# EpiMod: examples of usage

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## Introduction

In this document we describe how to use the R library *epimod*. In details, *epimod* implements a new general modeling framework to study epidemiological systems, whose novelties and strengths are:

1. the use of a graphical formalism to simplify the model creation phase;
2. the automatic generation of the deterministic and stochastic process underlying the system under study;
3. the implementation of an R package providing a friendly interface to access the analysis techniques implemented in the framework;
4. a high level of portability and reproducibility granted by the containerization (Veiga Leprevost et al. 2017) of all analysis techniques implemented in the framework;
5. a well-defined schema and related infrastructure to allow users to easily integrate their own analysis workflow in the framework.

The effectiveness of this framework is showed through the wellknown and simple SIR model.

# How to start

Before starting the analysis we have to install (1) GreatSPN GUI, (2) docker, and (3) the R package **devtools** for installing *EPIMOD*. First, from install.GreatSPN it is possible to download and install the GreatSPN editor tool, a Java Graphic UserInterface (GUI) based on Java Swing Class which allows to draw models using the Petri Net formalisms. Then, the user must have docker installed on its computer for exploiting the *epimod*'s docker images (for more information on the docker installation see: install.docker), and to have authorization to execute docker commands reported in the command page of function install docker. To do this the following commands must be executed.

1. Create the docker group.

```
$ sudo groupadd docker
```

2. Add your user to the docker group.

```
$ sudo usermod -aG docker $USER
```

The R package *devtools* has to be installed to run *epimod*:

```
install.packages("devtools")
library(devtools)
install_github("qBioTurin/epimod", dependencies=TRUE)
```

```
library(epimod)
```

Then, the following function must be used to download all the docker images used by *epimod*:

```
downloadContainers()
```

## Something to know

All the *epimod* functions print the following information:

- *Docker ID*, that is the CONTAINER ID which is executed by the function;
- *Docker exit status*, if 0 then the execution completed with success, otherwise an error log file is saved in the working directory.

# Cases of study

In this section we provide an example of *epimod* usage through a simple case study. In details, the SIR model is the simple case of disease diffusion that we have chosen and in the following subsections show how to use *epimod* to model, analyze and study this case. We refer to (Keeling and Rohani 2011) for all the details.

**SIR model**

The S-I-R model simulates a scenario of a disease spreading in which the population is categorized into three groups: (1) *Susceptible*, individuals unexposed to the disease, (2) *Infected*, individuals currently infected by the disease, and (3) *Recovered*, individuals which were successfully recovered by the infection. To consider the simplest case, we ignore the population demography (i.e., births and deaths of individuals are omitted), thus we consider only two possible events: the infection (passage from *Susceptible* to *Infected*), and the recovery (passage from *Infected* to *Recovered*). We are also assuming to neglect complex pattern of contacts, by considering an homogeneous mixing. From a mathematical point of view, the system behaviors can be investigated by exploiting the deterministic approach (Kurtz 1970) which approximates its dynamics through a system of ordinary differential equations (ODEs):

$$\begin{aligned} \frac{dS}{dt} &= -\frac{\beta}{N} SI, \\ \frac{dI}{dt} &= \frac{\beta}{N} SI - \gamma I, \\ \frac{dR}{dt} &= \gamma I, \end{aligned} \tag{1}$$

where:

- $S,\ I,\ R$ are the number of susceptible, infected, and recovered individuals, respectively;
- $\beta$ is the infection rate;
- $N$ is the constant population size;
- $\gamma$ is the recovery rate, which determines the mean infectious period.

**Model generation**

The first step is the model construction. Starting with the GreatSPN editor tool, a Java Graphic User Interface (GUI) based on Java Swing Class , it is possible to draw the model using the PN formalism and its generalizations.

Therefore, as represented in figure 1, we add one place for each variable of the system (i.e., S, I, and R represent the susceptible, infected, and recovered individuals respectively), and one transition for each possible event (i.e., *Infection* and *Recovery*). Finally, we save the PN model as a file with extension *.PNPRO* .

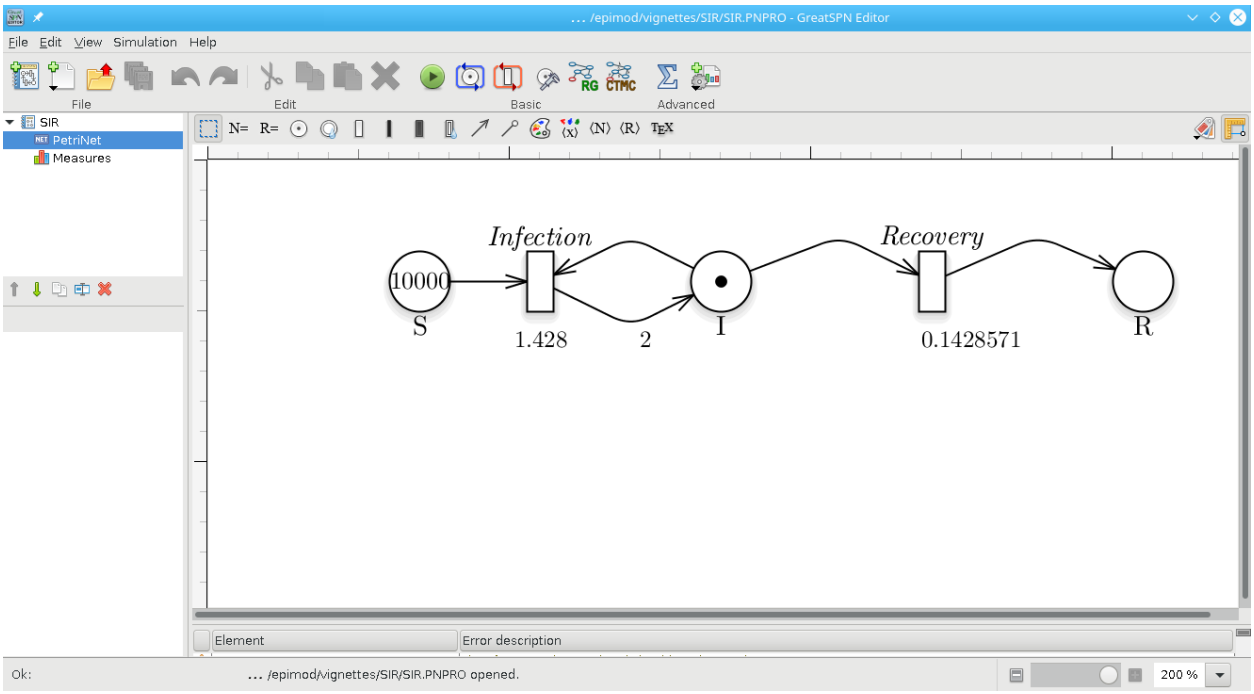


Figure 1: Petri Net representation of the SIR model.

