Dissertation Work Formulation

Dominic DiSanto; Tianxi Cai & Junwei Lu

Department of Biostatistics, Harvard University

September 6, 2024

Today's Goals/Questions

- Review (high-level) treatment patterns in our data
- Review the set-up and initial results of preliminary Hawkes modelling of RA-related PheCodes
  - Simple set-up: exponential kernel, binary treatment, cardiovascular phecodes
- Review what questions/materials to prepare for Kat/retreat on the 20th

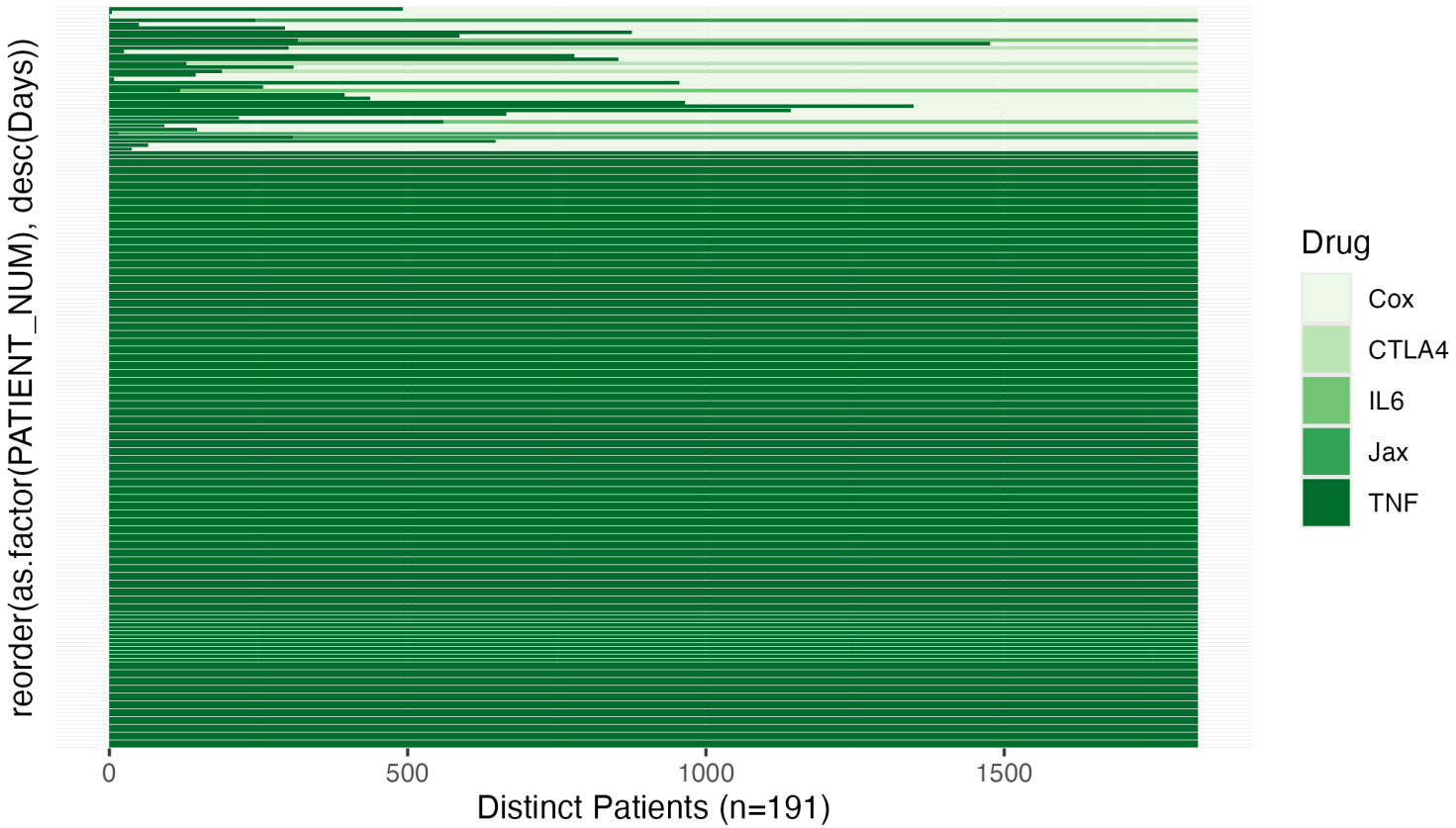
(Simple) Set-Up

- Began by focusing on cardiovascular related PheCodes (4**.**) codes, grouped at the three digit level (e.g. 400, 401, etc.)
  - These constitute our $p = 27$ mutually exciting processes
- Limited to patients with
  - RA diagnosis from 2016-Present
  - TNF-α treatment
  - No "other" treatment prior to TNF-α inhibitor initiation
- N=191 eligible patients, with P=364 distinct PheCodes
- When limiting to requiring cardiovascular codes, n=95 patients and p=27 PheCodes (after 3-digit truncation)
  - 72 ($\sim$75% remained on TNF-α medications throughout their history, 23 ($\sim$25% switched)

