Virtual Cross-Matching in Heart Transplantation
Large scale simulation of survival after heart transplantation using Artificial Neural Networks

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Associate Professor
Consultant Cardiothoracic Surgeon
The position

- Surgical Director, Lund Heart Transplant Program, Skane University Hospital, since 2013
- Investigator Director, Artificial Intelligence in Cardiothoracic Sciences, Lund University, since 2008
- Deputy Chairman, Swedish Cardiothoracic Registry since 2011
- Delegate, Scandiatransplant Council of Representatives since 2010
LUND UNIVERSITY
- One of Europe’s leading universities
- Education and research within; engineering, science, law, social sciences, economics and management, medicine, humanities, theology, fine art, music and theatre
- 47 000 students and 6 300 staff from all over the world
- 680 partner universities in more than 50 countries

SKÅNE UNIVERSITY HOSPITAL
- Third largest of Sweden’s seven university hospitals
- 12 500 employees
- The department of Cardiothoracic Surgery
  - 1 400 open heart surgery cases
  - 55 thoracic transplantations
- It is one of the two hospital which are allowed to perform heart and lung transplantation in Sweden. The other hospital is Sahlgrenska in Gothenburg.
History of thoracic organ transplantation

- James Hardy 1964, first lung transplant. 18 days.
- Christiaan Barnard 1967, first heart transplant. 18 days.
- Norman Shumway 1968, first heart transplant in USA.
- Jan-Otto Solem 1988, first heart transplant in Lund. 15 years.
Adult and Pediatric Heart Transplants
Number of Transplants by Year and Location

NOTE: This figure includes only the heart transplants that are reported to the ISHLT Transplant Registry. As such, the presented data may not mirror the changes in the number of heart transplants performed worldwide.
### GLOBAL ACTIVITY IN ORGAN TRANSPLANTATION 2011 ESTIMATES

<table>
<thead>
<tr>
<th></th>
<th>Kidney Transplants</th>
<th>Liver Transplants</th>
<th>Heart Transplants</th>
<th>Lung Transplants</th>
<th>Pancreas Transplants</th>
<th>Small Bowel Transplants</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>76118</td>
<td>23721</td>
<td>5741</td>
<td>4278</td>
<td>2564</td>
<td>209</td>
</tr>
</tbody>
</table>

### 112631 SOLID ORGANS REPORTED TO BE TRANSPLANTED

- Information of 103 Member States on organ transplantation activities is included in the GODT: 94 from 2011, 4 from 2010, 2 from 2009 and 3 from 2008.
Adult and Pediatric Heart Transplants
Kaplan-Meier Survival
(Transplants: January 1982 – June 2011)

- Median survival = 11 years
- Median survival conditional on surviving 1st year = 13 years

N = 103,299
N at risk at 26 years = 117

Survival (%) vs Years

JHLT. 2013 Oct; 32(10): 951-964
The Challenge
## Organ transplantation

<table>
<thead>
<tr>
<th>Source</th>
<th>Units</th>
<th>Donor examination</th>
<th>Extended donor examination (echo, angio, xmatch)</th>
<th>Potential recipients on waitinglist</th>
<th>Planning logistic, transportation for the team</th>
<th>Planning the logistic, transportation for the recipient</th>
<th>Prioritize recipients, contact recipient</th>
<th>Donor harvest operation</th>
<th>Recipient preparation</th>
<th>Donor/team transportation</th>
<th>Organ transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unassigned</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
UNOS (United Network for Organ Sharing)

- Private, non-profit organization that manage the nation organ transplant system
  - Blood type and size
  - Time spent on waitinglist
  - Distance (ischemic duration)
  - Medical urgency
  - The degree of immuno-system match
  - Child or an adult
- UNOS 1A, valid for 14 days
  - Mechanical circulatory support for acute hemodynamic decompensation that includes at least one of the following:
    - TAH, VAD, ECMO or IABP
    - Continuous mechanical ventilator
    - Continuous infusion of high-dose inotropes
    - Device-related complication
- UNOS 1B
  - VAD support
  - Continuous infusion of intravenous inotropes
How To Customize An Optimal Donor In Heart Transplantation?
• Use data from huge clinical databases
• Develop accurate computer-based models
• Perform realistic simulations
• Find new scientific solutions
• Achieve unprecedented excellence in science
### REGISTRY DATABASE:
Number of Transplants Reported

