Be-CoDiS: An epidemiological 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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Remark 1. \textit{Important changes done regarding the previous version of this paper (see [13]):}

\begin{itemize}
  \item Contacts with infected cadavers are now considered by the model.
  \item The methods used to estimate the model initial conditions and the model parameters have been corrected.
  \item The model parameters and the results have been updated to the situation on November \textsuperscript{9th}, 2014.
\end{itemize}

\textit{Results found with those changes fit better the last real data reported in [28].}

Abstract

Ebola virus disease (EVD) is a lethal human and primate disease that currently requires a particular attention from the national and international health authorities due to important outbreaks concurring 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 help the authorities to focus their efforts in important factors that can help to eradicate Ebola. Mathematical modeling and, more precisely, epidemiological modeling can help to predict the possible evolution of the Ebola outbreaks and to give some recommendations in the region to be prioritized for 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 world wide. This model is a particular adaptation of a previous epidemiological software, called Be-FAST, used to predict the spatial spread of animal diseases. The main interesting characteristics of Be-CoDiS are the consideration of the migratory
flux between countries and control measure effects (such as, hospitalized persons and quarantine areas) 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. Those experiments are based on both short and long term forecast of the EVD epidemic evolution. 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, taking into account that some empirical assumptions have been used regarding the coefficients of our model, a parameter sensitivity analysis is done. According to the results returned by the model, we found that France and United Kingdom are the countries, currently free of Ebola, with the higher probability to be infected by EVD within the next 30 days. However, the probability of EVD introduction in those countries during this time interval is quite low and is around 0.2%. Regarding the forecast at the end of the epidemic, we found that the EVD epidemic should disappear within 9 months and no major outbreaks (i.e., > 10 cases) should be reported except in Liberia, Guinea, Sierra Leone, Nigeria, Mali and Gambia. The magnitude of the epidemic could reach a total of 20043 cases, 8603 deaths and requires around 2115 beds in hospitals. The sensitivity analysis shows a linear relation between inputs and outputs precisions.

Keywords: epidemiological modelling, Ebola Virus Disease, risk analysis, Be-FAST model, Be-CoDiS model.

1 Introduction

Modeling and simulation are important decision tools that can be used to control or eradicate human and animal diseases [1, 26]. Each disease presents its own characteristics and, thus, most of them need a well-adapted simulation model in order to tackle real situations [3].

In this work, we present a first version of a new spatial-temporal epidemiological model, called Be-CoDiS (Between-Countries Disease Spread), adapted to the study of the spread of human disease in a considered area. This model is an adaptation of a previous software, called Be-FAST (Between Farm Animal Spatial Transmission), which focus 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 [12, 18] and validated on various cases as, for example: Classical swine fever in Spain and Bulgaria [17, 19], and Foot-and-Mouth disease in Peru [16]. Be-CoDiS is based on the combination of a deterministic Individual-Based model (where the countries are considered as individuals) [6], simulating the between-country interactions (here, migratory flux) and disease spread, with a deterministic compartmental model [3] (a system of ordinary differential equations), simulating the within-country disease spread. We note 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) [7, 23, 27]. EVD is a human and primates virus disease that causes a high mortality rate (between 50% and 90%). Currently, several important outbreaks have been reported in Western Africa (Guinea, Liberia, Sierra Leone and Nigeria). Furthermore, seven isolated cases were detected in Mali, Senegal, the USA and Spain and the risk to have a EVD propagation outside Africa (its natural reservoir) is real. 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) horizons. In order to validate our approach, results obtained by Be-CoDiS are compared to historical data and with other studies found in
the literature \cite{8,11,9,21,27,28,29} regarding the same 2014 EVD outbreaks. The work in \cite{9} 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 recall the main characteristics of the EVD. In Section 3, we give a detailed presentation of our model. In Section 4, we focus on the validation of Be-CoDiS by considering the 2014 EVD outbreaks. We compare the outputs given by our model, considering short time and long time horizons, with real observed data and results from other models. Then, we perform two EVD epidemic forecasts considering a 30 days time period 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 Main characteristics of Ebola Virus Disease

EVD is a lethal human and primates diseases caused by the Ebolavirus (EV, 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. This virus was first identified in Sudan and Zaire in 1976 \cite{7}.

Various important outbreaks have occurred in 1995, 2003 and 2007 in the Democratic Republic of Congo (315, 143 and 103 affected people, respectively), in 2000 and 2007 in Uganda (425 and 149 affected people, respectively), in 2003 \cite{23,5}. The 2014 outbreak started in December 2013 in Guinea and spread to Liberia and Sierra Leone. In March 2014, the international community was alerted about the gravity of the situation in those three countries. The situation on November 9th, 2014 (the date used to run our numerical experiments) was a total of 14098 affected people in Guinea, Liberia, Sierra Leone and Nigeria \cite{27,28}. The observed fatality percentage for this particular hazard was 70.8%. Moreover, 10 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.

From an epidemiological point of view, the EVD can be transmitted rarely between natural reservoirs (for instance, bats) and humans due to the contact with animal carcass \cite{14}. The most common way of EVD human transmission is due to contacts with blood or bodily fluids from an infected person (including dead person) or by contact with contaminated fomites (e.g., agriculture material).

Regarding data of the 2014 outbreak, 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 passes successively through the following states (see \cite{15,21,23,29}):

- 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 be infectious state.
- Infectious (denoted by $I$): The person can infect other people and start developing clinical signs. The mean duration is 5.0 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 this sate is 5 days (see \cite{15}). 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 [28]). On the one hand, after a mean duration of 4.2 days (range [1,11] days), 70.8% (range of [68,73]%) of the hospitalized persons die due to the EVD clinical signs and pass to the state Dead. On the other hand, the persons who have survived to EVD pass to the Recovered state.

- **Dead** (denoted by $D$): The person has not survived to the clinical signs. 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 by contact with infectious persons (see [15]). After a mean period of 2 days the body is buried.

- **Buried** (denoted by $B$): The person is dead. Its cadaver is buried and is no longer considered as infectious.

- **Recovered** (denoted by $R$): The person has survived to the clinical signs, is recovered from the EVD and is no longer infectious. It develops 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 any more by Ebola.

A person in the state $E$, $I$ or $H$ is called a contaminated person. Moreover, a person in the state $I$ or $H$ is also called a spreading person.

Once an EVD infected person is hospitalized, the authorities apply various control measures in order to control the EVD spread (see [27, 28, 8]):

- **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 [5]).

- **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.

We note that once a person is detected [28].

**Remark 2.** The above data are 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 [29]). 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.

**3 Mathematical formulation of the model**

In this Section, we describe in detail the Be-CoDiS model by presenting its general structure, the considered within and country countries disease spread sub-models. The main notations used in this work are summarized in Table 1.

**Remark 3.** 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 easily adapted to other disease. For instance, the classification of compartments in the SEIHR model can be changed to study other cases.
3.1 General description

The Be-CoDiS model is used to evaluate the spread of a considered 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 4.2). At the initial time \( t = 0 \), only susceptible people live in the countries that are free of diseases, whereas the number of persons in state \( E \), \( I \), \( H \), and \( R \) of the infected countries are set to their corresponding values (e.g., the current situation of 2014 Ebola outbreak). Then, during the time interval \( [0, T_{\text{max}}] \), with \( T_{\text{max}} \in \mathbb{N} \) the maximum number of simulation days, the within-country and between-country daily spread procedures (described in Section 3.2) are applied. If at the end of a simulation day \( t \) all the people in the considered countries are in the susceptible state, the simulation is stopped. Else, the simulation is stopped when \( t = T_{\text{max}} \). 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 an EVD epidemic.

