4.1 Artificial Intelligence and Organ Transplantation
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https://www.vanderschaar-lab.com/inspiration-exchange-ml-to-transform-organ-transplantation/

Importance of transplantation AI

- Supply and demand
    - Mortality waiting for liver
    - Limited increase in supply of donor organs
    - Organ donors deteriorating
- Paradigm for scarce healthcare resource
    - Rational approach

Liver transplantation

- Only solution for end-stage chronic liver disease
- Multiple causes for end stage liver disease
- 3 year survival without a transplant - 5%
- Good outcome: 94% survival at one year, 75% at 5 year
- Disease Severity, Donor quality can impact outcome
    - Disease severity impact magnified over time
    - Donor quality differences magnified over time
- Allocation principles varies:
    - US– sickest first – Need
        - Risk of poor outcome as disease severity is higher
    - Utility – best outcomes
    - Benefit: net life years gained; UK March 2018

Why is this a complex interesting area?

- Multi-dimensional donor and recipient space
    - Upt o 17 donor/recipient factors impact outcome
- Non-linear interactions
    - E.g. Na, K, urea/creatinine, BMI
- Counterfactuals
    - Impact of not receiving a transplants
- Assignment bias
    - Confound by various prejudice decisions and regulatory rules
- Informative censoring
    - Patients on transplant list are censored – never know what the outcome is

Which areas in transplantation might ML address?

- Optimal donor organ allocation
    - Organ declining – why
- Clinical variation in offer acceptance rates - quantitative epistemology

Previous work

- Spanish group
- SOM

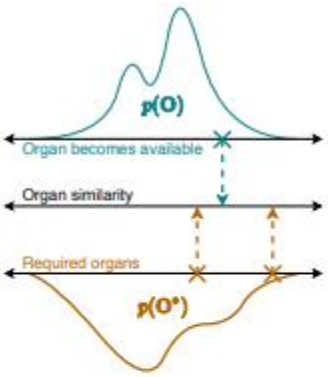
Organ allocation; principles and considerations

- Need: sickest patient first
- Utility: best match for outcome
- Benefit:
    - Incremental gain in survival
    - Net life years gained
    - Considerations
        - Time until better organ

Allocation process

[Diagram]

OrganITE

- **OrganITE: Optimal transplant donor organ offwering using an individual treatment effect**
- https://papers.nips.cc/paper/2020/file/e7c573c14a09b84f6b7782ce3965f335-Paper.pdf
- UK Transplant Database:
- Donor organ density
    - 

(a) Consider the density of organs, $p(\mathbf{O})$, above, and the density of required organs, $p(\mathbf{O}^*)$, below. While the available organ might be a better fit for the leftmost patient as it is similar to their required organ, we argue the available organ might be best assigned to the rightmost patient as their required organ is less probable to become available.
- OrganITE outperform other models
- Importance of organ density
    - During COVID, donor organs became less available
    - Prevalence of donor being available - Temperatur (organ availability)
        - OrganITE is more stable than FIFO, SPF, or BM

Organboard

- Demonstrating organ acceptability based on patient data
-

Characteristics of patients transplanted by OrganITE and CoxPH

- Characteristics can be visualized of overall comparing OrganITE and CoxPH
    - Cannot be explored for individual cases – why is one allocated to another?

OrganSync

- https://vanderschaar-lab.com/papers/ICML_2021_OrganSync.pdf

Table 2. **Results on organ allocation.** For each dataset we report the allocation performance of the benchmarks outlined in Table 1, in terms of added life-years (ALY), as well as total deaths over the course of one year. We set MELD as the baseline, to compare against. All results are reported in percentages ("%" is dropped for brevity) and ran over ten data-folds, standard deviation in brackets.

