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Research article

A network immuno-epidemiological model of HIV and opioid epidemics

Churni Gupta[1], **Necibe Tuncer**[2,*] **and Maia Martcheva**[3]

[1] Center for Pharmacometrics and Systems Pharmacology, University of Florida, USA
[2] Department of Mathematical Sciences, Florida Atlantic University, USA
[3] Department of Mathematics, University of Florida, USA

* **Correspondence:** Email: ntuncer@fau.edu.

Abstract: In this paper, we introduce a novel multi-scale network model of two epidemics: HIV infection and opioid addiction. The HIV infection dynamics is modeled on a complex network. We determine the basic reproduction number of HIV infection, $\mathcal{R}_v$, and the basic reproduction number of opioid addiction, $\mathcal{R}_u$. We show that the model has a unique disease-free equilibrium which is locally asymptotically stable when both $\mathcal{R}_u$ and $\mathcal{R}_v$ are less than one. If $\mathcal{R}_u > 1$ or $\mathcal{R}_v > 1$, then the disease-free equilibrium is unstable and there exists a unique semi-trivial equilibrium corresponding to each disease. The unique opioid only equilibrium exist when the basic reproduction number of opioid addiction is greater than one and it is locally asymptotically stable when the invasion number of HIV infection, $\mathcal{R}^1_{v_i}$ is less than one. Similarly, the unique HIV only equilibrium exist when the basic reproduction number of HIV is greater than one and it is locally asymptotically stable when the invasion number of opioid addiction, $\mathcal{R}^2_{u_i}$ is less than one. Existence and stability of co-existence equilibria remains an open problem. We performed numerical simulations to better understand the impact of three epidemiologically important parameters that are at the intersection of two epidemics: q_v the likelihood of an opioid user being infected with HIV, q_u the likelihood of an HIV-infected individual becoming addicted to opioids, and δ recovery from opioid addiction. Simulations suggest that as the recovery from opioid use increases, the prevalence of co-affected individuals, those who are addicted to opioids and are infected with HIV, increase significantly. We demonstrate that the dependence of the co-affected population on q_u and q_v are not monotone.

Keywords: HIV; opioid; network; basic reproduction number; invasion number

1. Introduction

In the last 15 years, US deaths due to the opioid epidemic have quadrupled from nearly 12,000 in 2002 to more than 47,000 in 2017 [1]. In October 2017, the US Department of Health and Human

Services declared the opioid crisis a national public health emergency [2]. The increase in injection drug use and reduction of behavioral inhibition have also contributed to the spread of infectious diseases, particularly HIV [3]. The two epidemics – opioid and HIV – are intertwined and modeling them in tandem will lead to understanding their interdependence [4].

The HIV epidemic, which begun in 1981, has been modeled extensively both on immunological level and on epidemiological level. On within-host level typically models involve healthy and infected CD4 cells and the virus [5–9]. On the between-host scale, the very basic models include susceptible, infected and AIDS classes [10, 11]. Multi-scale models of HIV, mostly of the nested type [12], have also received significant attention in the recent years [13–16].

Modeling of the opioid epidemic is more recent and picked up with the increasing importance of the substance abuse disorder. Early models [17] assume opioid use can be modeled similarly to infectious disease spread and that assumption has been used in current models of heroin use [18–21]. The transition to opioid use typically starts from prescription drug misuse and modeling of that has also been drawing attention lately [22].

Despite the importance of the HIV and the opioid epidemics and the clear interdependence between the two, relatively little modeling has been done at the interface of the two epidemics. The within-host modeling of the interplay between opioid and HIV has first drawn attention. Based on experiments in monkeys, Vaidya et al. [23–26] model the within-host dynamics of HIV and an opioid. The between host dynamics has been addressed even less. Duan et al. [27] models the two epidemics on population level and finds that the best control strategy should reduce the probability of opioid affected individuals getting HIV and should target the drug abuse epidemic. In this paper, we investigate the interplay of the two epidemics with a multi-scale model that incorporates both a within-host component and a between host component.

The sexual contacts leading to HIV are not homogeneous across the population. Typically, few individuals in the population partake in a lot of contacts, while most of the members of the population partake in few contacts. This type of heterogeneity of contacts in HIV transmission is modeled by scale-free networks. Modeling infectious disease dynamics on networks has been also drawing attention in the recent years, resulting in a book devoted to this topic [28]. We use here a network modeling approach introduced in [29] which gives a closed form model equations [30]. In this modeling framework of networks, ODE and age structured models have been investigated but the only multi-scale model on networks in closed form seems to be [16]. Here we expand the modeling framework developed in [16] to include the opioid epidemic thus considering for the first time a multi-scale network model of two diseases. This model is in closed form and we are able to perform analysis on it.

In Section 2 we introduce the multi-scale network model of HIV and opioid which consists of within-host component, between-host component and linking functions used to connect the two scales. In Section 3 we discuss the existence and stability of the disease-free equilibrium and compute an explicit form of the reproduction numbers. In Section 4 we focus on the existence and stability of the semi-trivial equilibria. In Section 4 we also compute the invasion numbers of the two epidemics. In Section 5 we perform simulations and consider different scenarios with differing parameter values. In Section 6 we summarize our results.

2. The model

2.1. The within-host model

We modify a well-known within-host model of HIV by explicitly including the opioid drug concentration $C(\tau)$ and its impact on the average susceptibility of target cells. The model takes the following form.

$$\begin{cases} \dfrac{dT}{d\tau} &= s - d_T T - k(C)V_i T, \\ \dfrac{dT_i}{d\tau} &= k(C)V_i T - \delta_i T_i, \\ \dfrac{dV_i}{d\tau} &= N_v \delta_i T_i - cV_i, \\ \dfrac{dC}{d\tau} &= \Lambda - d_c C, \end{cases} \tag{2.1}$$

Here T are the target cells, T_i are the infected target cells and V_i is the virus (HIV). Target cells are produced at rate s and cleared at rate d_T. Infected cells die at a rate δ_i, releasing N_v viral particles at death. The clearance rate of the virus is denoted by c. Opioid is taken at doses Λ is degraded at rate d_c. Infection rate of target cells by HIV in the presence of opioid is given by

$$k(C) = k_0 + \frac{k_1 C(\tau)}{C_0 + C(\tau)},$$

where C_0 is the half saturation constant, k_0 is the transmission coefficient in the absence of opioid and k_1 is a maximal increase in infection rate due to opioids.

Table 1. List of parameters of the within-host model.

Notation	Meaning
s	Production rate of healthy T-cells
d_T	Clearance rate of healthy T-cells
T	Number of healthy cells
T_i	Number of infected cells
V_i	Number of virions
δ_i	Death rate of infected cells
c	Clearance rate of virions
k_0	Transmission coeffiecient in absence of opioid
k_1	Maximal increase in infection rate due to opioid
C_0	Half saturation constant
d_c	Rate of degradation of opioid

A shortcoming of this model is that it does not consider multiple infection routes and drug resistant viral strains. This problem could have been remedied if a model such as the one formulated in [31] was used instead, as the base model. But because of the network structure, the system is already complicated, and addition of strains and infection route would further complicate it. We believe addition of strains and infection route would not give any different insights with the network structures.

2.2. The between-host model

To introduce the model, we define a complex network with size (number of nodes) N where each node is either occupied by an individual or vacant. The states for the epidemic transmission process on the network are divided into vacant state E, susceptible state S, opioid state U, infected state V, co-affected state $i(\tau, t)$ and AIDS state A. Nodes change states at rates to be introduced, and HIV transmission is governed by the network connections. A vacant state becomes susceptible state at the recruitment rate. Susceptible, opioid, infected, co-affected and AIDS states can change their state into a vacant state at natural death rate μ or at disease-induced death rates d_u, d_v, $d_i(\tau)$, d_a, respectively. A susceptible state can be infected with HIV and change into an infected state, or can become opioid-dependent and change into opioid state. HIV and opioid states can get co-affected by adding the other disease. An opioid state or co-affected state can move to a susceptible or HIV-infected states respectively due to treatment denoted as δ. HIV-infected or co-affected states can move to the AIDS state at rates γ_v and $\gamma_i(\tau)$.

For an epidemic network, 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 a potential for 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

$$< k >= \sum_{k=1}^{n} kp(k)\,,$$

where $p(k)$ is the probability that a randomly chosen node has degree k. That is, $< k >$ is a constant, when n is pre-specified. This is a standard notation for average degree. For further background, [32] is a good source for network science. Empirical studies suggest that many real-life HIV networks have scale-free degree distribution $p(k) \sim k^{-\eta}$, where $2 < \eta < 3$ [33, 34]. The conditional probability $p(j|k)$ that a node with degree k is connected to a node with degree j, is given by

$$p(j|k) = \frac{jp(j)}{< k >}\,.$$

Basically, $p(j|k)$ gives probability that an individual with k contacts is connected to an individual with j contacts. We assume contacts that lead to opioid addiction are homogeneous (transmission of opioid addiction can be between two nodes with the same probability). With the structure of a complex network and infection age, let $S_k(t)$, $U_k(t)$, $V_k(t)$, $A_k(t)$, be the number of susceptible, opioid-dependent, HIV infected and AIDS nodes respectively with degree k at time t for $k \in \{1, 2, \ldots, n\}$. Let $i_k(\tau, t)$ be the density of co-affected nodes of degree k at time t and with infection age τ. Then we can formulate the following network multi-scale model of HIV and opioid epidemics.

$$
\begin{cases}
\dfrac{dS_k(t)}{dt} = \Lambda_k - \lambda_u(t)S_k(t) - k\lambda_v(t)S_k(t) - \mu S_k(t) + \delta U_k(t), \\
\dfrac{dU_k(t)}{dt} = \lambda_u(t)S_k(t) - kq_v\lambda_v(t)U_k(t) - (\mu + d_u + \delta)U_k(t), \\
\dfrac{dV_k(t)}{dt} = k\lambda_v(t)S_k(t) - q_u\lambda_u(t)V_k(t) - (\mu + d_v + \gamma_v)V_k(t) + \delta\displaystyle\int_0^\infty \sigma(\tau)i_k(t,\tau)d\tau, \\
\dfrac{\partial i_k(t,\tau)}{dt} + \dfrac{\partial k_s i_k(t,\tau)}{d\tau} = -(\mu + d_i(\tau) + \gamma_i(\tau) + \delta\sigma(\tau))i_k(t,\tau), \\
k_s i_k(t,0) = kq_v\lambda_v(t)U_k(t) + q_u\lambda_u(t)V_k(t) \\
\dfrac{dA_k(t)}{dt} = \gamma_v V_k(t) + \displaystyle\int_0^\infty \gamma_i(\tau)i_k(t,\tau)d\tau - (\mu + d_a)A_k(t).
\end{cases}
\tag{2.2}
$$

The total population size of degree k is $N_k(t) = S_k(t) + U_k(t) + V_k(t) + I_k(t)$ where $I_k(t) = \int_0^\infty i_k(t,\tau)d\tau$. The force of HIV infection, $\lambda_v(t)$ takes into account the heterogeneous mixing in the network:

$$
\lambda_v(t) = \frac{1}{< k >}\sum_{k=1}^{n} kp(k)\lambda_v^k(t) \quad \text{where} \quad \lambda_v^k(t) = \frac{\beta_{v_1}^k V_k(t) + \displaystyle\int_0^\infty \beta_{v_2}^k(\tau)i_k(t,\tau)d\tau}{N_k(t)}. \tag{2.3}
$$

Thus $\lambda_v^k(t)$ denotes the force of infection from a node with degree k, where $\beta_{v_1}^k$ is the infection rate from $V_k(t)$ (HIV-infected node with degree k) per effective contact, and similarly, $\beta_{v_2}^k(\tau)$ is the time-since-infection dependent infection rate from $i_k(\tau,t)$ (co-affected node with degree k) per effective contact. Then the force of infection $\lambda_v(t)$ for the heterogeneous network model is obtained by summing over all the degrees of the network $\lambda_v^k(t)$ times the probability that the node with degree k is linked to the node with degree j. This is the average force of infection from each contact, and is therefore multiplied by k in the equations (2.2) for HIV transmission to nodes of degree k. The force of opioid addiction, $\lambda_u(t)$ is then given by,

$$
\lambda_u(t) = \sum_{k=1}^{n} \lambda_u^k(t) \quad \text{where} \quad \lambda_u^k(t) = \beta_u \frac{U_k(t) + \displaystyle\int_0^\infty i_k(t,\tau)d\tau}{N_k(t)}. \tag{2.4}
$$

Since the opioid contacts are homogeneous within the network, the force of addiction is obtained by summing over all the force of addictions of degree k, $\lambda_u^k(t)$. The within-host model remains the same as in (2.1) and the linking functions are given below.

