Mahidol University
Faculty of Medicine Ramathibodi Hospital
Department of Clinical Epidemiology and Biostatistics

Journal Club : Aug 18, 2023

Multivariate longitudinal data for survival analysis of cardiovascular event prediction in young adults: insights from a comparative explainable study

Ekapob Sangariyavanich, M.D.
(Commentator)

Wisdom of the Land

Topic

- Article : "Modelling of longitudinal data to predict cardiovascular disease risk: a methodological review"
- Deep learning in survival analysis
  - DeepSurv
  - DeepHit , Dynamic-DeepHit

Stevens *et al.*
BMC Medical Research Methodology (2021) 21:283
https://doi.org/10.1186/s12874-021-01472-x

BMC Medical Research Methodology

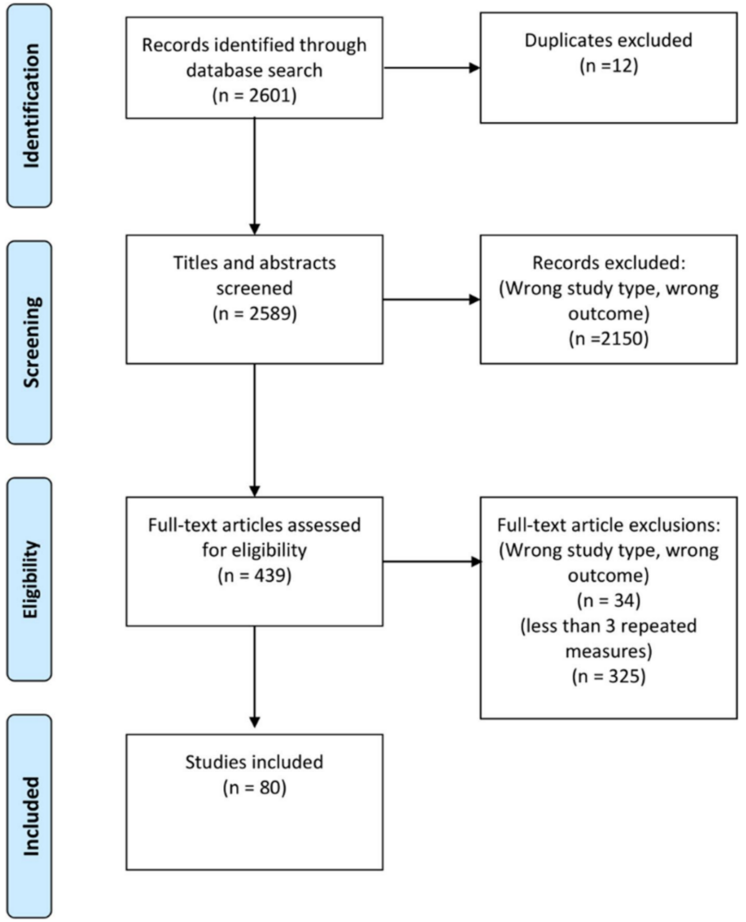
RESEARCH Open Access

Modelling of longitudinal data to predict cardiovascular disease risk: a methodological review

David Stevens[1,2], Deirdre A. Lane[1,2,3*], Stephanie L. Harrison[1,2], Gregory Y. H. Lip[1,2,3] and Ruwanthi Kolamunnage-Dona[4]

Study selection

1. They had a longitudinal design with data analyzed over at least three time points
2. The outcome was a clinical diagnosis of a cardiovascular disease(s) or mortality.
3. Cross-sectional, animal, and pediatric studies were excluded.



t of study selection

- 80 studies were included in studies
- 60 (75%) studies reported analyses on large sample sizes (≥1000 patients).
- 63 (78.8%) studies reported disease outcomes as time-to-event or survival outcomes.
- 69 (86.2%) longitudinal outcomes were continuous.

Modelling approaches

1. Single-stage approaches (40 studies (50%))
   - Cox proportional hazards (PH) model (25 studies (62.5%))
   - Time dependent covariate in cox model (6 studies (15%))
   - Other models : logistic regression(n=3), linear mixed effects model(n=4)
2. Two-stage models (29 studies (36.3%))
   - 2.1) Generate summaries from the longitudinal data
     - Group-based trajectory model (GBTMs) (17 studies (58.6%))
     - Linear regression model (9 studies (31%))
   - 2.2) Survival model
     - Cox PH model was used in most studies (26 studies (89.7%))

3. Joint modelling (8 studies (10%))

- Both the longitudinal variable and the survival model are fitted simultaneously.
- This approach makes full use of the available data and may be more statistically efficient than fitting a two-stage model; however, this increases the computational complexity.

