Uniformly accurate effective equations for disease transmission mediated by pair formation dynamics

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Abstract

We derive and asymptotically analyze mass-action models for disease spread that include transient pair formation and dissociation. Populations of unpaired susceptibles and infecteds are distinguished from the population of three types of pairs of individuals; both susceptible, one susceptible and one infected, and both infected. Disease transmission can occur only within a pair consisting of one susceptible individual and one infected individual. By considering the fast pair formation and fast pair dissociation limits, we use a perturbation expansion to formally derive a uniformly valid approximation for the dynamics of the total infected and susceptible populations. Under different parameter regimes, we derive uniformly valid effective equations for the total infected population and compare their results to those of the full mass-action model. Our results are derived from the fundamental mass-action system without implicitly imposing transmission mechanisms such as that used in frequency-dependent models. They provide a new formulation for effective pairing models and are compared with previous models.

Keywords: disease models, pairing dynamics,

1. Introduction

Ordinary differential equations have been widely used to model population biology and disease spread in systems where the agents are spatially homogeneous. Canonical mass-action theories include the SIS, SIR, SEIR/SEIS, and other models, which have been widely used to provide insight into the dynamics of infected populations [22, 1]. Such models are simplified, averaged representations of disease spread within complex, multispecies and heterogeneous populations. In this paper, we revisit and analyze transmission models and consider the effects of pairing dynamics on infectious disease propagation through a population.

Typically, the transmission rate is assumed to depend on three factors: a) rate at which an infected individual contacts other individuals; b) proportion of the contacts that are with susceptible individuals and c) the probability that a contact between the infected individual and a susceptible individual leads to the susceptible becoming infected. An important factor in determining the contact rate is the relative timescales of the time required for an infected individual to “find” another individual and the time required for behavior that is responsible for transmission.

Two widely used models dominate the literature [1]. Mass-action transmission models assume that the contact rate between any one infected individual and susceptible individuals is proportional to the density of susceptible individuals. That is, the transmission rate is given by $B_{m}\rho_{S}\rho_{I}$, where $\rho_{S}$ is the density of susceptible individuals, $\rho_{I}$ is the density of infected individuals, and $B_{m}$ is a constant rate $\times$ area. Mass-action models are appropriate when the time required to “find” other individuals is significantly longer than the time required for the behavior that spreads the disease and is probably more representative of diseases like tuberculosis (TB) where the required interaction can be just a fleeting contact [3].

Frequency-based transmission models [21] are independent of density and assume that an infected individual experiences the same number of contacts in a given time period regardless of the density. Given
that the populations are homogeneous, and that the contact mechanism does not distinguish between susceptible and infected individuals, the proportion of contacts that are with susceptibles will be $\rho_S / (\rho_S + \rho_I)$. The transmission rate will therefore be $B_1 \rho_I \rho_S / (\rho_S + \rho_I)$, where $B_1$ is a constant rate. Frequency-based models are appropriate when behavior that leads to disease transmission is the rate-limiting step and is appropriate for sexually transmitted diseases in populations that afford large numbers of partners. In other words, the frequency of new contacts is limited by some other social/behavioral process and not simply proportional to density. Moreover, there are examples of populations that follow neither mass-action nor frequency-dependent dynamics [6], or in which contact rates scale with density in nontrivial ways [15].

Various authors have also proposed models with infection rates of the form $B_1 B_m \rho_I \rho_S / [B_1 + B_m (\rho_S + \rho_I)]$. Such terms are similar to Holling’s Type II functional response in predator-prey models and asymptotically reproduce the mass-action transmission for low densities and the frequency-based transmission for large densities [6]. Whether or not this type of Holling’s type II model can be theoretically justified or whether an alternative functional response is more natural is also an important theoretical question. Heuristic frequency-based and Holling-type models implicitly incorporate behavior into the dynamics. However, qualitatively, one expects that these dynamics might arise from higher-dimensional mass-action ODEs that explicitly include intermediate “reactions” that reflect some of behavioral processes.

Here, we ask how can such behavior-induced frequency-based models be formally derived from the fundamental mass-action process by considering the simplest mass-action model in which lone susceptible and infected individuals associate to form pairs (either susceptible-susceptible, susceptible-infected or infected-infected) [11,12,18,4]. These models are similar to the class of household structure models in which groups of individuals form subgroups within which disease transmission spreads faster [10,8,9,14]. Pairs can also dissociate into their constituent lone individuals. In these pair formation type models, transmission can only occur from an infected to a susceptible in a susceptible-infected pair. We also include the effects of death and immigration of susceptibles which leads directly to a set of five differential equations: two ODEs for two types of lone individuals and three ODEs for the three different types of pairs. How these five equations can be reduced to effective equations under certain conditions will be the topic of our analyses. Previous treatments of the pairing models have been put forth but either do not consider certain parameter limits [12], are not systematic [21], implicitly force a frequency-dependent interaction through a “mixing matrix” [21], or only provide approximations at short times [20].

In this paper, we generate effective, mass-action-derived equations that are uniformly valid at all times. We first show that if pair dissociation and within-pair transmission is fast, to lowest order, the equations simply reduce to two mass-action-like equations, one for the total infected density and one for the total susceptible density, but with an effective transmission coefficient. Although no structural change is seen in this case, if association and dissociation are asymptotically faster than the other processes (death, transmission, and immigration), the resulting effective equations for the total infected and susceptible populations involve terms of rational fractions of polynomials. These equations further reduce to simpler forms in certain parameter limits.

On the other hand, if association is asymptotically faster than the other process (including dissociation), we show that the leading-order dynamics can only be reduced to three ODEs that bear a number of similarities to models that include an exposed subpopulation, such as the SEI (Susceptible-Exposed-Infected) class of models. This new type of model, derived from the fundamental mass-action pairing model, reflects a latency period in disease propagation but is still different from the typical SEI-type model.

2. Models

We start by reviewing the basic mass-action, frequency-based, and pairing models for disease propagation.

2.1. Simple Mass-Action Model

The simplest mass-action description for the dynamics of the susceptible and infected population densities $\rho_s(t)$ and $\rho_i(t)$ is given by the susceptible-infected (SI) model with immigration:
\[
\begin{align*}
\frac{d\rho_s(t)}{dt} &= \dot{\Pi} - \mu_s \rho_s(t) - B_m \rho_s(t) \rho_i(t) \\
\frac{d\rho_i(t)}{dt} &= -\mu_i \rho_i(t) + B_m \rho_s(t) \rho_i(t),
\end{align*}
\]

where \( \dot{\Pi} \) represents the rate at which the density of susceptible individuals increases via immigration from outside the region, and \( \mu_s \) and \( \mu_i \) are the death rates of susceptible and infected individuals, respectively.

