Analyzing transcriptomics data for understanding and predicting vaccine response in clinical trials

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and its environment…

euclid
F-CRIN platform for clinical trials

VRI
VACCINE RESEARCH INSTITUTE

anrs
MALADIES INFECTIEUSES ÉMERGENTES Inserm

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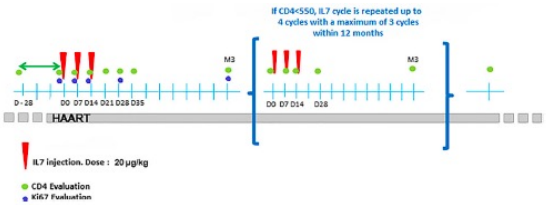
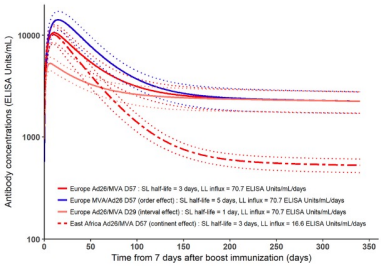
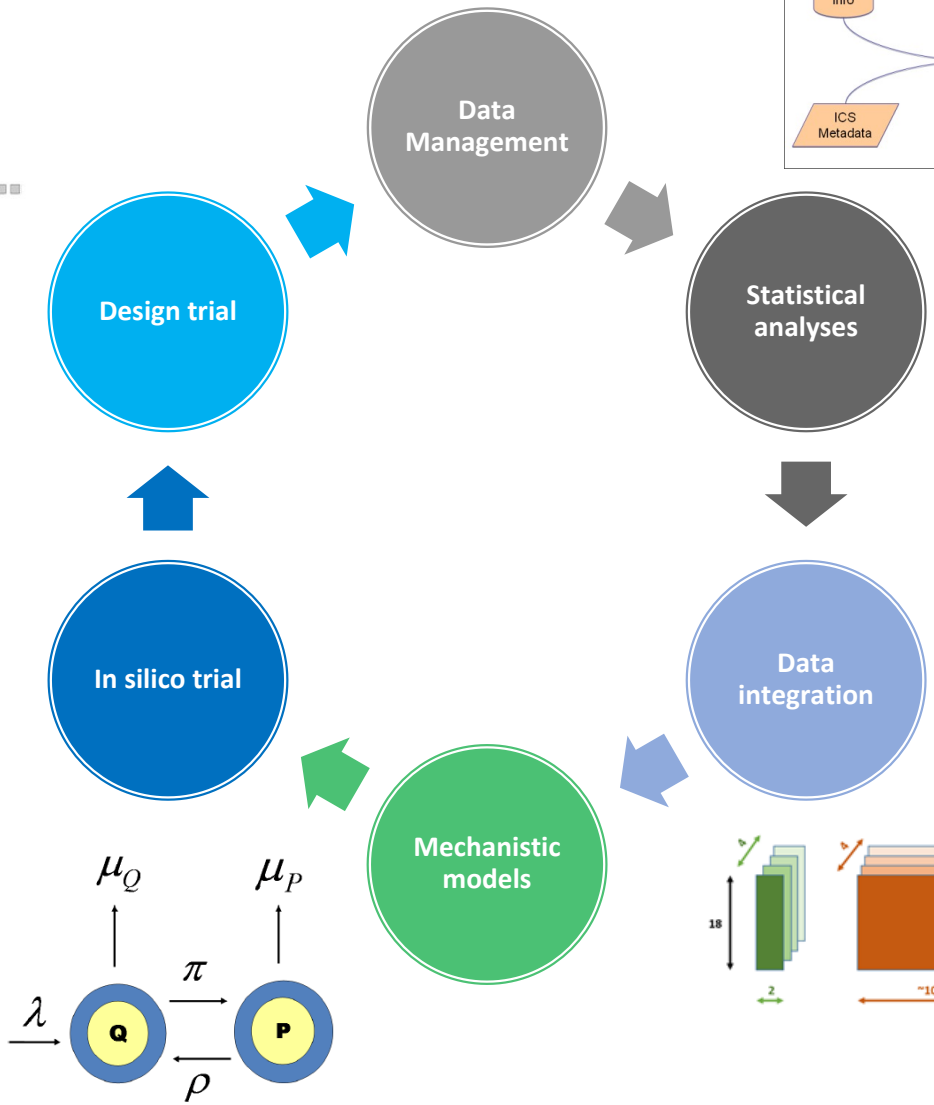
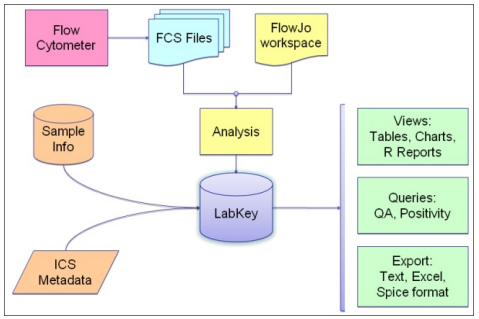
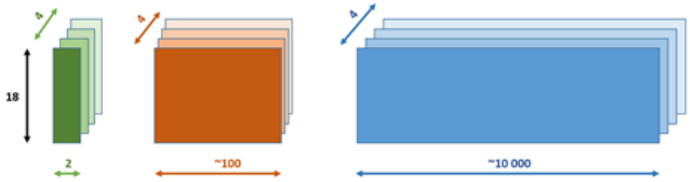
A big picture











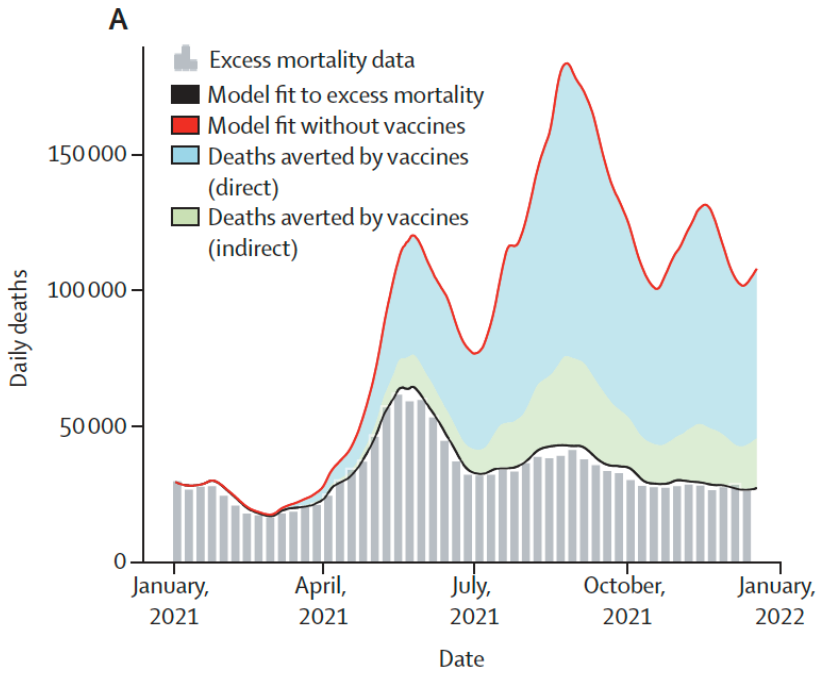
Outline

- Systems vaccinology
- Gene expression differential analysis
- Random forests for longitudinal data

Vaccines

Global impact of the first year of COVID-19 vaccination: a mathematical modelling study

Oliver J Watson, Gregory Barnsley*, Jaspreet Toor, Alexandra B Hogan, Peter Winskill, Azra C Ghani*

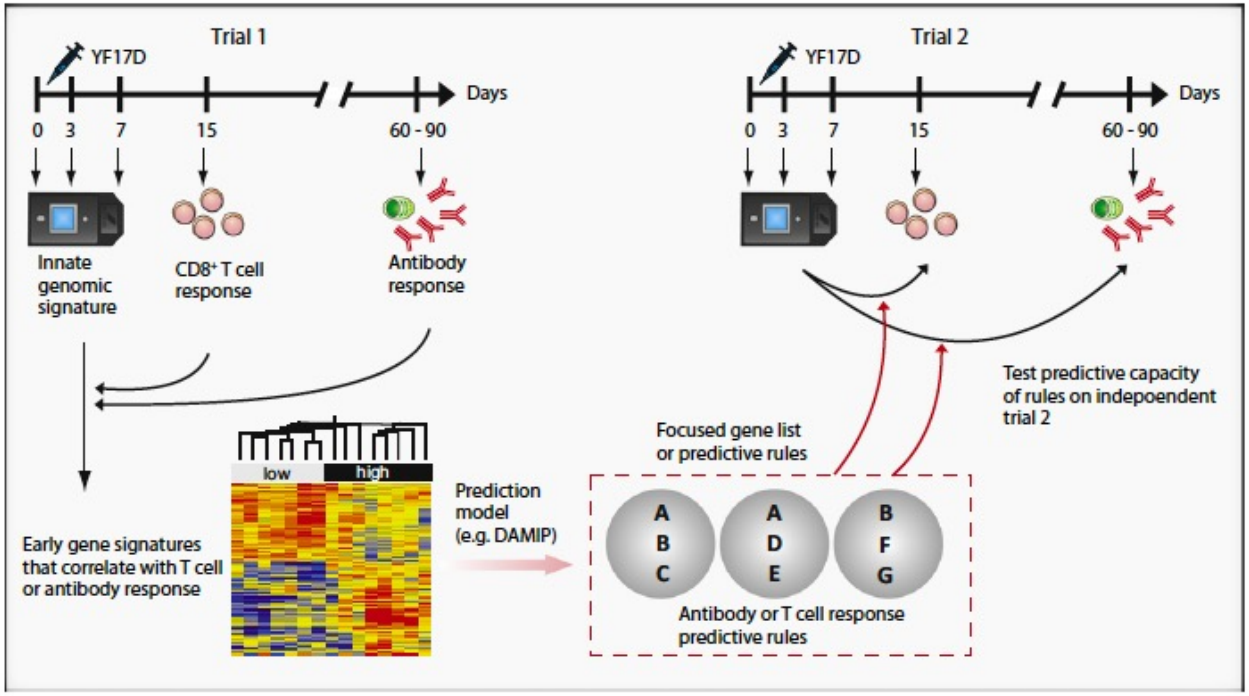


	Total COVID-19 deaths	Vaccination coverage (%)	Estimated deaths averted by vaccinations		
			Total	Per 10 000 people	Per 10 000 vaccines
Worldwide	5 469 000 (5 339 000–5 613 000)	38·30%	14 400 000 (13 650 000–15 900 000)	22·81 (21·63–25·18)	25·99 (24·64–28·69)

