Effects of Asymptomatic Infections on the Spatial Spread of Infectious Diseases

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Introduction

An asymptomatic case is an individual who tests positive but experiences no symptoms throughout the course of infection. Asymptomatic infection is very common for many infectious diseases including COVID-19, Ebola, influenza, cholera, Zika fever, and dengue fever. For example, a meta-analysis based on 28 studies estimated that 25% COVID-19 infections are asymptomatic. Asymptomatic infectives are hard to detect but may transmit the infection to others, acting as silent spreaders.

Global travel and tourism accelerate the spread of infectious diseases and constitute a major challenge for disease prevention and control (e.g., 2009 H1N1 pandemic, 2014-16 Ebola outbreak, 2015-16 Zika virus epidemic, 2019-21 COVID-19 pandemic). Entry and exit screening can hardly detect asymptomatic travelers who are more likely to spread the infectious agent from one area to another due to their uninterrupted mobility. There are many epidemic models on asymptomatic infection (e.g., Kemper, 1978; Arino et al., 2008) or human movement (e.g.,Rvachev and Longini, 1985; Lewis et al., 2006; Allen et al., 2008), but few consider their joint effect.

Model Formulation

The population in patch $i \in \Omega = \{1, \cdots, n\}$ is divided into classes consisting of susceptible, symptomatic, asymptomatic and recovered individuals, denoted by S_i, I_i, A_i and R_i, respectively. An SIAR patch model is given as follows

$$\begin{aligned}
\frac{dS_i}{dt} &= d_S \sum_{j\in\Omega} L_{ij}^S S_j + \Lambda_i - \beta_i \frac{I_i + \tau_i A_i}{N_i} S_i - \mu_i S_i, \quad i \in \Omega,\\
\frac{dI_i}{dt} &= d_I \sum_{j\in\Omega} L_{ij}^I I_j + \theta_i \beta_i \frac{I_i + \tau_i A_i}{N_i} S_i - (\mu_i + \gamma_i^I + \delta_i) I_i, \quad i \in \Omega,\\
\frac{dA_i}{dt} &= d_A \sum_{j\in\Omega} L_{ij}^A A_j + (1-\theta_i)\beta_i \frac{I_i + \tau_i A_i}{N_i} S_i - (\mu_i + \gamma_i^A) A_i, \quad i \in \Omega,\\
\frac{dR_i}{dt} &= d_R \sum_{j\in\Omega} L_{ij}^R R_j + \gamma_i^I I_i + \gamma_i^A A_i - \mu_i R_i, \quad i \in \Omega.
\end{aligned} \tag{1}$$

In patch i, Λ_i is the recruitment rate, β_i is the transmission coefficient between symptomatic and susceptible individuals, τ_i is the relative infectiousness of asymptomatic individuals to symptomatic individuals, $\theta_i \in (0,1)$ is the proportion of new infections that are symptomatic, γ_i^I and γ_i^A are the recovery rates of symptomatic and asymptomatic persons, respectively, μ_i and δ_i are the natural and disease-induced mortality rates, respectively, $d_\sharp$ and $L^\sharp = (L_{ij}^A)$ with $\sharp\in$\{S,I,A,R\} are dispersal rate and connectivity matrix, respectively, and N_i is the total population size of patch i.

Mathematical Analysis

I. Threshold Dynamics. Assume the connectivity matrices $L^\sharp$ with $\sharp\in$\{S,I,A,R\} are irreducible and essentially nonnegative with zero column sums. The model (1) has a unique disease-free equilibrium $E_0 = (\boldsymbol{S}^0, \boldsymbol{0}, \boldsymbol{0}, \boldsymbol{0})$ with $\boldsymbol{S}^0 \gg \boldsymbol{0}$.

