van Baalen and Rand, 1998; Dieckmann and Law, 2000; Ferrière and Le Galliard, 2001). To understand why, let us consider the vector  $\mathbf{q} = (q_{S/I} \quad q_{I/I} \quad q_{I'/I'})^T$ . From the definition of local densities, we have  $\mathbf{q} = \mathbf{p}/p_I$ , which allows us to write the dynamics of  $\mathbf{q}$  as

$$\frac{d\mathbf{q}}{dt} = \mathbf{A}\mathbf{q} - \lambda'\mathbf{q} \quad (13)$$

Coupled with equation

$$\frac{dp_{I'}}{dt} = \lambda' p_{I'}, \quad (14)$$

this gives another way of writing the system (12). Assuming that selection is weak, as we did previously, the system becomes

$$\begin{aligned}\frac{dp_{I'}}{dt} &= \epsilon \partial \lambda' p_{I'} + O(\epsilon^2) \\ \frac{d\mathbf{q}}{dt} &= (\bar{\mathbf{A}} + \epsilon \partial \mathbf{A})\mathbf{q} - \epsilon \partial \lambda' \mathbf{q} + O(\epsilon^2)\end{aligned} \quad (15)$$

where  $\bar{\mathbf{A}}$  is computed in the neutral model ( $\epsilon = 0$ ) and  $\partial \mathbf{A}$  is the first-order effect of selection of the matrix of pair transitions. It follows that the dynamics of  $p_{I'}$  is  $O(\epsilon)$  while the dynamics of  $\mathbf{q}$  is  $O(1)$ . Therefore, the global density of mutants is a slow variable under weak selection, whereas the local densities are fast variables.

Note that an analogous separation of time scales follows from assuming that the mutant is rare (as assumed for instance in Van Baalen and Rand, 1998; Ferrière and Le Galliard, 2001; Le Galliard et al., 2003), but the weak selection assumption is in general sufficient. However, the separation of time scales introduced by mutant rarity also allows the use of the quasi-equilibrium assumption, and justifies the use of the per-capita growth rate of rare mutants away from the diagonal in pairwise-invasibility plots typically used in adaptive dynamics (Geritz et al., 1998).

#### 3.4. Invasion fitness and selection gradient: quasi-equilibrium assumption

The quasi-equilibrium assumption implies that Eq. (13) can be set to zero. Hence

$$\tilde{\mathbf{A}}\tilde{\mathbf{q}} = \lambda'\tilde{\mathbf{q}} \quad (16)$$

where the tilde notation indicates quasi-equilibrium values. The latter equation shows, as expected, that the invasion fitness is the

dominant eigenvalue of the quasi-equilibrium matrix  $\tilde{\mathbf{A}}$ , with associated right eigenvector  $\tilde{\mathbf{q}}$ . A standard perturbation analysis leads to

$$\lambda' = \epsilon \frac{\bar{\mathbf{v}} \partial \tilde{\mathbf{A}} \bar{\mathbf{q}}}{\bar{\mathbf{v}} \bar{\mathbf{q}}} + O(\epsilon^2) \quad (17)$$

and we can compute the selection gradient as a function of matrix  $\partial \tilde{\mathbf{A}}$ , which gives the first-order effect of selection on the matrix of pair transitions, and of the right and left leading eigenvectors computed in the neutral model,  $\bar{\mathbf{q}}$  and  $\bar{\mathbf{v}}$ .

### 3.5. Genetic and demographic structure

#### 3.5.1. Right eigenvector: asymptotic local structure

As noted by Van Baalen and Rand (1998), the right eigenvector  $\bar{\mathbf{q}}$  can be thought of as a description of the local structure of the invading cluster of mutants after initial transient dynamics have decayed. For the SIS model, this vector can be written as follows:

$$\bar{\mathbf{q}} = \begin{pmatrix} \bar{q}_{S/I} \\ \bar{q}_{I/I} \\ \bar{q}_{I/S} \end{pmatrix} \quad (18)$$

In general, the local densities depend on both genetic and demographic structure. However, in the neutral model, we can decouple the two to a certain extent. A neutral mutant parasite will experience the same density of susceptible hosts as a resident parasite, hence  $\bar{q}_{S/I} = \hat{q}_{S/I}$ , the equilibrium local density of susceptible hosts experienced by an average infected host in a monomorphic population. Furthermore, the total density of infected hosts experienced by a neutral mutant parasite is equal to the local density of infected hosts experienced by an average infected host at equilibrium, and therefore  $\bar{q}_{I/I} + \bar{q}_{I/S} = \hat{q}_{I/I}$ . Following Lion (2009) and Lion and Gandon (2009, 2010), I introduce the following notation:

$$r = \frac{\bar{q}_{I/S}}{\hat{q}_{I/I}} \quad (19)$$

Then,  $\bar{\mathbf{q}}$  can be rewritten as

$$\bar{\mathbf{q}} = \begin{pmatrix} \hat{q}_{S/I} \\ \hat{q}_{I/I}(1-r) \\ \hat{q}_{I/I}r \end{pmatrix} \quad (20)$$

The latter equation allows us to express the right eigenvector as a function of demographic measures ( $\hat{q}_{S/I}$ ,  $\hat{q}_{I/I}$ ) which depend only on the location of individuals, and of genetic measures ( $r$ ) that depends on the location of alleles. For the SIS model, we further have  $\hat{q}_{S/I} = 1 - \hat{q}_{I/I} = \gamma/\beta$  (Eq. (10)).