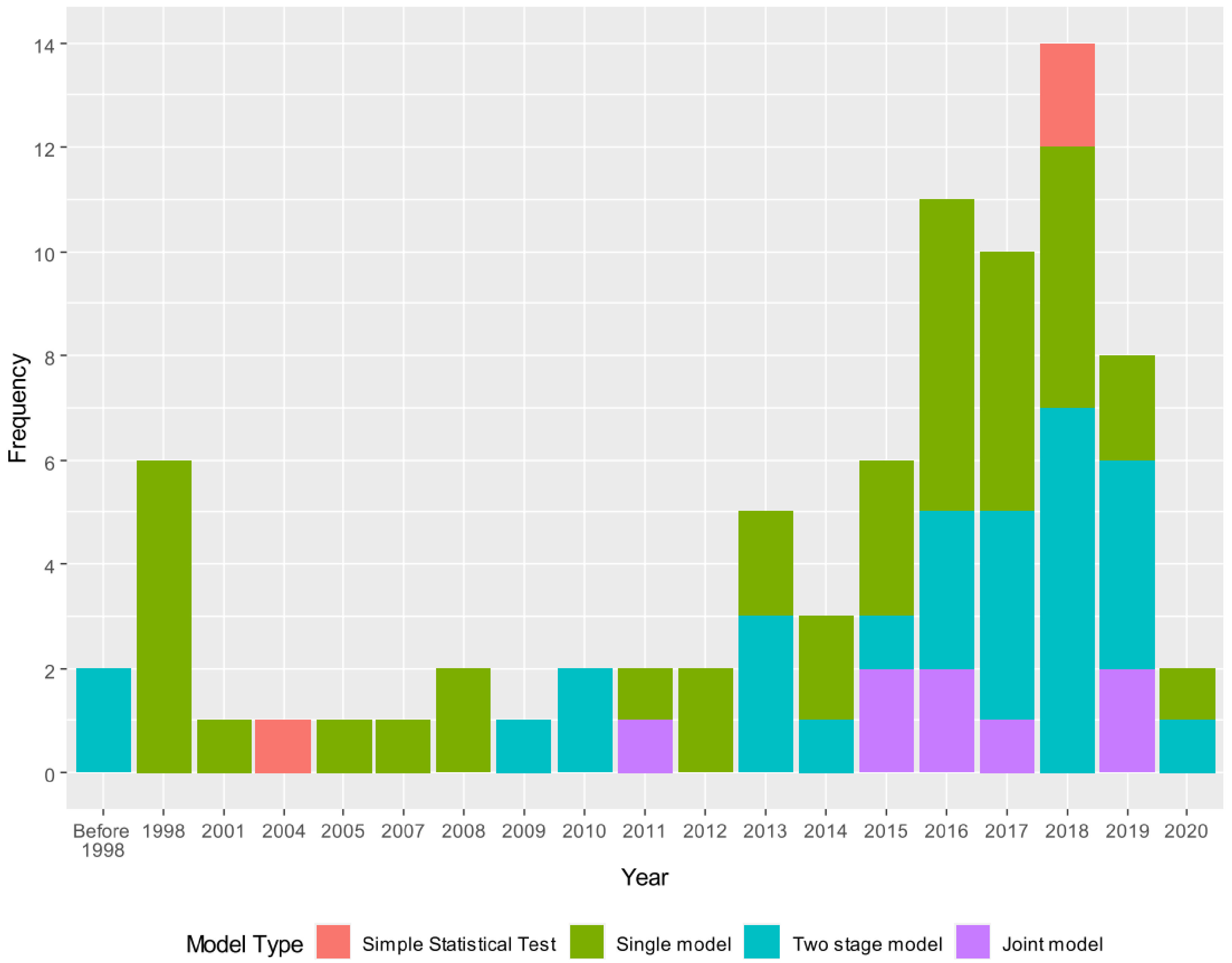


Fig. 3 Stacked bar chart showing the frequency of the statistical model types by year

Discussion

- There has been an increase in the complexity of methodology used over the past two decades.
- A time-dependent covariate Cox PH model provides an advantage by enabling risk estimates to be updated during follow-up for new individuals, the model assumes that values are constant between two time-points and are measured without error. This model is also prone to greater overfitting.
- Group-based trajectory model (GBTMs) is an effective way of identifying a fixed number of groups of individuals who follow similar trajectories.

