Population-based Simulation for Public Health: Generic Software Infrastructure and its Application to Osteoporosis

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Abstract

Policy-making in public health has great socio-economical consequences and must be done using the best available knowledge on the possible options. These processes are often too complex to be evaluated through analytical methods, such that computer simulations are often the best way to produce quantitative evaluations of their performances. For that purpose, we are proposing a complete software infrastructure for the simulation of public health processes. This software stack includes a generic population-based simulator called SCHNAPS, which has a modern object-oriented software architecture, and is completely configured through XML files. These configuration files can themselves be produced by a graphical user interface that allows modelling of public health simulation by non-programmers. This software infrastructure has been illustrated with the real-life case-study of osteoporosis prevention in adult women populations. This example, which is of great interest for Quebec health decision makers, provides insightful results for comparing several prevention strategies on a realistic population.

Keywords: Computer simulation, Discrete time systems, Computer aided analysis, Public health care.

1 Introduction

Health care decision makers are regularly involved in situations where they need to establish system-wide policies for purposes such as screening of preventable diseases or conducting vaccination campaigns. In these circumstances, they can benefit greatly from tools allowing them to compare available options and base their choices on specific relevant measures [28]. Otherwise, the decisions might be based on low quality results, opinions, political pressures, and/or pharmaceutical lobbying. Therefore, there is a great interest in providing decision makers with quantitative results comparing expected outcome of different public health policies. For this purpose, our team at Université Laval works in close collaboration with public health decision makers from the government of Quebec to support them with tools and resources, in order to facilitate their decisions.

Health care processes considered for evaluation are usually characterized by their great variability. The solution set is often too large and complex to be evaluated through some analytical methods. Moreover, it is generally not possible to experiment with different approaches on real populations given the cost and resources required, and some obvious ethical considerations. This explains the popularity of computer simulation in health care since the 1960s for comparing the various possible options [4]. However, even if the use of simulation in health care decision-making has greatly increased since the year 2000, the impact of simulations on policy-making or managerial decision-making is still limited. Indeed, Eldabi et al. [18] suggested that although there are many interfaces and packages that implement basic methods, there is still a lack of robust and easy-to-use tools that are accessible to clinicians and hospital managers.

Hence, this paper proposes a general simulation framework for supporting public health decision makers in the design of screening and prevention strategies. A flexible simulation engine is required since public health is concerned with a great variety of activities. Given that we cannot anticipate all possible models and uses that would be needed by those decision makers, we opted for developing a generic simulation software framework, allowing models of any kind – even models not related to public health – with the common denominator that simulations are conducted on populations. This simulation infrastructure has been successfully applied to the evaluation of various prevention strategies of osteoporosis in adult women populations.

In Sec. 2 an overview of various simulation with software systems available for public health is given. This is followed in Sec. 3 by a description of our proposed population-based generic simulator, and its execution in Sec. 4. An insight of

a graphical user interface for simulation modelling is given in Sec. 5. Finally, we present in Sec. 6 the recent application of this simulation infrastructure to the prevention of osteoporosis, which is a real-life case study of interest for Quebec public health decision makers.

2   Simulation Systems

According to Robinson [38], simulation and modelling environments can be classified into three main categories: spreadsheets, programming languages, and specialized software.

Spreadsheets   These are general software like Excel. They allow relatively basic calculations on numbers contained in cells of a two dimension grid. Up to some point, they can be used by non-programmers, but are limited to simple problems. Moreover, they do not encourage good programming practices such as code reuse and modularity.

Programming languages   It is possible to implement any simulation model using programming languages. However this requires good programming skills. Of course these languages support common software engineering practises like code reuse, abstractions, and modularity. There are many frameworks to facilitate simulation modelling using programming languages, e.g. DEVS/COM [7] and DEVSim++ [8].

Specialized Software   They usually facilitate simulation configuration using graphical user interfaces. However, they are specific to their application domain and thus it is often difficult to adapt them to other fields. Moreover, it is generally impossible for the user to extend these commercial software since the internal software is controlled by the vendor, e.g. ProModel [22] and AutoMod [40].

Simulation languages are in-between programming languages and specialized software. They consist of programming languages designed for simulation implementation, e.g. SIMULA [14], GPSS/H [9], and SLX [23]. They are more extensible and versatile than specialized software but more restrictive than programming languages. They propose general simulation concepts already implemented but adaptable by the user. Their goal is to facilitate reuse of components.

At the present time there are many simulators such as ProModel [22], SIMUL8 [44], and Arena [39] that claim to support health care modelling. However, they do not target medical strategies over the population, but are rather specialized in staff and resources optimization. Thus, they are not adapted to the needs cited above. There are also frameworks for simulating on populations such as SPLATCHE2 [37] and simuPOP [35], but they are specific to the modelling of genetic evolution. Hence, they do not correspond to our need for screening strategies and evaluating prevention campaigns. The closest existing application to what we are proposing is the Population Health Model (POHEM) [51, 52] developed by the Health Analysis Division of Statistics Canada. It consists in a set of models developed using the Modgen [46] programming language. It is designed for microsimulations over populations based on Canadian demography. However it is limited to microsimulations on regular desktop machines running Windows XP. We are striving for a simulator which could take advantage of modern supercomputer technology for large-scale simulations and that would not be restricted to Canadian models. Nevertheless, the ideas behind POHEM and Modgen are very interesting and inspiring for developing appropriate tools and resources.

We also have some experience [20, 21] with custom made simulators in several programming languages (VBA, C++, and Java). We learned from this work that unless a stable simulation framework is used, it is very difficult to take the material and knowledge developed in one work and reuse it in another. Moreover, proceeding directly with programming languages usually caused problems for validation by non-programmer specialists, thus showing the importance of using understandable tools. Finally, we observed a constant need for extension to other fields of the domain that could not be achieved using specialized software. Hence we decided to build our own simulator framework.

3   SCHNAPS Architecture

We designed SCHNAPS (SynCHroNous Agent- and Population-based Simulator) [17] as a hybrid between the three main approaches for simulation outlined in the previous section. The modelling used by this simulator is based on function descriptions similar to those of functional programming. Moreover each function can call sub-functions, which facilitates modularity and code reuse. These functions are described using predefined building blocks implementing mathematical, logical and Boolean operators, and even more specialized operators. Thus, defining a complex function using SCHNAPS is similar to the concatenation of multiple predefined functions in a spreadsheet, instead of using a complex syntax. It is also possible to extend the set of available blocks to include complex components that would facilitate the modelling in specific domains. The modelling thus becomes more similar to the use of specialized software.
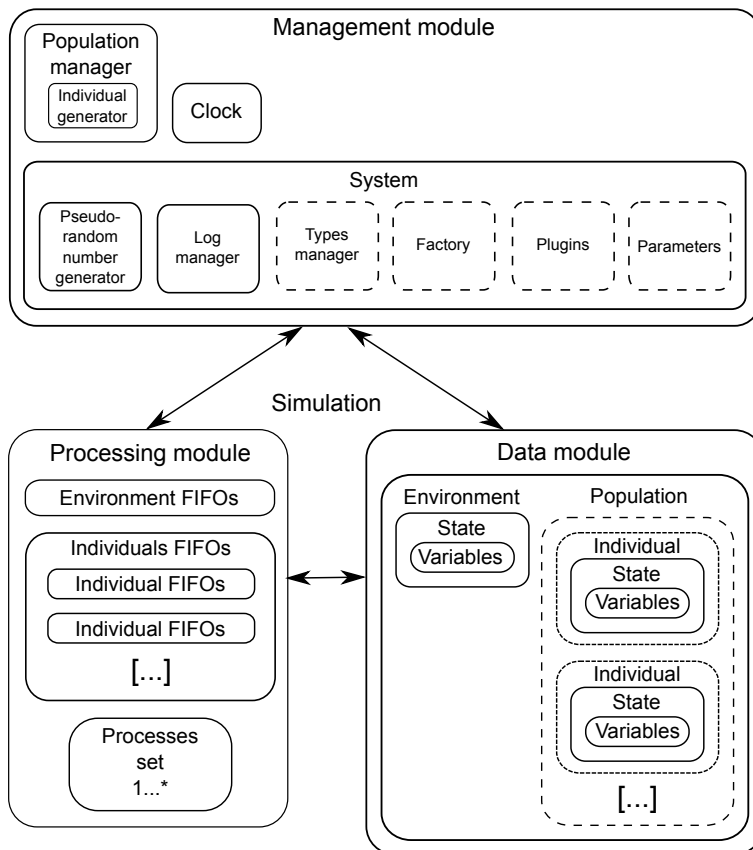
Figure 1: High-level view of the simulation framework.

