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Research article

Immuno-epidemiological co-affection model of HIV infection and opioid addiction

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Abstract: In this paper, we present a multi-scale co-affection model of HIV infection and opioid addiction. The population scale epidemiological model is linked to the within-host model which describes the HIV and opioid dynamics in a co-affected individual. CD4 cells and viral load data obtained from morphine addicted SIV-infected monkeys are used to validate the within-host model. AIDS diagnoses, HIV death and opioid mortality data are used to fit the between-host model. When the rates of viral clearance and morphine uptake are fixed, the within-host model is structurally identifiable. If in addition the morphine saturation and clearance rates are also fixed the model becomes practical identifiable. Analytical results of the multi-scale model suggest that in addition to the disease-addiction-free equilibrium, there is a unique HIV-only and opioid-only equilibrium. Each of the boundary equilibria is stable if the invasion number of the other epidemic is below one. Elasticity analysis suggests that the most sensitive number is the invasion number of opioid epidemic with respect to the parameter of enhancement of HIV infection of opioid-affected individual. We conclude that the most effective control strategy is to prevent opioid addicted individuals from getting HIV, and to treat the opioid addiction directly and independently from HIV.

Keywords: co-affection; multi-scale; HIV; opioid addiction; elasticity analysis; identifiable; invasion numbers; data fitting; immuno-epidemiological model

1. Introduction

The first cases of AIDS were reported in the United States in June 1981, and even after four decades, HIV/AIDS continues to be one of the biggest global epidemic of infectious disease the world faces. Since the beginning of the epidemic, 79.3 million (55.9–110 million) people have been infected with

the HIV virus and 36.3 million (27.2–47.8 million) people have died of HIV. Globally, 37.7 million (30.2–45.1 million) people were living with HIV at the end of 2020 [1]. Extensive research has been performed by researchers from different disciplines, e.g., Biology, Mathematics, Medicine, Public Health and Pharmaceutical Industries, trying to suppress the infection, while curbing or even eliminating the spread of HIV [2–6].

Opioids are a broad group of pain-relieving drugs that work by interacting with opioid receptors in human cells, resembling opium in addictive properties or physiological effects. This class of drugs include the illegal drug heroin, synthetic opioids such as fentanyl, and pain relievers available legally by prescription, such as oxycodone, hydrocodone, codeine, morphine, and many others. The opioid epidemic is one of the greatest public health problems in the USA. Opioid overdose death rates have increased steadily for more than a decade and doubled in the period 2013–2017, when the highly potent synthetic opioid fentanyl entered the drug supply [7]. Evidence supports that using prescription opioids can lead to opioid use disorder, and before 2010, the majority of deaths were linked to prescription opioids. Opioid use disorder is chronically relapsing, and requires chronic disease management [8].

In 1972, Hughes and Crawford introduced epidemiological field methodology to describe research and intervention in urban heroin spread. They concluded that "contagious" individuals tend to be in the early stages of heroin experimentation or addiction and to curb the spread, prevention and early intervention, along with more availability of treatment option would be effective [9]. In 1979, Mackintosh and Stewart introduced an exponential model to show that the spread of heroin usage follows an epidemic pattern and concluded that early intervention is key to stop the heroin epidemic from spreading [10]. Battista et al. investigated a mathematical model that considered opioid addiction originating from prescribed drug usage. The model considered illicit drug usage and treatment as well [11]. They reached the conclusion that to curb the prescription generated opioid epidemic, combatting addiction should be the primary control strategy.

The HIV and opioid epidemics are intimately linked, and not just because the demographic suffering most from both the epidemics are similar, people who are young, previously healthy and already stigmatized in some way [12]. People living with HIV often suffer from chronic pain. They are therefore prescribed opioids more often and at higher doses than people who do not have HIV, and disproportionately experience risk factors for substance use disorder, which suggests they could be at increased risk of the misuse of opioids. Opioid misuse among adults receiving ART (Anti-retroviral Therapy) is associated with inadequate ART adherence, insufficient durable viral suppression, and higher risk of HIV transmission to sexual partners [13]. Certain prescribed opioids for pain management also work as immunosuppressants, and increase infection risks, and HIV infected people are more susceptible to these effects [14]. It is also possible that HIV related neuropathogenesis in patients may be more severe, in case of significant opioid usage interfering with the ART treatment [15].

Opioids are associated with HIV risk behaviors such as needle sharing when infected and risky sexual behaviors, and have been linked to outbreaks of HIV and viral hepatitis. People who are addicted to opioids are also at risk of turning to other ways to get the drug, including trading sex for drugs or money, which increases HIV risk [16].

If the HIV infected and opioid dependent person is receiving treatment for both ailments simultaneously, research has shown that treatment for Opioid Use Disorder can help with HIV viral suppression, adherence to antiretroviral therapy, and overall mortality for patients [17].

In 2020, Duan et al. proposed a model of coinfection, featuring the joint spread of HIV and Heroin

usage, and concluded that in the United States, the two disease are in a state of coexistence. Further conclusion was the best control strategies would be to target the drug abuse epidemic, and to neutralize HIV risky behavior among drug users [18].

To model the spread of the disease in the population, it is to be noted that the pathogen is in dynamic interplay with each host body's immune system. The host's propensity to transmit the pathogen or die from it depends on the amount of the pathogen in the system as well as the intensity of the immune response. The spread of diseases on a population level therefore depends on these within-host disease characteristics of infectious individuals [19]. Following a method similar to Gilchrist and Sasaki's nested approach [20], in this paper we form an immuno-epidemiological model, where the within-host model is a simple pharmacokinetic model depicting both HIV and opioid usage. The between host model is an age structured expansion of the model utilized in [18]. The model developed addresses the question, "What control strategies will best combat the inter-connected spread of both the epidemics?"

The paper is organized as follows: In Section 2 the within-host model of HIV, and the subsequent modification to include opioid drug usage is introduced. Further, parameters for the models are estimated by fitting to data, and identifiability analysis is performed on both the models. In Section 3 the between-host model is introduced, along with the linking parameters to create the immuno-epidemiological model; Basic reproduction numbers for both the epidemics are defined, and stability analysis is performed for the disease free equilibrium. Both invasion numbers are defined and stability analysis is done on the boundary equilibriums. In Section 4 the parameters of the between-host model are estimated and sensitivity analysis is conducted on the invasion numbers, with respect to important parameters of the between-host model. Section 5 summarizes our results obtained, and Section 6 contains the Appendix.

2. Within-host models of HIV infection and opioid addiction

Before introducing a within-host model of HIV infection and opioid addiction, we first start with the well-known model of HIV [4, 21].

$$\textbf{Within-Host Model 1 } (\mathbf{M}_1)\textbf{:} \begin{cases} \dfrac{dT}{dt} = \lambda - \beta VT - dT, \\ \dfrac{dT_i}{dt} = \beta VT - \delta T_i, \\ \dfrac{dV}{dt} = \pi T_i - cV, \end{cases} \tag{M_1}$$

Here, $T(t)$ denotes the number target cells, specifically the number of CD4 cells per ml, $T_i(t)$ denotes the number of infected target cells and $V(t)$ denotes the virus (HIV), measured as vRNA copies per ml of plasma. Target cells are produced at rate λ and cleared at rate d. Virus infection of target cells is modeled by the mass action term βVT. Infected cells die at a rate δ and new viral particles are produced at a rate π. The clearance rate of the virus is denoted by c.

We modify the within-host model (M_1) by explicitly including the opioid drug concentration, $C(t)$,

(mg of opioid per kg of the host), and its impact on the average susceptibility of target cells:

$$\textbf{Within-Host Model 2 } (\mathrm{M}_2)\textbf{:} \begin{cases} \dfrac{dT}{dt} = \lambda - k(C)VT - dT, \\ \dfrac{dT_i}{dt} = k(C)VT - \delta T_i, \\ \dfrac{dV}{dt} = \pi T_i - cV, \\ \dfrac{dC}{dt} = \Lambda - d_c C, \end{cases} \tag{M_2}$$

Opioid is taken at doses Λ and it is degraded at rate d_c. Prior within-host models of HIV and opioids have been developed in [22], where the authors suggests that the morphine increases the susceptibility of target cells to HIV. Based on that result, we model the infection rate of target cells by HIV in the presence of opioid as

$$k(C) = \beta + \frac{\beta_1 C(t)}{C_0 + C(t)},$$

where C_0 is the half saturation constant, β is the transmission coefficient in the absence of opioid and β_1 is a maximal increase in infection rate due to opioids. The resulting within-host model is a pharmacokinetic type of model.

2.1. Parameter estimation

We use the viral load and CD4 measurements collected from 12 rhesus macaques in the experiment [23] to validate the within-host model of HIV and opioid addiction. The 12 animals were divided into two equal groups: six monkeys were morphine addicted and six monkeys served as controls. The simian-human immunodeficiency (SIV) virus was administered intravenously to all 12 animals, while 6 of them were given 5 mg/kg morphine three times a day to induce morphine addiction [23]. The averaged viral load and CD4 count of both the morphined and control groups are used to estimate within-host model parameters, which are as shown in Table 1.

Table 1. Average viral loads (vRNA copies/ml) and CD4 cell count (number of cells per ml) of morphine and control group. Average values are computed from the data given in [22].

	Week 0	Week 1	Week 2	Week 3	Week 4	Week 6	Week 8	Week 10	Week 12
Morphine Group									
Viral Load		7,031,667	11,433,333	815,150	281,833	320,650	2,856,850	2,367,767	8,457,567
Control Group									
Viral Load		8,510,000	11,300,000	917,000	382,000	273,000	157,000	155,000	95,100
Morphine Group									
CD4 Count	1,213,000	204,000	128,000	76,000	137,000	152,000	121,000	127,000	140,000
Control Group									
CD4 Count	1,304,000	619,500	371,167	151,667	235,833	241,167	270,000	379,167	246,167

In compact form the within-host models (M_1) and (M_2) can be rewritten as

$$\boldsymbol{x}'(t) = f(\boldsymbol{x}, \boldsymbol{p}), \quad \boldsymbol{x}(0) = \boldsymbol{x}_0, \quad \boldsymbol{y}(t) = h(\boldsymbol{x}, \boldsymbol{p}) \tag{2.1}$$

where $\boldsymbol{x}$ denote the state variables of the system. The system ($\boldsymbol{x}(t)$) evolves in time, depending on the parameters ($\boldsymbol{p}$) and the initial conditions ($\boldsymbol{x}_0$), while we observe the quantities ($\boldsymbol{y}$) which are functions of the state variables and model parameters. We assume that both observations, $\boldsymbol{y}(t) = (y_1(t), y_2(t))$, (viral load and CD4 count) are contaminated with measurements errors E_i and E_j respectively

$$Y_1^i = y_1(t_i) + E_i \quad i = 1, 2, \cdots, n \qquad \text{that is} \qquad Y_1^i = h_1(\boldsymbol{x}(t_i), \boldsymbol{p}) + E_i \quad i = 1, 2, \cdots, n \tag{2.2}$$

$$Y_2^j = y_2(t_j) + E_j \quad j = 1, 2, \cdots, m \qquad \text{that is} \qquad Y_2^j = h_2(\boldsymbol{x}(t_j), \boldsymbol{p}) + E_j \quad j = 1, 2, \cdots, m \tag{2.3}$$

Clearly,

$$h_1(\boldsymbol{x}(t_i), \boldsymbol{p}) = V(t_i, \boldsymbol{p}) \quad \text{and} \quad h_2(\boldsymbol{x}(t_j), \boldsymbol{p}) = T(t_j, \boldsymbol{p}).$$

The measurement errors cause the observations to deviate from their smooth path $V(t)$ and $T(t)$ and satisfy the following form

$$E_i = h_1(\boldsymbol{x}(t_i), \boldsymbol{p})\epsilon_i, \quad \text{and} \quad E_j = h_2(\boldsymbol{x}(t_j), \boldsymbol{p})\epsilon_j$$

where ϵ_i and ϵ_j are independent and identically distributed with mean zero and constant variance σ_0^2. Thus the observations, Y_1^i and Y_2^j have mean $h_1(\boldsymbol{x}(t_i), \boldsymbol{p})$, $h_2(\boldsymbol{x}(t_j), \boldsymbol{p})$ and variances $h_1(\boldsymbol{x}(t_i), \boldsymbol{p})^2\sigma_0^2$, $h_2(\boldsymbol{x}(t_j), \boldsymbol{p})^2\sigma_0^2$, respectively. We estimate the parameters of the within-host models (M_1) and (M_2) by fitting the logarithm of the predicted viral load and CD4 count to the log of the data in Table 1 via the following optimization problem.

$$\hat{\boldsymbol{p}} = \min_{\boldsymbol{p}} \left(\omega_1 \sum_{i=1}^{n} |\log_{10}(V(t_i, \boldsymbol{p})) - \log_{10}(Y_1^i)|^2 + \omega_2 \sum_{j=1}^{m} |\log_{10}(T(t_j, \boldsymbol{p})) - \log_{10}(Y_2^j)|^2 \right) \tag{2.4}$$

w.r.t the constraint $\quad \boldsymbol{p} > 0$

where ω_1 and ω_2 are appropriate weights. The optimization problem is just a least squares on the logarithms of data points. The weights are picked so that the range of the expressions in two summation terms are about the same magnitude.

The structural identifiability analysis of model (M_2) revealed that the within-host model is unidentifiable due to parameter correlations given in (2.11) and (2.12) (explained in detail in the following section). To improve the parameter identifiability, we fix parameters, c, Λ and d_c. It is worth mentioning at this point that, this would only improve the identifiability, but it would not result in structurally identifiable model because of the correlations between β, β_1 and C_0 in models (2.11) and (2.12). We fix the viral clearance rate as $c = 23$ day^{-1} [22], and $\Lambda = 15 \ \frac{\text{mg}}{\text{kg day}}$. The half life of morphine is 3 hours, thus we fixed $d_c = 5.5$ day^{-1}. Estimating the within-host model M_2 parameters, when c, Λ and d_c are fixed, reveals that $\beta = 0$ (see Table 2). So we update the HIV infection rate of target cells in an addicted host to

$$k(C) = \frac{\beta_1 C(t)}{C_0 + C(t)}.$$

We then refit the within-host model (M_2) by setting $\beta = 0$, and the estimated values are presented in Table 2. The fit of within-host models (M_1) and (M_2) are given in Figure 1.

