The Disparate Goals of Statistics and Machine Learning:
Survival Analysis and Prediction on Liver Transplantation Data

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I INVESTICIJSKI FONDOVI

Statistics and machine learning (1/2)

*statistics == (traditional) data models

- Traditional statistical (data) models
  - interpretable coefficients with CIs
  - inferences about the population: testing

- Machine Learning (ML) models
  - optimizes the generalization error (prediction accuracy) via cross-validation
  - can handle unwieldy amounts of variables
  - usually assumption-free => flexible

- Hard to compare in a quantifiable way
  - often compared exclusively in terms of prediction

nature methods

POINTS OF SIGNIFICANCE

Statistics versus machine learning

Statistics draws population inferences from a sample, and machine learning finds generalizable predictive patterns.

[1] D. Bzdok, N. Altman & M. Krzywinski , 2018

*Hidden/Extra

A few examples: comparison of (linear) Cox models to ML models

scientific reports

OPEN **Explainable machine learning can outperform Cox regression predictions and provide insights in breast cancer survival**

Arturo Moncada-Torres[1–4], Marissa C. van Maaren[1,2], Mathijs P. Hendriks[1,3], Sabine Siesling[1,2] & Gijs Geleijnse[1]

Our results showed that in the data at hand, ML-based approaches are capable of performing as good as a conventional CPH model or, in the case of the XGB model, even better. However, this comes at the cost of an increase in complexity/opacity. ML explainability techniques have arised as a solution for this issue. They can help us generate an explicit knowledge representation of how the model makes its predictions. In our case, SHAP values showed that the key difference between CPH's and XGB's performance can be attributed, at least partially, to the latter's ability to capture data nonlinearities and interactions between features, which can have important contributions to the outputs. Moreover, it does so automatically and without any additional effort required by the researcher. Furthermore, SHAP values also allowed us to investigate the impact of specific features on the model predictions, which can be a complex task even for experts. This type of modelling frameworks could speed up the process of generating and testing new hypothesis on new (NCR) data, which could contribute to a rapid learning health system.

There is a growing body of literature that shows how cancer patients, clinicians, epidemiologists, and researchers in general can benefit from ML techniques. However, in order to bring these solutions closer to the clinic, users need to be able to trust these novel approaches. We believe that ML explainability techniques, especially those with a solid theoretical background behind them (like SHAP values), are key to bridging the gap between everyday clinical practice and ML-based algorithms.

*t-test for CV results (optimistic variance estimation), Cox model is simply fit to the data (no interactions or transformations) and treated as a ML model

ELSEVIER

Physica Medica
Volume 82, February 2021, Pages 295-305

Original paper

A deep survival interpretable radiomics model of hepatocellular carcinoma patients

Lise Wei [a], Dawn Owen [b], Benjamin Rosen [a], Xinzhou Guo [c], Kyle Cuneo [a], Theodore S Lawrence [a], Randall Ten Haken [a], Issam El Naqa [d]

The DNN based models (individuals and combined) outperformed those of the Cox based models, showing superiority of the DNN based approach in modeling non-linear, complex relationships. Although the raw imaging based individual models performed worse than the clinical models, they are still significantly better than random. One possible reason of the low predictive power of the imaging features might be the lack of good soft tissue contrast in CT, low signal to noise ratio, etc. To improve the raw image CNN model performance, different strategies were applied, such as transfer learning, it turns out the performance were all pretty similar. Thus, we used the basic CNN structure for the CT image data. We also used random crop to augment the CT image input network.

*no statistical testing, Cox model is simply fit to the data (no interactions or transformations) and treated as a ML model

Zhang *et al. BMC Medical Imaging* (2020) 20:11
https://doi.org/10.1186/s12880-020-0418-1

BMC Medical Imaging

RESEARCH ARTICLE Open Access

CNN-based survival model for pancreatic ductal adenocarcinoma in medical imaging

Yucheng Zhang[1,2], Edrise M. Lobo-Mueller[3], Paul Karanicolas[4], Steven Gallinger[2], Masoom A. Haider[1,2,5] and Farzad Khalvati[1,2,5,6*]

Results: The proposed CNN-based survival model outperformed the traditional CPH-based radiomics approach in terms of concordance index and index of prediction accuracy, providing a better fit for patients' survival patterns.
Conclusions: The proposed CNN-based survival model outperforms CPH-based radiomics pipeline in PDAC prognosis. This approach offers a better fit for survival patterns based on CT images and overcomes the limitations of conventional survival models.

