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# Agent-Based Simulation of Colorectal Cancer Care Trajectory : Patient Model

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**Abstract.** Colorectal cancer is a diagnosis of particular concern for older Canadians. It is the second cancer in terms of rate of incidence and mortality among Canadians after lung cancer. Treatment of colorectal cancer requires a complex decision-making process of treatment. These treatments may involve surgery and either pre-operative or post-operative radiation or chemotherapy, which can have a great impact on 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 colorectal cancer patient care trajectories in a hospital. In this paper, we describe a virtual patient agent, which includes a cancer evolution model, capable of replicating cancer behaviour in response to treatment. Simulation results show promising interpolation capacity with respect to chemotherapy dosage. However, the model ability to interpolate different administration protocols is still limited, and therefore requires calibration for each protocol.

**Keywords:** Cancer evolution model, agent-based simulation, care pathways, colorectal cancer.

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# 1 Introduction

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, 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 colorectal cancer is the third most common 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. Colorectal cancer is 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. This study deals with this goal and is the first methodological step toward creating a simulation platform of care trajectories of 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.

First, this paper describes the general scope of this simulation project and presents a state of the art of agent-based simulation. Next, the general conceptual model of the simulation is described. Then, we present our cancer evolution, which, which is then tested and validated using two separate experiments.

## **2 Research Objective and General Methodology**

This section introduces the general objectives and limits of this study, and presents the general methodology used to achieve the objectives.

### **2.1 Project general and specific objectives**

Providing high-quality care is a priority among health professionals. However, resources are limited and their utilization must be optimized in order to meet high quality standard and patients unique profile. Therefore, the challenge faced by care providers and managers is to design organizational and medical processes that will deliver the right treatment, to the right patient, at the right time using the right resources. This study is part of a comprehensive project, which aims at developing a computer simulation environment of patient care trajectories in order to evaluate new approaches to increase hospital productivity and adapt hospital clinical practice conditions for the elderly and patients with multiple chronic diseases. Ultimately, 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. The expected result of this project is an innovative modeling of the interactions between the patients and the health care system, and ultimately, the development and validation of a new approach of providing cares. 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. This paper focuses specifically on the first developmental step of this simulation model, which concerns the development of an agent-based model of colorectal cancer patients. This includes a general conceptual model and a cancer evolution model under different kinds of treatment. The next section introduces agent-based simulation.

## **2.2 Agent-based modeling paradigm**

The general objective presented in the previous section requires the modeling and simulation of complex behaviours, decision-making processes and interactions between hospital staff and patients. The most appropriate technology to simulate these complex mechanisms is agent-based modeling and simulation (see Section 3 for a thorough discussion on that subject). 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, support staff) involved in the care trajectory and their interactions in a natural and anthropomorphic manner.

In brief, agent-based simulation is used in many scientific domains [3-5], such as ecology, biology, economics, social science, physics, engineering, and medicine. It is used to study complex systems by simulating the individual behaviours and the interactions of their elements. In order to create an agent-based simulation model, the researcher must identify the agent candidates, determine which one should be implemented as agents, and define their behaviour and how they interact with each other.

In this project, not all healthcare providers and hospital staff involved in care trajectories will be modeled as agents. For simplification purpose, an agent can also be used to model a function,

instead of the individual people responsible for that function. For instance, a tumour board can be model as an agent. This paper focuses on the design of the patient agent.

### **2.3 Research methodology**

As mentioned in Section 2.1, this paper presents the first step of this comprehensive project. The objective is 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. Although the general objectives of the project is to simulate a large number of patients treated simultaneously with the same resources of the hospital, this step of the project is only concerned with the general behaviour of the patient agent, and how well it can be configured in order to simulate colorectal cancer patients with different attributes.

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 organisational decisions and resource availability, as well as the patient condition, environment and support.

Therefore, having a representative cancer model is essential to this project. However, its domain of application goes beyond the evaluation of new organizational processes. For instance, an accurate model of cancer evolution can be used to replace clinical tests using simulation [6]. It can also be used to estimate recurrence rate after specific treatments, or for training purpose and decision support.

Although such simulation models can be useful in many contexts, and despite the fact that there are numerous models for specific aspects of cancer evolution (with and without treatment), to our

knowledge, there is no integrated model to simulate cancer evolution from its beginning to remission or death.

In order to define such a general cancer evolution model, we divide the problem into different parts, describing the evolution over time without treatment, and with each category of treatment. For each part, we first identified theoretical or empirical studies in the literature. Next, we adjusted partial models and integrated them into a general cancer evolution model.

Because our ultimate goal is to simulate the simultaneous treatment of many patients in a virtual hospital, each part of the model had to be solved reasonably quickly. Therefore, our main concern is the integration of these models by considering their validity domain.

At this stage of the project, our model does not take into account all available cancer treatments. Although there are currently only three main categories of treatments used in the world, surgery, chemotherapy and radiation therapy, each category treatment has a large number of different options that do not impact the patient and the cancer in the same way. In addition, these treatments can be administered alone or in combination, which then creates interactions that must be specifically studied. Consequently, the model presented in this article considers only few treatments, which are applied separately.

The second methodological challenge that must be addressed in this study concerns the validation of the cancer evolution model. This is done by testing the model in different configurations of treatment, as explained in Section 5.

The next section presents a state-of-the-art of simulation application to the medical domain.

### **3 State of art**

Simulation is a proven methodological tool to study the intrinsic complexity of dynamic systems, which behaviour emerges from the interactions of a multitude of elements. Artificial (e.g.,

emergency, health services), biological (e.g., immune system, tumour growth) as well as psychosocial (e.g., patient, family, physician) 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. Next, we introduce a detailed analysis of agent-based simulation applications in the medical domain, with an emphasis on the agents' functions.