More precisely,  $r$  is a measure of relatedness between parasites among pairs of hosts (Van Baalen and Rand, 1998; Lion and van Baalen, 2008; Lion, 2009; Lion and Gandon, 2009), and is identical to other measures of identity in state used in population genetics (Rousset, 2004; Lion, 2009). This provides the connection between ecological models based on spatial moment equations, and inclusive fitness theory. In both cases, weak selection ensures that the selection gradient can be written as a function of reproductive values, neutral measures of genetic structure (relatednesses), and first-order effects of selection on fitness (Taylor and Frank, 1996; Rousset and Billiard, 2000; Rousset, 2004; Taylor et al., 2007b).

#### 3.5.2. Left eigenvector: reproductive values

The vector of reproductive values collects the individual reproductive values of a mutant parasite in each of the various pairs. In the neutral model, we can compute them as the left eigenvector of the matrix  $\tilde{\mathbf{A}}$  associated with the eigenvalue 0. For

the SIS model, this gives

$$\bar{\mathbf{v}} = (2 \quad 1 \quad 1)$$

This result can be understood intuitively as follows. In the neutral model,  $v_{II} = v_{IS} = v_{\bullet\bullet}$ , where  $\bullet$  denotes any infected site. Consider a pair of infected sites in the neutral model. We want to express the reproductive value of a parasite in such a pair as a function of the reproductive value of a parasite which has a  $S$  neighbour. The reproductive value of a parasite in one of the infected individual of a  $\bullet\bullet$  pair is

$$\frac{1}{2} \times (\text{the amount of time spent as } \bullet\bullet) \times (\text{the rate of production of new } \bullet S \text{ pairs}) \times v_{\bullet S}$$

For the SIS model, the average duration of a  $\bullet\bullet$  pair is  $1/\gamma$ , while the rate of production of new  $\bullet S$  pairs is  $\gamma$ . Hence, we have

$$v_{\bullet\bullet} = \frac{1}{2} v_{\bullet S}$$

This is a particularly simple result, but for other life cycles, the vector of reproductive values may take more complex expressions (Lion and Boots, 2010).

### 3.6. Spatial moment expansion of selective pressures

The next step of our approach is to expand the matrix  $\partial \tilde{\mathbf{A}}$  to decouple selective effects on second-order local densities ( $\partial q_{x/y}$ ) from selective effects on third-order local densities ( $\partial q_{x/yz}$ ). To understand how we can do that, I shall again focus on the SIS model.

As shown in Appendix A.4, the matrix  $\mathbf{A}$  takes the following form:

$$\mathbf{A} = \begin{pmatrix} -\beta'(\phi + \bar{\phi} q_{I/SI} - \bar{\phi} q_{S/SI}) - \beta \bar{\phi} q_{I/SI} - \gamma' & \gamma & \gamma' \\ (\beta + \beta') \bar{\phi} q_{I/SI} & -\gamma - \gamma' & 0 \\ 2\beta'(\phi + \bar{\phi} q_{I/SI}) & 0 & -2\gamma' \end{pmatrix} \quad (21)$$

Note that I have dropped the “tilde” notation for convenience. It follows that the matrix  $\partial \mathbf{A}$  giving the first-order effect of selection on pair transitions can be split into two components. The first matrix contains the perturbed terms up to the order of pairs

$$\partial \mathbf{A}_1 \equiv \begin{pmatrix} -\partial\beta(\phi + \bar{\phi} q_{I/SI} - \bar{\phi} q_{S/SI}) - \partial\gamma & 0 & \partial\gamma \\ \partial\beta' \bar{\phi} q_{I/SI} & -\partial\gamma & 0 \\ 2\partial\beta(\phi + \bar{\phi} q_{I/SI}) & 0 & -2\partial\gamma \end{pmatrix} \quad (22)$$

and the second matrix contains the perturbed terms of higher-order

$$\partial \mathbf{A}_2 \equiv \begin{pmatrix} -\bar{\phi} \beta (\partial q_{I/SI} + \partial q_{I/SI} - \partial q_{S/SI}) & 0 & 0 \\ 2\bar{\phi} \beta \partial q_{I/SI} & 0 & 0 \\ 2\bar{\phi} \beta \partial q_{I/SI} & 0 & 0 \end{pmatrix} \quad (23)$$

The decomposition  $\partial \mathbf{A} = \partial \mathbf{A}_1 + \partial \mathbf{A}_2$  is exact in the sense that no moment closure approximation is needed. This flows directly from the weak selection approximation.

Now, using the expressions for  $\bar{\mathbf{v}}$  and  $\bar{\mathbf{q}}$ , some algebra allows us to rewrite Eq. (18) as

$$\lambda' = \epsilon \left( \frac{\bar{\mathbf{v}} \partial \mathbf{A}_1 \bar{\mathbf{q}}}{\bar{\mathbf{v}} \bar{\mathbf{q}}} + \bar{\phi} \beta \frac{2\hat{q}_{S/I}}{\bar{\mathbf{v}} \bar{\mathbf{q}}} \partial q_{S/SI} \right) + O(\epsilon^2) \quad (24)$$

In words, we have decoupled  $\lambda'$  into a first-order spatial component and a term that collects all higher-order spatial selective pressures.

