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Procedia Computer Science 100 (2016) 188 – 197

Procedia Computer Science

Conference on ENTERprise Information Systems / International Conference on Project MANagement / Conference on Health and Social Care Information Systems and Technologies, CENTERIS / ProjMAN / HCist 2016, October 5-7, 2016

Agent-Based Simulation Patient Model for Colon and Colorectal Cancer Care Trajectory

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Abstract

Colon and Colorectal cancer are a diagnosis of particular concern for older Canadians. They are the second cancer in terms of rate of incidence and mortality among Canadians after lung cancer. Treatment of colon and colorectal cancer requires a complex decision-making process of treatment. These treatments may involve surgery and either pre- or post-operative radiation or chemotherapy, which can have a great impact on the quality of life of patients due to the rigorous requirements of treatment and the inconvenient side effects. This paper is the first developmental step of an agent-based simulation platform aiming at simulating colon and colorectal cancer patient care trajectories in a hospital. In this study, we describe a virtual patient agent, which includes a cancer evolution model, capable of replicating cancer behavior in response to treatment. Simulation results show promising interpolation results with respect to chemotherapy dosage and radiotherapy dosage. However, the model ability to interpolate different administration protocols is still limited, and therefore require calibration for each protocol.

Peer-review under responsibility of the organizing committee of CENTERIS 2016

Keywords: Agent-based simulation; cancer evolution model; virtual patient.

1. Introduction and Motivation

Almost half Canadians (41 % women and 46 % men) will develop cancer during their lifetime and 88 % of them are older than fifty [1]. Lung, breast, colon, colorectal and prostate cancers represent more than half of all new cancer cases (52 %). Breast cancer is the leading type of cancer among women, while colon and colorectal cancer are the third most common

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Peer-review under responsibility of the organizing committee of CENTERIS 2016
doi:10.1016/j.procs.2016.09.140

cancer among men and women. Cancer is the leading cause of death in Canada and in the world [2] with 29.8 % of the population affected, compared to 26.6 % for cardiovascular diseases. Furthermore, in 2000, cancer was the fourth most expensive disease in Canada with $ 17.4 billions spent. Colon and Colorectal cancer are considered the second leading cause of cancer death among men and the third among women.

Cancer treatment is characterized by the convergence of many services including ambulatory, hospitals, clinical, nutritional, psychological, and sports medicine, which coordination and integration condition treatment success and patient quality of life. In order to reduce the impact of this disease and increase the cure rate and the patient quality of life, it is necessary to develop and evaluate new therapeutic and organizational approaches.

The general objective requires the modeling and simulation of complex behaviors, decision-making processes and interactions between hospital staff and patients, therefore to create and validate the patient agent model, which includes a physiological model of how the cancer evolves in time in response to specific treatments. This study deals with this goal and is the first methodological step toward creating a simulation platform of care trajectories of colon and colorectal cancer patients. This simulation platform aims at simulating many elements of the hospital environment, from care resources to patient physiology and psychology profiles, in order to evaluate the many impacts of organizational changes of care trajectories. Also, the simulation model will include: the physical health of the patient; the cognitive state of the patient; the psychosocial state of the patients; the hospital resources, staff and physicians. In other words, factors such as socio-demographic and environmental characteristics, as well as the characteristics of the organizational and decision-making systems, will be used to simulate patient care trajectories, from their diagnosis to the end of the treatment. This simulation environment will support the simultaneous optimization of resources utilization and care quality by assessing the performance of multiple patient care trajectories in a virtual hospital based on reengineered organizational and medical procedure of the Montreal General Jewish Hospital. In this study, agent-based simulation is used as the main modeling paradigm, because it allows the researcher to model the actors (e.g., patient, physician, nurse, and support staff) involved in the care trajectory and their interactions in a natural and anthropomorphic manner.