3.1 Properties

SCHNAPS is an agent-based simulator. It simulates over a set of explicit instances of individuals. Since these individuals are homogeneous and constitute a population, SCHNAPS is thus said to be population-based. Its population can be extended by adding new individuals as the simulation progresses, which is common to the population approach in health simulations. The environment where the population evolves is also represented as an agent. Because individuals interact with the environment, the simulations are said to be multi-agent. It is also possible to simulate over a heterogeneous population by explicitly managing each type of individual. Yet SCHNAPS has not been designed for pure multi-agent simulation and thus this use is reserved to advanced users. By simulating over populations, SCHNAPS supports dependencies between individuals evolving as a group.

Simulators can be classified according to their representation of simulated systems [6]. A state is discrete if all its contained variables belong to a finite set. It is said to be continuous if it is composed of real-valued numbers. SCHNAPS uses hybrid states so the states of its agents (individuals and environment) can contain both discrete and continuous variables. This offers significant flexibility when modelling, which is necessary for supporting models representing human individuals in health care simulations. These models may contain variables of different computer types (e.g. string, integer, float) possibly organized into data structures (e.g. lists, vectors). This great flexibility also facilitates the use of state variables to keep all essential information from past experiences. Hence, it is possible to make models of simulation processes that respect the Markov property.

SCHNAPS is said to be time-driven because its state transitions are synchronized with its internal clock [6]. The execution time required for simulating a model with events occurring at very specific moments over a very long period of time could be significant. Indeed, a time-driven simulator must go through each time step even when no event occurs. An event-driven simulator would be more appropriate to this kind of simulation because it would directly jump to time steps with events. However, the modelling of a time-driven system is usually much simpler than an event-driven one [6]. Since the target users of SCHNAPS include public health decision makers, a simpler and more intuitive modelling time-driven scheme was selected.

3.2 Framework

The main structures composing the framework of SCHNAPS are shown on Fig. 1.
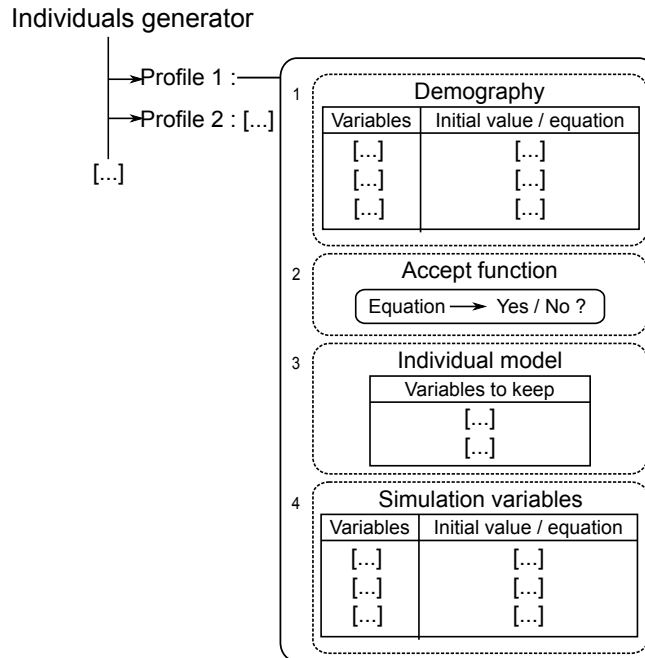
3

Individuals generator

	Demography	
Variables	Initial value / equation
[...]	[...]
[...]	[...]
[...]	[...]

Profile 1 :
Profile 2 : [...]
[...]

1

2 Accept function

Equation ⟶ Yes / No ?

3 Individual model

Variables to keep
[...]
[...]

4 Simulation variables

Variables	Initial value / equation
[...]	[...]
[...]	[...]
[...]	[...]

Figure 2: Generator of individuals for the simulation.

3.2.1 Management

The management module groups together every element linked to the planning of the simulation. The management module is divided into three main parts: the simulation system, the population manager, and the clock.

Simulation System The simulation system consists of a set of general tools. Some of these are visible to users (solid) while others are internal (dotted). It is also possible to define additional optional components. Simulating stochastic events and creating a population from statistical distributions require the use of a pseudo-random number generator. When modelling it is possible to specify the seed of generators in order to repeat the results of a simulation or to recreate exactly a given population. Because SCHNAPS simulates over populations of explicitly represented individuals, it is possible to closely follow each individual during the simulation. This is done by using the log manager to write down important information in a log file at specific times. As for the types manager, it is completely invisible to the user. Its role is to validate operations. Indeed, it must verify that the operators in function composing the simulation always receive valid data as operands. Moreover, it must ensure that the types match when assigning a new value to a variable. The factory is also hidden to the user. This data structure associates the name of each class to the allocator of the class. Hence, it is possible to create objects only using their name, implementing the so-called factory design pattern [19]. The plugins component allows the user to add specific modules to the simulator at run-time and handles the integration of optional components. It can be used to specialize SCHNAPS in certain fields, or to add a new functionality. Finally, the parameters can be used to customize the behaviour of the simulator. They are identified according to their role and/or the component to which they are related. Additional parameters can be defined when adding a new component using plugins. Every parameter has a default value which can be modified with the command line at the launch of SCHNAPS, or directly in the model. It is also possible to use parameters in the simulation to store recurring values.

Population Manager The population generator creates the population on which the simulation is applied. Since SCHNAPS allows the addition of individuals as the simulation progresses, the generator can be called at anytime. Each individual is generated from a population profile, and the generator may contain several profiles that can be used as sources for population, as shown on Fig. 2. The demography contains the general variables that characterize the given population. Each variable is either described by its initial state or by an equation, like a statistical distribution, from which the initial value can be computed. The computation of the initial value of a variable can also involve other variables already initialized. The individuals generated from a specific profile will all be composed of the corresponding demography variables. However, each individual is not necessarily appropriate for a given simulation. For example, when simulating a disease that only affects women, the population does not use male individuals. Hence, to maximize the use of resources, the individual generator includes an accept function. The newly created individual is the input to that function, which outputs whether the individual must be kept or rejected. If it is rejected, the generator creates a new one until it obtains a valid individual. This process is similar to the acceptance sampling used in random number generation from arbitrary

4

statistical distributions [41]. To lighten the simulation and facilitate posterior results analysis, only essential variables are kept in individuals. Thus, each population profile provides an individual model indicating which demography variables are retained for the simulation. Finally, individuals must be given additional variables specific to the simulation. The goal is to keep demography general enough so they can be re-used in different projects. The specialization of individuals for a given simulation is done using the simulation variables. For example, they can be used to represent the characteristics linked to the simulated disease or screening evaluation. They can also be used to accumulate information relative to the simulation such as the cumulative cost or to ensure the Markov property of the system by keeping all important information from the past. Like demography variables, these variables are either defined by an initial value or an equation and may involve other variables in their computation.