Table 2. Parameter estimation results of within-host models (M_1) and (M_2). Estimated values obtained by approximating the solutions of the optimization problem (2.4). In fitting model (M_2), the viral and morphine clearance rates together with morphine uptake are fixed at $c = 23$ day^{-1}, $\Lambda = 15 \frac{\text{mg}}{\text{kg day}}$ and $d_c = 5.5$ day^{-1}.

Parameter	λ	β	d	δ	π	c	β_1	C_0
Units	$\frac{\text{CD4 count}}{\text{ml} \times \text{day}}$	$\frac{\text{ml}}{\text{vRNA} \times \text{day}}$	$\frac{1}{\text{day}}$	$\frac{1}{\text{day}}$	$\frac{\text{vRNA}}{\text{CD4 count} \times \text{day}}$	$\frac{1}{\text{day}}$	$\frac{\text{vRNA}}{\text{CD4 count} \times \text{day}}$	$\frac{\text{mg}}{\text{kg}}$
Model (M_1) Estimated Value	45,885	1.08×10^{-8}	0.16	0.891	2841.5	10.1		
Model (M_2) Estimated Value	24,530	1.3×10^{-16}	0.11	0.61	4931	-	3.9×10^{-5}	6,757
Model (M_2) with $\beta = 0$ Estimated Value	24,603	-	0.11	0.60	4834	-	4.0×10^{-5}	6,530

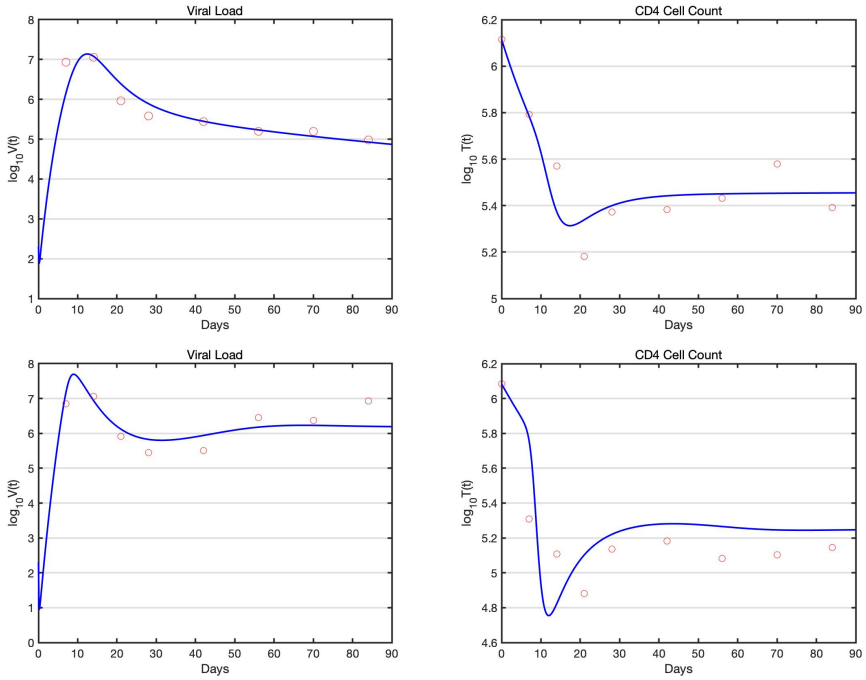

Figure 1. Fitting Results: Top Row : Within-host model (M_1) predictions (blue curve) to the (a) $\log_{10}$ viral load and (b) $\log_{10}$CD4 count data (red circles). Bottom Row : Within-host model (M_2) predictions (blue curve) to the (a) $\log_{10}$ viral load and (b) $\log_{10}$CD4 count data (red circles). The estimated values presented in Table 2. Initial conditions for model (M_1) are $T(0) = 1,304,000$, $V(0) = 200$ and initial conditions for model (M_2) are $T(0) = 1,213,000$, $V(0) = 200$, $C(0) = 0.04$.

2.2. Structural identifiability

In order to validate the within-host models with data, it is crucial to perform identifiability analysis. The first step in identifiability analysis is the structural identifiability. Structural identifiability is the property of the within-host model and the analysis assumes ideal, noise free data. To be specific it assumes that the smooth observations for the whole time interval are given. We use differential algebra approach in studying the structural identifiability analysis of the within-host models (M_1) and (M_2). For a review of other structural identifiability methods, we refer the reader to [24]. The first step in differential algebra approach is to obtain the input-output equations. We eliminate the unobserved state variable which is the infected target cell population, T_i from model (M_1) to obtain the following equivalent model (2.5). Within the identifiability analysis literature, we call the resulting equivalent system as input-output equations.

input-output equations for the within-host model (M_1):

$$\begin{aligned} V'' + (c+\delta)V' - \pi\beta VT + c\delta V &= 0 \\ T' + \beta VT + dT - \lambda &= 0 \end{aligned} \tag{2.5}$$

Solving input-output equations is equivalent to solving the model (M_1) for the viral load and target cell population. In the equivalent system, the viral load and target cell states depend on the parameters $\boldsymbol{p} = \{\lambda, \beta, d, \delta, \pi, c\}$. Structural identifiability of a within-host model using differential algebra approach has the following definition [24–27].

Definition 2.1. *Let $c(\boldsymbol{p})$ denote the coefficients of the input-output equations where $\boldsymbol{p}$ is the vector of model parameters. We say that the within-host model is structured to reveal its parameters from the observations if and only if*

$$c(\boldsymbol{p}) = c(\boldsymbol{q}) \quad \Longrightarrow \quad \boldsymbol{p} = \boldsymbol{q}.$$

Following the definition of the structural identifiability, suppose that another set of parameters $\boldsymbol{q} = \{\hat{\lambda}, \hat{\beta}, \hat{d}, \hat{\delta}, \hat{\pi}, \hat{c}\}$ would produce the same viral load and target cell populations. Thus first we would have

$$\begin{aligned} V'' + (\hat{c}+\hat{\delta})V' - \hat{\pi}\hat{\beta}VT + \hat{c}\hat{\delta}V &= 0, \\ T' + \hat{\beta}VT + \hat{d}T - \hat{\lambda} &= 0. \end{aligned} \tag{2.6}$$

Let $c(\boldsymbol{p})$ and $c(\boldsymbol{q})$ denote the coefficients of the differential polynomials in models (2.5) and (2.6) respectively. Since both models (2.5) and (2.6) are assumed to produce the same observations, solving the system of nonlinear equations $c(\boldsymbol{p}) = c(\boldsymbol{q})$,

$$c + \delta = \hat{c} + \hat{\delta}, \quad \pi\beta = \hat{\pi}\hat{\beta}, \quad c\delta = \hat{c}\hat{\delta}, \quad \beta = \hat{\beta}, \quad d = \hat{d}, \quad \lambda = \hat{\lambda} \tag{2.7}$$

we obtain two sets of solutions,

$$\{\lambda = \hat{\lambda}, \quad \beta = \hat{\beta}, \quad d = \hat{d}, \quad \pi = \hat{\pi}, \quad \delta = \hat{\delta}, \quad c = \hat{c}\}$$

and

$$\{\lambda = \hat{\lambda}, \quad \beta = \hat{\beta}, \quad d = \hat{d}, \quad \pi = \hat{\pi}, \quad \delta = \hat{c}, \quad c = \hat{\delta}\}.$$

So, we conclude that the model (M_1) is not structured to reveal all its parameters from the viral load and CD4 count data. Only the parameters λ, β, π and d can be uniquely identified. The within-host

model (M_1) is a locally identifiable model, since solving $c(\boldsymbol{p}) = c(\boldsymbol{q})$, resulted in two sets of solutions. As it is clear from the two sets of solutions, by fixing viral clearance rate to $c = \hat{c}$, we would obtain a structurally identifiable model. Thus we have showed the following Proposition 2.1.

Proposition 2.1. *The within-host model (M_1) is not structured to reveal its parameters from the viral load and target cell observations. Only the parameters λ, β, π and d can be uniquely identified. If the viral clearance rate is fixed, $c = \hat{c}$, then the model (M_1) reveals all its parameters uniquely.*

We continue with identifiability analysis of model (M_2). This time eliminating the unobserved state variables which are the infected target cell population and the concentration of opioid from the model is not a trivial task. We use DAISY to obtain the following equivalent system to model (M_2);

input-output equations for the within-host model (M_2):

$$\begin{aligned} V'' + (c+\delta)V' + \pi T' + c\delta V + \pi d T - \pi\lambda = 0 \\ \beta_1 C_0 V' T' T + \beta_1 C_0 d V' T^2 - \beta_1 C_0 \lambda V' T - T'' V T \beta_1 C_0 + T'^2 V \beta_1 C_0 - \\ T'^2(C_0 d_c + \Lambda) + T' V T(-2\beta C_0 d_c - 2\beta\Lambda - \beta_1 C_0 d_c - 2\beta_1\Lambda) - T' V \beta_1 C_0 \lambda - 2T' T d(C_0 d_c + \Lambda) + \\ 2T'\lambda(C_0 d_c + \Lambda) + V^2 T^2(-\beta^2 C_0 d_c - \beta^2\Lambda - \beta\beta_1 C_0 d_c - 2\beta\beta_1\Lambda - \beta_1^2\Lambda) + \\ V T^2 d(-2\beta C_0 d_c - 2\beta\Lambda - \beta_1 C_0 d_c - 2\beta_1\Lambda) + V T \lambda(2\beta C_0 d_c + 2\beta\Lambda + \beta_1 C_0 d_c + 2\beta_1\Lambda) - \\ T^2 d^2(C_0 d_c + \Lambda) + 2T d\lambda(C_0 d_c + \Lambda) - \lambda^2(C_0 d_c + \Lambda) = 0 \end{aligned} \tag{2.8}$$

Setting $c(\boldsymbol{p}) = c(\boldsymbol{q})$, we get

$$c + \delta = \hat{c} + \hat{\delta}, \quad \pi = \hat{\pi}, \quad c\delta = \hat{c}\hat{\delta}, \quad \pi d = \hat{\pi}\hat{d}, \quad \pi\lambda = \hat{\pi}\hat{\lambda}, \quad \frac{C_0 d_c + \Lambda}{\beta_1 C_0} = \frac{\hat{C}_0 \hat{d}_c + \hat{\Lambda}}{\hat{\beta}_1 \hat{C}_0}, \tag{2.9}$$

together with

$$\begin{aligned} \frac{2\beta C_0 d_c + 2\beta\Lambda + \beta_1 C_0 d_c + 2\beta_1\Lambda}{\beta_1 C_0} &= \frac{2\hat{\beta}\hat{C}_0\hat{d}_c + 2\hat{\beta}\hat{\Lambda} - \hat{\beta}_1\hat{C}_0\hat{d}_c + 2\hat{\beta}_1\hat{\Lambda}}{\hat{\beta}_1\hat{C}_0}, \\ \frac{\beta^2 C_0 d_c + \beta^2\Lambda + \beta\beta_1 C_0 d_c + 2\beta\beta_1\Lambda + \beta_1^2\Lambda}{\beta_1 C_0} &= \frac{\hat{\beta}^2\hat{C}_0\hat{d}_c + \hat{\beta}^2\hat{\Lambda} + \hat{\beta}\hat{\beta}_1\hat{C}_0\hat{d}_c + 2\hat{\beta}\hat{\beta}_1\hat{\Lambda} + \hat{\beta}_1^2\hat{\Lambda}}{\hat{\beta}_1\hat{C}_0} \end{aligned} \tag{2.10}$$

Solving the nonlinear systems (2.9) and (2.10), we obtain the following two sets of nonzero positive solutions,

$$\left\{\begin{aligned} &\lambda = \hat{\lambda}, \quad d = \hat{d}, \quad \pi = \hat{\pi}, \quad \delta = \hat{\delta}, \quad c = \hat{c}, \quad \beta + \beta_1 = \hat{\beta} + \hat{\beta}_1, \\ &\frac{d_c\beta_1}{\beta} = \frac{\hat{d}_c\hat{\beta}_1}{\hat{\beta}}, \quad \frac{\Lambda\beta_1}{\beta C_0} + \frac{(\hat{\Lambda} + \hat{C}_0\hat{d}_c)\beta}{\hat{C}_0\hat{\beta}} = \frac{\hat{\Lambda}\hat{\beta}_1}{\hat{\beta}\hat{C}_0} + \frac{(\hat{\Lambda} + \hat{C}_0\hat{d}_c)}{\hat{C}_0} \end{aligned}\right\} \tag{2.11}$$

and

$$\left\{\begin{aligned} &\lambda = \hat{\lambda}, \quad d = \hat{d}, \quad \pi = \hat{\pi}, \quad \delta = \hat{c}, \quad c = \hat{\delta}, \quad \beta + \beta_1 = \hat{\beta} + \hat{\beta}_1, \\ &\frac{d_c\beta_1}{\beta} = \frac{\hat{d}_c\hat{\beta}_1}{\hat{\beta}}, \quad \frac{\Lambda\beta_1}{\beta C_0} + \frac{(\hat{\Lambda} + \hat{C}_0\hat{d}_c)\beta}{\hat{C}_0\hat{\beta}} = \frac{\hat{\Lambda}\hat{\beta}_1}{\hat{\beta}\hat{C}_0} + \frac{(\hat{\Lambda} + \hat{C}_0\hat{d}_c)}{\hat{C}_0} \end{aligned}\right\} \tag{2.12}$$

This concludes that the model (M_2) is not structurally identifiable. It only reveals the parameters, λ, d and π from the viral load and CD4 cell count data.