Systems vaccinology

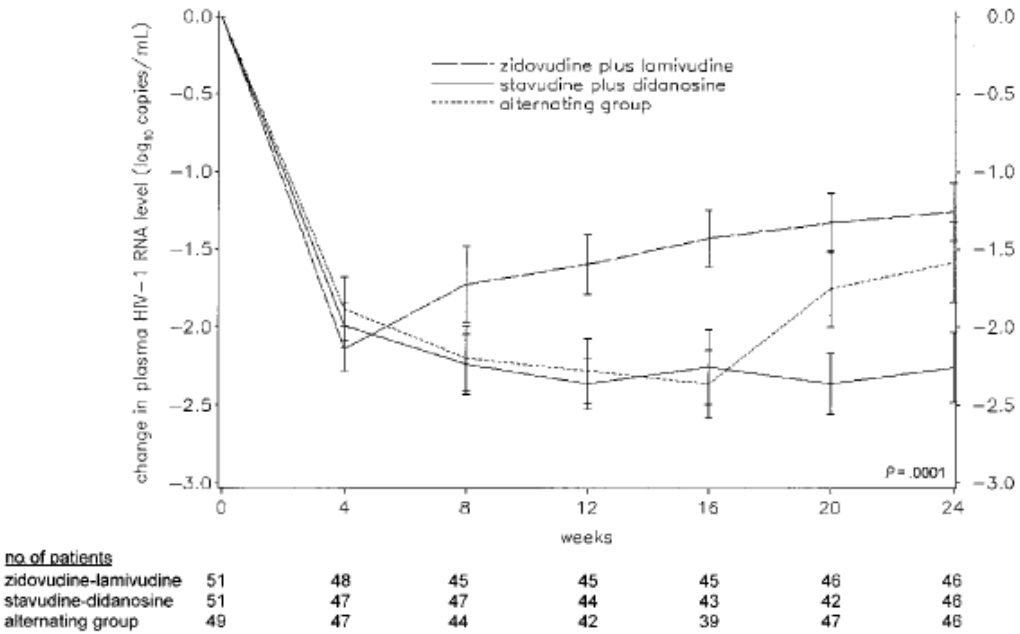
Systems biology approach predicts immunogenicity of the yellow fever vaccine in humans

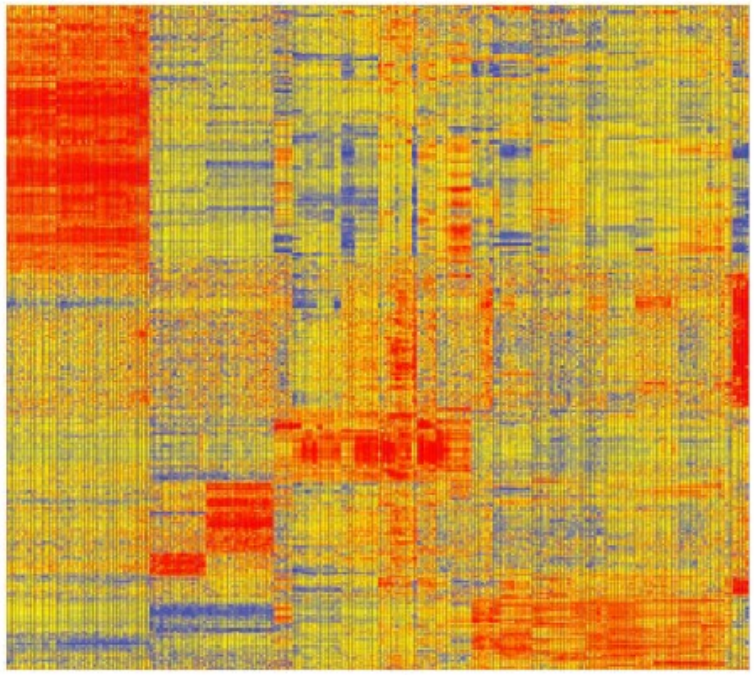
Troy D Querec[1,8], Rama S Akondy[1,8], Eva K Lee[2], Weiping Cao[1], Helder I Nakaya[1], Dirk Teuwen[3], Ali Pirani[4], Kim Gernert[4], Jiusheng Deng[1], Bruz Marzolf[5], Kathleen Kennedy[5], Haiyan Wu[5], Soumaya Bennouna[1], Herold Oluoch[1], Joseph Miller[1], Ricardo Z Vencio[5], Mark Mulligan[1,6], Alan Aderem[5], Rafi Ahmed[1] & Bali Pulendran[1,7]



Gene symbol	Gene ID	1	2	3
BEND4	Hs.120591			
	Hs.139006	X		
PFKFB3	Hs.195471		X	
TNFRSF17	Hs.2556	X	X	X
TPD52	Hs.368433			
	Hs.481166			
KBTBD7	Hs.63841	X	X	X
	Hs.649726			
NAP1L2	Hs.66180			X
		80	80	80
		100	100	100
		97	99	94

Data in vaccinology





Trial	Year	Sample size	Folder size
ALBI ANRS 070	1999	151	67 Ko
DALIA-1	2014	19	200 Go

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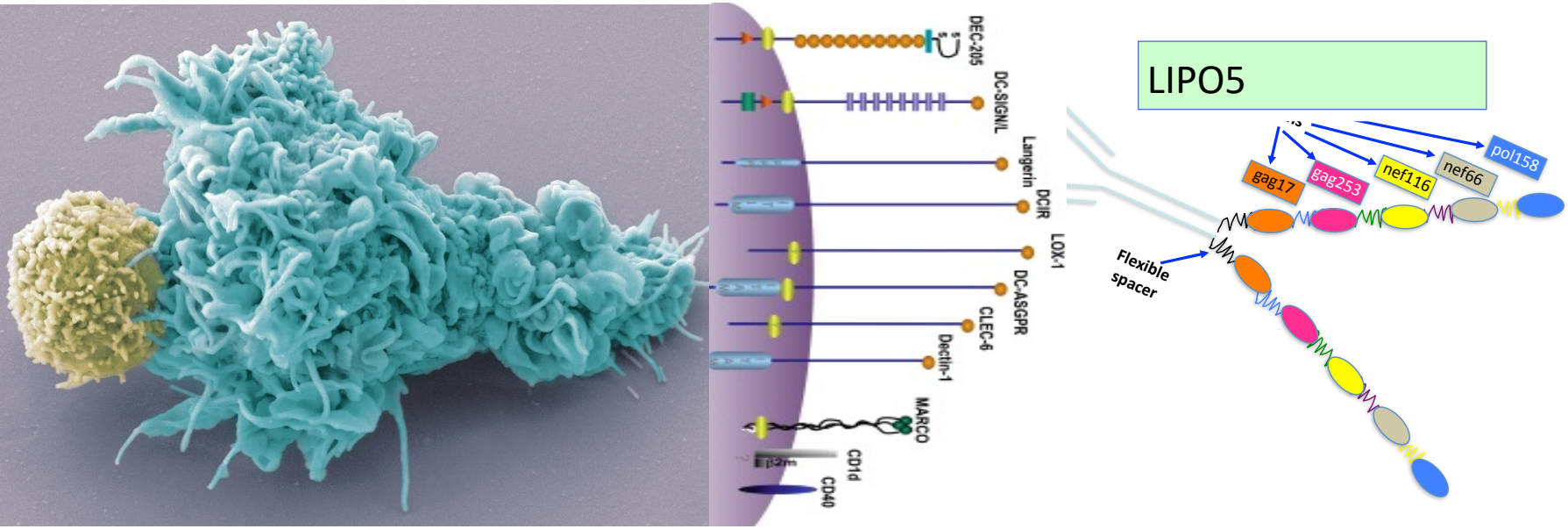
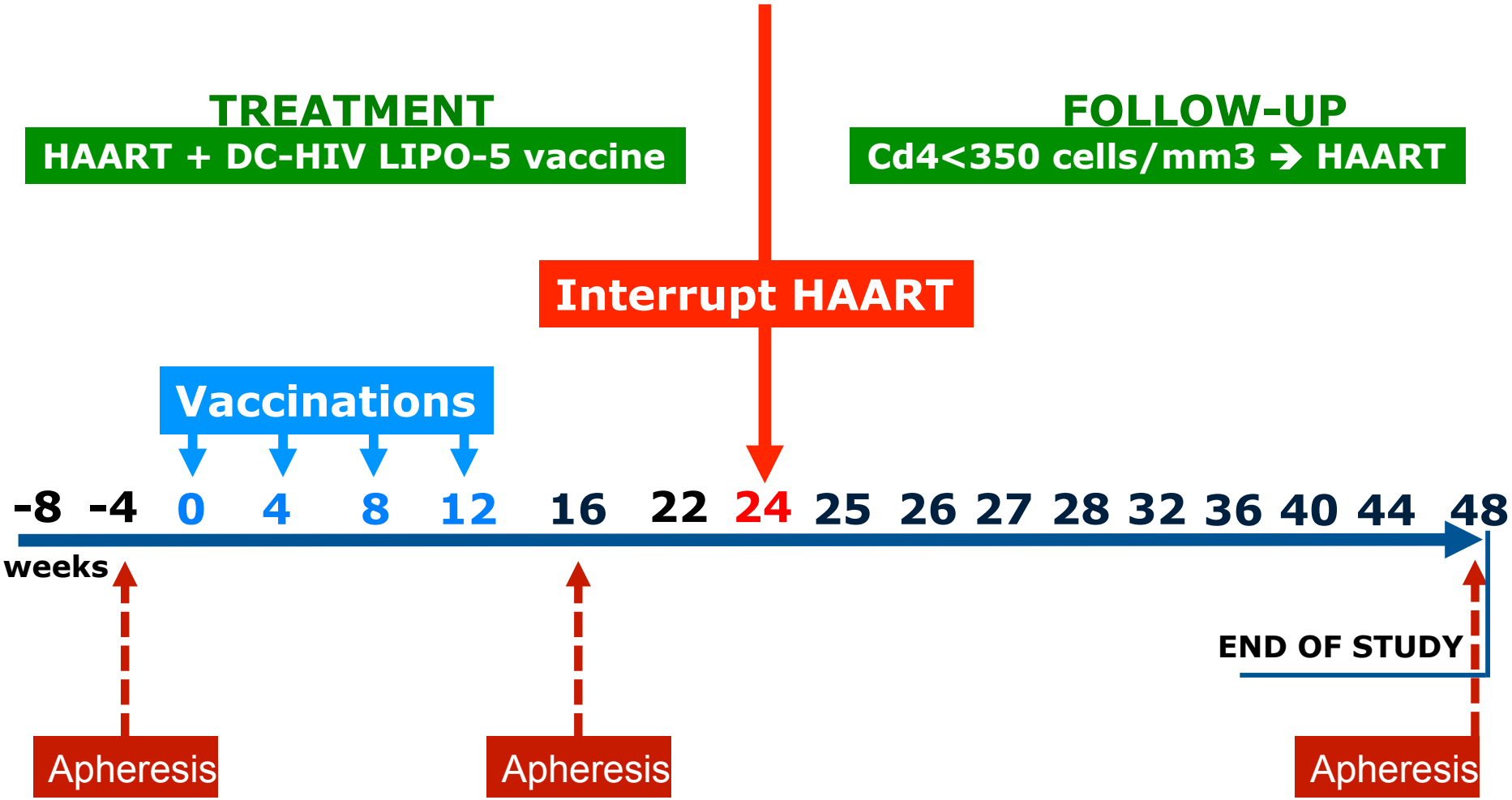
Dendritic cell based vaccine

