Web-based Supplementary Materials for Combinatorial Mixture Models for Single–Cell Assays with Application to Vaccine Studies by Greg Finak, SC De Rosa, Mario Roederer and Raphael Gottardo

Web Appendix A: HVTN065 Vaccine Trial ICS Data Description

HVTN065 is a phase 1 (safety and immunogenicity) trial of GeoVax HIV/AIDS DNA and MVA vaccine in 120 individuals (100 vaccinees, 20 placebo recipients, parts A and B). CD4 and CD8 T–cell epitope specific immune responses were measured via the ICS assay. Other humoral and cellular immune responses were measured via ELISA, and neutralizing antibody assays. Cytokines measured in the ICS assay included IFNg, TNFa, IL2, and IL4, and antigens included three Env, three Gag, and three Pol peptide pools. Results of the trial have been published (Nilu et al., 2006).

Web Appendix B: Constrained Beta–binomial model

We can define a model where we constrain the stimulated proportions under the alternative model such that $p_s > p_u$. In this case, the only changes required are for the alternative marginal likelihood L_1 defined in equation 1. The marginal likelihood for the constrained model becomes $\mathrm{L}_1 \times \mathrm{C}$, where C is a ratio of normalizing constants for the likelihood and the prior.

$$\mathrm{C} = \frac{\int_{p_{ui}=0}^{1} \left(\frac{1}{\mathrm{B}(n_{ui}+\alpha_u, N_{ui}-n_{ui}+\beta_u)} p_{ui}^{n_{ui}+\alpha_u-1}(1-p_{ui})^{N_{ui}-n_{ui}+\beta_u-1} \right) \left(\mathrm{I}_{1-\mathrm{p_{ui}}}(N_s^i - n_s^i + \beta_s, n_s^i + \alpha_s) \right) dp_{ui}}{\int_{p_{ui}=0}^{1} \left(\frac{1}{\mathrm{B}(\alpha_u,\beta_u)} p_{ui}^{\alpha_u-1}(1-p_{ui})^{\beta_u-1} \right) \left(\mathrm{I}_{1-\mathrm{p_{ui}}}(\beta_s, \alpha_s) \right) dp_{ui}}$$

The term $I_{1-p_{ui}}(\beta_s, \alpha_s) = 1 - I_{p_{ui}}(\alpha_s, \beta_s) = Pr(p_{si} > p_{ui}; \alpha_s, \beta_s)$ is the regularized incomplete Beta function, which is just the CDF of a Beta distribu-

tion with parameters α_s, β_s, resulting in a 1–dimensional integral that can be computed via Monte–Carlo integration (i.e. in our EM implementation). However, this can be computationally costly in the MCMC framework. In the latter case, we can compute the integral exactly if α_s and β_s are integers by using the identity:

$$I_{1-p_u}(\beta_s, \alpha_s) = \sum_{j=\beta_s}^{\beta_s+\alpha_s-1} \frac{(\beta_s+\alpha_s-1)!}{j!(\beta_s+\alpha_s-j)!}(1-p_u)^j(p_u)^{\beta_s+\alpha_s-j} \quad (1)$$

Typically, in ICS data $\beta_s >> \alpha_s$, leading to relatively few terms in the sum in equation 1. This leads to an exact expression for the normalizing constant:

$$f$$

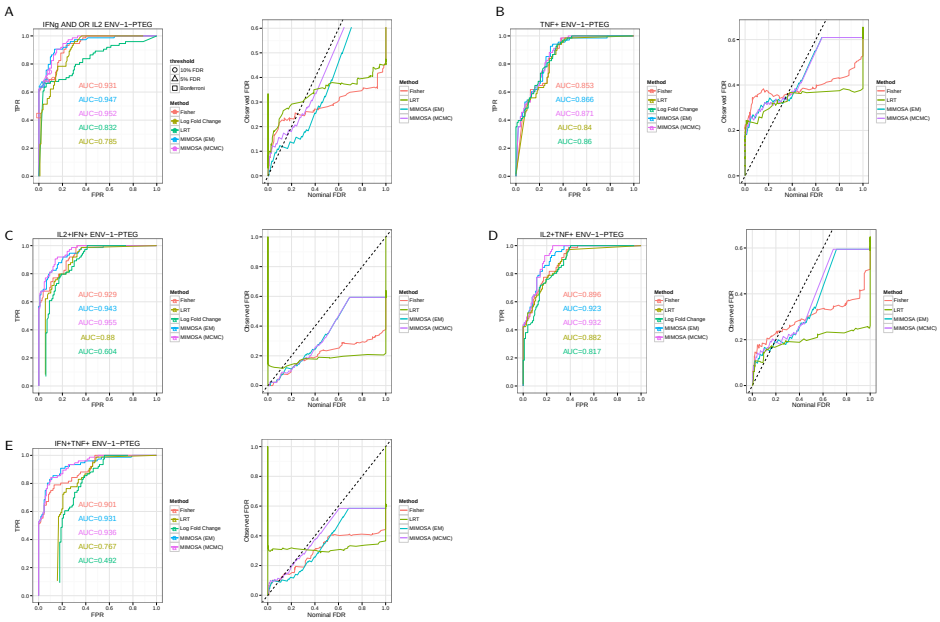
Web Appendix C: Derivation of Marginal Likelihoods for Beta–Binomial Model