In order to achieve this specific objective, several challenges must be addressed. The first methodological challenge concerns the development of the cancer evolution model. Cancer evolution in time, and particularly during treatment, is an important part of this study. It is the central model of proposed the simulation environment, because (a) it has an impact on resource utilization and decision processes, and (b) it is impacted by all medical and organizational decisions and resource availability, as well as the patient condition, environment and support. Therefore, having a representative cancer model is essential to this project.

This paper focuses specifically on the first developmental step of this simulation model, which concerns the development of an agent-based model of colon and colorectal cancer patients. This includes a general conceptual model and a cancer evolution model under different kinds of treatment. The next section presents a state-of-the-art of simulation application to the medical domain.

2. State of art

Simulation is a proven methodological tool to study the intrinsic complexity of dynamic systems, which behavior emerges from the interactions of a multitude of elements. Artificial, biological, as well as psychosocial systems involved in healthcare-related issues are complex in nature. Most simulation technics have been used to study and analyze these systems, including Monte Carlo simulation, Discrete-Event Simulation, System Dynamics and Agent-Based Simulation. In general, computer simulations are used to better understand the impacts of specific decisions, policies, or systems configurations through the use of virtual computer emulation of real systems. Computer simulations can also be used in educational settings in order to develop specific skills, in which students control part of the computer variables through user interfaces. This section presents different simulation applications in the medical domain as a tool to improve care quality and services.

2.1. Simulation technics and applications in the medical domain

As briefly mentioned, several simulation technics have being used in the medical domain. Each technic has its pros and cons and are appropriate for specific contexts. First, Monte Carlo simulation uses, repeatedly, random sets of numbers from known probability distribution of different sources of uncertainty (i.e., the environment), in order to compute the results of a mathematical model or algorithm (i.e., the system's model), from which we can infer the general behavior or performance of that system. It is used in practice when the behavior of the system cannot be easily calculated analytically. Discrete-Event

Simulation aims at creating simulation models in the form of queuing-type systems, in which time moves forward either by equal time increments or from one event to the next. In such models, events and flows between components occur according to probability distributions, which defines processing and transit times, and priority rules. Next, System Dynamics aims at modeling complex systems in order to analyze their general behavior. System Dynamics uses a top-down modeling approach based on stocks, flows, feedback loops and time delays. Such models only simulate the high-level interactions between the general components of a system by simulating the ripple effect of changes associated with their mutual dependencies. System Dynamics does not model the elementary interactions between the individual elements of the system, which is what Agent-Based Simulation aims to model and simulate. Agent-Based Simulation is an emerging simulation tool (Macal & North, 2006), which takes a bottom-up approach to model the individual behaviors and interactions of a system's elements, referred to as agents. Hence, instead of modeling the relationships between the components of a system, Agent-Based Simulation captures how the individual elements of a system behave with respect to their own local environment and state, and how they interact, communicate, make collective decisions, or influence each other. The Agent-Based Simulation modeling paradigm generally uses theoretical or empirical models to capture individual behaviors.

In the medical domain, [3] identifies 200 papers, in which simulation is used. More than 70% of these applications used Monte Carlo simulation, while 20% used Discrete-Event Simulation, less than 9% used System Dynamics, and finally only 1% used Agent-Based Simulation. Furthermore, the aims and scopes of these studies are extremely varied. [4] presents an extensive review of these applications. The authors classified these applications into two categories: the management of patient flow and the allocation of resources. More recently, [5] adds additional categories to the previous classification, including infection studies, communicable diseases, costs, economic evaluation and screening. Along the same line, [6] mentions the following domains of healthcare simulation: hospital systems, hospital departments, ambulatory care, health care systems planning, health care models, and medical decision making. Similarly, [3] mention that such models are used to study different types of issues including health risk, cost effectiveness of patient care strategies, transmission of diseases, health service organization and public health policy evaluation. For instance, [7] use ABS to reorganize hospital emergency departments. Recently, several simulation techniques have been used in conjunction to capture different dimensions. For instance, [8] use both DES and ABS to model a healthcare system, in which patients choose their hospital based on a linear additive service function of three factors (i.e., hospital reputation, travel distance, waiting time). Finally, [9] propose one of the first systematic studies aiming at comparing SD and ABS based on a simple mathematical model of interactions between a tumor and immune cells. The authors concluded that both modeling paradigms are not always equivalent. The next sub-sections first introduce the general concept of agent. Then, a state-of-the-art in agent-based simulation in the medical domain is presented.