- Therapeutic vaccine in HIV-infected patients
- Dendritic Cells are loaded with 5 HIV peptides



DALIA-1 trial design

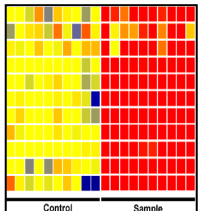


Levy et al. J Immunology 2014

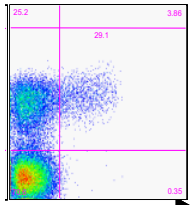
Data in vaccinology

- 846 000 probes (18 temps x 47 000 sondes) 26 Mo
- 18 612 000 beads (22 billes/sonde) 6 Go

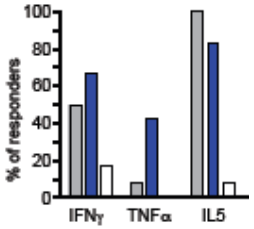
- 30 populations cellulaires 0.05 Mo
- 2160 anticorps (18 temps x 15 tubes x 8 anticorps) pour 2.6 Go



Gene profiling

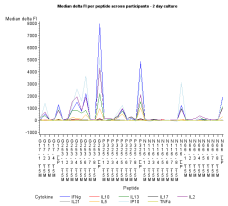


Cell responses

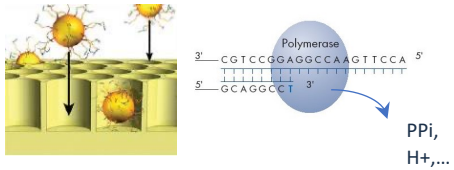


Cytokines

- 800 mesures/temps
- 0.35 Mo



Epitope mapping



Viral changes/ adaptation

- 200 séquences
- 20 Mo

Levy et al. J Immunology 2014

DALIA-1 results: HIV RNA viral load after treatment interruption

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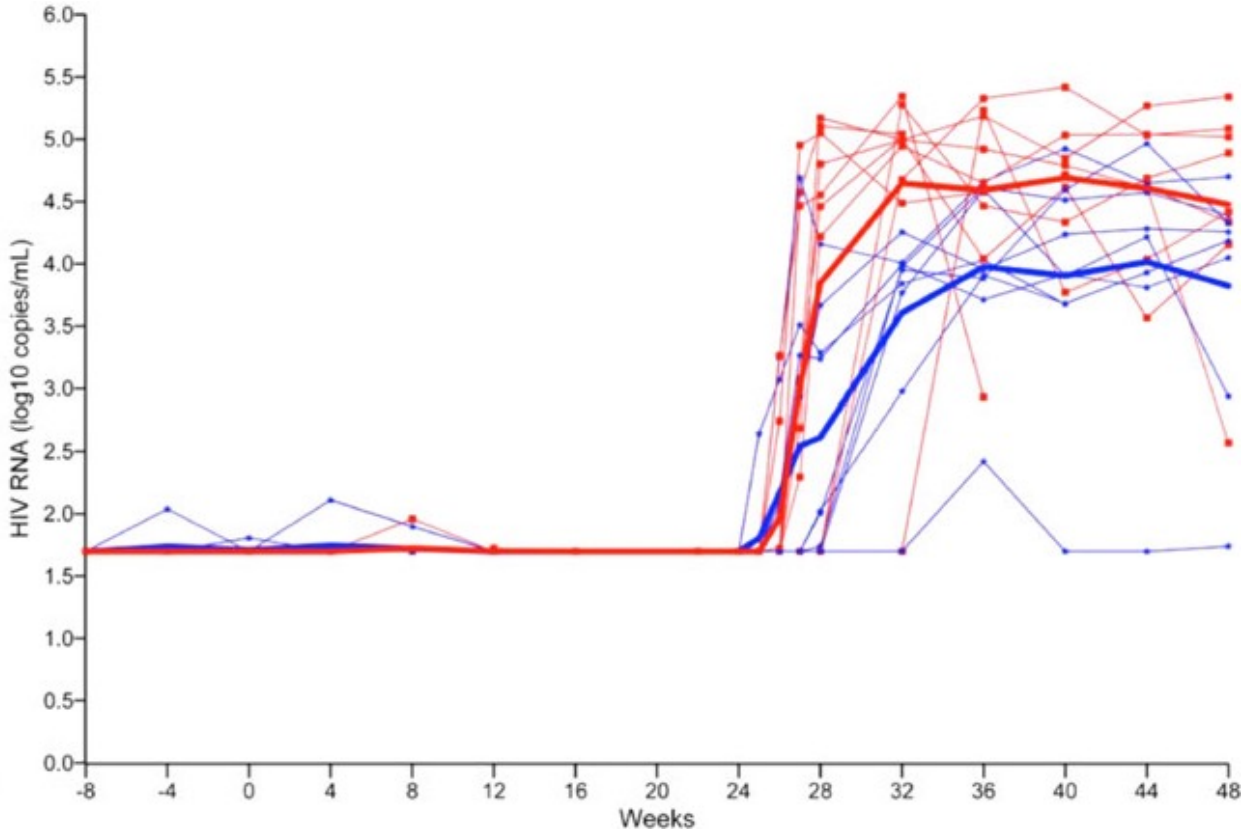
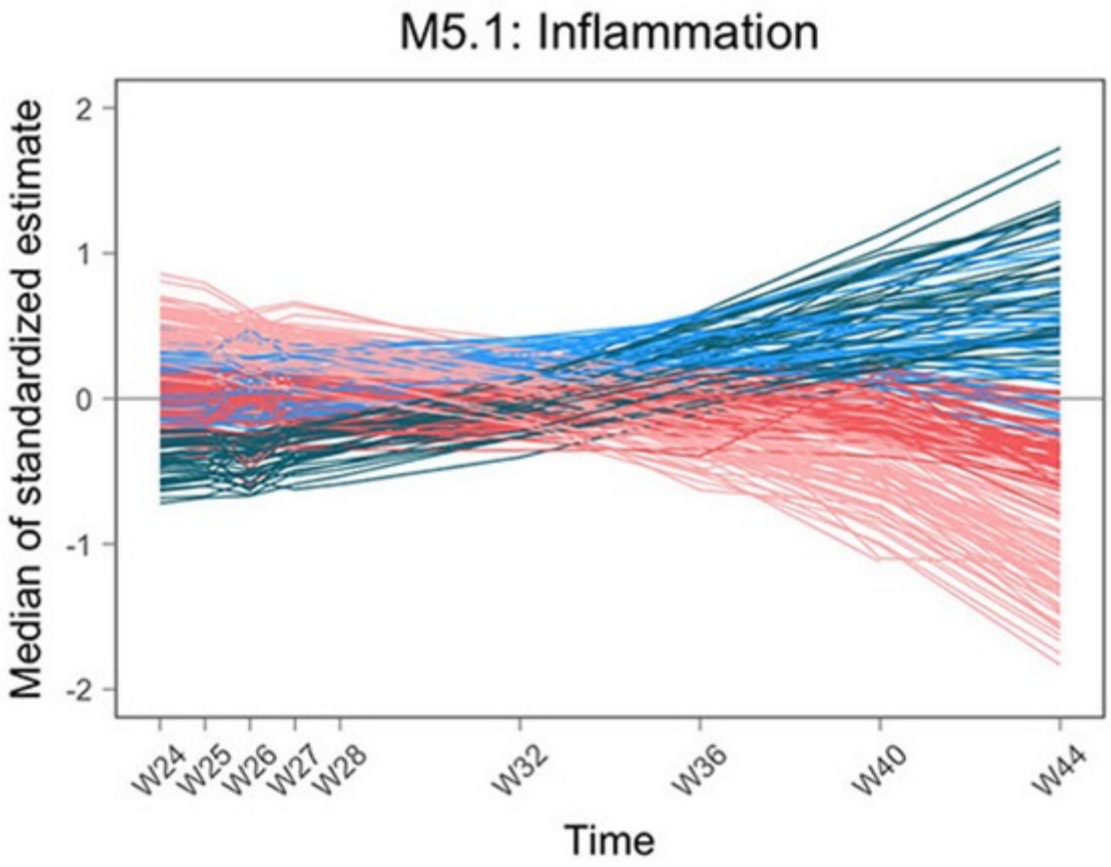


Levy et al. J Immunology 2014

DALIA-1 results: gene expression after treatment interruption

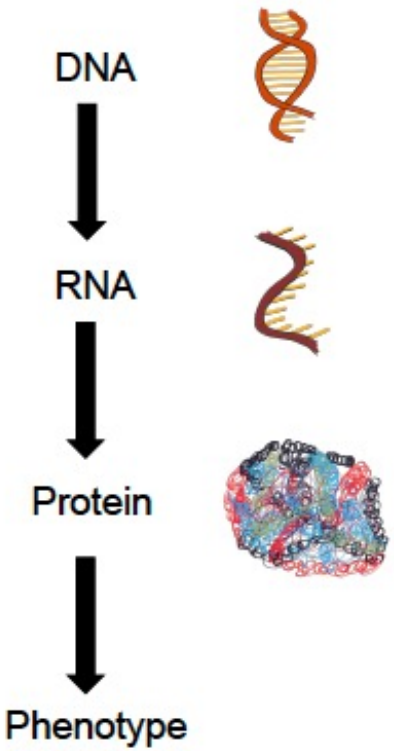


Thiebaut et al. Front Immunol 2019 & Hejblum Plos Comp Biol 2015

Aims

- To understand the mechanism of vaccine response
- To predict the vaccine response

The gene expression (transcriptome)

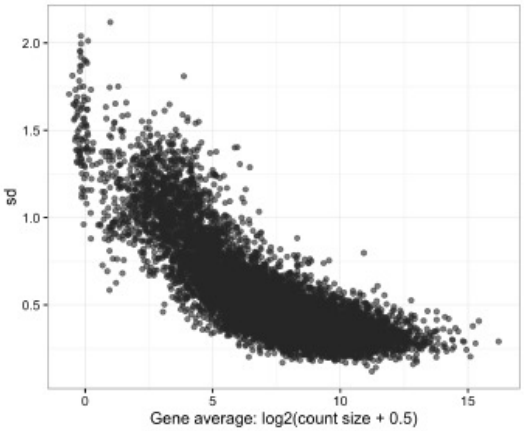


- Messenger RNA
- Measured by
  - Microarray: fluorescence intensity (continuous)
  - RNA-sequencing: count data
- Could be measured:
  - At the single-cell level
  - In the whole blood (bulk): gene abundance

