

# Be-CoDiS: A mathematical model to predict the risk of human diseases spread between countries. Validation and application to the 2014 Ebola Virus Disease epidemic.

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## Abstract

Ebola virus disease is a lethal human and primate disease that currently requires a particular attention from the international health authorities due to important outbreaks in some Western African countries and possible spread to other continents, which has already occurred in the USA and Spain. Regarding the emergency of this situation, there is a need of development of decision tools to assist the authorities to focus their efforts in important factors to eradicate Ebola. In particular, mathematical modelling can help to predict the possible evolution of the Ebola outbreaks and to give some recommendations about surveillance. In this work, we propose a novel spatial and temporal model, called Be-CoDiS (Between-Countries Disease Spread), to study the evolution of human diseases between countries. The goal is to simulate the spread of a particular disease and identify risk zones worldwide. The main interesting characteristics of Be-CoDiS are the consideration of the migratory flux between countries and control measure effects and the use of time dependent coefficients adapted to each country. First, we focus on the mathematical formulation of each component of the model. Next, in order to validate our approach, we consider various numerical experiments regarding the 2014 Ebola epidemic. In particular, we study the ability of the model in predicting the EVD evolution at 30 days and until the end of the epidemic. The results are compared to real data and other models outputs found in the literature. Finally, a brief parameter sensitivity analysis is done. **Keywords:** *Epidemiological modelling; Ebola Virus Disease*

## 1 Introduction

Modeling and simulation are important decision tools that can be used to control or eradicate human and animal diseases [1, 28]. Each disease presents its own characteristics and, thus, most of them need a well-

adapted simulation model in order to tackle real situations [3, 4].

In this work, we present a first version of a new spatial-temporal epidemiological model, called Be-CoDiS (Between-Countries Disease Spread), to simulate the spread of human disease in a considered area. This model is inspired from a previous software, called Be-FAST (Between Farm Animal Spatial Transmission), which focuses on the spread of animal diseases between and within farms. The major original ideas introduced by Be-FAST were the following: (i) the study of both within and between farms spread, (ii) the use of real database and (iii) dynamic coefficients calibrated in time according to farms characteristics (e.g., size, type of production, etc.). This model was deeply detailed in [16, 23] and validated on various cases as, for example: Classical Swine Fever in Spain and Bulgaria [21, 22], and Foot-and-Mouth disease in Peru [20]. Be-CoDiS is based on the combination of a deterministic Individual-Based model (where the countries are considered as individuals) [7], simulating the between-country interactions (here, migratory flux) and disease spread, with a deterministic compartmental model [4] (a system of ordinary differential equations), simulating the within-country disease spread. We observe that the coefficients of the model are calibrated dynamically according to the country indicators (e.g., economic situation, climatic conditions, etc.). At the end of a simulation, Be-CoDiS returns outputs referring to outbreaks characteristics (for instance, the epidemic magnitude, the risk of disease introduction or diffusion per country, the probability of having at least one infected per time unit, etc.). The principal characteristic of our approach is the consideration of the following effects at the same time: migratory flux between countries, control measure effects and time dynamic coefficients fitted to each country.

This work has two main goals. The first one, is to give a full and detailed mathematical formulation of Be-CoDiS in order to provide a transparent and understandable model for users. The second one is to validate our model by applying it to the current case of the Ebola Virus Disease (EVD) [8, 26, 29].

EVD is a lethal human and primates disease caused by the Ebola-virus (family of the Filoviridae) that causes important clinical signs, such as haemorrhages, fever or muscle pain. The fatality percentage (i.e., the percentage of infected persons who do not survive the disease) is evaluated to be within 25% and 90%, due to hypovolemic shock and multisystem organ failure, depending on the sanitary condition of the patient and the medical treatment. This virus was first identified in Sudan and Zaire in 1976 (see [8]). Various important outbreaks occurred in 1995, 2003 and 2007 in the Democratic Republic of Congo (315, 143 and 103 persons infected by EVD, respectively), in 2000 and 2007 in Uganda (425 and 149 persons infected by EVD, respectively), see [26, 6]. The 2014 outbreak started in December 2013 in Guinea and spread to Liberia and Sierra Leone. In March 2014, the international community was aware of the gravity of the situation in those three countries. The situation on December 7<sup>th</sup>, 2014 (the date used to run our numerical experiments) was a total of 17908 persons infected by EVD in Guinea, Liberia, Sierra Leone and Nigeria (see [29, 30]). Moreover, 34 isolated cases were detected in Mali, Senegal, Spain and the USA. Furthermore, in Spain and the USA, the first contagions between people outside Africa were observed. The observed mean fatality percentage for this particular hazard decreased from 70.8% (on March 24<sup>th</sup>, 2014) to 35.6% (on December 7<sup>th</sup>, 2014), see [19]. From an epidemiological point of view, the EVD can be transmitted between natural reservoirs (for instance, bats) and humans due to the contact with animal carcass [19]. The most common way of EVD human transmission is due to contacts with blood or bodily fluids from an infected person (including dead persons).

Starting from this particular context, we study the behaviour of our model in predicting the possible spread of EVD worldwide considering short time (i.e., a period of 30 days) and long time (i.e., until the end of the epidemic) intervals. In order to validate our approach, results obtained by Be-CoDiS are compared to historical data and with other studies found in the literature [5, 9, 12, 25, 29, 30, 31] regarding the same 2014 EVD outbreaks. The work in [12] is based on a time spatial model with flux between areas (considering a database based on airport traffic instead of, as done here, migratory flux) but with a different point of view regarding control measures (at the beginning of the simulation, if control measures are applied the authors set the disease transmission rate to a value lower than in the case without control measures) and model coefficients (considered as constant in time). We point out that most of the parameters used by our model are calibrated for African countries and few data are available about the behaviour of EVD in other countries. Thus, some empirical hypothesis are needed and a sensitivity analysis of Be-CoDiS regarding those

parameter is done. Finally, we also highlight the current limitations of the model and a way to improve it in future works.

This work is organized as follows. In Section 2, we describe the epidemiological behavior of EVD and give a detailed presentation of our model. In Section 3, we focus on the validation of Be-CoDiS by considering the 2014 EVD outbreaks. We compare the outputs given by our model with real data and with results from other models. Then, we perform two EVD epidemic forecasts considering a 30 days time interval and the end of the epidemic as the final date. Finally, we study the behavior of our model regarding changes in the value of its parameters.

## 2 Mathematical formulation of the model

In Section 2.1 we detail the epidemiological characteristics of EVD that are taken into account in our model. Then, in Sections 2.2, 2.3 and 2.4, we describe in detail the Be-CoDiS model by presenting its general structure, i.e., the considered within and between countries disease spread sub-models. Finally, in Section 2.5, we present the outputs used to analyse the results of the numerical simulations presented in Section 3. The main notations used in this work are summarized in Table 1.

**Remark 1.** *Be-CoDiS is designed to be able to study the spread of any human disease worldwide. Here, some particular details of the model are related to the specific EVD case but it can be adapted to other disease. For instance, the classification of compartments in the SEIHRDB model can be changed to study other cases.*

### 2.1 Epidemiological characteristics of Ebola Virus Disease

When a person is not infected by EVD, it is categorized in the Susceptible state (denoted by  $S$ ). If a person is infected, then they pass successively through the following states (see [17, 25, 26, 31]):

- Infected (denoted by  $E$ ): The person is infected by EVD but they cannot infect other people and has no visible clinical signs (i.e., fever, hemorrhages, etc.). The mean duration of a person in this state is 11.4 days (range of [2,21] days) and is called incubation period. Then, the person passes to the infectious state.
- Infectious (denoted by  $I$ ): The person can infect other people and start developing clinical signs. The mean duration is 5 days (range of [0,10] days) and is called infectious period. After this period, an infectious person is taken in charge by sanitary authorities and we classify them as Hospitalized.
- Hospitalized (denoted by  $H$ ): The person is hospitalized and can still infect other people, but with a lower probability. The mean duration in this state is 4.5 days (see [17]). Actually, it has been observed in practice that those patients can still infect other people with a probability 25 times lower than infectious people (see [30]). On the one hand, after a mean duration of 4.2 days (range [1,11] days), a percentage of the hospitalized persons, between 25% and 72.8% (depending on the sanitary services of the country), die due to the EVD clinical signs and pass to the Dead state. On the other hand, after a mean duration of 5 days, the persons who have survived to EVD pass to the Recovered state. We point out that state  $H$  does not include hospitalized persons which cannot infect other people any more. This last category of persons is included in the recovered state explained below. The mean of the total number of days that a EVD patient stays in hospital (from hospitalization to hospital discharge) is estimated to be  $C_o = 11.8$  days (range [7.7,17.9] days).
- Dead (denoted by  $D$ ): The person has not survived to the EVD. It has been observed in previous Ebola epidemics, that cadavers of infected persons can infect other people until they are buried. The probability to be infected by this kind of contact is the same as that of being infected by contact with infectious persons. Indeed, the daily number of contacts of a cadaver with persons is lower than that of an infectious person but, the risk of EVD transmission due to contacts with cadavers is larger than

Table 1: Summary of the main notations used in this work to describe Be-CoDiS. The values and reference are given in the corresponding section of the text.

Notation	Description
$T_{\max}$	Maximum number of simulation days (day)
$\Delta t$	Time discretisation step size (day)
$\beta_I(i)$	Disease contact rate of a person in state $I$ in country $i$ ( $\text{day}^{-1}$ )
$\beta_H(i)$	Disease contact rate of a person in state $H$ in country $i$ ( $\text{day}^{-1}$ )
$\beta_D(i)$	Disease contact rate of a person in state $D$ in country $i$ ( $\text{day}^{-1}$ )
$\gamma_E$	Transition rate of a person in state $E$ ( $\text{day}^{-1}$ )
$\gamma_I$	Transition rate of a person in state $I$ ( $\text{day}^{-1}$ )
$\gamma_{HR}$	Transition rate of a person in state $H$ to state $R$ ( $\text{day}^{-1}$ )
$\gamma_{HD}$	Transition rate of a person in state $H$ to state $D$ ( $\text{day}^{-1}$ )
$C_o$	Number of days that a person stays in hospital (day)
$\mu_m(i)$	Natural mortality rate in country $i$ ( $\text{day}^{-1}$ )
$\mu_n(i)$	Natural natality rate in country $i$ ( $\text{day}^{-1}$ )
$\omega(i)$	Disease fatality percentage in country $i$ (%)
$\kappa_i$	Efficiency of the control measures in country $i$ ( $\text{day}^{-1}$ )
$\lambda(i)$	First day of application of control measures in country $i$ (day)
$m_I(i, t)/m_H(i, t)$	Control measure efficiency (%) in country $i$ at time $t$ applied to persons in state $I$ or $H$ , respectively
$m_{\text{tr}}(i, j, t)$	Control measure efficiency (%) applied to persons migrating from country $i$ to country $j$ at time $t$
$\tau(i, t)$	Daily migratory rate from country $i$ to country $j$ ( $\text{day}^{-1}$ )
$N_{\text{CO}}$	Number of countries in the studied region
$NP(i, t)$	Number of persons in country $i$ at time $t$
$S(i, t)/E(i, t)/I(i, t)/H(i, t)/R(i, t)/D(i, t)/B(i, t)$	Number of persons in state $S, E, I, H, R, D, B$ in country $i$ at time $t$

the risk due to contacts with infectious persons (see [17]). After a mean period of 2 days (this could be different for some countries) the body is buried.

- Buried (denoted by  $B$ ): The person is dead because of EVD. Its cadaver is buried and they are no longer considered as infectious.
- Recovered (denoted by  $R$ ): The person has survived the EVD and is no longer infectious. They develop a natural immunity to EVD. Since it has never been observed a person who has recovered from Ebola and contracted the disease again during the period of time of the same epidemic, it is assumed that they cannot be infected again by Ebola.

Once an EVD infected person is hospitalized, the authorities apply various control measures in order to control the EVD spread (see [14, 9, 29, 30]):

- Isolation: Infected people are isolated from contact with other people. Only sanitary professionals are in contact with them. However, contamination of those professionals also occur (see [9]). Isolated persons receive an adequate medical treatment that reduces the EVD fatality rate.
- Quarantine: Movement of people in the area of origin of an infected person is restricted and controlled (e.g., quick sanitary check-points at the airports) to avoid that possible infected persons spread the disease.
- Tracing: The objective of tracing is to identify potential infectious contacts which may have infected a person or spread EVD to other people.
- Increase of sanitary conditions: The funerals of infected cadavers are controlled by sanitary personal in order to reduce the contacts between the dead bodies and susceptible persons.

