Impact of Eplet Mismatches on the Risk of Donor-Specific Antibodies and Antibody-Mediated Rejection in Simultaneous Pancreas-Kidney Transplant Recipients

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Organ and Tissue Donation Statistics in Australia (2020)

Organ Transplants

- **Recipients:** 1,270 individuals received organ transplants
- **Donors:** 463 deceased organ donors facilitated these transplants

- **Waiting List:** Over 1,600 individuals awaiting life-saving transplants
- **Dialysis Patients:** Over 12,000 individuals on dialysis, with many in need of kidney transplants

Tissue Transplants

- **Total Recipients:** 10,817 tissue transplants performed
- **Tissue Donors:** Contributions from 3,018 tissue donors
  - Living Donors: 2,728
  - Deceased Donors: 290

Eye and Corneal Transplants:

- Eye Donors: 1,318
- Corneal Transplants: 2,277 (Over double the number as there were in 2009)
- **Cumulative Impact:** Since 2009, more than 23,500 Australians have received corneal transplants

Data Source: Australian Government Department of Health

Managing Transplant Rejection

Transplant Rejection:

- Occurs when the immune system detects donor tissue as foreign, triggering a response.

- The goal is to 'trick' the immune system.

Importance of Matching: Success hinges on the compatibility of genetic markers between donor and recipient.

Managing Rejection: Immunosuppressive drugs

- Immunosuppression is able to modify, but do not nullify the immune response.

Potential risks of long-term immunosuppression:

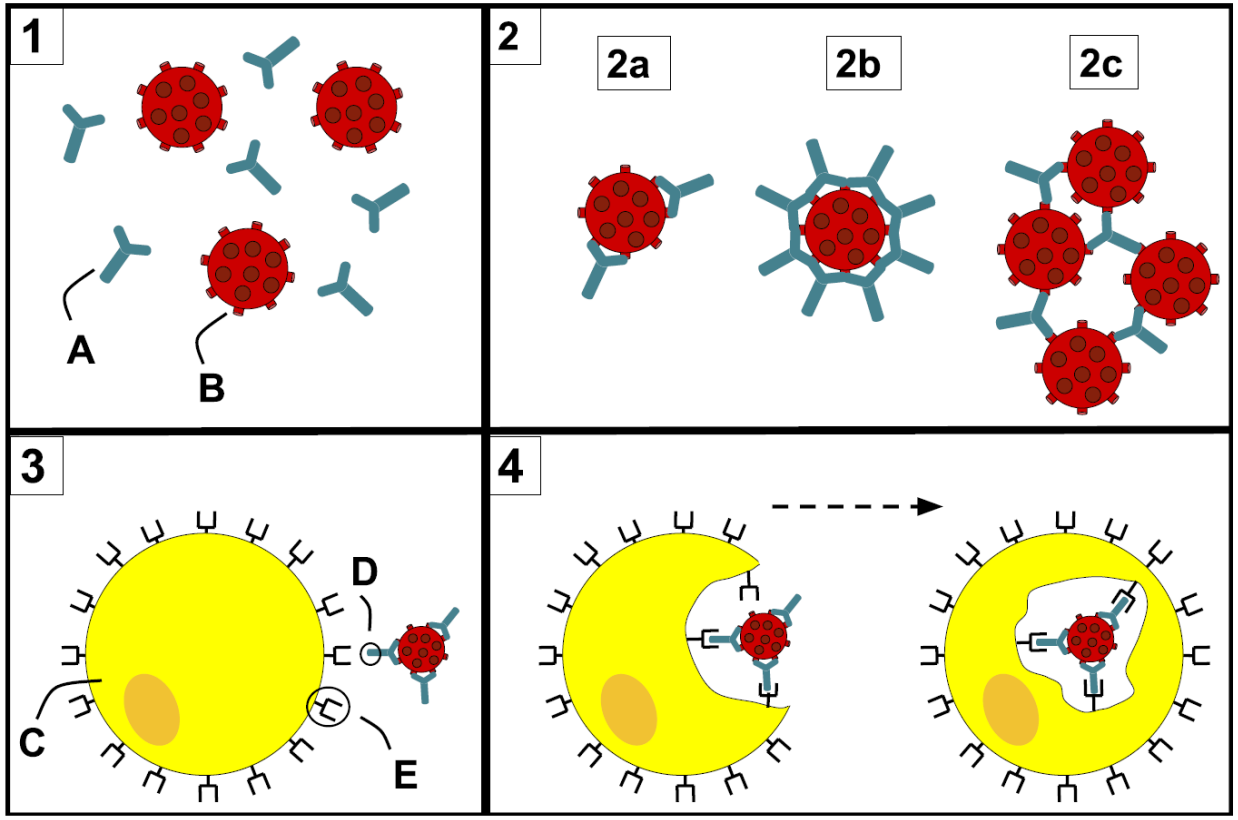
- Increased susceptibility to infections
- Drug toxicity and side effects

