HIV VACCINE TRIALS NETWORK

Inferring Dependency of HIV Vaccine Efficacy on HIV Divergence

Biostat 578A Lecture 8

Collaborators:

Ian McKeague
Columbia University

Yanqing Sun
University of North Carolina at Charlotte

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HIV Extraordinarily Diverse

HIV-1C pairwise amino acid diversity (n=73 sequences)

Protein	Mean (%)	Range (%)
Pol	6.4	0.2-10.2
Vif	11.6	0.5-22.1
Vpr	11.9	1.0-24.5
Rev	17.4	2.7-46.8
Tat	18.3	4.2-39.1
Nef	18.6	5.1-30.6
Env	20.0	7.4-26.4
Vpu	25.2	2.4-50.0

Objectives of HIV Vaccine Efficacy Trial

- **Primary objective:** Assess vaccine efficacy (VE) to prevent HIV infection
- **Secondary objective:** Assess if and how VE varies with genotypic/phenotypic characteristics of HIV
  - For each infected subject, measure the **distance** V between the infecting virus and the virus(es) represented in the vaccine
- **Available data:**
  - Vaccine group: $(X_{1i}, \delta_{1i}, \delta_{1i}V_{1i}), \quad i = 1, \cdots, n_1$
  - Placebo group: $(X_{2i}, \delta_{2i}, \delta_{2i}V_{2i}), \quad i = 1, \cdots, n_2$

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Categorization of HIV Strains

- **Case 1:** V a small number of ordered categories
  - E.g.: $V \in \{0, 1, 2, 3+\}$ substitutions/deletions in the HIV V3 loop tip sequence GPGRAF
  - For each strain category j, can study $VE(t, j)$ using cause-specific hazard functions or cumulative incidence functions:

$$VE(t,j) = 1 - \frac{\lambda_{1j}(t)}{\lambda_{2j}(t)} \quad \text{or} \quad VE(t,j) = 1 - \frac{F_{1j}(t)}{F_{2j}(t)}$$

$$\lambda_{kj}(t) = \lim_{h_1 \to 0} P\{T_k \in [t, t+h_1), V_k = j | T_k \geq t\}/h_1$$
$$F_{kj}(t) = P\{T_k \leq t, V_k = j\} = \int_0^t S_k(s-) d\Lambda_{kj}(s)$$

Some Literature on the Analysis of Discrete Competing Risks Data

- Prentice et al. (1978, Biometrics)
- Gray (1988, Ann Stat)
- Aly, Kochar, and McKeague (1994, JASA)
- Lunn and McNeil (1995, Biometrics)
- Lam (1998, Biometrika)
- Hu and Tsai (1999, Statistica Sinica)
- Luo and Turnbull (1999, Statistica Sinica)
- Sun (2001, J Nonpar Stat)
- McKeague, Gilbert, and Kanki (2001, Biometrics)
- Fine (2001, JASA)

Categorization of HIV Strains

- **Case 2:** V a large number of ordered categories
  - E.g.: $V =$ percent amino acid mismatch
    $\Rightarrow$ Treat V as continuous, $V \in [0, 1]$

Gag fragment alignment

```
PIVQNLQGQM VHQAISPRTL
.......... ..R......T
.......... ..R......T
.......... T.A.......
.......... ..R.......
.V........ T.A..G....
```

Previous Work on Inferring Dependency of VE on v

- Semiparametric modeling approach developed by Gilbert et al. (1999, Biometrika; 2000, Ann Stat)
- **Limitations of method:**
  - Interpretation conditional on infection
  - Functional form relating VE and v specified parametrically
  - Does not account for time to HIV infection

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Current Work on Statistical Methods

- **Objective:** Develop methods for testing and estimation of $VE(t,v)$ defined based on continuous mark-specific hazard and cumulative incidence functions
  - Mark-specific hazard functions:

$$\lambda_k(t,v) = \lim_{h_1,h_2 \to 0} P\{T_k \in [t, t+h_1), V_k \in [v, v+h_2) | T_k \geq t\}/h_1 h_2$$

  - Mark-specific cumulative incidence functions:

$$F_k(t,v) = \lim_{h_2 \to 0} P\{T_k \leq t, V_k \in [v, v+h_2)\}/h_2$$

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Vaccine Efficacy Parameters

Overall vaccine efficacy definitions:

- $VE(t) = 1 - \frac{\lambda_1(t)}{\lambda_2(t)}$
- $VE^c(t) = 1 - \frac{F_1(t)}{F_2(t)}$

Vaccine Efficacy Parameters

Mark-specific vaccine efficacy definitions:

- $VE(t,v) = 1 - \frac{\lambda_1(t,v)}{\lambda_2(t,v)}$
- $VE^c(t,v) = 1 - \frac{F_1(t,v)}{F_2(t,v)}$
- $VE^{dc}(t,v) = 1 - \frac{P\{T_1 \leq t, V_1 \leq v\}}{P\{T_2 \leq t, V_2 \leq v\}}$
- $VE^{int}(t,v) = \int_0^v VE^c(t,u)du$

Interpretation of $VE(t,v) = 1 - \frac{\lambda_1(t,v)}{\lambda_2(t,v)}$

- Interpretation of $\lambda_k(t,v)$ restricted to actual study conditions (*crude* hazard)
- Would like to study the *net* hazard: rate of failure by mark v in the absence of any competing viral strains
  - Unidentifiable

Interpretation of $VE(t,v) = 1 - \frac{\lambda_1(t,v)}{\lambda_2(t,v)}$

- Factorization:

$$\lambda_k(t,v) = \lambda_{Ek}(t,v) \times \lambda_{Tk}(t,v)$$

  - $\lambda_{Ek}(t,v) =$ **Exposure hazard**

    Markov intensity of exposures to strains with divergence v
  - $\lambda_{Tk}(t,v) =$ **Transmission probability** conditional on exposure to a strain with divergence v at time t

$$\lambda_{Tk}(t,v) = lim_{h_1,h_2 \to 0} \Pr(T_k \in [t, t+h_1), V_k \in [v, v+h_2) | T_k \geq t,$$

exposed in $[t, t+h_1)$ to HIV w/$V_k \in [v, v+h_1))/h_1 h_2$

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Interpretation of $VE(t,v) = 1 - \frac{\lambda_1(t,v)}{\lambda_2(t,v)}$

- $VE(t,v)$ measures a *mixture* of vaccine/placebo-group differences in:
  - mark-specific exposure rates
  - per-mark-specific exposure transmission probabilities
- Interest in vaccine efficacy parameter based on **transmission probabilities**: $VE^T(t,v) =$

$$lim_{h_1,h_2 \to 0} \frac{\Pr(T_1 \in [t,t+h_1), V_1 \in [v,v+h_2) | T_1 \geq t, \text{exp w/} V_1 \in [v,v+h_2))}{\Pr(T_2 \in [t,t+h_1), V_2 \in [v,v+h_2) | T_2 \geq t_2, \text{exp w/} V_2 \in [v,v+h_2))}$$

- **Approach**: Assume $\lambda_{E1}(t,v)/\lambda_{E2}(t,v) = 1$, so that the identifiable parameter $VE(t,v)$ equals $VE^T(t,v)$

Ignoring the Mark Variable Can Mislead in Assessing Vaccine Efficacy

- Consider a mark-specific PH model:

$$\lambda(t,v|z=0) = \lambda_0(v) = e^{\gamma v}$$

$$\lambda(t,v|z=1) = \lambda_0(v)e^{\alpha+\beta v}$$

- Marginal PH model (ignoring the mark):

$$\lambda_T(t|z) = \int_0^1 \lambda(t,v|z)\,dv = \left(\frac{e^{\gamma}-1}{\gamma}\right)e^{\beta^* z}$$

$$\beta^* = \alpha + \log\left(\frac{e^{\gamma+\beta}-1}{\gamma+\beta}\right) - \log\left(\frac{e^{\gamma}-1}{\gamma}\right)$$

Ignoring the Mark Variable Can Mislead in Assessing Vaccine Efficacy

- In the mark-specific PH model

$$VE(v) = 1 - e^{\alpha+\beta v}$$

- In the marginal PH model

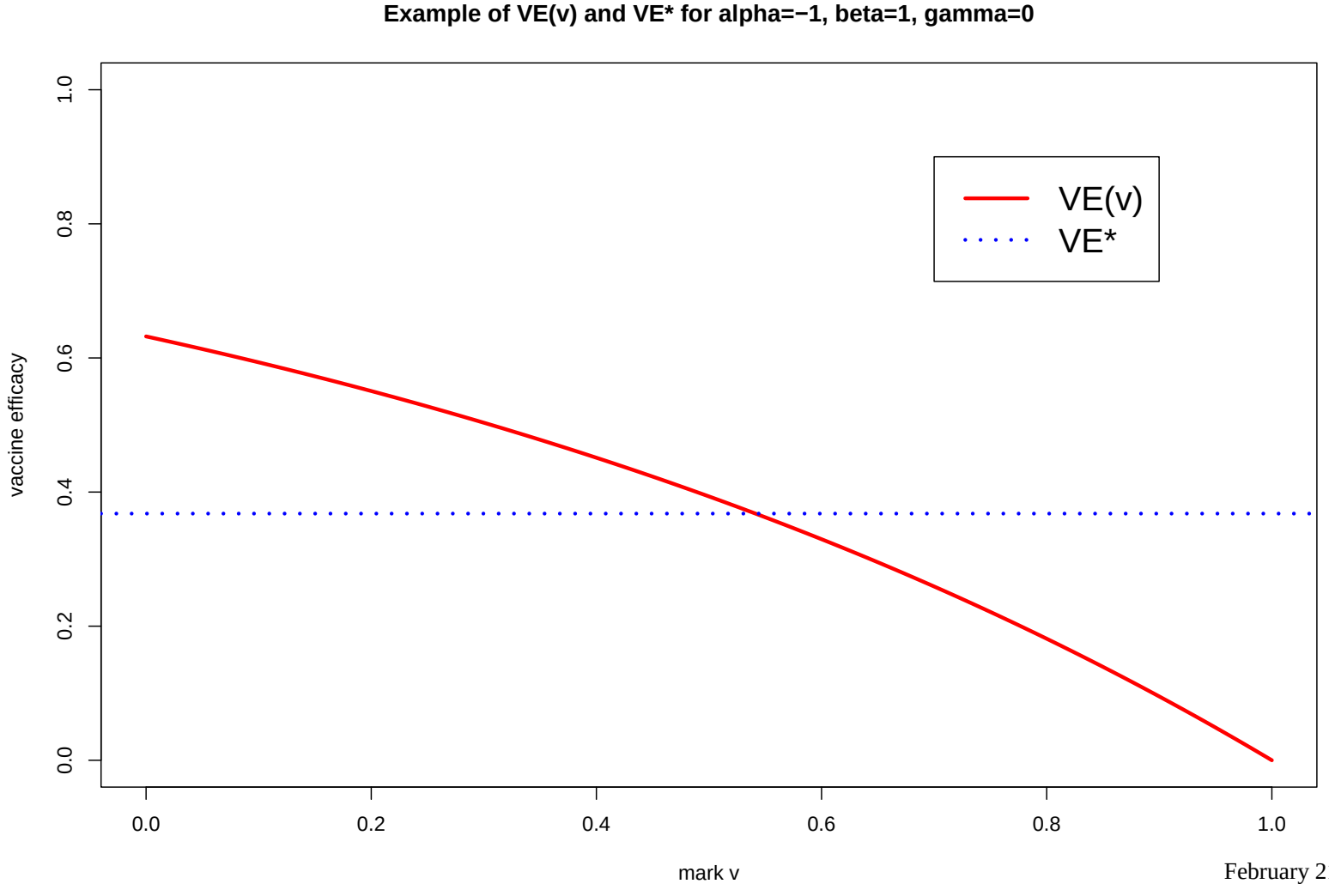
$$VE^* = 1 - \exp(\beta^*) = 1 - e^{\alpha}\left(\frac{e^{\gamma+\beta}-1}{\gamma+\beta}\right)\left(\frac{\gamma}{e^{\gamma}-1}\right)$$

- By varying γ over the real line, VE^* varies over all possible values of $VE(v)$ $(0 < v < 1)$
  - VE^* depends on the *baseline* mark-specific hazard

$\Rightarrow$ **The marginal estimand VE^* is affected by a model feature irrelevant for assessing vaccine efficacy**

Ignoring the Mark Variable Can Mislead in Assessing Vaccine Efficacy

- When the baseline does not involve the mark ($\gamma = 0$):
  $VE^* = \int_0^1 VE(v)\, dv$



Hypothesis Testing 1: Any Efficacy Against Any Virus?

- Consider $VE(t,v) = 1 - \frac{\lambda_1(t,v)}{\lambda_2(t,v)}$
- Test

$$
\begin{aligned}
H_0^0 : VE(t,v) &= 0 \text{ for all } v \in [0,1], t \in [0,\tau] \\
&\text{versus} \\
H_1^0 : VE(t,v) &\geq 1 \text{ for all } (t,v) \in [0,\tau] \times [0,1]; \\
H_2^0 : VE(t,v) &\neq 1 \text{ for some } (t,v) \in [0,\tau] \times [0,1]
\end{aligned}
$$

  with strict inequality for some $(t,v) \in [0,\tau] \times [0,1]$ in H_1^0

- $H_0^0 \Leftrightarrow \frac{\lambda_1(t,v)}{\lambda_2(t,v)} = 0$ for all $v \in [0,1], t \in [0,\tau]$

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Hypothesis Testing 1

- Doubly cumulative mark-specific hazard functions

$$\Lambda_k(t,v) = \int_0^v \int_0^t \lambda_k(s,u)\, ds\, du, \qquad k = 1,2$$

- **Idea of testing procedures:** Compare a nonparametric estimate of $\Lambda_1(t,v)$ with a nonparametric estimate of $\Lambda_2(t,v)$
- Large differences for some v indicate departures from H_0^0

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Nonparametric MLE of $\Lambda_k(t,v)$

- Likelihood:

$$\prod_o f_k(X_{ki},V_{ki}) \prod_c S_k(X_{ki}) = \prod_o \lambda_k(X_{ki},V_{ki}) \prod_{i=1}^{n_k} \exp\left\{ -\int_0^1 \int_0^{X_{ki}} \lambda_k(s,v)\, ds\, dv \right\}$$

- Log-likelihood:

$$\int_0^1 \int_0^\tau \log \lambda_k(s,v)\, N(ds,dv) - \int_0^1 \int_0^\tau Y_k(s) \lambda_k(s,v)\, ds\, dv$$

Nonparametric MLE of $\Lambda_k(t,v)$

$\Rightarrow$ Nonparametric MLE given by:

$$\widehat{\Lambda}_k(t,v) = \int_0^t \frac{N_k(ds,v)}{Y_k(s)},\ t \geq 0,\ v \in [0,1]$$

$$\begin{aligned} Y_k(t) &= \sum_{i=1}^{n_k} I(X_{ki} \geq t) \\ N_k(t,v) &= \sum_{i=1}^{n_k} I(X_{ki} \leq t, \delta_{ki} = 1, V_{ki} \leq v) \end{aligned}$$

- Huang and Louis (1998, Biometrika)

Test Process and Test Statistics for Evaluating H_0^0

- **Test process:**

$$L_n^1(t,v) = \sqrt{\frac{n_1 n_2}{n}} \int_a^t H_n(s) \left[\widehat{\Lambda}_1(ds,v) - \widehat{\Lambda}_2(ds,v)\right]$$

  where a is a constant > 0

- **Idea**: Use a functional of $L_n^1(\cdot,\cdot)$ that summarizes departures from H_0^0

Test Process and Test Statistics for Evaluating H_0^0

- Let $w_V(v)$ be a known nonnegative weight function
- Test statistics for detecting H_0^1

$$\widehat{U}_1^1 = L_n^1(\tau, 1)$$

$$\widehat{U}_2^1 = \int_0^1 w_V(v) L_n^1(\tau, v) dv$$

- Test statistics for detecting H_0^2

$$\widehat{U}_3^1 = |L_n^1(\tau, 1)|$$

$$\widehat{U}_4^1 = \int_0^1 w_V(v) (L_n^1(\tau, v))^2 dv$$

Hypothesis Testing 2: Differential Efficacy by Viral Divergence?

