Bulletin of Mathematical Biology (2021) 83:18
https://doi.org/10.1007/s11538-020-00855-3

Society for Mathematical Biology

ORIGINAL ARTICLE

A Network Immuno-Epidemiological HIV Model

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Received: 23 April 2020 / Accepted: 29 December 2020 / Published online: 16 January 2021

Abstract
In this paper we formulate a multi-scale nested immuno-epidemiological model of HIV on complex networks. The system is described by ordinary differential equations coupled with a partial differential equation. First, we prove the existence and uniqueness of the immunological model and then establish the well-posedness of the multi-scale model. We derive an explicit expression of the basic reproduction number $\mathscr{R}_0$ of the immuno-epidemiological model. The system has a disease-free equilibrium and an endemic equilibrium. The disease-free equilibrium is globally stable when $\mathscr{R}_0 < 1$ and unstable when $\mathscr{R}_0 > 1$. Numerical simulations suggest that $\mathscr{R}_0$ increases as the number of nodes in the network increases. Further, we find that for a scale-free network the number of infected individuals at equilibrium is a hump-like function of the within-host reproduction number; however, the dependence becomes monotone if the network has predominantly low connectivity nodes or high connectivity nodes.

Keywords HIV · Network · Age structured · Basic reproduction number · Epidemic model

1 Introduction

The human immunodeficiency virus (HIV), which causes acquired immune deficiency syndrome (AIDS), has been one of the major challenges for public health worldwide for the last few decades. There were approximately 37.9 million people globally with HIV/AIDS in 2018; an estimated 1.7 million individuals worldwide became newly

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infected with HIV in 2018; and an estimated 770,000 people died of AIDS and AIDS-related illnesses by the end of 2018 (https://www.unaids.org/en/resources/fact-sheet). HIV spreads via sexual contact, intravenous drug usage and vertical transmission, i.e., from mother to child. Therefore, the epidemic spread of HIV is mostly dependent on human behavior and contact.

Researchers from different disciplines, e.g., Biology, Mathematics, Medicine, Public Health and Pharmaceutical Industries, have been working on trying to eliminate or suppress HIV. Extensive research has been carried out on the immunological implication of HIV infection (Perelson and Nelson 1999; Rong et al. 2007; Huang et al. 2012). Similarly, epidemiological models have been studied to understand the viral dynamics of HIV within the population (Thieme and Castillo-Chavez 1993; Ruth and Blower 1993; Gumel et al. 2006). The dynamics of HIV/AIDS occurs at multiple scales, e.g., at the population level (transmission between humans) and the cellular level (within an infected human). However, research within the past decades has focused mainly on either within-host or between-host interactions. While it is easier to analyze disconnected (either between-host or within-host) models, certain questions can only be answered by looking at a multi-scale model. Gilchrist and Sasaki (2002) connected a simple within-host model in the nested fashion within a susceptible–infected–recovered (SIR) between-host model, and since then, many articles have followed a similar approach. Saenz and Bonhoeffer (2013) look at the way drug-resistant and drug-sensitive HIV strains in the immunological scale have an effect on the prevalence of those strains in the population. Martcheva and Li (2013) studied superinfection and its effect on the population dynamics. Shen et al. (2015) used a nested approach with partial differential equations to study the effects of antiretroviral therapy (ART) on viral load and the increase in prevalence of HIV. Lythgoe et al. (2013) used a nested integro-differential equation model to study competition between strains and its effect on HIV virulence. A similar approach was used in Doekes et al. (2017) to investigate how the latent reservoir of CD4+ T cells affects the evolution of HIV strains within and between host levels. Another approach has been to connect immunological to epidemiological models when both are described by ordinary differential equations (Cuadros and Garcia-Ramos 2012; Metzger et al. 2011), but in this approach the timescales variable for the within-host and between-host system remains the same.

The contact rate among individuals is not constant; some individuals may be in contact with a lot of other individuals, while others may be in contact with only a few. This is natural in a sexual or drug usage network. To describe this heterogeneity of contact, modelers have used complex networks. Pastor-Satorras and Vespignani (2001a) and Pastor-Satorras and Vespignani (2001b) used a complex network on an epidemic SIS model. The SIRS model on complex networks was studied in Li et al. (2014) and the SIR model in Wang et al. (2015). In Yang et al. (2016), the authors look into an age-since-infection SIS model integrated with a complex network. A similar approach was used in Yang and Chen (2017), and an age-since-infection SIR model on complex networks was investigated. A network of the small world type was used in Vieira et al. (2010) to model dynamics of HIV.

Epidemic spread on a static network, that is, without demography, has been thoroughly studied (Pastor-Satorras and Vespignani 2001b; Wang et al. 2012). For diseases

with a fast run time and recovery period, such as influenza or childhood diseases a static network can be appropriate, since the birth rate and death rate of individuals are on a much larger timescale. But for HIV, since it is a lifelong disease, demography does have a significant impact on disease dynamics. In such situations a dynamic network in which the network structure changes and nodes get occupied or vacated is considered (Zhang and Zhen 2011; Jin et al. 2014).

Here, we develop a multi-scale network model of HIV to address the question: "How do different network structures coupled with the within-host dynamics affect the between-host dynamics?" To our knowledge, no multi-scale model on a scale-free dynamic network of HIV has been developed or studied.

The paper is organized as follows: In Sect. 2 we introduce the within-host and between-host models and the parameters linking the two of them. In Sects. 3 and 4 we show the boundedness and existence of solutions for both the within-host and between-host model. In Sect. 5 we find the disease-free equilibrium and the threshold $\mathscr{R}_0$ and analyze the stability of the disease-free equilibrium, both local and global. We follow up in Sect. 6 with the existence and stability of the endemic equilibrium and establish that under certain conditions the endemic equilibrium is locally asymptotically stable. Finally, Sect. 7 contains simulations for our model. Section 8 summarizes our results.

2 A Multi-scale Network Model of HIV

In this section we develop a multi-scale network model of HIV. The model consist of a within-host immunological model of HIV which is common for all individuals in the population, regardless of their connection status. Furthermore, the model consists of a network age-since-infection structured compartment in which the individuals are separated into classes based on their connections.

2.1 Within-Host Model

The within-host model is a commonly used model in the literature (Nowak and May 2000) which tracks susceptible CD4+ cells $T(t)$, infected CD4+ cells $T_i(t)$ and the number of virions $V(t)$. The model takes the form:

$$\begin{aligned} T'(\tau) &= \lambda - k_v T V - dT, \\ T_i'(\tau) &= k_v T V - \mu_0 T_i, \\ V'(\tau) &= \pi T_i - cV. \end{aligned} \tag{1}$$

The immunological reproduction number is $R_0^{\text{host}} = \frac{\lambda k_v \pi}{\mu_0 dc}$. The immunological reproduction number gives the number of secondary viral particles that one viral particle will produce in an entirely susceptible target cell population. We assume that $R_0^{\text{host}} > 1$ as HIV persists within host. Model (1) has been analyzed before. It is known that if $R_0^{\text{host}} < 1$, it only has an infection-free equilibrium $E^0_{\text{host}} = (\frac{\lambda}{d}, 0, 0)$ which is globally asymptotically stable. When $R_0^{\text{host}} > 1$, the model also has an endemic equilibrium $E^*_{\text{host}} = (T^*, T_i^*, V^*)$ where

Table 1 Definitions of parameters and state variables of the within-host model

Notation	Meaning
λ	Production rate of healthy T-cells
k_v	Infection rate of healthy cells infected by virus
T	Number of healthy cells
T_i	Number of infected cells
d	Natural death rate of healthy cells
V	Number of virions
μ_0	Death rate of infected cells
c	Clearance rate of virions
π	Virus production rate of infected cells

$$T^* = \frac{\mu_0 c}{k_v \pi}, \qquad T_i^* = \frac{cd}{k_v \pi}(R_0^{\text{host}} - 1), \qquad V^* = \frac{d}{k_v}(R_0^{\text{host}} - 1).$$

It is also known that if $R_0^{\text{host}} > 1$, the infection-free equilibrium is unstable and the endemic equilibrium is globally stable (De Leenheer and Smith 2003). The immunological model parameters and state variables are defined in Table 1.

2.2 Linking Parameters

Linking parameters are epidemiological parameters that are expressed in terms of the within-host parameters and dependent variables. Their purpose is to link the within-host and the between-host models into a full immuno-epidemiological model. The linking functions in this model are $\beta(\tau)$, "the transmission rate of HIV" and $\gamma(\tau)$, " the rate of progression of infected individuals to AIDS." Typically, there are many ways to define the linking functions (Gilchrist and Coombs 2006). We assume the simplest linking functions, that is, $\beta_j(\tau)$ is proportional to the viral load at a given age since infection τ, and so

$$\beta_j(\tau) = \beta_j V(\tau).$$

The transition rate $\gamma(\tau)$ is assumed to be

$$\gamma(\tau) = \gamma_0 V(\tau).$$

2.3 Between-Host Model

We consider a dynamic network with total fixed number of vertices N_T. Some of the vertices are empty, but some are occupied by susceptible, infected or AIDS individuals. For an epidemic network, the degree of a node is the number of contacts the node has with other nodes. We assume that the network contacts are HIV-type contacts. That is, an edge between any two nodes represents transmission of HIV, either through sexual

contact or intravenous drug usage. For a network with maximal degree n, the average network degree is given by

$$\langle k \rangle = \sum_{k=1}^{n} kp(k)\,,$$

where $p(k)$ is the probability that a randomly chosen node has degree k. Empirical studies suggest that many real-life HIV networks have scale-free degree distribution $p(k) \sim k^{-\eta}$, where $2 < \eta < 3$ (Rotenberg 2009). A scale-free network is formed by adding a new person to the network one at a time following a connection mechanism that copies the natural formation of social contact (Keeling and Eames 2005). This type of network contains a few nodes which are connected to a large number of the other nodes (also called Hubs), and a majority of the nodes with very few edges. The conditional probability $p(j|k)$ is the probability that a node with degree k is connected to a node with degree j, which is given by

$$p(j|k) = \frac{jp(j)}{\langle k \rangle}\,.$$

Let n be the maximal number of connections in the complex network. For $k \in \{1, 2, ..., n\}$, let $S_k(t)$ be the number of susceptible vertices of degree k at time t, $i_k(t, \tau)$ stand for the density of infected vertices of degree k at time t and with infection age τ and $A_k(t)$ be the number of AIDS vertices which transferred from the infected class of degree k at time t. $N_k(t)$ is the total active population size of degree k at time t. We introduce an epidemiological model with infection in the host, as follows:

$$\begin{aligned} \frac{\mathrm{d}S_k}{\mathrm{d}t} &= \Lambda_k - k\lambda_v(t)S_k(t) - \mu S_k(t), \\ \frac{\partial i_k}{\partial t} + \frac{\partial i_k}{\partial \tau} &= -(\mu + \gamma(\tau))i_k(t, \tau), \\ i_k(0, t) &= k\lambda_v(t)S_k(t), \\ \frac{\mathrm{d}A_k}{\mathrm{d}t} &= \int_0^\infty \gamma(\tau)i_k(t, \tau)\mathrm{d}\tau - (\mu + \alpha)A_k(t). \end{aligned} \tag{2}$$

where $k \in \{1, 2, \cdots, n\}$. The force of infection $\lambda_v(t)$ is given by

$$\lambda_v(t) = \frac{1}{\langle k \rangle} \sum_{k=1}^{n} kp(k) \int_0^\infty \frac{\beta_k(\tau)i_k(t, \tau)}{N_k(t)}\mathrm{d}\tau.$$

