Causal PheWAS

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Verity Bioinformatics Retreat 2024

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Today's Agenda

- Describe a relevant set-up and motivation
- Review the set-up and preliminary analysis of a Hawkes Process approach
  - Currently a simplified set-up: limited to cardiovascular PheCodes, binary treatment comparison, and exponential Hawkes kernel
  - Review "results" for their relevance, intepretability
- Questions/Discussion Primers

Outline

PheWas Set-Up

- Phenome-Wide Association Study
  - A “inversion” of the GWAS

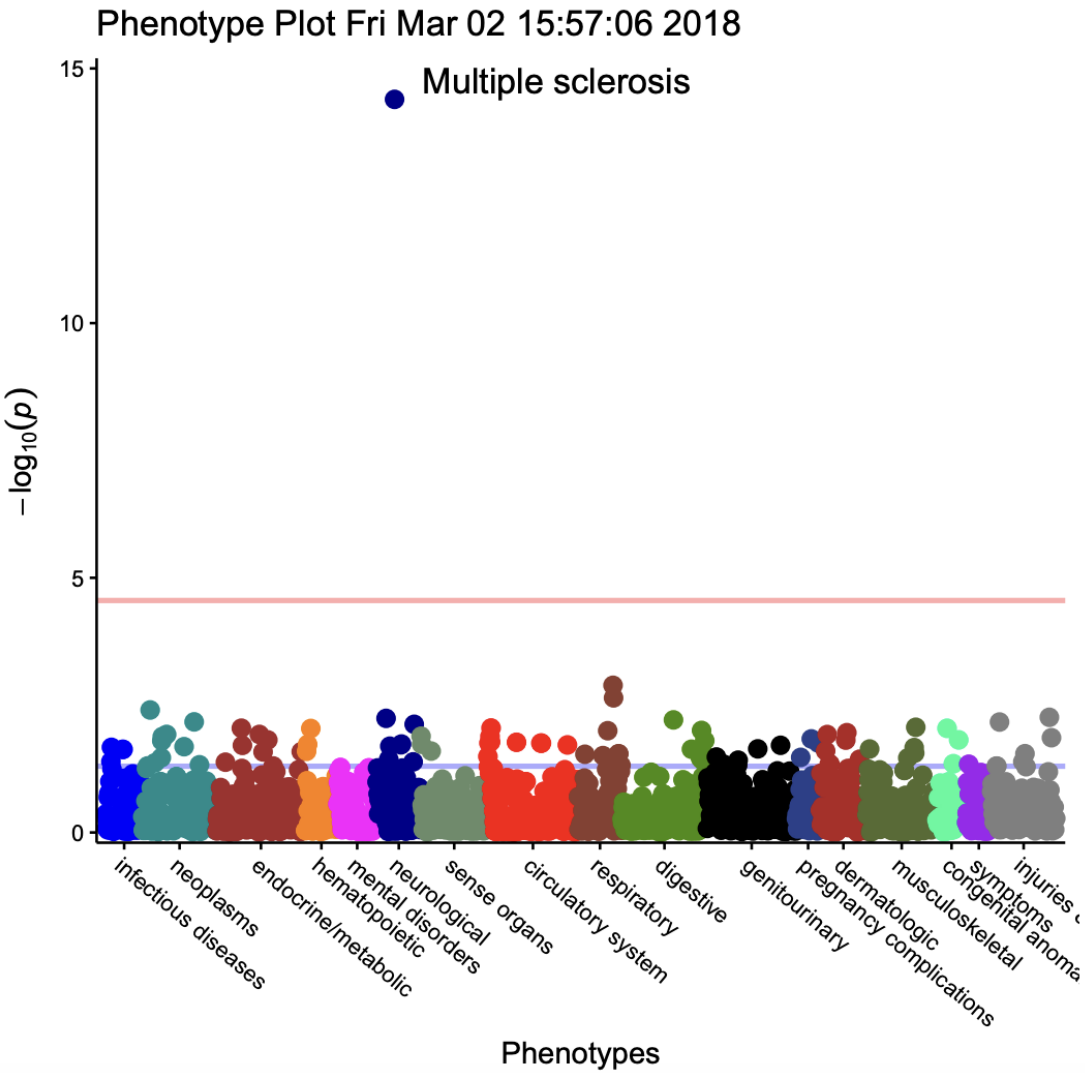

Figure: PheWAS Manhattan-Style Plot, via Carroll (2018) *Phenome Wide Association Studies (PheWAS) in R*

