

Deep Learning for Semi-Competing Risks and Statistics in the Community:

Some Thoughts, Current Work, and Future Directions

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Approximately 1 in 5 cancer deaths are attributed to lung cancer



5-year survival rate of **1** in **5** (Bade and Cruz, 2020), with prognosis depending on *individualized risk factors* (Ashworth et al., 2014)

World Health Organization, International Agency for Research on Cancer, Latest global cancer data: Cancer burden rises to 18.1 million new cases and 9.6 million cancer deaths in 2018.



Motivation comes from the **Boston Lung Cancer Study** (BLCS), a large cancer
epidemiology cohort examining:

- Complex mechanisms governing relationships between *risk factors*
- 2. Efficacy of treatments
- 3. Methods for accurately *predicting survival*

https://www.medicalnewstoday.com/articles/323434



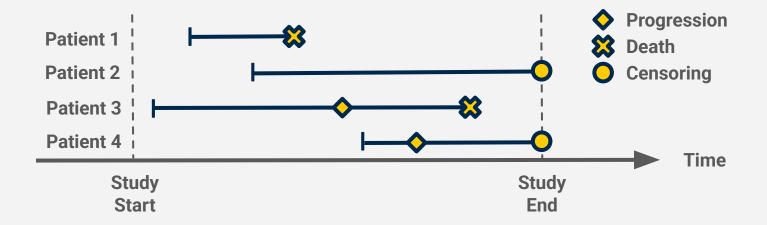
Mortality is often the **endpoint of choice** for clinical trials and cohort studies



Survival analysis deals with time-to-event outcomes which may be censored



Non-fatal events such as recurrence, progression may occur prior to death

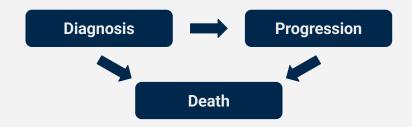


Non-fatal and fatal events are semi-competing (Fine et al., 2001)



Many studies report on lung cancer **outcomes**, however:

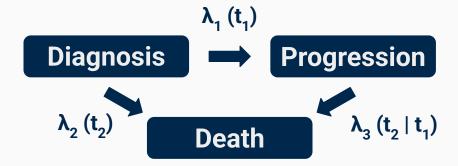
- Progression-free survival is used
- Mortality is considered
 without other events



When progression and death *do not correlate well*, this leads to *biased results* (Jazić et al., 2016)



Consider modeling the *hazards* of *transitioning* between *states*:





We can parameterize an *illness-death model* as:

$$\lambda_1\left(t_1\mid\gamma_i,x_i\right)=\gamma_i\times\lambda_{01}\left(t_1\right)\times\exp\left\{h_1(x_i)\right\};\quad t_1>0$$

$$\lambda_2\left(t_2\mid\gamma_i,x_i\right)=\gamma_i\times\lambda_{02}\left(t_2\right)\times\exp\left\{h_2(x_i)\right\};\quad t_2>0$$

$$\underbrace{\lambda_3\left(t_2\mid t_1,\gamma_i,x_i\right)}_{\text{Hazard Function}}=\underbrace{\gamma_i}_{\text{Frailty}}\times\underbrace{\lambda_{03}\left(t_2-t_1\right)}_{\text{Baseline Hazard}}\times\underbrace{\exp\left\{h_3(x_i)\right\};}_{\text{Risk Function}};\quad t_2>t_1>0$$

Hazard = **Frailty** × **Baseline Hazard** × **Risk Function**



The likelihood for the **observed data**, D, is given by:

$$L(\psi; \mathcal{D}) = \prod_{i=1}^{n} \int_{0}^{\infty} \frac{\theta^{-\frac{1}{\theta}}}{\Gamma(\frac{1}{\theta})} \times \gamma_{i}^{\frac{1}{\theta}-1} \times e^{-\frac{\gamma_{i}}{\theta}} \times \gamma_{i}^{\delta_{i1}+\delta_{i2}} \times \left[\lambda_{01}(Y_{i1})e^{h_{1}(\mathbf{x}_{i})}\right]^{\delta_{i1}}$$