Proposition 2.2. *The within-host model (M_2) is not structurally identifiable from the viral load and CD4 cell count observations.*

Since validating model (M_2) with data revealed that $\beta = 0$, we continue our analysis by modifying model (M_2), by setting $\beta = 0$. We obtain the following input-output equations in this case.
input-output equations for the within-host model (M_2) with $\beta = 0$:

$$V'' + V'(c+\delta) + T'\pi + Vc\delta + Td\pi - \lambda\pi = 0$$

$$V'T'T + V'T^2d - V'T\lambda - T''VT + T'^2V - T'^2\frac{(C_0dc+\Lambda)}{\beta_1C_0} +$$

$$T'VT\frac{(-C_0dc-2\Lambda)}{C_0} - T'V\lambda - 2T'T\frac{d(C_0dc+\Lambda)}{\beta_1C_0} + 2T'\frac{\lambda(C_0dc+\Lambda)}{\beta_1C_0} - V^2T^2\frac{\beta_1\Lambda}{C_0} +$$

$$VT^2\frac{d(-C_0dc-2\Lambda)}{C_0} + VT\frac{\lambda(C_0dc+2\Lambda)}{C_0} - T^2\frac{d^2(C_0dc+\Lambda)}{\beta_1C_0} + 2T\frac{d\lambda(C_0dc+\Lambda)}{\beta_1C_0} - \frac{\lambda^2(C_0dc+\Lambda)}{\beta_1C_0} = 0 \tag{2.13}$$

Note that $c(\boldsymbol{p}) = c(\boldsymbol{q})$ is the same as systems (2.9) and (2.10) with $\beta = 0$. Solving $c(\boldsymbol{p}) = c(\boldsymbol{q})$ we obtain,

$$\left\{\lambda = \hat{\lambda}, \quad d = \hat{d}, \quad \pi = \hat{\pi}, \quad \delta = \hat{\delta}, \quad c = \hat{c}, \quad \beta_1 = \hat{\beta}_1, \quad d_c = \hat{d}_c, \quad \frac{C_0}{\Lambda} = \frac{\hat{C}_0}{\hat{\Lambda}}\right\}$$

and

$$\left\{\lambda = \hat{\lambda}, \quad d = \hat{d}, \quad \pi = \hat{\pi}, \quad \delta = \hat{c}, \quad c = \hat{\delta}, \quad \beta_1 = \hat{\beta}_1, \quad d_c = \hat{d}_c, \quad \frac{C_0}{\Lambda} = \frac{\hat{C}_0}{\hat{\Lambda}}\right\}$$

So, the within-host model (M_2) with $\beta = 0$ is also not structurally identifiable from viral load and CD4 cell counts. It is not possible to identify parameters C_0 and Λ individually. It is only possible to identify their ratio $\frac{C_0}{\Lambda}$. If Λ is fixed, then C_0 would be identified. But even then, the within-host model (M_2) with $\beta = 0$ becomes locally identifiable since there exist two sets of solutions to $c(\boldsymbol{p}) = c(\boldsymbol{q})$. We summarize the structural identifiability in the following proposition.

Proposition 2.3. *The within-host model (M_2) with $\beta = 0$ is not structurally identifiable from the viral load and CD4 cell count observations.*

If the viral clearance and morphine recruitment rates are fixed, that is $c = \hat{c}$ and $\Lambda = \hat{\Lambda}$, then the model (M_2) with $\beta = 0$ becomes structurally identifiable.

2.3. Practical identifiability

Structural identifiability is a property of the within-host model and the analysis is performed without the actual data. A within-host model which is structurally identifiable may not be practically identifiable when the actual data is used in the parameter estimation problem. We continue our identifiability analysis with practical identifiability of within-host models (M_1) and (M_2) using Monte Carlo simulations (MCS). Using the estimated parameters $\hat{\boldsymbol{p}}$ as presented in Table 2; we generate synthetic data sets $\boldsymbol{Y} = (Y_1^i, Y_2^j)$ which are contaminated with error. In particular, we generate $M = 1000$ data sets of viral load and CD4 cell counts using normal distribution whose mean is the model predictions and standard deviations are $y_1(t_i)\sigma_0$ and $y_2(t_j)\sigma_0$ respectively. That is;

$$Y_1^i = \mathcal{N}\left(y_1(t_i, \hat{\boldsymbol{p}}), y_1(t_i, \hat{\boldsymbol{p}})\sigma_0\right) \quad \text{and} \quad Y_2^j = \mathcal{N}\left(y_2(t_j, \hat{\boldsymbol{p}}), y_2(t_j, \hat{\boldsymbol{p}})\sigma_0\right) \tag{2.14}$$

where $\mathcal{N}(\mu, \sigma)$ denotes the normal distribution with mean μ and standard deviation σ. The synthetic viral load and CD4 cell count data sets are generated for each measurement errors, by increasing the errors gradually from $\sigma_0 = 1\%$, to $\sigma_0 = 5\%, 10\%$ to $\sigma_0 = 30\%$. We then fit the within-host models (M_1) and (M_2) to each $M = 1000$ data sets by solving the optimization problem (2.4) and then calculate the Average Relative Errors (AREs) of each parameter for each noise level. The AREs are computed as

$$ARE(p^k) = 100\% \frac{1}{M} \sum_{j=1}^{M} \frac{|\hat{p}^k - p_j^k|}{\hat{p}^k} \tag{2.15}$$

where p^k is the k^{th} parameter in $\boldsymbol{p}$ and $\hat{\boldsymbol{p}}$ are the parameters that generate the random variables Y_1^i and Y_2^j. Since a population of parameter estimates results for each measurement error is obtained, we also compute the 95% confidence intervals. AREs of the parameters together with the confidence intervals for each measurement error are presented in Tables 3–6. Examining the AREs and the confidence intervals of the MCS for the within-host model (M_1) as presented in Table 3, we see that the AREs of parameters π and c are higher compared to measurement error levels (σ_0). Note that the within-host model (M_1) is only locally identifiable (see Proposition 2.1) and this is observed in AREs in Table 3. Next, we fix the viral clearance rate and run the MCS again for the within-host model (M_1), and as a result AREs of all parameters have decreased significantly (see Table 4). We conclude that the within-host model (M_1) is practically identifiable when the clearance rate is fixed. MCS results for the within-host model (M_2) with $\beta = 0$ and when Λ, d_c and c are fixed are presented in Table 5. As seen from AREs in Table 5 the parameters β_1 and C_0 have higher AREs especially when the measurement error is 30%, even though the model is structurally identifiable in that case (see Proposition 2.3). If in addition to Λ, d_c, c the half-saturation constant C_0 is fixed, then the within-host model (M_2) becomes practically identifiable as evident from Table 6.

3. A multi-scale model of opioid and HIV epidemics

Research shows that HIV infected individuals who use drugs of abuse maintain a higher HIV viral load and treatment is not as effective for them [22, 28]. The goal of this study is to understand the interplay between the two epidemics; HIV and opioid addiction. We use the term "co-affected" to characterize the individuals who are living with HIV and are also opioid drug users. Our previous research suggests that the role of the co-affected class is very important in the symbiotic relationship between the two epidemics [18]. To study the interplay of these two epidemics, we develop a multi-scale epidemic model where the total population is divided into five non-intersecting classes; susceptible individuals $S(t)$, opioid addicted individuals $U(t)$, HIV infected individuals $V(t)$, co-affected individuals $I(t)$, and individuals with AIDS $A(t)$. To understand the impact of within-host level opioid addiction on the population level HIV dynamics, we structure the co-affected class with time-since-co-affection parameter τ. The density of opioid addicted individuals who are also infected with HIV is then denoted by $i(t, \tau)$.

The number of co-affected individuals is determined by

$$I(t) = \int_0^\infty i(t,\tau)d\tau.$$

The multi-scale HIV-opioid epidemic model takes the following form;

$$\begin{cases} \dfrac{dS(t)}{dt} = \Lambda_S - \lambda_u(t)S(t) - \lambda_v(t)S(t) - \mu S(t) + \delta_u U(t), \\ \dfrac{dU(t)}{dt} = \lambda_u(t)S(t) - q_v\lambda_v(t)U(t) - (\mu + d_u + \delta_u)U(t), \\ \dfrac{dV(t)}{dt} = \lambda_v(t)S(t) - q_u\lambda_u(t)V(t) - (\mu + d_v + \gamma_v)V(t) + \delta_u \displaystyle\int_0^\infty \sigma(\tau)i(t,\tau)d\tau, \\ \dfrac{\partial i(t,\tau)}{dt} + \dfrac{\partial k_s i(t,\tau)}{d\tau} = -(\mu + d_i(\tau) + \gamma_i(\tau) + \delta_u\sigma(\tau))i(t,\tau), \\ k_s i(t,0) = q_v\lambda_v(t)U(t) + q_u\lambda_u(t)V(t) \\ \dfrac{dA(t)}{dt} = \gamma_v V(t) + \displaystyle\int_0^\infty \gamma_i(\tau)i(t,\tau)d\tau - (\mu + d_a)A(t), \end{cases} \tag{3.1}$$

where k_s is a scaling factor such that $\tau = k_s t$. Note that τ for the within-host scale is measured in days, while the between-host scale time t is measured in years. The scaling factor k_s allows us to convert between the two time units. Thus, k_s allows us to properly "zoom" on each scale and to consider both scales simultaneously in dynamic regime. The parameter Λ_S denotes the recruitment/birth rate and μ denotes the natural death rate of the population. A susceptible individual can get into contact with a HIV infected or opioid addicted individual and move to the corresponding class upon effective transmission of infection or addiction. The force of HIV-infection takes into account the different infectivity of co-affected individuals;

$$\lambda_v(t) = \frac{\beta_{v_1}V(t) + \displaystyle\int_0^\infty \beta_{v_2}(\tau)i(t,\tau)d\tau}{N(t)}. \tag{3.2}$$

Here β_{v_1} denotes the HIV infection rate of individuals living with HIV and $\beta_{v_2}(\tau)$ denotes the HIV infection rate of co-affected individuals which is assumed to vary with infection age τ. We use the data in [29] to determine the form of the linking for the transmission coefficient $\beta_{v_2}(\tau)$ to the viral load [19]. Fitting to data, we obtain the following form for $\beta_{v_2}(\tau)$;

$$\beta_{v_2}(\tau) = \frac{\beta_0 V(\tau)}{B + V(\tau)},$$

where $V(\tau)$ is the viral load in an HIV-infected host who is also opioid user. That is we obtain the transmission coefficient of the co-affected individual using the within-host model (M_2).

We suppose that individuals with AIDS are isolated and consider the following form for the total number of active population;

$$N(t) = S(t) + U(t) + V(t) + I(t).$$

The force of opioid addiction, $\lambda_u(t)$, has a similar formulation. Thus

$$\lambda_u(t) = \beta_u \frac{U(t) + \int_0^\infty i(t,\tau)d\tau}{N(t)}, \tag{3.3}$$

where β_u denotes the rate at which an effective contact with an opioid user will result in addiction. In system (3.1), the term $q_v\lambda_v$ denotes the force of infection of an opioid user to HIV infection. Similarly, the term $q_u\lambda_u$ denotes the force of addiction of an HIV-infected individual to opioid dependence.

Table 3. Monte Carlo Simulation results of Model (M_1). The AREs and 95% confidence intervals of parameters of within-host model (M_1) is presented for each measurement error σ_0.

	λ		d		β	
	ARE	95% CI	ARE	95% CI	ARE	95% CI
0%	10^{-14}	[45,885, 45,885]	0	[0.160, 0.160]	0	$[1.08\times10^{-8},\ 1.08\times10^{-8}]$
1%	0.8	[45,035, 46,841]	0.9	[0.157, 0.164]	1.0	$[1.05\times10^{-8},\ 1.11\times10^{-8}]$
5%	3.7	[42,148, 50,455]	4.0	[0.147, 0.178]	3.7	$[9.74\times10^{-9},\ 1.17\times10^{-8}]$
10%	7.2	[38,605, 54,658]	7.7	[0.135, 0.196]	6.7	$[9.13\times10^{-9},\ 1.27\times10^{-8}]$
20%	15.3	[31,862, 68,340]	16.1	[0.114, 0.249]	14.2	$[7.60\times10^{-9},\ 1.55\times10^{-8}]$
30%	26.7	[24,535, 90,430]	27.9	[0.09, 0.362]	50.5	$[6.05\times10^{-9},\ 2.07\times10^{-8}]$
	δ		π		l	
	ARE	95% CI	ARE	95% CI	ARE	95% CI
0%	0	[0.891, 0.891]	1.6×10^{-14}	[2841.5 2841.5]	1.8×10^{-14}	[10.1, 10.1]
1%	2.8	[0.842, 0.964]	18.2	[2068.5 5027.8]	22.1	[6.58, 19.24]
5%	9.1	[0.799, 1.174]	47.9	[1508.3 9460.4]	57.8	[3.91, 35.98]
10%	13.0	[0.748, 1.303]	63.1	[1297.1 13398]	74.4	[3.22, 49.67]
20%	22.1	[0.635, 1.625]	78.1	[1025.5 15496]	89.8	[2.63, 52.13]
30%	37.7	[0.538, 2.478]	114. 7	[590.1 20122]	114.2	[1.97, 65.88]

The parameters d_u, d_v and d_a denote additional death rates induced by addiction, HIV infection and AIDS respectively. Death rate of co-affected individuals is composed of two sources of additional death rates; HIV-infection which varies with infection age and opioid addiction. Namely,

$$d_i(\tau) = d_0\,(T(0) - T(\tau)) + d_1,$$

where $d_0\,(T(0) - T(\tau))$ represents death rate due to HIV and d_1 represents death rate due to addiction. The disease induced death rate does not depend explicitly on the viral load because the viral load is high during the acute HIV phase but the death rate is low during the same stage. The same relationship is also suggested in [30]. We assume that the opioid users recover at rate δ_u and move to the susceptible class. Similarly, co-affected individuals recover from addiction and move to the HIV infected class, with a rate $\delta_u\sigma(\tau)$ depending on their HIV infection age τ. γ_v denotes the transition into AIDS. As before, the transition into AIDS of co-affected individuals $\gamma_i(\tau)$ varies with infection age. We use the following function as suggested in [30]

$$\gamma_i(\tau) = \gamma_0\,(T(0) - T(\tau))\,.$$

Similarly, transition into AIDS does not depend explicitly on the viral load, because an HIV infected individual develop AIDS at average 8 to 10 years after the infection [31], and the viral load usually is not high during that transition time. The flowchart of the model is given in Figure 2. We previously proved the existence, uniqueness, positivity and boundedness of multi-scale models such as studied in this paper in [32–34]. Similar analysis can be adapted to this model (3.1) to establish the same results.

