Estimation of Causal Effects in the Presence of Unobserved Confounding in the Alzheimer's Continuum

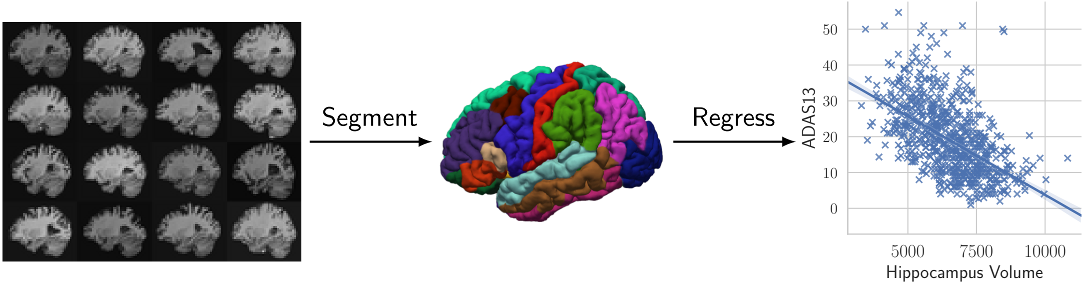
Sebastian Pölsterl and Christian Wachinger

Artificial Intelligence in Medical Imaging, Ludwig-Maximilians-Universität, Munich

International Conference on Information Processing in Medical Imaging

June 28–30th 2021

Cognitive Decline in Alzheimer's Disease

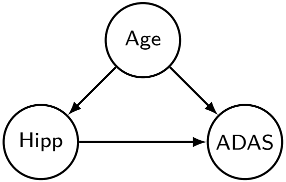


- **Goal**: Understand the **causal effect** of regional atrophy on cognition.
- The causal effect is the change in cognition when setting the hippocampus volume to x.

Causal Inference

- Standard machine learning usually does not provide estimates of causal effects. It provides estimates for

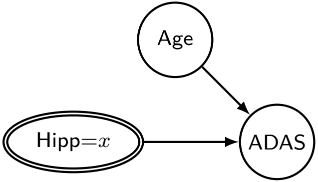
$$P(\text{ADAS} \mid \text{Hipp} = x) = \int_{age} P(\text{ADAS} \mid \text{Hipp} = x, age) P(age) \, dage$$



Observed distribution

- Causal inference is about **prediction under intervention**:

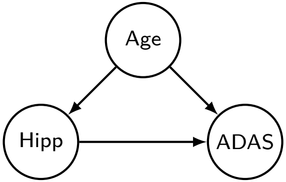
$$P(\text{ADAS} \mid do(\text{Hipp} = x)) \quad \neq \quad P(\text{ADAS} \mid \text{Hipp} = x)$$



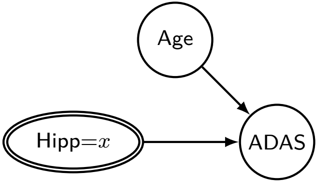
Interventional distribution

Answering Causal Questions

- The gold standard to answer a causal question is a randomized experiment.
  $\Rightarrow$ **Impossible in neuroimaging.**
- Need to resort to *observational data* and making **untestable assumptions** about the data-generating process.
- In particular, **no unmeasured confounder**.
- Alfaro-Almagro et al. (2021) identified **hundreds of potential confounders** just related to the image acquisition.
- **Identifiability**: Can the **post-intervention distribution** be estimated from the observed data?



Observed distribution



Interventional distribution

Prior Work

- Assumes that **all confounding variables are known** and have been measured.
- To account for observed confounders, use
  - Regress-out
  - Inverse Propensity Score Weighting

Regress-Out

- For j-th measurement, estimate regression model using observed confounders $\mathbf{z}$.
- For i-th patient, compute residuals

$$\tilde{X}_{ij} = X_{ij} - \mathbb{E}\left[X_{ij} \mid \mathbf{z_i}\right].$$

Confounders z_i	Regression Model	Reference
Age	Linear	Crary et al. (2014)
Age, Gender	Linear	Koikkalainen et al. (2012)
Brain volume	Linear	Salakhutdinov and Mnih (2008)
Imaging site	Linear	Fortin, Cullen, et al. (2018)
Imaging site, Scanner, Magnetic field strength	Linear	Wachinger et al. (2020)
Age, Gender, TIV, Scanner	Gaussian process	Kostro et al. (2014)