$$\times \left[\lambda_{02}(Y_{i2})e^{h_{2}(\mathbf{x}_{i})}\right]^{(1-\delta_{i1})\delta_{i2}} \times \left[\lambda_{03}(Y_{i2}-Y_{i1})e^{h_{3}(\mathbf{x}_{i})}\right]^{\delta_{i1}\delta_{i2}}$$

$$\times \exp\left\{-\gamma_{i}\left[\Lambda_{01}(Y_{i1})e^{h_{1}(\mathbf{x}_{i})}+\Lambda_{02}(Y_{i1})e^{h_{2}(\mathbf{x}_{i})}+\delta_{i1}\Lambda_{03}(Y_{i2}-Y_{i1})e^{h_{3}(\mathbf{x}_{i})}\right]\right\}d\gamma_{i}$$

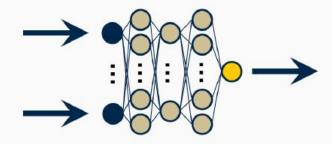
True risk functions governed by potentially complex relationships



How to **estimate/predict** these risk functions **more accurately**?



Deep learning has emerged as a powerful tool for **survival prediction**, but no work has been done on semi-competing outcomes



Artificial neural networks try to mirror how the human brain functions, with nodes connected through affine transformations



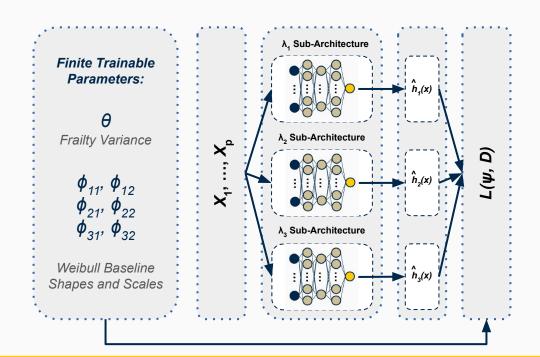
We proposes a *multi-task deep neural network* with three risk-specific *sub-networks*, corresponding to each state *transition*

And a finite set of **trainable parameters** to specify the **frailty variance** (θ) and the **baseline hazards** (φ_{q1} , φ_{q2}):

$$\lambda_{0g}(s) = \varphi_{g1}\varphi_{g2}s^{\varphi_{g2}-1}; g = 1, 2, 3$$



We propose the use of deep learning to estimate the *risk functions* for each *hazard* (i.e, state transition)





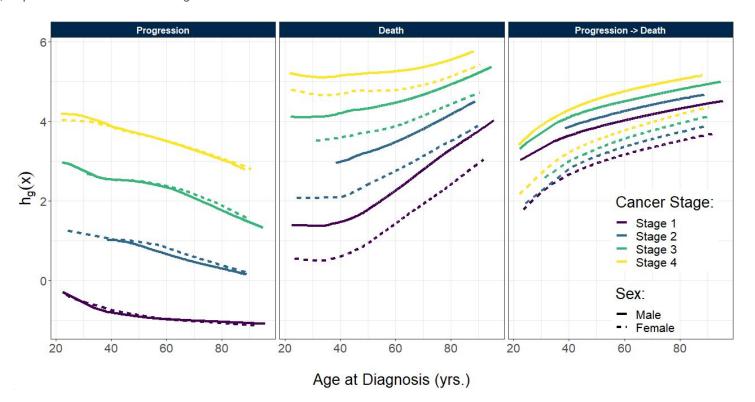
In our *first project*, focused on *5,296 patients* with non-small cell lung cancer, diagnosed between June 1983 and October 2021

Investigated time to *disease progression* and *death*, where progression might be censored by death or the study endpoint

	Progression Observed	Censored	
Death Observed	111 (2%) 1,916 (36%)		
Censored	224 (4%) 3,045 (58%		



Log-risk functions of age at diagnosis on each state transition, stratified by sex (solid versus dashed lines) and initial cancer stage (line color); https://www.annualreviews.org/doi/abs/10.1146/annurev-statistics-032921-022127



Estimated *frailty variance* (θ) to be 3.15, suggesting *progression* is *correlated with death*

Potential *nonlinear effects* of age that differ by event transition, *interactions* between cancer stage, and sex



We assumed *parametric* baseline hazards, *optimized directly*

But ...

We want a **non-parametric** model for both the **baseline hazards** and covariate **risk functions** to achieve greater flexibility and accuracy

But ...