RNA-seq differencial analysis

- Objective: to compare gene expression/abundance between/within groups

- Taking into account:
  - Test multiplicity
    (control of Type-I error and False Discovery rate)
  - RNA-seq data heterosckedasticity



RNA-seq differencial analysis

- The reference approaches
  - EdgeR: Robinson et al. Bioinformatics 2010 (>17K citations)
  - DESeq2: Love et al. Genome Biology 2014 (>24K citations)
  - Voom-lima: Law et al. Genome Biology 2014 (>2K citations)
- But limitations (Rapaport 2013, Rocke 2015, Germain 2016)
  - Strong parametric assumptions
  - Tailored for small studies

Dearseq method

Marine Gauthier

Boris Hejblum

We rely on the following **working model** for each gene g:

Model

$$\boldsymbol{y}_i = \boldsymbol{\alpha}_0 + X_i\boldsymbol{\alpha} + \Phi_i\boldsymbol{\beta} + \Phi_i\boldsymbol{\xi}_i + \boldsymbol{\epsilon}_i,$$

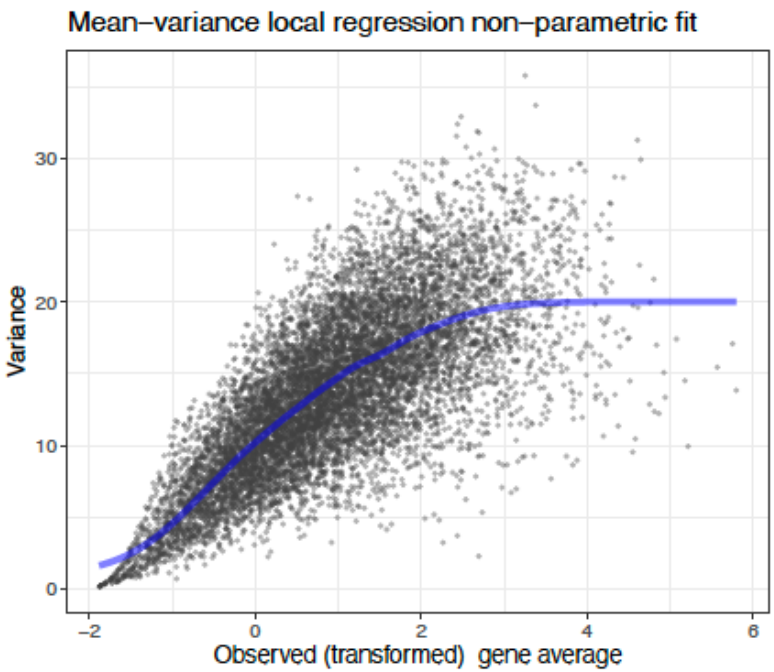
$$\boldsymbol{\xi}_i \sim N(0, \Sigma_\xi), \boldsymbol{\epsilon}_i \sim N(0, \Sigma_i)$$

$$\forall i = 1, ..., n$$

- $\boldsymbol{y}_i = (y_{i1}, \ldots, y_{in_i})$ is a $n_i \times 1$ vector of normalized gene expression measurements
- $\boldsymbol{\alpha}_0$ is a $n_i \times 1$ vector of intercepts
- X_i is the $n_i \times p$ matrix of covariates
- $\boldsymbol{\alpha}$ is a $p \times 1$ vector of fixed effects
- Φ_i is the $n_i \times m$ matrix of the variables of interest
- $\boldsymbol{\beta}$ is a $m \times 1$ vector of fixed effects
- $\boldsymbol{\xi}_i \sim N(0, \Sigma_\xi)$ is a $m \times 1$ vector of individual-level random effects of the variables of interest
- $\boldsymbol{\epsilon}_i$ is a $n_i \times 1$ vector of measurement error

Gauthier et al. NAR Genomics and Bioinformatics 2020

Dearseq method



Measurements errors: $\epsilon_i \sim N(0, \Sigma_i)$

$$v_{ij}^g = Var(y_{ij}^g \mid X_{ij}, \boldsymbol{\xi}_i^g) \quad m_{ij}^g = E(y_{ij}^g \mid X_{ij}, \boldsymbol{\xi}_i^g)$$

Following Law *et al.*, we model the mean-variance relationship at the gene level through Σ_i:

$$v^g = \omega(m^g) + e^g$$

for some unknown function $\omega(.)$ and

$$E(e^g) = 0, V(e^g) = \tau^2, \tau > 0.$$

$\Longrightarrow$ **Local linear regression** [Wasserman, 2006] **borrowing information across all genes**

$$diag(\widehat{\Sigma}_i^g) = \widehat{\omega}_n(\widehat{m}_{ij}^{(g)})$$

The parameters are estimated by Ordinary Least Square.

Gauthier et al. NAR Genomics and Bioinformatics 2020

Dearseq method

We derive a variance component score test statistic for the effects of interest. The null hypothesis of no effect of interest is:

$$H_0 : \text{“}\boldsymbol{\beta} = 0 \text{ and } \Sigma_\xi = 0\text{”}$$

Under H_0, $Q = q^T q$

$$\text{with } q^T = n^{-1/2} \sum_{i=1}^{n} \boldsymbol{y}_{\mu_i}^T \Sigma_i^{-1} \Phi_i$$

where $\boldsymbol{y}_{\mu_i} = \boldsymbol{y}_i - \boldsymbol{\mu}_i = \boldsymbol{y}_i - \boldsymbol{\alpha}_{i0} + X_i \boldsymbol{\alpha}$

Asymptotic test

$$Q \underset{+\infty}{\sim} \sum_{l=1}^{n_i} a_l \chi_1^2$$

where the mixing coefficients a_l depend on the covariance of $\boldsymbol{q}$

Permutation test

Permutations $\Rightarrow$ Naive p-values

[Phipson & Smyth (2010)]

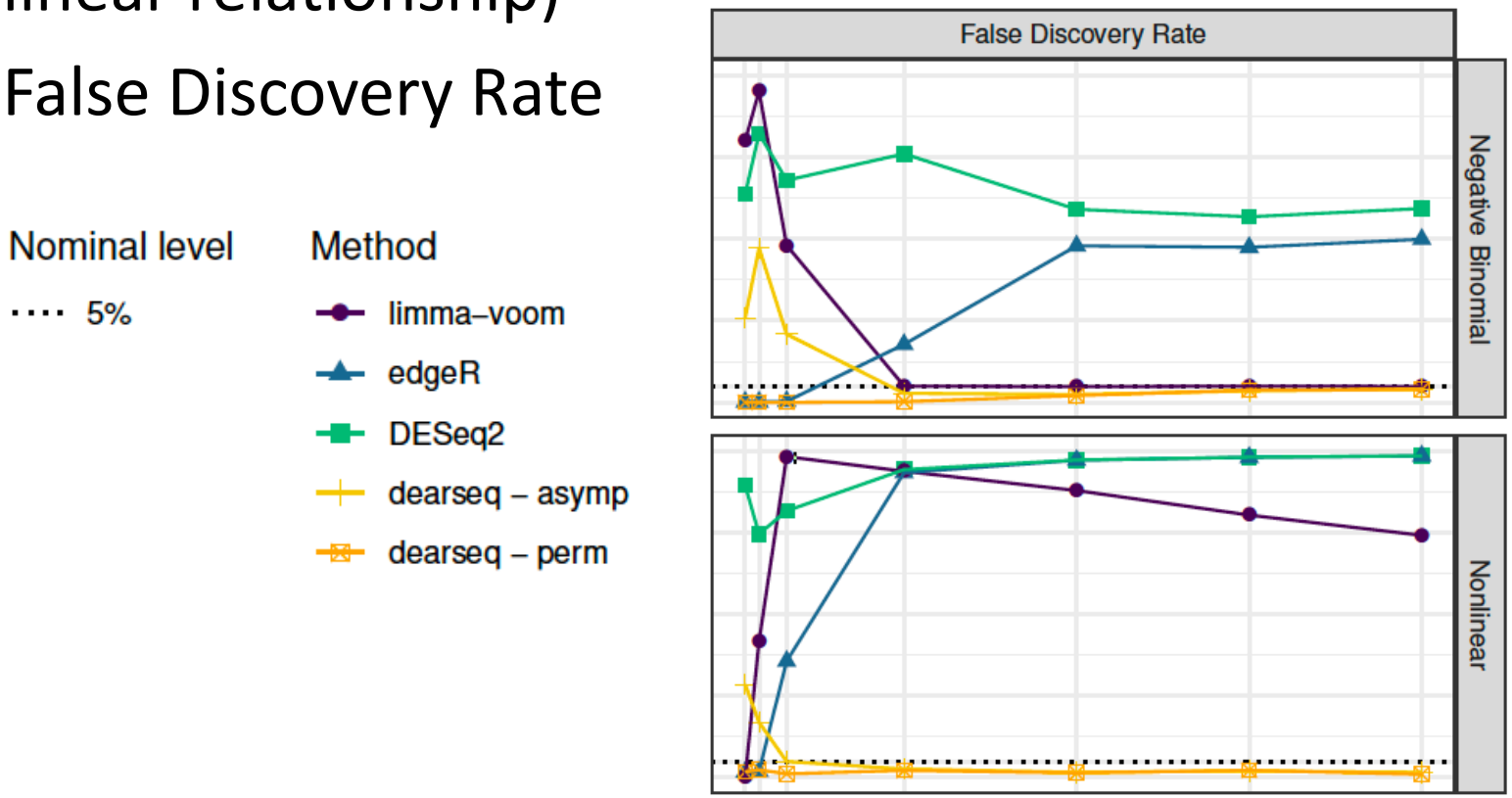
$\Rightarrow$ **exact p-values computations**

$\Longrightarrow$ Benjamini-Hochberg (1995) correction for multiple testing

Gauthier et al. NAR Genomics and Bioinformatics 2020

Simulations

- Monte Carlo estimation over 1000 simulations (non linear relationship)
- False Discovery Rate



Gauthier et al. NAR Genomics and Bioinformatics 2020

Valorisation

- Package dearseq

Volume 2, Issue 4
December 2020

dearseq: a variance component score test for RNA-seq differential analysis that effectively controls the false discovery rate

Marine Gauthier, Denis Agniel, Rodolphe Thiébaut, Boris P Hejblum

NAR Genomics and Bioinformatics, Volume 2, Issue 4, December 2020, lqaa093,
https://doi.org/10.1093/nargab/lqaa093
Published: 19 November 2020 **Article history** ▾

Oups, were we wrong?