Clock   The clock is used to synchronize the execution of events. The simulated time is initialized to zero which can correspond to any value in the real time when the simulation starts. Its value is incremented as long as the simulation progresses, and it is possible to stop the clock as needed. In SCHNAPS a clock tick corresponds to an increment Δt of time. It is then possible to adjust the size of Δt according to the precision wanted. However, the precision and the execution speed of simulation greatly depend on the selection of an appropriate Δt [2]. If it is too large, some events could happen during the same time unit while they should not, and if it is too small, the execution will be slowed down without any gain in precision.

3.2.2   Data

The data module comprises the structures on which the simulation is applied. This includes the environment and the contained population composed of individuals. For SCHNAPS the environment and the individuals are all agents. They are described by their state, which is composed of variables. Because hybrid states are used, some variables can be discrete (e.g. integers) while others are continuous (e.g. real values). The environment has its own state based on specific variables while each individual has its own state of the same variables as others, but with different values.

3.2.3   Processing

The last module brings together all structures linked to processes. Processes are an important concept which involves any operation that modifies the state of individuals or the environment. They are similar to programming functions composed of Boolean, mathematical, or logical operations. A process can call another one for immediate execution on the current individual processing. It can also push another process for a delayed execution. In the latter case, the pushed process can target either the environment, all individuals sequentially, or the current individual (default case). Processes can also watch the clock and trigger automatically on clock ticks. By randomly calling other processes, a clock observer can simulate the occurrence of sporadic events. Some processes are defined as scenarios. A scenario process is the first to be called automatically after the creation of a new individual. Hence, it is responsible for driving the simulation by calling and pushing other processes. All these processes working together constitute the simulation. SCHNAPS uses execution FIFO queues (first-in, first-out) to manage the execution of all processes. Each individual and the environment have their own FIFO set, one for each time step. These FIFOs are used to keep the order of events occurring according to calls and pushes.

4   Simulation Execution

Algorithm 1 presents the pseudo-code for a step-by-step simulation execution while the general information flow between components is illustrated in Fig. 3. At the beginning, the execution queues of all individuals and the environment are empty. The first processes to be executed are the scenarios. They are applied to their respective target at time zero. Then the clock starts, and on each time step each clock observer is triggered for immediate execution. A routine is then applied to process the FIFO associated with the current time step, for the environment and for each individual.

The processing of an execution queue consists of applying sequentially each process in the FIFO until it is empty. When a process is called by the current process, the current context is saved and the called process is immediately executed. Then the context is restored and the processing of the last process continues. When a process is pushed, it is not instantaneously added to the targeted FIFO. Instead the information relative to its occurrence is kept in a *blackboard* structure that is essentially a shared buffer where pushes are kept in memory before being pushed in correct order. When the current time FIFOs of the environment and all individuals are empty, the pushed processes waiting in the blackboard are sent to the FIFOs of their target associated to their specific delay. Processes pushed without delay are added to the current queues. Fig. 4 shows these interactions between processes.

Once the blackboard is empty, if no process was added to the current queues of environment nor individuals, the clock is incremented and the routine starts again. However, if some processes have been pushed without delay, there are FIFOs
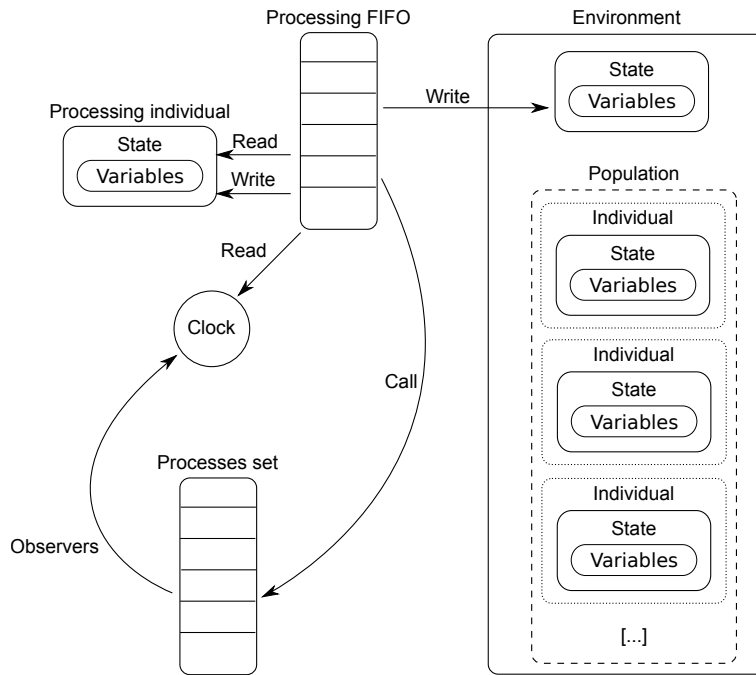
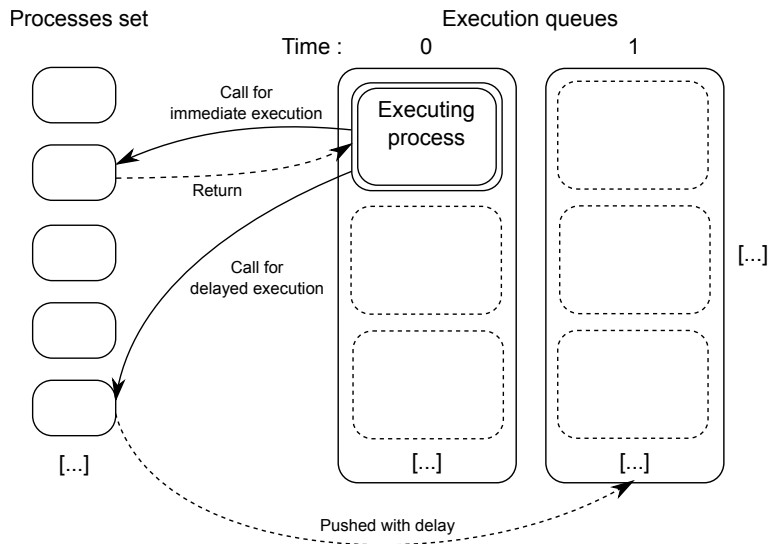Figure 3: General information flow during simulation.

Figure 4: Interactions between processes.

Algorithm 1 Step-by-step simulation.
```
execute scenario
for each clock tick do
    execute all clock observers
    repeat
        current_push = false
        while current_env_FIFO not empty do
            execute pop(current_env_FIFO)
        end while
        for each ind in population do
            while current_ind_FIFO not empty do
                execute pop(current_ind_FIFO)
            end while
        end for
        while blackboard_env not empty do
            pushed_process = pop(blackboard_env)
            if delay(pushed_process) is 0 then
                current_push = true
            end if
            push(delay_env_FIFO, pushed_process)
        end while
        for each individual in population do
            while blackboard_ind not empty do
                pushed_process = pop(blackboard_ind)
                if delay(pushed_process) is 0 then
                    current_push = true
                end if
                push(delay_ind_FIFO, pushed_process)
            end while
        end for
    until current_push is false
end for
```

for current step execution that are not empty. In that case, the routine starts over again in the current time. It is thus possible to model event occurrence inside a clock step.