### **3.1 Simulation technics and applications in the medical domain**

As briefly mentioned in Section 2.2, several simulation technics have been 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 behaviour or performance of that system. It is used in practice when the behaviour 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, [7] 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. [8] 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, [9] adds additional categories to the previous classification, including infection studies, communicable diseases, costs, economic evaluation and screening. Along the same line, [10] 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, [7] 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, [11] use ABS to reorganize hospital emergency departments. Recently, several simulation techniques have been used in conjunction to capture different dimensions. For instance, [12] 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, [13] propose one of the first systematic studies aiming at comparing SD and ABS based on a simple mathematical model of interactions between a tumour 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.

### 3.2 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 ([14]) "...a computer system situated in an environment, which is a way autonomous and flexible to achieve the objectives for which it was designed." Therefore, computer agents usually possess the following properties [15] :

- **Autonomous:** agents can act without the direct intervention of a third party (human or other) and they are not subject to any control on their action or their internal state;
- **Reactive:** agents can perceive their environment and cope with changes in their environment in a conducive manner;

- ***Pro-active:*** agents can demonstrate internal goals, taking initiatives behaviours;
- ***Social:*** agents can interact with each other through some form of communication languages and shared rules of sociability.

To these properties, agents may exhibit other properties to meet specific requirements ([16], [17], [18], [19]). Based on these concepts, agent-based simulation is growing rapidly in the medical domain. Several authors report the benefits and suitability of this simulation technics for the medical domain. The reasons lie in the complexity and dynamics of healthcare systems.

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 ([20], [21]).

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, [22-25] 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 [26]. In these models, the agents travelling times within the hospital is predefined. However, it can also be dynamically computed in the simulation as in [27], which models the evacuation of an hospital undergoing a fire, or in [28] that use simulation to study different transport configurations for clean and dirty equipment in the hospital.

In [12], the patient agent has a more advanced behavior because it can choose 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 whose behavior aims at maximizing a preference according to the state of its environment.

In [29], the authors go 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 [30], 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 colorectal cancer patient.

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

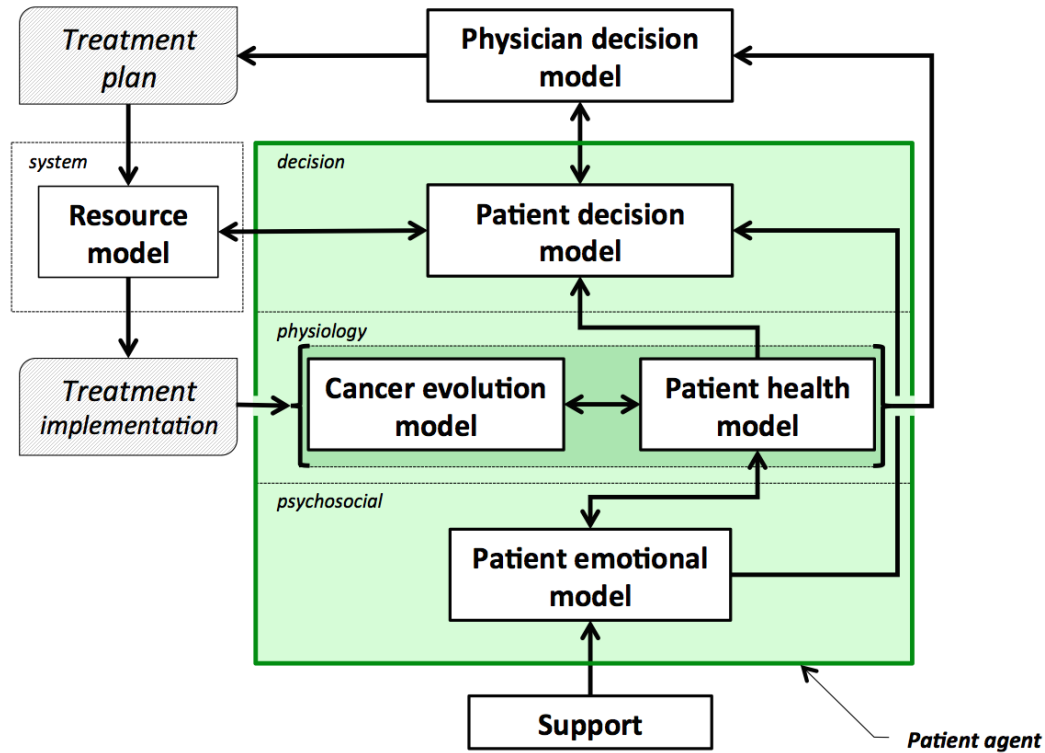
## **4 Patient agent models**

The patient is the central actor of the healthcare 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 behaviour.

### **4.1 Conceptual model**

The general conceptual model proposed in this study defines the main interactions between the patient and its environment (Figure 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 used to treat the patient. The links between the different aspects identified within

these four dimensions represent their mutual dependencies. The central 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).



**Fig. 1:** General conceptual model

**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.

**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, 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.

## 5 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 tumour 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 tumour. This may be an isolated cell traveling in the patient's body or a small tumour hooked somewhere else than the main tumour. The main tumour size and the number of metastases are two important information as they influence the decision about the treatment [31]. Both will be simulated from their appearance (size 1 cell for the tumour 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 tumour 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 tumour 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 tumour. If we neglect this impact, as we will see in Section 4.3, it is considered that they evolve in the same way as free evolution. Thus the only treatment affecting metastases is chemotherapy.

## 5.1 Tumour free growth

There is a lot of mathematical models of tumour growth based essentially on population-based models [32]. The original population-based model was developed by Maltus at the end of the 18<sup>e</sup> century, using equation (1):

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

Where  $X_p(t)$  is the tumour 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 [32], which describes the evolution of the main tumour from the appearance of the first cancerous cell to a larger tumour.