- If H_0^0 is rejected, then sensible to test

$$\begin{aligned} H_0 : VE(t,v) &= VE(t) \text{ for all } v \in [0,1], t \in [0,\tau] \\ \text{versus} & \\ H_1 : VE(t,v_1) &\geq VE(t,v_2) \text{ for all } v_1 \leq v_2, t \in [0,\tau] \\ H_2 : VE(t,v_1) &\neq VE(t,v_2) \text{ for some } v_1 \leq v_2, t \in [0,\tau] \end{aligned}$$

  with strict inequality for some t, v_1, v_2 in H_1

- $H_0 \Leftrightarrow \frac{\lambda_1(t,v)}{\lambda_2(t,v)}$ does not depend on v

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Hypothesis Testing 2

- **Idea of testing procedures:** Compare a nonparametric estimate of $\Lambda_1(t,v) - \Lambda_2(t,v)$ with an estimate under H_0
- H_0 holds $\Leftrightarrow$

$$\Lambda_1(t,v) = \int_0^t \frac{\lambda_1(s)}{\lambda_2(s)} \Lambda_2(ds,v)$$

- Under H_0, estimate $\Lambda_1(t,v) - \Lambda_2(t,v)$ by

$$\int_0^t \left[\frac{\widehat{\lambda}_1(s)}{\widehat{\lambda}_2(s)} - 1 \right] \widehat{\Lambda}_2(ds,v)$$

Hypothesis Testing 2

- Here

$$\widehat{\lambda}_k(t) = \frac{1}{b_k} \int_{u_1}^{u_2} K\left(\frac{t-s}{b_k}\right) d\widehat{\Lambda}_k(s)$$

- This is a standard kernel smoothing method to estimate the hazard functions, as described in Andersen, Borgan, Gill, and Keiding (1993)

Nonparametric Test Process for Evaluating H_0

- **Test process:**

$$L_n^{np}(t,v) = \sqrt{\frac{n_1 n_2}{n}} \int_a^t H_n(s) \left[\widehat{\Lambda}_1(ds,v) - \frac{\widehat{\lambda}_1(s)}{\widehat{\lambda}_2(s)} \widehat{\Lambda}_2(ds,v) \right]$$

- Let

$$\Delta_n^{np}(t,v_1,v_2) = L_n^{np}(t,v_1) + L_n^{np}(t,v_2) - 2L_n^{np}(t,(v_1+v_2)/2)$$

Nonparametric Test Statistics for Evaluating H_0

- **Idea**: Use a functional of $L_n^{np}(\cdot,\cdot)$ that summarizes departures from H_0
- **Nonparametric test statistics:**

$$\widehat{U}_1^{np} = \sup_{v_1<v_2} \sup_{0\le t_1<t_2<\tau} \left[\Delta_n^{np}(t_2,v_1,v_2) - \Delta_n^{np}(t_1,v_1,v_2)\right]$$

$$\widehat{U}_2^{np} = \sup_{v_1<v_2} \sup_{0\le t_1<t_2<\tau} \left|\Delta_n^{np}(t_2,v_1,v_2) - \Delta_n^{np}(t_1,v_1,v_2)\right|$$

Alternative Semiparametric Test Process for Evaluating H_0

- Replace the nonparametric kernel estimates $\frac{\widehat{\lambda}_1(s)}{\widehat{\lambda}_2(s)}$ with an estimate from a standard Cox model of the hazard ratio:

$$\frac{\widehat{\lambda}_1(s)}{\widehat{\lambda}_2(s)} = exp(\widehat{\beta})$$

  where β is the maximum partial likelihood estimator

- **Semiparametric test process:**

$$L_n^{sp}(t,v) = \sqrt{\frac{n_1 n_2}{n}} \int_a^t H_n(s) \left[\widehat{\Lambda}_1(ds,v) - exp(\widehat{\beta})\widehat{\Lambda}_2(ds,v)\right]$$

Semiparametric Test Statistics for Evaluating H_0

- Use the same functionals as for the nonparametric test statistics
- **Semiparametric test statistics:**

$$\widehat{U}_1^{sp} = \sup_{v_1<v_2} \sup_{0\le t_1<t_2<\tau} \left[\Delta_n^{sp}(t_2, v_1, v_2) - \Delta_n^{sp}(t_1, v_1, v_2)\right]$$

$$\widehat{U}_2^{sp} = \sup_{v_1<v_2} \sup_{0\le t_1<t_2<\tau} \left|\Delta_n^{sp}(t_2, v_1, v_2) - \Delta_n^{sp}(t_1, v_1, v_2)\right|$$

Common Framework for the Test Process

- General test process:

$$L_n^r(t,v) = \sqrt{\frac{n_1 n_2}{n}} \int_a^t H_n(s) \left[\widehat{\Lambda}_1(ds,v) - \widehat{r}(s)\widehat{\Lambda}_2(ds,v)\right]$$

- The superscript r reflects the choice of function $\widehat{r}(s)$ in the test process and indicates whether it is used to:
  - Test H_0^0 (r as 1 implies $\widehat{r}(s) = 1$)
  - Test H_0 nonparametrically (r as np implies $\widehat{r}(s) = \widehat{\lambda}_1(s)/\widehat{\lambda}_2(s)$)
  - Test H_0 semiparametrically (r as sp implies $\widehat{r}(s) = \exp(\widehat{\beta})$)

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Common Framework for the Test Process

- For $r = 1$, $[\cdot]$ in $L_n^r(t,v)$ compares $\widehat{\Lambda}_1(ds,v)$ and $\widehat{\Lambda}_2(ds,v)$
- For $r = np$ or $r = sp$, $[\cdot]$ in $L_n^r(t,v)$ compares $\widehat{\Lambda}_1(ds,v) - \widehat{\Lambda}_2(ds,v)$ to an estimate of $\Lambda_1(ds,v) - \Lambda_2(ds,v)$ under H_0

Why do the Statistics $\widehat{U}_j^{np}/\widehat{U}_j^{sp}$ Measure Departures From H_0?

- By the proof of Theorem 2 (stated later),

$$(n/n_1n_2)^{1/2}[\Delta_n^r(t_2,v_1,v_2)-\Delta_n^r(t_1,v_1,v_2)]$$

converges in probability to $\delta(t_1,t_2,v_1,v_2)=$

$$\int_{t_1}^{t_2}\int_{\frac{v_1+v_2}{2}}^{v_2} H(s)(\lambda_1(s,v)-r(s)\lambda_2(s,v))\,dv\,ds$$

$$-\int_{t_1}^{t_2}\int_{v_1}^{\frac{v_1+v_2}{2}} H(s)(\lambda_1(s,v)-r(s)\lambda_2(s,v))\,dv\,ds,$$

where $r(s)=\lambda_1(s)/\lambda_2(s)$ or $\exp(\beta)$

Why do the Statistics U_j^{np}/U_j^{sp} Measure Departures From H_0?

- Under H_0, $\delta(t_1, t_2, v_1, v_2) = 0$ for all $t_1, t_2 \in [0, \tau]$ and $v_1, v_2 \in [0, 1]$
- Under H_1 and some smoothness conditions, $\delta(t_1, t_2, v_1, v_2) > 0$ for some $t_1 < t_2 \in [0, \tau]$ and $v_1 < v_2 \in [0, 1]$
- Therefore a large value of $\widehat{U}_1^r$ provides evidence against H_0 in the direction of H_1
- Similarly a large value of $\widehat{U}_2^r$ provides evidence against H_0 in the direction of H_2

Summary of Asymptotic Properties of the Tests of H_0

- The following theoretical properties of all of the above tests are proved in Gilbert, McKeague, and Sun (2006)
  - Tests have asymptotically correct size
  - Tests are asymptotically consistent against H_1 and H_2, respectively
  - Critical values are unknown and are difficult to obtain
    $\Rightarrow$ Critical values approximated by the *Gaussian multipliers technique* (useful trick in survival analysis)
    - Idea stems from Lin et al. (1993, 1994, Biometrika)

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Theorems Stating Asymptotic Properties

Theorem 1: Suppose certain regularity conditions, including that $\lambda_k(t)$ is twice continuously differentiable over $[0, \tau+\delta], k=1,2$, $\lambda_2(t)$ is bounded away from zero on $[a/2, \tau+\delta]$, $\lambda_2(t,v) > 0$ and $\partial^2\Lambda_2(t,v)/\partial t^2$ is continuous on $[0,\tau+\delta]\times[0,1]$. Also assume the kernel function $K(\cdot)$ has bounded variation. Suppose $nb_k^2 \to \infty$ and $nb_k^6 \to 0$ for $k=1,2$. Then, under H_0

$$L_n^{np}(t,v) \xrightarrow{\mathscr{D}} L^{np}(t,v) \text{ in } D([a,\tau]\times[0,1]) \text{ as } n\to\infty.$$

(The limit process $L^{np}(t,v)$ is defined in Gilbert, McKeague, and Sun (2006))

Implication of Theorem 1: Asymptotically Correct Size

- Let U_j^{np} be defined the same as $\widehat{U}_j^{np}$, with $L_n^{np}(t,v)$ replaced with $L^{np}(t,v)$
- By the continuous mapping theorem, $\widehat{U}_j^{np} \xrightarrow{\mathscr{D}} U_j^{np}$ under H_0, so $P(\widehat{U}_j^{np} > c_{j\alpha}) \to \alpha$, where $c_{j\alpha}$ is the upper α-quantile of U_j^{np}
- However, the $c_{j\alpha}$ are unknown and very difficult to estimate due to the complicated nature of the limit process $L^{np}(t,v)$
  - $\Rightarrow$ Use the Gaussian multipliers simulation procedure to approximate $c_{j\alpha}$

Implication of Theorem 2: Asymptotically Consistent

Theorem 2: In addition to the conditions given in Theorem 1, assume that $\lambda_1(t,v)$ and $\lambda_2(t,v)$ are continuous and that $H(t,v) > 0$ on $[0,\tau] \times [0,1]$. Then,

$$P(\widehat{U}_1^{np} > c_{1\alpha}) \to 1 \text{ as } n \to \infty \text{ under } H_1,$$

and

$$P(\widehat{U}_2^{np} > c_{2\alpha}) \to 1 \text{ as } n \to \infty \text{ under } H_2$$

- Theorems 1 and 2 also hold for L_n^{sp} and $\widehat{U}_j^{sp}, j = 1,2,$ under the same conditions except that the conditions on $\lambda_k(t)$ are replaced by the proportional marginal hazards assumption $\lambda_1(t)/\lambda_2(t) = \exp(\beta)$

Multipliers Technique is Justified Asymptotically

- Heuristic summary of Gaussian Multipliers technique (details in Gilbert, McKeague, and Sun, 2006)
  - Formulate a null test process $L_n^{r*}(t,v)$, which is a function of the observed data sequence and of standard normal variables $W_{ki}, i = 1,\ldots,n_k, k = 1,2$
    - Martingales $M(ds,u)$ are replaced with $W_{ki}N_k(ds,u)$, where $W_{ki}, i = 1,\ldots,n_k, k = 1,2$ are independent standard normal variables
  - The weak limit of the process $L_n^{r*}(t,v)$ given the observed data is the same as the weak limit of $L_n^r(t,v)$ under the null hypothesis H_0
    - That is, Theorem 3 states that

$$L_n^{r*}(t,v) \xrightarrow{\mathscr{D}} L^r(t,v) \text{ in } D([a,\tau]\times[0,1]) \text{ under } H_0 \text{ as}$$

Multipliers Technique is Justified Asymptotically

- Theorem 3 justifies the following (simple) simulation procedure for obtaining a p-value based on $\widehat{U}_j^r$:
  - Compute $\widehat{U}_j^r$ based on the test process $L_n^r(t,v)$
  - Compute $\widehat{U}_j^{r*1}, \cdots, U_j^{r*B}$ based on simulated null test processes $L_n^{r*}(t,v)$ (e.g., $B = 1000$)
  - Set the $p-value$ as the fraction of the $\widehat{U}_j^{r*}$'s that are $\geq \widehat{U}_j^r$

Considerations in Choosing the Weight Process $H_n(s)$

$$L_n^r(t,v) = \sqrt{\frac{n_1 n_2}{n}} \int_a^t H_n(s) \left[\widehat{\Lambda}_1(ds,v) - \widehat{r}(s)\widehat{\Lambda}_2(ds,v)\right]$$

- Would like to choose $H_n(t)$ to make the testing procedure asymptotically distribution-free
  - Elusive
- Choose $H_n(t)$ to up-weight early or late differences
- Choose $H_n(t)$ to minimize variability in the test process; e.g., dampen instability in the right-tail

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Estimation of $VE(t,v)$

- Sample size too small to reliably estimate
  $VE(t,v) = 1 - \frac{\lambda_1(t,v)}{\lambda_2(t,v)}$
- Focus on

$$\begin{aligned} VE^c(t,v) &= 1 - \frac{F_1(t,v)}{F_2(t,v)} \\ &= 1 - \lim_{h\to 0} \frac{P(T_1 \le t, V_1 \in [v, v+h))}{P(T_2 \le t, V_2 \in [v, v+h))} \end{aligned}$$

Estimation of $VE^c(t,v)$

- Estimate $VE^c(t,v)$ by $1-\frac{\widehat{F}_1(t,v)}{\widehat{F}_2(t,v)}$, where

$$\hat{F}_k(t,v)=\frac{1}{b_k}\int_0^1\int_0^t \frac{\hat{S}_k(s-)}{Y_k(s)}K\left(\frac{v-u}{b_k}\right)N_k(ds,du),$$

$\widehat{S}_k(t)=$ Kaplan-Meier estimate of $S_k(t)$

- $\widehat{F}_k(t,v)=$ continuous analog of $\widehat{F}_{kj}(t)$ for discrete mark (Prentice et al., 1978)

$$\left(\widehat{F}_{kj}(t)=\int_0^t \frac{\widehat{S}_k(s-)}{Y_k(s)}N_{kj}(ds)\right)$$

Variance and Confidence Interval Estimation

- $\text{Var}\{\widehat{F}_k(t,v)\}$ can be estimated by

$$\frac{1}{b_k^2}\int_0^1\int_0^t\left[\frac{\hat{S}_k(s-)}{Y_k(s)}K\left(\frac{v-u}{b_k}\right)\right]^2 N_k(ds,du)$$

