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Predicting patient survival after liver transplantation using evolutionary multi-objective artificial neural networks

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ABSTRACT

Objective: The optimal allocation of organs in liver transplantation is a problem that can be resolved using machine-learning techniques. Classical methods of allocation included the assignment of an organ to the first patient on the waiting list without taking into account the characteristics of the donor and/or recipient. In this study, characteristics of the donor, recipient and transplant organ were used to determine graft survival. We utilised a dataset of liver transplants collected by eleven Spanish hospitals that provides data on the survival of patients three months after their operations.
Methods and material: To address the problem of organ allocation, the memetic Pareto evolutionary non-dominated sorting genetic algorithm 2 (MPENSGA2 algorithm), a multi-objective evolutionary algorithm, was used to train radial basis function neural networks, where accuracy was the measure used to evaluate model performance, along with the minimum sensitivity measurement. The neural network models obtained from the Pareto fronts were used to develop a rule-based system. This system will help medical experts allocate organs.
Results: The models obtained with the MPENSGA2 algorithm generally yielded competitive results for all performance metrics considered in this work, namely the correct classification rate (*C*), minimum sensitivity (*MS*), area under the receiver operating characteristic curve (*AUC*), root mean squared error (*RMSE*) and Cohen's kappa (*Kappa*). In general, the multi-objective evolutionary algorithm demonstrated a better performance than the mono-objective algorithm, especially with regard to the *MS* extreme of the Pareto front, which yielded the best values of *MS* (48.98) and *AUC* (0.5659).

The rule-based system efficiently complements the current allocation system (model for end-stage liver disease, MELD) based on the principles of efficiency and equity. This complementary effect occurred in 55% of the cases used in the simulation. The proposed rule-based system minimises the prediction probability error produced by two sets of models (one of them formed by models guided by one of the objectives (entropy) and the other composed of models guided by the other objective (*MS*)), such that it maximises the probability of success in liver transplants, with success based on graft survival three months post-transplant.
Conclusion: The proposed rule-based system is objective, because it does not involve medical experts (the expert's decision may be biased by several factors, such as his/her state of mind or familiarity with the patient). This system is a useful tool that aids medical experts in the allocation of organs; however, the final allocation decision must be made by an expert.

1. Introduction

Liver transplantation is an accepted treatment for patients with end-stage chronic liver disease, but it is strongly limited due to the limited availability of suitable liver donors. The imbalance between supply and demand unfortunately results in many waiting-list deaths. Several efforts have been made to expand the donor pool and to better prioritise recipients on waiting lists. Some examples of these efforts are the use of extended criteria donors (donors with extreme values of age, days in the intensive care unit (ICU), inotrope usage, body mass index (BMI) and cold ischemia time) and the adoption of the model for end-stage liver disease (MELD) score [1].

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In recent years, more relaxed criteria have been used for donors, with an accompanying increased risk of recipient and/or graft losses compared with the risk associated with the use of livers from non-extended criteria donors [2]. These risks should be carefully analysed because the combination of several of these marginal factors can result in graft loss [3]. Based on this point of view, Child [4] proposed the Child–Turcotte–Pugh (CTP) score for assessing the severity of a patient's liver disease. Feng [5] proposed a donor risk index (DRI), with the aim of establishing the quantitative risk associated with various combinations of donor characteristics. The MELD score model, which is based on the sickest-first principle, is the cornerstone of the current allocation policy and has been widely validated [6]. Nevertheless, these methods do not predict mortality after transplantation well. Rana et al. [7] devised a scoring system (SOFT) that predicts recipient survival three months following liver transplantation, which can complement the MELD-predicted waiting-list mortality rates. These methods only consider either the characteristics of the donors or the characteristics of the recipients and do not jointly consider the characteristics of the donor, recipient and transplant organ.

Statistics show that donor–recipient pairs (D–R pairs) after three months can be considered a classification problem of a non-balanced system with two possible solutions: the *survival class*, which is the most frequent class (approximately 90% of patterns), and the *non-survival class*, which is an infrequent class. In classifications with two classes, one of the most commonly used methods in biomedicine is logistic regression. Systems based on logistic regression can adequately classify the majority class (favourable events), but their predictive ability for the minor class (adverse events) is poor [8]. The CTP, DRI, MELD score and SOFT score are all based on logistic regression analysis, where we consider the linearity between the characteristics of the D–R pairs and the odds ratio of the survival probability after three months. Donor and graft acceptance (considering organ shortage and pool expansion), prioritisation of candidates (based on waiting-list mortality), and the allocation policy (combining the principles of equity, efficiency and fairness) depict a complex scenario that is not easily modelled. A large number of variables can be considered in a given clinical decision regarding donor and organ acceptance, allocation and donor–recipient matching. The risk of subjectivity and the likelihood of making an erroneous decision cannot be underestimated. Artificial intelligence tools for the decision-making process in liver transplantation can be useful despite their inherent complexity.

