

Design of a spatial and stochastic simulator for bird flu spreading in Corsica

Hill D.R.C.¹, Muzy A.², Barraud R.¹, Crozat B.¹, Madary J.², Leccia F.²

¹UMR CNRS 6158, LIMOS/ISIMA, Blaise Pascal University, BP 10125, 63177 Aubière CEDEX, FRANCE

²UMR CNRS 6240, LISA, Università di Corsica - Pasquale Paoli, 22, av. Jean Nicoli, 20250 Corti, FRANCE
drch@isima.fr

Keywords: Bird Flu, Corsica, Spatial Simulation, Stochastic simulation, Java.

Abstract

A stochastic spatial model of inter-human influenza spreading has been designed considering the adaptation of the avian H5N1 strain. The occurrence of this adaptation will take place and the model has been designed in order to test various scenarios in Corsica. The virulence of such an influenza pandemic is unknown, but the H5N1 strain has now been known for a decade as an extremely severe influenza virus. Since such a virus will be new to the human immune system, people who contract it will have no pre-existing immunity and the disease will be more serious than one caused by ordinary influenza. This paper presents an original simulation software, designed by a multi-disciplinary team, including doctors. The simulation is an individual based modeled, using current data on the existing medical areas of Corsica. The model takes into account geographical information and aims at being used for local public health decisions.

1. INTRODUCTION

Transmission between humans of a modified H5N1 “bird flu” strain was not proved until recent studies. In 2005, a study of the events which occurred in 2004 in 8 Asian countries suggested a Probable person-to-person transmission of avian influenza A (H5N1) [Ungchusak et al. 2005]. More recently, a Chinese group has presented a more convincing case of inter-human contamination [Wang et al. 2008]. However, even without more formal proof, we know that this event will occur in the near future, according to the World Health Organization. The cumulative number of confirmed human cases of avian influenza A (H5N1) reported to the World Health Organization has now reached 382 (with 241 deaths at the time of writing this article). Hence, the simulation of inter-human spreading is of interest to plan which actions to set up during a possible pandemic period. A possible inter-human spreading will be facilitated by air transportation, which will speed up a world spreading [Mangini and Gendreau 2005]. Major scientists in the domain have already proposed interesting models [Fergusson et al. 2005], [Longini et al. 2005] and [Colizza et al. 2007]. A survey of this kind of simulation model has

been recently proposed by [Bonmarin and Levy-Bruhl 2007]. The authors studied the models’ contribution to public health decisions. In Japan, a simulation model is proposing an agent-based simulation [Deguchi et al 2006] using SOARS (Spot Oriented Agent Role Simulator). They modeled the infection process taking into account the social activities of agents. Another individual based model, proposed by [Carrat et al 2006], simulates the spread of influenza within a community. In this community, meetings between individuals are simulated through randomly generated graphs according to [Andersson 1998] which exposes the limit theorems for a random graph epidemic model. This last model tests the impact of various intervention methods according to age, treatment, and vaccination status.

2. DESIGN CHOICES FOR THE SIMULATION

The design choices for the simulation have been made in accordance with current medical knowledge and policies. The medical knowledge is usually approximated making a stochastic modeling approach relevant. Because of the complexity of such spatial propagation at the moment, several modeling and implementation choices have to be made.

2.1. Local context and modeling choices

In France the modeling of interventions has been recently studied [Doyle et al. 2006]. To enhance the results provided for Corsica within this context, we have developed a stochastic spatial model of bird flu spreading in Corsica. The fact that the model concerns a small island was interesting in itself. We set up a multi-disciplinary team, involving doctors, specialists in geographical information systems and computer scientists. For health care purposes, the island is organized into areas for which both population and medical information are collected. The simulation is an individual based model, using current available data.

From the study carried out by [Longini and Al 2005], we retained that the population must first of all be divided into age groups. Each group has various meeting frequencies and ways of life. This changes the probabilities of infection between individuals of various classes. With regard to the procedure of virus transmission, the probability

that an individual will be infected by another previously infected individual is a parameter of the model. All the stochastic processes are handled through Monte Carlo experiments. In the contamination case a pseudo-random number is drawn according to a uniform law between 0 and 1. If the drawn number is lower than the probability of the individual age class, the individual enters into an incubation period. If not, contamination remains likely.

