Mean-field approximation to a spatial host-pathogen model

M. A. M. de Aguiar,[1,2] E. M. Rauch,[1,3] and Y. Bar-Yam[1,4]

[1]*New England Complex Systems Institute, Cambridge, Massachusetts 02138*
[2]*Instituto de Física Gleb Wataghin, Universidade Estadual de Campinas, 13083-970 Campinas, São Paulo, Brazil*
[3]*MIT Artificial Intelligence Laboratory, 200 Technology Square, Cambridge, Massachusetts 02139*
[4]*Department of Molecular and Cellular Biology, Harvard University, Cambridge, Massachusetts 02138*

We study the mean-field approximation to a simple spatial host-pathogen model that has been shown to display interesting evolutionary properties. We show that previous derivations of the mean-field equations for this model are actually only low-density approximations to the true mean-field limit. We derive the correct equations and the corresponding equations including pair correlations. The process of invasion by a mutant type of pathogen is also discussed.

Ecologists have become increasingly aware of the importance of space in evolution and epidemiology. It has become apparent that inhomogeneities in spatially distributed populations can fundamentally change the dynamics of these systems [1–5]. A simple lattice host-pathogen model, first introduced by Tainaka [6], has become a paradigm for the study of spatially extended dynamics. In epidemiology, the model was introduced by Comins *et al.* [7] and further studied in Refs. [8–11]. The model is a probabilistic cellular automaton, in which the state of each site is updated according to the state of nearby sites. Insight in the role of the parameters and global behavior of the system can be obtained from the mean field approximation, when all hosts and pathogens experience the same local environment. This first approximation to the dynamics can be improved by including pair correlations.

The mean-field equations for this host-pathogen model were first presented by Rand *et al.* [10] (see also Refs. [12,13]). Corrections due to pair correlations were considered in Ref. [13]. Satulovsky and Tome [14] have also derived the mean-field and pair-correlation equations for a similar model. In this paper, we argue that the mean-field equations and the pair approximation in Refs. [10,12,13] are actually only approximations to the correct equations. In the derivations in these works, the probability of infection of a susceptible host by an infected individual is overcounted, as is the probability of a susceptible host being born on a empty site. These equations are valid only for small rates of transmissibility of the pathogen and for small birth rates of susceptible hosts, when these overcountings are not important. We obtain the correct mean-field equations for the well established model of Tainaka [6] as well as the pair-correlation equations. The process of invasion by a mutant type is also discussed.

We consider a two-dimensional spatial lattice with N sites. The state of each site can be either empty (0), occupied by a susceptible (S), or occupied by an infected individual (I_τ). At each time step, the susceptible hosts reproduce into each nearby cell with probability g if that cell is not yet occupied. The probability of reproduction is independent for each neighbor. An infected host dies with probability v, the virulence. Finally, an infected host I_τ causes a neighboring un-

infected host to become infected with probability τ, the transmissibility. The subscript τ allows more than one type to be present on the lattice. For the sake of simplicity we shall relabel the state (S) as (1) and (I_τ) as (τ).

The state of the system is denoted by $\sigma = (\sigma_1, \sigma_2, \ldots, \sigma_N)$, where σ_i is the state at the ith site. We call $\omega_i(\sigma)$ the transition probability per unit time of the state at the site i. The transition probabilities are

$$\omega_i(\sigma) = \begin{cases} 1-(1-g)^{n_i} & \text{if} \quad \sigma_i=0 \\ 1-(1-\tau)^{m_i} & \text{if} \quad \sigma_i=1 \\ v & \text{if} \quad \sigma_i=\tau, \end{cases} \quad (1)$$

where $n_i = \Sigma_j \delta(\sigma_{i+j},1)$ is the number of susceptible neighbors to i, and $m_i = \Sigma_j \delta(\sigma_{i+j},\tau)$ is the number of infected neighbors to i. The sum over j runs through all the nearest neighbors. We call ζ the total number of nearest neighbors. Note that, since a susceptible cannot be infected twice, the probability of becoming infected has to be calculated as "one minus the probability of not becoming infected." This gives rise to the term $1-(1-\tau)^{m_i}$. Similarly, an empty site can become occupied only by offspring of a single susceptible neighbor host, thus the term $1-(1-g)^{n_i}$.