If recovery of infecteds back to the susceptible pool is included, Eqs. (1) becomes the standard SIS model when \( \dot{\Pi} = \mu_s = \mu_i = 0 \) and the total population is conserved. The steady-state solution to Eqs. (1) \( (\rho^*_s, \rho^*_i) = (\dot{\Pi}/\mu_s, 0) \), exists for all parameters and is linearly stable if the reproduction number

\[ R_m = \frac{B_m \dot{\Pi}}{\mu_s \mu_i} < 1 \]  

(2)

and linearly unstable if \( R_m > 1 \). A second steady state \( (\rho^*_s, \rho^*_i) = (\mu_i/B_m, \dot{\Pi}/\mu_i - \mu_s/B_m) \) only has positive densities and hence exists for \( R_m > 1 \) and is linearly stable. For values of \( R_m > 1 \), a non-zero infected population can be maintained indefinitely, whereas for \( R_m < 1 \), the infected population will ultimately die out.

2.2. Frequency-Dependent Model

A typical frequency-based model takes the form

\[
\begin{align*}
\frac{d\rho_s(t)}{dt} &= \dot{\Pi} - \mu_s \rho_s(t) - B_f \rho_s(t) \rho_i(t) \\
\frac{d\rho_i(t)}{dt} &= -\mu_i \rho_i(t) + B_f \rho_s(t) \rho_i(t) \rho_s(t),
\end{align*}
\]

which is often used to describe sexually transmitted disease in which the pair formation rate is thought to be intrinsic to the individual and largely population density-independent.

The steady state \( (\rho^*_s, \rho^*_i) = (\dot{\Pi}/\mu_s, 0) \) exists for all parameters and is linearly stable if

\[ R_f := \frac{B_f \dot{\Pi}}{\mu_i} < 1 \]  

(4)

and linearly unstable if \( R_f > 1 \). A second steady state

\[
(\rho^*_s, \rho^*_i) = \left( \frac{\dot{\Pi}}{\mu_s + B_f - \mu_i}, \frac{(B_f - \mu_i)\dot{\Pi}}{\mu_i(\mu_s + B_f - \mu_i)} \right)
\]

(5)

has only positive densities and hence exists for \( R_f > 1 \) and is linearly stable.

An important difference between the mass-action and frequency-based models is hence apparent. Under mass-action, the reproduction number depends on the influx of individuals \( \Pi \) and so reducing the influx of individuals will be an effective strategy in disease control. On the other hand, for the frequency model, the reproduction number is independent on the influx and so reducing the influx will not cause the disease to die out.

2.3. Mass-Action Pairing Model

We now consider the simplest mass-action model that explicitly includes population densities of transient pairs:
\[
\frac{d\rho_s}{dt} = \Pi - \mu_s \rho_s - 2\tilde{a}_{ss}\rho_s^2 - \tilde{a}_{si}\rho_s\rho_i + 2(\mu_{ss} + d_{ss})\rho_{ss} + (\mu_{si} + d_{si})\rho_{si}
\]
\[
\frac{d\rho_i}{dt} = -\mu_i \rho_i - 2\tilde{a}_{ii}\rho_i^2 - \tilde{a}_{si}\rho_s\rho_i + 2(\mu_{ii} + d_{ii})\rho_{ii} + (\mu_{si} + d_{si})\rho_{si}
\]
\[
\frac{d\rho_{ss}}{dt} = -(2\mu_{ss} + d_{ss})\rho_{ss} + \tilde{a}_{ss}\rho_s^2
\]
\[
\frac{d\rho_{si}}{dt} = -(\mu_{si} + \mu_{si} + d_{si} + \beta)\rho_{si} + \tilde{a}_{si}\rho_s\rho_i
\]
\[
\frac{d\rho_{ii}}{dt} = -(2\mu_{ii} + d_{ii})\rho_{ii} + \beta\rho_{si} + \tilde{a}_{ii}\rho_i^2
\]

where \(\rho_s\) and \(\rho_i\) are the densities of lone susceptible and infected individuals respectively. The quantities \(\rho_{ss}, \rho_{si}\) and \(\rho_{ii}\) are the densities of susceptible-susceptible, susceptible-infected and infected-infected pairs, respectively. In this model, transmission can occur only from infected to susceptibles who are in a susceptible-infected pair and happens at rate \(\beta\). The rate of immigration of density of lone susceptibles is denoted by \(\Pi\). In Eqs. 6, \(\mu\) represent the death rates of the indicated species; for example, \(\mu_{si}\) is the death rate for a susceptible in a susceptible-infected pair, and \(\mu_{is}\) is the death rate for an infected in a susceptible-infected pair. The quantities \(\tilde{a}\) represent the dissociation rate of the indicated pairs while \(\rho\), because they denote an interaction between two individuals and multiply terms quadratic in density, are association rates per density and have units of rate \(\times\) area.

In order to analyze the full model, we nondimensionalize by multiplying each equation by a reference area \(A_0\):

\[
\frac{dN_s}{dt} = \Pi - \mu_s N_s - 2a_{ss}N_s^2 - a_{si}N_sN_i + 2(\mu_{ss} + d_{ss})N_{ss} + (\mu_{is} + d_{si})N_{si}
\]
\[
\frac{dN_i}{dt} = -\mu_i N_i - 2a_{ii}N_i^2 - a_{si}N_sN_i + 2(\mu_{ii} + d_{ii})N_{ii} + (\mu_{si} + d_{si})N_{si}
\]
\[
\frac{dN_{ss}}{dt} = -(2\mu_{ss} + d_{ss})N_{ss} + a_{ss}N_s^2
\]
\[
\frac{dN_{si}}{dt} = -\left(\mu_{is} + \mu_{si} + d_{si} + \beta\right)N_{si} + a_{si}N_sN_i
\]
\[
\frac{dN_{ii}}{dt} = -(2\mu_{ii} + d_{ii})N_{ii} + \beta N_{si} + a_{ii}N_i^2
\]

where \(N = \rho A_0, a = \tilde{a}/A_0\), and \(\Pi = A_0\Pi\) are the dimensionless populations within area \(A_0\), the rate of association (with units of 1/time), and the immigration rate per density, respectively. The reference area \(A_0\) is arbitrary, but can be chosen to scale the magnitudes of \(N\) and the relative rates \(a/\mu\). Under any particular scaling, different limits of the magnitudes of \(N\) and \(a/\mu, d/\mu\) can be used to further analyze Eqs. 7a-7e.