PheWas Set-Up

- Phenome-Wide Association Study
  - A "inversion" of the GWAS
- Apt set-up for studying unintended (ideally positive) consequences of current treatments
  - Identifying targets for off-label use
  - Secondary outcome mitigation

Causal PheWAS

- A typical/simple causal problem may compare a single outcome between two treatment groups
  - e.g. $\mathbb{E}[Y(1) - Y(0)]$, the average treatment effect
- For multivariate (or high-dimensional) $\mathbf{Y}$, naïve (i.e. outcome-by-outcome) analysis is unsatisfactory
- Exising PheWAS papers and implementations tend to follow this more naïve analytic strategy

Hawkes Process Modelling

- Structured EHR data (such as PheCodes)[1] provide high-dimensional outcome data
  - Along with longitudinal/accumulation information
- Self-exciting counting processes are a natural modelling choice, i.e. mutually-exciting Hawkes processes
  - Adverse mental health events
  - Infectious period of a disease
  - Canonical example of earthquakes and aftershocks

[1] and related ontologies, e.g. RxNorms, CPT codes, etc.

Hawkes Process Modelling

- A process is uniquely identified by its "intensity function"
  - $\lambda_i(t) = \mathbb{P}(\text{An event occurs from } t \text{ and } t + \Delta t \mid \text{Patient's event history})$
  - "Instantaneous risk"

- Can parameterize the intensity function of a p-dimensional process as

$$\lambda_i(t; \boldsymbol{\mu_i}, \boldsymbol{\alpha}, \boldsymbol{\beta}) = \mu_i + \sum_{i=1}^{p} \sum_{t_{jk} < t} \alpha_{ij} \exp\{-\beta_{ij}(t - t_{jk})\}$$

  - μ_i - "baseline intensity" for event type i
  - α_{ij} - "intensity excitation for event of type i after an event of type j"
  - β_{ij} - "intensity decay for event of type i after an event of type j"

Hawkes Process Modelling

- Can write treatment-group specific intensities and compare
  - $\lambda_k^{(0)}(t)$ the hypothetical intensity function for a TNFi persister at time t
  - $\lambda_k^{(1)}(t)$ the hypothetical intensity function for a switcher at time t
- What can we compare about intensity functions (and what is useful to ask/compare)?
  - $\hat{\lambda}_k^{(1)}(t) - \hat{\lambda}_k^{(0)}(t)$
  - $\hat{\alpha}_{ij}^{(1)} - \hat{\alpha}_{ij}^{(0)}$
  - $\hat{\beta}_{ij}^{(1)} - \hat{\beta}_{ij}^{(0)}$

Outline

Preface

Goals include attempting to:

- Identify what research questions are useful to ask
- Interrogate how to pursue, estimate, present

Patients

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- RA diagnosis from 2016-Present
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Set a 4-year endpoint of observation window