2.2. Agent-based simulation in the medical domain

Research in agent-based simulation is prolific. It is known under different labels, including multi-agent simulation, individual-based models and agent-based models. These simulation tools are part of a more generic technology known as multi-agent systems, which domain of applications is much larger than simulation. In the literature, the concept of agent is generally defined as ([10]) "…a computer system situated in an environment, which is a way autonomous and flexible to achieve the objectives for which it was designed."

Healthcare operations management is a domain that is well suited to agent-based simulation because it involves many interacting people with their own decision-processes. With agent-based modeling, it is possible to explicitly model these individuals and their interactions. However, although agent-based simulation is growing in the medical domain, applications to the real world are still rare ([11], [12]).

In most organizational simulations in the medical field, agents, whether patients, doctors or nurses are of reactive type and their behavior are very specific to the purpose of the simulation. For instance, [13-14] use simulation in order to analyze the performance of an emergency department in different configurations. In these studies, agents are used to model resources that move through the hospital with predefined process time. Modeling in these studies deals mainly with the different types of treatment associated with their time and resources requirements, which then become predefined in the simulation. Only patients arrival time and resources availabilities change dynamically [15]. In these models, the agents travelling times within the hospital is predefined. However, it can also be dynamically computed in the simulation as in [16], which models the evacuation of an hospital undergoing a fire, or in [17] that use simulation to study different transport configurations for clean and dirty equipment in the hospital.

In [8], the patient agent has a more advanced behavior because it can chose the hospital for treatment according to various criteria such as quality of care and waiting times. Although, its choice is the result of a simple algorithm, this represents an agent which behavior aims at maximizing a preference according to the state of its environment.

In [18], the authors goes further and model the interaction between the type II diabetic patient and the doctor in order to study the impact of such negotiations on the effectiveness and cost of treatment. In [19], the authors model extensively a diabetic patient, taking into account the evolution of his illness according to choice of treatment. This is the aim of this paper, with a focus on colon and colorectal cancer patient.

In the next section we present our general conceptual model in order to guide the development the simulation platform.

3. Patient agent models

The patient is the central actor of the healthcare system or real system. It interacts with many resources, including physicians, nurses and equipment. Its dynamic condition is the main driver of resource utilization, and its reaction to treatment defines the system quality level. In order to design such an agent, different models are proposed to describe its place in the overall system, and its complex behavior. The general conceptual model proposed in this study defines the main interactions between the patient and its environment (Fig. 1). It is composed of four dimensions and includes different aspects of the patient, its environment, and the healthcare system. These dimensions are related to physiology of the patient, the psychosocial state and support of the patient, the decision processes and the resources use to treat the patient. The links between the different aspects identified within these four dimensions represent their mutual dependencies. The central (colored) part represents the patient agent. The other parts represent the hospital staff involved in the treatment selection, as well as patient support (e.g., family members, nurses).

Psychosocial dimension: The psychological dimension includes an emotional model of the patient agent and its social influences, especially in the form of support from family members and nurses. This model describes a response to specific situations. This model will eventually contribute to measuring the patient quality of life during treatment.