Note that if one mixes the mass-action model with frequency-dependent transmission, as has been often done \([21, 18]\), the quadratic pairing terms in Eqs. 6 would be replaced by, e.g., \(\tilde{a}_{si}\rho_s\rho_i/(\rho_i + \rho_s) = \tilde{a}_{si}N_iN_s/(N_i + N_s)\), where here, \(\tilde{a}_{si}\) has units of 1/time.

3. Asymptotic Analyses and Discussion

We now analyze the mass-action pairing model in different limits to reduce the model to simpler forms in order to illustrate how pairing and dissociation affect the overall propagation of infection.

3.1. Fast Dissociation and Transmission Limit

First, consider the simplest case where the dissociation and transmission rates are large by scaling them according to \(d_{ss} = d_{ss}/\varepsilon, d_{si} = d_{si}/\varepsilon, d_{ii} = d_{ii}/\varepsilon, \) and \(\beta = \beta/\varepsilon\), with \(\varepsilon \to 0^+\). In this limit, we expect the
number or density of pairs to be much smaller than the number of unpaired individuals. We adopt an
expansion of the form

$$N_s = N_s^{(0)} + \varepsilon N_s^{(1)} + \cdots$$
$$N_i = N_i^{(0)} + \varepsilon N_i^{(1)} + \cdots$$
$$N_{ss} = N_{ss}^{(0)} + \varepsilon N_{ss}^{(1)} + \cdots$$
$$N_{si} = N_{si}^{(0)} + \varepsilon N_{si}^{(1)} + \cdots$$
$$N_{ii} = N_{ii}^{(0)} + \varepsilon N_{ii}^{(1)} + \cdots$$

(8)

and substitute it into Eqs. 7a-7e. To leading order, we obtain

$$N_s^{(0)} = N_i^{(0)} = N_{ii}^{(0)} = 0,$$

while to the next order, we find

$$N_{ss}^{(1)} = \overline{a_{ss}} \overline{d_{ss}} N_s^{(0)} N_i^{(0)} / \beta + d_{ss},$$
$$N_{si}^{(1)} = \beta \overline{d_{si}} N_s^{(0)} N_i^{(0)} / \beta + d_{si},$$

(9)

Substitution of the above approximations for the pair populations in to the scaled equations for
$$N_s$$ and $$N_i$$ (derived from Eqs. 7a-7b), we find to lowest order

$$\frac{dN_s^{(0)}}{dt} = \Pi - \mu_s N_s^{(0)} - \left( \frac{a_{si} \beta}{\beta + d_{si}} \right) N_s^{(0)} N_i^{(0)}$$
$$\frac{dN_i^{(0)}}{dt} = -\mu_i N_i^{(0)} + \left( \frac{a_{si} \beta}{\beta + d_{si}} \right) N_s^{(0)} N_i^{(0)},$$

(10)

wherein an effective transmission rate can be defined as

$$B_{eff} := \frac{a_{si} \beta}{\beta + d_{si}} = \frac{a_{si} \beta}{\beta + d_{si}}$$

(11)

In this limit, the effective equations for infecteds and susceptibles retain the mass-action form, but with a
modified transmission parameter. The pair formation process mediates the disease transmission through
the association rate $$a_{si}$$. For $$\beta \ll d$$, the rate limiting step is transmission within a susceptible-infected
pair. When intrapair transmission is fast, $$\beta \gg d$$, the overall transmission rate $$B_{eff} \approx a_{si}$$ approaches the
association rate itself. Thus, in this limit, the five-dimensional mass-action pairing equations reduce to a
two-dimensional mass-action model with a modified transmission rate. Note that if we were to use the
frequency-dependent variant of the pairing model, the form would also be preserved to lowest order with
the corresponding transmission term $$B_{eff} N_s^{(0)} N_i^{(0)} / (N_i^{(0)} + N_s^{(0)})$$.

3.2. Fast Association and Dissociation Limit

We now consider the limit where both the association and dissociation coefficients are significantly larger
than the death and infection rates and define $$a_{ss} = a_{ss} / \varepsilon$$, $$a_{si} = \overline{a_{si}} / \varepsilon$$, $$a_{ii} = \overline{a_{ii}} / \varepsilon$$, $$d_{ss} = \overline{d_{ss}} / \varepsilon$$, $$d_{si} = \overline{d_{si}} / \varepsilon$$ and $$d_{ii} = \overline{d_{ii}} / \varepsilon$$, with $$\varepsilon \to 0^+$$. We also perform a linear transformation on Eqs. 7a-7b so that they describe
total susceptible and infected populations and are independent of $$\varepsilon$$. 

5
By using Eqs. 13c-13e to eliminate where

\[ N \]

them in terms of

\[ N \]

where

\[ 3.2.1. \text{Steady states and stability} \]

We now substitute the expansion in Eqs. 8 into Eqs. 12 and keep only the \( O(1) \) terms to find

\[
\begin{align*}
\frac{d}{dt} (N_s + 2N_{ss} + N_{ai}) &= \Pi - \mu_s N_s - 2\mu_{ss} N_{ss} - (\mu_{si} + \beta) N_{ai} \\
\frac{d}{dt} (N_i + 2N_{ii} + N_{ai}) &= -\mu_i N_i - 2\mu_{ii} N_{ii} - (\mu_{is} - \beta) N_{ai}
\end{align*}
\]

\[ \text{(12)} \]

We now substitute the expansion in Eqs. 8 into Eqs. 12 and keep only the \( O(1) \) terms to find

\[
\begin{align*}
\frac{d}{dt} \left( N_s^{(0)} + 2N_{ss}^{(0)} + N_{ai}^{(0)} \right) &= \Pi - \mu_s N_s^{(0)} - 2\mu_{ss} N_{ss}^{(0)} - (\mu_{si} + \beta) N_{ai}^{(0)} \\
\frac{d}{dt} \left( N_i^{(0)} + 2N_{ii}^{(0)} + N_{ai}^{(0)} \right) &= -\mu_i N_i^{(0)} - 2\mu_{ii} N_{ii}^{(0)} - (\mu_{is} - \beta) N_{ai}^{(0)}
\end{align*}
\]

\[ \text{(13a)} \]

\[ \text{(13b)} \]

\[ \text{(13c)} \]

\[ \text{(13d)} \]

\[ \text{(13e)} \]