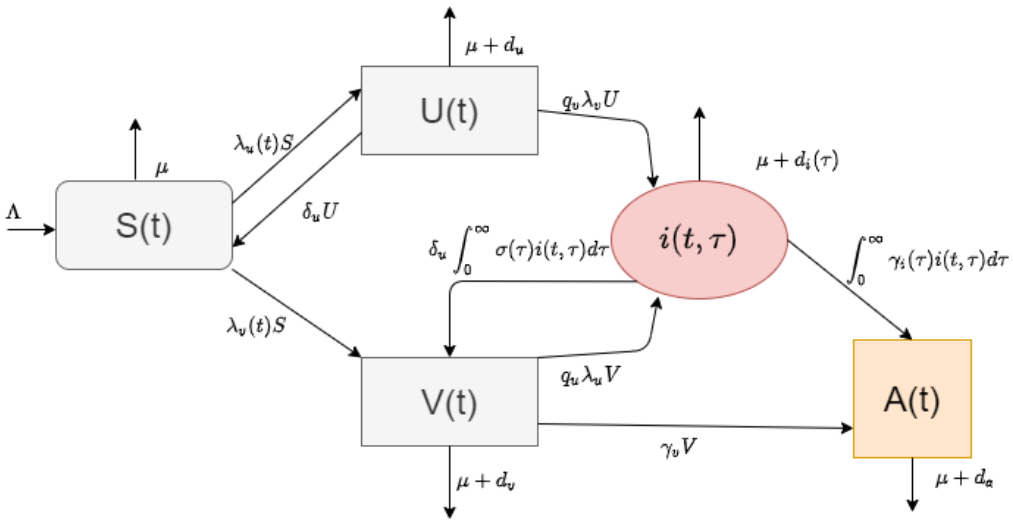

Figure 2. Flow chart of the multi-scale model of HIV and opioid epidemics: Susceptible individuals $S(t)$ are infected with HIV or acquire opioid addiction and move to the HIV infected compartment $V(t)$ or opioid addiction compartment $U(t)$. Opioid addicted individuals can be infected with HIV and move to the co-affected compartment $i(t,\tau)$. Similarly, individuals who are originally infected with HIV acquire opioid addiction and move to the co-affected compartment. Upon recovery from addiction, HIV infected individuals move to the susceptible compartment at rate δ_u, and co-affected individual move to the HIV infected only compartment with a rate $\delta_u\sigma(\tau)$ depending on HIV infection age τ. Co-affected individuals move to the AIDS compartment with a rate $\gamma_i(\tau)$, HIV infected individuals move to AIDS compartment with a constant rate γ_v.

3.1. Basic reproduction numbers and stability of disease-addiction free equilibrium

Table 4. Monte Carlo Simulation results of Model (M_1) when the viral clearance rate is fixed at $c = 10.1$. The AREs and 95% confidence intervals of parameters of within-host model M_1 is presented for each measurement error σ_0.

	λ		d		β	
	ARE	95% CI	ARE	95% CI	ARE	95% CI
0%	0	[45,885, 45,885]	0	[0.160, 0.160]	0	$[1.08 \times 10^{-8},\ 1.08 \times 10^{-8}]$
1%	0.7	[45,139, 46,639]	0.7	[0.157, 0.163]	0.6	$[1.07 \times 10^{-8},\ 1.10 \times 10^{-8}]$
5%	3.4	[42,248, 49,869]	3.6	[0.147, 0.176]	3.0	$[1.01 \times 10^{-9},\ 1.17 \times 10^{-8}]$
10%	7.0	[38,728, 54,348]	7.2	[0.135, 0.195]	6.2	$[9.48 \times 10^{-9},\ 1.28 \times 10^{-8}]$
20%	15.1	[31,976, 67,788]	15.8	[0.114, 0.250]	14.1	$[7.80 \times 10^{-9},\ 1.55 \times 10^{-8}]$
30%	26.3	[24,721, 97,073]	28.3	[0.09, 0.389]	25.8	$[5.97 \times 10^{-9},\ 2.05 \times 10^{-8}]$
	δ		π			
	ARE	95% CI	ARE	95% CI		
0%	0	[0.891, 0.891]	0	[2841.5 2841.5]		
1%	0.5	[0.879, 0.902]	0.8	[2781.5 2897.6]		
5%	2.7	[0.831, 0.948]	4.1	[2552.4 3133.8]		
10%	5.4	[0.771, 1.006]	8.5	[2270.2 3494.0		
20%	11.8	[0.648, 1.177]	20.3	[1718.8 4780.1]		
30%	21.6	[0.525, 1.646]	40.6	[1173.7 8817.3]		

We analyze the system (3.1) by first determining the equilibrium points. We set the differentials with respect to t equal to zero and obtain the following system. Since the individuals with AIDS are isolated, we study the following equivalent system.

$$\begin{cases} \Lambda_S - \lambda_u(t)S(t) - \lambda_v(t)S(t) - \mu S(t) + \delta_u U(t) = 0, \\ \lambda_u(t)S(t) - q_v\lambda_v(t)U(t) - (\mu + d_u + \delta_u)U(t) = 0, \\ \lambda_v(t)S(t) - q_u\lambda_u(t)V(t) - (\mu + d_v + \gamma_v)V(t) + \delta_u \int_0^\infty \sigma(\tau)i(t,\tau)d\tau = 0, \\ \dfrac{\partial k_s i(t,\tau)}{d\tau} = -(\mu + d_i(\tau) + \gamma_i(\tau) + \delta_u\sigma(\tau))i(t,\tau), \\ k_s i(0) = q_v\lambda_v(t)U(t) + q_u\lambda_u(t)V(t). \end{cases} \tag{3.4}$$

Table 5. Monte Carlo Simulation Results of the within-host model (M_2) with $\beta = 0$. The parameters Λ, d_c and c are fixed at $\Lambda = 15$, $d_c = 5.5$ and $c = 23$. The AREs and 95% confidence intervals of parameters of within-host model (M_2) is presented for each measurement error σ_0.

	λ		d		β_1	
	ARE	95% CI	ARE	95% CI	ARE	95% CI
0%	1.5×10^{-14}	[24,603, 24,603]	0	[0.114, 0.114]	0	$[4.0 \times 10^{-5},\ 4.0 \times 10^{-5}]$
1%	0.4	[24,343, 24,841]	0.5	[0.112, 0.115]	2.0	$[3.7 \times 10^{-5},\ 4.2 \times 10^{-5}]$
5%	2.1	[23,304, 25,782]	2.6	[0.107, 0.121]	6.4	$[3.1 \times 10^{-5},\ 4.9 \times 10^{-5}]$
10%	4.3	[21,967, 27,013]	5.2	[0.099, 0.129]	9.8	$[3.0 \times 10^{-5},\ 5.4 \times 10^{-5}]$
20%	8.9	[19,219, 29,775]	11.2	[0.083, 0.147]	72.1	$[2.8 \times 10^{-5},\ 6.9 \times 10^{-5}]$
30%	14.2	[15,849, 33,561]	20.0	[0.056, 0.175]	7×10^9	$[1.8 \times 10^{-5},\ 1.1 \times 10^{-4}]$
	δ		π		C_0	
	ARE	95% CI	ARE	95% CI	ARE	95% CI
0%	0	[0.603, 0.603]	0	[4834 4834]	0	[6530, 6530]
1%	0.4	[0.598, 0.608]	0.9	[4730 4938]	2.3	[6087, 7012]
5%	1.8	[0.577, 0.629]	4.6	[4310 5352]	8.1	[4991, 8244]
10%	3.6	[0.548, 0.634]	9.1	[3779 5883]	11.5	[4411, 9227]
20%	7.4	[0.488, 0.702]	18.6	[2713 6977]	44.0	[3482, 11349]
30%	12.0	[0.404, 0.7749]	29.1	[1600 7915]	6×10^9	[2020, 12812]

Table 6. Monte Carlo Simulation Results of the within-host model M_2 with $\beta = 0$. The parameters Λ, d_c, c and C_0 are fixed at $\Lambda = 15$, $d_c = 5.5$, $c = 23$ and $C_0 = 6530$. The AREs and 95% confidence intervals of parameters of within-host model M_2 is presented for each measurement error σ_0.

	λ		d		β_1	
	ARE	95% CI	ARE	95% CI	ARE	95% CI
0%	1.5×10^{-14}	[24,603, 24,603]	0	[0.114, 0.114]	0	$[4.0 \times 10^{-5},\ 4.0 \times 10^{-5}]$
1%	0.4	[24,339, 24,849]	0.5	[0.112, 0.115]	0.8	$[3.9 \times 10^{-5},\ 4.0 \times 10^{-5}]$
5%	2.2	[23,284, 25,829]	2.7	[0.106, 0.121]	4.1	$[3.6 \times 10^{-5},\ 4.4 \times 10^{-5}]$
10%	4.4	[21,965, 27,088]	5.6	[0.098, 0.129]	8.5	$[3.3 \times 10^{-5},\ 4.9 \times 10^{-5}]$
20%	9.0	[19,072, 29,843]	11.9	[0.081, 0.148]	19.5	$[2.8 \times 10^{-5},\ 6.5 \times 10^{-5}]$
30%	14.3	[15,714, 32,659]	21.1	[0.044, 0.175]	41.7	$[2.5 \times 10^{-5},\ 1.1 \times 10^{-4}]$
	δ		π			
	ARE	95% CI	ARE	95% CI		
0%	0	[0.603, 0.603]	0	[4834 4834]		
1%	0.4	[0.598, 0.608]	0.9	[4722 4943]		
5%	1.8	[0.577, 0.630]	4.7	[4276 5370]		
10%	3.7	[0.548, 0.655]	9.5	[3738 5937]		
20%	7.6	[0.488, 0.706]	19.4	[2631 7058]		
30%	12.3	[0.400, 0.751]	30.5	[1518 8119]		

When both HIV infection and addiction disappear in the population, we obtain the disease-addiction-free equilibrium for which the compartments $U(t)$, $V(t)$ and $i(t,\tau)$ are zero. The disease-addiction-free equilibrium for the system (3.4) is given as $E^0 = \left(S^0, 0, 0, 0\right) = \left(\frac{\Lambda_S}{\mu}, 0, 0, 0\right)$.

To determine the stability, we linearize the system around the disease-addiction-free equilibrium. We take $S(t) = S^0 + x(t)$, $U(t) = u(t)$,$V(t) = v(t)$, $N(t) = N^0 + n(t)$ and $i(t,\tau) = y(t,\tau)$, where $x(t), u(t), v(t), y(t,\tau)$ and $n(t)$ denote the perturbations around E^0. The linearized system for perturbations takes the following form,

$$\begin{cases} \dfrac{dx(t)}{dt} = -\lambda_u(t)S^0 - k\lambda_v(t)S^0 - \mu x(t) + \delta_u u(t), \\ \dfrac{du(t)}{dt} = \lambda_u(t)S^0 - (\mu + d_u + \delta_u)u(t), \\ \dfrac{dv(t)}{dt} = \lambda_v(t)S^0 - (\mu + d_v + \gamma_v)v(t) + \delta_u \displaystyle\int_0^\infty \sigma(\tau)y(t,\tau)d\tau, \\ \dfrac{\partial y(t,\tau)}{dt} + \dfrac{\partial k_s y(t,\tau)}{d\tau} = -(\mu + d_i(\tau) + \gamma_i(\tau) + \delta_u\sigma(\tau))y(t,\tau), \\ k_s y(t,0) = 0 \end{cases} \tag{3.5}$$

where

$$\lambda_u(t) = \beta_u \frac{u(t) + \displaystyle\int_0^\infty y(t,\tau)d\tau}{N^0}, \quad \lambda_v(t) = \frac{\beta_{v_1} v(t) + \displaystyle\int_0^\infty \beta_{v_2}(\tau)y(t,\tau)d\tau}{N^0}, \quad N^0 = S^0 = \frac{\Lambda_S}{\mu}.$$

Table 7. Definitions of parameters and dependent variables of the between-host model.

