Rev.R.Acad.Cienc.Exact.Fis.Nat. (Esp)
Vol. 92, N.º 4, pp 317-322, 1998
Monográfico: Problemas complejos de decisión

APPLICATIONS OF DECISION ANALYSIS TO EXTRACORPOREAL MEMBRANE OXYGENATION

(decision analysis/imprecise influence diagram/utility/ECMO)

A. MATEOS[*], S. RÍOS-INSUA[*], C. BIELZA[*], M. GÓMEZ[*], P. GARCÍA BARRENO[**], M. SÁNCHEZ LUNA[***] AND D. BLANCO[***]

[*] Department of Artificial Intelligence, Madrid Technical University, Spain
[**] Spanish Royal Academy, Madrid, Spain
[***] Neonatal Department, "Gregorio Marañón" Hospital, Madrid, Spain

ABSTRACT

The decision of whether to apply or not Extracorporeal Membrane Oxygenation (ECMO) to a neonate is a difficult medical decision making problem. To afford such problem, we are constructing a decision support system which integrates imprecise beliefs and preferences all structured in an influence diagram, to aid doctors in decision making. The basic methodology is decision analytic, and includes several uncertain factors and decisions to control the application of ECMO from the expected utilities of the different treatments. Since we deal with an influence diagram in which probabilities and utilities are partially assessed, we follow a Bayesian robust approach.

RESUMEN

La decisión de aplicar Oxigenación por Membrana Extracorpórea (ECMO) a neonatos es un difícil problema de decisión médica. Para afrontarlo, estamos construyendo un sistema de ayuda a la decisión que integra creencias y preferencias imprecisas, todo ello estructurado en un diagrama de influencia para ayudar a los médicos en la toma de decisiones. La metodología básica es analítica e incluye distintos factores inciertos y decisiones para controlar la aplicación de AREC a partir de las utilidades esperadas de los diferentes tratamientos. Como trabajamos sobre un diagrama de influencia con probabilidades y utilidades asignadas parcialmente, el enfoque es Bayesiano robusto.

1. INTRODUCTION

Extracorporeal Membrane Oxygenation (ECMO) is probably the last therapeutic link of the cardiorespiratory insufficiency of the neonate. Its use has evolved in the last years since the decade of 70's in which its applications were basically intractable forms of respiratory failure. At present it is considered an alternative to conventional treatments when these are no effective, or may negatively affect the baby prognosis.

ECMO has been the most used treatment of newborns since Dr. R.H. Bartlett in Michigan (USA) reported the first successful outcome of a neonate in 1975, see (2). This system is based on the use of a membrane oxygenator inserted in a complex circuit, consisting of roller pump, a blood heater and a blood reservoir, which switches off the movement of the roller pump when the circulating volume decreases. When operating as a venoarterial system, the circuit receives the blood through a venous cannula placed in the right atrium from the right internal jugular vein and, once it is oxygenated, injects the blood into the carotid arteria. When it works as venovenous system, oxygenated blood is reinjected to the right atrium without the need of cannulating the carotid artery.

This venovenous ECMO system can work with a single double cannula placed in the right internal jugular vein. The direction of flow is changed by a device that alternatively occludes the arterial and the venous limbs of the circuit and a nonocclusive pumps generates a tidal flow to the cannula. This system described by Chevalier and co-workers (see (8), (10), (7) and (6)) is called AREC (assistence respiratoire extra-corporelle) and avoids the complications derived from the arterial cannulation when it is not necessary for hemodynamic, and eliminates the problems of two cannula venovenous perfusion. The use of nonocclusive pumps also reduces the risk of rupture of the circuit and gas embolism. This venovenous tidal flow system works with lower dose of heparin reducing the risk of bleeding disorders.

A high distensible portion of the circuit located at the pump operates as a blood reservoir, and a double wall outside the circuit permits to circulate warm water in order to maintain the blood temperature. This system can be transformed to allow venoarterial support by simply removing the dispositive that alternatively clamps the limbs and cannulating the carotid, (14). This is the ECMO system actually used in the Neonatal Department of "Gregorio Marañón" Hospital in Madrid since October 1997.