By using Eqs. 13c-13e to eliminate \( N_{ss}^{(0)} \), \( N_{ai}^{(0)} \) and \( N_{ii}^{(0)} \) from Eqs. 13b-13a we obtain

\[
\begin{align*}
\frac{d}{dt} \left( N_s^{(0)} + 2\kappa_{ss} N_s^{(0)2} + \kappa_{si} N_s^{(0)} N_i^{(0)} \right) &= \Pi - \mu_s N_s^{(0)} - 2\mu_{ss} \kappa_{ss} N_s^{(0)2} - (\mu_{si} + \beta) \kappa_{si} N_s^{(0)} N_i^{(0)} \\
\frac{d}{dt} \left( N_i^{(0)} + 2\kappa_{ii} N_i^{(0)2} + \kappa_{si} N_s^{(0)} N_i^{(0)} \right) &= -\mu_i N_i^{(0)} - 2\mu_{ii} \kappa_{ii} N_i^{(0)2} - (\mu_{is} - \beta) \kappa_{si} N_s^{(0)} N_i^{(0)}
\end{align*}
\]

\[ \text{(14)} \]

where \( \kappa_{ss} = \bar{\alpha}_{ss}/\bar{d}_{ss}, \kappa_{si} = \kappa_{is} = \bar{\alpha}_{si}/\bar{d}_{si}, \) and \( \kappa_{ii} = \bar{a}_{ii}/\bar{d}_{ii} \).

3.2.1. Steady states and stability

The most convenient way to determine the steady states and/or further analyze Eqs. 13 is to unpack them in terms of \( N_s^{(0)} \) and \( N_i^{(0)} \) and write them in the form

\[
\frac{d}{dt} \begin{bmatrix} N_s^{(0)} \\ N_i^{(0)} \end{bmatrix} = M^{-1} \begin{bmatrix} \Pi - \mu_s N_s^{(0)} - 2\mu_{ss} \kappa_{ss} N_s^{(0)2} - (\mu_{si} + \beta) \kappa_{si} N_s^{(0)} N_i^{(0)} \\ -\mu_i N_i^{(0)} - 2\mu_{ii} \kappa_{ii} N_i^{(0)2} - (\mu_{is} - \beta) \kappa_{si} N_s^{(0)} N_i^{(0)} \end{bmatrix},
\]

\[ \text{(15)} \]

where

\[
M = \begin{bmatrix} 1 + 4\kappa_{ss} N_s^{(0)} + \kappa_{si} N_i^{(0)} & \kappa_{si} N_s^{(0)} \\ \kappa_{si} N_i^{(0)} & 1 + 4\kappa_{ii} N_i^{(0)} + \kappa_{si} N_s^{(0)} \end{bmatrix}
\]

Note that since \( N_s^{(0)}, N_i^{(0)}, \kappa_{ss}, \kappa_{si}, \kappa_{ii} \geq 0 \), the eigenvalues of \( M \) can never be zero and \( M \) is invertible.

One can readily show that the system of equations always supports an infection-free steady-state solution:
\( (N_s^{(0)}, N_i^{(0)}) = \left( \frac{-\mu_s + \sqrt{\mu_s^2 + 8\mu_{ss}\kappa_{ss}\Pi}}{4\mu_{ss}\kappa_{ss}}, 0 \right) \),

and that this solution is linearly stable if

\[ R := \frac{\kappa_{si}(\beta - \mu_{si})}{4\mu_{si}\kappa_{ss}} \left( -\mu_s + \sqrt{\mu_s^2 + 8\mu_{ss}\kappa_{ss}\Pi} \right) < 1. \]

and linearly unstable if \( R > 1 \). Another stable solution with positive \( N_s^{(0)} \) and \( N_i^{(0)} \) will exists if \( R > 1 \). This solution structure closely mirrors that of the mass-action and frequency-dependent models.

### 3.2.2. Comparison to mass-action and frequency-based models

In order to compare Eqs. (14) or (15) to the simpler classic models, it is preferable to rewrite the equations in terms of the leading-order expressions for the total susceptible and infected populations

\[
N_s^{(0)} = N_s^{(0)} + 2N_s^{(0)} + N_s^{(0)}
\]

\[
N_i^{(0)} = N_i^{(0)} + 2N_i^{(0)} + N_s^{(0)}.
\]

Again using Eqs. (15) or (16) to eliminate \( N_{ss}^{(0)} \), \( N_{si}^{(0)} \), and \( N_{ii}^{(0)} \), we find

\[
N_s^{(0)} = N_s^{(0)} + 2\kappa_{ss}N_s^{(0)} + \kappa_{si}N_s^{(0)}N_i^{(0)}
\]

\[
N_i^{(0)} = N_i^{(0)} + 2\kappa_{ii}N_i^{(0)} + \kappa_{si}N_s^{(0)}N_i^{(0)}.
\]

Next, we need to express the quantities \( N_s^{(0)} \) and \( N_i^{(0)} \) in terms of \( N_s^{(0)} \) and \( N_i^{(0)} \). Solving Eq. (19a) for \( N_i^{(0)} \) and substituting the result into Eq. (19a), we find a quartic equation for \( N_s^{(0)} \)

\[
2\kappa_{ss}(4\kappa_{ii}\kappa_{ss} - \kappa_{si}^2)N_s^{(0)} + (8\kappa_{ii}\kappa_{ss} - 2\kappa_{si}\kappa_{ss} - \kappa_{ii}^2)N_s^{(0)^3} + (\kappa_{si}^2N_s^{(0)} - N_i^{(0)}) - 8N_s^{(0)}(\kappa_{ii}\kappa_{ss} + 2\kappa_{ii} - \kappa_{si})N_s^{(0)^2} + N_s^{(0)}(\kappa_{si} - 4\kappa_{ii})N_s^{(0)} + 2N_s^{(0)^2} = 0.
\]