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

3.2 Within-Countries disease spread

The dynamic disease spread within a particular contaminated country \( i \) is modeled by using a deterministic compartmental model (see [3]).

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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 |
|----------|-------------|
| \( T_{\text{max}} \) | Maximum number of simulation days (day) |
| \( \Delta t \) | Time discretisation step size (day) |
| \( \beta_{I}(i,t) \) | Disease contact rate of a person in state \( I \) in country \( i \) at time \( t \) (day\(^{-1}\)) |
| \( \beta_{H}(i,t) \) | Disease contact rate of a person in state \( H \) in country \( i \) at time \( t \) (day\(^{-1}\)) |
| \( \beta_{D}(i,t) \) | Disease contact rate of a person in state \( D \) in country \( i \) at time \( t \) (day\(^{-1}\)) |
| \( \gamma_{E} \) | Transition rate of a person in state \( E \) (day\(^{-1}\)) |
| \( \gamma_{I} \) | Transition rate of a person in state \( I \) (day\(^{-1}\)) |
| \( \gamma_{HR} \) | Transition rate of a person in state \( H \) to state \( R \) (day\(^{-1}\)) |
| \( \mu_{m}(i) \) | Natural mortality rate in country \( i \) (day\(^{-1}\)) |
| \( \mu_{n}(i) \) | Natural natality rate in country \( i \) (day\(^{-1}\)) |
| \( \omega(i) \) | Disease fatality percentage in country \( i \) (\%) |
| \( m_{I}(i,t)/m_{H}(i,t) \) | Control measure efficiency (\%) in country \( i \) at time \( t \) applied to persons in state \( I \) or \( H \), respectively |
| \( m_{t}(i,j,t) \) | 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 \( j \) (day\(^{-1}\)) |
| \( N_{C} \) | Number of countries in the studied region |
| \( N_{P}(i,t) \) | Number of persons in country \( i \) at time \( t \) |
| \( S(i,t)/E(i,t)/I(i,t) \) | Number of persons in state \( S \), \( E \), \( I \), \( H \), \( R \), \( D \), \( B \) in country \( i \) at time \( t \) |
We assume that the people in a country are characterized to be in one of those states, described in Section 2: Susceptible (\(S\)), Infected (\(E\)), Infectious (\(I\)), Hospitalized (\(H\)) or Recovered (\(R\)). 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 3.2 we do not consider interaction between countries.

Under those assumptions, the evolution of \(S(i, t)\), \(E(i, t)\), \(I(i, t)\), \(H(i, t)\) and \(R(i, t)\), denoting the number of susceptible, infected, infectious, hospitalized and recovered persons in country \(i\) at time \(t\), respectively, is modeled by
\[
\frac{dS(i, t)}{dt} = \frac{-S(i, t)\left(\sum_{j}I(j, t)\beta_{ij(i, t)}I(i, t) + m_H(i, t)\beta_H(i, t)H(i, t) + m_D(i, t)\beta_D(i, t)D(i, t)\right)}{NP(i, t)} + \mu_n(i)\left(S(i, t) + E(i, t) + I(i, t) + H(i, t) + R(i, t)\right) - \mu_m(i)S(i, t),
\]
\[
\frac{dE(i, t)}{dt} = \frac{S(i, t)\left(\sum_{j}I(j, t)\beta_{ij(i, t)}I(i, t) + m_H(i, t)\beta_H(i, t)H(i, t) + m_D(i, t)\beta_D(i, t)D(i, t)\right)}{NP(i, t)} - \mu_m(i)E(i, t) - \gamma_EX_{fit}(E(i, t)),
\]
\[
\frac{dI(i, t)}{dt} = \gamma_EX_{fit}(E(i, t)) - (\mu_m(i) + \gamma_I)I(i, t),
\]
\[
\frac{dH(i, t)}{dt} = \gamma_II(i, t) - (\mu_m(i) + (1 - \omega(i))\gamma_HR + \omega(i)\gamma_HD)H(i, t),
\]
\[
\frac{dR(i, t)}{dt} = (1 - \omega(i))\gamma_HR\gamma_HD - \mu_m(i)R(i, t),
\]
\[
\frac{dD(i, t)}{dt} = \omega(i)\gamma_HD - \gamma_D D(i, t),
\]
\[
\frac{dB(i, t)}{dt} = \gamma_D D(i, t),
\]

where:

- \( i \in \{1, \ldots, N_{CO}\} \),
- \( X_{fit}(x) = x \) if \( x \geq \epsilon_{fit} \), and 0 elsewhere, with \( \epsilon_{fit} \in \mathbb{R}^{+} \) (small),
- \( N_{CO} \in \mathbb{N} \) is the number of countries,
- \( NP(i, t) = S(i, t) + E(i, t) + I(i, t) + H(i, t) + R(i, t) \) is the number of persons in country \( i \) at time \( t \),
- \( \mu_n(i) \in [0, 1] \) is the natality rate (day\(^{-1}\)) in country \( i \): the number of births per day and per capita,
- \( \mu_m(i) \in [0, 1] \) is the mortality rate (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),
- \( \omega(i) \in [0, 1] \) is the disease fatality percentage in country \( i \): the percentage of persons who do not survive the disease,
- \( \beta_{ij(i, t)} \in \mathbb{R}^{+} \) is the disease contact rate (day\(^{-1}\)) with people in state \( I \) in country \( i \) at time \( t \): the mean number of effective contacts (i.e., contacts with people in state \( I \) sufficient to transmit the disease) of a person per day before applying control measures,
- \( \beta_H(i, t) \in \mathbb{R}^{+} \) is the disease contact rate (day\(^{-1}\)) with people in state \( H \) in country \( i \) at time \( t \),
- \( \beta_D(i, t) \in \mathbb{R}^{+} \) is the disease contact rate (day\(^{-1}\)) with people in state \( D \) in country \( i \) at time \( t \),
• \( \gamma_E, \gamma_I, \gamma_{HR}, \gamma_{HD}, \gamma_D \in \mathbb{R}^+ \) denote the transition rate (day\(^{-1}\)) from a person in the \( E, I, H, H \) or \( D \) state to the \( I, H, R, D \) or \( B \) state, 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 \( E, I, H \) 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., \( \beta_I(i,t), \beta_H(i,t) \) and \( \beta_D(i,t) \)) 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 [24]):

\[
m_I(i,t) = m_H(i,t) = m_D(i,t) = \exp \left( -\kappa_i \max(t - \lambda(i), 0) \right),
\]

where \( \kappa_i \in \mathbb{R}^+ \) (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 \( S(i,0), E(i,0), I(i,0), H(i,0) \) and \( R(i,0) \) given in \( \mathbb{R} \), for \( i=1,..,N_{CO} \).

We note 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 4 for the EVD case.

Remark 4. In System (1), function \( X_{\text{fit}}(x) \) is a filter used to avoid artificial spread of the epidemic due to negligible values of \( x \).