Inverse Propensity Score Weighting

- Create a balanced pseudo-population by using instance weights w_i in the outcome model.
- Instance weights are based on the conditional probability of the outcome given the observed confounders:

$$w_i = \frac{P(y_i)}{P(y_i \mid \mathbf{z}_i)}.$$

Confounders z_i	Outcome	Outcome Model	Weight Model	Reference
Age	Healthy/MCI	SVM	Logistic reg	Linn et al. (2016)
Gender, Imaging site	MMSE	Gaussian process	Gaussian process	Rao et al. (2017)

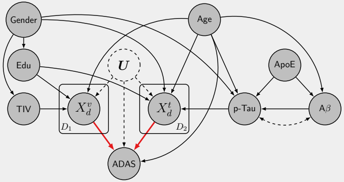
Identifiability

Identifiability

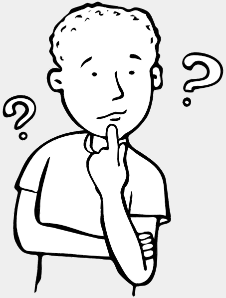
None of the previous work studied whether causal effects can actually be **identified** from observed data!

Causal inference from observational data requires a **holistic approach** (Pearl, 2000):

Define the Causal Graph



What can be Answered?

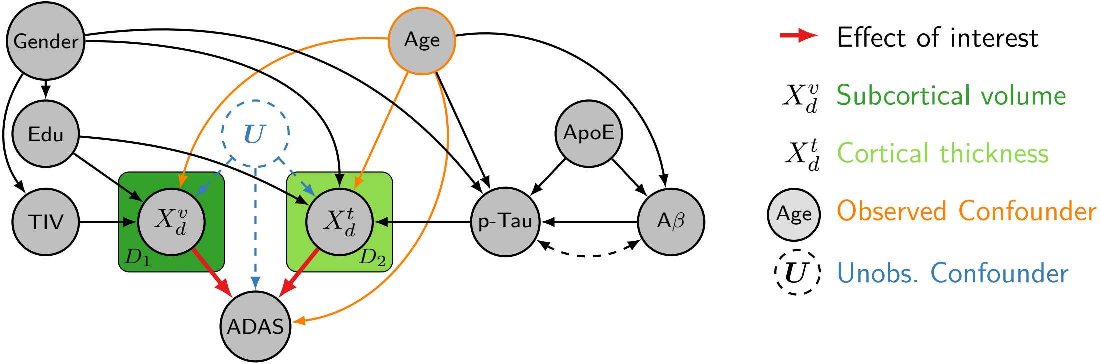


Estimation of Causal Effects

$$\mathbb{E}\left[\text{ADAS} \mid do(x'_{\mathcal{S}})\right]$$
$$= \mathbb{E}_{age, x_{\bar{\mathcal{S}}}, z}\left[\mathbb{E}\left[\text{ADAS} \mid x'_{\mathcal{S}}, x_{\bar{\mathcal{S}}}, age, \mathbf{z}\right]\right]$$

Causal Question

What is the *average causal effect* of changes in volume/thickness of a subset of neuroanatomical structures on the ADAS13 score in patients with an Alzheimer's pathologic change?