Human Leukocyte Antigen (HLA)

- **Location of HLA Genes:** Found on chromosome 6.
- **Detection of Foreign HLA markers:**
  - Donor organs carry the donor's specific HLA markers.
  - Recipient's immune system recognizes foreign HLA when blood circulates through the transplanted organ.
- HLA compatibility is crucial for the immune response and determining transplant success.
  - **HLAMatchmaker:** A computer algorithm used for HLA matching.

Eplets

- Rather than binding to the entire HLA antigen, antibodies specifically target eplets.
- Eplets are distinct, localized areas on HLA antigens where antibodies attach.
- A single HLA antigen can possess various eplets. These eplets can be public or private.
- The likelihood of transplant rejection increases with the number of eplet mismatches.



Copied from Wikipedia

Advancing Eplet Mismatch Scoring for Transplant Success

Current Scoring Limitations:

- Presently, mismatch scores are calculated by considering all eplets equally.

Research Hypothesis:

- Not all eplets contribute equally to the immune response; some have a higher immunogenic activity than others.

Challenge:

- Identifying the eplets that are critical to match is a significant challenge.

Our Approach:

- We are employing statistical models to isolate the subset of eplets that are more immunogenetically active.
- Successfully identifying the more active eplets would help clinicians to select recipients for successful transplantation.