The CPH-based survival models can help clinicians make more personalized treatment decisions for individual patients. Traditional CPH models assume that the independent variables make a linear contribution to the model, with respect to time [13]. In many conditions,

*no statistical testing, Cox model is simply fit to the data (no interactions or transformations) and treated as a ML model

Statistics and machine learning (2/2)

- The difference between the two is not as clear-cut
  - can they switch roles?

- Antagonisms:
  - **accurate information vs. interpretability**
  - **interpetability (reliability) vs. black box prediction**

Statistical Science
2001, Vol. 16, No. 3, 199–231

Statistical Modeling: The Two Cultures

[2] L. Breiman, 2001

Choosing Prediction Over Explanation in Psychology: Lessons From Machine Learning

ASSOCIATION FOR PSYCHOLOGICAL SCIENCE

[3] Tal Yarkoni, Jacob Westfall, 2017

PERSPECTIVE
https://doi.org/10.1038/s42256-019-0048-x

nature machine intelligence

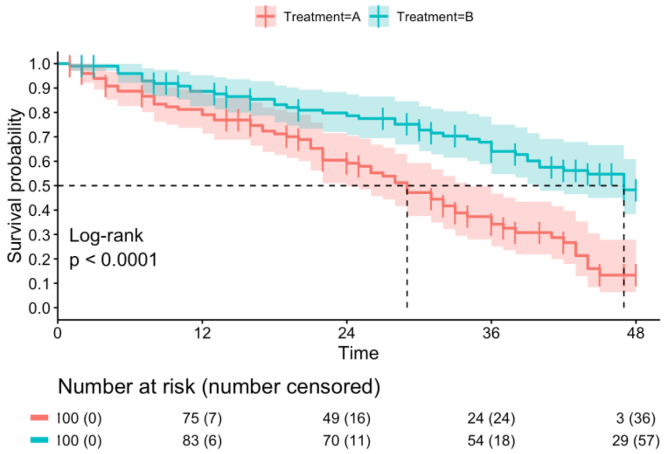
Stop explaining black box machine learning models for high stakes decisions and use interpretable models instead

[4] C. Rudin, 2019

Survival analysis

- An approach to analyzing the duration of time until an event occurs
  - **events:** death, organ failure, system failure, customer loss, job retention, ...
  - **domains:** medicine, engineering (reliability), social sciences, ...

- Specifics of survival analysis
  - **censorship:** time-to-event variable is not fully known
  - analysis via the survival and hazard functions



- Most commonly used:
  - **Kaplan-Meier survival function estimator** (nonparametric)
  - **Cox proportional hazards model** (semiparametric; linear regression for survival)

*Hidden/Extra

Survival and hazard functions

$$S(t) = P(\{T > t\}) = \int_t^{\infty} f(u)\,du = 1 - F(t).$$

$$h(t) = \lim_{\Delta t \to 0} \frac{R(t) - R(t + \Delta t)}{\Delta t \cdot R(t)}$$

$$f(t) = -S'(t)$$

$$\lambda(t) = -\frac{d}{dt} \log S(t)$$

Cox PH model

$$\begin{aligned}\lambda(t|X_i) &= \lambda_0(t)\exp(\beta_1 X_{i1} + \cdots + \beta_p X_{ip}) \\ &= \lambda_0(t)\exp(X_i \cdot \beta)\end{aligned}$$

$$L_i(\beta) = \frac{\lambda(Y_i \mid X_i)}{\sum_{j:Y_j \geq Y_i} \lambda(Y_i \mid X_j)} = \frac{\lambda_0(Y_i)\theta_i}{\sum_{j:Y_j \geq Y_i} \lambda_0(Y_i)\theta_j} = \frac{\theta_i}{\sum_{j:Y_j \geq Y_i} \theta_j}$$

