

# EpiMod: SIR model

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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*. GreatSPN GUI, the graphical editor for drawing Petri Nets formalisms, is available online ([link to install GreatSPN](#)), and it can be installed following the steps showed therein. 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: [link to 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 show the steps necessary to model, study and analyze a simple case study. To this aim, we choose to study the diffusion of a disease following the SIR dynamics. We refer to (Keeling and Rohani 2011) for all the details.

## SIR model

The S-I-R models the diffusion of an infection in a population assuming three possible states (or compartments) in which any individual in the population may move. Specifically, (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 it is possible to draw the model using the PN formalism and its generalizations. We recall that the Petri Nets are bipartite graphs in which we have two type of nodes, places and transitions. Graphically, places are represented as circles and those are the variables of our systems. On the other hand, transitions are depicted as rectangles and are the possible events happening in the system. Variables and events (i.e., places and transitions) are connected through arcs, showing what variable(s) is (are) affected by a specific event. For more details we refer to (Marsan et al. 1995).

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*.

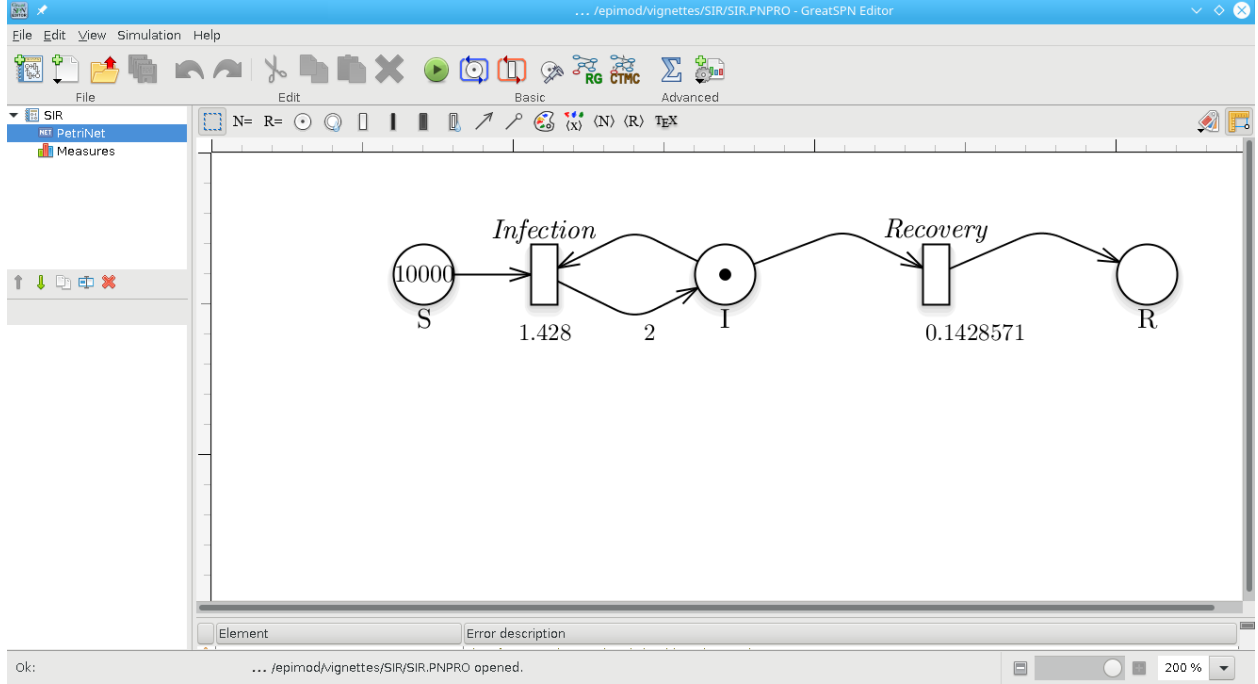


Figure 1: Petri Net representation of the SIR model.