Cohort/Treatment Summary Slide

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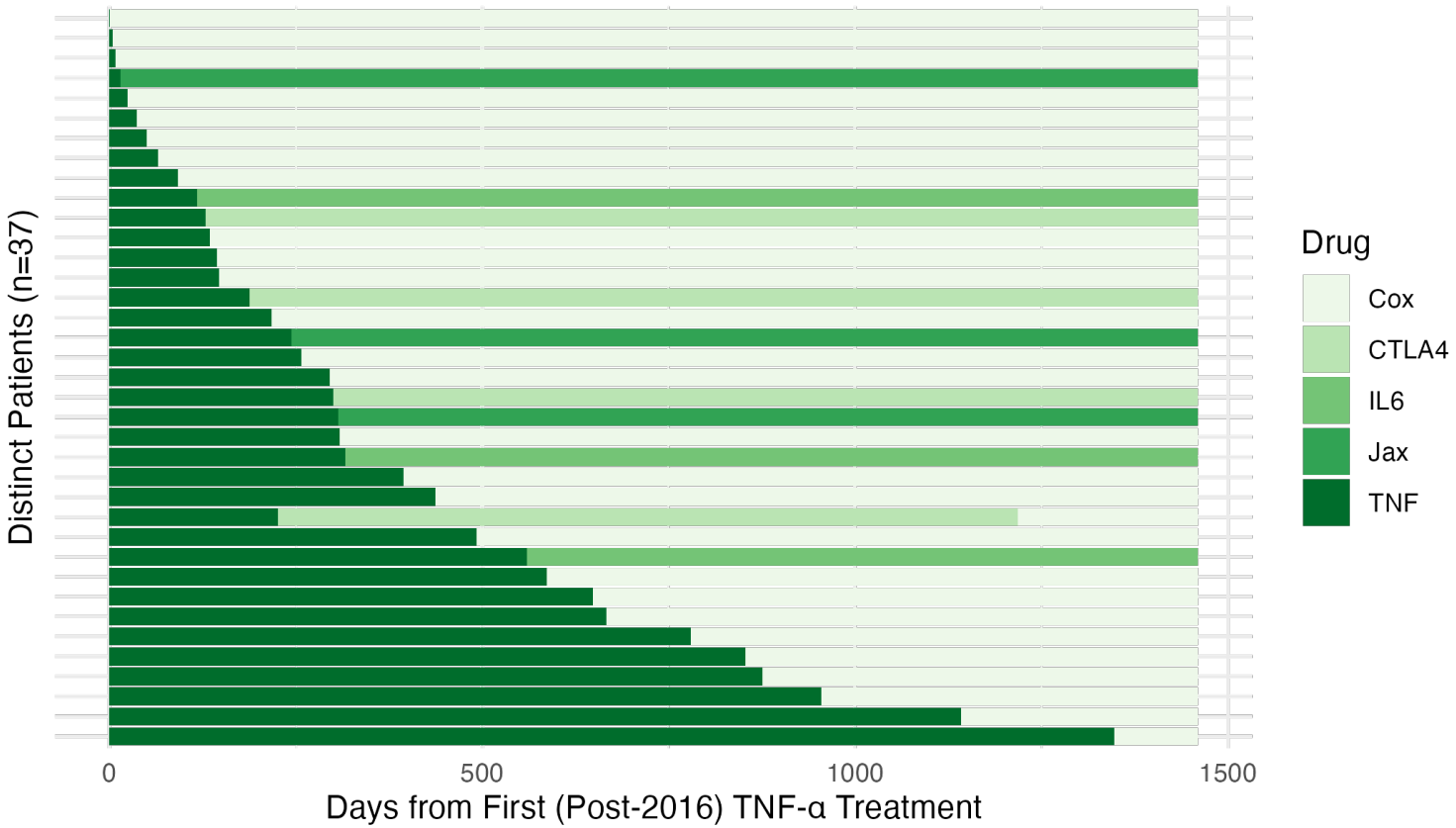

Figure: Timing and class of treatment change (among $n = 37$ "switchers")

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  - These constitute our $p = 27$ mutually exciting processes
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  - These constitute our $p = 27$ mutually exciting processes
  - Solely a convenience/simplifying construction for our analysis
- $n = 94$ patients has at least one event among these $p = 27$ PheCodes (after 3-digit truncation)
  - 71 ($\sim$75% remained on TNF-α medications throughout their history, 23 ($\sim$25% switched)

Observed PheCodes as Hawkes Processes

- Assigned binary treatment, "TNF-α inhibitors only" compared to "any-time drug-switch"
  - "Drug-switch" is any post-TNF records of IL-6, COX, JAK, CTLA6, or Anti-CD20 related medications
  - Currently excluding patients who received non-TNF drugs prior to TNF start date
- Began observation period at TNF initiation date
  - i.e. Day 0 is earliest date of TNF receipt

Hawkes Process Parameterization

- We observed these $p = 27$ inter-related counting processes (i.e. PheCodes occurring across time)
- We can parameterize their intensity functions $\lambda_i(t)$
  - Most easily interpreted as an "instantaneous risk" of an event occurring at time t

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- Eliding some details, we can write separate intensity functions for events under TNF-α inhibitors and under other treatments
  - $\hat{\lambda}^{(0)}$ describes the intensity function for an event occurring for a patient treated by a TNF-α inhibitor
  - $\hat{\lambda}^{(1)}$ for the intensity function of events observed under any other treatment

Hawkes Process Parameterization

- $\lambda_i(t) = \mu_i + \sum_{i=1}^{p} \sum_{t_{jk}<t} \alpha_{ij} \exp\{-\beta_{ij}(t - t_{jk})\}$
  - μ - "baseline intensity"
  - α_{ij} - "intensity excitation"
  - β_{ij} - "intensity decay"