Parameter/Variable	Description
$S(t)$	Number of susceptible individuals at time t
$V(t)$	Number of HIV infected individuals at time t
$U(t)$	Number of opioid addicted individuals at time t
$i(t,\tau)$	Density of co-affected individuals with co-affection age τ at time t
$A(t)$	Number of individuals with AIDS at time t
Λ_S	Constant recruitment rate
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 co-affected 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 co-affection at co-affection age τ
d_a	Death rate induced by AIDS
δ_u	Recovery rate from Opioid addiction
$\sigma(\tau)$	Addiction recovery rate for co-affected individuals
q_u	Increase/decrease of HIV infection due to opioid addiction
q_v	Increase/decrease of opioid addiction due to HIV infection
γ_v	Rate of transition from HIV to AIDS
$\gamma_i(\tau)$	Rate of transition into AIDS for co-affected individuals

We look for solutions of the form $x(t) = x_0e^{\lambda t}$,$u(t) = u_0e^{\lambda t}$, $v(t) = v_0e^{\lambda t}$, $y(t,\tau) = y(\tau)e^{\lambda t}$ and obtain the following eigenvalue problem,

$$\begin{cases} (\lambda+\mu)x_0 + \left(\beta_u \dfrac{u_0 + \displaystyle\int_0^\infty y(\tau)d\tau}{N^0}\right)S^0 + k\left(\dfrac{\beta_{v_1}v_0 + \displaystyle\int_0^\infty \beta_{v_2}(\tau)y(\tau)d\tau}{N^0}\right)S^0 - \delta_u u_0 = 0, \\ (\lambda+\mu+d_u+\delta_u)u_0 - \left(\beta_u \dfrac{u_0 + \displaystyle\int_0^\infty y(\tau)d\tau}{N^0}\right)S^0 = 0, \\ (\lambda+\mu+d_v+\gamma_v)v_0 - \left(\dfrac{\beta_{v_1}v_0 + \displaystyle\int_0^\infty \beta_{v_2}(\tau)y(\tau)d\tau}{N^0}\right)S^0 + \delta_u\displaystyle\int_0^\infty \sigma(\tau)y(\tau)d\tau = 0, \\ \dfrac{\partial k_s y(\tau)}{d\tau} + \lambda y(\tau) = -(\mu + d_i(\tau) + \gamma_i(\tau) + \delta_u\sigma(\tau))y(\tau), \\ k_s y(0) = 0 \end{cases} \tag{3.6}$$

Solving the fourth equation of system (3.6) we get

$$y(\tau) = y(0)\pi(\tau)e^{-\lambda\tau/k_s} = 0. \tag{3.7}$$

where

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

Using Eq (3.7) and the second equation of system (3.6), we obtain,

$$(\lambda+\mu+d_u+\delta_u)u_0 - \beta_u\frac{u_0}{N^0}S^0 = 0 \tag{3.8}$$

Solving this equation we obtain,

$$u_0\left(1 - \frac{\beta_u}{\lambda+\mu+d_u+\delta_u}\right) = 0. \tag{3.9}$$

Since $u_0 \neq 0$, we set the following equation,

$$1 = \frac{\beta_u}{\lambda+\mu+d_u+\delta_u}. \tag{3.10}$$

We define the basic reproduction number of opioid addiction $\mathscr{R}_u$ as

$$\mathscr{R}_u = \frac{\beta_u}{\mu+d_u+\delta_u}. \tag{3.11}$$

Similarly using Eq (3.7) and the third equation of system (3.6), we obtain,

$$1 = \frac{\beta_{v_1}}{\lambda + \mu + d_v + \gamma_v}$$

Then, we define the basic reproduction number of HIV-infection $\mathscr{R}_v$ as

$$\mathscr{R}_v = \frac{\beta_{v_1}}{\mu + d_v + \gamma_v}. \tag{3.12}$$

Now we state the following theorem,

Theorem 1. *If* $\max\{\mathscr{R}_u, \mathscr{R}_v\} < 1$ *then disease-addiction-free equilibrium* E^0 *is locally asymptotically stable. If* $\max\{\mathscr{R}_u, \mathscr{R}_v\} > 1$ *then the equilibrium* E^0 *is unstable.*

Proof. Suppose

$$\mathscr{G}_1(\lambda) = \frac{\beta_u}{\lambda + \mu + d_u + \delta},$$

$$\mathscr{G}_2(\lambda) = \frac{\beta_{v_1}}{(\lambda + \mu + d_v + \gamma_v)}.$$

Then we notice that $\mathscr{G}_1(0) = \mathscr{R}_u$, $\mathscr{G}_2(0) = \mathscr{R}_v$, $\lim_{\lambda\to\infty} \mathscr{G}_1(\lambda) = 0, \lim_{\lambda\to\infty} \mathscr{G}_2(\lambda) = 0$. We claim that if $\max\{\mathscr{R}_u, \mathscr{R}_v\} < 1$ then the disease free equilibrium is locally asymptotically stable, that is all the roots of system (3.6) have negative real parts. To show this, we proceed by way of contradiction. Suppose system (3.6) has a root λ_0 with $\Re(\lambda_0) \geq 0$. Then,

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

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

This is a contradiction. Hence E^0 is locally asymptotically stable when $\max\{\mathscr{R}_u, \mathscr{R}_v\} < 1$.

3.2. Stability of boundary equilibria and invasion numbers

To obtain the opioid-only boundary equilibrium $E_1^* = \left(S_1^*, U_1^*, 0, 0\right)$, we set $S(t) = S_1^*$, $U(t) = U_1^*$, $V(t) = 0$ and $i(t, \tau) = 0$ in system (3.4), then the system reduces to the following,

$$\begin{aligned} \Lambda_S - \mu S_1^* - S_1^* \lambda_u(U_1^*) + \delta_u U_1^* &= 0 \\ S_1^* \lambda_u(U_1^*) - (\mu + d_u + \delta_u) U_1^* &= 0 \\ \lambda_u(U_1^*) = \beta_u \frac{U_1^*}{N_1^*} & \end{aligned} \tag{3.13}$$

Solving system (3.13) we obtain,

$$\frac{S_1^*}{N_1^*} = \frac{1}{\mathscr{R}_u}, \quad \text{and} \quad \frac{U_1^*}{N_1^*} = 1 - \frac{1}{\mathscr{R}_u}.$$

At the HIV-only equilibrium, $E_2^* = (S_2^*, 0, V_2^*, 0)$, the system (3.4) reduces to

$$\begin{aligned} \Lambda_S - \mu S_2^* - S_2^* \lambda_v(V_2^*) &= 0 \\ S_2^* \lambda_v(V_2^*) - (\mu + d_v + \gamma_v) V_2^* &= 0 \\ \lambda_v(V_2^*) &= \frac{\beta_{v_1} V_2^*}{N_2^*} \end{aligned} \tag{3.14}$$

Solving system (3.14) we obtain,

$$\frac{S_2^*}{N_2^*} = \frac{1}{\mathscr{R}_v}, \quad \text{and} \quad \frac{V_2^*}{N_2^*} = 1 - \frac{1}{\mathscr{R}_v}.$$

We state the following lemma,

Lemma 1. *Given* $\min\{\mathscr{R}_u, \mathscr{R}_v\} > 1$*, then there exist an opioid-only boundary equilibrium, and an HIV-only boundary equilibrium of system* (3.1)*.*

To find the invasion number of HIV and stability of E_1^* we linearize the system (3.1) around E_1^*. We set $S(t) = x(t) + S_1^*$, $U(t) = u(t) + U_1^*$, $V(t) = v(t)$, $i(t, \tau) = y(t, \tau)$ and $N(t) = n(t) + N_1^*$, then the system for the perturbations becomes,

$$\begin{cases} \dfrac{dx(t)}{dt} = -S_1^* \lambda_u(u, y) - x(t)\beta_u \dfrac{U_1^*}{N_1^*} + S_1^* \beta_u \dfrac{U_1^* n(t)}{N_1^{*2}} - \mu x(t) + \delta_u u(t) - S_1^* \lambda_v(v, y), \\ \dfrac{du(t)}{dt} = S_1^* \lambda_u(u, y) + x(t)\beta_u \dfrac{U_1^*}{N_1^*} - S_1^* \beta_u \dfrac{U_1^* n(t)}{N_1^{*2}} - q_v U_1^* \lambda_v(v, y) - (\mu + d_u + \delta_u) u(t), \\ \dfrac{dv(t)}{dt} = S_1^* \lambda_v(v, y) - q_u v(t)\beta_u \dfrac{U_1^*}{N_1^*} - (\mu + d_v + \gamma_v) v(t) + \delta_u \displaystyle\int_0^\infty \sigma(\tau) y(t, \tau) d\tau, \\ \dfrac{\partial y(t, \tau)}{dt} + \dfrac{\partial k_s y(t, \tau)}{d\tau} = -(\mu + d_i(\tau) + \gamma_i(\tau) + \delta_u \sigma(\tau)) y(t, \tau), \\ k_s y(t, 0) = q_v U_1^* \lambda_v(v, y) + q_u v(t) \beta_u \frac{U_1^*}{N_1^*}, \end{cases} \tag{3.15}$$

where,

$$\lambda_u(u, y) = \beta_u \frac{u + \displaystyle\int_0^\infty y(t, \tau)}{N_1^*}, \quad \lambda_v(v, y) = \frac{\beta_{v_1} v(t) + \displaystyle\int_0^\infty \beta_{v_2}(\tau) y(t, \tau) d\tau}{N_1^*}.$$

We look for solutions of the form $x(t) = xe^{\lambda t}$,$u(t) = ue^{\lambda t}$,$v(t) = ve^{\lambda t}$, $y(\tau, t) = y(\tau)e^{\lambda t}$ and obtain the

following eigenvalue problem,

$$\begin{cases} \lambda x = -S_1^*\lambda_u(u,y) - x\beta_u\frac{U_1^*}{N_1^*} + S_1^*\beta_u\frac{U_1^*n}{N_1^{*2}} - \mu x + \delta_u u - S_1^*\lambda_v(v,y), \\ \lambda u = S_1^*\lambda_u(u,y) + x\beta_u\frac{U_1^*}{N_1^*} - S_1^*\beta_u\frac{U_1^*n}{N_1^{*2}} - q_v U_1^*\lambda_v(v,y) - (\mu + d_u + \delta_u)u, \\ \lambda v = S_1^*\lambda_v(v,y) - q_u v\beta_u\frac{U_1^*}{N_1^*} - (\mu + d_v + \gamma_v)v + \delta_u\int_0^\infty \sigma(\tau)y(\tau)d\tau, \\ \frac{\partial k_s y(\tau)}{d\tau} + \lambda y = -(\mu + d_i(\tau) + \gamma_i(\tau) + \delta_u\sigma(\tau))y(\tau), \\ k_s y(0) = q_v U_1^*\lambda_v(v,y) + q_u v\beta_u\frac{U_1^*}{N_1^*}, \end{cases} \tag{3.16}$$

where,

$$\lambda_u(u,y) = \beta_u\frac{u + \int_0^\infty y(\tau)}{N_1^*}, \quad \lambda_v(v,y) = \frac{\beta_{v_1}v(t) + \int_0^\infty \beta_{v_2}(\tau)y(\tau)d\tau}{N_1^*}.$$

From the third, fourth and fifth equation of system (3.16) we obtain,

$$\begin{cases} (\lambda + \mu + d_v + \gamma_v)v = S_1^*\lambda_v(v,y) - q_u v\beta_u\frac{U_1^*}{N_1^*} + \delta_u\int_0^\infty \sigma(\tau)y(\tau)d\tau, \\ \frac{\partial k_s y(\tau)}{d\tau} + \lambda y = -(\mu + d_i(\tau) + \gamma_i(\tau) + \delta_u\sigma(\tau))y(\tau), \\ k_s y(0) = q_v U_1^*\lambda_v(v,y) + q_u v\beta_u\frac{U_1^*}{N_1^*}. \end{cases} \tag{3.17}$$

From the second equation of system (3.17) we get $y(\tau) = y(0)\pi(\tau)e^{-\lambda\tau/k_s}$. Setting

$$K = \beta_u q_u\frac{U_1^*}{N_1^*} \text{ and } Q(\lambda) = \delta_u\int_0^\infty \sigma(\tau)\pi(\tau)e^{-\lambda\tau/k_s}d\tau$$

the first and third equations of system (3.17) become,

$$\begin{array}{ll} (\lambda + \mu + d_v + \gamma_v + K)v - Q(\lambda)y(0) & = S_1^*\lambda_v(v,y) \\ -Kv + k_s y(0) & = q_v U_1^*\lambda_v(v,y) \end{array} \tag{3.18}$$

Solving for v and $y(0)$ we obtain,

$$v = \frac{k_s S_1^* + q_v U_1^* Q(\lambda)}{k_s(\lambda + \mu + d_v + \gamma_v + K) - KQ(\lambda)}\lambda_v(v,y),$$
$$y(0) = \frac{q_v(\lambda + \mu + d_v + \gamma_v + K)U_1^* + KS_1^*}{k_s(\lambda + \mu + d_v + \gamma_v + K) - KQ(\lambda)}\lambda_v(v,y).$$

Substituting these values into the following equation,

$$\lambda_v(v,y) = \frac{\beta_{v_1}v(t) + \int_0^\infty \beta_{v_2}(\tau)y(\tau)d\tau}{N_1^*},$$

and cancelling $\lambda_v(v, y)$ from both sides of the equation, we obtain;

$$1 = \frac{\beta_{v_1}}{N_1^*} \frac{k_s S_1^* + q_v U_1^* Q(\lambda)}{k_s(\lambda + \mu + d_v + \gamma_v + K) - KQ(\lambda)} + \frac{\int_0^\infty \beta_{v_2}(\tau) e^{-\lambda\tau/k_s} \pi(\tau) d\tau}{N_1^*} \frac{q_v(\lambda + \mu + d_v + \gamma_v + K)U_1^* + KS_1^*}{k_s(\lambda + \mu + d_v + \gamma_v + K) - KQ(\lambda)}. \tag{3.19}$$

We then define invasion number of HIV infection, $\mathscr{R}^1_{v_i}$ as

$$\begin{aligned} \mathscr{R}^1_{v_i} = & \frac{\beta_{v_1}}{N_1^*} \frac{k_s S_1^* + q_v U_1^* \delta_u \int_0^\infty \sigma(\tau)\pi(\tau) d\tau}{k_s(\mu + d_v + \gamma_v + K) - K\delta_u \int_0^\infty \sigma(\tau)\pi(\tau) d\tau} \\ & + \frac{\int_0^\infty \beta_{v_2}(\tau)\pi(\tau) d\tau}{N_1^*} \frac{q_v(\mu + d_v + \gamma_v + K)U_1^* + KS_1^*}{k_s(\mu + d_v + \gamma_v + K) - K\delta_u \int_0^\infty \sigma(\tau)\pi(\tau) d\tau} \end{aligned} \tag{3.20}$$

Let

$$\mathscr{G}_{vi}(\lambda) = \frac{\beta_{v_1}}{N_1^*} \frac{k_s S_1^* + q_v U_1^* Q(\lambda)}{k_s(\lambda + \mu + d_v + \gamma_v + K) - KQ(\lambda)} + \frac{\int_0^\infty \beta_{v_2}(\tau) e^{-\lambda\tau/k_s} \pi(\tau) d\tau}{N_1^*} \frac{q_v(\lambda + \mu + d_v + \gamma_v + K)U_1^* + KS_1^*}{k_s(\lambda + \mu + d_v + \gamma_v + K) - KQ(\lambda)}$$

$$\hat{\beta}(\lambda) = \int_0^\infty \beta_{v_2}(\tau) e^{-\lambda\tau/k_s} \pi(\tau) d\tau$$