For the SIS model, the first-order spatial component of the selection gradient can be computed exactly. Indeed, the expression of  $\partial \mathbf{A}_1$  depends on the triple local densities  $q_{S/S'}$ ,  $q_{I/S'}$  and  $q_{I'/S}$  evaluated in the neutral model at equilibrium. In the neutral model, we have  $\bar{\mathbf{A}}\bar{\mathbf{q}} = \mathbf{0}$ , which can be rewritten as the system

$$\bar{\phi}\bar{q}_{S/S'} = \bar{q}_{S/I'} \quad (25)$$

$$\bar{\phi}\bar{q}_{I/S'} = \bar{q}_{I/I'} \quad (26)$$

$$\phi + \bar{\phi}\bar{q}_{I'/S} = \bar{q}_{I'/I'} \quad (27)$$

Using these relationships between second-order and third-order measures of genetic and demographic structure, we can write Eq. (24) as follows (Appendix A.5)

$$\lambda' = \epsilon \left[ \left( 1 - r \frac{1 - \hat{q}_{S/I}}{1 + \hat{q}_{S/I}} \right) S_0 + \bar{\phi} \beta \frac{2\hat{q}_{S/I}}{1 + \hat{q}_{S/I}} \partial q_{S/S'} \right] + O(\epsilon^2) \quad (28)$$

where  $\hat{q}_{S/I} = \gamma/\beta$  and

$$S_0 = \hat{q}_{S/I} \partial \beta - \partial \gamma = \frac{\gamma}{\beta} \partial \beta - \partial \gamma \quad (29)$$

is the selection gradient in the non-spatial model.

### 3.7. Moment closure approximations

Up to now, we have not used any approximation of the spatial structure. Provided the network is large enough and mutation is weak, Eq. (28) is an exact computation giving the direction of selection. However, Eq. (28) still contains two unknowns, which are the relatedness,  $r$ , and the selective pressure due to triple correlations,  $\partial q_{S/S'}$ . Moment closure approximations can be used to make further progress.

#### 3.7.1. Approximating the selective effect of higher-order correlations

On a random regular network, the local densities are generally well approximated by the ordinary pair approximation,  $q_{x/yz} \approx q_{x/y}$  (Matsuda et al., 1992; Rand, 1999; Van Baalen, 2000). Using this moment closure, we obtain

$$q_{S/S'} \approx q_{S/S} \quad (30)$$

and as a consequence the impact of the mutant trait on the local density  $q_{S/S'}$  can be neglected. We thus have  $\partial q_{S/S'} \approx 0$ .

However, ordinary pair approximation does not take into account network clustering, as typically encountered on square or triangular lattices. To deal with this limitation, Morris (1997), Rand (1999), and Van Baalen (2000) introduced an improved pair approximation for clustered networks. Let  $\theta$  be the global clustering coefficient of the network (the probability of finding a triplet in closed form). The improved pair approximation gives the following estimate for  $q_{S/S'}$

$$q_{S/S'} \approx q_{S/S} \left( 1 - \theta + \theta \frac{q_{S/I}}{p_S} \right). \quad (31)$$

Note that the ordinary pair approximation is recovered for  $\theta = 0$  (no clustering).

This improved approximation yields

$$\partial q_{S/S'} \approx \theta \frac{q_{S/S}}{p_S} \partial q_{S/I'}. \quad (32)$$

Plugging this relationship into Eq. (28), I show in Appendix A.5 that this yields the following expression for the selection gradient

on a clustered network

$$\lambda' = \epsilon \left( \frac{1 - r \frac{1 - \hat{q}_{S/I}}{1 + \hat{q}_{S/I}} - \theta C}{1 - \theta C} \right) S_0 + O(\epsilon^2) \quad (33)$$

where

$$C = \bar{\phi} \frac{2\hat{q}_{S/I}}{1 + \hat{q}_{S/I}} \frac{\hat{q}_{S/S}}{p_S}$$

denotes the effect of clustering.

Three key lessons can be drawn from the latter equation:

1. Potential evolutionary endpoints are obtained by setting  $S_0 = \hat{q}_{S/I} \partial \beta - \partial \gamma$  to zero. Because  $\hat{q}_{S/I} = \gamma/\beta$ , spatial structure has no effect on the evolutionarily stable strategy of the parasite, which is given by the marginal value theorem  $\partial \beta/\beta = \partial \gamma/\gamma$ , as in a well-mixed population.
2. Genetic structure ( $r$ ) only affects the rate of evolution; a higher relatedness slows down the speed at which the evolutionary attractor is reached.
3. Similarly, network clustering does not seem to affect the evolutionary endpoint, but only the rate of evolution.

These predictions are borne out by stochastic simulations on random networks ( $\theta = 0$ ) and square lattices (Lion, 2010; Lion and Boots, 2010). It is important to note, however, that, for other life cycles, the evolutionary endpoint is generically affected by spatial structure, relatedness and network clustering (see e.g. Lion and Boots, 2010 for an application of the present method to the SIRS and SI models).

#### 3.7.2. Approximating relatedness

If quantitative results are needed, relatedness can be computed from the neutral model at equilibrium. Unfortunately, unlike in models with constant population size where exact results and methods are available for computing neutral measures of relatedness (reviewed in Rousset, 2004), no such results are currently available for the SIS model. Lion (2009) gives two approximations of relatedness in the SIS model (a pair approximation, which underestimates the true value of relatedness, and a triple approximation, which is more accurate). The pair approximation can be obtained directly from Eq. (27) by setting  $q_{I'/S}$  to zero, and yields  $r = \phi/(1 - \gamma/\beta)$ . However, it is important to note that Eq. (27) is only the starting point of an infinite recursion linking neutral measures of relatedness between individuals at different distances. Again, this is analogous to the recursion derived in population genetics to compute measures of genetic identities. Using pair approximation amounts to breaking this recursion at second-order. This introduces a bias that a triple approximation is in part able to reduce (Lion, 2009).