<table>
<thead>
<tr>
<th>ORGAN</th>
<th>Transplants Reported from July 1, 2011, through June 30, 2012</th>
<th>Total Transplants Reported through June 30, 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>3,776</td>
<td>111,068</td>
</tr>
<tr>
<td>Heart-Lung</td>
<td>71</td>
<td>4,405</td>
</tr>
<tr>
<td>Lung</td>
<td>3,271</td>
<td>45,314</td>
</tr>
</tbody>
</table>
Countries Participating in the ISHLT International Registry for Heart and Lung Transplantation*

* Red flag indicates national or collaborative data submission; yellow flag indicates direct submission of data by individual centers.
The majority of donors were men (69%). The study material was 26,047 patients (44%). The average donor age was 32 years. The mean age of the overall cohort was 51 years.

### Results

#### Weight (kg)
- Derivation Cohort: 48,042
- Validation Cohort: 76

#### Peripheral vascular disease
- Derivation Cohort: 23,783
- Validation Cohort: 648 (3%)

#### COPD
- Derivation Cohort: 23,791
- Validation Cohort: 714 (4%)

#### History of cerebrovascular disease
- Derivation Cohort: 23,783
- Validation Cohort: 714 (4%)

#### Inotropic support prior to transplant
- Derivation Cohort: 39,128
- Validation Cohort: 12,901 (39%)

#### ICU
- Derivation Cohort: 13,446
- Validation Cohort: 2,657 (27%)

#### ECMO
- Derivation Cohort: 36,542
- Validation Cohort: 92 (0%)

#### Female gender
- Derivation Cohort: 59,698
- Validation Cohort: 15,470 (31%)

#### Cytomegalovirus status
- Derivation Cohort: 43,209
- Validation Cohort: 20,425 (57%)

#### Donor age was the variable that influenced outcome at most of the cases, Table 3.

#### Donor blood group
- Derivation Cohort: 49,856
- Validation Cohort: 5,842

#### Recipient-donor match
- Derivation Cohort: 49,856
- Validation Cohort: 5,842

#### Table 1a | Demographics and clinical characteristics of the study population (1998–2006)

<table>
<thead>
<tr>
<th>Description</th>
<th>Derivation Cohort</th>
<th>Validation Cohort</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>59,698</td>
<td>9,842</td>
<td>0.937</td>
</tr>
<tr>
<td>Recipient's diagnosis</td>
<td>Nonischemic cardiomyopathy 21,789 (44%) 4,258 (43%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ischemic cardiomyopathy 21,911 (44%) 4,355 (44%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Graft failure 971 (2%) 203 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vascular disease 1,533 (3%) 296 (3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Congenital 950 (2%) 191 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Miscellaneous 2,703 (5%) 439 (5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>51 ± 11</td>
<td>121 ± 22</td>
<td>0.212</td>
</tr>
<tr>
<td>Female gender</td>
<td>59,698</td>
<td>10,052 (20%) 1,978 (20%)</td>
