

**ARTICLE TYPE****Reduction of discrete-time infectious disease models**

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Henares, Spain. Email: rafael.bravo@uah.es**Abstract**

In this work we propose the construction of discrete-time systems with two time scales in which infectious diseases dynamics are involved. We deal with two general situations. In the first, we consider that individuals affected by the disease move between generalized sites on a faster time scale than the dynamics of the disease itself. The second situation includes the dynamics of the disease acting faster together with another slower general process.

Once the models have been built, conditions are established so that the analysis of the asymptotic behavior of their solutions can be carried out through reduced models. This is done using known reduction results for discrete-time systems with two time scales. These results are applied in the analysis of two new models. The first of them illustrates the first proposed situation, being the local dynamics of the SIS-type disease. Conditions are found for the eradication or global endemicity of the disease. In the second model, a case of co-infection with a primary disease and an opportunistic disease is treated, the latter acting faster than the former. Conditions for eradication and endemicity of co-infection are proposed.

**KEYWORDS:**

discrete-time model; time scales; metapopulation; compartmental disease models

**1 | INTRODUCTION**

Mathematical models in epidemiology already have a long history. Recent events worldwide have shown that they are a very useful tool, both theoretical and practical. It has been widely understood that their contribution in the management of epidemics is practically essential.

Most mathematical models in epidemiology are built in continuous time. However, so far this century, the number of discrete-time models has been growing steadily. Important authors within this area have published articles presenting discrete-time

<sup>0</sup>**Abbreviations:** DFE, Disease free equilibrium; EE, Endemic equilibrium; GAS, Globally asymptotically stable; LAS, Locally asymptotically stable; SIS, Susceptible–Infectious–Susceptible; SEIRS, Susceptible–Exposed–Infectious–Recovered–Susceptible

models<sup>1,2,5,13,28,29,14</sup>. The recognized advantages of discrete-time models over continuous-time models have to do with their better implementation in numerical simulations and their better adaptation to data, normally collected periodically<sup>16</sup>.

In basic epidemiological models demographic and spatial issues are not considered<sup>19,6</sup>. Individuals in the population are classified into large compartments that reflect their disease status (Susceptible, Exposed, Infected, Recovered, etc.). The introduction of demography, or space, or both is a very natural second step to gain realism. These models can entail the existence of different time scales when the different processes involved in the dynamics act at speeds of different order.

In this work we propose a general framework for discrete-time models with two time scales in which the dynamics of some infectious disease intervene. The type of discrete-time model with two time scales that we use can be seen developed in<sup>7,23</sup>. The slow process is assumed to be defined by a map  $L$  that gives its result after a slow unit of time. In turn, the effect of the fast process on a fast unit of time is defined by another map  $F$ . In a slow unit of time, the fast process acts  $k$  times, where  $k$  represents the ratio between the time scales. The model that combines the two processes is defined on the slow time scale considering that the fast process acts  $k$  times followed by an episode of the slow process. As a function of  $L$  and  $F$ , and denoting by  $X$  the state vector of the population and by  $t$  the slow time variable, the model has the following expression

$$X(t+1) = L\left(F^{(k)}(X(t))\right), \quad (1)$$

where the superscript  $(k)$  represents the  $k$ -th iterate. We will see that the existence of time scales in the same system allows us, in some cases, to simplify its analysis.

We want to deal here with two basic situations: (I) *Slow disease dynamics* (SDD), it includes rapid transitions of individuals between sites, understood in a generalized way, together with an epidemiological or eco-epidemiological process that acts on a slower time scale; (II) *Fast disease dynamics* (FDD), it includes the epidemiological process acting this time on the fast scale, while a second process does so on the slow time scale.

The aim of this work is the construction and analysis of discrete-time models with two time scales that include the dynamics of a disease. The analysis of the models is done with the help of known reduction results<sup>23,7</sup>. These results propose, from the initial models, new reduced models, which are easier to study. In addition, they establish how to study some relevant issues of the asymptotic behavior of the solutions of the initial model from this same study in the reduced model. As an illustration of this, two new models are presented. In one of them the dynamics of the disease develops on the slow time scale, and in the other on the fast time scale.

Although it is recognized and systematized the multiscale modeling in epidemiology<sup>12,15</sup>, few of these models end up taking the form of a single system, continuous or discrete, including two time scales. In continuous time, we could cite a few recent works<sup>17,18,22,25</sup> and, in discrete time, our publications<sup>8,9,10,11</sup>.

To introduce situation (I), SDD, with fast movements we will use models of metapopulations. These are very useful mathematical models to understand the spatio-temporal spread of infectious diseases<sup>27,3,4</sup>, either in humans, animals or plants. In them the space is considered discrete, divided into a finite number of sites. These sites, depending on the model, can range from a house or small natural environment to a country or a continent. Usually, in these models, the movements are considered explicitly. On the one hand, locally, in each site, the model defines the dynamics of the disease together with demography and, on the other hand, globally, the movements of individuals between sites. A detailed review of this topic in continuous time, without considering time scales, is carried out in<sup>3</sup>. In<sup>11</sup> a discrete-time model with two time scales of the mentioned characteristics is presented and analyzed. The local model used is a SEIRS model and the movement rates are considered constant.

Returning to the second basic situation, FDD, fast disease dynamics together with another slower process, we try to establish a framework, as general as possible, in which already published works<sup>8,9,10</sup> can be included. In the first two of these works, a parasite affects one of the two populations that make up the community, and in the third, the parasite affects both. The fast part of the models describes the dynamics of the disease associated with the parasite and the slow part includes the demography of the community, in which individuals are distinguished by their disease status. In the proposed framework we consider a general compartmental model for the dynamics of the disease and a general process for slow dynamics represented by a general map.

This work is organised as follows. First, in Section 2 the general models of the SDD and FDD types are built. Also, particular cases of each of these two types of models are proposed, and will be studied later. Section 3 is dedicated to the construction of the reduced models associated with the original models of Section 2, and to state the results that relate the asymptotic behavior of the original and reduced models. Sections 4 and 5 carry out the analysis of the particular models proposed in Section 2 with the techniques presented in Section 3. Finally, Section 6 presents some conclusion and perspectives.

## 2 | MODELS

We consider discrete-time models with two time scales (1). This type of model can be understood in a general way as containing two processes, one that acts on the fast scale, represented by  $F$ , and the other on the slow scale, represented by  $L$ . Thus, we will talk about fast process and slow process, and also about fast dynamics and slow dynamics.

In this section we will present two types of discrete-time models with two time scales. The first type, called SDD, includes as a rapid process the transitions of individuals between spatial sites or, more generally, between different activities that establish a partition of the set of individuals. Along with this rapid process, the dynamics of an infectious disease is included as a slow process. The second type of model, called FDD, considers the dynamics of a disease as a fast process, and a general slow process, which may be related to demography, behavior, another disease, etc.

## 2.1 | SDD: Fast movements-Slow disease

The population can be considered divided into  $m$  groups, which we call sites thinking of a kind of *generalized metapopulation*. In many applications these sites will represent actual spatial sites. Individuals move between the  $m$  sites. At each site, the disease dynamics is described by the same model, in which parameters values can change to fit the local situation. We consider the disease model as a general compartmental model. The generic notation for each of the compartments of the model is  $C$ , and the set of all of them will be denoted  $\mathcal{C}$ .