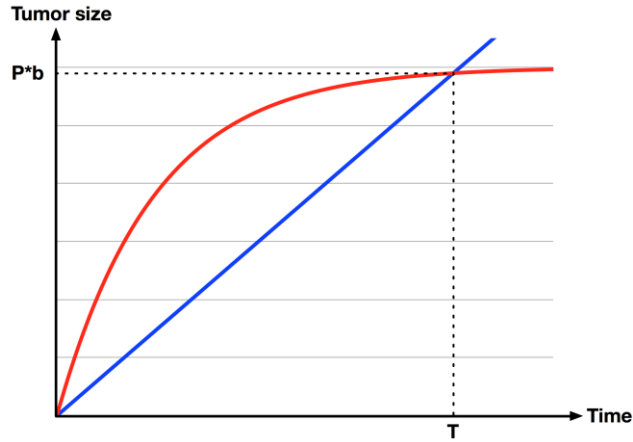
$$g(x) = a * x * \ln\left(\frac{b}{x}\right) \quad (2)$$

with  $a$  being the rate of tumour growth (it is related to doubling time (DT) of the tumour);  $b$  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 tumour in different phases depending on its size in order to describe its evolution more precisely [33].

In our simulation, we use the Gompertzian formula for the tumour free evolution. In order to determine  $a$ , we used [34], which characterizes the tumour 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 tumour growth, this allows us to calculate the time it takes for the tumour to be a given percentage  $P$  of the maximum size  $b$  using equation (3).

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

Once the  $T$  is known,  $a$  is calculated using the Gompertz curve function, as shown in Figure 2.



**Fig. 2:** Estimation of parameters  $a$  (red = Gompertz curve ; blue = Exponential curve)

Therefore, the link between the doubling time and  $a$  can be calculated using equation (4).

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

### 5.1.1 Tumour growth after radiation therapy

First, only external radiation therapy is modeled. Its impact on the size of the tumour 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 [35].

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

with  $\alpha$  and  $\beta$  being constants for colorectal cancer, respectively 0.339 and 0.067, as empirically estimated by [36];  $d$  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 [36]. 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 tumour keeps growing freely between sessions.

### 5.1.2 Tumour 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 colorectal cancer [37]. Based on this study, the function  $g(x)$  in equation (1) is described by equations (6) and (7) :

$$g(x) = (a_c - E(t)) * x \quad (6)$$

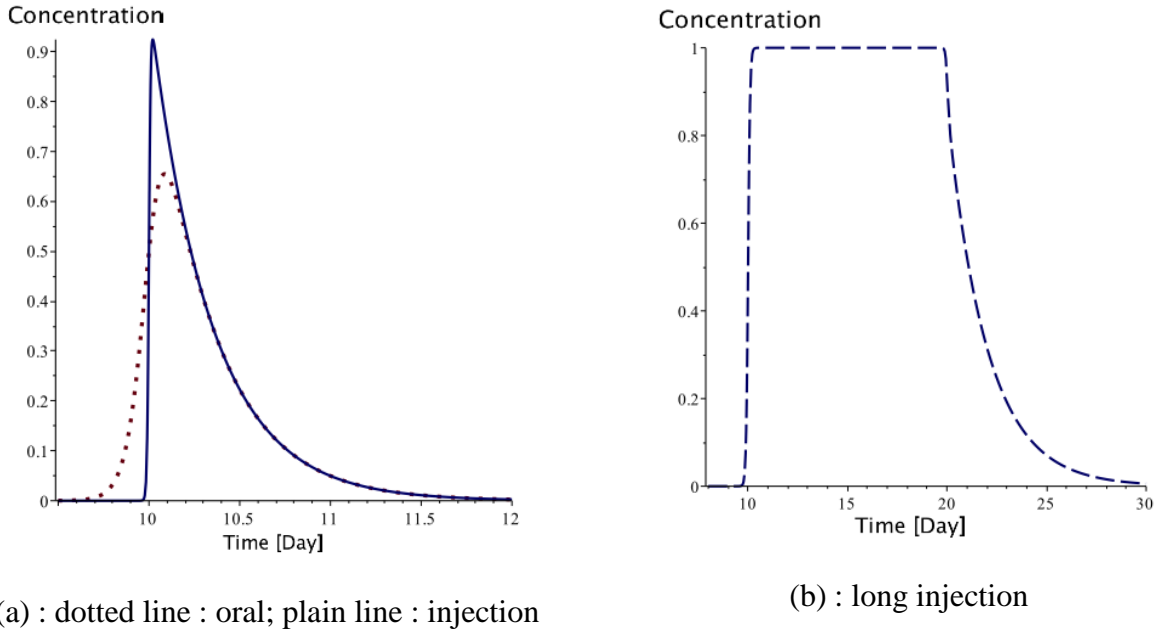
$$E(t) = E0 * \sum_i \text{Concentration}(t, T_i) \quad (7)$$

With  $a_c$  being the exponential growth factor of the tumour. It is determined according to the parameters of the Gompertzien growth and the tumour size at the beginning of chemotherapy.  $\text{Concentration}(t, T_i)$  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 tumour [32].  $E0$  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 [38] and Piccline [39]. 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 [37] and [32].

**For injection with syringe and oral administration:**

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

with  $\text{Absorption}$  being the speed of drug elimination from the patient's body;  $k$  is the speed of drug assimilation; and  $\text{Dose}$  is the dose injected during the session. The only different between injection with syringe and oral administration is  $k$ , which is bigger for injection (see Figure 3a).