The blackboard has been designed to support parallel simulation of the population. Indeed, SCHNAPS has the capacity to use multiple cores to simulate the progression of individuals. The blackboard is then used to avoid the conflicts of several processes trying to push in the same FIFO and to ensure a constant order of the pushes based on the index of the individual in the population. The multiprocessors feature of SCHNAPS is interesting because machines with multiple cores are now common and that can make good use of this functionnality to speed up simulation execution.

4.1   Configuration

The configuration for the simulation is passed to SCHNAPS through configuration files. The specification of systems is quite straightforward. However, the definition of input variables and the description of all processes is more sophisticated; they are similar to computer programming functions. The representation of these functions in SCHNAPS is very important since it greatly influences the approach used for modelling.

4.1.1   Tree Modelling

The modelling of functions is mainly based on implementing functions as a tree, as shown in Fig. 5a. The information propagates from bottom to top, i.e. from leaves to root. Any Boolean, mathematical or logical operation can be represented by a tree made of an operator (root) and its operands (child nodes). Child nodes can be sub-trees made of an operator, its operands, and so on. The execution of such a function consists in the recursive computation of operands of the root until the leaves are reached. Leaves are the operands of their parent node. Fig. 5b gives an example of the modelling of the mathematical function $Z \times Y + 6/(X + 1)$.
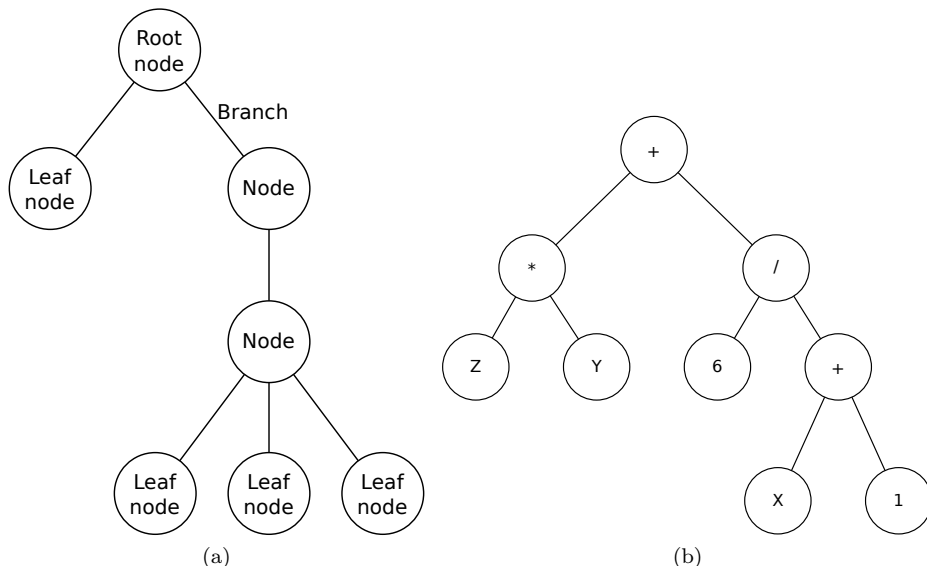
Figure 5: Function representation: (a) general tree structure; (b) function $Z \times Y + 6/(X + 1)$.

4.1.2 Operators and Operands

In the software architecture of SCHNAPS, all operators are implemented as primitive objects. These primitives are packaged in plugins dynamically loaded at run-time. SCHNAPS already has four standard plugins implementing basic operations: operators, control flow, data access and modifiers, and medical specific operations. The operators plugin includes the mathematical, relational, and logical operations. The control flow plugin consists of all primitives implementing branching operations such as switch cases and conditions. It also includes primitives for pushing and calling processes. The data plugin contains the primitives required to reference and modify variables, parameters, and the clock (read-only). Finally, the medical plugin consists of primitives used to facilitate the implementation of simulations linked to the medical domain. This includes primitives for screening, prevention, diagnosis, and events. Table 1 gives an example of primitives contained in these plugins.

4.1.3 Configuration Files

Because of its natural organization as a tree, the XML language (eXtensible Markup Language) [36] is ideal for modelling the functions in the configuration of a simulation with SCHNAPS. Therefore each object defined in the framework has methods for reading and writing itself using XML. Using the factory, it is possible to instantiate each component by reading its name in the configuration file. In order to standardize parameter files, a XSD (XML Schema Definition) [49] describes the appropriate form for these files. It also specifies the name and options of each available component.

The advantage of using XML configuration files is that the syntax of this text format is robust, self-descriptive, and explicit, thus easily understandable and editable by humans. It is recognized as a standard mechanism for representing, storing, and exchanging information [15]. Moreover, the complete specification of a dialect and all the components using XSD schema facilitates the development of third-party applications for managing these files. Hence SCHNAPS does not integrate any parameter files editor, but its design is made possible and encouraged.

5 Graphical Input Interface

A graphical user interface has been developed to facilitate the modelling of simulations for non-programming users. It completely handles the creation and management of configuration files. This interface relies on XSD descriptors of SCHNAPS input to propose different views required to model each component described above. Thus the user is guided through several tabs to input all information that is directly transposed in a configuration file intended for SCHNAPS. The modelling of a complete simulation does not require any XML knowledge. Fig. 6 shows the population tab of the input GUI. This is where the user can specify the population variables to keep (thus making an individual model) and define additional variables specific to the simulation (referred to here as *Event variables*). The interface also includes tabs for defining process trees, parameters, simulation processes, outcomes (variables to print) and specifying sensitivity analysis.

As described above, functions are represented as trees. The tree editor shown in Fig. 7 is used to describe every function required at each step of the modelling. A list of available primitives according to the specific modules currently

Table 1: Samples of operator primitives contained in basic plugins.