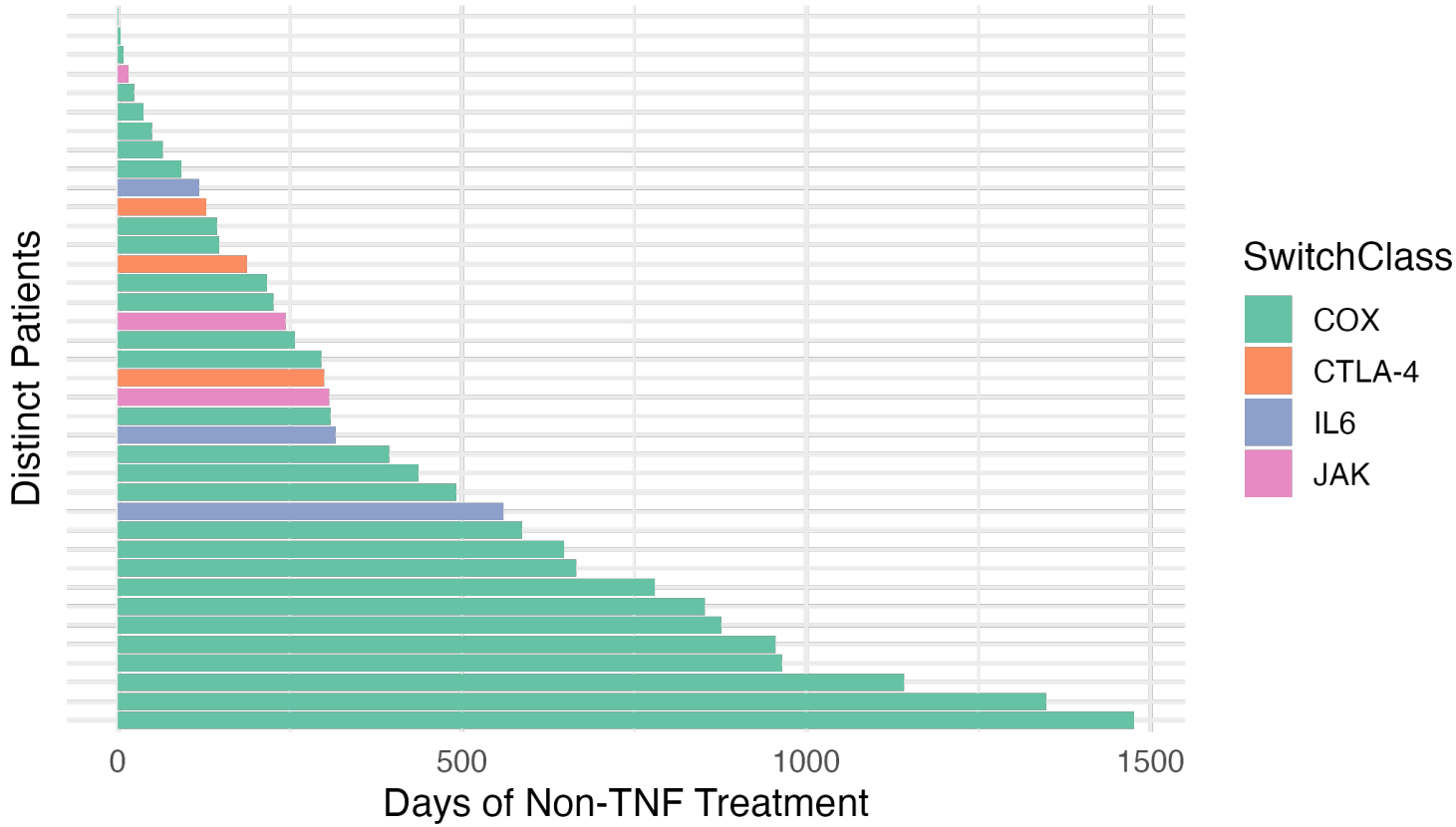
(Simple) Set-Up

- 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

Cohort/Treatment Summary Slide



Cohort/Treatment Summary Slide



(Simple) Estimation Set-Up

- Parameterize the Hawkes process with exponential decay kernel
  - $\lambda_i(t) = \mu_i + \sum_{j=1}^{p} \sum_{t_k < t} \alpha_{ij} \exp\{-\beta_{ij}(t - t_k)\}$

