Precision Medicine with Imprecise Measurements: Exploring Measurement Error in Personalized Decision Making

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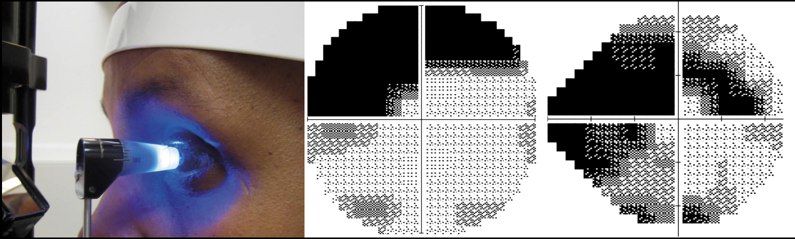
Slide deck and Shiny app links available at:
`mpwallace.github.io`

Glaucoma: group of eye diseases associated with elevated intraocular pressure (IOP).

Elevated IOP can lead to vision loss.



Glaucoma: One Disease, Many Treatments

Treatment options attempt to lower IOP (and by extension preserve visual field), they include:

- Lifestyle changes.
- Eye drops (numerous options).
- Surgery.

Treatment decisions based on numerous factors.

Example: Patient is currently taking Azarga eye drops. A personalized treatment rule could be:

> "*If current IOP is 15 or higher, add Alphagan eye drops, otherwise continue with only Azarga.*"

- Question: How do we choose the best decision rule?

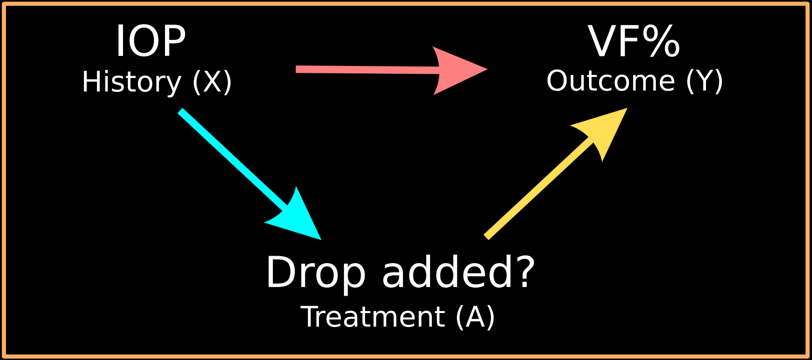
  Should our IOP cut-off be 13, 15, 20?

Some hypothetical data:

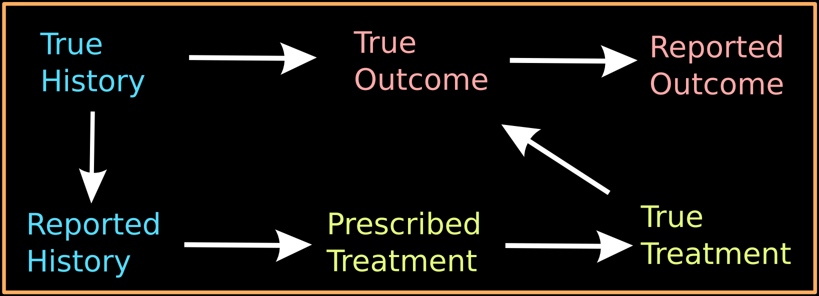
Patient	Observed IOP	Drop added?	VF% at 3 months
1	16	No	73
2	20	Yes	55
3	21	Yes	50
4	16	Yes	61
5	15	No	42
...	...	...	...