- 95% pointwise CIs for $VE^c(t,v) = 1 - F_1(t,v)/F_2(t,v)$:

$$1-\left(1-\widehat{VE}^c(t,v)\right)\exp\left(\pm z_{\alpha/2}\sqrt{\frac{\widehat{\text{Var}}\{\widehat{F}_1(t,v)\}}{\widehat{F}_1(t,v)^2}+\frac{\widehat{\text{Var}}\{\widehat{F}_2(t,v)\}}{\widehat{F}_2(t,v)^2}}\right)$$

Alternative Mark-Specific Vaccine Efficacy Parameter

- Consider

$$VE^{dc}(t,v) = 1 - \frac{P\{T_1 \leq t, V_1 \leq v\}}{P\{T_2 \leq t, V_2 \leq v\}}$$

  - Equivalent to discrete mark case
  - Estimate each cumulative probability by nonparametric MLE
    (Huang and Louis, 1998, Biometrika)
  - Can obtain empirical likelihood-based CIs for $VE^{dc}(t,v)$

HIV VACCINE TRIALS NETWORK

Bandwidth Selection

- Nonparametric testing procedure requires bandwidths b_1, b_2 for $\widehat{\lambda}_1(t)$ and $\widehat{\lambda}_2(t)$
- Estimation procedure requires bandwidths b_{v1}, b_{v2} for $\widehat{F}_1(t,v)$ and $\widehat{F}_2(t,v)$
- **Approach:** Minimize an estimate of the mean integrated squared error (MISE); e.g., as in Andersen, Borgan, Gill, and Keiding (1993)
  - e.g., $\text{MISE}(\widehat{\lambda}_k(\cdot)) = E\int\{\widehat{\lambda}_k(t) - \lambda_k(t)\}^2 dt$

HIV VACCINE TRIALS NETWORK

Simulation Experiment

- Results presented for 8 experiments:
  - No. of HIV infections in placebo arm: 48, 95, 190
  - $VE^c(36) = 1 - \frac{F_1(36)}{F_2(36)}$: 0.33 or 0.67
  - Exponential failure times [20% random dropout], uniform marks in placebo arm, vaccine arm marks from density

$$f_V(v) = \frac{1}{\beta\left(1.5^{1/\beta} - 0.5^{1/\beta}\right)}(v+0.5)^{(1/\beta)-1}$$

  - $\beta = 1$ corresponds to H_0
  - $\beta = 0.5, 0.25$ correspond to H_1 (monotone altern)
  - Also consider a 2-sided alternative:
    $f_V(v) = \frac{16}{3}vI(v < \frac{1}{2}) + (\frac{8}{3} - \frac{8}{3}v)I(v \geq \frac{1}{2})$

Size of Tests of H_0^0

- Results for null case of $VE(t,v) = 0$

Empirical Power ($\times$ 100%) for Testing H_1^0 and H_2^0

		$n_k = 100$	$n_k = 200$	$n_k = 400$
Test	*Altern.*	$(48)^2$	(95)	(190)
Cox[1]		5.2	5.0	5.8
$\widehat{U}_1^1$	H_1^0	7.9	5.0	6.6
$\widehat{U}_2^1$	H_1^0	7.7	5.3	6.0
$\widehat{U}_3^1$	H_2^0	5.9	7.0	5.3
$\widehat{U}_4^1$	H_2^0	6.7	5.3	5.2

[1]Wald Z-test from standard Cox model, ignoring the mark

[2]Average number of subjects infected in group 2 (placebo)

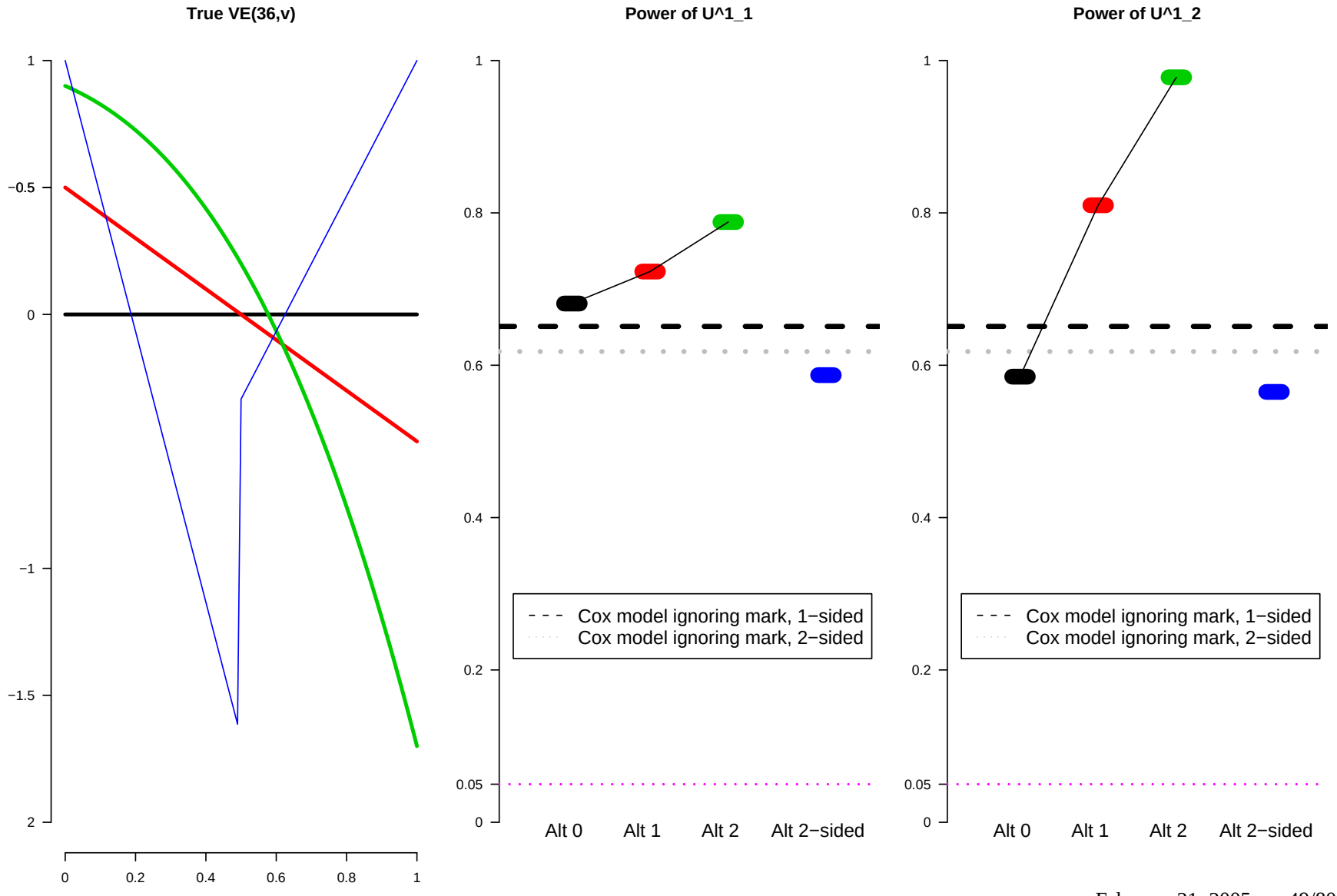
HIV VACCINE TRIALS NETWORK

Power of $\widehat{U}_1^1$ and $\widehat{U}_2^1$ for Testing H_0^0

- The tests of H_0^0 have correct size (near 0.05)
- Next assess power of the tests
- In the following 2 plots, Alt 0, Alt 1, Alt 2 correspond to $\beta = 1, 0.5, 0.25$, respectively
- Power achieved with the test statistics $\widehat{U}_1^1$ and $\widehat{U}_2^1$ is compared to the power of the ordinary Cox model Wald test of $VE(t) = 0$ that ignores the mark variable

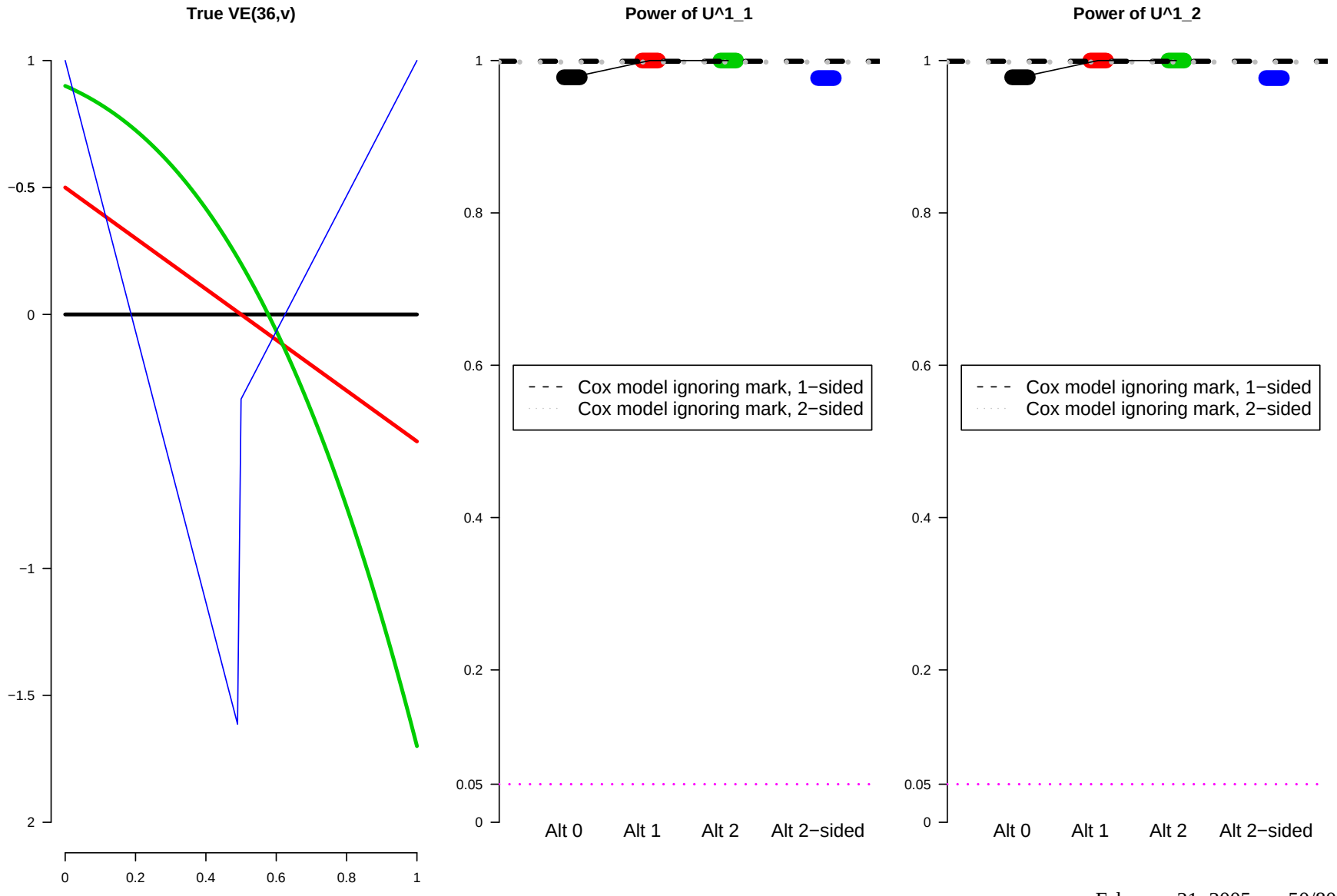
Simulation Experiment: Tests of H_0^0

Power for testing VE(t,v) = 0, 48 placebo infections, VE = 0.33



Simulation Experiment: Tests of H_0^0

Power for testing VE(t,v) = 0, 48 placebo infections, VE = 0.67



HIV VACCINE TRIALS NETWORK

Summary of Results for Tests of H_0^0

- The tests of H_0^0 have appropriate sizes and high powers
- When $VE(t,v)$ declines with v, they have greater power than the Cox model Wald test of $VE = 0$
  - Therefore accounting for the mark variable can substantially improve efficiency
  - For clinical trials with strong reasons to suspect that the mark-specific relative risk is monotone in the mark, consider accounting for the mark in a secondary analysis of the treatment effect

HIV VACCINE TRIALS NETWORK

Simulation Results for Tests of H_0

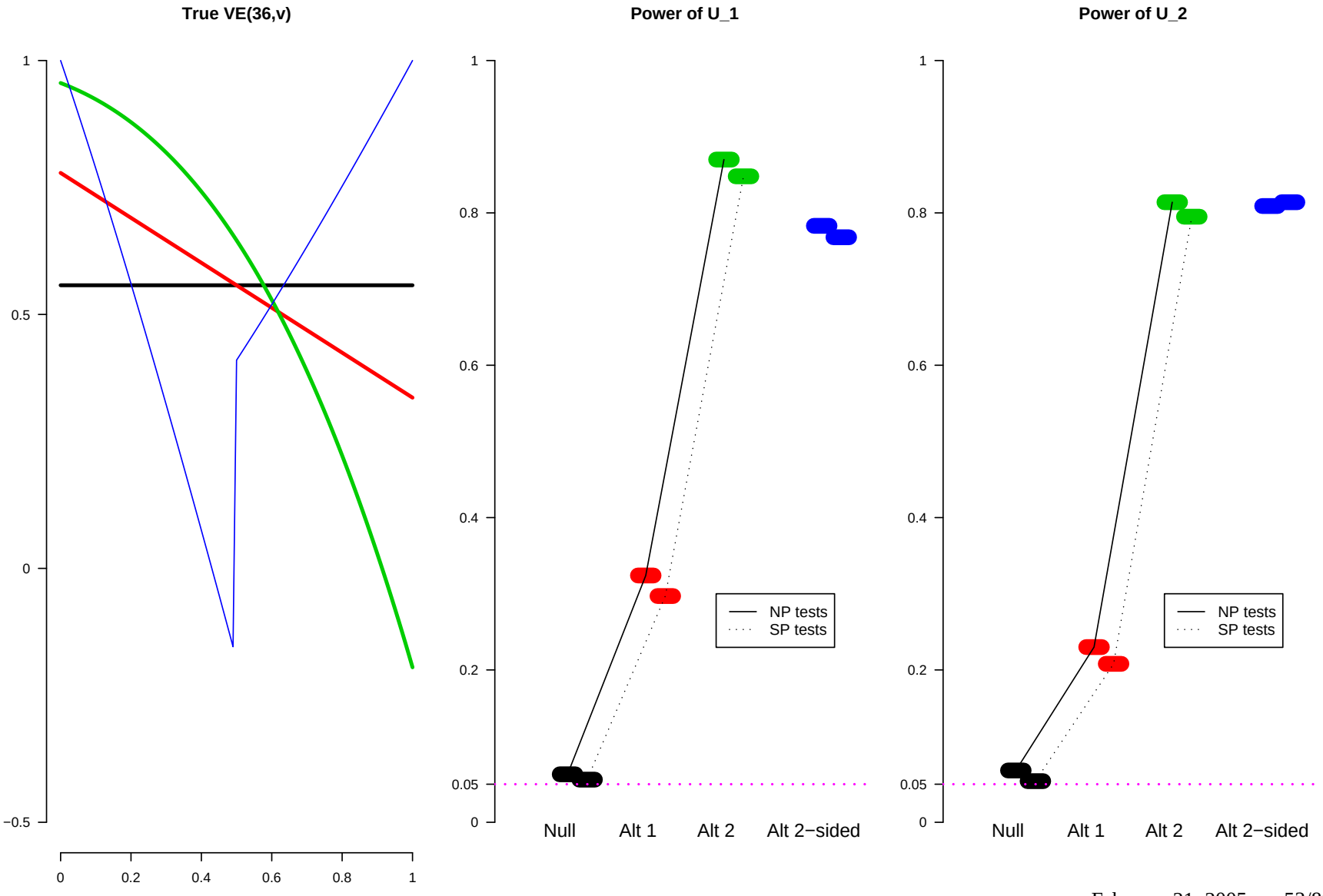
- Next consider simulation results for testing

$$H_0 : VE(t, v) = VE(t)$$

- In the following 4 plots, Null, Alt 1, Alt 2 correspond to $\beta = 1.0, 0.5, 0.25$, respectively