Direct maximization of the likelihood function is challenging



Treating **frailties** as **unobserved**, the **complete data likelihood** is:

$$\begin{split} L\left(\psi;\mathcal{D},\gamma\right) &= \prod_{i=1}^{n} \frac{\theta^{-\frac{1}{\theta}}}{\Gamma\left(\frac{1}{\theta}\right)} \times \gamma_{i}^{\frac{1}{\theta}-1} \times e^{-\frac{\gamma_{i}}{\theta}} \times \gamma_{i}^{\delta_{i1}+\delta_{i2}} \times \left[\lambda_{01}\left(Y_{i1}\right)e^{h_{1}\left(\mathbf{x}_{i}\right)}\right]^{\delta_{i1}} \\ &\times \left[\lambda_{02}\left(Y_{i2}\right)e^{h_{2}\left(\mathbf{x}_{i}\right)}\right]^{(1-\delta_{i1})\delta_{i2}} \times \left[\lambda_{03}\left(Y_{i2}-Y_{i1}\right)e^{h_{3}\left(\mathbf{x}_{i}\right)}\right]^{\delta_{i1}\delta_{i2}} \\ &\times \exp\left\{-\gamma_{i}\left[\Lambda_{01}\left(Y_{i1}\right)e^{h_{1}\left(\mathbf{x}_{i}\right)}+\Lambda_{02}\left(Y_{i1}\right)e^{h_{2}\left(\mathbf{x}_{i}\right)}+\delta_{i1}\Lambda_{03}\left(Y_{i2}-Y_{i1}\right)e^{h_{3}\left(\mathbf{x}_{i}\right)}\right]\right\} \end{split}$$

EM algorithm provides a numerically stable approach to estimation



The expected log-complete data likelihood, or 'Q' function, is

$$Q\left(\psi \mid \mathcal{D}, \psi^{(m)}\right) = Q_1 + Q_2 + Q_3 + Q_4,$$

where Q_1 , Q_2 , Q_3 , and Q_4 are **separable** w.r.t the **model parameters**



'Q' function components:

Sorry for the eye chart!

$$Q_{1} = \sum_{i=1}^{n} \delta_{i1} \mathbb{E}[\log(\gamma_{i}) | \mathcal{D}, \psi^{(m)}] + \delta_{i1} \{ \log[\lambda_{01}(Y_{i1})] + h_{1}(x_{i}) \} - \mathbb{E}[\gamma_{i} | \mathcal{D}, \psi^{(m)}] \Lambda_{01}(Y_{i1}) e^{h_{1}(x_{i})}$$

$$Q_{2} = \sum_{i=1}^{n} \delta_{i2} \mathbb{E}[\log(\gamma_{i}) | \mathcal{D}, \psi^{(m)}] + (1 - \delta_{i1}) \delta_{i2} \{ \log [\lambda_{02} (Y_{i2})] + h_{2}(\mathbf{x}_{i}) \} - \mathbb{E}[\gamma_{i} | \mathcal{D}, \psi^{(m)}] \Lambda_{02} (Y_{i1}) e^{h_{2}(\mathbf{x}_{i})}$$

$$Q_{3} = \sum_{i=1}^{n} \delta_{i1} \delta_{i2} \left\{ \log \left[\lambda_{03} (Y_{i2}) \right] + h_{3}(\mathbf{x}_{i}) \right\} - \mathbb{E}[\gamma_{i} | \mathcal{D}, \psi^{(m)}] \delta_{i1} (\Lambda_{03} (Y_{i2} - Y_{i1})) e^{h_{3}(\mathbf{x}_{i})}$$

$$Q_4 = \sum_{i=1}^n -\frac{1}{\theta} \log(\theta) + \left(\frac{1}{\theta} - 1\right) \mathbb{E}[\log(\gamma_i) | \mathcal{D}, \psi^{(m)}] - \frac{1}{\theta} \mathbb{E}[\gamma_i | \mathcal{D}, \psi^{(m)}] - \log \Gamma\left(\frac{1}{\theta}\right)$$



We **extend** the EM algorithm to a **hybrid multi-task deep learning** approach for semi-competing risk prediction:

E-Step: Frailties *imputed* given data, current M-Step estimates

M-Step: Estimate non-parametric **cumulative baseline hazard** by non-decreasing step functions and **frailty variance**