  Limitation: They are computationally difficult to fit, difficult to apply in clinical practice.

- The reasons for the slow increase in the utilization of two-stage and joint models.
  1) Computationally these models can be much harder to fit than single-stage models
  2) There is poor awareness of inefficiency in simple methods.
  3) Many studies may not include a statistician as part of the research team and therefore, authors may not have the requisite experience of analyzing longitudinal data.
- Two-stage and joint models become more common, and software to fit the models becomes more accessible and computationally more powerful, the utilization of more efficient methods should increase over time.

Conclusions

- The use of two-stage and joint models is a critical part of understanding the relationship between the longitudinal risk factors and CVD.
- Many studies still employ single stage approaches which often underutilize available longitudinal data when modelling cardiovascular risk.
- Further studies should aim to optimize the use of longitudinal data by using two-stage and joint models whenever possible for a more accurate estimation of cardiovascular risk.

Topic

- Article : “Modelling of longitudinal data to predict cardiovascular disease risk: a methodological review”
- Deep learning in survival analysis
  - DeepSurv
  - DeepHit , Dynamic-DeepHit

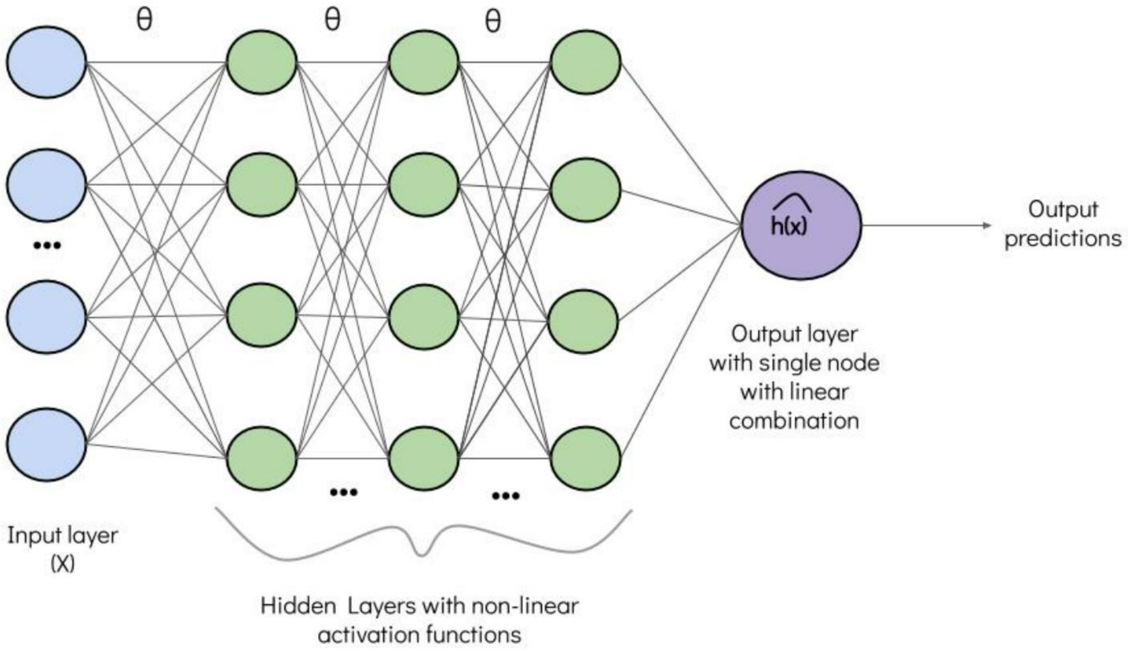
Research article | Open Access | Published: 26 February 2018