- Estimate MLE's $\hat{\boldsymbol{\alpha}}, \hat{\boldsymbol{\beta}}$
  - Estimated separately by treatment group (with pre-switch observations contributing to the TNF-only model until treatment-switching observed
  - More accurately can write $\hat{\boldsymbol{\alpha}}^{(0)}, \hat{\boldsymbol{\beta}}^{(0)}$ and $\hat{\boldsymbol{\alpha}}^{(1)}, \hat{\boldsymbol{\beta}}^{(1)}$

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

Example Conditional Intensity Comparison

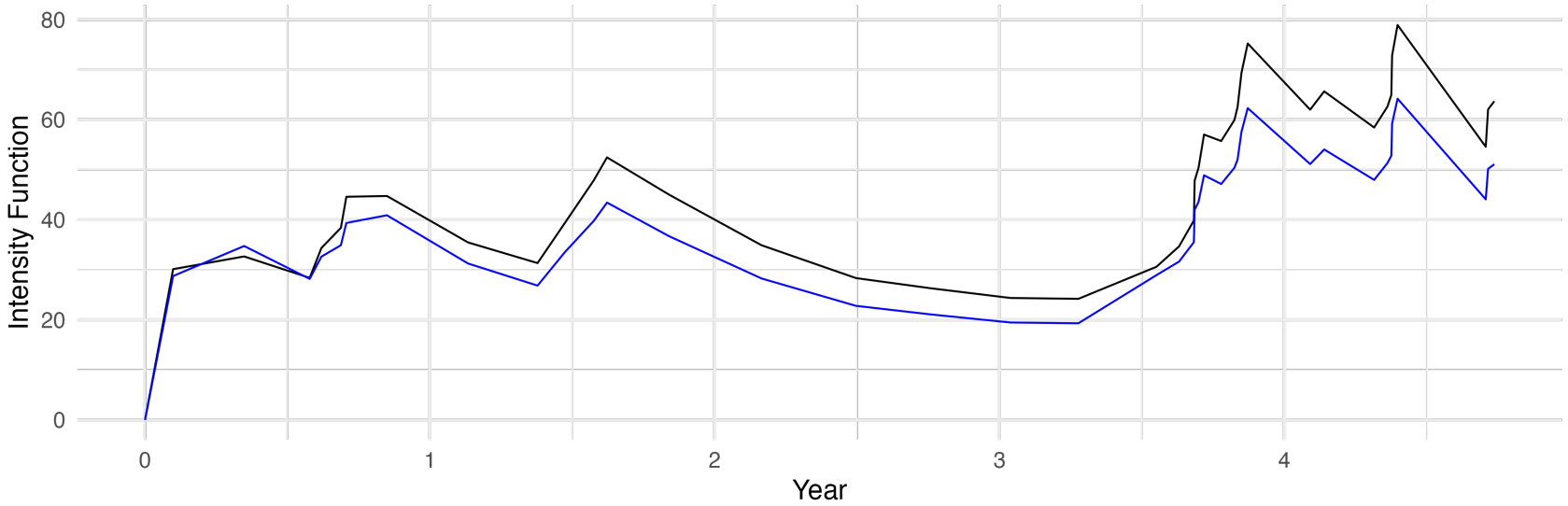


Figure: Conditional intensity function of for a single patient's 427.** pheCodes

Blue line represents $\lambda^{(0)}$ intensity function estimated under drug switching.
Black line the $\lambda^{(1)}$ under TNF-α inhibitors only.
Plotted for for an arbitrary patient, focusing on cardiac arrest codes (427.**)

Parameter Estimates

Parameter	Role	TNF-Only	Any-Drug Switch
μ_i	Baseline Intensity	0.957	0.002
$\alpha_{i,i}$	Event Excitation	3.533	2.437
$\beta_{i,i}$	Intensity Decay	1.542	1.252

Here i corresponds to the process representing PheCode 427.**, i.e. $\alpha_{i,i}$ is the self-excitation from other 427.** codes and $\beta_{i,i}$ the exponential decay parameter from other 427.** codes.

Summary/Questions

- 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
- Other useful results to prepare and present for Kat?
  - Plot about PheCode/event frequency

Logistics: Committee

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

Parameter Distribution by Treatment Group