ECMO is recommended only for the treatment of those pathologies that might be reversible in a reasonable period of time, usually no longer than two weeks. The possibility of a reversible pathology must be, at least, according to the recovery time, good oxygenation or surgical treatment. The most frequent pathologies to need ECMO are: persistent pulmonary hypertension syndrome of the newborn, respiratory distress syndrome, meconium aspiration syndrome, congenital diaphragmatic hernia, respiratory failure by alveolar leak syndrome, septic shock, and those situations where cardiac failures are frequent as, after a cardiac repair of congenital cardiac defects and a stabilization of hypoxemic crisis. Because of risks of bleeding disorders and the need of sufficient blood flow, selection criteria for ECMO also include a gestational age greater than 34 weeks, a birth weight greater than 2000 grams, absence of intracranial hemorrhage and intractable coagulation disorders.

During ECMO some complications for the patient may arise like, thrombocytopenia and bleeding problems as intracranial and gastrointestinal hemorrhage, bleeding of the cannula side, cardiac malfunction, generalized edema, renal failure and need for ultrafiltration or dialysis, systemic arterial hypertension, glucose or electrolyte disfunction, hemolysis, cardiac arrhythmia, damages in the central nervous system and convulsions, cerebral edema, decrease of venous return, hypovolemia and hypervolemia, and mechanical problems: cannula problems, oxygenator failure, tubing rupture, pump failure, heat exchanger malfunction, or even air in circuit. The risk of infection during ECMO (it does not include existent infections at the entrance of ECMO) is difficult to estimate due to the limited published data. It is always necessary to take into account that during ECMO the inflammatory cascade is activated by the foreign surfaces of blood-contacting devices. There is a host-defense reaction organized around the neutrophil, the macrophage, and the immune system.

The withdrawal of the ECMO support is carried out by considering recovery of the pulmonary function and gasometric criteria. The need for a low extracorporeal flow support is signal to begin the weaning of ECMO.

The aim of the application of this medical treatment, is the survival of the highest number of newborns, providing them an acceptable level of quality of life with the lowest cost. To achieve such global objective, we are constructing a decision support system (DSS) which integrates beliefs and preferences, represented in an influence diagram (ID), (9), (19) and (21), to aid doctors in decision making about the use of ECMO. The methodology is based on Decision Analysis (DA), see e.g., (13), and integrates several uncertain factors and decisions to control the application of ECMO and thus, to determine the expected utilities of the different medical treatments.

An ID is a tool used to represent and solve complex inference and DA problems. Under the classical Bayesian approach, decision makers (DM) must provide precise judgments (preferences and beliefs) for its nodes. However, the robust Bayesian approach, see e.g., (3), has shown the difficulties of such precise elicitations, considering the advantages of a more flexible point of view, as the robust one that we adopt in this system.

This paper provides the methodological description of the DSS based on an ID with a multi-attribute analysis. The paper includes five more sections. In Section 2, we consider the generation of objectives and attributes for the problem, constructing an objectives hierarchy to allow the disaggregation of this complex problem into components. In Section 3, we introduce the relevant variables which influence the objectives and their relations. Section 4 provides the doctors' beliefs and preferences modelling under partial information. Section 5 describes the evaluation of the imprecise influence diagram, considering different rules to take advantage of the solution process. Finally some conclusions are given.

2. GENERATION OF OBJECTIVES AND ATTRIBUTES

Each strategy of treatment must specify objectives and attributes, i.e., measures of effectiveness, to measure the degree of achievement of the objectives by each treatment. The distinct aspect of the DA approach is the degree of formality with which this specification is conducted.

We begin identifying the global objective which, as we indicated, in our case is the achievement of survival of the highest number of neonates with an acceptable level of quality of life and minimum cost. From this global objective, other subobjectives stem which can be grouped in "tangible effects" and "intangible effects". In the first case we have several subobjectives like costs of equipments and treatment, number of days in the intensive care unit,... but we note that, to avoid redundancies and to have a simpler multi-attribute model, all these might be included and condensed in only one objective named "minimize cost of stay at hospital". We also incorporated in this group the subobjective "maximize the number of survivals". For intangible effects, we included the subobjective "minimize the number of sequels". We took care to assure that all facets of the higher objective were accounted for in the subobjectives. Furthermore, tests of *importance* were repeatedly considered before any objective was included in the hierarchy, and doctors were asked if they felt the best course of action could be altered if that objective was excluded. Thus, with the aid of the doctors, we constructed an objectives hierarchy (15), see Figure 1.