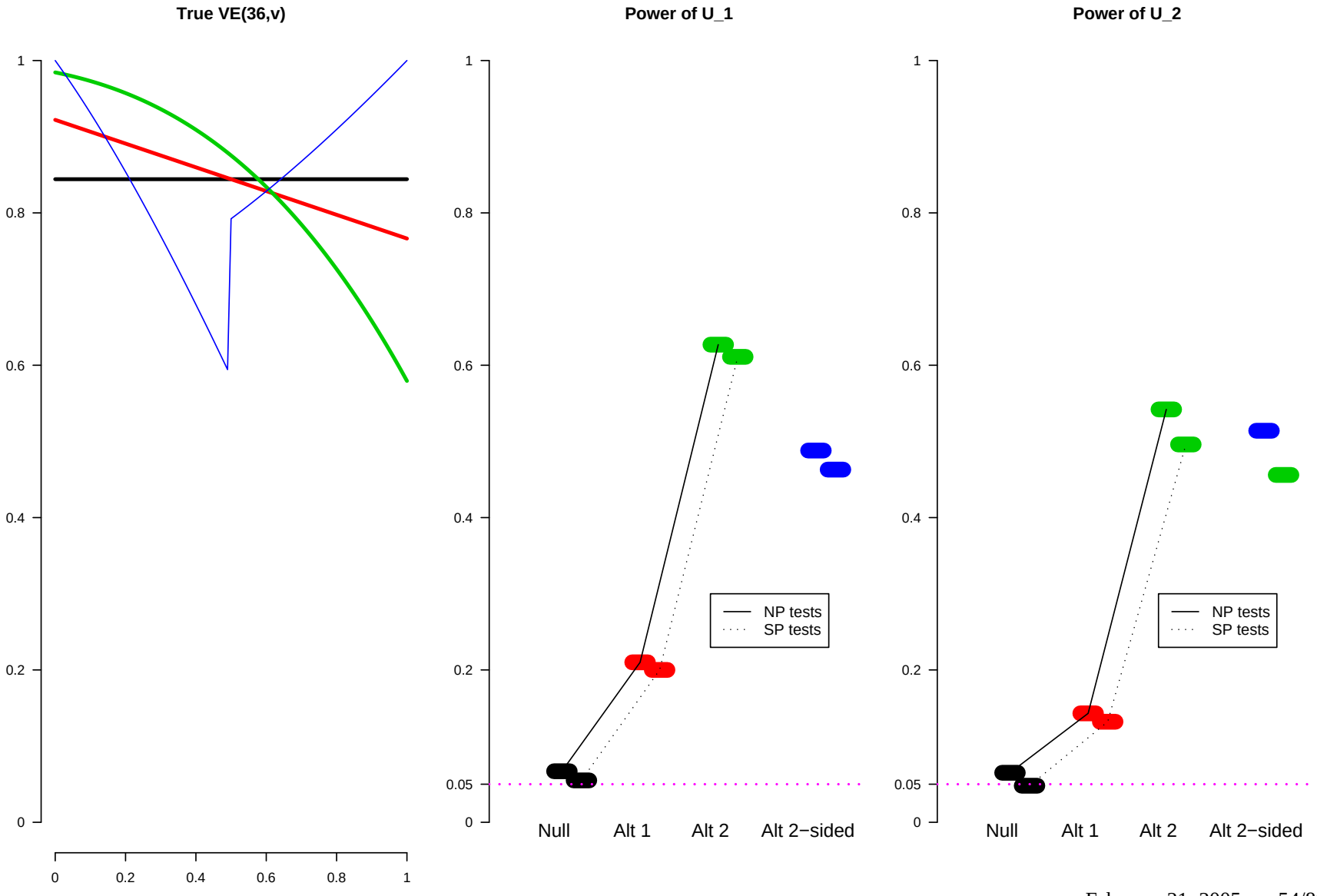
Simulation Results for Tests of H_0

Power for testing VE(t,v) independent of v, 95 placebo infections, VE = 0.33



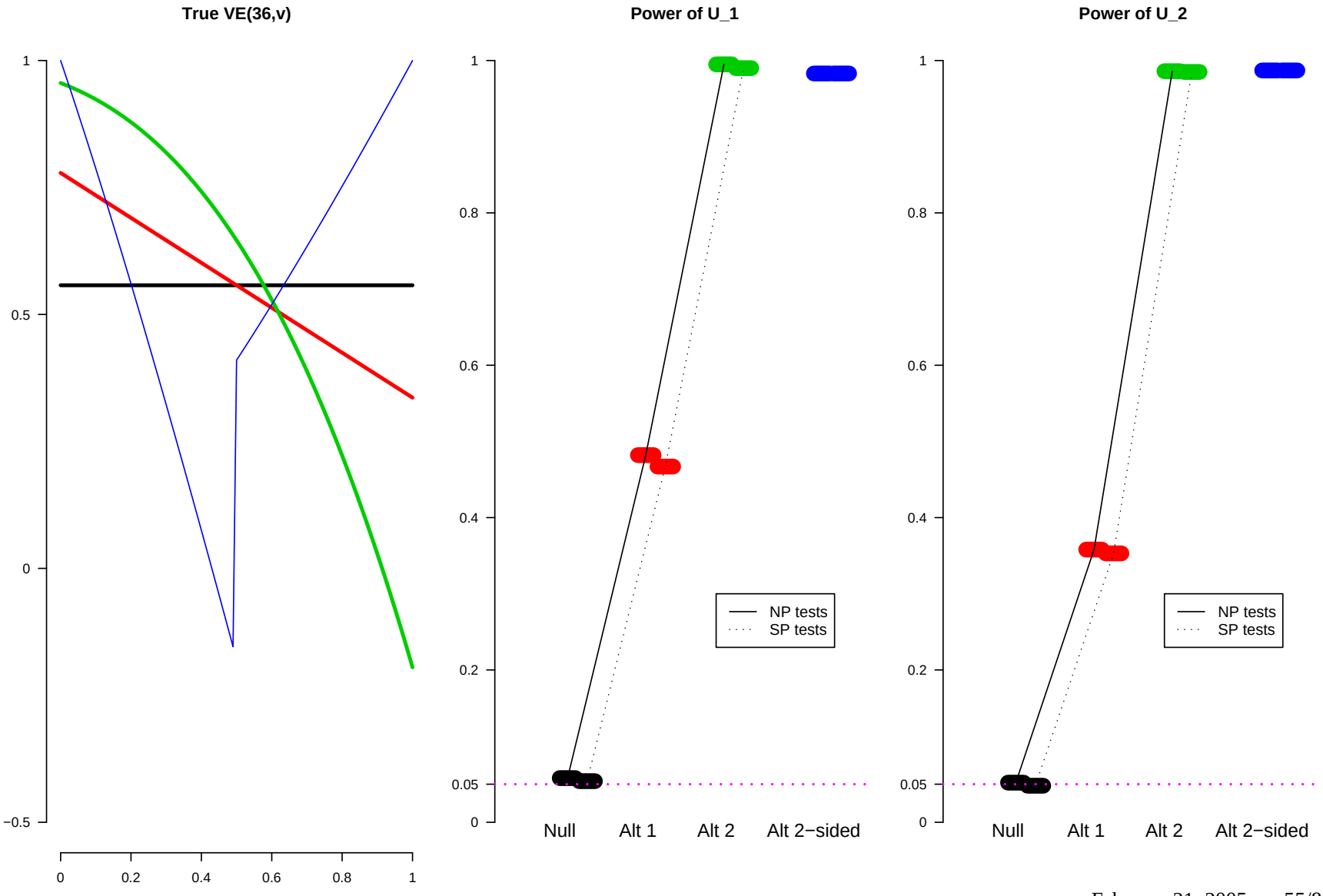
Simulation Results for Tests of H_0

Power for testing VE(t,v) independent of v, 95 placebo infections, VE = 0.67



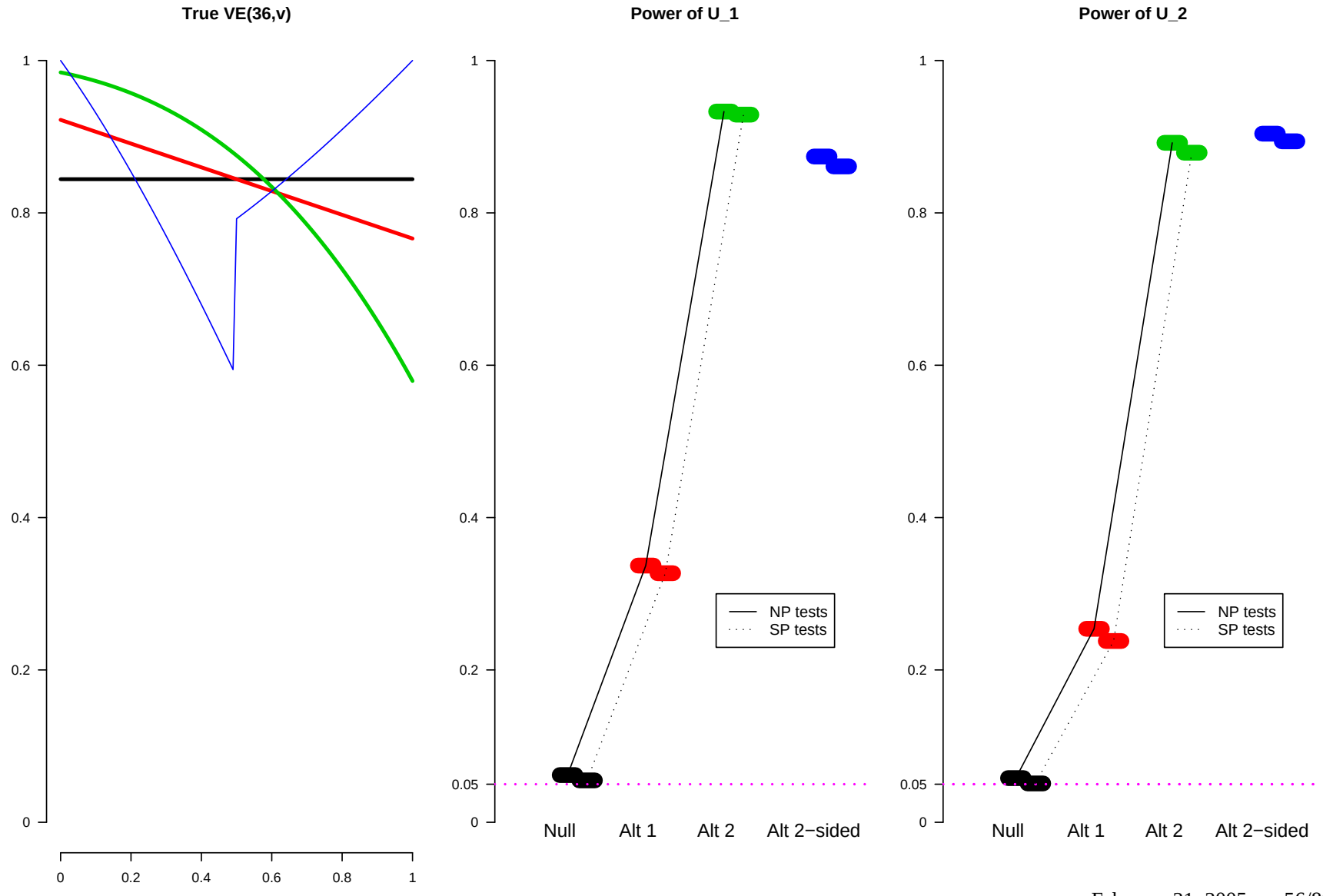
Simulation Results for Tests of H_0

Power for testing VE(t,v) independent of v, 190 placebo infections, VE = 0.33



Simulation Results for Tests of H_0

Power for testing VE(t,v) independent of v, 190 placebo infections, VE = 0.67



HIV VACCINE TRIALS NETWORK

Summary of Results for Testing H_0

- Satisfactory performance at moderate sample sizes
- Somewhat surprisingly, for small/moderate samples the semiparametric tests did not provide greater power than the nonparametric tests in the case that the failure times had proportional hazards
  - **Explanation**: Test process involves contrasts

$$\widehat{\Lambda}_1(dt, v) - \widehat{r}(t)\widehat{\Lambda}_2(dt, v)$$

with $\widehat{r}(t) = \frac{widehat\lambda_1(t)}{\widehat{\lambda}_2(t)}$ or $\exp(\widehat{\beta})$

HIV VACCINE TRIALS NETWORK

Summary of Results for Testing H_0

- Additional simulations were conducted to assess performance of tests when the proportional hazards assumption fails
- The empirical sizes of $\widehat{U}_1^{sp}$ and $\widehat{U}_2^{sp}$ frequently missed 0.05 by an amount more than 2 or 3 Monte Carlo standard deviations (results not shown)
- As predicted from theory, the semiparametric tests fail when the proportional hazards assumption fails
- Nonparametric tests recommended in practice