Having constructed the model, the generation of both the stochastic (the Continuous Time Markov Chain) and deterministic (ODEs) processes underlying the model is implemented by the *model_generation()* function. This function takes as input the file generated by the graphical editor, in this case called *SIR.PNPRO*, and automatically derives the processes.

```
model_generation(net_fname = "./SIR.PNPRO")
#> docker run --privileged=true  --user=1000:1000 --cidfile=dockerID --volume /home/pernice/GIT/R_packa
#>
#>
#> Docker ID is:
#>  afd4fa5f0e79
#> ..
#>
#>
#> Docker exit status: 0
#>
#> docker run --privileged=true  --user=1000:1000 --cidfile=dockerID --volume /home/pernice/GIT/R_packa
#>
#>
#> Docker ID is:
#>  619cc3acc70a
#> ..
#>
#>
#> Docker exit status: 0
```

The binary file *SIR.solver* is generated in which the derived processes and the library used for their simulation are packaged.

Notice that *model_generation()* might take as input parameter the C++ file defining the functions characterizing the behavior of general transitions (Pernice et al. 2019), namely *functions_fname*. For instance, if we want to define the transition *Infection* as a general transition then we have firstly to set, through the GreatSPN GUI tool, the transition as *General* and name the corresponding rate name as **FN:NameGeneralFN**, where in this case the *NameGeneralFN* is **InfectionFunction**. An example is shown in figure 2.

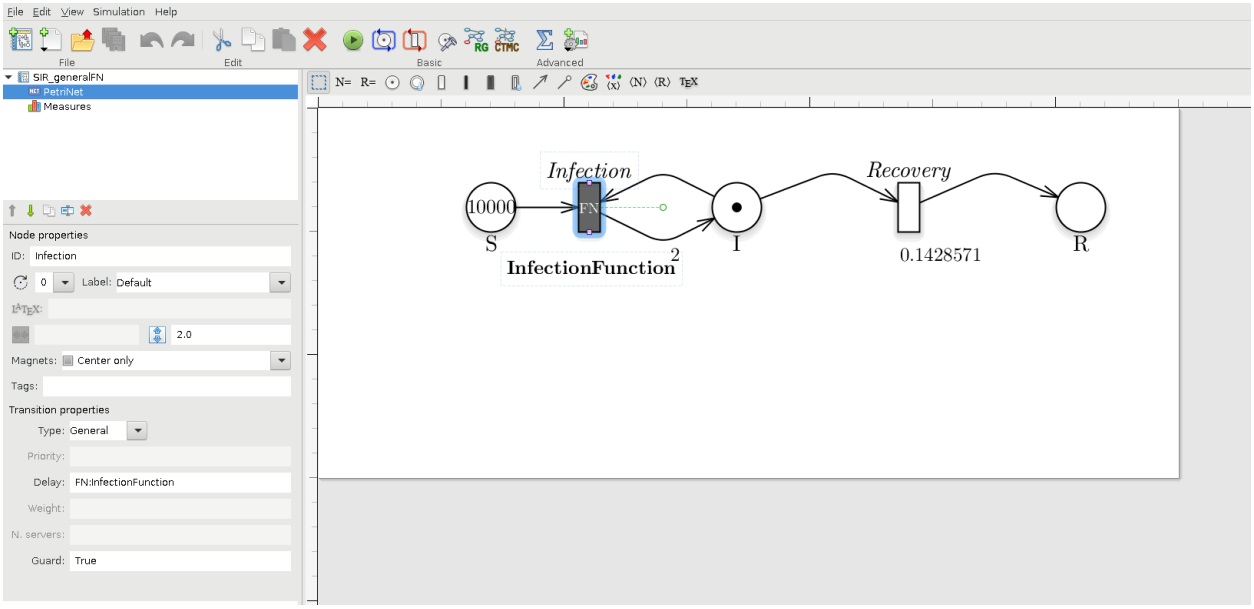


Figure 2: Petri Net representation of the SIR model, modelling the Infection transition as a general transition.

Successively, we to define the C++ file, for instance *transition.cpp*, storing the general transition definition, which has to be structured as follow:

```
static double Infection_rate = 1.428;

double InfectionFunction(double *Value,
                         map <string,int>& NumTrans,
                         map <string,int>& NumPlaces,
                         const vector<string> & NameTrans,
                         const struct InfTr* Trans,
                         const int T,
                         const double& time)
{

    // Definition of the function exploited to calculate the rate,
    // in this case for semplicity we define it throught the Mass Action  law

    double intensity = 1.0;

    for (unsigned int k=0; k<Trans[T].InPlaces.size(); k++)
    {
        intensity *= pow(Value[Trans[T].InPlaces[k].Id],Trans[T].InPlaces[k].Card);
    }
```

```
    double rate = Infection_rate * intensity;

    return(rate);
}
```

where the fixed input parameters are:

- **double *Value**: marking of the Petri Net at time *time*;
- **map <string,int>& NumTrans**: map which associates the transition name with the corresponding index position in the *NameTrans* vector;
- **map <string,int>& NumPlaces**: map which associates the place name with the corresponding index position in the *Value* vector;
- **const vector & NameTrans**: vector of the transition names;
- **const struct InfTr* Trans**: structure generated by GreatSPN, in which, given a transition index $T$, it is possible to obtain its input places (*Trans[T].InPlaces*), and considering the $k$ input place with *Trans[T].InPlaces[k].Id* and *Trans[T].InPlaces[k].Card* it is possible to obtain the corresponding place index position in the *Value* vector and the arc (linking the $k$ place with the $T$ transition) molteplicity, respectively. For instance, with *Value[Trans[T].InPlaces[k].Id]* it is possible to obtain the marking of the $k$-th input place of $T$-th transition;
- **const int T**: index of the firing transition;
- **const double& time** : time.

Notice that the function name has to correspond to the rate name associated with the general transition, in this case *InfectionFunction*.

Finally, the process can be derived be the *model_generation()* function as follow.

```
model_generation(net_fname = "./SIR_generalFN.PNPRO",
                 functions_fname = "./transition.cpp")
```

### Sensitivity analysis

The second step is represented by the sensitivity analysis, in which the deterministic process is solved several times varying the values of the unknown parameters to identify which are the sensitive ones (i.e., those that have a greater effect on the model behavior), by exploiting the Pearson Ranking Correlation Coefficients (PRCCs). This may simplify the calibration step reducing (1) the number of variables to be estimated and (2) the search space associated with each estimated parameter. With this purpose, the function *sensitivity_analysis()* calculates the PRCCs, and, given a reference dataset and a distance measure, it ranks the simulations according to the distance of each solution with respect to the reference one.