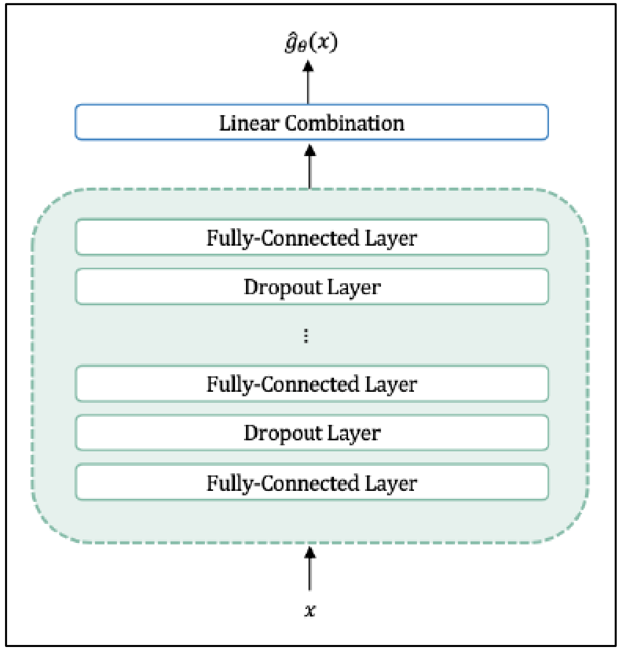
DeepSurv: personalized treatment recommender system using a Cox proportional hazards deep neural network

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

DeepSurv





- DeepSurv has an advantage over traditional Cox regression because it does not require an *a priori* selection of covariates, but learns them adaptively.

Table 1: Experimental Results for All Experiments: C-index (95% Confidence Interval)

Experiment	CPH	DeepSurv	RSF
Simulated Linear	0.773677 (0.772,0.775)	**0.774019 (0.772,0.776)**	0.764925 (0.763,0.766)
Simulated Non-linear	0.506951 (0.505,0.509)	**0.648902 (0.647, 0.651)**	0.645540 (0.643,0.648)
WHAS	0.817620 (0.814, 0.821)	0.862620 (0.859,0.866)	**0.893623 (0.891,0.896)**
SUPPORT	0.582870 (0.581,0.585)	**0.618308 (0.616,0.620)**	0.613022 (0.611,0.615)
METABRIC	0.630618 (0.627,0.635)	**0.643374 (0.639,0.647)**	0.624331 (0.620,0.629)
Simulated Treatment	0.481540 (0.480,0.483)	**0.582774 (0.580,0.585)**	0.569870 (0.568,0.572)
Rotterdam & GBSG	0.657750 (0.654, 0.661)	**0.668402 (0.665,0.671)**	0.651190 (0.648, 0.654)

Katzman JL, Shaham U, Cloninger A, Bates J, Jiang T, Kluger Y. DeepSurv: personalized treatment recommender system using a Cox proportional hazards deep neural network. BMC Med Res Methodol. 2018 Feb 26;18(1):24. doi: 10.1186/s12874-018-0482-1. PMID: 29482517; PMCID: PMC5828433.

DeepHit

C. Lee, W. R. Zame, J. Yoon, M. van der Schaar, "DeepHit: A Deep Learning Approach to Survival Analysis with Competing Risks," AAAI Conference on Artificial Intelligence (AAAI), 2018

Dynamic-DeepHit

C. Lee, J. Yoon and M. v. d. Schaar, "Dynamic-DeepHit: A Deep Learning Approach for Dynamic Survival Analysis With Competing Risks Based on Longitudinal Data," in IEEE Transactions on Biomedical Engineering, vol. 67, no. 1, pp. 122-133, Jan. 2020, doi: 10.1109/TBME.2019.2909027.