**Remark 2.** *Data given above were calibrated for the cases of African countries, the natural reservoir of EVD. However, due to the spread of this disease out of Africa, new studies should be performed to analyze the behavior of EVD in other sanitary, population and climatic conditions. Currently, very few studies are available. One of them is about the survival of the Ebola virus (EV) according to changes in temperature (see [27]). It has been found that the lower is the temperature the greater is the survival period of the EV) outside the host. Thus, in this work some empirical hypothesis, which seems to be reasonable, have been done. We have assumed that the transmission parameter of EV decreases when the temperature or the sanitary expenses of a country increase and increases when the people density of a country increases.*

## 2.2 General description

The Be-CoDiS model is used to evaluate the spread of a human disease within and between countries during a fixed time interval.

At the beginning of the simulation, the model parameters are set by the user (for instance, the values considered in the EVD case are described in Section 3.1). At the initial time ( $t = 0$ ), only susceptible people live in the countries that are free of the disease, whereas the number of persons in states  $S$ ,  $E$ ,  $I$ ,  $H$ ,  $R$ ,  $D$  and  $B$  of the infected countries are set to their corresponding values (e.g., the current situation of 2014 Ebola outbreak). Then, during the time interval  $[0, T_{\max}]$ , with  $T_{\max} \in \mathbb{N}$  the maximum number of simulation days, the within-country and between-country daily spread procedures (described in Section 2.3) are applied. If at the end of a simulation day  $t$  all the people in all the considered countries are in the susceptible state, the simulation is stopped. Else, the simulation is stopped when  $t = T_{\max}$ . Furthermore, the control measures are also implemented and they can be activated or deactivated, when starting the model, in order to quantify their effectiveness to reduce the magnitude and duration of a EVD epidemic.

A diagram summarizing the main structure of our model is presented in Figure 1.

## 2.3 Within-Countries disease spread

The dynamic disease spread within a particular contaminated country  $i$  is modeled by using a deterministic compartmental model (see [4]).

We assume that the people in a country are characterized to be in one of those states, described in Section 2.1: Susceptible ( $S$ ), Infected ( $E$ ), Infectious ( $I$ ), Hospitalized ( $H$ ), Recovered ( $R$ ), Dead ( $D$ ) or Buried ( $B$ ). For the sake of simplicity we assume that, at each time, the population inside a country is homogeneously distributed (this can be improved by dividing some countries into a set of smaller regions with similar characteristics). Thus, the spatial distribution of the epidemic inside a country can be omitted. We assume that new births are susceptible persons. In Section 2.3, we do not consider interaction between countries. Under those assumptions, the evolution of  $S(i, t)$ ,  $E(i, t)$ ,  $I(i, t)$ ,  $H(i, t)$ ,  $R(i, t)$ ,  $D(i, t)$  and  $B(i, t)$ , denoting the number of susceptible, infected, infectious, hospitalized, recovered, dead and buried persons in

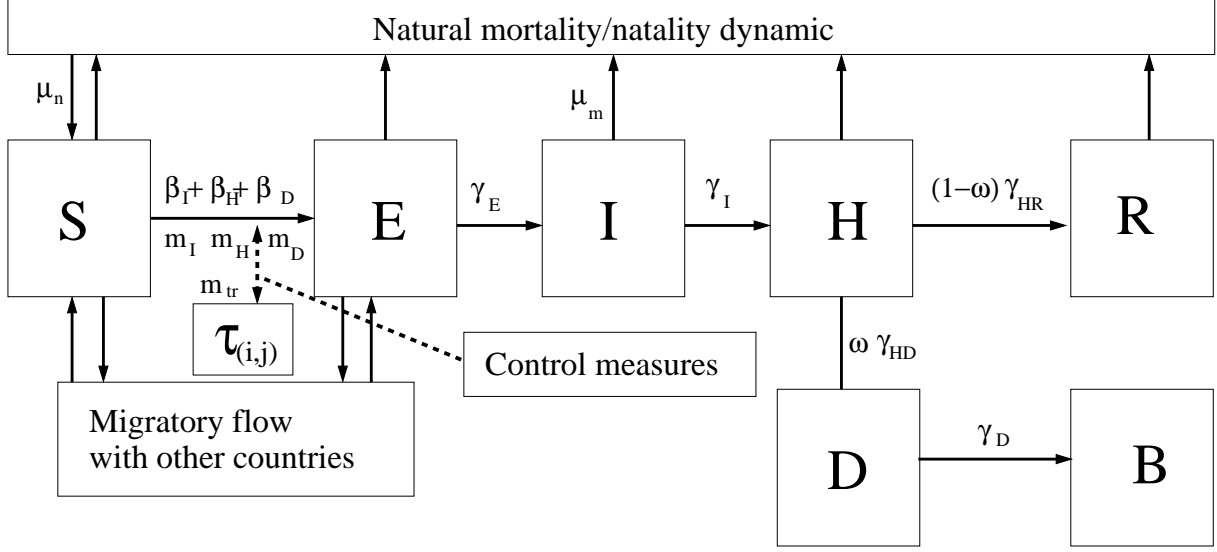


Figure 1: Diagram summarizing the Be-CoDiS model.

country  $i$  at time  $t$ , respectively, is modeled by the following system of ordinary differential equations

$$\begin{aligned}
\frac{dS(i,t)}{dt} &= -\frac{S(i,t)\left(m_I(i,t)\beta_I(i)I(i,t) + m_H(i,t)\beta_H(i)H(i,t)\right)}{NP(i,t)} \\
&\quad -\frac{S(i,t)\left(m_D(i,t)\beta_D(i)D(i,t)\right)}{NP(i,t)} - \mu_m(i)S(i,t) \\
&\quad + \mu_n(i)\left(S(i,t) + E(i,t) + I(i,t) + H(i,t) + R(i,t)\right), \\
\frac{dE(i,t)}{dt} &= \frac{S(i,t)\left(m_I(i,t)\beta_I(i)I(i,t) + m_H(i,t)\beta_H(i)H(i,t)\right)}{NP(i,t)} \\
&\quad + \frac{S(i,t)\left(m_D(i,t)\beta_D(i)D(i,t)\right)}{NP(i,t)} - \mu_m(i)E(i,t) - \gamma_E \mathcal{X}_{\epsilon_{\text{fit}}}(E(i,t)), \\
\frac{dI(i,t)}{dt} &= \gamma_E \mathcal{X}_{\epsilon_{\text{fit}}}(E(i,t)) - (\mu_m(i) + \gamma_I)I(i,t), \\
\frac{dH(i,t)}{dt} &= \gamma_I I(i,t) - \left(\mu_m(i) + (1 - \omega(i))\gamma_{HR} + \omega(i)\gamma_{HD}\right)H(i,t), \\
\frac{dR(i,t)}{dt} &= (1 - \omega(i))\gamma_{HR}H(i,t) - \mu_m(i)R(i,t), \\
\frac{dD(i,t)}{dt} &= \omega(i)\gamma_{HD}H(i,t) - \gamma_D D(i,t), \\
\frac{dB(i,t)}{dt} &= \gamma_D D(i,t),
\end{aligned} \tag{1}$$

where:

- $i \in \{1, \dots, N_{CO}\}$ ,
- $N_{CO} \in \mathbb{N}$  is the number of countries,
- $NP(i, t) = S(i, t) + E(i, t) + I(i, t) + H(i, t) + R(i, t) + D(i, t) + B(i, t)$  is the number of persons (alive and also died or buried because of EVD) in country  $i$  at time  $t$ ,
- $\mu_n(i) \in [0, 1]$  is the natality rate ( $\text{day}^{-1}$ ) in country  $i$ : the number of births per day and per capita,
- $\mu_m(i) \in [0, 1]$  is the mortality rate ( $\text{day}^{-1}$ ) in country  $i$ : the number of deaths per day and per capita (or, equivalently, the inverse of the mean life expectancy (day) of a person),
- $\mathcal{X}_{\epsilon_{\text{fit}}}(x) = x$  if  $x \geq \epsilon_{\text{fit}}$ ,  $\mathcal{X}_{\epsilon_{\text{fit}}}(x) = 2 \cdot x - \epsilon_{\text{fit}}$  if  $(\epsilon_{\text{fit}}/2) \leq x \leq \epsilon_{\text{fit}}$ , and 0 elsewhere, with  $\epsilon_{\text{fit}} \in [0, +\infty)$  (small tolerance parameter),
- $\omega(i) \in [0, 1]$  is the disease fatality percentage in country  $i$ : the percentage of persons who do not survive the disease,
- $\beta_I(i) \in \mathbb{R}^+$  is the disease effective contact rate ( $\text{day}^{-1}$ ) of a person in state  $I$  in country  $i$ : the mean number of effective contacts (i.e., contacts sufficient to transmit the disease) of a person in state  $I$  per day before applying control measures,
- $\beta_H(i) \in \mathbb{R}^+$  is the disease effective contact rate ( $\text{day}^{-1}$ ) of a person in state  $H$  in country  $i$ ,
- $\beta_D(i) \in \mathbb{R}^+$  is the disease effective contact rate ( $\text{day}^{-1}$ ) of a person in state  $D$  in country  $i$ ,
- $\gamma_E, \gamma_I, \gamma_{HR}, \gamma_{HD}, \gamma_D \in \mathbb{R}^+$  denote the transition rate ( $\text{day}^{-1}$ ) from a person in state  $E, I, H, H$  or  $D$  to state  $I, H, R, D$  or  $B$ , respectively: the number of persons per day and per capita passing from one state to the other (or, equivalently, the inverse of the mean duration of one of those persons in state  $E, I, H, H$ , or  $D$ , respectively),
- $m_I(i, t), m_H(i, t), m_D(i, t) \in [0, 1]$  (%) are functions representing the efficiency of the control measures applied to non-hospitalized persons, hospitalized persons and infected cadavers respectively, in country  $i$  at time  $t$  to eradicate the outbreaks. Focusing on the application of the control measures, which in the EVD consists in isolating persons/areas of risks and in improving sanitary conditions of funerals, we multiply the disease contact rates (i.e.,  $\beta_I(i), \beta_H(i)$  and  $\beta_D(i)$ ) by decreasing functions simulating the reduction of the number of effective contacts as the control measures efficiency is improved. Here, we have considered the functions (see [18]):

$$m_I(i, t) = m_H(i, t) = m_D(i, t) = \exp\left(-\kappa_i \max(t - \lambda(i), 0)\right), \quad (2)$$

where  $\kappa_i \in [0, +\infty)$  ( $\text{day}^{-1}$ ) simulates the efficiency of the control measures (greater value implies lower value of disease contact rates) and  $\lambda(i) \in \mathbb{R} \cup \{+\infty\}$  (day) denotes the first day of application of those control measures.

System (1) is completed with initial data  $S(i, 0), E(i, 0), I(i, 0), H(i, 0), R(i, 0), D(i, 0)$  and  $B(i, 0)$  given in  $\mathbb{R}$ , for  $i=1, \dots, N_{CO}$ .

We observe that all parameters of system (1) should be adapted to the considered disease and countries. Generally, they are calibrated considering real data as explained in Section 3 for the EVD case.

**Remark 3.** In system (1), function  $\mathcal{X}_{\epsilon_{\text{fit}}}(x)$  is a filter used to avoid artificial spread of the epidemic due to negligible values of  $x$ .



## 2.4 Between-Countries disease spread

The disease spread between countries is modeled by using a spatial deterministic Individual-Based model (see [7]). Countries are classified in one of the following states: free of disease ( $F$ ) or with outbreaks ( $O$ ). We assume that at time  $t$  country  $i$  is in state  $O$  if  $I(i, t) + H(i, t) \geq 1$  (i.e., there exist at least one infected person in this country), else it is in state  $F$ .