These logistic regression models have been developed to estimate the risk of death by considering the underlying disease and the urgency of a transplant for a recipient patient, assuming that all donor livers carry the same risk of failure. However, this does not always hold; specifically, it has been shown in recent years that the risk of graft failure and even patient death after transplantation differ among recipients. While some patients may "tolerate" and overcome the initially poor functioning of a compromised donor organ (for example, one received from an extended criteria donor), others may not. Increasing awareness of the diversity in donor organ quality has stimulated the debate regarding the matching of specific recipient and donor factors to avoid not only futility but also personal and institutional differences in organ acceptance. The insufficient supply of deceased-donor livers for transplantation has motivated the expansion of acceptance criteria; the additional organs that are available due to the extension of these criteria are known as "marginal" and "expanded criteria" livers. This policy of aggressive liver utilisation has motivated the derivation of a donor risk index that is a quantitative, objective, and continuous metric of liver quality based on factors that are known or knowable at the time of an organ offer.

The aim of this study was to develop a liver allocation system based on donor and recipient matching. There are numerous motivations for developing this system: (1) current selection/allocation systems are based on the risk of waiting-list patient death and do not recognise distinctions in donor organ quality; (2) efforts to increase the number of organ donations are likely to result in a relatively high proportion of extended criteria donors; (3) matching donors and recipients may offer the prospect of predicting outcomes at the time when a specific donor liver is allocated to a specific recipient; (4) differences in local acceptance rates and policies may be diminished; and (5) overall outcome and efficacy may improve.

This liver allocation system was developed using artificial intelligence methods that offer significant advantages over conventional statistical techniques that are limited by several hypotheses associated with the distributions of predictor variables and the relationships that may exist between them. In this study, we used artificial neural network models (ANNs) trained by a multi-objective evolutionary algorithm (MOEA) [9]. The use of ANNs in biomedicine as an alternative to other classification methods has been very common in the last two decades. As a result, ANNs have been used to detect tumours in the small bowel [10], to predict graft survival for heart-lung and thoracic transplantation patients [11,12] and to diagnose cytomegalovirus disease [13]. With the ANN models obtained from the Pareto fronts built by the MOEA, a rule-based system was developed to help medical experts make decisions about liver transplants. This system determines the best match between different D–R pairs, with the aim of maintaining graft survival for three months after the transplant.

The goal of this study was to develop a rule-based system for allocating donors to recipients, using all the ANN models extracted from the extremes of the Pareto fronts obtained by the memetic Pareto evolutionary non-dominated sorting genetic algorithm 2 (MPENSGA2). In this MOEA, a local optimisation process is used to improve the prediction of individuals in the population during the evolutionary process.

The paper is organised as follows: Section 2 presents a brief description of the materials used, Section 3 describes the MPENSGA2 method, Section 4 describes the experimental design and presents the results obtained, and the conclusions and future research are outlined in Section 5.

2. Materials

2.1. Evolutionary artificial neural networks

ANNs [14] have been an object of renewed interest among researchers in statistics and computer science owing to the significant results obtained in a wide range of classification and pattern recognition problems. The research in neural classification has established that neural networks are a promising alternative to various conventional classification methods [15].

Evolutionary computation (EC) is a subfield of artificial intelligence that involves combinatorial optimisation problems. EC uses iterative progress, such as growth or development in a population. This population is then selected in a guided random search until the desired end is achieved. Such processes are often inspired by evolutionary biological mechanisms. In the EC, there are two main operators that form the basis of evolutionary systems: recombination (the generation of a new individual from parents) and mutation (the modification of an individual in the population).

EC has been widely used in recent years to evolve neural network architectures and weights. These evolutionary artificial neural networks (EANNs) have many applications [16,17]. EANNs provide a more successful method for optimising network performance and architecture simultaneously. A major advantage of the evolutionary approach over traditional learning algorithms such as the back-propagation algorithm (BP) is the ability to escape a