N-Step: Maximize the 'Q' function w.r.t. the **deep neural network parameters** for each risk function, $h_g(x_i)$; g = 1, 2, 3



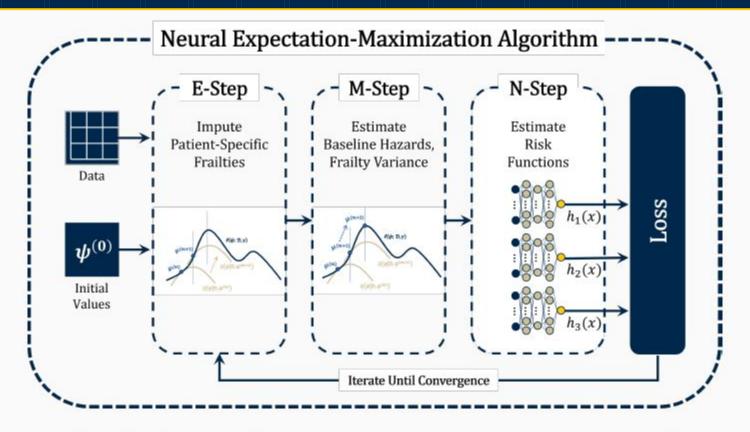


Figure: Overview of our proposed neural expectation-maximization algorithm



Further, no tailored metrics to assess *predictive accuracy*. We propose a *bivariate extension* to the *Brier Score* [Brier et al., 1950]

$$\begin{split} BBS_{c}(t) &= \frac{\pi_{i}(t)^{2} \cdot \mathbb{I} \left\{ Y_{i1} \leq t, \ \delta_{i1} = 1, \ Y_{i1} \leq Y_{i2} \right\}}{\hat{G}_{i}(Y_{i1})} \\ &+ \frac{\pi_{i}(t)^{2} \cdot \mathbb{I} \left\{ Y_{i1} \leq t, \ Y_{i2} \leq t, \ \delta_{i1} = 0, \ \delta_{i2} = 1, \ Y_{i1} \leq Y_{i2} \right\}}{\hat{G}_{i}(Y_{i2})} \\ &+ \frac{[1 - \pi_{i}(t)]^{2} \cdot \mathbb{I} \left\{ Y_{i1} > t, \ Y_{i2} > t \right\}}{\hat{G}_{i}(t)} \end{split}$$

$$\pi_{i}(t)$$
 is an **estimate of** $S_{i}(t) = Pr(T_{i1} > t, T_{i2} > t), G_{i}(t) = Pr(C_{i} > t) > 0$

E[BBS_c(t)] equals **MSE** of $\pi_i(t)$, plus a **constant** w.r.t. $\pi_i(t)$

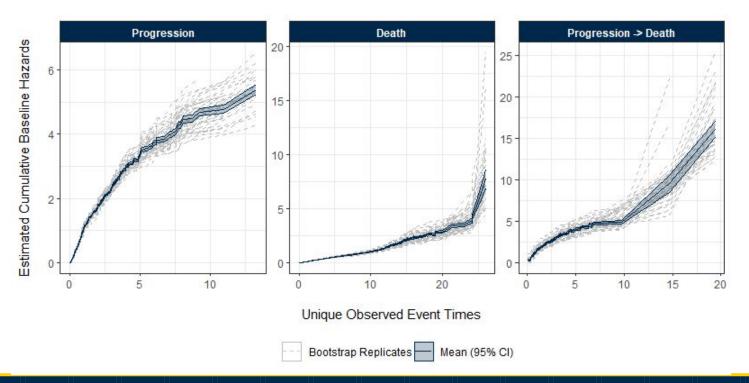


Returning to the Boston Lung Cancer Study, baseline hazards highest in sojourn time between progression and death

5-year *iBBS* for our method was 0.32 vs. 0.68 from a traditional model, suggesting that a linear model might not be *as predictive*



Estimated *cumulative baseline hazards* and 95% bootstrap CI





Our current work considers:



Efficiency



Interpretability



Causality



Some thoughts...

- Non-fatal events impact illness trajectories/treatment decisions
- Interested in 'true' effect of intervention/exposure on progression
- Progression is difficult to estimate and associations with risk factors/treatments are forgone despite being of clinical interest



Our proposal...