**Fig. 3:** Drug concentration**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), and Figure 3b.

*Concentration* ( $t, T_i$ ) =

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

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

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

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

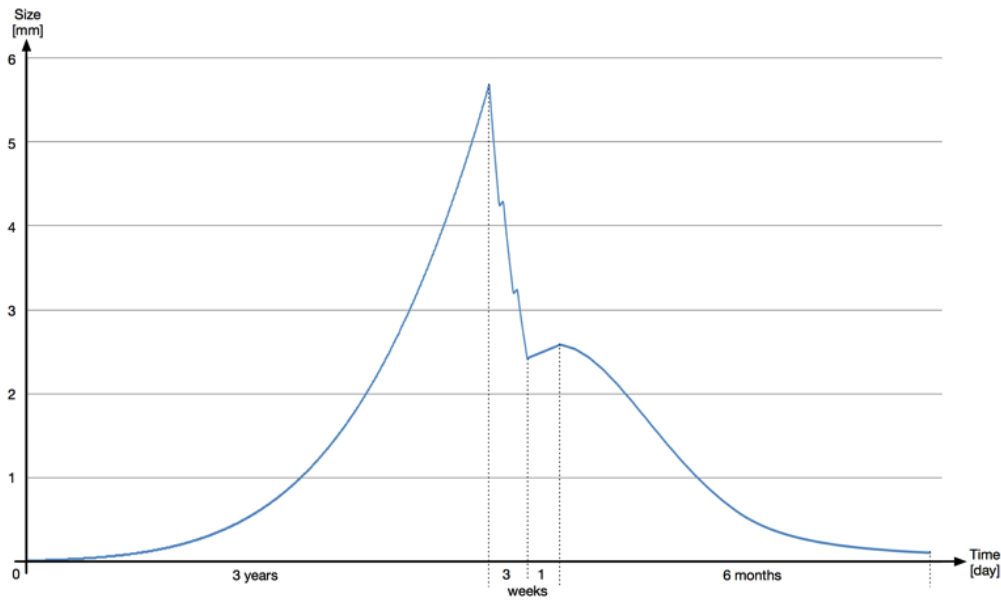
**5.1.3 Tumour growth after surgery**

The effect of surgery on the size of the tumour 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 tumour

remaining in the body. The next section presents an illustrative example of a cancer patient treated with two treatments.

#### 5.1.4 Illustrative example

In order to illustrate the evolution of a main tumour, before, during and after treatment, this example, shown in Figure 4, shows the tumour's diameter in mm over time. First, there is a three-year evolution phase before any treatment. Then, there are three weeks with 5 radiation therapy sessions per week, followed by one week of rest, and finally six months of chemotherapy.



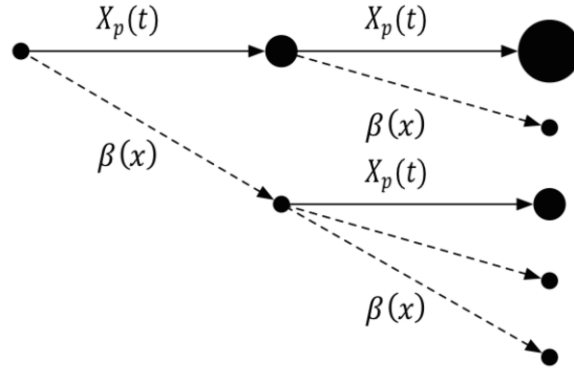
**Fig. 4:** Tumour's diameter in mm over time

## 5.2 Metastases growth

For the development of metastases, we use a model developed by Iwata ([40]). In this model, the growth of main tumour and the metastases are described by a set of mathematical equations. The tumour 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 tumour and other metastases, is described by equation (11).

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

with  $m$  being the coefficient of colonization, and  $\alpha_2$  being the fractal dimension of blood vessels infiltrating the tumour. In turn, as shown in Figure 5, new tumours grow according to  $X_p(t)$ , and produce cancerous cells according to  $\beta(x)$ .



**Fig. 5:** Metastases growth dynamic

Considering that all tumours evolve similarly is not entirely correct. Indeed, although they all originate from the main tumour (i.e., their nature is similar), their spread and evolution depend on their location. However, accurately modeled movement of each tumour 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):

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

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  $\alpha_2$  are specific to each patient and have a normal distribution, which are determined thanks to [31] and [40].

The value of interest for the decision-making is the Metastatic Index ( $MI_n$ ). It is defined by equation (13) in [31]. It represents the total number of metastatic tumours of size between  $n$  and  $X_p(t)$  in the patient's body at time  $T$ .

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

The resolution of the Iwata model is more complex than that of the primary tumour. 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).

### 5.2.1 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 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):

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

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

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

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

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

### 5.3 Model integration

Each of these individual models describes part of the entire cancer evolution with and without treatment. For the purpose of building a simulation model, they must be integrated. However, they are continuity gaps at the interface of each model that require some adjustments. More specifically, because the Iwata model is difficult to solve when initial conditions are changed (e.g., after a chemotherapy session), we made hypothesis in order to simplify the integration of the different models.

First, between surgery and chemotherapy, the primary tumour does not produce metastases because it has been removed. However, an opposite effect occurs after the removal of the main tumour favouring metastases development through angiogenesis [41]. Therefore, because we do not know which effect is dominant, the metastases growth model proposed in Section 4.2.2.1 is used after surgery.

Similarly, concerning radiation therapy, the decreased metastases production by the main tumour is neglected. Indeed, at this stage of the cancer, the production of metastasis is partly due to metastases themselves [42]. Furthermore, for staging, as seen in the next section, we only consider metastatic tumours of size greater than  $5 \times 10^6$  cells. Consequently, this effect has little

impact on metastases of this size, because metastatic cells produced during radiation therapy do not have enough time to grow bigger than this size before chemotherapy.

Next, between consecutive chemotherapy sessions, or during chemotherapy breaks due to fatigue of the patient, we assume that the  $E(t)$ , which defines the impact of chemotherapy drug in the tumour growth model during chemotherapy (i.e., equation (7)), is equal to zero until the next session due to a lack of drug in the body. Therefore, we model the tumour growth between sessions as exponential (i.e., equation (3)), because it is sufficiently accurate for short period of time (the difference between the gomptertz and exponential growth over three weeks is less than 0.5% in most cases). However, note that the gomptertz growth was used for the evolution of the tumour over the large period before any treatment. In order to calculate the parameter  $a_c$  (from equation (6)), we used the technic described in Section 4.2.1.

Another challenge, for the integration these models, lies in the calculation of the metastatic index (MI). Indeed, the upper limit of the integral (equation (15)) is the tumour size during free evolution. However, during a treatment, the upper limit is no longer equal to the size of the tumour. For example, during radiation treatment, the tumour size decreases a lot, although the treatment has no direct impact on metastases. Therefore, the tumour size after radiotherapy cannot be taken as the upper limit of the integral. To solve this problem, we take as an upper bound the fictitious tumour size corresponding to its free evolution. For chemotherapy treatment, the upper bound is also the size of the fictitious tumour, which evolution is described by the evolution of the tumour with the chemotherapy model.