In details, the function *sensitivity_analysis()* takes in input

1. **solver_fname**: the *.solver* file generated by the *model_generation* function, that is *SIR.solver*;
2. **n_config**: the total number of samples to be performed, for instance 200;
3. **f_time**: the final solution time, for instance 10 weeks (70 days);
4. **s_time**: the time step defining the frequency at which explicit estimates for the system values are desired, in this case it could be set to 1 day;
5. **parameters_fname**: a textual file in which the parameters to be studied are listed associated with their range of variability. This file is defined by three mandatory columns: (1) a tag representing the parameter type: $i$ for the complete initial marking (or condition), $p$ for a single parameter (either a single rate or initial marking), and $g$ for a rate associated with general transitions (Pernice et al. 2019) (the user must define a file name coherently with the one used in the general transitions file); (2) the

name of the transition or place which is varying (this must correspond to name used in the PN draw in GreatSPN editor), if the complete initial marking is considered (i.e., with tag *i*) then *init* should be inserted; (3) the function used for sampling the value of the variable considered, it could be either R function or user-defined function (in this case it has to be implemented into the R script passed from the *functions_fname* input parameter). Let us note that the output of this function must have size equal to the length of the varying parameter, that is 1 when tags *p* or *g* are used, and the size of the marking (number of places) when *i* is used. The remaining columns represent the input parameters needed by the functions defined in the third column. An example is given by the file *Functions_list.csv*, where we decided to vary the rates of the *Recovery* and *Infection* transitions by using the R function which generates values following the uniform probability distribution on the interval from *min* to *max*. We set *n=1* because we must generate one value for each sample.

```
#>   Tag       Name Function Parameter1   Parameter2 Parameter3
#> 1   p   Recovery    runif        n=1      min = 0      max=1
#> 2   p  Infection    runif        n=1  min = 1e-05  max=2e-04
```

Another example might be *Functions_list2.csv*, where we decide to vary the initial marking using the following function *init_generation* defined in the R script *Functions.R* (see *functions_fname* parameter).

```
#>   Tag       Name         Function           Parameter1        Parameter2
#> 1   i       init  init_generation  min_init = 10000*.8  max_init = 10000
#> 2   p   Recovery            runif                 n=1           min = 0
#> 3   p  Infection            runif                 n=1       min = 1e-05
#>   Parameter3
#> 1
#> 2      max=1
#> 3  max=2e-04
```

6. **functions_fname**: an R file storing the user defined functions to generate instances of the parameters summarized in the *parameters_fname* file. An example is given by *Functions.R*, where the function *init_generation* introduced in *Functions_list2.csv* file is defined in order to sample the initial number of susceptible between *min_init* and *max_init*, and fixing the number of infected and recovered to 1 and 0 respectively.

```
init_generation<-function(min_init , max_init, n)
{
    S=runif(n=1,min=min_init,max=max_init)
# It returns a vector of lenght equal to 3 since the marking is
# defined by the three places: S, I, and R.
    return( c(S, 1,0) )
}
```

7. **target_value_fname**: an R file providing the function to obtain the place or a combination of places from which the PRCCs over the time have to be calculated. In details, the function takes in input a *data.frame*, namely *output*, defined by a number of columns equal to the number of places plus one corresponding to the time, and number of rows equals to number of time steps defined previously. Finally, it must return the column (or a combination of columns, see Sec. Sensitivity Analysis Pertussis ) corresponding to the place (or combination of places) for which the PRCCs have to be calculated for each time step. An example is given in *Target.R*, where the PRCCs are calculated with respect to place *I* (infected individuals).

```
Target<-function(output)
{
    I <- output[,"I"]
    return(I)
}
```

8. **reference_data**: a csv file storing the data to be compared with the simulations' result. In *reference_data.csv* we report the SIR evolution starting with 10000 susceptible, one infected and zero recovered, with a recovery and infection rates equals to 0.1428 and 1.428 respectively.

```
#>           Time         S        I          R
#> TimeStep1  0.0 10000.000 1.000000 0.00000000
#> TimeStep2  0.1  9999.848 1.137136 0.01524425
#> TimeStep3  0.2  9999.674 1.293078 0.03257922
#> TimeStep4  0.3  9999.477 1.470399 0.05229125
#> TimeStep5  0.4  9999.253 1.672030 0.07470625
#> TimeStep6  0.5  9998.998 1.901306 0.10019506
```

9. **distance_measure_fname**: the R file storing the function to compute the distance (or error) between the model output and the reference dataset itself. The function defining the distance takes in input only the reference data and the simulation's output (i.e. a trajectory); an example is given by *msqd.R* where a distance measure (based on the squared error distance) as function of the infected individuals is defined:

```
msqd<-function(reference, output)
{
    Infect <- output[,"I"]

    diff.Infect <- sum(( Infect - reference )^2 )

    return(diff.Infect)
}
```

Let us observe that: (i) the distance and target functions must have the same name of the corresponding R file,(ii) *sensitivity_analysis* exploits also the parallel processing capabilities, and (iii) if the user is not interested on the ranking calculation then the **distance_measure_fname** and **reference_data** are not necessary and can be omitted.

```
## Simple version where only the transition rates vary.
sensitivity<-sensitivity_analysis(n_config = 200,
                                  parameters_fname = "Functions_list.csv",
                                  solver_fname = "SIR.solver",
                                  reference_data = "reference_data.csv",
                                  distance_measure_fname = "msqd.R" ,
                                  target_value_fname = "Target.R" ,
                                  f_time = 7*10, # weeks
                                  s_time = 1 # days
                                  )
#> docker run --privileged=true  --user=1000:1000 --cidfile=dockerID --volume /home/pernice/GIT/R_packa
#>
#>
```

```
#> Docker ID is:
#>  e5120c18d279
#> ...
#>
#>
#> Docker exit status: 0
```

Hence, considering the SIR model we can run the *sensitivity_analysis* varying the *Infection* and *Recovery* transitions rates in order to characterized their effect on the number of infected individuals.

