TOOL FOR THE EVALUATION OF INNOVATIVE THERAPIES
Multi-agent based System

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Abstract: The paper contains the main lines of the modeling of a prototype for both medical and economical evaluation of radiotherapy centers using innovative therapies. We consider uncertainties according to patients and hospital complexes participating in the study. The corresponding part of the tool is called recruitment model. It evaluates a theoretical number of patients interested in treatments of one center, using spatialization into a context of competition. Moreover we developed a scheduling model, described briefly here and two shortly presented economical models in charge of the evaluation of the average price per treatment and the comparison between different radiotherapy strategies. We present preliminary results of the recruitment model.

1 INTRODUCTION

1.1 Context and Objectives

Innovative therapies used by centers involve uncertainties according to the installation of facilities and/or the expected therapeutic gain, after the treatment (as hadrontherapy, stereotaxy, cyberknife). Medical benefits results are often unknown, and patients are hostile to choose between a new therapy and a well known treatment, thus it is a hard decision to equip a complex, using only economical methods.

We model a generic progressive prototype evaluating the position of a center from both medical and economical point of view. To proceed we first evaluate a theoretical number of patients interested in these therapies, then its medical position regarding competition and medical politics fixed in advance. A recruitment model is in charge of the theoretical number of patients. It uses a suitable scheduling model to plan the internal organization of the hospital, giving us the possibility to have a good response for the demand of a patient. The general prototype consist of two economical models, one evaluating the price per treatment of a therapy in a hospital, and another one used to compare different strategies of treatment between them and with the cost reimbursed by the health insurance of a country. Moreover we include the cost per year gained after a treatment according to a strategy of treatment. The economical part of the prototype is not described here. The tool supports the development of innovative therapies and medical structures.

1.2 Modeling Method

The tool is composed by the four independant models, thanks to links between them they could be used altogether (Fig. 1). We implemented them in a generic way using the multi-agent theory (L.R.Coutinho et al., 2005) and techniques such as (J.Ferber et al., 2004; J.F.Hübner et al., ; Wagner, 2003), to describe the global system, the interactions and organizational information system. This provides us a flexible organization (Nicholas, 2000).

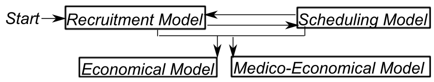

Figure 1: Interaction between mains models.

Let us explain the execution of the global schema:

1. The recruitment model(RM) generates patients and spreads them out to suitable centers. Items are located into the geography, thus the distance between them is known. The RM calculates a theoretical number of recruited patients per complex. One time step is equal to one week, according to the common

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hospital organization.

2. The RM uses the scheduling model (SM) which gives the response of acceptance or not for the current patient, according to all constraints (functioning, capacity, medical politics). The two models are correlated, and the last one could be replaced easily.

3. The use of the economical model (EM) is possible iff the evaluated center knows the number of recruited patients by disease. It is estimated by the RM model or done directly by the user. This model computes the cost per treatment using the Activity based costing method (ABC, 2011; I.Durand-Zaleski, 2005; K.Kesteloot et al., 2000). We modeled, with medical experts, the description of a treatment composed by two phases (preparation and irradiation), each one is presented by activities included in.

4. The medico-economical model estimates a price per strategy, using a price per method of treatment (protocol) included in one strategy. One strategy is composed by multiple protocols describing the path followed by the patient during his treatment. The user could use the EM to get a price per treatment or give an estimation by himself. In addition we compare it with the cost corresponding to the French Health Insurance System.

The global representation of the system is close to the Information Systems As Agents (Hayes-Roth, 1995). Each model could be associated to an institutional agent (Wagner, 2003), thus the communication between agents is done by the transfer of information or messages (Genesereth and P.Ketchpel, 1994).

The four main parts are designed as separate agents, implemented in JAVA. They are acting in a common environment, represented by a knowledge dictionary and constructed especially for the tool. This dictionary embraces all definitions for different domains (geography, medicine, epidemiology, economy). We built up the ontology, the kernel of all links between the four models, using the XML, XSD properties, to control the quality of the required information. The collective interpretation allows common discussions and interactions. In addition the global brute space controls the dictionary (J.Ferber et al., 2009). Moreover the Social level, the knowledge, is a part of the Structural Specification of the tool (J.F.Hübner et al., 2002).