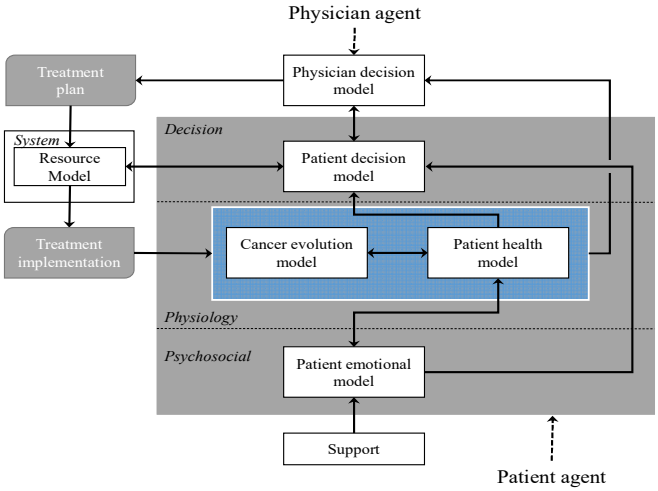

Fig. 1. General conceptual model

Physiological dimension: this dimension includes both the patient's health model (its general physical and health condition) and its cancer evolution model. Both are affected by treatment in different manners, while influencing each other. In practice, this dimension includes on the one hand, the absolute physiological state of the patient and cancer, and, on the other hand, the perception of this state obtained from observations (e.g., analysis, scans, and biopsies). While the first information is not necessarily known, the second can be out-dated, and more or less accurate. The variable describing the cancer evolution model in particular is described in the next section. Finally, in this model, the patient health model is influenced by his or her emotional model.

Decision dimension: This dimension includes both the patient's and the physician's decision models. It represents the main actors' decision-making processes and preferences that contribute to treatment selection and treatment implementation. It is the part of the conceptual model that directly contributes to the decision and implementation of patient care trajectories. Here, the patient decision model is influenced by its health and emotional models, while the physician decision model is influenced by the patient cancer and health models. The patient decision model also contributes to plan each individual treatment according to the system resource availabilities.

System dimension: The system dimension represents the virtual hospital resources and processes. When a physician requests a type of treatment, it must be plan according to the hospital priority, the workload of the resources required for this kind of treatment, as well as the preferences of the patient.

The different sub-models of these dimensions influences each other in order to emulate the general relationships between the patient, his/her cancer, the medical staff, and the patient's support. The relationship between the patient and the hospital processes and resources are addressed through the dynamic specification of the treatment program into the care trajectories, which defines how the patient interacts with the different resources for his/her treatment and tests/scans. The next section focuses on the cancer evolution model and the link between cancer evolution and the physician decision model.

4. Cancer evolution model

Modeling the evolution of cancer is an important step for the simulation of care trajectories. In order to do this, the cancer will be modeled into two parts, the main tumor and metastases. Metastases are meant as a general term referring to every cancerous cell found in the patient's body that are not part of the main tumor. This may be an isolated cell traveling in the patient's body or a small tumor hooked somewhere else than the main tumor. The main tumor size and the number of metastases are two important information as they influence the decision about the treatment [20]. Both will be simulated from their appearance (size 1 cell for the tumor and no metastasis) to the end of the treatment. It is useful to model the evolution of the cancer before the diagnosis so that out of treatment evolution parameters can be validated and the distribution of metastasis density can be known. The evolution of the tumor model that will be described later has four parts: a free evolution and the three evolutions under each of the three treatments, which are radiation therapy, surgery and chemotherapy developments.

For the metastases evolution model, there are only two parts: as for the tumor model, a free evolution and an evolution under chemotherapy. There is no special evolution under radiation therapy because it has no effect on metastasis other than to reduce the emission of cancerous cells by the main tumor.

