Dynamic Treatment Regime in Parkinson's Disease

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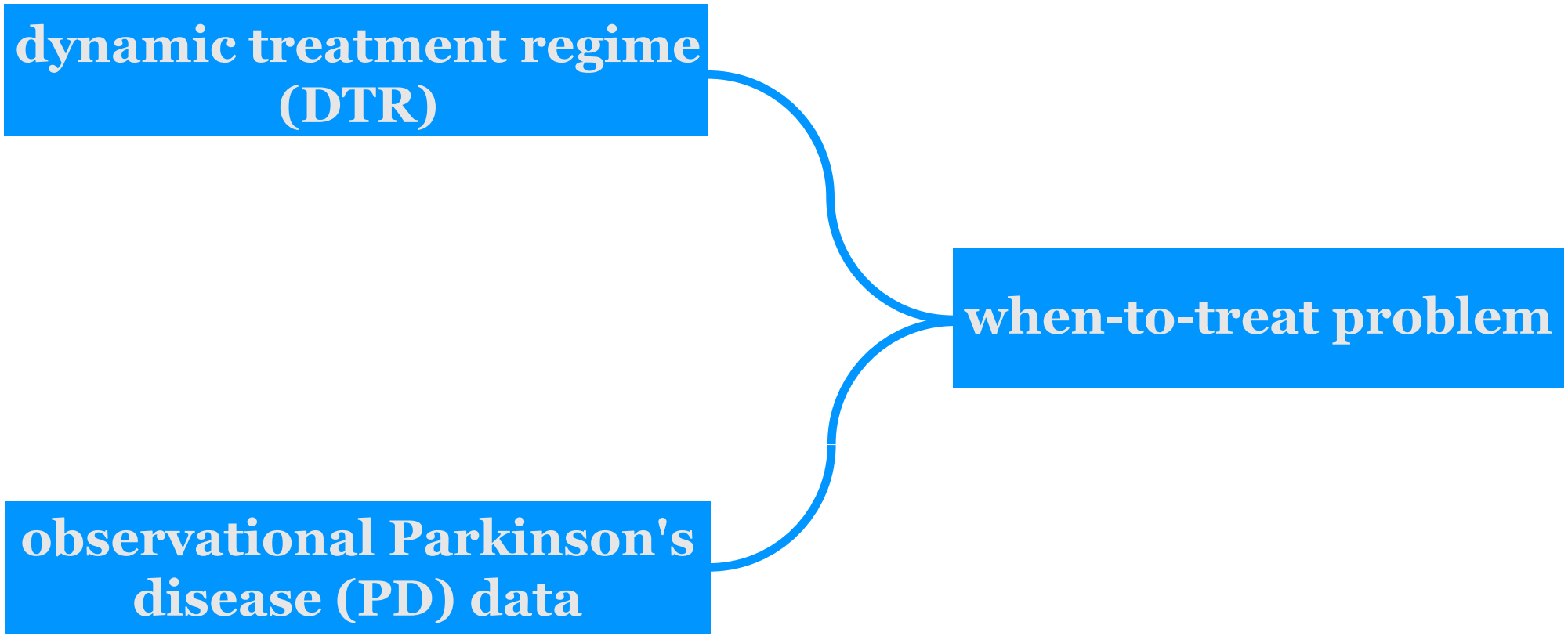
CONTENTS

GOAL


dynamic treatment regime (DTR)
observational Parkinson's disease (PD) data
when-to-treat problem

VALUE

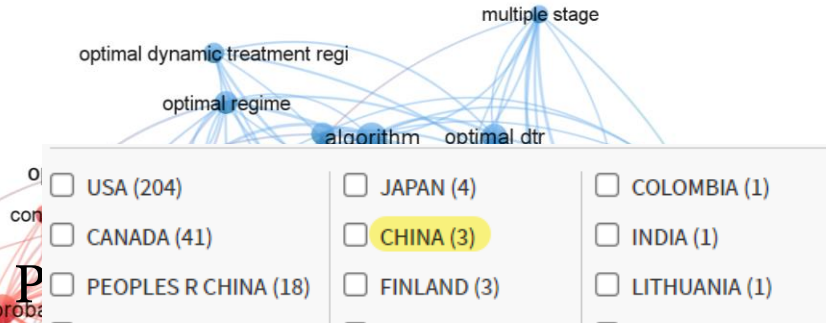
- for application: PD’s treatment guidance
- for methodology work: DTR + observational study

NECESSITY

- VOSviewr plot
- unbalanced development
- already has funding: DTR + PD

NECESSITY

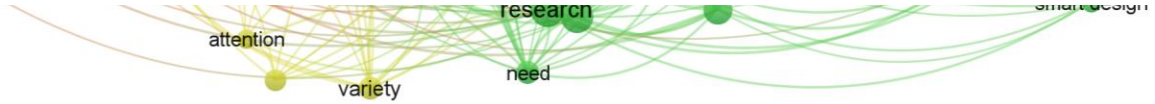
- VOSviewr plot
- unbalanced development
- already has funding: DTR + P