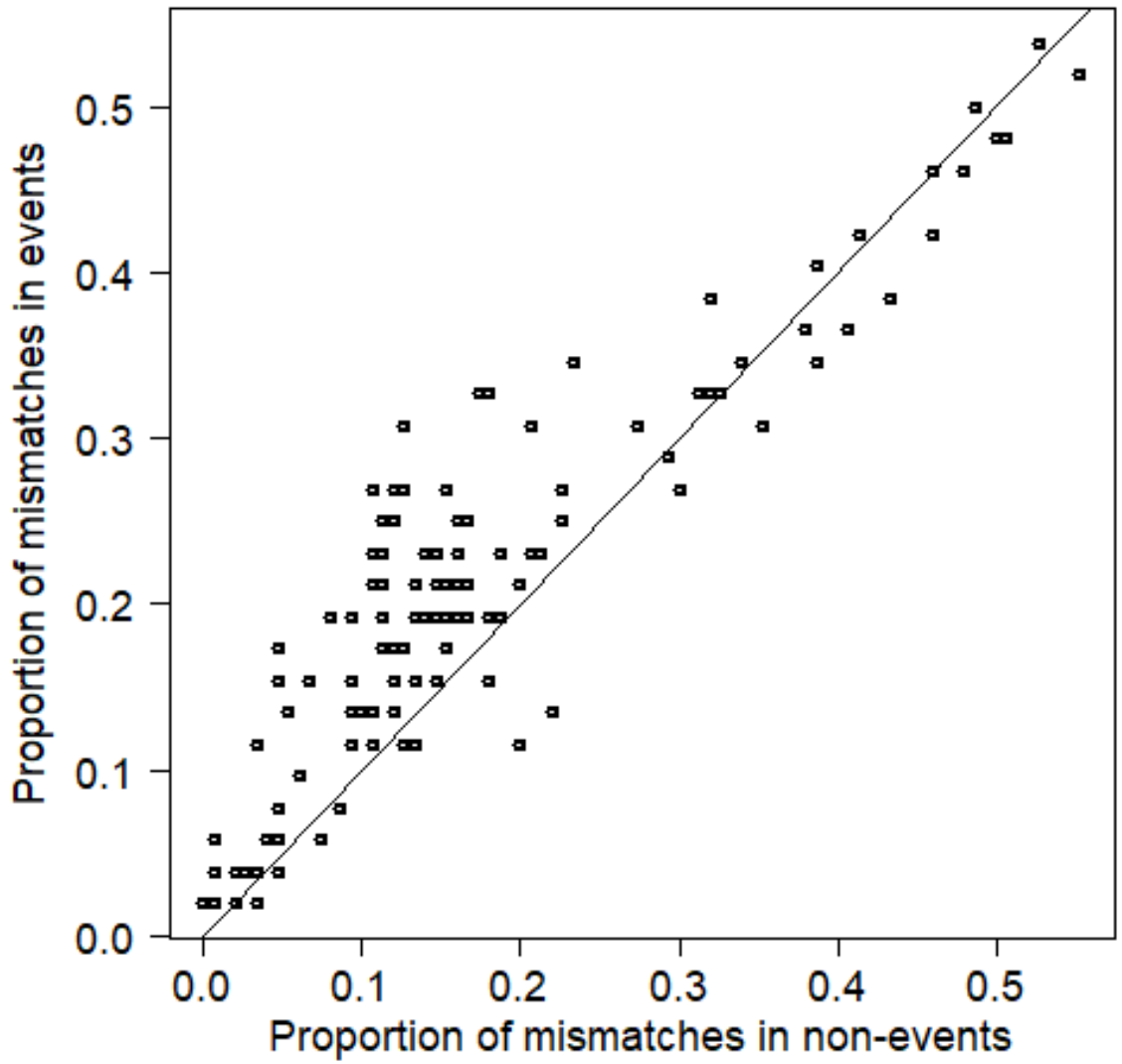
Analysis of de novo Donor-Specific Antibody Production

- De novo Donor Specific Antibody (dnDSA)" refers to new antibodies produced by the recipient against the donor's HLA post-transplant.
- **Study Overview:**
  - Sample Size: Analysis was conducted on 202 samples.
  - response variable: Time-to-dnDSA development.
  - Covariates: 321 binary covariates were used (match=0, mismatch=1).
- **Demographic Variables**:
  - Age and gender of donor and recipient, ischemia time, and presence of pre-formed DSA.
- **dnDSA Incidence:** 52 out of 202 recipients developed dnDSA (experienced rejection).

Analysis of Mismatch Proportions (Unadjusted for Time to Rejection)

- **Data Points:** Each point represents the observed proportion of eplet mismatches for events (transplant rejections) and non-events.
- **Reference Line:** The 45-degree line illustrates the point of equality where the proportion of mismatches in events equals that in non-events.

		Match	Mismatch	
Rejection	No	131	19	150
	Yes	38	14	52



Modeling challenges in active eplet identification

- **Overfitting Risk:** With 321 covariates compared to 203 samples, overfitting is a concern.

Statistical Approaches that can be utilized:

  - **Regularized Cox Regression & Random Survival Forest:** These methods are suitable for the time-to-event data.

- **Interpreting Challenge:** Negative coefficients pose interpretation challenges as they suggest more mismatches could decrease the chance of rejection.
- **Complete Separation Issue:** Eplets with rare mismatches that always lead to rejections, causing model distortion.

Solutions Implemented:

- **Constrained Coefficients:** The glmnet package's Regularized Cox Regression is utilized for constrained optimization, allowing coefficients to be restricted to non-negative values to better reflect clinical expectations.
- Regularization solves our complete separation problem too.