Allowing for the simultaneous existence of different types of pathogens, and mutation between the types, enables the study of evolutionary dynamics, where different types compete for the same susceptibles. When a pathogen of transmissibility τ reproduces, its offspring has probability μ of having transmissibility $\tau \pm \epsilon$. For simplicity we assume that τ may take only discrete values $\tau_k = k\epsilon$, $k=1,2,\ldots,M$, where $M=1/\epsilon$. The state occupied by a host infected with pathogen τ_k will be labeled (τ_k). The transition probability per unit time of the state at the site i is then given by

$$\omega_{ik}(\sigma) = \begin{cases} 1-(1-g)^{n_i} & \text{if} \quad \sigma_i=0 \\ \Omega_k & \text{if} \quad \sigma_i=1 \\ v & \text{if} \quad \sigma_i=\tau_{k'}, \end{cases} \quad (2)$$

where Ω_k is the probability that susceptible hosts become infected by the pathogen with transmissibility τ_k:

$$\Omega_k = \chi \left[\frac{\mu}{2} p_{k-1} + \frac{\mu}{2} p_{k+1} + (1-\mu) p_k \right] \qquad (3)$$

with

$$\chi = \frac{1 - \prod_j (1-\tau_j)^{m_j}}{\sum_j p_j} \qquad (4)$$

and $p_k = 1 - (1-\tau_k)^{m_k}$. For Ω_1 and Ω_M the terms in p_0 and p_{M+1} should be discarded and the factor $(1-\mu)$ replaced by $(1-\mu/2)$.

Approximate mean-field equations for the lattice model with a single pathogen type were obtained using simple considerations in Refs. [12,13] in the context of the same spatial model and in Ref. [14] for a similar spatial predator-prey model. These equations fail to take into account the fact that a susceptible cannot be infected twice or that an empty site cannot accommodate more than one offspring. In order to find the correct mean-field limit of the spatial model, we have derived the master equation for the probability of the system as a whole. For the present case of multiple pathogen types, it reads

$$\frac{dP(\sigma,t)}{dt} = \sum_{i=1}^{N} \sum_{k'} [P(\sigma_{k'}^i) \omega_{i\sigma_i}(\sigma_{k'}^i) - P(\sigma)\omega_{ik'}(\sigma)], \qquad (5)$$

where $P(\sigma,t)$ is the probability of finding the system in the state σ at time t. The sum over k' should be included only when the argument of $\omega_{ik'}$ is $\tau_{k'}$ in the first term and when it is 1 in the second term. We refer to Ref. [15] for the derivation.

Given any function of the states, $f(\sigma)$, its ensemble average is given by $\langle f(\sigma) \rangle = \sum_\sigma P(\sigma,t) f(\sigma)$. Differentiating with respect to t and using Eq. (5) we find

$$\frac{d\langle f(\sigma) \rangle}{dt} = \sum_{i=1}^{N} \sum_{k'} \langle [f(^i\sigma_{k'}) - f(\sigma)]\omega_{ik'}(\sigma) \rangle, \qquad (6)$$

where again the sum over k' exists only when the argument of $\omega_{ik'}$ is $\tau_{k'}$ in the first term and when it is 1 in the second term.

Single type of pathogen. In the case of a single type of pathogen the sum over k' disappears and the transition probabilities simplify to Eq. (1). To obtain an equation for the average probability of empty sites, we consider $f(\sigma) = \delta(\sigma_i,0)$. Then $P_i(0,t) \equiv \langle \delta(\sigma_i,0) \rangle$ is the average probability that site i is in the state (0) in the time t. Similarly we define $P_i(1,t)$ for the average probability of susceptible hosts and $P_i(\tau,t)$ for the average probability of infected hosts. In the approximation, where the P_i's are independent of the site, they become the mean-field probabilities of each state, which we call $x(t) = P(1,t)$, $y(t) = P(\tau,t)$, and $z(t) = P(0,t) = 1 - x(t) - y(t)$. According to Eq. (6),

$$\frac{dP_i(1,t)}{dt} = \sum_{n=1}^{N} \langle f(^n\sigma)\omega_n(\sigma) - f(\sigma)\omega_n(\sigma) \rangle. \qquad (7)$$

Since $f(^n\sigma)$ differs from $f(\sigma)$ only if $n=i$, only this term contributes to the sum. Noticing that $\delta(^i\sigma,1) = \delta(\sigma_i,0)$ we get

$$\frac{dP_i(1,t)}{dt} = \langle \delta(\sigma_i,0)[1-(1-g)^{n_i}] \rangle$$
$$- \langle \delta(\sigma_i,1)[1-(1-\tau)^{m_i}] \rangle. \qquad (8)$$