In this work we consider that the flow of people between countries  $i$  and  $j$  at time  $t$  (i.e., the number of persons traveling per day from  $i$  to  $j$  at time  $t$ ), is the only way to introduce the disease from country  $i$ , in state  $O$ , to country  $j$ . To do so, we consider the matrix  $(\tau(i, j))_{i, j=1}^{N_{CO}}$ , where  $\tau(i, j) \in [0, 1]$  is the rate of transfer (day<sup>-1</sup>) of persons from country  $i$  to country  $j$ , which is expressed in % of population in  $i$  per unit of time. Furthermore, we assume that only persons in the  $S$  and  $E$  sates can travel, as other categories are not in condition to perform trips due to the importance of clinical signs or to quarantine. Moreover, due to control measures in both  $i$  and  $j$  countries, we assume that those rates can vary in time and are multiplied by a function denoted by  $m_{tr}(i, j, t)$ . Thus, we consider the following modified version of system (1):

$$\begin{aligned}
\frac{dS(i, t)}{dt} &= -\frac{S(i, t) \left( m_I(i, t) \beta_I(i) I(i, t) + m_H(i, t) \beta_H(i) H(i, t) \right)}{NP(i, t)} \\
&\quad - \frac{S(i, t) \left( m_D(i, t) \beta_D(i) D(i, t) \right)}{NP(i, t)} - \mu_m(i) S(i, t) \\
&\quad + \mu_n(i) \left( S(i, t) + E(i, t) + I(i, t) + H(i, t) + R(i, t) \right) \\
&\quad + \sum_{i \neq j} m_{tr}(j, i, t) \tau(j, i) S(j, t) - \sum_{i \neq j} m_{tr}(i, j, t) \tau(i, j) S(i, t), \\
\frac{dE(i, t)}{dt} &= \frac{S(i, t) \left( m_I(i, t) \beta_I(i) I(i, t) + m_H(i, t) \beta_H(i) H(i, t) \right)}{NP(i, t)} \\
&\quad + \frac{S(i, t) \left( m_D(i, t) \beta_D(i) D(i, t) \right)}{NP(i, t)} - \mu_m(i) E(i, t) - \gamma_E \mathcal{X}_{\epsilon_{fit}}(E(i, t)) \\
&\quad + \sum_{i \neq j} m_{tr}(j, i, t) \tau(j, i) \mathcal{X}_{\epsilon_{fit}}(E(j, t)) - \sum_{i \neq j} m_{tr}(i, j, t) \tau(i, j) \mathcal{X}_{\epsilon_{fit}}(E(i, t)), \\
\frac{dI(i, t)}{dt} &= \gamma_E \mathcal{X}_{\epsilon_{fit}}(E(i, t)) - (\mu_m(i) + \gamma_I) I(i, t), \\
\frac{dH(i, t)}{dt} &= \gamma_I I(i, t) - \left( \mu_m(i) + (1 - \omega(i)) \gamma_{HR} + \omega(i) \gamma_{HD} \right) H(i, t), \\
\frac{dR(i, t)}{dt} &= (1 - \omega(i)) \gamma_{HR} H(i, t) - \mu_m(i) R(i, t), \\
\frac{dD(i, t)}{dt} &= \omega(i) \gamma_{HD} H(i, t) - \gamma_D D(i, t), \\
\frac{dB(i, t)}{dt} &= \gamma_D D(i, t).
\end{aligned} \tag{3}$$



System (3) is completed with initial data  $S(i, 0)$ ,  $E(i, 0)$ ,  $I(i, 0)$ ,  $H(i, 0)$ ,  $R(i, 0)$ ,  $D(i, 0)$  and  $B(i, 0)$  given in  $[0, +\infty)$ ; for  $i=1, \dots, N_{CO}$ .

This full model (3), which is summarized in Figure 1, is called Be-CoDiS.

**Remark 4.** *The explicit solution of (3) and the corresponding initial values are not (in general) available. In order to get an approximation of the solution one can use a suitable numerical solver. Here, we use the explicit Euler scheme with a time step of 1 day and  $\epsilon_{\text{filt}} = 10^{-3}$ .*

## 2.5 Outputs of the model

Here, we present the outputs used to analyse the results of the simulations performed in Section 3. In particular, considering a time interval  $[0, T]$ , for each country  $i$  we compute the following values:

- $\text{cumul}_{\text{cases}}(i, t)$ : the cumulative number of EVD cases in country  $i$  at day  $t$ , which can be computed as:

$$\text{cumul}_{\text{cases}}(i, t) = \text{cumul}_{\text{cases}}(i, 0) + \int_0^t \gamma_I \cdot I(i, t) dt.$$

- $\text{cumul}_{\text{deaths}}(i, t)$ : cumulative number of deaths (due to EVD) in country  $i$  at day  $t$ , which can be computed as:

$$\text{cumul}_{\text{deaths}}(i, t) = \text{cumul}_{\text{deaths}}(i, 0) + \omega(i) \int_0^t \gamma_{HD} \cdot H(i, t) dt.$$

- $\text{RS}(i)$ : the initial risk of country  $i$  to spread EVD to other countries, given by:

$$\text{RS}(i) = \sum_{i \neq j} \tau(i, j) m_{tr}(i, j, 0) E(i, 0).$$

$\text{RS}$  (persons-day<sup>-1</sup>) is the daily amount of infected persons who leave country  $j$  at time  $t = 0$ .

- $\text{TRS}(i)$ : the total risk of country  $i$  to spread EVD to other countries, considering the time interval  $[0, T]$ , computed as:

$$\text{TRS}(i) = \sum_{t=0}^T \sum_{i \neq j} \tau(i, j) m_{tr}(i, j, t) E(i, t).$$

$\text{TRS}$  (persons) is the number of infected persons send to other countries during the considered time interval.

- $\text{RI}(i)$ : the initial risk of EVD introduction into country  $i$  from other countries, given by:

$$\text{RI}(i) = \sum_{j \neq i} \tau(j, i) m_{tr}(j, i, 0) E(j, 0).$$

$\text{RI}$  (persons-day<sup>-1</sup>) is the daily amount of infected persons entering country  $i$  at time  $t = 0$ .

- $\text{TRI}(i)$ : the total risk of EVD introduction into country  $i$  from other countries considering the time interval  $[0, T]$ , computed as:

$$\text{TRI}(i) = \sum_{t=0}^T \sum_{i \neq j} \tau(j, i) m_{tr}(j, i, t) E(j, t).$$

$\text{TRI}$  (persons) is the number of EVD infected persons received from other countries during the time interval  $[0, T]$ .

- $MNH(i)$ : the maximum number of hospitalized persons at the same time at country  $i$  during the time interval  $[0, T]$ . It is computed as:

$$MNH(i) = \max_{t=0\dots T} \left\{ H(i, t) + R(i, t) - R(i, t - C_o) \right\}.$$

We remind (see Section 2.1) that  $C_o$  is the total number of days that a person stays in hospital, including the period of convalescence. This number can help to estimate and plan the number of clinical beds needed to treat all the EVD cases.

- $Emf(i)$ : the total emigration flow ( $\text{day}^{-1}$ ). It is the percentage of the population leaving the country each day, which can be computed as:

$$Emf(i) = \sum_{i \neq j} \tau(i, j).$$

### 3 Application to the 2014 Ebola case

We are now interested in validating our approach by considering the Ebola epidemic currently occurring worldwide. The advantage of this case is that some real and simulated data are now available and, thus, we are able to compare our model outputs with the information available in the following literature [9, 2, 29].

To this aim, we first explain in Section 3.1 how to estimate the model parameters for the EVD. Then, we present the results and discuss them in Section 3.2. Finally, in Section 3.3, we carry out a brief sensitivity analysis regarding the parameters values.

#### 3.1 Be-CoDiS parameters estimation for EVD

Some of the parameters used in the simulations presented in Section 3.2, have been found in the literature [9, 2, 6, 12] and in the daily reports on the Ebola evolution available online (see [5, 30]). Despite the effort to use the maximum amount of robust parameters as possible, due to lack of information of the behavior of Ebola out of Africa, some of them have been estimated using empirical assumptions. This part should be clearly improved as soon as missing information is available.

We now detail each kind of parameter by its category.

##### 3.1.1 Country indicators

We use the following data regarding country  $i$ :

- $TMP_i(t) \in \mathbb{R}$ : Mean temperature ( $\hat{A}^\circ\text{C}$ ) at day  $t$ .
- $DEN_i \in \mathbb{R}^+$ : Population density (persons/ $\text{km}^2$ ).
- $NP(i, 0) \in \mathbb{N}$ : Total number of persons alive and also died or buried because of EVD.
- $GNI_i \in \mathbb{R}^+$ : Gross National Income per year per capita ( $\text{US}\$. \text{person}^{-1} \cdot \text{ye} \cdot \text{ar}^{-1}$ ). We remind that the Gross National Income is an indicator of the economy of the country: the total domestic and foreign output claimed by residents of a country.
- $SAN_i \in \mathbb{R}^+$ : The mean Health expenditure per year per capita ( $\text{US}\$. \text{per} \cdot \text{son}^{-1} \cdot \text{year}^{-1}$ ). This is an economical indicator of the sanitary system of a country given by the amount of money inverted by public and private institutions (national or international) in the sanitary system of the country.
- $MLE_i \in \mathbb{R}^+$ : The mean life expectancy (days).
- $\mu_n(i) \in [0, 1]$ : See Section 2.3.

All those data have been freely obtained for year 2013 from the following World Data Bank website: <http://data.worldbank.org>.

### 3.1.2 Initial conditions

We have considered the initial conditions for our system (3) corresponding to the state of the EVD epidemic at several dates reported in [30].

In [30], only the cumulative numbers of reported cases (i.e., persons who have ever been in state  $H$ , as stated in [31]) and deaths (i.e., a person in state  $D$  or  $B$ ) in each country  $i$  at date  $t$ , denoted by  $NRC(i, t)$  and  $NRD(i, t)$ , are given for dates starting on March, 23<sup>rd</sup> 2014. Thus, taking into account the characteristics of the EVD presented in Section 2.1, we estimate the amount of persons in states  $E$ ,  $I$ ,  $H$ ,  $R$ ,  $D$  and  $B$  at  $t = 0$  as follows:

- Since the main duration in state  $H$  is 4.5 days, we compute  $H(i, 0)$  by considering the number of reported cases that are alive at time  $t = 0$  minus the number of reported cases that are alive 4.5 days before

$$H(i, 0) = ((NRC(i, 0) - NRD(i, 0)) - (NRC(i, -4.5) - NRD(i, -4.5))).$$

- Since the main duration in state  $D$  is 2 days, we compute  $D(i, t)$  as

$$D(i, 0) = (NRD(i, 0) - NRD(i, -2)).$$

- Since the main duration in states  $E$ ,  $I$  and  $H$  is 11.4, 5 and 4.5 days, respectively, we consider

$$E(i, 0) = \frac{11.4}{4.5} \cdot TH(i, 0) \text{ and } I(i, 0) = \frac{5}{4.5} \cdot TH(i, 0),$$

where  $TH(i, 0) = NRC(i, 0) - NRC(i, -4.5)$  is the total number of persons who have ever been in state  $H$  any of the last 4.5 days.

- The number of recovered persons  $R(i, 0)$  is given by

$$R(i, 0) = (NRC(i, 0) - NRD(i, 0) - H(i, 0)).$$

- The number of buried cadaver  $B(i, 0)$  is

$$B(i, 0) = (NRD(i, 0) - D(i, 0)).$$

- The number of susceptible persons  $S(i, 0)$  is

$$S(i, 0) = (NP(i, 0) - E(i, 0) - I(i, 0) - H(i, 0) - R(i, 0) - D(i, 0) - B(i, 0)).$$

All these numbers are rounded to the nearest integer.

### 3.1.3 Human Migration flow rate $\tau(i, j)$

This information, regarding the 2005-2010 human migratory fluxes between countries, was taken from [13] and the free database available in <http://www.global-migration.info>. The original data, denoted by  $\tilde{\tau}(i, j)$ , represent the number of persons who moved from country  $i$  to country  $j$  from 2005 to 2010. We set  $\tau(i, j) = \tilde{\tau}(i, j)/(5 \cdot 365 \cdot NP(i, 0))$ , which represents the percentage of persons in country  $i$  who move to country  $j$  per day.