One can readily show that only one of the four roots gives values of \( N_s^{(0)} \) and \( N_i^{(0)} \) that are both positive when \( N_s^{(0)} \) and \( N_i^{(0)} \) are positive. Upon using this physical root for \( N_i^{(0)} \) as functions of \( N_s^{(0)} \) and \( N_i^{(0)} \) in Eq. (19a), we find the unique physical root for \( N_i^{(0)} \), expressed in terms of \( N_s^{(0)} \) and \( N_i^{(0)} \). Explicit formulae for the solution of a quartic are known and so we can express \( N_s^{(0)} \equiv F_s(N_s^{(0)}, N_i^{(0)}) \) and \( N_i^{(0)} \equiv F_i(N_s^{(0)}, N_i^{(0)}) \) as functions \( F_s \) and \( F_i \) that are obtained by the procedure described above. One can then rewrite

\[
\frac{dN_s^{(0)}}{dt} = \Pi - \mu_sN_s^{(0)} + 2(\mu_s - \mu_{ss})\kappa_{ss}F_s^2 + (\mu_s - \mu_{si} - \beta)\kappa_{si}F_sF_i
\]

\[
\frac{dN_i^{(0)}}{dt} = -\mu_iN_i^{(0)} + 2(\mu_i - \mu_{ii})\kappa_{ii}F_i^2 + (\mu_i - \mu_{is} + \beta)\kappa_{si}F_sF_i.
\]

Although \( F_s(N_s^{(0)}, N_i^{(0)}) \) and \( F_i(N_s^{(0)}, N_i^{(0)}) \) are unwieldy functions of \( N_s^{(0)} \) and \( N_i^{(0)} \), Eqs. (21) represent a systematic projection of the original five-dimensional problem to two equations describing the total susceptible and infected populations. These two equations can be further simplified in the following limits.
3.2.3. Low density asymptotics

Consider the solutions to \( N_S^{(0)} \) and \( N_1^{(0)} \) in the limit where the populations in the reference area \( A_0 \) are small, \( N_S^{(0)}, N_1^{(0)} \ll 1 \). Upon Taylor expansion of the solutions to Eqs. \ref{eq:19a} and \ref{eq:19b}, we find \( F_S(N_S^{(0)}, N_1^{(0)}) \approx N_S^{(0)} - (\kappa_{si} N_1^{(0)} + 2 \kappa_{ss} N_S^{(0)}) N_S^{(0)} + O(N_S^{(0)^3}) \) and \( F_1(N_S^{(0)}, N_1^{(0)}) \approx N_1^{(0)} - (\kappa_{si} N_S^{(0)} + 2 \kappa_{ii} N_1^{(0)}) N_1^{(0)} + O(N_S^{(0)^3}) \), and Eqs. \ref{eq:21} to lowest order becomes

\[
\begin{align*}
\frac{dN_S^{(0)}}{dt} &\approx \Pi - \mu_s N_S^{(0)} + 2(\mu_s - \mu_{ss})\kappa_{ss} N_S^{(0)^2} + (\mu_s - \mu_{si} - \beta)\kappa_{si} N_S^{(0)} N_1^{(0)} \\
\frac{dN_1^{(0)}}{dt} &\approx -\mu_1 N_1^{(0)} + 2(\mu_i - \mu_{ii})\kappa_{ii} N_1^{(0)^2} + (\mu_i - \mu_{is} + \beta)\kappa_{si} N_S^{(0)} N_1^{(0)}
\end{align*}
\]

(22)

The dynamics in this low-density limit are dominated by immigration and death, but are also qualitatively different from those of the standard mass-action model in that Eqs. \ref{eq:22} contain \( N_S^{(0)^2} \) and \( N_1^{(0)^2} \) terms. These quadratic terms arise from the difference in death rates between paired and unpaired susceptible individuals \( \mu_s - \mu_{ss} \) and paired and unpaired infected individuals \( \mu_i - \mu_{ii} \). However, if we assume that the death rate is independent of the pairing status, i.e., \( \mu_{ss} = \mu_s \), \( \mu_{ii} = \mu_i \), \( \mu_{si} = \mu_s \) and \( \mu_{is} = \mu_i \), we obtain the standard mass-action model with \( B_{ss} \propto \kappa_{si} \beta \).

3.2.4. High density asymptotics

If \( N_S^{(0)}, N_1^{(0)} \gg 1 \), and hence \( N_S^{(0)}, N_1^{(0)} \gg 1 \), the physical solutions to Eqs. \ref{eq:19a} and \ref{eq:19b} are approximately

\[
\begin{align*}
F_S(N_S^{(0)}, N_1^{(0)}) &\approx \frac{N_1^{(0)} + (2 K - 1) N_S^{(0)} - \sqrt{\left(N_1^{(0)} - N_S^{(0)}\right)^2 + 4 K N_S^{(0)} N_1^{(0)}}}{4 \kappa_{ss} (K - 1)} \\
F_1(N_S^{(0)}, N_1^{(0)}) &\approx \frac{N_S^{(0)} + (2 K - 1) N_1^{(0)} - \sqrt{\left(N_1^{(0)} - N_S^{(0)}\right)^2 + 4 K N_S^{(0)} N_1^{(0)}}}{4 \kappa_{ii} (K - 1)}
\end{align*}
\]

(23)

where \( K \equiv 4 \kappa_{ss} \kappa_{ii} / \kappa_{si}^2 \). Upon substituting Eqs. \ref{eq:23} into Eqs. \ref{eq:21}, we find the effective, though unwieldy, equations for \( N_S^{(0)}, N_1^{(0)} \gg 1 \). In this case, even if \( \mu_{ss} = \mu_s, \mu_{ii} = \mu_i, \mu_{si} = \mu_s \) and \( \mu_{is} = \mu_i \), the effective model differs significantly in form from both the mass-action and frequency-dependent models. In Figs. \ref{fig:1} we compare the exact solutions of \( N_S(t) \) and \( N_1(t) \) from Eqs. \ref{eq:7a} to \ref{eq:7c} to \( N_S^{(0)}(t) \) and \( N_1^{(0)}(t) \) derived from solving Eqs. \ref{eq:21} using Eqs. \ref{eq:23}. The agreement is excellent for all times.