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 = "./Net/SIR.PNPRO")
```

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 a 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 to set the transition as *General* and name the corresponding rate name as **FN:NameGeneralFN**, where in this case the *NameGeneralFN* is **InfectionFunction**. As showed in figure 2, where the transition type is set to *General* and the delay (i.e., the rate) to **FN:InfectionFunction**.

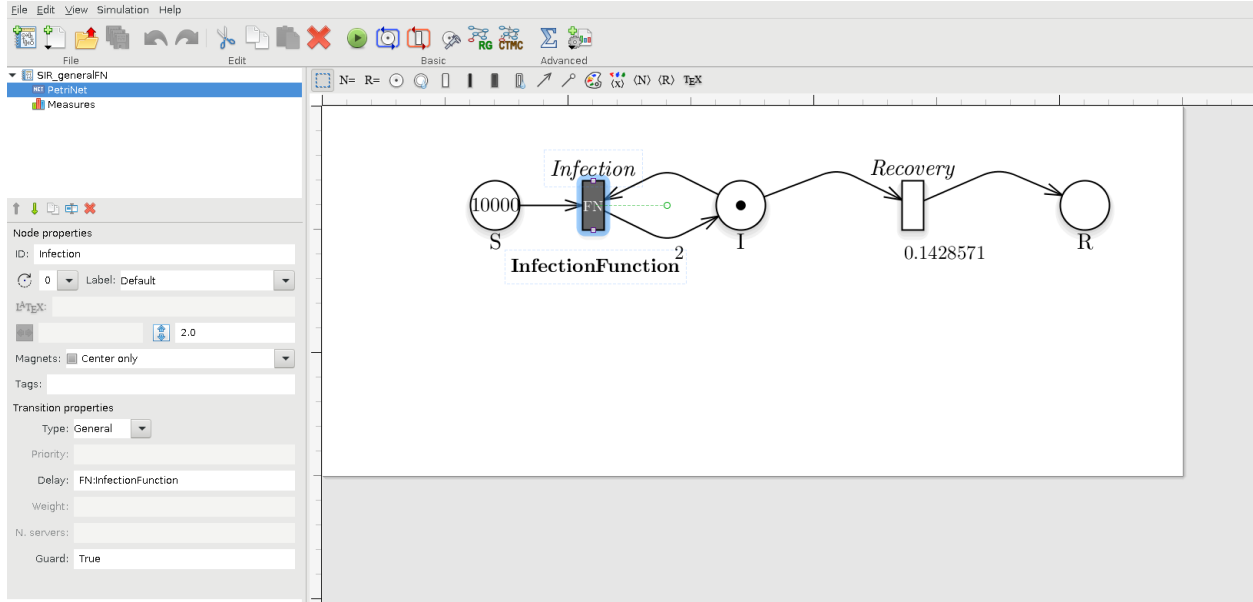


Figure 2: Petri Net representation of the SIR model, modelling the Infection transition as a general transition.

Then, we have to properly define a C++ function implementing the specific behavior of the transition and save it, for instance in a file named *transition.cpp*, 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 simplicity we define it through 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**: association between the transition name and the corresponding index of the *NameTrans* vector;
- **map <string,int>& NumPlaces**: association between the place's name and the corresponding index of the *Value* vector;
- **const vector & NameTrans**: transition names;
- **const struct InfTr\* Trans**: array of *InfTr* structures (implemented in GreatSPN) which is indexed using the transition index. The structure *InfTr* has the following fields: (1) *InPlaces*: the input places to a transition, which is characterized by the input place index position in the *Value* vector (*Trans[T].InPlaces[k].Id*) and the arc (linking the *k* place with the *T* transition) multiplicity (*Trans[T].InPlaces[k].Card*). (2) ....
- **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 by the *model\_generation()* function as follow.

```
model_generation(net_fname = "./Net/SIR_generalFN.PNPRO",
                 functions_fname = "./Cpp/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 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 by default the name *init* is used; (3) the function used for sampling the value of the variable considered, it could be either a R function or an user-defined function (in this case it has to be implemented into the R script passed through 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) 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. Notice that the **reference\_data**'s rows must be the variable time serie, and so the columns the corresponding values at a specific time.

```

#>      TimeStep1      TimeStep2      TimeStep3      TimeStep4      TimeStep5      TimeStep6
#> Time           0 1.000000e-01 2.000000e-01 3.000000e-01 4.000000e-01 0.5000000
#> S           10000 9.999848e+03 9.999674e+03 9.999477e+03 9.999253e+03 9998.9984994
#> I              1 1.137136e+00 1.293078e+00 1.470399e+00 1.672030e+00 1.9013056
#> R              0 1.524425e-02 3.257922e-02 5.229125e-02 7.470625e-02 0.1001951
#>      TimeStep7
#> Time           0.6000000
#> S           9998.7088095
#> I              2.1620116
#> R              0.1291789