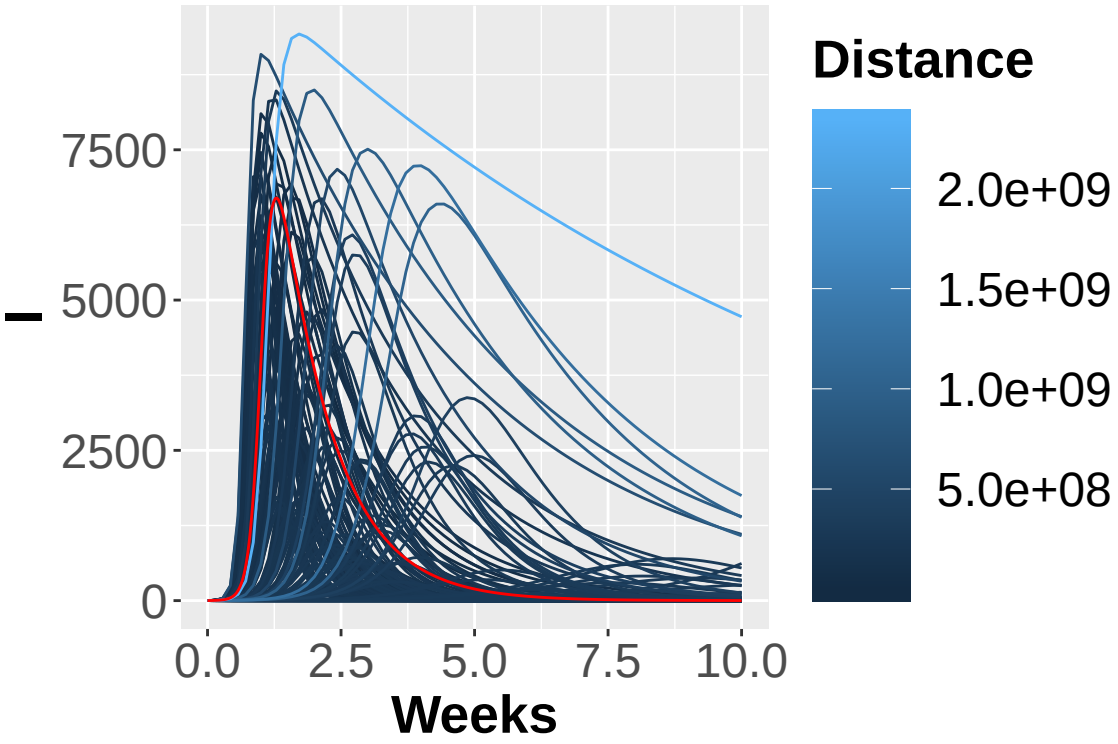


Figure 3: The 200 trajectories considering the I place obtained from different parameters configurations.

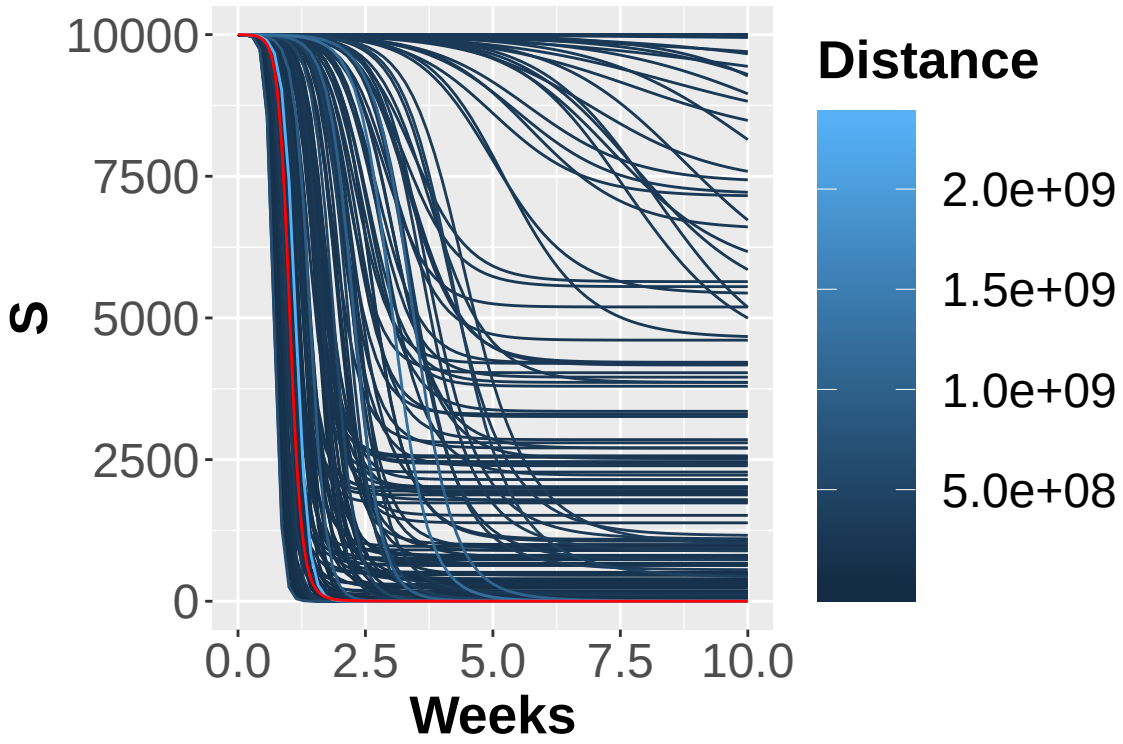


Figure 4: The 200 trajectories considering the S place obtained from different parameters configurations.