Clearly, $\hat{\beta}(\lambda)$ is bounded above by $\hat{\beta}(0)$ and $Q(\lambda)$ is bounded above by $Q(0)$ for λ real. Note that, $\mathscr{G}_{vi}(0) = \mathscr{R}^1_{v_i}$ and $\lim_{\lambda\to\infty} \mathscr{G}_{vi}(\lambda) = 0$. Suppose system (3.19) has a root $\lambda = x + iy$ with $\Re(\lambda) = x > 0$. We first, prove the following inequaltiy.

$$\frac{\left|q_v(\lambda + \mu + d_v + \gamma_v + K)\frac{U_1^*}{N_1^*}\right| + \left|K\frac{S_1^*}{N_1^*}\right|}{|k_s(\lambda + \mu + d_v + \gamma_v + K)| - |KQ(0)|} \leq \frac{\left|q_v(\mu + d_v + \gamma_v + K)\frac{U_1^*}{N_1^*}\right| + \left|K\frac{S_1^*}{N_1^*}\right|}{|k_s(\mu + d_v + \gamma_v + K)| - |KQ(0)|} \tag{3.21}$$

To prove inequality (Eq 3.21) we write down the left hand side of the inequality,

$$\frac{\left|q_v(\lambda + \mu + d_v + \gamma_v + K)\frac{U_1^*}{N_1^*}\right| + \left|K\frac{S_1^*}{N_1^*}\right|}{|k_s(\lambda + \mu + d_v + \gamma_v + K)| - |KQ(0)|} = \frac{q_v C_1 z + KC_2}{k_s z - KQ(0)} = f(z),$$

where, $C_1 = \dfrac{U_1^*}{N_1^*}$, $C_2 = \dfrac{S_1^*}{N_1^*}$ and $z = \sqrt{(x + \mu + d_v + \gamma_v + K)^2 + y^2}$ where $z = x + yi$. Since $f'(|z|) < 0$, $f(|z|)$ is a decreasing function. That is when $z(0, 0) \leq z(x, y)$, $f(z(0, 0)) \geq f(z(x, y))$ when $x \geq 0$. But $f(z(0, 0))$ is just the right hand side of inequality (Eq 3.21). This proves the inequality (Eq 3.21). Using inequality (Eq 3.21) we now state the following,

$$1 = |\mathscr{G}_{vi}(\lambda)| \leq |\mathscr{G}_{vi}(0)| = \mathscr{R}^1_{vi} < 1$$

This is a contradiction. So system (3.19) can only have roots with non-negative real parts when $\mathscr{R}^1_{vi} < 1$. If $\mathscr{R}^1_{vi} > 1$ then $\mathscr{G}_{vi}(\lambda) \to 0$ as $\lambda \to 0$ and λ real. Thus E^*_1 is unstable. Note that,

$$\frac{U^*_1}{N^*_1} = 1 - \frac{1}{\mathscr{R}_u}, \quad \frac{S^*_1}{N^*_1} = \frac{1}{\mathscr{R}_u}. \tag{3.22}$$

To find the further eigenvalues, satisfying the third, fourth and fifth equation of system (3.16), $y(t,\tau) = 0$ and $v(t) = 0$. The first two equations in system (3.16) then reduce to

$$\begin{aligned} \lambda x &= -S^*_1\beta_u\frac{u}{N^*_1} - x\beta_u\frac{U^*_1}{N^*_1} + S^*_1\beta_u\frac{U^*_1 n}{N^{*2}_1} - \mu x + \delta_u u, \\ \lambda u &= S^*_1\beta_u\frac{u}{N^*_1} + x\beta_u\frac{U^*_1}{N^*_1} - S^*_1\beta_u\frac{U^*_1 n}{N^{*2}_1} - (\mu + d_u + \delta_u)u. \end{aligned} \tag{3.23}$$

Adding the two equations and solving for n we get

$$n = -\frac{d_u u}{(\lambda+\mu)} \quad \text{which implies} \quad x = -\frac{\lambda+\mu+d_u}{\lambda+\mu}u.$$

Replacing x and n in the second equation of system (3.16) we get,

$$\begin{aligned} (\lambda+\mu+d_u+\delta_u)u &= S^*_1\beta_u\frac{u}{N^*_1} - \frac{\lambda+\mu+d_u}{\lambda+\mu}u\beta_u\frac{U^*_1}{N^*_1} + S^*_1\beta_u\frac{U^*_1}{N^{*2}_1}\frac{d_u u}{(\lambda+\mu)} \\ \implies \left(\lambda+\mu+d_u+\delta_u+\beta_u(1-\frac{1}{\mathscr{R}_u})\frac{\lambda+\mu+d_u}{\lambda+\mu}\right)u &= S^*_1\beta_u\frac{u}{N^*_1}\left(1+\frac{d_u\frac{U^*_1}{N^*_1}}{\lambda+\mu}\right) \end{aligned} \tag{3.24}$$

Multiplying both sides of the equation $\frac{1}{N^*_1}$,

$$\left(\lambda+\mu+d_u+\delta_u+\beta_u n(1-\frac{1}{\mathscr{R}_u})\frac{\lambda+\mu+d_u}{\lambda+\mu}\right)\frac{u}{N^*_1} = \frac{S^*_1}{N^*_1}\beta_u\frac{u}{N^*_1}\left(1+\frac{d_u\frac{U^*_1}{N^*_1}}{\lambda+\mu}\right) \tag{3.25}$$

$\frac{u}{N^*_1} = 0$ implies from system (3.24) u would be zero, which would not be of interest. Thus $\frac{u}{N^*_1} \neq 0$ and canceling the expression on both sides, then the characteristic equation becomes,

$$(\lambda+\mu+d_u+\delta_u)(\lambda+\mu) + \beta_u(\lambda+\mu+d_u)\left(1-\frac{1}{\mathscr{R}_u}\right) = \beta_u\left(\lambda+\mu+d_u(1-\frac{1}{\mathscr{R}_u})\right)\frac{1}{\mathscr{R}_u} \tag{3.26}$$

Rewriting this equation as a quadratic equation, we get

$$\lambda^2 + (2\mu+d_u+\delta_u+\beta_u-2\beta_u\frac{1}{\mathscr{R}_u})\lambda + (\mu+d_u+\delta)\mu + \beta_u\left(1-\frac{1}{\mathscr{R}_u}\right)(\mu+d_u) - \beta_u\frac{1}{\mathscr{R}_u}\left(\mu+d_u(1-\frac{1}{\mathscr{R}_u})\right) = 0 \tag{3.27}$$

Simplifying the equation, we have $\lambda^2 + b\lambda + c = 0$ where $b = \beta_u - d_u - \delta_u > 0$ and

$$c = \left(1 - \frac{1}{\mathscr{R}_u}\right)(\beta_u(\mu + d_u) - (\mu + d_u + \delta_u)d_u) > 0$$

since $\beta_u > (\mu + d_u + \delta_u)$ when $\mathscr{R}_u > 1$. 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 $\mathscr{R}_{v_i}^1 < 1$, and it is unstable if $\mathscr{R}_{v_i}^1 > 1$.*

To find the invasion number of Opioid addiction and stability of E_2^* we first linearize the system (3.1) around E_2^*. We set $S(t) = x(t) + S_2^*$, $U(t) = u(t)$, $V(t) = v(t) + V_2^*$, $i(t,\tau) = y(t,\tau)$ and $N(t) = n(t) + N_2^*$, the system for the perturbations become,

$$\begin{cases} \dfrac{dx(t)}{dt} = -S_2^*\lambda_u^2(u,y) - \mu x(t) + \delta_u u(t) - S_2^*\lambda_v^2(v,y) - C_1 x + S_2^*\dfrac{\beta_{v_1}V_2^* n}{N_2^{*2}}, \\ \dfrac{du(t)}{dt} = S_2^*\lambda_u^2(u,y) - q_v u C_1 - (\mu + d_u + \delta_u)u(t), \\ \dfrac{dv(t)}{dt} = xC_1 + S_2^*\lambda_v^2(v,y) - S_2^*\dfrac{\beta_{v_1}V_2^* n}{N_2^{*2}} - q_u V_2^*\lambda_u^2(u,y) \\ -(\mu + d_v + \gamma_v)v(t) + \delta_u\int_0^\infty \sigma(\tau)y(t,\tau)d\tau, \\ \dfrac{\partial y(t,\tau)}{dt} + \dfrac{\partial k_s y(t,\tau)}{d\tau} = -(\mu + d_i(\tau) + \gamma_i(\tau) + \delta_u\sigma(\tau))y(t,\tau), \\ k_s y(t,0) = q_v C_1 u + q_u V_2^*\lambda_u^2(u,y) \end{cases} \tag{3.28}$$

Where,

$$\lambda_u^2(u,y) = \beta_u\frac{u + \int_0^\infty y(t,\tau)}{N_2^*}$$

$$\lambda_v^2(v,y) = \frac{\beta_{v_1}v(t) + \displaystyle\int_0^\infty \beta_{v_2}(\tau)y(t,\tau)d\tau}{N_2^*}$$

and

$$C_1 = \frac{\beta_{v_1}V_2^*}{N_2^*}.$$

We look for solutions of the form $x(t) = xe^{\lambda t}$, $u(t) = ue^{\lambda t}$, $v(t) = ve^{\lambda t}$, $y(\tau,t) = y(\tau)e^{\lambda t}$ and obtain the following eigenvalue problem,

$$\begin{cases} \lambda x = -S_2^*\lambda_u^2(u,y) - \mu x + \delta_u u - S_2^*\lambda_v^2(v,y) - C_1 x + S_2^*\frac{\beta_{v_1}V_2^* n}{N_2^{*2}}, \\ \lambda u = S_2^*\lambda_u^2(u,y) - q_v u C_1 - (\mu + d_u + \delta_u)u, \\ \lambda v = xC_1 + S_2^*\lambda_v^2(v,y) - S_2^*\frac{\beta_{v_1}V_2^* n}{N_2^{*2}} - q_u V_2^*\lambda_u^2(u,y) - (\mu + d_v + \gamma_v)v + \delta_u\int_0^\infty \sigma(\tau)y(\tau)d\tau, \\ \frac{\partial k_s y(\tau)}{d\tau} + \lambda y = -(\mu + d_i(\tau) + \gamma_i(\tau) + \delta_u\sigma(\tau))y(\tau), \\ k_s y(0) = q_v C_1 u + q_u V_2^*\lambda_u^2(u,y) \end{cases} \tag{3.29}$$

Where,

$$\lambda_u^2(u,y) = \beta_u\frac{u + \int_0^\infty y(\tau)d\tau}{N_2^*}$$

$$\lambda_v^2(v,y) = \frac{\beta_{v_1}v + \int_0^\infty \beta_{v_2}(\tau)y(\tau)d\tau}{N_2^*}$$

From the fourth equation of system (3.29) we get

$$y(\tau) = y(0)\pi(\tau)e^{-\lambda\tau/k_s} \tag{3.30}$$

Let $Q(\lambda) = \int_0^\infty \pi(\tau)e^{-\lambda\tau/k_s}d\tau$.
From the second equation of system (3.29) we get

$$u = \frac{S_2^*}{\lambda + \mu + d_u + \delta_u + q_v C_1}\lambda_u^2(u,y)$$

Multiplying both sides of this equation with $\frac{1}{N_2^*}$ we get,

$$\frac{u}{N_2^*} = \frac{S_2^*}{(\lambda + \mu + d_u + \delta_u + q_v C_1)N_2^*}\lambda_u^2(u,y). \tag{3.31}$$

From the fifth equation of system (3.29) we get,

$$\frac{y(0)}{N_2^*} = \frac{q_v C_1 u}{k_s N_2^*} + \frac{q_u V_2^*}{k_s N_2^*}\lambda_u^2(u,y).$$

Supplying these values in the equation,

$$\lambda_u^2(u,y) = \beta_u\frac{u + \int_0^\infty y(\tau)d\tau}{N_2^*},$$

and canceling $\lambda_u^2(u,y)$ from both sides we obtain,

$$1 = \beta_u[\frac{S_2^*}{(\lambda + \mu + d_u + \delta_u + q_v C_1)N_2^*} + Q(\lambda)(\frac{q_v C_1}{k_s N_2^*}\frac{S_2^*}{\lambda + \mu + d_u + \delta + q_v C_1} + \frac{q_u V_2^*}{k_s N_2^*})] \tag{3.32}$$

We then define the invasion number of opioid epidemic as,

$$\mathscr{R}^2_{u_i} = \frac{(k_s + q_v C_1 \Pi)\beta_u S_2^*}{(\mu + d_u + \delta_u + q_v C_1)k_s N_2^*} + \Pi q_u \beta_u \frac{V_2^*}{k_s N_2^*} \tag{3.33}$$

where $\Pi = \int_0^\infty \pi(\tau)d\tau$ and $C_1 = \frac{\beta_{v_1} V_2^*}{N_2^*}$. We call $\mathscr{R}^2_{ui}$ the invasion number of opioid addiction. We claim that when $\mathscr{R}^2_{u_i} < 1$, the boundary equilibrium E_2^* is locally asymptotically stable, that is all the roots of Eq (3.32) have negative real parts.

Suppose

$$\mathscr{G}_{ui}(\lambda) = \frac{(1 + q_v C_1 Q(\lambda))\beta_u S_2^*}{k_s(\lambda + \mu + d_u + \delta_u + q_v C_1)N_2^*} + Q(\lambda)\frac{q_u \beta_u}{k_s}\frac{V_2^*}{N_2^*}.$$

Then $\mathscr{G}_{ui}(0) = \mathscr{R}^2_{u_i}$ and $\lim_{\lambda\to\infty} \mathscr{G}_{ui}(\lambda) = 0$.