### 3.3 Between-Countries disease spread

The disease spread between countries is modeled by using a spatial deterministic Individual-Based model (see [6]). 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 the O state 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 the F state.

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 O state, 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\(^{-1}\)) 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 \( E \) states 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, which is nonincreasing in time, denoted by \( m_{tr}(i,j,t) \). Here, we consider

\[
m_{tr}(i,j,t) = m_I(i,t)m_I(j,t).
\]

Thus, we consider the following modified version of System (1):
We solve numerically the System (3) with the corresponding initial values by using the explicit Euler scheme. Next, we are able to compare our model outputs with the information available in the following literature [8, 2, 27].

To do so, we first introduce in Section 4.1 a numerical model approximating the solution of continuous model (3). Then, we explain in Section 4.2 how to estimate the model parameters for the EVD. Next, we present the results and discuss them in Section 4.3. Finally, in Section 4.4, we carry out a brief sensitivity analysis regarding the parameters values.

4 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 [8, 2, 27].

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

4.1 Numerical implementation of Be-CoDiS

We solve numerically the System (3) with the corresponding initial values by using the explicit Euler scheme with a time step of 1 day and $\epsilon_{\text{fit}} = 10^{-5}$. System 3 is completed with initial data $S(i, 0), E(i, 0), I(i, 0), H(i, 0)$ and $R(i, 0)$ given in $\mathbb{R}$; for $i=1,.., N_{\text{CO}}$.
This algorithm was implemented in Matlab 2014a and runs on a laptop with a quadcore i7-3740QM 2.7GHz CPUs with 16Gb of ram. One simulation with $T_{\text{max}}=365$ days and the parameters given below requires around 25 seconds.

4.2 Be-CoDiS parameters estimation for EVD

The parameters used in the simulations presented in Section 4.3 have been found in the literature \cite{8, 2, 5, 9} and in the daily reports on the Ebola evolution available online (see \cite{4, 28}). 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.

4.2.1 Country indicators

We have done some assumption regarding the dependence of the parameters described below with respect to some characteristics of the countries. More precisely, we have considered information regarding country $i$:

- $\text{TMP}_i(t) \in \mathbb{R}$: Mean temperature ($^\circ$C) at day $t$.
- $\text{DEN}_i \in \mathbb{R}^+$: People density (persons/m$^2$).
- $N_P(i, 0) \in \mathbb{N}$: Total number of persons.
- $\text{GNI}_i \in \mathbb{R}^+$: Gross National Income per year per capita (US$.\text{person}^{-1} \cdot \text{year}^{-1})$. We remind that the Gross National Income is an indicator of the economy in country: the total domestic and foreign output claimed by residents of a country.
- $\text{SAN}_i \in \mathbb{R}^+$: The mean Health expenditure per year per capita (US$.\text{person}^{-1} \cdot \text{year}^{-1})$. This is an economical indicator of the sanitary system of a country.
- $\text{MLE}_i \in \mathbb{R}^+$: The mean life expectancy (days).
- $\mu_n(i) \in [0, 1]$: See Section 3.2

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

4.2.2 Initial conditions

We have considered the initial conditions for our System (3) corresponding to the state of the EVD epidemic at a date reported in \cite{28}.

However, in previous reference, only the cumulative numbers of reported cases (i.e., a person in state $H$, see \cite{29}) and deaths in the affected country $i$ at date $t$, denoted by $\text{NRC}(i, t)$ and $\text{NRD}(i, t)$, are given for dates starting on March, 23rd 2014. Thus, we estimate the amount of persons in state $E, I, H, R, D$ and $B$ at $t = 0$ by taking into account the characteristics of the EVD presented in Section 2.

- As the main duration from state $H$ is 5 days, we compute $H(i, t)$ we have computed $H(i, t)$ by considering the number of cases alive reported at date $t$ minus the number of cases alive reported 5 days before
  \[ H(i, 0) = ((\text{NRC}(i, 0) - \text{NRD}(i, 0)) - (\text{NRC}(i, -5) - \text{NRD}(i, -5))). \]

- As the main duration from state $D$ is 2 days, we compute $D(i, t)$ as
  \[ D(i, 0) = (\text{NRD}(i, 0) - \text{NRD}(i, -2))). \]
The number of persons in states $I$ and $E$ are estimated by considering the mean duration of a person in those states, the mean duration of a person in state $H$ in country $i$ denoted by $\gamma_H(i)$, and the number of persons who have been in state $H$ during the last 5 days denoted by $TH(i,0) = NRC(i,0) - NRC(i,-5)$. Thus, we consider

We compute $E(i,t) = \frac{\gamma_H(i)}{\gamma_E} \cdot TH(i,0)$ and $I(i,t) = \frac{\gamma_H(i)}{\gamma_I} \cdot TH(i,0)$,

where $\gamma_H(i) = (\omega(i) \cdot \gamma_{HD} + (1 - \omega(i)) \cdot \gamma_{HR})$.

- 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.

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

This information, regarding the 2005-2010 human migratory fluxes between countries, was found in [10] and the free database available in [http://www.global-migration.info/](http://www.global-migration.info/). The original data, denoted by $\tilde{\tau}(i,j)$, represent the number of persons who have 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.

We compute for a country $i$, $EmF(i) = \sum_{i \neq j} \tau(i,j)$, the total emigration flow.

### 4.2.4 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 4.2.1 and 2, we estimate the following parameters for our model:

- $\mu_m(i) = 1/\text{MLE}_i$ (day$^{-1}$)
- $\omega(i) = 0.25 \cdot \frac{\text{SAN}_i}{\max_i(\text{SAN}_i)} + 0.70 \cdot (1 - \frac{\text{SAN}_i}{\max_i(\text{SAN}_i)})$, as we know that the EVD fatality percentage oscillate between $[25, 70]$, depending on the quality of the sanitary service (see [21]).
- $\gamma_E = 1/11.4$ (day$^{-1}$), $\gamma_I = 1/5.0$ (day$^{-1}$), $\gamma_{HR} = 1/5.0$ (day$^{-1}$), $\gamma_{HD} = 1/4.2$ (day$^{-1}$), $\gamma_D = 1/2$ (day$^{-1}$).
- $\beta_I(i,t)$: There exists various works on the computation of the EVD effective contact rate $\beta_I(i,t)$ considering various SIR model (see [2, 4]). 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 [28, 4]).
– In Guinea, identified as the country of origin of the EVD epidemic, the index case was identified as a young boy who died on December 6th, 2013 and infected 3 persons of its family. On March 24th, 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 [28]). 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 thus, we fit those data with the solution given by System (1). To do so, System (1) is started at $t = 0$ (corresponding to December 06th, 2013) with 3 persons in the state $I$ in Guinea, 1 person in state $D$ and all other persons being free of disease. The model is run with $T_{\text{max}} = 108$ days (corresponding to March 24th, 2014 as the final date). In this simulation, we do not consider control measures (i.e., for any $(i,j,t) \in \mathbb{N} \times \mathbb{N} \times \mathbb{R}$, $m_I(i,t) = m_H(i,t) = m_D(i,j,t) = 1$). All other parameters are set to the values introduced previously. Considering a particular value $\beta_I^{\text{(Guinea)}} \in \mathbb{R}^+$, at the end of this simulation we compute the model error $\text{Err}(\beta_I^{\text{(Guinea)}})$, defined as absolute value of the the cumulative number of reported cases at the end of our simulation (see Section 4.3.2) minus NRC(\text{Guinea}, T_{\text{max}}). We minimized $\text{Err}(\beta_I(\text{Guinea}))$ by considering a dichotomy algorithm starting from $\beta_I(\text{Guinea})=0.117$ (day$^{-1}$) (value reported in [2]) and found an optimal value of $\beta_I(\text{Guinea})=0.2135$ (day$^{-1}$).