| Operators	
Primitive	Description
Add	$Operand_1 + Operand_2$
Sub	$Operand_1 - Operand_2$
Mult	$Operand_1 \times Operand_2$
And	$Operand_1 \wedge Operand_2$
Or	$Operand_1 \vee Operand_2$
Control flow	
Primitive	Description
If Then Else	If $Operand_1$ is true then $Operand_2$ else $Operand_3$
Choice	Execute different operand according to a variable value
Push process	Push specified process on target with some delay
Call process	Call specified process for immediate execution
Data	
Primitive	Description
Variable	Read the value of a variable
Set variable	Assign a value to a variable
Parameter	Read the value of a parameter
Clock	Read the current value of the clock
Medical	
Primitive	Description
Screening test	Perform a test with specified sensitivity, specificity, and cost
Prevention campaign	Apply the costs of a prevention campaign to the population
Event	Apply (or not) an event with some probability
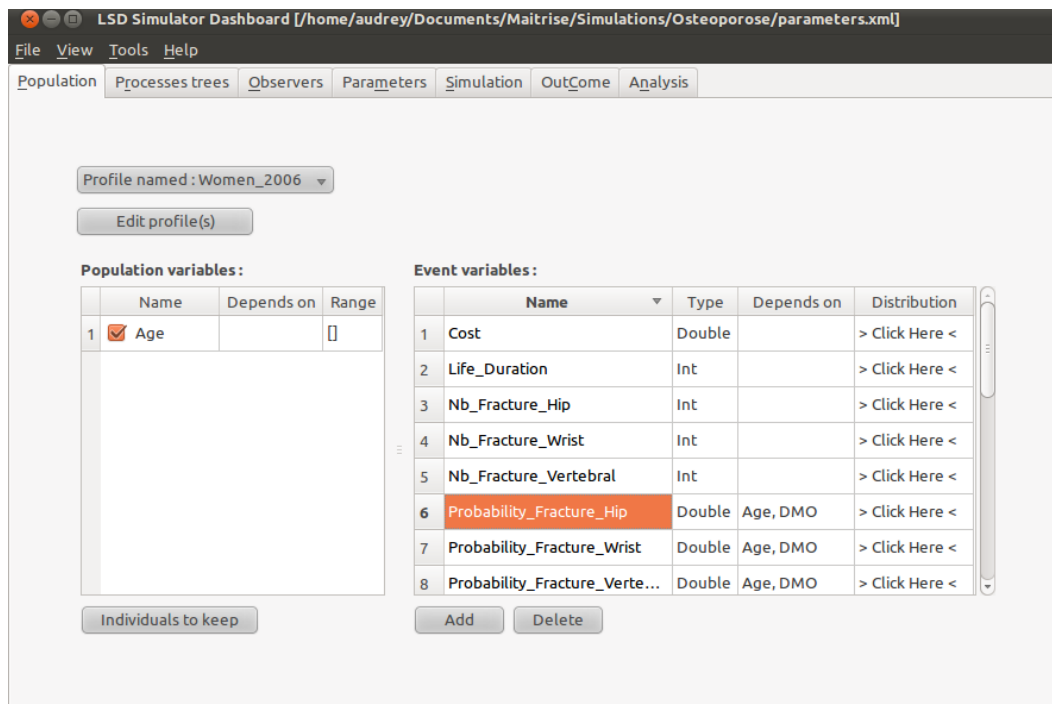
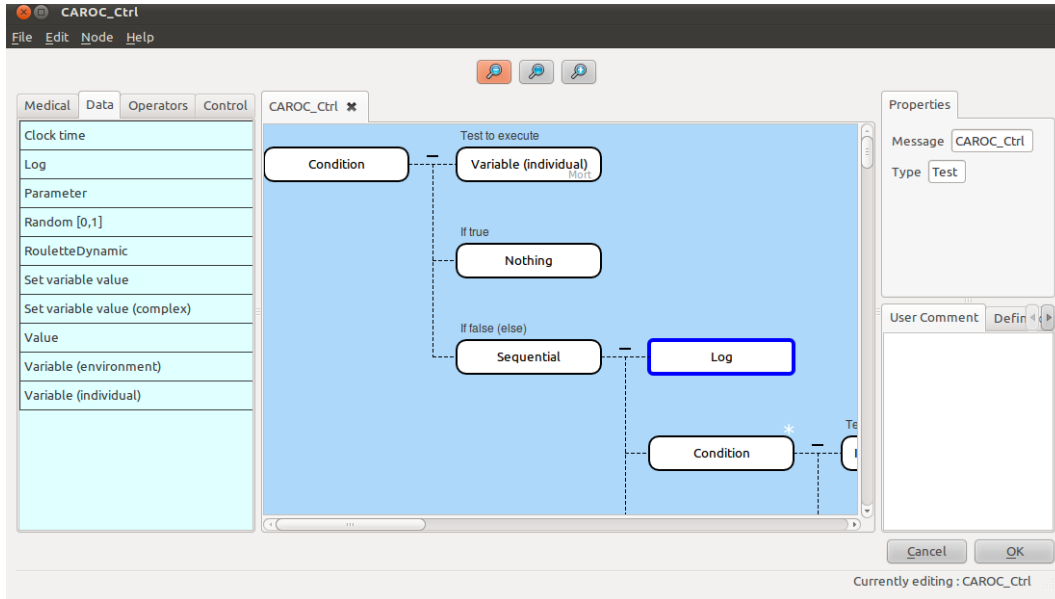Figure 6: Input GUI: population configuration tab.

Figure 7: Input GUI: tree editor.

loaded is given to the user. The editor uses the XSD schema of these plugins to display their contained primitives and their associated properties. Hence the user can build functions using drag-and-drop from the list (left) to the tree on the drawing pane (centre). When selecting a primitive node on the tree, the editor automatically generates input fields needed for specifying the properties of the primitive (right).

Moreover this input interface supports a set of additional parameters that can be integrated directly into the XSD schema by plugin developers. This information can be used to validate input values. It can also be used to indicate the return type of the primitives and the type of their operands. The interface uses that information to guide the user when modelling functions. Some parameters can also be defined to indicate specific display properties of primitives. It is then possible for plugin developers to specify in their XSD schema, for example, the display name of the primitives and to indicate that some attributes must be associated with specific operands.

6 Application: Osteoporosis

Osteoporosis is a disease characterized by the deterioration in the micro-architecture of bone tissue, which leads to increased bone fragilty and susceptibility to fractures. The occurence of two osteoporosis related fractures per hour in the Quebec population of 2 million women aged of 50 years or more has led to an estimated annual cost of 300 million Canadian dollars [1]. The following section describes the modelling and the simulation of this problematics. The data used are directly related to the health care procedures in Quebec, thus all costs are given in Canadian dollars (CAD). However, SCHNAPS is not limited to models of public health care from Quebec. Indeed, any systems can be modelled and any population demography can be used as input.

6.1 Population

Since this disease mainly targets menopaused women, the population used for simulation is composed of women who are at least 40 years old. Their bone mineral density (BMD) is discretised into three classes: normal BMD, osteopenia, and osteoporosis. Their BMD is initialised according to their age and is subjected to an annual deterioration.

6.2 Modelling

The intervention scenarios currently considered by the public health system correspond either to a uniform prevention strategy or to the coupling of a screening method with a prevention strategy. In addition to status quo, which is the scenario without any intervention, the following prevention strategies are considered [34, 47]:

- physical activity (which can be simply walking every day);

- supplements of calcium and vitamin D;

- a combination of physical activity and supplements of calcium and vitamin D.

Table 2: Parameters of osteoporosis screening questionnaires.

Questionnaire	Sensitivity (%)	Specificity (%)
ORAI	90.0	45.1
OST	76.8	51.6
SCORE	90.0	32.0

Screening strategies are [42]:

- CAROC (Canadian Association of Radiologists and Osteoporosis Canada) procedure;

- ORAI (Osteoporosis Risk Assessment Instrument) questionnaire;

- OST (Osteoporosis Self-assessment Tool) questionnaire;

- SCORE (Simple Calculated Osteoporosis Risk Estimation) questionnaire.

In prevention scenarios, prevention is applied to all compliant individuals not already practicing this form of prevention. In screening scenarios, a screening strategy is applied to all compliant individuals. According to the screening result, some treatment or prevention is suggested to the individuals. Individuals compliant to the screening are considered compliant to the prevention. Again, only individuals that do not already practice the prevention can receive its benefits. 53.1% [25] of individuals are compliant.