DeepHit

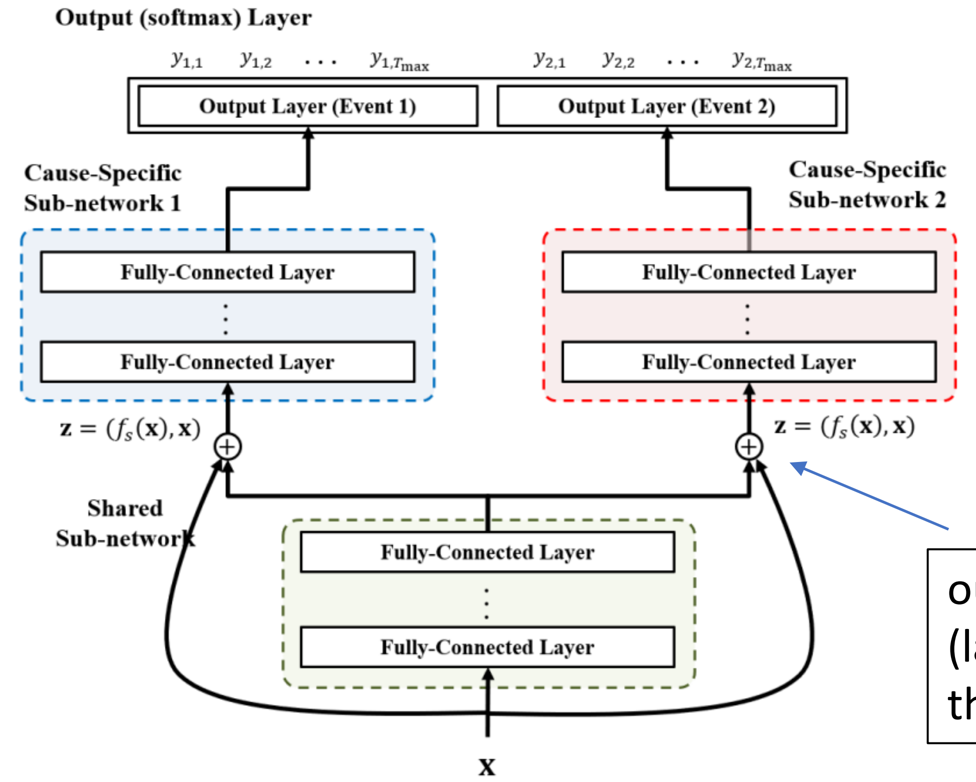
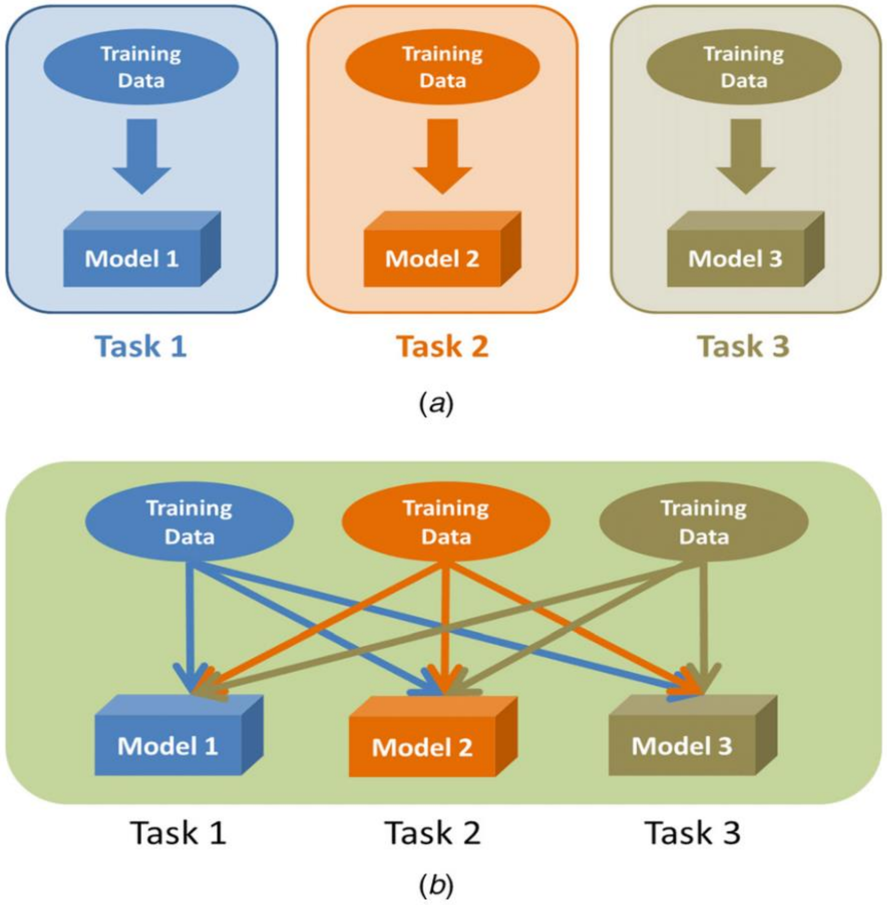