Further, $\gamma(\tau)$ is the transition rate at infection age τ from the infected class to the AIDS stage class, and $\beta_k(\tau)$ is the transmission rate at infection age τ. The Λ_k is the recruitment rate of susceptibles, μ is the natural death rate of all classes, and α is the disease-induced mortality rate. We consider the total active population size of degree

k as:

$$N_k(t) = S_k(t) + \int_0^\infty i_k(t, \tau)\mathrm{d}\tau.$$

A shortcoming of this model due to the simple linking functions would be that all individuals in the population experience the same within-host dynamics. This problem could have been remedied if multiple groups of infected individuals were included in the population. Such a multi-group multi-scale model is studied in Numfor et al. (2016). But because of the network structure, the system is already complicated, and addition of multiple groups of infection classes would further complicate it. We believe addition of infection classes would not give any different insights with the network structures.

3 Existence and Boundedness of the Solution of Within-Host Model

The existence and boundedness of the solutions of the within-host model will be necessary to prove the existence and uniqueness of the multi-scale system. We state the following theorem without proof.

Theorem 1 (Thieme 2003) *Let $\mathbb{R}^n_+ = [0, \infty)^n$ be the cone of nonnegative vectors in $\mathbb{R}^n$. Let $F : \mathbb{R}^n_+ \to \mathbb{R}^n$ be locally Lipschitz,*

$$F(t, x) = (F_1(t, x), \cdots, F_n(t, x)), x = (x_1, \cdots, x_n),$$

and satisfy

$$F_j(t, x) \geq 0 \text{ whenever } t \geq 0, x \in \mathbb{R}^n_+, x_j = 0.$$

Then for every $x^0 \in \mathbb{R}^n_+$, there exists a unique solution of $x' = F(t, x), x(0) = x^0$ with values in $\mathbb{R}^n_+$, which is defined on some interval $[0, b)$, $b > 0$. If $b < \infty$, then

$$\limsup_{t \to b} \sum_{j=1}^{n} x_j(t) = \infty.$$

We apply Theorem 1 to system (1). Since the system equations are bilinear, the system is locally Lipschitz. When $(T, T_i, V) \geq 0$, taking $T(\tau) = 0$, we have

$$T'(\tau) = \lambda > 0.$$

Similarly, taking $T_i(\tau) = 0$,

$$T_i'(\tau) = k_v T V \geq 0,$$

and lastly taking $V(\tau) = 0$,

$$V'(\tau) = \pi T_i \geq 0.$$

So system (1) satisfies the conditions of Theorem 1 and has a unique nonnegative solution.

Now the following computation shows that $T(\tau)$, $T_i(\tau)$, $V(\tau)$ are bounded.

For all τ

$$\begin{aligned} T'(\tau) + T_i'(\tau) &= (T + T_i)'(\tau) = \lambda - dT - \mu_0 T_i \\ &\leq \lambda - \min\{d, \mu_0\}(T + T_i) \end{aligned}$$

which implies

$$(T + T_i) \leq \frac{\lambda}{\min\{d, \mu_0\}} + c_0 e^{-\min\{d,\mu_0\}\tau},$$

where $c_0 = T(0) + T_i(0) - \frac{\lambda}{\min\{d,\mu_0\}}$.

Since $T + T_i$ is bounded, so is T_i. Let $T_i \leq C_2$. So

$$V'(\tau) = \pi T_i - cV \leq \pi C_2 - cV,$$

which implies

$$V \leq \frac{\pi C_2}{c} + c_1 e^{-c\tau},$$

where $c_1 = V(0) - \frac{\pi C_2}{c}$.

So,

$$\limsup_{\tau\to\infty} (T + T_i + V) \leq \frac{\lambda}{\min\{d, \mu_0\}} + \frac{\pi C_2}{c}.$$

Hence, according to Theorem 1, (1) has a solution for the interval $[0, b)$ when $b > 0$. Since the solutions are bounded, we have that $b = \infty$. We get the following theorem.

Theorem 2 *Given Eq. (1) with positive initial conditions* $T(0) = T^0, T_i(0) = T_i^0, V(0) = V^0$, *there exist constants* C_1, C_2, C_3 *such that* $0 \leq T(\tau) \leq C_1, 0 \leq T_i(\tau) \leq C_2, 0 \leq V(\tau) \leq C_3$ *for all* $\tau > 0$.

4 Boundedness and Existence of Solutions

Using the method of integrating factors and the characteristics, we find a integral formulation of Eq. (2). For the well-posedness of the between-host system, we use an

approach similar to the one used in Numfor et al. (2014).

$$S_k(t) = S_{k0}e^{-(\alpha+\mu)t} + \frac{\Lambda_k}{\mu+\alpha}(1-e^{-(\alpha+\mu)t}) + \int_0^t e^{-(\mu+\alpha)(t-s)} S_k(s)\left(\alpha - \frac{k}{\langle k\rangle}\sum_{j=1}^{n}\frac{jp(j)}{N_j(s)}\int_0^\infty \beta_j V(\tau) i_j(t,\tau)\mathrm{d}\tau\right)\mathrm{d}s,$$

$$i_k(t,\tau) = \begin{cases} \frac{k}{\langle k\rangle} S_k(t-\tau)\pi(\tau)\sum_{k=1}^{n}\frac{jp(j)}{N_j(t-\tau)}\int_0^\infty \beta_j V(\tau) i_j(t-\tau,r)\mathrm{d}r, & \text{if } t \geq \tau \\ i_k(\tau-t,0)\frac{\pi(\tau)}{\pi(\tau-t)} & t < \tau \end{cases} \tag{3}$$

where $\alpha \geq n\beta C_3$, and $\beta = \max\{\beta_1, \cdots, \beta_n\}$ and $\pi(\tau) = e^{-\int_0^\tau (\mu+\gamma(\sigma))\mathrm{d}\sigma}$.

To prove the existence and uniqueness, we define our state solution space as

$$X = \Big\{(X_1 \times X_2)^n, X_1 = \mathbb{R}, X_2 = L^1(\mathbb{R}), S_k(t) \geq \epsilon_k > 0, i_k(t,\tau) \geq 0, \limsup S_k(t) < \infty \text{ and } \limsup \int_0^\infty i_k(t,\tau)\mathrm{d}\tau < \infty \text{ for } k = 1, 2, ..., n\Big\},$$

where $\epsilon_k = \min\{S_{k0}, \frac{\Lambda_k}{\mu+\alpha}\}$.

Now we define a map

$$\mathscr{L}_k : X \to (X_1 \times X_2), \mathscr{L}_k(S,i) = (L_{k1}(S,i), L_{k2}(S,i)),$$

where

$$L_{k1}(S,i) = S_{k0}e^{-(\alpha+\mu)t} + \frac{\Lambda_k}{\mu+\alpha}(1-e^{-(\alpha+\mu)t}) + \int_0^t e^{-(\mu+\alpha)(t-s)} S_k(s)\left(\alpha - \frac{k}{\langle k\rangle}\sum_{j=1}^{n}\frac{jp(j)}{N_j(s)}\int_0^\infty \beta_j V(\tau) i_j(t,\tau)\mathrm{d}\tau\right)\mathrm{d}s, \tag{4}$$

and

$$L_{k2}(S,i) = \begin{cases} \frac{k}{\langle k\rangle} S_k(t-\tau)\pi(\tau)\sum_{k=1}^{n}\frac{jp(j)}{N_j(t-\tau)}\int_0^\infty \beta_j V(\tau) i_j(t-\tau,r)\mathrm{d}r, & \text{if } t \geq \tau \\ i_k^0(\tau-t)\frac{\pi(\tau)}{\pi(\tau-t)} & t < \tau. \end{cases} \tag{5}$$

The following assumptions are made:

- $S_{k0}, \mu, \Lambda_k, \beta_k$ are positive constants for all $k = 1, 2, \cdots, n$,
- $\mu + \gamma_0(s)$ is positive and Lipschitz continuous,
- $i_k^0(\tau - t)$ is nonnegative for all $\tau > t$, for all $k = 1, 2, \cdots, n$,

- $\int_0^\infty i_k^0(\tau)\mathrm{d}\tau \le M$ and $0 < S_{k0} \le M$ for all $k = 1, 2, \cdots, n$,
- $\limsup S_k(t) < M$ for all $k = 1, 2, \cdots, n$.