### 3.1.4 EVD characteristics

The following parameters are assumed to be well studied due to several data sets available about the current 2014 Ebola outbreak. Using data from Sections 2.1 and 3.1.1, we estimate the following parameters for our model:

- $\mu_m(i) = 1/\text{MLE}_i$  (day<sup>-1</sup>)
- $\omega(i) = 0.25 \cdot \frac{\text{SAN}_i}{\max_i(\text{SAN}_i)} + (0.728 \cdot m_I(i, t)) \cdot (1 - \frac{\text{SAN}_i}{\max_i(\text{SAN}_i)})$ , as we know that, for this particular epidemic, the EVD fatality percentage oscillate between [25,72.8]%, depending on the quality of the sanitary service (see [25]). Moreover, according to [30], the maximum fatality rate has been decreased with the application of the control measures. Thus, we have modelled this effect by multiplying the maximum fatality rate by  $m_I(i, t)$ .
- $\gamma_E = 1/11.4$  (day<sup>-1</sup>),  $\gamma_I = 1/5$  (day<sup>-1</sup>),  $\gamma_{HR} = 1/5$  (day<sup>-1</sup>),  $\gamma_{HD} = 1/4.2$  (day<sup>-1</sup>),  $\gamma_D = 1/2$  (day<sup>-1</sup>).
- $\beta_I(i)$ : There exists several works on the computation of the EVD effective contact rate  $\beta_I(i)$  considering various SIR model (see [2, 6]). However, the value of this rate depend on the epidemic characteristics (country, year, etc.). Furthermore, our model includes novel characteristics regarding those articles, as it includes movement between countries, hospitalized people and control measures. Thus, we have computed our own rates by using a regression method considering three particular sets of data associated with the evolution of the EVD epidemic in Guinea, Liberia and Sierra Leone (see [30, 5]).
  - In Guinea, the country of origin of the EVD epidemic, the index case was identified as a young boy who died on December 6<sup>th</sup>, 2013 and infected 3 persons of its family. On March 24<sup>th</sup>, 2014, before the application of major control measures by national and international authorities, a total cumulative number of 86 cases and 59 dead persons were reported (see [30]). After this date, international help was sent to fight this epidemic and this changed the initial EVD effective contact rate in Guinea, denoted by  $\beta_I(\text{Guinea})$ . Thus, we fit those data with the solution given by system (1). To this end, system (1) was started at  $t = 0$  (corresponding to December 6<sup>th</sup>, 2013) with 3 persons in state  $I$  in Guinea, 1 person in state  $D$  and all other persons being free of disease. The model was run with  $T_{\max} = 108$  days (corresponding to March 24<sup>th</sup>, 2014 as the final date). In this simulation, we did not consider control measures (i.e., for any  $(i, j, t) \in \mathbb{N} \times \mathbb{N} \times \mathbb{R}$ ,  $m_I(i, t) = m_H(i, t) = m_{\text{tr}}(i, j, t) = 1$ ). All other parameters were set to the values introduced previously. Considering a particular value  $\beta_{\text{Guinea}}^I \in \mathbb{R}^+$ , at the end of this simulation we computed the model error  $\text{Err}(\beta_{\text{Guinea}}^I)$ , defined as absolute value of the the cumulative number of reported cases at the end of our simulation (see Section 3.2.2) minus  $\text{NRC}(\text{Guinea}, T_{\max})$ . We minimized  $\text{Err}(\beta_I(\text{Guinea}))$  by considering a dichotomy algorithm starting from  $\beta_I(\text{Guinea})=0.117$  (day<sup>-1</sup>) (value reported in [2]) and found an optimal value of  $\beta_I(\text{Guinea})=0.2095$  (day<sup>-1</sup>).
  - In Sierra Leone, 33 cases and 10 deaths were reported on July 6<sup>th</sup>, 2014. Major control measures were applied on July 27<sup>th</sup>, 2014, when the cumulative number of reported cases was 533 with 233 deaths. We used the same fitting technique as in the case of Guinea, with system (1), without control measures, starting at  $t = 0$  (corresponding to July 6<sup>th</sup>, 2014) with 85, 37, 33, 10, 145 and 117 persons in states  $E, I, H, D, R$  and  $B$ , respectively (considering the estimation method presented in Section 3.1.2) and all other persons being free of disease. The system was run with  $T_{\max} = 21$  days (i.e., final date at July 27<sup>th</sup>, 2014). We found  $\beta_I(\text{SierraLeone})=0.3140$  (day<sup>-1</sup>).
  - In Liberia, 131 cases and 84 death were reported on July 6<sup>th</sup>, 2014. On August 4<sup>st</sup>, 2014, before the application of control measures, 516 cases and 282 deaths were observed. System (1), without control measures, was started at  $t = 0$  (i.e., corresponding to July 6<sup>st</sup>, 2014) with 38, 17, 15, 9, 116 and 75 persons in the states  $E, I, H, D, R$  and  $B$ , respectively (see Section 3.1.2). This system was run during  $T_{\max} = 29$  days. Applying the same technique as for Guinea and Sierra Leone, we found  $\beta_I(\text{Liberia})=0.5055$  (day<sup>-1</sup>).

Taking into account those three rates, since the rate of other countries (especially the non African ones) remains unknown (due to the lack of data), we have performed an empirical non linear regression to estimate  $\beta_I(i)$ . To this aim,  $\beta_I(i)$  is assumed to be a non-decreasing function  $\beta_I(r_\beta \cdot \text{DEN}_i / \text{GNI}_i)$ , where  $r_\beta \in [0, +\infty)$  (km<sup>2</sup>·US\$·persons<sup>-2</sup>·year<sup>-1</sup>) is a balance parameter which determines the importance of  $\text{DEN}_i$  on the value of  $\beta_I$  in comparison to  $\text{GNI}_i$ . Indeed, the variable  $r_\beta \cdot \text{DEN}_i / \text{GNI}_i$  is chosen because

of the following reasons: 1) we assume that the higher the population of a country is, the higher the probability of contagion is and the higher  $\beta_I(i)$  is; 2) the higher the economy level of a country is, the higher its education level is, the lower the EVD risk habits of persons are (for instance, touching cadavers during funerals, see [10, 15]) and the lower  $\beta_I(i)$  is. In addition, we propose to use a function of the form

$$\beta_I\left(r_\beta \cdot \frac{\text{DEN}_i}{\text{GNI}_i}\right) = a_\beta \cdot \arctan\left(r_\beta \cdot \frac{\text{DEN}_i}{\text{GNI}_i} + b_\beta\right) + c_\beta,$$

where  $a_\beta$  (day<sup>-1</sup>),  $b_\beta$  (non-dimensional) and  $c_\beta$  (day<sup>-1</sup>)  $\in \mathbb{R}$ . We found, by considering the nonlinear regression method 'nlinfit' implemented in Matlab using the points

- (DEN<sub>Guinea</sub>/GNI<sub>Guinea</sub>,  $\beta_I(\text{Guinea})$ ) = (0.1820, 0.2095),
- (DEN<sub>SierraLeone</sub>/GNI<sub>SierraLeone</sub>,  $\beta_I(\text{Sierra Leone})$ ) = (0.2357, 0.314),
- (DEN<sub>Liberia</sub>/GNI<sub>Liberia</sub>,  $\beta_I(\text{Liberia})$ ) = (0.3307, 0.50555),

that  $a_\beta = 0.2574$ ,  $b_\beta = -2.2026$ ,  $c_\beta = 0.3515$  and  $r_\beta = 8.7223$ .

**Remark 5.** *If needed,  $\beta_I$  can be also considered as time dependent (see, for example, [11]). For instance, as said in Section 2.1, it has been observed that Ebola Virus survives better outside the host for lower temperatures (see [27]). Thus, it could be interesting to introduce a slight dependence of  $\beta_I(i)$  on the temperature of the country  $i$ . For instance, we could consider:*

$$\bar{\beta}_I(i, t) = \beta_I\left(r_\beta \cdot \frac{\text{DEN}_i}{\text{GNI}_i}\right) \left(1 - \alpha \cdot \frac{\text{TMP}_i(t) - \text{TMP}_{\text{ref}}}{\max_{(i,t)} |\text{TMP}_i(t) - \text{TMP}_{\text{ref}}|}\right), \quad (4)$$

where  $\text{TMP}_{\text{ref}}$  ( $^{\circ}\text{C}$ ) is a reference temperature; and  $\alpha$  (%) represent the maximum percent variation of the value  $\beta_I$ . However, as no data are available in literature to estimate a suitable value of  $\alpha$ , the effect of the temperature is neglected in our model.

- $\beta_H(i) = (\beta_I(i)/26)$  (day<sup>-1</sup>), as the probability of being infected by contact with persons in state  $H$  is 26 times lower than the probability of being infected by contact with persons in state  $I$ , as explained in Section 2.1,
- $\beta_D(i) = \beta_I(i)$  (day<sup>-1</sup>), as the probability of being infected by contact with persons in state  $D$  is the same as the probability of being infected by contact with persons in state  $I$ , see Section 2.1.

### 3.1.5 Control measures

Here, we estimate the parameters used in Equation 2:

- $\lambda(i)$ : It is the first day  $t$  such that  $H(i, t) \geq 1$  for all countries except for Guinea, Liberia, Mali, Nigeria and Sierra Leone. For these countries, intensive control measures were not applied right after the apparition of the first person in state  $H$ , but some time later (as reported in [30]). Thus, in the simulations presented in Section 3.2, we considered for these countries a reported delay between the detection of the first EVD case and the application of the control measures.
- $\kappa_i$ : In order to fit  $\kappa_i$ , we use data from Guinea, Sierra Leone and Liberia. Moreover, for all the numerical experiments considered in this work, we consider  $m_{\text{tr}}(i, j, t) = m_I(i, t)m_I(j, t)$ .
  - In Guinea, control measures were applied starting on March 24<sup>th</sup>, 2014. On December 7<sup>th</sup>, 2014, the number of reported cases in Guinea was 1878. Again, we fit those data with system (1) starting at  $t = 0$  (corresponding to December 6<sup>th</sup>, 2013) with 3 persons in state  $I$  and 1 person in state  $D$  in Guinea and all other persons being free of the disease. The model was run with  $T_{\text{max}}=306$  days (corresponding to December 7<sup>th</sup>, 2014). In this simulation, the control measures were applied after  $t = 108$  days (i.e.,  $\lambda(\text{Guinea})=108$  days). Considering a particular value  $\kappa_{\text{Guinea}}$ ,

we computed the model error  $\text{Err}(\kappa_{\text{Guinea}})$ , as defined previously. We minimized  $\text{Err}(\kappa_{\text{Guinea}})$  by considering a dichotomy algorithm starting from  $\kappa_{\text{Guinea}}=0.001$  and found an optimal value of  $\kappa_{\text{Guinea}}=0.001874$  ( $\text{day}^{-1}$ ).

- In Sierra Leone, control measures were applied starting on July 27<sup>th</sup>, 2014. On November, 9<sup>th</sup>, 2014, the number of reported cases in Sierra Leone was 5368. We used the same fitting method as in Guinea and started system (1) with the same conditions as those used for computing  $\beta_{\text{SierraLeone}}^I$ . The system was started with  $T_{\text{max}}=133$  days and control measures were applied at day  $\lambda(\text{Sierra Leone})=64$  (i.e., corresponding to July 27<sup>th</sup>, 2014). We found  $\kappa_{\text{SierraLeone}}=0.011039$ .
- In Liberia, extensive control measures started on August 4<sup>th</sup>, 2014. On December 7<sup>th</sup>, 2014, the number of reported cases was 6822. We used the same fitting method as the one used for Guinea and started system (1) with the same conditions as those used for computing  $\beta_{\text{Liberia}}^I$ . This system was run with  $T_{\text{max}}=99$  days and control measures were applied at day  $\lambda_{\text{Liberia}}=36$ . We found  $\kappa_{\text{Liberia}}=0.042883$ .

Taking into account those three values, we perform a regression method, similar to the one introduced in Section 3.1.4, estimating  $\kappa_i$ . To this end,  $\kappa_i$  is assumed to be a non-decreasing function  $\bar{\kappa}(r_\kappa \cdot \text{SAN}_i/\text{DEN}_i)$ , where  $r_\kappa \in [0, +\infty)$  ( $\text{persons}^2 \cdot \text{year} \cdot \text{km}^{-2} \cdot \text{US\$}^{-1}$ ) is a balance parameter which determines the importance of  $\text{SAN}_i$  on the value of  $\beta_I$  in comparison to  $\text{DEN}_i$ . Indeed, the variable  $r_\beta \cdot \text{SAN}_i/\text{DEN}_i$  is chosen because of the following reasons: 1) the higher the sanitary expenses are, the more efficient the control measures are and the higher  $\kappa_i$  is; 2) the higher the value of  $\text{DEN}_i$  is, the harder to respect the control measures is and the lower  $\kappa_i$  is.

