Proportional Hazards Models With Continuous Marks

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Scientific Motivation

- Randomized HIV vaccine trials
- Major difficulty: Differential vaccine efficacy (VE)
- Vaccines don't protect as well against unfamiliar viruses
- Can quantify genetic diversity using Hamming distance (continuous)

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PIVQNLQGQM VHQAISPRTL NAWVKVVEEK
.......... ..R......T ..........
.......... ..R......T ..........
.......... T.A....... ..........
.......... ..R....... ..........
.V........ T.A..G.... ....G.....
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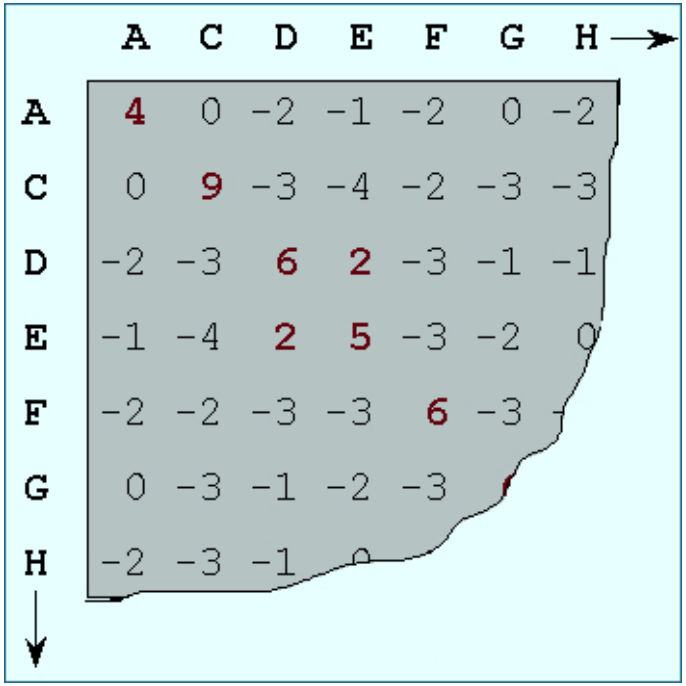
GAG fragment alignment



Part of the Hamming substitution matrix

Statistical Motivation

- Want to perform inference on vaccine efficacy, accounting for infecting type in the model.
- Measures on infecting type **only observed in infected subjects** - *cannot* be treated as ordinary covariates!

i	1	2	3	4	5	6	7	8	...
T	13.3	7.4	4.8	16.3	1.5	14.2	16.3	7.0	...
δ	1	1	1	0	0	0	0	1	...
V	0.72	0.80	0.51					0.06	...
X	1	0	1	0	0	1	1	0	...
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	

  - T: follow-up time
  - δ: failure indicator
  - V: mark variable
  - X: Vaccine (1) or placebo(0). Could be a vector, including other covariates of interest (possibly time-varying).

Parameter of interest...sort of

- We are interested in the **strain-specific vaccine efficacy:**

$$VE(v) = 1 - \frac{\lambda(t, v|X_1 = 1)}{\lambda(t, v|X_1 = 0)}$$

- $\lambda(t, v|X)$ is a conditional strain-specific hazard.
  - Interpretable as instantaneous failure rate due to type v at time t, conditional on having survived up to t.
  - Also conditional on X, which includes vaccination status.
- Gilbert (2000) demonstrates the above, based on two assumptions:
  - A.1) Vaccination reduces strain-specific transmission probability per exposure uniformly.
  - A.2) Risk behavior and exposure equal among participants regardless of vaccination status.

