Rank-Based Identification of High-Dimensional Surrogate Markers : Application to Vaccinology

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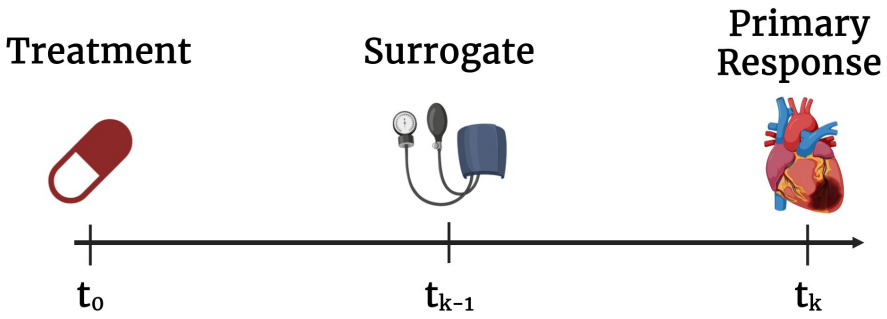
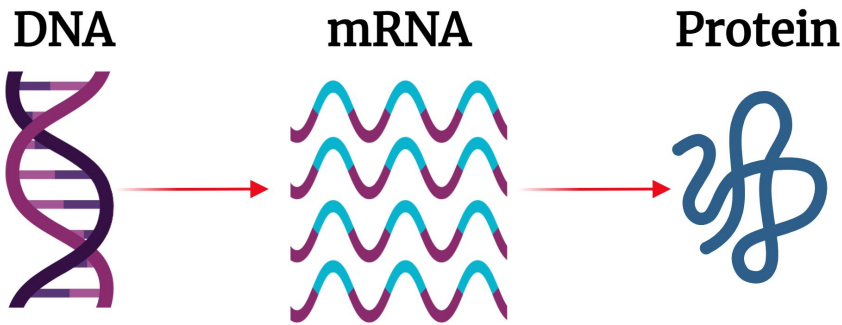
Background

What is a surrogate marker?

- **Intermediate endpoint**
- Treatment effect on surrogate **predicts treatment effect on primary outcome**



Transcriptomics



Could gene expression markers serve as surrogates?

Limitations of Current Methodology

Existing methods require...

- **Restrictive assumptions**
- **Large sample sizes**
- **Low-dimensional setting**

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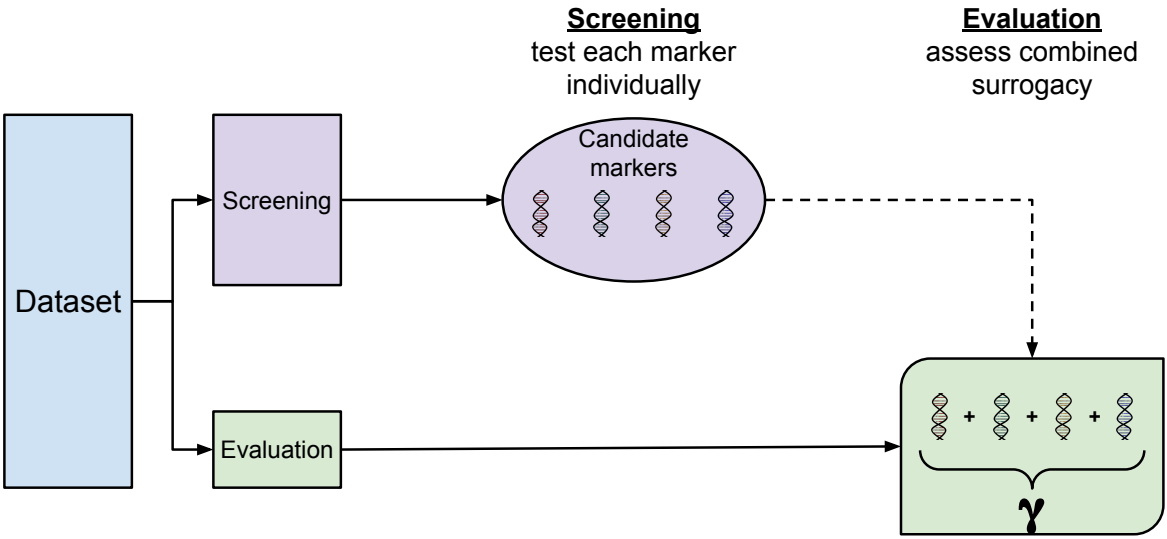
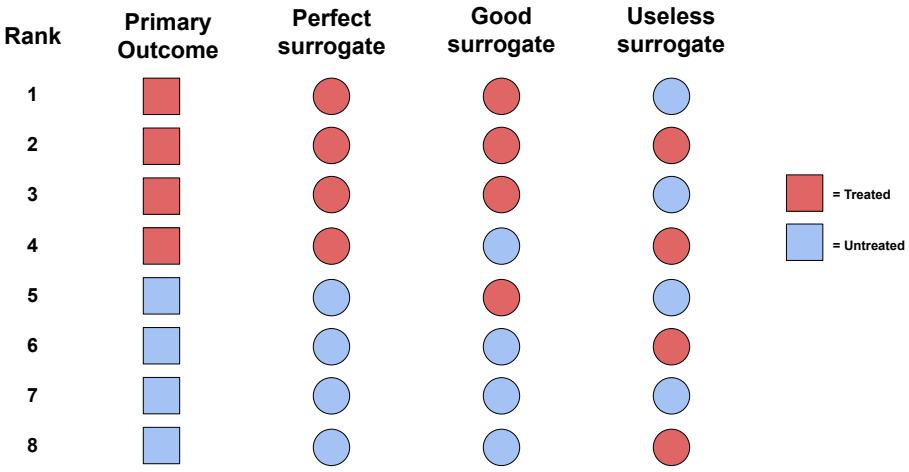
New approach to **evaluate high-dimensional surrogate markers** in small-sample setting