Assume the Eq (3.32) has roots with non-negative real part $\Re(\lambda) > 0$. The Eq (3.32) satisfies,

$$\begin{aligned}
1 &= \left|\frac{(1 + q_v C_1 Q(\lambda))\beta_u S_2^*}{k_s(\lambda + \mu + d_u + \delta_u + q_v C_1)N_2^*} + Q(\lambda)\frac{q_u \beta_u}{k_s}\frac{V_2^*}{N_2^*}\right| \\
&\le \left|\frac{(1 + q_v C_1 Q(\lambda))\beta_u S_2^*}{k_s(\lambda + \mu + d_u + \delta_u + q_v C_1)N_2^*}\right| + \left|Q(\lambda)\frac{q_u \beta_u}{k_s}\frac{V_2^*}{N_2^*}\right| \\
&\le \left|\frac{(1 + q_v C_1 Q(\Re(\lambda)))\beta_u S_2^*}{k_s(\lambda + \mu + d_u + \delta_u + q_v C_1)N_2^*}\right| + \left|Q(\Re(\lambda))\frac{q_u \beta_u}{k_s}\frac{V_2^*}{N_2^*}\right| \\
&\le \left|\frac{(1 + q_v C_1 \Pi)\beta_u S_2^*}{k_s(\mu + d_u + \delta_u + q_v C_1)N_2^*}\right| + \left|\Pi\frac{q_u \beta_u}{k_s}\frac{V_2^*}{N_2^*}\right| \\
&\le \mathscr{R}^2_{u_i} < 1
\end{aligned} \tag{3.34}$$

This is a contradiction. Hence all roots of Eq (3.32) have negative real parts when $\mathscr{R}^2_{u_i} < 1$.

Now let us suppose, $\mathscr{R}^2_{u_i} > 1$. Then since $\mathscr{G}'_{ui}(\lambda) < 0$ when $\lambda > 0$ and real, $\mathscr{G}_{ui}(\lambda)$ is decreasing when $\lambda > 0$ and real. But we have, $\mathscr{G}_{ui}(0) = \mathscr{R}^2_{u_i} > 1$ and $\lim_{\lambda\to\infty} \mathscr{G}_{ui}(\lambda) = 0$. Then Eq (3.32) has at least one positive root when $\mathscr{R}^2_{u_i} > 1$.

If λ is not a solution of characteristic Eq (3.32), we have $u = 0$, $y(0) = 0$, the first two equations of system (3.29) reduce to

$$\begin{aligned}
\lambda x &= -\mu x - S_2^*\frac{\beta_{v_1} v}{N_2^*} - C_1 x + S_2^*\frac{\beta_{v_1} V_2^* n}{N_2^{*2}}, \\
\lambda v &= x C_1 + S_2^*\frac{\beta_{v_1} v}{N_2^*} - S_2^*\frac{\beta_{v_1} V_2^* n}{N_2^{*2}} - (\mu + d_v + \gamma_v)v.
\end{aligned} \tag{3.35}$$

Adding the two equations and solving for n we get

$$n = -\frac{(d_v + \gamma_v)v}{(\lambda + \mu)},$$

i.e.

$$x = -\frac{\lambda + \mu + d_v + \gamma_v}{\lambda + \mu}v.$$

Using these values in the second equation of system (3.35) we get,

$$\left(\lambda+\mu+d_v+\gamma_v+\frac{C_1(\lambda+\mu+d_v+\gamma_v)}{\lambda+\mu}\right)v=S_2^*\frac{\beta_{v_1}v}{N_2^*}\left(\frac{\lambda+\mu+(d_v+\gamma_v)\frac{V_2^*}{N_2^*}}{\lambda+\mu}\right). \tag{3.36}$$

Since $v\neq 0$ we can cancel $\frac{v}{\lambda+\mu}$ from both sides and get the following equation,

$$1=S_2^*\frac{\beta_{v_1}}{N_2^*}\left(\frac{\lambda+\mu+(d_v+\gamma_v)\frac{V_2^*}{N_2^*}}{(\lambda+\mu+C_1)(\lambda+\mu+d_v+\gamma_v)}\right). \tag{3.37}$$

Now we know for the boundary equilibrium E_2^*, $S_2^*+U_2^*=N_2^*$, i.e both $\frac{S_2^*}{N_2^*}$ and $\frac{U_2^*}{N_2^*}$ are less than one. We also have the following,

$$\frac{C_1}{\beta_{v_1}}=\frac{V_2^*}{N_2^*},$$

and since $\mathscr{R}_v>1, \beta_{v_1}>\mu+d_v+\gamma_v$. Assume the Eq (3.37) has roots with non-negative real part. With $\Re(\lambda)\geq 0$ the Eq (3.37) satisfies,

$$\begin{aligned}1&=\left|\beta_{v_1}\frac{S_2^*}{N_2^*}\frac{(\lambda+\mu+(d_v+\gamma_v)\frac{V_2^*}{N_2^*})}{(\lambda+\mu+d_v+\gamma_v)(\lambda+\mu+C_1)}\right|\\&=\left|\beta_{v_1}\frac{1}{\mathscr{R}_v}\frac{(\lambda+\mu+(d_v+\gamma_v)\frac{C_1}{\beta_{v_1}}}{(\lambda+\mu+d_v+\gamma_v)(\lambda+\mu+C_1)}\right|\\<\left|\beta_{v_1}\frac{1}{\mathscr{R}_v}\frac{1}{(\lambda+\mu+d_v+\gamma_v)}\right|&\leq\left|\beta_{v_1}\frac{1}{\mathscr{R}_v}\frac{1}{(\mu+d_v+\gamma_v)}\right|=1.\end{aligned} \tag{3.38}$$

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

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

3.3. Estimating parameters of the multi-scale model of HIV and opioid epidemics

The Centers for Disease Control (CDC) collects and reports the surveillance data on persons diagnosed with HIV infection. The time series data of HIV diagnoses, which is defined by CDC as the number of HIV infections, confirmed by laboratory or clinical evidence in one calendar year, regardless of the stage of HIV-infection [31] is available at their website [35] starting from 2008. AIDS diagnoses are the individuals who were diagnosed with HIV infection and classified as AIDS. We obtain the HIV deaths and AIDS diagnoses from the CDC website to estimate the parameters of the multi-scale model (3.1) [35]. We report the time series data in Appendix Table A. National Center for Health Statistics reports the drug overdose deaths in the US from 1999–2018 [36]. The report gives any drug overdose mortality, but we used only the opioid deaths as given in complimentary pdf file [37]. We present the time series opioid overdose data in Appendix Table A.

We would like to estimate the parameters of the multi-scale model (3.1). As explained above the parameters of the co-affected class are linked to the viral load and target cell population within-infected host who abuse opioid drugs. Let $\boldsymbol{p}_e$ denote the parameters of the between host model (3.1) and let $\boldsymbol{p}$ denote the parameters of the within-host model M_2, then using the multi-scale data, we will estimate the following parameters;

$$[\boldsymbol{p}_e, \boldsymbol{p}] = [\underbrace{\beta_u, \beta_{v_1}, \beta_0, B, \delta_u, q_u, q_v, d_u, d_v, d_a, d_0, d_1, \gamma_v, \gamma_0, \sigma}_{\text{between-host model (3.1)}}, \quad \underbrace{\lambda, d, \beta_1, \delta, \pi}_{\text{within-host model } M_2} \ ].$$

For simplicity, we set $\sigma(\tau) = \sigma$. Recruitment and natural death rates are fixed at $\Lambda_S = 50,000,000\mu$ and $\mu = 1/75$. To define the multi-scale parameter estimation problem based on the data available in US, we set $\boldsymbol{y}_p(t) = (y_{p1}(t), y_{p2}(t), y_{p3}(t))$ to denote the observations. Observations for the between-host model parameter estimation are AIDS cases, denoted by $y_{p1}(t)$, HIV deaths denoted by $y_{p2}(t)$ and deaths due to opioid addiction denoted by $y_{p3}(t)$. Based on the model (3.1) observations are given as the following

$$\begin{aligned} y_{p1}(t) &= \gamma_v V(t) + \int_0^\infty \gamma_i(\tau) i(t,\tau) d\tau \\ y_{p2}(t) &= d_v V(t) + \int_0^\infty d_0 \left(T(0) - T(\tau)\right) i(t,\tau) d\tau \\ y_{p3}(t) &= d_u U(t) + \int_0^\infty d_1 i(t,\tau) d\tau \end{aligned} \tag{3.39}$$

Clearly, each observation depends on both the between-host parameters $\boldsymbol{p}_e$ and within-host parameters $\boldsymbol{p}$. Let $t_k^i = \{t_1^i, t_2^i, t_3^i, \cdots, t_{n_i}^i\}$, for $i = 1, 2, 3$ denote the discrete time points measured in years when the AIDS diagnoses, ($i = 1$), HIV deaths ($i = 2$) and opioid deaths ($i = 3$) are reported. Let Z_k^i denote the number of AIDS diagnoses ($i = 1$), HIV deaths ($i = 2$) and opioid deaths ($i = 3$) at the corresponding discrete times. Then we use the following optimization problem to estimate the parameters of the multi-scale system (3.1).

$$\begin{aligned} &\min_{\boldsymbol{p}_e, \boldsymbol{p}} \Bigg(\frac{\omega_1}{n_1} \sum_{k=1}^{n_1} \frac{|y_{p1}(t_k^1, \boldsymbol{p}_e, \boldsymbol{p}) - Z_k^1)|^2}{\hat{Z}^1} + \frac{\omega_2}{n_2} \sum_{k=1}^{n_2} \frac{|y_{p2}(t_k^2, \boldsymbol{p}_e, \boldsymbol{p}) - Z_k^2)|^2}{\hat{Z}^2} + \frac{\omega_3}{n_3} \sum_{k=1}^{n_3} \frac{|y_{p3}(t_k^3, \boldsymbol{p}_e, \boldsymbol{p}) - Z_k^3)|^2}{\hat{Z}^3} \\ &+ \frac{\omega_4}{n} \sum_{i=1}^{n} \frac{|\log_{10}(V(t_i, \boldsymbol{p})) - \log_{10}(Y_1^i)|^2}{\hat{Y}_1} + \frac{\omega_5}{m} \sum_{j=1}^{m} \frac{|\log_{10}(T(t_j, \boldsymbol{p})) - \log_{10}(Y_2^j)|^2}{\hat{Y}_2} \Bigg) \\ &\text{w.r.t the constraints } \ \boldsymbol{p}_e > 0, \ \boldsymbol{p} > 0, \ \beta_u = \mathscr{R}_u(\mu + d_u + \delta_u) \text{ and } \beta_{v_1} = \mathscr{R}_v(\mu + d_v + \gamma_v). \end{aligned} \tag{3.40}$$

Note that we use multi-scale data to estimate parameters of the multi-scale model. The within-host scale data and population scale data have different magnitudes. For instance, the weekly log viral load data is within range 5–8, and the yearly AIDS cases is within range $1 \times 10^4 - 4 \times 10^4$. Furthermore, the number of data points varies significantly for each observation. In such a case, the iterative numerical algorithm which approximates the minimization problem (3.40) tends to minimize the data with the highest magnitude at price of deviating from the small magnitude data. To overcome this issue, we normalize with the average data value. Thus in problem (3.40),

$$\hat{Z}^1 = \frac{1}{n_1}\sum_{k=1}^{n_1} Z_k^1, \quad \hat{Z}^2 = \frac{1}{n_2}\sum_{k=1}^{n_2} Z_k^2, \quad \hat{Z}^3 = \frac{1}{n_3}\sum_{k=1}^{n_3} Z_k^3, \quad \text{and}$$
$$\hat{Y}_1 = \frac{1}{n}\sum_{i=1}^{n} \log_{10}(Y_1^i), \quad \hat{Y}_2 = \frac{1}{m}\sum_{j=1}^{m} \log_{10}(Y_2^j).$$

Also note, that in problem (3.40), $\omega_1, \ldots, \omega_5$ are weights given to each data sets.

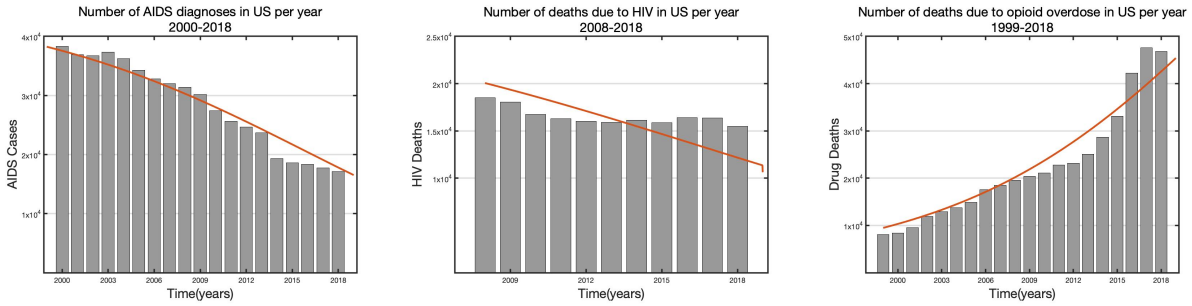

Figure 3. Model fit to data.

3.4. Sensitivity analysis

In this section we are interested in performing elasticity analysis of the invasion numbers with respect to the reproduction numbers as well as several important parameters. In article [18], we computed the elasticities of the two invasion numbers of an ODE model similar to the one here with parameters estimated from fitting to data. We found out that the invasion numbers are most sensitive to the parameter q_v that gives the enhancement of HIV infection of opioid-addicted individuals. We concluded that "decreasing the HIV infection in drug users is the most efficient way to decouple the two epidemics". In this section, we want to see whether the results from [18] can be confirmed. Thus, in this section we compute the corresponding elasticities. To do that we set, $M_1 = \mu + d_u + \delta_u$, $M_2 = \mu + d_v + \gamma_v$, and $\beta_{v_2} = \int_0^\infty \beta_{v_2}(\tau)\pi(\tau)d\tau$. The analytical expressions of the derivatives of the invasion reproduction numbers with respect to the corresponding parameters are given as in the following.