Again, we propose to use

$$\bar{\kappa}\left(r_\kappa \cdot \frac{\text{SAN}_i}{\text{DEN}_i}\right) = a_\kappa \cdot \arctan\left(r_\kappa \cdot \frac{\text{SAN}_i}{\text{DEN}_i} + b_\kappa\right) + c_\kappa$$

where  $a_\kappa$  ( $\text{day}^{-1}$ ),  $b_\kappa$  (non-dimensional) and  $c_\kappa$  ( $\text{day}^{-1}$ )  $\in \mathbb{R}$ . We found, by considering the nonlinear regression method *'nlinfit'* implemented in Matlab using the points

- $(\text{SAN}_{\text{Guinea}}/\text{DEN}_{\text{Guinea}}, \bar{\kappa}(\text{Guinea}))=(0.6697, 0.001874)$ ,
- $(\text{SAN}_{\text{SierraLeone}}/\text{DEN}_{\text{SierraLeone}}, \bar{\kappa}(\text{Sierra Leone}))=(1.1344, 0.011039)$ ,
- $(\text{SAN}_{\text{Liberia}}/\text{DEN}_{\text{Liberia}}, \bar{\kappa}(\text{Liberia}))=(1.4686, 0.042883)$ ,

that  $a_\kappa = 0.0292$ ,  $b_\kappa = -7.2086$ ,  $c_\kappa = 0.0404$  and  $r_\kappa = 4.9661$ .

However, regarding the evolution of the control measures during the current EVD epidemic, since the beginning of August the international community have sent important sanitary and financial help to affected countries to help them to eradicate the EVD outbreaks. Thus, we assume that all countries affected by EVD will have a control measure coefficient  $\kappa_i$  at least as efficient as  $(\kappa_{\text{Liberia}} + \kappa_{\text{Sierra Leone}})/2=0.026961$ . Thus, we consider

$$\kappa_i = \max\left(\bar{\kappa}\left(r_\kappa \cdot \frac{\text{SAN}_i}{\text{DEN}_i}\right), 0.026961\right).$$

### 3.2 Numerical experiments

We consider the parameters presented in Section 3.1 and carry out several numerical experiments in order to estimate some relevant values of the 2014 Ebola outbreak. First in Section 3.2.1, we study the initial risk of introduction and diffusion of EVD for each country, taking into account only some of the inputs of the model. Next, in Section 3.2.2, we validate our model by comparing the outputs of two numerical experiments with real data. Finally, in Section 3.2.3, we predict the possible EVD evolution during various time intervals ( $T_{\text{max}}=30$  days and the end of the epidemic).

Table 2: Initial conditions for the countries affected by EVD on December 7<sup>th</sup>, 2014.

Country	$E(i, 0)$	$I(i, 0)$	$H(i, 0)$	$R(i, 0)$	$D(i, 0)$	$B(i, 0)$	$\lambda(i)$
Sierra Leone	1007	442	418	5711	53	1715	-131
Liberia	145	64	60	4482	10	3167	-123
Guinea	222	98	92	772	29	1399	-256
Mali	0	0	0	2	0	6	-43
USA	0	0	0	3	0	1	-66
Senegal	0	0	0	1	0	0	-98
Spain	0	0	0	1	0	0	-60

Table 3: Risk of EVD spread to other countries (RS) on December 7<sup>th</sup>, 2014 for countries affected by EVD).

Country	RS
Guinea	$4.3 \times 10^{-4}$
Sierra Leone	$9.9 \times 10^{-6}$
Liberia	$6.8 \times 10^{-8}$

### 3.2.1 Initial Risk of EVD Introduction and Diffusion

Here, we consider  $t = 0$  corresponding to December 7<sup>th</sup>, 2014, the date of the last EVD situation report available in [30] when those experiments were performed. The values of  $E_{i,0}$ ,  $m_{i,0}$  and  $m_{j,0}$  are obtained by using the methodology presented in Section 3.1.2 and 3.1.5. For the countries that had been affected by EVD on December 7<sup>th</sup>, 2014, we use the initial conditions presented in Table 2 obtained by using the methodology presented in Section 3.1.2.

In Table 3, we present the value of RS for the countries with a strictly positive value of RS on December 7<sup>th</sup>, 2014. We observe that Guinea had the major risk for EVD spread to other countries with a risk of around  $4.3 \times 10^{-4}$  persons sent to other countries per day (i.e., a probability of 0.043% to contaminate another country per day). The initial risk of other countries is negligible.

In Table 4, we report the 20 countries with the highest value of RI. We observe that Liberia and Sierra Leone are the first countries in this list, which is logical since those countries receive an important migration flux from Guinea. This result is consistent with the 2014 Ebola situation, with the disease starting from Guinea and then spreading to Liberia and Sierra Leone. We also observe that the USA, Spain, Nigeria and Senegal are in this top 20 (all affected by EVD cases). Indeed, they receive an important migratory flux from Guinea, Liberia and Sierra Leone. The USA, France and United Kingdom had (on December 7<sup>th</sup>, 2014) a probability of receiving an infected person per day of 0.006%, this value is more than twice higher than the risk of other countries in the list (except Liberia and Sierra Leone). A world map showing the distributions of RI for each country is included in Figure 2. We see that Western Europe, Western Africa, North America and Australia were the areas with the highest risk of EVD introduction.

Such a study is interesting as it reveals the countries with the most immediate risk of EVD introduction or spread. Effort for controlling the movements of people entering or leaving those regions could be prioritized in order to reduce the spread of EVD world wide.

### 3.2.2 Validation of the model

We are now interested in checking the validity of the EVD epidemic evolution predicted by our model. In particular, we want to check its ability to generate good predictions when considering short time ( $T_{\max} \leq 30$  days) and long time ( $T_{\max} \geq 90$  days) intervals. To this aim, we have performed the two following experiments.



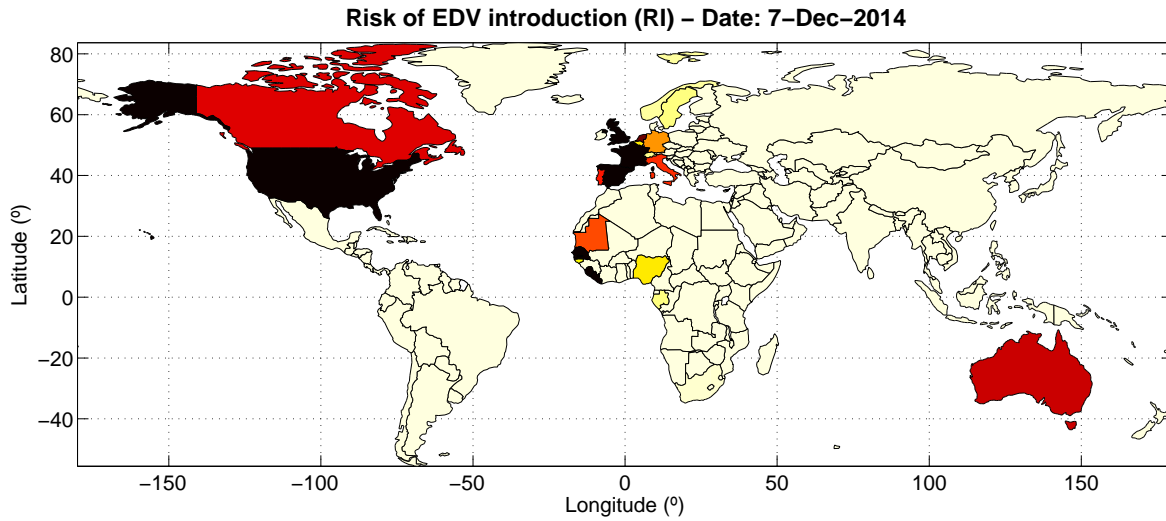


Figure 2: Risk of EVD Introduction (RI) of each country, corresponding to data on December 7<sup>th</sup>, 2014. Darker zones correspond to higher risk values.

Table 4: Risk of EVD introduction (RI) on December 7<sup>th</sup>, 2014 for each country. Only the Top 20 is reported.

Country	RI
Liberia	$1.3 \times 10^{-3}$
Sierra Leone	$4.1 \times 10^{-4}$
USA	$8.9 \times 10^{-5}$
France	$7.4 \times 10^{-5}$
United Kingdom	$6.9 \times 10^{-5}$
Spain	$3.4 \times 10^{-5}$
Senegal	$2.7 \times 10^{-5}$
Netherlands	$2.1 \times 10^{-5}$
Gambia	$1.9 \times 10^{-5}$
Australia	$1.8 \times 10^{-5}$
Canada	$1.7 \times 10^{-5}$
Portugal	$1.5 \times 10^{-5}$
Italy	$1.4 \times 10^{-5}$
Mauritania	$1.3 \times 10^{-5}$
Germany	$1.1 \times 10^{-5}$
Belgium	$7.3 \times 10^{-6}$
Nigeria	$7.2 \times 10^{-6}$
Guinea Bissau	$6.7 \times 10^{-6}$
Sweden	$3.9 \times 10^{-6}$
Gabon	$3.5 \times 10^{-6}$

Table 5: Initial conditions for the countries affected by EVD on November 9<sup>th</sup>, 2014.

Country	$E(i, 0)$	$I(i, 0)$	$H(i, 0)$	$R(i, 0)$	$D(i, 0)$	$B(i, 0)$	$\lambda(i)$
Sierra Leone	1298	569	467	3732	16	1153	-103
Liberia	520	228	133	3853	28	2808	-95
Guinea	288	127	30	706	36	1106	-228
Mali	8	4	3	0	2	2	-15
USA	0	0	0	3	0	1	-38
Senegal	0	0	0	1	0	0	-70
Spain	0	0	0	1	0	0	-32

Table 6: Validation for short time intervals: Cumulative numbers of cases predicted by Be-CoDiS (**BC**), real observed data reported in [30] (**Real**) and percentage error done by the model (**Err.**) on November 23<sup>th</sup>, 2014 and December 7<sup>th</sup>, 2014 for countries affected by EVD at those dates. We also report the cumulative number of deaths.

Date	23-11-2014			07-12-2014		
Country	BC	Real	Err. (%)	BC	Real	Err. (%)
Total cases	16107	15935	1	17521	17942	2
Total deaths	5654	5689	1	6059	6388	5
Guinea	2193	2134	3	2494	2292	9
Liberia	7275	7168	2	7465	7719	3
Sierra Leone	6626	6599	1	7519	7897	5
Mali	12	8	50	16	8	100

**Validation for short time intervals:** We run system (3) with  $T_{\max}=29$  days from November 9<sup>th</sup>, 2014 to December 7<sup>th</sup>, 2014, with the model parameters introduced in Section 3.1 and the initial conditions presented in Table 5 obtained by using the methodology presented in Section 3.1.2.

The evolution of the cumulative numbers of total cases and deaths predicted by the model (see Section 3.1.5) is presented in Figure 3. We also report in this figure the cumulative numbers of cases and deaths observed by the authorities during the epidemic for some dates (see [30]). Moreover, in Table 6, we summarize the number of simulated and observed cumulative numbers of cases and deaths for each affected country on November 23<sup>th</sup>, 2014 and December 7<sup>th</sup>, 2014. In addition, we computed and show in this table the percentage error of the model defined as the absolute value of the difference between the predicted and the real values divided by the real observation and multiplied by 100. We point out that the real observations are also based on estimations done by the authorities and are periodically corrected (for instance, they count suspected cases of EVD and remove them if the serological EVD tests are negative). This explain the oscillation in the cumulative numbers of cases and deaths.

We observe on both, Figure 3 and Table 6, that the model predicts a stabilization of the epidemic during the considered period of time with a deceleration of the number of new cases. This is consistent with the general behavior of the real reported data. When comparing the magnitude of the predicted cumulative numbers with the real ones, we observe that the order between those values is preserved. Regarding the relative error done in predicting the number of cases and deaths, we observe that the model predicts the number of cumulative cases with an error lower than 10% for those countries with big numbers of reported cases. Regarding Mali, the country with the smaller number of cases, the relative errors can be important (up to 100%) which is normal as the reference value for computing the error is small. Those results tends to show that our model seems to predict a reasonable EVD epidemic behavior for short time intervals.