– In Sierra Leone, 305 cases and 127 deaths were reported on July 6th, 2014. Major control measures were applied on July 27th, 2014, when the cumulative number of reported cases was 533 with 233 deaths. We use the same fitting technique as in the case of Guinea, with System (1) started at $t = 0$ (corresponding to May 28th, 2014) with 85, 37, 33, 10, 145 and 117 persons in the state $E$, $I$, $H$, $D$, $R$ and $B$, respectively (considering the estimation method presented in Section 4.2.2) and all other persons being free of disease. The system is run with $T_{\text{max}} = 21$ days (i.e., final date at July 30th, 2014). We found $\beta_I(\text{Sierra Leone})=0.3180$ (day$^{-1}$).

– In Liberia, 131 cases and 84 death were reported on July 6th, 2014. On August 4th, 2014, before the application of control measures, 516 cases and 282 deaths were observed. System (1) is started at $t = 0$ (i.e., corresponding to July 1st, 2014) with 38, 17, 15, 9, 116 and 75 persons in the state $E$, $I$, $H$, $D$, $R$ and $B$, respectively (see Section 4.2.2). This system is run during $T_{\text{max}} = 29$ days. Applying the same technique as for Guinea and Sierra Leone, we found $\beta_I(\text{Liberia})=0.5294$ (day$^{-1}$).

Considering 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 create function $\beta_I(r_\beta \cdot \text{GNI}_i/\text{DEN}_i)$, where $r_\beta \in \mathbb{R}$ (m$^{-2}$ · US$^{-1}$ · persons$^2$ year$^{-1}$) is a balance parameter which determines the importance of GNI$^i$ on the value of $\beta_I$ in comparison to DEN$^i$. Indeed, the variable $r_\beta \cdot \text{GNI}_i/\text{DEN}_i$ is chosen because of the following reasons: 1) we assume that the more dense is a country, the higher is the probability of contagion; 2) the higher the economy level of country is, the higher is the education level and the lower the EVD risk habits of persons are (for instance, touching cadavers during funerals, see [22, 11]). We note that $\text{GNI}_{\text{Guinea}}/\text{DEN}_{\text{Guinea}} = 5.49$ (m$^2$ · US$^{-1}$ · persons$^2$ year$^{-1}$), $\text{GNI}_{\text{Sierra Leone}}/\text{DEN}_{\text{Sierra Leone}} = 4.24$ (m$^2$ · US$^{-1}$ · persons$^2$ year$^{-1}$) and $\text{GNI}_{\text{Liberia}}/\text{DEN}_{\text{Liberia}} = 3.0236$ (m$^2$ · US$^{-1}$ · persons$^2$ year$^{-1}$). In addition, we propose to use a function of the form

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

where $a_\beta$ (day$^{-1}$), $b_\beta$ and $c_\beta$ (day$^{-1}$) $\in \mathbb{R}$. We found, by considering the nonlinear regression method ‘nlinfit’ implemented in Matlab for $\beta_I$ with the points $(r_\beta \cdot \text{GNI}_{\text{Guinea}}/\text{DEN}_{\text{Guinea}}, \beta_I(\text{Guinea}))$, $(r_\beta \cdot \text{GNI}_{\text{Sierra Leone}}/\text{DEN}_{\text{Sierra Leone}}, \beta_I(\text{Sierra Leone}))$ and $(r_\beta \cdot \text{GNI}_{\text{Liberia}}/\text{DEN}_{\text{Liberia}}, \beta_I(\text{Liberia}))$ detailed previously, that $a_\beta = 15.2106$, $b_\beta = -0.1168$, $c_\beta = 0.3746$ and $r_\beta = -3.7097$.

**Remark 5.** As said in Section 3, it has been observed that Ebola Virus survives better outside the host for lower temperatures (see [22]). Thus, it could be interesting to introduce a slight dependence of
\( \beta_i(t, \tau) \) on the temperature of the country \( i \). For instance, we could consider:

\[
\bar{\beta}_i(t, \tau) = \beta_i \left( r_\beta \cdot \frac{\text{GNI}_i}{\text{DEN}_i} \right) \left( 1 - \alpha \cdot \frac{\text{TMP}_i(t) - \text{TMP}_{\text{ref}}}{\max_{i,t} |\text{TMP}_i(t) - \text{TMP}_{\text{ref}}|} \right),
\]

where \( \text{TMP}_{\text{ref}} \) (°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.

- \( \beta_H(i, \tau) = \frac{\beta_i(t, \tau)}{26} \) (day\(^{-1}\)),
- \( \beta_D(i, \tau) = \beta_i(t, \tau) \) (day\(^{-1}\)).

### 4.2.5 Control measure rate \( \kappa_i \)

In order to fit \( \kappa_i \) we use data from Guinea, Sierra Leone and Liberia.

- In Guinea, control measures were applied starting on March 24th, 2014. On November, 9th, 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 6th, 2013) with 3 persons in the state \( I \) and 1 person in the state \( D \) in Guinea and all other persons being free of the disease. The model is run with \( T_{\text{max}} = 306 \) days (corresponding to the date November, 9th, 2014). In this simulation, the control measures are applied after \( t = 107 \) days (i.e., \( \lambda(\text{Guinea}) = 108 \) days). Considering a particular value \( \kappa_{\text{Guinea}} \), we compute 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 \( \kappa_{\text{Guinea}} = 0.002378 \) (day\(^{-1}\)).

- In Sierra Leone, control measures were applied starting on July 27th, 2014. On November, 9th, 2014, the number of reported cases in Sierra Leone was 5368. We use the same fitting method as in Guinea and started System (1) with the same conditions as those used for computing \( \beta_i^{\text{Sierra Leone}} \). The system was started with \( T_{\text{max}} = 133 \) days and control measures are applied at day \( \lambda(\text{Sierra Leone}) = 64 \) (i.e., corresponding to July 27th, 2014). We found \( \kappa_{\text{Sierra Leone}} = 0.011557 \).

- In Liberia, extensive control measures started on August 4th, 2014. At November 9th, 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 \( \beta_i^{\text{Liberia}} \). This system was run with \( T_{\text{max}} = 99 \) days and control measures were applied at day 36. We found \( \kappa_{\text{Liberia}} = 0.047635 \).