Next, taking into account the desirable properties of a set of attributes, we identified an attribute for each one of the lowest-level objectives. For the objective "minimize cost of stay at hospital", we considered the natural-proxy attri-

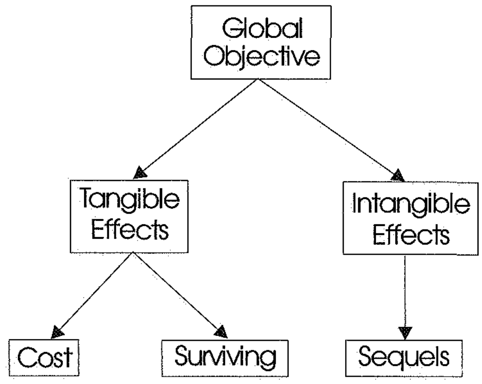

Figure 1. Objectives hierarchy for the ECMO problem

bute thousands of pesetas. At first, this measurable attribute can be thought of as easy. However, it does not result so easy because we should consider four kinds of costs (20), which depend also on several more variables: (1) ECMO program development cost: ECMO equipment, coordinator's salary, specialists' salaries during training, consultants' fees: bioengineer and perfusion, laboratory training, office and storage space; (2) ECMO program operating cost: coordinator's salary, specialists' salaries, consulting salaries, office, maintenance and replacement of equipment, retraining, supplies: medical/surgical and office; (3) potential indirect costs of ECMO: effects on critical resources such as nursing and on the intensive care unit since two bed spaces may be needed for one ECMO patient thus consuming considerable resources; and (4) ECMO program follow-up cost. In our case, we have considered mean costs per day and we have discretized the range to have a discrete attribute.

However, for the objective "sequels" (mainly of neurological kind, see (17) and (22), it was much harder to determine an attribute and we had to construct one specially for this objective, thus considering a constructed scale developed *ad hoc,* where each value represents a degree of the neurologic problem. However, it is not yet very clear the causes of the sequels that a neonate exhibits after the application of ECMO. Doctors do not know if they are due to the treatment or to the initial pathology. For that reason and because only data about surviving neonates with and without sequels are known, without considering the kind of sequel and its degree, both objectives (survivings and sequels) have been jointly considered as a unique one, discerning only between survivors with or without sequels, being necessary to drop the *ad hoc* first scale constructed.

For all the cases, we passed the *clairvoyance test,* (16), trying to avoid ambiguous scales and to balance the effort spent to develop the scale against the ease of assessing alternatives and communicating the results of the analysis.

3. DEFINITION OF VARIABLES

In this section we provide the variables which influence the objectives as well as their relationships. To conduct this phase of the modelling process, it was necessary several working periods with the doctors, to adaptively model the real problem. The medical decision is to decide whether to apply or not ECMO to the neonate. This decision depends on a previous test (Test), which is applied to the neonate to know if he is suitable for the treatment and depends on three variables: viability (Viab.), weight (Weight) and gestational age (Gest. Age), as well as the oxygenation index (OI). This four variables are binary taking the values 0 and 1. For variable viability, the value 0 means no feasible (irreversible pathology) and 1 otherwise. Variable weight takes the value 0 when the neonate has a weight under 2000 grams and 1 otherwise. Gestational age takes the value 0 when the neonate is less than 34 weeks old and 1 otherwise. OI takes the value 0 when it is less than 40 in 3 out of 5 blood samples taken between intervals of at least 30 minutes but at most 60 minutes and 1 otherwise.