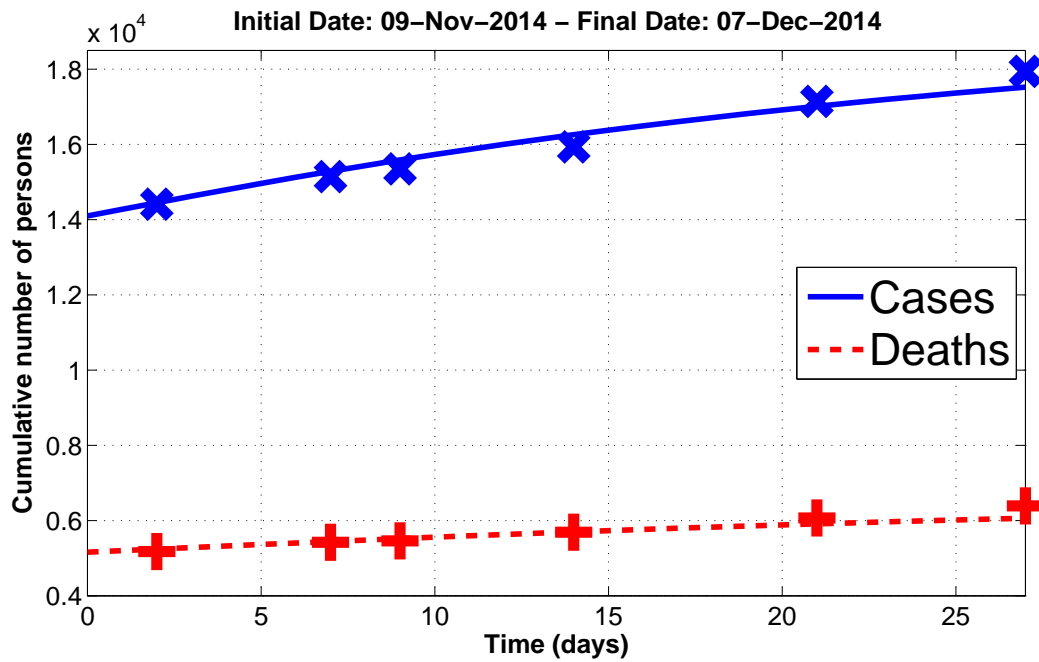


Figure 3: Evolution of the cumulative numbers of total EVD cases (continuous line) and deaths (dotted line) predicted by the Be-CoDiS model from November 9<sup>th</sup>, 2014 to December 7<sup>th</sup>, 2014. We also show for some dates the cumulative amount of total cases (X) and deaths (+) reported in [30].

Table 7: Validation for long time intervals: Date of the first reported case (**Date**), cumulative numbers of cases (**Cases**) and deaths (**Deaths**) for countries affected by EVD predicted by Be-CoDiS (**BC**) and in the real epidemic (**Real**). Real observed data reported in [30] on December 7<sup>th</sup>, 2014 are also shown.

Country	BC			Real		
	Date	Cases	Deaths	Date	Cases	Deaths
Sierra Leone	18-Jun-2014	9824	4105	26-May-2014	7897	1768
Liberia	5-Apr-2014	9776	2363	31-Mar-2014	7719	3177
Guinea	6-Dec-2013	2606	1607	06-Dec-2013	2292	1428
Nigeria	4-Dec-2014	17	7	20-Jul-2014	20	8
Gambia	15-Sep-2014	98	20	-	0	0
Senegal	-	0	0	29-Aug-2014	1	0
USA	-	0	0	30-Sep-2014	4	1
Mali	-	0	0	23-Oct-2014	8	6
Spain	-	0	0	06-Oct-2014	1	0

**Validation for long time intervals:** We considered a simulation starting from the known index cases of the current EVD epidemic on December 6<sup>th</sup>, 2013 and let the epidemic run until its ending (i.e., the approximated time for which the numbers of persons in states  $E$ ,  $I$ ,  $H$  and  $D$  are all lower than 1). To this aim, system (3) was started at  $t = 0$  (corresponding to December 6<sup>th</sup>, 2013) with 3 persons in state  $I$  and 1 person in state  $D$  in Guinea and all other persons being free of the disease. All the parameters were set to the values introduced previously in Section 3.1. In particular taking into account Section 3.1.5, we set the delay between the first day  $t$  such that  $H(i, t) \geq 1$  and the first day of application of control measures for Guinea, Sierra Leone, Liberia and Nigeria to 108, 120, 70 and 23 days, respectively.

The evolution of the cumulative numbers of total cases and deaths predicted by the model is presented in Figure 4. We also show in this figure the cumulative numbers of cases and deaths observed by the authorities during the epidemic (see [30]) for several dates. In addition, in Table 7, we report the date of the first infection (i.e., the first time for which the cumulative number of infected cases is greater than 1), the final cumulative numbers of cases and the final cumulative numbers of deaths for countries affected by EVD predicted by Be-CoDiS. Moreover, we also show the data reported in [30] for those countries for December 7<sup>th</sup>, 2014.

From Table 7, we observe that our model predicts the infection of Liberia, Nigeria and Sierra Leone. Moreover, the magnitude in those countries and Guinea is similar to the one observed on December 7<sup>th</sup>, 2014. In addition, on the one side, our model also predicts the infection of Gambia with relatively low epidemics, which has not occurred before this work was done. On the other side, starting just with data from December 6<sup>th</sup>, 2013, our model fails to predict infection in Mali, Senegal, Spain and USA. However, when this work was done, in those four countries the EVD epidemic seemed to be sporadic and limited.

Regarding Figure 4, we see that, in general, the model predicts an increase of the cumulated number of cases and deaths higher than the one given by reported data, which could be due to real cases non counted on the reports of [30] (in those reports it is explained the problems of recording all the cases). However, it also indicates a first stabilization of the situation at the end of October 2014. This phenomenon is actually observed regarding real observations (see [30]). According to the model, the epidemic should end on June 25<sup>th</sup>, 2015.

From those results, and taking into account the difficulty of epidemiological models for predicting long time intervals (see [24]), Be-CoDiS seems to generate reasonable behaviour of the evolution of the epidemic when considering a long time interval, even when using just the initial index cases as initial data. In particular, it seems that the model may help to detect, from the start of an epidemic to its end, the countries with more probabilities to develop important outbreaks and to simulate the relevant values of affected cases.

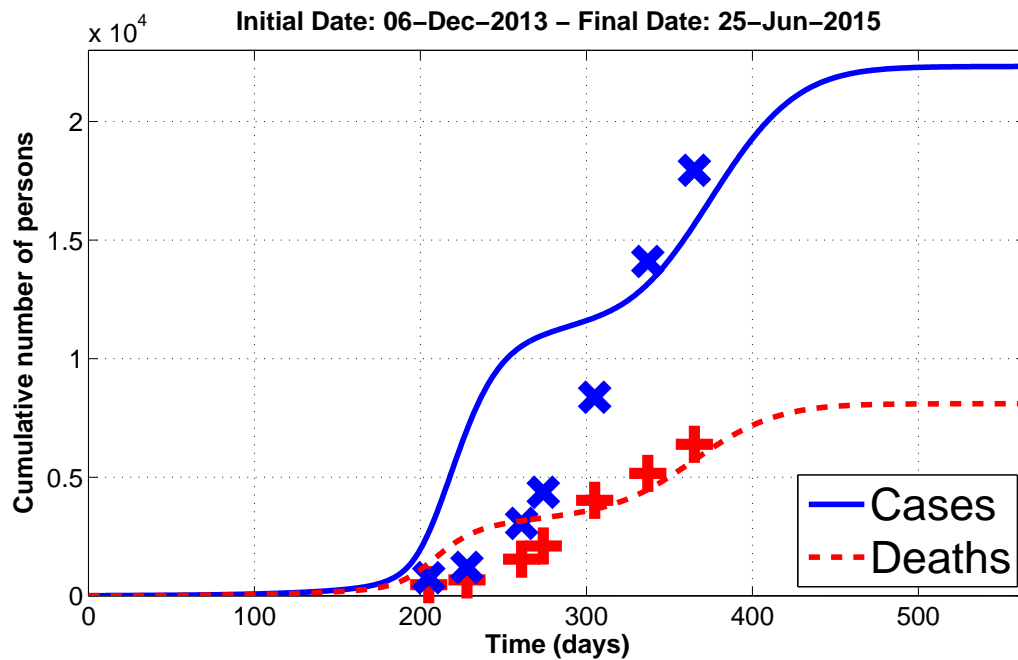


Figure 4: Evolution of the cumulative numbers of total EVD cases (continuous line) and deaths (dashed line) predicted by the Be-CoDiS model from December 6<sup>th</sup>, 2013 to June 25<sup>th</sup>, 2015. We also show for some dates the cumulative amount of total cases (X) and deaths (+) reported in [30].

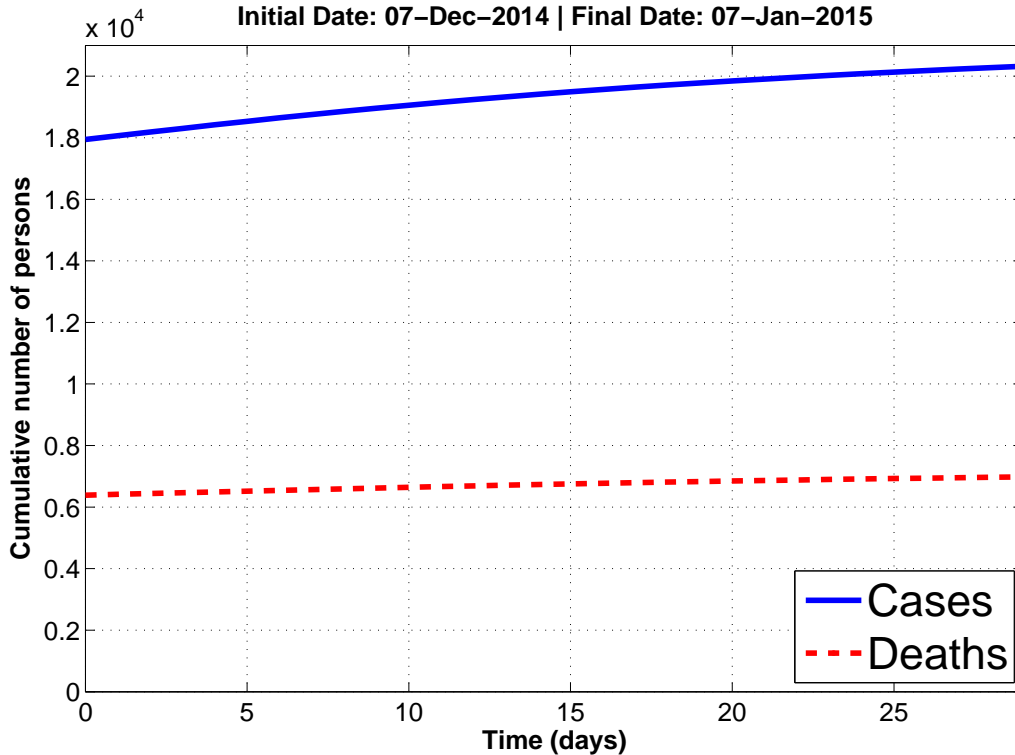


Figure 5: Evolution of the cumulative numbers of total EVD cases (continuous line) and deaths (dashed line) predicted by the Be-CoDiS model from December 7<sup>th</sup>, 2014 to January 7<sup>th</sup>, 2015.

### 3.2.3 Forecast for the 2014 EVD epidemic starting with data for December 7<sup>th</sup>, 2014

Now, we are interested in running our model starting with real data for December 7<sup>th</sup>, 2014 (the last date available at [30] when our numerical experiments were run) and analyse the obtained predictions. To this end, system (3) was started with the parameters presented in Section 3.1 and the initial conditions reported in Table 2 obtained by using the methodology presented in Section 3.1.2. The system was run until the end of the epidemic (i.e., the time for which the numbers of persons in states  $E$ ,  $I$ ,  $H$  and  $D$  are all lower than 1). We performed the study of the pandemic for a short time interval (by considering results on January 7<sup>th</sup>, 2015) and a long time interval (by considering the final date of the simulation) analysis.

**Short time interval forecast until January 7<sup>th</sup>, 2014:** The evolution of the cumulative numbers of total cases and deaths predicted by the model is presented in Figure 5. The evolution of the total numbers persons in states  $E$ ,  $I$ ,  $H$  and  $D$  is shown in Figure 6. The cumulative number of simulated cases and deaths, at the end of this interval, are 20366 and 6993, respectively. The epidemic seems to become stabilized with a slope that decreases progressively. As said previously, this tendency seems to be confirmed by the last reported data (see [30]). This is also clear in Figure 6, where it can be seen that the number of person in states  $E$ ,  $I$ ,  $H$  and  $D$  decreases significantly.