2.3. Linking functions

To link the within-host and between host models, we use data [35] to determine the form of the linking of the transmission coefficient $\beta_{v_2}^k(\tau)$ [36] to the viral load. Fitting to the data [36], we obtain the following function for $\beta_{v_2}^k(\tau)$:

$$
\beta_{v_2}^k(\tau) = \frac{\beta_0^k V_i^r(\tau)}{B + V_i^r(\tau)},
$$

where $r \approx 1$. Further, we use the suggested functions in [37] to link the remaining τ-dependent rates:

$$
d_i(\tau) = d_0\,(T(0) - T) + d_1, \qquad \gamma_i(\tau) = \gamma_0\,(T(0) - T)\,, \qquad \sigma(\tau) = \sigma_0,
$$

where $\beta_0^k, B, d_0, d_1, \gamma_0, \sigma_0$, are constants. Disease-induced death rate d_i and transition to AIDS rate γ_i do not depend explicitly on the viral load because the viral load is high during the acute HIV phase but these rates are low during this same stage.

Table 2. Definitions of parameters and dependent variables of the between-host model.

Parameter/Variable	Description
$S_k(t)$	Number of susceptible individuals at time t with degree k
$V_k(t)$	Number of HIV infected individuals at time t with degree k
$U_k(t)$	Number of opioid addicted individuals at time t with degree k
$i_k(t,\tau)$	Density of co-affected individuals with coinfection age τ at time t with degree k
$A_k(t)$	Number of individuals with AIDS at time t with degree k
Λ_k	Constant recruitment rate for nodes with degree k
β_u	Transmission rate of opioid addiction
β_{v_1}	Transmission rate of HIV infection of HIV infected only individuals
$\beta_{v_2}(\tau)$	Transmission rate of HIV infection of coinfected individuals
μ	Natural death rate
d_u	Death rate induced by opioid addiction
d_v	Death rate induced by HIV infection
$d_i(\tau)$	Death rate induced by coaffection at coaffection age τ
d_a	Death rate induced by AIDS
δ	Recovery rate from opioid addiction
$\sigma(\tau)$	Recovery rate from coinfection to HIV only
q_u	Increase coefficient of HIV infection due to opioid usage
q_v	Increase coefficient of opioid usage due to HIV infection
γ_v	Rate of transition from HIV to AIDS
$\gamma_i(\tau)$	Rate of transition from coinfection to AIDS

3. Existence and stability of the disease free equilibrium

Equilibria are time-independent solutions of the system and often determine its long-term behavior. We find the equilibria of this system by setting the derivatives with respect to t equal to zero.

$$\begin{cases} \Lambda_k - \lambda_u(t)S_k(t) - k\lambda_v(t)S_k(t) - \mu S_k(t) + \delta U_k(t) = 0, \\ \lambda_u(t)S_k(t) - kq_v\lambda_v(t)U_k(t) - (\mu + d_u + \delta)U_k(t) = 0, \\ k\lambda_v(t)S_k(t) - q_u\lambda_u(t)V_k(t) - (\mu + d_v + \gamma_v)V_k(t) + \delta\int_0^\infty \sigma(\tau)i_k(t,\tau)d\tau = 0, \\ \dfrac{\partial k_s i_k(t,\tau)}{d\tau} = -(\mu + d_i(\tau) + \gamma_i(\tau) + \delta\sigma(\tau))i_k(t,\tau), \\ k_s i_k(0) = kq_v\lambda_v(t)U_k(t) + q_u\lambda_u(t)V_k(t). \end{cases} \tag{3.1}$$

At the disease-free equilibrium $U_k(t)$, $V_k(t)$ and $i_k(t,\tau)$ are zero for all k. So, the disease-free equilibrium is given by

$$\varepsilon^0 = \left(\frac{\Lambda_1}{\mu}, 0, 0, 0, \cdots, \frac{\Lambda_n}{\mu}, 0, 0, 0\right).$$

To determine the stability of the disease free equilibrium and to find the basic reproduction numbers of HIV infection and opioid addiction, denoted by $\mathcal{R}_u$ and $\mathcal{R}_v$ respectively, we linearize the system around the disease-free equilibrium. We take $S_k(t) = S_k^0 + x_k(t)$, $U_k(t) = u_k(t)$, $V_k(t) = v_k(t)$, $N_k(t) = N_k^0 + n_k(t)$ and $i_k(t,\tau) = y_k(t,\tau)$. Then linearizing the system (2.2) takes the following form

$$\begin{cases} \dfrac{dx_k(t)}{dt} = -\lambda_u(t)S_k^0 - k\lambda_v(t)S_k^0 - \mu x_k(t) + \delta u_k(t), \\ \dfrac{du_k(t)}{dt} = \lambda_u(t)S_k^0 - (\mu + d_u + \delta)u_k(t), \\ \dfrac{dv_k(t)}{dt} = k\lambda_v(t)S_k^0 - (\mu + d_v + \gamma_v)v_k(t) + \delta\displaystyle\int_0^\infty \sigma(\tau)y_k(t,\tau)d\tau, \\ \dfrac{\partial y_k(t,\tau)}{dt} + \dfrac{\partial k_s y_k(t,\tau)}{d\tau} = -(\mu + d_i(\tau) + \gamma_i(\tau) + \delta\sigma(\tau))y_k(t,\tau), \\ k_s y_k(t,0) = 0 \end{cases} \tag{3.2}$$

where,

$$\lambda_u(t) = \sum_{k=1}^{n}\beta_u \frac{u_k(t) + \displaystyle\int_0^\infty y_k(t,\tau)d\tau}{N_k^0},$$

$$\lambda_v(t) = \frac{1}{< k >}\sum_{k=1}^{n} kp(k)\frac{\beta_{v_1}^k v_k(t) + \displaystyle\int_0^\infty \beta_{v_2}^k(\tau)y_k(t,\tau)d\tau}{N_k^0}, \quad \text{and} \quad N_k^0 = S_k^0 = \frac{\Lambda_k}{\mu}.$$

We look for solutions of the form $x_k(t) = x_{k0}e^{\lambda t}$, $u_k(t) = u_{k0}e^{\lambda t}$, $v_k(t) = v_{k0}e^{\lambda t}$, $y_k(t,\tau) = y_k(\tau)e^{\lambda t}$ and obtain the following eigenvalue problem,

$$\begin{cases} (\lambda + \mu)x_{k0} + \lambda_u(t)S_k^0 + k\lambda_v(t)S_k^0 - \delta u_{k0} = 0, \\ (\lambda + \mu + d_u + \delta)u_{k0} - \lambda_u(t)S_k^0 = 0, \\ (\lambda + \mu + d_v + \gamma_v)v_{k0} - k\lambda_v(t)S_k^0 - \delta\displaystyle\int_0^\infty \sigma(\tau)y_k(\tau)d\tau = 0, \\ \dfrac{\partial k_s y_k(t,\tau)}{d\tau} + \lambda y_k(\tau) = -(\mu + d_i(\tau) + \gamma_i(\tau) + \delta\sigma(\tau))y_k(\tau), \\ k_s y_k(0) = 0 \end{cases} \tag{3.3}$$

Solving the fourth equation of (3.3) we get

$$y_k(\tau) = y_k(0)\pi(\tau)e^{\frac{-\lambda\tau}{k_s}} = 0 \tag{3.4}$$

where

$$\pi(\tau) = e^{-\frac{1}{k_s}\int_0^\tau \mu + d_i(\xi) + \gamma_i(\xi) + \delta\sigma(\xi)d\xi}.$$

Substituting (3.4) in the second equation of (3.3) we have,

$$u_{k0} = \frac{S_k^0}{(\lambda + \mu + d_u + \delta)}\beta_u \sum_{j=1}^{n} \frac{u_{j0}}{N_j^0}. \tag{3.5}$$

We notice that all u_{k0} have the same sign. Summing both sides from 1 to n after dividing with N_k^0, we get

$$\sum_{k=1}^{n} \frac{u_{k0}}{N_k^0} = \frac{\beta_u}{(\lambda + \mu + d_u + \delta)} \sum_{k=1}^{n} \frac{S_k^0}{N_k^0} \sum_{j=1}^{n} \frac{u_{j0}}{N_j^0} \tag{3.6}$$

If $\sum_{k=1}^{n} \frac{u_{k0}}{N_k^0} = 0$ then $u_{k0} = 0$ for all k which is not the case. So cancelling $\sum_{k=1}^{n} \frac{u_{k0}}{N_k^0}$ from both sides of the equation we obtain,

$$1 = \frac{\beta_u}{(\lambda + \mu + d_u + \delta)} \sum_{k=1}^{n} \frac{S_k^0}{N_k^0} = \frac{n\beta_u}{(\lambda + \mu + d_u + \delta)} \tag{3.7}$$

since $N_k^0 = S_k^0 = \frac{\Lambda_k}{\mu}$. We define

$$\mathcal{R}_u = \frac{n\beta_u}{\mu + d_u + \delta}. \tag{3.8}$$

Substituting (3.4) in the third equation of (3.3) we have,

$$v_{k0} = \frac{kS_k^0}{(\lambda + \mu + d_v + \gamma_v)} \frac{1}{< k >} \sum_{j=1}^{n} jp(j) \frac{\beta_{v_1}^j v_{j0}}{N_j^0}. \tag{3.9}$$

We note that all v_{k0} have the same sign. Multiplying both sides by $\frac{1}{<k>} \sum_{k=1}^{n} kp(k) \frac{\beta_{v_1}^k}{N_k^0}$ and summing from 1 to n we obtain,

$$\frac{1}{< k >} \sum_{k=1}^{n} kp(k) \frac{\beta_{v_1}^k v_{k0}}{N_k^0} = \frac{1}{< k >} \sum_{k=1}^{n} k^2 p(k) \frac{\beta_{v_1}^k S_k^0}{N_k^0(\lambda + \mu + d_v + \gamma_v)} \frac{1}{< k >} \sum_{j=1}^{n} jp(j) \frac{\beta_{v_1}^j v_{j0}}{N_j^0}. \tag{3.10}$$

If $\frac{1}{<k>} \sum_{k=1}^{n} kp(k) \frac{\beta_{v_1}^k v_{k0}}{N_k^0} = 0$, then $v_{k0} = 0$ for all k which is not the case. So cancelling $\frac{1}{<k>} \sum_{k=1}^{n} kp(k) \frac{\beta_{v_1}^k v_{k0}}{N_k^0}$ from both sides we get,

$$1 = \frac{1}{< k >} \sum_{k=1}^{n} k^2 p(k) \frac{\beta_{v_1}^k S_k^0}{N_k^0(\lambda + \mu + d_v + \gamma_v)} = \frac{1}{< k >} \sum_{k=1}^{n} k^2 p(k) \frac{\beta_{v_1}^k}{(\lambda + \mu + d_v + \gamma_v)}. \tag{3.11}$$

So we define

$$\mathcal{R}_v = \frac{1}{< k >} \sum_{k=1}^{n} k^2 p(k) \frac{\beta_{v_1}^k}{(\mu + d_v + \gamma_v)}. \tag{3.12}$$

Now we can prove the following theorem,

Theorem 1. If $\max\{\mathcal{R}_u, \mathcal{R}_v\} < 1$ then the disease free equilibrium is locally asymptotically stable. If $\max\{\mathcal{R}_u, \mathcal{R}_v\} > 1$, then the disease-free equilibrium is unstable.

Proof. Suppose

$$\begin{aligned} \mathcal{G}_1(\lambda) &= \frac{n\beta_u}{\lambda + \mu + d_u + \delta}, \\ \mathcal{G}_2(\lambda) &= \frac{1}{< k >} \sum_{k=1}^{n} k^2 p(k) \frac{\beta_{v_1}^k}{(\lambda + \mu + d_v + \gamma_v)}. \end{aligned} \tag{3.13}$$

Then we notice that $\mathcal{G}_1(0) = \mathcal{R}_u$, $\mathcal{G}_2(0) = \mathcal{R}_v$, $\lim_{\lambda\to\infty} \mathcal{G}_1(\lambda) = 0, \lim_{\lambda\to\infty} \mathcal{G}_2(\lambda) = 0$.