## 5.4 Cancer observed state and actual state

The physician's decision on which treatment to be performed on the patient is not based on the output values of the mathematical models presented above, which represent a simulation of the

actual state of the cancer that can never be completely known. Instead, treatment decisions, which will eventually be simulated as well, are based on criteria such as TNM staging of cancer [43]. TNM staging can be considered as the observed state of the cancer. Consequently, we must link both the observed state and the actual state in order to be able to define what treatment to be performed for each patient.

In the simulation environment, TNM staging is only determined before deciding which treatment to follow. During treatment, physicians are more interested by the reactions of the cancer and the general health of the patient in order to interrupt or adjust the treatment.

The NCCN Guideline [44] explain the TNM staging for colorectal cancer in details. However, for simplification purpose, this staging was adjusted, as described in Sections 4.4.1 and 4.4.2. Here, T only corresponds to the general stages of cancer (i.e., 1, 2, 3 or 4), while N and M are Boolean variables specifying respectively if there are or not metastases lymph node (i.e., N), and if there are or not distant metastasis (i.e., M). This simplified staging identifies the most important aspect to know for treatment decision, using the NCCN guideline.

#### 5.4.1 Tumour

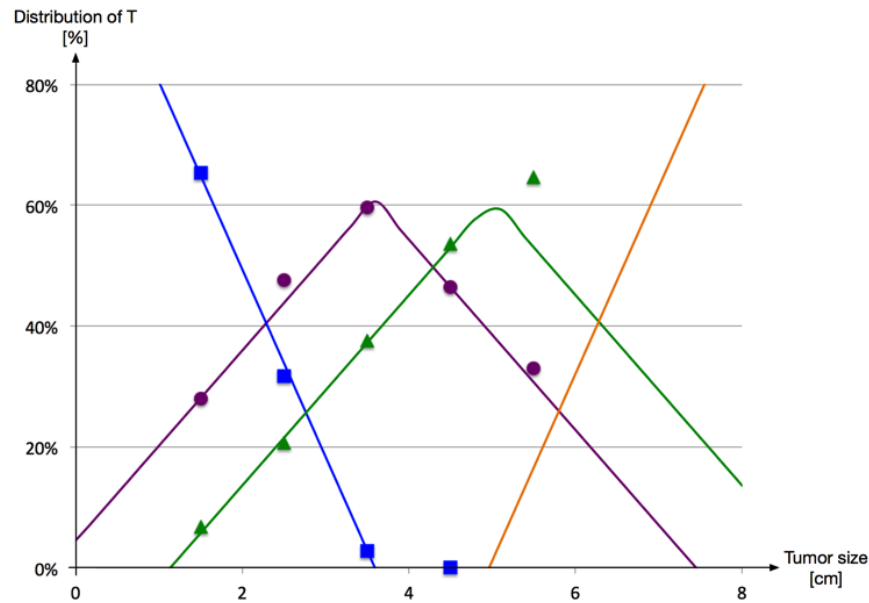
The output of the tumour model is its size given in numbers of cells. In order to convert the number of cells into the diameter of the tumour, we assume that  $1 \text{ mm}^3 = 10^6$  cells, as explained in [43], and that the tumour is a sphere [44]. With these assumptions, the conversion can be done using equation (16).

$$D_{mm} = \left( \frac{6 * N_c}{\pi * 10^6} \right)^{1/3} \quad (17)$$

with  $N_c$  is the number of cells in the tumour.

In the TNM classification, T corresponds to the penetration of the tumour through the various tissue layers of the colon and not directly to the tumour size [45]. However, based on [46] and

[47], it is possible to estimate the tumour penetration distributions according to its tumour size, as shown in Figure 6.



**Fig. 6:** Distribution of T1 to T4 according to tumour size.

Therefore, from the size of the tumour given by the mathematical model, a probability of belonging to a particular penetration (i.e., T1 to T4) is determined. For example, a tumour with a 4-centimetre diameter has a 45% chance of being a type T3 penetration, and a 55% chance of being a type T2 penetration.

#### 5.4.2 Nodes and metastases

In order to determine  $M$ , the same method as [31] was applied. If  $IM_{10^8}$  is greater than 1 at the time of diagnosis, we consider that the patient has metastases in at least one organ and his  $M$  is equal to one. Concerning  $N$ , we proceed similarly. However but we use  $IM_{5 \times 10^6}$  instead of  $IM_{10^8}$  because a size of  $5 \times 10^6$  cells corresponds to 2.1 mm, which is the difference between the average size of the tumour-free lymph nodes and the average size of lymph nodes with metastatic infiltration, measured in [48]. Furthermore, below this size, there is very little chance that the analysis of nodules comes out positive for the presence of cancerous cells [31].

## 6 Model validation

In order to validate the model, we carried out two experiments, using the Maple software package version 16.0 with a 2,5GHz Intel Core i5 processor and 8 Go of RAM. The first experiment aims at assessing the ability of the model to replicate the results of different clinical studies with specific treatment protocols. The second experiment extends the first by assessing the ability of the model to interpolate the results of several clinical studies with different treatment (i.e., different dosage, different protocols, different treatment duration). In other words, this second experiment aims at analyzing the ability of the model to estimate the outcome of treatments for which we do not have clinical studies.

In both experiments, in order to compare the simulation results with actual data, we used the standard classification criteria of the World Health Organization [49], 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 practice, this classification is based on the evolution of the size of the tumours. More specifically, practitioners calculate the sum of the products of the greatest perpendicular diameters (SPD) of the measurable metastases, which is a measure of an area, and analyze their evolution between observations. However, in our model, we can approximate the sum of the volume of tumours using Equation (18).

$$M_{Icell_n}(T) = \int_n^{X_p(T)} x * \rho(x, T) dx \quad (18)$$

with  $n$  being the minimal size of tumours to be included (in number of cells).