The OI has influence on the survival (Surviving) which, as we pointed out, can take three values: death, surviving without sequels and surviving with sequels, and is also influenced both by the application or not of ECMO and the kind of pathology. The latter can be: meconium aspiration syndrome (MAS), congenital diaphragmatic hernia (CDH), sepsis (Sepsis), respiratory distress syndrome (RDS), pulmonary hypertension of ideopatic kind (PH), cardiac patients that demand extracorporeal cirugy (CEC) and other pathologies (OP). All the variables which represent pathologies are binary, taking the values 0 or 1, depending on the pathology being exhibited or not by the neonate. Variable surviving depends also on the seriousness of the raised mechanical problems like oxygenator failure (OF), tubing rupture (TR), cannula problem (CP), pump failure (PF), heat exchanger malfunction (HEM), air intake (AI), blood coagulation (BC) and other mechanical complications (OMC). The variables which represent also these problems are binary too, because the mechanical problems may appear or not. Depending on the occurred mechanical problems thus will be the seriousness, which we have considered that may be of three kinds: light, moderate and very serious. This variable is represented by the node seriousness of the mechanical problem (MP Ser.). Finally, since our main aim is the survival of the neonate with the small number of sequels and minimum cost, the value node will depend on the nodes: surviving and cost. Node cost is implicitly in node ECMO, because costs come from the application or not of ECMO. To represent these relations we use an influence diagram, see Figure 2.

Once we have constructed the diagram, we must consider the problem of filling it with the possible actions at the decision node, the probability distributions for the uncertain nodes and an appropriate utility function for the value node, which will be considered in the next section.

4. BELIEFS AND PREFERENCES MODELLING

This section outlines the elicitation of doctors' beliefs and preferences. The beliefs have been represented by me-

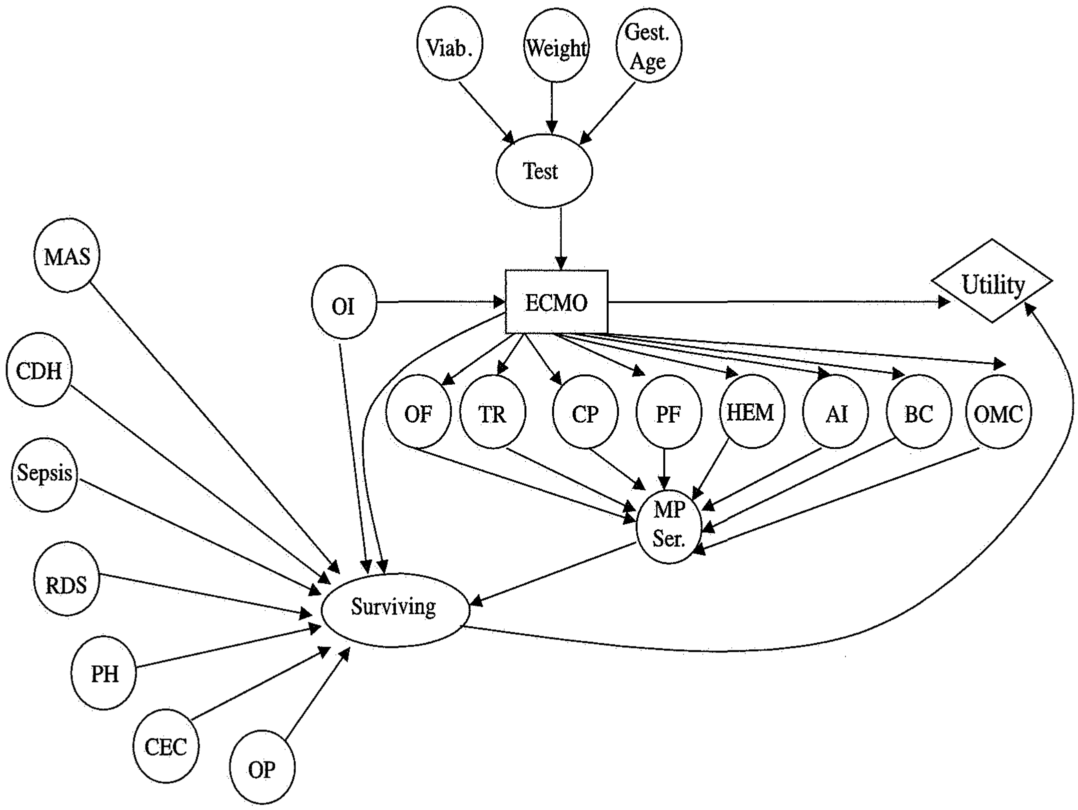

Figure 2. The influence diagram for our problem.

ans of discrete probability distributions. These have been provided directly by the doctors with the support of data which appear in (1) and (11), from questions of the type:

— What is the probability that a neonate presents meconium aspiration syndrome?

— What is the probability that a neonate has a weight under 2000 grams?

— ...