Estimation of $\beta(v)$ using partial likelihood

- Proportional hazards assumption (Cox [1972]):

$$\lambda(v, t|X) = \lambda_0(t, v) \exp(\beta(v)^T X)$$

- Localized log partial likelihood:

$$\ell_v(\beta_v) = \sum_{i=1}^{n} \int_0^1 \int_0^\tau K_h(u - v) \times \left[\beta^T(v) X_i(t) - \log \left(\sum_{j=1}^{n} Y_j(t) e^{\beta^T(v) X_j} \right) \right] \times N_i(dt, du)$$

  - Counting process $N_i = I(X_i \leq t, \delta_i = 1, V_i \leq v)$: jumps from 0 to 1 at $u = V_i$ and $t = T_i$ if ith subject is uncensored.
  - Weighted by risk set of all subjects at time T_i ["At risk" $Y_j(t)$].
  - ...and by V_i being close to v of interest [Kernel function $K_h(\cdot)$].
- For $v \in [0, 1]$, the MPLE is $\hat{\beta}(v) = \arg\max_\beta(v) \mathcal{L}(\beta(v))$

Other quantities of interest based on the MPLE

- In the PH model, $\beta_1(v)$ is the hazard ratio for vaccinees vs. non-vaccinees
- Thus, $\hat{VE}(v) = 1$ - exp$(\widehat{\beta}_1(v))$
- Calculations of asymptotic variance: (similar to Cox ['72]):

$$S^{(j)}(t,\beta) = n^{-1}\sum_{i=1}^{n} Y_i(t)e^{\beta_T Z_i} Z_i^{\otimes j}$$

$$J_n(t,\beta) = \frac{S^{(2)}(t,\beta)}{S^{(0)}(t,\beta)} - \left(\frac{S^{(1)}(t,\beta)}{S^{(0)}(t,\beta)}\right)^{\otimes 2}$$

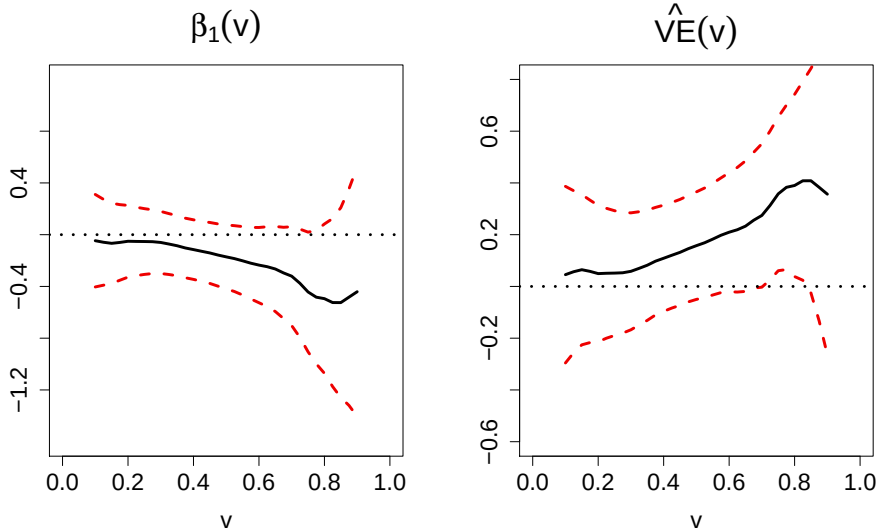
$$\ddot{\ell}_\beta(v,\beta(v)) = -\sum_{i=1}^{n}\int_0^1\int_0^\tau K_h(u-v)J_n(t,\beta)N_i(dt,du)$$

More asymptotic properties of the MPLE

$$\sqrt{nh}(\hat{\beta}(v) - \beta(v)) \to_d N(0, \nu_0 \Sigma^{-1}(v))$$

$\nu_0 = 3/5$ (integral of squared kernel function)

$$\sqrt{nh}(\widehat{VE}(v) - VE(v)) \to_d N(0, \nu_0 \sigma_1^2(v) e^{2\beta_1(v)})$$



Pointwise estimates and confidence bands for VaxGen004 dataset:
$n = 5403$; 2:1 randomization; 336 failures with observed marks