Web Appendix D: The MCMC Algorithm

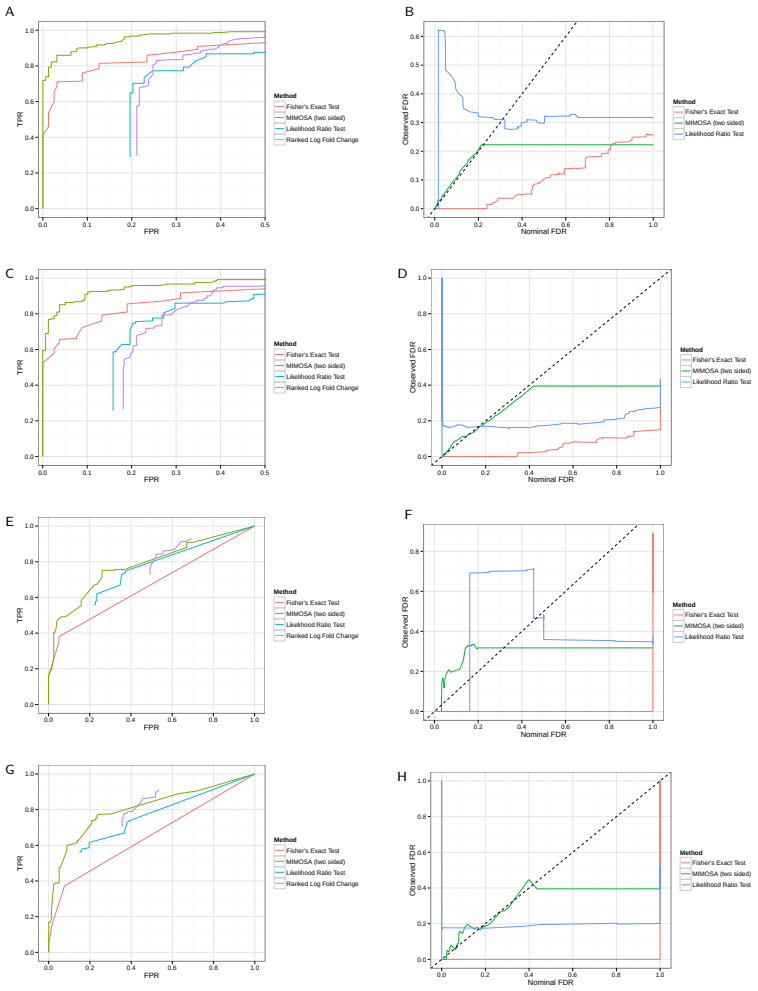
Web Appendix E: Marginal Likelihoods for the Multivariate Model

References

Nilu G. et al., 2006, J Virol, 80, 4717



Web Figure A: Comparison of MIMOSA on other cytokines and cytokine combinations for ENV-1-PTEG stimulated CD4+ T-cells from the HVTN065 trial.



Web Figure B: Unconstrained MIMOSA model fit to two–sided data (A,B,E,F) or to data where model assumptions are violated (C,D,G,H). Two–sided data were simulated from a standard model. A) Average ROC curves and B) average observed vs nominal FDR from 10 simulations with N=5,000, and E-F) N=1,000. Unconstrained MIMOSA fit to two–sided data simulated from a model where the proportions were drawn from a truncated normal distribution over $[0, 1]$, rather than a Beta distribution. C) Average ROC curves and D) average observed vs nominal FDR from 10 simulations at N=5,000, and G-H) N=1,000.