We allowed doctors to provide answers to these questions with intervals rather than point-valued probabilities because in such case the reality is more faithfully represented since there were some differences, in some cases, between both data sources and also several years should be considered jointly. Based on that information, we considered unnecessary any other elicitation method for probabilities, see (9). We asked the doctors also to provide the precise value on each interval, that considered as the best approximation to what happens at the "Gregorio Marañón" Hospital.

Preferences have been represented by means of utilities and obtained from doctors' elicitations through questions like:

— What is the utility that a neonate survives without sequels after applying ECMO?

— What is the utility that a neonate survives with sequels without applying ECMO?

— ...

Due to the difficulty to answer such questions, we also allowed doctors to provide intervals instead of unique values to facilitate the elicitation process, being less demanding. In this case, we took the midpoint of each interval to obtain an initial ranking.

Thus, in the spirit of the robust Bayesian approach, we used probability intervals, (4) and (12), and utility intervals, (4), rather than unique values. However, precise values have been also provided by the doctors of the Neonatology Service to be utilised in a first stage of the research. The remaining information will be used when we study the robustness via sensitivity analysis. We shall see, in next section, how to conduct the evaluation of an ID when only some constraints on the probabilities and utilities have been obtained, see (5).

5. EVALUATION PROCESS OF IMPRECISE INFLUENCE DIAGRAMS

The foundations for this framework are those of (18), who suggests a model for imprecise beliefs and preferences via a class of probability distributions and a class of utility functions. Beliefs are updated by applying Bayes' formula to each member in the probability class. A parametric model associates with each alternative a_j an evaluation function $\psi_j(w)$, typically the expected utility, which depends on parameters $w \in S$ modeling imprecision in the DM's beliefs and preferences: an alternative a_j is at most as preferred as an alternative a_k if and only if $\psi_j(w) \leq \psi_k(w)$, $\forall w \in S$. Consequently, we must look for nondominated alternatives, which will be optimal in a Pareto sense.

Suppose we have built a structural ID but we are only able to collect information on the necessary assessments at chance and value nodes, expressed in parametric form, thus having an ID under partial information (IDPI), see (5). So, we consider IDs in which we have assigned a class of probability distributions to chance nodes and a class of utility functions to the value node.

Our target is to obtain the set of nondominated alternatives with respect to a class of expected utilities. This can be done in an IDPI by applying similar operations to those used when solving a conventional ID, like Shachter's, (19). Following (4), the conditional expectations for chance node removals have to be parametrically taken and probability assessments are changed for arc reversals by applying Bayes' formula parametrically. To remove a decision node, we register the set of nondominated alternatives by solving a sequence of optimization problems. It will often be non unique and their elements non equivalents.

The above operations can be combined in a similar fashion to those used in the evaluation of precise IDs, having then the algorithm for the evaluation of IDPI. In (4) it is shown all these ideas and how the evaluation algorithm for IDPI leads to obtain all the nondominated strategies of the associated decision problem.

Also, (4) provides some rules for the efficient computation of nondominated alternatives when reducing a decision node, estimations of the potential loss in expected utility, and an evaluation of the ranks of the expected utilities as long as the algorithm progresses. Furthermore, it introduces some additional criteria to limit the size of the nondominated sets since they may grow tremendously as we proceed backwards in the computation. Several criteria from decision making under uncertainty can be adapted to this context: maximin, maximax, Laplace, potentially optimal,... But we must take care of how to compute the nondominated strategies that verify the criterion chosen by the DM, since for various criteria we cannot do it through similar algorithms to that for evaluating IDPIs, i.e., computing at each decision node the actions which satisfy the criterion and selecting the nondominated ones among these at the end of the process.

6. CONCLUSIONS

The decision of whether to apply or not ECMO to a neonate is a difficult medical decision making problem. Doctors demanded a DSS to aid them to find the most appropriate decision for each patient. This paper presents the decision making tools used to develop such system. It is based on an influence diagram to represent doctors' preferences and beliefs and the dependencies among the relevant variables. We adopt a robust Bayesian point of view by eliciting and representing beliefs and preferences through intervals instead of unique numbers. The system developed will be used by the Neonatology Service of the "Gregorio Marañón" Hospital.