#### 3.7.3. The pros and cons of moment closure approximations

Although moment closure approximations are unavoidable, there is some danger in using them as a starting point of the analysis. After using the ordinary pair approximation directly in  $\partial \mathbf{A}_1$ , for instance, the resulting matrix only depends on measures of demographic structure  $q_{S/S}$  and  $q_{I/S}$ , and the impact of genetic structure is apparently lost. This is due to the combination of mutant rarity and pair approximation. The correct way to handle this is to first use the equilibrium relationships (25)–(27), which are true for any network structure and any frequency of the mutant. Apparent discrepancies between various published results for the evolution of altruism have been shown to directly flow

from a misuse of pair approximation (see Lion and Gandon, 2009 for a discussion).

A general limitation of moment closure approximations for invasion analyses is that their accuracy tends to decrease near neutrality (Murrell et al., 2004; Lion and Gandon, 2009; Lion, 2009). This is the main reason why pair approximation performs so badly when estimating neutral coefficients of relatedness, even on random networks (Lion, 2009). This has led to the suggestion that the invasion fitness of a mutant under neutrality can serve as a good test of what constitutes a 'good' moment closure method (Murrell et al., 2004). Further work is needed to improve the accuracy of moment closure approximations in both discrete- and continuous-space models.

### 3.8. Conclusion

The SIS model forms a baseline model for studying the evolution of parasite traits. The technique briefly described in this chapter can be used to explore more complex life cycles, at the price of greater analytical developments. Mostly, this is an exercise in bookkeeping and matrix algebra, although in general, a closed solution (as in the SIS model) is beyond our reach. Nonetheless, this approach may be used to obtain analytical expressions that, although not fully solvable, yield qualitative insight into the effect of spatial structure on the evolution of various life-history traits (see e.g. Lion and Boots, 2010 for other host-parasite life cycles).

## 4. Discussion

### 4.1. Feedback loop between spatial ecology and evolution

Central to the recent progress of evolutionary ecology is the recognition that selective pressures are shaped by ecological conditions (e.g. population and environmental dynamics), and that the evolution of traits in turn affects ecology through effects on population density or resource availability. This feedback loop between ecology and evolution requires us to adopt an ecological definition of fitness (Metz et al., 1992; Metz, 2008). In general, fitness will be a property of a given type in a given environment, where the environment is defined from a strictly individually-centred perspective. The environment collects all the relevant information necessary to compute the reproduction and survival of individuals. This includes any effects external to the focal population, and any direct effects of conspecifics. We may write fitness as  $r_i(\mathbf{E})$ , where  $i$  the focal (geno- or pheno-) type and  $\mathbf{E}$  is a vector describing the environment.

In spatially structured populations, the feedback loop between ecological dynamics and evolution may be taken into account in two ways. First, one may describe spatial structure as a form of class structure, for instance by tracking the densities of demes with different compositions (Metz and Gyllenberg, 2001; Ajar, 2003; Rousset, 2004; Rousset and Ronce, 2004). Alternatively, one may only use class structure to describe differences between individual of a given type that are unrelated to their spatial location, and take spatial structure into account only through the environmental variable  $\mathbf{E}$ . This is the approach I outline in this review. By so doing, we obtain analytical expressions that retain only the key ecological aspects of spatial structuring (e.g.  $q_{S/I}$  in the SIS model) and can be directly compared with the corresponding non-spatial expressions. This provides theoreticians with a simple and direct way to "add space" to a well-understood non-spatial model, thereby shedding light onto how spatial structuring shapes the feedback loop between ecology and evolution.

### 4.2. Decoupling genetic and ecological structuring

Spatially structured populations are structured at different levels, which feed back on the evolution of traits. Spatial genetic structuring describes the spatial distribution of alleles. In spatially structured populations, mutant alleles are locally abundant, even when they are globally rare, and this is a key departure from what happens in well-mixed populations. Tracking the dynamics of spatial genetic structure has long been a cornerstone of spatial population genetics (Wright, 1943; Kimura, 1953; Malécot, 1975; Rousset, 2004).

However, the selective pressures at work in natural populations will generally be shaped by the interplay between genetic structuring (the spatial distribution of alleles) and demographic structuring (the spatial distribution of individuals) (Lion and Boots, 2010; Lion et al., 2011). In general, the joint action of the two structuring processes will be difficult to tease apart, as it is quite clear that genetic structuring will be influenced by demographic structuring.

Most population genetics models solve this conundrum by positing that population size is constant (but see Rousset and Ronce, 2004; Lehmann et al., 2006), thereby neglecting the role of demographic structuring. This allows theoreticians to focus on spatial genetic structuring only, but also neglects the feedback between population dynamics and selection. The approach I present in this paper uses a weak selection argument to effectively decouple the effects of genetic and demographic structuring in the neutral process. An interesting application is to investigate the impact of different levels of habitat saturation and epidemiological dynamics on the evolution of traits (Lion and Gandon, 2009, 2010; Lion and Boots, 2010).