Theorem 3 *For $T < \infty$, there exists a unique nonnegative solution (S, i) to the epidemiological system (2).*

Proof First, we show $\mathscr{L}_k$ maps X into $(X_1 \times X_2)$.

$$\begin{aligned}
|L_{k1}(S,i)|(t) &\le |S_{k0}e^{-(\alpha+\mu)t}| \\
&\quad + \left|\frac{\Lambda_k}{\mu+\alpha}(1-e^{-(\alpha+\mu)t})\right| + \alpha\left|\int_0^t S_k(s)e^{-(\mu+\alpha)(t-s)}\mathrm{d}s\right| \\
&\quad + \left|\int_0^t e^{-(\mu+\alpha)(t-s)}S_k(s)\frac{k}{\langle k\rangle}\sum_{j=1}^n \frac{jp(j)}{N_j(s)}\int_0^\infty \beta_j V(\tau) i_j(t,\tau)\mathrm{d}\tau\mathrm{d}s\right| \\
&\le M + \frac{\Lambda_k}{\alpha+\mu} + \frac{\alpha}{\alpha+\mu}\limsup S_k(s) + \frac{k\beta C_3}{\mu+\alpha}\limsup S_k(s) < \infty.
\end{aligned}$$

Next we consider the second component.

$$\begin{aligned}
&\int_0^\infty |L_{k2}(S,i)|(t,\tau)\mathrm{d}\tau \\
&= \int_0^t \left|\frac{k}{\langle k\rangle}S_k(t-\tau)\pi(\tau)\sum_{k=1}^n \frac{jp(j)}{N_j(t-\tau)}\int_0^\infty \beta_j V(\tau) i_j(t-\tau,r)\mathrm{d}r\right|\mathrm{d}\tau \\
&\quad + \int_t^\infty |i_k^0(\tau-t)e^{-\int_0^t \mu+\gamma_0 V(\tau-t-s)\mathrm{d}s}|\mathrm{d}\tau \\
&\le k\beta C_3 T\limsup S_k(s) + M < \infty.
\end{aligned}$$

Now

$$L_{k1}(S,i)(t) \ge S_{k0}e^{-(\mu+\alpha)t} + \frac{\Lambda_k}{\mu+\alpha}(1-e^{-(\mu+\alpha)t}) \ge \epsilon_k > 0,$$

due to the convex combination of S_{k0} and $\frac{\Lambda_k}{\mu+\alpha}$. Also, $L_{k2}(S,i)(t) \ge 0$ since $S_k(t) \ge \epsilon_k > 0$ and $i_k(t,\tau) \ge 0$. Hence, $\mathscr{L}_k$ maps X to $X_1 \times X_2$.

Next, we show that $\mathscr{L}_k$ admits a unique fixed point. We define the following iterative sequence:

$$(S_k^{m+1}(t), i_k^{m+1}(t,\tau)) = (L_{k1}(S^m(t), i^m(t,\tau)), L_{k2}(S^m(t), i^m(t,\tau))), \tag{6}$$

where

$$S_k^{m+1}(t) = S_{k0}e^{-(\mu+\alpha)t} + \frac{\Lambda_k}{\mu+\alpha}\left(1 - e^{-(\mu+\alpha)t}\right) + \int_0^t e^{-(\mu+\alpha)(t-s)} S_k^m(s)\left(\alpha - \frac{k}{\langle k\rangle}\sum_{j=1}^{n}\frac{jp(j)}{N_j^m(s)}\int_0^\infty \beta_j V(\tau) i_j^m(t,\tau)\mathrm{d}\tau\right)\mathrm{d}s,$$

$$i_k^{m+1}(t,\tau) = \begin{cases} \frac{k}{\langle k\rangle} S_k^n(t-\tau)\pi(\tau)\sum_{k=1}^{n}\frac{jp(j)}{N_j^n(t-\tau)}\int_0^\infty \beta_j V(\tau) i_j^n(t-\tau,r)\mathrm{d}r, & \text{if } t \geq \tau \\ i_k^0(\tau - t)\frac{\pi(\tau)}{\pi(\tau-t)} & t < \tau. \end{cases}$$

We set $S_k^0(t) = 0$ and $i_k^0(t,\tau) = 0$. Then,

$$S_k^1(t) = S_{k0}e^{-(\mu+\alpha)t} + \frac{\Lambda_k}{\mu+\alpha}\left(1 - e^{-(\mu+\alpha)t}\right),$$

$$i_k^1(t,\tau) = \begin{cases} 0, & \text{if } t \geq \tau \\ i_k^0(\tau - t)\frac{\pi(\tau)}{\pi(\tau-t)} & t < \tau, \end{cases}$$

and define a sequence of total population as

$$N_k^m(t) = S_k^m(t) + \int_0^\infty i_k^m(t,\tau)\mathrm{d}\tau.$$

To show the sequence of functions $(S_k^{m+1}(t), i_k^{m+1}(t,\tau))$ converges for all $m \geq 0$, we define the following notation

$$\begin{aligned} \mathbb{F}_k^m(t) &= |S_k^{m+1}(t) - S_k^m(t)|, \\ \mathbb{I}_k^m(t) &= \int_0^\infty |i_k^{m+1}(t,\tau) - i_k^m(t,\tau)|\mathrm{d}\tau, \end{aligned} \tag{7}$$

where

$$\mathbb{N}^m(t) = \sum_{k=1}^{n} kp(k)(\mathbb{F}_k^m(t) + \mathbb{I}_k^m(t)).$$

We have $\mathbb{F}_k^0 = S_{k0}e^{-(\mu+\alpha)t} + \frac{\Lambda_k}{\mu+\alpha}(1 - e^{-(\mu+\alpha)t}) \leq \max\{S_{k0}, \frac{\Lambda_k}{\mu+\alpha}\}$, $\mathbb{I}_k^0 = \int_0^\infty i_k^0(\tau)\mathrm{d}\tau$ and so $\mathbb{N}^0 = \sum_{k=1}^{n} kp(k)(\max\{S_{k0}, \frac{\Lambda_k}{\mu+\alpha}\} + \int_0^\infty i_k^0(\tau)\mathrm{d}\tau)$.

For $n = 1$, we get

$$\begin{aligned} \mathbb{F}_k^1(t) &= |S_k^2(t) - S_k^1(t)| \\ &= \left|\int_0^t e^{-(\mu+\alpha)(t-s)} S_k^1(s)\left(\alpha - \frac{k}{\langle k\rangle}\sum_{j=1}^{n}\frac{jp(j)}{N_j^1(s)}\int_0^\infty \beta_j V(\tau) i_j^1(t,\tau)\mathrm{d}\tau\right)\mathrm{d}s\right| \\ &\leq \max\left\{S_{k0}, \frac{\Lambda}{\mu+\alpha}\right\}\left(\frac{\alpha + n\beta C_3}{\alpha+\mu}\right), \end{aligned} \tag{8}$$

and

$$\begin{aligned}\mathbb{I}_k^1(t) &= \int_0^\infty |i_k^2(t,\tau) - i_k^1(t,\tau)|\mathrm{d}\tau \\ &= \int_0^t \frac{k}{\langle k\rangle} S_k^1(t-\tau) \sum_{j=1}^n jp(j) \frac{\int_t^\infty \beta_j V(s) i_k^0(s+\tau-t)\frac{\pi(\tau)}{\pi(\tau-s)} ds}{N_j^1(t-\tau)} \mathrm{d}\tau \\ &\le K\beta C_3 \int_0^t S_k^1(t-\tau)\mathrm{d}\tau = K\beta C_3 T \max\{S_{k0}, \frac{\Lambda_k}{\mu+\alpha}\}. \end{aligned} \tag{9}$$

From (8) and (9) we get $\mathbb{N}^1(t) = \sum_{k=1}^n kp(k)(\mathbb{F}_k^1(t) + \mathbb{I}_k^1(t)) \le C\mathbb{N}^0$.

$$\begin{aligned}\mathbb{F}_k^m(t) = |S_k^{m+1}(t) - S_k^m(t)| &\le \alpha \int_0^t e^{-(\mu+\alpha)(t-\xi)} |S_k^m(\xi) - S_k^{m-1}(\xi)|\mathrm{d}\xi \\ &+ \int_0^t e^{-(\mu+\alpha)(t-\xi)} \frac{k}{\langle k\rangle} \sum_{j=1}^n jp(j)\beta_j C_3 \int_0^\infty \Big| S_k^m(\xi)\frac{i_j^m(\xi,\tau)}{N_j^m(\xi)} \\ &- S_k^{m-1}(\xi)\frac{i_j^{m-1}(\xi,\tau)}{N_j^{m-1}(\xi)}\Big|\mathrm{d}\tau, \end{aligned} \tag{10}$$

where

$$\begin{aligned}&\sum_{j=1}^n jp(j)\int_0^\infty \left| S_k^m(\xi)\frac{i_j^m(\xi,\tau)}{N_j^m(\xi)} - S_k^{m-1}(\xi)\frac{i_j^{m-1}(\xi,\tau)}{N_j^{m-1}(\xi)}\right|\mathrm{d}\tau \\ &\le \sum_{j=1}^n jp(j)\left(|S_k^m(\xi) - S_k^{m-1}(\xi)| \int_0^\infty \frac{i_j^m(\xi,\tau)}{N_j^m(\xi)} d\tau + S_k^{m-1}(\xi)\int_0^\infty \left|\frac{i_j^n(\xi,\tau)}{N_j^m(\xi)} - \frac{i_j^{m-1}(\xi,\tau)}{N_j^{m-1}(\xi)}\right|\mathrm{d}\tau\right) \\ &\le \sum_{j=1}^n jp(j)\left(|S_k^m(\xi) - S_k^{m-1}(\xi)| + S_k^{m-1}(\xi)\int_0^\infty i_j^m(\xi,\tau)\left|\frac{N_j^{m-1}(\xi) - N_j^m(\xi)}{N_j^{m-1}(\xi)N_j^m(\xi)}\right|\mathrm{d}\tau\right) \\ &+ \sum_{j=1}^n jp(j)\frac{S_k^{m-1}(\xi)}{N_j^{m-1}(\xi)}\int_0^\infty |i_j^m(\xi,\tau) - i_j^{m-1}(\xi,\tau)|\mathrm{d}\tau) \\ &\le \sum_{j=1}^n jp(j)\left(|S_k^m(\xi) - S_k^{m-1}(\xi)| + \frac{\limsup S_k}{\epsilon_j}(|S_j^{m-1}(\xi) - S_j^m(\xi)| + \int_0^\infty 2|i_j^m(\xi,\tau) - i_j^{m-1}(\xi,\tau)|\mathrm{d}\tau)\right). \end{aligned} \tag{11}$$

From (10) and (11), we get

$$\mathbb{F}_k^m(t) \le (\alpha+k)\int_0^t \mathbb{F}_k^{m-1}(\xi)\mathrm{d}\xi + \frac{kK_1}{\langle k\rangle}\sum_{j=1}^n jp(j)\int_0^t (\mathbb{F}_j^{m-1}(\xi) + 2\mathbb{I}_j^{m-1}(\xi))\mathrm{d}\xi. \tag{12}$$

