Causal Inference in the Closed-Loop: Marginal Structural Models for Sequential Excursion Effects

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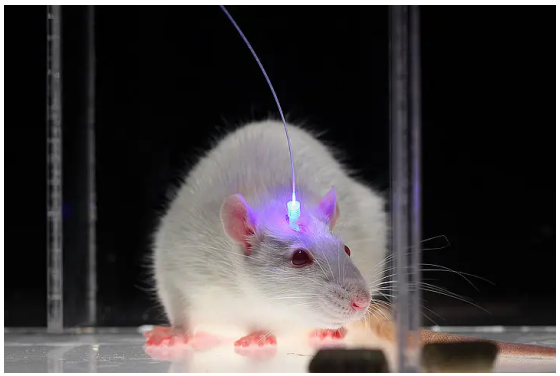
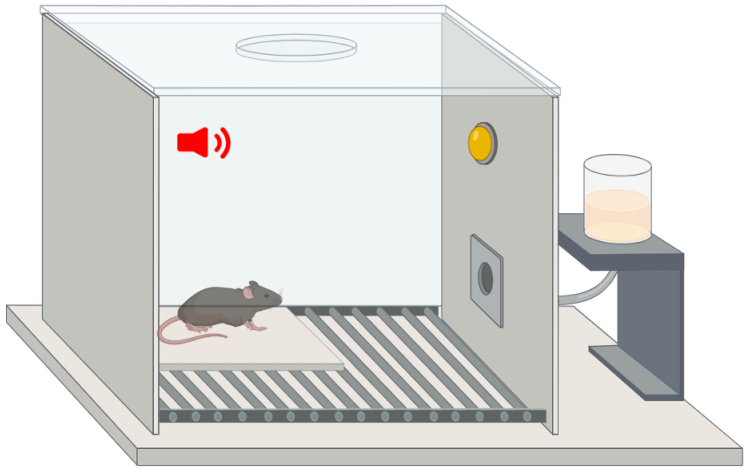
Sequentially randomized experiments in neuroscience

- Optogenetics is a widely used neuroscience technique that allows experimenters to briefly stimulate/inhibit neural pathways (millisecond time resolution) in vivo in sequentially randomized experiments
- $\sim 8,400$ references to optogenetics in 2023





Rich sequence info in sequentially randomized experiments not currently probed in neuro

- Despite deep connections to causal inference literature on sequentially randomized experiments, paucity of causal inference work has resulted in analysis conventions that
  - ⋆ coarsen the rich experimental data
  - ⋆ use simplistic estimands ("macro" longitudinal effects) that rely on between-group differences and potentially miss effects
- We set out to propose an analysis framework that would enable estimation of contrasts for regimes that dissect the rich sequence info (w/in treatment group)
  - ⋆ "Does stimulating on two consecutive trials have a greater effect than stimulating on two non-consecutive trials?"
  - ⋆ Floor/ceiling, potentiating/antagonistic, dose-response

Positivity violations

- Positivity violations ("availability") are often inherent to experimental designs (e.g., "randomly stimulate only on trials when an animal presses a lever")
  - ⋆ Stochastic dynamic treatment regimes with sequence of trials, where, for example, treatment probability on trial t: $\mathbb{P}(A_t = a \mid I_t = 1) = 0.5$, for $a \in \{0, 1\}$, and $\mathbb{P}(A_t = 1 \mid I_t = 0) = 0$
- $I_t = 0 \iff$ subject is forced into the control condition, i.e., no randomization
- We consider a class of dynamic treatment regimes that are compatible with positivity violations inherent to experimental design/scientific question:

$$\mathscr{D}_j = \{d_j : \mathscr{H}_j \to \{0, 1\} \mid d_j(H_j) = 0 \text{ if } I_j = 0\}$$

- Our focus: contrasts of deterministic dynamic regimes:
  - ⋆ $d_j^{(1)} = I_j$, or $d_j^{(0)} = 0$
  - ⋆ always treat when available, or never treat

Estimands

- Multiple time-point analogs of excursion effects: letting $\boldsymbol{d}_{\Delta,t} = (d_{t-\Delta+1}, \ldots, d_t)$,

$$\mathbb{E}[Y_t(\boldsymbol{d}_{\Delta,t})] \equiv \mathbb{E}[Y_t(A_1, \ldots, A_{t-\Delta}, d_{t-\Delta+1}(H_{t-\Delta+1}), \ldots, d_t(H_t(\boldsymbol{d}_{\Delta-1,t-1})))]$$

- Straightforward to incorporate baseline (at $t-\Delta+1$) effect modifiers, and lag effects (take outcome to be Y_{t+k})
- To borrow strength across time and treatment patterns, we put forth a marginal structural model (MSM):

$$m(t, \boldsymbol{d}_{\Delta,t}; \boldsymbol{\beta}) \approx \mathbb{E}[Y_t(\boldsymbol{d}_{\Delta,t})]$$

- These are essentially history-restricted marginal structural models (Neugebauer et al., 2007; Guo et al., 2021), but extended to handle dynamic policies
- We derive our estimators by treating MSM parameters as projections

Results

- We derive an inverse probability of treatment-weighted estimator, $\widehat{\boldsymbol{\beta}}$, valid in closed-loop experiments

Theorem 1

Under mild assumptions, $\widehat{\boldsymbol{\beta}}$ is asymptotically normal, with a closed-form variance expression.

- Our asymptotic result yields simple inferential tools, e.g., Wald-based confidence intervals and hypothesis tests for $\boldsymbol{\beta}$
- Through different MSM specifications, time-varying effect modification, as well as classic patterns like dose-response effects and treatment response duration
- The paper lays out detailed simulation studies, and an analysis of a real optogenetics study

References I

Guo, F. R., Richardson, T. S., and Robins, J. M. (2021). Discussion of 'Estimating time-varying causal excursion effects in mobile health with binary outcomes'. *Biometrika*, 108(3):541–550.

Neugebauer, R., van der Laan, M. J., Joffe, M. M., and Tager, I. B. (2007). Causal inference in longitudinal studies with history-restricted marginal structural models. *Electronic journal of statistics*, 1:119.