Considering those three values, we perform a regression method similar to the one introduced in Section 4.2.4 for computing \( \tilde{\kappa}(r_\kappa \cdot \text{SAN}_i / \text{DEN}_i) \). In this function, the efficiency of the control measures depends on: 1) the sanitary expenses \( \text{SAN}_i \), as this value represent the amount of money inverted by public and private institutions (national or international) in the sanitary system of a country; 2) the higher is the value \( \text{DEN}_i \), the harder is to respect the control measures are. We note that \( \text{GNI}_{\text{Guinea}} / \text{DEN}_{\text{Guinea}} = 5.70 \cdot 10^{-8} \) (m\(^2\) · US$ · persons\(^{-2}\) · year\(^{-1}\)), \( \text{GNI}_{\text{Sierra Leone}} / \text{DEN}_{\text{Sierra Leone}} = 1.86 \cdot 10^{-7} \) (m\(^2\) · US$ · persons\(^{-2}\) · year\(^{-1}\)) and \( \text{GNI}_{\text{Liberia}} / \text{DEN}_{\text{Liberia}} = 3.42 \cdot 10^{-7} \) (m\(^2\) · US$ · persons\(^{-2}\) · year\(^{-1}\)).

Again, we propose to use

\[
\tilde{\kappa}(r_\kappa \cdot \frac{\text{SAN}_i}{\text{DEN}_i}) = a_\kappa \cdot \arctan (r_\kappa \cdot \frac{\text{SAN}_i}{\text{DEN}_i} + b_\kappa) + c_\kappa,
\]

where \( a_\kappa \) (day\(^{-1}\)), \( b_\kappa \) and \( c_\kappa \) (day\(^{-1}\)) \( \in \mathbb{R} \). We found, by considering the nonlinear regression method ’\text{nlmfit}’ implemented in Matlab for \( \beta_i \) with the points \( (r_\kappa \cdot \text{SAN}_{\text{Guinea}} / \text{DEN}_{\text{Guinea}}, \tilde{\kappa}(\text{Guinea})) \), \( (r_\kappa \cdot \text{SAN}_{\text{Sierra Leone}} / \text{DEN}_{\text{Sierra Leone}}, \tilde{\kappa}(\text{Sierra Leone})) \), \( (r_\kappa \cdot \text{SAN}_{\text{Liberia}} / \text{DEN}_{\text{Liberia}}, \tilde{\kappa}(\text{Liberia})) \), and the point \((0,0)\) (i.e., we assume that no sanitary expense implies no control measures) that \( a_\kappa = 0.0316 \), \( b_\kappa = -8.9408 \), \( c_\kappa = 0.0217 \) and \( r_\kappa = 6.7102 \).
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 $\left(\kappa_{\text{Liberia}} + \kappa_{\text{Sierra Leone}}\right)/2=0.029596$. Thus, we consider

$$\kappa_i = \max\left(\kappa\left(\text{SAN}_i,\text{DEN}_i\right), 0.029596\right).$$

In order to illustrate the considered fitting method, we show on Figure 2 the evolution for Guinea of the cumulative numbers of EVD cases and deaths predicted with Be-CoDiS and some real observations. More precisely, for a particular country $i$, we compute the cumulative number of EVD cases at day $t$ as following:

$$\text{cumul_cases}(i, t) = \text{cumul_cases}(i, 0) + \int_0^t \gamma_I \cdot I(i, t) dt \approx \text{cumul_cases}(i, 0) + \sum_{k=0}^t \gamma_I \cdot I(i, k),$$

where $\text{cumul_cases}(i, 0) \in \mathbb{R}$ is given (see [28]). On a similar way, we compute its cumulative number of deaths (due to EVD) at day $t$ as:

$$\text{cumul_deaths}(i, t) = \text{cumul_deaths}(i, 0) + \omega(i) \int_0^t \gamma_{HD} \cdot H(i, t) dt \approx \text{cumul_deaths}(i, 0) + \omega(i) \sum_{k=0}^t \gamma_{HD} \cdot H(i, k),$$

where $\text{cumul_deaths}(i, 0) \in \mathbb{R}$ is given (see [28]). We see that the number of cases fit well the real data whereas the number of deaths presents a slight variation. This is due to the fact that since the reception of international sanitary help in affected countries, the disease mortality has been drastically reduced compared to the beginning of the epidemic. A study of the evolution of the EVD mortality rate is required to improve this part in our model.

Regarding the suitability of the proposed functions $\kappa_i$ and $\beta_i(i, t)$ in countries with no or few data, we note that in the experiments presented in Section 4.3.2, the cumulative number of infected cases in Nigeria simulated by our model (i.e., 16 cases) is of the same order than the real data (i.e., 20 cases).

4.3 Numerical experiments

We consider the parameters presented in Section 4.2 and carry out several numerical experiments in order to estimate some relevant values of the 2014 Ebola outbreak. First in Section 4.3.1 regarding only the input of the model we do an a priori study of the risk of introduction and diffusion of EVD for each country. Next, in Section 4.3.2 we validate our approach by comparing the outputs of two numerical experiments with real data. Finally, in Section 4.3.3 we predict the possible EVD evolution during various time intervals ($T_{\text{max}}=1$ month and to the end of the epidemic).

4.3.1 Initial Risk of EVD Introduction and Diffusion

We have computed, for each country $i$, the risks of introduction and spread of Ebola, denoted by $\text{RI}(i)$ and $\text{RS}(i)$, by only considering the immigration flow matrix $(\tau(i, j))$ as following:

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

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

$\text{RI}$ (persons·day$^{-1}$) corresponds to the daily amount of infected persons which enter in country $i$ at time $t = 0$. $\text{RS}$ (persons·day$^{-1}$) correspond to the daily amount of infected persons who leave the country $j$ at time $t = 0$. 

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Figure 2: Evolution for Guinea of the cumulative numbers of total EVD cases (continuous line) and deaths (dotted line) predicted by the Be-CoDiS model from December 6th, 2013 up to November 9th, 2014. We also show at some days the cumulative amount of total cases (X) and deaths (+) reported in [28].
Liberia and Sierra Leone. The USA, United Kingdom and France present a risk of introducing EVD in this top 20 (all affected by EVD cases). Indeed, they receive an important migratory flux from Guinea, from Guinea. This result is consistent with the 2014 Ebola situation, with the disease starting from Guinea are the first countries in this list, which is logical since those countries receive an important migration flux country per day). The initial risk of other countries is negligible.

In order to reduce the spread of EVD worldwide, effort for controlling the movements of people entering or leaving those regions should be prioritized

Western Africa, North America and Australia are the most affected areas.

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 should be prioritized in order to reduce the spread of EVD world wide.

Table 2: Risk of EVD spread to other countries (RS) on November 9th, 2014 for countries affected by EVD).

| Country   | RS     |
|-----------|--------|
| Guinea    | 1.3e-02|
| Sierra Leone | 2.8e-04|
| Mali      | 7.0e-05|
| Liberia   | 4.0e-05|

Here, we consider $t = 0$ corresponding to November 9th, 2014, the date of the last EVD situation report available in [28] when those experiments were performed. The values of $m_{i,0}$, $m_{j,0}$ and $E_{i,0}$ are obtained by using the methodology presented in Section 4.2.2. On November 9th, 2014, we set