Following the next generation matrix method, the basic reproduction number is

$$\mathcal{R}_0 = \rho(F_{11}V_{11}^{-1} + F_{22}V_{22}^{-1}),$$

where $F_{11} = \mathrm{diag}\{\theta_1\beta_1, \cdots, \theta_n\beta_n\}, F_{22} = \mathrm{diag}\{(1-\theta_1)\tau_1\beta_1, \cdots, (1-\theta_n)\tau_n\beta_n\}, V_{11} = D_I - d_I L^I, V_{22} = D_A - d_A L^A, D_I = \mathrm{diag}\{r_1^I, \cdots, r_n^I\}$, $D_A = \mathrm{diag}\{r_1^A, \cdots, r_n^A\}$ with $r_i^I = \mu_i + \gamma_i^I + \delta_i$ and $r_i^A = \mu_i + \gamma_i^A$ for $i \in \Omega$.

Proposition 1. For model (1), the basic reproduction number $\mathcal{R}_0$ satisfies

$$\min_{i\in\Omega} \mathcal{R}_{0I}^{(i)} + \min_{i\in\Omega} \mathcal{R}_{0A}^{(i)} \le \mathcal{R}_0 \le \max_{i\in\Omega} \mathcal{R}_{0I}^{(i)} + \max_{i\in\Omega} \mathcal{R}_{0A}^{(i)},$$

where $\mathcal{R}_{0I}^{(i)} = \frac{\theta_i\beta_i}{r_i^I}$ and $\mathcal{R}_{0A}^{(i)} = \frac{(1-\theta_i)\tau_i\beta_i}{r_i^A}$ with $\mathcal{R}_0^{(i)} = \mathcal{R}_{0I}^{(i)} + \mathcal{R}_{0A}^{(i)}$ representing the basic reproduction number of patch i in isolation.

Theorem 1. For model (1), if $\mathcal{R}_0 \le 1$, then the disease-free equilibrium E_0 is globally asymptotically stable; if $\mathcal{R}_0 > 1$, then the disease is uniformly persistent and there exists at least one endemic equilibrium $E^* = (\boldsymbol{S}^*, \boldsymbol{I}^*, \boldsymbol{A}^*, \boldsymbol{R}^*)$.

II. Dependence of $\mathcal{R}_0$ on Dispersal Rates. In case of no asymptomatic infection, model (1) is reduced to an SIR patch model and its reproduction number is the same as that of an SIS patch model (e.g., Allen et al., 2007; Gao and Ruan, 2011).

Theorem 2. (Gao, 2019; Gao and Dong, 2020) For model (1) with $\theta_i = 1$ for all $i \in \Omega$, the basic reproduction number $\mathcal{R}_0(d_I) = \rho(F_{11}V_{11}^{-1})$ and the spectral bound $s(d_I) := s(F_{11} - V_{11})$ are strictly decreasing and strictly convex in $d_I \in [0, \infty)$ if $\mathcal{R}_0^{(i)} = \beta_i / r_i^I$ and $\beta_i - r_i^I$ are respectively nonconstant in $i \in \Omega$, and constant otherwise.

However, for the SIAR patch model (1) with $n = 2$, it is shown that $\mathcal{R}_0$ is either strictly decreasing or strictly increasing or constant with respect to d_I and d_A. Nonmonotone dependence of $\mathcal{R}_0$ on dispersal rates can occur with more patches.

Theorem 3. Suppose $\theta_i = \theta$ and $\tau_i = \tau$ for all $i \in \Omega$, and L^I and L^A are symmetric. Then the basic reproduction number $\mathcal{R}_0(d_I)$ of model (1) is constant in terms of d_I if $(F_{11}D_I^{-1} + F_{22}V_{22}^{-1})D_I\boldsymbol{1} = \mathcal{R}_0(0)D_I\boldsymbol{1}$, and strictly decreasing otherwise.

Proposition 2. Assume that: (i) $\theta_i = \theta$ and $\tau_i = \tau$ for $i \in \Omega$, (ii) $L^I = L^A := L$, (iii) there is a positive diagonal matrix C such that CLC^{-1} is symmetric. Let $\boldsymbol{v}$ be a positive right eigenvector of L corresponding to eigenvalue zero Then the basic reproduction number $\mathcal{R}_0(d_I)$ of model (1) is constant in terms of d_I if $(F_{11}D_I^{-1} + F_{22}V_{22}^{-1})D_I\boldsymbol{v} = \mathcal{R}_0(0)D_I\boldsymbol{v}$, and strictly decreasing otherwise.