$$L(\beta) = \prod_{i:C_i=1} L_i(\beta)$$

Kaplan-Meier survival estimator

$$\widehat{S}(t) = \prod_{i:\ t_i \leq t} \left(1 - \frac{d_i}{n_i}\right)$$

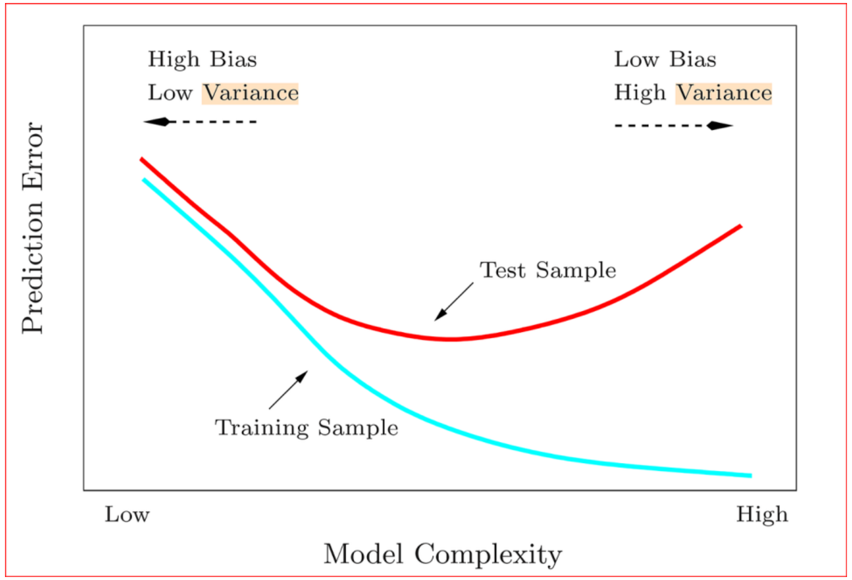
Accelerated failure time model

$\lambda(t|\theta) = \theta\lambda_0(\theta t)$, typically $\theta = \exp(-[\beta_1 X_1 + \cdots + \beta_p X_p])$

$$\log(T) = -\log(\theta) + \log(T\theta) := -\log(\theta) + \epsilon$$

Survival prediction (1/2)

- machine-learning (ML) based approach
  - focus on prediction over interpretation



- **designed to generalize on unseen data**
  - regularization techniques to tackle overfitting
  - crossvalidation for model selection and evaluation

- evaluated using the concordance index
  - the ratio of correctly-ordered pairs to comparable pairs:

$$\text{C-index} = \frac{\sum_{i,j} 1_{T_j < T_i} \cdot 1_{\eta_j > \eta_i} \cdot \delta_j}{\sum_{i,j} 1_{T_j < T_i} \cdot \delta_j}$$

- often treated as a classification problem

*Hidden/Extra

Survival turned to classification

LATE BREAKER ARTICLES

Multicenter Comparison of Machine Learning Methods and Conventional Regression for Predicting Clinical Deterioration on the Wards

Churpek, Matthew M. MD, MPH, PhD[1]; Yuen, Trevor C. MS[1]; Winslow, Christopher MD[2]; Meltzer, David O. MD, PhD[1]; Kattan, Michael W. MBA, PhD[3]; Edelson, Dana P. MD, MS[1]

Author Information

Critical Care Medicine 44(2):p 368-374, February 2016. | *DOI:* 10.1097/CCM.0000000000001571

Conferences > 2018 IEEE International Confe...

Predicting Time to First Treatment in Chronic Lymphocytic Leukemia Using Machine Learning Survival and Classification Methods

Publisher: IEEE Cite This PDF

David Chen; Gaurav Goyal; Ronald Go; Sameer Parikh; Che Ngufor **All Authors**

ELSEVIER

Biology of Blood and Marrow Transplantation

Volume 24, Issue 6, June 2018, Pages 1299-1306

Evaluation of a Machine Learning-Based Prognostic Model for Unrelated Hematopoietic Cell Transplantation Donor Selection

Ljubomir Buturovic[1], Jason Shelton[2], Stephen R. Spellman[3], Tao Wang[4 5], Lyssa Friedman[2], David Loftus[2], Lyndal Hesterberg[2], Todd Woodring[2], Katharina Fleischhauer[6], Katharine C. Hsu[7], Michael R. Verneris[8], Mike Haagenson[3], Stephanie J. Lee[3 9]

nature > npj breast cancer > articles > article

Article | Open Access | Published: 16 August 2018

Exploration of PET and MRI radiomic features for decoding breast cancer phenotypes and prognosis

Shih-ying Huang, Benjamin L. Franc, Roy J. Harnish, Gengbo Liu, Debasis Mitra, Timothy P. Copeland, Vignesh A. Arasu, John Kornak, Ella F. Jones, Spencer C. Behr, Nola M. Hylton, Elissa R. Price, Laura Esserman & Youngho Seo

npj Breast Cancer **4**, Article number: 24 (2018) | Cite this article

Article | Open Access | Published: 27 March 2020

Predicting Short-term Survival after Liver Transplantation using Machine Learning

Chien-Liang Liu, Ruey-Shyang Soong, Wei-Chen Lee, Guo-Wei Jiang & Yun-Chun Lin

Scientific Reports **10**, Article number: 5654 (2020) | Cite this article

ORIGINAL ARTICLES

Impact of Machine Learning With Multiparametric Magnetic Resonance Imaging of the Breast for Early Prediction of Response to Neoadjuvant Chemotherapy and Survival Outcomes in Breast Cancer Patients