In the scenarios with physical activity as a prevention strategy, the cost of the prevention campaign is set to $5.00/year per individual, no matter if she is compliant or not or if she already practice it. The cost for taking supplements of calcium and vitamin D is only computed for compliant individuals that do not already practice this prevention ($149.65/year for women under 50 years old, $164.25/year otherwise). In the scenario combining the two approaches, the cost of the prevention campaign for physical activity is considered in addition to the cost for taking calcium and vitamin D supplements.

Concerning screening strategies, all compliant individuals must initially proceed with a medical visit ($99.53 for women under 70 years old, $102.78 otherwise). The initial CAROC procedure begins with a DXA (Dual-emission X-ray Absorptiometry) test of *perfect* sensitivity and specificity. This determines each individual's BMD and assigns them a prevention activity or treatment based on the result [3, 29]:

- Women with normal BMD must take a control CAROC in 5 years. 9% of them are advised to follow a prevention strategy if they do not already practice it.

- Women with osteopenia must take a spinal radiography ($72.65) in addition to a laboratory examination ($105.16). They must take a control CAROC in 5 years. 29.4% of them are advised to follow a prevention strategy if they do not already practice it.

- Women with osteoporosis must also take a spinal radiography ($72.65) in addition to a laboratory examination ($105.16). They must take a control CAROC in 2 years. According to their age, a proportion of them are advised a treatment. 75.6% of them are compliant. To those who are not advised the treatment, 75.6% are compliant with a prevention strategy. Only those who do not already practice it are considered.

Strategies involving a questionnaire all operate on the same principle. Each questionnaire is characterized by sensitivity and specificity given by Table 2. Individuals are either assigned a prevention strategy or proceed to the initial CAROC procedure according to their BMD (as computed by the questionnaire) [3, 29]:

- Women with normal BMD must return to complete the questionnaire in 5 years. 9% of them are assigned a prevention strategy if they do not already practice it.

- The others proceed to the initial CAROC procedure. Questionnaires do not distinguish between osteopenia and osteoporosis.

Individuals who enter the screening procedure CAROC or receive a treatment systematically stop the screening questionnaire.

The control CAROC procedure begins with a medical visit ($99.53 for women under 70 years old, $102.78 otherwise). Subsequently, each woman is treated according to specific rules [3, 29]:

- All women already receiving a treatment continue and must undergo a control CAROC in 2 years.

- Otherwise, women who have had a spine or hip fracture must undergo a control CAROC in 2 years. 9% of those with normal BMD, 29.4% of those with osteopenia, and 75.6% of those with osteoporosis are assigned a treatment.

Table 3: Prevention and treatment weighting on fracture probability for women with normal BMD [31, 47].

Prevention or treatment	Spine %	Hip %	Wrist %
Physical activity	100	62	100
Vitamin D and calcium	100	72	79
Physical activity + vitamin D and calcium	100	62	79
Risedronate	53	55	55

Table 4: Prevention and treatment weighting on fracture probability for women with osteopenia or osteoporosis [31, 47].

Prevention or treatment	Spine %	Hip %	Wrist %
Physical activity	100	62	100
Vitamin D and calcium	88	88	88
Physical activity + vitamin D and calcium	88	62	88
Risedronate	53	55	55

- Otherwise, women over 64 years old who have had a wrist fracture must undergo a control CAROC in 2 years. 9% of those with normal BMD, 29.4% of those with osteopenia, and 75.6% of those with osteoporosis are assigned a treatment.

- The others are assigned a treatment or a prevention strategy according to their BMD following the same logic as in the initial CAROC procedure.

Individuals following the control CAROC procedure are considered in the screening process.

The treatment advised for individuals applies differently depending on age and history of fractures [3, 29]:

- All women who have had a spine or hip fracture need must receive a treatment using risedronate ($149.65/year).

- Otherwise, women over 64 years old who have had a wrist fracture must receive a treatment using risedronate ($149.65/year).

- The others are assigned the prevention strategy considered in the scenario. Supplements of vitamin D and calcium is the prevention strategy used for the scenario without prevention.

Prevention and treatment lead to a reduction of fracture probability. Only the three most common and expensive types of fractures are considered: spine, hip, and wrist [11,13,30]. The effects are given by Table 3 for women with normal BMD and by Table 4 for women with osteopenia or osteoporosis. The effects of an approach correspond to a weighting on the current probability of fractures. Thus, the lower the weight, the better it is. The probability of fracture P' following a prevention or treatment with weight W is given by

$$P' = P \times W,$$

where P is the fracture probability before the prevention or treatment. In the simulation, these effects are applied during the year following the prevention or treatment. In order to benefit from the effects, individuals must follow the procedure correctly. For the supplement of vitamin D and calcium, for example, individuals must follow the dosage on a regular basis. It is considered that 49% of individuals comply with prevention or treatment [5].

In all scenarios, each year of an individual's life begins with the application of treatment, if necessary. Otherwise, prevention is applied, if applicable. Then, each type of fracture can occur once in the following order: hip, wrist and spine. Annual fracture probabilities according to the BMD for each age group are given by Tables 5a, 5b, and 5c. Individuals thus see their annual number of fractures of each type limited to one. In addition, the number of hip fractures during life is limited to two. Indeed, as a fractured hip is usually replaced, it is very unlikely to be broken again. Following a fracture, individuals who already receive a treatment continue. Otherwise, those who participate in the screening program (i.e. are followed by a CAROC control) follow the CAROC procedure based on the same rules as the control CAROC procedure. However, the cost of the medical visit is not computed as it is assumed that it has been taken into account by the control CAROC. 21% of individuals that do not already participate in the screening program are sent to the post-fracture CAROC based on the same rules as the control CAROC procedure [3]. The medical cost is not computed as it is assumed that the individual has already been seen by a practitioner following the fracture. However, the procedure includes the cost associated with the DXA (as in the initial CAROC described before). 10.5% of individuals that are not sent to the post-fracture CAROC begin a treatment [3, 32]. At the end of each year, some individuals die according to the mortal rates of their age group, possibly modulated by earlier fractures.

Age Group (Years)	Normal %	Osteopenia %	Osteoporosis %
40-44	0.0088	0.0170	0.0310
45-49	0.0160	0.0300	0.0560
50-54	0.0320	0.0630	0.1100
55-59	0.0400	0.0790	0.1400
60-64	0.0800	0.1600	0.2900
65-69	0.0950	0.1700	0.3400
70-74	0.1200	0.1700	0.4200
75-79	0.3700	0.5200	1.3000
80-84	0.7800	1.1000	2.7000
85-89	1.0000	1.5000	3.7000
90 +	1.0000	1.5000	3.7000

(a) Hip fracture

Age Group (Years)	Normal %	Osteopenia %	Osteoporosis %
40-44	0.077	0.150	0.270
45-49	0.077	0.150	0.270
50-54	0.140	0.280	0.500
55-59	0.200	0.400	0.750
60-64	0.390	0.770	1.400
65-69	0.350	0.500	1.200
70-74	0.350	0.500	1.200
75-79	0.360	0.500	1.300
80-84	0.370	0.530	1.300
85-89	0.360	0.520	1.300
90 +	0.360	0.520	1.300

(b) Wrist fracture

Age Group (Years)	Normal %	Osteopenia %	Osteoporosis %
40-44	0.021	0.042	0.077
45-49	0.067	0.130	0.240
50-54	0.054	0.100	0.190
55-59	0.150	0.300	0.550
60-64	0.150	0.300	0.550
65-69	0.280	0.400	1.000
70-74	0.280	0.400	1.000
75-79	0.440	0.630	1.600
80-84	0.440	0.630	1.600
85-89	0.540	0.770	1.900
90 +	0.540	0.770	1.900

(c) Spine fracture

Table 5: Annual fracture probability among Quebec women according to age and BMD [31, 47].