Theorem 4. For model (1), if $d_I = 0$ (or $d_A = 0$), then the basic reproduction number $\mathcal{R}_0$ is strictly decreasing with respect to d_A (or d_I) whenever $\mathcal{R}_0^{(i)}$ is nonconstant in $i \in \Omega$, and constant otherwise.

III. Independence of $\mathcal{R}_0$ on Dispersal and Dispersal Rates. We consider under what conditions $\mathcal{R}_0(d_I, d_A, L^I, L^A)$ and $\mathcal{R}_0(d_I, d_A)$ are constant, respectively.

Proposition 3. For model (1), the following statements on $\mathcal{R}_0$ hold:

a) $\mathcal{R}_0$ is independent of dispersal iff both $\mathcal{R}_{0I}^{(i)}$ and $\mathcal{R}_{0A}^{(i)}$ are constant in $i \in \Omega$.

b) $\mathcal{R}_0$ is independent of dispersal rates iff $\mathcal{R}_0^{(i)}$ is constant in $i \in \Omega$ and $s\left((D_A F_{22}^{-1} F_{11} D_I^{-1} - d_A L^A F_{22}^{-1})^{-1} - D_I F_{11}^{-1} F_{22} D_A^{-1} + d_I L^I F_{11}^{-1}\right) = 0$ for any $d_I, d_A \ge 0$.

c) $\mathcal{R}_0$ is independent of dispersal rates if $\mathcal{R}_0^{(i)}$ is constant in $i \in \Omega$ and $D_I \boldsymbol{v}^I = k D_A \boldsymbol{v}^A$ for some $k > 0$, where $\boldsymbol{v}^\sharp$ is a right positive eigenvector with eigenvalue zero of matrix $L^\sharp$ for $\sharp\in$\{I,A\}, but not conversely.

d) $\mathcal{R}_0$ is independent of dispersal rates if $\mathcal{R}_0$ is independent of dispersal, but not conversely.

Numerical Simulations

Example 1. Infection risk versus dispersal rates.