### 4.3. The link with inclusive fitness theory

There is a striking analogy with inclusive fitness techniques used to analyse evolution in spatially subdivided populations (Rousset and Billiard, 2000; Rousset, 2004; Taylor et al., 2007a,b). This is not surprising because both techniques use similar approximations of the mutation process. In practice, the core of inclusive fitness theory (deriving the selection gradient as a function of spatial measures of genetic structure in the neutral process) matches exactly the approach we have described. Both methods are also faced with the difficult task of computing those neutral measures of relatedness from the dynamics of the neutral process. For models with demography, exact numerical solutions exist for the infinite island model (Rousset and Ronce, 2004; Alizon and Taylor, 2008), but not for other models of spatial structure. Moment closure approximations provide an alternative path to computing approximations for these neutral measures of genetic structure (Lion, 2009), but the scope of this approach is for the moment limited to nearest-neighbour relatedness and to simple spatial structure (such as random regular networks). Potential extensions could build on other formalisms incorporating more complex dispersal kernels on networks (Ellner, 2001; Filipe and Maule, 2003) and in continuous space (Bolker and Pacala, 1997; Dieckmann and Law, 2000; Robledo-Arnuncio and Rousset, 2010).

Nonetheless, spatial moment equations provide an alternative route to the key insight of inclusive fitness theory that selection depends both on direct and indirect fitness effects, and that indirect fitness effects should be weighted by measures of genetic similarity. Because limited dispersal tends to produce genetic correlations between individuals, it is not surprising that spatial moment equations lead to expressions for the selection gradient that depend on measures of relatedness. For evolutionary ecologists unfamiliar with the population genetics literature on



inclusive fitness, this provides perhaps a more intuitive way of understanding how relatedness (or other measures of genetic structure) arises from spatial ecological dynamics.

#### 4.4. Biological applications: limitations and perspectives

Although I have focused on a simple biological model to illustrate the inner workings of the method, the approach described here is more general and applies to any life cycle where events only change the state of one site. In particular, the analysis described above can be extended to account for a mixture of local and global dispersal (Boots and Sasaki, 2000; Lion and Boots, 2010). With some additions, it can also be extended to events that change the state of two sites at the same time, such as migration. However, as life cycles become more complex, so does the dimensionality of the matrix needed to represent mutant dynamics. This typically hampers progress for many biological scenarios of interest. Nonetheless, spatial moment equations have been used to tackle a variety of biological questions. These include the evolution of helping behaviours (Van Baalen and Rand, 1998; Le Galliard et al., 2003, 2005; Ohtsuki et al., 2006; Lion and Gandon, 2009, 2010), parasite traits (Boots and Sasaki, 1999, 2000; Kamo and Boots, 2006; Kamo et al., 2007; Lion and Boots, 2010; Messinger and Ostling, 2013; Webb et al., 2013), host defence strategies (Brown and Hastings, 2003; Best et al., 2011; Débarre et al., 2012), and dispersal (Harada, 1999; Le Galliard et al., 2005; Kamo and Boots, 2006; Lion et al., 2006).

To date, the applicability of the method is bounded by three main limitations. First, analytical simplifications are less straightforward when the focal population is structured in discrete classes (e.g. juveniles and adults, treated and naive hosts). Although analytical expressions for the selection gradient can be obtained (Lion and van Baalen, 2007; Débarre et al., 2012; Zurita-Gutiérrez and Lion, 2015), they depend on unknown variables that cannot be easily expressed in terms of measures of genetic or demographic structure, mostly because of the increased dimensionality of the system. This calls for further work.

Second, the approach I have presented focuses on convergence stability and yields prediction on the direction of selection and on evolutionary singularities, but not on the stability of these singularities (Geritz et al., 1998). To determine whether the singularity corresponds to an ESS or a branching point, for instance, one needs to compute the second-order effects of selection on invasion fitness, which typically requires us to compute relatedness coefficients between three individuals, as well as potential effects of selection on genetic structure (i.e., neutral measures of relatedness are not sufficient, Ajar, 2003). This area has been largely untouched, as researchers typically rely on numerical integration or stochastic simulations to check the stability of potential evolutionary endpoints.

Third, the accuracy and usefulness of pair approximations remain open problems. The method I described in this paper relies on measures of genetic and demographic structure computed at neutrality, but pair approximation tends to perform badly in a neutral model (Lion, 2009). When quantitative accuracy is sought, this has motivated the use of a mixed approximation, where third-order spatial selective effects are neglected, but relatedness is computed using a triple approximation in the neutral model (Lion and Gandon, 2009). However, there is no guarantee that third-order spatial selective effects are always negligible. For instance, in the absence of a trade-off between transmission and virulence, selection for intermediate transmissibility can only be observed on networks with sufficient degrees of clustering (Haraguchi and Sasaki, 2000; Lion and Boots, 2010).

This has led to the observation that the use of pair approximation and other moment closure schemes is more an art than a science (Bolker, 2004; Ovaskainen et al., 2014). Because moment closure is

inevitable in spatial models, what is needed is a less heuristic and more rigorous method to reduce the dimensionality of the system. Recently, an alternative approach has been proposed that aims at writing a perturbation expansion of spatial moment equations in terms of a small parameter  $1/L$ , where  $L$  is the characteristic length of the dispersal kernel (Ovaskainen and Cornell, 2006; Cornell and Ovaskainen, 2008; Ovaskainen et al., 2014). Although applications to evolution have been limited so far (but see North et al., 2011; Barraquand and Murrell, 2012a,b), this looks like a promising avenue for research. A further benefit of this approach is that it can be applied to continuous-space models, thus paving the way for a fruitful interaction between theoretical models, field data and the statistical theory of spatial point processes. Although, up to now, theoretical studies of evolution in spatially structured populations have mainly been applied to discrete space models, extensions to continuous space would be a welcome addition to the literature.

