LIVER TRANSPLANT WAITING LIST SIMULATION
An Agent based Model

Alexander Flávio de Oliveira
Instituto de Informática, Pontifícia Universidade Católica de Minas Gerais, Belo Horizonte, Brazil

Ricardo Poley Martins Ferreira
Departamento de Engenharia Mecânica, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil

Agnaldo Soares de Lima
Instituto Alfa de Gastroenterologia do Hospital das Clínicas, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil

Keywords: Multi-agent systems, Agent based simulation, Simulation, Liver transplant waiting list, Queue discipline.

Abstract: Generally, Prioritizing is not a simple task. Given a waiting list for organ transplantation with dozens of patients, which patient must be prioritized at the time of an organ donation? Which patient has been waiting for longer time or which patient has the worst health? What policy would be fairer and more efficient? The search for an answer to this question can become a complex decision-making problem. The process for testing various policies and verifying whether each one of them can bring benefits or not, can be slow and consume valuable resources. Computer simulations can help by allowing, at a lower cost and with greater security and flexibility, reproduction and study of events whose real occurrence would not be desirable or even possible. These efforts result in the creation of tools for modeling and simulation. In this work, a model based on multi-agent systems was developed and implemented by using the Repast framework. The model was calibrated by using information taken from a real situation. Experiments were carried out illustrating situations in which the simulation model could be used. The results demonstrated the ability of the model to capture details of reality and to simulate defined situations.

1 INTRODUCTION

Waiting lists exist in many situations and their study and analysis attract researchers from different areas of knowledge. As a result of their research, models are proposed to represent queues and their applications (Gross and Harris, 1998). However, although useful, the mathematical models have difficulty to capture details of the environment and to represent qualitative aspects such as preferences and behaviors, which are usually associated with individual characteristics. Given these limits of classical queue mathematical models, there have been studies using approaches based on agents. Their main feature is the fact that the focus is kept on individuals, being able to capture details of reality (North and Macal, 2007).

Medical science has made organ transplants possible, and many lives have been saved. In Brazil, there were more than 1,000 liver transplants in 2006, and in 2007 more than 7,000 were waiting for a liver transplant. Patients waiting for a donated organ are organized in waiting lists. This measure, however, raises some questions: What queue priority policy should be used? How should the waiting list be organized? Which patients are to be prioritized? Who has been waiting for more time or who has the worst clinical condition? Studies on priority policies (Howard, 2001)(Thompson et al., 2004) seek answers to these complex decision-making questions. They seek to improve the system efficiency, respecting medical ethics, human rights and distributive justice.

In 1997, the liver transplant waiting list was organized by order of patient registration. The objective was to inhibit frauds in an attempt to minimally fair organize the access to the grafts (Freeman et al., 2002). Although objective and transparent, this first-come first-served service policy caused side effects.

Flávio de Oliveira A., Poley Martins Ferreira R. and Soares de Lima A..
LIVER TRANSPLANT WAITING LIST SIMULATION - An Agent based Model.
DOI: 10.5220/0003188904620468
In *Proceedings of the 3rd International Conference on Agents and Artificial Intelligence* (ICAART-2011), pages 462-468
ISBN: 978-989-8425-41-6

Knowing that in the future, their patients will need a transplant, doctors began to enroll them early in the waiting list, in order that, when they would need the transplant, the patients would be in top positions of the queue and thus they would have a greater chance of receiving the transplant(Freeman et al., 2002). This behavior caused a generalized queue swelling, harming those patients with urgent transplant needs who arrived in the waiting list with lower priority than patients with better health who were already waiting. To inhibit early enrollment, and especially to reduce mortality on the waiting list (Oton-Nieto et al., 2005), the first policy was changed in July 2006 in Brazil when a health based policy was adopted. The new policy is based on an index of severity MELD(Model of End-Stage Liver Disease) of the patient. The patient's MELD is calculated using a formula that takes into consideration results obtained from three blood tests, which measure how effectively the liver produces bile; how effectively the liver produces blood clotting agents, and how effectively the kidneys are functioning. The MELD score is used to estimate the patient chances of dying within the next three months.