For  $C \in \mathcal{C}$ ,  $j \in \{1, \dots, m\}$ , and  $t \in \{0, 1, 2, \dots\}$ , we define the state variables of the model as

$$n_j^C(t) = \text{density of individuals with disease state } C, \text{ at site } j, \text{ at time } t.$$

The total population at site  $j$  is denoted

$$n_j = \sum_{C \in \mathcal{C}} n_j^C.$$

The vector of individuals in compartment  $C \in \mathcal{C}$  across the  $m$  sites is denoted  $\bar{n}_C = \text{col}(n_1^C, \dots, n_m^C)$ . The population state vector is called

$$X = \text{col}(\bar{n}_C)_{C \in \mathcal{C}}.$$

In the next section, reduced models will be built associated with the models with two time scales that we are presenting in this section. The state variables of these reduced models will be, in the SDD case, the total number of individuals in each disease compartment across all sites. For each  $C \in \mathcal{C}$

$$n^C = \sum_{j=1}^m n_j^C(t),$$

that we collect in the vector of global variables

$$Y = \text{col}(n^C)_{C \in \mathcal{C}},$$

whose sum yields the total number of individuals in the population

$$N = \sum_{C \in \mathcal{C}} n^C = \sum_{j=1}^m n_j.$$

We can express the global variables in terms of the state variables with the help of matrix  $U = \text{diag}(\bar{1}, \dots, \bar{1}) \in \mathbb{R}_+^{p \times p \cdot m}$ , where  $\bar{1} = (1, \dots, 1) \in \mathbb{R}_+^m$  is a row vector, and  $p$  is the number of disease compartments, i.e. the cardinal of set  $\mathcal{C}$ :

$$Y = UX.$$

Once we have established the necessary notations, we first define the fast process of the model, which is associated with the movements of individuals between sites. Although we could define movement rates between sites more generally, we are going to assume that they depend just on global variables  $Y$ . This will ensure the existence of a reduced model with good properties. For each disease compartment, movements are represented by a regular stochastic matrix depending on  $Y \in \mathbb{R}_+^p$ :

$$M^C(Y) \in \mathbb{R}_+^{m \times m}, \text{ for every } C \in \mathcal{C}.$$

The movements of the whole population are then defined through the following matrix

$$M(Y) = \text{diag} \left( M^C(Y) \right)_{C \in \mathcal{C}} \in \mathbb{R}_+^{p \cdot m \times p \cdot m}.$$

The state  $X$  of the population after one movement episode is defined by the following map

$$F(X) = M(UX)X,$$

that represents the fast process in system (1).

The slow process corresponds to the dynamics of the disease. As we have already discussed, we consider the same disease model, possibly with different parameter values, at each site. Due to the order that we have established in the state variables, it is not obvious how to write the global dynamics of the disease from the local dynamics. Therefore, we will simply denote  $D$  the map that defines a disease episode along a slow unit of time, and write model (1), for the SDD case, in the following form:

$$X(t+1) = D \left( F^{(k)}(X(t)) \right).$$

The effect of the fast process is to exchange individuals between sites while maintaining their disease state. This implies that the global variables,  $n^C$ , are invariant for movements between sites. It can be shown in the following form

$$UF(X) = UM(UX)X = UX.$$

A consequence of it is that the  $k$ -th iterate of  $F$  can be expressed in terms of the  $k$ -power  $M(Y)^k$  of matrix  $M(Y)$ :

$$F^{(k)}(X) = M(UX)^k X,$$

and so the complete model, for the SDD case, can be expressed as:

$$X(t+1) = D\left(M\left(UX(t)\right)^k X(t)\right). \quad (2)$$

A model that fits the framework of (2) is analyzed in<sup>11</sup>. The local dynamics is of SEIRS type and the movements are made between two sites.

*SIS model in an m-site environment.*

Next, we introduce an example of model (2). We generally assume that the individuals in the population move between  $m$  different sites on a faster time scale than that associated with the local dynamics of the disease. We assume that the disease develops locally according to a SIS model<sup>1</sup> with specific parameters for each site.

As we are considering only two disease compartments, susceptible and infective, we can simplify the notation that we have presented in a general way. Thus, the system state variables,  $S_j$  and  $I_j$  ( $j = 1, \dots, m$ ), represent the density of susceptible and infective individuals, respectively, at site  $j$ . The total population at site  $j$  is  $n_j = S_j + I_j$ . We denote  $\bar{n}_S = \text{col}(S_1, \dots, S_m)$ , and  $\bar{n}_I = \text{col}(I_1, \dots, I_m)$ , the state vectors of susceptible and infective individuals across the  $m$  sites. The population state vector is

$$X = \text{col}(S_1, \dots, S_m, I_1, \dots, I_m).$$

The global variables, that will serve as state variables of the associated reduced system, are the total number of susceptible individuals  $S = \sum_{j=1}^m S_j$  and the total number of infective individuals  $I = \sum_{j=1}^m I_j$ . Thus, the vector of global variables is as follows

$$Y = \text{col}(S, I),$$

The fast process, movements between sites, is defined by two regular stochastic matrices,  $M^S$  and  $M^I$ , which represent the movements of susceptible and infective individuals, respectively. As we mentioned above, these matrices could be considered dependent on global variables, but in this case we assume that they are constant:

$$F(X) = (M_S \bar{n}_S, M_I \bar{n}_I) = MX,$$

where  $M = \text{diag}(M_S, M_I)$ . Its  $k$ -th iterate is expressed as  $F^{(k)}(X) = M^k X$ .

The slow process, the disease dynamics, is defined locally, i.e., in each site  $j \in \{1, \dots, m\}$ , by an SIS model<sup>1</sup>:

$$\begin{aligned} S_j(t+1) &= S_j(t) - \beta_j \frac{S_j(t)I_j(t)}{S_j(t) + I_j(t)} + \gamma_j I_j(t), \\ I_j(t+1) &= I_j(t) + \beta_j \frac{S_j(t)I_j(t)}{S_j(t) + I_j(t)} - \gamma_j I_j(t), \end{aligned} \quad (3)$$

where we assume that transmission and recovery coefficients satisfy  $\beta_j, \gamma_j \in (0, 1)$ . By rearranging the equations (3) to adjust the order of the state variables in  $X$ , we can define the map  $D$  in (2) that represents the slow process:

$$D(X) = \left( S_1 - \beta_1 \frac{S_1 I_1}{S_1 + I_1} + \gamma_1 I_1, \dots, S_m - \beta_m \frac{S_m I_m}{S_m + I_m} + \gamma_m I_m, I_1 + \beta_1 \frac{S_1 I_1}{S_1 + I_1} - \gamma_1 I_1, \dots, I_m + \beta_m \frac{S_m I_m}{S_m + I_m} - \gamma_m I_m \right) \quad (4)$$

Finally, the complete two time scale model takes the form of system (2)

$$X(t+1) = D \left( M^k X(t) \right). \quad (5)$$

## 2.2 | FDD: Slow process-Fast disease

In this case we are going to keep to the largest possible framework. In fact, except for the fact that the fast process is represented by the dynamics of a disease, the approach corresponds to the general one of a discrete-time system with two time scales<sup>7,23</sup>.

Some models of this type already exist in the literature. In<sup>8</sup>, the slow process corresponds to the demography associated to a predator-prey community. A disease affects the prey population. The fast process causes prey to change disease status, while leaving predators unchanged. A similar model is treated in<sup>9</sup>, where the relationship of the community is one of competition. In<sup>10</sup>, on a similar scheme, the fast dynamics is more complicated because the populations that make up the community share the disease.

To establish a broad framework we consider the population divided into groups, and each of these groups divided into subgroups. The choice of groups and subgroups is linked to the two processes that take place on different time scales. The fast process occurs within each group with transfers of individuals between the corresponding subgroups. On the other hand, the slow process has to do with transfers between groups.

The state of the population at time  $t$  with  $p$  groups is represented by a vector

$$X(t) := \text{col}(\bar{n}_1(t), \dots, \bar{n}_p(t)) \in \mathbb{R}_+^{N \times N},$$

where vector

$$\bar{n}_i(t) := \text{col} \left( n_1^i(t), \dots, n_{N^i}^i(t) \right) \in \mathbb{R}_+^{N^i}, \quad \text{for } i = 1, \dots, p,$$

represents the state of the  $i$  group which is divided into  $N^i$  subgroups.  $N = N^1 + \dots + N^p$  is the number of state variables of the model.

In<sup>8</sup> there are two groups, prey and predators, and the prey group is divided into two subgroups, susceptible and infected individuals, while the predator group itself constitutes its only subgroup. The fast process, disease dynamics, concerns the subgroups and the slow process, demography, will be finally related to the groups prey and predators. A similar structure is used in<sup>8</sup>. In<sup>10</sup>, still there are two groups, but each of them is subdivided into two subgroups because the disease affects in this case both populations.