- $E_{\text{Guinea},0} = 288, I_{\text{Guinea},0} = 127, H_{\text{Guinea},0} = 30, R_{\text{Guinea},0} = 706, D_{\text{Guinea},0} = 36, B_{\text{Guinea},0} = 1106, \lambda(\text{Guinea}) = -228$;
- $E_{\text{Liberia},0} = 520, I_{\text{Liberia},0} = 228, H_{\text{Liberia},0} = 133, R_{\text{Liberia},0} = 3853, D_{\text{Liberia},0} = 28, B_{\text{Liberia},0} = 2808, \lambda(\text{Liberia}) = -95$;
- $E_{\text{Sierra Leone},0} = 1298, I_{\text{Sierra Leone},0} = 569, H_{\text{Sierra Leone},0} = 467, R_{\text{Sierra Leone},0} = 3732, D_{\text{Sierra Leone},0} = 16, B_{\text{Sierra Leone},0} = 1153, \lambda(\text{Sierra Leone}) = -103$;
- $E_{\text{USA},0} = 0, I_{\text{USA},0} = 0, H_{\text{USA},0} = 0, R_{\text{USA},0} = 3, D_{\text{USA},0} = 0, B_{\text{USA},0} = 1, \lambda(\text{USA}) = -38$;
- $E_{\text{Mali},0} = 8, I_{\text{Mali},0} = 4, H_{\text{Mali},0} = 0, R_{\text{Mali},0} = 0, D_{\text{Mali},0} = 2, B_{\text{Mali},0} = 2, \lambda(\text{Mali}) = -15$.
- $E_{\text{Nigeria},0} = 0, I_{\text{Nigeria},0} = 0, H_{\text{Nigeria},0} = 0, R_{\text{Nigeria},0} = 12, D_{\text{Nigeria},0} = 0, B_{\text{Nigeria},0} = 8, \lambda(\text{Nigeria}) = -106$;
- $E_{\text{Senegal},0} = 0, I_{\text{Senegal},0} = 0, H_{\text{Senegal},0} = 0, R_{\text{Senegal},0} = 1, D_{\text{Senegal},0} = 0, B_{\text{Senegal},0} = 0, \lambda(\text{Senegal}) = -70$;
- $E_{\text{Spain},0} = 0, I_{\text{Spain},0} = 0, H_{\text{Spain},0} = 0, R_{\text{Spain},0} = 1, D_{\text{Spain},0} = 0, B_{\text{Spain},0} = 0, \lambda(\text{Spain}) = -32$.

Table 2 presents the value of RS for all the countries with a strictly positive value of RS on November 9th, 2014. We observe that Guinea has the major risk for EVD spread to other countries with a risk of around $6 \times 10^{-3}$ persons sent to other countries per day (i.e., 0.6% of probability to contaminate another country per day). The initial risk of other countries is negligible.

In Table 3 we report the 20 countries with the highest value of RI. We note 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 note 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, United Kingdom and France present a risk of introducing $6 \times 10^{-5}$ infected people per day (i.e., 0.006% of probability to receive an infected person per day), 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 3. We see that Western Europe, Western Africa, North America and Australia are the most affected areas.

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 should be prioritized in order to reduce the spread of EVD world wide.
Figure 3: Risk of EVD Introduction (RI) of each country, corresponding to data on November 9th, 2014. Darker zones correspond to higher risk values.

Table 3: Risk of EVD introduction (RI) on November 9th, 2014 for each country. Only the Top 20 is reported.

| Country       | RI     |
|---------------|--------|
| Liberia       | 1.7e-03|
| Sierra Leone  | 5.1e-04|
| USA           | 1.1e-04|
| France        | 9.4e-05|
| United Kingdom| 8.5e-05|
| Spain         | 4.3e-05|
| Senegal       | 3.3e-05|
| Netherlands   | 2.5e-05|
| Gambia        | 2.3e-05|
| Australia     | 2.2e-05|
| Canada        | 2.1e-05|
| Portugal      | 1.9e-05|
| Italy         | 1.8e-05|
| Mauritania    | 1.6e-05|
| Germany       | 1.3e-05|
| Nigeria       | 1.1e-05|
| Belgium       | 8.9e-06|
| Guinea Bissau | 8.1e-06|
| Gabon         | 5.3e-06|
| Sweden        | 4.9e-06|
4.3.2 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 intervals (i.e., $T_{\text{max}} \leq 1$ month) and long time (i.e., $T_{\text{max}} \geq 3$ months) horizons. To do so, we have performed the two following experiments.

Validation for short time intervals: We run System (3) with $T_{\text{max}} = 31$ days from October 8th, 2014 to November 9th, 2014, with the model parameters introduced in Section 4.2.2 and the the following initial conditions obtained by using the methodology presented in Section 4.2.2.

- $E_{\text{Guinea},0} = 368, I_{\text{Guinea},0} = 162, H_{\text{Guinea},0} = 112, R_{\text{Guinea},0} = 460, D_{\text{Guinea},0} = 16, B_{\text{Guinea},0} = 762, \lambda(\text{Guinea}) = -196$;
- $E_{\text{Liberia},0} = 620, I_{\text{Liberia},0} = 272, H_{\text{Liberia},0} = 242, R_{\text{Liberia},0} = 1518, D_{\text{Liberia},0} = 99, B_{\text{Liberia},0} = 2217, \lambda(\text{Liberia}) = -63$;
- $E_{\text{Sierra Leone},0} = 1316, I_{\text{Sierra Leone},0} = 577, H_{\text{Sierra Leone},0} = 513, R_{\text{Sierra Leone},0} = 1507, D_{\text{Sierra Leone},0} = 123, B_{\text{Sierra Leone},0} = 807, \lambda(\text{Sierra Leone}) = -71$;
- $E_{\text{USA},0} = 3, I_{\text{USA},0} = 2, H_{\text{USA},0} = 1, R_{\text{USA},0} = 0, D_{\text{USA},0} = 0, B_{\text{USA},0} = 0, \lambda(\text{USA}) = -6$;
- $E_{\text{Spain},0} = 3, I_{\text{Spain},0} = 2, H_{\text{Spain},0} = 1, R_{\text{Spain},0} = 0, D_{\text{Spain},0} = 0, B_{\text{Spain},0} = 0, \lambda(\text{Spain}) = -2$;
- $E_{\text{Nigeria},0} = 0, I_{\text{Nigeria},0} = 0, H_{\text{Nigeria},0} = 0, R_{\text{Nigeria},0} = 12, D_{\text{Nigeria},0} = 0, B_{\text{Nigeria},0} = 8, \lambda(\text{Nigeria}) = -78$;
- $E_{\text{Senegal},0} = 0, I_{\text{Senegal},0} = 0, H_{\text{Senegal},0} = 0, R_{\text{Senegal},0} = 1, D_{\text{Senegal},0} = 0, B_{\text{Senegal},0} = 0, \lambda(\text{Senegal}) = -38$.

The evolution of the cumulative numbers of total cases and deaths predicted by the model (see Section 4.2.5) is presented in Figure 4. We also report on this figure the cumulative numbers of cases and deaths observed by the authorities during the epidemic for some dates (see Table 3). Moreover, in Table 4, we summarize the number of simulated and observed cumulative numbers of cases and deaths for each affected country on October 22nd, 2013 and let the epidemic run until its ending (i.e., $T_{\text{max}} = 3$ months). To do so, System (3) is started at $t = 0$ (corresponding to December 6th, 2013) with 3 persons in the state $I$ and 1 person in the $D$ state in Guinea and all other persons being free of the disease. Furthermore, as

Validation for long time intervals: We have considered a simulation starting from the known index cases of the current EVD epidemic on December 6th, 2013 and let the epidemic run until its ending (i.e., the approximated time for which the numbers of persons in states $E$, $I$ and $H$ are all lower than 1). To do so, System (3) is started at $t = 0$ (corresponding to December 6th, 2013) with 3 persons in the state $I$ and 1 person in the $D$ state in Guinea and all other persons being free of the disease. Furthermore, as
Figure 4: Evolution of the cumulative numbers of total EVD cases (continuous line) and deaths (dotted line) predicted by the Be-CoDiS model from October 8th, 2014 up to November 9th, 2014. We also show for some dates the cumulative amount of total cases (X) and deaths (+) reported in [28].