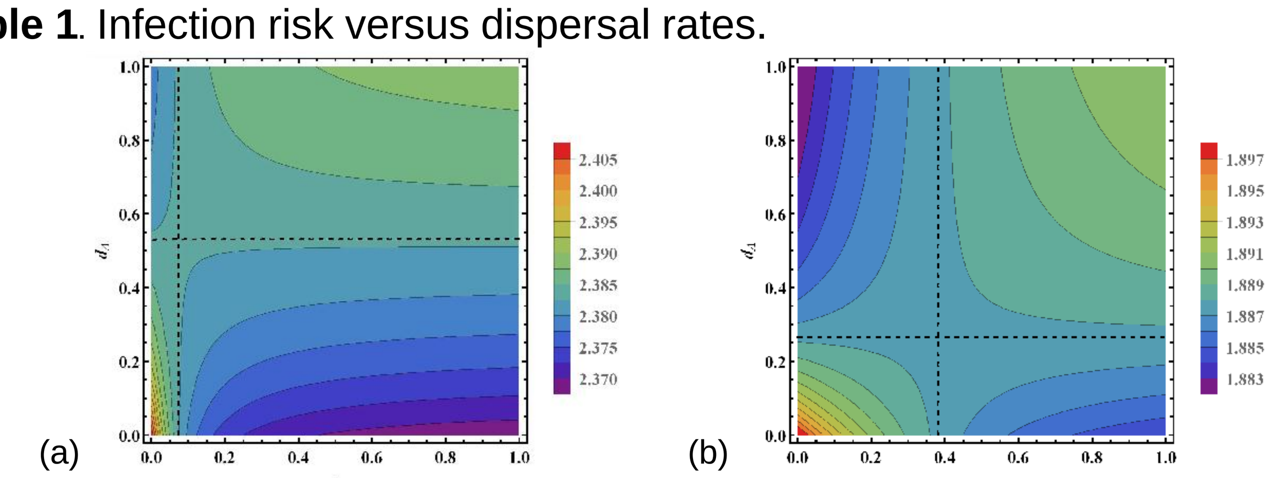

Figure 1. The contour plots of $\mathcal{R}_0$ versus d_I and d_A under parameter settings: (a) $\beta_1 = 0.77, \beta_2 = 0.35$, $r_1^I = 0.24$, $r_2^I = 0.13, r_1^A = 0.18$, $r_2^A = 0.21, \theta_1 = \theta_2 = 0.66, \tau_1 = 0.2, \tau_2 = 0.92, L_{12}^I = L_{21}^I = 0.08$, and $L^A = L^I$; (b) $\beta_1 = 0.59, \beta_2 = 0.44$, $r_1^I = 0.25$, $r_2^I = 0.22, r_1^A = 0.24$, $r_2^A = 0.11, \theta_1 = \theta_2 = 0.72, \tau_1 = \tau_2 = 0.29, L_{12}^I = 0.06$, $L_{21}^I = 0.01$, and $L_{12}^A = L_{21}^A = 0.1$. The dashed lines are the contours of $\mathcal{R}_0(d_I) = \mathrm{const}$ or $\mathcal{R}_0(d_A) = \mathrm{const}$.

Example 2. Ignoring asymptomatic infection underestimates the infection risk.

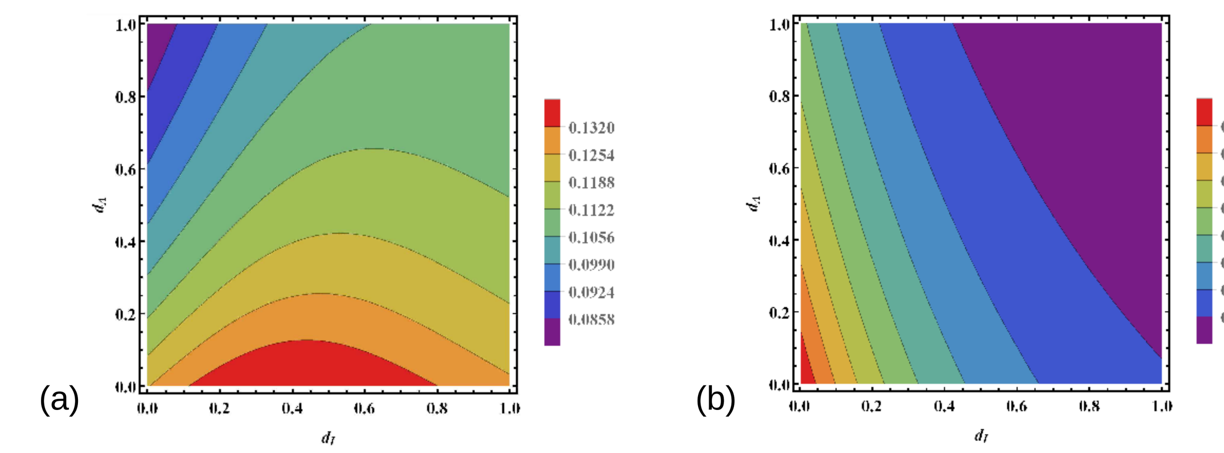

Figure 2. The contour plots of the relative underestimation of the reproduction number, $1 - \mathcal{R}_{0I}(d_I)/\mathcal{R}_0(d_I, d_A)$,under parameter settings: (a) $\beta_1 = 0.42, \beta_2 = 0.32$, $r_1^I = 0.16$, $r_2^I = 0.18, r_1^A = 0.14$, $r_2^A = 0.17, \theta_1 = \theta_2 = 0.8, \tau_1 = 0.5, \tau_2 = 0.36, L_{12}^I = 0.02$, $L_{21}^I = 0.1$, and $L^A = L^I$; (b) the same as (a) except that $r_1^I = 0.21$, $r_2^I = 0.16, \tau_2 = 0.5, L_{12}^I = 0.01$ and $L_{21}^I = 0.02$. Here $\mathcal{R}_{0I}(d_I) = \rho(F_{11}V_{11}^{-1})$.