The *real* quantity of interest

- Cumulative vaccine efficacy

$$\widehat{CV}(v) = \int_a^b \widehat{VE}(u)du, \quad [a,b] \in [0,1]$$

- $\sqrt{n}(\widehat{CV}(v) - CV(v))$ converges to a mean-zero Gaussian process.
- Naive variance estimate: $\int_a^b \hat{\Sigma}^2(u)_{(1,1)} e^{2\hat{\beta}_1(u)} du$
  - Ignores correlations at discrete values of v in finite samples.
- Instead use $\hat{\rho}^2(v) = \hat{\Sigma}_{\hat{A}}(v)_{(1,1)}$, where

$$\Sigma_{\hat{A}}(v) = n^{-1} \sum_{i=1}^{n} \int_a^v \int_0^\tau \hat{A}(u) J_n(t, \hat{\beta}(u)) \hat{A}(u)^T N_i(dt, du)$$

$$\hat{A}(v) = e^{\hat{\beta}_1(v)} \hat{\Sigma}(v)^{-1}$$

(1-α) confidence bands for $\widehat{CV}(v)$

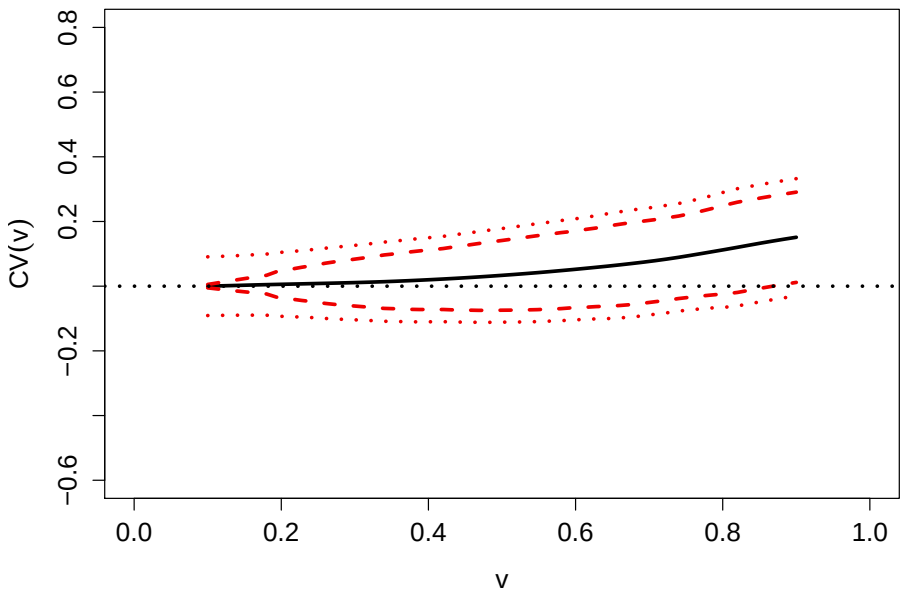
Pointwise:

$$\widehat{CV}(v) \pm n^{1/2} \mathcal{Z}_{\alpha/2} \hat{\rho}(v)$$

Simultaneous:

$$\widehat{CV}(v) \pm n^{1/2} \mathcal{U}_{\alpha} \left(\frac{\hat{\rho}(v)+\hat{\rho}(b)}{\hat{\rho}(b)} \right)$$

$\mathcal{U}_{\alpha}$ is the upper α-quantile of $\sup_{v \in [0,0.5]} |B(v)|$, where $B(v)$ is a Brownian bridge.



Estimate of cumulative VE with pointwise (—) and simultaneous ($\cdots$) confidence bands for VaxGen004 dataset

Hypothesis testing

Goal: Test overall and differential vaccine efficacy on $v \in [a, b]$

- H_{10} (Overall Null): vaccine efficacy zero for *all* v
  - H_{1a} (General alternative): VE nonzero for *some* v
  - H_{1m} (Monotone alternative): VE non-negative for *all* v, and positive for *some* v.

- H_{20} (Differential Null): vaccine efficacy does not depend on v
  - H_{2a} (General alternative): VE depends on v
  - H_{2m} (Monotone alternative): VE decreases with increasing v.