Similarly, we obtain

$$\frac{dP_i(\tau,t)}{dt} = \langle \delta(\sigma_i,1)[1-(1-\tau)^{m_i}] - \delta(\sigma_i,\tau)v \rangle. \qquad (9)$$

The averages can be calculated expanding the binomials $(1-g)^{n_i}$ and $(1-\tau)^{m_i}$ and approximating all pair (and higher) correlations by simple products of one-site averages [14,16]. We obtain

$$\frac{dx}{dt} = zh_\zeta(gx) - xh_\zeta(\tau y) \qquad (10)$$

and

$$\frac{dy}{dt} = xh_\zeta(\tau y) - vy, \qquad (11)$$

where we have defined the auxiliary function

$$h_\zeta(\alpha) \equiv 1 - (1-\alpha)^\zeta. \qquad (12)$$

These are the correct mean-field equations for the host-pathogen model, taking fully into account the fact that a susceptible host cannot become infected twice and that an empty site can accommodate only one offspring. One important consequence of including this feature, usually present in spatial models (see, however, Ref. [14]), is that the equations become nonlinear in g and τ, losing the scaling invariance that allows one to consider only $g+\tau+v=1$ [14]. The approximate equations in Refs. [10,12–14] correspond to taking $h_\zeta(\alpha) \approx \zeta\alpha$.

Two types of pathogens. When two types of pathogens are present, the competition that arises between them gives rise to a very rich dynamics. We assume that the two types, that we call resident and mutant, have the same virulence v, but different transmissibility rates, τ_1 for the resident and τ_2 for the mutant. There are four one-site variables, z, x, y_1, and y_2, corresponding to the probabilities of empty sites, susceptible hosts, infected by the resident pathogen, and infected by the mutant pathogen respectively. Once again $z = 1 - x - y_1 - y_2$.

The calculation of the mean-field equations in this case is more involved, and we refer to Ref. [15] for the details. The result is

$$\frac{dx}{dt} = zh_\zeta(gx) - xh_\zeta(y_1\tau_1 + y_2\tau_2), \qquad (13)$$

$$\frac{dy_1}{dt} = \bar{\chi}\left\{\frac{\mu}{2}h_\zeta(\tau_2 y_2) + \left(1-\frac{\mu}{2}\right)h_\zeta(\tau_1 y_1)\right\}x - v y_1,$$

(14)

$$\frac{dy_2}{dt} = \bar{\chi}\left\{\frac{\mu}{2}h_\zeta(\tau_1 y_1) + \left(1-\frac{\mu}{2}\right)h_\zeta(\tau_2 y_2)\right\}x - v y_2,$$

(15)

where

$$\bar{\chi} = \frac{h_\zeta(\tau_1 y_1 + \tau_2 y_2)}{h_\zeta(\tau_1 y_1) + h_\zeta(\tau_2 y_2)}.$$

(16)

It can be shown [15] that the approximate equations lead to complete invasion if a small amount of a more transmissible mutant pathogen is introduced in the resident population, whereas the full mean-field equations lead to coexistence if $|\tau_2 - \tau_1|$ is sufficiently small. Invasion happens only if $|\tau_2 - \tau_1|$ is larger than a threshold that depends on τ_1.

The mean-field equations can be improved by including pair correlations. This is done by keeping two-site probabilities $P_{ij}(\alpha\beta)$ in the equations while reducing higher-order correlations to at most two-site terms. We do this reduction according to the truncation scheme in Refs. [14,16–19].

Pair correlations for a single type of pathogen. For a single type there are three possible states per site, (0), (1), and (τ), and six two-site correlations. Since $\Sigma_j P(ij) = P(i)$, only three of them are independent. We call the independent correlations $u = P(10)$, $r = P(1\tau)$, and $w = P(0\tau)$. The other three are given by $q \equiv P(00) = z - u - w$, $p \equiv P(11) = x - r - u$, and $s \equiv P(\tau\tau) = y - r - w$, with $z = 1 - x - y$. The five independent variables are, therefore, x, y, u, r, and w. The details of the calculation can be found in Ref. [15]. The result is

$$\frac{dx}{dt} = z h_\zeta(gu/z) - x h_\zeta(\tau r/x),$$

(17)

$$\frac{dy}{dt} = x h_\zeta(\tau r/x)^\zeta - v y,$$

(18)

$$\frac{du}{dt} = (q-u)h_{\zeta-1}(gu/z) + vr - u h_{\zeta-1}(\tau r/x)$$

$$- gu[1 - h_{\zeta-1}(gu/z)],$$

(19)

$$\frac{dr}{dt} = (p-r)h_{\zeta-1}(\tau r/x) - vr - w h_{\zeta-1}(gu/z)$$

$$- \tau r[1 - h_{\zeta-1}(\tau r/x)],$$

(20)

$$\frac{dw}{dt} = u h_{\zeta-1}(\tau r/x) + v(s-w) - w h_{\zeta-1}(gu/z).$$

(21)