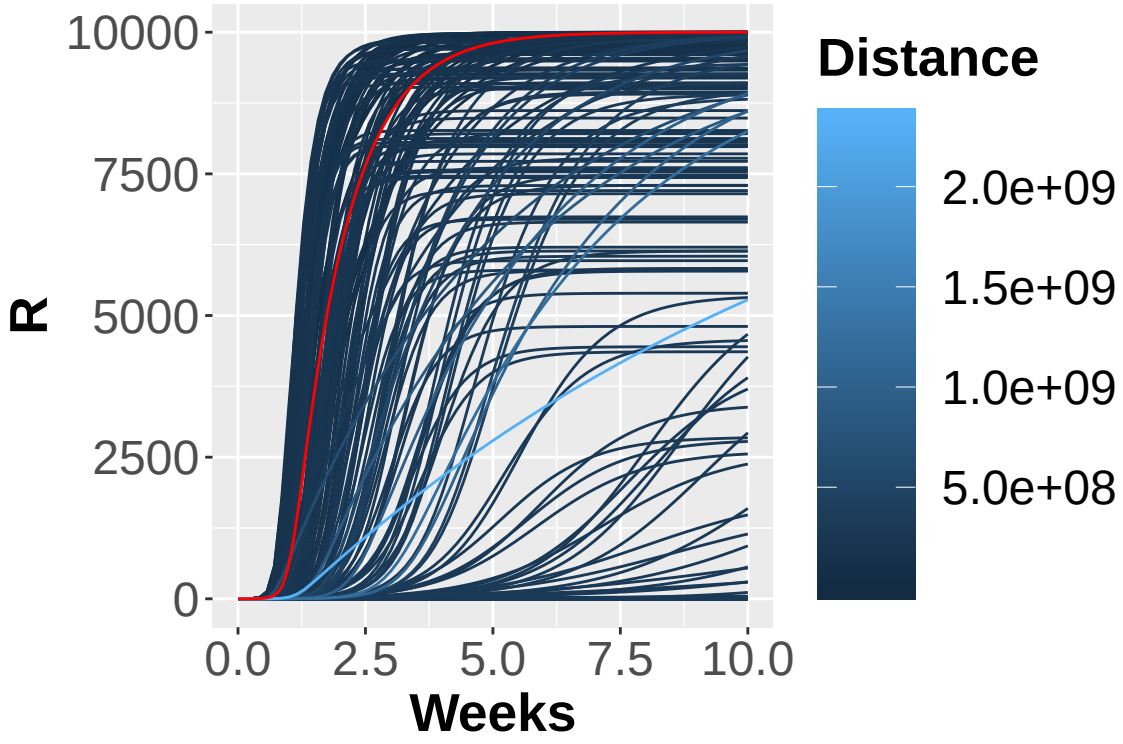


Figure 5: The 200 trajectories considering the R place obtained from different parameters configuration.

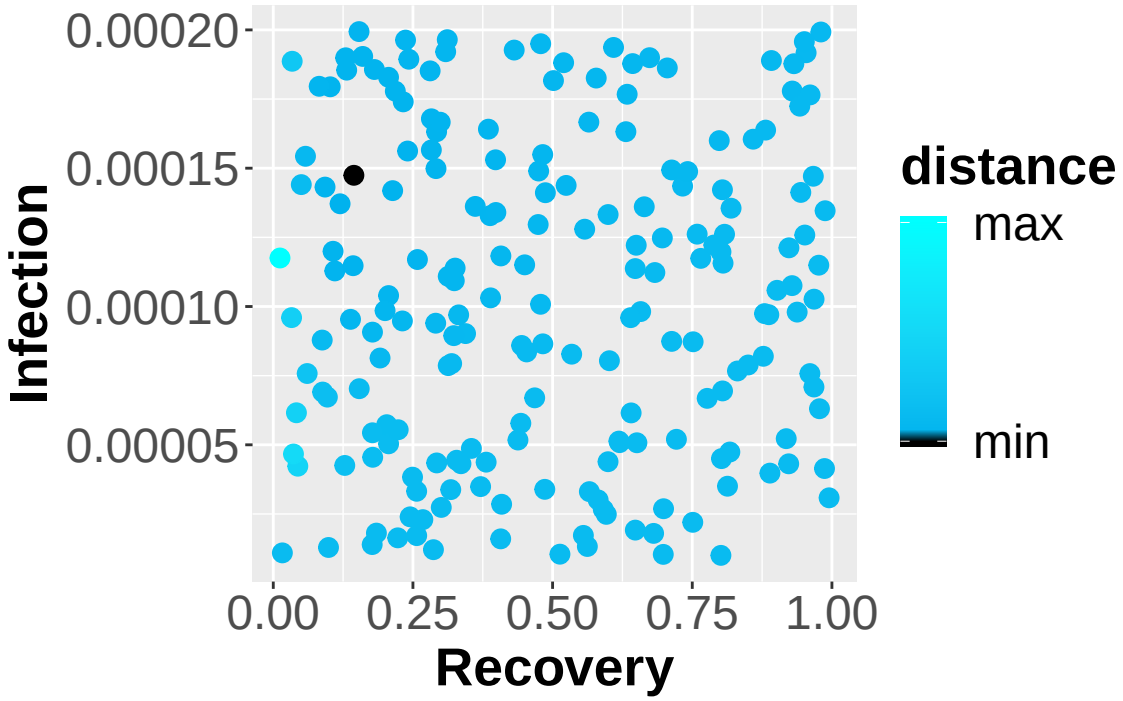


Figure 6: Scatter plot showing the squared error between the reference data and simulated number of infected. The dark blue points represent the parameters configuration with minimum error.

From the figures 3, 5, and 4, it is possible to observe the different trajectories obtained by solving the system of ODEs, represented by eq. 1, with different parameters configurations, sampled by exploiting the function passed through **parameters_fname**. In figure 6 the distance values, obtained using the measure definition described before, are plotted varying the *Recovery* parameter (on the x-axis) and *Infection* parameter (on the y-axis). Each point is colored according to a nonlinear gradient function starting from color dark blue (i.e., lower value) and moving to color light blue (i.e., higher values). From this plot we can observe that lower squared errors are obtained when *Recovery* is around 0.13 and *Infection* around 0.00015, thus we can reduce the search space associated with the two parameters around these two values.