Defining test processes and statistics

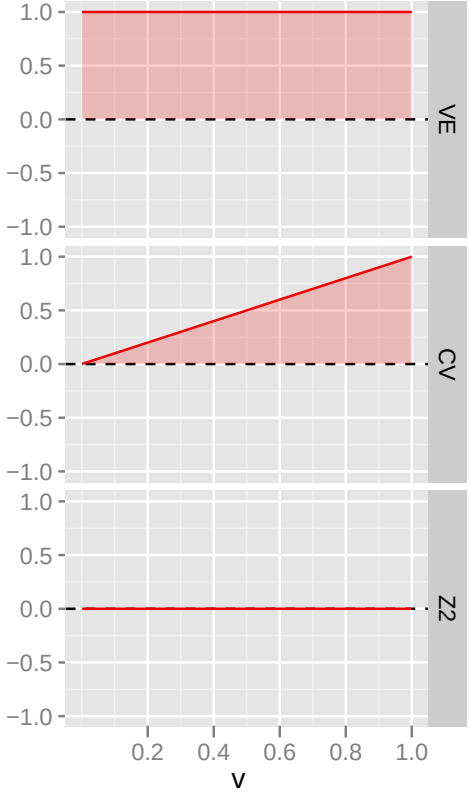
Define: test processes $\hat{Z}$ and test statistics T for each alternative:

- H_{10}: $\hat{Z}^{(1)}(v) = \sqrt{n}\widehat{CV}(v)/\hat{\rho}(b)$ and $\hat{t}(v) = \hat{\rho}^2(v)/\hat{\rho}^2(b)$
  - H_{1a}: $T_a^{(1)} = \int_a^b (\hat{Z}^{(1)}(v))^2 d\hat{t}(v)$
  - H_{1m}: $T_{m1}^{(1)} = \int_a^b \hat{Z}^{(1)}(v) d\hat{t}(v)$

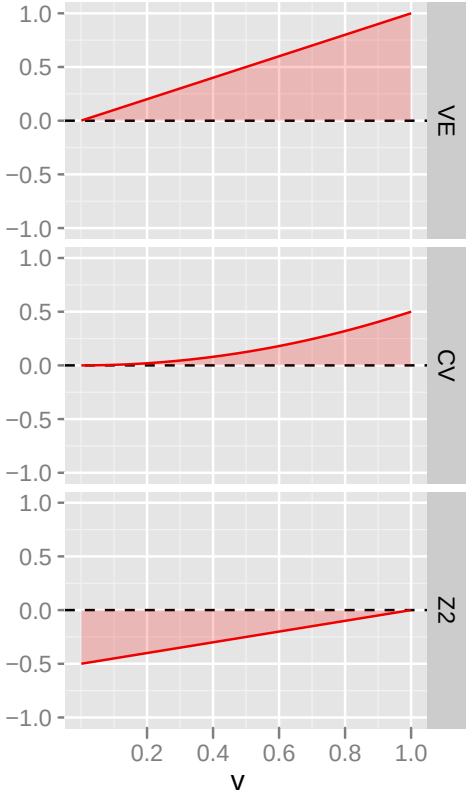
- H_{20}: $\hat{Z}^{(2)}(v) = \sqrt{n}(\frac{\widehat{CV}(v)}{v-a} - \frac{\widehat{CV}(b)}{b-a})/\hat{\rho}(b)$
  - H_{2a}: $T_a^{(2)} = \int_a^b (\hat{Z}^{(2)}(v))^2 d\hat{t}(v)$
  - H_{2m}: $T_{m1}^{(2)} = \int_a^b \hat{Z}^{(2)}(v) d\hat{t}(v)$