Materials and Methods


Screening
test each marker
individually
Evaluation
assess combined
surrogacy
Dataset
Screening
Candidate
markers
Evaluation
γ

Intuition of the rank-based test



Notation

- n - sample size
- $A \in \{0, 1\}$ - binary treatment indicator
- Y - continuous response
- $\boldsymbol{S} = (S_1, ..., S_p)$ - candidate surrogates
- Y^a - response had treatment been a
- S^a - surrogate candidates had treatment been a

A non-parametric test for surrogacy of a single marker

- $U_Y = \mathbb{P}(Y^1 > Y^0) + \frac{1}{2}\mathbb{P}(Y^1 = Y^0)$
  - $0.5 < U_Y \leq 1 \implies$ positive treatment effect
- $U_{S_j} = \mathbb{P}(S_j^1 > S_j^0) + \frac{1}{2}\mathbb{P}(S_j^1 = S_j^0)$
- $\delta_j = U_Y - U_{S_j}$
  - i.e. $\delta_j \approx 0 \implies S_j$ approximates treatment effect on Y
- **Non-Inferiority Test** $H_0 : \delta_j \geq \epsilon$ vs $H_1 : \delta_j < \epsilon$

Estimation with rank-sum statistics

- Define $G(A,B) = \begin{cases} 1, & \text{if} \quad A > B \\ \frac{1}{2}, & \text{if} \quad A = B \\ 0, & \text{if} \quad B < A \end{cases}$
- $\widehat{U_Y} = (n_1 n_0)^{-1} \sum_{i=1}^{n_1} \sum_{k=1}^{n_0} G(Y_{i1}, Y_{k0})$
- $\widehat{U_{S_j}} = (n_1 n_0)^{-1} \sum_{i=1}^{n_1} \sum_{k=1}^{n_0} G(S_{ji1}, S_{jk0})$
- $\widehat{\delta_j} = \widehat{U_Y} - \widehat{U_{S_j}}$

Screening stage

- One-sided $(1-\alpha)\%$ C.I. estimated as $[-1, \widehat{\delta}_j + \Phi^{-1}(1-\alpha)\widehat{\sigma}_{\delta_j}]$
- p-value is $p_j = P(Z < \widehat{\delta}_j)$ where $Z \sim N(\epsilon, \widehat{\sigma}_{\delta_j})$
- Test every candidate $S_1, ..., S_p$ and correct p-values for test multiplicity
- Define candidate surrogates $\mathcal{S} = \{j : p_{j,\text{adj}} \leq \alpha\}$

Evaluation Step

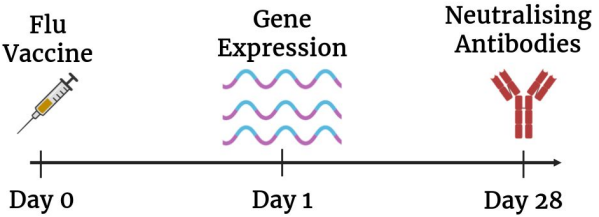
Evaluate combined surrogacy of candidates

- $\widehat{\gamma_{\mathcal{S}}} := \sum_{j \in \mathcal{S}} \widehat{\delta_j}^{-1} \bar{S}_j$
  - $\bar{S}_j$ is S_j standardised
  - Weighted by $\widehat{\delta_j}^{-1} \implies$ stronger surrogates contribute more
- Re-apply rank-test to evaluate $\widehat{\gamma_{\mathcal{S}}}$