Coxnet: Cox regression with elastic-net regularization

- The traditional Cox regression model is

$$h(t|X) = h_0(t)e^{X^t\beta}$$

- The estimates of the coefficients are obtained using

$$\hat{\beta} = \max_{\beta}\left[\frac{n}{2}\left(\sum_{i=1}^{m} X_{i(j)}^T\beta - \log\left(\sum_{j\in R_i} e^{X_j^T\beta}\right)\right) - \lambda p_\alpha(\beta)\right]$$

where λ>0.

- The Elastic-net penalty is

$$p_\alpha(\beta) = \alpha\sum_{j=1}^{p}|\beta_j| + (1-\alpha)\sum_{j=1}^{p}\beta_j^2/2$$

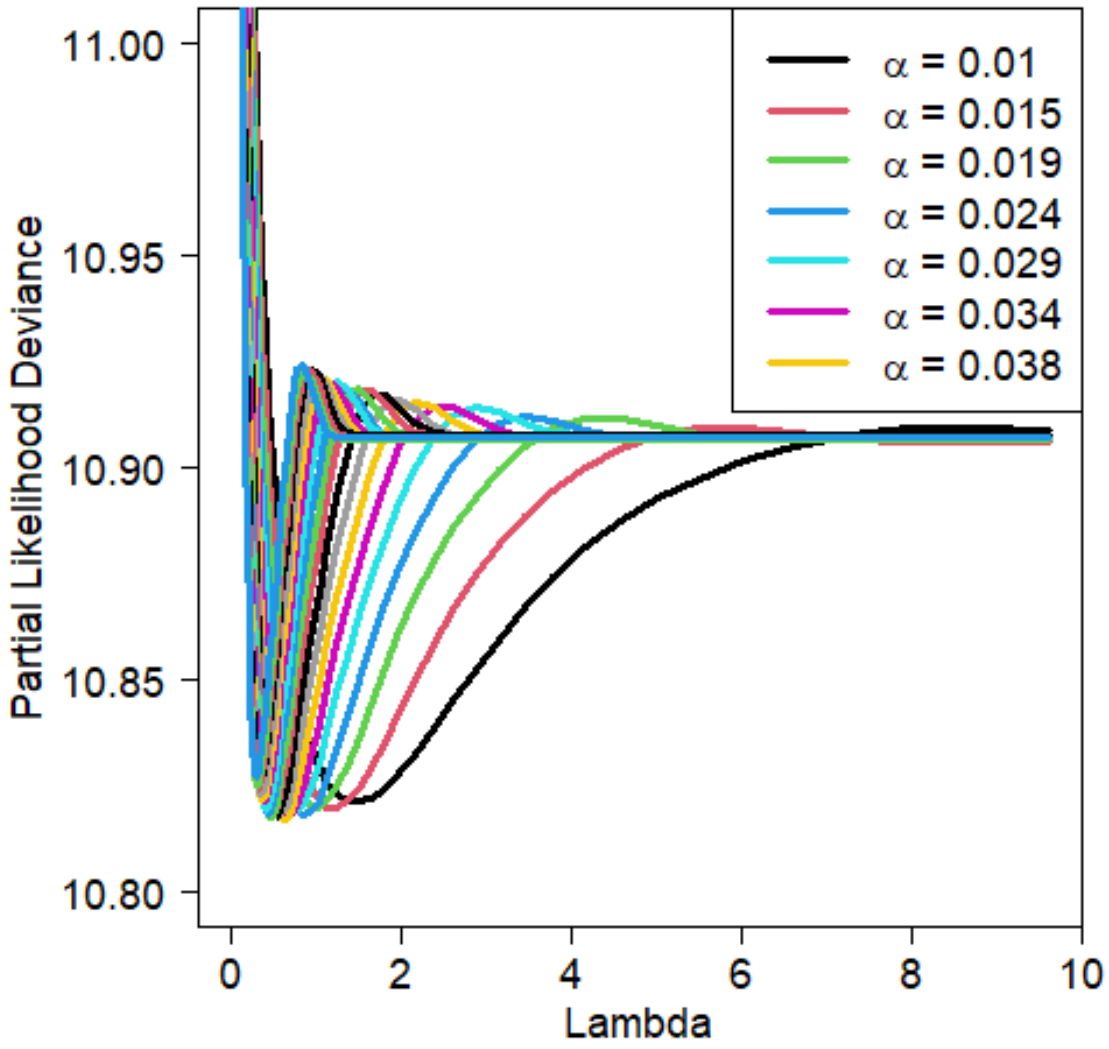
where 0≤α≤1 is the mixing parameters.