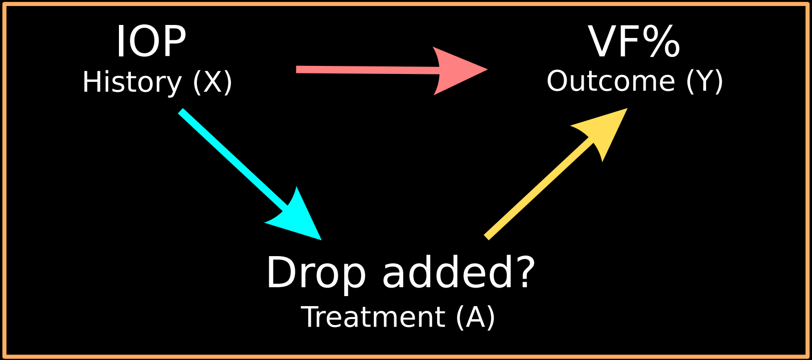
VF% = Visual Field Percentage

Question: How do these variates relate?



Goal: Identify treatment A that optimizes $E[Y|X, A]$


True History
True Outcome
Reported Outcome
Reported History
Prescribed Treatment
True Treatment



First: error-free setting using dWOLS.

$$\underbrace{E[Y|X,A]}_{\substack{\text{Expected outcome}\\ \text{(to be maximized)}}} \qquad A \in \{0,1\}$$

- We might propose the following model

$$E[Y|X,A;\beta,\psi] = \beta_0 + \beta_1 \text{IOP} + A(\psi_0 + \psi_1 \text{IOP})$$

"Add drop ($A = 1$) if $\psi_0 + \psi_1 \text{IOP} > 0$"

- More generally:

$$\overbrace{E[Y|X,A;\beta,\psi]}^{\substack{\text{Expected outcome}\\ \text{(to be maximized)}}} = \overbrace{G(X;\beta)}^{\text{Treatment-free}} + \overbrace{\gamma(X,A;\psi)}^{\text{Blip}}$$

- Simplifies focus: choose A that maximizes $\gamma(X,A;\psi)$.

Identifying the best treatment regime

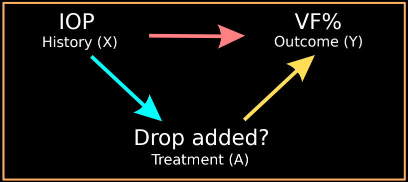
- Suppose the true outcome model is:

$$E[Y|X, A; \beta, \psi] = \beta_0 + \beta_1 \text{IOP} + \beta_2 \text{IOP}^2 + A(\psi_0 + \psi_1 \text{IOP})$$

- But we propose:

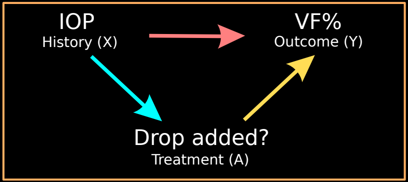
$$E[Y|X, A; \beta, \psi] = \beta_0 + \beta_1 \text{IOP} + A(\psi_0 + \psi_1 \text{IOP})$$

- Problem: A depends on IOP $\implies \psi_0, \psi_1$ mis-estimated.
- Solution: Account for this dependency.



$$E[Y|X, A; \beta, \psi] = G(X; \beta) + \gamma(X, A; \psi)$$

- Three models to specify:
    1. Treatment-free model: $G(X; \beta)$.
    2. Blip model: $\gamma(X, A; \psi)$.
    3. Treatment model: $P(A = 1|X; \alpha)$.
- Estimate ψ via WOLS of Y on covariates in blip and treatment-free models, with weights $w = |A - P(A = 1|X; \hat{\alpha})|$.



Identifying the best treatment regime

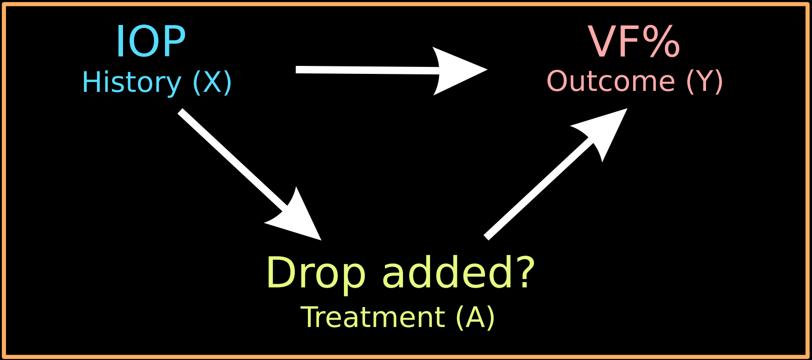
- Suppose the true outcome model is:

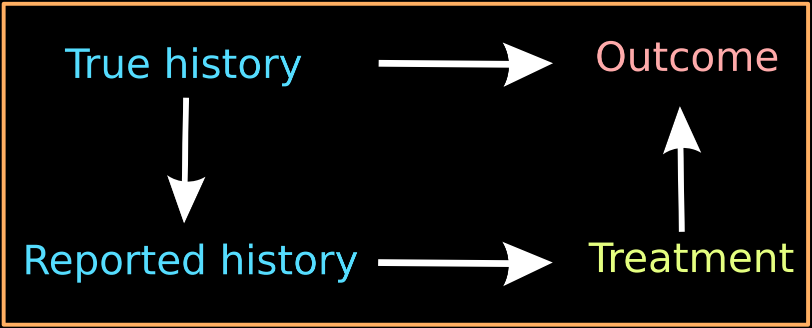
$$E[Y|X, A; \beta, \psi] = \beta_0 + \beta_1 \text{IOP} + \beta_2 \text{IOP}^2 + A(\psi_0 + \psi_1 \text{IOP})$$

- But we propose:

$$E[Y|X, A; \beta, \psi] = \beta_0 + \beta_1 \text{IOP} + A(\psi_0 + \psi_1 \text{IOP})$$

- WOLS with weights $w = |A - P(A = 1|X; \hat{\alpha})|$ will still yield consistent estimators of ψ_0, ψ_1.
- Estimators are "doubly robust": consistent if at least one of treatment-free or treatment components correctly specified.
- The blip must always be correct.


IOP
History (X)
VF%
Outcome (Y)
Drop added?
Treatment (A)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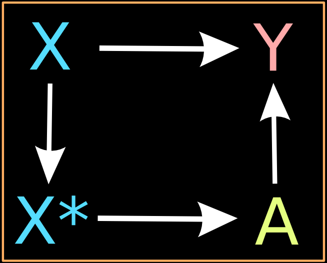
Treatment

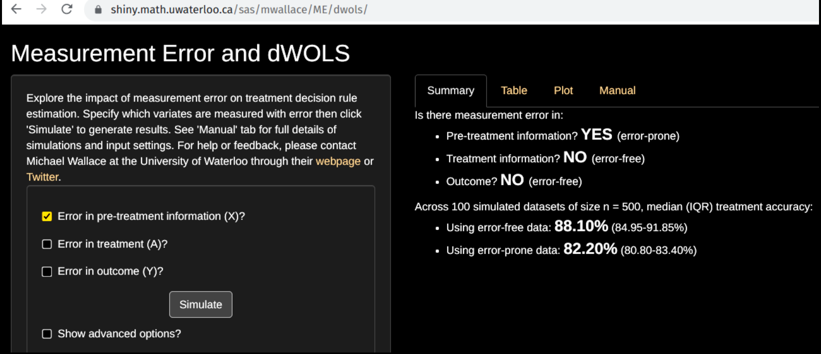


Estimation: suppose the true outcome model is:

$$E[Y|X, A; \beta, \psi] = \beta_0 + \beta_1 X + \beta_2 X^2 + A(\psi_0 + \psi_1 X)$$