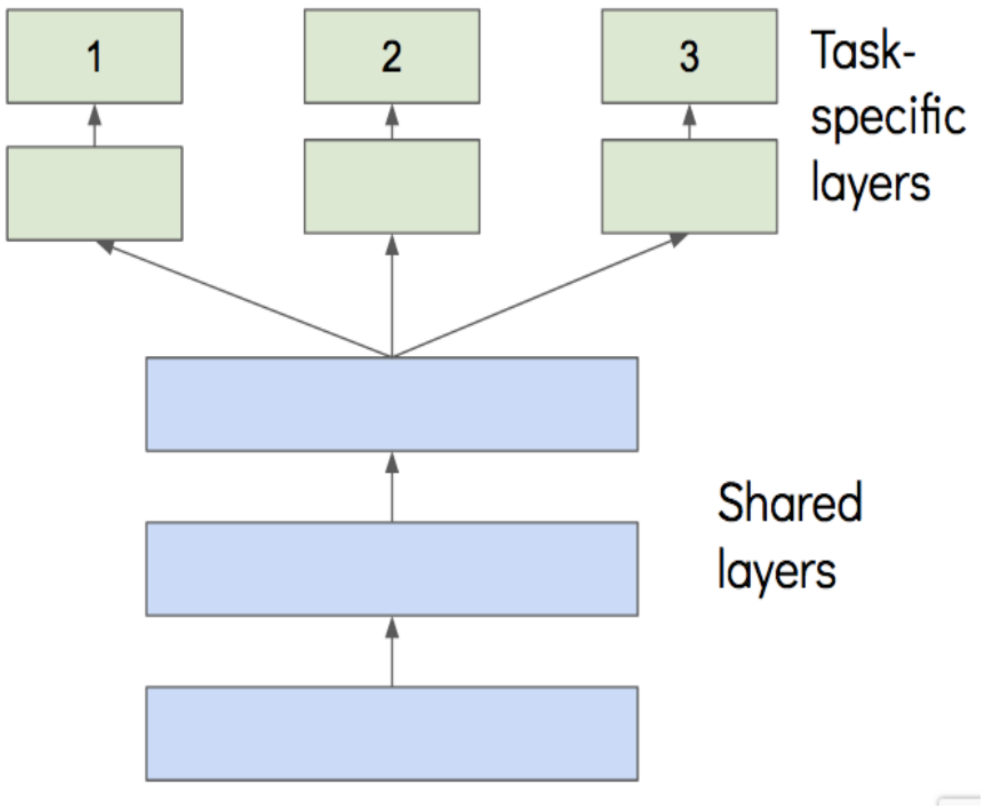
Figure 2: The architecture of DeepHit with two competing events.

- A deep neural network that learns the distribution of first hitting times directly.
- Handles situations in which there is a single underlying risk (cause) and situations in which there are multiple competing risks (causes).

- DeepHit is a multi-task network which consists of
  - a shared sub-network
  - K cause-specific sub-networks

output a vector fs(x) that captures the (latent) representation that is common to the K competing events.