Starting from model (1), if we call  $D$  the map, linked to the dynamics of the disease, that defines the fast process, and we keep the notation  $L$  for the map that represents the general slow process, then the complete model, for the FDD case, has the following form:

$$X(t+1) = L\left(D^{(k)}(X(t))\right). \quad (6)$$

*Opportunistic disease model.*

To illustrate the case FDD, fast disease dynamics, we consider a discrete-time version of a particular model of coinfection that it is studied by means of a continuous time model in<sup>20</sup>. The population is affected by a primary disease and those individuals infected by it can then contract a second so-called opportunistic disease. Coinfected individuals can recover from the opportunistic disease and only then from the primary disease. We divide the population being studied into three classes labeled  $S$ ,  $I$ , and  $C$ . Let  $S(t)$  denote the number of individuals who are susceptible to the primary disease at time  $t$ .  $I(t)$  denotes the number of infected individuals by the primary disease that are susceptible to, but not yet infected by, the opportunistic disease. Finally,  $C(t)$  denotes the number of coinfecting individuals, that is, those who have been infected by both diseases.

The discrete-time model includes the dynamics of each disease at a different time scale. The slow one is associated to the primary disease, and the fast one to the opportunistic disease. We consider no demography. The opportunistic disease dynamics is described by means of an SIS model,<sup>1</sup> with frequency-dependent transmission and constant recovery fraction. Let  $\beta^{op}$ ,  $\gamma^{op} \in (0, 1)$  be, respectively, the transmission and recovery coefficients. The map defining the dynamics of the opportunistic disease at the fast time scale is then

$$(I, C) \rightarrow \left( I - \frac{\beta^{op} IC}{I + C} + \gamma^{op} C, C + \frac{\beta^{op} IC}{I + C} - \gamma^{op} C \right).$$

The primary disease dynamics is also represented by an SIS model. Susceptible individuals can be infected, at different rates, by infected and coinfecting individuals. Let  $\beta_I$ ,  $\beta_C \in (0, 1)$  be the respective transmission coefficients. The recovery coefficient is  $\gamma \in (0, 1)$ . The corresponding map defining its dynamics at the slow time scale, for constant  $C$ , is



$$(S, I) \rightarrow \left( S - \frac{(\beta_I I + \beta_C C)S}{S + I + C} + \gamma I, I + \frac{(\beta_I I + \beta_C C)S}{S + I + C} - \gamma I \right).$$

Let us next write the two time scales discrete-time system in the form of system (6). Considering that  $S$  does not change at the fast time scale, we define the map  $D$  representing the fast dynamics

$$D(S, I, C) = \left( S, I - \frac{\beta^{op} I C}{I + C} + \gamma^{op} C, C + \frac{\beta^{op} I C}{I + C} - \gamma^{op} C \right), \quad (7)$$

and, considering the changes of  $C$  only at the fast time scale, we define the map  $L$  to describe the slow dynamics

$$L(S, I, C) = \left( S - \frac{(\beta_I I + \beta_C C)S}{S + I + C} + \gamma I, I + \frac{(\beta_I I + \beta_C C)S}{S + I + C} - \gamma I, C \right). \quad (8)$$

Denoting  $X(t) = (S(t), I(t), C(t))$ , the proposed model has the following form:

$$X(t+1) = L(D^{(k)}(X(t))). \quad (9)$$

### 3 | REDUCTION OF THE MODELS

In this section we present the reduction techniques of the models (2) and (6) introduced in Section 2. These techniques require two steps. The first consists in the construction of a reduced model that is, therefore, easier to study than the original model. This model will necessarily only give us approximate information about the initial model. The second necessary step in the reduction is to specify what we can find out about the initial model through the study of the reduced model.

The characteristic of the models that allows us to address their reduction is the existence of two time scales. Discrete-time models like (2) and (6) propose the superposition of two processes, one slow and one fast. The unit of time chosen to formulate the model is the one associated with the slow process. Thus, the action of the fast process in a slow unit of time is reflected in the iteration of the map that defines it. The arguments to approximately reduce the initial model will be supported by the possible existence of a limit for these iterates. This limit will decide part of the dynamics of the initial model, leaving the other part to be leaded by the slow process. The reduced model can be seen as a model in which the fast process has already acted and which reflects what remains to be decided by the slow process. Obviously, this can only be an approximation, since the passage to the limit is equivalent to considering that the ratio between the time scales tends to infinity.

The reduction process is easier to understand in the case of SDD models. The hypotheses for its reduction are already included in the construction of the models (2). With the help of these hypotheses we will formulate, in a more abstract way, those corresponding to the FDD models (6). These hypotheses are generally not easy to test. We will see, however, how to do it in the model on opportunistic diseases (9).

### 3.1 | SDD: Fast movements-Slow disease

We start with the reduction of SDD. In system (2) we assume that both  $D$  and  $M$  are smooth enough.

As we have commented before, we are going to first look for the limit of the iterates of the fast process. In this case, it suffices to calculate the limit of the powers of the matrix  $M(UX)$ . We have that  $M(UX) = \text{diag} \left( M^C(UX) \right)_{C \in \mathcal{C}} \in \mathbb{R}_+^{p \cdot m \times p \cdot m}$  and that  $M^C(UX)$  is a regular stochastic matrix for any  $X \in \mathbb{R}_+^{p \cdot m}$  and  $C \in \mathcal{C}$ .

With the help of the Perron-Frobenius theorem we know that 1 is the strictly dominant eigenvalue of  $M^C(UX)$ ,  $\bar{1} = (1, \dots, 1) \in \mathbb{R}_+^m$  its associated row left-eigenvector, and there exists a unique  $\bar{v}^C(UX) = (v_1^C(UX), \dots, v_m^C(UX)) \in \mathbb{R}_+^m$  associated strictly positive column right-eigenvector whose entries sum up to 1:

$$M^C(UX)\bar{v}^C(UX) = \bar{v}^C(UX), \quad \bar{1}\bar{v}^C(UX) = 1. \quad (10)$$

Moreover, the limit of the powers of matrices  $M^C(UX)$  and  $M(UX)$  are easily expressed in terms of these eigenelements:

$$\lim_{k \rightarrow \infty} \left( M^C(UX) \right)^k = \bar{v}^C(UX)\bar{1},$$

from where, taking into account that  $U = \text{diag} \left( \bar{1}, \dots, \bar{1} \right)$  and calling  $V(UX) := \text{diag} \left( \bar{v}^C(UX) \right)_{C \in \mathcal{C}}$ , we obtain

$$\lim_{k \rightarrow \infty} \left( M(UX) \right)^k = V(UX)U. \quad (11)$$

From system (2) to arrive at expression (11), it is enough to calculate the eigenvectors  $\bar{v}^C(UX)$ . These eigenvectors have a clear interpretation. The fast process, the movements between sites, tends to distribute the individuals of each compartment  $C \in \mathcal{C}$  among the sites according to the proportions indicated by  $\bar{v}^C(UX)$ . For each compartment  $C$ , the fast dynamics keeps its total density constant. These constants are nothing but what we called global variables,  $Y = UX$ . Therefore, the fast process drives the distribution between sites but does not act on the global densities. The dynamics of these global variables will be driven by the slow process and will be represented by a reduced system.

Reaching this reduced model is now straightforward. If in system (2) we replace the iterates of the fast process by its limit,  $X(t+1) = D \left( V(UX(t))U X(t) \right)$ , we arrive at the following reduced system for the global variables

$$Y(t+1) = UD \left( V(Y(t))Y(t) \right) \quad (12)$$

The fast process effect is already included in the parameters of this new reduced system.

The following theorem, that establishes the relationship between the asymptotic behavior of the solutions of system (12) and system (2), is published in<sup>21</sup> as a special case of the general results appeared in<sup>23</sup>. In order to make the statement clearer, it is exposed in the case of equilibrium points, but an analogous result is valid in the case of periodic solutions.