<td>0.884</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>173 ± 9</td>
<td>173 ± 9</td>
<td>0.605</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>48,042</td>
<td>76 ± 15</td>
<td>0.412</td>
</tr>
<tr>
<td>COPD</td>
<td>23,035</td>
<td>615 ± 211</td>
<td>0.217</td>
</tr>
<tr>
<td>Hypertension</td>
<td>23,764</td>
<td>7,682 (38%)</td>
<td>0.605</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>23,764</td>
<td>648 (3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>29,089</td>
<td>2,373 (10%)</td>
<td>0.010</td>
</tr>
<tr>
<td>History of cerebrovascular disease</td>
<td>23,791</td>
<td>714 (4%)</td>
<td>0.360</td>
</tr>
<tr>
<td>Infection within two weeks</td>
<td>23,516</td>
<td>2,077 (10%)</td>
<td>0.124</td>
</tr>
<tr>
<td>Cytochrome oxidase status</td>
<td>31,998</td>
<td>18,823 (70%)</td>
<td>0.504</td>
</tr>
<tr>
<td>Amodarone prior to transplant</td>
<td>23,794</td>
<td>4,727 (24%)</td>
<td>0.122</td>
</tr>
<tr>
<td>Antithrombin</td>
<td>22,134</td>
<td>6,196 (37%)</td>
<td>0.947</td>
</tr>
<tr>
<td>Previous transplant</td>
<td>47,311</td>
<td>1,263 (3%)</td>
<td>0.412</td>
</tr>
<tr>
<td>Previous cardiac surgery</td>
<td>5,600</td>
<td>2,056 (44%)</td>
<td>0.993</td>
</tr>
<tr>
<td>PVR (wood units)</td>
<td>21,689</td>
<td>2 (1.4–3.2)</td>
<td>0.718</td>
</tr>
<tr>
<td>Creatinine (µmol/l)</td>
<td>27,909</td>
<td>106 (88–132)</td>
<td>0.834</td>
</tr>
<tr>
<td>Serum bilirubin (mg/dl)</td>
<td>25,181</td>
<td>0.9 (0.6–1.4)</td>
<td>0.482</td>
</tr>
<tr>
<td>Dialysis pre-transplanted</td>
<td>2,033</td>
<td>28 (2%)</td>
<td>0.334</td>
</tr>
<tr>
<td>Medical condition at transplant</td>
<td>59,698</td>
<td>3,157 (63%)</td>
<td>0.549</td>
</tr>
<tr>
<td>Not hospitalized</td>
<td>59,698</td>
<td>6,225 (44%)</td>
<td>0.549</td>
</tr>
<tr>
<td>Hospitalized</td>
<td>4,903 (10%)</td>
<td>933 (10%)</td>
<td>0.377</td>
</tr>
<tr>
<td>ICU</td>
<td>13,446 (27%)</td>
<td>2,657 (27%)</td>
<td>0.754</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>39,128</td>
<td>12,901 (39%)</td>
<td>0.754</td>
</tr>
<tr>
<td>Intra-aortic balloon pump</td>
<td>37,399</td>
<td>1,013 (3%)</td>
<td>0.435</td>
</tr>
<tr>
<td>ECMO</td>
<td>36,542</td>
<td>92 (0%)</td>
<td>0.377</td>
</tr>
<tr>
<td>Donor age (years)</td>
<td>59,698</td>
<td>32 ± 13</td>
<td>0.278</td>
</tr>
<tr>
<td>Female gender</td>
<td>59,698</td>
<td>15,470 (31%)</td>
<td>0.402</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>28,421</td>
<td>2,636 (11%)</td>
<td>0.311</td>
</tr>
<tr>
<td>Cytochrome oxidase status</td>
<td>43,209</td>
<td>20,425 (57%)</td>
<td>0.774</td>
</tr>
<tr>
<td>Insulin time [mincluded]</td>
<td>42,519</td>
<td>178 ± 63</td>
<td>0.416</td>
</tr>
<tr>
<td>Era of transplantation</td>
<td>59,698</td>
<td>13,933 (28%)</td>
<td>0.824</td>
</tr>
</tbody>
</table>