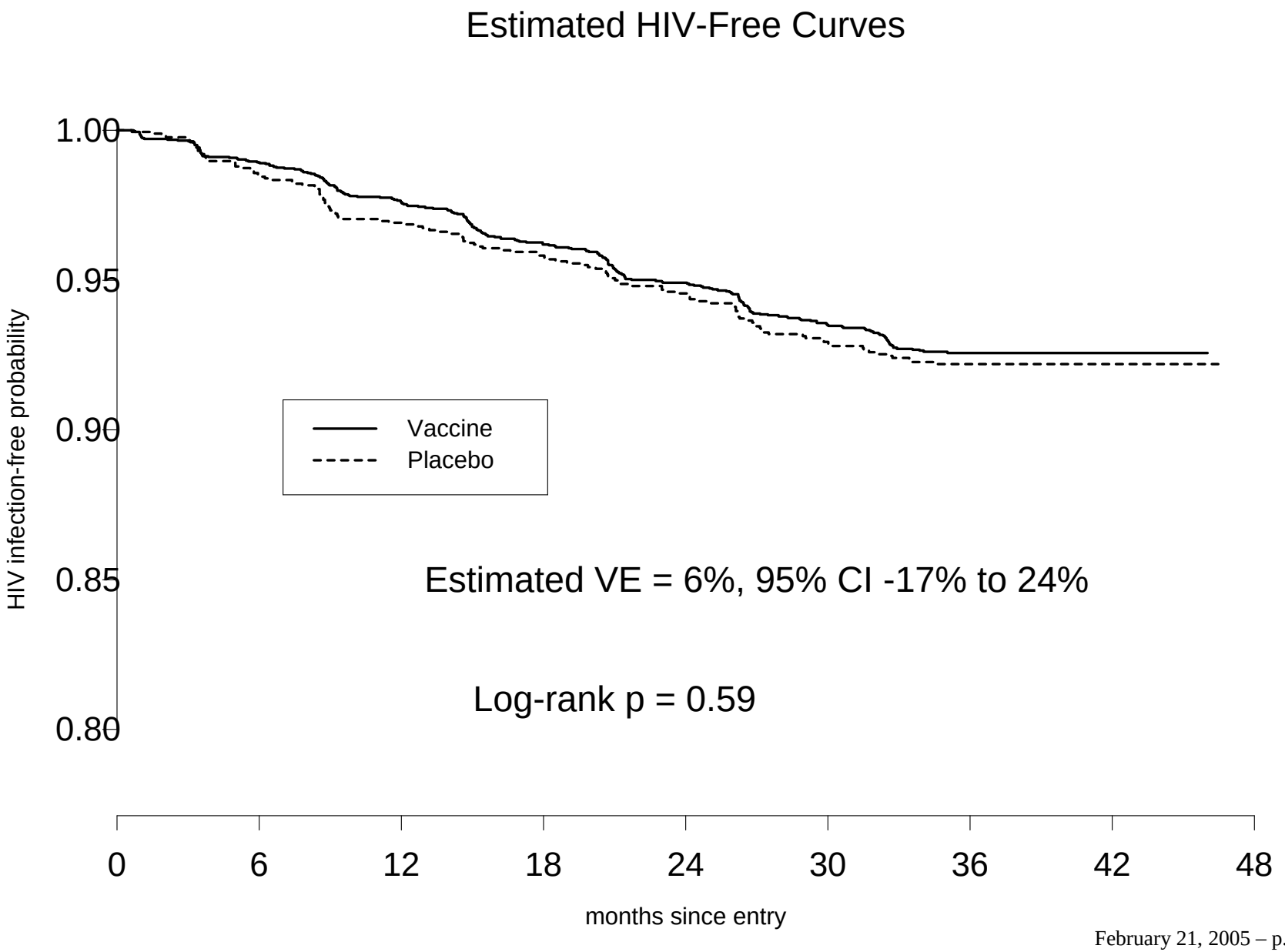
Example: Vax004 Efficacy Trial

- **Primary analysis: No vaccine efficacy to prevent HIV infection**

	Number Randomized	Number Infected	Percent Infected
Vaccine	3598	241	6.7%
Placebo	1805	127	7.0%

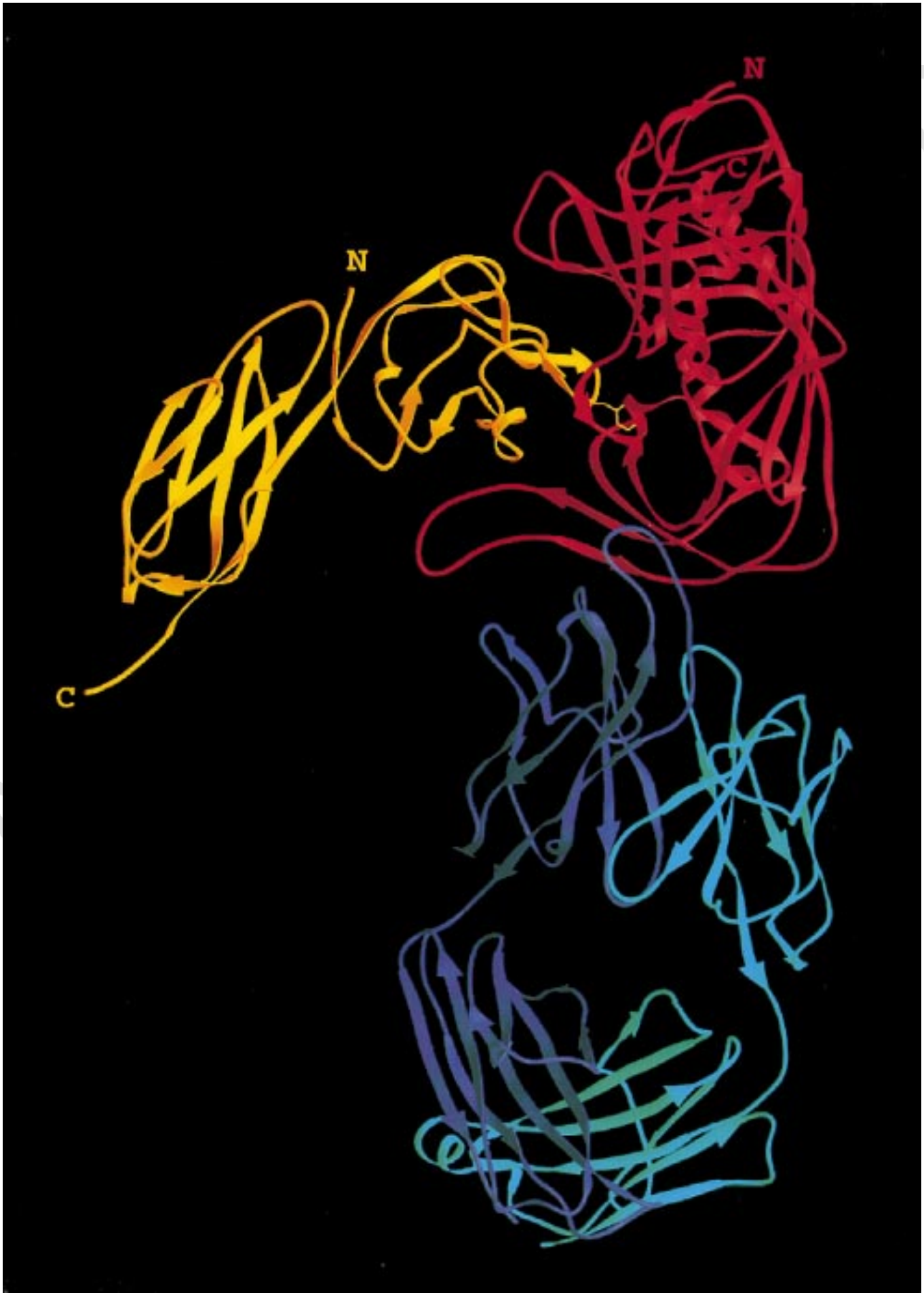
$$\widehat{VE} = 5.7\%, \quad 95\% \text{ CI } -17.0\% \text{ to } 24.0\%, p = 0.59$$

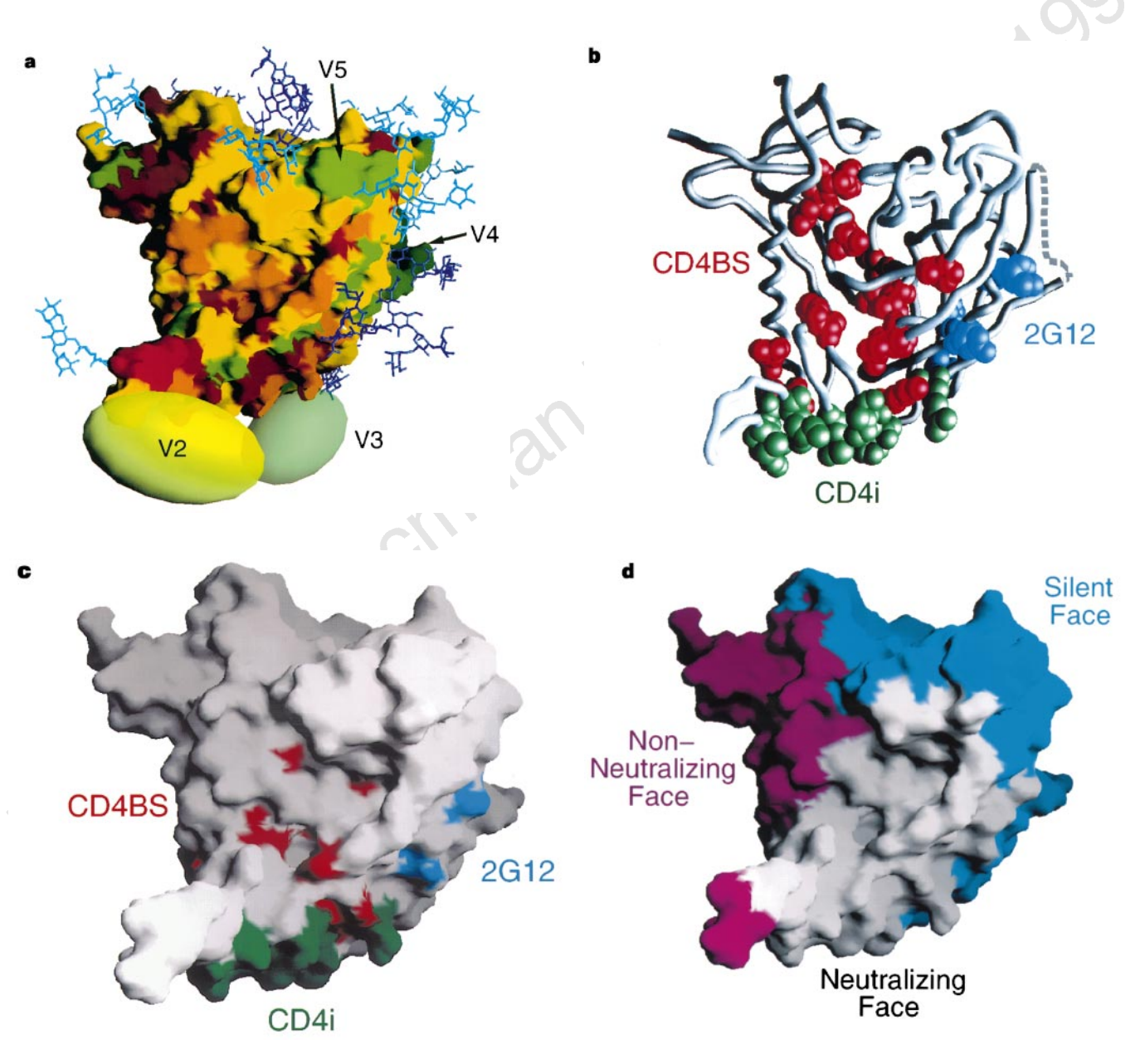
Time to HIV Infection Similar in Vaccine and Placebo Arms



Evaluating $VE(t,v)$ for Pre-specified Marks $V = v$

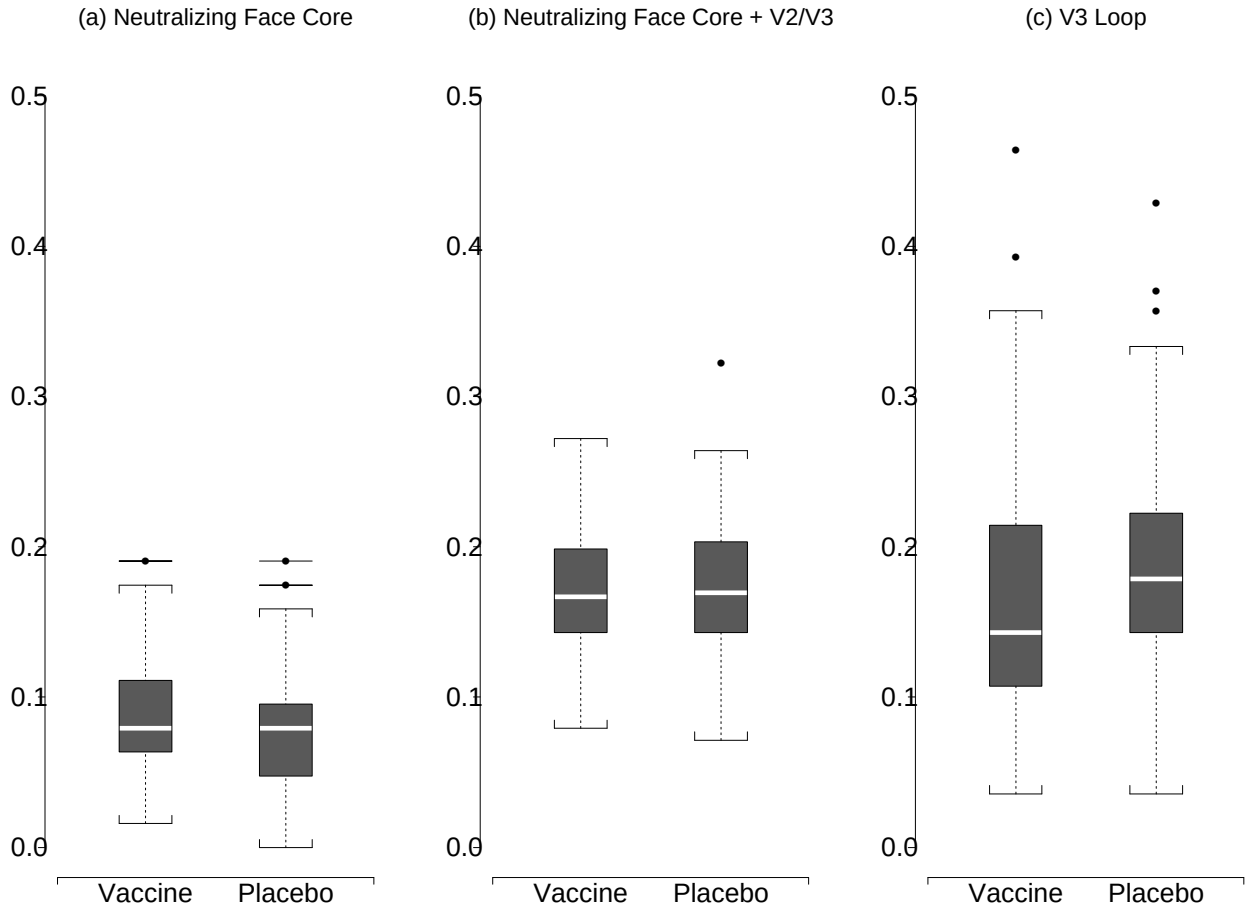
- $V_{MN} =$ percent aa mismatch in a region of gp120 of the infecting strain relative to the MN vaccine strain
- V_{GNE8} defined similarly for the reference strain GNE8
- $V = \min(V_{MN}, V_{GNE8})$
  "distance to the nearest immunogen"
- Regions for distances:
  - Neutralizing face core ($\sim$ 30 amino acids)
  - Neutralizing face core + V2/V3 loop regions ($\sim$ 110 amino acids)
  - V3 loop region ($\sim$ 33 amino acids)


N
C
N
C


a
V5
V4
V2
V3
b
CD4BS
2G12
CD4i
c
CD4BS
2G12
CD4i
d
Silent
Face
Non–
Neutralizing
Face
Neutralizing
Face

Distributions of Genetic Distances V

- 337/368 (92%) infected subjects have sequence data



Implementation of Inferential Procedures

- Weight process within test process:

$$H_n(t) = \sqrt{\frac{\overline{Y}_1(t)}{n_1}\frac{\overline{Y}_2(t)}{n_2}}$$

- Epanechnikov kernel $K(x) = 0.75(1-x^2)I(|x| \leq 1)$; Gasser and Müller (1979) tail correction
- Bandwidths for $\widehat{\lambda}_k(t)$:
  - Optimal bandwidths $b_1 = 1.83, b_2 = 2.10$
- Bandwidths for $\widehat{F}_k(36, v)$:
  - b_{v1} and $b_{v2} =$ separately optimized using 2-fold cross-validation