In the rest we present the recruitment model, rules used to built it up and sub-processes developed in collaboration with medical experts. The elaboration process is: a response with feasible results is needed for every situation. We used the medical knowledge to construct basic rules, which are represented like a *n* node tree. A node is a rule and edges are possible actions to undertake, regarding the constraints. When the complete tree is constructed, and not resolved situations exist, we use the main rules again. The process is repeated until all situations are resolved. This mechanism belongs to the Cased-Based Reasoning methodology (A.Aamodt and E.Plaza, 1994; S.Ontañon and E.Plaza, 2008). The process of collecting all required data for the prototype is complex, thus a simpler versions of some hypothesis exist.

2 THE GENERATOR OF PATIENTS

The generation of patients is a process lead by the RM during every time step. It depends on the simulated geography and indications (deseases), and makes the link with the process of research of centers. It as an agent, composed by multiple mechanisms, described in the two following subsections.

2.1 Geographic Position

To represent the epidemiology data the geography is composed by different level of details.

Definition: Geography *is an hierarchical structure, composed by items. Items are the smallest non partitionable elements (Fig. 2).*

Every geographic element is referenced by an indication. Epidemiological data couples with well known statistical laws permits us to generate patients according to an indication and an item.Thus generated patients know their geographic position.

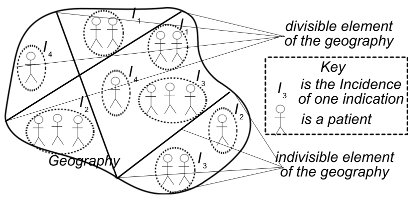

Figure 2: Elements of the geography and Incidences. We subdivide the geography into indivisible zones, which are as small as possible.One element of the geography refers to several indications.

Definition: Incidence *is the number of patients according to one geographic element (Fig. 2). Incidences compose the generated population for every time step.*

2.2 The Disease Description of a Patient

The patient is described by a couple of [indication/protocol](IP). The protocol is the description of the treatment according to technical constraints and the planning of all sessions. As multiple protocols could be coupled with one indication, the chances for the patient to find one treatment are larger. We suggest a method to classify them in a specific order, which facilitates the patient to find a center.

***Definition:* Priority group** *The couple IP is characterized by a priority group, combination of the medical benefit and the proof of the innovative therapy.*

The priority group defines a mutable order for treatments. The patient initially starts the research of centers with its best priority group.

We suggest a final date for patient, obliging him to find a center for a treatment before. It allows the patient to ask centers for a treatment multiple times if he is not accepted immediately. We introduce in this way the multi-demand of the patient to centers. So the final date for the treatment depends on the generator, which acts at the beginning of every time step. Its discussions with the recruitment model create the patients in an environment of competition of radiotherapy centers. This is an institutional agent operating with biological agents.

3 THE PROCESS OF RESEARCH OF CENTERS

The process of research of centers is based on technical requirements of the disease of the patient, his general healthy state, his preferences to the existing offer and geographical position of centers.

3.1 Description of the Center

The choice of the patient is influenced by possible treatments, available facilities in centers, their geographic position and their medical politics.

1. The Mechanism of Medical Politics

***Definition:* Medical Politics** *represents preferences of a center to the accepted indications. When it exists, it gives priority of some treatments and/or eliminates others, composed by several rules being a part of the planning.*

***Definition:* Reserved Time** *represents reserved slots in the hospital planning for a number of patients described, by special characteristics as an indication and a protocol.*

We suggest some rules for medical politics, defined as independent structures and not essential for the functioning of the center, as well as the existence of the mechanism of medical politics.

- A *Reserved Time for a Couple of IP*. The center constitutes a group of couples, composed by reserved slots for IP treatments. This way the center gives priority to treatments with a better therapeutic gain.

- A *List of Priorities*, with reserved slots for one or multiple priority groups. The last two rules could introduce a conflict situation. If the priority group and the couple of the same IP have reserved time, the medical knowledge gives priority to the rule of the couple.

- *limit the Usage of Particles* such as Carbone, for hadrontherapy centers. We estimate the annual use of the particle and control it to not exceed a fixed limit.

2. The Scheduling Model

The scheduling model is a simple model, which plans treatments and calculates the probability of acceptance of one patient according to its time of waiting. We estimate the probability of acceptance with a mobile mean computed for each IP accepted in a center. A response is then given to the patient.

We constructed the SM in order to be able to test the RM. The number of treated patients is maximized regarding medical politics. We used linear programming in $0,1$ to implement it. Constraints are not listed here, but we illustrate the use of the model on the Fig. 3. The SM is used whenever the recruitment model needs to have a response for one patient. It also plans treatments for patients already in the waiting queue and when it is not possible, the patient stays in the waiting queue considering his preferences. The SM is used for planning treatments for each room and during the whole simulation, we use the RLE encoding (RLE, 2010). It matches each day with the planning of a room. When the scheduling model doesn't find a place for one patient, not corresponding to medical politics, he is rejected directly and he has to search for another center. As depicted on Fig. 3 there are some rules to use during the discussion between the SM and the agent of the center. We can identify them in the same way as it has been done in (Wagner, 2003; Taveter and Wagner, 2001).