Therefore, because our model returns a number of cells, which is a proxy of the tumour's volume, we converted the threshold value of each class based on the volume a sphere and the area of the disk ( $volume = constant \cdot \sqrt[3/2]{area}$ ). For example, Partial Response (PR) is defined as a SPD reduction larger or equal to 50%, which corresponds to a decrease of at least 64.65% (*i.e.*,  $1 - \sqrt[3/2]{5}$ ) in the total number of metastatic cells.

Concerning complete response (*i.e.*, CR), a patient is considered with a complete response if his or her  $MI_{10^8} < 1$ , which mean that all metastases of at least  $10^8$  cells are gone.

Finally, in order to measure the performance of the calibration and the capacity of the model to replicate the results of clinical studies, we used the average Euclidean distance between the simulation results and the clinical studies, as calculated with equation (19).

$$E = \sqrt{(CR_1 - CR_2)^2 + (PR_1 - PR_2)^2 + (SD_1 - SD_2)^2 + (PD_1 - PD_2)^2} \quad (19)$$

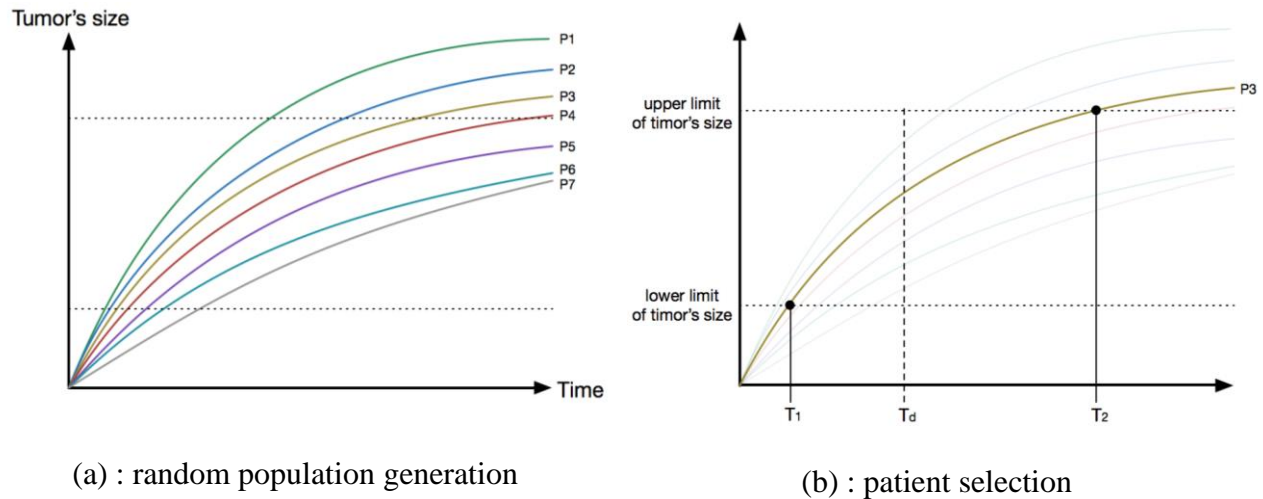
## 6.1 First experiment

In this first experiment, we must first calibrate the model's parameters. In order to do so, we use data from two clinical studies [50, 51], 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. The first study tested two administration protocols (*i.e.*, a and b) on a sample of 35 and 40 patients. The second study tested only the first protocol (*i.e.*, a) of the first study on a sample of 301 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.

### 6.1.1 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 tumour because they share parameters. Therefore, we have to simulate all virtual patients starting at  $T_0$ , when the first cancer cell appears. Subsequently, we determine two dates per patient.  $T_1$  and  $T_2$ , respectively, when the tumour size falls within the range of value of interest, as defined by the studies, and when it comes out of this range. The date of diagnosis  $T_d$  is selected randomly between  $T_1$  and  $T_2$ , as shown in the Figure 7:



**Fig. 7:** Curves explaining the selection of  $T_1$ ,  $T_2$  and  $T_d$

Once the diagnosis date is fixed, we determine the stage of the patient. Among this large population of virtual patient, we select those whose characteristics are similar to the actual population to create our population test. Thus the total number of virtual patients is not 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 ([50, 51]), we took patients with stage 4 and with  $MI_{5*10^8}$  greater than 1, which corresponds to metastasis larger than 10mm.

### 6.1.2 Calibration

In order to calibrate the model for the three configurations of the two clinical studies, we first need to estimate the impact of each parameter on the results based on their role in the model. For example, the percentage of progressive disease is only defined by the parameter of the Gompertz evolution  $a$  and the parameters of the chemotherapy  $E0$ , *Absorption* and *Dose*. Other parameters such as  $m$ ,  $\alpha$  and the maximum and minimum size of the tumour in the selection of the virtual population only affects the distribution of patients in the three categories: CR, PR and SD.

Thus, to calibrate the model, we proceed by try-and-error, using a dichotomy approach to set each parameter and replicate the results of the clinical studies as best as possible.

Concerning the duration of the simulated treatments, the median duration reported in both studies was used for the corresponding tests. The dose of chemotherapy was considered constant throughout the treatment. Because our model does not take into account side effects and patients mortality rate, we adjusted the results of clinical studies to remove these cases for comparison purpose. The final values of the parameters for each calibration are shown in Table 1. Concerning the parameter *Absorption*, it has been set equal to its defined in [32] value, while the average value of  $\alpha$  2 was taken in [40].