	UNOS		**UKReg**	
Method	Deaths	ALY	Deaths	ALY
MELD	compared against			
FIFO	-0.9 (.01)	-2.0 (.11)	-1.1 (.16)	-5 (.01)
M-na	-0.3 (.13)	+1.2 (.10)	-2.1 (.18)	+6 (.01)
TB	+7.0 (.19)	+2.4 (.21)	+0.9 (.11)	+8 (.03)
CM	-0.01 (.09)	+12.8 (.31)	+0.1 (.11)	+7 (.02)
O-ITE	**-3.6 (.18)**	+11.1 (.28)	-3.3 (.12)	+11 (.15)
OS	-3.5 (.15)	**+13.1 (.19)**	**-4.1 (.21)**	**+ 13 (.03)**

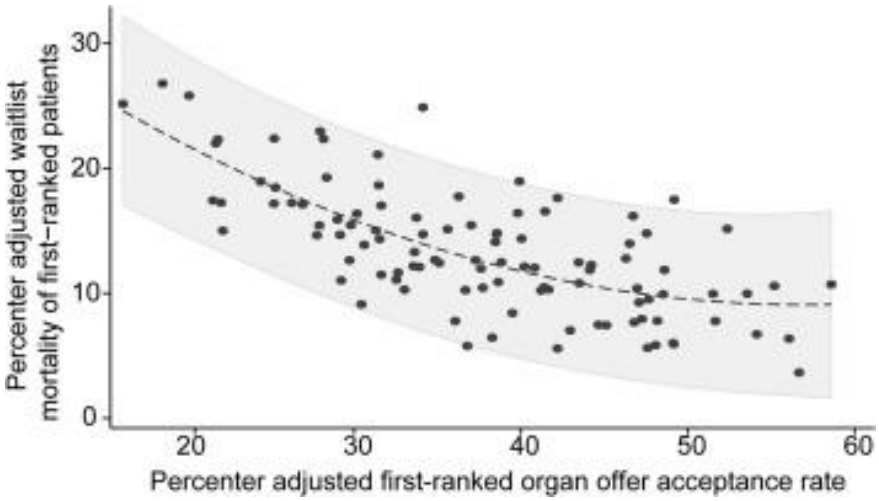
- Based on k-means clustering
    - Each cluster differ by donor feature and recipient parameter
    - Allocation based on the cluster
    - Allowing identification of different clusters
        - Greater granularity of why one is allocated than the other
    - Number of clusters can be adjusted depending on the database size

Optimal organ allocation processes

- Outcome without a donor
- Outcome with a specific donor
- Time til another "better/optimal" donor appears

Clinical variation

- Variability in clinical care and decisions
- Variance can impact the outcome of transplantation
    - **Liver transplant center variability in accepting organ offers and its impact on patient survival**
    - https://linkinghub.elsevier.com/retrieve/pii/S0168-8278(15)00773-4



- Identifying drivers of clinical decisions
  - **Closing the loop in medical decision support by understanding clinical decision-making: A case study on organ transplantation**
  - https://proceedings.neurips.cc/paper/2021/file/c344336196d5ec19bd54fd14befdde87-Paper.pdf
  - Discover which criteria are most important to clinicians to organ offer acceptance
  - Identify patient-specific organ preferences of centers
  - Explore variations in transplantation practices between different transplant centers.