Li *et al. Genome Biology* (2022) 23:79
https://doi.org/10.1186/s13059-022-02648-4

Genome Biology

SHORT REPORT Open Access

Exaggerated false positives by popular differential expression methods when analyzing human population samples

Yumei Li[1†], Xinzhou Ge[2†], Fanglue Peng[3], Wei Li[1*] and Jingyi Jessica Li[2,4,5,6,7*]

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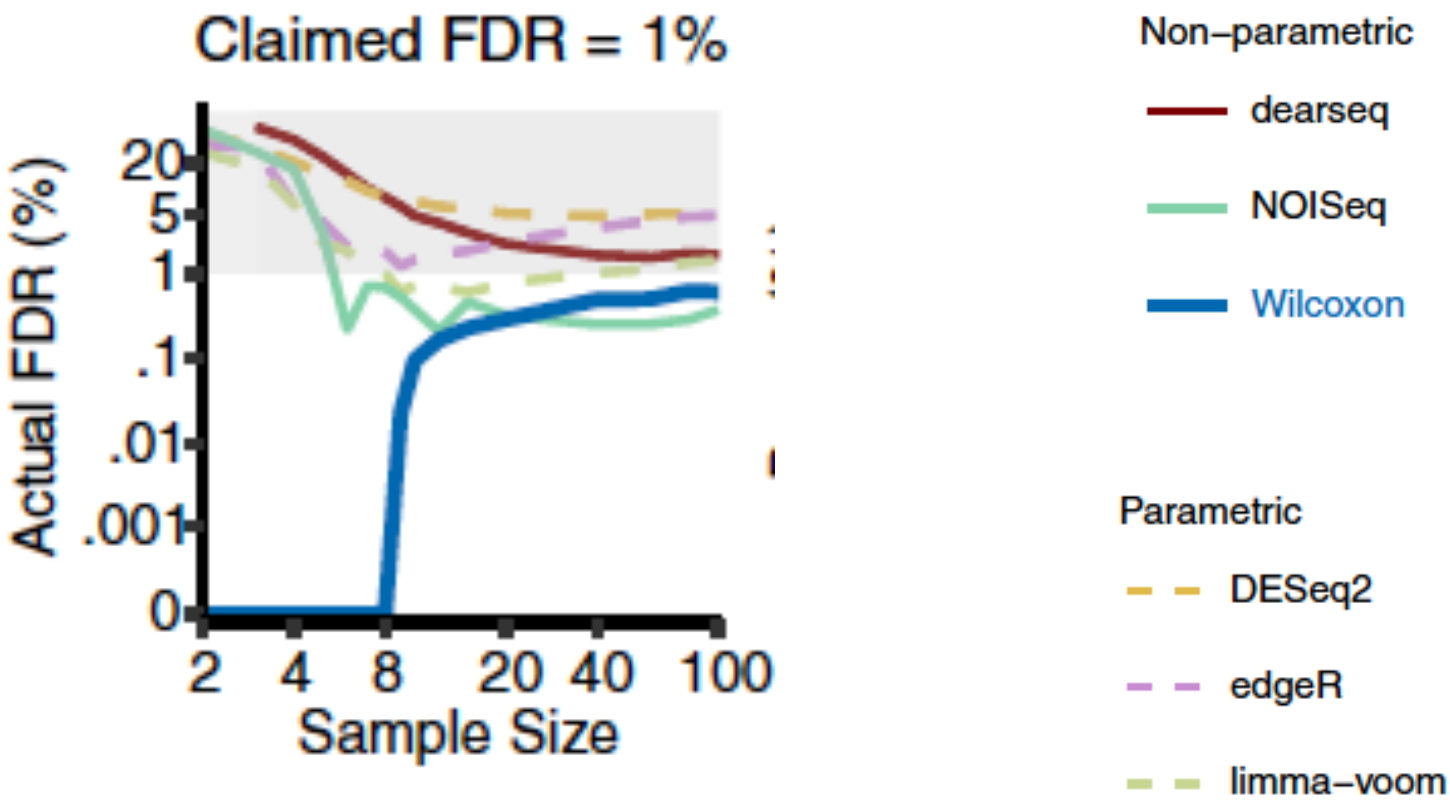
[2] Department of Statistics,

Abstract

When identifying differentially expressed genes between two conditions using human population RNA-seq samples, we found a phenomenon by permutation analysis: two popular bioinformatics methods, DESeq2 and edgeR, have unexpectedly high false discovery rates. Expanding the analysis to limma-voom, NOISeq, dearseq, and Wilcoxon rank-sum test, we found that FDR control is often failed except for the Wilcoxon rank-sum test. Particularly, the actual FDRs of DESeq2 and edgeR sometimes exceed 20% when the target FDR is 5%. Based on these results, for population-level RNA-seq studies with large sample sizes, we recommend the Wilcoxon rank-sum test.

Oups, were we wrong?

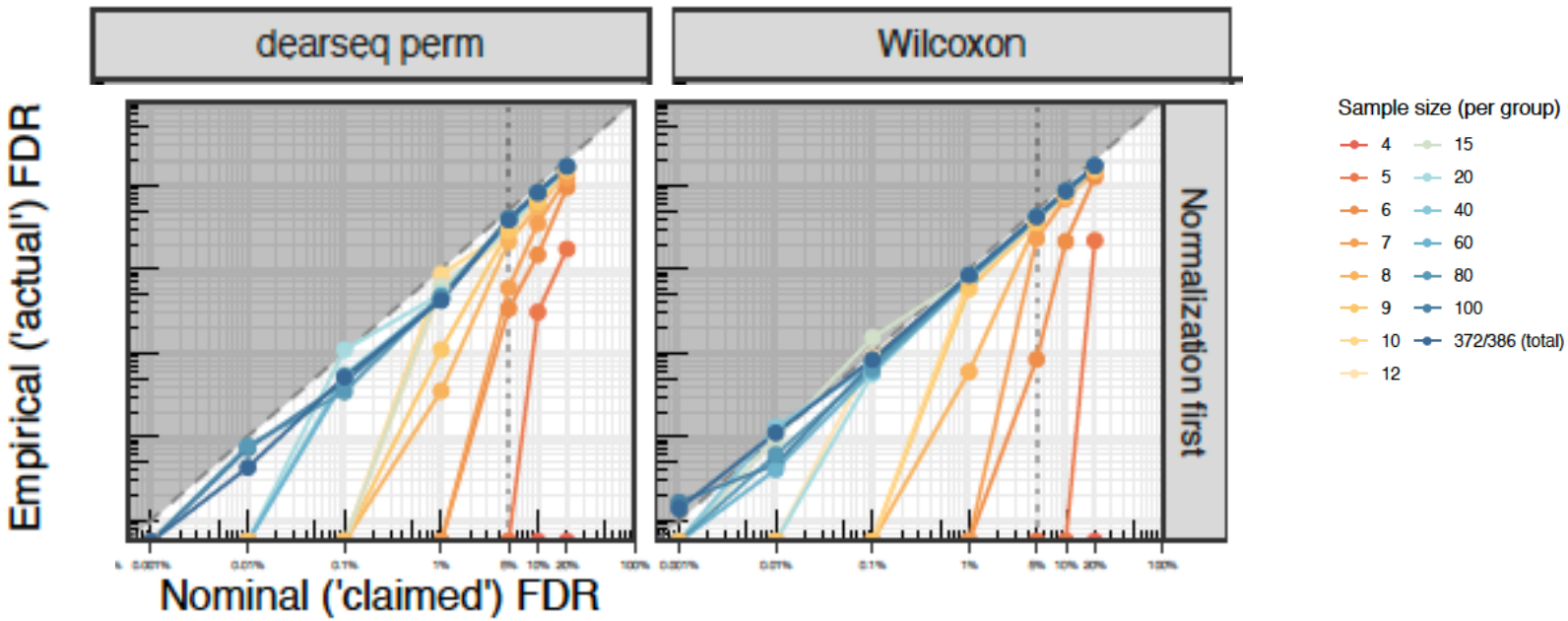


Li et al. Genome Biology 2022

Actually, no. It is ok.

Neglecting normalization impact in semi-synthetic RNA-seq data simulation generates artificial false positives

Boris P Hejblum[1,2,*], Kalidou Ba[1,2], Rodolphe Thiébaut[1,2,3], Denis Agniel[4,5]



https://www.biorxiv.org/content/10.1101/2022.05.10.490529v1

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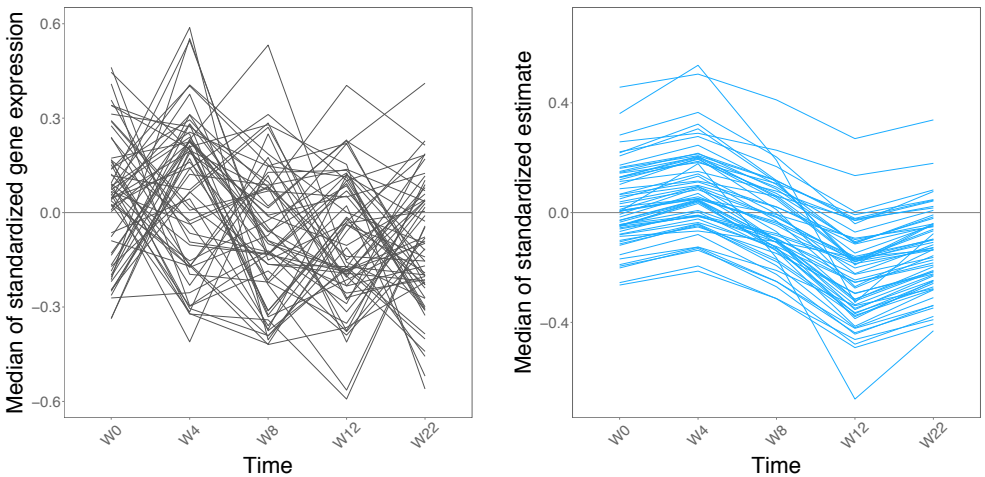
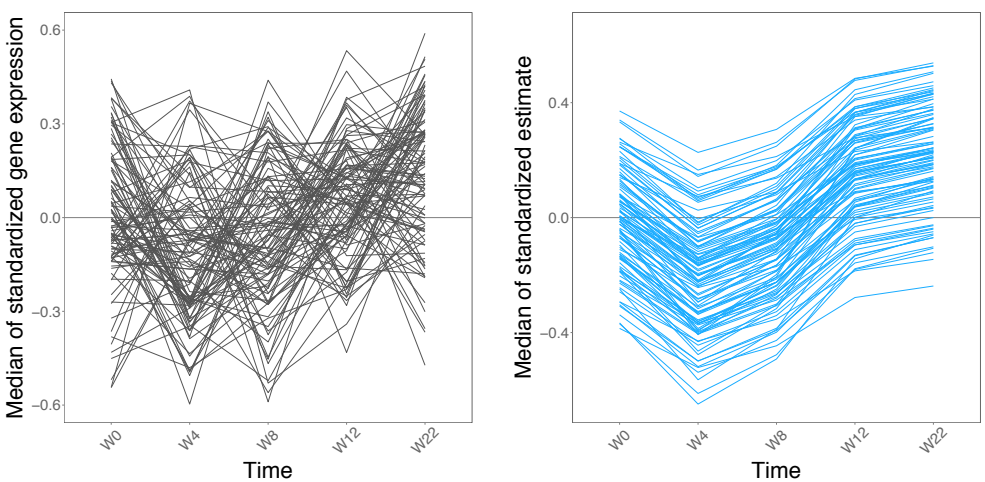
Time course geneset analysis