We claim that if $\max\{\mathcal{R}_u, \mathcal{R}_v\} < 1$ then the disease free equilibrium is locally asymptotically stable, that is all the solutions of $\mathcal{G}_1(\lambda) = 1$ and $\mathcal{G}_2(\lambda) = 1$, have negative real parts. To show this, we proceed by way of contradiction. Suppose one of the equations $\mathcal{G}_1(\lambda) = 1$ and $\mathcal{G}_2(\lambda) = 1$ has a solution λ_0 with $\Re(\lambda_0) \geq 0$. Then,

$$1 = |\mathcal{G}_1(\lambda_0)| \leq |\mathcal{G}_1(\Re\lambda_0)| \leq |\mathcal{G}_1(0)| = \mathcal{R}_u,$$

or

$$1 = |\mathcal{G}_2(\lambda_0)| \leq |\mathcal{G}_2(\Re\lambda_0)| \leq |\mathcal{G}_2(0)| = \mathcal{R}_v.$$

This is a contradiction. Hence ε^0 is locally asymptotically stable when $\max\{\mathcal{R}_u, \mathcal{R}_v\} < 1$. If $\max\{\mathcal{R}_u, \mathcal{R}_v\} > 1$, let us assume, without loss of generality, $\mathcal{R}_u > 1$. Then $\mathcal{G}_1(\lambda) = 1$ has a positive solution, λ^*. Thus, the disease free equilbrium is unstable.

4. Semi-trivial (Boundary) equilibria

4.1. Existence of semi-trivial equilibria

In this section, we prove the existence and stability of the two boundary equilibria E_1^* and E_2^* corresponding to opioid addiction and HIV transmission in a single population respectively. To obtain E_1^* we let $S_k(t) = S_{k1}^*$, $U_k(t) = U_{k1}^*$ and $V_k(t) = 0$ and $i_k(t,\tau) = 0$ for all k, i.e., $E_1^* = (S_{11}^*, U_{11}^*, 0, 0, \cdots, S_{n1}^*, U_{n1}^*, 0, 0)$. We get the following equations

$$\begin{aligned} \Lambda_k - \mu S_{k1}^* - S_{k1}^* \lambda_u(U_1^*) + \delta U_{k1}^* &= 0 \\ S_{k1}^* \lambda_u(U_1^*) - (\mu + d_u + \delta) U_{k1}^* &= 0 \\ \lambda_u(U_1^*) = \beta_u \sum_{k=1}^{n} \frac{U_{k1}^*}{N_{k1}^*} & \end{aligned} \tag{4.1}$$

From the second equation of (4.1) we get,

$$S_{k1}^* = \frac{\mu + d_u + \delta}{\beta_u} \frac{U_{k1}^*}{\sum_{j=1}^{n} \frac{U_{j1}^*}{N_{j1}^*}}.$$

Summing both sides of the equation from $k = 1$ to $k = n$, and dividing by N_{k1}^* we get,

$$\sum_{k=1}^{n} \frac{S_{k1}^*}{N_{k1}^*} = \frac{\mu + d_u + \delta}{\beta_u} = \frac{n}{\mathcal{R}_u} \tag{4.2}$$

We know $\frac{S^*_{k1}+U^*_{k1}}{N^*_{k1}} = 1$, and so

$$\sum_{k=1}^{n} \frac{S^*_{k1} + U^*_{k1}}{N^*_{k1}} = n \tag{4.3}$$

i.e.,

$$\sum_{k=1}^{n} \frac{U^*_{k1}}{N^*_{k1}} = n\left(1 - \frac{1}{\mathcal{R}_u}\right)$$

Plugging in the values in the first equation of (4.1) and solving for U^*_{k1} we get

$$U^*_{k1} = \frac{\Lambda_k}{\frac{\mu}{\mathcal{R}_u - 1} + \mu + d_u} = \frac{\Lambda_k}{(\mu + d_u)(1 - \frac{\mu}{(1-\mathcal{R}_u)(\mu+d_u)})} \tag{4.4}$$

Now when $\mathcal{R}_u < 1$, $\sum_{k=1}^{n} \frac{U^*_{k1}}{N^*_{k1}} < 0$, which implies $U^*_{k1} < 0$ for at least one k. When $\mathcal{R}_u > 1$, $U^*_{k1} > 0$. Thus, E^*_1 exists if and only if $\mathcal{R}_u > 1$.

To obtain E^*_2 we let $S_k(t) = S^*_{k2}$, $V_k(t) = V^*_{k2}$ and $U_k(t) = 0$ and $i_k(t, \tau) = 0$ for all k, i.e., $E^*_2 = (S^*_{12}, 0, V^*_{12}, 0, \cdots, S^*_{n2}, 0, V^*_{n2}, 0)$. We get the following equations

$$\begin{aligned} \Lambda_k - \mu S^*_{k2} - k S^*_{k2} \lambda_v(V^*_2) &= 0, \\ k S^*_{k2} \lambda_v(V^*_2) - (\mu + d_v + \gamma_v) V^*_{k2} &= 0, \\ \lambda_v(V^*_2) = \frac{1}{< k >} \sum_{j=1}^{n} jp(j) \frac{\beta^j_{v_1} V^*_{j2}}{N^*_{j2}}&. \end{aligned} \tag{4.5}$$

From the second equation of (4.5) we get

$$k S^*_{k2} = \frac{\mu + d_v + \gamma_v}{\lambda_v(V^*_2)} V^*_{k2}.$$

Dividing both sides by N^*_{k2} and multiplying with $\frac{1}{<k>} \sum_{k=1}^{n} kp(k)\beta^k_{v_1}$ and adding from 1 to n we get,

$$\frac{1}{< k >} \sum_{k=1}^{n} k^2 p(k) \frac{\beta^k_{v_1} S^*_{k2}}{N^*_{k2}} = (\mu + d_v + \gamma_v). \tag{4.6}$$

We know $\frac{S^*_{k2}+V^*_{k2}}{N^*_{k2}} = 1$, and so

$$\frac{1}{< k >} \sum_{k=1}^{n} k^2 p(k) \frac{\beta^k_{v_1}(V^*_{k2} + S^*_{k2})}{N^*_{k2}} = (\mu + d_v + \gamma_v)\mathcal{R}_v, \tag{4.7}$$

which gives us,

$$\frac{1}{< k >} \sum_{k=1}^{n} k^2 p(k) \frac{\beta^k_{v_1} V^*_{k2}}{N^*_{k2}} = (\mu + d_v + \gamma_v)(\mathcal{R}_v - 1).$$

So when $\mathcal{R}_v < 1$, E^*_2 does not exist. Now

$$N^*_{k2} = V^*_{k2} + S^*_{k2} = V^*_{k2} + V^*_{k2}(\frac{\mu + d_v + \gamma_v}{k\lambda_v(V^*_2)}),$$

and so we obtain,

$$\frac{V_{k2}^*}{N_{k2}^*} = \frac{1}{1 + \frac{\mu+d_v+\gamma_v}{k\lambda_v(V_2^*)}}, \tag{4.8}$$

$$\lambda_v(V_2^*) = \frac{1}{< k >} \sum_{k=1}^{n} kp(k)\beta_{v_1}^k \frac{1}{1 + \frac{\mu+d_v+\gamma_v}{k\lambda_v(V_2^*)}} = \frac{1}{< k >} \sum_{k=1}^{n} kp(k)\beta_{v_1}^k \frac{k\lambda_v(V_2^*)}{k\lambda_v(V_2^*) + (\mu + d_v + \gamma_v)}. \tag{4.9}$$

$\lambda_v(V_2^*) = 0$ is a solution to (4.5) which gives the disease free equilibrium. Then for a boundary equilibrium, $\lambda_v(V_2^*) > 0$ is a root of $f(\lambda_v)$, where

$$f(\lambda_v) = \frac{1}{< k >} \sum_{k=1}^{n} k^2 p(k) \frac{\beta_{v_1}^k}{k\lambda_v(V_2^*) + (\mu + d_v + \gamma_v)} - 1.$$

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

4.2. Stability of boundary equilibria and invasion numbers

To find the invasion number of HIV and stability of E_1^* we first linearize the system (2.2) around E_1^*. We set $S_k(t) = x_k(t) + S_{k1}^*$, $U_k(t) = u_k(t) + U_{k1}^*$, $V_k(t) = v_k(t)$, $i_k(t,\tau) = y_k(t,\tau)$ and $N_k(t) = n_k(t) + N_{k1}^*$, the system for the perturbations becomes,

$$\begin{cases} \dfrac{dx_k(t)}{dt} = -S_{k1}^*\lambda_u(u,y) - x_k(t)\beta_u \displaystyle\sum_{j=1}^{n} \frac{U_{j1}^*}{N_{j1}^*} + S_{k1}^*\beta_u \sum_{j=1}^{n} \frac{U_{j1}^* n_k}{N_{j1}^{*2}} - \mu x_k(t) + \delta u_k(t) - kS_{k1}^*\lambda_v(v,y), \\ \dfrac{du_k(t)}{dt} = S_{k1}^*\lambda_u(u,y) + x_k(t)\beta_u \displaystyle\sum_{j=1}^{n} \frac{U_{j1}^*}{N_{j1}^*} - S_{k1}^*\beta_u \sum_{j=1}^{n} \frac{U_{j1}^* n_k}{N_{j1}^{*2}} - kq_v U_{k1}^*\lambda_v(v,y) - (\mu + d_u + \delta)u_k(t), \\ \dfrac{dv_k(t)}{dt} = kS_{k1}^*\lambda_v(v,y) - q_u v_k(t)\beta_u \displaystyle\sum_{j=1}^{n} \frac{U_{j1}^*}{N_{j1}^*} - (\mu + d_v + \gamma_v)v_k(t) + \delta \int_0^\infty \sigma(\tau)y_k(t,\tau)d\tau, \\ \dfrac{\partial y_k(t,\tau)}{dt} + \dfrac{\partial k_s y_k(t,\tau)}{d\tau} = -(\mu + d_i(\tau) + \gamma_i(\tau) + \delta\sigma(\tau))y_k(t,\tau), \\ k_s y_k(t,0) = kq_v U_{k1}^*\lambda_v(v,y) + q_u v_k(t)\beta_u \sum_{j=1}^{n} \frac{U_{j1}^*}{N_{j1}^*}, \end{cases} \tag{4.10}$$

where,

$$\lambda_u(u,y) = \beta_u \sum_{j=1}^{n} \frac{u_j + \int_0^\infty y_j(t,\tau)}{N_{j1}^*},$$

$$\lambda_v(v,y) = \frac{1}{< k >} \sum_{j=1}^{n} jp(j) \frac{\beta_{v_1}^j v_j(t) + \int_0^\infty \beta_{v_2}^j(\tau) y_j(t,\tau)d\tau}{N_{j1}^*}.$$

We look for solutions of the form $x_k(t) = x_k e^{\lambda t}$, $u_k(t) = u_k e^{\lambda t}$, $v_k(t) = v_k e^{\lambda t}$, $y_k(\tau, t) = y_k(\tau)e^{\lambda t}$ and obtain the following eigenvalue problem,

$$\begin{cases} \lambda x_k = -S^*_{k1}\lambda_u(u,y) - x_k\beta_u \sum_{j=1}^n \frac{U^*_{j1}}{N^*_{j1}} + S^*_{k1}\beta_u \sum_{j=1}^n \frac{U^*_{j1}n_k}{N^{*2}_{j1}} - \mu x_k + \delta u_k - kS^*_{k1}\lambda_v(v,y), \\ \lambda u_k = S^*_{k1}\lambda_u(u,y) + x_k\beta_u \sum_{j=1}^n \frac{U^*_{j1}}{N^*_{j1}} - S^*_{k1}\beta_u \sum_{j=1}^n \frac{U^*_{j1}n_k}{N^{*2}_{j1}} - kq_v U^*_{k1}\lambda_v(v,y) - (\mu + d_u + \delta)u_k, \\ \lambda v_k = kS^*_{k1}\lambda_v(v,y) - q_u v_k\beta_u \sum_{j=1}^n \frac{U^*_{j1}}{N^*_{j1}} - (\mu + d_v + \gamma_v)v_k + \delta \int_0^\infty \sigma(\tau)y_k(\tau)d\tau, \\ \frac{\partial k_s y_k(\tau)}{d\tau} + \lambda y_k = -(\mu + d_i(\tau) + \gamma_i(\tau) + \delta\sigma(\tau))y_k(\tau), \\ k_s y_k(0) = kq_v U^*_{k1}\lambda_v(v,y) + q_u v_k\beta_u \sum_{k=1}^n \frac{U^*_{k1}}{N^*_{k1}}, \end{cases} \tag{4.11}$$

where,

$$\lambda_u(u,y) = \beta_u \sum_{j=1}^n \frac{u_j + \int_0^\infty y_j(\tau)d\tau}{N^*_{j1}},$$

and

$$\lambda_v(v,y) = \frac{1}{< k >} \sum_{j=1}^n jp(j) \frac{\beta^j_{v_1} v_j + \int_0^\infty \beta^j_{v_2}(\tau)y_j(\tau)d\tau}{N^*_{j1}}. \tag{4.12}$$