but we only observe

$$X^* = X + U \qquad U \sim N(\mu_{ux}, \sigma^2_{ux})$$

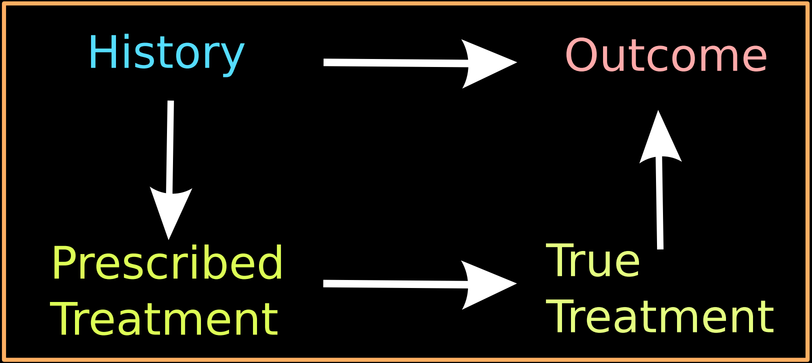


All links available at `https://mpwallace.github.io/`

$$E[Y|X, A; \beta, \psi] = \beta_0 + \beta_1 X + \beta_2 X^2 + A(\psi_0 + \psi_1 X)$$

$$X^* = X + U \qquad U \sim N(\mu_{ux}, \sigma^2_{ux})$$

- Much established theory on errors in X in linear regression.
- Because dWOLS grounded in standard regression theory, existing measurement error correction methods can be used.
- Result: Regression Calibration can be used with dWOLS and maintain double robustness.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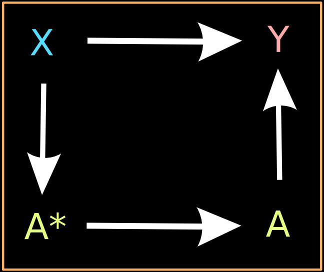
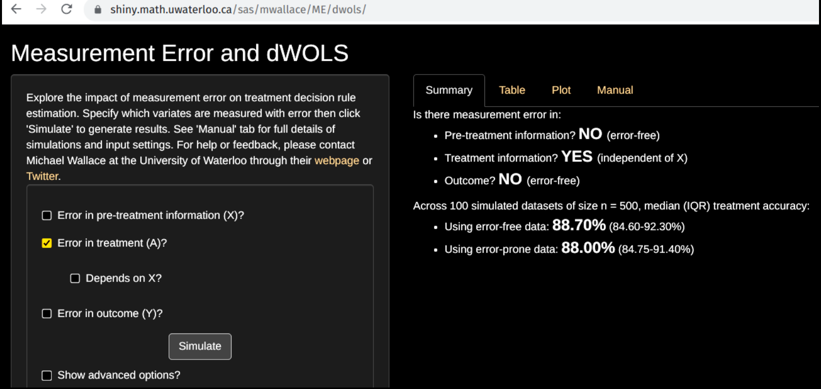


For binary A, misclassification can be characterized by the positive and negative predictive values:

$$PPV = P(A = 1 | A^* = 1) \qquad NPV = P(A = 0 | A^* = 0)$$

Key question: Do the misclassification probabilities depend on X?



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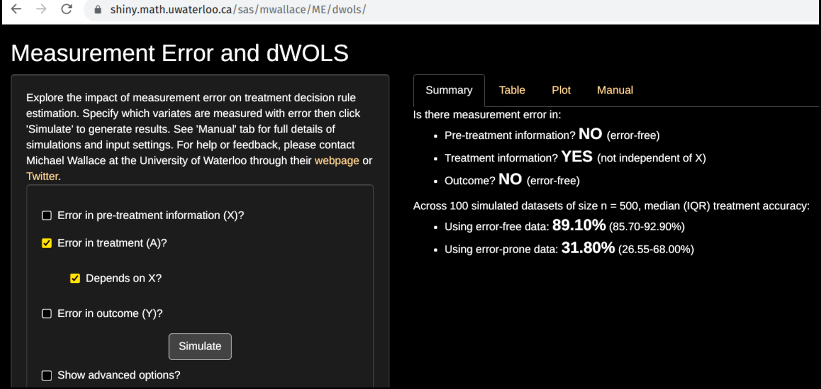
shiny.math.uwaterloo.ca/sas/mwallace/ME/dwols/

Measurement Error and dWOLS

Explore the impact of measurement error on treatment decision rule estimation. Specify which variates are measured with error then click 'Simulate' to generate results. See 'Manual' tab for full details of simulations and input settings. For help or feedback, please contact Michael Wallace at the University of Waterloo through their webpage or Twitter.