Tahmassebi, Amirhessam PhD[*]; Wengert, Georg J. MD[†]; Helbich, Thomas H. MD[†]; Bago-Horvath, Zsuzsanna MD, PhD[‡]; Alaei, Sousan MD[‡]; Bartsch, Rupert MD[§]; Dubsky, Peter MD[‖]; Baltzer, Pascal MD[†]; Clauser, Paola MD[†]; Kapetas, Panagiotis MD[†]; Morris, Elizabeth A. MD[¶]; Meyer-Baese, Anke PhD[*]; Pinker, Katja MD, PhD[*,¶]

Author Information

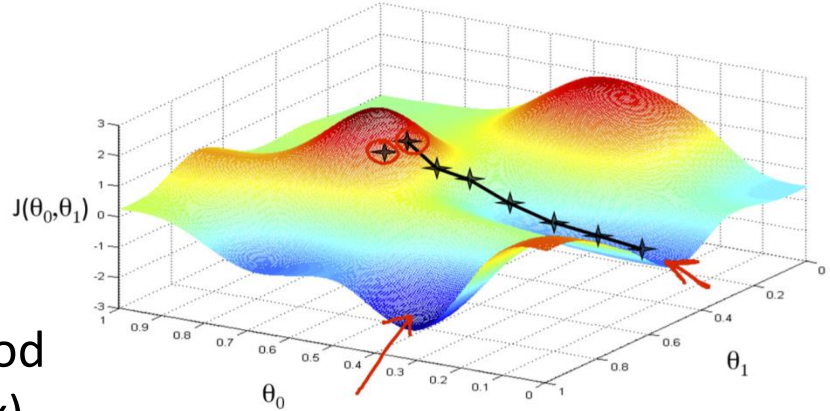
Investigative Radiology 54(2):p 110-117, February 2019. | *DOI:* 10.1097/RLI.0000000000000518

Survival prediction (2/2)

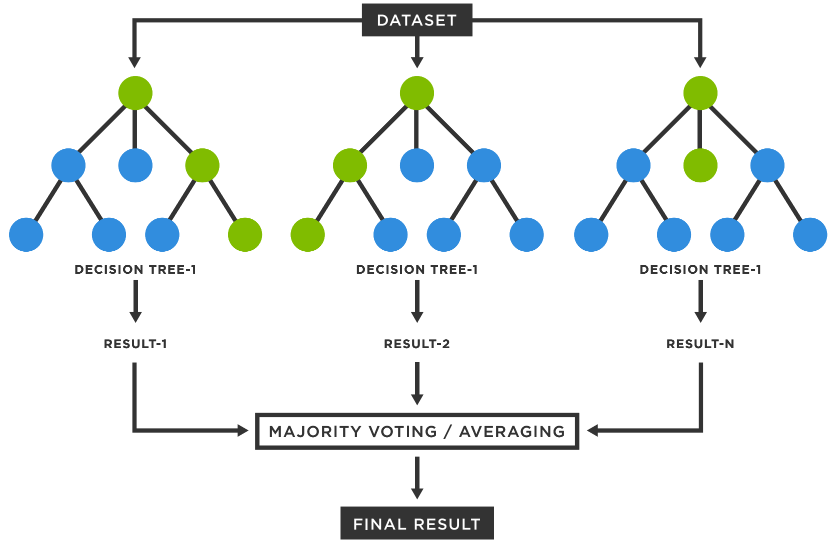
- CoxNet (regularized Cox PH model)
- gradient boosting methods
- XGBoost
- neural nets (e.g., DeepSurv)

Cox, AFT (diff. f's)

Cox likelihood (c-index)



- random survival forests
- survival support vector machines (SSVMs)



- others (variational clustering, MCMC, ...)

*Hidden/Extra

Regularization Paths for Cox's Proportional Hazards Model via Coordinate Descent

Noah Simon, **Jerome H. Friedman**, **Trevor Hastie**, **Rob Tibshirani**

How to Cite

Simon, N., Friedman, J. H., Hastie, T., & Tibshirani, R. (2011). Regularization Paths for Cox's Proportional Hazards Model via Coordinate Descent. *Journal of Statistical Software, 39*(5), 1–13. https://doi.org/10.18637/jss.v039.i05

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JOURNAL ARTICLE

Survival ensembles FREE

Torsten Hothorn ✉, Peter Bühlmann, Sandrine Dudoit, Annette Molinaro, Mark J. Van Der Laan

Biostatistics, Volume 7, Issue 3, July 2006, Pages 355–373, https://doi.org/10.1093/biostatistics/kxj011

Published: 12 December 2005 **Article history** ▾

Research article | Open Access | Published: 26 February 2018

DeepSurv: personalized treatment recommender system using a Cox proportional hazards deep neural network