A three-stage approach for estimating the *causal effect* of treatment on a *non-fatal outcome* in the presence of *dependent censoring*:

- 1. Derive the marginal, non-fatal survival function
- 2. Impute our outcome using jackknife pseudo-values
- 3. Estimate average treatment effect using causal deep learning



1. Derive the marginal, non-fatal survival function

$$S_1(t) = [S_*(t)^{1-\theta} - S_2(t)^{1-\theta} + 1]^{1/(1-\theta)}$$

Where $S_*(t)$ is the **progression-free** survival function, $S_2(t)$ is the marginal **fatal survival** function, and θ is the **copula parameter**

Based on Clayton copula with connection to previous GFCMM



1. Marginal distribution of non-fatal event time as a function of event-free survival and fatal event survival is always estimable

Need to **estimate** θ , the frailty variance (restricted GFCMM) and equivalent **dependency parameter** (Clayton Copula) "ad hoc"

→ Using extended *concordance estimator* of Oakes (1982) proposed in Fine et al. (2001)



2. Impute our outcome using jackknife pseudo-values

$$\hat{S}_{1}^{i}(t) = n \hat{S}_{1}(t) - (n-1) \hat{S}_{1}^{-i}(t)$$

where $\hat{S}_1(t)$ and $\hat{S}_1^{-i}(t)$ are the **estimates** of $S_1(t)$ using **all** n subjects and **excluding** the ith subject, respectively.

This *leave-one-out* estimator for $S_1(t)$ represents the *contribution* of the *i*th individual in estimating $E[S_1(t)]$ in the sample



3. Estimate average treatment effect using causal deep learning

The average causal risk difference is given by:

$$E[I(T_{i1}^{1} > t)] - E[I(T_{i1}^{0} > t)]$$

An estimate of the **ATE** for the average causal risk difference is:

$$\hat{ATE} = 1/n \sum_{i} \hat{S}_{i1}(t \mid X_i, Z = 1) - \hat{S}_{i1}(t \mid X_i, Z = 0)$$

For a causal variable of interest, **Z**

3. Estimate average treatment effect using causal deep learning

Predict *potential outcomes* and estimate the survival ATE by modeling pseudo-values conditional on *risk factors* in *DNN*

Network output optimized under the common **binary cross-entropy** loss function

→ Faster *learning rate/convergence* than MSE due to *steeper gradient* when the predicted output is far from the true output



- Survival probabilities are more natural to interpret than hazards
- Because we have a **consistent estimate** of $S_1(t)$
 - 1. $S_1^i(t)$ is approximately independent of $S_1^j(t)$ for $i \neq j$ as $n \to \infty$
 - 2. $\lim_{n\to\infty} E[S_1^i(t) \mid Z_i, X_i] = S_1(t \mid Z, X)$
- With (1) and (2), these *pseudo-values* can be used as a *response* variables in our deep learning framework
- Imputed outcome *more efficient* for deep learning



Preliminary Simulations:

Example comparison ATE calculation for parametric vs. proposed method with *linear* vs. *non-linear* risks generated

Risk Function	Empirical ATE	Parametric		Proposed	
		Bias	MSE	Bias	MSE
Linear	0.3100	0.0183	0.0003	0.0157	0.0002
Non-Linear	0.3283	0.0590	0.0035	0.0343	0.0012



Preliminary Analysis of the BLCS Study:

Considered n = 4,700 patients in the BLCS with **NSCLC** and **stage 1-3a** (considered operable) at diagnosis

Estimated **average difference** in probability of 5-year time-to-progression between **first-line treatment** options

→ *Surgical resection* vs. *chemotherapy or radiation*, adjusting for socio-demographic and genetic risk factors



Preliminary Analysis of the BLCS Study:

Estimated survival conditional **ATE of 0.156**, suggesting potential **longer-term benefit** of surgery, consistent with current literature

Estimated **copula dependence** between progression and survival to be θ = 4.38, corresponding to a **Kendall's** τ = 0.6865



Overall...

Clinical motivation for this work comes from the semi-competing nature of patient health events in the Boston Lung Cancer Study

Statistical motivation comes from **interest in methods** for high-dimensional survival analysis, deep learning, causal inference

Many exciting opportunities for future development



Some next steps...