Thus,

$$\sum_{k=1}^{n} kp(k)\mathbb{F}_k^m(t) \le (\alpha+n)\sum_{k=1}^{n} kp(k)\int_0^t \mathbb{F}_k^{m-1}(\xi)\mathrm{d}\xi + \sum_{k=1}^{n}\frac{k^2K_1p(k)}{\langle k\rangle} \times \left[\sum_{j=1}^{n} jp(j)\int_0^t (\mathbb{F}_j^{m-1}(\xi)+2\mathbb{I}_j^{m-1}(\xi))\mathrm{d}\xi\right] \le \mathbf{K}_1\left[\sum_{k=1}^{n} kp(k)\int_0^t (\mathbb{F}_k^{m-1}(\xi)+\mathbb{I}_k^{m-1}(\xi))\mathrm{d}\xi\right]. \tag{13}$$

Next we consider the second component.

$$\mathbb{I}_k^m(t) = \int_0^\infty |i_k^{m+1}(t,\tau)-i_k^m(t,\tau)|\mathrm{d}\tau \le \int_0^t \frac{k}{\langle k\rangle}\pi(\tau)\sum_{j=1}^{n} jp(j)\int_0^\infty \beta C_3\left|\frac{S_k^m(t-\tau)i_j^m(t-\tau,r)}{N_j^m(t-\tau)} - \frac{S_k^{m-1}(t-\tau)i_j^{m-1}(t-\tau,r)}{N_j^{m-1}(t-\tau)}\right|\mathrm{d}r\mathrm{d}\tau \le \mathbf{K}_2\left[\sum_{k=1}^{n} kp(k)\int_0^t (\mathbb{F}_k^{m-1}(\xi)+\mathbb{I}_k^{m-1}(\xi))\mathrm{d}\xi\right], \tag{14}$$

where we used a similar method to the first component and used the substitution $\xi = t-\tau$. Combining (13) and (14) we notice the following recurrence relation

$$\mathbb{N}^m(t) \le \mathbf{K}\int_0^t \mathbb{N}^{m-1}(\xi)\mathrm{d}\xi,$$

with $\mathbb{N}^1(t) \le C\mathbb{N}^0$, where $\mathbf{K} = \mathbf{K}_1 + \mathbf{K}_2$.

Now,

$$\mathbb{N}^2(t) \le \mathbf{K}\int_0^t \mathbb{N}^1(\xi)\mathrm{d}\xi \le \mathbf{K}C\mathbb{N}^0 t,$$

and

$$\mathbb{N}^3(t) \le \mathbf{K}\int_0^t \mathbf{K}C\mathbb{N}^0\xi\mathrm{d}\xi \le C\mathbb{N}^0\frac{\mathbf{K}^2t^2}{2}.$$

Thus by induction, it follows that

$$\mathbb{N}^m(t) \le C\mathbb{N}^0\frac{\mathbf{K}^{m-1}t^{m-1}}{(m-1)!} \le C\mathbb{N}^0\frac{\mathbf{K}^{m-1}T^{m-1}}{(m-1)!}.$$

Next we see that

$$\left|S_k^{l+m}(t) - S_k^m(t)\right| \leq \sum_{j=m+1}^{l+m} \mathbb{N}^j(t) \leq C\mathbb{N}^0 \sum_{j=m+1}^{\infty} \frac{\mathbf{K}^{j-1}T^{j-1}}{(j-1)!} \to 0, \text{ as } m \to \infty$$

Also,

$$\begin{aligned}\int_0^\infty \left|i_k^{l+m}(t,\tau) - i_k^m(t,\tau)\right| \mathrm{d}\tau &\leq \sum_{j=m+1}^{l+m} \int_0^\infty |i_k^j(t,\tau) - i_k^{j-1}(t,\tau)| \mathrm{d}\tau \\ &\leq \sum_{j=m+1}^{l+m} \mathbb{N}^j(t) \leq C\mathbb{N}^0 \sum_{j=m+1}^{\infty} \frac{\mathbf{K}^{j-1}T^{j-1}}{(j-1)!} \to 0, \text{ as } m \to \infty\end{aligned}$$

It can be concluded that the sequence $\{S_k^m(t), i_k^m(t,\tau)\}$ generated by (6) is a Cauchy sequence in $X_1 \times X_2$, and is convergent since $X_1 \times X_2$ is complete. Thus, there exists $(S_k(t), i_k(t,\tau))$ in $X_1 \times X_2$ which is the limit of the given sequence, and a fixed point of the operator $\mathscr{L}_k$. Therefore, there exists a solution to the between-host model for all $T < \infty$.

To prove uniqueness, we assume there are two solutions $(S_k(t), i_k(t,\tau))$ and $(\overline{S}_k(t), \overline{i}_k(t,\tau))$, which satisfy the following equations,

$$(S_k(t), i_k(t,\tau)) = (L_{k1}((S_k(t), i_k(t,\tau))), L_{k2}((S_k(t), i_k(t,\tau)))),$$

and

$$(\overline{S}_k(t), \overline{i}_k(t,\tau)) = (L_{k1}((\overline{S}_k(t), \overline{i}_k(t,\tau))), L_{k2}((\overline{S}_k(t), \overline{i}_k(t,\tau)))).$$

We substitute $(S_k(t), i_k(t,\tau))$ and $(\overline{S}_k(t), \overline{i}_k(t,\tau))$ in place of $(S_k^m(t), i_k^m(t,\tau))$ and $(S_k^{m-1}(t), i_k^{m-1}(t,\tau))$, respectively, in the proof of existence of solution above, and set

$$\hat{\mathbb{F}}_k(t) = \left|S_k(t) - \overline{S_k}(t)\right| \text{ and } \hat{\mathbb{I}}_k(t) = \int_0^\infty \left|i_k(t,\tau) - \overline{i}_k(t,\tau)\right| \mathrm{d}\tau.$$

From the recurrence relation, we get

$$\hat{\mathbb{N}}(t) \leq \mathbf{K} \int_0^t \hat{\mathbb{N}}(\xi)\mathrm{d}\xi,$$

so that by Gronwall's inequality in integral form $\hat{\mathbb{N}}(t) = 0$. Thus, $\sum_{k=1}^n kp(k)(\hat{\mathbb{F}}_k(t) + \hat{\mathbb{I}}_k(t)) = 0$. Since $\hat{\mathbb{F}}_k(t) \geq 0$ and $\hat{\mathbb{I}}_k(t) \geq 0$ and $\sum_{k=1}^n kp(k)(\hat{\mathbb{F}}_k(t) + \hat{\mathbb{I}}_k(t)) = 0$, there can be two cases, either $p(k) = 0$, in which case there are no vertices with degree k, or both $\hat{\mathbb{F}}_k(t)$ and $\hat{\mathbb{I}}_k(t)$ are equal to 0 for all $t > 0$. Hence, the solution $(S_k(t), i_k(t,\tau))$ to the epidemiological model is unique.

□

5 The Disease-Free Equilibrium

5.1 Existence and Stability of the Disease-Free Equilibrium

Equilibria are time-independent solutions of the system. We look at the equilibria of this system, and we set the differentials with respect to t equal to zero.

$$\begin{aligned} \Lambda_k - k\lambda_v S_k - \mu S_k &= 0, \\ \frac{\partial i_k}{\partial \tau} &= -(\mu + \gamma(\tau)) i_k(\tau), \\ i_k(0) &= k\lambda_v S_k. \end{aligned} \tag{15}$$

At the disease-free equilibrium $i_k(\tau)$ is zero for all k. So $\varepsilon^0 = \left(\frac{\Lambda_1}{\mu}, 0, \cdots, \frac{\Lambda_n}{\mu}, 0\right)$.

To determine the stability of the disease-free equilibrium and the immuno-epidemiological reproduction number, we linearize around the disease-free equilibrium. We take $S_k(t) = S_k^0 + x_k(t)$, $N_k(t) = N_k^0 + n_k(t)$ and $i_k(t, \tau) = y_k(t, \tau)$. Then, linearizing Eq. (15) takes the following form:

$$\begin{aligned} \frac{\mathrm{d}x_k}{\mathrm{d}t} &= -k\lambda_v(t) S_k^0 - \mu x_k(t), \\ \frac{\partial y_k}{\partial t} + \frac{\partial y_k}{\partial \tau} &= -(\mu + \gamma(\tau)) y_k(t, \tau), \\ y_k(0, t) &= k\lambda_v(t) S_k^0, \\ \lambda_v(t) = \frac{1}{\langle k \rangle} \sum_{k=1}^{n} kp(k) \int_0^\infty & \frac{\beta_k(\tau) y_k(t, \tau)}{N_k^0} \mathrm{d}\tau. \end{aligned} \tag{16}$$

where $N_k^0 = S_k^0 = \frac{\Lambda_k}{\mu}$. We look for solutions of the form $x_k(t) = x_{k0} e^{\lambda t}$, $y_k(\tau, t) = y_k(\tau) e^{\lambda t}$ and obtain the following eigenvalue problem,

$$\begin{aligned} 0 &= -(\lambda + \mu) x_{k0} - k\lambda_v(y_k(\tau)) S_k^0, \\ \frac{\partial y_k}{\partial \tau} + \lambda y_k(\tau) &= -(\mu + \gamma(\tau)) y_k(\tau), \\ y_k(0) &= k\lambda_v(y_k(\tau)) S_k^0. \end{aligned} \tag{17}$$

Solving the second equation of (17) we get

$$y_k(\tau) = y_k(0) \pi(\tau) e^{-\lambda \tau}. \tag{18}$$

Substituting (18) in the third equation of (17) we obtain,

$$y_k(0) = k\lambda_v(y_l(\lambda)) S_k^0, \tag{19}$$

where $\lambda_v(y_l(\lambda)) = \frac{1}{\langle k\rangle}\sum_{l=1}^{n} lp(l)\int_0^\infty \frac{\beta_l(\tau)y_l(0)\pi(\tau)e^{-\lambda\tau}}{N_l^0}\mathrm{d}\tau$. Simplifying we have:

$$\begin{aligned} y_k(0) &= kS_k^0\frac{1}{\langle k\rangle}\sum_{l=1}^{n} lp(l)\int_0^\infty \frac{\beta_l(\tau)\pi(\tau)e^{-\lambda\tau}\mathrm{d}\tau}{N_l^0}y_l(0),\\ \frac{y_k(0)}{S_k^0} &= k\frac{1}{\langle k\rangle}\sum_{l=1}^{n} lp(l)\int_0^\infty \frac{\beta_l(\tau)\pi(\tau)e^{-\lambda\tau}\mathrm{d}\tau}{N_l^0}y_l(0). \end{aligned} \tag{20}$$