Jared L. Katzman, Uri Shaham, Alexander Cloninger, Jonathan Bates, Tingting Jiang & Yuval Kluger ✉

BMC Medical Research Methodology **18**, Article number: 24 (2018) | Cite this article

The Annals of Applied Statistics
2008, Vol. 2, No. 3, 841–860
DOI: 10.1214/08-AOAS169
In the Public Domain

RANDOM SURVIVAL FORESTS[1]

BY HEMANT ISHWARAN, UDAYA B. KOGALUR, EUGENE H. BLACKSTONE AND MICHAEL S. LAUER

Cleveland Clinic, Columbia University, Cleveland Clinic and National Heart, Lung, and Blood Institute

CONFERENCE PROCEEDING

Support vector machines for survival analysis

Van Belle, Vanya; Pelckmans, Kristiaan; Suykens, Johan; Van Huffel, Sabine

Proc. of the Third International Conference on Computational Intelligence in Medicine and Healthcare (CIMED2007); 2007

Comparative Study > Artif Intell Med. 2011 Oct;53(2):107-18. doi: 10.1016/j.artmed.2011.06.006. Epub 2011 Aug 6.

Support vector methods for survival analysis: a comparison between ranking and regression approaches

Vanya Van Belle [1], Kristiaan Pelckmans, Sabine Van Huffel, Johan A K Suykens

Affiliations + expand

PMID: 21821401 DOI: 10.1016/j.artmed.2011.06.006

An Efficient Training Algorithm for Kernel Survival Support Vector Machines

Sebastian Pölsterl[1(✉)], Nassir Navab[2,3], and Amin Katouzian[4]

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Survival regression with accelerated failure time model in XGBoost

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August 24, 2021

Published as a conference paper at ICLR 2022

A DEEP VARIATIONAL APPROACH TO CLUSTERING SURVIVAL DATA

Laura Manduchi,[1] Ričards Marcinkevičs,[1] Michela C. Massi,[2,3] Thomas Weikert,[4] Alexander Sauter,[4] Verena Gotta,[5] Timothy Müller,[6] Flavio Vasella,[6] Marian C. Neidert,[7] Marc Pfister,[5] Bram Stieltjes[4] & Julia E. Vogt[1]
[1]ETH Zürich; [2]Politecnico di Milano; [3]CADS, Human Technopole; [4]University Hospital Basel; [5]University Children's Hospital Basel; [6]University of Zürich; [7]St. Gallen Cantonal Hospital

Article | Open Access | Published: 29 June 2021

Approximation of the Cox survival regression model by MCMC Bayesian Hierarchical Poisson modelling of factors associated with childhood mortality in Nigeria

A. F. Fagbamigbe ✉, M. M. Salawu, S. M. Abatan & O. Ajumobi

Scientific Reports **11**, Article number: 13497 (2021) | Cite this article

Survival stacking: casting survival analysis as a classification problem

Erin Craig[1], Chenyang Zhong[2], and Robert Tibshirani[3]

[1]Department of Biomedical Data Science, Stanford University
[2]Department of Statistics, Stanford University
[3]Departments of Biomedical Data Science and Statistics, Stanford University

July 29, 2021

On Ranking in Survival Analysis: Bounds on the Concordance Index

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Cary Dehing-Oberije, Philippe Lambin
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Abstract

In this paper, we show that classical survival analysis involving censored data can naturally be cast as a ranking problem. The concordance index (CI), which quantifies the quality of rankings, is the standard performance measure for model *assessment* in survival analysis. In contrast, the standard approach to *learning* the popular proportional hazard (PH) model is based on Cox's partial likelihood. We devise two bounds on CI–one of which emerges directly from the properties of PH models–and optimize them *directly*. Our experimental results suggest that all three methods perform about equally well, with our new approach giving slightly better results. We also explain why a method designed to maximize the Cox's partial likelihood also ends up (approximately) maximizing the CI.

ORIGINAL RESEARCH article

Front. Oncol., 20 January 2021
Sec. Cancer Imaging and Image-directed Interventions
Volume 10 - 2020 | https://doi.org/10.3389/fonc.2020.588990

This article is part of the Research Topic
Bottom-Up Approach: a Route for Effective Multi-modal Imaging of Tumors
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SurvNet: A Novel Deep Neural Network for Lung Cancer Survival Analysis With Missing Values