Tuning Regularization Parameters with Repeated Cross-Validation

Challenge of Limited Data: Traditional k-fold cross-validation can lead to high variance in model evaluation due to a small sample size.

Solution: Repeated Cross-Validation:

- Method: We perform 10-fold cross-validation multiple times (1000 replicates) to obtain a more stable estimate of model performance.
- Outcome: This repetition reduces the variance of the error estimate.



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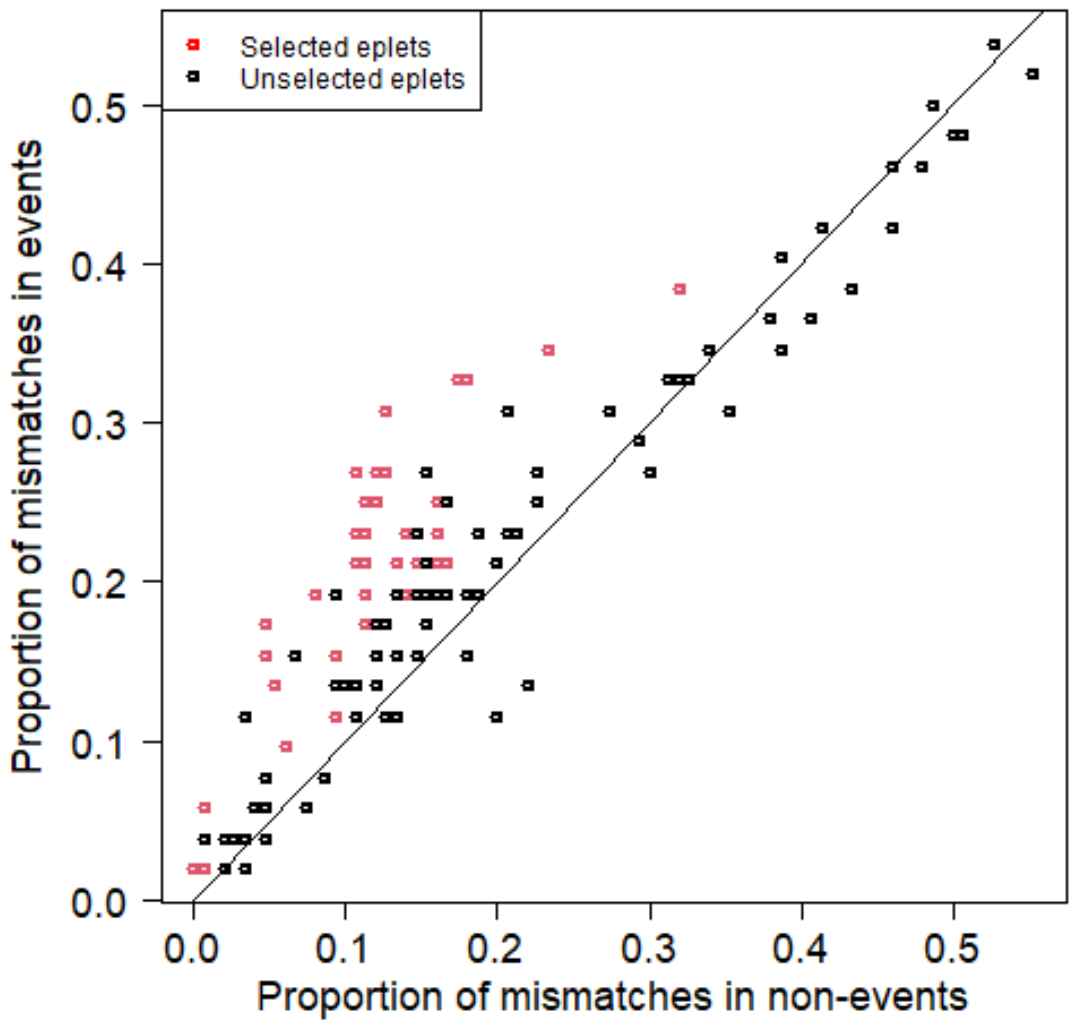