In our model, we also include contamination between medical areas. In addition, the major factors have been taken into account and can be parameterized to design various experiments. The main medical measures have been included. These measures help to reduce the contamination and to avoid a pandemic until a strain-specific vaccine is available. First, the use of masks [Inouye et al 2006] and antivirals [Longini et al 2004] [Jefferson et al 2006] have been considered in our model, as well as a possible quarantine [Mniszewski et al 2008]. Second, the introduction of a vaccine (current influenza vaccine or an H5N1 strain-specific) is also taken into account. The European Commission recently approved a new pre-pandemic vaccine against influenza. If the following virus structure is close to the current virus structure, this pre-pandemic vaccine would be helpful. Otherwise, only a vaccine developed during the pandemics, quarantine, Tamiflu treatments and the use of masks by doctors, can diminish the propagation.

2.2. Development language, libraries and tools

To implement our project, we chose the Java language for its portability on several operating systems such as Unix, Microsoft Windows, Mac OS or Linux with little or no modifications. We worked with the JDK SE 6 (Java Development Kit). The JDK is downloadable with the following URL:

<http://java.sun.com/javase/downloads/index.jsp>.

With regard to libraries, we first used the SSJ (Stochastic Simulation in Java) worked out by Pierre L'Ecuyer of Montreal University. SSJ is a Java library, providing tools for stochastic simulation. SSJ contains various packages facilitating the development of Monte Carlo simulations. The version used is SSJ-2.0. It is downloadable at this URL:

<http://www.iro.umontreal.ca/~simardr/ssj/>

At the end of prototyping, considering that the whole library was too large for our project we implemented only a few methods and a revised version of the Mersenne Twister for pseudo-random numbers generation [Mastumoto and Nishimura 1997]. For the graphical interface (GUI), we imported the "Swing-Layout-1.0.jar" library.

The development environment we retained is Eclipse 3.1.1. Free and largely widespread, this tool makes it possible to be effective in the writing of the code thanks to many edition functionalities and with a fast navigation through all the files and classes of a project. This tool is available at the following URL:

<http://www.eclipse.org/downloads/>

There is a plugin allowing the edition, of visual graphical interfaces named Visual Editor. However, this plugin is under development for version 3.1.1 of Eclipse, and for this reason we used the NetBeans software for the GUI design. The version used is the 6.0 and is downloadable with the URL following:

<http://download.netbeans.org/netbeans/6.0/final/>

We created a full documentation of our source code thanks to the Javadoc, which is a reference for the generation of Java documentation. Finally, memory and computing performance benchmarks were carried out with the JProfiler 5.1.2 tool.

2.3. A simulation focused on active elements

In our model we take into account that Corsica is divided into medical areas, which themselves include several administrative sub-divisions. These administrative sub-divisions comprise a population of people divided into various age groups. Medical areas were geographically defined by medical authorities depending on the number of doctors, nurses and pharmacists. In our IBM (Individual Based Model) we focus only on active individuals, people who are able to contaminate others. This choice is a traditional technique of optimization in simulation [Hill 1996]. For each individual we must have attributes which tell us in which state the person is. According to [Colizza et al. 2007], we point out that the person can be in the "likely" state, *i.e.*, the individual is healthy but likely to be contaminated. The person can be in a "latent" state of incubation, *i.e.*, this person is in a non-contagious period. The individual can be in the "infected" state, and is then contagious. Finally a person is known as "related" if the person is sick but non-contagious. From this state, the people can then die or survive. In this last case, this individual becomes likely to contract the disease again after a period of one year. The class representing the individual must have all the methods necessary to modify the characteristics of a person and to cause his death. In addition, for each person, the duration of incubation as well as the duration of the contagious state must be calculated.

We chose initially, according to [Colizza et al. 2007], to calculate these durations thanks to a random drawing according to a negative exponential distribution (around a

mean specified as an input parameter by the user). We will see in the results section that such parameters are of course considered sensitive for the evolution of the transmission.

