DEEP LEARNING BASED DECEASED-DONOR KIDNEY ALLOCATION MODEL FOR INDIA

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ABSTRACT

Deep learning, also known as deep structured learning and deep machine learning (DML), is a subfield of machine learning. It consists of complex algorithms called artificial neural networks (ANN) and deep neural networks (DNN) that form an architecture consisting of hierarchically connected multiple processing levels similar to structure and function of human brain.

There is a huge shortage of organs for transplant. If we consider subjects on the waiting list for kidney transplantation, they remain a huge risk of mortality from chronic kidney disease while on dialysis. The longer the wait, the greater is the risk of death. Kidneys from deceased donors are allocated to kidney failure patients on the waiting list on the basis of a number of criteria, like blood group, tissue matching, age, time on dialysis, urgency, and survival benefit. The criteria used for allocation may be different for different countries.

The organ allocation system needs to be precise and highly efficient- and the best model can be an artificial intelligence model. Computer-based organ allocation models exist in Europe and United States of America. These models are based on scientific principles and government policies and exemplify an effort to make organs available to the neediest, and with best tissue matching. The distance the organ needs to be transported is also taken into account when allocating an organ, as lesser the delay in transplanting such organ, lesser is the cold ischemia time and chances of delayed graft function.

We aim to develop a deep-learning based artificial intelligence (AI) model built on deep neural network hierarchical architecture. Besides helping in the allocation of kidneys, the deep learning based AI will give HLA matching details and HLA matching score that will help clinicians decide immunosuppression protocol and will give an insight regarding the success of transplantation. Better HLA match improves the chances of a successful kidney transplantation.

The deep learning model will use the database on blood group, PRA (panel reactive antibodies), age, anti-HLA antibodies, and other important variables. The database used to train and test the model is based on statistical data collected from OPTN (Organ Procurement and Transplantation Network), USA and Wikipedia. We have made the model based on the guidelines for organ transplantation from NOTTO (National Organ and Tissue Transplant Organization, India), as the model aims to help allocation of a kidney from deceased donors in India.

We expect to develop a highly efficient allocation tool based on AI that can also give details of HLA match that is vital for the clinical management of transplanted organ.

Keywords: Deep Learning, Kidney Transplant, Transplantation, Artificial Neural Networks, Deep Neural Networks.

1. INTRODUCTION

Though the concept of artificial intelligence- machines that could think and act like humans do- was actively being discussed and presented in the scientific community earlier, the term 'Artificial Intelligence' was first coined by John McCarthy in 1956 (Smith et al., 2006). The artificial intelligence concept has continuously intrigued scientific minds since then. Machines have evolved inefficiency, and so has artificial intelligence, and the applications have permeated literally every field- from space travel to human healthcare. Today we are keenly watching the success of robotic surgeries, teleradiology, telemedicine, and application of artificial intelligence in clinical decision making. Deep learning per se has found its use in many fields like big data analytics (Najafabadi et al., 2015), speech recognition, understanding language, computer vision (Luckow et al, 2016), intelligent video surveillance (Sun, Shao and He, 2017) and histopathology (Zhang et al., 2017). Application of deep learning in healthcare is rapidly gaining grounds.

We have made an effort to build a deep learning model that helps in kidney allocation from deceased donors to chronic kidney disease patients on waiting list. This is a benchmark kidney allocation model for deceased donor renal transplant using deep learning methodology. The model builds a priority list and allocates the kidneys to patients on a waiting list based on a number of criteria. Multiple layers of decision making are involved, and on some occasions, a few variables are suppressed from making an effect on the final decision of allocation guidance provided by our model, something that is a key feature of many artificial intelligence algorithms. For example, if there is HLA- DR match (HLA: Human Leucocyte Antigen), the other HLA variables match is inhibited from making an effect on kidney allocation guidance provided by the model, as HLA DR match is of paramount importance when compared with other HLA antigen matches (Brennan, 2017).