```

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 = "Input/Functions_list.csv",
                                solver_fname = "Net/SIR.solver",
                                reference_data = "Input/reference_data.csv",
                                distance_measure_fname = "Rfunction/msqd.R" ,
                                target_value_fname = "Rfunction/Target.R" ,
                                f_time = 7*10, # weeks
                                s_time = 1, # days
                                parallel_processors = 24
                                )

```

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.



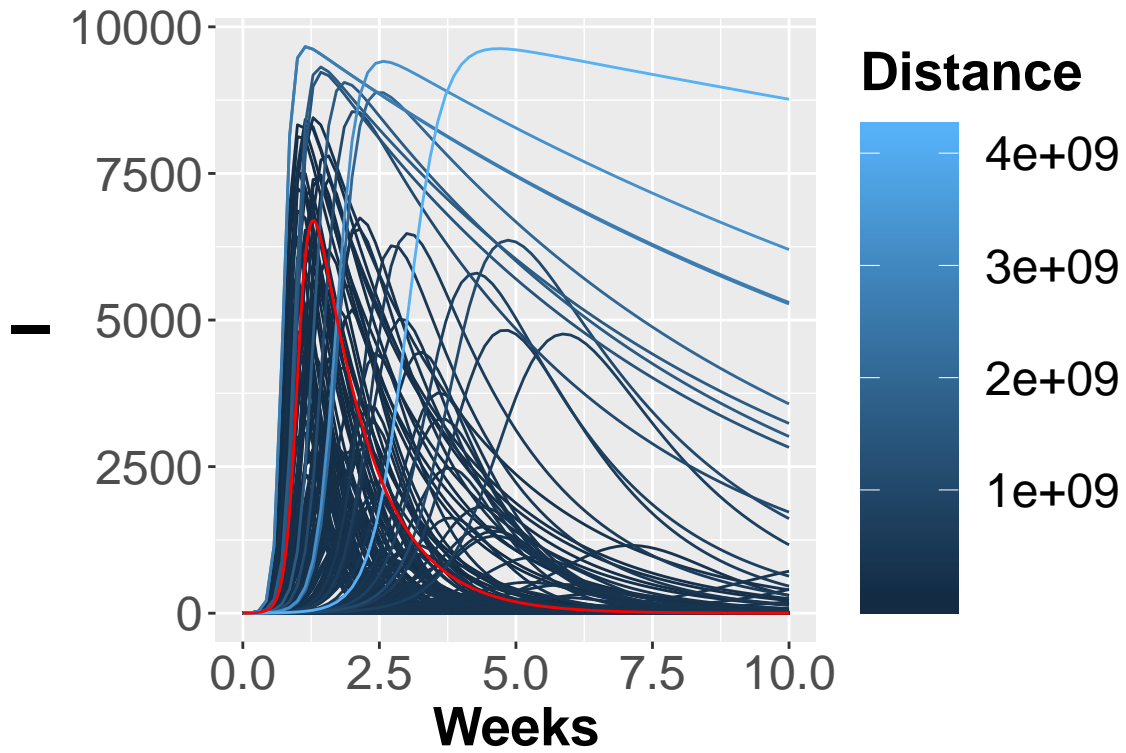


Figure 3: The 200 trajectories considering the I place obtained from different parameters configurations.

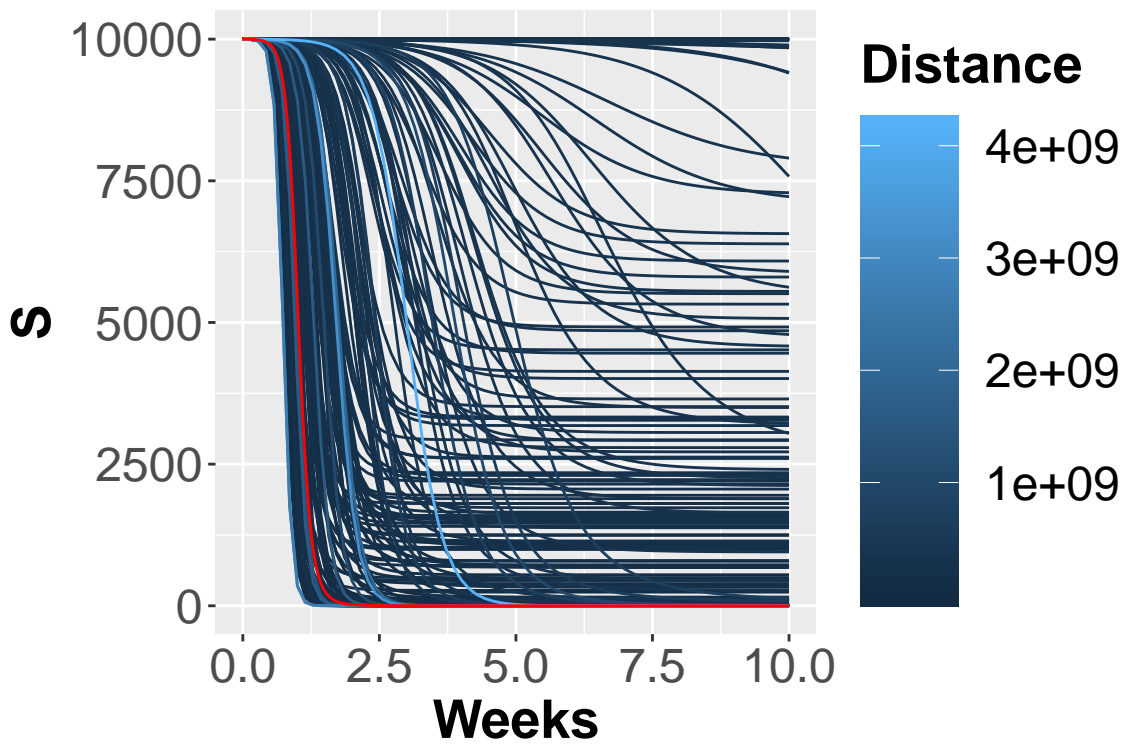


Figure 4: The 200 trajectories considering the S place obtained from different parameters configurations.