### Table 1b | Blood groups and HLA for the study population

<table>
<thead>
<tr>
<th>Description</th>
<th>Derivation Cohort</th>
<th>Validation Cohort</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient blood group</td>
<td>Derivation Cohort</td>
<td>Validation Cohort</td>
<td>P-value</td>
</tr>
<tr>
<td>A</td>
<td>22,152 (44%) 4,369 (44%)</td>
<td></td>
<td>0.655</td>
</tr>
<tr>
<td>B</td>
<td>6,238 (13%) 1,271 (13%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AB</td>
<td>2,990 (6%) 599 (6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O</td>
<td>18,476 (37%) 3,603 (37%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donor blood group</td>
<td>Derivation Cohort</td>
<td>Validation Cohort</td>
<td>P-value</td>
</tr>
<tr>
<td>A</td>
<td>19,979 (40%) 3,943 (40%)</td>
<td></td>
<td>0.820</td>
</tr>
<tr>
<td>B</td>
<td>4,985 (10%) 1,014 (10%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AB</td>
<td>1,333 (3%) 259 (3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O</td>
<td>23,559 (47%) 4,626 (47%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recipient-donor match</td>
<td>Derivation Cohort</td>
<td>Validation Cohort</td>
<td>P-value</td>
</tr>
<tr>
<td>HLA-A, 1 mismatch</td>
<td>11,417 (41%) 2,405 (41%)</td>
<td></td>
<td>0.994</td>
</tr>
<tr>
<td>HLA-A, 2 mismatch</td>
<td>15,372 (35%) 3,320 (35%)</td>
<td></td>
<td>0.161</td>
</tr>
<tr>
<td>HLA-B, 1 mismatch</td>
<td>9,543 (36%) 1,900 (36%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLA-B, 2 mismatch</td>
<td>16,555 (62%) 3,246 (61%)</td>
<td></td>
<td>0.172</td>
</tr>
<tr>
<td>HLA-DR, 1 mismatch</td>
<td>23,559 (47%) 4,626 (47%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are mean ± SD, number (%). The numbers are calculated on patients with available data. HLA, Human Leukocyte Antigen.
Pattern recognition problem

a Complete linear separation
b Poor linear separation
c Almost complete non-linear separation
d Complete non-linear separation

Fig. 3 Solution for a two-dimensional classification problem.

a Complete linear separation of the two classes, using a biostatistical method based on a generalized linear model with assumptions of linearity—arbitrary correlations in medicine.

b Poor linear separation of a non-linear classification problem, performed by the same linear model.

c An almost complete non-linear separation of the two classes, using a biostatistical method based on a non-linear model such as an artificial neural network (ANN) with four hidden nodes.

The aim of this study was to perform a systematic review of published reports of ANNs as predictive systems in pancreatic disease. The experiences learned provide a basis for discussion of how ANNs can be used to improve both diagnosis and prediction in acute pancreatitis and pancreatic cancer.

Methods
Electronic searches were conducted to identify reports of published studies. Searches were restricted to articles published in English. The US National Library of Medicine's PubMed database, including Medline citations from 1950 to 2007, was searched for articles on the use of ANNs in pancreatic disease using the MeSH terms 'neural networks (computer)' combined with 'pancreatic neoplasms', 'pancreatitis' or 'pancreatic diseases'. Additional articles were retrieved through hyperlinks and by manually searching reference lists in original published articles. A systematic review of the articles was performed.

Artificial neural networks
An ANN consists of a set of processing units (nodes) that simulate neurones. These nodes are interconnected.
Technical resources

- Neural Network Toolbox
  - Cross-entropy error function
  - Regularization - weight decay
  - Calibrated and Optimised using
    - 5-fold cross validation
    - C-Index
    - Ensemble approach
- MATLAB Distributed Computing Server
- Parallel Computing Toolbox
- High Performance Computer Cluster, an
  - Apple Xserve, 96 processors, and a
  - VTrak E-Class (16TB) storage unit

Biganzoli et al. showed that by treating the time interval as an input variable in a standard feed-forward ANN with a cross-entropy error function, it was possible to estimate smoothed discrete hazards as conditional probabilities of failure
Simulated Annealing

Generate the initial configuration
Randomly select a recipient from registry
Save the Recipient-Donor profile as \( RD_{\text{best}} \)

Predict survival
\( S_{\text{best}} = \text{ANN}(RD_{\text{best}}) \)

Generate new Recipient-Donor profile
Select feature to be Toggled
\( \text{togg}` \sim \text{randsample}[1-5] \)
Save the new profile as \( RD_{\text{togg}} \)

Predict survival
\( S_{\text{togg}} = \text{ANN}(RD_{\text{togg}}) \)

Calculate difference
\( \Delta = S_{\text{togg}} - S_{\text{best}} \)

Generate acceptance cut-off
\( u \sim \text{randsample}[0-1] \)

\( u < \exp(\Delta / t) \)

Yes

\( t' = t \times k \)

No

\( t' = t \times k \)

Yes

Save the best Recipient-Donor profile, \( RD_{\text{best}} \)