2. LITERATURE REVIEW

2.1 Significance of HLA matching in Renal Transplant

The human leukocyte antigen (HLA) system is a gene complex encoding the major histocompatibility complex (MHC) proteins in humans. These cell-surface proteins are responsible for the regulation of the immune system in humans.

HLA System: The genes comprising the HLA system are encoded on the short arm of chromosome 6. More than 250 genes are present in this highly gene-dense HLA system. Each locus in this gene architecture has two alleles of HLA types (Choo, 2007; Fuggle et al, 2014). The haplotypes from parents are co-dominantly inherited in Mandelian fashion (Choo SY, 2007). The HLA system is classified into two classes, HLA class I and HLA class II (Choo, 2007; Fuggle et al, 2014).

HLA class I consists of antigens like HLA-A, HLA-B, HLA-C, HLA- E, HLA-F and HLA-G. These antigens are found in nearly all nucleated cells (Choo, 2007; Fuggle et al, 2014). HLA- E, HLA-F, HLA-G serve as ligands for receptors of Natural Killer (NK) cells, and have been shown to be important in defence from viruses. These loci may be important in bone marrow transplantation where NK cells are involved in rejection. Their relevance in solid-organ transplantation (like kidney, liver, lung and heart transplantation) has not been established yet (Fuggle et al, 2014).

HLA class II consists of antigens such as HLA-DR, HLA-DQ, and HLA-DP. They are expressed on Antigen presenting cells (monocytes, macrophages, and dendritic cells), B lymphocytes, and activated T lymphocytes (Choo, 2007; Fuggle et al, 2014) HLA class II antigens are recognized by CD4+ T lymphocytes (Fuggle et al, 2014).

Significance of HLA Matching: HLA match that has important consequences on the survival of patient and/or the graft (transplanted organ) (Zhou et al, 1993; Tang et al, 2007; Choo, 2007; Contreras et al, 2010; Tinckam, 2012; Cecka, 2016; Takemoto et al, 2017).

High HLA match is associated with better graft survival and is the most important modifiable risk factors in kidney transplantation (Zhou et al, 1993; Tang et al, 2007; Contreras et al, 2010; Cecka, 2016; Takemoto et al, 2017). HLA matching can decrease the risk of renal (kidney) graft loss by about 40%. Even a single HLA mismatch may result in the poorer outcome (Zhou et al, 1993). However, the effect of HLA DR match was found to be higher than HLA A and B match on graft survival (Zhou et al, 1993; Takemoto et al, 2017).

HLA matching is not only important in kidney transplantation, but in other areas as well like hemopoietic stem cell transplantation, and computer models have been developed to help in allocation in this area as well (Bochtler, 2016). Computer-based models based on HLA analysis have been used in other areas as well like to study adverse drug reactions (Luo H et al, 2015).

Anti-HLA antibodies: A person may develop antibodies against foreign HLA antigen due to blood transfusion, pregnancy or previous organ transplantation (Choo, 2007; Fuggle et al, 2014). These HLA antibodies are very important when considering organ transplantation. If a patient having anti-HLA antibodies against any of the HLA antigens of the donor, it may result in rapid, hyper-acute rejection of the transplanted organ.

2.2 Transplant From Deceased Donors

Even though patient and graft survival is lesser in a transplant from deceased donors as compared with live-donor transplantation, transplantation from deceased donors is encouraged as there is a shortage of organs from living donors (Nemati et al, 2014).

Many transplant centres enlist in deceased donor programs. Kidneys are allocated to recipients according to age, blood group, HLA matching, anti-HLA antibodies (donor-specific antibodies), urgency, and priority- the rules may vary from country to country.

Every effort is made to reduce the delay in transporting the organ to the recipient, as faster delivery reduces the cold ischemia time considerably, and reduces the chances of delayed graft function (Nguyen et al, 2013; BSHI and BTS, 2016).

Also, chronic kidney disease patients waiting for kidney transplantation are required to do Panel Reactive Antibody (PRA) test, which indicates how likely is the recipient to get a suitable, crossmatch-compatible donor (Cecka, 2010).