Results of Tests of $H_0^0 : VE(t,v) = 0$

- Time-span $t \in [2, 36]$ months
- P-values obtained using 10000 simulations

Distance	Test Stat.	p-value
Neut face	$\widehat{U}_1^1$	$p = 0.15$
	$\widehat{U}_2^1$	$p = 0.05$
	$\widehat{U}_3^1$	$p = 0.32$
	$\widehat{U}_4^1$	$p = 0.14$
Neut face + V2/V3	$\widehat{U}_1^1$	$p = 0.18$
	$\widehat{U}_2^1$	$p = 0.26$
	$\widehat{U}_3^1$	$p = 0.36$
	$\widehat{U}_4^1$	$p = 0.59$
V3 loop	$\widehat{U}_1^1$	$p = 0.15$
	$\widehat{U}_2^1$	$p = 0.61$
	$\widehat{U}_3^1$	$p = 0.30$
	$\widehat{U}_4^1$	$p = 0.72$

HIV VACCINE TRIALS NETWORK

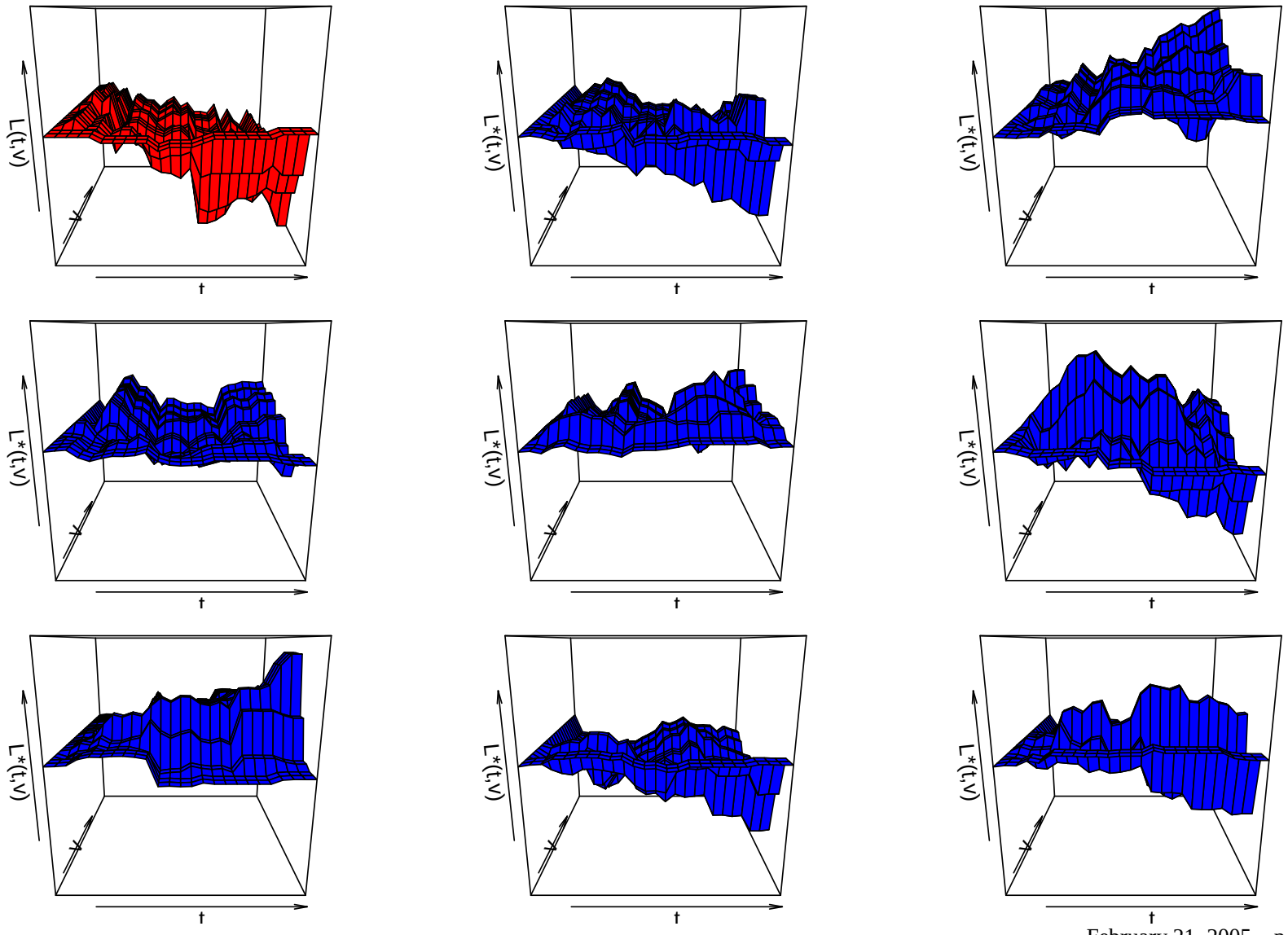
Results of Tests of $H_0 : VE(t,v) = VE(t)$

- Time-span $t \in [2, 36]$ months
- P-values obtained using 10000 simulations

Distance	Test Stat.	p-value
Neut face	$\widehat{U}_1^{np}/\widehat{U}_1^{sp}$	$p = 0.041/0.095$
	$\widehat{U}_2^{np}/\widehat{U}_2^{sp}$	$p = 0.24/0.11$
Neut face + V2/V3	$\widehat{U}_1^{np}/\widehat{U}_1^{sp}$	$p = 0.62/0.60$
	$\widehat{U}_2^{np}/\widehat{U}_2^{sp}$	$p = 0.84/0.26$
V3 loop	$\widehat{U}_1^{np}/\widehat{U}_1^{sp}$	$p = 0.96/0.95$
	$\widehat{U}_2^{np}/\widehat{U}_2^{sp}$	$p = 0.94/0.73$

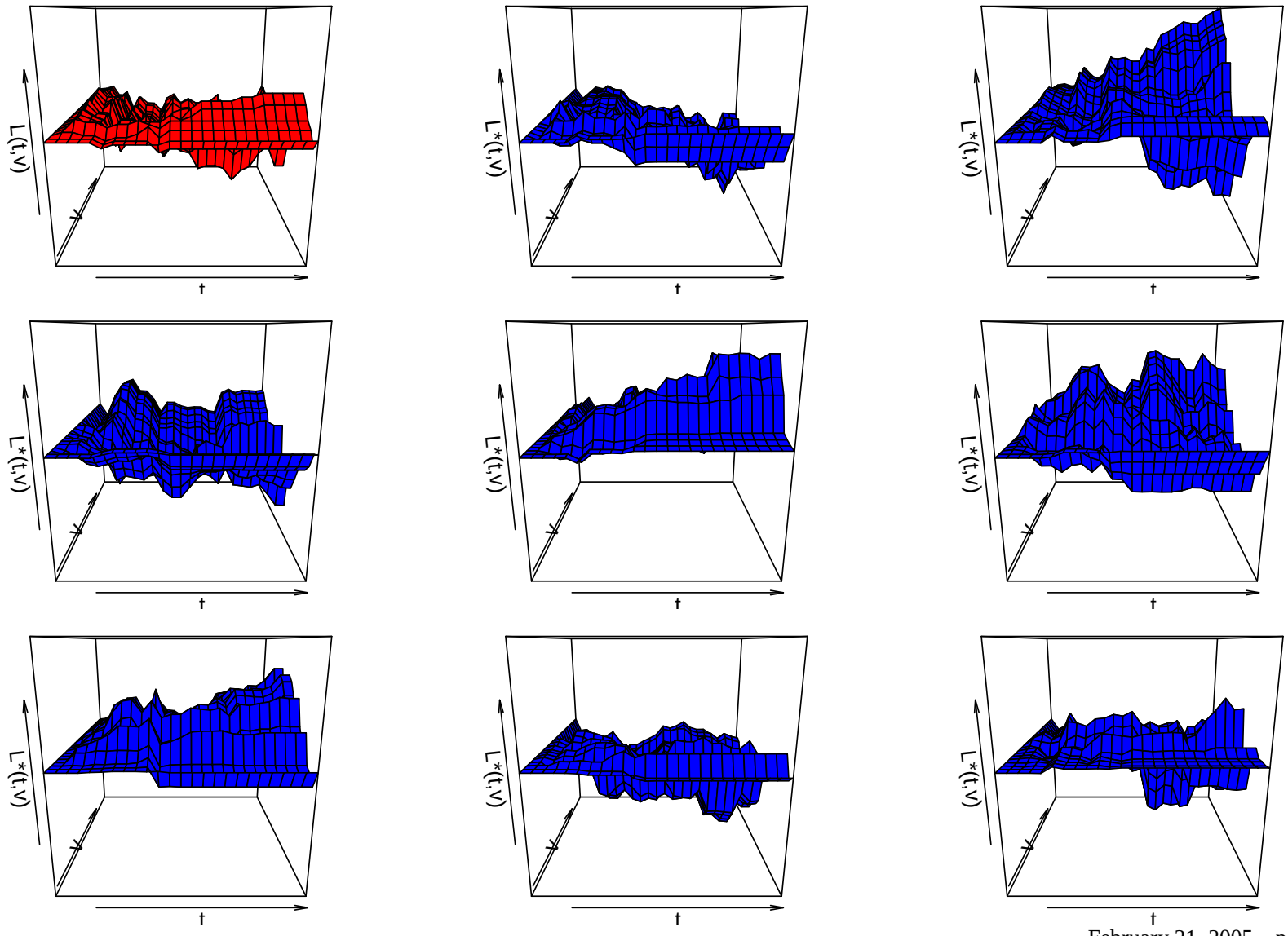
$L_n^{np}(t,v)$ and 8 $L_n^{np*}(t,v)$: Neut face

Test process and 8 simulated test processes for neutralizing face core distance



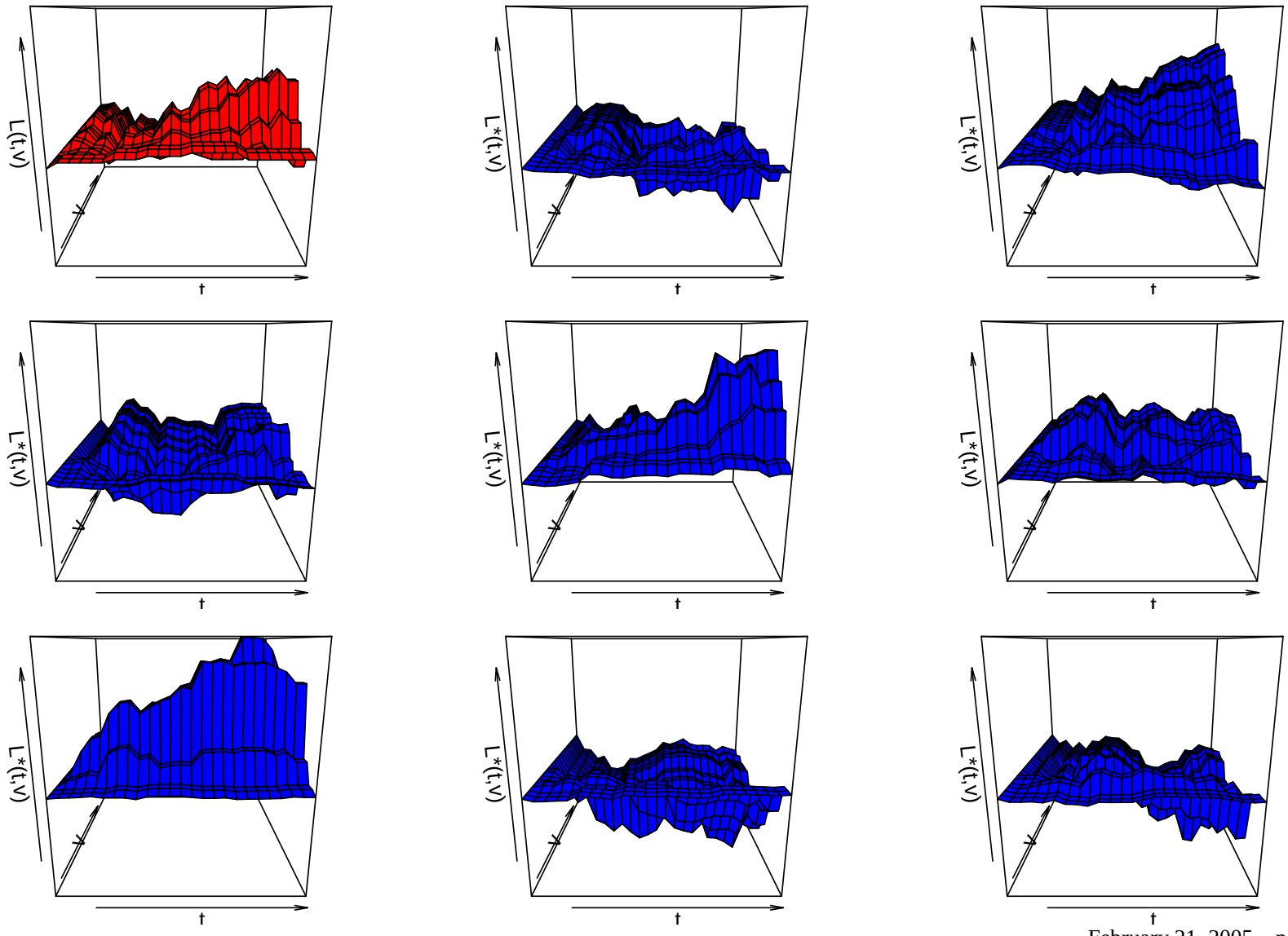
$L_n^{np}(t,v)$ and 8 $L_n^{np*}(t,v)$: Neut face + V2/V3

Test process and 8 simulated test processes for neutralizing face core + V2/V3 distance