Application

Data description

- **Open data** from Human Immune Project Consortium
- SDY1276 - GE/Antibody response for *Trivalent Inactivated Influenza* ($n = 103$)



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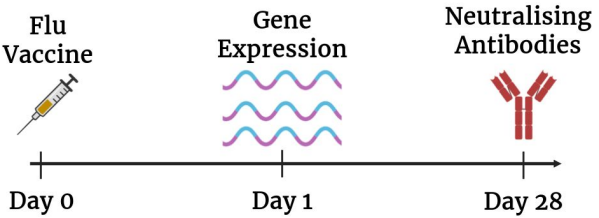


Can the treatment effect on GE at day 1 predict the treatment effect on day 28 on the antibodies?

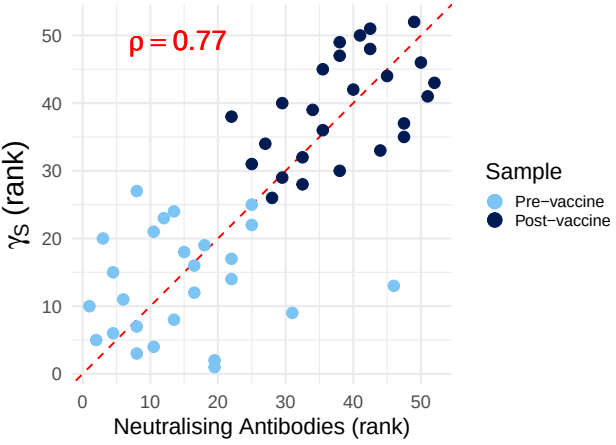
Screening Results

222 significant genes after multiple testing correction

Gene	Gene set	δ (95% C.I.)	p_{adj}
CNDP2		-0.026 (-0.056, 0.004)	1.6e-43
IFI44L	M8.3 (Type 1 Interferon)	-0.026 (-0.056, 0.004)	1.6e-43
IFITM3	M15.127 (Interferon)	-0.026 (-0.056, 0.004)	1.6e-43
NPC2		-0.026 (-0.056, 0.004)	1.6e-43
PSME1		-0.026 (-0.056, 0.004)	1.6e-43
SERPING1	M15.127 (Interferon)	-0.026 (-0.056, 0.004)	1.6e-43
VAMP5		-0.026 (-0.056, 0.004)	1.6e-43
EPB41L3	M12.2 (Monocytes)	-0.013 (-0.05, 0.024)	1.1e-30
IFI6	M8.3 (Type 1 Interferon)	-0.013 (-0.05, 0.024)	1.1e-30
IRF7	M10.1 (Interferon)	-0.013 (-0.05, 0.024)	1.1e-30
MX1	M8.3 (Type 1 Interferon)	-0.013 (-0.05, 0.024)	1.1e-30
MYOF	M16.6 (Monocytes), M16.15 (Cell death)	-0.013 (-0.05, 0.024)	1.1e-30
OAS3	M8.3 (Type 1 Interferon)	-0.013 (-0.05, 0.024)	1.1e-30
PSMB9	M13.17 (Interferon),M15.64 (Interferon)	-0.013 (-0.05, 0.024)	1.1e-30
RHBDF2	M15.37 (Inflammation), M15.64 (Interferon)	-0.013 (-0.05, 0.024)	1.1e-30

Table: Top 15 genes by adjusted p-value from screening stage on 75% of the data.

Evaluation results



- $\delta_{\gamma_S} = -0.0385(-0.102, 0.0248)$
- $p = 0.00311$
- $\implies \gamma_S$ a suitable surrogate for the day 28 treatment effect of TIV on neutralising antibodies

Discussion

Conclusions

- New method to **identify high-dimensional surrogate markers** of continuous responses
- Application to influenza vaccination
  - **222-gene signature** of mainly interferon genes **predicts vaccine effect** on antibodies
- Perspectives
  - Generalisability : other years of TIV, other vaccines?
  - Extension to other data types (survival, binary outcome) and complex designs

arXiv > stat > arXiv:2502.03030

Statistics > Methodology

[Submitted on 5 Feb 2025]

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Thank you for listening

Appendix

How to choose the threshold ϵ?