**Theorem 1.** Let  $Y^* \in \mathbb{R}_+^p$  be a hyperbolic equilibrium point of system (12). Then, there exists an integer  $k_0 \geq 0$  such that for all  $k \geq k_0$  system (2) has an equilibrium point  $X_k^*$  which is hyperbolic and satisfies

$$\lim_{k \rightarrow \infty} X_k^* = X^*, \text{ with } X^* := D(V(Y^*)Y^*).$$

Moreover, the following holds:

1.  $X_k^*$  is asymptotically stable (resp. unstable) if and only if  $Y^*$  is asymptotically stable (resp. unstable).
2. Let  $Y^*$  be asymptotically stable and let  $X_0$  be such that the solution  $Y(t)$  to (12) corresponding to the initial data  $Y(0) = UX_0$  satisfies that  $\lim_{t \rightarrow \infty} Y(t) = Y^*$ . Then, for all  $k \geq k_0$ , the solution  $X(t)$  to (2) with  $X(0) = X_0$  satisfies that  $\lim_{t \rightarrow \infty} X(t) = X_k^*$ .

If the reduced model (12) has a hyperbolic equilibrium, the initial model (2), for  $k$  large enough, has a hyperbolic equilibrium that can be approximated by the expression  $D(V(Y^*)Y^*)$ . This expression is built from the equilibrium of the reduced system, the equilibrium distributions of the fast process and the map of the slow process. In addition, the stability of the equilibrium and its basin of attraction, if it is stable, can be studied in the reduced model.

I repeat that the same result is true for a periodic solution rather than an equilibrium.

*SIS model in an m-site environment. Reduced model.*

As an illustration of the reduction process that we have just presented, we are going to build the reduced model associated with model (5). To do this, we must start from the column right-eigenvectors whose entries sum up to 1 of the matrices  $M_S$  and  $M_I$ . Suppose that  $\bar{v}^S = \text{col}(v_1^S, \dots, v_m^S)$  and  $\bar{v}^I = \text{col}(v_1^I, \dots, v_m^I)$  are these vectors that verify  $M_S \bar{v}^S = \bar{v}^S$  and  $\bar{1} \bar{v}^S = 1$ , and  $M_I \bar{v}^I = \bar{v}^I$  and  $\bar{1} \bar{v}^I = 1$ , then the (2m)-dimensional system (5) has an associated 2-dimensional system, for the state variables  $S$  and  $I$  (total number of susceptible and infected individuals), with the form (12)

$$\begin{pmatrix} S(t+1) \\ I(t+1) \end{pmatrix} = Y(t+1) = UD(V(Y(t))Y(t)) = \begin{pmatrix} \bar{1} & \bar{0} \\ \bar{0} & \bar{1} \end{pmatrix} D\left(\begin{pmatrix} \bar{v}^S & \bar{0} \\ \bar{0} & \bar{v}^I \end{pmatrix} \begin{pmatrix} S(t) \\ I(t) \end{pmatrix}\right),$$

that yields the following system:

$$\begin{aligned} S(t+1) &= S(t) - \left( \sum_{j=1}^m \frac{\beta_j v_j^S v_j^I}{v_j^S S(t) + v_j^I I(t)} \right) S(t) I(t) + \left( \sum_{j=1}^m v_j^I \gamma_j \right) I(t), \\ I(t+1) &= I(t) + \left( \sum_{j=1}^m \frac{\beta_j v_j^S v_j^I}{v_j^S S(t) + v_j^I I(t)} \right) S(t) I(t) - \left( \sum_{j=1}^m v_j^I \gamma_j \right) I(t). \end{aligned} \tag{13}$$

### 3.2 | FDD: Slow process-Fast disease

We proceed with the reduction of the FDD model (6). For that, we establish hypotheses that allow us to reproduce the two characteristics of the SDD model that allowed its reduction. The first one is that the iterates of the fast process have a limit that decides part of the dynamics. The second is that the rest of the dynamics can be decided from a smaller number of variables, those that we have called global variables, that are invariant for the fast dynamics.

**Hypothesis 1.** The sequence of iterates of  $D$ ,  $\{D^{(k)}\}_{k \in \mathbb{N}}$ , converges pointwise on  $\Omega_N \subset \mathbb{R}_+^N$  to a map  $\bar{D} : \Omega_N \rightarrow \Omega_N$ , such that  $\bar{D} \in C^1(\Omega_N)$ .

**Hypothesis 2.** There exist a non-empty open subset  $\Omega_q \subset \mathbb{R}^q$  with  $q < N$  and two maps  $G : \Omega_N \rightarrow \Omega_q$  and  $E : \Omega_q \rightarrow \Omega_N$  with  $G \in C^1(\Omega_N)$ ,  $E \in C^1(\Omega_q)$ , such that the map  $\bar{D}$  can be expressed as  $\bar{D} = E \circ G$ .

Now, if we substitute the  $k$ -th iterate of  $D$  for its limit in the right-hand side of system (6),  $L(E \circ G(X(t)))$ , we see that we can obtain a reduced system for the global variables  $Y = G(X) \in \mathbb{R}^q$ :

$$Y(t+1) = (G \circ L \circ E)(Y(t)) := \bar{L}(Y(t)). \quad (14)$$

The reduction of the SDD case could also be thought through an  $E \circ G$  decomposition of the limit of the iterates of its fast process. In that case, the reduction would be done with  $E(Y) = V(Y)Y$  and  $G(X) = UX$ .

The following theorem,<sup>23</sup> contains a result with the same thesis as Theorem 1. On the other hand, to achieve it, it is necessary to impose some conditions on the convergence of the iterates of  $D$  that can be difficult to verify depending on the cases. The iterates of  $D$  and their differentials must converge uniformly on compact sets.

**Theorem 2.** Let us assume that  $D$  verify Hypotheses 1 and 2, and that

$$\lim_{k \rightarrow \infty} D^{(k)} = \bar{D} \text{ and } \lim_{k \rightarrow \infty} d(D^{(k)}) = d(\bar{D})$$

uniformly on any compact set  $K \subset \Omega_N$ .

Let  $Y^* \in \Omega_q$  be a hyperbolic equilibrium point of system (14). Then, there exists an integer  $k_0 \geq 0$  such that for each  $k \geq k_0$  system (6) has an equilibrium point  $X_k^*$  which is hyperbolic and satisfies

$$\lim_{k \rightarrow \infty} X_k^* = X^*, \text{ with } X^* = (L \circ E)(Y^*).$$

Moreover, the following holds:

1.  $X_k^*$  is asymptotically stable (resp. unstable) if and only if  $Y^*$  is asymptotically stable (resp. unstable).

2. Let  $Y^*$  be asymptotically stable and let  $X_0 \in \Omega_N$  be such that the solution  $Y(t)$  to (14) corresponding to the initial data  $Y(0) = G(X_0)$  satisfies that  $\lim_{t \rightarrow \infty} Y(t) = Y^*$ . Then, for all  $k \geq k_0$ , the solution  $X(t)$  to (6) with  $X(0) = X_0$  satisfies that  $\lim_{t \rightarrow \infty} X(t) = X_k^*$ .

The theorem states that, for large enough time scales ratio, we can approximate equilibrium points of the complete system and study their stability, together with their domains of attraction, performing the corresponding analysis in the aggregated system. An analogous result can be stated for periodic solutions, see<sup>23</sup>.

The hypotheses of the theorem are in general difficult to check in practical applications, particularly the uniform convergence of the differentials of the iterates of map  $D$ . In<sup>24</sup> (Theorem 2) a result of these same characteristics is presented that avoids the hypothesis of convergence of the differentials. On the other hand, in the thesis it cannot be ensured that the solutions of the initial system tend to the attractors (equilibria or periodic solutions) that are obtained from the reduced system. However, it does prove that the dynamics remains as close to these attractors as desired, as long as  $k$  is large enough. From the point of view of eco-epidemiological models this last property is good enough to obtain valuable qualitative results.