3.2.5. Equal association rates and equal dissociation rates

A further simplification can be made in the special case in which both the pairing rates and unpairing rates for all possible pairings are equal. This implies that the dissociation coefficients for each of the pairings are the same \( d_{ss} = d_{ii} = d_{si} \). For association, there are three possible pairings: susceptible-susceptible, infected-infected, and susceptible-infected. A pair with one infected and one susceptible can combinatorially arise in two ways so \( \kappa_{si} = 2 \kappa_{ss} = 2 \kappa_{ii} \). Thus, \( \kappa_{si} = 2 \kappa_{ss} = 2 \kappa_{ii} \equiv \kappa \) and \( K = 1 \). The physical solution to Eqs. \ref{eq:19a} and \ref{eq:19b} then reduces to

\[
\begin{align*}
F_S(N_S^{(0)}, N_1^{(0)}) &= \frac{N_S^{(0)}}{4 \kappa} \left( N_S^{(0)} + N_1^{(0)} \right) \left( \sqrt{8 \kappa \left( N_1^{(0)} + N_S^{(0)} \right) + 1} - 1 \right) \\
F_1(N_S^{(0)}, N_1^{(0)}) &= \frac{N_1^{(0)}}{4 \kappa} \left( N_S^{(0)} + N_1^{(0)} \right) \left( \sqrt{8 \kappa \left( N_1^{(0)} + N_S^{(0)} \right) + 1} - 1 \right)
\end{align*}
\]

(24)

8
Figure 1: Fast association and dissociation - high density limit: Comparison of the exact numerical solution of Eqs. \(7a-7e\) with the numerical solution of the high-density asymptotic approximation derived from using Eqs. \(23\) in Eqs. \(24\). We plot the total susceptible and infected populations, \(N_s + N_{si} + 2N_{ss}\) and \(N_i + N_{ii} + 2N_{si}\), derived from Eqs. \(16\) (solid black) versus \(N_s^{(0)}\) and \(N_i^{(0)}\) from Eqs. \(20\) and \(21\) (dashed blue and dashed red) as functions of \(\ln t\). (a) The parameters used are \(\hat{a} = \hat{d} = 1\), \(\epsilon = 0.3\), \(\mu_s = \mu_{ss} = \mu_{si} = 0\), \(\mu_i = \mu_{ii} = \mu_{si} = 0.01\), \(\Pi = 2\), and \(\beta = 0.5\), with initial conditions \(N_s^{(0)}(0) = 100\) and \(N_i^{(0)}(0) = 10\). (b) Using the same parameters and initial conditions, but with \(\epsilon = 0.0003\). In both plots, the decreasing and increasing curves indicate \(N_s^{(0)}(t)\) and \(N_i^{(0)}(t)\), respectively. The asymptotic approximations are quite accurate even for \(\epsilon = 0.3\).

Using these expressions, Eqs. \(21\) in the \(N_s^{(0)} + N_i^{(0)} \gg 1\) limit simplify to

\[
\begin{align*}
\frac{dN_s^{(0)}}{dt} &= \Pi - \mu_s N_s^{(0)} + (\mu_s - \mu_{ss}) \frac{N_s^{(0)^2}}{N_s^{(0)} + N_i^{(0)}} + \frac{(\mu_s - \mu_{si} - \beta)}{2} \frac{N_s^{(0)} N_i^{(0)}}{N_s^{(0)} + N_i^{(0)}} \\
\frac{dN_i^{(0)}}{dt} &= -\mu_i N_i^{(0)} + (\mu_i - \mu_{ii}) \frac{N_i^{(0)^2}}{N_s^{(0)} + N_i^{(0)}} + \frac{(\mu_i - \mu_{si} + \beta)}{2} \frac{N_s^{(0)} N_i^{(0)}}{N_s^{(0)} + N_i^{(0)}}.
\end{align*}
\]

(25)

which is similar to a frequency-dependent model with effective transmission rate \(B_f = \beta/2\). Thus, we have found a specific limit where pairing and unpairing dynamics within a mass-action model reduces it to an effective frequency-dependent model.

3.3. Fast Association Limit

We now consider a different limit in which we relax the fast dissociation constraint and assume only the association rates are significantly larger than all other (dissociation, death, and infection) rates. Upon defining \(a_{ss} = a_{ss}/\epsilon\), \(a_{si} = a_{si}/\epsilon\) and \(a_{ii} = a_{ii}/\epsilon\), with \(\epsilon \to 0^+\), Eqs. \(16\) become

\[
\begin{align*}
\frac{dN_s}{dt} &= \Pi - \mu_s N_s + 2 \frac{a_{ss}}{\epsilon} N_s^2 - \frac{a_{si}}{\epsilon} N_s N_i + 2(\mu_{ss} + d_{ss}) N_{ss} + (\mu_{si} + d_{si}) N_{si} \\
\frac{dN_i}{dt} &= -\mu_i N_i - 2 \frac{a_{ii}}{\epsilon} N_i^2 - \frac{a_{si}}{\epsilon} N_s N_i + 2(\mu_{ii} + d_{ii}) N_{ii} + (\mu_{si} + d_{si}) N_{si} \\
\frac{dN_{ss}}{dt} &= - (2\mu_{ss} + d_{ss}) N_{ss} + \frac{a_{ss}}{\epsilon} N_s^2 \\
\frac{dN_{si}}{dt} &= - (\mu_{is} + \mu_{si} + d_{si} + \beta) N_{si} + \frac{a_{si}}{\epsilon} N_s N_i \\
\frac{dN_{ii}}{dt} &= - (2\mu_{ii} + d_{ii}) N_{ii} + \beta N_{si} + \frac{a_{ii}}{\epsilon} N_i^2.
\end{align*}
\]