We propose and implement an agent based simulation model for the liver transplant waiting list (Weiss, 2000) (Sandholm, 1999). The proposed model is used to explore, empirically, different situations and to answer ”what-if” questions. The objective is to develop a model which can help medical decision makers to understand and to answer questions like: given an organ transplant list with dozens of patients enrolled, how to prioritize who has been waiting for a longer time or who has the worst clinical condition? What policy would be more fair and efficient? To choose a priority policy is not a simple task and can become a complex decision-making problem.

In literature simulation models to study liver transplant waiting lists were developed (Howard, 2001)(Teng and Kong, 2008)(Thompson et al., 2004). Most of these models use discrete event simulation.

Teng and Kong (Teng and Kong, 2008) proposed an agent based simulation, describing their ideas and presenting some design decisions. Their article is aimed to study the allocation policy of donated livers from a geographical distribution point of view taking into consideration aspects related to organ deliver logistics and organ quality at the of transplant time. However, the article does not present results and states that the simulator had not yet been calibrated and validated.

Shechter et al (Shechter et al., 2005) proposed a biologically based discrete-event simulation that represents the biology of end-stage liver disease and the health care organization of transplantation in the United States. They studied changes in the allocation policies.

Thompson et al (Thompson et al., 2004) presented a tool called LSAM (*Liver Simulated Allocation Model* capable of simulating different aspects of a liver transplant waiting list as the allocation policies. They argue that the simulation-based analysis can inform the policy process by predicting the likely effects of alternative policies.

In (Howard, 2001), they study how the ratio between liver demand and supply affects the waiting time. The main conclusion was that the rule of ”worst-first” is fair, but its efficiency, measured by the loss of patient's health decreases as the ratio of demand-supply increases.

The outline of this paper is as follows. We first present the liver transplant waiting list model. Then follows a section that presents computational experiments made to calibrate and test the simulator, and to show how it can be used to deal with a transplant waiting list. Concluding remarks appear in section 4.

2 LIVER TRANSPLANT WAITING LIST SIMULATION MODEL

The proposed agent-based simulation model represents each recipient patient and his or her liver disease, the donated liver and its characteristics, the waiting list, and the interactions among them. Each agent interacts with other agents and entities according to specific needs and objectives (North and Macal, 2007).

To overview the model some considerations are presented: The model reproduces the liver transplantation process from the moment an organ is available until the end of post-transplant care which can last up to one year; The model considers as available resources: medical staff, material, equipment and operating room necessary for the transplant; The model considers that a donated liver can be used for only one patient and it considers only adult patients.

The modeled process begins when a patient is placed on the waiting list following the MELD based assortment policy. While the patients wait for a compatible liver donation, their health changes because of their diseases. During the waiting time, a patient can die, but still has chance of recovering his or her liver function, showing an improvement and no longer needing a transplant. Waiting in the transplant list, the patient might prefer to be transferred to another waiting list, to give up the transplant, or simply loose contact with the transplant control center for whatever reason. These events define the abandon list.

When a liver becomes available, there is an effort to allocate it to a patient who meets compatibility criteria, respecting his/her position in the waiting list. Compatibility criteria consider ABO blood type, body size of the donor and recipient, degree of medical urgency and MELD score (Model for End-Stage Liver Disease). The patient's position in the waiting list, in turn, will depend on the assortment discipline, which may be first-in first-served, a random order, the worst-first or the best-first. When a compatible patient is found, the service is started, and the donated liver is transplanted. After a liver transplant, the patient enters post-transplant care where he or she can stay for up to one year. During the post-transplant care, the patient can die or a graft rejection may occur and the patient must return to the transplant waiting list. The model dynamic can be seen in the Figure 1.

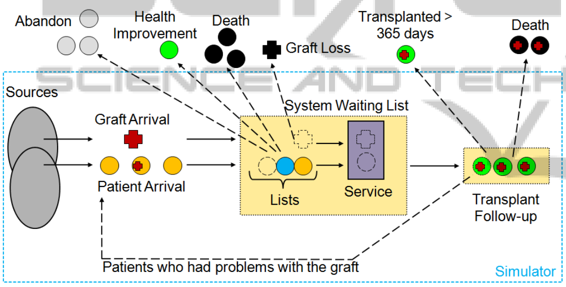

Figure 1: Simulation model dinamics.