Table 4: Validation for short time intervals: Cumulative numbers of cases predicted by Be-CoDiS (BC), real observed data reported in [28] (Real) and percentage error done by the model (Err.) on October 19th, 2014 and November 9th, 2014 for countries affected by EVD at those dates. We also report the cumulative number of deaths.

| Date    | 19-10-2014 | 09-11-2014 |
|---------|------------|------------|
|         | BC         | Real       | Err. (%) | BC         | Real       | Err. (%) |
| Total cases | 10837      | 9936       | 9        | 13205      | 14098      | 6        |
| Total deaths | 5192       | 4887       | 6        | 6479       | 5160       | 25       |
| Guinea  | 1756       | 1540       | 14       | 2255       | 1878       | 20       |
| Liberia | 4662       | 4665       | 1        | 4969       | 6822       | 27       |
| Sierra Leone | 4338     | 3706       | 17       | 5944       | 5368       | 10       |
| Mali    | 0          | 0          | 0        | 0          | 4          | 100      |
| Spain   | 5          | 1          | 150      | 8          | 1          | 700      |
| USA     | 5          | 2          |          | 7          | 4          | 75       |
Table 5: 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 [28] on November 9th, 2014 are also shown.

| Country     | BC Date       | BC Cases | BC Deaths | Real Date       | Real Cases | Real Deaths |
|-------------|---------------|----------|-----------|-----------------|------------|-------------|
| Liberia     | 7-Apr-2014    | 10828    | 4600      | 31-Mar-2014     | 6525       | 2697        |
| Sierra Leone| 01-Jul-2014   | 7372     | 3039      | 26-May-2014     | 4759       | 1070        |
| Guinea      | 06-Dec-2013   | 2270     | 1724      | 06-Dec-2013     | 1731       | 1041        |
| Nigeria     | 14-Dec-2014   | 15       | 12        | 20-Jul-2014     | 20         | 8           |
| Senegal     | 23-Apr-2015   | 2        | 1         | 29-Aug-2014     | 1          | 0           |
| USA         | 16-May-2015   | 1        | 0         | 30-Sep-2014     | 4          | 1           |
| Gambia      | 04-Oct-2014   | 44       | 20        | -               | 0          | 0           |
| United Kingdom | 23-May-2015 | 1        | 0         | -               | 0          | 0           |
| Mali        | -             | 0        | 0         | 23-Oct-2014     | 4          | 4           |
| Spain       | -             | 0        | 0         | 06-Oct-2014     | 1          | 0           |

mentioned in Section 4.2.5, we have considered a delay between the detection of the first EVD case in a country and the applications of intensive control measures observed during the real EVD epidemic. More precisely, for Guinea, Sierra Leone, Liberia and Nigeria, we have considered a delay of 107, 140, 75 and 22 days, respectively. For other countries, this delay has been set to 0 day (as no data is available). All other parameters are set to the values introduced previously in Section 4.2.

The evolution of the cumulative numbers of total cases and deaths predicted by the model is presented in Figure 5. We also show on this figure the cumulative numbers of cases and deaths observed by the authorities during the epidemic (see [28]) for several dates. In addition, in Table 5 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 and in the real epidemic. Furthermore, we also show the real data observed for those countries on November 9th, 2014.

From Table 5, we note that our model predicts the infection of Liberia, Sierra Leone, Nigeria, Senegal and the USA. Moreover, the magnitude in those countries and Guinea is similar to the one observed on November 9th, 2014. In addition, on the one side, our model also predicts the infection of Gambia and United Kingdom with low epidemics, which has not occurred before this work was done. On the other side, our model fails to predict infection in Spain and Mali. However, for the moment in those two countries the EVD epidemic seems to be sporadic and limited.

Regarding Figure 5, we see that the model predicts an increase of the cumulated number of cases and deaths smoother than the one given by the real data. 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 [28]). According to the model, the epidemic should end on July 10th, 2015.

From those results, and taking into account the difficulty of epidemiological models for predicting long time intervals (see [20]), Be-CoDiS seems to generate reasonable behaviour of the evolution of the epidemic when considering a long time horizon. In particular, it seems that the model may help to detect the countries with more probabilities to develop important outbreaks.

4.3.3 Forecast for the EVD epidemic starting with data from November 9th, 2014

Now, we are interested in running our model starting on November 9th, 2014 (the last date available at [28] when those experiments were run) and analyse the obtained predictions. To do so, System 4 is started with the initial conditions corresponding to November 9th, 2014 (see Section 4.3.1) and parameters presented in Section 4.2. The system is run until the end of the epidemic (i.e., the approximated time for which the
Figure 5: Evolution of the cumulative numbers of total EVD cases (continuous line) and deaths (dotted line) predicted by the Be-CoDiS model from December 6\textsuperscript{th}, 2013 to June 27\textsuperscript{th}, 2015. We also show for some dates the cumulative amount of total cases (X) and deaths (+) reported in [28].
numbers of persons in states $E$, $I$ and $H$ are all lower than 1). We perform a short time horizon (by considering results on December 5th, 2014) and a long time horizon (by considering the final date of the simulation) analysis.

In particular, we report the countries who have at least one cumulative EVD case at the end of the considered time interval $[0, T]$. For those, countries we compute the following values:

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

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

TRS (persons) measures the number of infected persons send to other countries during the considered time interval.

- **TRI($i$)**: the total risk of EVD introduction from other countries considering the time interval $[0, T]$, computed as

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

TRI (persons) measures 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 $[0, T]$. Taking into account that the mean duration of a person in the state $H$ is 5 days and the mean duration from hospitalization to discharge is 12 days (see [29]), it is computed as

$$\text{MNH} (i) = \max_{t=0 \ldots T} \left( H(i, t) \right) \cdot \frac{12}{5}.$$

This number can help to estimate and plan the number of clinical beds needed to treat all the EVD cases.

- **Emf($i$) (%)**.

**Short time horizon forecast on December 9th, 2014**: The evolution of the cumulative numbers of total cases and deaths predicted by the model is presented in Figure 6. The evolution of the total numbers persons in the state $E$, $I$, $H$ and $D$ is shown in Figure 7. The total number of reported cases and deaths, at the end of this interval, are 17846 and 7114, 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 [28]). This is also visible in Figure 7, where the number of person in states $E$, $I$, $H$ and $D$ decreases with values which are at least reduced by 3.