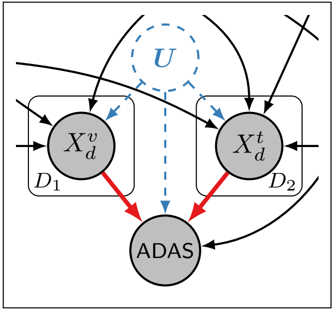


Non-Identifiability Due to Unobserved Confounding

- **Average causal effect** of a subset $\mathcal{S} \subset \{X_1, \ldots, X_D\}$ of neuroanatomical structures on the ADAS score:

$$\mathbb{E}\left[\mathrm{ADAS} \,|\, do(X_{\mathcal{S}} = x'_{\mathcal{S}})\right] = \int \text{adas} \cdot P(\text{adas} \,|\, do(x'_{\mathcal{S}}))\, d\text{adas}.$$

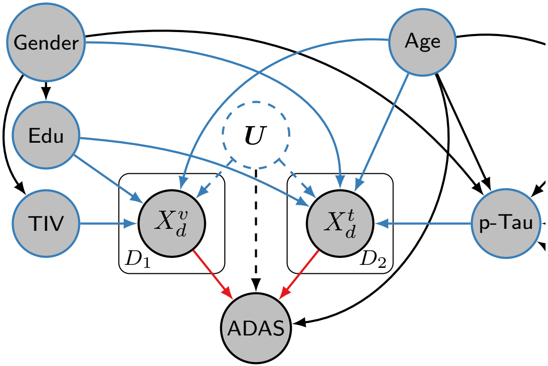
- **Identifiability**: Can the **post-intervention distribution** be estimated from the observed joint distribution over X and ADAS?
- **Answer: NO!**
Because of **unobserved confounding** due to $\boldsymbol{U}$ (Pearl, 2000).



Estimating a Substitute Confounder

- Due to unobserved confounding, we have to make **assumptions on the data-generating process**.
- Note that all causes $X_1, \dots, X_D$ become **conditionally independent**, given their **parents**:

$$P(x_1, \dots x_D \mid PA_{X_1,\dots,X_D}) = \prod_{d=1}^{D} P(x_d \mid PA_{X_1,\dots,X_D}).$$



Substitute Confounder (Wang and Blei, 2019)

- Conditional probability

$$P(x_1, \ldots x_D \,|\, PA_{X_1,\ldots,X_D}) = \prod_{d=1}^{D} P(x_d \,|\, PA_{X_1,\ldots,X_D}).$$

  has the same form as a **probabilistic latent factor model** (PLFM).
- Estimate a **substitute confounder $\mathbf{z}$** for the unobserved confounder via a PLFM.

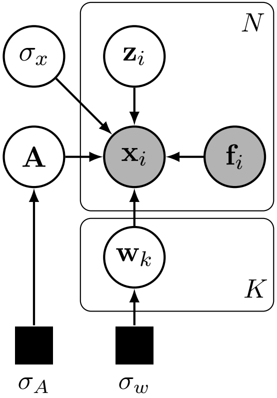
Latent Factor Model – PPCA

Probabilistic Principal Component Analysis (Tipping and Bishop, 1999):

- Represent the D causes in terms of the known causes $\mathbf{f}_i$ and the latent substitute confounder $\mathbf{z}_i \in \mathbb{R}^K$:

$$\mathbf{x}_i \sim \mathcal{N}_D(\mathbf{W}\mathbf{z}_i + \mathbf{A}\mathbf{f}_i, \sigma_x^2 \mathbf{I}_D), \qquad \forall i = 1, \ldots, N.$$

- Estimate posterior distribution of:
  - Substitute confounder $\mathbf{z}$,
  - Loading matrix $\mathbf{W}$,
  - Coefficients $\mathbf{A}$,
  - Variance term σ_x^2.



Identifiability of the Average Causal Effect

- Proof that using the substitute confounder $\mathbf{z}$ in place of the unobserved confounder $\boldsymbol{U}$, $P(\text{adas} \mid do(x'_{\mathcal{S}}))$ becomes **identifiable** from observed data.
- Need to eliminate the **do-operator** by applying rules from do-calculus (Pearl, 2000):

$$\mathbb{E}\left[\text{ADAS} \mid do(x'_{\mathcal{S}})\right]$$

Eliminating the do-Operator

Apply the rules of do-calculus (Pearl, 2000, Theorem 3.4.1):