The list of countries with a number of persons in states  $E$ ,  $I$ ,  $H$  or  $D$  greater than 1 at least at one moment from December 7<sup>th</sup>, 2014 to January 7<sup>th</sup>, 2014 and their characteristics is reported in Table 8. We observe in this table that Guinea is the country with the higher risk of spreading EVD to other countries (the probability of sending one infected person during the time interval is around 1%). The other countries

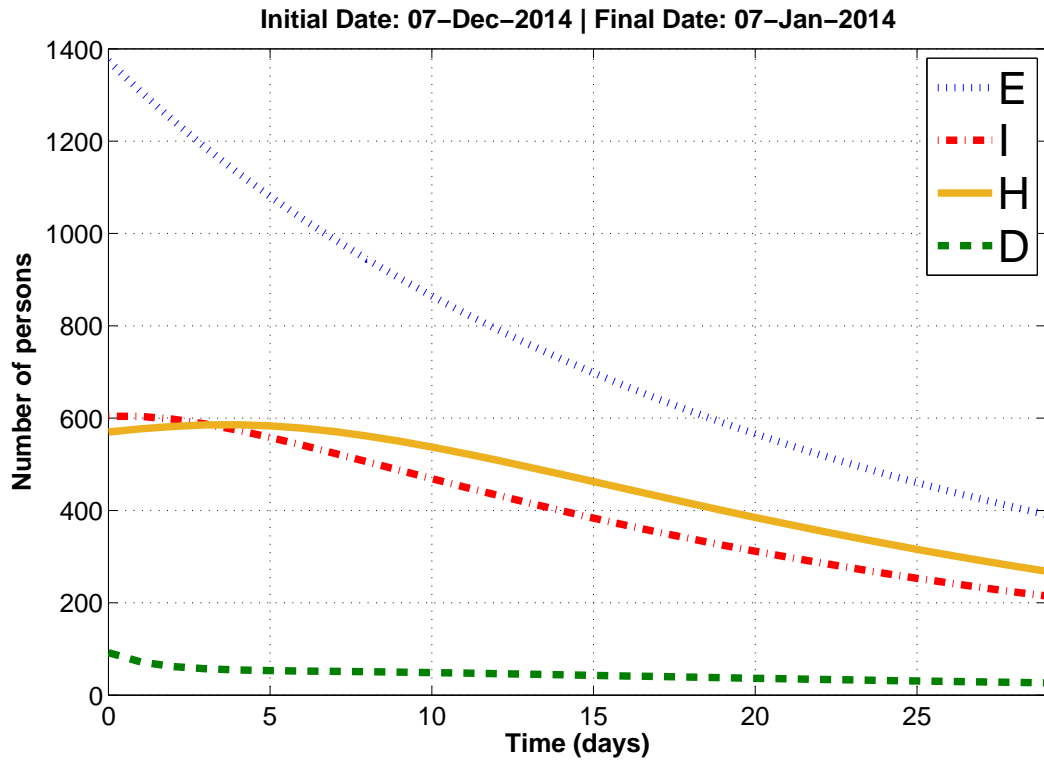


Figure 6: Evolution of the total numbers of persons in states  $E$  (dashed line),  $I$  (slash-dashed line),  $H$  (continuous line) and  $D$  (slashed line) predicted by the Be-CoDiS model from December 7<sup>th</sup>, 2014 to January 7<sup>th</sup>, 2015.



Table 8: Short time interval forecast: cumulative numbers of EVD cases (**Cases**), cumulative numbers of deaths (**Deaths**), maximum number of persons hospitalized at the same time (**MNH**), TRS and EmF values for countries affected by EVD predicted by Be-CoDiS on January 7<sup>th</sup>, 2015. We also report the cumulative number of EVD cases (**I.C.**) and the cumulative number of deaths (**I.D.**) reported on December 7<sup>th</sup>, 2014.

Country	Cases	Deaths	MNH	TRS	EmF	I.C.	I.D.
Total	20366	6993	1536	-	-	17521	6059
Sierra Leone	9617	2105	1125	$1.3 \times 10^{-4}$	$1.2 \times 10^{-4}$	7897	1768
Liberia	7913	3178	163	$4.9 \times 10^{-6}$	$1.8 \times 10^{-4}$	7719	3177
Guinea	2802	1695	250	$1.0 \times 10^{-2}$	$1.4 \times 10^{-3}$	2292	1428

present a much lower risk. This results is consistent with the fact that Guinea presents the highest value of EmF (at least ten times greater than other countries) combined with a large number of EVD cases. Regarding the magnitude of the epidemic, the model predicts that the number of cases in Sierra Leone can increase dramatically (around 1700 new cases) next month. On the opposite side the situation in Guinea and Liberia seems to be stabilized with a lower increase of cases (around 500 new cases). Regarding the values MNH of each country, we see that a maximum number of 1536 beds (obtained at December 13<sup>th</sup>, 2014 for this 1 month period) in hospitals dedicated to treat EVD cases should be planned to take care of the affected persons. This maximum number was estimated to be around 1733 in [30] (report date: December 7<sup>th</sup>, 2014) and, currently, 1269 beds are used.

Finally in Figure 7, we present a bar representation of the countries with the 20 highest values of TRI. More precisely, we report  $100 \times \text{TRI}$ , as this value represents the probability of introduction of at least 1 EVD case due to migration flow (%). We see that Sierra Leone, France and United Kingdom are the countries that clearly have the highest probabilities to receive an infected person during this 1 month period. Considering France and United Kingdom, which are currently free of EVD epidemic, their probabilities are around 0.17%. This list includes other African and European countries and Australia, but they present a low risk with probabilities lower than 0.05%. This classification seems to be consistent with the results found in [12], where France and United Kingdom are the countries with the highest probabilities to receive an infected person. However, in the former article, the probabilities of infection are around 75%.

**Long time interval forecast until the end of the EVD epidemic:** In this case, the model was started with real data for December 7<sup>th</sup>, 2014 and was run until October 29<sup>th</sup>, 2015 (i.e., the day that the EVD epidemic is assumed to be extinguished according to the model).

The evolution of the cumulative numbers of total cases and deaths predicted by the model is presented in Figure 8. The evolution of the total number of persons in states  $E$ ,  $I$ ,  $H$  and  $D$  is shown in Figure 9. The final numbers of reported cases and deaths, at the end of the time interval, are 21673 and 7452, respectively. As it can be observe on both Figures, within the next two months the epidemic seems to be controlled and no major increases should be observed after this period.

The list of countries with a number of persons in states  $E$ ,  $I$ ,  $H$  or  $D$  greater than 1 at least at one moment from December 7<sup>th</sup>, 2014 to October 29<sup>th</sup>, 2015 and their characteristics is reported in Table 9. We can see in this table that, the model predicts a medium outbreak in Gambia (around 96 cases and 20 deaths). The risk of spread from Guinea during the whole period is now 0.021, which corresponds to a probability of 2.1% of spreading at least one EVD case to other countries. Comparing the magnitude of the epidemic with the one observed at the end of the short time prediction done before, the number of new cases after two months is clearly reduced and, after this period, no major new cases should be reported. The maximum number of required beds in hospitals is still 1536 (as in the forecast for a short time interval studied above).

Finally in Figure 10, we present a bar representation of the countries with the 20 highest probabilities of introduction of EVD. Again, United Kingdom, France and Sierra Leone are the countries with the highest probabilities to receive an infected person (around 0.4%). Other countries in the list have a risk lower than 0.12%. A world map showing the distributions of TRI by countries is included in Figure 11. We see

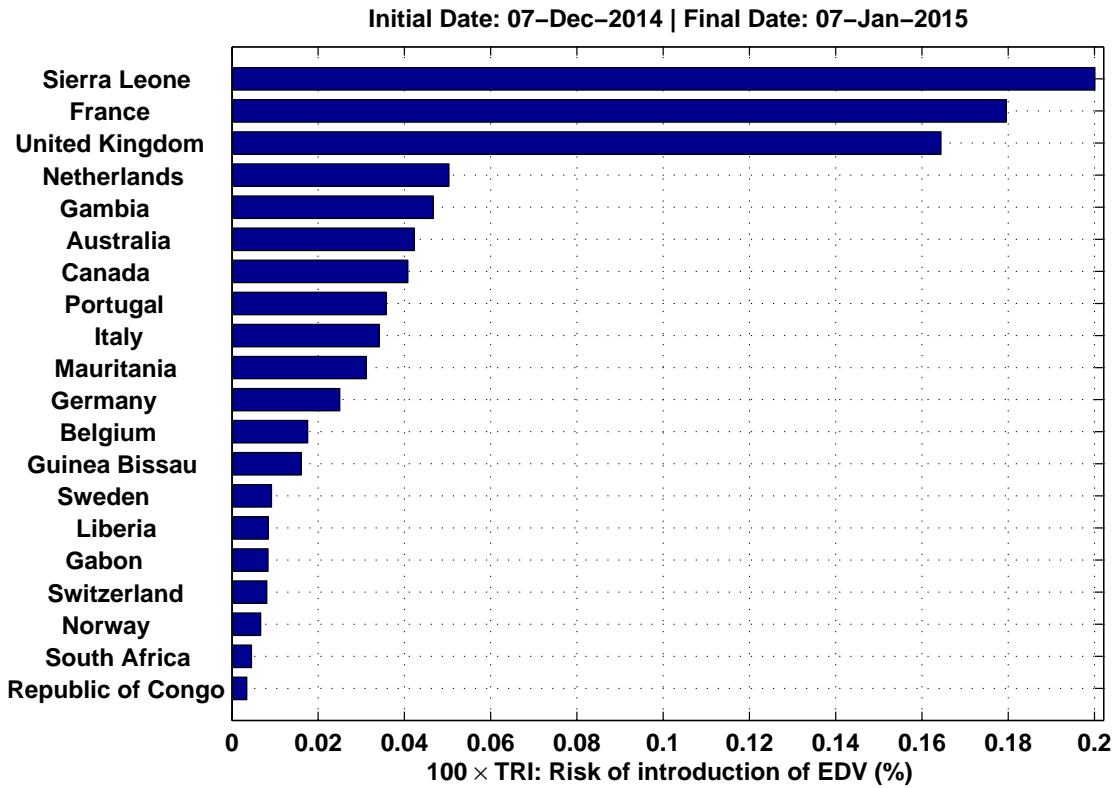


Figure 7: Countries with the 20 highest probabilities (%) of introduction of EVD, predicted by the Be-CoDiS model from December 7<sup>th</sup>, 2014 to January 7<sup>th</sup>, 2015.

Table 9: Long time interval forecast: cumulative number of EVD cases (**Cases**), cumulative number of deaths (**Deaths**), maximum number of persons hospitalized at the same time (**MNH**), TRS and EmF values for countries affected by EVD predicted by Be-CoDiS on October 29<sup>th</sup>, 2015.

Country	Cases	Deaths	MNH	TRS	EmF
Total	21673	7452	1536	-	-
Sierra Leone	10084	2182	1125	$1.5 \times 10^{-4}$	$1.2 \times 10^{-4}$
Liberia	7930	3178	163	$5.0 \times 10^{-6}$	$1.8 \times 10^{-4}$
Guinea	3531	2058	250	$2.1 \times 10^{-2}$	$1.4 \times 10^{-3}$
Gambia	96	20	21	$1.4 \times 10^{-3}$	$7.3 \times 10^{-4}$

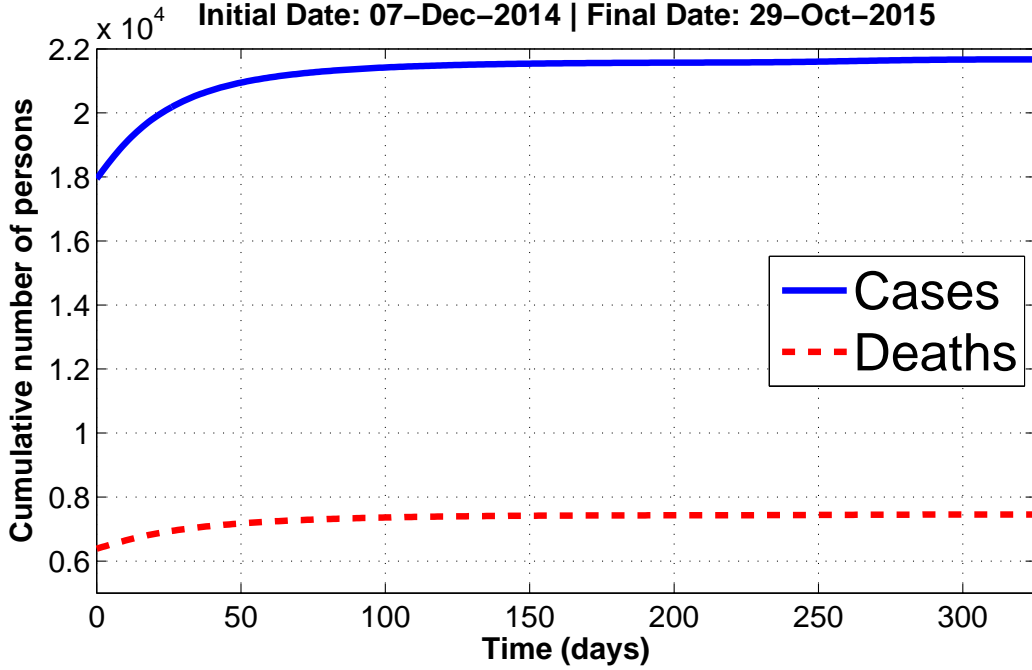


Figure 8: Evolution of the cumulative numbers of total EVD cases (continuous line) and deaths (dashed line) predicted by the Be-CoDiS model from December 7<sup>th</sup>, 2014 to October 29<sup>th</sup>, 2015.