At the beginning of simulation, all the individuals are in the “likely state” (*i.e.*, healthy). In addition, it is necessary to distinguish if a person belonged to the medical personnel. Indeed, we know that the doctors will be particularly affected, because of their strong exposure to the virus. However, if they are strongly struck by the disease, then the expansion of the disease is likely to be higher and the death rate much more important. Indeed, if the medical personnel is strongly affected, they will no longer be available to look after the rest of the population. Every day a random drawing is completed. If this number is lower than the medical population proportion, a doctor dies.

The next kind of active element for the simulation is the notion of medical areas. For each medical area we have divided the population into three distinct age groups. The first group, that we name “young people” (ranging from 0 to 19 years); the “adult” group (ranging from 20 to 64 years), whereas the last class named “senior”, (represents individuals over 64 years).

Moreover, we have also decided that our simulation must take into account the density of population to represent the significant and realistic impact of the geographical data at our disposal. The class “Medical area” class presents a surface attribute as well as an attribute representing its number of inhabitants and the methods allowing us to obtain, for each state and each age group, the number of people concerned in each disease status.

2.4. Data sources

Real data are available for all medical areas, provided by a Geographical Information System (GIS). Thanks to the latter and the work of Julien Madary, we had at our disposal maps as well as enough data to instantiate the programming objects, which we presented previously. We stored the data necessary for the simulation in a CSV file (Coma Separated Variables). Such files are uploaded in input of the simulation program instantiating real updated data of medical areas. For every administrative sub-division of Corsica, we had at our disposal files containing:

- The number of inhabitants;
- The surface;
- The coordinates on the map.

We also had files containing aggregated data for medical areas:

- Number of inhabitants;
- Coordinates on the map;
- Number of doctors;
- Number of individuals for each age group.

2.5. Implementation of active elements

A “Person” class presents the attributes and the essential methods to describe an “Individual” in our simulation. In particular, our simulator will instantiate this class while carrying out a random drawing to determine for each person, the duration of incubation and the duration of the infectious period, these values being variable from one individual to another. This drawing is carried out with a uniform law between the maximum and minimum of the durations for the incubation and infectious period.

A “Medical Area” is a class containing “Persons”, thus we have arrays to store the people according to their state (healthy, in incubation period, surviving or dead) but also according to their age group. To avoid the instantiation of a very great number of persons, we optimized the implementation of the Medical Area class with meters to count people according to their status and age group.

3. SIMULATOR STRUCTURE AND BEHAVIOR

Depending on previous design choices, transition functions and data structures of the simulator can be specified.

3.1. Main input parameters

It has been noticed in our bibliographical study that the first parameter to be taken into account is the global attack rate. This rate will enable us to obtain the number of individuals in contact with a sick and contagious person who will then be infected. Considering an infected individual the attack rate is given hereafter:

$$(1) \text{ Global Attack Rate} = \frac{\text{number of infected people}}{\text{Number of people with sufficient contacts with the contagious people.}}$$

However, the attack rate is variable according to the age group of the individuals considered. We thus propose, first of all, to define a factor to be applied to the global rate of attack. This will give the specific attack rate to a population of a definite age group. These factors are taken as input parameters in our program.

Another variation factor can be applied to the global attack rate to make it possible to take into account the density of population of a given medical area. Indeed, it is known that the rate of attack will be weaker for a zone where the population density is low. The medical areas are thus classified by their density. We decided to apply a factor of 100% for the city having the strongest density. However, since these factors cannot be nil or close to zero, we gave a minimum threshold of 50% for the medical area having the lowest density. The global attack rate will then be reduced by multiplying it by the density factor corresponding to the

medical area. Knowing the maximum and minimum threshold, we proposed a normalization of this factor for all medical areas depending on their population density.

The average duration of the incubation period as well as the average duration of the contagious state (“infected”) must also be given as input parameters because they strongly influence the propagation velocity of the virus. A random drawing between a minimum and maximum of duration of these states is used at run time.

The average number of contacts that an individual has with the people of the same age group, as well as with people of different age groups, is an input parameter for our simulator. The death rate is also specified as an input model parameter, we retained 10% as default value despite the fact that World Health Organization consider a much higher mortality.

Other parameters are also taken into account in our simulation such as the distribution of the infected individuals between medical areas. Neighboring medical areas of an index infected individual have higher contamination probabilities. The other main input parameters are the number of simulation days, the number of replications as well as the possible activation of a percentage of success for medical treatments (mask, vaccine and Tamiflu antiviral).