	Protocol b Study 1	Protocol a Study 1	Protocol a Study 2
Parameters	Average (Standard deviation)	Average (Standard deviation)	Average (Standard deviation)
<b>m</b>	$6 * 10^{-8}$ ( $3 * 10^{-9}$ )	$6 * 10^{-8}$ ( $2 * 10^{-9}$ )	$6 * 10^{-8}$ ( $2 * 10^{-9}$ )
<b><math>\alpha_2</math></b>	0,66 (0,03)	0,66 (0,02)	0,66 (0,02)
<b>P</b>	0,87	0,0035	0,006
<b>Lower Limit</b>	39	35	39
<b>Upper Limit</b>	39	37	41
<b>E0</b>	$3,4 * 10^{-3}$	$1,6899 * 10^{-3}$	$1,69 * 10^{-3}$
<b>Absorption</b>	0,6	0,6	0,6
<b>Dose</b>	0,732	1,25	1,25

Table 1: Calibration results

### 6.1.3 Simulation results

Three 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, and protocol *a* of study 2, was tested with samples of 300 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 simulation results presented in Table 2 are fairly consistent with the results of the studies, and our model can adequately reproduce reality. Figure 8 presents the average value of *E* of the simulation tests for each experiment.

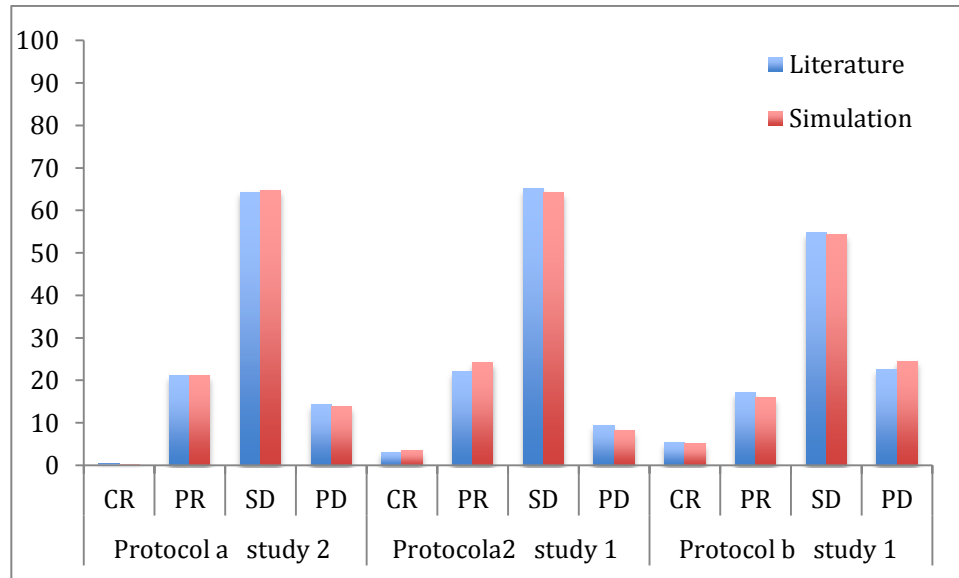


Fig. 8: Comparative analysis

		Study (literature)	Average of simulation tests	E	Standard Deviation
Protocol a study 2	CR	0,34	0,33	0,69	0,35
	PR	21,06	21,10		1,20
	SD	64,33	64,80		1
	PD	14,27	13,77		1,27
Protocol a study 1	CR	3,16	3,5	2,73	2,99
	PR	22,11	24,19		7,11
	SD	65,26	64,19		9,28
	PD	9,47	8,12		4,60
Protocol b study 1	CR	5,38	5,06	2,3	4,44
	PR	17,20	16,08		8,47
	SD	54,84	54,30		8,01
	PD	22,58	24,56		10,10

Table 2: Comparative analysis and Euclidian distance

#### 6.1.4 Discussion

The calibration was more difficult to carry out in the cases of clinical test with small population sample. This difficulty can come from several reasons. First, the small number of patients tested can cause an inhomogeneous population. Similarly, random number generation can also affect

the distribution of the population with such small size. Next, the relative inaccuracy of the model may be too large with such small patient populations, which may lead to results that are more significantly different from actual data.

In addition, it is interesting to note that the set of parameters to reach accurate results is not unique. Indeed, it was possible to find another set of parameters (Table 3) with a value of *Absorption* equal to 0.4, while keeping the others parameters within the acceptable boundary, which also gave a good calibration for the protocol a of the study 1. Indeed,  $E$  was equal to 3,5 and here it is the new set of parameter:

<b>Protocol a Study 1</b>	
<b>Parameters</b>	<b>Average (Standard deviation)</b>
<b>m</b>	$6 * 10^{-8}$ ( $1 * 10^{-9}$ )
<b><math>\alpha 2</math></b>	0,66 (0,01)
<b>P</b>	0,004
<b>Lower Limit</b>	34
<b>Upper Limit</b>	34
<b>Dose</b>	1,25
<b>E0</b>	1,13E-03
<b>Absorption</b>	0,4

Table 3: second set of parameters for Protocol a Study 1.

Next, the parameters of Protocol *a* of studies 1 and 2 are similar and it is possible to use the parameters of one to simulate the other with  $E < 7$  for study 2, and  $E < 4,5$  for study 1. Unfortunately, using the parameters of one protocol to simulate the other has not given good results. This may be due in part to the simplifications we introduced in order to simulate these protocols. Indeed, we made two assumptions. The first was to consider a constant dose for all patients during the entire treatment. This assumption is correct insofar as both studies administered at least 90% of the planned dose. However, the second assumption was to take the

same treatment duration for all patients matching the median treatment duration recorded in the clinical studies. Unfortunately, in practice, treatment duration varies greatly from one patient to another, especially due to the side effects and patient's response. Consequently, a second phase of validation will be performed with more specific data for each patient from the Montreal Jewish General Hospital.

Finally, once model calibration is extensively tested with several protocols, it could eventually be used to simulate the outcome of various treatments and protocols for specific patients, and thus, serves as a medical decision support system. Indeed, with some medical tests it would be possible to estimate parameters  $a$ ,  $m$  and  $\alpha^2$  of the patient within a certain margin of error. For instance,  $a$  could be approximated using two imaging tests of the primary tumour to determine its size at two different dates.  $m$  and  $\alpha^2$  could be determined by estimating the mass of visible metastases using imaging, which should be equal to the one given by the Iwata model at the same tumour's size and time of diagnosis. Using these estimated parameters, the outcome of a treatment for a patient could be simulated with specific statistical distributions for the unknown parameters, which would then give probable outcomes for that patient.