The Del Monte Institute awards a $50,000 grant to Dr. Ertefaie to study the comparative effectiveness of treatment strategies in Parkinson's Disease

March 2020

Among neurological disorders, the fastest growing is now Parkinson's disease (PD), surpassing Alzheimer's disease. Existing guidelines for symptomatic drug therapy for PD can best be described as "permissive". The relative lack of comparative evidence for different classes of drugs has created challenges in devising recommendations to follow any specific therapeutic strategy; indeed, there remains substantial heterogeneity in the choice of treatment strategies. The proposal aims to fill this important gap. A specific goal is to use the data collected as part of the Parkinson's Progression Markers Initiative (PPMI) study to identify a sequence of treatment decisions (drug classes) to optimize an outcome of interest; and construct a set of best treatment strategies. We will focus on motor complications, anxiety and depression scores measured at 3 and 24 months of treatment initiation as important clinical outcomes. Dr. Charles Venuto (URMC) is a co-investigator on this grant.



INTRODUCTION

- Parkinson's disease
  - progress measurements: MDS-UPDRS[1]
  - drugs: L-Dopa and DA-agonists
  - Parkinson's Progression Markers Initiative (PPMI)

[1] GOETZ C G, TILLEY B C, SHAFTMAN S R, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results [J]. Movement Disorders, 2008, 23(15): 2129-70.

INTRODUCTION

- dynamic treatment regimes
  - personalized medicine, reinforcement learning
  - concepts, notations
    - $x1 \rightarrow a1 \rightarrow x2 \rightarrow a2 \rightarrow x3 \rightarrow a3 \rightarrow y$ (h_3)
    - **blip function[1]**

$$\gamma_k(\boldsymbol{h}_k, a_k) = \mathbb{E}\left[Y^{\bar{\boldsymbol{a}}_{k-1}, a_k, \underline{\boldsymbol{a}}_{k+1}^{opt}} - Y^{\bar{\boldsymbol{a}}_{k-1}, a_k=0, \underline{\boldsymbol{a}}_{k+1}^{opt}} \mid \boldsymbol{H}_k = \boldsymbol{h}_k\right] \qquad a_k \; vs. \; a_k = 0$$

  - finding the optimal DTR

[1] ROBINS J M. Optimal Structural Nested Models for Optimal Sequential Decisions [Z]. Proceedings of the Second Seattle Symposium in Biostatistics. Springer New York. 2004: 189-326.10.1007/978-1-4419-9076-1_11

INTRODUCTION

- **blip function**

$$\gamma_k(\boldsymbol{h}_k, a_k) = \mathbb{E}\left[Y^{\bar{\boldsymbol{a}}_{k-1}, a_k, \underline{\boldsymbol{a}}_{k+1}^{opt}} - Y^{\bar{\boldsymbol{a}}_{k-1}, a_k=0, \underline{\boldsymbol{a}}_{k+1}^{opt}} \mid \boldsymbol{H}_k = \boldsymbol{h}_k\right]$$

  - decompose decision value

$$\mathbb{E}[Y^a \mid \mathbf{H} = \mathbf{h}; \boldsymbol{\beta}, \boldsymbol{\psi}] = \underbrace{f(\mathbf{h}_0; \boldsymbol{\beta})}_{\text{treatment-free model}} + \sum_{k=1}^{K} \underbrace{\gamma_k(\mathbf{h}_k, a_k; \boldsymbol{\psi}_k)}_{\text{blip function}}$$

  - optimal treatment regime

$$\begin{cases} a_k = 1, \gamma_k(\mathbf{h}_k, 1; \boldsymbol{\psi}_k) > 0 \\ a_k = 0, \gamma_k(\mathbf{h}_k, 1; \boldsymbol{\psi}_k) \leq 0 \end{cases}$$

METHODOLOGY

- Q-learning
  - Q-functions

    $Q_K(\mathbf{h}_K, a_K) = \mathbb{E}[Y \mid \mathbf{H}_K = \mathbf{h}_k]$ and

    $Q_k(\mathbf{h}_k, a_k) = \mathbb{E}\left[\max_{A_{k+1}} Q_{k+1}(\mathbf{H}_{k+1}, A_{k+1} \mid \mathbf{H}_k = \mathbf{h}_k, A_k = a_k)\right]$ for $k < K$.

  - function approximation

    $Q_k(\mathbf{h}_k, a_k; \boldsymbol{\beta}_k, \boldsymbol{\psi}_k) = \boldsymbol{\beta}_k^T \mathbf{h}_k^{\beta} + \boldsymbol{\psi}_k^T a_k \mathbf{h}_k^{\psi}$.