4.1. Tumor free growth

There is a lot of mathematical models of tumor growth based essentially on population-based models [21]. The original population-based model was developed by Maltus at the end of the 18e century, using equation (1):

$$\underbrace{Variation}_{X_p'(t)} = \underbrace{Number\ of\ birth - Number\ of\ death}_{g(X_p(t))} \tag{1}$$

Where Xp(t) is the tumor size over time given in numbers of cells. One of the most common formulas used for g(x) is an empirical law (see equation 2) described by Gompertz in 1825 [21], which describes the evolution of the main tumor from the appearance of the first cancerous cell to a larger tumor.

$$g(x) = a * x * \ln\left(\frac{b}{x}\right) \tag{2}$$

with a being the rate of tumor growth (it is related to doubling time (DT) of the tumor); b is a constant equals 10^{12} and represents a maximum diameter of 12.4 cm (this value is used in most studies on solid tumours). Other tumour growth models exist, such as logistic and exponential models. The Gyllenberg-Webb model divides the evolution of the tumor in different phases depending on its size in order to describe its evolution more precisely [22].

In the simulation, the Gompertzian formula for the tumor free evolution was used. In order to determine a, we used [23], which characterizes the tumor growth of 27 patients suffering from colorectal cancer. Using this empirical study, we computed a Weibull distribution law of the doubling time, from which we randomly generated a doubling time DT. Assuming

that this doubling time is a constant over the tumor growth, this allows us to calculate the time it takes for the tumor to be a given percentage P of the maximum size b using equation (3).

$$TumourSize(t) = e^{\frac{\ln(2)}{DT} * t} \tag{3}$$

Once the T is known, a is calculated using the Gompertz curve function, therefore, the link between the doubling time and a can be calculated using equation (4).

$$a = -\frac{\ln\left(-\frac{\ln(P)}{\ln(b)}\right) * \frac{\ln(2)}{DT}}{\ln(P*b)} \tag{4}$$

4.2. Tumor growth after radiation therapy

First, only external radiation therapy is modeled. Its impact on the size of the tumor is calculated one session at a time. Consequently, the remaining number of cells is the number of cells before treatment multiplied by the percentage of surviving cells S represented by equation (5) from [24].

$$S = e^{-A(\alpha*d+\beta*d^2)+B} \tag{5}$$

with α and β being constants for colon and colorectal cancer, respectively 0.339 and 0.067, as empirically estimated by [25]; d is the dose used during the session; and A and B are two parameters associated with the patient, corresponding to the effect of a variety of factors. They follow a normal distribution determined using [25]. This model is based on two assumptions. First, each cell that cannot further divide itself after the radiation therapy session, is considered dead. Second, the tumor keeps growing freely between sessions.

4.3. Tumor growth during chemotherapy

The action of chemotherapy is determined using a model developed and tested with two types of chemotherapy drug (i.e., Fluorouracil and Capecitabine) on colon and colorectal cancer [26]. Based on this study, the function g(x) in equation (1) is described by equations (6) and (7):

$$g(x) = \left(a_c - E(t)\right) * x \tag{6}$$

$$E(t) = E0 * \sum_i Concentration(t, T_i) \tag{7}$$

With a_c being the exponential growth factor of the tumor. It is determined according to the parameters of the Gompertzien growth and the tumor size at the beginning of chemotherapy. Concentration (t, Ti) represents the function of drug concentration injected at time T during session i, in the patient's body over time. E0 is the effect of the drug on the decrease of the tumor [21]. E0 depends on the patient and on the type of treatment. We model three types of drug administration: Oral, injection with syringe and long injection like Portacaths [27] and Piccline [28]. The function of concentration of drug in the patient's body over time is different for these three types of administration (see equations 8, 9 and 10), based on [26] and [21].

For injection with syringe and oral administration:

$$Concentration\ (t, T_i) = Dose * \left(\frac{1}{2} + \frac{1}{2} * tanh\big(k(t - T_i)\big)\right) * e^{(Absorption*(T_i - t))} \tag{8}$$

with Absorption being the speed of drug elimination from the patient's body; k is the speed of drug assimilation; and Dose is the dose injected during the session. The only different between injection with syringe and oral administration is k, which is bigger for injection.