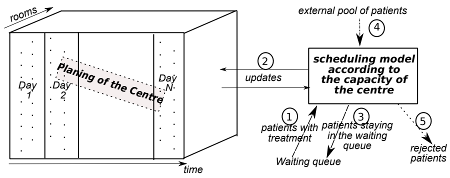

Figure 3: Interaction between the SM and the RM. We make updates during the planning of treatments, in consequence coming patients are evaluated and accepted or rejected.

3. The Waiting Queue

The waiting queue is a consequence of the mechanism of medical politics. When a patient being a part from medical politics arrives with a demand, and no place is available for him, than if he could "wait" according to his final date of treatment, he goes in an waiting queue if he agrees. The situation of this patient is evaluated at every time step (Fig. 4). Moreover the entry of new patients could force the exit of a patient.

A special way of ordering is applied to the waiting

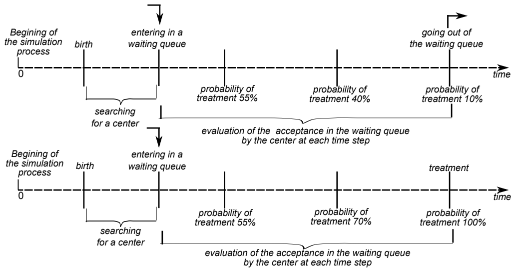

Figure 4: Evaluation of the state of the patient in an waiting queue, rejection or successful issue.

queue, considering the entry date and the priority group of the patient. The center keeps unchanged the medical politics and the priority of patients, which are always planned in the slots of reserved time. The waiting queue implies waiting possibilities for a patient. When a center does not consider medical politics, the waiting queue does not exist and the patient will not wait for a response.

4. Choice of Patients by the Center
We suggest a mechanism organizing demands of patients. For every time step of the simulation the mechanism groups demands for the same center. Thus the center receives a group of patients and applies medical politics. The possible responses are:

- How many patients could be taken for an immediate treatment. Patients evaluated to be probably placed in the planning are part of medical politics. When there are places available after the setting of those patients, the other patients are set up.

- Number of patients directed to the waiting queue.

- Number of rejected patients, when they are not a part of medical politics and there is no place in the planning for them.

The response by the center is a result of the interaction of the agents of medical politics, the SM and the RM. They are using the common knowledge and according to the environment they discuss on the possible actions to undertake. The full description of the center is a part of the mind of the center reflection the decisions taken during discussions with other agents in the system.

3.2 Characterize the Distance and the Attractivity

As the geographic distance is an important parameter, we define crowns of influence over each center representing the hesitation of the patient.

Definition: Crown of Influence (Zone) *is composed of one or multiple geographic elements. Over the center one can find multiple crowns. The influence is smaller when the crown is distant from the center.*

In consequence when the patient is in the first crown the center is more attractive, than if he is in another crown (Fig. 5). The patient prefers centers situated nearly, thus we introduce a list of center around him, ordered according to the geographic distance. This model of crowns is mutable.

We mentioned the healthy state of the patient, in consequence the medical benefit of the treatment depends on. This medical parameter is part of a mechanism called attractivity.

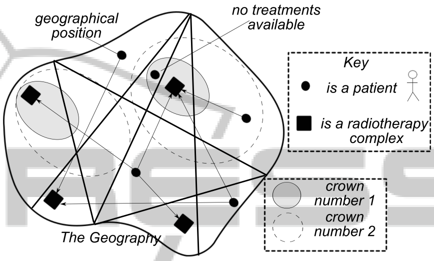

Figure 5: Spatialization for patients and center.

Definition: Attractivity *is a combination between the level of proof the treatment and the priority group of the couple IP attributed to a patient.*

We use the attractivity coefficient as a test if a patient wants to go to one center capable to treat him. The result of the use of the geographic distance in the attractivity, is a list obtained by a patient for all centers around him and capable to treat him. The mechanism of the attractivity is a part of the process of research of centers, which is the leading agent of the RM. All links for this process are connected with the global environment of competition (Fig. 5).