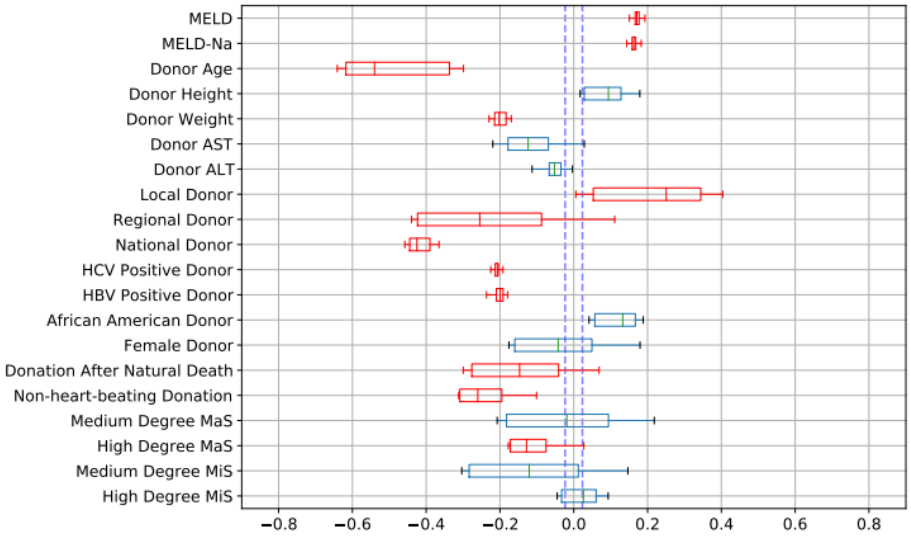


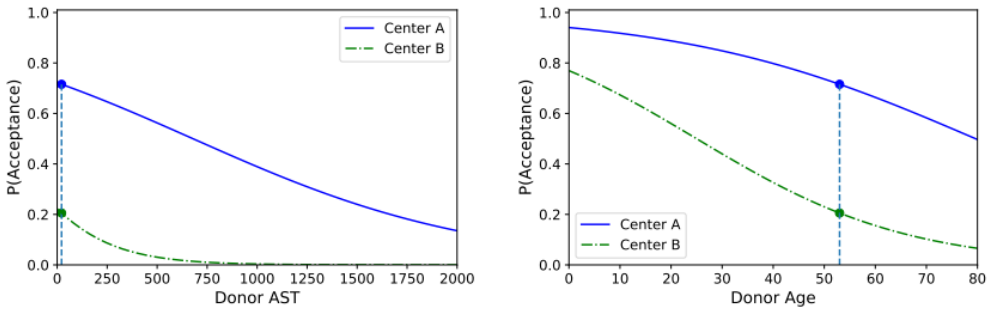
Figure 3: Distribution of normalized policy signature $\tilde{\rho}$ (x-axis) over match criteria (y-axis), see the Appendix for explanation. Criteria with weights between the dotted blue lines could be ignored with no more than 0.1% loss in the average precision score.

Table 2: Benchmark of different methods on decision prediction.

METHOD	AUC-ROC	AUC-PRC	LL
LOGISTIC REGRESSION	0.794±0.054	0.341±0.061	-0.538±0.051
PER-CLUSTER LOGISTIC REGRESSION	0.803±0.049	0.352±0.063	-0.527±0.048
DECISION TREE	0.775±0.057	0.274±0.069	-0.552±0.060
PER-CLUSTER DECISION TREE	0.773±0.052	0.281±0.066	-0.564±0.064
LOCALLY WEIGHTED REGRESSION	0.865±0.044	0.429±0.066	-0.256±0.089
LASSO	0.777±0.064	0.314±0.068	-0.570±0.045
RANDOM FOREST	0.852±0.064	0.421±0.106	-0.271±0.092
INVASE	0.790±0.062	0.341±0.071	-0.541±0.064
BEHAVIORAL CLONING	0.899±0.043	0.502±0.067	-0.383±0.067
ITRANSPLANT (OURS)	0.895±0.045	0.502±0.062	-0.396±0.069

As shown in Table 2, iTransplant significantly outperforms all baseline methods and performs similarly to the upper bound provided by BC while maintaining interpretability of policies identified for each patient. Although the policy learned by iTransplant uses logistic regression as the decision function, by learning individualized policies, iTransplant greatly outperformed both global logistic regression and per-cluster logistic regression (see Appendix for further details).

- All these parameters have been previously associated with declined donation
    - ITransplant was better in prediction compared to other models
- ITransplant able to show why clinical decision was different between two centers



(a) Counterfactual impact of donor AST test value. (b) Counterfactual impact of donor age.