- Can write treatment-group specific intensities
  - $\lambda_i(t)^{(0)} = \mu_i^{(0)} + \sum_{i=1}^{p} \sum_{t_{jk}<t} \mathbb{1}(t_{jk} \leq t_{switch}) \alpha_{ij}^{(0)} \exp\left\{-\beta_{ij}^{(0)}(t - t_{jk})\right\}$
  - t_{switch} is time of switch from TNF-inhibitor

Cohort/Treatment Summary Slide

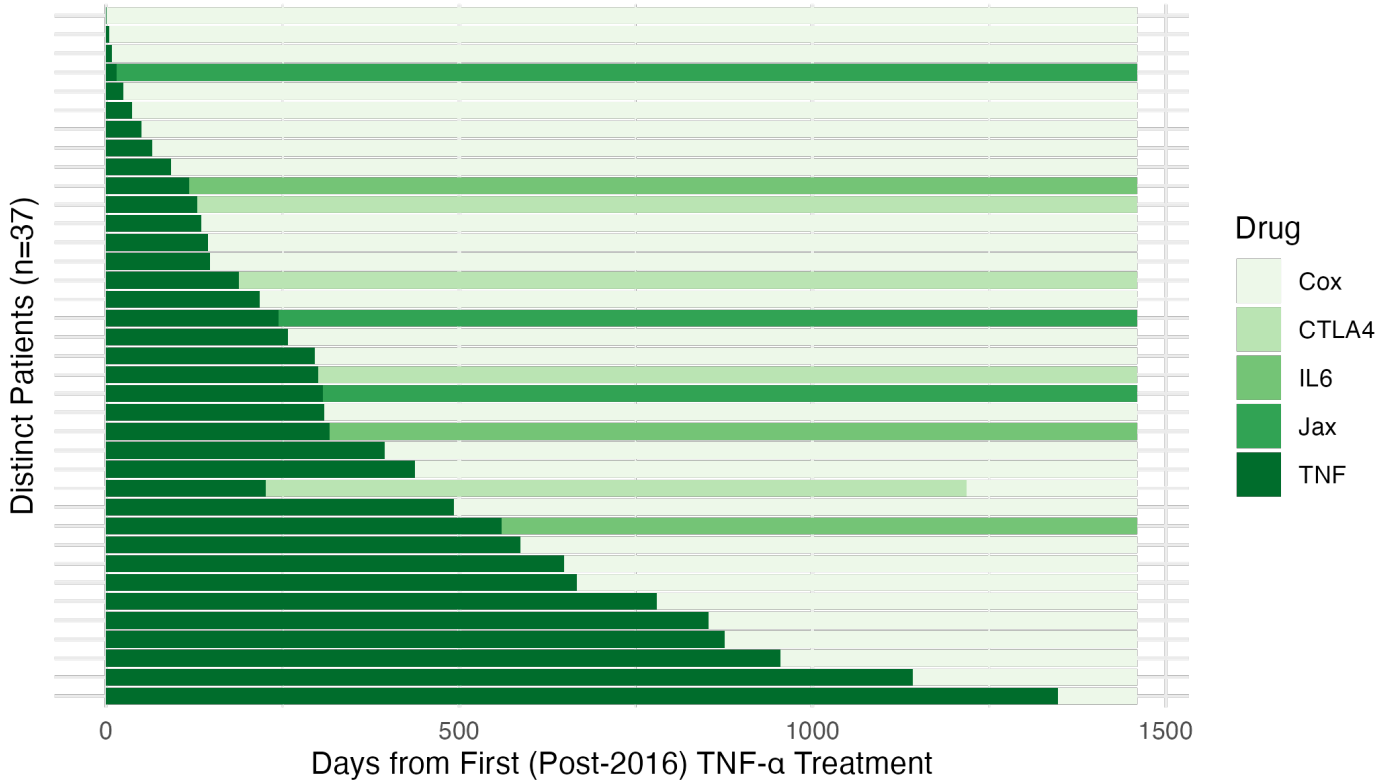


Figure: Timing and class of treatment change (among $n = 37$ "switchers")

Darkest green, pre-switch events contributed to estimation of $\hat{\alpha}^{(0)}, \hat{\beta}^{(0)}$