3.3 The Patient and his Actions

We use the laws of Poisson and Gauss from the Epidemiological data to generate patients with a couple of IP attributed to every one. The patient changes his states during the simulation. He appears in the beginning of one time step and starts searching of a radiotherapy centers. When he founds one, he could go in for a treatment, using the attractivity coefficient. In some cases the patient does not find a hospital complex, because he does not suit to the medical politics included in the study and/or there is no available place. For well known techniques the patient is treated out of the system, thus we evaluate only the participation of new and innovative techniques in the therapy center. The next figure 6 resumes the set of states of the patient during the simulation, related to the RM and the process of search of centers.

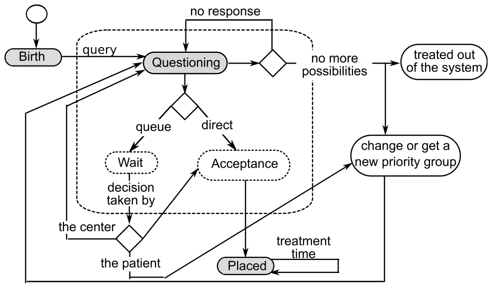

Figure 6: States of the patient: genesis, searching process, waiting queue, acceptance of a treatment and the modification of the priority group.

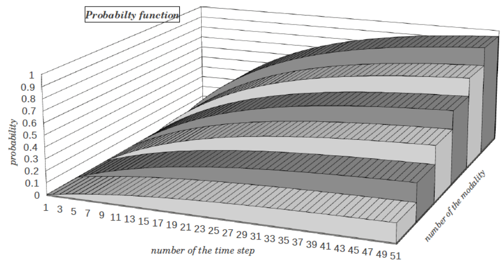

Figure 7: Curve of the probability function used by the patient to estimate the degradation of his priority group.

1. The order of Couples Describing the Disease and the Treatment, The Choice of Lower Priority Group

One indication is coupled to more than one protocol, thus the patient has more chances to find a treatment. The research of centers starts with his best couple IP. All the couples are ordered according to their priority group, describing a different ways of treatment. We model the behaviour of the patient as a multiple demands to all centers corresponding to the treatments (protocols), of the given priority group. When this situation appears the patient evaluates the responses of each center and send them back a response. The evaluation is based on the date of treatment done by the center, the distance and the attractivity. When the patient is accepted by one center and he accepts to go in, the other centers with a positive responses are alerted by a mechanism, lead by the RM.

When the patient does not find a center capable to treat him, he could degrade the current priority group, taking the next available in his list. If a lower priority group does not exist, then he has to search with the current one, or he has to choose to take a well known treatment and to be treated out of our system.

To model the degradation of the priority group, we use a decision parameter based on a probability law, combination of the number of weeks available for waiting and the priority group. An example of the graph of this curve is shown on the Fig. 7. In the example there are 51 time steps period and 6 priority groups.

In consequence the probability law is used by the agent of the patient as a measure to estimate his need to change his priority group and search for new treatments. Less time available implies a faster choice of lower priority group.

2. The Waiting State, Waiting Queue and Priority Groups

The waiting state of the patient corresponds to an awaiting queue. This is possible when the patient is scouring for center and he is a part of medical politics of one center. If the designed center does not find enough place for a treatment, then the patient goes automatically in a waiting queue. When multiple centers are available for the patient, and he is a part from their medical politics, then he goes in the waiting queues of all centers. The first complex that finds a place for a treatment is referred for the patient. When this situation appears the other centers are informed by a message that they have to liberate the place.

The evaluation of the place of the patient at every time step is a process described in the previous section for the center. When the center evaluates that the patient has no chances to be treated before his limit date, the patient is forced to quit the waiting queue. In addition when the patient has available time to wait, he could stay in the waiting queue of the hospital for several weeks. When he waits too long time, he could decided to exit it. This mechanism makes a link between the waiting time of the patient and its priority group. When the patient is in a waiting queue, he could choose to stay in and start to search centers for a less advantageous treatment. This action degrades his priority group but gives him more chances for a treatment (Fig. 7). A patient in an queue, is described by a passive state, i.e. he doesn't change its priority group. At each time step his need to pass from the passive state to a searching state is evaluated using the probability law. Thus the agent uses a rule, which validation implies the change of the state. When he passes in an active state, i.e. keeps its current place in the queue, he can try to find centers with a new lower priority group (Fig. 8).

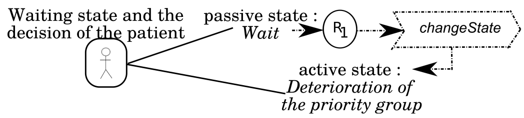

Figure 8: The rule for changing the state of the patient.