#### *Opportunistic disease model. Reduced model.*

Before proceeding to the reduction of the system associated with the opportunistic disease model (9), let us observe that both map  $D$  and map  $L$  leave the total number of individuals in the population,  $N$ , invariant, so that

$$S(t) + I(t) + C(t) = S(0) + I(0) + C(0) = N.$$

This allows us to make the substitution  $S(t) = N - I(t) - C(t)$ , transforming the system (9) into a 2-dimensional system for the variables  $I$  and  $C$ . The associated reduced system will turn out to be 1-dimensional for the global variable  $\bar{I} = I + C$ .

In variables  $I$  and  $C$  the map  $\tilde{D}$  defining the fast dynamics, that of the opportunistic disease, is

$$\tilde{D}(I, C) = \left( I - \frac{\beta^{op} IC}{I + C} + \gamma^{op} C, C + \frac{\beta^{op} IC}{I + C} - \gamma^{op} C \right), \quad (15)$$

and the map  $\tilde{L}$  defining the slow dynamics associated with the primary disease is

$$\tilde{L}(I, C) = \left( I + \frac{1}{N}(\beta_I I + \beta_C C)(N - I - C) - \gamma I, C \right), \quad (16)$$

Denoting  $\tilde{X}(t) = (I(t), C(t))$ , the 2-dimensional model equivalent to model (9) has the following form:

$$\tilde{X}(t+1) = \tilde{L}(\tilde{D}^{(k)}(\tilde{X}(t))). \quad (17)$$

To build the reduced system associated with the opportunistic disease model (17), we have to start by finding the limit of the iterates of  $\tilde{D}$  (15).

The analysis of the discrete-time SIS model involved in the definition of  $\tilde{D}$  is carried out in<sup>1</sup>. Defining the basic reproduction number as the ratio transmission coefficient to recovery coefficient, in the case of the opportunistic disease

$$R_0^{op} = \frac{\beta^{op}}{\gamma^{op}}, \quad (18)$$

we have that if  $R_0^{op} \leq 1$  then the opportunistic disease is eradicated with  $C(t)$  tending to zero, on the other hand, if  $R_0^{op} > 1$  then the disease becomes endemic with stable fractions of  $I$  and  $C$  individuals being  $\frac{1}{R_0^{op}} = \frac{\gamma^{op}}{\beta^{op}}$  and  $1 - \frac{1}{R_0^{op}} = 1 - \frac{\gamma^{op}}{\beta^{op}}$ , respectively.

From this result we can readily obtain the following

$$\lim_{k \rightarrow \infty} \tilde{D}^{(k)}(I, C) = \bar{D}(I, C) := (\nu(I + C), (1 - \nu)(I + C)), \quad (19)$$

where,  $\nu = 1$  if  $R_0^{op} \leq 1$ , and  $\nu = \frac{1}{R_0^{op}}$  if  $R_0^{op} > 1$ .

We can observe in the expression of  $\bar{D}$  that it depends on only one variable  $I + C$ . This allow us to establish the  $E \circ G$  decomposition of  $\bar{D}$  necessary for the reduction of the system. If we define  $\bar{I} = I + C$  as the global variable,  $G(I, C) = I + C$ , it is straightforward that defining  $E(\bar{I}) = (\nu\bar{I}, (1 - \nu)\bar{I})$  we get  $\bar{D} = E \circ G$ . Therefore, the reduced system associated to (17) is

$$\bar{I}(t + 1) = \bar{L}(I(t)) := (G \circ \bar{L} \circ E)(\bar{I}(t)).$$

In detailed form

$$\bar{I}(t + 1) = \bar{I}(t) + \frac{(\beta_I \nu + \beta_C(1 - \nu))}{N} \bar{I}(t)(N - \bar{I}(t)) - \gamma \nu \bar{I}(t). \quad (20)$$

## 4 | SIS MODEL IN AN M-PATCH ENVIRONMENT.

In this section we study the SIS model in an m-site environment (5) with the help of the reduced system (13) and Theorem 1.

In system (13) it is immediate to check that the total number of individuals is constant  $S(t) + I(t) = S(0) + I(0) = N$ , which allows us to reduce it to a scalar equation. To do it, in the  $I$  equation we eliminate the variable  $S$  replacing it with  $N - I$ . The equation to be studied is

$$I(t + 1) = I(t) + \left( \sum_{j=1}^m \frac{\beta_j v_j^S v_j^I}{v_j^S (N - I(t)) + v_j^I I(t)} \right) (N - I(t)) I(t) - \left( \sum_{j=1}^m v_j^I \gamma_j \right) I(t). \quad (21)$$

Let us introduce the following notation

$$\bar{\beta} := \sum_{j=1}^m v_j^I \beta_j \text{ and } \bar{\gamma} := \sum_{j=1}^m v_j^I \gamma_j. \quad (22)$$

In Appendix 6.1, the analysis of equation (21) is carried out. The discussion of the asymptotic behavior of its solutions is characterised in terms of the basic reproduction number defined as follows

$$\bar{R}_0 = \frac{\bar{\beta}}{\bar{\gamma}}. \quad (23)$$

The analysis tells us that if  $\bar{R}_0 < 1$  then the disease is eradicated, while if  $\bar{R}_0 > 1$  the endemicity of the disease follows from the existence of a hyperbolic and asymptotically stable endemic equilibrium.

**Proposition 1.** Let it be  $I(t)$  be equation (21). Then

1. If  $\bar{R}_0 < 1$  then the equilibrium  $I_0^* = 0$  is hyperbolic and asymptotically stable and  $\lim_{t \rightarrow \infty} I(t) = 0$  for any solution with initial data  $I(0) > 0$ .
2. If  $\bar{R}_0 > 1$  then there exists an unique hyperbolic and asymptotically stable equilibrium  $I_+^* \in (0, N)$ .

*Proof.* See Appendix 6.1. □

This result can be transferred to the SIS model in an m-site environment (5) with the help of Theorem 1:

**Theorem 3.** Let  $X(t)$  be the solution to system (5) for any initial data  $X(0) \in \mathbb{R}_+^{2m}$  with  $I(0) = \sum_{j=1}^m I_j(0) > 0$ , and  $N = S(0) + I(0) = \sum_{j=1}^m (S_j(0) + I_j(0))$ . Then

1. If  $\bar{R}_0 < 1$  then there exists an integer  $k_0 \geq 0$  such that for all  $k \geq k_0$  system (5) has an equilibrium  $X_k^*$  which is hyperbolic and asymptotically stable, that satisfies

$$\lim_{k \rightarrow \infty} X_k^* = X^* = D(\text{diag}(\bar{v}^S, \bar{v}^I) \text{col}(N, 0)) = \text{col}(v_1^S N, \dots, v_m^S N, 0, \dots, 0)$$

and

$$\lim_{t \rightarrow \infty} X(t) = X_k^*.$$

2. If  $\bar{R}_0 > 1$  then there exists an integer  $k_0 \geq 0$  such that for all  $k \geq k_0$  system (5) has an equilibrium  $X_k^*$  which is hyperbolic and asymptotically stable, that satisfies

$$\lim_{k \rightarrow \infty} X_k^* = X^* = D(\text{diag}(\bar{v}^S, \bar{v}^I) \text{col}(N - I_+^*, I_+^*)) = D(v_1^S(N - I_+^*), \dots, v_m^S(N - I_+^*), v_1^I I_+^*, \dots, v_m^I I_+^*).$$

Moreover, if the solution  $I(t)$  to (21) with  $I(0) = \sum_{j=1}^m I_j(0) > 0$  satisfies that  $\lim_{t \rightarrow \infty} I(t) = I_+^*$  then  $\lim_{t \rightarrow \infty} X(t) = X_k^*$ .

It can be seen that  $\bar{R}_0$  plays the role of basic reproduction number for model (5).