Some simplified examples

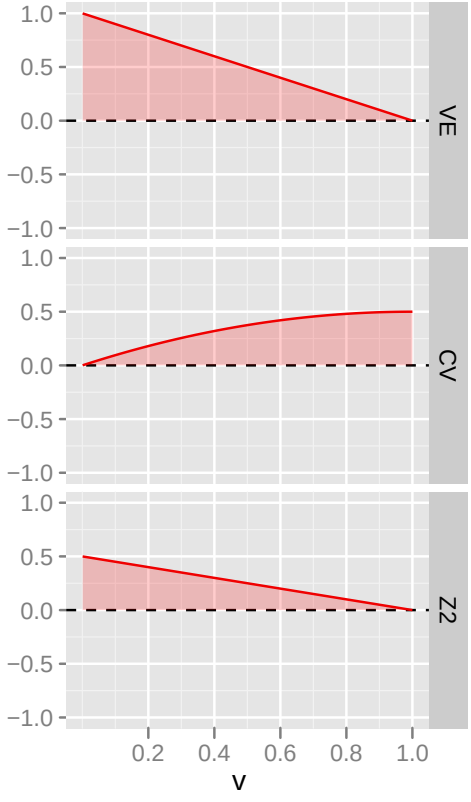
$$VE(v) = 1$$
$$CV(v) = v$$
$$Z^{(1)} \propto \widehat{CV}(v) = v$$
$$Z^{(2)} \propto \frac{\widehat{CV}(v)}{v} - \widehat{CV}(1) = 0$$



$$VE(v) = v$$
$$CV(v) = v^2/2$$
$$\hat{Z}^{(1)} \propto \widehat{CV}(v) = \frac{v^2}{2}$$
$$\hat{Z}^{(2)} \propto \frac{\widehat{CV}(v)}{v} - \widehat{CV}(1) = \frac{v-1}{2}$$



$$VE(v) = 1 - v$$
$$CV(v) = v - v^2/2$$
$$\hat{Z}^{(1)} \propto \widehat{CV}(v) = v - \frac{v^2}{2}$$
$$\hat{Z}^{(2)} \propto \frac{\widehat{CV}(v)}{v} - \widehat{CV}(1) = \frac{1-v}{2}$$



Test statistic distributions

- Under their respective nulls, the test processes $\hat{Z}^{(1)}(v)$ and $\hat{Z}^{(2)}(v)$ converge to Wiener processes indexed by $t(v) = \rho^2(v)/\rho^2(b)$.
- Test statistics $T_a^{(1)}$, $T_{m1}^{(1)}$, $T_a^{(2)}$, $T_{m1}^{(2)}$ converge to the respective functionals, so their null distributions can be simulated.
- Discretized versions of the monotone alternative test statistics $T_{m2}^{(2)}$, $T_{m2}^{(2)}$ also exist.

Simulation study

- Generate time-to-failure data from given hazard function:

$$\lambda(t, v|x) = \exp(\gamma v + (\alpha + \beta v)x \qquad t \geq 0, v \in [0, 1]$$