(Simple) Estimation Set-Up

- Estimate $\hat{\boldsymbol{\mu}}, \hat{\boldsymbol{\alpha}}, \hat{\boldsymbol{\beta}}$ by maximum likelihood separately by pre- and post-switch events
  - $\hat{\boldsymbol{\mu}}^{(\mathbf{0})}, \hat{\boldsymbol{\alpha}}^{(\mathbf{0})}, \hat{\boldsymbol{\beta}}^{(\mathbf{0})}$ (under TNF-α inhibitors)
  - $\hat{\boldsymbol{\mu}}^{(\mathbf{1})}, \hat{\boldsymbol{\alpha}}^{(\mathbf{1})}, \hat{\boldsymbol{\beta}}^{(\mathbf{1})}$ (under treatment switching)

- Compare the calculated intensity functions
  - $\lambda^{(0)}(t; \boldsymbol{\mu}^{(\mathbf{0})}, \boldsymbol{\alpha}^{(\mathbf{0})}, \boldsymbol{\beta}^{(\mathbf{0})})$ and $\lambda^{(1)}(t; \boldsymbol{\mu}^{(\mathbf{1})}, \boldsymbol{\alpha}^{(\mathbf{1})}, \boldsymbol{\beta}^{(\mathbf{1})})$
  - The related research question is somewhat diffuse: "Is drug-switching effective?"

Example Conditional Intensity Comparison

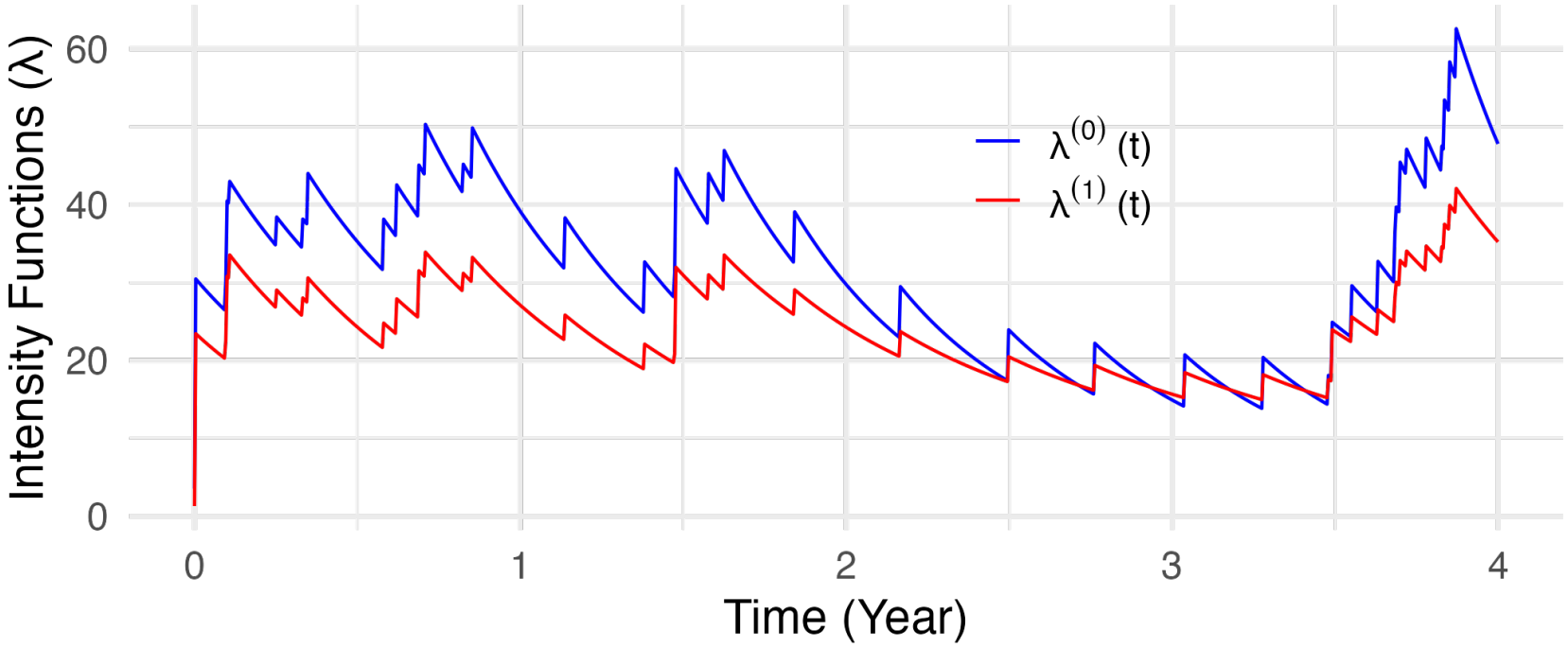


Figure: Conditional intensity function of for a single (arbitrary) patient's 427.** PheCodes