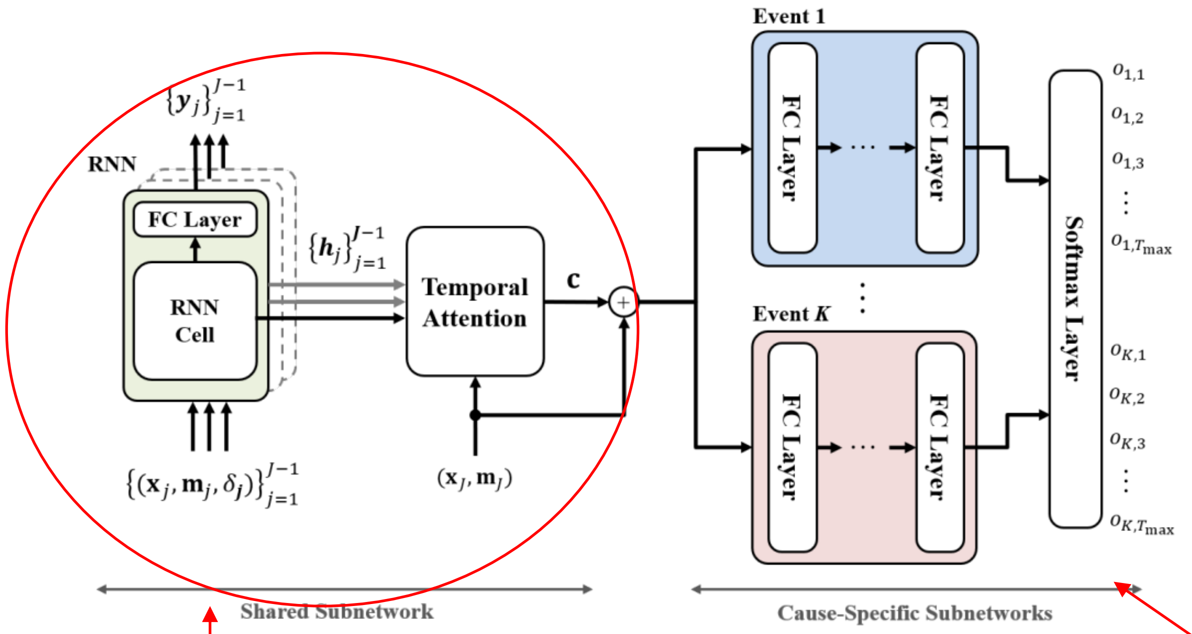




Multi-task learning model

https://humboldt-wi.github.io/blog/research/information_systems_1920/group2_survivalanalysis/#coxph

Dynamic-DeepHit



(a) The network architecture with K competing risks.

- The existing works provide only static survival analysis: they use only the current information to perform the survival predictions and most of the works focus on a single risk rather than multiple risks.

We employ a temporal attention mechanism in the hidden states of the RNN structure when constructing the context vector.

-The cause-specific subnetworks take the context vector and the last measurements as an input and estimate the joint distribution of the first hitting time and competing events that is further used for risk predictions.

TABLE I: Comparison of $C_k(t, \Delta t)$ (mean $\pm$ std) for various methods. Higher the better.