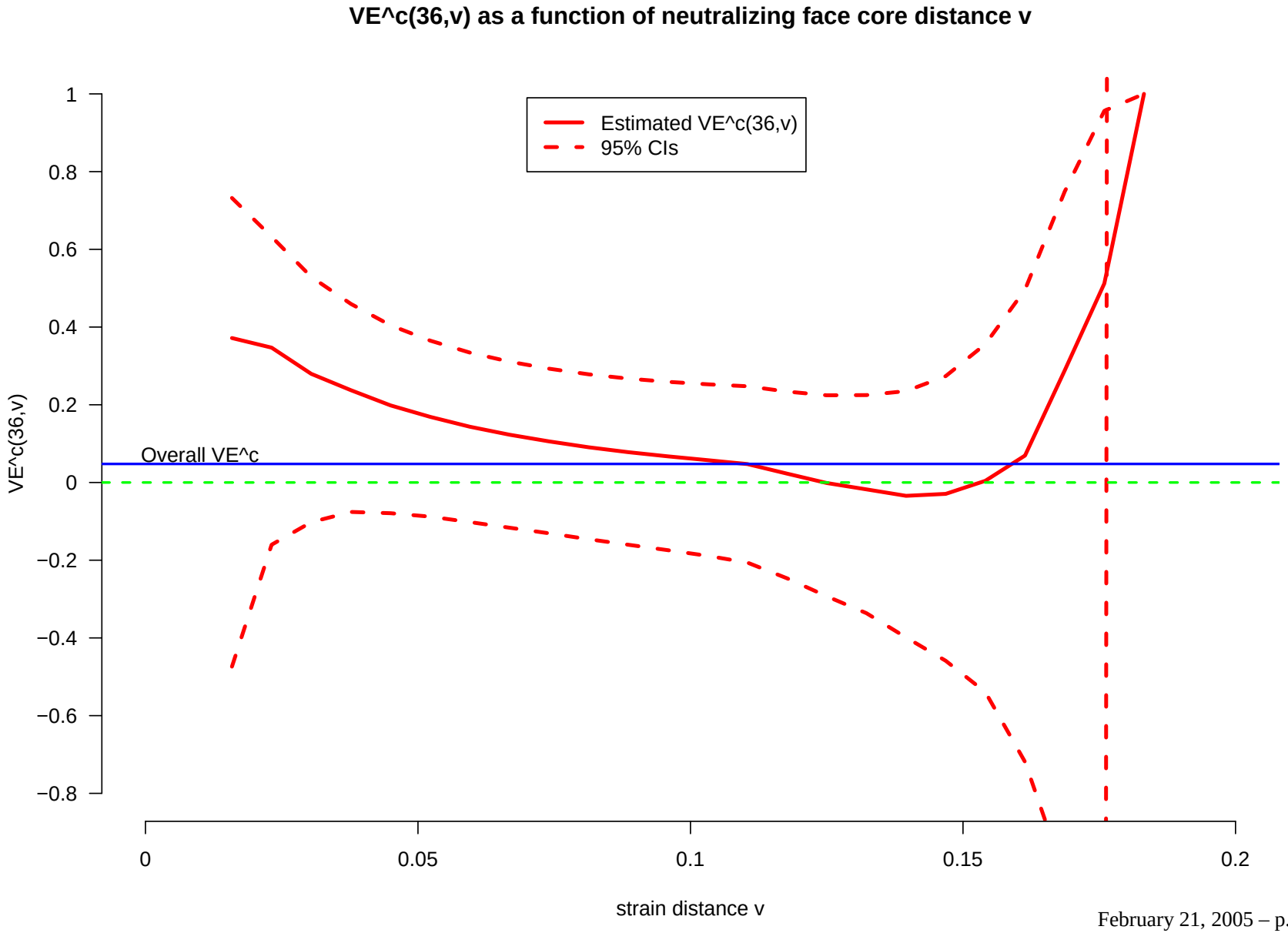


$L_n^{np}(t,v)$ and 8 $L_n^{np*}(t,v)$: V3 loop

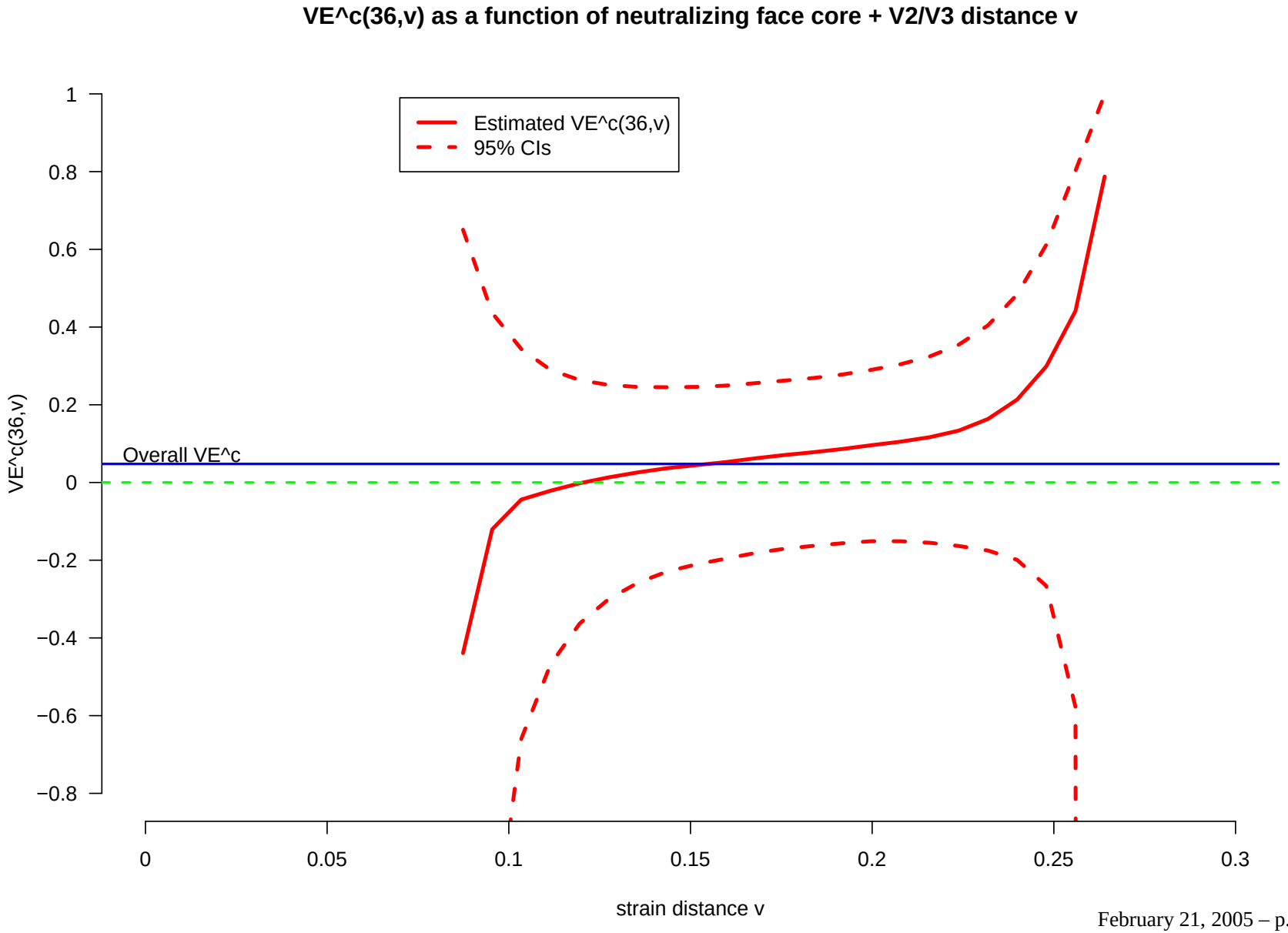
Test process and 8 simulated test processes for V3 loop distance



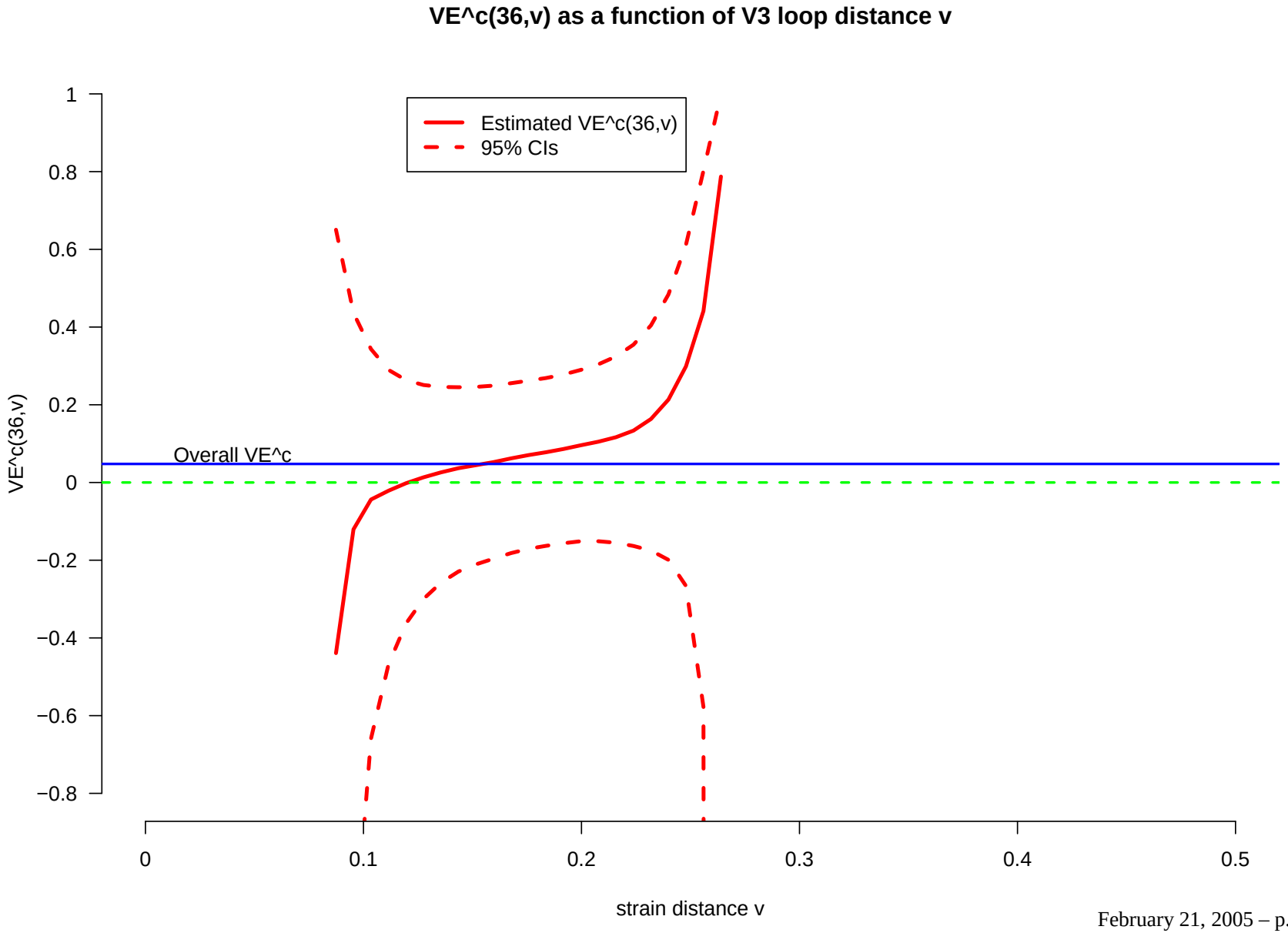
$VE^c(36, v)$ versus v: Neut face



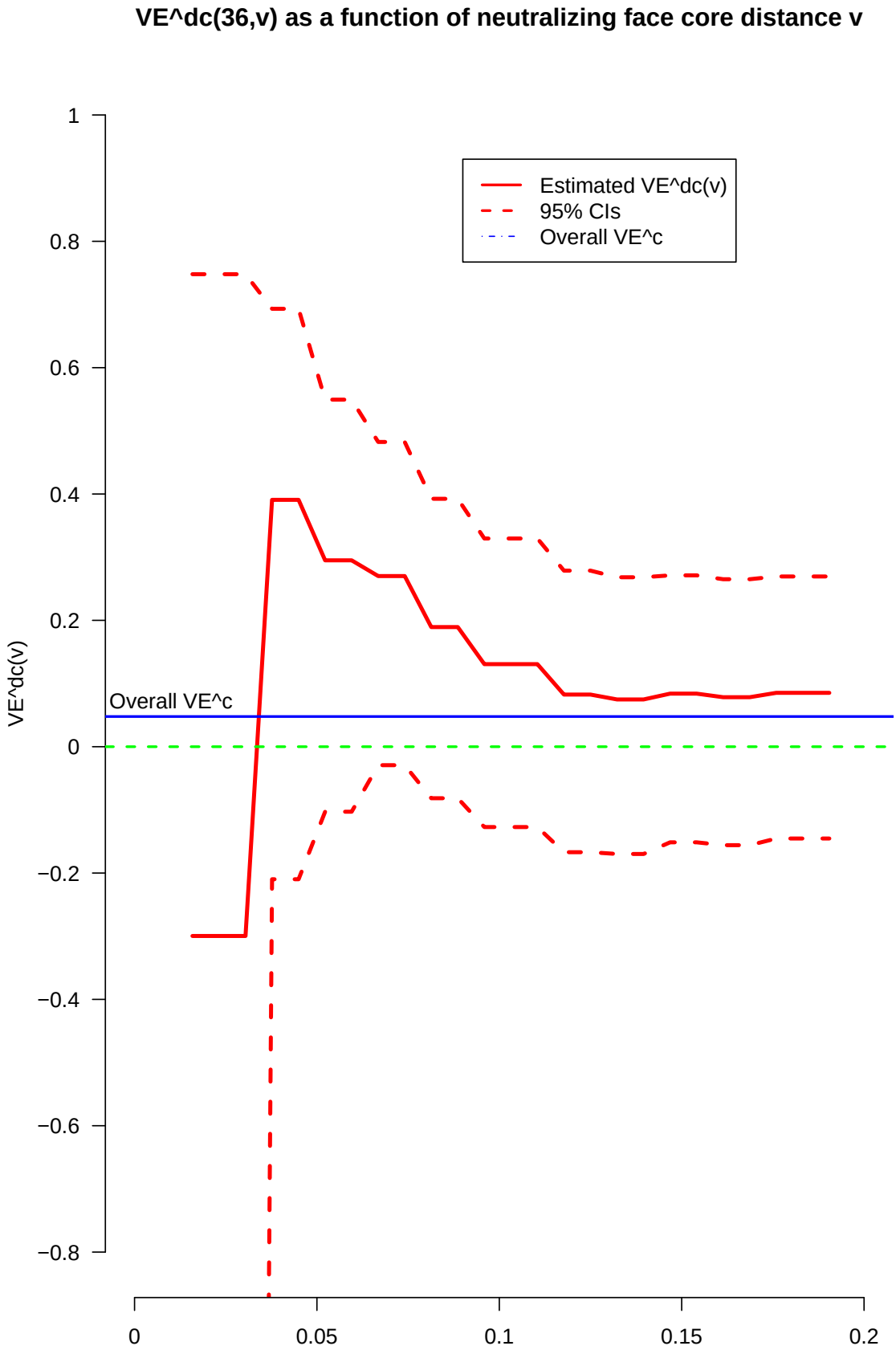
$VE^c(36, v)$ versus v: Neut face + V2/V3