$$
\begin{aligned}
\mathbb{E}\left[\mathrm{ADAS} \,|\, do(x'_{\mathcal{S}})\right] &= \mathbb{E}_{age, x_{\bar{\mathcal{S}}}, z}\left[\mathbb{E}\left[\mathrm{ADAS} \,|\, do(x'_{\mathcal{S}}), x_{\bar{\mathcal{S}}}, age, \mathbf{z}\right]\right] && (1)\\
&\overset{R3}{=} \mathbb{E}_{age, x_{\bar{\mathcal{S}}}, z}\left[\mathbb{E}\left[\mathrm{ADAS} \,|\, do(x'_{\mathcal{S}}), x_{\bar{\mathcal{S}}}, do(ptau), age, \mathbf{z}\right]\right] && (2)\\
&\overset{R2}{=} \mathbb{E}_{age, x_{\bar{\mathcal{S}}}, z}\left[\mathbb{E}\left[\mathrm{ADAS} \,|\, x'_{\mathcal{S}}, x_{\bar{\mathcal{S}}}, do(ptau), age, \mathbf{z}\right]\right] && (3)\\
&\overset{R2}{=} \mathbb{E}_{age, x_{\bar{\mathcal{S}}}, z}\left[\mathbb{E}\left[\mathrm{ADAS} \,|\, x'_{\mathcal{S}}, x_{\bar{\mathcal{S}}}, ptau, age, \mathbf{z}\right]\right] && (4)\\
&= \mathbb{E}_{age, x_{\bar{\mathcal{S}}}, z}\left[\mathbb{E}\left[\mathrm{ADAS} \,|\, x'_{\mathcal{S}}, x_{\bar{\mathcal{S}}}, age, \mathbf{z}\right]\right] && (5)\\
&\approx \frac{1}{N}\sum_{i=1}^{N} \hat{\mathbb{E}}\left[\mathrm{ADAS} \,|\, x'_{\mathcal{S}}, \mathbf{x}_{i,\bar{\mathcal{S}}}, age_i, \mathbf{z}_i\right] && (6)
\end{aligned}
$$

Estimating the Average Causal Effect

- Is the post-intervention distribution identifiable? ✔
- **Average causal effect** and can be estimated by a Bayesian Linear Beta regression model (Ferrari and Cribari-Neto, 2004).

$$\mathbb{E}\left[\mathrm{ADAS} \mid do(x'_{\mathcal{S}})\right] \approx \frac{1}{N} \sum_{i=1}^{N} \hat{\mathbb{E}}\left[\mathrm{ADAS} \mid x'_{\mathcal{S}}, \mathbf{x}_{i,\bar{\mathcal{S}}}, age_i, \mathbf{z}_i\right].$$

- **CAUTION**: Depends on several assumptions that are specific to the causal question!

Assumptions

1. The data-generating process is **faithful** to the graphical model.
   $\Rightarrow$ *Untestable*.
2. The unknown **confounder affects multiple brain regions** and not just a single region.
   $\Rightarrow$ *Confounding due to scanner, imaging protocol, and aging affect the brain as a whole*.
3. The PLFM **captures all multi-cause confounders**.
   $\Rightarrow$ *Posterior predictive checking*.
4. The PLFM estimates the substitute confounder with **consistency**, i.e., deterministicly, as the number of causes grows large.
   $\Rightarrow$ *Holds for a large class of models (Chen et al., 2020)*.
5. $P(x_{\mathcal{S}} \,|\, PA_{X_1,\ldots,X_D}) > 0$ for any subset S.
   $\Rightarrow$ Holds for PPCA, because conditional distribution is a normal distribution.

Semi-Synthetic Data

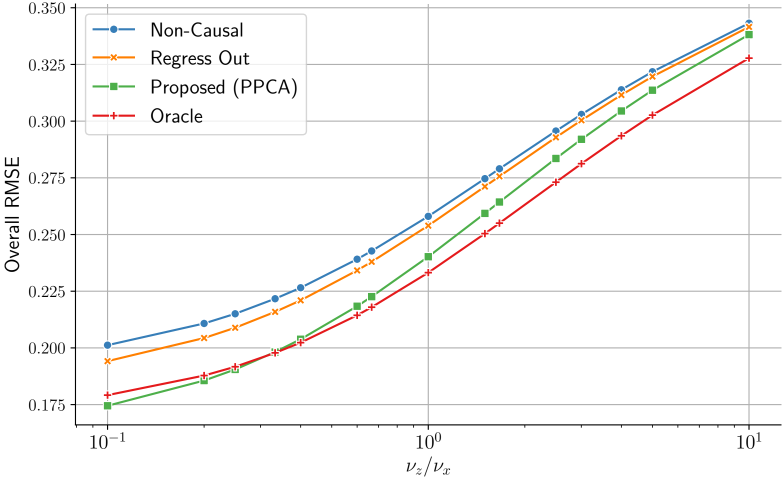
Perform 1,000 simulations for varying strength of confounding:

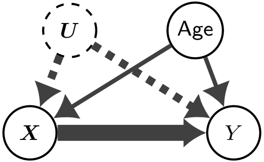
- 19 regional brain volumes of 11,800 subjects from UK Biobank (Miller et al., 2016).
- Observed confounder: Age.
- Unobserved confounder: Generated (via clustering).
- Outcome: Binary (generated).

Methods:

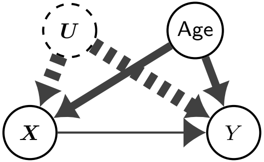
- **Proposed**: Uses age-aware PPCA to estimate 5 substitute confounders.
- **Regress Out**: Only accounts for age.
- **Non-causal**: Ignores all confounders.
- *Oracle*: Accounts for observed *and* unobserved confounder.

Evaluation on Semi-Synthetic Data





Left: Least confounded



Right: Most confounded

Alzheimer's Disease Data

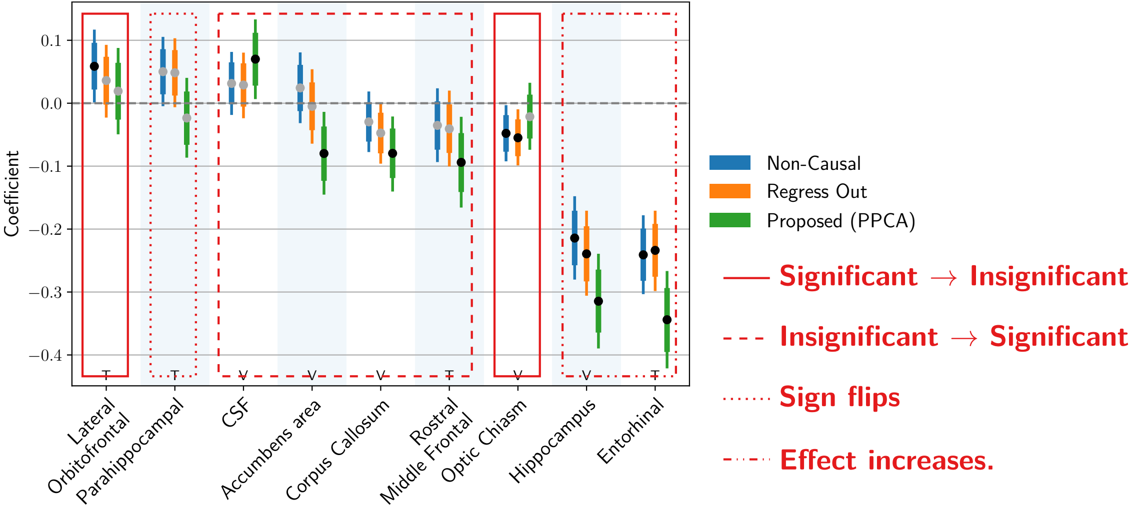
Alzheimer's Disease Neuroimaging Initiative (Jack, Bernstein, et al., 2008):

- 14 volume and 8 thickness measures of 711 subjects.
- Only include patients with abnormal amyloid biomarkers (Jack, Bennett, et al., 2018).
- Estimate 6 substitute confounders.
- Outcome: ADAS13 (proportion).

Methods:

- **Proposed**: Uses PPCA to estimate 6 substitute confounders, while accounting for age, gender, education, TIV.
- **Regress Out**: Only accounts for age, gender, education, TIV.
- **Non-causal**: Ignores all confounders.
- **CAUTION**: Quantitative evaluation is impossible!