For long injection:

Concerning long injection, the only new parameter is duration, which is the length of time of the injection, as shown in equation (9).

$$Concentration\ (t, T_i) = Dose * \left(\frac{1}{2} + \frac{1}{2} * tanh\big(k(t - T_i)\big)\right) * e^{\left(\frac{1}{2}+\frac{1}{2}*tanh\left(10(t-T_i-duration)\right)\right)*\left(Absorption*(T_i-t+duration)\right)} \tag{9}$$

Finally, the function of the tumor's size during chemotherapy is:

$$X_{pc}\left(S_{T_c}, t\right) = S_{T_c} e^{\int_{T_c}^{t}(a_c - E(s))ds} \quad with\ t > T_c \tag{10}$$

with S_{T_c} is the tumour's size before the beginning of chemotherapy. This value is also used in the metastatic evolution model.

4.4. Tumor growth after surgery

The effect of surgery on the size of the tumor is simpler than the other two treatments described above. Indeed, depending on the cancer (colon or rectum) and the type of surgery, the effect of the surgery can be described as a probability of having cancerous cells from the main tumor remaining in the body. The next section presents an illustrative example of a cancer patient treated with two treatments.

4.5. Metastases growth

For the development of metastases, we use a model developed by Iwata ([29]). In this model, the growth of main tumor and the metastases are described by a set of mathematical equations. The tumor growth is modeled by $X_p(t)$, which can either be the Gompertzian function (2) or the exponential function (3). Next metastases growth, produced by the main tumor and other metastases, is described by equation (11).

$$\beta(x) = m * x^{\alpha 2} \tag{11}$$

with m being the coefficient of colonization, and α2 being the fractal dimension of blood vessels infiltrating the tumor.

Considering that all tumors evolve similarly is not entirely correct. Indeed, although they all originate from the main tumor (i.e., their nature is similar), their spread and evolution depend on their location. However, accurately modeled movement of each tumor cell in the body is impossible. The Iwata model and its assumptions are considered valid and used in the majority of evolution models of metastases. Iwata's model is defined by the system of equation (12):

$$\begin{cases} \frac{\partial \rho(x,t)}{\partial t} + \frac{\partial g(x) * \rho(x,t)}{\partial x} = 0, \\ \rho(x,0) = 0, \\ g(1) * \rho(1,t) = \int_1^{\infty} \beta(x) * \rho(x,t) dx + \beta\left(X_p(t)\right). \end{cases} \tag{12}$$

with $\rho(x,t)$ being the density of metastases in the patient's body (i.e., the number of tumours containing x cells at time t), and $g(x)$ being the function defined in Section 4.2.1. Both parameters m and α2 are specific to each patient and have a normal distribution, which are determined thanks to [20] and [29].

The value of interest for the decision-making is the Metastatic Index (MIn). It is defined by equation (13) in [20]. It represents the total number of metastatic tumors of size between n and $X_p(t)$ in the patient's body at time T.

$$MI_n(T) = \int_n^{X_p(T)} \rho(x,T)\, dx \tag{13}$$

The resolution of the Iwata model is more complex than that of the primary tumor. Furthermore, there is general solution of this model with a function $g(x)$ with chemotherapy. Therefore, in order to keep calculation time reasonable within the simulation environment, the Iwata model is only used to describe the evolution of metastases without treatment using function $g(x)$ defined in equation (2).

4.6. Metastases growth during chemotherapy:

Granted there is no general solution to the Iwata model with chemotherapy, in order to determine the effects of chemotherapy on metastases, we first made three assumptions:

Cancer cell dispersion in the body (i.e., $\beta(x)$) is neglected. Because cancer cell progressing through the patient's body is directly in contact with the drug, we assume it is automatically destroyed.

All metastatic tumours evolve along the same decay law as the primary tumour under chemotherapy. In this study, we use equation (6):

The number of tumours given by$\rho(x,T_c)$, as defined in (12) at the end of the free evolution of metastases, remains unchanged during the chemotherapy treatment. Only the tumour's size is affected.