ACKNOWLEDGMENTS

This paper has been supported by DGESIC project PB97-0856 and CAM project 07/0009/1997.

REFERENCES

1. Avroy, A.F. & Martin, R. J. (eds.) (1997) Neonatal-Perinatal medicine. Diseases of the fetus and infant, 6th edition, Mosby.

2. Bartlett, R.H., Gazzaniga A.B., Jefferies R., *et al.* (1976) Extracorporeal membrane oxygenation (ECMO) cardiopulmonary support in infancy, *ASAIO Trans.* **22,** 80-88.

3. Berger, J.O. (1994) An overview of robust Bayesian analysis, *Test* **3,** 5-125 (with discussion).

4. Bielza, C. (1996) Contribuciones al análisis de problemas supercomplejos de toma de decisiones, *PhD. dissertation*, School of Computer Science, Madrid Technical University.

5. Bielza, C., Ríos Insua, D. & Ríos-Insua, S. (1996) Influence diagrams under partial information, in *Bayesian Statistics 5.*, J.M. Bernardo, J.O. Berger, A.P. Dawid and A.F.M. Smith (eds.), Oxford University Press, 491-498.

6. Chevalier, J.Y. (1993) Extracorporeal respiratory assistance for pediatric acute respiratory failure, *Crit. Care Med.* **21,** S382-383.

7. Chevalier, J.Y., Couprie, C., Larroquet, M., Renolleau, S., Durandy. Y. & Costil, J. (1993) Venovenous single lumen cannula extracorporeal lung support in neonates. A five year experience, *Asaio J.* **39,** M654-658.

8. Chevalier, J.Y., Durandy, Y., Batisse, A., Mathe J.C. & Costil J. (1990) Preliminary report: extracorporeal lung support for neonatal acute respiratory failure, *Lancet* **335,** 1364-1366.

9. Clemen, R.T. (1996) *Making Hard Decisions: An Introduction to Decision Analysis,* Duxbury, 2nd edition.

10. Durandy, Y., Chevalier, J.Y. & Lecompte, Y. (1990) Single-cannula venovenous bypass for respiratory membrane lung support, *J. Thorac. Cardiovasc. Surg.* **99,** 404-409.

11. ELSO, http://www.elso.med.umich.edu/

12. Fertig, K.W. & Breese, J.S. (1993) probability intervals over IDs, *IEEE Trans. on Pattern Analysis and Machine Intelligence* **15,** 3, 280-286.

13. French, S. (1986) *Decision Theory: An Introduction to the Mathematics of Rationality,* Ellis Horwood.

14. Germain, J.F., Casadevall, I., Desplanques, L., Mercier, J.C., Hartmen, J.F. & Beaufils, F. (1994) Doppler echocardiographic assessment of pulmonary circulation in severe respiratory failure of the neonate: an aid for extracorporeal lung support indications, *J. Pediatr. Surg.* **29,** 873-877.

15. Keeney, R.L. & Raiffa, H. (1976) *Decision with Multiple Objectives: Preferences and Value Tradeoffs,* Wiley.

16. Kirkwood, C.W. (1997) *Strategic Decision Making,* Duxbury Press.

17. Luisiri, A., Graviss, E.R., Weber, T., Silberstein, M.J., Tantana, S., Connors, R. & Brodeur, A.E. (1988) Neuro-sonographic changes in newborns treated with extracorporeal membrane oxygenation, *J. Ultrasound Med.* **7,** 429-438.

18. Ríos Insua, D. (1990) *Sensitivity Analysis in Multiobjective Decision Making,* LNEMS 347, Springer, Berlin.

19. Shachter, R.D. (1986) Evaluating influence diagrams, *Operations Research* **34,** 871-882.

20. Short, B.L. & Pearson, G. D. (1993) The economics of ECMO therapy, in *Extracorporeal Life Support,* R.M. Arensman and J.D. Cornish (eds.), Blackwell Scientific Publications, 331-336.

21. Smith, J.Q. (1989) Influence diagrams for Bayesian decision analysis, *European Journal of Operational Research,* **40,** 363-376.

22. Taylor, G.A., Class, P., Fitz, C.R. & Miller, M.K. (1987) Neurologic status in infants treated with extracorporeal membrane oxygenation: correlation of imaging findings with developmental outcome, *Radiology,* **165,** 155-161.