All these parameters are gathered in a file named “BFParam.txt”, which is uploaded at the beginning of simulation. In this file, we propose the default values of the simulation parameters. Of course the user can change the values of all factors either by specifying them in the file, or by interacting with a graphical interface.

3.2. Propagation inside a medical area

In a first phase, we carried out the simulation inside a single medical area. The simulator first takes into account the global attack rate and the first infected individual. We can then determine how many people will be infected later. We indicated that this global rate must be multiplied by various factors according to age groups of the population of the medical area. Moreover, it is advisable to determine for each person the average number of contacts that an individual has with other people of his own age group. This average number is obtained thanks to a random drawing according to a distribution by the normal law (with mean and standard deviation). The average number of contacts and the global attack rate multiplied by the various factors, will determine the number of individuals recently infected in each age group. It is noticed that it would be necessary to carry out this calculation for every inhabitant of the medical area. To scale the simulation to all medical areas, we chose to carry out these calculations before developing the final version of the simulator. We did some pre-simulations at the level of a single medical area with a sufficient number of replications to obtain a satisfactory confidence interval.

With this approach we pre-calculated the number of people that an individual will infect in each age group and we inserted these results in a static matrix of the simulator (this matrix being uploaded in the input parameter file). This aggregation avoids calculating for each inhabitant the number of individuals with whom it is in contact. This means reducing calculations and thus execution time. With the results of these calculations, we fixed the number of people whom an individual infects according to the age groups. Once completed, this pre-computing is stored in memory, and day after day, new people of the current medical area are infected, starting from each contagious person (“infected”). To handle this we manipulated the following tables:

- A table of people in incubation period (“latent”);
- A table of people in contagious state (“infected”);
- A table of people sick, but in a non-contagious state (“related”).

These tables behave like stacks, *i.e.*, when a person of class “young people” (for example) is infected, we then transfer this person to the table “latent” period and we remove it from the table of people likely to be infected (still of the “young people” class). Then, when the duration of incubation has passed, we transfer the person to the “infected” table. With the same approach, when the duration of the infectious period has passed, we transfer this person to the “related” table and so on. It is to be noticed that people who are in the tables representing the contagious people (“infected”) can then infect again individuals in the tables of healthy people likely to contract the virus.

Considering the attack rate and the various factors seen previously, the infection is obtained by using the following simple formula:

$$\begin{aligned}
 (2) \text{ Number of infected people} &= \\
 &\quad \text{Number of contacts of the infected people} \\
 &\quad \times \\
 &\quad \text{Global Attack Rate} \\
 &\quad \times \\
 &\quad \text{Reduction factors to be applied}
 \end{aligned}$$

The factors to be applied are the factors of density of population of the medical area, the factors according to the age group, as well as the proportion of infected individuals. This last variable is important because it is necessary to take into account the fact that an individual can have a contact with already infected individuals. Once the calculation is carried out, we draw a pseudo-random number between 0 and 1 (according to a uniform law). If this number is lower than the calculated rate, a new individual is then infected.

In addition, with the table of the “related”, *i.e.* representing non-contagious people, a drawing is achieved

following a normal law (of average and standard deviation specified as input parameters). This drawing determines the number of individuals deceased as well as the number of survivors. The surviving people are replaced in the table of the individuals likely to be infected by the virus after a one year period. We are conscious that an individual who has already been in contact with the virus has the antibodies necessary to fight against this one and thus is not likely to contract the disease again. However, we consider that the virus can transfer between two influenza periods and thus the individual could then again be infected. In addition, we take into account that if the number of doctors is strongly affected, the death rate will then be increased. For this last point, a factor is also applied to the death rate. According to the previous remarks, the following formula is obtained:

(3) *Number of deaths* =

$$\begin{aligned}
 & \text{A number of people in the state "related"} \\
 \times & \\
 & \text{Death rate} \\
 \times & \\
 & \text{Factor specific to each medical area (depending on} \\
 & \text{the remaining number of "operational" doctors)}
 \end{aligned}$$

3.3. Propagation between medical areas

We distinguished the transmission between adjacent medical areas and the transmission between distant medical areas. Indeed, the probability that an individual moves in a close area is definitely more important than his displacement towards a distant area. At this point our application is different from other applications (mentioned in our bibliographical study). Indeed, starting from the number of people whom an individual in the infectious state infects, we "divide" these new infected people between the various medical areas according to the percentages specified as input parameters by the user. For instance, we propose a distribution of 80% of infected people in the medical area of origin, 15% in the neighboring area and finally 5% in the more distant areas (this is the default settings in the basic parameter file of the simulator).