- [ ] Error in pre-treatment information (X)?
- [x] Error in treatment (A)?
  - [x] Depends on X?
- [ ] Error in outcome (Y)?

Simulate

- [ ] Show advanced options?

Summary | Table | Plot | Manual

Is there measurement error in:

- Pre-treatment information? **NO** (error-free)
- Treatment information? **YES** (not independent of X)
- Outcome? **NO** (error-free)

Across 100 simulated datasets of size n = 500, median (IQR) treatment accuracy:

- Using error-free data: **89.10%** (85.70-92.90%)
- Using error-prone data: **31.80%** (26.55-68.00%)

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$$E[Y|X, A; \beta, \psi] = \beta_0 + \beta_1 X + \beta_2 X^2 + A(\psi_0 + \psi_1 X)$$

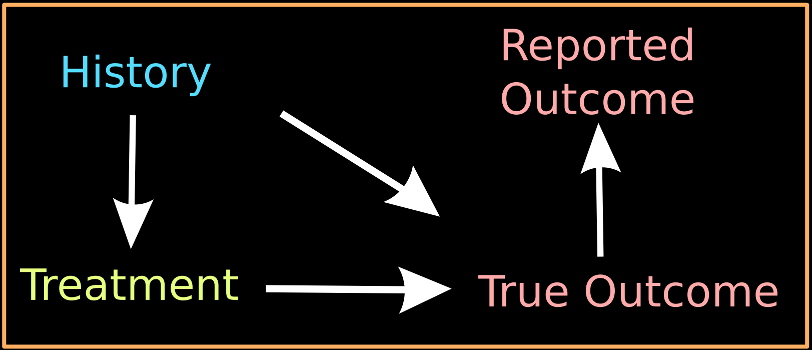
If misclassification does not depend on X, then our estimates of ψ_0, ψ_1 will be biased:

$$\psi_0^* = (PPV + NPV - 1)\psi_0 \qquad \psi_1^* = (PPV + NPV - 1)\psi_1$$

However: our treatment rule is of the form

$$A = 1 \text{ if } \psi_0 + \psi_1 X > 0$$

which is unaffected if ψ_0, ψ_1 are biased by the same factor.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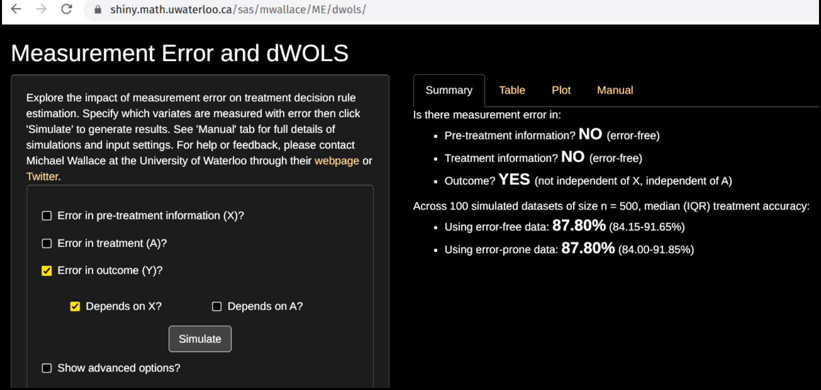
True Outcome

$$E[Y|X,A;\beta,\psi] = \beta_0 + \beta_1 X + \beta_2 X^2 + A(\psi_0 + \psi_1 X)$$

$$Y^* = Y + U \qquad U \sim N(\mu_{uy}, \sigma^2_{uy})$$



Error independent of A: ψ estimators still consistent.