Panel reactive antibodies (PRA): PRA has been an established measure of sensitization since the 1960s. In this method, HLA of a panel of donors that represent the local population is identified. Recipients are tested for HLA antibodies against HLA antigens from these panel of donors that represent the local population (Cecka, 2010). PRA is calculated based on the result and is reported as the percentage of these predefined antigens to which the recipient has

reactive antibodies (Cecka, 2010). The PRA indirectly gives an estimate of the percentage of the local population that is having those HLA antigens that the recipient has antibodies in his blood (Cecka, 2010; Nguyen et al, 2013). For example, if a recipient's PRA is 60%, it means he has HLA antibodies against 60% of the donors in the local population, and so these donors will not be crossmatched compatible (Cecka, 2010; Nguyen et al, 2013).

Highly sensitized patients (those with PRA greater than 80%) have to be on a long waiting list, as they are less likely to get a suitable crossmatch compatible donor. A study showed that in Australia, highly sensitized individuals might have to wait for twice as much time as those who are not sensitized, for a kidney from a deceased donor (Nguyen et al, 2013). Hence, those patients with high PRA score are placed on a higher priority on the transplant waiting list (this is done by giving points for PRA score that affects the ranking).

3. METHODOLOGY

Our methods use the variables like age, blood group, HLA (Human leucocyte antigen), PRA (panel reactive antibody), anti-HLA antibodies (unacceptable HLA antigens), time on dialysis, and other important factors to make a deep learning artificial intelligence model to allocate kidney from the deceased donor to the kidney failure patient on waiting list. The model actively updates the waiting list of kidney failure patients according to the waiting list and generates a priority list based on survival benefit and urgency to receive a kidney. NOTTO guidelines have been followed as the model is developed to help kidney allocation for patients in India (Notto, 2017).
The making of the AI model involves 3 stages.

- Stage 1: Building the model.
- Stage 2: Training the model.
- Stage 3: Testing the model.

We have built a model based on NOTTO guidelines (INDIA) (Notto, 2017).

3.1 Data Preparation

We have used the data from organ procurement and transplantation network (OPTN) in the USA (a very generous support from OPTN, http://optn.transplant.hrsa.gov) to train and test our model as an adequate database from India could not be procured to develop, train or test our model (Massie, 2014).

The statistical data available from OPTN website for New York State was used to generate a random data for 25,001 donors and 25,000 recipients. Also, for creating a random data for blood groups for 25,001 donors, reference was taken from Wikipedia for percentages of ABO blood group distribution in the USA, and calculations were done to create a random data (Wikipedia, 2017).

HLA antigens and unacceptable antigen details were taken from OPTN website, and a random data for donors and recipients was created using the information provided (OPTN, 2017).
Donor and recipient age data was taken from OPTN website. The data was used to create a random data of 25001 donors and 25000 recipients (OPTN, 2017).

The data on time on dialysis, previous immunological graft failure, within 3 months of transplantation, Vascular access: Failed all AV Fistula sites (Yes or No), Vascular access: Failed AV Graft after failed all AV Fistula sites, PRA, previous living donor transplantation

now in need of transplantation, near relative of previous deceased donor now requiring transplantation, is completely imaginary. This data was used for training and testing our model.

3.2 Model Building

The model uses multilayer perceptrons having an architecture of deep neural networks. Each variable is encoded in a single perceptron with a hidden node that can alter the strength or weight of the impact of the perceptron on decision making. There is an activation function node as well that fires only if it reaches a significant threshold- otherwise, the variable the perceptron represents has no effect on the final decision of organ allocation.