Note that $\frac{S_k^0}{N_k^0} = 1$. Multiplying both sides of (20) by $\frac{1}{\langle k\rangle}\sum_{l=1}^{n} kp(k)\int_0^\infty \beta_k(\tau)\pi(\tau)e^{-\lambda\tau}\mathrm{d}\tau$ and then adding together, we have

$$\begin{aligned} \frac{1}{\langle k\rangle}\sum_{l=1}^{n} lp(l)\frac{y_l(0)}{N_l^0}\int_0^\infty \beta_l(\tau)\pi(\tau)e^{-\lambda\tau}\mathrm{d}\tau &= \frac{1}{\langle k\rangle}\sum_{k=1}^{n} k^2p(k)\int_0^\infty \beta_k(\tau)\pi(\tau)e^{-\lambda\tau}\mathrm{d}\tau\\ &\quad \sum_{l=1}^{n} lp(l)\int_0^\infty \frac{\beta_l(\tau)\pi(\tau)e^{-\lambda\tau}\mathrm{d}\tau}{N_l^0}y_l(0),\\ \lambda_v(y_k(\lambda)) &= \frac{1}{\langle k\rangle}\sum_{k=1}^{n} k^2p(k)\int_0^\infty \beta_k(\tau)\pi(\tau)e^{-\lambda\tau}\mathrm{d}\tau\lambda_v(y_l(\lambda)). \end{aligned} \tag{21}$$

If $\lambda_v(y_k(\lambda)) = 0$, then $y_k(\tau) = 0$ which is not the case for all ks.
Canceling out $\lambda_v(y_k(\lambda))$ from both sides of (21) we get,

$$1 = \frac{1}{\langle k\rangle}\sum_{k=1}^{n} k^2p(k)\int_0^\infty \beta_k(\tau)\pi(\tau)e^{-\lambda\tau}\mathrm{d}\tau. \tag{22}$$

We define

$$\mathscr{R}_0 = \frac{1}{\langle k\rangle}\sum_{k=1}^{n} k^2p(k)\int_0^\infty \beta_k(\tau)\pi(\tau)\mathrm{d}\tau. \tag{23}$$

The formulation of between-host reproduction number $\mathscr{R}_0$ is dependent on $\beta_k(\tau)$ and $\gamma(\tau)$, since

$$\pi(\tau) = e^{-\int_0^\tau(\mu+\gamma(\sigma))\mathrm{d}\sigma}.$$

We compute $\mathscr{R}_0$ when the within-host model is at equilibrium. In such a situation transmission rate $\beta_k(\tau)$ and transition into AIDS rate $\gamma(\tau)$ become,

$$\beta_k(\tau) = \beta_k V(\tau) = \beta_k\frac{d(R_0^{\text{host}}-1)}{k_v}, \text{ and } \gamma(\tau) = \gamma_0\frac{d(R_0^{\text{host}}-1)}{k_v}.$$

With this setting $\pi(\tau)$ can be computed as

$$\pi(\tau) = e^{-(\mu+\gamma_0 \frac{d(R_0^{\text{host}}-1)}{k_v})\tau}.$$

Since

$$\mathscr{R}_0 = \frac{1}{\langle k \rangle} \sum_{k=1}^{n} k^2 p(k) \int_0^{\infty} \beta_k(\tau)\pi(\tau)\mathrm{d}\tau,$$

when the within-host system is at equilibrium, then $\mathscr{R}_0$ equals to

$$\mathscr{R}_0 = \frac{1}{\langle k \rangle} \sum_{k=1}^{n} k^2 p(k) \frac{\beta_k d(R_0^{\text{host}}-1)}{\mu k_v + \gamma_0 d(R_0^{\text{host}}-1)}.$$

$\mathscr{R}_0$ is explicitly dependent on R_0^{host} and the other between-host parameters. In general $\mathscr{R}_0$ is dependent on within-host dynamics as well.

Next we prove the following theorem.

Theorem 4 *If $\mathscr{R}_0 < 1$, then the disease-free equilibrium is locally asymptotically stable. If $\mathscr{R}_0 > 1$, it is unstable.*

Proof Suppose

$$\mathscr{G}(\lambda) = \frac{1}{\langle k \rangle} \sum_{k=1}^{n} k^2 p(k) \int_0^{\infty} \beta_k(\tau)\pi(\tau)e^{-\lambda\tau}\mathrm{d}\tau$$

Then, we notice that $\mathscr{G}(0) = \mathscr{R}_0$, $\lim_{\lambda\to\infty} \mathscr{G}(\lambda) = 0$

We claim that if $\mathscr{R}_0 < 1$, then the disease-free equilibrium is locally asymptotically stable, that is, all the roots of (22) have negative real parts. To show this, we proceed by way of contradiction. Suppose (22) has a root λ_0 with $\Re(\lambda_0) \geq 0$. Then,

$$1 = |\mathscr{G}(\lambda_0)| = |\mathscr{G}(\Re\lambda_0)| \leq |\mathscr{G}(0)| \leq \mathscr{R}_0$$

This is a contradiction. Hence, ε^0 is locally asymptotically stable when $\mathscr{R}_0 < 1$.

Now let us suppose $\mathscr{R}_0 > 1$. Then since $\mathscr{G}'(\lambda) < 0$, $\mathscr{G}(\lambda)$ is a decreasing function, with $\mathscr{G}(0) = \mathscr{R}_0 > 1$ and $\lim_{\lambda\to\infty} \mathscr{G}(\lambda) = 0$. Then, (22) has at least one positive root, and therefore, ε^0 is unstable if $\mathscr{R}_0 > 1$.

□

5.2 Global Stability of the Disease-Free Equilibrium

We use the Fluctuation Lemma to establish the global stability of the disease-free equilibrium. The following notation is used,

$$f^{\infty} = \lim_{t\to\infty} \sup f(t),$$

and

$$f_\infty = \lim_{t\to\infty} \inf f(t).$$

Then, the Fluctuation Lemma (Thieme 2003) is given as follows:

Lemma 1 (Fluctuation Lemma) *Let $g : \mathbb{R}_+ \to \mathbb{R}$ be a bounded and continuously differentiable function. Then, there exist sequences $\{s_n\}$ and $\{t_n\}$ such that $s_n \to \infty$, $t_n \to \infty$, $g(s_n) \to g_\infty$, $g'(s_n) \to 0$, $g(t_n) \to g^\infty$ and $g'(t_n) \to 0$ as $n \to \infty$.*

Lemma 2 *Suppose $f : \mathbb{R}_+ \to \mathbb{R}_+$ is a bounded function and $h(t) \geq 0$. Then,*

$$\lim_{t\to\infty} sup \int_0^t h(\theta) f(t-\theta) d\theta \leq f^\infty \int_0^\infty h(s) \mathrm{d}s$$

Using integration along the characteristic lines, $i_k(t,\tau)$ satisfies the following Volterra formulation:

$$i_k(t,\tau) = \begin{cases} B_k(t-\tau)\pi(\tau), & \text{if } t \geq \tau \\ i_k(\tau - t, 0)\frac{\pi(\tau)}{\pi(\tau - t)} & t < \tau \end{cases} \tag{24}$$

where $B_k(t) = kS_k\lambda_v(t)$ for $k = 1, ..., n$.

Theorem 5 *If $\mathscr{R}_0 < 1$, then the disease-free equilibrium is globally asymptotically stable.*

Proof Theorem 4 shows that the disease-free equilibrium ε^0 of system (2) is locally stable if $\mathscr{R}_0 < 1$. To use the Fluctuation Lemma, we substitute the expressions of $i_k(t,\tau)$, to get

$$\begin{aligned} B_k(t) = kS_k\lambda_v(t) &= kS_k(t)\frac{1}{\langle k\rangle}\sum_{j=1}^{n} jp(j)\int_0^\infty \frac{\beta_j(\tau) i_j(t,\tau)}{N_j(t)}\mathrm{d}\tau, \\ Q_k(t) = \frac{B_k(t)}{N_k(t)} &= k\frac{S_k(t)}{N_k(t)}\frac{1}{\langle k\rangle}\sum_{j=1}^{n}\frac{jp(j)}{N_j(t)}\left(\int_0^t \beta_j(\tau)B_j(t-\tau)\pi(\tau)\mathrm{d}\tau + F_j(t)\right) \\ &\leq k\frac{1}{\langle k\rangle}\sum_{j=1}^{n}\frac{jp(j)}{N_j(t)}\left(\int_0^t \beta_j(\tau)B_j(t-\tau)\pi(\tau)\mathrm{d}\tau + F_j(t)\right), \end{aligned} \tag{25}$$

where

$$F_j(t) = \int_t^\infty \beta_j(\tau) i_j(\tau - t, 0)\frac{\pi(\tau)}{\pi(\tau - t)}\mathrm{d}\tau,$$

with $\lim_{t\to\infty} F_j(t) = 0$.