The model entities involved in the simulation:

- Patient: an agent that represents the recipient patient;
- Liver: an agent that represents the donated organ;
- Assortment discipline: entity that defines the waiting list assortment policy;
- Source: an agent responsible for generate patients and donated livers. We defined two sources types: patient source and liver source;
- Service: an agent that represents the transplant surgery, where the donated liver is transplanted into the recipient patient;
- System Waiting List: an agent responsible for controlling the entry and the exit in the waiting list by applying an assortment discipline, and to verify the compatibility criteria, in order to allocate the donated liver to the chosen patient and to create services;
- Transplant Follow-up: an agent responsible for maintaining in the simulation transplanted patients and to accompany them during a period of one year. It is also responsible for removing from the simulation those patients who died post-transplant and to re-apply on the waiting list those who have problems with the graft;
- Disease: entity responsible for changes in the patient's MELD;
- Report: entity responsible for accounting and recording on file the simulation results and indicators.

The patient agent can assume different states: "sick", "sick again", "transplanted","retransplanted", "cured" and "deceased". The state in which the patient lies defines its behavior. Figure 2 shows the patient agent states and the events that trigger the transition between these states.

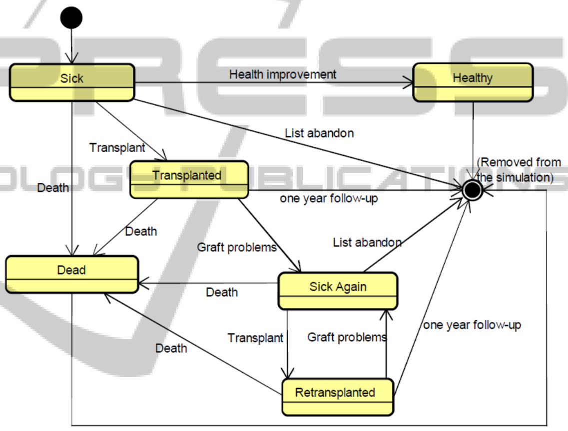

Figure 2: Patient's state diagram.

As the patient agent, the liver agent can assume different states: "useful", "useless" and "used". Its state defines its behavior.

The patient and the donated liver arrivals are controlled by the sources already defined. When the simulation begins, the patient source populates the waiting list with an initial number of patients reported by the user. This step aims to leave the waiting list with an initial size, defined by the situation being simulated. The source creates agents according to a Poisson distribution, assuming a central value entered by the user. For each created agent, the source provides, probabilistically, values for some of its attributes. Figure 3 presents the simulator class model.

Considering the basic elements that describe the waiting list system (Gross and Harris, 1998), some model details are given below:

- Patient arrival pattern in the waiting list is represented by a Poisson distribution;
- The server pattern: each service attends a patient, and the service time is predetermined and equal

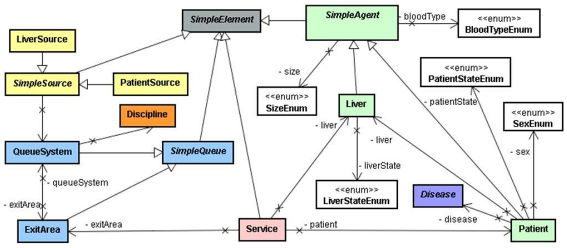

Figure 3: Simulator class diagram.

for all services;

- Discipline: discipline implemented were: worst-first MELD based, Fist-In First-Served;
- System capacity: there is no restriction on the size of the waiting list which is capable of receiving a not-bounded number of patients;
- number of service channels: there is no restriction on the amount of simultaneous services;
- Number of service stages: service (transplant) is performed in one stage.

In this model, agents use probabilities as a basis for controlling their behavior. The probability values used were taken from historical database analysis and defined by expert ad hoc decision.

The abstract class *Disease* represents the common behavior of all diseases that can affect the patient. A disease has an attribute *bonus* which contains a value passed as a parameter by the user. The bonus is a correction value that is added to the patient MELD according to their disease, since some disease types, such as carcinomas, compromise the patient's health rapidly requiring urgent transplant.

The disease types implemented by the model are: ethanolic cirrhosis, post-viral B and C cirrhosis, cryptogenic cirrhosis, Hepatocellular Carcinoma and others. These types make up represents diseases that can lead a patient to the transplant waiting list. Generic graft rejection is implemented as a disease which affects transplant patients who have problems after surgery and require a new transplant.