When  $\bar{R}_0 < 1$  we can consider that the disease is driven to extinction. The non-negative solutions of system (5) tend towards a disease-free equilibrium (DFE) that has approximately the following form:

$$X_0^* = (v_1^S N, \dots, v_m^S N, 0, \dots, 0).$$

On the other hand, if  $\bar{R}_0 > 1$ , we could consider the disease to be endemic. In this case, there exists an asymptotically stable endemic equilibrium (EE) close to:

$$X_+^* = D(v_1^S(N - I_+^*), \dots, v_m^S(N - I_+^*), v_1^I I_+^*, \dots, v_m^I I_+^*),$$

whose domain of attraction can be calculated with the help of the domain of attraction of equilibrium  $I_+^*$  in equation (21).

A simple case where equilibrium  $I_+^*$  is GAS, and therefore also  $X_+^*$ , is where movements bring susceptible and infective individuals to the same spatial distribution,  $v_j^S = v_j^I$  ( $j = 1, \dots, m$ ). Equation (21) reduces to

$$I(t+1) = I(t) + \frac{\bar{\beta}}{N}(N - I(t))I(t) - \bar{\gamma}I(t),$$

which is a classical SIS model, whose positive equilibrium  $I_+^* = (1 - \bar{\gamma}/\bar{\beta})N$  is GAS whenever  $\bar{R}_0 = \bar{\beta}/\bar{\gamma} > 1$ .

It should be noted that the previous statements can be assured for  $k$  large enough, that is, if the ratio between time scales is large enough.

From the analysis of system (5) we can try to answer some questions about the effect of rapid movements between sites on the dynamics of the disease. For this, it is enough to take into account that, globally,  $\bar{R}_0$  decides between eradication or endemicity of the disease, and that, locally, in each site, the corresponding basic reproduction number,  $R_0^j = \beta_j/\gamma_j$ , plays this same role.

We are going to limit ourselves to giving two examples of these possible questions. Is it possible to have a locally endemic disease in every site that is nonetheless eradicated when the sites are connected by the right fast movements? Or, the other way around, can we go from local eradication to global endemicity?

The answer to both questions is negative. Let us see it with the first one. Endemic disease at each site means that  $R_0^j > 1$  for all  $j$  or, equivalently, that  $\beta_j > \gamma_j$ . We now have to see the consequences of this hypothesis on the global basic reproduction number  $\bar{R}_0$ , but it is straightforward that

$$\bar{\beta} - \bar{\gamma} = \sum_{j=1}^m v_j^I \beta_j - \sum_{j=1}^m v_j^I \gamma_j = \sum_{j=1}^m v_j^I (\beta_j - \gamma_j) > 0,$$

and, thus,  $\bar{R}_0 > 1$ .



In<sup>11</sup>, a model similar to (5) is studied with a local dynamic that corresponds to an SEIRS model. The fact of having two states of infected individuals, exposed and infective, to which different movement patterns can be associated allows an affirmative answer to the previous question.

A second example of question is the following. If locally only one of the sites eradicates the disease while it is endemic everywhere else, can patterns of movement be found that lead to global eradication of the disease?

Suppose that it is site 1 in which the disease is driven to extinction,  $R_0^1 < 1$ , and that the opposite occurs in the rest of the sites,  $R_0^j > 1$  for  $j = 2, \dots, m$ . We are going to reflect the movement pattern in a single parameter  $\alpha \in (0, 1)$ . To do this, we suppose that the vector  $\bar{v}^I$  can be written as follows

$$\bar{v}^I = (\alpha, (1 - \alpha)v_2, \dots, (1 - \alpha)v_m)$$

where  $v_i \in (0, 1)$  and  $v_2 + \dots + v_m = 1$ . To get a positive answer to our question we need to find values of  $\alpha \in (0, 1)$  that make  $\bar{R}_0 < 1$ . We can prove that they exist by solving the inequality  $\bar{\beta} < \bar{\gamma}$ :

$$\alpha\beta_1 + (1 - \alpha) \sum_{j=2}^m v_j\beta_j < \alpha\gamma_1 + (1 - \alpha) \sum_{j=2}^m v_j\gamma_j,$$

whose solution is

$$\alpha > \frac{\sum_{j=2}^m v_j(\beta_j - \gamma_j)}{\gamma_1 - \beta_1 + \sum_{j=2}^m v_j(\beta_j - \gamma_j)} \in (0, 1).$$

## 5 | OPPORTUNISTIC DISEASE MODEL.

We complete in this section the analysis of the opportunistic disease model (9) by means of the reduced system (20) and Theorem 2.

Considering  $\bar{\beta} = \beta_I\nu + \beta_C(1 - \nu)$  as the transmission coefficient and  $\bar{\gamma} = \nu\gamma$  as the recovery coefficient, the reduced system (20) turns out to be an SIS model of the form studied in<sup>1</sup> expressed in terms of the infective individuals variable  $\bar{I}$ :

$$\bar{I}(t + 1) = \bar{I}(t) + \frac{\bar{\beta}}{N} \bar{I}(t)(N - \bar{I}(t)) - \bar{\gamma} \bar{I}(t). \quad (24)$$

We recall that  $\nu = 1$  if  $R_0^{op} \leq 1$ , and  $\nu = 1/R_0^{op}$  if  $R_0^{op} > 1$ , with  $R_0^{op} = \beta^{op}/\gamma^{op}$  being the basic reproduction number associated to the opportunistic disease.

The asymptotic behavior of the solutions of equation (24) depends on the ratio  $\bar{\beta}$  to  $\bar{\gamma}$ , which we denote

$$\bar{R}_0 = \frac{\bar{\beta}}{\bar{\gamma}}, \quad (25)$$

and which can be considered as the basic reproductive number of the complete opportunistic disease model (9).

**Proposition 2.** Let  $\bar{I}(t)$  be the solution to equation (24) for any initial data  $\bar{I}(0) > 0$  and  $N = S(0) + \bar{I}(0)$ . Then

1. If  $\bar{R}_0 < 1$ , the equilibrium  $\bar{I}_0^* = 0$  is hyperbolic and asymptotically stable and  $\lim_{t \rightarrow \infty} \bar{I}(t) = 0$ .
2. If  $\bar{R}_0 > 1$ ,  $\bar{I}_+^* = N(1 - \frac{1}{\bar{R}_0})$  is a hyperbolic and asymptotically stable equilibrium such that  $\lim_{t \rightarrow \infty} \bar{I}(t) = \bar{I}_+^*$ .

*Proof.* See<sup>1</sup> Section 4. □

As stated in the previous proposition, the asymptotic behavior of the solutions of equation (24) is defined by hyperbolic and asymptotically stable equilibria, with regions of attraction that contain the interval  $(0, N]$ .

This allows us to apply Theorem 2 to obtain the same type of result on the solutions of system (17) and, therefore, of the opportunistic disease model (9). To do this, we first need to ensure that the hypotheses of the theorem hold. It remains for us to check that the convergence of the iterates of map  $\tilde{D}$  (19), and their differentials, to map  $\bar{D}$ , and its differential, is uniform on compact sets. The proof of this question can be found in<sup>8</sup> Lemma A.1.

Before applying Theorem 2, let us note that, as the reproduction number  $\bar{R}_0$  depends on  $\nu$ , we have two different cases in Proposition 2.