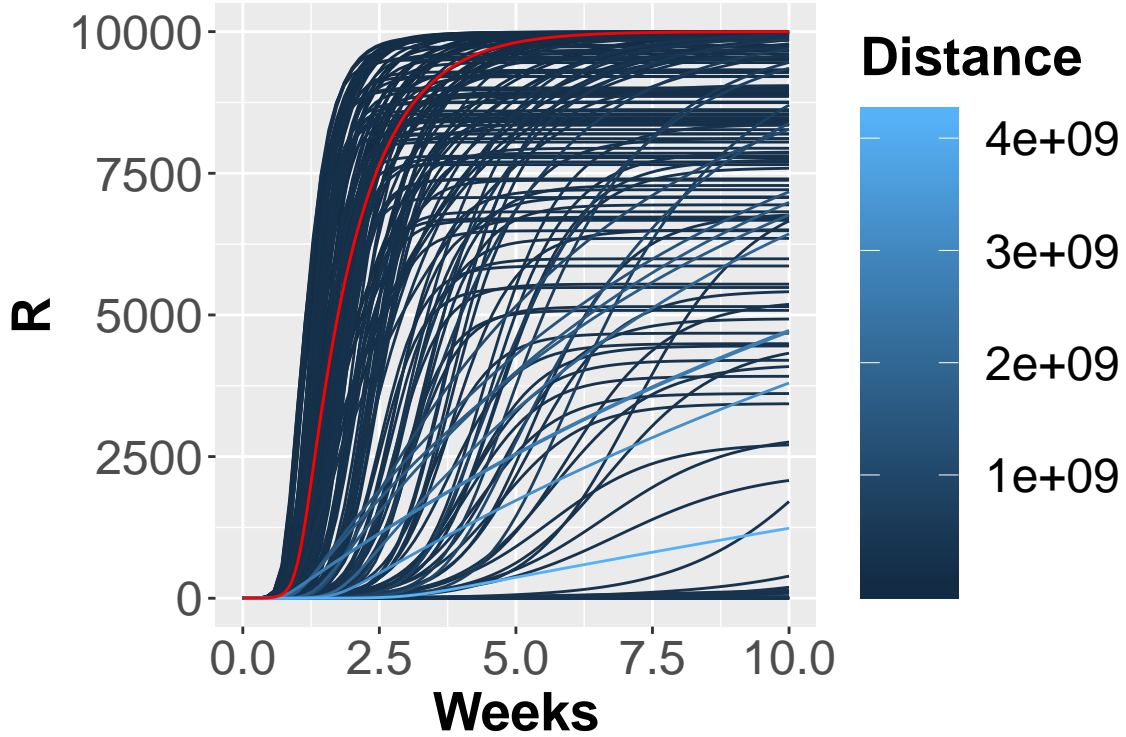


Figure 5: The 200 trajectories considering the R place obtained from different parameters configuration.

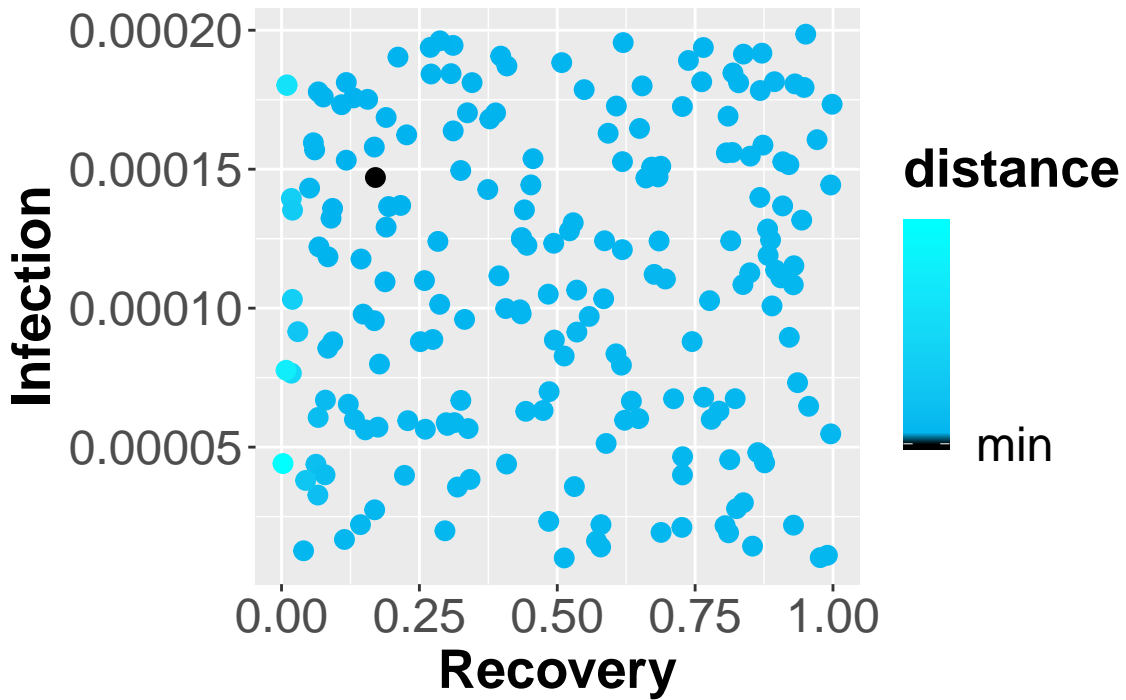


Figure 6: Scatter plot showing the squared error between the reference data and simulated number of infected. The dark blue points represent the parameters configuration with minimum error.

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.

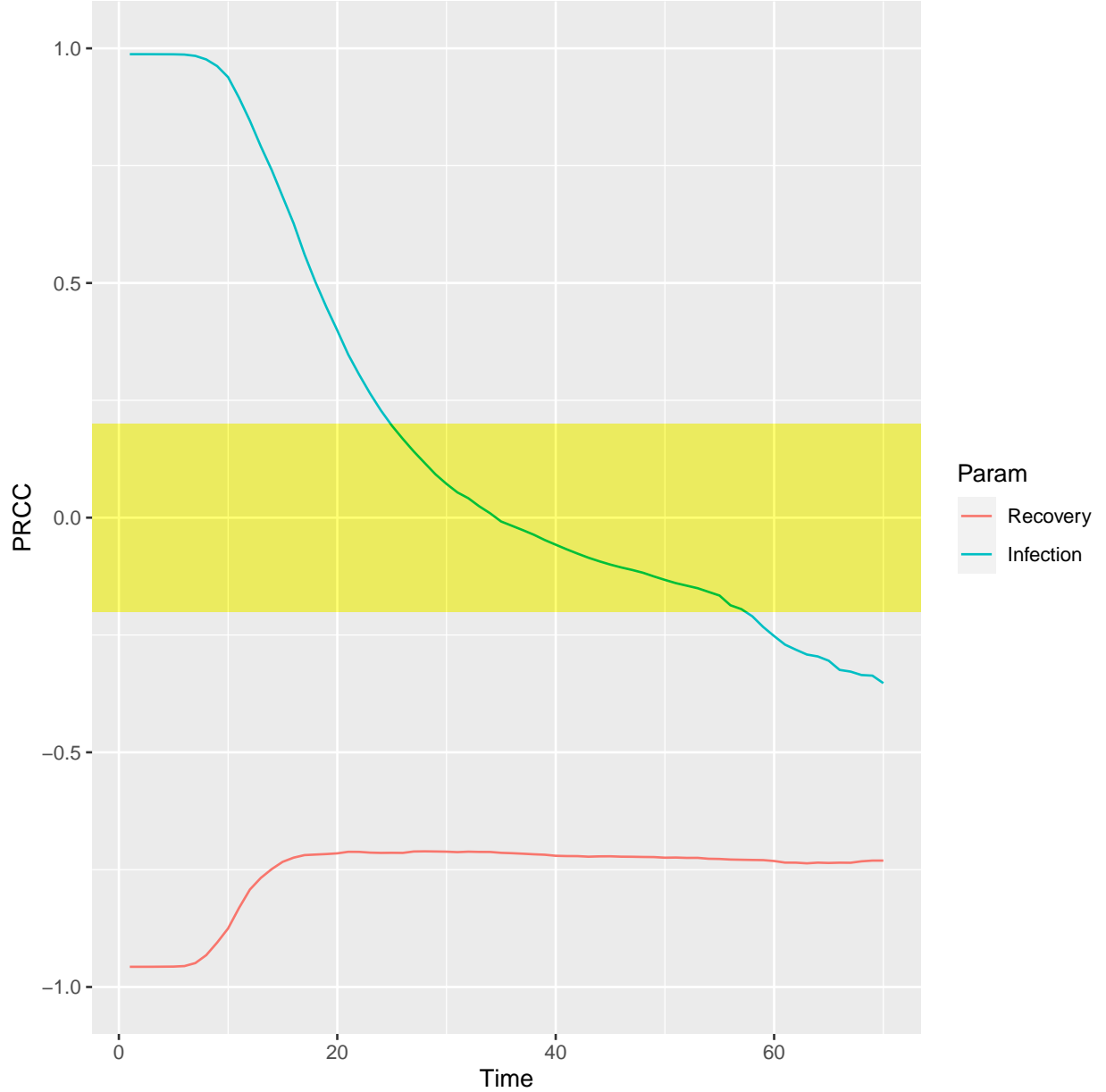


Figure 7: PRCC for the I place over time.

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 = "Input/Functions_list.csv",
                                functions_fname = "Rfunction/Functions.R",
                                solver_fname = "Net/SIR.solver",
                                target_value_fname = "Rfunction/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 = "Input/Functions_list.csv",
                                functions_fname = "Rfunction/Functions.R",
                                solver_fname = "Net/SIR.solver",
                                reference_data = "Input/reference_data.csv",
                                distance_measure_fname = "Rfunction/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 = "Input/Functions_list2.csv",
                                functions_fname = "Rfunction/Functions.R",
                                solver_fname = "Net/SIR.solver",
                                reference_data = "Input/reference_data.csv",
                                distance_measure_fname = "Rfunction/msqd.R" ,
                                target_value_fname = "Rfunction/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 Mass Action law. Generally, in order to define the rate of a transition it is required to provide some inputs and, hence, we need to define an R function (in the **functions\_fname** file) which provides all the input parameters necessary to the C++ function.

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 *transition.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\n": 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 simplicity we define it through 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 distance between the simulated data and the reference data is minimized, according to the definition of distance provided by the user (**distance\_fname**)

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. 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(parameters_fname = "Input/Functions_list_Calibration.csv",
  functions_fname = "Rfunction/FunctionCalibration.R",
  solver_fname = "Net/SIR.solver",
  reference_data = "Input/reference_data.csv",
  distance_measure_fname = "Rfunction/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
)