A connection network between the different medical areas has been stored in a CVS file format according to their geographical positions. Loaded at the beginning of the simulation this matrix enables the simulator to determine how to realistically distribute the new infected individuals between the different medical areas. This connection network can be improved to follow the main road traffic.

In addition, we implemented a function allowing the reading of a scenario file, which enables the user to determine the appearance of several contagious individuals in a specific medical area (arrivals at ports and airports). The scenario file is a simple text file named "scenario.txt" such as the one of figure 1.

```

# ----- #
# Fichier scenario #
# ----- #

#Nombre d'évènements
NBRE_EVT      2

# ----- #
ZONE  10      //zones de recours cible
AGE   1      //classe d'âge de l'individu
JOUR  8      //jour d'apparition
NB    400    //nombre d'individus contagieux
                //intégrés dans la zone de Recours

# ----- #
ZONE  23
AGE   2
JOUR  9
NB    50

```

Figure 1. Sample scenario file

4. FIRT SIMULATION RESULTS AND VERIFICATION

4.1. Use of the simulator

4.1.1. Command line execution

We have previously stated that it is possible to launch our application in two different ways (through a graphical user interface or through a command line). After having launched the "JBirdFluCommandLines.exe" program, a console appears. The main simulation parameters are then displayed (number of simulation days, number of replications, durations of incubation and infection, etc.) The console also informs the user of the normal simulation end. It should be noted that the user must edit the "BFParams.csv" file to modify the input parameters of the simulation. At exit, the application generates the following files at the root directory of the simulation application:

1. "ResultatsStatistiques.txt" presenting a summary of the results for each medical area;
2. "ResultatsIntervalleConfiance.txt" presenting the confidence intervals of the results;
3. "log.txt" having the detailed trace of the execution.

The number of replications necessary to obtain a confidence interval of 95% is automatically evaluated. However, by modifying the file of "BFParams.txt" parameters, it is possible to fix the number of desired replications.

4.1.2 Use of the graphical interface

Launched, the "JBirdFluGUI.exe" application will display the graphic interface in figure 2. Within this first application window, we can modify the main parameters of the simulator, such as the duration of simulation, the

number of replications, the selection of medical decisions as well as the position of the first contamination.