Pair correlations for two types of pathogens. We assume once again that both the resident and mutant pathogens have the same virulence v, but different transmissibility rates: τ_1 for the resident and τ_2 for the mutant. There are four one-site variables, z, x, y_1 and y_2 and ten two-site variables: u

$= P(10)$, $r_1 = P(1\tau_1)$, $r_2 = P(1\tau_2)$, $w_1 = P(0\tau_1)$, $w_2 = P(0\tau_2)$, $q = P(00)$, $p = P(1q)$, $s_1 = P(\tau_1\tau_1)$, $s_2 = P(\tau_2\tau_2)$, and $s_{12} = P(\tau_1\tau_2)$. Of these 14 variables, only nine are independent. We choose them to be x, y_1, y_2, u, r_1, r_2, w_1, w_2, and s_{12}. The other five are related to them by $q = z - u - w_1 - w_2$, $p = x - u - r_1 - r_2$, $s_1 = y_1 - w_1 - r_1 - s_{12}$, and $s_2 = y_2 - w_2 - r_2 - s_{12}$. We obtain

$$\frac{dx}{dt} = z h_\zeta(gu/z) - x h_\zeta((\tau_1 r_1 + \tau_2 r_2)/x),$$

$$\frac{dy_1}{dt} = \bar{\chi}x\left\{\frac{\mu}{2}h_\zeta(\tau_2 r_2/x) + \left(1-\frac{\mu}{2}\right)h_\zeta(\tau_1 r_1/x)\right\} - v y_1,$$

$$\frac{du}{dt} = (q-u)h_{\zeta-1}(gu/z) - gu[1 - h_{\zeta-1}(gu/z)]$$

$$- u h_{\zeta-1}((\tau_1 r_1 + \tau_2 r_2)/x) + v(r_1 + r_2),$$

$$\frac{dr_1}{dt} = \bar{\bar{\chi}}\frac{\mu}{2}p h_{\zeta-1}(\tau_2 r_2/x) + \bar{\omega}\left(1-\frac{\mu}{2}\right)p h_{\zeta-1}(\tau_1 r_1/x)$$

$$- w_1 h_{\zeta-1}(gu/z) - \tau_1 r_1[1 - h_{\zeta-1}((\tau_1 r_1 + \tau_2 r_2)/x)]$$

$$- r_1 h_{\zeta-1}((\tau_1 r_1 + \tau_2 r_2)/x)) - v r_1,$$

$$\frac{dw_1}{dt} = \bar{\bar{\chi}}\frac{\mu}{2}u h_{\zeta-1}(\tau_2 r_2/x) + \bar{\omega}\left(1-\frac{\mu}{2}\right)u h_{\zeta-1}(\tau_1 r_1/x)$$

$$+ v(s_1 + s_{12} - w_1) - w_1 h_{\zeta-1}(gu/z),$$

$$\frac{ds_{12}}{dt} = \bar{\bar{\chi}}\frac{\mu}{2}r_2\{\tau_2[1 - h_{\zeta-1}(\tau_2 r_2/x)] + h_{\zeta-1}(\tau_2 r_2/x)\}$$

$$+ \bar{\bar{\chi}}\frac{\mu}{2}r_1\{\tau_1[1 - h_{\zeta-1}(\tau_1 r_1/x)] + h_{\zeta-1}(\tau_1 r_1/x)\}$$

$$+ \bar{\bar{\chi}}\left(1-\frac{\mu}{2}\right)r_2 h_{\zeta-1}(\tau_1 r_1/x)$$

$$+ \bar{\bar{\chi}}\left(1-\frac{\mu}{2}\right)r_1 h_{\zeta-1}(\tau_2 r_2/x) - 2 v s_{12},$$

where

$$\bar{\bar{\chi}} \equiv \frac{h_{\zeta-1}(\tau_1 y_1 + \tau_2 y_2)}{h_{\zeta-1}(\tau_1 y_1) + h_{\zeta-1}(\tau_2 y_2)}.$$

The equations for y_2, r_2, and w_2 can be obtained by exchanging the subindices 1 and 2 in the equations for y_1, r_1, and w_1, respectively.