(26)
Substituting the expansion
\[ N_s = N_s^{(0)} + \varepsilon^{1/2} N_s^{(1)} + \cdots \]
\[ N_i = N_i^{(0)} + \varepsilon^{1/2} N_i^{(1)} + \cdots \]
\[ N_{ss} = N_{ss}^{(0)} + \varepsilon^{1/2} N_{ss}^{(1)} + \cdots \]
\[ N_{si} = N_{si}^{(0)} + \varepsilon^{1/2} N_{si}^{(1)} + \cdots \]
\[ N_{ii} = N_{ii}^{(0)} + \varepsilon^{1/2} N_{ii}^{(1)} + \cdots \]
(27)
into Eqs. 28 and retaining only terms of size \( O(\varepsilon^{-1}) \), we find \( N_s^{(0)} = N_i^{(0)} = 0 \). Next, collecting terms of size \( O(1) \) we obtain
\[ 0 = \Pi - 2\bar{a}_{ss} N_s^{(1)} - \bar{a}_{si} N_i^{(1)} + 2(\mu_{ss} + d_{ss}) N_{ss}^{(0)} + (\mu_{is} + d_{si}) N_{si}^{(0)} \]  
(28a)
\[ 0 = -2\bar{a}_{ii} N_i^{(1)} - \bar{a}_{si} N_s^{(1)} + 2(\mu_{ii} + d_{ii}) N_{ii}^{(0)} + (\mu_{si} + d_{si}) N_{si}^{(0)} \]  
(28b)
\[ \frac{dN_{ss}^{(0)}}{dt} = - (2\mu_{ss} + d_{ss}) N_{ss}^{(0)} + \bar{a}_{ss} N_s^{(1)} \]  
(28c)
\[ \frac{dN_{si}^{(0)}}{dt} = - (\mu_{is} + \mu_{si} + d_{si} + \beta) N_{si}^{(0)} + \bar{a}_{si} N_s^{(1)} N_i^{(1)} \]  
(28d)
\[ \frac{dN_{ii}^{(0)}}{dt} = - (2\mu_{ii} + d_{ii}) N_{ii}^{(0)} + \bar{a}_{ii} N_i^{(1)} \]  
(28e)
Solving Eqs. 28a and 28b we find
\[ N_s^{(1)} = \frac{P_s + (2f - 1) P_s - \sqrt{(P_i - P_s)^2 + 4fPP_s}}{4\bar{a}_{ss}(f - 1)} \]  
(29)
\[ N_i^{(1)} = \frac{P_i + (2f - 1) P_i - \sqrt{(P_i - P_s)^2 + 4fPP_i}}{4\bar{a}_{ii}(f - 1)} \]

where \( f \equiv 4\bar{a}_{ss}\bar{a}_{ii}/\bar{a}_{si}^2 \) and
\[ P_s = 2(\mu_{ss} + d_{ss}) N_{ss}^{(0)} + (\mu_{is} + d_{si}) N_{si}^{(0)} + \Pi \]
\[ P_i = 2(\mu_{ii} + d_{ii}) N_{ii}^{(0)} + (\mu_{si} + d_{si}) N_{si}^{(0)} \]  
(30)
Thus, to lowest order in the fast association limit, the infected population is \( N_i^{(0)} \approx 2N_{ss}^{(0)} + N_{si}^{(0)} \). In what follows, it will be useful to define the susceptibles who are in susceptible-infected pairs, \( N_s^{(0)} \equiv N_{si}^{(0)} \), as an “exposed” population. Analogously, the “unexposed” susceptible population not in mixed pairs is dominated by susceptible-susceptible pairs and is \( N_s^{(0)} \approx 2N_{ss}^{(0)} \).

Rewriting Eqs. 28d 28e using Eqs. 28 we find
\[ \frac{dN_s^{(0)}}{dt} = - (2\mu_{ss} + d_{ss}) N_s^{(0)} + \frac{P_i + (2f - 1) P_i - \sqrt{(P_i - P_s)^2 + 4fPP_i}}{2(f - 1)} \]  
(31)
\[ \frac{dN_i^{(0)}}{dt} = - (\mu_{si} + \mu_{si} + d_{si} + \beta) N_i^{(0)} + \frac{\sqrt{(P_i - P_s)^2 + 4fPP_s}}{2(f - 1)} \]  
\[ \frac{dN_i^{(0)}}{dt} = - \mu_i N_i^{(0)} + (\mu_{ii} + \mu_{ii} + \beta) N_{ii}^{(0)} \]
where $P_s$ and $P_i$ can also be expressed as

$$
P_s = (\mu_{ss} + d_{ss})N_S^{(0)} + (\mu_{is} + d_{si})N_E^{(0)} + \Pi \\
P_i = (\mu_{ii} + d_{ii})N_I^{(0)} + (\mu_{ii} - \mu_{si} + d_{si} - d_{ii})N_E^{(0)}.
$$

(Eq. 32)

Eqs. 31 and 32 constitute a self-contained system of equations for the three subpopulations $N_S^{(0)}(t)$, $N_E^{(0)}(t)$, and $N_I^{(0)}(t)$.

An alternative formulation is to group all susceptibles and write

$$
\frac{d}{dt} (N_S^{(0)} + N_E^{(0)}) = \Pi - \mu_{ss} (N_S^{(0)} + N_E^{(0)}) + (\mu_{ss} - \mu_{si} - \beta) N_E^{(0)} + \sqrt{(P_i - P_s)^2 + 4fP_sP_i - (P_1 + P_3)}
$$

(Eq. 33)

$$
\frac{dN_S^{(0)}}{dt} = -\mu_{is} N_S^{(0)} + (\mu_{ii} - \mu_{is} + \beta) N_I^{(0)}
$$

$$
\frac{dN_E^{(0)}}{dt} = -\mu_{ii} N_I^{(0)} + (\mu_{ii} - \mu_{si} + \beta) N_E^{(0)}.
$$

In the case $a_{ii}^2 \to 4a_{ss}a_{ii}$ ($f \to 1$), we apply L’Hôpital’s rule on Eqs. 31 to further simplify it to

$$
\frac{dN_S^{(0)}}{dt} = -2(\mu_{ss} + d_{ss}) N_S^{(0)} + \frac{P_s^2}{P_s + P_i}
$$

$$
\frac{dN_E^{(0)}}{dt} = - (\mu_{is} + \mu_{si} + d_{si} + \beta) N_E^{(0)} + \frac{P_i}{P_s + P_i}
$$

$$
\frac{dN_I^{(0)}}{dt} = -\mu_{ii} N_I^{(0)} + (\mu_{ii} - \mu_{si} + \beta) N_E^{(0)}.
$$

(Eq. 34)

which is reminiscent of simple SEI-type models [19, 13, 23]. A comparison between $N_S$ and $N_I$ derived from the exact Eqs. 7a-7e and those derived from solving Eqs. 34 is given in Figs. 2. The approximations are accurate for all valid parameter regimes across all times.