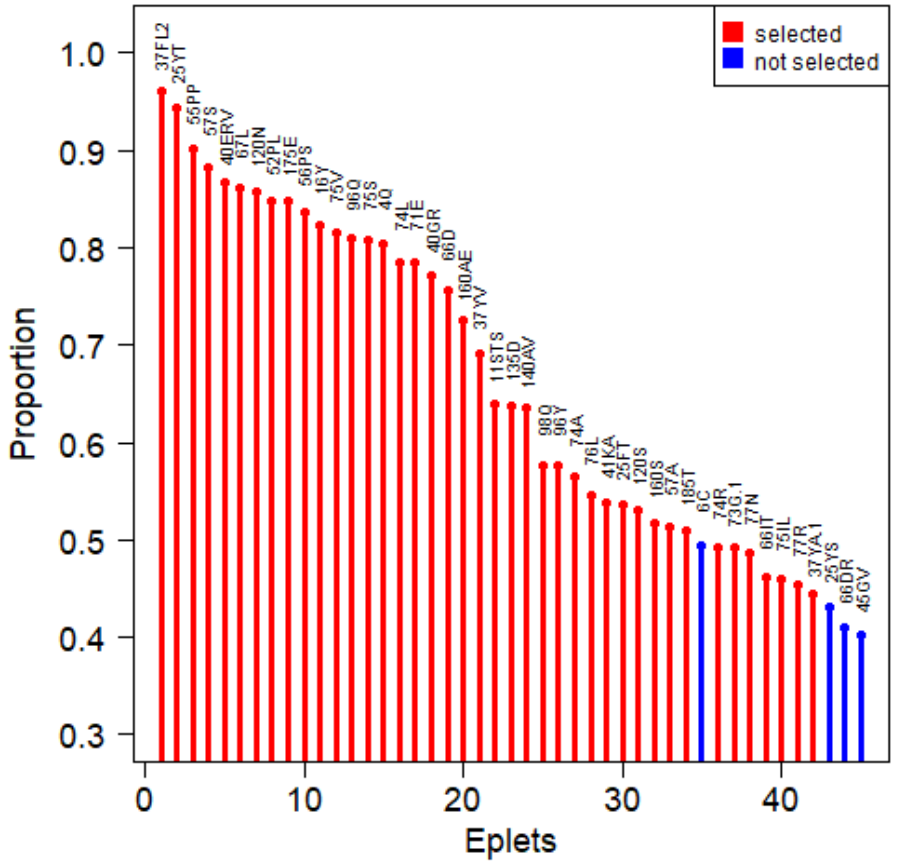
Bootstrap Methods for Inference in Elastic-Net Regularization

Inference Challenge:

- Inference procedures for models with elastic-net penalties are not yet well established.

Bootstrap Approach:

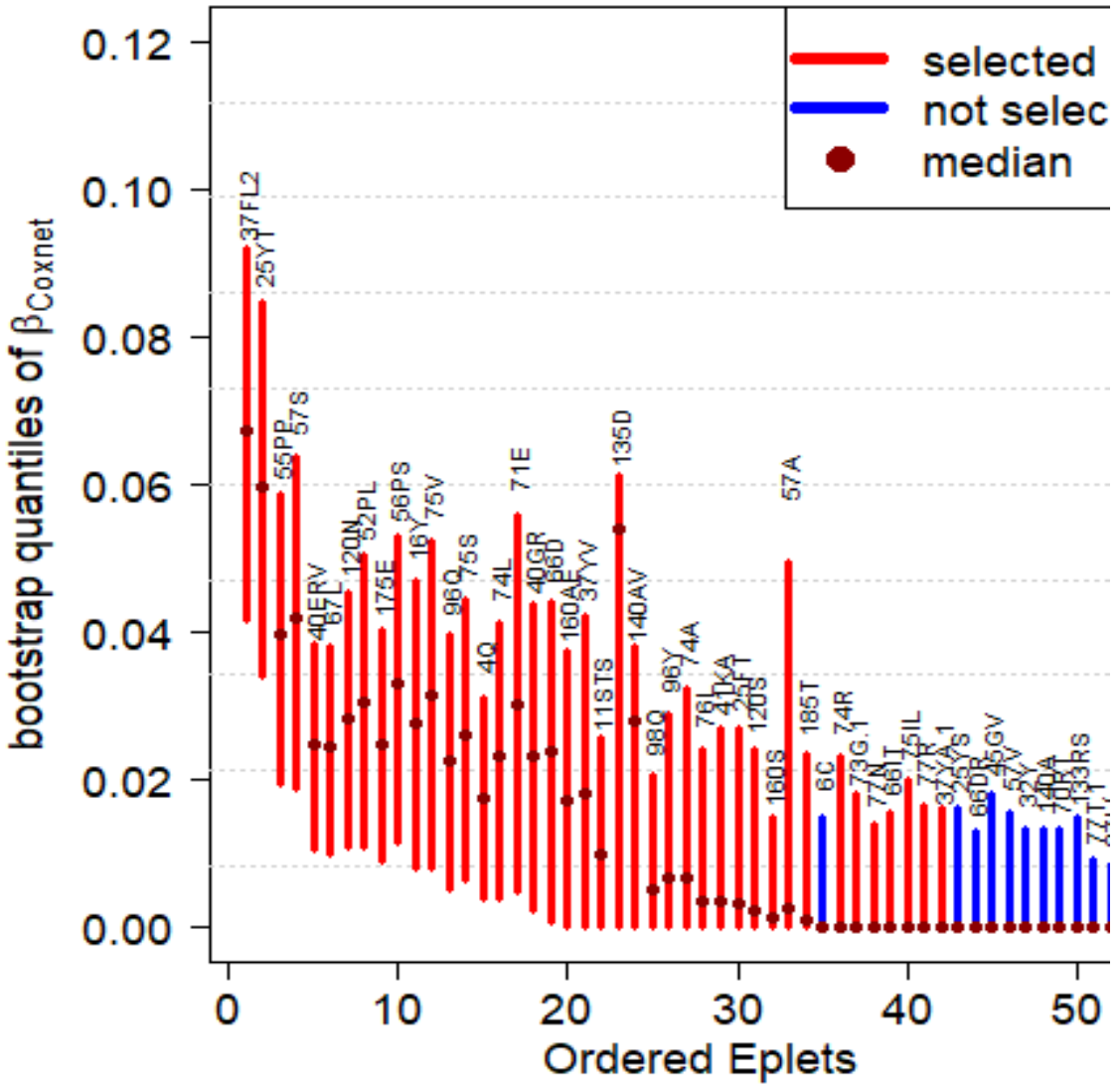
- We utilize bootstrap resampling with 1000 samples to evaluate the stability of feature (eplet) selection.
- Eplet selection frequency is calculated to gauge selection confidence.



Bootstrap Methods for Inference in Elastic-Net Regularization

Coefficient Uncertainty:

- Bootstrap quantiles offer insight into the variability of coefficient estimates.



Conclusions and next steps in eplet mismatch analysis.

Key Findings:

- Specific eplet mismatches are linked to an increased risk of developing dnDSA.
- Avoiding these mismatches may reduce the incidence of dnDSA.

Future Research and Recommendations:

- Validation with larger independent datasets is necessary for confirming these findings.
- Implement matching strategies that rely on high-risk eplet mismatches.

Independent dataset:

- We have recently received a new independent dataset of similar size, but some of the covariates are missing, posing another challenge.