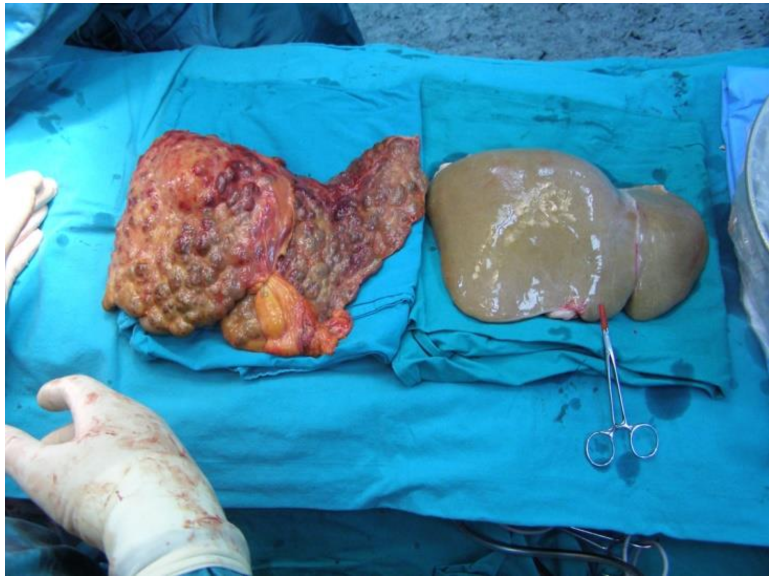
Jianyong Wang[1], Nan Chen[2], Jixiang Guo[1], Xiuyuan Xu[1], Lunxu Liu[2*] and Zhang Yi[1*]

[1] Machine Intelligence Laboratory, College of Computer Science, Sichuan University, Chengdu, China
[2] Department of Thoracic Surgery, West China Hospital and West China School of Medicine, Sichuan University, Chengdu, China

Survival analysis is important for guiding further treatment and improving lung cancer prognosis. It is a challenging task because of the poor distinguishability of features and the missing values in practice. A novel multi-task based neural network, SurvNet, is proposed in this paper. The proposed SurvNet model is trained in a multi-task learning framework to jointly learn across three related tasks: input reconstruction, survival classification, and Cox regression. It uses an input reconstruction mechanism cooperating with incomplete-

Survival data in liver transplantation

- Orthotopic liver transplantation (OLT) – surgical procedure where diseased liver is replaced with a healthy liver from a live/cadaveric donor
- Vital surgical indication; various etiologies
- Survival data:
  - recipient data
  - donor data/graft data
- Applications:
  - imaging assessment
  - waitlist dropout assessment
  - survival analysis – risk factor analysis
  - donor-recipient matching/donor allocation policies
  - prognostic models - clinical decision making tool

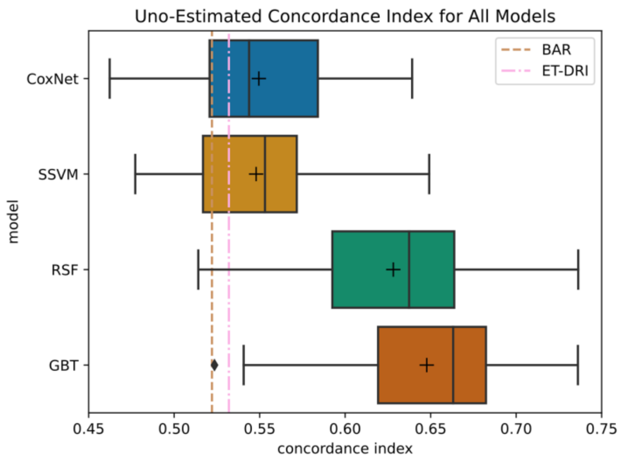


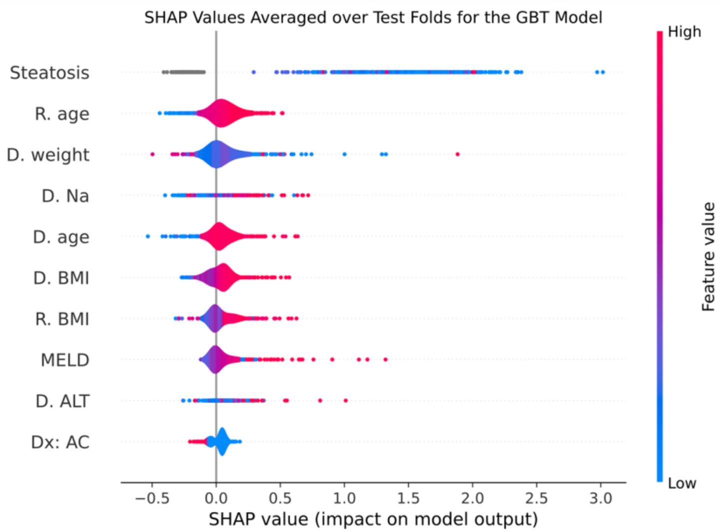
Machine-Learning-Assisted Donor-Recipient Matching for Orthotopic Liver Transplantation