Choose the sequence $t_n^1 \to \infty$ such that $Q_k(t_n^1) \to Q_k^\infty$. We recall that $F_j(t) \to 0$ as $t \to \infty$. With the help of Lemmas 1 and 2, it follows from (23)

$$Q_k^\infty \leq k \frac{1}{\langle k \rangle} \sum_{j=1}^{n} jp(j) Q_j^\infty \int_0^\infty \beta_j(\tau)\pi(\tau)\mathrm{d}\tau. \tag{26}$$

Multiplying both sides of Eq. (26) with $kp(k)K_k$, where $K_k = \int_0^\infty \beta_k(\tau)\pi(\tau)\mathrm{d}\tau$, and summing from 1 to n, we get

$$\sum_{k=1}^{n} kp(k)K_k Q_k^\infty \leq \frac{1}{\langle k \rangle} \sum_{k=1}^{n} k^2 p(k) K_k \sum_{j=1}^{n} jp(j) Q_j^\infty \int_0^\infty \beta_j(\tau)\pi(\tau)\mathrm{d}\tau. \tag{27}$$

Then, (27) reduces to

$$Q \leq \mathscr{R}_0 Q \text{ where } Q = \sum_{k=1}^{n} kp(k)K_k Q_k^\infty.$$

Since $\mathscr{R}_0 < 1$, $Q = 0$, that is, $Q_k^\infty = 0$ which in turn implies $B_k^\infty = 0$. It follows from (24) we have that $\lim_{t\to\infty} i_k(t,\tau) = 0$

Next we show that $\lim_{t\to\infty} \int_0^\infty i_k(t,\tau)\mathrm{d}\tau = 0$. To show that we use (24) again and see that

$$\begin{aligned} \int_0^\infty i_k(t,\tau)\mathrm{d}\tau &= \int_0^t B_k(t-\tau)\pi(\tau)\mathrm{d}\tau + \int_t^\infty i_k(\tau - t, 0)\frac{\pi(\tau)}{\pi(\tau - t)}\mathrm{d}\tau \\ &\leq \int_0^t B_k(t-\tau)\pi(\tau)\mathrm{d}\tau + e^{-\mu t}\int_t^\infty i_k(\tau - t, 0)\mathrm{d}\tau. \end{aligned} \tag{28}$$

Using Lemma 2, we get

$$\limsup_{t\to\infty} \int_0^\infty i_k(t,\tau)\mathrm{d}\tau \leq B_k^\infty \int_0^\infty \pi(s)\mathrm{d}s \leq \frac{1}{\mu} B_k^\infty = 0.$$

This implies $\lim_{t\to\infty} \int_0^\infty i_k(t,\tau)\mathrm{d}\tau = 0$

Since $\beta_k(\tau)$ is a bounded function, the last result also implies $\lim_{t\to\infty} \lambda_v(t) = 0$.

Using Lemma 1, there exists a sequence t_n^2 such that as $n \to \infty$, $t_n^2 \to \infty$, $S_k(t_n^2) \to S_\infty$ and $S_k'(t_n^2) \to 0$.

It follows from

$$\frac{\mathrm{d}S_k(t_n^2)}{\mathrm{d}t} = \Lambda_k - \mu S_k(t_n^2) - K S_k(t_n^2)\lambda_v(t_n^2) \tag{29}$$

that

$$0 = \Lambda_k - \mu S_{k\infty} \implies S_{k\infty} = \frac{\Lambda_k}{\mu}. \tag{30}$$

Now, we know that

$$\begin{aligned}\frac{\mathrm{d}N_k}{\mathrm{d}t} &= \frac{\mathrm{d}S_k}{\mathrm{d}t} + \int_0^\infty \frac{\partial i_k}{\partial t}\mathrm{d}\tau \\ &= \Lambda_k - i_k(0,t) - \mu S_k(t) - \mu\int_0^\infty i_k(t,\tau)\mathrm{d}\tau - \int_0^\infty \gamma(\tau) i_k(t,\tau)\mathrm{d}\tau - \int_0^\infty \frac{\partial i_k}{\partial \tau}\mathrm{d}\tau \\ &= \Lambda_k - \mu N_k(t) - \int_0^\infty \gamma(\tau) i_k(t,\tau)\mathrm{d}\tau.\end{aligned} \tag{31}$$

Then, $N_k^\infty \leq \frac{\Lambda_k}{\mu}$ and so $S_k^\infty \leq \frac{\Lambda_k}{\mu}$. This implies $\lim_{t\to\infty} S_k(t) = \frac{\Lambda_k}{\mu}$. This completes the proof. □

6 Existence and Stability of the Endemic Equilibrium

Now we assume $\mathscr{R}_0 > 1$. Then, the disease-free equilibrium of system (2) is unstable. We look for at least one positive endemic equilibrium $\mathscr{E}^* = (S_1^*, i_1^*, \cdots, S_n^*, i_n^*)$. Consider the system for the endemic equilibria,

$$\begin{aligned}\Lambda_k - \mu S_k^* - k S_k^* \lambda_v(i^*) &= 0, \\ \frac{\partial i_k^*}{\partial \tau} &= -(\mu + \gamma(\tau)) i_k^*(\tau), \\ i_k^*(0) &= k S_k^* \lambda_v(i^*),\end{aligned} \tag{32}$$

where

$$\lambda_v(i^*) = \frac{1}{\langle k\rangle}\sum_{k=1}^n k p(k)\int_0^\infty \frac{\beta_k(\tau) i_k^*(\tau)}{N_k^*}\mathrm{d}\tau.$$

From the first equation of (32) we get $S_k^* = \frac{\Lambda_k}{\mu + k\lambda_v(i^*)}$ and from the second equation we get, $i_k^*(\tau) = i_k^*(0)\pi(\tau)$. Let

$$\int_0^\infty \beta_k(\tau)\pi(\tau)\mathrm{d}\tau = K_k.$$

Then,

$$\begin{aligned}\lambda_v(i^*) &= \frac{1}{\langle k\rangle}\sum_{k=1}^n k p(k)\frac{i_k^*(0) K_k}{N_k^*} \\ &= \frac{1}{\langle k\rangle}\sum_{k=1}^n k^2 p(k)\frac{S_k^*}{N_k^*}\lambda_v(i^*) K_k.\end{aligned} \tag{33}$$

Now,

$$N_k^* = S_k^* + i_k^*(0)\int_0^\infty \pi(\tau)\mathrm{d}\tau = S_k^* + kS_k^*\lambda_v(i^*)\int_0^\infty \pi(\tau)\mathrm{d}\tau$$
$$= S_k^*\left(1 + k\lambda_v(i^*)\int_0^\infty \pi(\tau)\mathrm{d}\tau\right), \tag{34}$$

that implies

$$\frac{S_k^*}{N_k^*} = \frac{1}{1 + k\lambda_v(i^*)\Pi},$$

where

$$\Pi = \int_0^\infty \pi(\tau)\mathrm{d}\tau.$$

$\lambda_v(i^*) = 0$ is a solution to (33) which gives the disease-free equilibrium. Then for an endemic equilibrium, $\lambda_v(i^*) > 0$ is a root of $f(\lambda_v)$, where

$$f(\lambda_v) = \frac{1}{\langle k\rangle}\sum_{k=1}^{n} k^2 p(k)\frac{1}{1 + k\lambda_v(i^*)\Pi}K_k - 1.$$

As λ_v increases f decreases. $\lim_{\lambda_v\to\infty} f(\lambda_v) = -1$. But $f(0) = \mathscr{R}_0 - 1 > 0$. Then, $f(\lambda_v)$ has a unique zero, giving us a unique endemic equilibrium for the system.

To establish the stability of the endemic equilibrium $\mathcal{E}^*$ we need to linearize system (2) around the endemic equilibrium and then analyze the characteristic equation obtained by it. An important part of that stability result (Martcheva and Li 2013) is the assumption that

$$\beta_k(\tau) = \frac{\beta_k}{\gamma_0}\gamma(\tau)$$

which is satisfied by some linking functions, including the ones we have assumed for this article.

Let $B_j = \int_0^\infty \beta_j(\tau)i_j^*\mathrm{d}\tau$. Then, we obtain the following sufficient but not necessary condition for the endemic equilibrium.

Theorem 6 *Suppose $\mathscr{R}_0 > 1$ and $\frac{B_k\gamma_0}{N_k^*\beta_k} < k\lambda_v(i^*)$ for all k. Then, the endemic equilibrium $\mathcal{E}^*$ of system (2) is locally asymptotically stable.*

Proof We linearize system (2) at the endemic equilibrium $\mathcal{E}^*$, that is, we set $S_k(t) = x_k(t) + S_k^*$, $i_k(t,\tau) = y_k(t,\tau) + i_k^*$ and $N_k(t) = n_k(t) + n_k^*$. The systems for the perturbations becomes:

$$\frac{\mathrm{d}x_k}{\mathrm{d}t} = \frac{-k}{\langle k\rangle}\sum_{j=1}^{n}\frac{jp(j)}{N_j^*}[S_k^*\int_0^\infty \beta_j(\tau)y_j(\tau,t)\mathrm{d}\tau - S_k^*\frac{n_j}{N_j^*}B_j + x_kB_j] - \mu x_k,$$

$$\frac{\partial y_k}{\partial t} + \frac{\partial y_k}{\partial \tau} = -(\mu + \gamma(\tau))y_k(t,\tau),$$
$$y_k(0,t) = \frac{k}{\langle k\rangle}\sum_{j=1}^{n}\frac{jp(j)}{N_j^*}[S_k^*\int_0^\infty \beta_j(\tau)y_j(\tau,t)\mathrm{d}\tau - S_k^*\frac{n_j}{N_j^*}B_j + x_kB_j], \tag{35}$$

where $B_j = \int_0^\infty \beta_j(\tau)i_j^*\mathrm{d}\tau$.

$N_k(t) = n_k(t) + N_k^* = (x_k(t) + \int_0^\infty y_k(t,\tau)d\tau) + (S_k^* + \int_0^\infty i_k^*\mathrm{d}\tau)$, giving us

$$n_k(t) = x_k(t) + \int_0^\infty y_k(t,\tau)\mathrm{d}\tau.$$

We look for solutions of the form $x_k(t) = x_ke^{\lambda t}$, $y_k(t,\tau) = y_k(\tau)e^{\lambda t}$. So

$$n_k(t) = e^{\lambda t}\left(x_k + \int_0^\infty y_k(\tau)\mathrm{d}\tau\right) = n_ke^{\lambda t},$$

where $n_k = x_k + \int_0^\infty y_k(\tau)\mathrm{d}\tau$.