One corresponds to the opportunistic disease being rapidly eradicated,  $R_0^{op} < 1$ , then  $\nu = 1$ , and equation (20) is nothing but the SIS model associated to the primary disease in the absence of the opportunistic disease, expressed in terms of the infective variable  $\bar{I}$ :

$$\bar{I}(t+1) = \bar{I}(t) + \frac{\beta_I}{N} \bar{I}(t)(N - \bar{I}(t)) - \gamma \bar{I}(t).$$

Using the basic reproduction number of the primary disease

$$R_0^{pr} := \frac{\beta_I}{\gamma}, \quad (26)$$

and assuming  $R_0^{pr} \leq 1$ , we can expressed the asymptotic behaviour of the solutions of equation (20) with  $\bar{I}(0) > 0$ , and  $N = S(0) + \bar{I}(0)$  in the following form:

1. If  $R_0^{pr} \leq 1$ ,

$$\lim_{t \rightarrow \infty} \bar{I}(t) = 0. \quad (27)$$

2. If  $R_0^{pr} > 1$ ,

$$\lim_{t \rightarrow \infty} \bar{I}(t) = N \left( 1 - \frac{1}{R_0^{pr}} \right). \quad (28)$$

The second case is where the opportunistic disease rapidly attains a positive equilibrium,  $R_0^{op} > 1$  and  $\nu = 1/R_0^{op}$ . In this case  $\bar{\beta} = \beta_I/R_0^{op} + (1 - 1/R_0^{op})\beta_C$  and  $\bar{\gamma} = \gamma/R_0^{op}$ . So, the basic reproduction number (25) of equation (20), that we call  $R_0^{coi}$ , is

$$R_0^{coi} = \frac{\beta_I}{\gamma} + (R_0^{op} - 1) \frac{\beta_C}{\gamma} = R_0^{pr} \left( 1 + (R_0^{op} - 1) \frac{\beta_C}{\beta_I} \right). \quad (29)$$

The asymptotic behaviour of the solutions of equation (20) with  $\bar{I}(0) > 0$ , and  $N = S(0) + \bar{I}(0)$  is the following:

1. If  $R_0^{coi} \leq 1$  then

$$\lim_{t \rightarrow \infty} \bar{I}(t) = 0. \quad (30)$$

2. If  $R_0^{coi} > 1$  then

$$\lim_{t \rightarrow \infty} \bar{I}(t) = N \left( 1 - \frac{1}{R_0^{coi}} \right). \quad (31)$$

When  $R_0^{op} < 1$  the opportunistic disease is eradicated and the basic reproductive number of the primary disease  $R_0^{pr}$  decides what happens to it, either it is eradicated or it becomes endemic. On the other hand, if the opportunistic disease becomes endemic among those infected with the primary disease,  $R_0^{op} > 1$ , it is then the basic reproductive number of the co-infection  $R_0^{coi}$  that leads either to the endemicity of the co-infection or to the eradication of both diseases.

If we return to the initial opportunistic disease model (9) with three variables, the application of the reduction method tells us that the asymptotic behavior of its solutions can be described with a good approximation (the better the greater the ratio between the time scales) through one of the following steady state situations:

1.  $E_0 = (N, 0, 0)$ ; both diseases are eradicated.

2.  $E_{pr} = (S_{pr}^*, I_{pr}^*, 0) = (N/R_0^{pr}, N(1 - 1/R_0^{pr}), 0)$ ; the opportunistic disease is eradicated and the primary disease is endemic.

3.  $E_{coi} = (S_{coi}^*, I_{coi}^*, C_{coi}^*) = (N/R_0^{coi}, N(1 - 1/R_0^{coi})/R_0^{op}, N(1 - 1/R_0^{coi})(1 - 1/R_0^{op}))$ ; the coinfection becomes endemic.

Using the asymptotic results (19), (27), (28), (30) and (31), and Theorem 2, we summarize the long-term behaviour of the solutions of system (9):

Let  $X(t) = (S(t), I(t), C(t))$  be any solution of system (9) with initial conditions verifying  $S(0) \geq 0$ ,  $I(0) > 0$ ,  $C(0) > 0$ , and  $S(0) + I(0) + C(0) = N$ .

1. If  $R_0^{op} < 1$ , then  $R_0^{pr} < 1$  implies that  $X(t)$  approaches  $E_0$  while  $R_0^{pr} > 1$  implies that it approaches  $E_{pr}$ .

2. If  $R_0^{op} > 1$ , then  $R_0^{coi} < 1$  implies that  $X(t)$  approaches  $E_0$  while  $R_0^{coi} > 1$  implies that it approaches  $E_{coi}$ .

To draw some conclusions from the model analysis, we are going to focus on the potential impact of the opportunistic disease and, for this, we are left with the case of  $R_0^{op} > 1$  in which the isolated opportunistic disease becomes endemic.

A first observation is that a sufficiently large recovery rate  $\gamma$  from the primary disease can always lead to disease-free status.

For any  $R_0^{op} > 1$  both diseases are eradicated whenever  $R_0^{coi} < 1$ , that is, if

$$\beta_I + (R_0^{op} - 1)\beta_C < \gamma.$$

A sufficient reduction in the average period of infection of the primary disease,  $1/\gamma$ , allows both diseases to be eradicated. This can be achieved by isolating the infected and devoting more resources to recovery. This might lead one to think that it is enough to concentrate on the treatment of the primary disease, but this is not the case. On the one hand, the average period of infection could be reduced but up to a certain value and, on the other hand, it is easy to see that no matter how small the basic number of reproduction of the primary disease,  $R_0^{pr} < 1$ , it can be compensated with a basic number of reproduction of the opportunistic disease large enough,  $R_0^{op}$ , so that  $R_0^{coi} > 1$ , which implies the endemicity of co-infection:

$$R_0^{op} > 1 + \left( \frac{1}{R_0^{pr}} - 1 \right) \frac{\beta_I}{\beta_C}.$$

A sufficiently strong opportunistic disease can maintain co-infection in a population that, if only affected by the primary disease, would tend towards a disease-free state. The opportunistic disease acts as a reservoir for the primary disease that strengthens it. If we compare for the cases of co-infection and infection only through the primary disease, the number of susceptible individuals, those not affected by either of the two diseases, to which the dynamics of the model leads us we can clearly observe the aforementioned reservoir effect

$$\frac{S_{pr}^*}{S_{coi}^*} = 1 + (R_0^{op} - 1) \frac{\beta_C}{\beta_I},$$

which is reflected in the term  $(R_0^{op} - 1) \frac{\beta_C}{\beta_I}$ .

## 6 | CONCLUSION AND PERSPECTIVES

In this work, models have been presented including at least one infectious process together with a second process, these acting on different time scales. The models have been expressed in the form of discrete-time systems. Unlike what happens in continuous time, in discrete time the references including models with two time scales are very scarce.

The framework chosen to present these models has been intended to be general enough. However, two limitations have been observed. The first of these is a limitation introduced primarily for notational reasons. Infectious disease models have been proposed in the form of compartmental models. It is clear that extending this framework to more general models of infectious diseases is feasible.

The other limitation has to do with the type of discrete-time system with two time scales that can be studied through a reduced system. The analysis of a discrete-time system is usually complicated to carry out. In the case of the systems presented in this work, even more so due to the possible high number of variables and the existence of time scales. Therefore, we have presented a framework of systems in which the existing reduction results<sup>23,24</sup> can be applied. This does not ensure that a deep analysis of the model is feasible, but it does increase the chances that this will be the case.

We have established two main types of models, depending on whether the infectious process acts on the slow or fast time scale. The first of these (SDD) consists of a disease process acting on a slow time scale together with a second process acting on a faster time scale. The disease process is represented by a general compartmental model. The second process has been given the form of individual movements between widely understood sites. This last choice has two fundamental reasons. The first of them is the significant number of applications that it can host. The second reason is that this type of fast dynamics makes it easier to reduce the entire model<sup>21</sup>. Sites can obviously be understood in very different ways (activities, behaviors, etc.), but the most common case of being spatial sites is highly relevant in the study of disease models. The reduction procedure for these models leads us to a disease model in which the sites no longer appear explicitly. The result of the fast dynamics is reflected within the parameters that appear in this last model. From it, a good approximation of the basic reproduction number of the complete model can be found and thus distinguish between eradication or endemicity of the disease at a global level. The reduction procedure has important value, not only in justifiably simplifying models of relative complexity, but also in offering explanations of simpler models that are directly presented in compact form.

As an illustration of the reduction procedure in SDD models, a multi-site SIS model has been analyzed. Locally, at each site, the dynamics of the disease have been represented by a classical SIS model with specific parameters. The reduced model has turned out to be a global SIS model in which both the transmission coefficient and the recovery coefficient are obtained from the corresponding local ones and from the stable distribution of individuals as a result of their movements between sites. The eradication or global endemicity of the disease can then be characterized from a global basic reproduction number,  $\bar{R}_0$ , and thus establish the influence of the movements in the development of the disease.