#### 4.5. Conclusion

Modelling approaches in evolutionary ecology all have their strengths and limitations, but most importantly, they all rely on some biological and mathematical assumptions that it is important to present explicitly. I have tried to clarify the assumptions and limitations used in analyses based on spatial moment equations by showing how this framework fits more broadly within evolutionary game theory and adaptive dynamics. The links with related approaches such as inclusive fitness theory and population genetics have been highlighted. My main message is that spatial moment equations (especially pair models) should be viewed as alternative spatial models, and not merely as approximations of “real” spatial models. More than 20 years after their introduction to spatial ecology, I think that, despite their limitations, spatial moment equations are mature enough to be envisioned as a credible alternative modelling approach to non-spatial evolutionary models, and as a fruitful technique with which to unravel the tangled feedback loop between spatial ecology and evolution.

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#### Appendix A. Derivation of moment equations

##### A.1. Singlet equations

Our aim is to evaluate the expression for the generator (1) for the function  $f(\sigma) = \sum_k c_k(\sigma)$ . Noting that

$$c_k(\sigma + (b-a)\mathbf{e}_i) = c_k(\sigma) + (\delta_{cb} - \delta_{ca})\delta_{ik},$$

where  $\delta_{ij}$  is Kronecker's symbol, Eq. (1) can be rewritten as

$$\mathcal{L}f(\sigma) = \sum_{i=1}^N \sum_{a,b \in \Omega} r_i^{a \rightarrow b} (\delta_{cb} - \delta_{ca}) = \sum_{a \in \Omega} \left( \sum_{i=1}^N r_i^{a \rightarrow c} - \sum_{i=1}^N r_i^{c \rightarrow a} \right).$$

Taking the expectation over the RHS and plugging into Eq. (2), we obtain

$$\frac{d\langle c \rangle}{dt} = \sum_{a \in \Omega} (\langle r^{a \rightarrow c} \rangle - \langle r^{c \rightarrow a} \rangle). \quad (\text{A.1})$$

A.2. Pair equations

We now turn to the dynamics of the densities of the densities of *cd* pairs, using the function  $f(\sigma) = \mathbf{c}^T \mathbf{J} \mathbf{d}$ . We have

$$\begin{aligned} f(\sigma + (b-a)\mathbf{e}_i) &= \sum_{j=1}^N \sum_{k=1}^N J_{jk} c_j (\sigma + (b-a)\mathbf{e}_i) d_k (\sigma + (b-a)\mathbf{e}_i) \\ &= \sum_{j=1}^N \sum_{k=1}^N J_{jk} [c_j(\sigma) + (\delta_{cb} - \delta_{ca})\delta_{ij}] [d_k(\sigma) + (\delta_{db} - \delta_{da})\delta_{ik}] \\ &= f(\sigma) + \sum_{j=1}^N \sum_{k=1}^N J_{jk} (\delta_{cb} - \delta_{ca}) \delta_{ij} d_k(\sigma) + \sum_{j=1}^N \sum_{k=1}^N J_{jk} c_j(\sigma) (\delta_{db} - \delta_{da}) \delta_{ik}. \end{aligned}$$

Plugging the result into Eq. (1), we obtain

$$\begin{aligned} \mathcal{L}f(\sigma) &= \sum_{i=1}^N \sum_{a,b \in \Omega} r_i^{a \rightarrow b} \left[ \sum_{j=1}^N \sum_{k=1}^N J_{jk} (\delta_{cb} - \delta_{ca}) \delta_{ij} d_k(\sigma) \right. \\ &\quad \left. + \sum_{j=1}^N \sum_{k=1}^N J_{jk} c_j(\sigma) (\delta_{db} - \delta_{da}) \delta_{ik} \right] \\ &= \sum_{a,b \in \Omega} \left[ \sum_{j=1}^N \sum_{k=1}^N J_{jk} r_j^{a \rightarrow b} (\delta_{cb} - \delta_{ca}) d_k(\sigma) \right. \\ &\quad \left. + \sum_{j=1}^N \sum_{k=1}^N J_{jk} r_k^{a \rightarrow b} c_j(\sigma) (\delta_{db} - \delta_{da}) \right] \\ &= \sum_{a \in \Omega} \sum_{j=1}^N \sum_{k=1}^N J_{jk} r_j^{a \rightarrow c} d_k(\sigma) - \sum_{b \in \Omega} \sum_{j=1}^N \sum_{k=1}^N J_{jk} r_j^{c \rightarrow b} d_k(\sigma) \\ &\quad + \sum_{a \in \Omega} \sum_{j=1}^N \sum_{k=1}^N J_{jk} r_k^{a \rightarrow d} c_j(\sigma) - \sum_{b \in \Omega} \sum_{j=1}^N \sum_{k=1}^N J_{jk} r_k^{d \rightarrow b} c_j(\sigma). \end{aligned}$$

Replacing the dummy variable *b* by *a* and using the notation

$$\langle f : g \rangle = \mathbb{E} \sum_{j=1}^N \sum_{k=1}^N J_{jk} f_j(\sigma) g_k(\sigma),$$

we finally obtain

$$\frac{d\langle c : d \rangle}{dt} = \sum_{a \in \Omega} \left[ \langle r^{a \rightarrow c} : d \rangle + \langle c : r^{a \rightarrow d} \rangle - \langle r^{c \rightarrow a} : d \rangle - \langle c : r^{d \rightarrow a} \rangle \right]. \quad (\text{A.2})$$