```

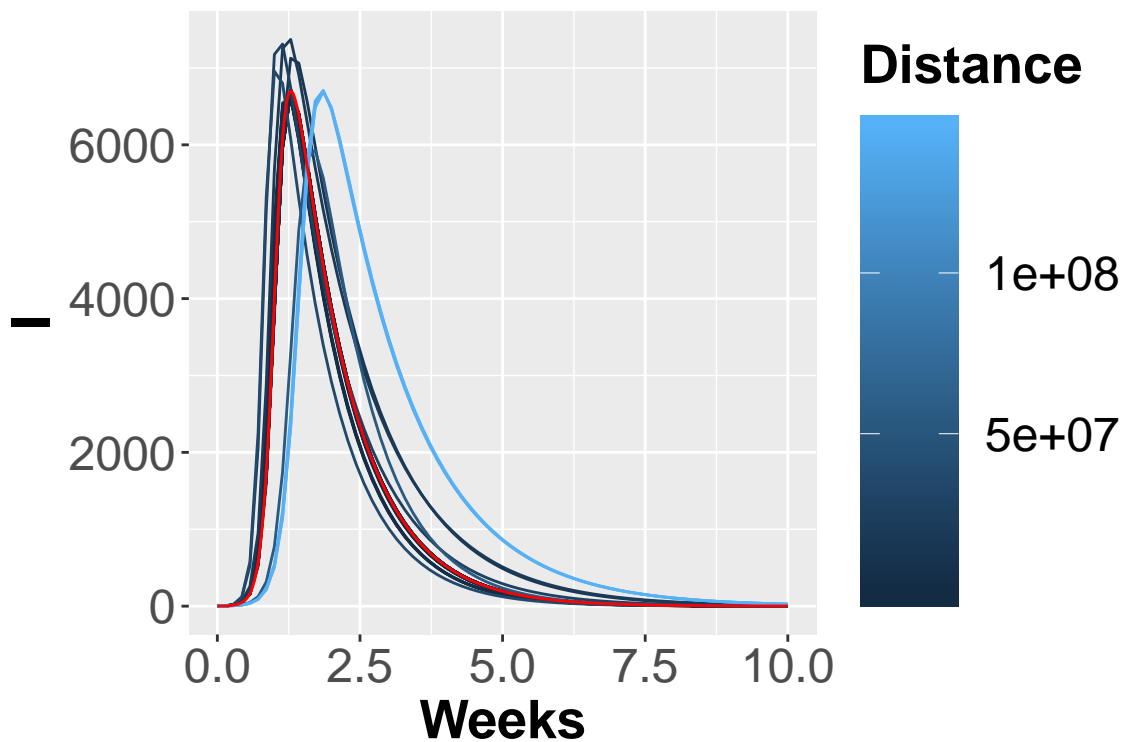


Figure 8: Trajectories considering the I place.