M 4.1: T cell – 86th percentile



M 4.6: Inflammation – 96th percentile

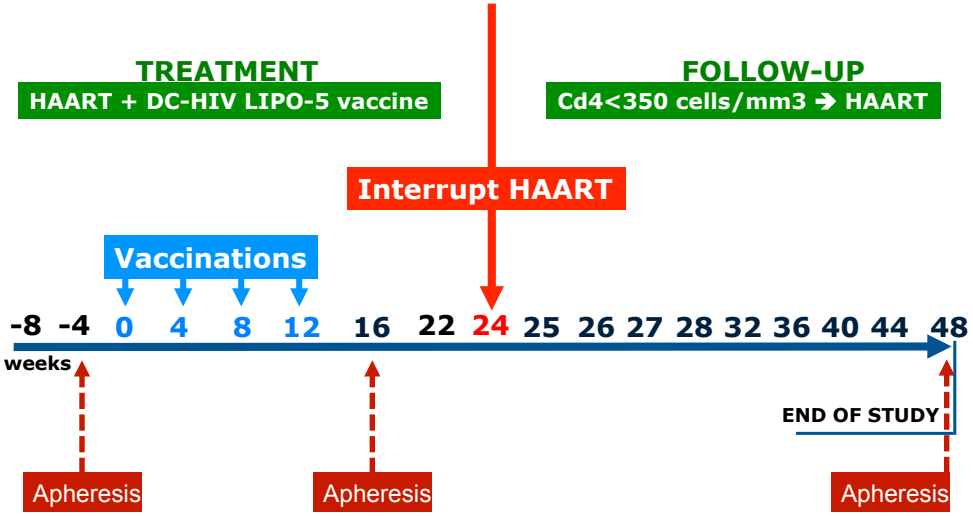
M3.2[99th pctile]: Inflammation 1/1
M1.1[99th pctile]: Platelets 1/1
M4.13[98th pctile]: Inflammation 1/1
M5.10[97th pctile]: Mitochondrial Respiration 1/1
M4.6[96th pctile]: Inflammation 1/1
M5.6[96th pctile]: Mitochondrial Stress / Proteasome 1/1
M3.5[95th pctile]: Cell Cycle 1/1
M5.7[94th pctile]: Inflammation 1/1
M3.1[94th pctile]: Erythrocytes 1/1
M2.3[94th pctile]: Erythrocytes 1/1
M7.1[93th pctile]: Inflammation 1/1
M6.2[93th pctile]: Mitochondrial Respiration 1/1
M4.3[91th pctile]: Protein Synthesis 1/1
M4.11[91th pctile]: Plasma Cells 1/3
M4.11[91th pctile]: Plasma Cells 2/3
M4.11[91th pctile]: Plasma Cells 3/3
M6.13[90th pctile]: Cell Death 1/1
M4.5[89th pctile]: Protein Synthesis 1/1
M4.14[88th pctile]: Monocytes 1/1
M4.2[88th pctile]: Inflammation 1/1
M4.7[87th pctile]: Cell Cycle 1/1
M4.1[86th pctile]: T cell 1/1
M3.6[85th pctile]: Cytotoxic/NK Cell 1/1
M5.9[84th pctile]: Protein Synthesis 1/1
M5.15[82th pctile]: Neutrophils 1/1
M4.15[81th pctile]: T cells 1/1
M6.6[80th pctile]: Apoptosis / Survival 1/1
M5.1[74th pctile]: Inflammation 1/1

Hejblum Plos Comp Biol 2015

Question

- Knowing which genes / genesets are moving over time,

- which ones are associated to the viral load dynamics?



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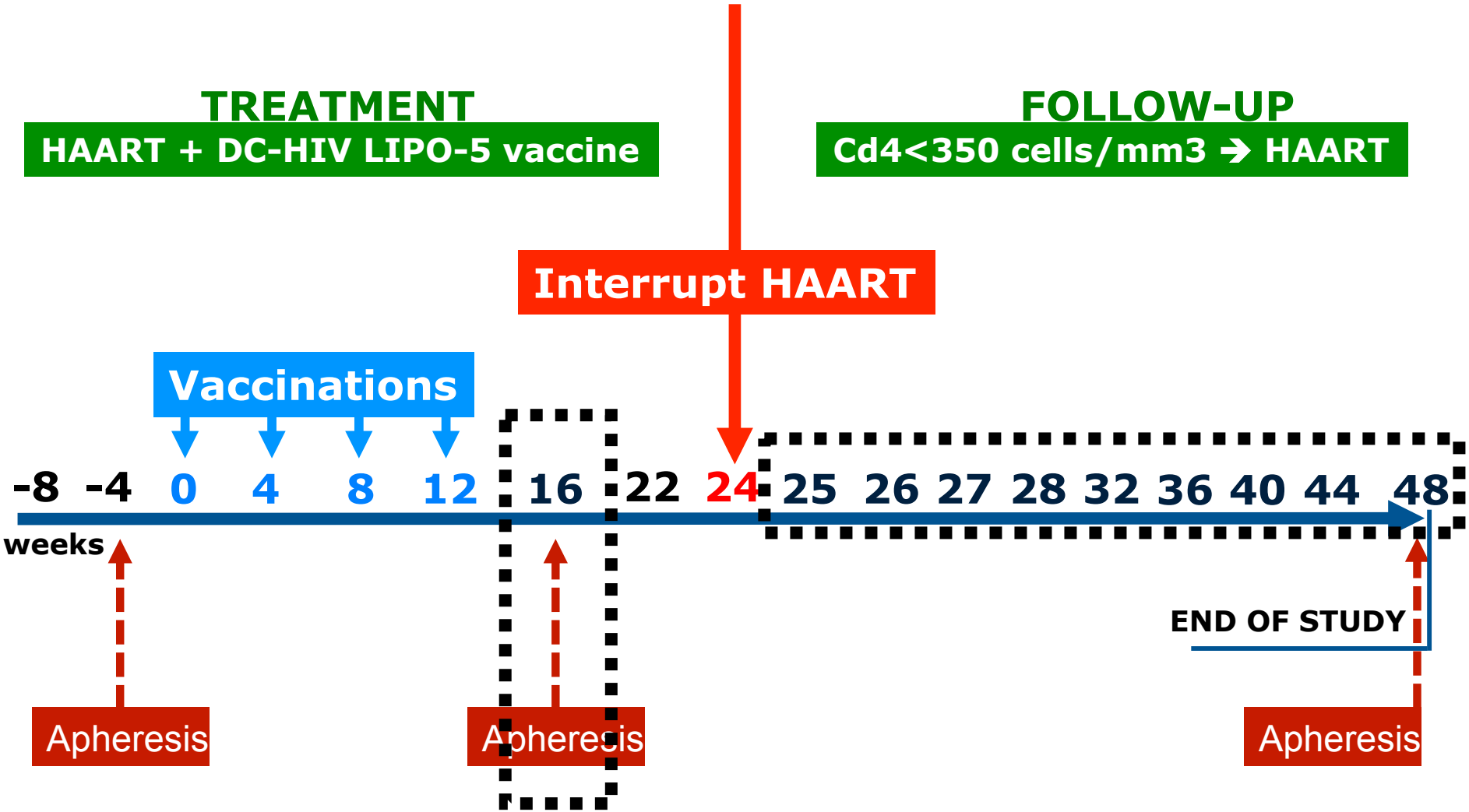
DALIA-1 trial design
Integrative Analysis



Sparse group Partial Least Squares method

Benoit Liquet

Number of predictors (genes) > number of patients:

PLS + LASSO

Regression method

- Independent linear combinations of predictors, ie **genes**
- Independent linear combinations of explaining variables, ie **immunological measures**
- Components **maximize their covariance**

Penalization method

- Select only a few predictors, i.e. **genes**
- **Sparse**: all non selected predictor Coefficients are estimated **as exactly 0**

- *Each **sPLS** component is **sparse:** only a few variables contributes to each components*
- *Selection could be done by **group** of genes*

Liquet et al. Bioinformatics 2015; Sutton et al. Statist Med 2018;37:3338

Group PLS

Aim: Select group variables taking into account the data structures

- PLS components
  $C^k = u_1 \times X_1 + u_2 \times X_2 + u_3 \times X_3 + \ldots + u_p \times X_p$
- sparse PLS components (sPLS)
  $C^k = u_1 \times X_1 + \underbrace{u_2}_{=0} \times X_2 + \underbrace{u_3}_{=0} \times X_3 + \ldots + u_p \times X_p$
- group PLS components (gPLS)