A.3. Moment equations for the SIS model

For the SIS model, the expected dynamics of the number of infected hosts is

$$\frac{d\langle I \rangle}{dt} = \langle r^{S \rightarrow I} \rangle - \langle r^{I \rightarrow S} \rangle$$

with the following transition rates

$$r_i^{S \rightarrow I} = \beta \sum_{j=1}^N J_{ij} I_j S_i$$

$$r_i^{I \rightarrow S} = \gamma I_i.$$

We thus have

$$\frac{d\langle I \rangle}{dt} = \left[ \sum_{i=1}^N \beta \sum_{j=1}^N J_{ij} I_j S_i \right] - \mathbb{E} \left[ \sum_{i=1}^N \gamma I_i \right] = \beta \langle S : I \rangle - \gamma \langle I \rangle.$$

The dynamics of the expected number of infected hosts thus depends on the dynamics of the number of connected pairs of infected and susceptible hosts,  $\langle S : I \rangle$ . In turn, we can write down this equation as follows:

$$\frac{d\langle I : S \rangle}{dt} = \langle r^{S \rightarrow I} : S \rangle + \langle I : r^{I \rightarrow S} \rangle - \langle r^{I \rightarrow S} : S \rangle - \langle I : r^{S \rightarrow I} \rangle$$

$$\begin{aligned} &= \beta \mathbb{E} \left[ \sum_{i=1}^N \sum_{j=1}^N \sum_{k=1}^N J_{ij} J_{ik} I_k S_i S_j \right] + \gamma \mathbb{E} \left[ \sum_{i=1}^N \sum_{j=1}^N J_{ij} I_i I_j \right] \\ &\quad - \gamma \mathbb{E} \left[ \sum_{i=1}^N \sum_{j=1}^N J_{ij} I_i S_j \right] \\ &\quad - \beta \mathbb{E} \left[ \sum_{i=1}^N \sum_{j=1}^N \sum_{k=1}^N J_{ij} J_{jk} I_i S_j I_k \right]. \end{aligned}$$

Note that, for a set of indicator functions *a, b, c*, the number of *abc* triplets is given by

$$\sum_{i=1}^N \sum_{j=1}^N \sum_{k=1}^N J_{ij} J_{jk} a_i b_j c_k.$$

If  $a \neq c$ , this is the number of true triplets,  $[a : b : c]$ . However, if  $a = c$ , the above computation also includes the number of *ab* pairs (triplets for which  $i = k$ ). In other words, we have

$$\sum_{i=1}^N \sum_{j=1}^N \sum_{k=1}^N J_{ij} J_{jk} a_i b_j c_k = \begin{cases} [a : b : c] & \text{if } a \neq c, \\ [a : b] + [a : b : c] & \text{if } a = c. \end{cases}$$

Plugging these expressions in the equation for the dynamics of  $\langle I : S \rangle$  yields

$$\frac{d\langle I : S \rangle}{dt} = \beta \langle I : S : S \rangle + \gamma \langle I : I \rangle - \gamma \langle I : S \rangle - \beta (\langle I : S \rangle + \langle I : S : I \rangle).$$

A similar equation can be obtained for the dynamics of *II* pairs, as follows:

$$\begin{aligned} \frac{d\langle I : I \rangle}{dt} &= \langle r^{S \rightarrow I} : I \rangle + \langle I : r^{S \rightarrow I} \rangle - \langle r^{I \rightarrow S} : I \rangle - \langle I : r^{I \rightarrow S} \rangle \\ &= 2\beta \langle I : S \rangle + \langle I : S : I \rangle - 2\gamma \langle I : I \rangle. \end{aligned}$$

When the network is regular, we can obtain another, more interpretable formulation as follows. Dividing by the total number of pairs,  $Nn$ , and rescaling the transmission rate  $\beta$  as a per-capita rate, we have

$$\frac{dp_{IS}}{dt} = \beta \bar{\phi} p_{ISS} + \gamma p_{II} - \gamma p_{IS} - \beta (\phi p_{IS} + \bar{\phi} p_{ISI}),$$

where  $\phi = 1/n$  and  $\bar{\phi} = 1 - \phi$ . Alternatively, this is often written as

$$\frac{dp_{IS}}{dt} = \beta \bar{\phi} q_{I/SS} p_{SS} + \gamma p_{II} - (\gamma + \beta (\phi + \bar{\phi} q_{I/SI})) p_{IS}. \quad (\text{A.3})$$

The first term on the RHS represents transition from SS to IS pairs due to new infections from one of the infected individuals in the neighbourhood of a susceptible host in a SS pair (there are  $(n-1)q_{I/SS}$  such infected neighbours). The second term on the RHS represents transition from II to IS pairs due to recovery. The third term on the RHS represents the destruction of IS pairs, either due to recovery (transition from IS to SS) or to infection (transition from IS to II, either because of infection through the anchored infected individual, or through one of the  $(n-1)q_{I/SI}$  infected neighbours).

Similarly, the dynamics of *II* pairs on a regular network can be written as

$$\frac{dp_{II}}{dt} = 2\beta (\phi + \bar{\phi} q_{I/SI}) p_{SI} - 2\gamma p_{II}. \quad (\text{A.4})$$

With practice, it is often straightforward (and faster) to write down directly Eq. (A.3) and (A.4). An excellent vademecum on how to do so can be found in Van Baalen (2000).