Now, using the third, fourth and fifth equation of (4.11) we will compute the invasion number of HIV.

$$\begin{cases} (\lambda + \mu + d_v + \gamma_v)v_k = kS^*_{k1}\lambda_v(v,y) - q_u v_k\beta_u \sum_{j=1}^n \frac{U^*_{j1}}{N^*_{j1}} + \delta \int_0^\infty \sigma(\tau)y_k(\tau)d\tau, \\ \frac{\partial k_s y_k(\tau)}{d\tau} + \lambda y_k = -(\mu + d_i(\tau) + \gamma_i(\tau) + \delta\sigma(\tau))y_k(\tau), \\ k_s y_k(0) = kq_v U^*_{k1}\lambda_v(v,y) + q_u v_k\beta_u \sum_{j=1}^n \frac{U^*_{j1}}{N^*_{j1}}. \end{cases}$$

From the second equation of (4.2) we get $y_k(\tau) = y_k(0)\pi(\tau)e^{-\frac{\lambda\tau}{k_s}}$, where $\pi(\tau)$ is as defined before. Suppose $K = \beta_u q_u \sum_{k=1}^n \frac{U^*_{k1}}{N^*_{k1}}$ and $Q(\lambda) = \delta[\int_0^\infty \sigma(\tau)\pi(\tau)e^{-\frac{\lambda\tau}{k_s}}d\tau]$. Then from the first and third equations of (4.2) we get,

$$\begin{cases} (\lambda + \mu + d_v + \gamma_v + K)v_k - Q(\lambda)y_k(0) &= kS^*_{k1}\lambda_v(v,y), \\ -Kv_k + k_s y_k(0) &= kq_v U^*_{k1}\lambda_v(v,y). \end{cases} \tag{4.13}$$

Solving for v_k and $y_k(0)$ we obtain,

$$v_k = \frac{k_s kS^*_{k1} + kq_v U^*_{k1}Q(\lambda)}{k_s(\lambda + \mu + d_v + \gamma_v + K) - KQ(\lambda)}\lambda_v(v,y),$$
$$y_k(0) = \frac{kq_v(\lambda + \mu + d_v + \gamma_v + K)U^*_{k1} + KkS^*_{k1}}{k_s(\lambda + \mu + d_v + \gamma_v + K) - KQ(\lambda)}\lambda_v(v,y).$$

Supplying these values in Eq (4.12), and cancelling $\lambda_v(v, y)$ from both sides of the equation, we obtain,

$$1 = \frac{1}{< k >}\sum_{j=1}^{n} j^2 p(j)\Bigg[\frac{\beta_{v_1}^j}{N_{j1}^*}\frac{k_s j S_{j1}^* + j q_v U_{j1}^* Q(\lambda)}{k_s(\lambda+\mu+d_v+\gamma_v+K) - KQ(\lambda)} + \frac{\int_0^\infty \beta_{v_2}^j(\tau)\pi(\tau)d\tau}{N_{j1}^*}\frac{j q_v(\lambda+\mu+d_v+\gamma_v+K)U_{j1}^* + K j S_{j1}^*}{k_s(\lambda+\mu+d_v+\gamma_v+K) - KQ(\lambda)}\Bigg]. \tag{4.14}$$

We define

$$\mathcal{R}_{v_i}^1 = \frac{1}{< k >}\sum_{j=1}^{n} j^2 p(j)\Bigg[\frac{\beta_{v_1}^j}{N_{j1}^*}\frac{k_s j S_{j1}^* + j q_v U_{j1}^* \delta[\int_0^\infty \sigma(\tau)\pi(\tau)d\tau]}{k_s(\mu+d_v+\gamma_v+K) - K\delta[\int_0^\infty \sigma(\tau)\pi(\tau)d\tau]} + \frac{\int_0^\infty \beta_{v_2}^j(\tau)\pi(\tau)d\tau}{N_{j1}^*}\frac{j q_v(\mu+d_v+\gamma_v+K)U_{j1}^* + K j S_{j1}^*}{k_s(\mu+d_v+\gamma_v+K) - K\delta[\int_0^\infty \sigma(\tau)\pi(\tau)d\tau]}\Bigg]. \tag{4.15}$$

We call $\mathcal{R}_{v_i}^1$ the invasion reproduction number of HIV infection. Now suppose,

$$\mathcal{G}_{vi}(\lambda) = \frac{1}{< k >}\sum_{j=1}^{n} j^2 p(j)\Bigg[\frac{\beta_{v_1}^j}{N_{j1}^*}\frac{k_s S_{j1}^* + q_v U_{j1}^* Q(\lambda)}{k_s(\lambda+\mu+d_v+\gamma_v+K) - KQ(\lambda)} + \frac{\int_0^\infty \beta_{v_2}^j(\tau)e^{-\lambda\tau}\pi(\tau)d\tau}{N_{j1}^*}\frac{q_v(\lambda+\mu+d_v+\gamma_v+K)U_{j1}^* + K S_{j1}^*}{k_s(\lambda+\mu+d_v+\gamma_v+K) - KQ(\lambda)}\Bigg]$$

$\int_0^\infty \beta_{v_2}^j(\tau)e^{-\lambda\tau}\pi(\tau)d\tau = \beta_j(\lambda)$. $\beta_j(\lambda)$ is bounded above by $\beta_j(0)$ and $Q(\lambda)$ is bounded above by $Q(0)$. Then $\mathcal{G}_{vi}(0) = \mathcal{R}_{v_i}^1$ and $\lim_{\lambda\to\infty}\mathcal{G}_{vi}(\lambda) = 0$. Suppose (4.14) has a solution $\lambda = x + iy$ with $\Re(\lambda) = x \geq 0$ and $\mathcal{R}_{vi}^1 < 1$. First we prove the following result.

$$\frac{\left|q_v(\lambda+\mu+d_v+\gamma_v+K)\frac{U_{j1}^*}{N_{j1}^*}\right| + \left|K\frac{S_{j1}^*}{N_{j1}^*}\right|}{|k_s(\lambda+\mu+d_v+\gamma_v+K)| - |KQ(0)|} \leq \frac{\left|q_v(\mu+d_v+\gamma_v+K)\frac{U_{j1}^*}{N_{j1}^*}\right| + \left|K\frac{S_{j1}^*}{N_{j1}^*}\right|}{|k_s(\mu+d_v+\gamma_v+K)| - |KQ(0)|} \tag{4.16}$$

Proof. To prove (4.16) we write down the left hand side of the inequality,

$$\frac{\left|q_v(\lambda+\mu+d_v+\gamma_v+K)\frac{U_{j1}^*}{N_{j1}^*}\right| + \left|K\frac{S_{j1}^*}{N_{j1}^*}\right|}{|k_s(\lambda+\mu+d_v+\gamma_v+K)| - |KQ(0)|} = \frac{q_v C_1 z + KC_2}{k_s z - KQ(0)} = f(z),$$

where, $C_1 = \frac{U_{j1}^*}{N_{j1}^*}$, $C_2 = \frac{S_{j1}^*}{N_{j1}^*}$ and $z = \sqrt{(x+\mu+d_v+\gamma_v+K)^2 + y^2}$. Since $f'(z) < 0$, $f(z)$ is a decreasing function. That is when $z(0,0) \leq z(x,y)$, $f(z(0,0)) \geq f(z(x,y))$. But $f(z(0,0))$ is just the right hand side of (4.16).

Using (4.16) we can now state the following,

$$
\begin{aligned}
1 = |\mathcal{G}_{vi}(\lambda)| &= \left| \frac{1}{< k >} \sum_{j=1}^{n} j^2 p(j) \left[\frac{\beta_{v_1}^j}{N_{j1}^*} \frac{k_s S_{j1}^* + q_v U_{j1}^* Q(\lambda)}{k_s(\lambda + \mu + d_v + \gamma_v + K) - KQ(\lambda)} \right.\right. \\
&\quad \left.\left. + \frac{\beta_j(\lambda)}{N_{j1}^*} \frac{q_v(\lambda + \mu + d_v + \gamma_v + K) U_{j1}^* + K S_{j1}^*}{k_s(\lambda + \mu + d_v + \gamma_v + K) - KQ(\lambda)} \right] \right| \\
&\leq \frac{1}{< k >} \sum_{j=1}^{n} j^2 p(j) \left[\left| \frac{\beta_{v_1}^j}{N_{j1}^*} \frac{k_s S_{j1}^* + q_v U_{j1}^* Q(0)}{k_s(\mu + d_v + \gamma_v + K) - KQ(0)} \right| \right. \\
&\quad \left. + \left| \beta_j(0) \frac{q_v(\lambda + \mu + d_v + \gamma_v + K) \frac{U_{j1}^*}{N_{j1}^*} + K \frac{S_{j1}^*}{N_{j1}^*}}{k_s(\lambda + \mu + d_v + \gamma_v + K) - KQ(0)} \right| \right] \\
&\leq \frac{1}{< k >} \sum_{j=1}^{n} j^2 p(j) \left[\left| \frac{\beta_{v_1}^j}{N_{j1}^*} \frac{k_s S_{j1}^* + q_v U_{j1}^* Q(0)}{k_s(\mu + d_v + \gamma_v + K) - KQ(0)} \right| \right. \\
&\quad \left. + \beta_j(0) \frac{\left| q_v(\lambda + \mu + d_v + \gamma_v + K) \frac{U_{j1}^*}{N_{j1}^*} \right| + \left| K \frac{S_{j1}^*}{N_{j1}^*} \right|}{|k_s(\lambda + \mu + d_v + \gamma_v + K)| - |KQ(0)|} \right] \\
&\leq \frac{1}{< k >} \sum_{j=1}^{n} j^2 p(j) \left[\left| \frac{\beta_{v_1}^j}{N_{j1}^*} \frac{k_s S_{j1}^* + q_v U_{j1}^* Q(0)}{k_s(\mu + d_v + \gamma_v + K) - KQ(0)} \right| \right. \\
&\quad \left. + \frac{\left| q_v(\mu + d_v + \gamma_v + K) \frac{U_{j1}^*}{N_{j1}^*} \right| + \left| K \frac{S_{j1}^*}{N_{j1}^*} \right|}{|k_s(\mu + d_v + \gamma_v + K)| - |KQ(0)|} \right] \\
&= |\mathcal{G}_{vi}(0)| = \mathcal{R}_{vi}^1 < 1.
\end{aligned}
\tag{4.17}
$$

This is a contradiction. So (4.14) only has solutions with non-negative real parts when $\mathcal{R}_{vi}^1 < 1$.