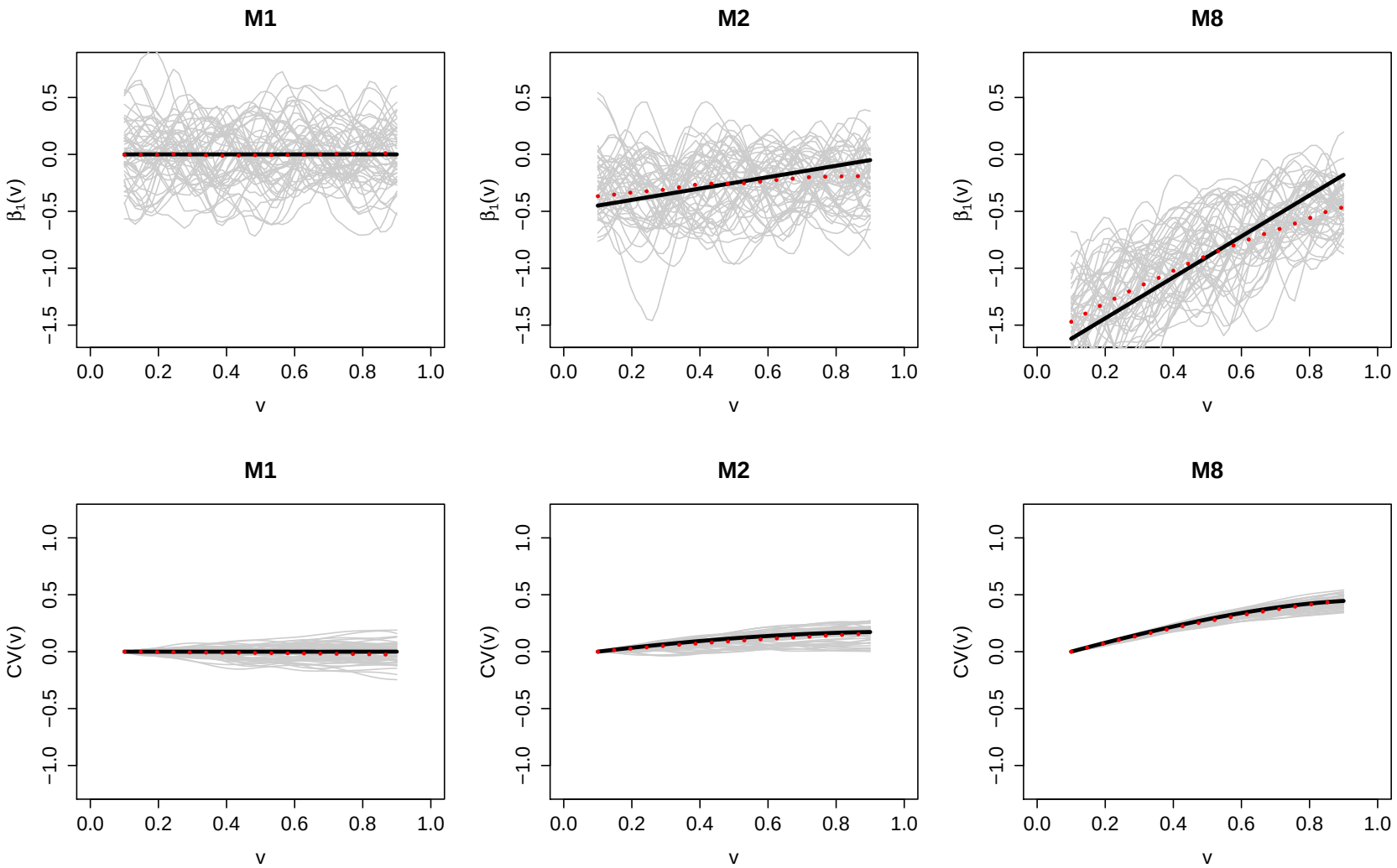
  - v generated from uniform distribution
  - x vaccination status 0 or 1 with probability 0.5
  - t simulated from exponential distribution, using the hazard function conditional on v, x
  - Censoring simulated from an independent exponential distribution with rates of 20 to 30 %

- Results in true $\beta(v) = \alpha + \beta v$ and $VE(v) = 1 - \exp(\alpha + \beta v)$

Simulation setup

- H_{10} : $VE(v) = 0$ for all $v \in [a, b]$
  - Model 1: $(\alpha, \beta, \gamma) =$ (0.0,0.0,0.3) (Null)
  - Model 2: $(\alpha, \beta, \gamma) =$ (-0.5,0.5,0.3) (Alternative)
  - Model 3: $(\alpha, \beta, \gamma) =$ (-0.6,0.6,0.3) (Alternative)
  - Model 4: $(\alpha, \beta, \gamma) =$ (-0.6,0.0,0.3) (Alternative)
- H_{20} : $VE(v)$ does not depend on $v \in [a, b]$
  - Model 5: $(\alpha, \beta, \gamma) =$ (-0.7,0.0,0.3) (Nul)
  - Model 6: $(\alpha, \beta, \gamma) =$ (-1.2,1.2,0.3) (Alternative)
  - Model 7: $(\alpha, \beta, \gamma) =$ (-1.5,1.5,0.3) (Alternative)
  - Model 8: $(\alpha, \beta, \gamma) =$ (-1.8,1.8,0.3) (Alternative)
- Models 1, 2, 5, 8: 1,000 simulations each with $n = 500, 800$; $h = 0.05, 0.10, 0.15$
- Models 3, 4, 6, 7: $n = 500$ and $h = 0.10$ only.