	Algorithms	Resp. Failure $\Delta t = 1$	Resp. Failure $\Delta t = 3$	Resp. Failure $\Delta t = 5$	Resp. Failure $\Delta t = 10$	Other Causes $\Delta t = 1$	Other Causes $\Delta t = 3$	Other Causes $\Delta t = 5$	Other Causes $\Delta t = 10$
$t = 30$	cs-Cox	0.840±0.09†	0.837±0.08†	0.837±0.08†	0.837±0.08†	0.667±0.10*	0.664±0.10*	0.665±0.10*	0.665±0.10*
	RSF	0.936±0.01†	0.932±0.01	0.931±0.02†	0.929±0.01†	0.798±0.04*	0.792±0.04*	0.773±0.05*	0.776±0.05*
	JM	0.882±0.03*	0.896±0.01*	0.896±0.01*	0.897±0.01*	0.760±0.02*	0.795±0.03*	0.802±0.02*	0.812±0.01*
	JM-LC	0.897±0.04†	0.894±0.05†	0.894±0.05†	0.894±0.05†	0.856±0.02*	0.855±0.02*	0.855±0.02*	0.855±0.02*
	[5]	0.910±0.02*	0.907±0.02*	0.907±0.02*	0.907±0.01*	0.819±0.07†	0.831±0.07†	0.834±0.07†	0.839±0.07†
	Exponential	0.895±0.03*	0.890±0.03*	0.890±0.03*	0.890±0.02*	0.824±0.05*	0.825±0.05*	0.824±0.05*	0.824±0.05*
	Proposed								
	FEV$_1$%	0.948±0.01	0.939±0.01	0.938±0.01	0.937±0.01	0.924±0.02	0.922±0.02	0.921±0.02	0.921±0.02
	cause-spec.	0.946±0.01	0.937±0.02	0.936±0.02	0.933±0.02	0.875±0.04†	0.867±0.05†	0.862±0.05†	0.866±0.05†
	full-fledged	**0.949±0.01**	**0.941±0.01**	**0.942±0.01**	**0.941±0.01**	**0.929±0.02**	**0.927±0.02**	**0.925±0.02**	**0.926±0.02**
$t = 40$	cs-Cox	0.842±0.03*	0.842±0.03*	0.842±0.03*	0.842±0.03*	0.748±0.10*	0.749±0.10*	0.749±0.10*	0.749±0.10*
	RSF	0.888±0.01*	0.887±0.02*	0.886±0.03*	0.891±0.03*	0.803±0.06†	0.771±0.05*	0.749±0.05*	0.746±0.05*
	JM	0.906±0.01*	0.905±0.01*	0.908±0.01*	0.909±0.01*	0.818±0.03*	0.814±0.03*	0.813±0.02*	0.840±0.02*
	JM-LC	0.911±0.04†	0.910±0.04†	0.910±0.04†	0.910±0.04†	0.851±0.02*	0.851±0.02*	0.850±0.02*	0.850±0.02*
	[5]	0.913±0.02*	0.923±0.02*	0.923±0.01*	0.923±0.01*	0.837±0.07†	0.845±0.07†	0.846±0.07†	0.849±0.07†
	Exponential	0.883±0.03*	0.883±0.03*	0.882±0.03*	0.882±0.03*	0.816±0.04*	0.817±0.04*	0.816±0.04*	0.816±0.04*
	Proposed								
	FEV$_1$%	0.956±0.01	0.958±0.01	0.957±0.01	0.957±0.01	0.934±0.02	0.931±0.02	0.931±0.02	0.931±0.02
	cause-spec.	0.955±0.01	0.957±0.01	0.957±0.01	0.958±0.01	0.907±0.02†	0.909±0.02†	0.906±0.03†	0.909±0.02†
	full-fledged	**0.961±0.01**	**0.963±0.01**	**0.963±0.01**	**0.963±0.01**	**0.939±0.01**	**0.938±0.01**	**0.939±0.01**	**0.939±0.01**
$t = 50$	cs-Cox	0.851±0.11†	0.851±0.11†	0.851±0.11†	0.851±0.11†	0.721±0.09*	0.720±0.09*	0.720±0.09*	0.720±0.09*
	RSF	0.898±0.01*	0.890±0.03*	0.892±0.02*	0.891±0.02*	0.741±0.05*	0.764±0.03*	0.763±0.03*	0.768±0.04*
	JM	0.900±0.01*	0.902±0.01*	0.908±0.01*	0.908±0.01*	0.824±0.03*	0.823±0.02*	0.826±0.01*	0.843±0.02*
	JM-LC	0.916±0.04*	0.916±0.04*	0.916±0.04*	0.916±0.04*	0.852±0.02*	0.852±0.02*	0.852±0.02*	0.853±0.02*
	[5]	0.929±0.01*	0.929±0.01*	0.929±0.01*	0.929±0.01*	0.851±0.07†	0.858±0.06†	0.859±0.06†	0.862±0.06†
	Exponential	0.875±0.02*	0.874±0.02*	0.874±0.02*	0.873±0.02*	0.806±0.04*	0.806±0.04*	0.806±0.04*	0.806±0.04*
	Proposed								
	FEV$_1$%	0.962±0.01	0.962±0.00	0.962±0.00	0.961±0.00	0.926±0.03	0.935±0.02	0.930±0.02	0.934±0.02
	cause-spec.	0.962±0.01	0.961±0.01	0.944±0.03	0.954±0.02	0.896±0.04†	0.929±0.03	0.929±0.03	0.925±0.03
	full-fledged	**0.968±0.00**	**0.968±0.01**	**0.967±0.01**	**0.967±0.01**	**0.941±0.01**	**0.942±0.01**	**0.943±0.01**	**0.936±0.02**

$*$ indicates p-value < 0.01, † indicates p-value < 0.05

Lee C, Yoon J, Schaar MV. Dynamic-DeepHit: A Deep Learning Approach for Dynamic Survival Analysis With Competing Risks Based on Longitudinal Data. IEEE Trans Biomed Eng. 2020 Jan;67(1):122-133. doi: 10.1109/TBME.2019.2909027. Epub 2019 Apr 3. PMID: 30951460.

Thank you