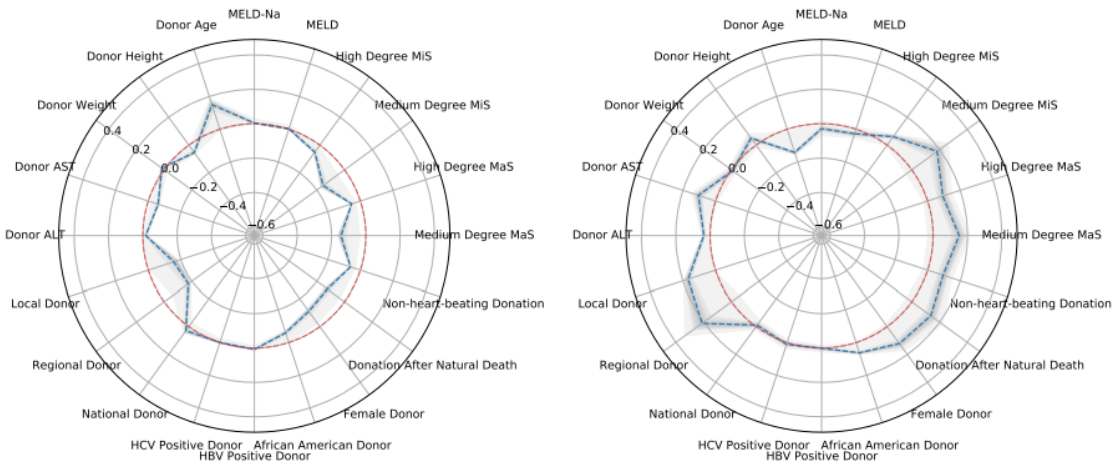
Figure 5: Patient-level variations in policies from two different transplant centers.

The AST test value is an indirect measure of liver cell integrity, with a higher value in a donor suggesting more severe damage and therefore potentially worse post transplant outcome. Both policy $\hat{\pi}^A$ and $\hat{\pi}^B$ show preferences for organ offers with lower AST test value. However, for the considered patient, policy $\hat{\pi}^A$ is more tolerant to changes in donor AST test results. The low AST test result of the donor leads to a significantly higher likelihood of offer acceptance compared to policy $\hat{\pi}^B$ (Figure 5(a)). We find similar variations when examining the impact of donor age on the offer acceptance probability. While policy $\hat{\pi}^B$ has a high chance of accepting the organ offer from a young donor, the acceptance rate decreases steadily as the counterfactual donor age increases. For the policy $\hat{\pi}^A$, the acceptance rate is largely insensitive to the donor age until the age of the donor exceeds 30.

With the counterfactual impacts of donor features plotted in Figure 5, we can intuitively observe the variations in transplantation practices in the investigated transplant centers. This demonstrates the potential of iTransplant as a tool for clinicians to examine their own decision-making policies with existing transplantation data and the impact of changes to patient and donor characteristics.

- Itransplant was able to identify within clusters, why an organ is being accepted or not

patient features. In Figure 4, we provide an overview of the policies for patients in cluster 1 and 2 displaying the deviation in policy with respect to the averaged policy signature $\bar{\rho}$ for all patients (see the Appendix for detailed discussion).



(a) Patient cluster 1. (b) Patient cluster 2.

Figure 4: The deviations of policy signature $\Delta\rho = \rho - \bar{\rho}$ of two patient clusters.

Implementing ML technologies: lesson from transplantation

- Implementation of changes with Medicine maybe slow
- Clinical trials of organ allocation have not been undertaken
- Multiple simulations
- Interpretability is only one component of trust in new AI methodologies
- Regulatory authorities
- Public Patient involvement
- Laws of Tort

Developing, implementing, and governing AI in medicine (Transplantation)

Phase 1	Preparation prior to AI development	
	Define clinical problem	
	Evaluate available models	
	Collate relevant data, consider bias	
	Ensure privacy	
Phase 2	AI model development	

	Applicable regulatory requirements	
	Prepare data	
	Train & validate	
	Evaluate performance	
Phase 3	Asses AI performance & reliability	
	Externally validate	
	Simulate results and prepare a clinical study	