Each disease type is a concrete implementation of *Disease*. Thus, the method *getHealthTransition ()*, responsible for defining the evolution of the patient's MELD is defined in *Disease*, but behaves as the implementation of each patient disease (polymorphism). This design allows each disease to cause a distinct impact on the patient's MELD evolution and allows a greater model detail.

The possibility to register as the patient's health changes over time, according to (Howard, 2001), is important to better capture the dynamic nature of the problem. However, due to the lack of information, all the diseases modeled used the same evolution of the MELD. During this work, no information was found on the impact of each disease type on MELD value. So, all diseases evolve in the same way and the value of the patient's MELD is increased by a random number between 0 and 1 in each time interval, *each day*.

System Waiting List is the agent responsible for controling and organizing the list agents (patients and livers), to find patients compatible with the available organs respecting the defined discipline, and to create the service care . The class that represents this agent is *QueueSystem*.

3 COMPUTATIONAL EXPERIMENTS

Computational experiments were made in order to calibrate and to test the simulator, as well as to illustrate how it can be used to deal with real situations and to study the transplant waiting list. The experiments described in this section were performed with a notebook with a *AMD Athlon 64 X2 QL-64* processor and 4 GB of RAM memory. Running *Windows Vista H.E.* 64 bits and the Java version used was 1.6.0_17. The model was implemented using the *Repast http://repast.sourceforge.net/*).

3.1 Model Calibration

The chosen calibration situation was the liver transplantation waiting list of the state of São Paulo, Brazil. The obtained data was from the 2008 census produced by the State Health Department (Censo 2007 and 2008). This information is presented in Table 3. The comparison among the simulation results *output data* and the real situation *reference data* was made.

The model agents use information and probabilities to control their behavior. These parameters were obtained from data and were calibrated:

- Probability of health improve: in this context, the improvement consists in the liver function recovery: 1,15%;
- Probability of death after transplant: 31,78%;
- Probability of re-transplant: 10%.;
- Probability of death in a three months waiting period: depending on the patient's MELD;
- Probability of abandon the list: 23,03%;
- Patient gender probability: 65,7% to be male;
- Patient and liver donor blood types probabilities - Table 1;

- Patient and liver donor body sizes probabilities: Small 30%, Medium 40%, Large 30%;
- Initial MELD index probability - Table 2;
- Patient disease type probability: Ethanolic cirrhosis 25,71% , Post-viral B and C cirrhosis 28,57%, Cryptogenic cirrhosis 14,29%,Hepatocellular Carcinoma 1,43%, Others 30%.

Table 1: Patient and liver donor Brazil blood types probabilities.

Type	-	+
O	5,3%	42%
A	4,1%	32,2%
B	1,4%	11,1%
AB	0,4%	3,5%

The probability of death in the waiting list is not a predefined *parameter*, because the death is related to the patients MELD. To initialize the simulation the simulated situation must be defined. The situation is set up from input data. The data are shown in Table 3. Table 6 shows the obtained results. The ”initial available livers” and ”special situation bonuses” received the value 0, because these informations were not available. Calculation methods for obtaining the values of reference data are presented in Table 4 and applying the formulas Reference and Input data were obtained. Once defined the situation, the values of the input data, the comparison indicators and the reference data, five simulations were performed and the average of the results were compared with the reference data. To compare the results of simulation with real data we used the defined error in the calibration process. The error represents the relative difference between output and the reference data. Table 6 shows the obtained results. The *error* represents the relative difference between the *output data* and the *reference data*, and is defined by the following formula:

$$erro_i = (\frac{OutputData_i}{ReferenceData_i} - 1) \times 100 \qquad (1)$$

Table 2: Initial MELD index probability.

MELD	Probability
6 - 10	43,22%
11 - 14	32,63%
15 - 20	19,92%
21 - 30	3,81%
30	0,42%

3.2 Testing the Simulation Model

A second test was made to observe the behavior of the simulation model using another situation. The chosen situation was the 2007 São Paulo liver transplant waiting list. Table 3 does not contain any information about removed patients from the list because their MELD three blood tests were not made in the last 365 days. In the 2008 census, 835 patients were in this situation. This represents 17.75% of the total number of patients. Therefore, the abandon probability used in the validation process had to be adjusted. The *input* values to the model were obtained using Table 4 formula.

Table 3: 2007 and 2008 waiting list census of the state of São Paulo, Brazil.