Table 6: Utility values

Health state	Utility	Length
Perfect health [33]	1	Up to next event
Hip fracture		
Health state	Utility	Length
Hospitalization [12]	0.3	14 days
Rehabilitation [12]	0.56	30 days
Post-rehabilitation [12]	0.85	Up to next event
Clinical vertebral fracture		
Health state	Utility	Length
Hospitalization [10]	0.33	10 days
Rehabilitation [10]	0.68	49 days
Post-rehabilitation [33]	0.85	Up to next event
Wrist fracture before hip/clinical vertebral fracture		
Health state	Utility	Length
Emergency room [10]	0.61	1 day
Rehabilitation [10]	0.88	24 days
Post-rehabilitation [33]	1	Up to next event
Wrist fracture after hip/clinical vertebral fracture		
Health state	Utility	Length
Emergency room	0.54	1 day
Rehabilitation	0.79	24 days
Post-rehabilitation	0.85	Up to next event

6.2.1 Hip Fracture

All individuals with a hip fracture are sent to the emergency ($256.69), they undergo an operation ($3 808.94), and they are hospitalized ($19 759.91). Then, 52% of individuals receive physiotherapy ($536.69) in addition to an activity to prevent falls ($2 328.48). The others follow the acute rehabilitation process ($24 639.53) combined either with long-term care ($74 646.00) for 42% of individuals, and with physiotherapy ($536.69) and an activity to prevent falls ($2 328.48) for the others [29]. The probability of death is modulated by a factor 4.31 for the current year, 1.14 for the second year, and 1.89 for the third year [26].

6.2.2 Wrist Fracture

All individuals with a wrist fracture are sent to the emergency ($256.69). 18% undergo surgery ($3 334.74) while others receive a conservative treatment ($385.34) [27]. Then, all individuals receive physiotherapy ($536.69) and perform a medical examination ($110.92) in addition to an activity to prevent falls ($2 328.48) [29, 50]. The probability of death is modulated by a factor 1.36 for the current year and 2.05 for the second year [26].

6.2.3 Spine Fracture

All individuals with a spine fracture are sent to the emergency ($256.69) and 10% are hospitalized ($8 076.00). Follow up ($455.28) is performed on all individuals in addition with physiotherapy ($536.69) and an activity to prevent falls ($2 328.48) [29]. The probability of death is modulatd by a factor 2.85 for the current year and 2.65 for the second year [26].

6.3 Utilities

The Health Utilities Index III (HUI3) [24] was used to score the utility of the different possible health states that occur in the model over time given by Table 6. The measures are given in Quality-Adjusted Life Years (QALYs). It measures the desirability of a given health state.

6.4 Simulation

Simulations have been performed on the CLUMEQ Colosse supercomputer installed on the Université Laval campus. Each option was repeated 100 times in order to produce a distribution curve. Costs and QALYs are discounted at a base rate of 3% annually. Simulations are performed under 2 conditions:

1. screening and/or preventive interventions targeting a single cohort of women 40 years old and older, and applied until their death;

2. programs applied to this cohort to which are added new cohorts of 40 year old newcomers, each year during the 10 following years.

The model and simulation data have been validated by three osteoporosis experts. The results for a single cohort using status quo have been compared to the real data in order to validate the system. Data produced have then been compared with expected data (such as the number of fractures, mortality rates per age, costs, effectiveness of interventions, etc.).

6.5 Results

The simulated results of an option lie in the average total cost $\mathbb{E}(C)$, the average total number of fractures $\mathbb{E}(F)$, and the average cumulated QALYs $\mathbb{E}(Q)$ given by

$$\mathbb{E}(C) = \frac{\sum_{i=1}^{100} C_i}{100},$$

$$\mathbb{E}(F) = \frac{\sum_{i=1}^{100} F_i}{100}, \quad \text{and}$$

$$\mathbb{E}(Q) = \frac{\sum_{i=1}^{100} Q_i}{100},$$

where C_i, F_i and Q_i are respectively the total cost, the total number of fractures, and the cumulated QALYs obtained during the ith repetition.

The options are also compared on the basis of their average cost-effectiveness ratio $\mathbb{E}(C/E)$ (ACER) and their average cost-effectiveness ratio relatively to the status quo $\mathbb{E}(\Delta C/\Delta E)$ [16]. Two effectiveness measures are considered: the number of avoided fractures in comparison with the baseline option and the utilities (QALYs). The number of avoided fractures obtained during the ith repetition for an option is given by

$$F_{\text{avoided},i} = F_{\text{status quo},i} - F_i,$$

where $F_{\text{status quo},i}$ is the number of fractures in the scenario without any intervention obtained during the ith repetition. Using the number of avoided fractures, $\mathbb{E}(C/E)$ and $\mathbb{E}(\Delta C/\Delta E)$ are given by

$$\mathbb{E}(C/F_{\text{avoided}}) = \frac{\sum\limits_{i=1}^{100} \dfrac{C_i}{F_{\text{avoided},i}}}{100}$$

$$\mathbb{E}(\Delta C/\Delta F_{\text{avoided}}) = \frac{\sum\limits_{i=1}^{100} \dfrac{C_i - C_{\text{status quo},i}}{F_{\text{avoided},i}}}{100}$$

where $C_{\text{status quo},i}$ is the total cost of the baseline option (status quo) obtained during the ith repetition. Using the utilities, $\mathbb{E}(C/E)$ and $\mathbb{E}(\Delta C/\Delta E)$ are given by

$$\mathbb{E}(C/Q) = \frac{\sum\limits_{i=1}^{100} \dfrac{C_i}{Q_i}}{100}$$

$$\mathbb{E}(\Delta C/\Delta Q) = \frac{\sum\limits_{i=1}^{100} \dfrac{C_i - C_{\text{status quo},i}}{Q_i - Q_{\text{status quo},i}}}{100}$$

where $Q_{\text{status quo},i}$ is the cumulated QALYs of the baseline option (status quo) obtained during the ith repetition.

Table 7 compares the options based on their simulation output and their $\mathbb{E}(C/E)$ and $\mathbb{E}(\Delta C/\Delta E)$ on avoided fractures and utilities. These are the results of simulation using 10 cohorts of menopaused women. The results for a single cohort do not affect the general ranking between the options. For each measure, bold font indicates the best result. For the simulation outputs (cost, number of fractures, and QALYs), paired t-tests have been done to compare the best result with the others. When the best is not significantly better (95% confidence), the other result is underlined. Paired t-tests were not used on $\mathbb{E}(C/E)$ and $\mathbb{E}(\Delta C/\Delta E)$ as they are not well suited to these procedures.

Table 7: Simulation results for osteoporosis prevention and screening options for 10 cohorts of menopaused women.