Example Conditional Intensity Comparison

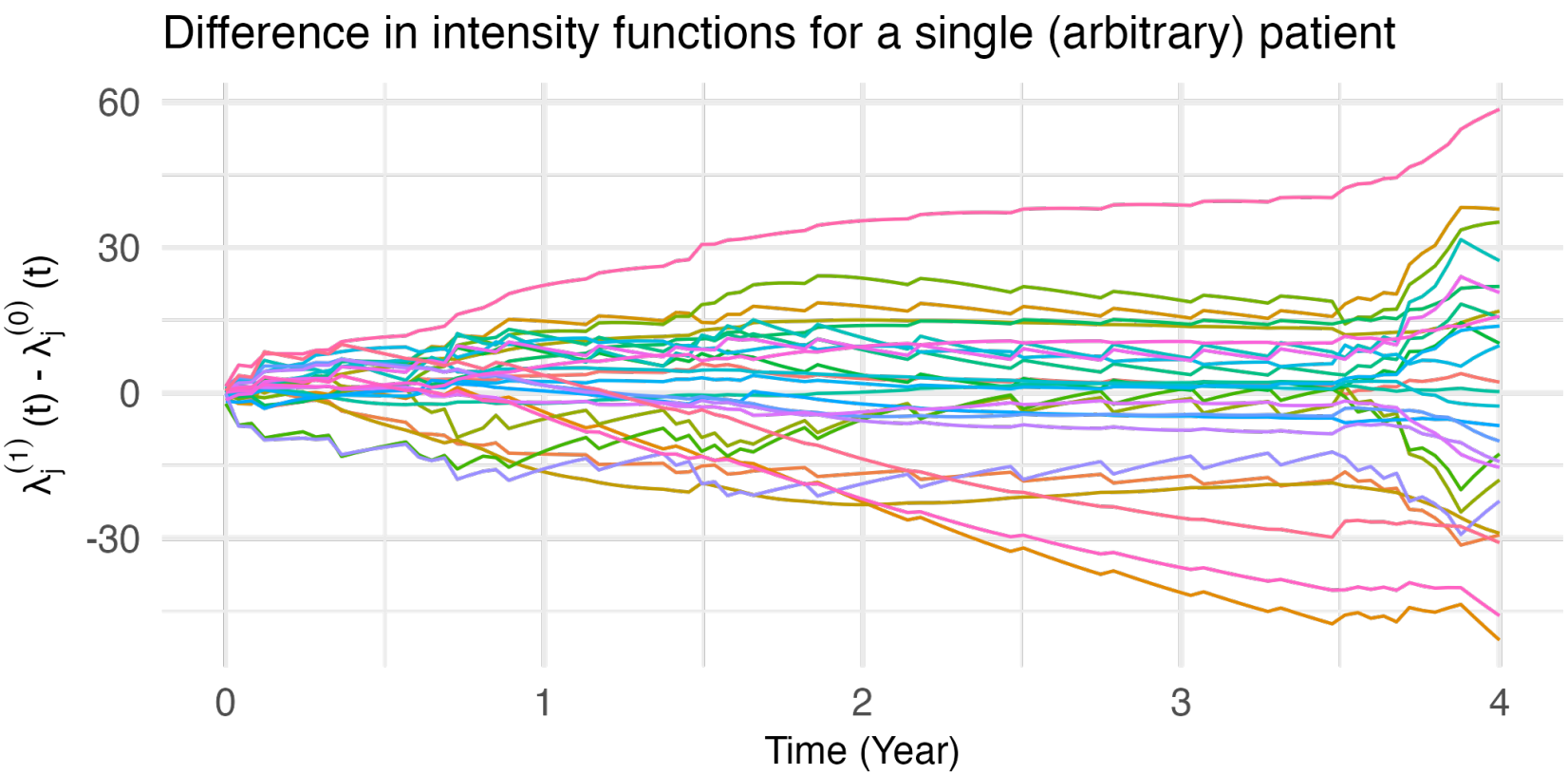