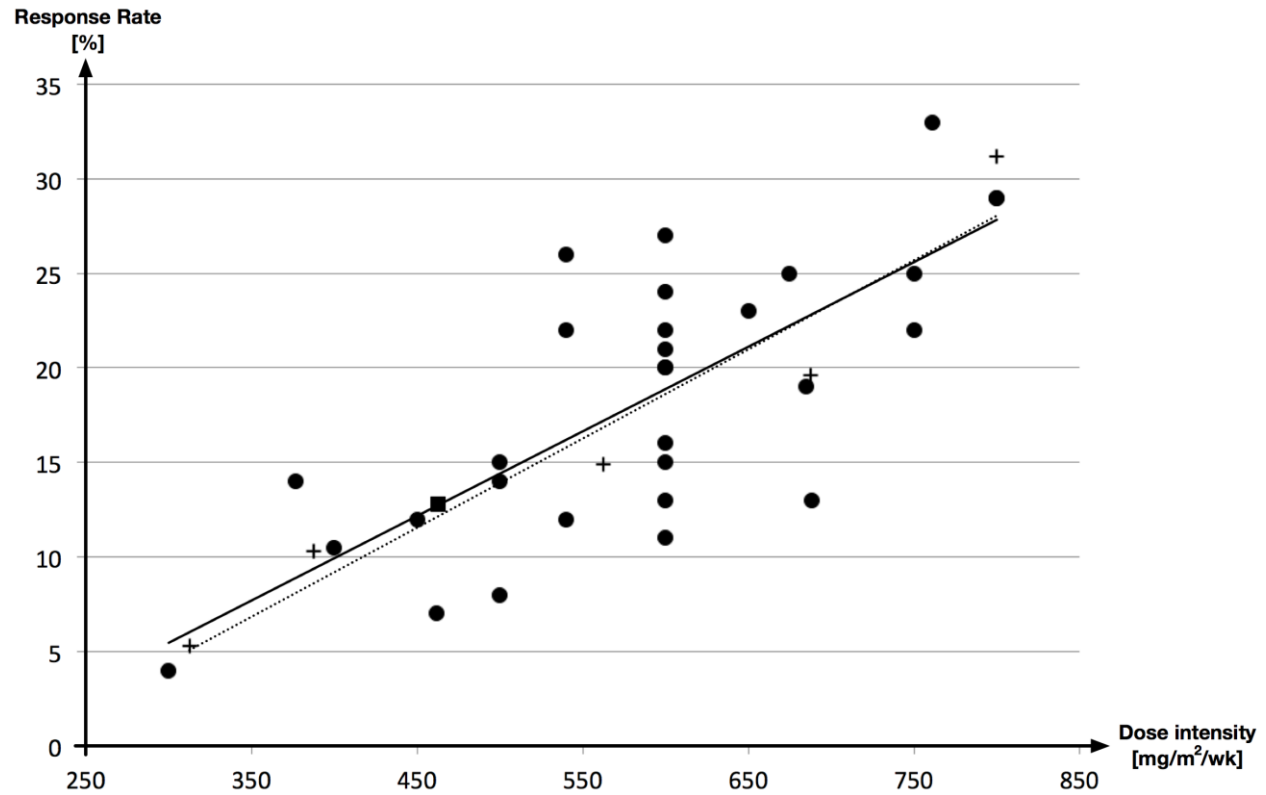
## 6.2 Second experiment

In this second experiments, we aim at assessing the capacity of the model to interpolate the results of clinical studies with different treatments, such as different dosage, different protocols, different treatment durations. To do so, we used another set of studies conducted with another type of chemotherapy used in colorectal cancer, the 5-fluorouracil (5-FU), which is well documented in the literature. In particular, we used [52], which regroup a number of clinical studies on 5-FU, in order to define the response (CR + PR) as a function of the average dose per time unit (for one cycle of chemotherapy), using linear regression (Figure 10).

First, we calibrated the model using [53] ( $E = 1.06$ ). The protocol targeted in this study is 5 day of 5-FU repeat every four weeks. Once calibrated, we varied the dose (all other parameters being unchanged). As see in Figure 10, that the variation of the dose in the model has a greater impact than in reality. In order to adjust this, we assumed that parameter  $E0$ , which describes the effect of the drug on the decrease of the tumour, should be a function of the dose. Therefore, in order to adjust the impact of the dose, we introduced a new  $E0$ , as a function of dose (Equation 20).

$$E0 = \frac{a}{Dose} - b \quad (20)$$

Once  $a$  et  $b$  were calibrated, the new results show an excellent capacity of the model to interpolate the impact of the dose (Figure 10). Similarly, we also tested the capacity of the model to interpolate the impact the total treatment duration. Once again, the impact of the treatment duration was more significant than in reality. However, we were not able to find a simple mathematical function capable of taking the impact of treatment duration into account. We suspect that  $E0$  must either be a function of the total treatment duration, or must change in time during treatment as if some sort of mechanism would affect the capacity of the drug to decrease tumour size. However, because the time of treatment described in the literature, when available, is only an average, it is difficult to properly define  $E0$  with the data available. This must be done with more specific data



**Fig. 9:** Response rate as a function of the dose intensity

(Black dots are from [54], the black line is the associated linear regression of these dots; the black square is from [53]; the black plus are the results of the model with E0 as function of the dose, the dotted line is the associated linear regression).

## 7 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 Figure 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 actual data for a hospital will be part of an extensive aspect of the project. Once validated, this simulation environment 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 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 [41]. In addition, long-term effects of treatment should be integrated as the tumour 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. This should be fairly easy insofar as mortality models based on the evolution of cancer already exist [54, 55].

Along the same line, the model must also include side effects because they are important causes of resource utilization variability between patients, as well as indicators of patient quality of life. Finally, this model of cancer colorectal evolution is easily adaptable to other type of carcinoma cancer [56], because the equation used was made for general cancer and not only for the colorectal. For example Iwata use his model on liver cancer.

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