- 656 patients who underwent OLT from Mar 2013 – Dec 2018 at University Hospital Merkur, Zagreb
- 24 donor and recipient variables
- CoxNet, Random Survival Forest, gradient boosted trees, Survival Support Vector Machines

	1 year	3 years	5 years	Overall
Survival Rate	74.8%	55.2%	20.3%	–
Censorship Rate	15.9%	39.5%	64.6%	71.6%
Survival Median	629 days			

Donor variables	age, weight, height, BMI, sex, blood type, anti-HBc, steatosis, sodium, CRP, ALT, GGT, bilirubin, CIT
Recipient variables	age, weight, height, BMI, sex, blood type, MELD, cardiac arrest, pancreas, diagnosis
Missing values	steatosis (125), CRP (46), bilirubin (24), GGT (8), ALT (2), sodium (2), CIT (2)

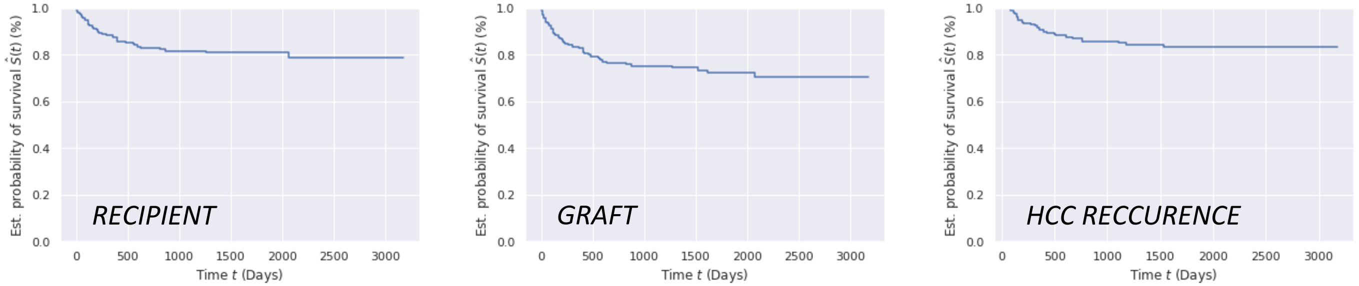




Use of ML models for identification of predictors of survival and tumour reccurence in patients undergoing LT for hepatocellular carcinoma

- 170 patients who underwent OLT from Mar 2013 – Dec 2018 at University Hospital Merkur, Zagreb
- 34 donor and recipient and tumour specific parameters
- Kaplan Meier:recipient, graft, HCC reccurence
- Cox proportional hazards, CoxNET, RSF, SSVM, survival gradient boosting

METHOD	CI
CoxPH	0.52
CoxNet	0.62
Survival random forest	**0.72**
Survival support vector machine	0.70
Survival gradient boosting	0.60



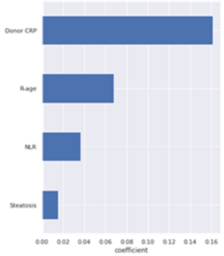
Survival random forest
- AFP
- D-CRP
- R-age
- NLR

Random Survival Forest
Concordance index:0.7162162162162162

Weight	Feature
0.0950 ± 0.0563	AFP
0.0544 ± 0.0859	CRP
0.0429 ± 0.0741	R-age
0.0276 ± 0.0238	NLR
0.0129 ± 0.0219	D-age
0.0072 ± 0.0204	PLR
0.0050 ± 0.0158	Lab MELD
0.0020 ± 0.0122	Cold-ischaemic-period
0.0012 ± 0.0097	ALT>105
0 ± 0.0000	Pancreas=ne
0 ± 0.0000	R-sex=M
0 ± 0.0000	TACE=NE
0 ± 0.0000	Number of TACE treatments
-0.0011 ± 0.0036	GGT>90
-0.0015 ± 0.0048	Imaging Milan=NE
-0.0018 ± 0.0050	Cardiac arrest=ne
-0.0021 ± 0.0208	D-sex=M
-0.0024 ± 0.0089	Bilirubin>50
-0.0065 ± 0.0134	R-BMI
-0.0096 ± 0.0261	Steatosis
… 4 more …	