Causal Effects in Alzheimer's Disease



Conclusion

1. The causal effect of neuroanatomical measures on cognition is **unidentifiable in the presence on unobserved confounders**.
2. We proved that using the substitute confounder **enables identifiability** of the causal effect.
3. We do need to rely on several assumptions ...
4. Code available at `https://github.com/ai-med/causal-effects-in-alzheimers-continuum`.

References I

Alfaro-Almagro, F., P. McCarthy, S. Afyouni, J. L. R. Andersson, M. Bastiani, et al. (2021). "Confound modelling in UK Biobank brain imaging". In: *Neuroimage* 224, p. 117002.

Chen, Y., X. Li, and S. Zhang (2020). "Structured Latent Factor Analysis for Large-scale Data: Identifiability, Estimability, and Their Implications". In: *J Am Stat Assoc* 115 (532), pp. 1756–1770.

Crary, J. F., J. Q. Trojanowski, J. A. Schneider, J. F. Abisambra, E. L. Abner, et al. (2014). "Primary age-related tauopathy (PART): a common pathology associated with human aging". In: *Acta Neuropathol* 128.6, pp. 755–766.

Ferrari, S. and F. Cribari-Neto (2004). "Beta Regression for Modelling Rates and Proportions". In: *J Appl Stat* 31.7, pp. 799–815.

Fortin, J.-P., N. Cullen, et al. (2018). "Harmonization of cortical thickness measurements across scanners and sites". In: *Neuroimage* 167, pp. 104–120.

Jack, C. R., D. A. Bennett, K. Blennow, M. C. Carrillo, B. Dunn, et al. (2018). "NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease". In: *Alzheimers Dement* 14.4, pp. 535–562.

References II

Jack, C. R., M. A. Bernstein, N. C. Fox, P. Thompson, et al. (2008). "The Alzheimer's disease neuroimaging initiative (ADNI): MRI methods". In: *J Magn Reson Imaging* 27.4, pp. 685–691.

Koikkalainen, J., H. Pölönen, J. Mattila, M. van Gils, H. Soininen, J. Lötjönen, et al. (2012). "Improved Classification of Alzheimer's Disease Data via Removal of Nuisance Variability". In: *PLoS One* 7.2, e31112.

Kostro, D., A. Abdulkadir, A. Durr, R. Roos, B. R. Leavitt, et al. (2014). "Correction of inter-scanner and within-subject variance in structural MRI based automated diagnosing". In: *Neuroimage* 98, pp. 405–415.

Linn, K. A., B. Gaonkar, J. Doshi, C. Davatzikos, and R. T. Shinohara (2016). "Addressing confounding in predictive models with an application to neuroimaging". In: *Int J Biostat* 12.1, pp. 31–44.

Miller, K. L., F. Alfaro-Almagro, N. K. Bangerter, D. L. Thomas, E. Yacoub, et al. (2016). "Multimodal population brain imaging in the UK Biobank prospective epidemiological study". In: *Nat Neurosci* 19.11, pp. 1523–1536.

Pearl, J. (2000). *Causality: Models, reasoning, and inference*. Cambridge University Press.

Rao, A., J. M. Monteiro, and J. Mourao-Miranda (2017). "Predictive modelling using neuroimaging data in the presence of confounds". In: *Neuroimage* 150, pp. 23–49.

References III

Salakhutdinov, R. and A. Mnih (2008). “Bayesian Probabilistic Matrix Factorization Using Markov Chain Monte Carlo”. In: *ICML*, pp. 880–887.

Tipping, M. E. and C. M. Bishop (1999). “Probabilistic Principal Component Analysis”. In: *J R Stat Soc Series B Stat Methodol* 61.3, pp. 611–622.

Wachinger, C., A. Rieckmann, and S. Pölsterl (Oct. 21, 2020). “Detect and Correct Bias in Multi-Site Neuroimaging Datasets”. In: *Med Image Anal.*

Wang, Y. and D. M. Blei (2019). “The Blessings of Multiple Causes”. In: *J Am Stat Assoc*, pp. 1–71.