Now let us suppose, $\mathcal{R}_{vi}^1 > 1$. It can be shown that $\mathcal{G}_{vi}(\lambda)$ is decreasing. Then since $\mathcal{G}_{vi}(0) = \mathcal{R}_{v_i}^1 > 1$ and $\lim_{\lambda \to \infty} \mathcal{G}_{vi}(\lambda) = 0$ for real and positive λ, (4.14) must have at least one positive root when $\mathcal{R}_{vi} > 1$. Now, from (4.1)–(4.3) we get,

$$
S_{k1}^* = \frac{n}{\mathcal{R}_u} \frac{U_{k1}^*}{n\left(1 - \frac{1}{\mathcal{R}_u}\right)} = \frac{U_{k1}^*}{\mathcal{R}_u - 1},
$$

i.e.,

$$
\frac{\frac{U_{k1}^*}{\mathcal{R}_u - 1} + U_{k1}^*}{N_{k1}^*} = \frac{U_{k1}^*}{N_{k1}^*} \left(\frac{1}{\mathcal{R}_u - 1} + 1 \right) = 1.
$$

Solving the equation we get,

$$
\begin{aligned}
\frac{U_{k1}^*}{N_{k1}^*} &= 1 - \frac{1}{\mathcal{R}_u}, \\
\frac{S_{k1}^*}{N_{k1}^*} &= \frac{1}{\mathcal{R}_u}.
\end{aligned}
\tag{4.18}
$$

To find the remaining eigenvalues, satisfying the third, fourth and fifth equation of (4.11), $y_j(\tau) = 0$ and $v_j = 0$ for all $j = 1, 2, \cdots, n$. The first two equations then just reduce to

$$\begin{aligned}\lambda x_k &= -S^*_{k1}\beta_u \sum_{j=1}^{n} \frac{u_j}{N^*_j} - x_k\beta_u \sum_{j=1}^{n} \frac{U^*_{j1}}{N^*_{j1}} + S^*_{k1}\beta_u \sum_{j=1}^{n} \frac{U^*_{j1}n_k}{N^{*2}_{j1}} - \mu x_k + \delta u_k,\\ \lambda u_k &= S^*_{k1}\beta_u \sum_{j=1}^{n} \frac{u_j}{N^*_j} + x_k\beta_u \sum_{j=1}^{n} \frac{U^*_{j1}}{N^*_{j1}} - S^*_{k1}\beta_u \sum_{j=1}^{n} \frac{U^*_{j1}n_k}{N^{*2}_{j1}} - (\mu + d_u + \delta)u_k,\end{aligned} \tag{4.19}$$

Adding the two equations and solving for n_k we get

$$n_k = -\frac{d_u u_k}{(\lambda + \mu),}$$

i.e.,

$$x_k = -\frac{\lambda + \mu + d_u}{\lambda + \mu} u_k.$$

Replacing x_k and n_k in the second equation of (4.19) we get,

$$\begin{aligned}(\lambda + \mu + d_u + \delta)u_k &= S^*_{k1}\beta_u \sum_{j=1}^{n} \frac{u_j}{N^*_{j1}} - \frac{\lambda + \mu + d_u}{\lambda + \mu} u_k\beta_u \sum_{j=1}^{n} \frac{U^*_{j1}}{N^*_{j1}} + S^*_{k1}\beta_u \sum_{j=1}^{n} \frac{U^*_{j1}}{N^{*2}_{j1}} \frac{d_u u_j}{(\lambda + \mu)}\\ \implies \left(\lambda + \mu + d_u + \delta + \beta_u n\left(1 - \frac{1}{\mathcal{R}_u}\right)\frac{\lambda + \mu + d_u}{\lambda + \mu}\right)u_k &= S^*_{k1}\beta_u \sum_{j=1}^{n} \frac{u_j}{N^*_{j1}} \left(1 + \frac{d_u \frac{U^*_{j1}}{N^*_{j1}}}{\lambda + \mu}\right).\end{aligned} \tag{4.20}$$

Multiplying both sides of the equation $\frac{1}{N^*_{k1}}$ and summing over 1 to n,

$$\left(\lambda + \mu + d_u + \delta + \beta_u n\left(1 - \frac{1}{\mathcal{R}_u}\right)\frac{\lambda + \mu + d_u}{\lambda + \mu}\right)\sum_{k=1}^{n} \frac{u_k}{N^*_{k1}} = \sum_{k=1}^{n} \frac{S^*_{k1}}{N^*_{k1}}\beta_u \sum_{j=1}^{n} \frac{u_j}{N^*_{j1}} \left(1 + \frac{d_u \frac{U^*_{j1}}{N^*_{j1}}}{\lambda + \mu}\right). \tag{4.21}$$

$\sum_{j=1}^{n} \frac{u_j}{N^*_{j1}} = 0$ implies from (4.20) all u_k would be zero, which would not be of interest. $\sum_{j=1}^{n} \frac{u_j}{N^*_{j1}} \neq 0$ for non-equilibrium points, and cancelling the expression on both sides, then the characteristic equation becomes,

$$(\lambda + \mu + d_u + \delta)(\lambda + \mu) + \beta_u(\lambda + \mu + d_u)n\left(1 - \frac{1}{\mathcal{R}_u}\right) = \beta_u\left(\lambda + \mu + d_u\left(1 - \frac{1}{\mathcal{R}_u}\right)\right)\frac{n}{\mathcal{R}_u}. \tag{4.22}$$

Rewriting this equation as a quadratic equation, we get

$$\lambda^2 + (2\mu + d_u + \delta + \beta_u n - \beta_u \frac{n}{\mathcal{R}_u})\lambda + (\mu + d_u + \delta)\mu + \beta_u n\left(1 - \frac{1}{\mathcal{R}_u}\right)(\mu + d_u) - \beta_u n \frac{1}{\mathcal{R}_u}\left(\mu + d_u\left(1 - \frac{1}{\mathcal{R}_u}\right)\right) = 0 \tag{4.23}$$

Simplifying the equation, we have $\lambda^2 + b\lambda + c = 0$ where $b = \mu + \beta_u n > 0$ and $c = \left(1 - \frac{1}{\mathcal{R}_u}\right)(\beta_u n(\mu + d_u) - (\mu + d_u + \delta)d_u) > 0$ since, $\beta_u n > (\mu + d_u + \delta)$ when $\mathcal{R}_u > 1$. Hence this quadratic equation has only roots with negative real parts. Combining the work above we can conclude,

Theorem 2. The unique boundary equilibrium E_1^* is locally asymptotically stable if $\mathcal{R}_{v_i}^1 < 1$, and it is unstable if $\mathcal{R}_{v_i}^1 > 1$.

To find the invasion number of opioid addiction and stability of E_2^* we first linearize the system (2.2) around E_2^*. We set $S_k(t) = x_k(t) + S_{k2}^*$, $U_k(t) = u_k(t)$, $V_k(t) = v_k(t) + V_{k2}^*$, $i_k(t,\tau) = y_k(t,\tau)$ and $N_k(t) = n_k(t) + N_{k2}^*$. The system for the perturbations becomes,

$$\begin{cases} \dfrac{dx_k(t)}{dt} = -S_{k2}^*\lambda_u^2(u,y) - \mu x_k(t) + \delta u_k(t) - kS_{k2}^*\lambda_v^2(v,y) - C_1 k x_k + kS_{k2}^* \dfrac{1}{< k >}\displaystyle\sum_{j=1}^{n} jp(j)\frac{\beta_{v_1}^j V_{j2}^* n_j}{N_{j2}^{*2}}, \\ \dfrac{du_k(t)}{dt} = S_{k2}^*\lambda_u^2(u,y) - kq_v u_k C_1 - (\mu + d_u + \delta)u_k(t), \\ \dfrac{dv_k(t)}{dt} = kx_k C_1 + kS_{k2}^*\lambda_v^2(v,y) - kS_{k2}^* \dfrac{1}{< k >}\displaystyle\sum_{j=1}^{n} jp(j)\frac{\beta_{v_1}^j V_{j2}^* n_j}{N_{j2}^{*2}} - q_u V_{k2}^*\lambda_u^2(u,y) \\ -(\mu + d_v + \gamma_v)v_k(t) + \delta\int_0^\infty \sigma(\tau)y_k(t,\tau)d\tau, \\ \dfrac{\partial y_k(t,\tau)}{dt} + \dfrac{\partial k_s y_k(t,\tau)}{d\tau} = -(\mu + d_i(\tau) + \gamma_i(\tau) + \delta\sigma(\tau))y_k(t,\tau), \\ k_s y_k(t,0) = kq_v C_1 u_k + q_u V_{k2}^*\lambda_u^2(u,y), \end{cases} \tag{4.24}$$

where,

$$\lambda_u^2(u,y) = \beta_u \sum_{j=1}^{n} \frac{u_j + \int_0^\infty y_j(t,\tau)}{N_{j2}^*}$$

$$\lambda_v^2(v,y) = \frac{1}{< k >}\sum_{j=1}^{n} jp(j)\frac{\beta_{v_1}^j v_j(t) + \displaystyle\int_0^\infty \beta_{v_2}^j(\tau)y_j(t,\tau)d\tau}{N_{j2}^*}$$

and

$$C_1 = \frac{1}{< k >}\sum_{j=1}^{n} jp(j)\frac{\beta_{v_1}^j V_{j2}^*}{N_{j2}^*}.$$

We look for solutions of the form $x_k(t) = x_k e^{\lambda t}$, $u_k(t) = u_k e^{\lambda t}$, $v_k(t) = v_k e^{\lambda t}$, $y_k(t,\tau) = y_k(\tau)e^{\lambda t}$ and obtain the following eigenvalue problem,

$$\begin{cases} \lambda x_k = -S^*_{k2}\lambda^2_u(u,y) - \mu x_k + \delta u_k - kS^*_{k2}\lambda^2_v(v,y) - C_1 k x_k + kS^*_{k2}\frac{1}{<k>}\sum_{j=1}^{n} jp(j)\frac{\beta^k_{v_1} V^*_{j2} n_j}{N^{*2}_{j2}}, \\ \lambda u_k = S^*_{k2}\lambda^2_u(u,y) - kq_v u_k C_1 - (\mu + d_u + \delta)u_k, \\ \lambda v_k = kx_k C_1 + kS^*_{k2}\lambda^2_v(v,y) - kS^*_{k2}\frac{1}{<k>}\sum_{j=1}^{n} jp(j)\frac{\beta^k_{v_1} V^*_{j2} n_j}{N^{*2}_{j2}} - q_u V^*_{k2}\lambda^2_u(u,y) \\ \qquad -(\mu + d_v + \gamma_v)v_k + \delta\int_0^\infty \sigma(\tau)y_k(\tau)d\tau, \\ \frac{\partial k_s y_k(\tau)}{d\tau} + \lambda y_k = -(\mu + d_i(\tau) + \gamma_i(\tau) + \delta\sigma(\tau))y_k(\tau), \\ k_s y_k(0) = kq_v C_1 u_k + q_u V^*_{k2}\lambda^2_u(u,y). \end{cases} \tag{4.25}$$

From the fourth equation of (4.25) we get

$$y_k(\tau) = y_k(0)\pi(\tau)e^{\frac{-\lambda}{k_s}\tau}. \tag{4.26}$$

Let $Q(\lambda) = \int_0^\infty \pi(\tau)e^{\frac{-\lambda}{k_s}\tau}d\tau$. From the second equation of (4.25) we get

$$u_k = \frac{S^*_{k2}}{\lambda + \mu + d_u + \delta + kq_v C_1}\beta_u \sum_{j=1}^{n}\frac{u_j + y_j(0)Q(\lambda)}{N^*_{j2}}.$$

Multiplying both sides of this equation with $\frac{1}{N^*_{k2}}$ we get,

$$\frac{u_k}{N^*_{k2}} = \frac{\beta_u S^*_{k2}}{(\lambda + \mu + d_u + \delta + kq_v C_1)N^*_{k2}}\sum_{j=1}^{n}\frac{u_j + y_j(0)Q(\lambda)}{N^*_{j2}}. \tag{4.27}$$

From the fifth equation of (4.25) we get,

$$k_s y_k(0) = kq_v C_1 u_k + q_u V^*_{k2}\beta_u \sum_{j=1}^{n}\frac{u_j + y_j(0)Q(\lambda)}{N^*_{j2}}.$$

Multiplying both sides of this equation with $\frac{Q(\lambda)}{N^*_{k2}}$ we get,

$$\frac{y_k(0)Q(\lambda)}{N^*_{k2}} = \frac{kq_v C_1 Q(\lambda)\beta_u S^*_{k2}}{k_s(\lambda + \mu + d_u + \delta + kq_v C_1)N^*_{k2}}\sum_{j=1}^{n}\frac{u_j + y_j(0)Q(\lambda)}{N^*_{j2}} + Q(\lambda)q_u\frac{V^*_{k2}\beta_u}{N^*_{k2}k_s}\sum_{j=1}^{n}\frac{u_j + y_j(0)Q(\lambda)}{N^*_{j2}}. \tag{4.28}$$