*(P)*Time	01/01/2007 31/12/2007	01/01/2008 31/12/2008
(Ci) Initial size of the waiting list	3.904	3.493
*(E)*Arrival patients	1.021	1.212
*(I)*Inscriptions	1.021	1.212
(S) Patients who left	1.439	2.132
*(Tdv)*Living donor transplants	95	79
*(Tfe)*Transp. outside the State	5	8
*(Tps)*Transp. inside the State	331	455
*(Tsc)*Transp. without confirmation	5	3
*(A)*Abandon	5	10
*(FHr)*Liver function recovered	45	54
*(NQT)*Patient do not want be transplanted	14	15
*(Rid)*Rem. (duplicate)	5	2
*(Rmv)*Rem. MELD/PELD (overdue 365 days)	not informed	835
*(Rs)*Rem.(suspended 365days)	119	113
*(Rpe)*Rem. by the medical	44	32
*(Rsc)*Rem. without clinical conditions	50	50
*(Toe)*Moved to another state	15	17
*(O)*Pre-transplant death	706	459
*(Cf)*FINAL RECORD	3.486	2.573

Removed(Rem.), Transplanted(Transp.).
Based on: (Censo 2007 and 2008).

The data presented in Table 3 refers to an assorted waiting list using the MELD index. Applying the formulas presented in Table 4, we obtain the values shown in the Table 5.

Once defined the case to be studied, the *input data* values, the *comparison indicators* and the *reference data*, five simulations were performed and the average results were compared with the real data. Results presented in the Table 6 indicates the difference between the real situation and the simulation results. The health improvement rate increased by 31,59% in relation to the real situation The pre-transplant death and the abandon rates are larger than the real rates. But the number of patients who died in the waiting list and the number of patients who abandoned the list were smaller than pre-transplant deaths increase.

Table 6: Calibration results *Simulation results* versus *Reference data* 2008 census and Validation results *Simulation results* versus *Reference data* 2007 census.

Result Year	Indicator	*Reference Data*	*Simulation Result*	*error*
	Waiting list size	4.703	4.722	0,41%
Calibration	Patients per day arrival rate	3,32	3,37	1,50%
	Donated livers per day arrival rate	1,46	1,46	-0,23%*
2008	Health improvement rate	1,15%	1,10%	-4,20%
	Pre-transplant death rate	9,76%	9,64%	-1,27%
	Abandon rate	23,03%	23,46%	1,88%
	Waiting list size	4.920	4.928	0,15%
Validation	Patients per day arrival rate	2,78	2,80	0,71%
	Average livers arrival rate per day	1,17	1,20	2,77%
2007	Health improvement rate	0,91%	1,20%	31,59%
	Pre-transplant death rate	14,35%	11,22%	-21,78%
	Abandon rate	5,22%	6,39%	22,42%

Table 7: Comparing WF-Meld based versus First-in First-Served disciplines.

Comparison indicator	2008 Values	Simulation results
List size	4.703	4717
Number of patients with health improved	54	58
Pre-transplant number of deaths	459	428
Number of patient's abandon	1083	1067
Discipline	*WF-MELD Based*	*FIFS*

Table 4: *Input data* equations and *Reference data* formulas.

Input data	Formula
Number of simulated days	*(P)*
Initial number of patients in the waiting list	*(Ci)*
Initial number of disponible livers	-
Average patient arrival rate per day	$\frac{(I)-(Rid)}{(P)}$
Average liver arrival rate per day	$\frac{(Tdv)+(Tps)}{(P)}$
Spacial situation bonus	-
Discipline	*Worst-First*
***Reference data* Indicators**	**Formula**
List size	$(I)-(Rid)+(E)$
Average patient arrival rate per day	$\frac{(I)-(Rid)}{(P)}$
Average liver arrival rate per day	$\frac{(Tdv)+(Tps)}{(P)}$
Health improvement rate	$\frac{(FHr)}{(Ci)+(E)} \times 100$
Pre-transplant death rate	$\frac{(O)}{(Ci)+(E)} \times 100$

The simulator allows the inclusion of other details. As long as more information is available about a situation, you can represent them in the model. This versatility allows the model gradually becomes more complete and capable of reproducing complex situations.