Simulation results: estimation



For selected models with n=500 and h = 0.1, random sample of 50 point estimates for $\beta_1(v)$ and CV(v) (—), true values (—) and mean of 1000 estimates ($\cdots$)

Selected results: coverage and power

Tests of overall vaccine efficacy

Model	(α, β, γ)	n	h	Size/Power (%) $T_a^{(1)}$	$T_{m1}^{(1)}$	$T_{m2}^{(1)}$	Coverage (%)
M1	(0.0,0.0,0.3)	500	0.10	7.0	2.8	9.6	96.5
M2	(-0.5,0.5,0.3)	500	0.05	49.0	57.3	69.0	93.9
			0.10	58.7	68.6	70.0	99.6
			0.15	63.7	69.8	74.5	98.8
		800	0.05	70.8	76.9	85.5	94.9
			0.10	74.7	81.5	87.1	99.1
			0.15	70.2	71.8	86.4	98.8
M3	(-0.6,0.6,0.3)	500	0.10	75.4	82.2	84.7	96.5
M4	(-0.6,0.0,0.3)	500	0.10	96.5	98.4	99.8	96.7

Selected results: coverage and power

Tests of differential vaccine efficacy

Model	(α, β, γ)	n	h	Size/Power (%) $T_a^{(1)}$	$T_{m1}^{(2)}$	$T_{m2}^{(2)}$	Coverage (%)
M5	(-0.7,0.0,0.3)	500	0.10	4.2	3.3	**12.1**	98.4
M6	(-1.2,1.2,0.3)	500	0.10	**38.0**	42.3	48.8	96.7
M7	(-1.5,1.5,0.3)	500	0.15	61.7	66.0	73.0	94.8
M8	(-1.8,1.8,0.3)	500	0.10	60.7	60.7	77.2	95.5
			0.10	65.6	68.0	83.2	98.1
			0.15	81.2	80.2	89.9	95.3
		800	0.05	92.5	87.1	92.0	93.9
			0.10	96.2	94.1	96.9	93.2
			0.15	96.2	94.4	97.6	96.0

Criticisms & Conclusions

- Many calculation details weren't explicitly stated - needed author code to clarify:
  - Integrals implemented differently from paper text
  - Bandwidth-dependent measures to avoid the lower boundary - not mentioned in text
  - Simulation results difficult to reproduce from details in paper
- Possible next steps:
  - Simulate from more complex distributions (distinguish between monotone and general alternatives)
  - Compare to finite competing risks (Prentice *et al.* 1975)
  - Clarify calculation details and justify the additional procedures.

Thank you!

HIV plushie from www.giantmicrobes.com

Discretized monotone alternative test statistics

- Defined by inverting covariance estimates of Wiener processes on a finite grid:
  - $T_{m2}^{(1)} = (K-1)^{1/2} \sum_{k=2}^{K} \frac{Z^{(1)}(v_k) - Z^{(1)}(v_{k-1})}{\sqrt{t(v_k) - t(v_{k-1})}}$
  - $T_{m2}^{(2)} = \hat{\Pi}_K^{-1} \sum_{k=2}^{K} Z^{(2)}(v_k) - Z^{(2)}(v_{k-1}) / \hat{\pi}_k$

$$\hat{\pi}_k^2 = \hat{\tau}_{k-1,k-1} - 2\hat{\tau}_{k-1,k} + \hat{\tau}_{k,k}$$

$$\hat{\tau}_{i,j} = \widehat{Cov}(Z^{(2)}(v_i), Z^{(2)}(v_j))$$

$$= \frac{\hat{t}(v_i)}{(v_i - a)(v_j - a)} - \frac{\hat{t}(v_i)}{(v_i - a)(b - a)} - \frac{\hat{t}(v_j)}{(b - a)(v_j - a)} + \frac{1}{(b - a)^2}$$

$$\Gamma = (\hat{\tau}_{i,j})_{K \times K}$$

$$\xi = (\hat{\pi}_2^{-1}, \hat{\pi}_3^{-1} - \hat{\pi}_2^{-1}, \ldots, \hat{\pi}_K^{-1} - \hat{\pi}_{K-1}^{-1}, \hat{\pi}_K^{-1})$$

$$\hat{\Pi}_K = \xi^T \Gamma \xi$$