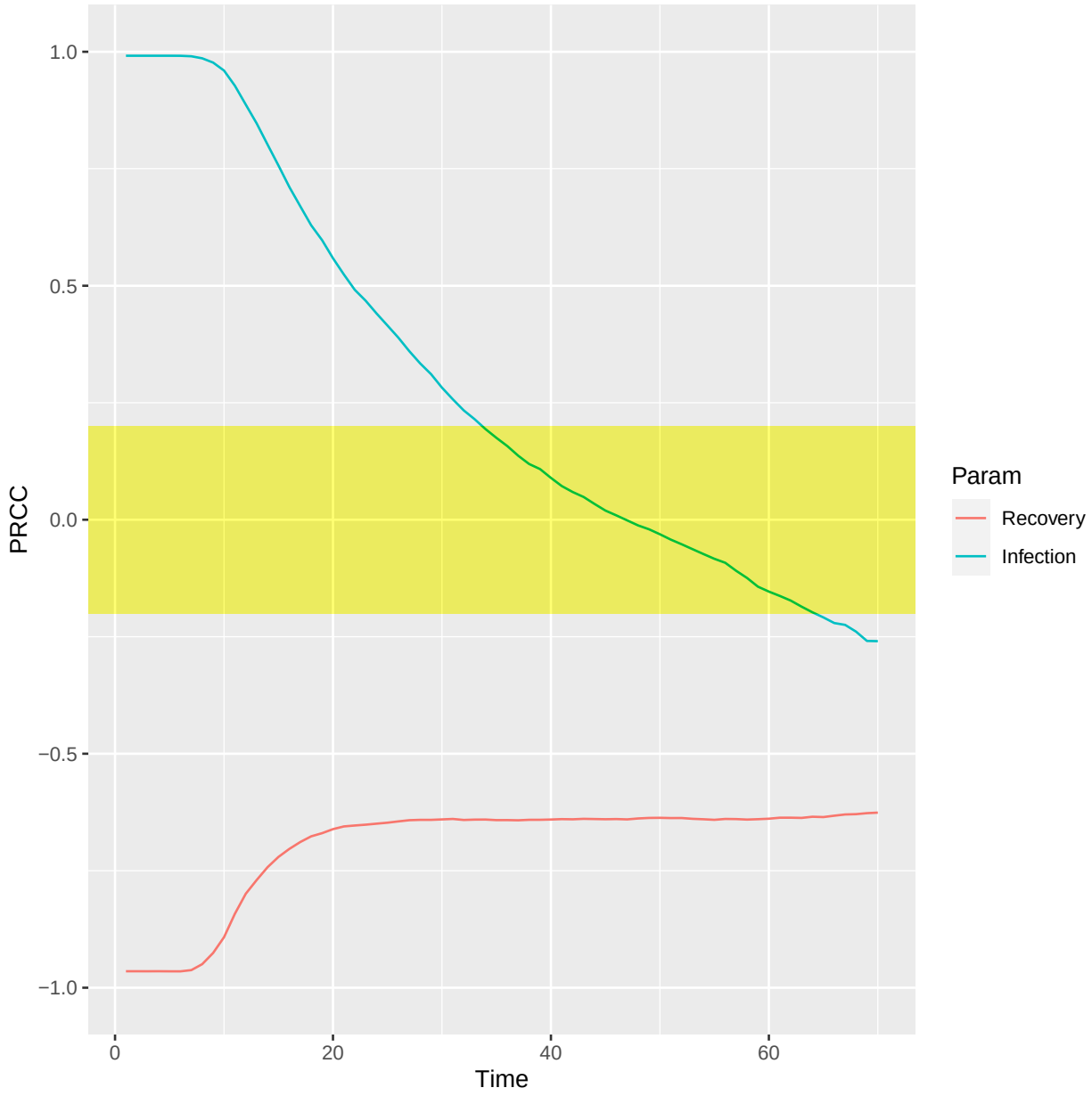


Figure 7: PRCC for the I place over time.

The PRCCs values for these two parameters, depicted in figure 7, with respect the number of infections over the entire simulated period are both meaningful, especially in the first part of the simulation, corresponding to the transient part where the parameters affect mostly the output. Differently, this effect decreases after the fifth week where all the deterministic trajectories obtained with different parameters configurations converge to the same states, see figure 3.

Other possible examples of how to use this function are reported hereafter:

```
## Version where only the PRCC is calculated
sensitivity<-sensitivity_analysis(n_config = 100,
                                  parameters_fname = "Functions_list.csv",
                                  solver_fname = "SIR.solver",
```

```
                                    target_value_fname = "Target.R" ,
                                    parallel_processors = 1,
                                    f_time = 7*10, # weeks
                                    s_time = 1 # days
                                    )

## Version where only the ranking is calculated
sensitivity<-sensitivity_analysis(n_config = 100,
                                    parameters_fname = "Functions_list.csv",
                                    solver_fname = "SIR.solver",
                                    reference_data = "reference_data.csv",
                                    distance_measure_fname = "msqd.R" ,
                                    parallel_processors = 1,
                                    f_time = 7*10, # weeks
                                    s_time = 1 # days
                                    )

## Complete and more complex version where all the parameters for calculating
## the PRCC and the ranking are considered, and the initial conditions vary too.

sensitivity<-sensitivity_analysis(n_config = 100,
                                    parameters_fname = "Functions_list2.csv",
                                    functions_fname = "Functions.R",
                                    solver_fname = "SIR.solver",
                                    reference_data = "reference_data.csv",
                                    distance_measure_fname = "msqd.R" ,
                                    target_value_fname = "Target.R" ,
                                    parallel_processors = 2,
                                    f_time = 7*10, # weeks
                                    s_time = 1 # days
                                    )
```

**Sensitivity analysis with general transitions** Let us consider the example of the SIR model where the *Infection* transition is defined as general transition, with the porpoise to varying the *Infection_rate* constant of the corresponding MA law. Generally, since all the transition constants are used in the file C++, then we need to define an R function into the **functions_fname** which returns the values that have to be used into the file C++. Therefore, we have to modify the *Functions_list* csv as follow in order to associate with the general transition *Infection* the R function, *InfectionValuesGeneration*, which generates the values exploited by the respective function defined in the C++ file, called *trasition.cpp*.

```
#>   Tag       Name                    Function Parameter1 Parameter2 Parameter3
#> 1   p   Recovery                       runif        n=1    min = 0      max=1
#> 2   g  Infection  InfectionValuesGeneration    min = 0      max=1
```

Successively, we have to define the *InfectionValuesGeneration* in *Functions.R*.

```
InfectionValuesGeneration<-function(min, max)
{
    rate_value <-  runif(n=1, min = min, max = max)
    return(rate_value)
}
```

Notice that the value (or values) generated are temporarily saved in a file named as the corresponding name in the *Functions_list*, in this case *Infection*. Hence, the file *transition.cpp* has to be modified in order to read and use the value generated from the R function *InfectionValuesGeneration*. An example of implementation is the following, where two functions are defined: (1) *read_constant()* in order to read the generated value, which is associated with the right variable, and (2) *init_data_structures()* in order to read the file only the first time that the function is called.

```
static double Flag = -1;
static double Infection_rate = 1.428;

void read_constant(string fname, double& Infection_rate)
{
    ifstream f (fname);
    string line;
    if(f.is_open())
    {
        int i = 1;
        while (getline(f,line))
        {
            switch(i)
            {
                case 1:
                    Infection_rate = stod(line);
                    //cout << "p" << i << ": " << line << "\t" << p1 << endl;
                    break;
            }
            ++i;
        }
        f.close();
    }
    else
    {
        std::cerr<<"\nUnable to open " << fname << ": file do not exists\": file do not exists\n";
        exit(EXIT_FAILURE);
    }
}

void init_data_structures()
{
    read_constant("./Infection", Infection_rate);
    Flag = 1;

}

double InfectionFunction(double *Value,
                         map <string,int>& NumTrans,
                         map <string,int>& NumPlaces,
                         const vector<string> & NameTrans,
                         const struct InfTr* Trans,
                         const int T,
                         const double& time)
{
```

```
    // Definition of the function exploited to calculate the rate,
    // in this case for semplicity we define it throught the Mass Action  law

    if( Flag == -1)   init_data_structures();

    double intensity = 1.0;

    for (unsigned int k=0; k<Trans[T].InPlaces.size(); k++)
    {
        intensity *= pow(Value[Trans[T].InPlaces[k].Id],Trans[T].InPlaces[k].Card);
    }

    double rate = Infection_rate * intensity;

    return(rate);
}
```

### Calibration analysis

The aim of this phase is to optimize the fit of the simulated behavior to the reference data by adjusting the parameters associated with both Recovery and Infection transitions. This step is performed by the function *model_calibration()*, characterized by the solution of an optimization problem in which the input distance function with respect to a reference data is minimized.