A.4. Invasion matrix

Let us now consider that the host population can be infected by two parasite strains. We now have three states in the system ( $\Omega = \{S, I, I'\}$ ). To track the invasion dynamics of the mutant strain, we need to follow the dynamics of the pairs *SI'*, *II'* and *I'I*. Using

the same method as above, we obtain the following system of equations:

$$\frac{dp_{S'I'}}{dt} = \beta\bar{\phi}q_{I'/SS}p_{SS} + \gamma p_{I'I'} + \gamma' p_{I'I'} - (\gamma' + \beta'(\phi + \bar{\phi}q_{I'/S'}) + \beta\bar{\phi}q_{I'/S'})p_{S'I'} \quad (\text{A.5})$$

$$\frac{dp_{I'I'}}{dt} = \beta\bar{\phi}q_{I'/S'}p_{S'I'} + \beta'\bar{\phi}q_{I'/SI}p_{SI} - (\gamma + \gamma')p_{I'I'} \quad (\text{A.6})$$

$$\frac{dp_{I'I'}}{dt} = 2\beta'(\phi + \bar{\phi}q_{I'/S'})p_{S'I'} - 2\gamma'p_{I'I'}. \quad (\text{A.7})$$

With the relationships  $p_{I'SS} = q_{I'/SS}p_{SS} = q_{S'/S'}p_{S'I'}$  and  $p_{I'SI} = q_{I'/SI}p_{SI} = q_{I'/S'}p_{S'I'}$ , this can be rewritten in matrix form,

$$\frac{d}{dt} \begin{pmatrix} p_{S'I'} \\ p_{I'I'} \\ p_{I'I'} \end{pmatrix} = \begin{pmatrix} \beta\bar{\phi}q_{S'/S'} - (\gamma' + \beta'(\phi + \bar{\phi}q_{I'/S'}) + \beta\bar{\phi}q_{I'/S'}) & \gamma & \gamma' \\ (\beta + \beta')\bar{\phi}q_{I'/S'} & -(\gamma + \gamma') & 0 \\ 2\beta'(\phi + \bar{\phi}q_{I'/S'}) & 0 & -2\gamma' \end{pmatrix} \begin{pmatrix} p_{S'I'} \\ p_{I'I'} \\ p_{I'I'} \end{pmatrix}, \quad (\text{A.8})$$

where we recognise matrix **A** in the main text.

#### A.5. Selection gradient

Under weak selection, the matrix **A** can be partitioned into two matrices  $\partial\mathbf{A}_1$  and  $\partial\mathbf{A}_2$ , the expressions of which are given in the main text. Using the equilibrium relationships (25)–(27), the matrix  $\partial\mathbf{A}_1$  can be written as

$$\partial\mathbf{A}_1 = \begin{pmatrix} -\partial\beta(\bar{q}_{I'/I'} - \bar{q}_{S'/I'}) - \partial\gamma & 0 & \partial\gamma \\ \partial\beta\bar{q}_{I'/I'} & -\partial\gamma & 0 \\ 2\partial\beta\bar{q}_{I'/I'} & 0 & -2\partial\gamma \end{pmatrix}. \quad (\text{A.9})$$

Left- and right-multiplying by the eigenvectors  $\bar{\mathbf{v}}$  and  $\bar{\mathbf{q}}$ , one obtains

$$\frac{\bar{\mathbf{v}}\partial\mathbf{A}_1\bar{\mathbf{q}}}{\bar{\mathbf{v}}\bar{\mathbf{q}}} = \frac{2\bar{q}_{S'/I'} + \bar{q}_{I'/I'}}{2\bar{q}_{S'/I'} + \bar{q}_{I'/I'} + \bar{q}_{I'/I'}} (\partial\beta\bar{q}_{S'/I'} - \partial\gamma). \quad (\text{A.10})$$

With the relationships  $\bar{q}_{S'/I'} = \hat{q}_{S/I}$ ,  $\bar{q}_{I'/I'} = \hat{q}_{I/I}(1-r)$  and  $\bar{q}_{I'/I'} = \hat{q}_{I/I}r$ , one finally obtains

$$\frac{\bar{\mathbf{v}}\partial\mathbf{A}_1\bar{\mathbf{q}}}{\bar{\mathbf{v}}\bar{\mathbf{q}}} = \frac{1 + \hat{q}_{S/I} - \hat{q}_{I/I}r}{1 + \hat{q}_{S/I}} (\partial\beta\bar{q}_{S'/I'} - \partial\gamma), \quad (\text{A.11})$$

which is the first term in Eq. (28). The second term depends on a selective effect  $\partial q_{S'/I'}$  which can be estimated using the improved pair approximation detailed in the main text. Noting  $\partial\lambda'$  the selection gradient, we then have two equations with two unknowns ( $\partial\lambda'$  and  $\partial q_{S'/I'}$ )

$$\partial\lambda' = AS_0 + \theta C\beta\partial q_{S'/I'},$$

$$\partial\lambda' = S_0 + \beta\partial q_{S'/I'},$$

where the expressions and interpretations of  $A$ ,  $S_0$  and  $C$  are given in the main text.

The second equation comes from the expression of the per-capita growth rate computed from the dynamics of the global density  $p_I$  (Eq. (9)). Eliminating  $\partial q_{S'/I'}$ , we finally obtain

$$\partial\lambda' = \frac{A - \theta C}{1 - \theta C} S_0, \quad (\text{A.12})$$

which is Eq. (33) in the main text.

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