Summing both side of (4.27) and (4.28) from 1 to n and adding together we get,

$$S(\lambda) = S(\lambda)\left[\sum_{k=1}^{n}\frac{(1 + kq_v C_1 Q(\lambda))\beta_u S^*_{k2}}{k_s(\lambda + \mu + d_u + \delta + kq_v C_1)N^*_{k2}} + Q(\lambda)\frac{q_u\beta_u}{k_s}\sum_{k=1}^{n}\frac{V^*_{k2}}{N^*_{k2}}\right] \tag{4.29}$$

where, $S(\lambda) = \sum_{j=1}^{n}\frac{u_j + y_j(0)Q(\lambda)}{N^*_{j2}}$. Since $S(\lambda) = 0$ implies from (4.27) $u_k = 0$ for all k, $S(\lambda) \neq 0$. We cancel $S(\lambda)$ from both sides and get,

$$1 = \sum_{k=1}^{n}\frac{(1 + kq_v C_1 Q(\lambda))\beta_u S^*_{k2}}{k_s(\lambda + \mu + d_u + \delta + kq_v C_1)N^*_{k2}} + Q(\lambda)\frac{q_u\beta_u}{k_s}\sum_{k=1}^{n}\frac{V^*_{k2}}{N^*_{k2}}. \tag{4.30}$$

Let $\Pi = \int_0^\infty \pi(\tau)d\tau$. We define

$$\mathcal{R}^2_{u_i} = \sum_{k=1}^{n} \frac{(1 + kq_vC_1\Pi)\beta_u S^*_{k2}}{k_s(\mu + d_u + \delta + kq_vC_1)N^*_{k2}} + \Pi\frac{q_u\beta_u}{k_s}\sum_{k=1}^{n}\frac{V^*_{k2}}{N^*_{k2}}. \tag{4.31}$$

We call $\mathcal{R}^2_{u_i}$ the invasion reproduction number of opioid addiction. We claim that when $\mathcal{R}^2_{u_i} < 1$ the boundary equilibrium E^*_2 is locally asymptotically stable, that is all the roots of (4.30) have negative real parts. Suppose

$$\mathcal{G}_{ui}(\lambda) = \sum_{k=1}^{n} \frac{(1 + kq_vC_1Q(\lambda))\beta_u S^*_{k2}}{k_s(\lambda + \mu + d_u + \delta + kq_vC_1)N^*_{k2}} + Q(\lambda)\frac{q_u\beta_u}{k_s}\sum_{k=1}^{n}\frac{V^*_{k2}}{N^*_{k2}}.$$

Then $\mathcal{G}_{ui}(0) = \mathcal{R}^2_{u_i}$ and $\lim_{\lambda\to\infty}\mathcal{G}_{ui}(\lambda) = 0$. Assume the Eq (4.30) has roots with non-negative real part $\Re(\lambda) > 0$. The Eq (4.30) satisfies,

$$\begin{aligned}
1 &= \left|\sum_{k=1}^{n} \frac{(1 + kq_vC_1Q(\lambda))\beta_u S^*_{k2}}{k_s(\lambda + \mu + d_u + \delta + kq_vC_1)N^*_{k2}} + Q(\lambda)\frac{q_u\beta_u}{k_s}\sum_{k=1}^{n}\frac{V^*_{k2}}{N^*_{k2}}\right| \\
&\le \left|\sum_{k=1}^{n} \frac{(1 + kq_vC_1Q(\lambda))\beta_u S^*_{k2}}{k_s(\lambda + \mu + d_u + \delta + kq_vC_1)N^*_{k2}}\right| + \left|Q(\lambda)\frac{q_u\beta_u}{k_s}\sum_{k=1}^{n}\frac{V^*_{k2}}{N^*_{k2}}\right| \\
&\le \left|\sum_{k=1}^{n} \frac{(1 + kq_vC_1Q(\Re(\lambda)))\beta_u S^*_{k2}}{k_s(\lambda + \mu + d_u + \delta + kq_vC_1)N^*_{k2}}\right| + \left|Q(\Re(\lambda))\frac{q_u\beta_u}{k_s}\sum_{k=1}^{n}\frac{V^*_{k2}}{N^*_{k2}}\right| \\
&\le \left|\sum_{k=1}^{n} \frac{(1 + kq_vC_1\Pi)\beta_u S^*_{k2}}{k_s(\mu + d_u + \delta + kq_vC_1)N^*_{k2}}\right| + \left|\Pi\frac{q_u\beta_u}{k_s}\sum_{k=1}^{n}\frac{V^*_{k2}}{N^*_{k2}}\right| \\
&\le \mathcal{R}^2_{u_i} < 1
\end{aligned} \tag{4.32}$$

This is a contradiction. Hence all roots of (4.30) have negative real parts when $\mathcal{R}^2_{u_i} < 1$. Now let us suppose, $\mathcal{R}^2_{u_i} > 1$. Then since $\mathcal{G}'_{ui}(\lambda) < 0$ when $\lambda > 0$, $\mathcal{G}_{ui}(\lambda)$ is decreasing when $\lambda > 0$. But we have, $\mathcal{G}_{ui}(0) = \mathcal{R}^2_{u_i} > 1$ and $\lim_{\lambda\to\infty}\mathcal{G}_{ui}(\lambda) = 0$. Then (4.30) has at least one positive root when $\mathcal{R}^2_{u_i} > 1$. If λ is not a solution of characteristic equation (4.30),we have $u_j = 0$, $y_j(0) = 0$, the remaining two equations of (4.25) then just reduce to

$$\begin{aligned}
\lambda x_k &= -\mu x_k - kS^*_{k2}\frac{1}{<k>}\sum_{j=1}^{n} jp(j)\frac{\beta^j_{v_1}v_j}{N^*_{j2}} - C_1kx_k + kS^*_{k2}\frac{1}{<k>}\sum_{j=1}^{n} jp(j)\frac{\beta^j_{v_1}V^*_{j2}n_j}{N^{*2}_{j2}}, \\
\lambda v_k &= kx_kC_1 + kS^*_{k2}\frac{1}{<k>}\sum_{j=1}^{n} jp(j)\frac{\beta^j_{v_1}v_j}{N^*_{j2}} - kS^*_{k2}\frac{1}{<k>}\sum_{j=1}^{n} jp(j)\frac{\beta^j_{v_1}V^*_{j2}n_j}{N^{*2}_{j2}} - (\mu + d_v + \gamma_v)v_k.
\end{aligned} \tag{4.33}$$

Adding the two equations and solving for n_k we get

$$n_k = -\frac{(d_v + \gamma_v)v_k}{(\lambda + \mu)},$$

i.e.,

$$x_k = -\frac{\lambda + \mu + d_v + \gamma_v}{\lambda + \mu}v_k.$$

Using these values for n_k and x_k in the second equation of (4.33) we get

$$\left(\lambda+\mu+d_v+\gamma_v+\frac{kC_1(\lambda+\mu+d_v+\gamma_v)}{\lambda+\mu}\right)v_k = kS^*_{k2}\frac{1}{<k>}\sum_{j=1}^{n} jp(j)\frac{\beta^j_{v_1}V^*_{j2}}{N^*_{j2}}\left(\frac{\lambda+\mu+(d_v+\gamma_v)\frac{V^*_{j2}}{N^*_{j2}}}{\lambda+\mu}\right). \tag{4.34}$$

Dividing both sides by N^*_{k2} and readjusting we obtain,

$$\frac{v_k}{N^*_{k2}} = \frac{kS^*_{k2}}{N^*_{k2}}\frac{1}{(\lambda+\mu+d_v+\gamma_v)(\lambda+\mu+kC_1)}\frac{1}{<k>}\sum_{j=1}^{n} jp(j)\frac{\beta^j_{v_1}v_j}{N^*_{j2}}\left(\lambda+\mu+(d_v+\gamma_v)\frac{V^*_{j2}}{N^*_{j2}}\right). \tag{4.35}$$

Multiplying both sides of this equation with $\frac{1}{<k>}\sum_{k=1}^{n} kp(k)\beta^k_{v_1}(\lambda+\mu+(d_v+\gamma_v)\frac{V^*_{k2}}{N^*_{k2}})$, we get,

$$T(\lambda) = \frac{1}{<k>}\sum_{k=1}^{n} k^2p(k)\beta^k_{v_1}\frac{S^*_{k2}}{N^*_{k2}}\frac{(\lambda+\mu+(d_v+\gamma_v)\frac{V^*_{k2}}{N^*_{k2}})}{(\lambda+\mu+d_v+\gamma_v)(\lambda+\mu+kC_1)}T(\lambda), \tag{4.36}$$

where $T(\lambda) = \frac{1}{<k>}\sum_{j=1}^{n} jp(j)\frac{\beta^j_{v_1}v_j}{N^*_{j2}}\left(\lambda+\mu+(d_v+\gamma_v)\frac{V^*_{j2}}{N^*_{j2}}\right)$. Since $T(\lambda)=0$ implies from (4.35), $v_k=0$ for all k, $T(\lambda)\neq 0$ and we get the following characteristic equation,

$$1 = \frac{1}{<k>}\sum_{k=1}^{n} k^2p(k)\beta^k_{v_1}\frac{S^*_{k2}}{N^*_{k2}}\frac{(\lambda+\mu+(d_v+\gamma_v)\frac{V^*_{k2}}{N^*_{k2}})}{(\lambda+\mu+d_v+\gamma_v)(\lambda+\mu+kC_1)}. \tag{4.37}$$

From (4.8) we obtain,

$$\frac{V^*_{k2}}{N^*_{k2}} = \frac{kC_1}{kC_1+\mu+d_v+\gamma_v},$$
$$\frac{S^*_{k2}}{N^*_{k2}} = \frac{\mu+d_v+\gamma_v}{kC_1+\mu+d_v+\gamma_v}.$$

Assume the Eq (4.37) has roots with non-negative real part. Using (4.9), $\Re\lambda \geq 0$ the Eq (4.37) satisfies,

$$\begin{aligned}
1 &= \left|\frac{1}{<k>}\sum_{k=1}^{n} k^2p(k)\beta^k_{v_1}\frac{S^*_{k2}}{N^*_{k2}}\frac{(\lambda+\mu+(d_v+\gamma_v)\frac{V^*_{k2}}{N^*_{k2}})}{(\lambda+\mu+d_v+\gamma_v)(\lambda+\mu+kC_1)}\right| \\
&= \left|\frac{1}{<k>}\sum_{k=1}^{n} k^2p(k)\beta^k_{v_1}\frac{\mu+d_v+\gamma_v}{kC_1+\mu+d_v+\gamma_v}\frac{(\lambda+\mu+(d_v+\gamma_v)\frac{kC_1}{kC_1+\mu+d_v+\gamma_v})}{(\lambda+\mu+d_v+\gamma_v)(\lambda+\mu+kC_1)}\right| \\
&< \left|\frac{1}{<k>}\sum_{k=1}^{n} k^2p(k)\beta^k_{v_1}\frac{\mu+d_v+\gamma_v}{kC_1+\mu+d_v+\gamma_v}\frac{1}{(\lambda+\mu+d_v+\gamma_v)}\right| \\
&\leq \frac{1}{<k>}\sum_{k=1}^{n} k^2p(k)\beta^k_{v_1}\frac{\mu+d_v+\gamma_v}{kC_1+\mu+d_v+\gamma_v}\frac{1}{(\mu+d_v+\gamma_v)} = 1
\end{aligned} \tag{4.38}$$

This is a contradiction. So we can state the following theorem,

Theorem 3. The unique boundary equilibrium E_2^* is locally asymptotically stable if $\mathcal{R}_{u_i}^2 < 1$, and is unstable if $\mathcal{R}_{u_i}^2 > 1$.

5. Numerical simulations

5.1. Numerical scheme and simulation

We present a numerical scheme for the immuno-epidemiological models (2.1) and (2.2). The within-host model, consisting of ordinary differential equations can be solved by a stiff ODE solver in MATLAB.