The second type of established model (FDD) considers the disease process acting on a faster time scale than that of a second process that accompanies it. The disease process is still represented by a general compartmental model. The second process is represented in a general way because, unlike what happens in the SDD type, there is no clear advantage of choosing any particular case. Obviously, there is a toll to pay for such generality and the hypotheses to satisfy in order to carry out the reduction may

be too difficult, if not impossible, to establish. When the reduction can be carried out, it obviously has the same advantages as described above.

As an illustration, we have analyzed a co-infection model in which the reduction procedure can be applied without major problems. The rapid process is an opportunistic disease that acts when a primary disease has sufficiently weakened the individual's immune system. The dynamics of the primary disease plays the role of a slow process with respect to that of the opportunistic disease. Both processes are represented by SIS models and the reduced global model of co-infection is also a SIS model. The latter can be defined from a single global variable, the sum of infected by the primary disease and co-infected. A simple analysis of the reduced model allows us to establish the conditions for the eradication of both diseases and the endemicity of co-infection.

The presented reduction results allow establishing the stability of the equilibria of the initial model from the reduced model, including the attractive domains of the asymptotically stable equilibria. These results apply very well in the case of the disease free equilibrium (DFE). It is usually easy to find the DFE in the reduced model and even demonstrate that it is GAS when the basic global reproduction number is less than 1. Thus, there is a simple characterization of the eradication of the disease at a global level.

As far as the endemicity of the disease is concerned, things are not so simple. If endemicity is characterized by a positive endemic equilibrium (EE) in the reduced model, then the reduction results allow us to characterize global endemicity in the initial model in the same way. A first difficulty that we frequently face is that of finding the EE in the reduced model. This may be infeasible and, even if it is, the difficulty will grow to establish its stability. Sometimes endemicity is not characterized by an EE but is established from the uniform persistence<sup>26</sup> of infectious states. Studying the uniform persistence in the reduced model may be easier than finding the EE and proving its stability. This helps to overcome the previously proposed difficulty but leads us to propose a new theoretical work. At the moment, the reduction results do not allow us to conclude the uniform persistence of the initial model from that of the reduced model. In addition to this more specific task, in the proposed framework any result that simplifies the reduction hypotheses, such as the one that appears in<sup>24</sup>, would be of great help in the applications.

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## Conflict of interest

Author declares no potential conflict of interests.

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## APPENDIX

### 6.1 | Analysis of equation (21)

In this section we present the details of the study of the asymptotic behavior of the solutions of equation (21), which we recall to facilitate reading

$$I(t+1) = I(t) + \left( \sum_{j=1}^m \frac{\beta_j v_j^S v_j^I}{v_j^S (N - I(t)) + v_j^I I(t)} \right) (N - I(t)) I(t) - \left( \sum_{j=1}^m v_j^I \gamma_j \right) I(t). \quad (32)$$

To simplify the writing, we introduce the following notation:

$$B(S, I) = \sum_{j=1}^m \frac{\beta_j v_j^S v_j^I}{v_j^S S + v_j^I I}$$

and use the defined parameters (22)

$$\bar{\beta} = \sum_{j=1}^m v_j^I \beta_j \text{ and } \bar{\gamma} = \sum_{j=1}^m v_j^I \gamma_j.$$

Equation (32) can be written as

$$I(t+1) = I(t) + B(N - I(t), I(t)) (N - I(t)) I(t) - \bar{\gamma} I(t) = f(I(t)) = g(I(t)) I(t),$$

where  $g(I) = 1 - \bar{\gamma} + B(N - I, I)(N - I)$  and  $f(I) = g(I)I$ .

The equilibria of equation (32), that we are interested in, are  $I_0^* = 0$  (DFE) and the solutions to  $g(I) = 1$  in  $(0, N]$ .

As  $f'(I) = g'(I)I + g(I)$ , we have  $f'(0) = g(0) = 1 - \bar{\gamma} + \bar{\beta}$ . Recalling that  $\gamma_j, \beta_j \in (0, 1)$ , we also have  $\bar{\gamma}, \bar{\beta} \in (0, 1)$ . Thus,  $f'(0) > 0$ . Now,  $I_0^*$  is hyperbolic and asymptotically stable if  $f'(0) < 1$ , that is, if  $\bar{\gamma} > \bar{\beta}$ . This corresponds to the condition  $\bar{R}_0 = \bar{\beta}/\bar{\gamma} < 1$ . If this the case, we can prove that  $[0, N]$  is in the region of attraction of  $I_0^*$ . Let  $I(0) \in [0, N]$ :

$$B(N - I, I)(N - I) = \sum_{j=1}^m \frac{\beta_j v_j^S v_j^I (N - I)}{v_j^S (N - I) + v_j^I I} \leq \sum_{j=1}^m \frac{\beta_j v_j^S v_j^I (N - I)}{v_j^S (N - I)} = \bar{\beta},$$

therefore,  $f(I) \leq (1 - \bar{\gamma} + \bar{\beta})I$ , which implies

$$I(t) \leq (1 - \bar{\gamma} + \bar{\beta})^t I(0) = (f'(0))^t I(0) \xrightarrow{t \rightarrow \infty} 0.$$

We are now going to prove that when  $\bar{R}_0 > 1$  there exists an endemic equilibrium  $I_+^* \in (0, N]$  which is hyperbolic and asymptotically stable.

It is easy to express the derivative of  $g$  as follows

$$g'(I) = - \sum_{j=1}^m \frac{\beta_j v_j^S (v_j^I)^2 N}{(v_j^S (N - I) + v_j^I I)^2}.$$

523 Since  $g'$  is negative,  $g$  is decreasing. Furthermore,  $g(0) = 1 - \bar{\gamma} + \bar{\beta} > 1$  and  $g(N) = 1 - \bar{\gamma} < 1$ , so that there exists an unique

524  $I_+^* \in (0, N]$  satysfying  $g(I_+^*) = 1$  as required.

525 To prove the properties of  $I_+^*$ , we first set a lower bound on the derivative of  $f$ :

$$\begin{aligned} f'(I) = g'(I)I + g(I) &= - \sum_{j=1}^m \frac{\beta_j v_j^S (v_j^I)^2 N I}{(v_j^S (N - I) + v_j^I I)^2} + 1 - \bar{\gamma} + \sum_{j=1}^m \frac{\beta_j v_j^S v_j^I (N - I)}{v_j^S (N - I) + v_j^I I} \\ &= 1 - \bar{\gamma} + \sum_{j=1}^m \left( \frac{\beta_j v_j^S v_j^I}{v_j^S (N - I) + v_j^I I} \cdot \frac{v_j^S (N - I)^2 - v_j^I I^2}{v_j^S (N - I) + v_j^I I} \right). \end{aligned}$$

526 We note that the second factor in the parenthesis can be written as the following convex combination

$$\frac{v_j^S (N - I)^2 - v_j^I I^2}{v_j^S (N - I) + v_j^I I} = \frac{v_j^S (N - I)}{v_j^S (N - I) + v_j^I I} (N - I) + \frac{v_j^I I}{v_j^S (N - I) + v_j^I I} (-I),$$

527 and, thus, it admits the following lower bound

$$-I < \frac{v_j^S (N - I)^2 - v_j^I I^2}{v_j^S (N - I) + v_j^I I}.$$

528 Using this bounds in the expression of  $f'(I)$  we obtain

$$f'(I) > 1 - \bar{\gamma} - \sum_{j=1}^m \frac{\beta_j v_j^S v_j^I I}{v_j^S (N - I) + v_j^I I} > 1 - \bar{\gamma} - \sum_{j=1}^m \frac{\beta_j v_j^S v_j^I I}{v_j^I I} = 1 - \bar{\gamma} - \sum_{j=1}^m \beta_j v_j^S > -1.$$

529 In particular we have that  $f'(I_+^*) > -1$ . So, to prove that  $I_+^*$  (EE) is hyperbolic and asymptotically stable, we only have to

530 show that  $f'(I_+^*) < 1$ . This is readily obtained since  $f'(I_+^*) = g'(I_+^*)I_+^* + g(I_+^*) = g'(I_+^*)I_+^* + 1$  and  $g'(I_+^*) < 0$ .

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