The list of countries with a number of persons in state $E$, $I$, $H$ or $D$ greater than 1 at a moment from November 9th, 2014 to December 9th, 2014 and their characteristics are reported in Table 6. 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 0.7 %). Other countries present a much lower risk. This results is consistent with the fact that Guinea presents the highest value of EmF (at least ten time greater than other countries) combined with a large number of EVD cases. Regarding the magnitude of the epidemic, the model reports the number of cases in Sierra Leone can increase dramatically (around 2000 new cases) in next month. On the opposite the situation in Guinea and Liberia seems to be stabilized with a lower increase of cases (around 700 new cases). The situation in Mali is reduced to a limited outbreak of EVD. Regarding the values MNH of each country, we see that a maximum number of 2115 beds in hospitals dedicated to treat EVD cases should be planned to cure the affected persons. This maximum number was estimated to be around 4288 in [28] (report date: October 8th, 2014) and, currently, 1100 beds are used.
Figure 6: Evolution of the cumulative numbers of total EVD cases (continuous line) and deaths (dotted line) predicted by the Be-CoDiS model from November 9th, 2014 to December 9th, 2014.

Table 6: Short time horizon 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 December 5th, 2014. We also report the cumulative numbers of EVD cases (Init. Cases) and the cumulative numbers of deaths (Init. Deaths) observed on November 9th, 2014.

| Country  | Cases | Deaths | MNH  | TRS   | EmF    | Init. Cases | Init. Deaths |
|----------|-------|--------|------|-------|--------|-------------|--------------|
| Sierra Leone | 7759   | 2244   | 517  | 4.e-06 | 1.2e-4 | 5368        | 1169         |
| Liberia  | 7515   | 3195   | 1299 | 9.e-09 | 1.8e-4 | 6822        | 2836         |
| Guinea   | 2527   | 1649   | 296  | 7.e-03 | 1.4e-3 | 1878        | 1142         |
| Mali     | 17     | 16     | 8    | 5.e-08 | 4.5e-4 | 4           | 4            |
| Total    | 17846  | 7114   | 2115 | -     | -      | 14098       | 5160         |
Figure 7: Evolution of the total numbers of persons in states $E$ (dotted line), $I$ (slash-dotted line), $H$ (continuous line) and $D$ (slashed line) predicted by the Be-CoDiS model from November 9th, 2014 to December 9th, 2014.
Figure 8: Countries with the 20 highest probabilities (%) of introduction of at least 1 EVD case due to migration flow predicted by the Be-CoDiS model from November 9th, 2014 to December 9th, 2014.

Finally in Figure 8, 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. Considering France and United Kingdom, which are currently free of EVD epidemic, the time interval their probabilities are around 0.2%. This list includes African and European countries and Australia. However, they present a low risk with a probability lower than 0.07%. This classification seems to be consistent with the results found in [9], 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%. Such a difference may be explained by the considered input data (in particular the movement of people is calibrated from the air-planes traffic). However, as no deep details are given in [9] about the considered parameters, doing a direct comparison with those results is difficult.

**Long time horizon forecast until the end of the EVD epidemic:** In this case, the model starts on November 9th, 2014 and is run until August 1st, 2015 (i.e., the date for which 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 9. The evolution of the total number of persons in the state $E$, $I$, $H$ and $D$ is shown in Figure 10. The final numbers of reported cases and deaths, at the end of the time interval, are 20043 and 8603, 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 noted after this period.

The list of countries with a number of persons in state $E$, $I$, $H$ or $D$ greater than 1 at a moment from
Figure 9: Evolution of the cumulative numbers of total EVD cases (continuous line) and deaths (dotted line) predicted by the Be-CoDiS model from November 9th, 2014 to August 01st, 2015.
Figure 10: Evolution of the total numbers of persons in states $E$ (dotted line), $I$ (slash-dotted line), $H$ (continuous line) and $D$ (slashed line) predicted by the Be-CoDiS model from November 9$^{th}$, 2014 to August 14$^{th}$, 2015. We note that the Y axis is presented in log scale.
Table 7: Long time horizon 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 August 1st, 2015.

| Country    | Cases | Deaths | MNH  | TRS     | EmF  |
|------------|-------|--------|------|---------|------|
| Total      | 20043 | 8603   | 2115 | -       | -    |
| Sierra Leone| 8800  | 2793   | 1299 | 3.3e-04 | 1.2e-04 |
| Liberia    | 7585  | 3247   | 517  | 4.5e-05 | 1.8e-04 |
| Guinea     | 3572  | 2519   | 296  | 2.7e-02 | 1.4e-03 |
| Gambia     | 41    | 19     | 8    | 6.8e-04 | 7.3e-04 |
| Mali       | 20    | 18     | 8    | 7.2e-05 | 4.5e-04 |

Table 8: Results of the sensibility analysis presented in Section 4.4. We report the mean, median, minimum and maximum percentage variation of the considered outputs regarding their non perturbed value.

| α   | Mean | Minimum | Maximum |
|-----|------|---------|---------|
| 1%  | 1.2  | 0.06    | 10.6    |
| 5%  | 5.1  | 0.6     | 18.5    |
| 10% | 9.8  | 0.79    | 31.2    |

November 9th, 2014 to August 1st, 2014 and their characteristics are reported in Table 7. We can see in this table that, the model predicts medium outbreaks in Gambia (around 40 cases). The risk of spread of Guinea during the whole period is now 0.027, which corresponds to a probability of 2.7% of spreading at least one EVD case to other countries. New infected countries also present a risk of EVD spread higher than other countries in this list (probability of 0.07%). 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 881 (as in the forecast for short time interval).

Finally in Figure 11 we present a bar representation of the countries with the 20 highest probabilities of introduction of at least 1 EVD cases due to migration flow (%). Again, France and United Kingdom are the countries with the highest probabilities to receive an infected person (around 0.5%). Other countries in the list have a risk lower than 0.15%. A world map showing the distributions of TRI by countries is included in Figure 12. We see that Western Europe, Western Africa, Canada and Australia are the most affected areas.

4.4 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 is run 100 times by considering random uniform perturbations of amplitude $[-\alpha, +\alpha]$% on all the parameters, with $\alpha =1\%$, $5\%$, $10\%$ and $20\%$. We consider the short time horizon forecast on December 9th, 2014 scenario presented in Section 4.3.3. The mean percentage variations, considering all countries, of TRS, TRI, MNH, cumul_cases and cumul_deaths regarding their respective non perturbed value are studied. For each value of $\alpha$, we report the average minimum, maximum, median and mean value considering all those variables. Results are reported in Table 8.

From this table, we observe that perturbations of $\alpha\%$ in the inputs generates mean output variations of around $\alpha\%$. Therefore, it seems that there is a linear relationship between input and output perturbations. The maximum observed mean perturbation is 58% 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 analysis should be performed in order to identify the more influential model parameters and, thus, give recommendation about the result precision to possible users.
Figure 11: Countries with the 20 highest probability (%) of introduction of at least 1 EVD cases due to migration flow predicted by the Be-CoDiS model from November 9th, 2014 to August 01st, 2015.

Figure 12: Total risk of EVD introduction (TRI) of each country, corresponding to the period from November 9th, 2014 to August 1st, 2015. Darker zones correspond to higher risk values.
5 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 from November 9th, 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 [9]. However, the probability of infection is of 0.2%, which is low in comparison to the result found in other works.

Regarding forecast considering the end of the epidemic, it should disappear within nine months and no major outbreaks (i.e., more than 10 infected cases) should be reported except in Liberia, Guinea, Sierra Leone, Nigeria, Mali and Gambia. This last country is currently free of the disease, and a particular vigilance should be paid to it. According to the model, the magnitude of the epidemic could reach a total of 20043 cases, 8603 deaths and requires around 2115 beds in hospitals.

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 cost).

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