For the between-host model we introduce a finite-difference method. We discretize the domain

$$\mathcal{D} = \{(t, \tau) : \ 0 \le t \le T, \ 0 \le \tau \le A\}$$

where A is a maximal infection age and time $T < \infty$, a maximal time. We take $\Delta t = \Delta\tau$, with $k_s = 1$, and so the points in age and line direction can be computed as,

$$\tau_m = m\Delta t \quad t_j = j\Delta t.$$

Setting $M = \left[\frac{A}{\Delta t}\right]$ and $N = \left[\frac{T}{\Delta t}\right]$, we obtain $A = M\Delta t$, $T = N\Delta t$. The numerical method computes approximations to the solution at the mesh points. We assume $S_k(t_j) = S_k^j$, $U_k(t_j) = U_k^j$, $V_k(t_j) = V_k^j$ and $i_k(t_j, \tau_m) = i_{m,k}^j$. We summarize the numerical method below,

$$\begin{cases} \lambda_v^j = \frac{1}{\langle k\rangle}\sum_{k=1}^n \frac{\beta_{v_1} V_k^j + \sum_{m=1}^M \Delta t \beta_{v_{2_m}} i_{m,k}^{j+1}}{N_k^j}, & j = 0, \cdots, N-1; \\ \lambda_u^j = \sum_{k=1}^n \frac{\beta_u U_k^j + \sum_{m=1}^M \Delta t i_{m,k}^{j+1}}{N_k^j}, & j = 0, \cdots, N-1; \\ S_k^{j+1} = \frac{S_k^j + \Lambda\Delta t + \delta U_k^j \Delta t}{1 + k\lambda_v^j \Delta t + \lambda_u^j \Delta t + \mu\Delta t}, & j = 0, \cdots, N-1; \\ U_k^{j+1} = \frac{U_k^j + \lambda_u^j S_k^{j+1}\Delta t}{1 + kq_v\lambda_v^j \Delta t + (\mu + d_u + \delta)\Delta t}, & j = 0, \cdots, N-1; \\ V_k^{j+1} = \frac{V_k^j + k\lambda_v^j S_k^{j+1}\Delta t + \delta\Delta t \sum_{m=1}^M \sigma_m i_{m,k}^{j+1}\Delta t}{1 + q_u\lambda_u^j \Delta t + (\mu + d_v + \gamma_v)\Delta t}, & j = 0, \cdots, N-1; \\ i_{m+1,k}^{j+1} = \frac{i_{m,k}^j}{1 + \mu\Delta t + (d_m + \gamma_m + \delta\sigma_m)\Delta t}, & j = 0, \cdots, N-1; \\ & m = 0, \cdots, M-1, \\ i_{0,k}^{j+1} = kq_v U_k^{j+1}\lambda_v^j + q_u V_k^{j+1}\lambda_u^j, & j = 0, \cdots, N-1; \\ N_k^{j+1} = \frac{N_k^j + \Delta t(\Lambda - d_u U_k^{j+1} - (d_v + \gamma_v)V_k^{j+1} - \sum_{m=1}^M (d_m + \gamma_m) i_{m,k}^j)}{1 + \mu\Delta t}, & j = 0, \cdots, N-1. \end{cases} \tag{5.1}$$

To study the coexistence equilibrium analytically is not feasible for this model. So we take the help of simulations to predict the existence of coexistence equilibrium in a scale free network scenario. We consider specific parameter values for which $\mathcal{R}^2_{u_i}$ and $\mathcal{R}^1_{v_i}$ are greater than 1. The simulations suggest that the coexistence equilibrium exists and is stable. Given parameter values are constant, the invasion number of HIV, $\mathcal{R}^1_{v_i}$, seem to show dependence on the size of the network used. With the same parameter values given in Table 3, when the network contains 200 nodes, $\mathcal{R}^1_{v_i}$ is close to 1.4, while with 300 nodes, $\mathcal{R}^1_{v_i}$ increases to 2.9. The invasion number of opioid addiction $\mathcal{R}^1_{v_i}$ remains stable near the same value 1.2 when size of the network is increased from 200 nodes to 300 nodes. This is to be expected since the spread of opioid has been considered homogeneous over the network. Simulations suggesting a coexistence equilibrium are shown in Figure 1.

Table 3. Parameter estimation results from [38].

Parameter	Estimated Value	Units
β_u	0.385676	1/time
β_{v_1}	0.0551	1/time
k_0	0.00011046	1/time
B	15318.9	vRNA/ml
δ	0.118227	1/time
q_u	0.867138	Unitless
q_v	30.6189	Unitless
d_u	0.00817752	1/time
d_v	0.0144092	1/time
d_a	1.2766e+11	1/time
d_0	2.72895e-07	ml/(time × cells)
d_1	3.4671e-06	1/time
γ_v	0.0223488	1/time
γ_0	1.63927e-12	1/time
σ	0.000270006	Unitless
s	22843.6	CD4 count/(time × ml)
d	0.0766824	1/time
k_1	2.02785e-05	vRNA/(CD4 count × time)
δ_i	0.725266	1/time
$N_v\delta_i$	8465.63	vRNA/(CD4 count × time)

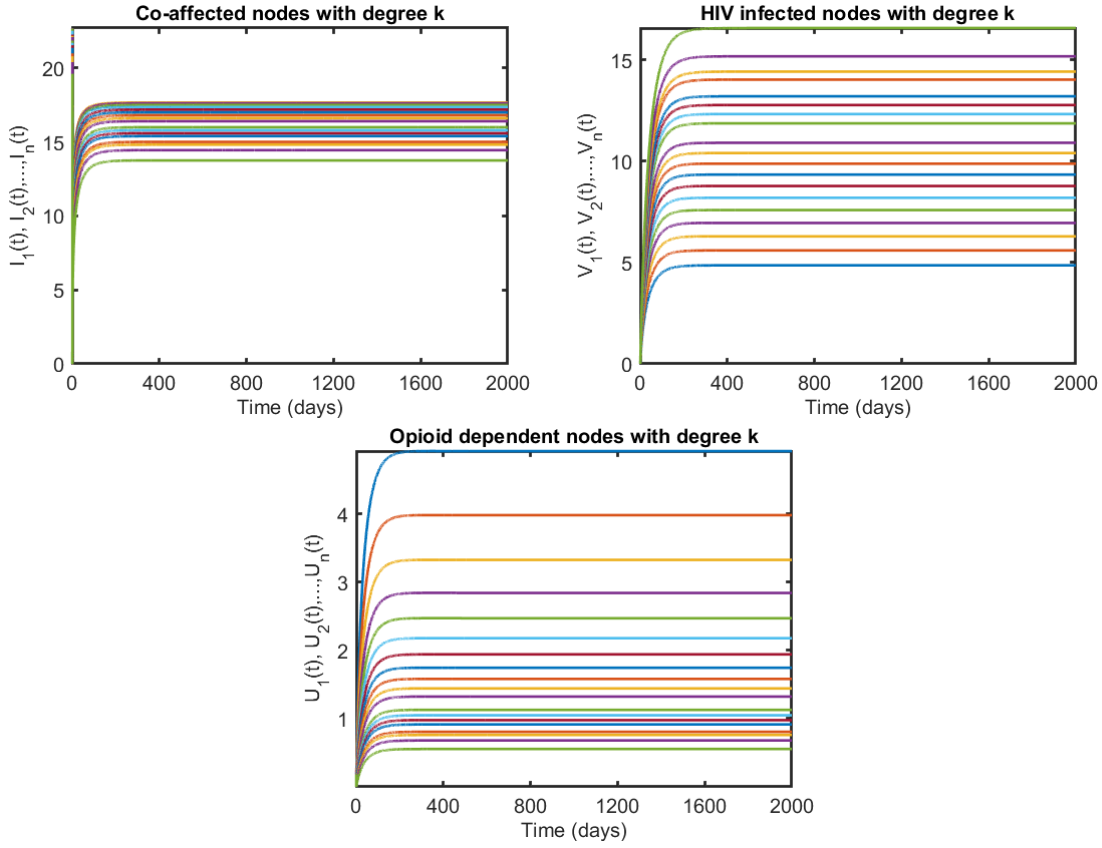

Figure 1. Simulations with the network model. In this simulation the average degree is 7.63 and $\mathcal{R}_{vi}^1 = 1.2173$, $\mathcal{R}_{ui}^2 = 1.1607$. The number of nodes is 100. The maximal degree is 28 but there are no occupied nodes with degree 1, 2, 3.

5.2. *Effects of the parametric values of q_u, q_v and δ*

We define U(t)=$\sum_{k=1}^{n} U_k(t)$ as the total opioid addicted population. Similarly we define $V(t)$, $I(t)$ and $S(t)$ as the total HIV infected, total co-infected and total susceptible population respectively. The network utilized had 200 nodes. The parameters β_u and $\beta_{v_1}^k$ are estimated by the following formulas, $\beta_u = \mathcal{R}_u(\mu + d_u + \delta)$; and $\beta_{v1}^k = \mathcal{R}_v(\mu + d_v + \gamma_v)$. Since the model we consider does not include treatment for HIV, we consider $\mathcal{R}_v = 5.5$. This estimate is an average value collected from [39], which gives an estimation of basic reproduction number of HIV in Rural South West Uganda. Estimated value of $\mathcal{R}_u$ according to [27] would be close to 1.1. Given the fact that a high percentage of US citizens mentioned it would be easy for someone to access opioids for illicit purposes, according to a poll conducted in 2018 (46 percent) and people who misuse opioids often get them from a family member or friend who has a prescription [40], we considered the $\mathcal{R}_u$ to be higher in range, around 3.25. The maximal degree n for the following simulations (except Figure 1) is 43, with number of nodes being 200.

The two parameters in (2.2) that are of particular interest are q_u and q_v, which determine how much one epidemics impacts the other. That is q_v determines how likely opioid users are to get infected by HIV compared to non-users, and q_u determines how likely HIV infected people are to become opioid addicted compared to non-infected people. In [27] the estimated value of the q_v term equivalent was

94.5, and in [38], the estimated value of q_v was 30.62. Both estimates suggest a high dependence effect of opioid usage on HIV infection. In our simulations we take the lesser estimate of $q_v = 30.62$. The total co-affected population due to varying values of q_v is simulated, such as $0.5q_v, q_v, 1.5q_v, 2q_v, 2.5q_v, 3q_v$. The estimated value for q_u in [38] was below 1, but HIV-infected persons are more likely to have chronic pain, receive opioid analgesic treatment, receive higher doses of opioids, and to have substance use disorders and mental illness compared with the general population, putting them at increased risk for opioid use disorder [41]. So the simulations were done with the fitted value for q_u along with double, five times and ten times the fitted value. While the total number of co-affected varies according to the network, the trend seems to be similar, with q_v increasing, the total number of co-affected increases (Figure 2). A definite situation of interest is when $q_u = 4.3$, the maximum value seems to be achieved when q_v is close to 60, not at the highest value of approximately 90. The simulation was repeated with these values for different network sizes and provided the same result.

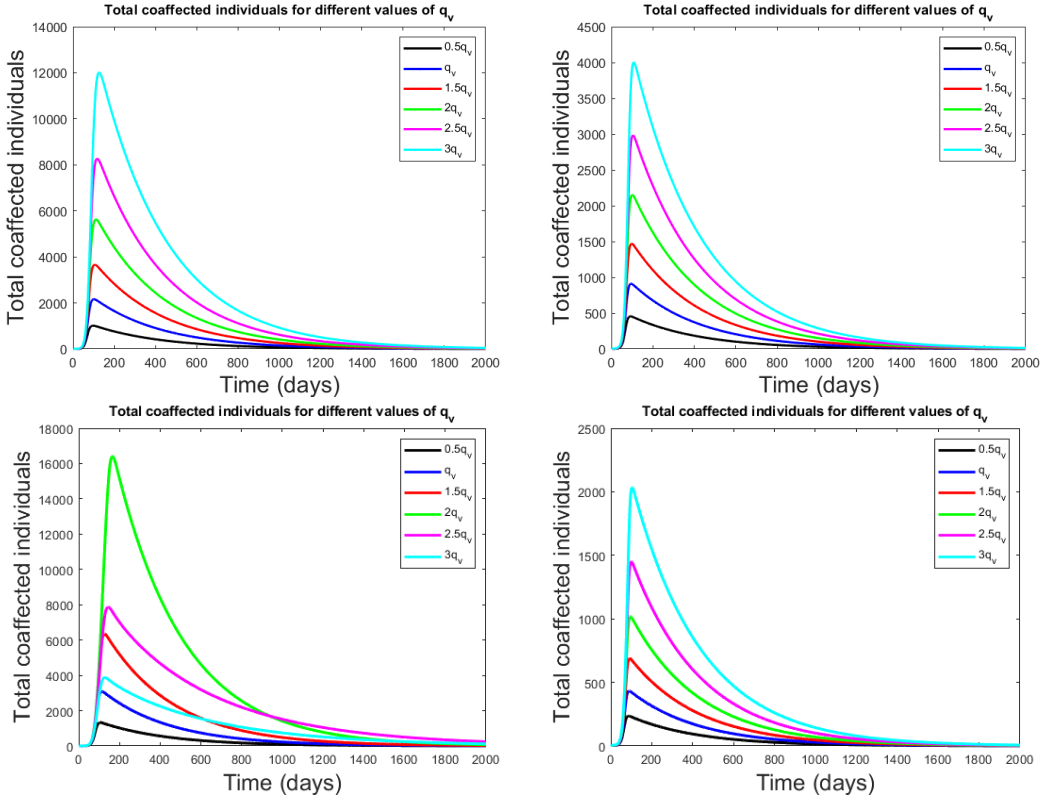

Figure 2. Figure shows total co-affected individuals for six different values of q_v. Top Left: $q_u = 0.86$, Top Right: $q_u = 1.72$, Bottom Left: $q_u = 4.3$, Bottom Right: $q_u = 8.6$. The other parameters used are given in Table 3.