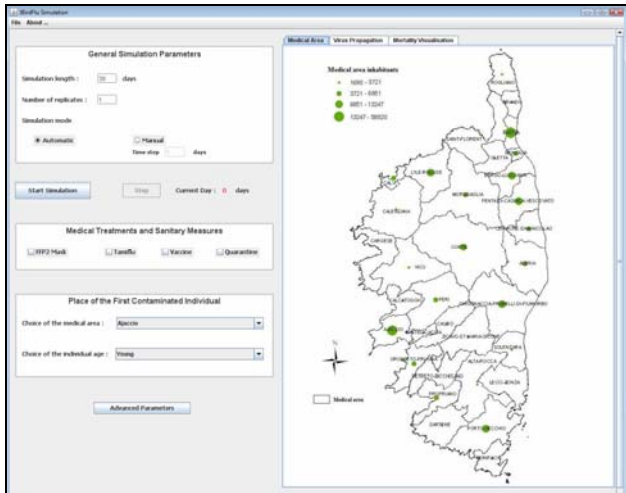


Figure 2. Main window of the simulator

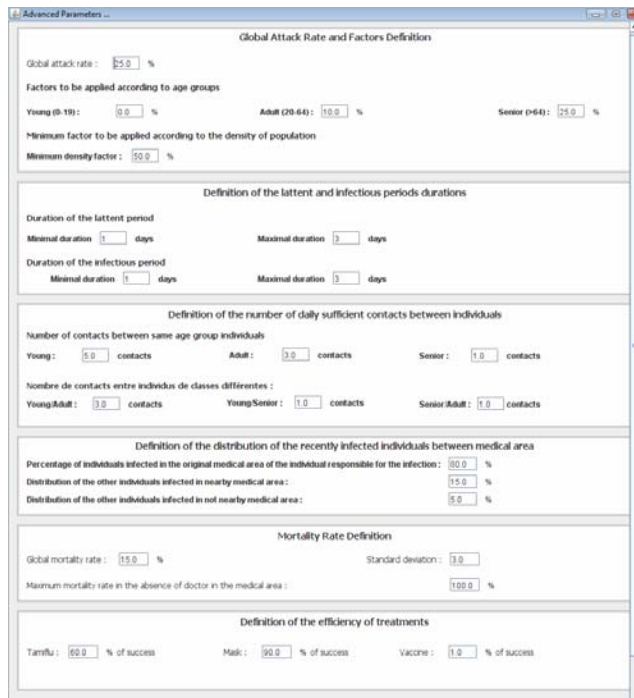


Figure 3. Secondary window enabling the modification of advanced parameters

Through this interface, it is possible to launch a number of simulations in an automatic mode (the display of an average map is postponed to the end of the simulation). In addition, we also provide a more manual mode, step by step, specifying the time base to trace the transient behavior of the simulation model. When doing this, it is important to remember that we are watching only a very small sample of a stochastic process.

While clicking on the “File” menu, it is then possible to activate or deactivate the reading of a scenario file. The map displayed with the launching of the application makes it possible to visualize the various medical areas with their respective density. The two other tabs present the propagation map of the virus as well as a map giving the evolution of speculative mortality in the medical areas. Finally the button “Advanced Parameters” makes it possible to modify the detailed simulation parameters as shown in the figure 3. The output files previously cited are also generated during the execution in graphic mode.

4.2. Testing and verification

During the testing phase, we realized that the parameters largely influencing the results are the duration of incubation as well as the duration of infection. With the command line version we quickly discovered that a small number of replications (around 6) were needed to obtain a confidence interval of 95%. Figure 4 presents the visual results obtained with the default parameters after a single replication, a total rate of attack of 25% and after 90 days.

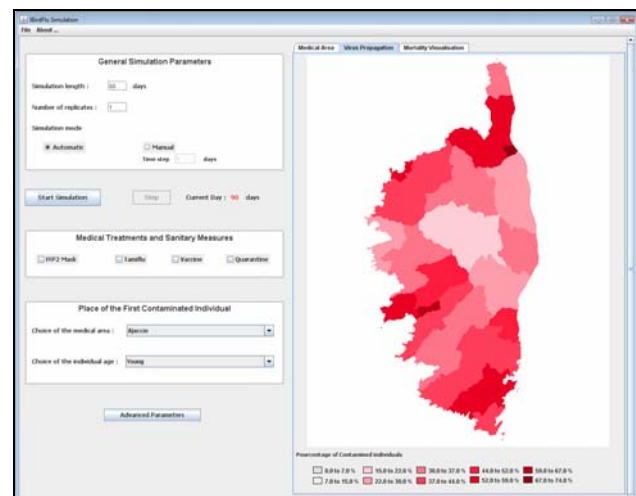


Figure 4. Propagation of the virus: percentage of contaminated individuals

We notice that one of the most affected areas is that which is at the origin of the propagation. Then, the areas having the strongest density are also strongly affected. This result is obvious since, as we saw in our bibliographical study, the propagation is clearly increased when the population is strongly interconnected, in particular in the cities with a large population on a limited surface.

In addition, we can see that some medical areas are less affected by the disease, in particular in the center of Corsica (Corte). This result appears logical since the greatest concentration of the population is located on the littoral coasts. However, the presence of the University and the fact that many young adults are traveling on the Ajaccio – Corte

– Bastia axis should be considered. With our software design, we can modify the connection network for this axis. However, it has to be noticed that during a hypothetic bird flu propagation, quarantine policies are enforced and public institutions (like universities) are closed.

With the default settings, *i.e.*, with in particular a duration of incubation ranging between 1 and 3 days, the same duration of the infectious period, and a sufficient number of contacts per person (ranging between 1 and 6 according to age groups), the maximum contamination percentage obtained is of 76% for certain areas at the end of one year of simulation. On the other hand, if one increases the duration of the infectious period (for example from 1 to 7 days), the maximum percentage approaches 90% (with percentages being spread out from 50% to 90% for all medical areas).