4. Summary and Conclusions

We have revisited the canonical mass-action susceptible-infected disease transmission models and systematically incorporated pairing dynamics. The purpose is to rigorously find uniformly valid effective equations from mass-action models with pairing and unpairing steps. After nondimensionalization of the five fundamental mass-action equations, we find parameter regimes that allow us to develop uniformly valid approximations to the total infectious and susceptible populations. Our results were compared with lower-dimensional mass-action and frequency-dependent models without pairing.

First, in the fast transmission and pair dissociation limit, we found that the mass-action pairing model reduces to a standard mass-action susceptible-infected (SI) model (Eqs. 10) without pairing, but with an effective disease transmission rate given by Eq. 11.

Next, if pair formation and break-up are assumed fast, we found effective equations for the total susceptible and infected populations. Although the resulting two ODEs can be unwieldy, this system differs fundamentally from the basic SI model. However, if death rates do not depend on the pairing status, we show that, in the low-density limit, the simple mass-action response is recovered (Eq. 22). In this low-density limit, the pairing dynamics do not affect the leading-order form of the functional response. However, in the high-density limit, a frequency-dependent response is recovered (Eq. 25) if the association and dissociation rates are the same for each of the three different types of pairs. Under these assumptions, we showed that, for finite densities, a Holling’s Type II response does not arise. Nevertheless, we derived a simple functional
response that contains the same number of parameters as a model using Holling’s type II response, but with a clear mathematical justification.

Finally, we relaxed the fast dissociation constraint and assumed that only the association rates are large. In this case, we could only reduce the five-dimensional system of mass-action equations to a three-dimensional system that includes susceptible, infecteds, and an exposed population describing susceptible in susceptible-infected pairs (Eqs. 31 or 34). These equations share features with the canonical SEI-type models [2, 13, 19].

Although the two- or three-dimensional system of equations we derived are typically more complicated in form, our formulae allow one to incorporate the effects of pair formation and dissociation in a self-consistent, uniformly valid way in the limits described. We have also numerically compared our solutions with those from the full five-dimensional mass-action system and found excellent agreement in the limits analyzed (Figs. 1 and 2).

Our asymptotic analysis can be, in principle, straightforwardly extended to richer disease models including SIS, SIR, and models with birth processes. It would be interesting to apply similar asymptotic approaches to analyze disease dynamics occurring under group interactions or household structures [10, 8, 14, 16] or with aging [5].

Mass-action chemical reaction models in which an enzyme and substrate must first associate before a reaction can occur have also been treated using related asymptotic analyses. A classic example is Michaelis-Menten kinetics in which an inner and outer solution are pieced together to describe substrate and product concentrations at short and long times [17]. In our problem, we have only considered the “outer” solutions, yet for all cases studied, our lowest order approximations are valid at all times. A more detailed and rigorous examination of bimolecular interactions in mass-action chemical kinetics in certain reaction rate limits may provide new mathematical insights on approximating complex reaction networks.

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References

[1] Anderson RM (1982) Population Dynamics of Infectious Diseases: Theory and Applications. Chapman and Hall, London-New York
[2] Anderson RM, May RM (1991) Infectious Diseases of Humans, Dynamics and Control. Oxford university Press, Oxford
[3] Blower SM, Chou T (2004) Modeling the emergence of the “hot zones”: tuberculosis and the amplification dynamics of drug resistance. Nature Medicine 10:1111–1116
[4] Chen MJ, Ghani AC (2010) Populations and partnerships: insights from metapopulation and pair models into the epidemiology of gonorrhoea and other sexually transmitted infections. Sexually Transmitted Infections 86:433–439
[5] Chou T, Greenman CD (2016) A Hierarchical Kinetic Theory of Birth, Death and Fission in Age-Structured Interacting Populations. Journal of Statistical Physics 164:49–76
[6] Cross PC, Creech TG, Ebinger MR, Manlove K, Irvine K, Henningsen J, Rogerson J, Scurlock BM, Creel S (2013) Female elk contacts are neither frequency nor density dependent. Ecology 94:2076–2086
[7] Dawes JHP, Souza MO (2013) A derivation of Holling’s type I, II and III functional responses in predator-prey systems. J Theor Biol 327:11–22
[8] Dodd PJ, Ferguson NM (2007) Approximate disease dynamics in household-structured populations. Journal of the Royal Society Interface 4:1103–1106
[9] Fraser C (2007) Estimating individual and household reproduction numbers in an emerging epidemic. PLoS ONE 2:e758
[10] Ghoshal G, Sander LM, Sokolov I (2004) SIS epidemics with household structure: the self-consistent field method. Mathematical Biosciences 190(1):71–85
[11] Hadeler KP, Waldstätter R, Wörz-Busekros A (1988) Models for pair formation in bisexual populations. J Math Biol 26:635–649
[12] Heesterbeek JAP, Metz JAJ (1993) The saturating contact rate in marriage and epidemic models. J Math Biol 31:529–539
[13] Hethcote HW (2000) The Mathematics of Infectious Diseases. SIAM Review 42:599–653
[14] House T, Keeling MJ (2008) Deterministic epidemic models with explicit household structure. Mathematical Biosciences 213:29–39
[15] Hu H, Nigmatulina K, Eckhoff P (2013) The scaling of contact rates with population density for the infectious disease models. Mathematical Biosciences 244:125–134
[16] Keeling MJ, House T, Cooper AJ, Pellis L (2016) Systematic Approximations to Susceptible- Infectious- Susceptible Dynamics on Networks. PLoS Computational Biology 12:e1005296
[17] Keener J, Sneyd J (1998) Mathematical Physiology. Springer
[18] Kretzschmar M, Dietz K (1998) The effect of pair formation and variable infectivity on the spread of an infection without recovery. Mathematical Biosciences 148:83–113
[19] Li MY, Graef JR, Wang L, Karsai J (1999) Global dynamics of a SEIR model with varying total population size. Mathematical Biosciences 160:191–213
[20] Llensa C, Juher D, na JS (2014) On the early epidemic dynamics for pairwise models. Journal of Theoretical Biology 352:71–81
[21] Lloyd-Smith JO, Getz WM, Westerhoff HV (2004) Frequency-dependent incidence in sexually-transmitted disease models: portrayal of pair-based transmission and effects of illness on contact behaviour. Proc Royal Soc London B 271:625–634
[22] Murray JD (2002) Mathematical Biology: I. An Introduction, 3rd Ed. Springer, New York
[23] Yan P, Liu S (2006) SEIR epidemic model with delay. ANZIAM Journal 48:119–134