$VE^c(36, v)$ versus v: V3 loop

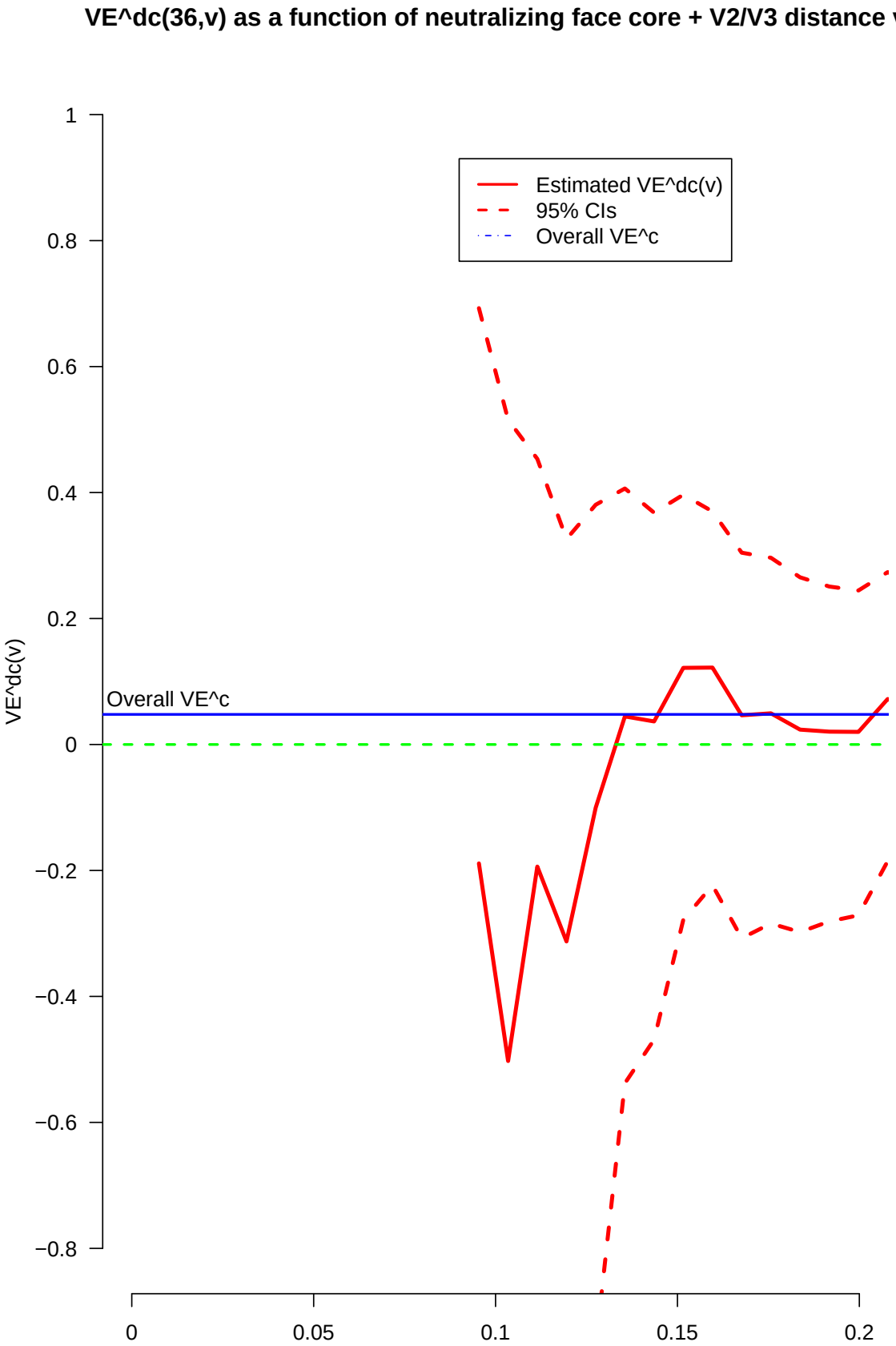


$VE^{dc}(36, v)$ versus v: Neut face



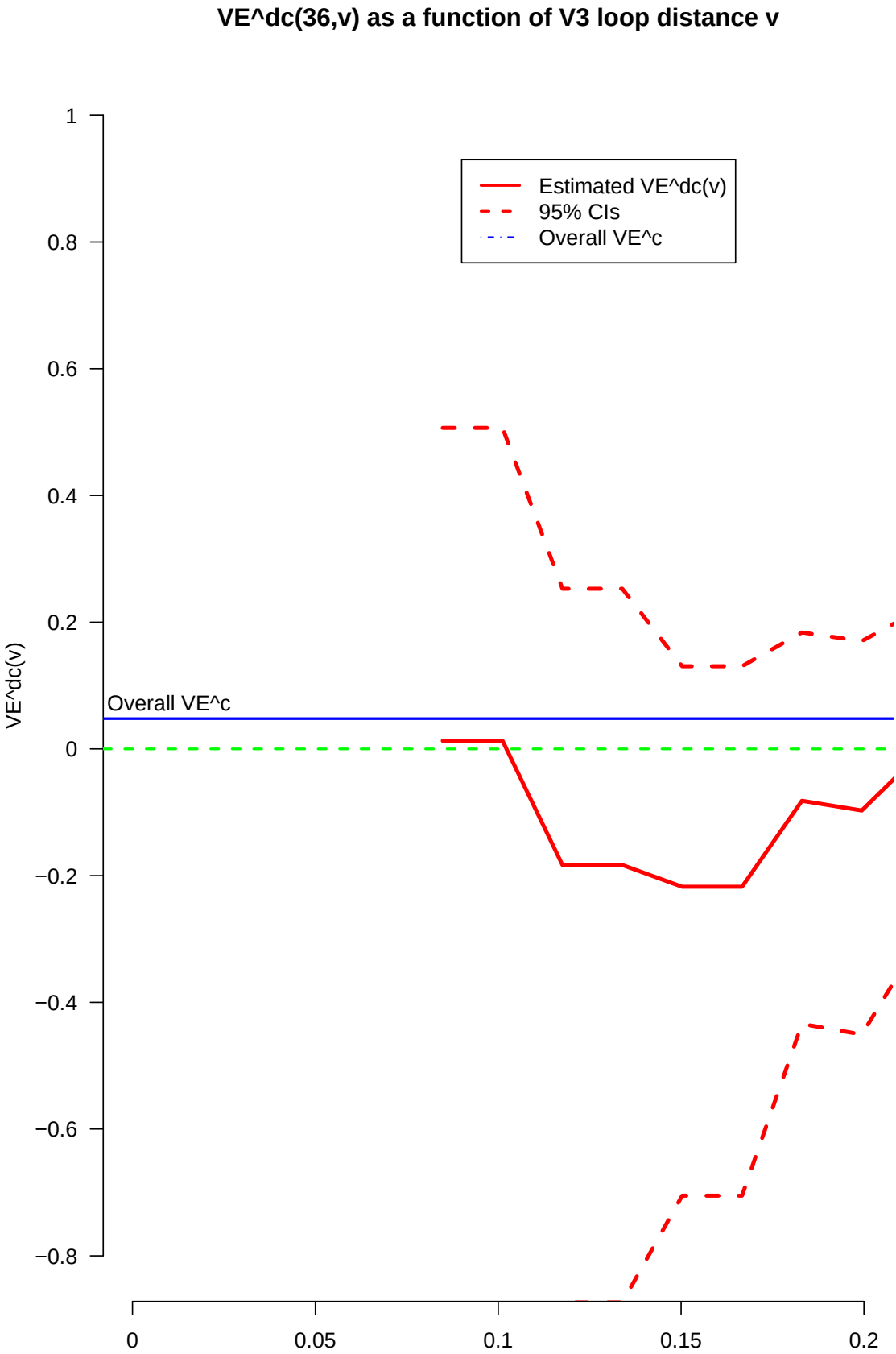
HIV VACCINE TRIALS NETWORK

$VE^{dc}(36, v)$ versus v: Neut face + V2/V3



HIV VACCINE TRIALS NETWORK

$VE^{dc}(36, v)$ versus v: V3 loop



HIV VACCINE TRIALS NETWORK

Key Question: How Define the HIV Metric V?

- The approach is inter-collaborative: virologists/immunologists/structural biologists/statisticians seek to identify an **immunologically relevant** HIV sequence metric V
  - Problem complicated for antibody vaccines (need knowledge of 3-D structure)
  - Simpler for T cell vaccines (linear epitopes)
    - E.g., weighted potential T cell epitope (WPTE) distance: one minus the fraction of 9-mers in the infecting virus also in the vaccine

Current Research: Regression Modeling

- Conditional mark-specific hazard: $\lambda(t,v|z(t)) =$

$$\lim_{h_1,h_2\to 0} P\left\{T \in [t,t+h_1), V \in [v,v+h_2) | T \geq t, Z(t) = z(t)\right\} / h_1 h_2$$

- Mark-specific proportional hazards model:

$$\lambda(t,v|z(t)) = \lambda_0(t,v)\exp\left\{\beta(v)^T z(t)\right\}$$

$$\beta(v) = (\beta_1(v), \beta_2(v)^T)^T$$

$\beta_1(v)$ corresponds to vaccine/placebo status (parametric or unspecified)

$\beta_2(v)$ corresponds to other covariates (parametric)

HIV VACCINE TRIALS NETWORK

Applications to Vaccine Efficacy Trials

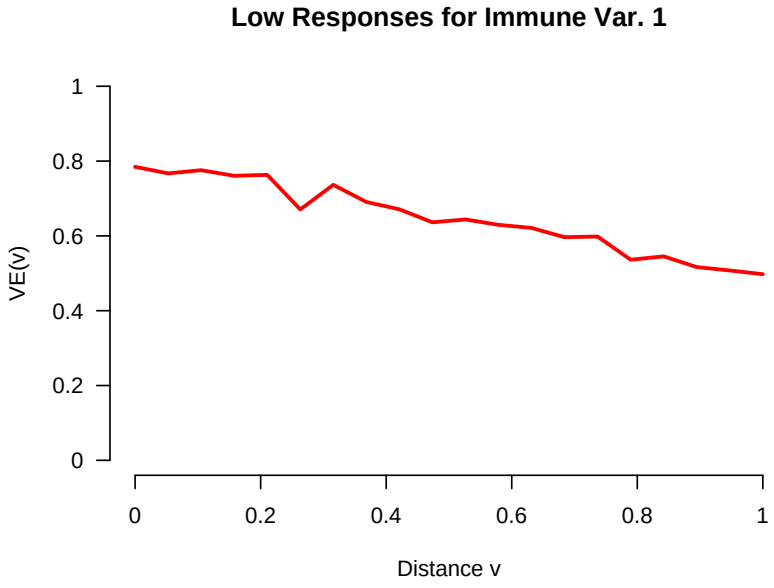
- Test for vaccine efficacy varying with the mark: $H_0 : VE(v) = VE$
  - Model-based alternative to the nonparametric tests
- Test for vaccine efficacy at any mark value: $H_0 : VE(v) = 0$ for all v
- Estimate $VE(v)$ both for $\beta_1(v)$ unspecified and specified parametrically

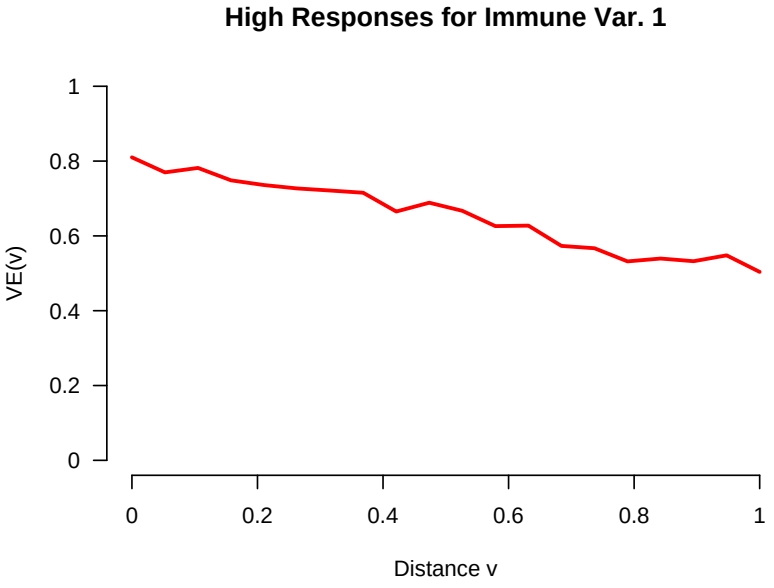
HIV VACCINE TRIALS NETWORK

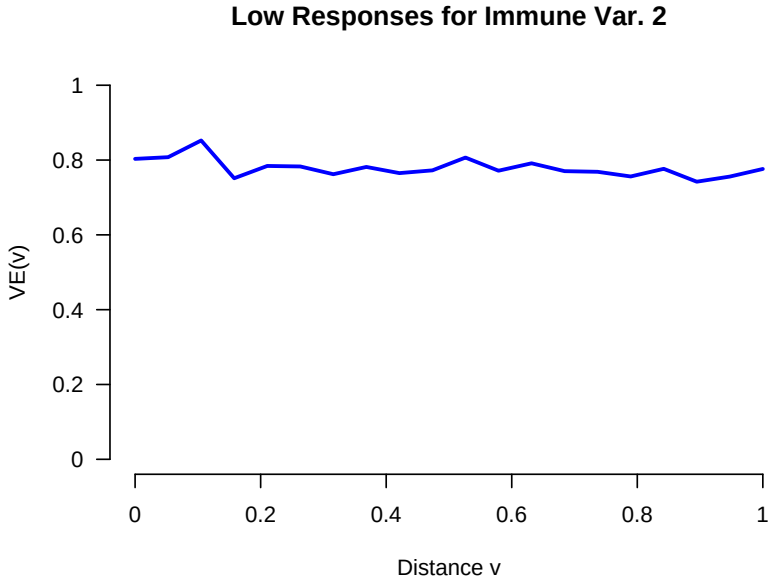
Applications to Vaccine Efficacy Trials

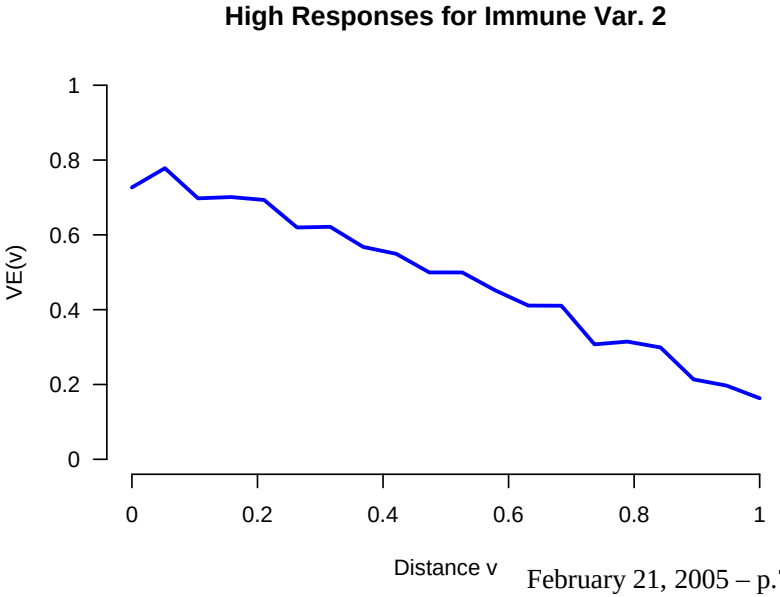
- Include covariates
  - Control for confounders, estimate covariate-adjusted $VE(v)$
  - Assess possible differences in $VE(v)$ at different covariate levels [interactions]
    - Does a genetic trait affect whether the vaccine selectively protects?
    - Does the level of immune response to vaccination affect whether the vaccine selectively protects?

Example of $VE(v)$ Depending on Immune Reponse









Complimentary Approach: Antigen Scanning (Addressed in Lecture 9)

- Scan all peptide regions of length 9
- **Goal:** Identify regions where peptide sequences from infected vaccinees are more divergent from the immunogen peptide than peptide sequences from infected placebo recipients [Topic of Lecture 9]