With a number of contacts ranging between 1 and 10 according to age groups, a duration of incubation ranging between 1 and 3 days and a duration of the infectious period ranging between 1 and 7 days, one then realizes that at the end of one year, all the zones of recourse are contaminated with a spread out percentage from 90% to 95%. This result proves that the durations of incubation and infection are very significant parameters in our simulator.

Lastly, the most effective medical measures are the wearing of mask as well as the setting in quarantine (with the default values raised at the time of our bibliographical study). Indeed with medical measures it is possible to strongly limit the propagation of the disease (reduction of approximately 70%). The effectiveness of medical measures can be modified and adjusted by the user with the advanced parameters. During the testing and verification phases, all the results were computed with a confidence interval of 95%.

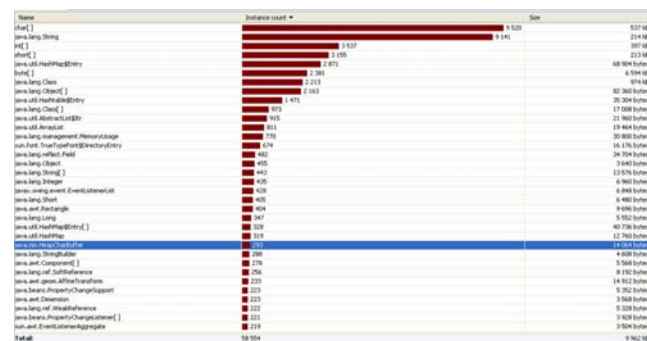


Figure 5. Performance analysis with JProfiler

4.3. Performance of the simulator

With regard to the performance evaluation of our application, we carried out tests with the JProfiler tool. We have studied the memory used by the various instances and also the number of method calls. Our application can be used easily on a current microcomputer. Figure 5 presents the diagram of memory usage for various instances. The two

main peaks deal with Character and String instances (less than 10000 instances). We also noticed on other diagrams that the method presenting the greatest execution time is the one allowing the transmission between medical areas, despite a low number of calls. The details of this method will be carefully studied in the near future.

5. CONCLUSION

The main goal of our application was to provide the user with a modular tool, enabling him to define the various factors which influence the propagation of the avian flu on the island of Corsica. For that, we have proposed an object-oriented simulation software with text configuration files and we have also developed graphical interfaces to interactively test the modifications of the main parameters. The spatial aspects have been taken into account thanks to a Geographical Information System providing maps and valuable data for all the Corsican medical areas. The simulation developed is stochastic and can be considered as a spatial individual based model. The main factors of the space propagation of the avian flu were taken into account and modeled following our detailed bibliographical study. Two versions of the application were developed. The first corresponds to a command line launching mode for further statistical studies following specific design of experiments. The second version implies the launching of the application using a graphic interface having as an advantage the visualization of the space propagation of the virus, as well as associated mortality. This is achieved on two distinct maps of Corsica. Scenarios of propagation are possible on the two versions and the results at exit of the simulator are proposed with a 95% confidence interval. This confidence interval is just a classical approach to present results of stochastic experiments. It is important to understand that no one can propose accurate predictions of mortality before the emergence and spreading of the pandemic virus. Therefore all the speculative estimates can only serve to test scenarios.

Medical actions were considered and integrated in our simulator. Among them, we considered the setting in quarantine, the use of a regular or customized influenza vaccine, the wearing of masks by the population as well as the use of the Tamiflu antiviral. The percentages of success of these various treatments and preventions can be specified by expert users. In its current status, we will need to improve the transmission of the virus between individuals living in medical areas separated over long distances. At the present time, this modeling is simplified and would deserve to be improved by a dedicated contact network. This supposes the inclusion of data on the use of the road networks which are currently at our disposal thanks to local geographical information data.

Moreover, despite the fact that our program was designed for the island of Corsica, it could evolve with a view to allowing a simulation on wider scales. After

thorough testing on a local scale, this work could be envisaged, provided enough geographical information is available.

Reference List

[Andersson 1998] Andersson H, 1998, "Limit theorems for a random graph epidemic model". *Ann Appl Prob*, 8, pp. 1331-1349.