Shiny App: Error in Y

$$E[Y|X, A; \beta, \psi] = \beta_0 + \beta_1 X + \beta_2 X^2 + A(\psi_0 + \psi_1 X)$$

$$Y^* = Y + U \qquad U \sim N(\mu_{uy}, \sigma^2_{uy})$$

shiny.math.uwaterloo.ca/sas/mwallace/ME/dwols/

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- [ ] Error in pre-treatment information (X)?
- [ ] Error in treatment (A)?
- [x] Error in outcome (Y)?
  - [x] Depends on X?
  - [x] Depends on A?

Simulate

- [ ] Show advanced options?

Summary | Table | Plot | Manual

Is there measurement error in:

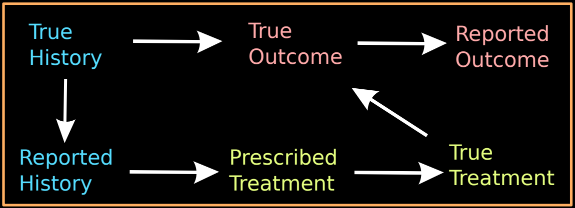
- Pre-treatment information? **NO** (error-free)
- Treatment information? **NO** (error-free)
- Outcome? **YES** (not independent of X, not independent of A)

Across 100 simulated datasets of size n = 500, median (IQR) treatment accuracy:

- Using error-free data: **87.90%** (84.40-91.40%)
- Using error-prone data: **56.20%** (45.75-67.80%)

Error not independent of A: ψ estimators no longer reliable.

- Measurement error an important consideration in all elements of precision medicine problems.
- There are some special cases where errors have limited impact, or may be corrected for with standard theory.
- But: many more cases to explore.



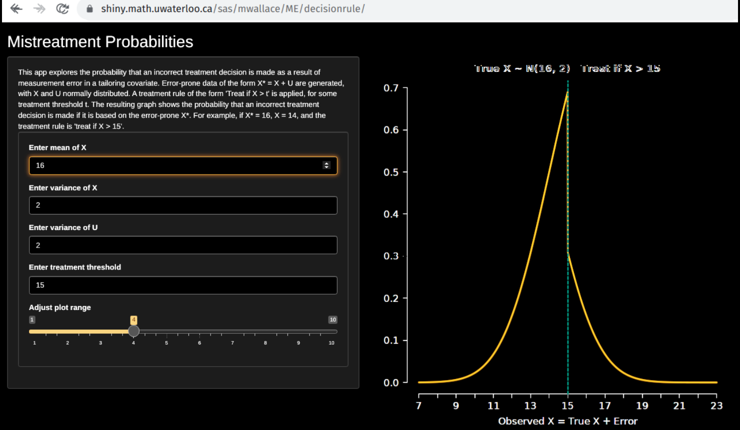
Looking Ahead: Future Treatment

Suppose we conclude that our treatment rule should be:

"If 3-month average IOP $\geq$ 15 add secondary drop, otherwise, maintain current treatment regime."

I go to the clinic and my IOP measurement is 16. Then what?

Exploring these probabilities through a Shiny app:



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Acknowledgments

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Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

NSERC
CRSNG

- **dWOLS**: M. P. Wallace and E. E. M. Moodie (2015). Doubly-robust dynamic treatment regimen estimation via weighted least squares. *Biometrics* **71(3)** 636-644.

- **Precision Medicine and Measurement Error in Tailoring Variates**: D. Spicker and M. P. Wallace (2020). Measurement error and precision medicine: error-prone tailoring covariates in dynamic treatment regimes. *Statistics in Medicine* **39(26)**

- **R Package DTRreg**: Available on CRAN.

- **Precision Medicine and Measurement Error More Broadly**: M. P. Wallace. Measurement error and precision medicine. In Cai T., Chakraborty B., Laber E., Moodie E. and van der Laan M. (Eds), Handbook of Statistical Methods for Precision Medicine. Chapman & Hall/CRC Handbooks of Modern Statistical Methods. Expected publication 2023.

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