Prediction intervals to quantify uncertainty

Extending these methods and our analysis to incorporate

- Longitudinal risk factors over disease course
- High-dimensional covariate, such as CT imaging features
- More comprehensive events (e.g. second primaries)





Data science is ubiquitous in big business and academic research

What about ...



A **community foundation** allocating \$18 million to improve **quality of life** services for seniors?

A *mobile food pantry* determining optimal *service locations* in low-income areas?

A **youth center** predicting **crisis calls** from high-risk, runaway, and homeless youth?







Community organizations also stand to benefit from statistical insight ...

... they may lack the time, resources, or knowledge to collect and analyze data



Statilicom | Statistics in the Community

A community outreach program that offers the expertise of graduate students, free of charge, to non-profit governmental and community partners in the areas of data organization, analysis, and interpretation.



2001: STATCOM founded at Purdue

2006: ASA Member Initiatives Grant

2006: 10 chapters chartered, including Michigan!

2016: Most defunct, Michigan growing

2023: Michigan STATCOM is thriving

STATCOM'S ENGAGEMENT

TAKEN FROM WHEN I STARTED IN 2016 UNTIL TODAY

62

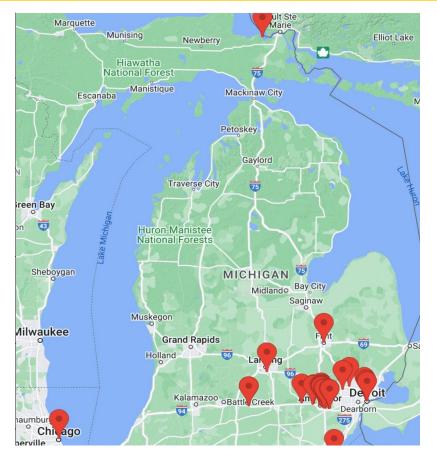
PROJECTS COMPLETED

255

MEMBERS ENGAGED 10

DEPARTMENTS REPRESENTED













Ann Arbor Area Community Foundation



ADVOCATE CELEBRATE



Alliance for Contraception in Cats & Dogs





PUBLIC HEALTH





Answers you can trust



Genesee County Health Department

gatherers

Your Health. Our Work.





statilicom **60+ Survey of Washtenaw County**



The AAACF received \$18 million dollars to help improve the quality of life of older adults aging in place within the county, especially those with lower life expectancy and socioeconomic status



Project Overview

AAACF partnered with STATCOM and the Ginsberg Center at UM to write, distribute, and analyze a survey assessing the quality of life of older adults (60+) aging in place in Washtenaw County



\$



Zip Code

48197 48198 Rent Assistance

Medicaid Not Enough Money

Financial

Living Alone

Living Alone

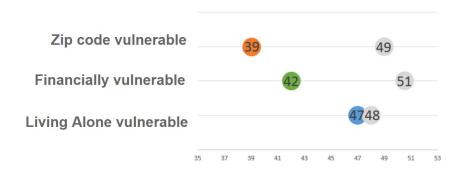




Why This Matters

Results are being used to allocate funding for services to older adult populations within the county, and community reports have informed decision making for local governments in smaller regions of the county

Vulnerable older adults have lower quality of life

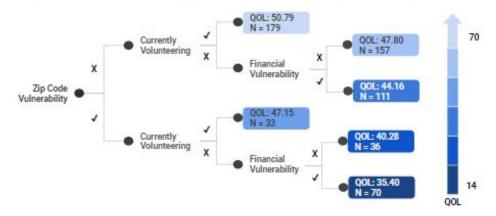




- Our Results

Tree-based modeling showed that respondents living in vulnerable zip codes, who were not volunteering, and who were financially vulnerable comprised the lowest average quality of life group.

Zip Code + Not Volunteering + Financial Vulnerability = Lowest QOL





Why was this a good project?

- 1. STATCOM involved from conception to conclusion
- 2. Leveraged community partnerships for success
- 3. Findings were used to inform policy decisions
- 4. Students directly impacted this population

Our Current Projects (mine in yellow):

- Starr Commonwealth
- The Konnection
- Stand with Trans
- Michigan Center for Youth Justice
- Poverty Solutions

66

It's incredibly beneficial having highly trained & knowledgeable STATCOM representatives help us analyze our data on recent graduate outcomes. They helped us get to the 'aha' moment of understanding the story about what the data was telling us. I am so thankful for the help I received at STATCOM.