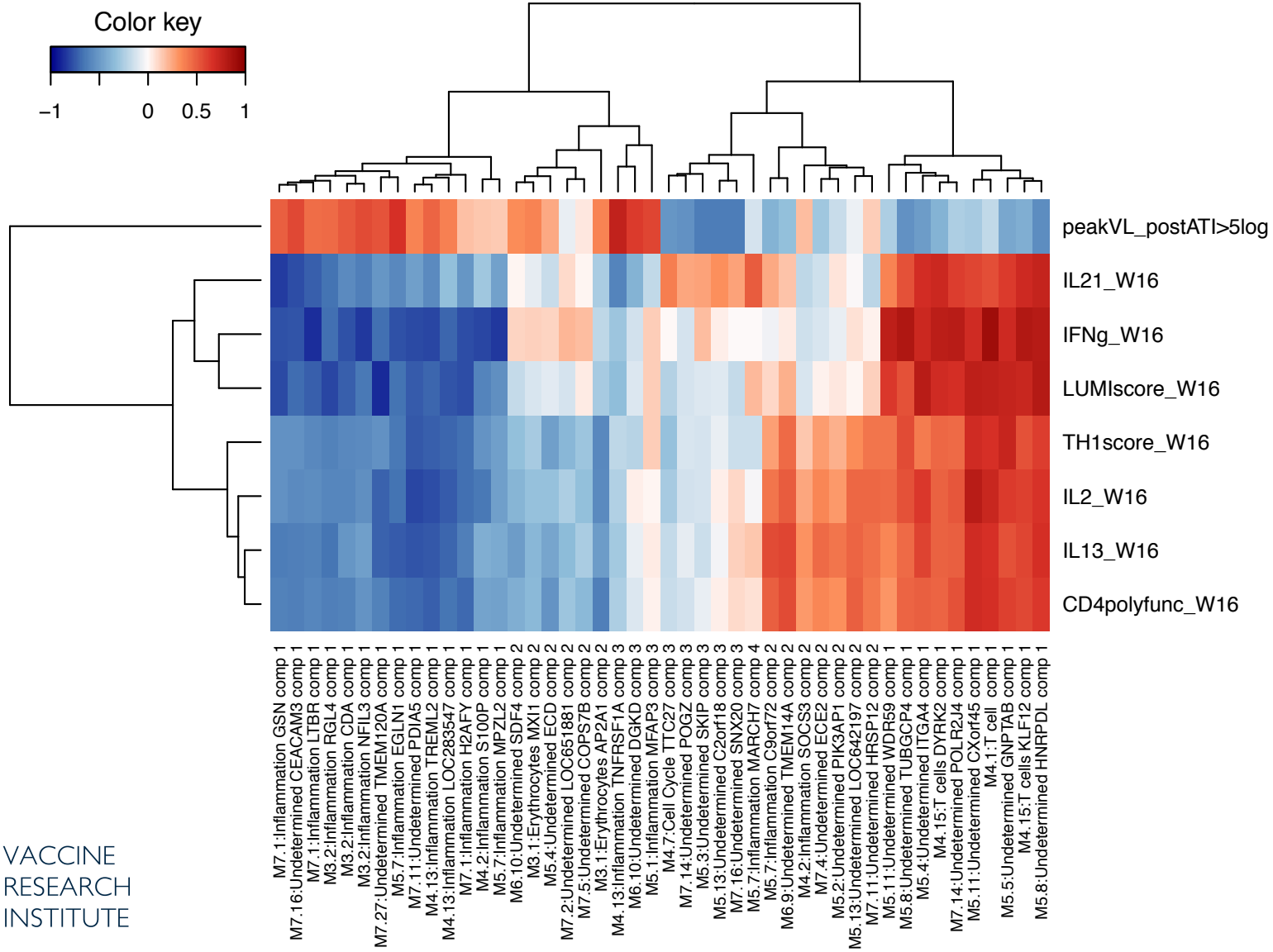
$$C^k = \overbrace{\underbrace{u_1}_{=0} X_1 + \underbrace{u_2}_{=0} X_2}^{module_1} + \overbrace{\underbrace{u_3}_{\neq 0} X_3 + \underbrace{u_4}_{\neq 0} X_1 + \underbrace{u_5}_{\neq 0} X_5}^{module_2} \ldots \overbrace{\underbrace{u_{p-1}}_{=0} X_{p-1} + \underbrace{u_p}_{=0} X_p}^{module_K}$$

$\hookrightarrow$ select group of variables; all the variables within a group are selected otherwise none of them are selected

sgPLS

Liquet et al. Bioinformatics 2015; Sutton et al. Statist Med 2018;37:3338

Correlations with immune response (W16) and peak of viral load (post ATI)



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Need more

- To take into account longitudinal setting
- Repeated measures of HIV RNA viral load
- Repeated measures of gene abundance

Random forest for longitudinal data

Article

SMMR
STATISTICAL METHODS IN MEDICAL RESEARCH

Statistical Methods in Medical Research
0(0) 1–19

DOI: 10.1177/0962280220946080
journals.sagepub.com/home/smm
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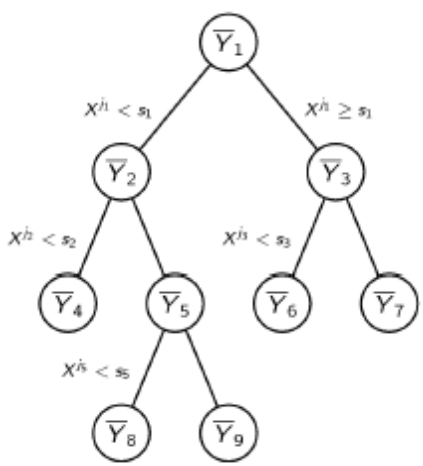
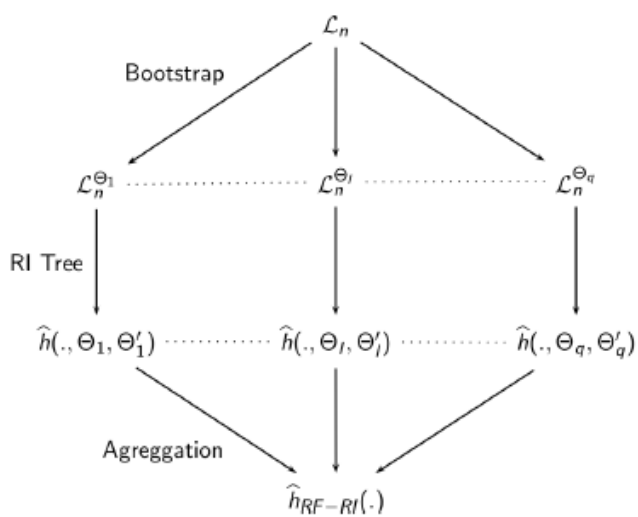
Random forests for high-dimensional longitudinal data

Louis Capitaine, Robin Genuer and Rodolphe Thiébaut





Random forest for longitudinal data

Model

Suppose Y_{ij}, the viral load of the ith individual at time t_{ij}, satisfies

$$Y_{ij} = f(X_{ij}) + Z_{ij} b_i + \omega_i(t_{ij}) + \varepsilon_i \quad \forall i = 1, \ldots, n; j = 1, \ldots, n_i$$

- $f : \mathbb{R}^p \longrightarrow \mathbb{R}$: unknown regression function
  X_{ij} the $p \times 1$ vector of covariates : fixed effects matrix *(gene expressions)*
- $b_i \underset{i.i.d}{\sim} \mathcal{N}(0, B)$: random effects, Z_{ij} the $1 \times q$ random effects covariates
- $(\omega_i(t))_{t \geq 0}$: centered Gaussian process with covariance function $\gamma^2 K_i(s,t)$
- $\varepsilon_{ij} \underset{i.i.d}{\sim} \mathcal{N}(0, \sigma^2)$: residual error

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Random forest for longitudinal data

Algorithm 1: General estimation procedure for model (1)

Initialization: Let $r = 0$, $\hat{b}_{i,(0)} = 0_q$, $\hat{\omega}_{i,(0)} = 0_{n_i}$, $\hat{B}_{(0)} = I_q$, $\hat{\gamma}^2_{(0)} = 1$ and $\hat{\sigma}^2_{(0)} = 1$.

Repeat

1. Set $r = r + 1$, compute $\tilde{Y}_{ij,(r-1)} = Y_{ij} - Z_{ij}\hat{b}_{i,(r-1)} - \hat{\omega}_{ij,(r-1)}$ estimate f in the standard regression framework (with all N observations):

$$\tilde{Y}_{ij,(r-1)} = f(X_{ij}) + \varepsilon_{ij}$$

   to get $\hat{f}_{i,(r)}$.
   Then predict $\hat{b}_{i,(r)}$ and $\hat{\omega}_{i,(r)}$ using $\hat{B}_{(r-1)}, \hat{\gamma}^2_{(r-1)}, \hat{\sigma}^2_{(r-1)}$ and $\hat{f}_{i,(r)}$.

2. Update $\hat{B}_{(r)}$, $\hat{\gamma}^2_{(r)}$ and $\hat{\sigma}^2_{(r)}$ using $\hat{f}_{i,(r)}$, $\hat{b}_{i,(r)}$ and $\hat{\omega}_{i,(r)}$,

until *convergence*;

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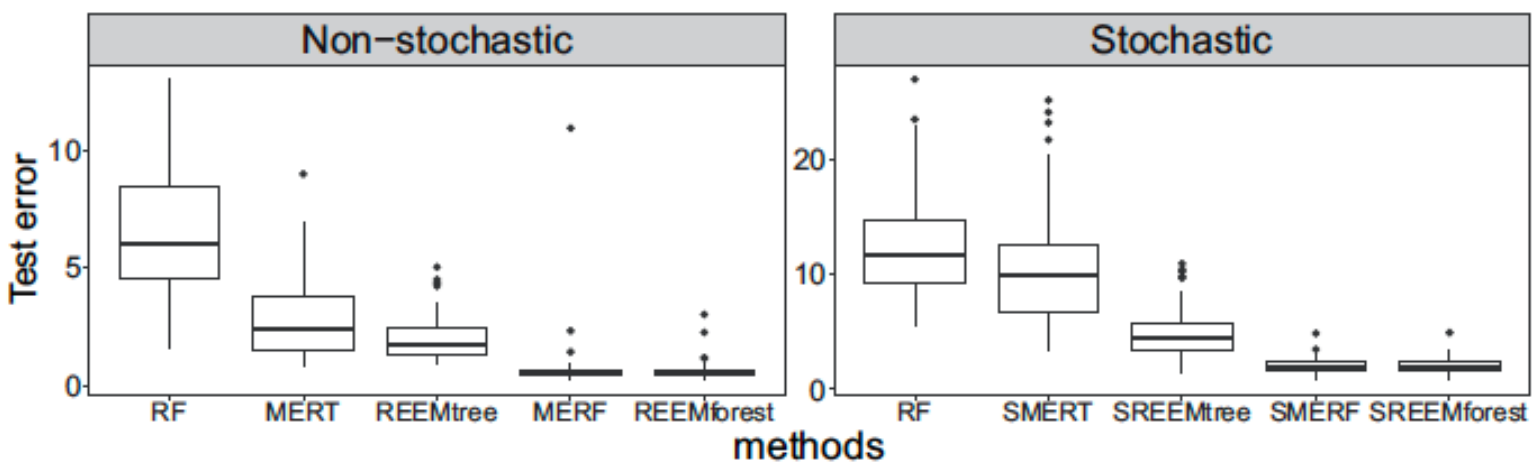
LongituRF

Random forest for longitudinal data

Table 3. Squared bias of the estimated parameters, averaged on 100 datasets respectively simulated under model (4) and (5) in the high-dimensional case.

	f	B	γ^2	σ^2
Non-stochastic model				
MERT	1.902	0.603	*	0.112
REEMtree	1.543	0.499	*	0.070
MERF	0.750	0.504	*	0.005
REEMforest	0.729	0.493	*	0.005
Stochastic model				
SMERT	5.229	0.926	0.113	0.590
SREEMtree	3.519	0.738	0.071	0.065
SMERF	1.378	0.511	0.024	0.010
SREEMforest	1.367	0.496	0.023	0.011



Application to DALIA-1

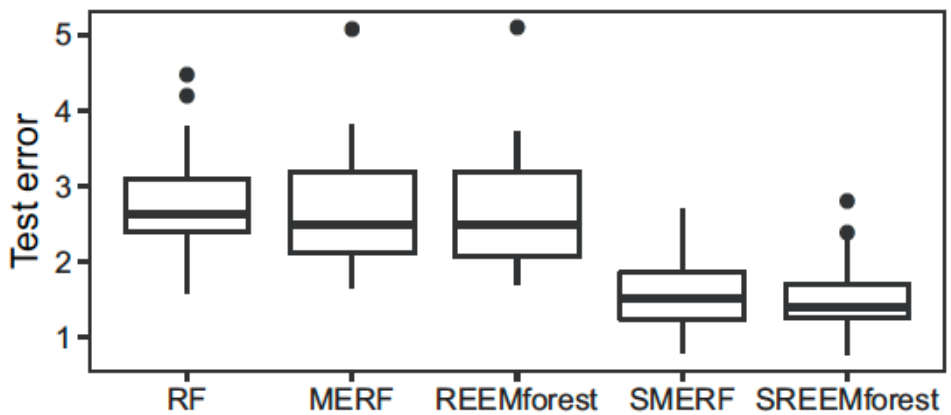


Figure 10. Boxplots of test errors computed using 25 training/test sets random splits, for Breiman's RF, **MERF**, **REEMforest**, **SMERF**, and **SREEMforest**, DALIA trial.