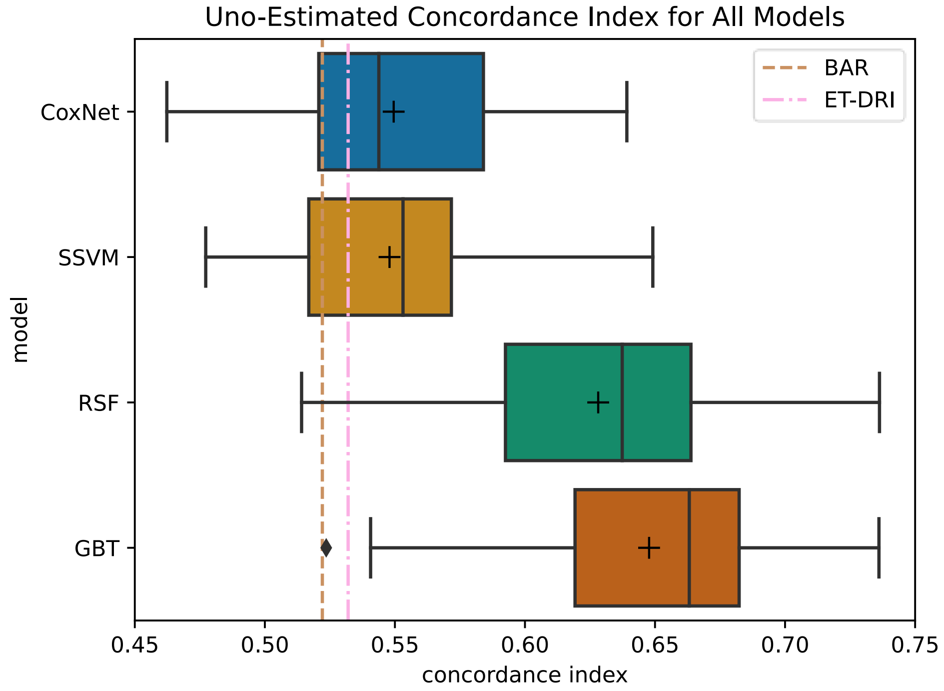
CoxPH
- D-age
- D-CRP
- AFP
- Number of TACE

CoxNET (regularization)
- D-CRP
- R-age
- NLR
- Graft steatosis



Our experience in terms of statistics and ML

- Statistics can handle inference
  - what about prediction?
- (Regularized) Cox is often quite good
  - and it's interepretable!
  - *what when it is significantly worse?*
- ML in medicine
  - **ML outperforms statistical models**
  - *but: lack of reliability*
  - how to move forwards?



Conclusion

- Statistical models makes inference about a population
- ML models extract generalizable patterns more efficiently
- Not clear:
  - are accurate predictions compatible with interpretability?
  - can explanations of ML models sometimes be more informative than statistical interpretation?

- Adapt to the problem and the data:
  - an **interdisciplinary approach**
- In the case of liver transplantation:
  - we use **statistical models for inference** about our population
  - we use **ML to get accurate predictions** of survival (**donor allocation**)
  - plenty of work to do in producing both accurate and reliable models

The New York Times

Noam Chomsky: The False Promise of ChatGPT

March 8, 2023

Perversely, some machine learning enthusiasts seem to be proud that their creations can generate correct "scientific" predictions (say, about the motion of physical bodies) without making use of explanations (involving, say, Newton's laws of motion and universal gravitation). But this kind of prediction, even when successful, is pseudoscience. While scientists certainly seek theories that have a high degree of empirical corroboration, as the philosopher Karl Popper noted, "we do not seek highly probable theories but explanations; that is to say, powerful and highly improbable theories."

[5] Noam Chomsky et al., 2023

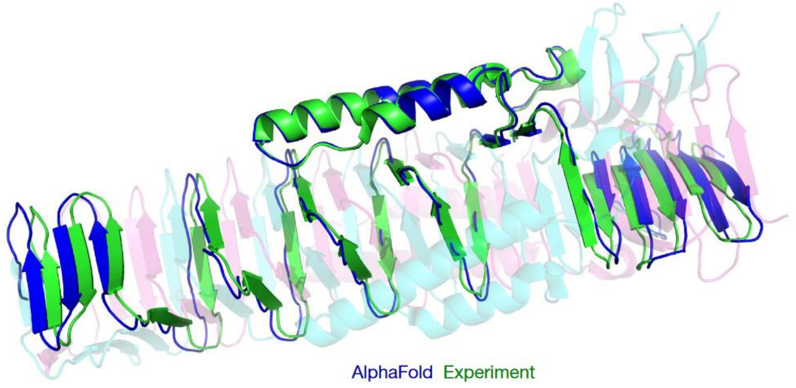
nature

Article

Highly accurate protein structure prediction with AlphaFold

Accelerating scientific discovery

AlphaFold can accurately predict 3D models of protein structures and is accelerating research in nearly every field of biology.



[6] John Jumper et al., 2021

Thank you!

ivan.stresec@fer.hr; miran.bezjak@gmail.com; bojana.dalbelo@fer.hr

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