Shelagh Saenz, STATCOM Community Partner





What has contributed to our growth?

- Departmental Support/Encouragement
- Dedicated Student Volunteers
- Strong University Partnerships



Our department supports experiential learning

STATCOM is a natural way for students to apply what they have learned in class while working in a team-based paradigm

It develops important skills all students should have when pursuing a graduate degree while giving back to the community

66

STATCOM provides a **great opportunity** to use data to help organizations focused on **public good**. It allows me to use my skills to help these organizations run more efficiently and **answer important questions**.

Tim NeCampFormer STATCOM President



University Partnerships





















NCSU-STATCOM

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STATCOM: Revitalization of Statistica **Community Service at Universities**

1 APRIL 2018 2 938 VIEWS ONE COMMENT

Evan Revnolds and Timothy NeCamp

Universities provide valuable resources for providing pro-bono statistical services, include connections and many statistically inclined students eager to apply their skills. STATCO of Michigan is leveraging these resources to increase its benefit to both the community While several universities with graduate statistics and biostatistics programs founded ST the 2000s, much of their activity has declined since then. In contrast, STATCOM is large than ever at the University of Michigan.

National Outreach

8 People Statistics in the Community At Columbia University's Mailman School of Public Health

reach program provided to New York City by graduate students in the Department of Biostatistics at Mailman nal statistical consulting, free of charge, to non-profit community and local governmental groups in the areas of data organization, analysis, and interpretation

Our History

ras founded in 2001 at Purdue University's Department of Statistics with support from a Member Initiatives Grant Association (ASA). Since then a network of STATCOM programs has been established and active chapters are nd Ricetatistics departments throughout the country. The Columbia University chanter was founded in 2021 by

+ Add to My Program Thu, 8/6/2020, 3:00 PM - 4:50 PM

Teaching Data Science for Good: How University-Based Initiatives Are Shaping Future Statisticians Section on Statistical Consulting, Social Statistics Section, Section on Statistics and Data Science Educ

Organizer(s): Emily L Morris, Department of Biostatistics, University of Michigan

Chair(s): Emily L Morris, Department of Biostatistics, University of Michigan

3:05 PM Data for Good in Your Neighborhood: How Graduate Students and Local Communities Benefit from Collaborative

Partnerships Presentation

Stephen Salerno, University of Michigan

3:35 PM "Data for Good" at Columbia's Data Science Institute Tian Zheng, Columbia University

4:05 PM Data Science Education as an Economic and Public Health Intervention: How (Bio)Statisticians Can Lead Change in the World Jeff Leek, Johns Hopkins Bloomberg School of Public Health

4:35 PM Floor Discussion

Organizer(s): Leah Jager, Johns Hopkins Bloomberg School of Public Health

Chair(s): Leah Jager, Johns Hopkins Bloomberg School of Public Health

Can Data Science Education Be Used as a Tool for Upward Mobility?

sentation Aboozar Hadavand, Johns Hopkins University, Bloomberg School of Public Health

Incorporating Community-Based Learning Into the Classroom resentation Lynne Steuerle Schofield, Swarthmore College

2:25 PM Statistics in the Community: Community-University Partnerships Fostering Data Science Education

Stephen Salerno, Department of Biostatistics, University of Michigan

Bloomberg D4GX (2018)



Data for Good In Your Neighborhood: A case study on how data can benefit your local community

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Data for Public Good Symposium

STATCOM, CTAC, CEDER, and MIDAS host a symposium to showcase research efforts and community-based partnerships that improve humanity by using data for good





Abstract:





STATCOM hosts a series of workshops in R syntax, exploratory data analysis, data visualization, and reproducible research with RMarkdown/Projects:





Learn R, in R.

swirl teaches you R programming and data science interactively, at your own pace, and right in the R console!



Current Priorities/Goals:

- Engage more community partners and students
- Create sustainable processes and documentation
- Continue national outreach efforts
- Fund a student coordinator in our department



















personal ones,



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arxiv.org/abs/2212.12028



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