When τ_1, τ_2, and g are small, the functions $h_\zeta(\alpha)$ can again be approximated by $\zeta\alpha$ and the approximate pair correlation equations are obtained. We found that the approximate equations present limit cycles in a much larger range of parameters than the true mean-field equations [15]. Once again, when the process of invasion is studied, we find coexistence of similar types if $|\tau_2 - \tau_1|$ is small. However, the more transmissible pathogen type still wins over any less transmissible ones, in the sense that either the less transmissible type goes extinct, or its average number is always
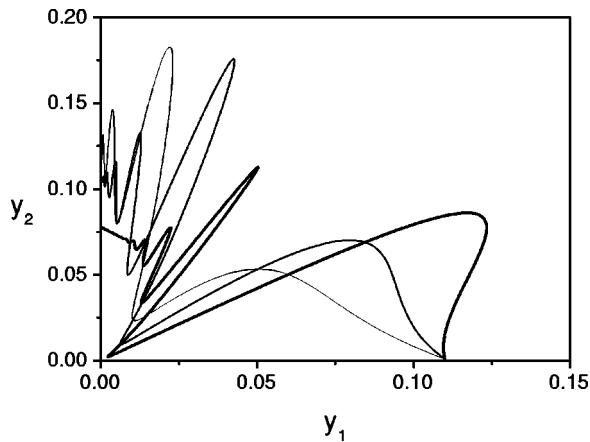
FIG. 1. Invasion in the pair approximation for $g=0.05$, $v=0.2$, and $\tau_2=\tau_1+0.05$. The curves show the time evolution of y_1 and y_2 (dimensionless units) for $\tau_1=0.2$ (thin), 0.3 (thicker), and 0.5 (thickest). The initial conditions are $x=0.28$, $y_1=0.11$, and $y_2=0.001$. The larger the value of τ_1, the closer to extinction the population gets.

smaller than the mutant invader. The emergence of an intermediate-transmissibility evolutionarily stable type [4,5] is not observed even in the pair approximation.

However, the oscillatory approach to equilibrium revealed by the pair approximation does give us a clue to understand how the evolutionarily stable type appears in the spatial model. In Fig. 1 we show y_1 versus y_2 for $g=0.05$, $v=0.2$ and $\tau_2=\tau_1+0.05$ for $\tau_1=0.2$, 0.3, and 0.5. The initial population consists of an equilibrium between health individuals and individuals infected by the resident type plus a very small amount of individuals infected by the mutant type. Although invasion occurs in all cases (y_1 goes to zero), the higher the value of τ_1, the closer the population of infected

hosts gets to extinction (when y_1 and y_2 get close to zero simultaneously). If we assume that the initial population is structured in patches, those patches receiving the mutant type are indeed likely to go extinct. If the patches are very large, Fig. 1 shows that the number of infected hosts rises again after the near extinction leading to invasion by the more transmissible type. However, if the patches are finite, the population of infected may die. We can estimate the minimum size of these patches so that extinction can be prevented. If n_p is the total number of sites in the patch and y_{1min}, y_{2min} are the values assumed by y_1 and y_2 at the near extinction time, then the actual number of individuals (sites) infected by the resident and the mutant pathogen types at this time is $n_p y_{1min}$, and $n_p y_{2min}$, respectively. When this number goes below 1 there is less than one infected site in the whole patch, and the corresponding pathogen goes extinct. For $\tau_1=0.2$ the resident type disappears if n_p is less than 100, whereas the mutant type disappears only if the patch falls below 45 sites. Typical patches observed in numerical simulations are larger than this, implying that invasion is indeed expected. For $\tau_1=0.5$ extinction of both resident and mutant pathogens is prevented only if patches are larger than about 450. However, for $\tau_1=0.7$, the mutant pathogen with $\tau_2=0.75$ is more likely to go extinct than the resident. If patches are larger than about 780 the resident pathogen survives, whereas the mutant type disappears unless patches are larger than 890. Therefore, if the actual size of the system, or the patch where the mutant first appears, is sufficiently small, extinction does happen for pathogens of large transmissibility, preventing invasion and leading naturally to the survival of an intermediate type.

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