Table 10: Results of the sensibility analysis presented in Section 3.3. We report the mean, median, minimum and maximum percentage variation of the considered outputs regarding their non perturbed value.

$\alpha$	Mean	Minimum	Maximum
1%	0.9	0.06	3.7
5%	3.7	0.3	14.9
10%	6.9	0.4	26.1

that Western Europe, Western Africa, Canada and Australia are the areas with the highest risk of EVD introduction in the whole studied period of time.

### 3.3 Model sensitivity analysis

The goal of this section is to provide a quick analysis of the variation of the Be-CoDiS outputs regarding perturbations on the input data. To do so the model was run 100 times, considering random uniform perturbations of amplitude  $[-\alpha, +\alpha]\%$  on all the parameters, with  $\alpha = 1\%$ ,  $5\%$ ,  $10\%$  and  $20\%$ . We considered the short time interval case studied in Section 3.2.3. We computed the mean percentage variations, considering all countries, of TRS, TRI, MNH,  $\text{cumul}_{\text{cases}}$  and  $\text{cumul}_{\text{deaths}}$ , regarding their respective non perturbed value. For each value of  $\alpha$ , we report the average minimum, maximum, median and mean value considering all those variables. Results are reported in Table 10.

From this table, we observe that perturbations of  $\alpha\%$  in the inputs generates mean output variations lower than  $\alpha\%$ . Therefore, it seems that there is a linear relationship between input and output perturbations. The maximum observed mean perturbation is 26.1% and is obtained for  $\alpha=10\%$ . This indicates that important variations in results can be obtained if input data are not good enough. A more extensive sensitivity

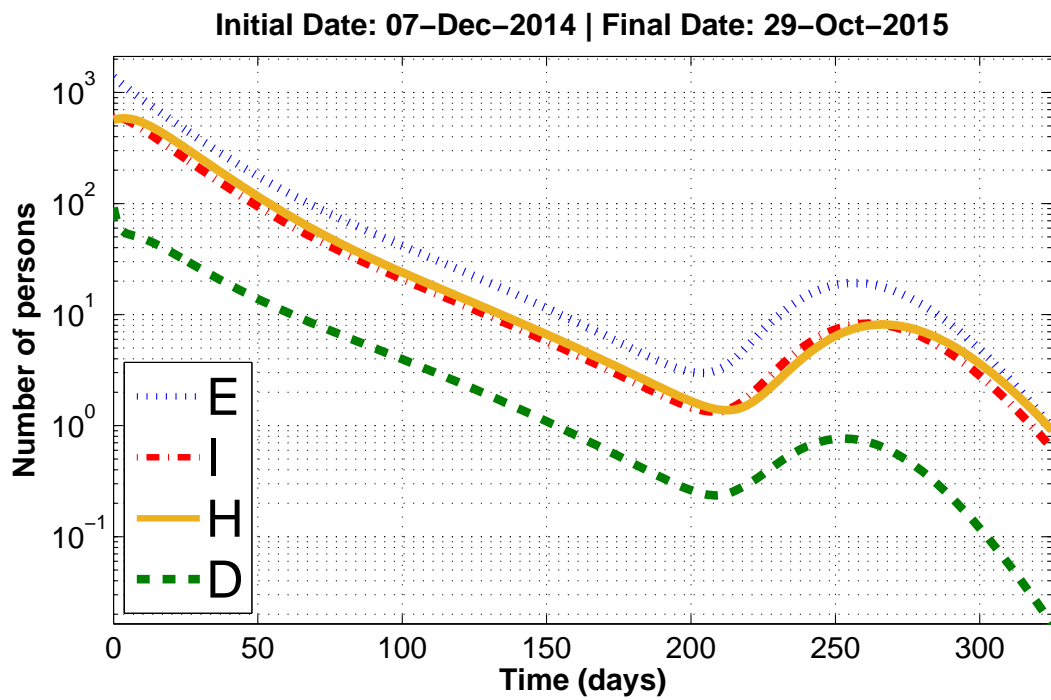


Figure 9: Evolution of the total numbers of persons in states  $E$  (dashed line),  $I$  (slash-dashed line),  $H$  (continuous line) and  $D$  (slashed line) predicted by the Be-CoDiS model from December 7<sup>th</sup>, 2014 to October 29<sup>th</sup>, 2015. We point out, the Y axis is presented in log scale.

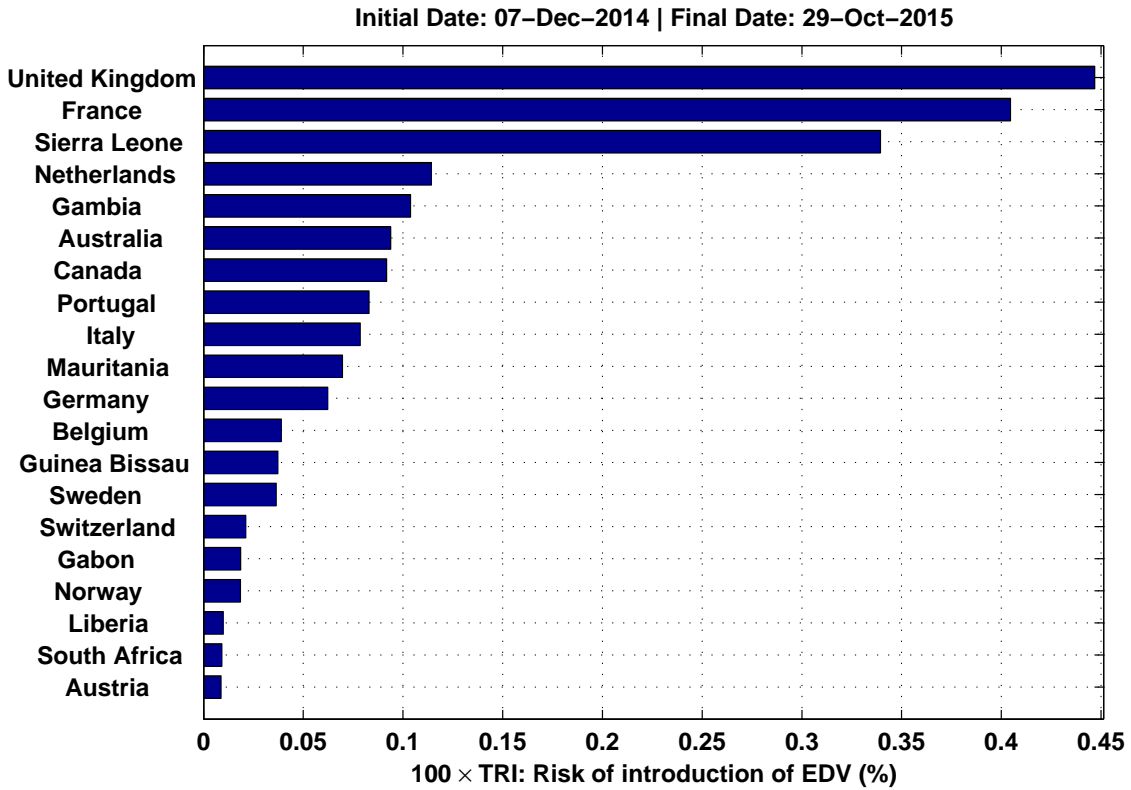


Figure 10: Countries with the 20 highest probability (%) of introduction of EVD, predicted by the Be-CoDiS model from December 7<sup>th</sup>, 2014 to October 29<sup>th</sup>, 2015.

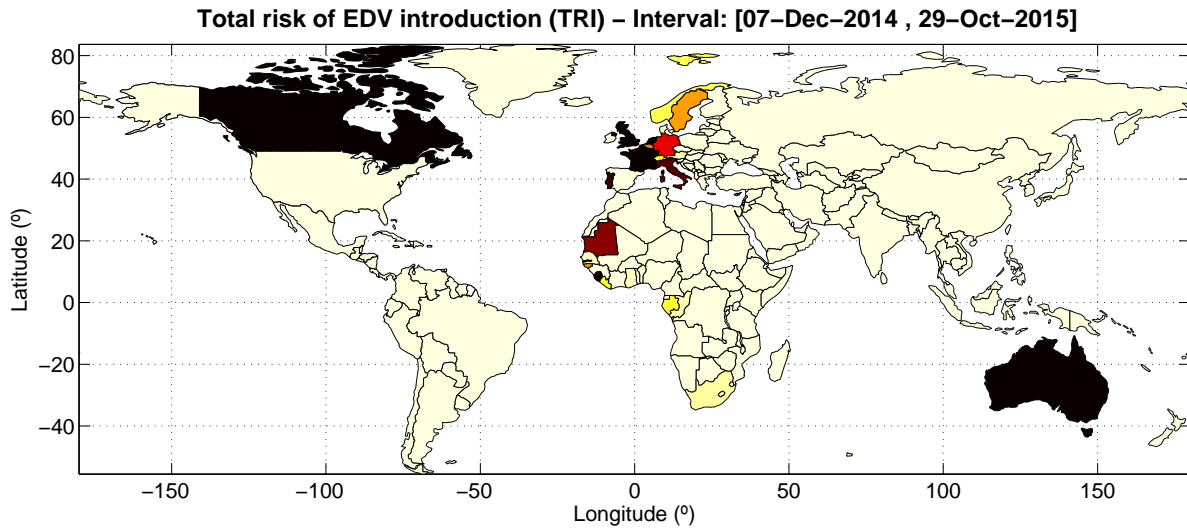


Figure 11: Total risk of EVD introduction (TRI) of each country, corresponding to the period from December 7<sup>th</sup>, 2014 to October 29<sup>th</sup>, 2015. Darker zones correspond to higher risk values.

analysis should be performed in order to identify the more influential model parameters and, thus, give recommendation about the result precision to possible users.

## 4 Conclusions

In this work, we have presented a first formulation of a new spatial-temporal epidemiological model, called Be-CoDiS, based on the combination of a deterministic Individual-Based model (modelling the interaction between countries, considered as individual) for between country spread with a deterministic compartmental model, based on ordinary differential equations, for within-country spread. The main characteristics of this model are the combination of the effects of the migratory flux between countries and control measures and the use of dynamic model coefficients. The model has been validated considering the current 2014 EVD epidemic that strikes several countries around the world and with the threat of a global extension.

Considering short and long time interval validation experiments, the model reproduces in a reasonable way the real epidemic evolution. Those results seems to indicate the validity of our approach.

Regarding the 30 days forecast results, starting with data reported for December 7<sup>th</sup>, 2014, Sierra Leone, France and United Kingdom are the countries with the highest probabilities of receiving an infected person, which is consistent with other studies, such as [12]. However, the probability of infection is 0.17%, which is low in comparison to the result found in other works.

Regarding a long time forecast, the epidemic should disappear within eleven months and no major outbreaks (i.e., more than 10 infected cases) should be reported except in Gambia, Guinea, Liberia and Sierra Leone. We observe that Gambia is currently free of the disease, and a particular vigilance could be considered. According to the model, the magnitude of the epidemic could reach a total of 21673 cases, with 7452 deaths. Moreover, the model estimates that maximum number of beds required in hospital was 1536 (for December 13<sup>th</sup>, 2014).

Finally, we have performed a brief sensitivity analysis of our model that seems to indicate a linear relation between perturbation in the inputs and outputs. However, in some cases, high variation can be obtained.

In this work, we have also highlighted the current limitation of our approach: simplified assumptions in the mathematical model, lack of precision in some data and the use of empirical assumptions. Those parts should be improved in the future.

The next steps should be the validation of the results found for short term intervals by using more recent data. Moreover, we should recalibrate the model coefficients using those new data. In addition, a more extensive sensitivity analysis should be performed in order to identify the parameters that have a strong impact on the model outputs. Finally, the model can be used to study the economical impact of the 2014 Ebola epidemic and to solve associated optimization resource problems (for instance, controlling the epidemic considering a constrained economical budget).

## acknowledgements

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