We now obtain the following eigenvalue problem,

$$\lambda x_k = -\frac{-k}{\langle k\rangle}\sum_{j=1}^{n}\frac{jp(j)}{N_j^*}[S_k^*\int_0^\infty \beta_j(\tau)y_j(\tau)\mathrm{d}\tau - S_k^*\frac{n_j}{N_j^*}B_j + x_kB_j] - \mu x_k,$$
$$\lambda y_k + \frac{\partial y_k}{\partial \tau} = -(\mu + \gamma(\tau))y_k(\tau),$$
$$y_k(0) = \frac{k}{\langle k\rangle}\sum_{j=1}^{n}\frac{jp(j)}{N_j^*}[S_k^*\int_0^\infty \beta_j(\tau)y_j(\tau)\mathrm{d}\tau - S_k^*\frac{n_j}{N_j^*}B_j + x_kB_j]. \tag{36}$$

Now, $y_j(\tau) = y_j(0)\int_0^\infty e^{-\lambda t}\pi(\tau)\mathrm{d}\tau$, which gives us

$$n_j = x_j + y_j(0)\Pi(\lambda),$$

where $\Pi(\lambda) = \int_0^\infty e^{-\lambda t}\pi(\tau)\mathrm{d}\tau$. If we rewrite the equation for x_k as $\lambda x_k = -y_k(0) - \mu x_k$, we get

$$x_k = \frac{-y_k(0)}{\lambda + \mu}.$$

Then,

$$n_j = y_j(0)\left[\frac{-1}{\lambda + \mu} + \Pi(\lambda)\right].$$

First we notice that all $y_k(0)$ have the same sign for all k. Indeed,

$$y_k(0) = \frac{k}{\langle k \rangle} S_k^* \sum_{j=1}^{n} \frac{jp(j)}{N_j^*} \left[\int_0^\infty \beta_j(\tau) y_j(\tau) \mathrm{d}\tau - \frac{n_j}{N_j^*} B_j \right] + x_k \lambda_v(i^*).$$

Hence, with the relation between x_k and $y_k(0)$ we have:

$$y_k(0) = \frac{k}{\langle k \rangle} S_k^* \frac{\lambda + \mu}{\lambda + \mu + \lambda_v(i^*)} \sum_{j=1}^{n} \frac{jp(j)}{N_j^*} \left[\int_0^\infty \beta_j(\tau) y_j(\tau) \mathrm{d}\tau - \frac{n_j}{N_j^*} B_j \right].$$

We see that the sign of $y_k(0)$ depends on the last two terms but neither of them depends on k. Hence, $y_k(0)$ has the same sign for all k.

Using values for x_k and n_k, the equations of eigenvalue problem reduce to,

$$\begin{aligned} y_k(0) &= \frac{k}{\langle k \rangle} S_k^* \sum_{j=1}^{n} \frac{jp(j)}{N_j^*} \left[\frac{B_j y_j(0)}{N_j^*(\lambda + \mu)} - \frac{B_j}{N_j^*} y_j(0) \Pi(\lambda) + y_j(0) K_j(\lambda) \right] - k \frac{y_k(0)}{\lambda + \mu} \lambda_v(i^*) \\ &\implies (1 + \frac{k\lambda_v(i^*)}{\lambda + \mu}) y_k(0) = \frac{k}{\langle k \rangle} S_k^* \sum_{j=1}^{n} \frac{jp(j)}{N_j^*} y_j(0) \left[\frac{B_j}{N_j^*(\lambda + \mu)} - \frac{B_j}{N_j^*} \Pi(\lambda) + K_j(\lambda) \right] \\ &\implies y_k(0) = \frac{k}{\langle k \rangle} S_k^* \frac{\lambda + \mu}{\lambda + \mu + k\lambda_v(i^*)} \sum_{j=1}^{n} \frac{jp(j)}{N_j^*} y_j(0) \left[\frac{B_j}{N_j^*(\lambda + \mu)} - \frac{B_j}{N_j^*} \Pi(\lambda) + K_j(\lambda) \right]. \end{aligned} \tag{37}$$

where $K_k(\lambda) = \int_0^\infty \beta_k(\tau) e^{-\lambda\tau} \pi(\tau) \mathrm{d}\tau$. In the next step we multiply both sides of the equation by $\frac{kp(k)}{N_k^*}(\frac{B_k}{N_k^*(\lambda+\mu)} - \frac{B_k \Pi(\lambda)}{N_k^*} + K_k(\lambda))$. To avoid introducing roots to the characteristic equation, we will assume that λ is such that $\frac{kp(k)}{N_k^*}(\frac{B_k}{N_k^*(\lambda+\mu)} - \frac{B_k \Pi(\lambda)}{N_k^*} + K_k(\lambda)) \neq 0$ for every k. Summing over 1 to n,

$$\begin{aligned} &\sum_{k=1}^{n} y_k(0) \frac{kp(k)}{N_k^*} \left(\frac{B_k}{N_k^*(\lambda + \mu)} - \frac{B_k \Pi(\lambda)}{N_k^*} + K_k(\lambda) \right) \\ &= \sum_{k=1}^{n} \frac{1}{\langle k \rangle} \frac{k^2 p(k) S_k^*(\lambda + \mu)}{N_k^*(\lambda + \mu + k\lambda_v(i^*))} \left(\frac{B_k}{N_k^*(\lambda + \mu)} - \frac{B_k \Pi(\lambda)}{N_k^*} + K_k(\lambda) \right) \\ &\quad \sum_{j=1}^{n} \frac{jp(j)}{N_j^*} y_j(0) \left[\frac{B_j}{N_j^*(\lambda + \mu)} - \frac{B_j}{N_j^*} \Pi(\lambda) + K_j(\lambda) \right]. \end{aligned} \tag{38}$$

Because all $y_k(0)$ have the same sign and from our assumption above that λ is such that $\frac{kp(k)}{N_k^*}(\frac{B_k}{N_k^*(\lambda+\mu)} - \frac{B_k \Pi(\lambda)}{N_k^*} + K_k(\lambda)) \neq 0$ for every k, we have that for λ with $\Re\lambda \geq 0$,

$$\sum_{k=1}^{n} y_k(0)\frac{kp(k)}{N_k^*}\left(\frac{B_k}{N_k^*(\lambda+\mu)}-\frac{B_k\Pi(\lambda)}{N_k^*}+K_k(\lambda\right)\neq 0.$$

We cancel that expression, and then, Eq. (38) reduces to

$$\begin{aligned}1&=\sum_{k=1}^{n}\frac{1}{\langle k\rangle}\frac{k^2p(k)S_k^*(\lambda+\mu)}{N_k^*(\lambda+\mu+k\lambda_v(i^*))}\left(\frac{B_k}{N_k^*(\lambda+\mu)}-\frac{B_k\Pi(\lambda)}{N_k^*}+K_k(\lambda\right)\\&=\sum_{k=1}^{n}\frac{1}{\langle k\rangle}\frac{k^2p(k)S_k^*}{N_k^*(\lambda+\mu+k\lambda_v(i^*))}\left(\frac{B_k\gamma_0}{N_k^*\beta_k}+\lambda+\mu\right)K_k(\lambda).\end{aligned}\tag{39}$$

Assume the above equation has roots with nonnegative real part. Since we have $\frac{B_k\gamma_0}{N_k^*\beta_k} < k\lambda_v(i^*)$, and $\Re\lambda \geq 0$ Eq. (39) satisfies,

$$\begin{aligned}1&=\left|\frac{1}{\langle k\rangle}\sum_{k=1}^{n}\frac{k^2p(k)S_k^*}{N_k^*(\lambda+\mu+k\lambda_v(i^*))}\left(\frac{B_k\gamma_0}{N_k^*\beta_k}+\lambda+\mu\right)K_k(\lambda)\right|\\&=\left|\frac{1}{\langle k\rangle}\sum_{k=1}^{n}\frac{k^2p(k)}{1+k\lambda_v(i^*)\Pi}\left(\frac{\frac{B_k\gamma_0}{N_k^*\beta_k}+\lambda+\mu}{(\lambda+\mu+k\lambda_v(i^*))}\right)K_k(\lambda)\right|\\&\leq\frac{1}{\langle k\rangle}\sum_{k=1}^{n}\frac{k^2p(k)}{1+k\lambda_v(i^*)\Pi}\left|\left(\frac{\frac{B_k\gamma_0}{N_k^*\beta_k}+\lambda+\mu}{(\lambda+\mu+k\lambda_v(i^*))}\right)\right||K_k(\lambda)|\\&<\frac{1}{\langle k\rangle}\sum_{k=1}^{n}\frac{k^2p(k)}{1+k\lambda_v(i^*)\Pi}K_j(0)=1.\end{aligned}\tag{40}$$

This is a contradiction. Hence, the endemic equilibrium E^* is locally asymptotically stable when $\mathscr{R}_0 > 1$. □

7 Simulations

7.1 Simulation of the Dynamical Model

We write a MATLAB code to simulate the model. We focus on scale-free networks, that is, networks whose degree distribution follows a power law, at least asymptotically. Such network is pictured in Fig. 1.

We use such a network as a foundation of the HIV model. The network describes the HIV contacts between the individuals represented by the nodes of the network. The code computes $p(k)$ as

$$p(k)=\frac{N_k}{\sum_{j=1}^{n}N_j}.$$

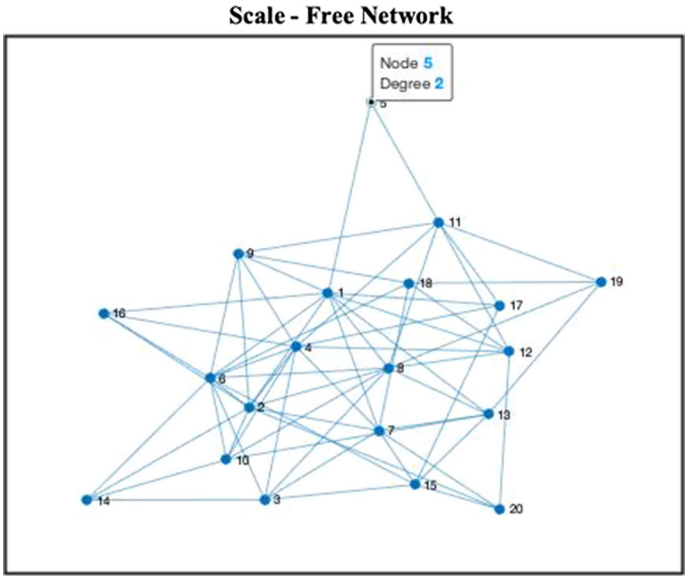

Fig. 1 A scale-free network with 20 nodes (Color figure online)

This approach to the computation of the $p(k)$s modifies somewhat our original model, but the general concept remains the same. Simulations with the model are included in Fig. 2.