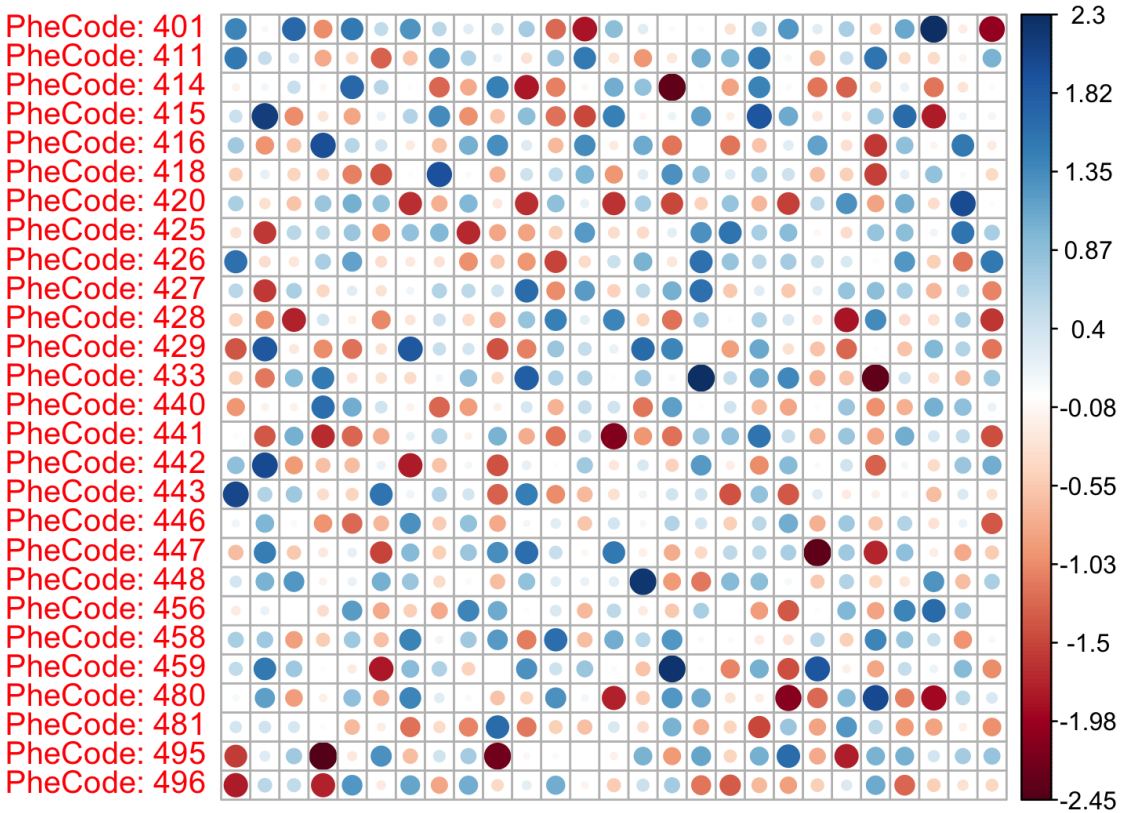