Based on these hypothesis, the new distribution of metastases during chemotherapy ($t > T_c$) can be calculated based on $\rho(x,T_c)$ as defined at the end of the free evolution of metastases, using equation (14):

$$\rho(X_1,t) = \rho(X_2,T_c) \quad with \quad X_1 = X_{pc}(X_2,t) \tag{14}$$

We define a new function ${X_{pc}}^{-1}$ as.

$$ {X_{pc}}^{-1}(X_1, t) = X_2 = \frac{X_1}{e^{\int_{T_c}^{t}(a_c - E(s))ds}} \tag{15} $$

Therefore, MI during chemotherapy can be calculated using equation (15):

$$ MI_n(t) = \int_n^{X_{pc}(X_p(T_c),t)} \rho\left({X_{pc}}^{-1}(x, t), T_c\right)dx \tag{16} $$

5. Model validation

In order to validate the model, we carried out one experiment, using our simulation platform (based in the JADE Platform) with a 3,5GHz Intel Core i7 processor and 32 Go of RAM. This experiment aim at assessing the ability of the model to replicate the results of different clinical studies with specific treatment protocols. In this experiment, in order to compare the simulation results with actual data, we used the standard classification criteria of the World Health Organization [31], which are also used in the clinical studies used for validation. This classification distinguishes patients according to the cancer response (i.e., partial response (PR); complete response (CR); stable disease (SD); and progressive disease (PD)). Due to the limits of our model, which does not currently take into account patient mortality, it was not possible to consider other criteria such as the overall survival (OS), the disease free survival (DFS) and the progression free survival (PFS).

In this experiment, we must first calibrate the model's parameters. In order to do so, we use data from two clinical studies [32, 33], which allows us to validate our metastases growth model during chemotherapy treatment. Indeed, as it is the least documented and modeled part of the cancer evolution, we prioritize the validation of this part of the model. The data from these clinical studies includes the stage of the cancer, the method of patient selection and the protocol of treatment received by patients for Capecitabine chemotherapy. This study tested two administration protocols (i.e., a and b) on a sample of 35 and 40 patients. Patients in the protocol a received two daily doses from day 1 to 14, followed by a period of rest (day 15 until 21), and followed by a new treatment cycle starting on day 22. Patients in the protocol b received two daily doses continuously without rest periods. The model was calibrated for these two administrations protocols and for both sample sizes.

5.1. Selection of the virtual population

For each protocol/population we aim to replicate, we must first create several populations of virtual patients. To do so, it is not possible to simply create a virtual population with similar statistics as the real population. Indeed, the metastases distribution is correlated with the characteristics of the primary tumor because they share parameters. Therefore, we have to simulate all virtual patients starting at T0, when the first cancer cell appears. Subsequently, we determine two dates per patient, T1 and T2, respectively, when the tumor size falls within the range of interest, as defined by the studies, and when it comes out of this range. The date of diagnosis Td is selected randomly between T1 and T2.

Once the diagnosis date is fixed, we determine the stage of the patient. From this large population of virtual patients, we select those whose characteristics are similar to the actual population to create our population test. Thus the total number of virtual patients is known in advance and it is necessary to initially simulate a large number of patients to have a sufficiently large test population. In order to select a virtual population similar to the actual populations selected in clinical trials ([32, 33]), in the experiment below we took patients with stage 4 and with MI_{5*10^8} greater than 1, which corresponds to metastasis larger than 10mm.

There are two ways to generate populations: we can generate the populations randomly or we can generate populations based on the real data stored in the access document. In the following, all generated data must be stored in txt file, this file contains all the necessary information (Age, diagnosis day, cancer type, tumor size, stage and treatment plan) to start the treatment phase. During the generation of populations (Agent patients), the physician agents are used in collaboration with the nurses agents to diagnose patients and to establish a treatment plan for each patient.