With the objective of verifying what could be the results if other waiting list assortment discipline was used, a simulation was performed taking the 2008 scenario and changing the discipline from worst-first MELD based to the First-In First-Served discipline which was adopted before 2006. The simulation results presented in Table 7 suggests that the old policy

Table 5: *Input data* extracted from the 2007 Census and from the 2008 Census.

Input data	2007	2008
Number of simulated days	365	365
Initial number of patients in the waiting list	3.904	3.493
Initial number of disponible livers	0	0
Average patient arrival rate per day	2,78	3,32
Average liver arrival rate per day	1,17	1,46
Spacial situation bonus	0	0
Discipline	*WF-MELD Based*	*WF-MELD Based*

FIFS (First-In First-Served) was more efficient than the new MELD based policy. According to the results, the FIFS policy provides a greater number of patients with the improved health, a reduction in the pre-transplant number of deaths, and in the number of patients who abandon the list.

4 CONCLUDING REMARKS

This research is interested in the liver transplant patient waiting list organization, and considers problems that arise from the decision-making process to define what assortment policies to adopt.

Seeking to contribute to the study of this problem, this work developed an agent based simulation model. The free open source framework Repast was used. Each component of the process - the patient, the liver, the waiting list, the transplantation, and the sources of livers and patients were modeled as agents. This approach allowed the characterization of the process in detail and with a finer granularity.

The simulator was calibrated and some exploratory experiments were performed. The performed experiments in this study have a demonstrative nature, i.e. they were performed in order to illustrate situations where the simulation model could be used. For these experiments, comparison indicators were defined and measured to compare the performance of the waiting using a different waiting list assortment discipline.

The obtained results show the expected behavior. A more detailed interpretation of the results requires further study. This effort, while important, goes beyond the scope of this paper. The experiments demonstrated the ability of the model to capture details of reality and to reproduce real situations. The model can be extended, as needed, to represent more complex situations.

ACKNOWLEDGEMENTS

This work has been supported by FAPEMIG (PPM-00399-09), CNPQ (371756/2008-1).

REFERENCES

Freeman, R. B., Wiesner, R. H., Harper, A., McDiarmid, S. V., Lake, J., Edwards, E., Merion, R., Wolfe, R., Turcotte, J., Teperman, L., UNOS/OPTN Liver Disease Severity Score, U. L., Intestine, and Committees, U. P. T. (2002). The new liver allocation system: moving toward evidence-based transplantation policy. *Liver transplantation*, 8:851–858.

Gross, D. and Harris, C. M. (1998). *Fundamentals of Queueing Theory (Wiley Series in Probability and Statistics)*. Wiley-Interscience.

Howard, D. H. (2001). Dynamic analysis of liver allocation policies. *Medical Decision Making*, 21(4):257–266.

North, M. J. and Macal, C. M. (2007). *Managing Business Complexity: Discovering Strategic Solutions with Agent-Based Modeling and Simulation*. Oxford University Press, USA.

Oton-Nieto, E., Barcena-Marugan, R., Carrera-Alonso, E., Blesa-Radigales, C., Garcia-Gonzalez, M., J. Nuo, G. P.-P., and Garcia-Plaza, A. (2005). Variability of meld score during the year before liver transplantation. In *Transplantation Proceedings*, volume 37, pages 3887 – 3888.

Sandholm, T. (1999). *Multi-agent Systems: A Modern Introduction to Distributed Artificial Intelligence*, chapter Distributed Rational Decision Making, pages 201 – 258. MIT Press.

Shechter, S., Bryce, C., Alagoz, O., Kreke, J., Stahl, J., Schaefer, A., Angus, D., and Roberts, M. (2005). A clinically based discrete-event simulation of end-stage liver disease and the organ allocation process. *Medical Decision Making*, 25(2):199–209.

Teng, Y. and Kong, N. (2008). Applying agent-based modeling and simulation (abms) to the u.s. organ transplantation and allocation network. In *3rd INFORMS Workshop on Data Mining and Health Informatics (DM-HI 2008)*, pages 331–338.

Thompson, D., Waisanen, L., Wolfe, R., Merion, R., McCullough, K., and Rodgers, A. (2004). Simulating the allocation of organs for transplantation. In *Health Care Management Science 7*, pages 331–338.

Weiss, G. (2000). *Multiagent Systems: A Modern Approach to Distributed Artificial Intelligence*. The MIT Press.