The patient is a biological agent (Wagner, 2003)) acting into the RM with his beliefs and goal. His mental components (Shoham, 1993) force him to discuss and interact with other agents present in the global system. The environment creates the resources and the conditions for resolving the situations that appears. According to the context the mind of the patient decides for the best action to do (J.Ferber, 1999; Dignum, 2009).

4 THE GLOBAL PROCESS, FIRST RESULTS AND CONCLUSIONS

The global process of the recruitment model is an institutional agent, he guides all discussions (R.Searle, 1995). The rules are illustrated on the Fig. 9. We use the schema introduced by (Wagner, 2003). The algorithm modeled for the RM is:

- Initialization and preparation of the environment.
- Generation of patients. The patient is described by four elements: geographic element, indication, protocol and priority group.
- Creation of a list of centers, for every patient, capable to accept him and according to the geographic distance and the attractivity.
- Updates for the waiting list of all centers.
- The medical politics are activated for centers.
- Choice by the patient from the available centers.
- The SM plans treatments of accepted patients.

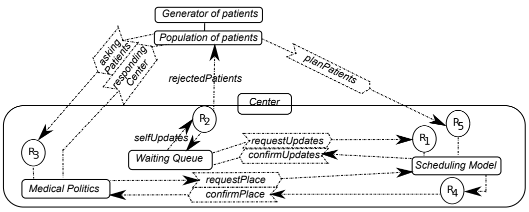

Figure 9: Rules according to the general institutional process of the recruitment model.

The first results obtained by the prototype use data from the three French radiotherapy centers: CPO (C), NICE (N) and ETOILE (E), with corresponding capacities 489920 hours, and tree treatment rooms, for C and E, and 16554 and one treatment room for N. The geography included in the study is the territory of France, divided into 23 geographic elements. There are 24 indications and 22 protocols with average duration for the whole treatment spread out over 10 sessions. The couples IP are organized into 8 priority groups. We use both, the recruitment and the scheduling model for one year simulation time. Our results, based on a week with 5 days of working time, show that when there is more time before the start of the treatment, the recruitment is more important. Details are shown in the next tables. We present results regarding the full capacity and according to every priority group, being a part of medical politics of the centers. The results present different situations of recruitment with 0_w, 3_w and 20_w weeks of delay before the treatment. The tables are also ordered according to the possible number of patients recruited for the first priority group. When the limit of recruitment of patients for the first priority group is more important, the recruitment increase. CPO and ETOILE increase the number of treated patients for different values of accepted capacity of the first priority group. We suggest that medical politics have to be planed carefully, in order to have a well structured recruitment.

Table 1: Treated patients by centers for one year. The first priority group is 12% of the global planning for C and E.

	0_w			3_w			20_w		
PG	C	E	N	C	E	N	C	E	N
1	30	1	84	35	10	97	28	11	105
2	26	19	-	24	12	-	26	23	-
3	-	-	-	-	-	-	-	-	-
4	23	33	-	63	115	-	125	113	-
5	11	23	-	90	132	-	0	165	-
6	-	-	-	-	-	-	70	-	-
7	140	327	-	524	797	-	477	902	-
8	-	-	-	25	50	-	31	49	-

Table 2: Treated patients by centers for one year. The first priority group is 42% of the planning for C and E.

	0_w			3_w			20_w		
PG	C	E	N	C	E	N	C	E	N
1	50	43	95	49	42	105	47	34	117
2	42	46	-	42	47	-	49	61	-
3	20	-	-	18	-	-	27	-	-
4	24	76	-	63	123	-	127	138	-
5	12	22	-	87	153	-	97	160	-
6	-	-	-	-	-	-	-	-	-
7	152	368	-	607	917	-	522	1151	-
8	-	-	-	22	41	-	27	51	-

1. Conclusion

We use concepts from multi-agent systems for the construction of a reusable and independent tool presented in this paper. The different models used for it are presented as separate agents, thus they are reusable and could be replaced. The link between them is done by the ontology presented in the global environment. The dictionary is related to multiple fields such as medicine, economy or informatics. All input data respect the structure of the ontology and results were validated by medical experts.

The recruitment model, the main part of the prototype, takes into account the situation of competition between radiotherapy centers and the spatialization of centers and patients in the geography. With our model it is possible to evaluate the right geographic location of a treatment center in order to optimize the recruitment. We show preliminary results obtained by the collaboration of the recruitment model and the scheduling model. In future works we plan to replace the existing scheduling model with a complex one, including definitions of staff and taking into account critical resources.

Compare to the actual economical methods we evaluate the efficiency of a center using its potential recruitment. Our prototype could be used as a decision making tool for new innovative facilities, thus allowing to test different scenarios with respect to staff or treatment capacity as well as medical politics.

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