The function input parameters are very similar to those introduced for the *sensitivity_analysis()*, we have just to modify the **parameters_fname** since we do not need to sample the parameter values. An example is given in *Functions_list_Calibration.csv*, where the first two columns (i.e., type and name) remain unchanged, differently the functions associated with each rate (defined *FunctionCalibration.R*) have to return the value (or a linear transformation) of the vector of the unknown parameters generated from the optimization algorithm, namely $x$, whose size is equal to number of parameters in **parameters_fname**. Let us note that the output of these functions must return a value for each input parameter.

```
#>   Tag       Name   Function Parameter
#> 1   p   Recovery   recovery       n=1
#> 2   p  Infection  infection       n=1
```

For instance, to calibrate the transition rates associated with *Recovery* and *Infection*, the functions *recovery* and *infection* have to be defined, returning just the corresponding value from the vector $x$, where *x[1]= "Recovery rate"*, *x[2]= "Infection rate"*, since we do not want to change the vector generated from the optimization algorithm (see Sec. Calibration Analysis Pertussis). The order of values in $x$ is given by the order of the parameters in **parameters_fname**.

```
recovery<-function(x)
{
    return(x[1])
}

infection<-function(x)
{
    return(x[2])
}
```

The remaining parameters are necessary for the optimization process, such as the vector defining the upper/lower bound limits, the initial parameters value, and the control parameters of the optimization (see the R package GenSa (Yang Xiang et al. 2012)).

```
model_calibration(out_fname = "calibration",
                  parameters_fname = "Functions_list_Calibration.csv",
                  functions_fname = "FunctionCalibration.R",
                  solver_fname = "SIR.solver",
                  reference_data = "reference_data.csv",
                  distance_measure_fname = "msqd.R" ,
                  f_time = 7*10, # weeks
                  s_time = 1, # days
                  # Vectors to control the optimization
                  ini_v = c(0.15,0.00015),
                  ub_v = c(0.2, 0.0002),
                  lb_v = c(0.1, 0.0001),
                  max.call = 50
                  )
#> docker run --privileged=true  --user=1000:1000 --cidfile=dockerID --volume /home/pernice/GIT/R_packa
#>
#>
#> Docker ID is:
#>  04047ef12384
#> ....
#>
#>
#> Docker exit status: 0
#> [1] 0
```

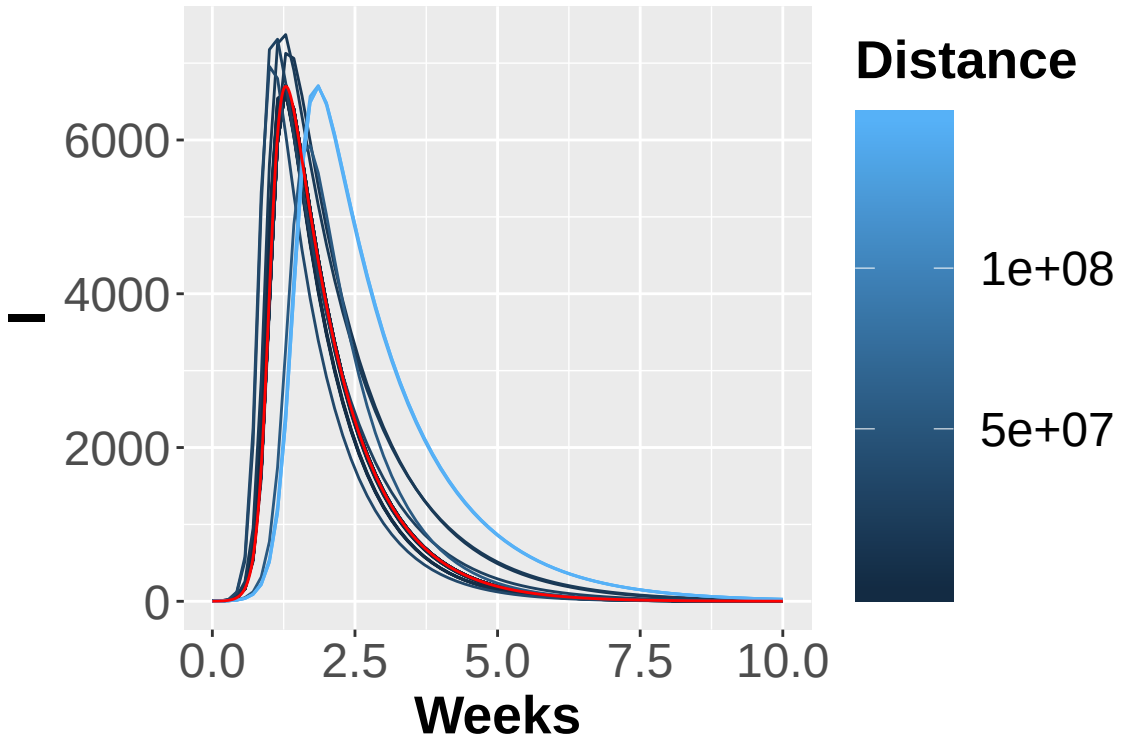


Figure 8: Trajectories considering the I place.