Perceptrons once developed, go through a training or learning process as exemplified in following figure 1(Veloso, 2001):

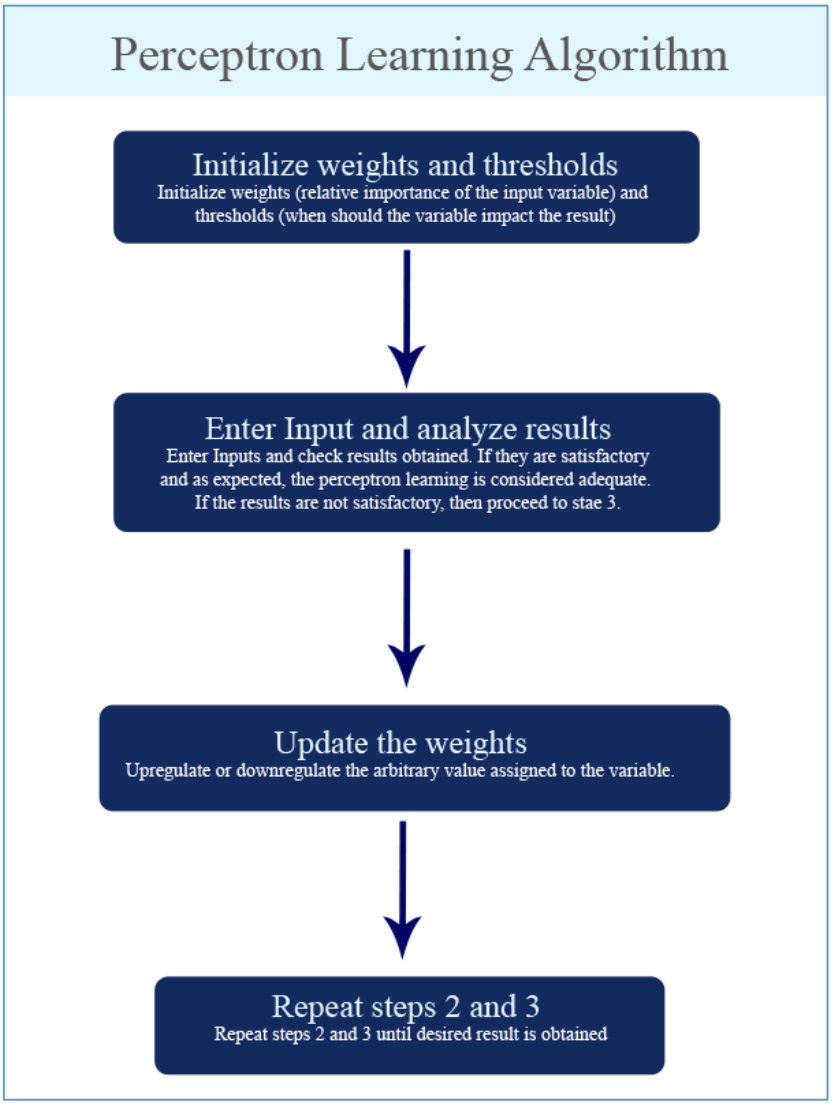

Figure 1 Perceptron Learning Algorithm

The model gives two sets of outputs for matching candidates (patients on the waiting list). The first set is according to NOTTO guidelines, where blood group and unacceptable HLA antigens are considered. The second set is based on HLA Matching, as HLA matching has a significant contribution towards the probability of success of kidney transplantation, as is the

most important modifiable risk factors in this area. HLA-DR match is given a priority, as it has more importance than other HLA antigens match, as shown in a number of studies (Zhou et al, 1993; Tang et al, 2007; Contreras et al, 2010; Cecka, 2016; Takemoto et al, 2017). In our model, if there is an HLA-DR match, perceptrons representing other HLA antigens are inhibited from making any major impact on the final outcome. This is done by inhibiting the activation function. If there is no HLA-DR match, then all the perceptrons related to HLA are allowed to make a full impact on the choice of allocating the kidneys, as shown in the second set of candidates as output.