5.2. Simulation results

Two simulation tests were carried out for each set of parameters. In all tests, the virtual population samples were, like for calibration, similar in size to those of the two studies. In other words, protocol b of study 1 was tested with samples of 40 patients, protocol a of study 1 was tested with samples of 35 patients. During the simulation tests, to

reduce the possible variations, we tested an average of 10 samples of population for study 1, and an average of 3 for study 2. The model results of the simulation tests are fairly consistent with the results of the studies, and our model can adequately reproduce reality.

Fig. 2 describes the average value of E of the simulation tests for each experiment.

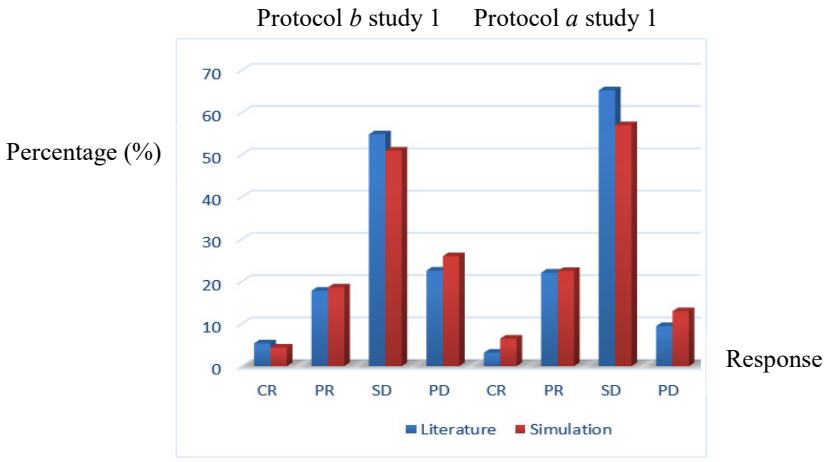

Fig. 2. Comparative analysis

6. Conclusion and future work

This paper introduced a conceptual model aiming at the development of a simulation environment capable of emulating the simultaneous care trajectories of several of cancer patients. More specifically, this paper introduces a cancer evolution model, which is the first developmental step of such a simulation environment.

Before this model can be implemented and tested within the simulation environment, several other aspects of the conceptual model presented in Fig. 1 will have to be developed. Along the same line, the hospital resources and management processes will have to be modeled as well. But one of the first things to do before its integration into the simulation platform will be to validate the entire model with actual data from the hospital.

Once completed, the configuration of the many agents of this simulation platform will be adjusted in order to emulate accurately reality. This paper shows that preliminary results indicate that it is possible to develop such a model, although development and analysis are required.

The validation of the entire simulation environment with respect to actually data for a hospital will be part of an extensive aspect of the project. Once validated, this simulation will be used by the hospital in order to evaluate the benefits of specific organizational changes to both the hospital performance and the patients' quality of life.

Concerning the development of the simulation platform, the next step is be to calibrate and test this model with other chemotherapies and treatment protocols with specific patient data. However, there is still much work to do to improve this overall model. For instance, one general improvement concerns the modeling of the combined effects of radiation and chemotherapy administered simultaneously. Another important aspect concerns the modeling of the interactions between cancer treatments and the treatments of other health issues (i.e., co-morbidity).

Concerning the modeling of new treatment, the second should also be adapted to include the impact of internal radiation therapy (i.e., brachytherapy) as it is more and more used in hospitals. Moreover, it would also be useful to take into account the interactions between the different treatments as surgery impacts metastasis' angiogenesis, which makes metastasis grow faster [30]. In addition, long-term effects of treatment should be integrated as the tumor may take some time to regrow after radiation therapy. However, these effects are often random and causes for their presence or absence are unknown, making them difficult to model. Eventually, the model must also include mortality and its expected step for any medium term following work.

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