Example 3. Nonsusceptible ratio versus dispersal rates (Gao, 2020; Gao and Lou, 2021). The ratio of nonsusceptible population over both patches and the difference of nonsusceptible ratios of patches 1 and 2 at the endemic equilibrium are respectively

$$1 - (S_1^* + S_2^*)/(N_1^* + N_2^*) \quad \text{and} \quad S_2^*/N_2^* - S_1^*/N_1^*.$$

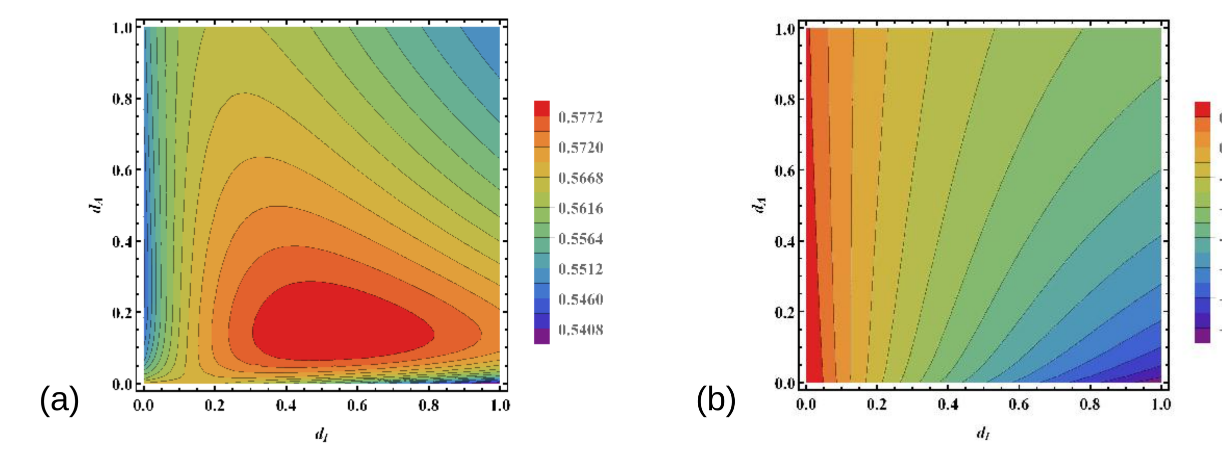

Figure 3. The contour plots of the nonsusceptible ratio over two patches and the difference of the nonsusceptible ratios of patches 1 and 2 at E^* under parameter setting: $\beta_1 = 0.4, \beta_2 = 0.54$, $r_1^I = 0.15$, $r_2^I = 0.24, r_1^A = 0.17$, $r_2^A = 0.19, \theta_i = 0.9, \tau_i = 0.4, \Lambda_1 = 50, \Lambda_2 = 21$, $\mu_i = 0.004$, $\delta_i = 0$ for $i = 1,2, L_{12}^I = 0.012$, $L_{21}^I = 0.06, L^S = L^I = L^A = L^R$, and $d_S = d_A = d_R$. Here $1 - 1/\mathcal{R}_0^{(1)} = 0.59$ and$1 - 1/\mathcal{R}_0^{(2)} = 0.52$.

Discussion

We propose an SIAR patch model to address asymptomatic infection and spatial heterogeneity. The reproduction number $\mathcal{R}_0$ is defined and estimated. The relation between $\mathcal{R}_0$ and dispersal rates is analyzed. Ignoring asymptomatic infections will underestimate the infection risk, and the level of underestimation significantly varies with dispersal rates. The inconsistence between $\mathcal{R}_0$ and the nonsusceptible ratio in response to fast dispersal highlights the necessity of assessing the effectiveness of control measures with other quantities besides the basic reproduction number.

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