Figure: $\lambda_j^{(1)}(t) - \lambda_j^{(0)}(t)$ for all $p = 27$ processes (for a single arbitrary patient)

Parameter Difference Plots

$$\beta_{ij}^{(1)} - \beta_{ij}^{(0)}$$



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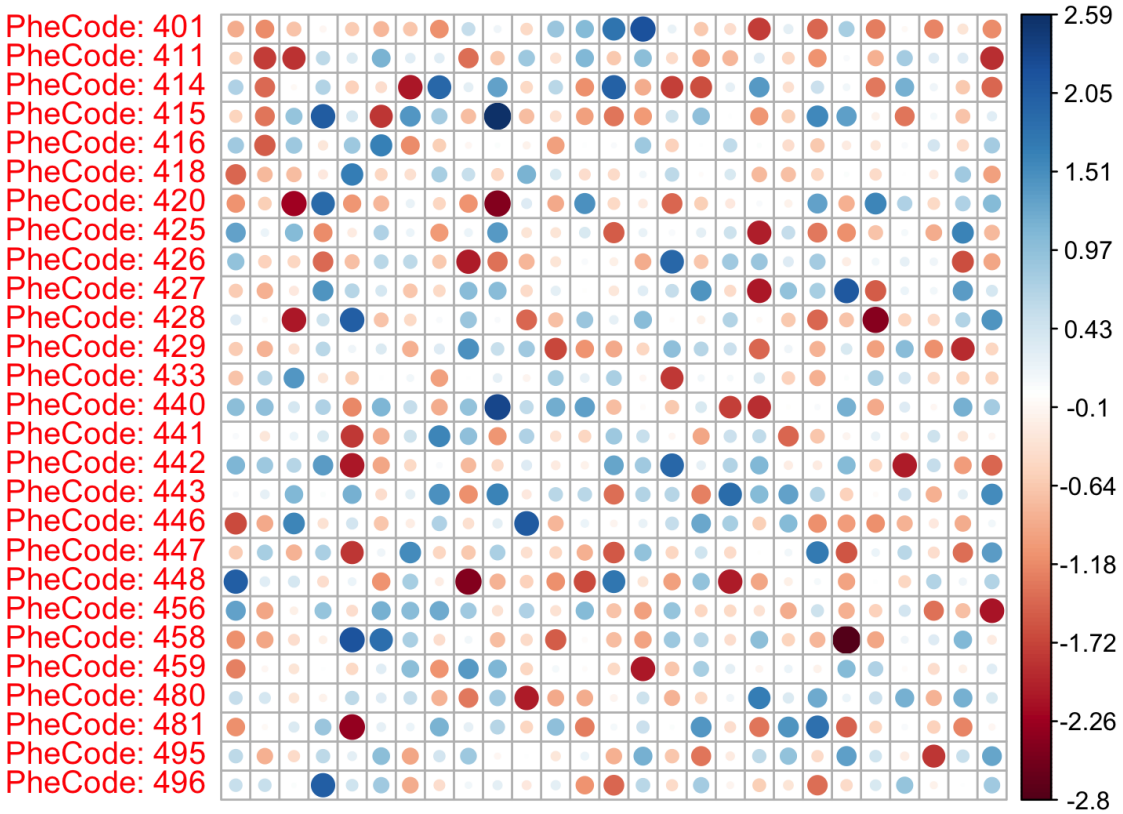

Summary

- The Hawkes process framework for PheWAS allows for nice, joint (and longitudinal) modelling
- Comparison of intensity functions $\lambda^{(1)}, \lambda^{(0)}$ is a natural and immediate estimand
  - Can compare parameters $\hat{\boldsymbol{\alpha}}, \hat{\boldsymbol{\beta}}$

References I

- PheWAS package in R https://github.com/PheWAS/PheWAS
- Darrous (2023) MR-PheWAS https://www.nature.com/articles/s41467-024-45655-8
- Lin (2024) RR-PheWas https://pubmed.ncbi.nlm.nih.gov/38699370/

Appendix

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Summary/Questions I

- What does the analysis comparing $\lambda^{(1)}, \lambda^{(0)}$ actually answer?
- Are other questions/estimands more relevant?
  - Optimal timing of drug-switching (related to assignment operator in LMTP's)
    - More of a policy-evaluation/learning question
  - Identifying related diseases with similar observed effects
    - Trying to build evidence of effectiveness by observing signal/differences among related pathologies
    - i.e. for disease i, examining $\boldsymbol{\beta}_{i,j_c:j_d}$ for "clusters" or relevant cooccurring code $\beta j_c, \cdots, \beta j_d$'s
  - What confounder medications to include as additional processes for cohort of persons with RA? Steroids/NSAIDS?

Summary/Questions II

- Symmetry of Hawkes parameters, that is should $\beta_{i,j} = \beta_{j,i}$ and/or $\alpha_{i,j} = \alpha_{j,i}$?
  - That is, should occurrence of PheCode j affect subsequent PheCode i in the same way as preceding PheCode i affects subsequent PheCode j
- Identifying assumptions (allowing us to argue more formally for causality)
- How to aggregate information across all patients? Solely through inference on parameters $\boldsymbol{\mu}, \boldsymbol{\alpha}, \boldsymbol{\beta}$?
  - Complication is that λ is a function of event history (i.e. arrival times)

Drugs/Drug Classes Considered I

Other drugs included but only the following observed in our cohort:

- **TNF Blockers:**
  - adalimumab
  - certolizumab
  - etanercept
  - golimumab
  - infliximab
- **IL-6 Inhibitors:**
  - sarilumab
  - tocilizumab
- **JAK Inhibitors:**
  - tofacitinib
  - baricitinib
  - upadacitinib

Drugs/Drug Classes Considered II

- **CTLA-4 Inhibitors:**
  - abatacept
- **COX Inhibitors:**
  - celecoxib
  - diclofenac
  - diflunisal
  - meloxicam
  - nabumetone
  - naproxen
  - piroxicam
  - rofecoxib
  - sulindac