Simulations suggest that the nodes with the maximal number of individuals have the same connectivity among the susceptible and AIDS individuals as in the total population. The maximal number of individuals in these classes have 11 connections. This is somewhat unexpected, particularly for AIDS individuals. However, the infected nodes that dominate the group of infected individuals have 6 connections. Simulations further show that if we increase the number of nodes to a 100, the properties of the solution remain the same, except the reproduction number which increases to 2.

7.2 Simulation of the Equilibria

In this subsection we assume that the within-host model is at equilibrium. That makes the linking coefficients β_k and γ independent of τ and the between-host model becomes an ODE. Looking at the equilibrium values of susceptible and infected individuals we obtain:

$$S_k = \frac{\Lambda_k}{k\lambda_v + \mu} \qquad I_k = \frac{k\lambda_v \Lambda_k}{(\mu + \gamma)(k\lambda_v + \mu)}$$

where λ_v is the solution of the equation:

$$1 = \frac{1}{< k >} \sum_{k=1}^{n} k^2 p(k) \frac{\beta_k}{\mu + \gamma + k\lambda_v}.$$

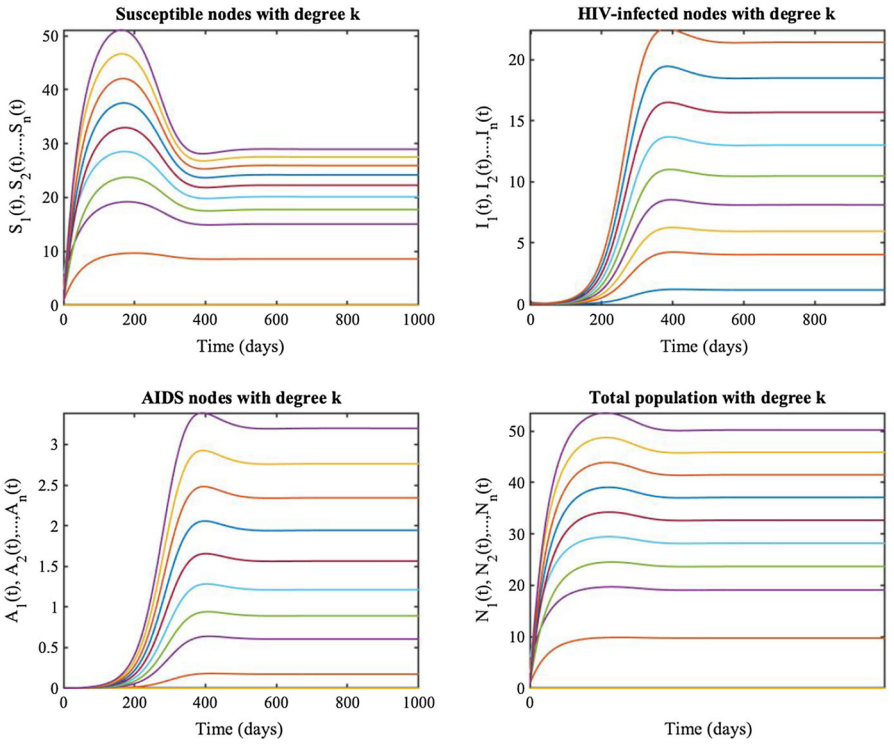

Fig. 2 Simulations with the network model. In this simulation the average degree is 6.4 and $\mathscr{R}_0 = 1.3173$. The number of nodes is 200. The maximal degree is 63, but there are no occupied nodes with degree 1, 3 (Color figure online)

To understand the impact of the within-host reproduction number on the equilibrial population level of infected individuals and their interaction with the network specifics, we define $\gamma(R_0^{\text{host}})$ and $\beta_k(R_0^{\text{host}})$, that is, the linking parameters β_k and γ as functions of the within-host reproduction number. In a similar way we define the force of infection $\lambda_v(R_0^{\text{host}})$ and $I_k(R_0^{\text{host}})$. We define the total equilibrium infected population by $I = \sum_{k=1}^{n} I_k$, and we plot it in Fig. 3 for different network scenarios.

Simulations in Fig. 3 suggest several things. First, under "regular" distribution of the nodes connectivity, that is, most nodes have few connections and few nodes have many connections, the total number of infected I at equilibrium is a non-monotone function of the within-host reproduction number (red curve). For small R_0^{host}, the total number of infected in the population increases as R_0^{host} increases. However, if R_0^{host} is larger, then increase in R_0^{host} decreases the total number of infected in the population. The non-monotone nature of the dependence is somewhat expected as for small R_0^{host} the prevalence increases as the within-host viral load increases, but when the within-host viral load becomes large, too many people are progressing to AIDS and the HIV prevalence decreases with further increase in R_0^{host}. However, this non-monotone relationship seems to depend on the network. If the network consist of nodes with low connectivity only, then the total prevalence only increases with R_0^{host} (blue curve). In

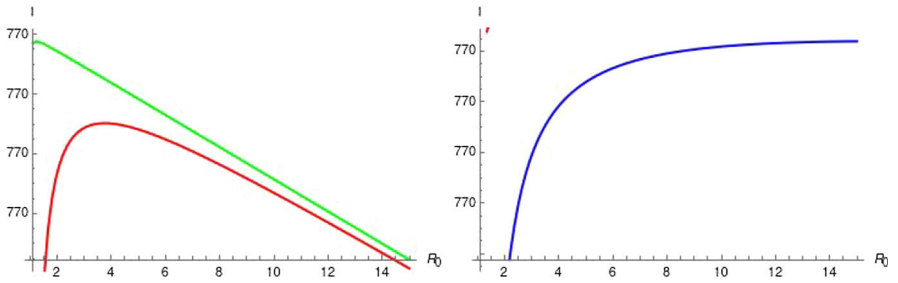

Fig. 3 Simulations with the equilibria of the network model. Each curve shows I as a function of the within-host reproduction number R_0^{host}. For the red curve most nodes have degree 1 and a few nodes have higher degree. For the green curve all nodes have high degree. For the blue curve all nodes have low degree. The changes on the graph are small enough that Mathematica cannot detect the difference on the Y-axis (Color figure online)

fact decrease does occur under this scenario but for much larger, possibly unrealistic, values of R_0^{host}. In contrast, if the network consists of nodes of high connectivity only, then the prevalence is a decreasing function of the R_0^{host} (green curve). The decreasing dependence of the prevalence on R_0^{host} is a sign of "too much" pathogen in the system, and too fast progression of individuals to AIDS. Interestingly, this property can be also captured by the connectivity in the network, even if all other properties of the within-host viral load are the same. Finally, the connectivity of the network leads to tiny differences in the prevalence of HIV on population level. The highly connected network leads to higher prevalence than the "regular" network (green curve is above red curve) and they are both higher than the blue curve (not pictured).

8 Discussion

We formulate a within-host model linked with a dynamic network epidemiological model with demography, through epidemiological parameters. The system is described by ordinary differential equations coupled with partial differential equations in a nested fashion. First, existence and uniqueness results of the immunological system are proved. Next, well-posedness of the epidemiological system is established using functional analytic approach which we adapt from article (Numfor et al. 2014). We derive an explicit expression of the basic reproduction number $\mathscr{R}_0$ of the immuno-epidemiological model. The immuno-epidemiological model always has a disease-free equilibrium. When $\mathscr{R}_0 < 1$, the disease-free equilibrium is locally asymptotically stable. We use the Fluctuation Lemma to prove that the disease-free equilibrium is also globally asymptotically stable. When $\mathscr{R}_0 > 1$, the disease-free equilibrium is unstable and a unique endemic equilibrium exists. We show that the endemic equilibrium is locally asymptotically stable, provided the linking functions have a specific simple form, and the population size of degree k's large enough. Compared to article (Martcheva and Li 2013), the network model needs an additional condition for stability which bounds the population size of each degree from below and requires population sizes of smaller degree to be larger. In general, the question of stability of the endemic

equilibrium remains open, but simulations with the network lead consistently to stable endemic equilibrium.

Numerical simulations using scale-free networks suggest that given parameters fixed, the basic reproduction number $\mathscr{R}_0$ increases with the increase in number of nodes. When the number of nodes is 20, $\mathscr{R}_0$ is close to but greater than one, whereas increasing the number of nodes to 100, $\mathscr{R}_0$ is close to or greater than two.

We also use simulations considering the within-host system at equilibrium, defining the prevalence in terms of R_0^{host}. Simulations suggest that prevalence is a non-monotone hump-like function of R_0^{host}, the immunological reproduction number, when a scale-free network is considered. With high network connectivity, the prevalence decreases with R_0^{host}, but with very low network connectivity of the network the prevalence increases with R_0^{host}. These observations suggest that lowering the within-host reproduction number, e.g., by using medications, can have very different effects on population level, depending on the HIV network and its connectivity. The non-monotone dependence of the prevalence on the within-host reproduction number is perhaps not unexpected. Such non-monotone dependence occurs in multi-scale models with homogeneous mixing (Gulbudak et al. 2017) where it is believed to be a consequence of the trade-off between transmission and virulence of pathogens. However, here the non-monotone dependence of prevalence in terms of R_0^{host} occurs as a consequence of the network connectivity, which in turn may be magnifying the trade-offs between transmission and virulence. A similar scenario where a hump-like dependence of prevalence on connectivity and the reproduction number also occurs in multi-patch models in which increasing migration rates de facto increase connectivity of the patch network (Acevedo et al. 2015).

Our simulation also shows that the higher the connectivity, the higher the prevalence. Therefore, control measures may focus on the following directions, applied simultaneously:

- Behavioral change via limiting number of partners, usage of condoms and PREP therapy. Limiting number of partners would bring down the connectivity in the social network, usage of condoms and PREP therapy would lower the transmission rate of HIV.
- Lower $\mathscr{R}_0$ below 1 by lowering the viral load via ART and combination medications. This will also lower the transition rate to AIDS stage.

Control measures should be applied with the understanding of the possible non-monotone dependence of prevalence on the within-host reproduction number.

Funding Maia Martcheva was partially supported by NSF DMS-1951595. Necibe Tuncer was partially supported by NSF DMS-1951626.

Code availability The code was written by one of the authors and is available on request.

Compliance with Ethical Standards

Conflict of interest Not applicable.

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