Option	$\mathbb{E}(C)$ (M\$)	$\mathbb{E}(F)$	$\mathbb{E}(Q)$ (QALYs)	$\mathbb{E}(C/F_{\text{avoided}})$ (\$/avoided fracture)	$\mathbb{E}(\Delta C/\Delta F_{\text{avoided}})$ (\$/avoided fracture)	$\mathbb{E}(C/Q)$ (\$/QALY)	$\mathbb{E}(\Delta C/\Delta Q)$ (\$/QALY)
Status quo	3 638	355 585	12 023 438	∞	Baseline	302.57	Baseline
Prevention							
Physical activity	**3 517**	348 979	12 030 580	532 429.57	**−18 271.46**	**292.36**	−16 900.26
Vitamin D and calcium	4 226	348 771	12 028 982	620 178.88	86 288.22	351.31	106 052.42
Combination	4 177	343 687	**12 034 074**	351 048.86	45 288.98	347.08	50 665.41
CAROC procedure							
Physical activity	3 813	344 841	12 031 555	354 908.35	16 307.18	316.93	21 586.39
Vitamin D and calcium	4 148	344 898	12 030 489	388 161.48	47 754.36	344.81	72 387.43
Combination	4 132	341 559	12 033 732	294 599.54	35 229.02	343.37	48 003.66
ORAI questionnaire							
Physical activity	3 803	344 964	12 031 330	358 024.53	15 502.07	316.06	20 862.81
Vitamin D and calcium	4 130	344 807	12 030 052	383 234.05	45 701.02	343.35	74 480.20
Combination	4 113	**341 460**	12 033 657	**291 186.75**	33 634.12	341.79	46 493.09
OST questionnaire							
Physical activity	3 797	344 940	12 031 350	356 678.40	**14 928.19**	315.58	**20 086.54**
Vitamin D and calcium	4 117	345 024	12 030 086	389 800.02	45 331.60	342.20	72 014.47
Combination	4 102	341 824	12 033 783	298 098.07	33 732.77	340.88	44 870.61
SCORE questionnaire							
Physical activity	3 804	344 900	12 031 339	356 025.56	15 554.72	316.19	21 036.42
Vitamin D and calcium	4 134	344 884	12 030 411	386 327.76	46 365.98	343.64	71 157.81
Combination	4 119	341 567	12 033 835	293 840.47	34 321.93	342.29	46 274.45

We observe that the prevention strategy using physical activity has the lowest cost. In fact it even costs less than the status quo. We also note that the options implicating either a CAROC procedure or a questionnaire are similar for the same prevention strategy. Thus, the options with the lowest number of fractures are those composed of either a CAROC, ORAI, or SCORE screening combined with prevention using physical activity in addition to supplements of vitamin D and calcium. These options also obtain the highest cumulated QALYs, together with prevention using physical activity in addition to supplements of vitamin D and calcium, and OST screening combined with that same prevention. We observe that $\mathbb{E}(C/F_{\text{avoided}})$ is infinite for the status quo. Indeed, the number of avoided fractures in this scenario is zero. The options that maximize this measure are those that minimize the number of fractures. We note that $\mathbb{E}(\Delta C/\Delta F_{\text{avoided}})$ and $\mathbb{E}(\Delta C/\Delta Q)$ are negative for the option of prevention using physical activity. This happens because the cost of this option is lower than the cost of the baseline (status quo). Hence, these values cannot be compared with the others. The options that minimize these values are thus the options that combine a screening strategy with prevention using physical activity. Finally, $\mathbb{E}(C/Q)$ is minimized with the option of prevention using physical activity.

6.6 Discussion

The main limitations of such a study are related to the mapping of a reality [43, 45]. Indeed, some simplifications had to be brought to the representation of the "real life". For example, the side effects of drug treatments are not modeled because taking all of them into account is deemed too complicated, and because their impact on costs would probably be marginal. Also, patients are just considered as compliant or not: the model does not consider the reduced effects of poor compliance. More importantly, the model does not consider the additional effect of various interventions carried out concomitantly, for instance physical exercise in addition to vitamin D and calcium intake, as no data exist on the combined effect of different interventions. It is thus impossible to estimate what is often prescribed, namely a combination of preventive interventions. Finally, it is worth remembering that the simulation is limited to considering the topic of osteoporosis related fractures. Beneficial effects of the options considered (such as physical activity) on other issues (for example, obesity and its consequences) have not been modeled.

In spite of these limitations, some main observations can be drawn from this study. When the utility measure is considered, the promotion of physical activity among women who do not exercise stands out as the most favorable option. These results can be explained by the fact that total costs are lower in the these options and QALYs are relatively similar across all options. This similarity in QALYs between the options is probably due to the fact that life expectancy differs very little from one option to another, and that the impact of events on utilities does not significantly influence the average utility of the entire population. $\mathbb{E}(C/F_{\text{avoided}})$ and $\mathbb{E}(\Delta C/\Delta F_{\text{avoided}})$ lead to different best options because the first does not take into account the money already invested in the status quo, while the latter measures the investment to make in order to avoid a fracture. The fact that $\mathbb{E}(C/F_{\text{avoided}})$ and $\mathbb{E}(C/Q)$ produce different ordering and lead to a different preferred option is probably the most interesting issue of the present case study. It reflects the complexity of the decision making process in health care. In the field of prevention, the complexity is particularly acute considering the diverse benefit of preventive activities (from health gains to a general feeling of well-being). Supporting rational (i.e. avoided fractures) interventions is as important in this field as it is in a clinical setting. However, one should be aware of the risk

to forgo some essential issues by focusing on only one methodological approach. Realizing concomitantly various types of analyses might provide less definitive answers, but a more realistic perspective on the evaluated topic.

7 Conclusion

This paper proposes a new software infrastructure for simulation in a context of public health. Its main element is SCHNAPS, a highly generic simulator that can be configured to simulate virtually any situation. The simulator is organized into three main elements: 1) the agents, which include an environment and a population of homogeneous individuals, each agent being defined by a set of variables of various types composing its state; 2) processes, which are much like program functions applied to the states for modifying the environment and individual values, and can be executed in numerous ways; and 3) the management facilities, which include various helpful mechanisms to generate random numbers, log activities, etc. The population is generated from real demographic data, with a selection of relevant simulation variables according to the problem at hand. A simulation with SCHNAPS can be completely specified through a XML configuration file. The software infrastructure also includes an input GUI, for a convivial production of configuration files by non-programmers. For instance, this allows health specialists, who develop the conceptual simulation model, to directly interact with the computer modelling. This is necessary to allow public health specialists – possibly decision makers – to edit simulation models proposed for some given applications, to modify them according to their needs, and even to quickly prepare simulation models when the situation requires (e.g., to evaluate different vaccination strategies to avoid a flu epidemic). An application of that infrastructure to the prevention of osteoporosis provides detailed results on a real-life case study of interest for Quebec public health policy-makers, comparing the cost-effectiveness and cost-utility of various prevention programs.

This software infrastructure has been developed to facilitate implementation of public health simulation. There are several on-going projects for analyzing various health topics with these tools: strategies for vaccination against influenza, prenatal screening of cystic fibrosis, screening of breast cancer, and some others. We are also experimenting with an extension of the simulator, based on Monte Carlo learning [48], that allows an automatic optimization of strategies to improve interventions over the one proposed in the literature and guidelines. Although still actively under development, preliminary results with the techniques on the prevention of osteoporosis are encouraging, showing that the approach is working well and is able to propose refined strategies. Furthermore, there is another project, still in its infancy, for the analysis of administrative health databases with data mining techniques, to extract different patient management procedures commonly used in real-life health practices. One of our objectives in this area is to feed our software infrastructure with these procedures, in order to simulate current strategies and analyze their performances.

The simulation infrastructure is composed of open source tools that are freely available on the Web at `http://schnaps.googlecode.com` (SCHNAPS) and `http://sourceforge.net/projects/lsdsimulatorinp` (input GUI).

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