    ➡ optimal treatment regime: $\begin{cases} a_k = 1, \widehat{\boldsymbol{\psi}}_k^T \boldsymbol{h}_k^{\psi} > 0 \\ a_k = 0, \text{ otherwise} \end{cases}$

METHODOLOGY

- **dynamic weighted** ordinary least square (dWOLS)
  - why
  - how
    - propensity score weighting[1]
      $\pi(\mathbf{h})w(1,\mathbf{h}) = \big(1-\pi(\mathbf{h})\big)w(0,\mathbf{h}),\ \pi(\mathbf{h}) = P(A=1|\mathbf{h})$
    - pseudo outcomes
      $\tilde{y}_K = y \quad \text{and}$
      $\tilde{y}_k = y + \sum_{k+1}^{K} \mu_k\left(\mathbf{h}_k, a_k; \widehat{\boldsymbol{\psi}}_k\right) \quad \text{for } k < K.$
  - $\mathbb{E}[\tilde{Y}_k \mid \mathbf{h}_k, a_k; \boldsymbol{\beta}_k, \boldsymbol{\psi}_k] = \boldsymbol{\beta}_k^T \mathbf{h}_k^{\beta} + \boldsymbol{\psi}_k^T a_k \mathbf{h}_k^{\psi}$

[1] ROSENBAUM P R, RUBIN D B. The central role of the propensity score in observational studies for causal effects [J]. Biometrika, 1983, 70(1): 41-55.

METHODOLOGY

- **dynamic weighted** ordinary least square (dWOLS)
  - weighting

    $$\pi(\mathbf{h})w(1,\mathbf{h}) = \big(1-\pi(\mathbf{h})\big)w(0,\mathbf{h}),\ \underbrace{\pi(\mathbf{h}) = P(A=1|\mathbf{h})}_{treatment\ model}$$

  - regress on pseudo outcomes

    $$\mathbb{E}[\tilde{Y}_k \mid \mathbf{h}_k, a_k; \boldsymbol{\beta}_k, \boldsymbol{\psi}_k] = \underbrace{\boldsymbol{\beta}_k^T \mathbf{h}_k^{\beta}}_{treatment-free\ model} + \underbrace{\boldsymbol{\psi}_k^T a_k \mathbf{h}_k^{\psi}}_{(stage\ k)\ blip\ function}$$

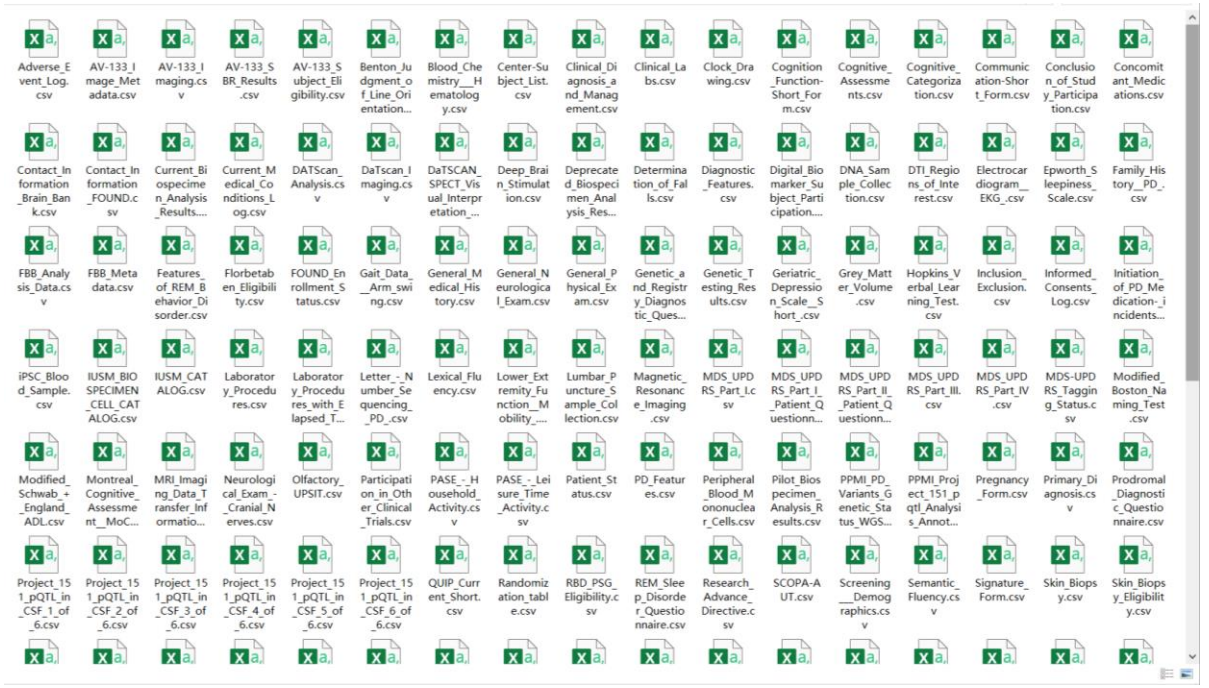
  - what property

    $$\Rightarrow \begin{cases} a_k = 1, \widehat{\boldsymbol{\psi}}_k^T \boldsymbol{h}_k^{\psi} > 0 \\ a_k = 0, \text{ otherwise} \end{cases}$$