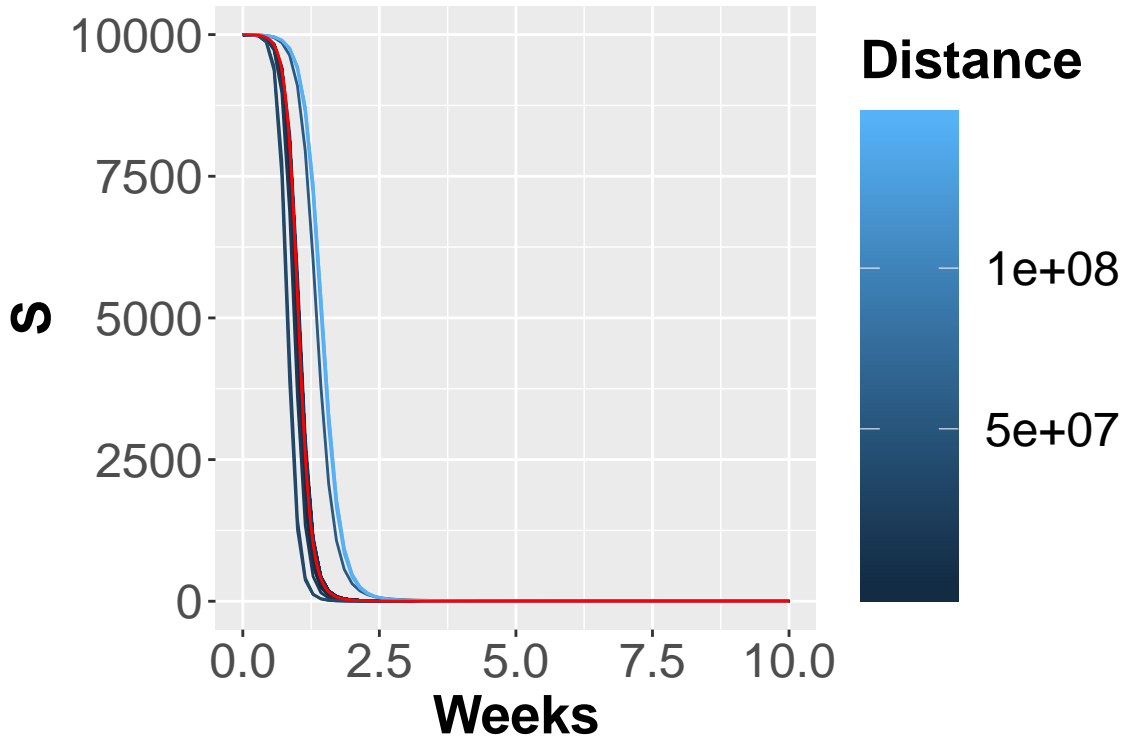


Figure 9: Trajectories considering the S place.

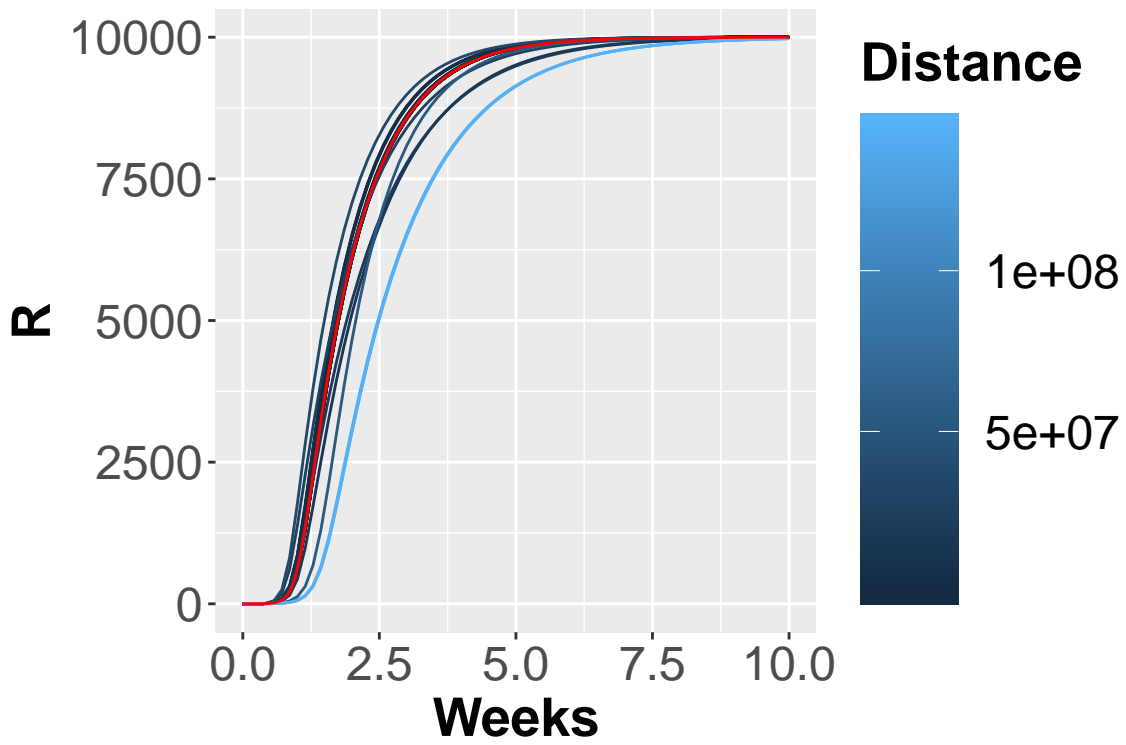


Figure 10: Trajectories considering the R place.

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 optimization 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 Analysis 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 = "Net/SIR.solver",
               parameters_fname = "Results/Functions_list_ModelAnalysis.csv",
               f_time = 7*10, # weeks
               s_time = 1
               )
```

## References

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