- ϵ depends on n, treatment effect on Y, desired power and significance
- If desired power $100 \times (1-\beta)\%$ to test a treatment effect on Y based on a test with S_j
- ϵ can be chosen adaptively as $\epsilon = \max\{0, \widehat{u}_Y - u^*_{\alpha,\beta}\}$
  - where $u^*_{\alpha,\beta} = \frac{1}{2} - \sqrt{\frac{n_0+n_1+1}{12 n_0 n_1}}[\Phi^{-1}(\beta) - \Phi^{-1}(1-\alpha)]$

Estimation - paired case

- **Data:** $\boldsymbol{Y_i} = (Y_i^1, Y_i^0)^T$ and surrogate candidate $\boldsymbol{S_{ij}} = (S_{ij}^1, S_{ij}^0)^T$.
- $\widehat{U}_Y = n^{-1}\sum_{i=1}^{n} G(Y_i^1, Y_i^0)$
- $\widehat{U}_{S_j} = n^{-1}\sum_{i=1}^{n} G(S_{ij}^1, S_{ij}^0)$

Two one-sided test procedure

We want to test $\delta \in [-\epsilon, \epsilon]$
Perform **Two one-sided tests** :

$$H_0^{(1)} : \delta \geq \epsilon, \quad \text{and} \quad H_0^{(2)} : \delta \leq -\epsilon.$$

resulting in two p-values $p^{(1)} = \Phi\left(\frac{\widehat{\delta}-\epsilon}{\widehat{\sigma}_\delta}\right)$, $p^{(2)} = 1 - \Phi\left(\frac{\widehat{\delta}+\epsilon}{\widehat{\sigma}_\delta}\right)$
Final p-value is $p = \max\{p^{(1)}, p^{(2)}\}$ and $(1-2\alpha) \times 100\%$ C.I. is

$$\left[\widehat{\delta} - \Phi^{-1}(1-\alpha)\,\widehat{\sigma}_\delta,\ \widehat{\delta} + \Phi^{-1}(1-\alpha)\,\widehat{\sigma}_\delta\right]$$

Simulation Setup

- $P = 500$ candidate surrogates
- Response : $Y_a \sim \mathcal{N}(\mu_{y_a}, \sigma_{y_a})$,
  - with $\mu_{y_1} = 3$, $\mu_{y_0} = 0$, and $\sigma_{y_a} = 1$
- Setting 1 : 100% invalid surrogates $S_{j,a} \sim \mathcal{N}(m_j, \sigma_j)$
  - $m_j \sim U(0.5, 2.5)$, $\sigma_j \sim U(0.5, 2)$
- Setting 2 : 10% valid surrogates $S_{j,a} = y_a + \mathcal{N}(0, \sigma_{\text{valid}})$
  - σ_{valid} controls surrogate strength

Setting 1 : no true surrogates

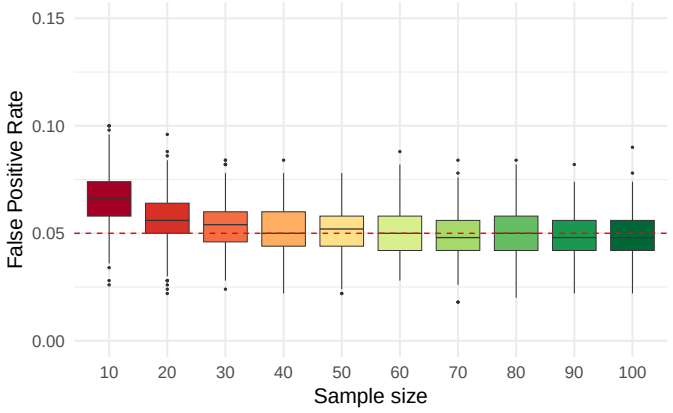

Figure: False positive rate across 500 data generations.

Setting 2 : 10% true surrogates

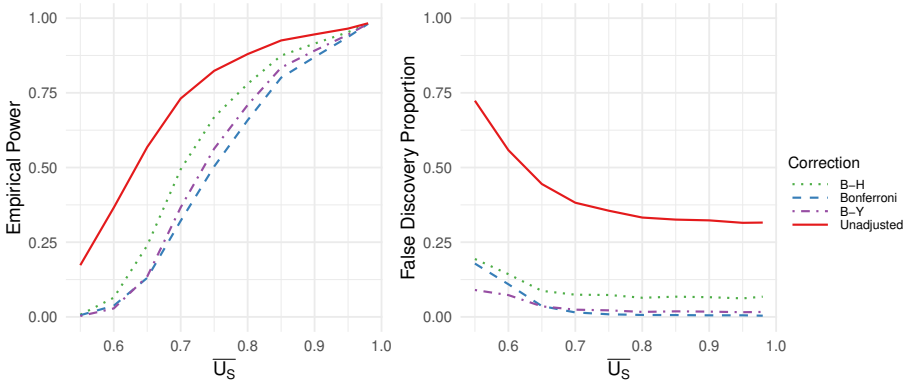

Figure: Power and FDP across 500 data generations with different multiple correction methods.