    - double robustness

PROCESS

- preprocessing the data
- variable selection



PROCESS

- preprocessing the data
  - missing data
  - remove data
  - contradiction
  - descriptive analysis

PATNO	STAGE	MDS_UPDRS_III_OFF	MoCA	GENDER	……
3001	1	19	30	Male	……
3001	2	33		Male	……
3001	3	23	29	Male	……

TABLE 1

PDMEDYN
NA

TABLE 2

MED TYPE
2

TABLE 3

MED DOSE
120

Gender	6 months (1)	28
	12 months (2)	153
Family History of PD		
	18 months (3)	42
	24 months (4)	25
	>24 months (>4)	38

Male: 66.08
Female: 33.92
0 family: 72.03
1 family: 21.68
2 families: 4.90
3 families: 0.70
4 families: 0.35
5 families: 0.35

Duration (Months)	6.40 (6.31; 1.00; 35.00)
MDS-UPDRS part III score (OFF)	20.31 (8.59; 6.00; 47.00)
RBDSQ score	4.42 (2.84; 0.00; 13.00)
MoCA score	27.14 (2.29; 17.00; 30.00)

PROCESS

- variable selection
  - previous papers[1][2]
  - stepAIC analysis

$$\underbrace{\pi(\mathbf{h}) = P(A = 1|\mathbf{h})}_{treatment\ model}$$

$$\mathbb{E}[\tilde{Y}_k \mid \mathbf{h}_k, a_k; \boldsymbol{\beta}_k, \boldsymbol{\psi}_k] = \underbrace{\boldsymbol{\beta}_k^T \mathbf{h}_k^{\beta}}_{treatment-free\ model} + \underbrace{\boldsymbol{\psi}_k^T a_k \mathbf{h}_k^{\psi}}_{(stage\ k)\ blip\ function}$$

MDS-UPDRS Part III score
at stage 8 (24 months)

MDS-UPDRS Part III score
MoCA score
RBDSQ score
MDS-UPDRS Part II score

[1] MA L-Y, TIAN Y, PAN C-R, et al. Motor Progression in Early-Stage Parkinson's Disease: A Clinical Prediction Model and the Role of Cerebrospinal Fluid Biomarkers [J]. Frontiers in Aging Neuroscience, 2021, 12.

[2] SCHRAG A, SIDDIQUI U F, ANASTASIOU Z, et al. Clinical variables and biomarkers in prediction of cognitive impairment in patients with newly diagnosed Parkinson's disease: a cohort study [J]. The Lancet Neurology, 2017, 16(1): 66-75.

RESULTS

- 4-stage DTR
- model diagnostics

TABLE 3 DTR Analysis of PPMI Data (Using dWOLS)

Stage (k)	$\widehat{\psi}_{k0}$	$\widehat{\psi}_{k1}$	$\widehat{\psi}_{k2}$	$\widehat{\psi}_{k3}$	$\widehat{\psi}_{k4}$
6 months (1)	-43.79	-0.12	-0.08	1.77	-0.35
12 months (2)	14.46	0.01	-0.27	-0.38	-0.26
18 months (3)	-44.64	-0.17	1.47	1.58	0.1
24 months (4)	21.09	-0.36	-2.05	-0.24	0.76

$$21.09 - 0.36 * \text{MDS-UPDRS III.4} - 2.05 * \text{RBDSQ.4} - 0.24 * \text{MOCA.4} + 0.76 * \text{MDS-UPDRS II.4} \; (> OR \leq) \; 0$$

$$\mathbb{E}[\tilde{Y}_k \mid \mathbf{h}_k, a_k; \boldsymbol{\beta}_k, \boldsymbol{\psi}_k] = \underbrace{\boldsymbol{\beta}_k^T \mathbf{h}_k^{\beta}}_{treatment-free\ model} + \underbrace{\boldsymbol{\psi}_k^T a_k \mathbf{h}_k^{\psi}}_{(stage\ k)\ blip\ function}$$

DISCUSSION

- limitations
  - imputation methods
  - non-regularity
  - Matthew effect
- future work
  - combine non-motor scores
  - import penalty terms
  - drug type/dose

MAIN REFERNCES

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THANK YOU!

Q&A