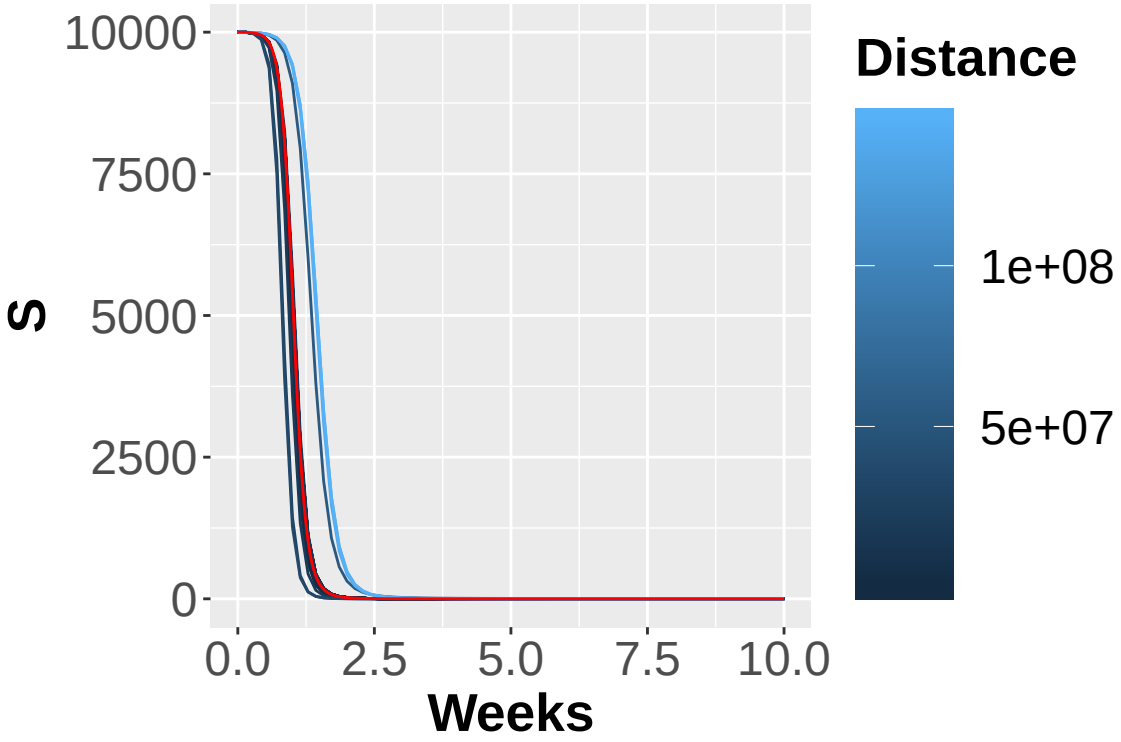


Figure 9: Trajectories considering the S place.

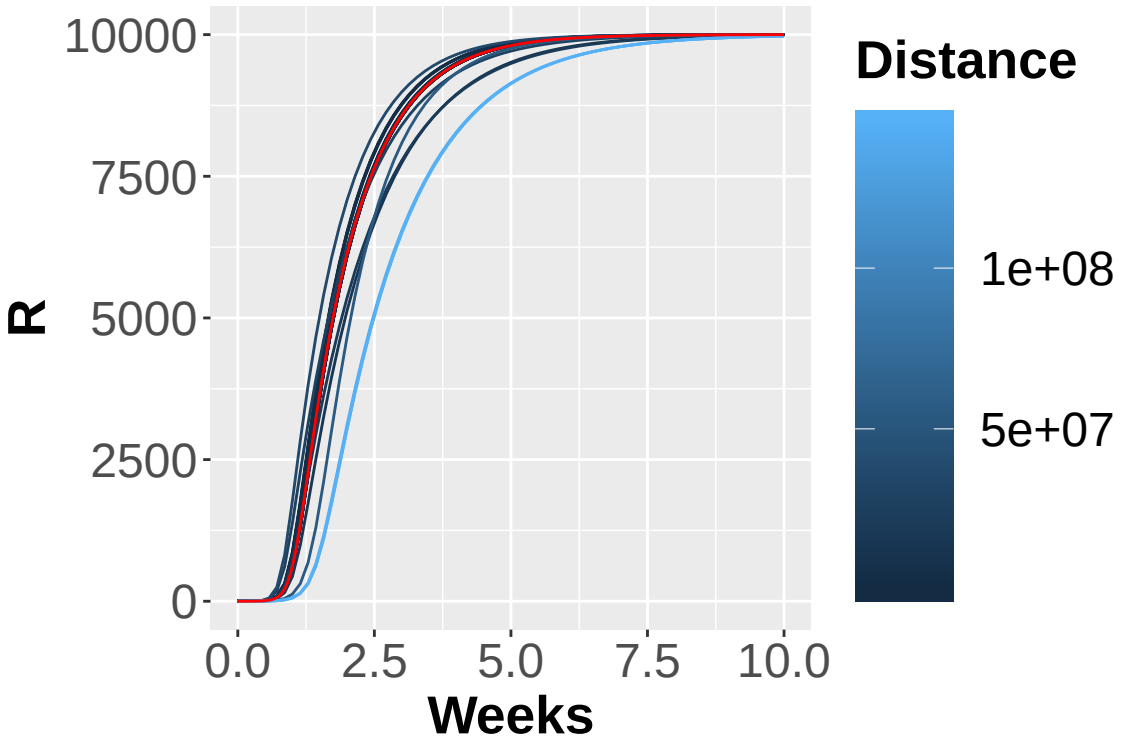


Figure 10: Trajectories considering the R place.

In figures 8,9 and 10 the trajectories with color depending on the squared error w.r.t. reference trend are plotted. In this case, fixing a maximum number of objective function calls, we obtain the following optimal value for the two parameters:

```
#> [1] 0.1428522382 0.0001428038
```

**Calibration analysis with general transitions** Starting from the changes made in the Sensitivity Analysis phase, we have to add the possibility to save the value passed by the optmization algorithm instead of the value generated by the function defined by the user. By default in the calibration phase, the vector $x$ of the unknown parameters, in this case the *Recovery* and *Infection* rates, is passed to the R functions defined in *Functions.R*. Therefore, we have to modify the *InfectionValuesGeneration* in order to return the value contained in $x$, i.e. the second one ( the order is given by the order of the parameters in **parameters_fname**). Notice that in the Sensitivity Analisys phase, the vector $x$ is not passed in input so we can generalized the *InfectionValuesGeneration* as follow in order to use it in both the analysis phases.

```
InfectionValuesGeneration<-function(min, max, x= NULL)
{
    if(is.null(x))  rate_value <-  runif(n=1, min = min, max = max)
    else rate_value <- x[2]

    return(rate_value)
}
```

### Model Analysis

The last step is the model analysis, where the corresponding function *model_analysis()* executes and tests the behavior of the developed model. Furthermore, by changing the input parameters, it is possible to perform a *what-if* analysis or forecasting the evolution of the diffusion process. This function solves the system given a specific parameters configuration which is passed through the function parameter, *parameters_fname*. In this case, instead of writing a function to sample or define the parameter variability, we can pass the specific value obtained from the calibration for generating the corresponding trajectory.

```
#>   Tag       Name Specific value
#> 1   p   Recovery   0.1428522382
#> 2   p  Infection   0.0001428038
```

```
model_analysis(out_fname = "model_analysis",
               solver_fname = "SIR.solver",
               f_time = 7*10, # weeks
               s_time = 1,
               parameters_fname = "Functions_list_ModelAnalysis.csv"
               )
```

# References


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