A second set of simulations were performed, taking the base value of $q_u = 1.72$. The four individual cases have all other parameters and network values same, only q_v is varied, from $15, 31, 62$ and 93 respectively. While some of the cases do have permutations, over all the trend is similar, and opposite to the simulations in Figure 2. That is q_u increasing causes the total number of co-affected to decrease

(Figure 3). Again we notice a situation of interest, when $q_v = 60$, the maximum value seems to be achieved when q_u is close to 1.72, not at the lowest value of approximately 0.86. Repeated simulation with differing sized networks did not show changes in the results.

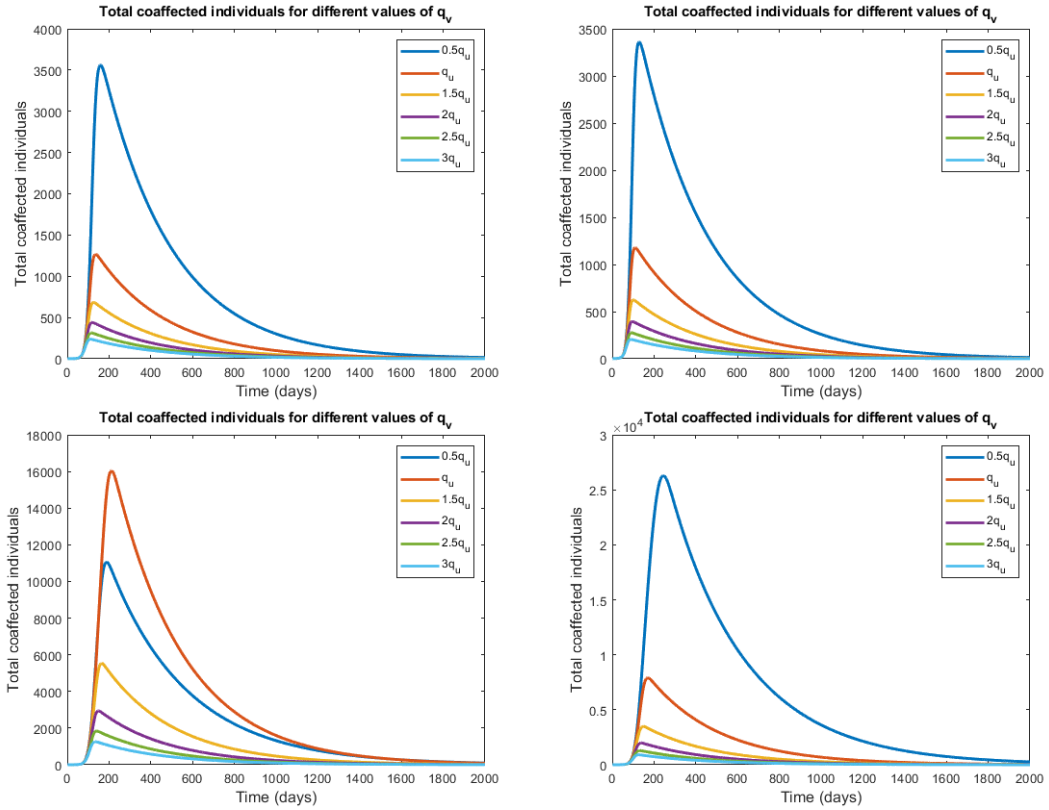

Figure 3. Figure shows total co-affected individuals for six different values of q_u, Top Left: $q_v = 15$, Top Right: $q_v = 30$, Bottom Left: $q_v = 60$, Bottom Right: $q_v = 90$. The other parameters used are given in Table 3.

Another parameter of interest is δ, which denotes the rate of recovery from addiction in the epidemiological model. The estimate for that in [27] is close to 0.033, while in [38] the estimate is approximately 0.11. If successful treatment is considered without subtracting the relapses, the rate would probably be close to 0.05 [42]. To simulate for differing values of δ, we consider β_u and β_{v1}^k as constants, directly taking the values from Table 3. All the other parameter values are as mentioned in Table 3. We consider four differing situations for δ, with the value being 0.02, the fitted value 0.11, and target high values of 0.5 and $\delta = 1$. We also investigated different scenarios with differing network sizes, with number of nodes being 100, 300 and 500 respectively. Interestingly, irrespective of network size, the total number of co-affected people appeared to be higher with the value of δ increasing (Figure 4). One quite plausible explanation would be the higher recovery would decrease the number of opioid overdose deaths significantly, thereby increasing the co-affected prevalence.

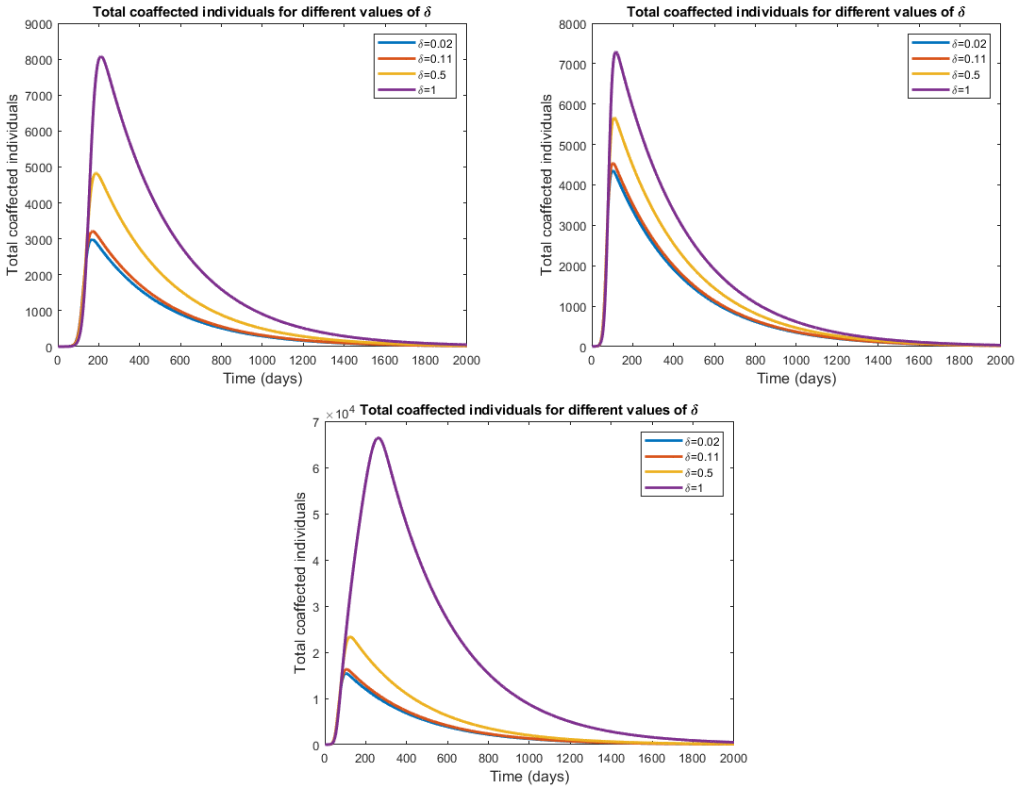

Figure 4. Figure shows total co-affected individuals for four different values of δ, Top Left: Network Size 100, Top Right: Network Size 300, Bottom: Network size 500. The other parameters used are given in Table 3.

6. Discussion

We formulate a within-host model linked with a dynamic network HIV/opioid coinfection epidemiological model with demography, through epidemiological parameters. The system is described by ordinary differential equations coupled with partial differential equations in a nested fashion. The network multi-scale model here is an extension of the multi-scale model considered in [38]. The disease free equilibrium of the system always exists and is locally asymptotically stable when both the basic reproduction numbers of opioid and HIV, $\mathcal{R}_u$ and $\mathcal{R}_v$ are less than 1.

The boundary equilibrium E_1^* exists when $\mathcal{R}_u$ is more than 1 and E_2^* exist when $\mathcal{R}_v$ is more than 1. We define the invasion reproduction numbers $\mathcal{R}^1_{v_i}$ and $\mathcal{R}^2_{u_i}$. The invasion reproduction number $\mathcal{R}^2_{u_i}$ gives the reproduction of the opioid users when the population is at the equilibrium E_2^*, that is, when HIV infection alone is at equilibrium in the single population. The invasion reproduction number $\mathcal{R}^1_{v_i}$ gives the reproduction of the HIV infection at the equilibrium E_1^*, that is when the opioid transmission alone is at equilibrium in the single population. When $\mathcal{R}^1_{v_i} < 1$, E_1^* is locally stable and when $\mathcal{R}^1_{v_i} > 1$, E_1^* is unstable. When $\mathcal{R}^2_{u_i} < 1$, E_2^* is locally stable and when $\mathcal{R}^2_{u_i} > 1$, E_2^* is unstable. The model is too complicated to compute or consider the stability of an endemic equilibrium, analytically, but simulations suggest that there is an interior equilibrium potentially under the condition that both invasion numbers are larger than one.

We use fitted parameters from [38], to perform simulations, to explore the effect of the change of the parameters q_u, q_v and δ. The parameters q_u and q_v represent the effect of one epidemic on the other, and we simulated for plausible values of q_u and q_v, to get estimates of co-affected prevalence. The estimate of q_v, the likelihood of a heroin user to be infected with HIV, in [27] was approximately 94, and since a large number of opioid users progress to becoming heroin users, (Data from 2011 showed that an estimated 4 to 6 percent who misuse prescription opioids switch to heroin and about 80 percent of people who used heroin first misused prescription opioids) [43], chances of the q_v estimate for all illicit opioid usage being close to the "heroin only" estimate is high. We notice that increase in q_v causes the co-affected population to rise significantly, which indicates that control strategies focusing on reducing HIV infection among the opioid addicted population would be effective in decoupling the epidemics, corroborating with the conclusions in [27].

To the best of our knowledge, there have not been previous models with a parameter similar to q_u, that provides an estimate for the effect of HIV infection on opioid use. The simulations from our model show that increase of q_u in general causes the number of co-affected to decline. That is the prevalence of co-affected people declines sharply with the increase to more HIV infected people being addicted to opioids. This does corroborate real life data, since deaths due to overdose in the US per year were aproximately 120,000 in the year 2020, and the number increased 15 percent by 2021 [44], compared to the number of deaths due to HIV being around 18,500 in 2020 [45]. We noticed significant increase in the prevalence of co-affected individuals, when the parameter δ, representing the recovery from opioid usage was increased significantly. The sharp increase points to the idea that control measures should focus more on treatment of opioid use disorder, and that uncoupling the two epidemics is a priority to prevent loss of human lives. Counseling about the dangers of opioid addiction for HIV infected people must be provided, and similarly counseling about the dangers of getting infected with HIV should be provided to reported opioid addicts.

In summary, we have developed a novel multi-scale network model of HIV and opioid epidemics. We have analized the model and obtained conditions for HIV-only to persist or opioid-only to persist. Simulations suggest that the two epidemics can co-exist for some parameter values. Simulations further suggest that decreasing q_v decreases the number of co-affected and may lead to decopuling the epidemics. Thus control measures targeted at reducing q_v should be coupled with treatment of opioid affected individuals which is consistent with our previois findings.

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Conflict of interest

The authors declare there is no conflict of interest.

Code availability

The code was written by one of the authors and is available on request by contacting Churni Gupta.

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