Expressions for $\mathscr{R}_{ui}^2$

$$\frac{\partial \mathscr{R}_{ui}^2}{\partial \mathscr{R}_u} = \frac{M_1}{\mathscr{R}_v}\left[\frac{(k_s + q_v M_2(\mathscr{R}_v - 1)\Pi)}{(M_1 + q_v M_2(\mathscr{R}_v - 1))k_s} + \frac{\Pi q_u(\mathscr{R}_v - 1)}{k_s}\right],$$
$$\frac{\partial \mathscr{R}_{ui}^2}{\partial \mathscr{R}_v} = M_1\mathscr{R}_u\left[\frac{\Pi q_u}{k_s\mathscr{R}_v^2} + \frac{q_v M_2\Pi}{\mathscr{R}_v^2(M_1 + q_v M_2(\mathscr{R}_v - 1))k_s} - \frac{(k_s\mathscr{R}_v + q_v M_2(\mathscr{R}_v - 1)\Pi)(q_v M_2 k_s)}{\mathscr{R}_v(M_1 + q_v M_2(\mathscr{R}_v - 1))^2 k_s^2}\right],$$
$$\frac{\partial \mathscr{R}_{ui}^2}{\partial q_u} = \frac{\Pi M_1\mathscr{R}_u(\mathscr{R}_v - 1)}{k_s\mathscr{R}_v},$$
$$\frac{\partial \mathscr{R}_{ui}^2}{\partial q_v} = \frac{M_1 M_2\mathscr{R}_u(\mathscr{R}_v - 1)(M_1\Pi - k_s)}{\mathscr{R}_v[M_1 + q_v M_2(\mathscr{R}_v - 1)]^2}.$$

Expressions for $\mathscr{R}^1_{vi}$

$$\frac{\partial \mathscr{R}^1_{v_i}}{\partial \mathscr{R}_v} = \frac{M_2(k_s + q_v\delta_u(\mathscr{R}_u - 1)[\int_0^\infty \sigma(\tau)\pi(\tau)d\tau])}{\mathscr{R}_u k_s M_2 + \mathscr{R}_u q_u(\mathscr{R}_u - 1)M_1[k_s - \delta_u \int_0^\infty \sigma(\tau)\pi(\tau)d\tau]},$$

$$\frac{\partial \mathscr{R}^1_{v_i}}{\partial \mathscr{R}_v} = \frac{A_1B_1 - A_2B_2}{A_1^2},$$

$$\frac{\partial \mathscr{R}^1_{v_i}}{\partial q_v} = \frac{M_2\mathscr{R}_v\delta_u[\int_0^\infty \sigma(\tau)\pi(\tau)d\tau](\mathscr{R}_u - 1) + \beta_{v_2}(M_2(\mathscr{R}_u - 1) + q_u(\mathscr{R}_u - 1)\mathscr{R}_u M_1)}{\mathscr{R}_u[k_s M_2 + q_u(\mathscr{R}_u - 1)M_1(k_s - \delta \int_0^\infty \sigma(\tau)\pi(\tau)d\tau)]},$$

$$\frac{\partial \mathscr{R}^1_{v_i}}{\partial q_u} = \frac{A_1C_1 - A_2C_2}{A_1^2},$$

Where,

$$A_1 = k_s M_2 + q_u(\mathscr{R}_u - 1)M_1[k_s - \delta_u \int_0^\infty \sigma(\tau)\pi(\tau)d\tau],$$

$$A_2 = M_2\frac{\mathscr{R}_v}{\mathscr{R}_u}(k_s + q_v\delta_u[\int_0^\infty \sigma(\tau)\pi(\tau)d\tau](\mathscr{R}_u - 1)) + \frac{\beta_{v_2}}{\mathscr{R}_u}[q_v(M_2(\mathscr{R}_u - 1) + q_u(\mathscr{R}_u - 1)^2 M_1) + q_u(\mathscr{R}_u - 1)M_1],$$

$$B_1 = M_2\mathscr{R}_v\left(\frac{-k_s}{\mathscr{R}_u^2} + \frac{q_v\delta_u\int_0^\infty \sigma(\tau)\pi(\tau)d\tau}{\mathscr{R}_u^2}\right) + \frac{\beta_{v_2}}{\mathscr{R}_u^2}\left(q_v M_2 + q_v q_u M_1(\mathscr{R}_u^2 - 1) + M_1 q_u\right),$$

$$B_2 = q_u M_1(k_s - \delta_u \int_0^\infty \sigma(\tau)\pi(\tau)d\tau),$$

$$C_1 = \beta_{v_2} M_1(\mathscr{R}_u - 1),$$

$$C_2 = (\mathscr{R}_u - 1)M_1[k_s - \delta_u \int_0^\infty \sigma(\tau)\pi(\tau)d\tau].$$

To determine the best control measures, knowledge of the relative importance of the different parameters responsible for transmission is useful. Elasticity is a measure of the relative change of a quantity Q with respect to the parameter p, and it is defined as follows:

$$\varepsilon_p^Q = \frac{\partial Q}{\partial p}\frac{p}{Q}.$$

We denote the elasticities of the invasion numbers with respect to the reproduction numbers as follows:

$$A = \frac{\partial \mathscr{R}^2_{u_i}}{\partial \mathscr{R}_u}\frac{\mathscr{R}_u}{\mathscr{R}^2_{u_i}} \qquad B = \frac{\partial \mathscr{R}^2_{u_i}}{\partial \mathscr{R}_v}\frac{\mathscr{R}_v}{\mathscr{R}^2_{u_i}} \qquad C = \frac{\partial \mathscr{R}^1_{v_i}}{\partial \mathscr{R}_u}\frac{\mathscr{R}_u}{\mathscr{R}^1_{v_i}} \qquad D = \frac{\partial \mathscr{R}^1_{v_i}}{\partial \mathscr{R}_v}\frac{\mathscr{R}_v}{\mathscr{R}^1_{v_i}}$$

Table 8. Parameter estimation results of multi-scale fitting problem (3.40) to multi-scale data via multi-scale models (3.1) and (M_2).

Parameter	Estimated Value	Units
β_u	0.385676	1/time
β_{v_1}	0.0551	1/time
β_0	0.00011046	1/time
B	15318.9	vRNA/ml
δ_u	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 $\times$ 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
λ	22843.6	CD4 count/(time $\times$ ml)
d	0.0766824	1/time
β_1	2.02785e-05	vRNA/(CD4 count $\times$ time)
δ	0.725266	1/time
π	8465.63	vRNA/(CD4 count $\times$ time)
$\mathscr{R}_u$	2.76	Unitless
$\mathscr{R}_v$	1.1	Unitless

Figure 4 gives the elasticities of the invasion number with respect to the reproduction numbers. One immediate observation is that these elasticities are not all positive. In particular, the elasticity of $\mathscr{R}^1_{v_i}$ with respect to $\mathcal{R}_u$ is negative which means that increase in opioid addicted individuals decreases the invasibility of HIV and may decouple the two pandemics. The negative sign is in a sense natural

because it signifies competition between the two diseases. At the same time Figure 4 reveals that the elasticity of $\mathscr{R}^2_{u_i}$ with respect to $\mathcal{R}_v$ is positive but very small. This means that an increase in HIV-infected individuals barely affects the invasion capabilities of the opioid affected. Looking at Table 9 the largest number in magnitude is the elasticity of $\mathscr{R}^2_{u_i}$ with respect to q_v. This is the same elasticity that in [18] had maximal magnitude. This suggests that the key to controlling these two pandemics is to decrease the HIV infection in drug users – this is the point where the control measures will have maximum impact. Decreasing q_v will increase the invasion capabilities of opioid addiction. To counter that effect, we have to simultaneously control the opioid epidemic.

Parameters not involved in the reproduction numbers but potentially important for control are q_u and q_v. We denote the elasticities of the invasion numbers with respect to these parameters as follows:

$$W = \frac{\partial \mathscr{R}^1_{v_i}}{\partial q_u}\frac{q_u}{\mathscr{R}^1_{v_i}} \quad X = \frac{\partial \mathscr{R}^1_{v_i}}{\partial q_v}\frac{q_v}{\mathscr{R}^1_{v_i}} \quad Y = \frac{\partial \mathscr{R}^2_{u_i}}{\partial q_u}\frac{q_u}{\mathscr{R}^2_{u_i}} \quad Z = \frac{\partial \mathscr{R}^2_{u_i}}{\partial q_v}\frac{q_v}{\mathscr{R}^2_{u_i}}$$

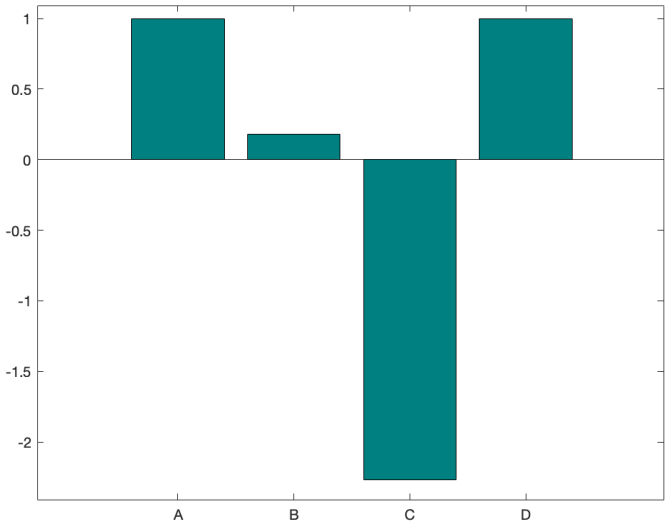

Figure 4. Figure shows elasticities of the invasion numbers with respect to the reproduction numbers. The parameters used are given in Table 8.

Table 9. Table shows elasticities of the invasion numbers with respect to the parameters q_u, q_v and δ_u. The parameters used are given in Table 8.

Elasticity	Estimated Value
W	-0.8097
X	0.0023
Y	0.0014
Z	-187.7127

4. Discussion and conclusions

In this paper we formulate a multi-scale immuno-epidemiological model of HIV-Opioid epidemics coinfection using the nested approach [20]. The system consists of a within-host model of ordinary differential equations describing the dynamics within the co-affected individuals. The within-host model is linked with an epidemiological model via epidemiological parameters. The multi-scale model here is an extension of the ODE model considered in [18].

To estimate the parameters for the within-host model, the viral load and CD4 measurements obtained from [23] are utilized. Structural identifiability analysis is performed for the estimated parameters, and we conclude that model (M_2) is not structurally identifiable as developed. Validation of the model (M_2) with data suggests that $\beta = 0$. Then the within-host model with $\beta = 0$, is structural identifiable if we fix the drug-infusion and the viral clearance rates. Furthermore the model becomes practically identifiable, when the opioid clearance rate and saturation constant are fixed. We fit the full multi-scale model to the within-host data [23] and the number of AIDS diagnoses in the US, number of HIV deaths and number of opioid deaths. We choose to fit the within-host and between-host models simultaneously to all five data sets because our prior research suggests that simultaneous fitting improves the identifiability of the parameters [26]. This allows us to determine the parameters of the full model.

We study the multi-scale immuno-epidemiological model analytically. We compute the reproduction numbers of HIV and opioid epidemics. We show that the unique disease-addiction-free equilibrium is locally stable if both reproduction numbers are below one and unstable if an least one reproduction number is grater than one. If the reproduction number of HIV is greater than one, there is a unique equilibrium corresponding to HIV only. We show further that the HIV only equilibrium is locally asymptotically stable if the opioid invasion number is smaller than one, and it is unstable if the opioid invasion number is greater than one. Similarly, if the reproduction number of the opioid is greater than one there exists a unique equilibrium corresponding to the opioid epidemic only. We show that the opioid-only equilibrium is locally asymptotically stable if the HIV invasion number is smaller than one. If the HIV invasion number is greater than one, the opioid only equilibrium is unstable. Simulations suggest that there is an interior equilibrium potentially under the condition that both invasion numbers are larger than one; however proving that analytically has not been possible. In the ODE case [18], simulation suggested that the interior equilibrium may not be unique. Thus we expect possible non-uniqueness in this case too.

Using the fitted parameters we compute the elasticities of the invasion numbers with respect to the reproduction numbers as well as with respect to some of the parameters. The elasticities of the invasion number of the opioid with respect to the reproduction number of HIV is very small and positive. In terms of control the HIV epidemic has very little impact on the invasion capabilities of the opioid epidemic. On the other hand, the elasticity of the invasion number of HIV with respect to the opiod reproduction number is very large and negative suggesting that the opioid epidemic has a big impact on the invasion capabilities of HIV. In particular decreasing HIV prevalence increases the opioid epidemic invasion capabilities and strengthens the opioid epidemic. This is what we observe in reality – HIV incidence and deaths drop but the opioid deaths rise in numbers. The largest in modulus elasticity is that of the opioid invasion number with respect to q_v – the coefficient of enhancement of HIV infection of opioid affected individuals. This coefficient is already very large – we estimate it at 30, but it also has a very large effect on the invasion capabilities of the opioid epidemic. We find that this elasticity

is the largest also in our previous article [18] and we surmise that targeting HIV infection of opioid affected individuals will have the largest impact on the both epidemics. Decreasing HIV-infection of opioid affected individuals will strengthen the invasion capabilities of the opioid epidemic and should be coupled with systematic control of the opioid epidemic alone. Thus, even though our model is different and our data are different in this article compared to [18], we reach similar conclusion about control strategies for the coupled epidemics.

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Conflict of interest

All authors declare that there is no conflict of interest.

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Appendix

Table A. HIV deaths, AIDS diagnoses and opioid deaths. Resources are [35] and [36].

Years	HIV deaths	AIDS cases	Opioid deaths
1999	—	—	8050
2000	—	38,285	8407
2001	—	36,922	9496
2002	—	36,726	11,920
2003	—	37,317	12,940
2004	—	36,220	13,756
2005	—	34,261	14,918
2006	—	32,790	17,545
2007	—	31,984	18,516
2008	18,525	31,384	19,582
2009	18,043	30,187	20,422
2010	16,742	27,401	21,089
2011	16,300	25,620	22,784
2012	16,018	24,684	23,166
2013	15,908	23,656	25,052
2014	16,145	19,313	28,647
2015	15,860	18,590	33,091
2016	16,395	18,375	42,249
2017	16,358	17,749	47,600
2018	15,483	17,113	46,802