[Bonmarin and Levy-Bruhl 2007] Bonmarin, I., Levy-Bruhl, D., 2007, "Contribution of simulation models to public health decisions: the influenza pandemic", *Medecine et Maladies Infectieuses* 37 (suppl. 3), pp. 204-209.

[Carrat et al 2006] Carrat F., Luong J., Lao H., Sallé A., Lajaunie C. and Wackernage H., 2006, "A 'small-world-like' model for comparing interventions aimed at preventing and controlling influenza pandemics". *BMC Medicine*, 4, no.26. An electronic version of this article can be found online at: <http://www.biomedcentral.com/1741-7015/4/26>.

[Colizza et al. 2007] V. Colizza, A. Barrat, M. Barthelemy, A.-J. Valleron, A. Vespignani, 2007, "Modeling the world-wide spread of pandemic influenza: baseline case and containment interventions", *PLoS Medicine*, 4, no.1, pp.13-23.

[Deguchi et al 2006] Deguchi, H., Kanatani, Y., Kaneda, T., Koyama, Y., Ichikawa, M., Tanuma, H., 2006, "Anti pandemic simulation by SOARS", *SICE-ICASE International Joint Conference*, art. no. 4108485, pp. 4581-4586.

[Ferguson et al. 2005] Ferguson N.M., Cummings D.A.T., Cauchemez S., Fraser C., Riley S., Meechai A., Iamsrithaworn S., Burke D.S., 2005, "Strategies for containing an emerging influenza pandemic in Southeast Asia", *Nature* 437, pp. 209-214.

[Hill 1996] Hill D.R.C., 1996, *Object-Oriented Analysis and Simulation*, Addison-Wesley Longman, 291p.

[Inouye et al. 2006] Inouye, S., Matsudaira, Y., Sugihara, Y., 2006, "Masks for influenza patients: Measurement of airflow from the mouth", *Japanese Journal of Infectious Diseases*, 59, no.3, pp. 179-181.

[Jefferson et al. 2006] Jefferson, T., Demicheli, V., Rivetti, D., Jones, M., Di Pietrantonj, C., Rivetti, A., 2006, "Antivirals for influenza in healthy adults: Systematic review", *Lancet*, 367 (9507), pp. 303-313.

[Longini et al 2004] Longini Jr., I.M., Halloran, M.E., Nizam, A., Yang, Y., 2004, "Containing Pandemic Influenza with Antiviral Agents", *American Journal of Epidemiology*, 159, no.7, pp. 623-633.

[Longini et al. 2005] M. Longini, A. Nizam, S.Xu, K. Ungchusak, W. Hanshaoworakul, D. A.T. Cummings, M. Halloran, 2005, "Containing Pandemic Influenza at the Source", *Science*, 2005. July 12th.

[Mangili and Gendreau 2005] Mangili, A., Gendreau, M.A., 2005, "Transmission of infectious diseases during commercial air travel", *Lancet*, 365 (9463), pp. 989-996.

[Mastumto and Nishimura 1997] M. Matsumoto, Nishimura, 1997, "Mersenne Twister: A 623-dimensionally equidistributed uniform pseudorandom number generator," *In Proc. 29th Winter Simulation Conf.*, pp. 127-134.

[Mniszewski et al 2008] Mniszewski, S.M., Del Valle, S.Y., Stroud, P.D., Riese, J.M., Sydoriak, S.J., 2008, "Pandemic simulation of antivirals + school closures: buying time until strain-specific vaccine is available", *Computational and Mathematical Organization Theory*, pp. 1-13, In press.

[Ungchusak et al. 2005] Ungchusak, K., Auewarakul, P., Dowell, S.F., Kitphati, R., Auwanit, W., Puthavathana, P., Uiprasertkul, M., (...), Chunsuttiwat, S., 2005, "Probable person-to-person transmission of avian influenza A (H5N1)", *New England Journal of Medicine*, 352, no. 4, pp. 333-340.

[Wang et al. 2008] Wang, H., Feng, Z., Shu, Y., Yu, H., Zhou, L., Zu, R., Huai, Y., (...), Wang, Y., 2008, "Probable limited person-to-person transmission of highly pathogenic avian influenza A (H5N1) virus in China", *The Lancet* 371 (9622), pp. 1427-1434.