There are three sequential steps used in this AI model for allocation:

Step 1: Make and maintain a priority list based on the guidelines from NOTTO, considering age, blood group, time on dialysis, previously failed transplantation, difficulty in getting a vascular access for dialysis, PRA, and other factors. A cumulative score is generated based on these criteria. Also, a record of unacceptable donors is made based on anti HLA antibodies. The list is classified into a priority list. Another list called urgent priority list is provided by government authorized special committees. Each of these two lists is further subdivided into ‘less than 18 years’ and ’18 years and more’ groups.

The classification into urgent cases is actually based on a committee’s decision as per the NOTTO’s guidelines and follows a proper evaluation of patient’s condition to decide whether transplantation need is urgent or not.

Step 2: Deceased donor’s age, blood group, and HLA are taken into consideration to develop criteria for acceptable recipients. Also, a kidney from younger age group deceased donors are allocated to younger age patient first. If a younger age patient is not available or is unable to accept the donor's kidney, then the kidneys are offered to an adult.

Step 3: The criteria for acceptable recipients is matched against the candidates on the priority list. One kidney goes to one ‘priority list’ patient and another to those on ‘urgent’ list. Figure 2 elaborates the flow of decision process

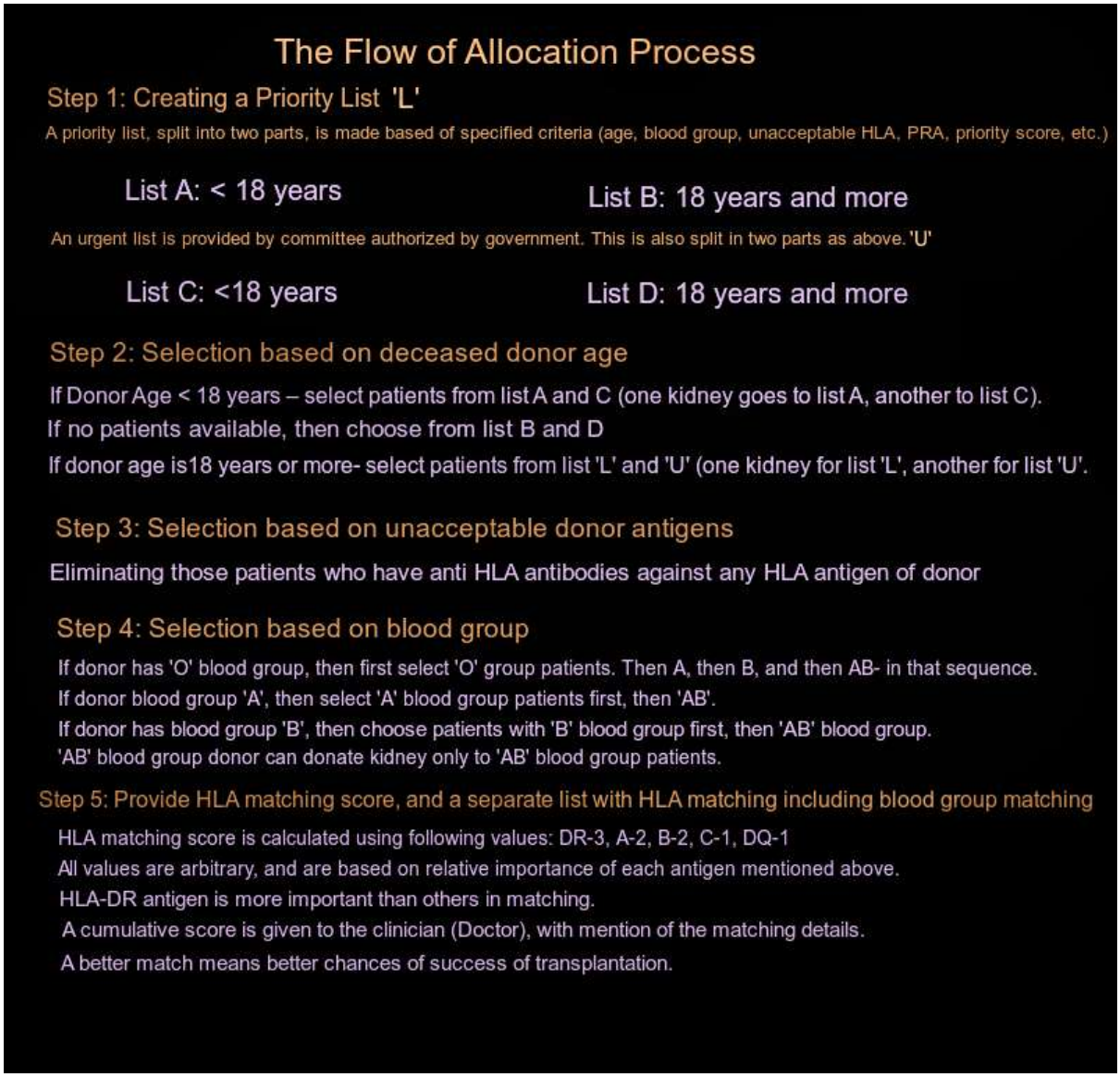

Figure 2 Allocation Process

3.3 Scoring System to Make Priority List

A cumulative score is calculated based on the details given below. Based on this cumulative score the priority list is created. The Greater score puts the patient higher on the priority list.

- 1 point for each month on dialysis (Notto, n.d).
- 3 points for each kidney transplant failure due to immunological rejection within 3 months of kidney transplantation (Notto, n.d).
- 3 points for patient's age less than 6 years, 2 points for age 6 to less than 12 years, and 1 point for age 12 years to less than 18 years (Notto, n.d).
- 2 points if all possible Arteriovenous fistula sites (vascular access for haemodialysis) and the patient is on temporary vascular access. 4 points are given if besides all AV fistula sites being failed, even AV graft has failed, and the patient is on temporary vascular access (Notto, n.d).
- PRA 20% and more, 0.5 points for every 10% increase (Notto, n.d).
- For previous living donor now in need of kidney transplant, 5 points are given (Notto, n.d).