Start of a new trial set of a given temperature

\( t = t \times k \)

\( t < t_{\text{min}} \)

Calculate difference
\( \Delta = S_{\text{togg}} - S_{\text{best}} \)

Generate acceptance cut-off
\( u \sim \text{randsample}[0-1] \)

\( u < \exp(\Delta / t) \)

Yes

Test of a possible "hill climbing" or improved survival

No

No

No

Yes

Start of a new trial set of a given temperature

Update best profile

No

Yes

Temperature loop

Trial at a given temperature

Simulated Annealing
The Results
Figure 3 | Customize Optimal Donor Using Simulated Annealing (CODUSA). Panel (A): Random selection of 1,000 patients and their respective survival curve based on the best case customized donor profile. Panel (B): Random selection of 1,000 patients and their respective survival curve based on the worse case customized donor profile.
Virtual Recipient Donor Match Simulation

Figure 1A.

- Actual Survival
- Predicted Survival Test data (ANN)
- Predicted Survival Validation data (ANN)
- Best Donor-Recipient match
- Worse Donor-Recipient match
- Best Simulated match
- Worse Simulated match

Overall survival (%)

Time after transplantation (years)

* 574,580,900 recipient-donor match
** Bets/Worse match using simulated annealing technique

Figure 1B.

Monitoring the simulation of identifying a worse case cross-matching

Duration of ischemia (min)

Donor age (years)

Area under survival curve

Area: 0.56

19 October, 2009

Lund University, Artificial Intelligence in Cardiothoracic Science (http://www.med.lu.se/aicts)
CODUSA - Customize Optimal Donor Using Simulated Annealing In Heart Transplantation

Daniel Ansari1, Bodil Andersson1, Mattias Ohlsson2, Peter Höglund3, Roland Andersson1 & Johan Nilsson4

1Lund University and Skåne University Hospital, Department of Clinical Sciences Lund, Surgery, 2Lund University, Department of Astronomy and Theoretical Physics, Computational Biology and Biological Physics, 3Skåne University Hospital, Department of Competence Centre for Clinical Research, 4Lund University and Skåne University Hospital, Department of Clinical Sciences Lund, Cardiothoracic Surgery.

In heart transplantation, selection of an optimal recipient-donor match has been constrained by the lack of individualized prediction models. Here we developed a customized donor-matching model (CODUSA) for patients requiring heart transplantations. Using Simulated Annealing and artificial neural networks. Using this approach, by analyzing 59 heart transplants, we found that donor age matching was the variable most strongly associated with improved survival. Female hearts were given to 21% of the women and 0% of the men, and recipients with blood group B received identical matched blood group in only 18% of best-case match compared to 73% for the original match. By optimizing the donor profile, the survival could be improved with 33 months. These findings strongly suggest that the CODUSA model can improve the ability to select optimal match and avoid worst-case match in the clinical setting. This is an important step towards personalized medicine.

The Results

Prospective five-year survival rate raised by up to 10%. “In a simulated randomized trial, the preliminary results show that the ANN model we developed using MATLAB and Neural Network Toolbox would transplant approximately 20% more patients than would have been considered using traditional selection criteria,” says Nilsson. “The prospective five-year survival rate for the ANN-selected patients was 5–10% higher than those matched with the criteria physicians use today.”

Network training time reduced by more than two-thirds. “Using Neural Network Toolbox and MATLAB, it took us 5 to 10 minutes to train our ANNs,” says Nilsson. “Training took 30 to 60 minutes using open-source software. That is a big difference, because we were training and evaluating hundreds of network configurations.”

Simulation time cut from weeks to days. “When we switched to MATLAB and MathWorks parallel computing technologies, we completed experiments that regularly took 3 to 4 weeks in about 5 days,” says Nilsson. “More importantly, the simulations were completed reliably, with no crashes.”
• ANN could be used to predict individual long-term survival

• A VRDM model using ANN allows transplant physicians to risk stratify risk-benefit analysis inherent to any donor offer

• Simulation of future outcome for each recipient on the waiting list would make it possible to avoid worse case match, and to choose best possible match in the clinical
Thank You!