- Near relative of a previous deceased donor who now needs a kidney transplant, 5 points are given (Notto, n.d).

4. DISCUSSION

The Python scripts used to build the model is uploaded to GitHub. The link is here. The model we developed successfully creates the priority list, subdivided into two- ('less than 18 years', and '18 years and more')- based on the scoring system using age, PRA score, previous transplant, failed AV fistula sites, and other parameters. It also allocates one kidney from the deceased donor to the above-mentioned priority list, and another kidney to the 'urgent list' we get from the committee formed by government authorities. The model successfully finds the right recipients based on blood group, age, unacceptable HLA antigens, and the priority score. The model can further be modified to allocate kidneys retrieved from government hospitals to patients in government hospitals first, and later to others, as defined in NOTTO guidelines (Notto, 2017).

The model can also give two sets of acceptable recipients, one based on blood group and unacceptable antigens as defined in NOTTO guidelines, and another set based on previously mentioned criteria, plus the HLA match.

While the program can successfully give results like priority score, priority list, allocating kidneys to patients on a priority list based on ABO blood group matching, and considering unacceptable HLA antigens, the model needs further development to incorporate higher features like allocating kidneys based on HLA match giving higher priority to those with HLA-DR match. Also, UI (user interface) to help medical professionals enter patient and deceased donor data is being developed. After the development is complete, the program will give a priority list based on HLA matching, with higher importance given to HLA-DR match (if HLA- DR match occurs, other antigens will make a lesser impact on kidney allocation).

5. IMPLICATIONS

This is a User Interface based benchmark model in which deep learning method is used for allocation. We believe that deep learning methodology can make a big impact on the quality of kidney allocation process in deceased donor kidney allocation program where medical professionals need to enter the few mandatory details of the donor through the user interface and the deep learning based tool will predict top 10 recipients based on blood group match, and another list of 10 recipients based on HLA and blood group match. These two lists will aid medical professionals to allocate the kidneys to the right individuals waiting for kidney transplantation.

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