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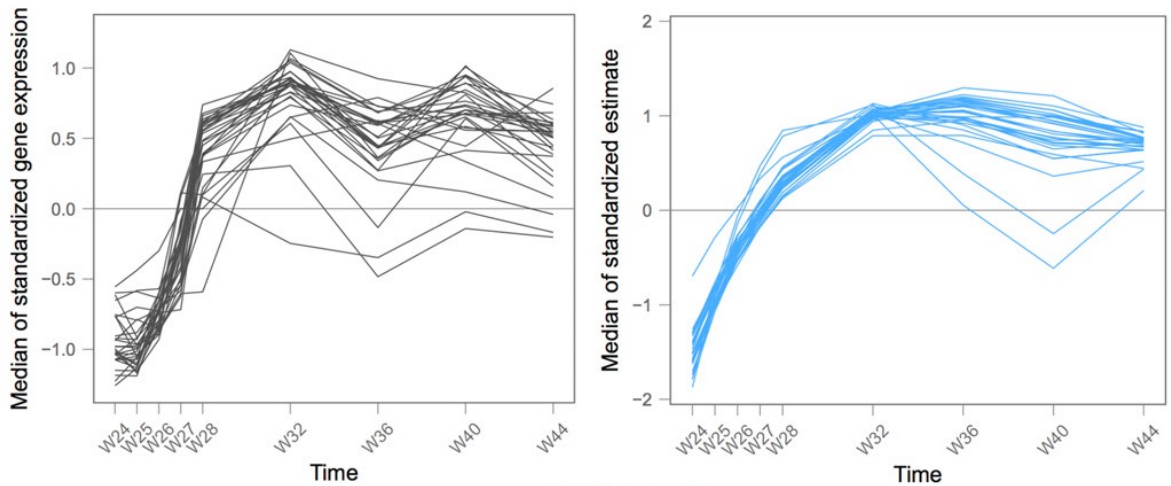
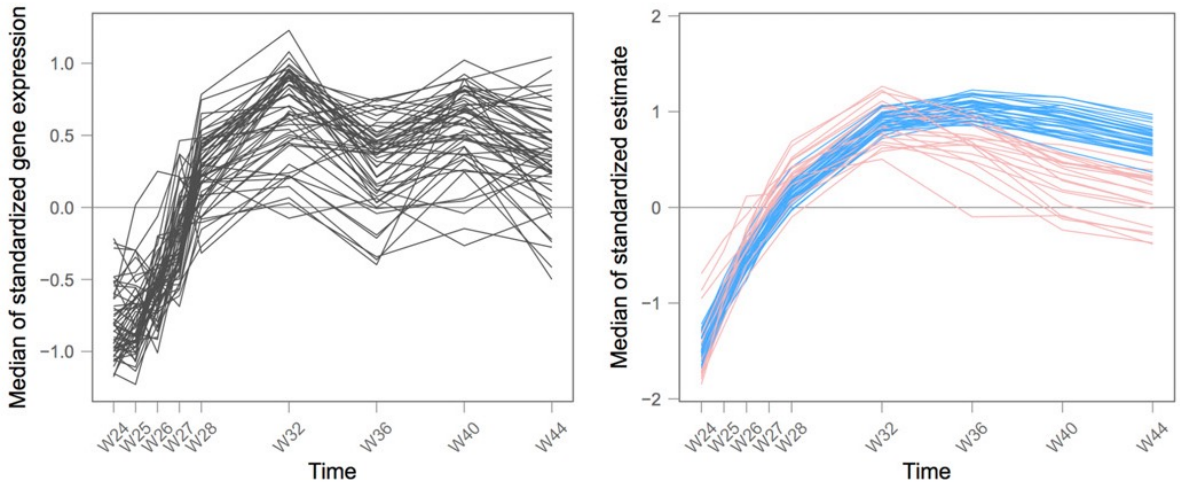
Application to DALIA-1



M1.2: Interferon



M3.4: Interferon

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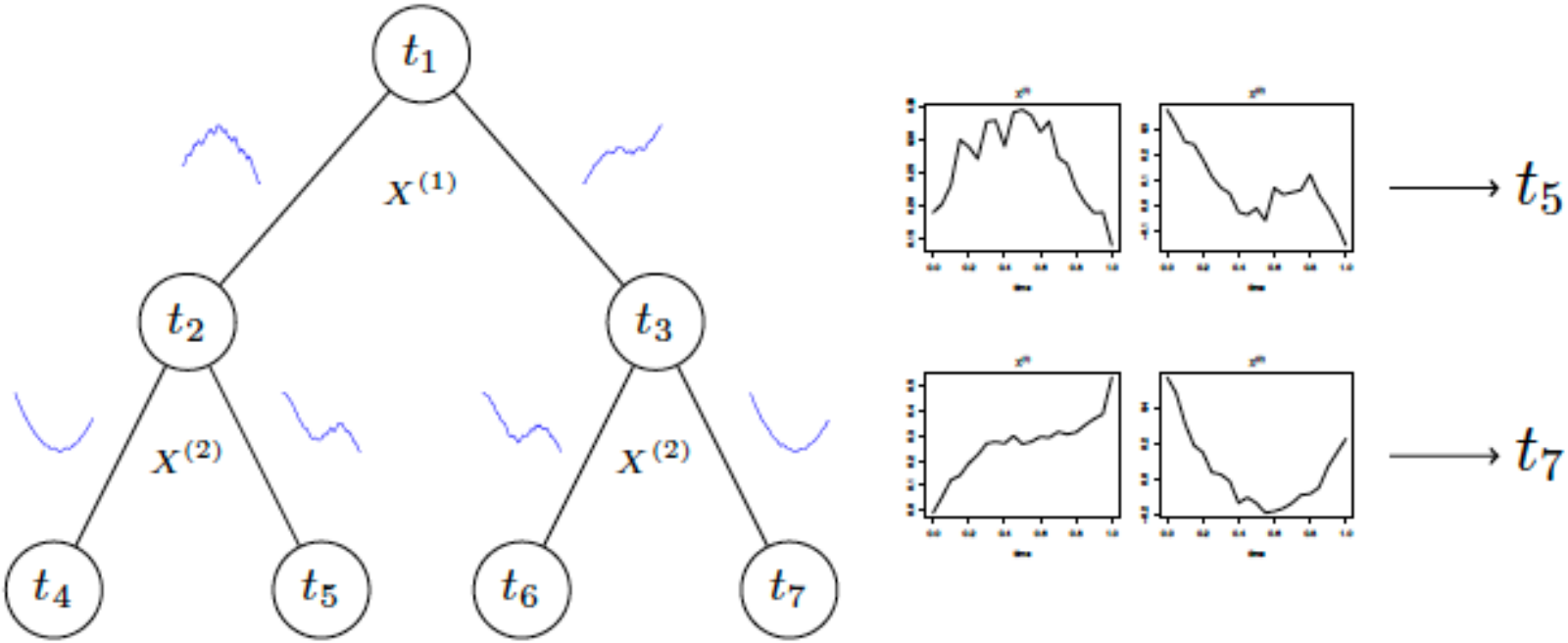
Frechet random forest

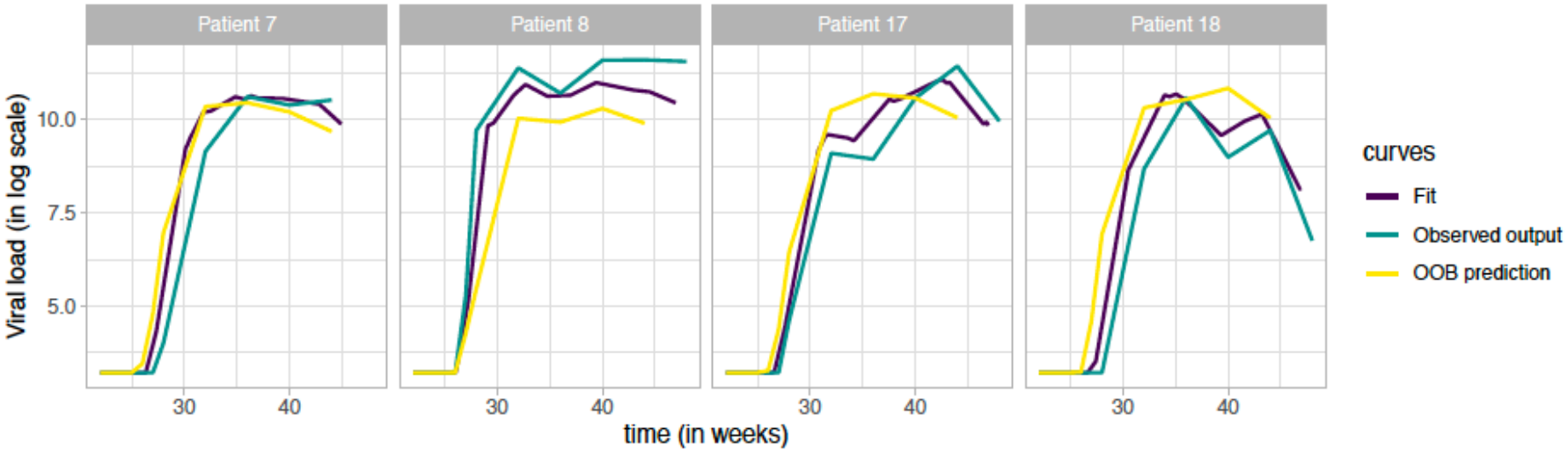
- We use a shape-based distance between curves: the Fréchet distance.
- The split function is the 2-means algorithm adapted to curves (Genolini et.al. 2016).

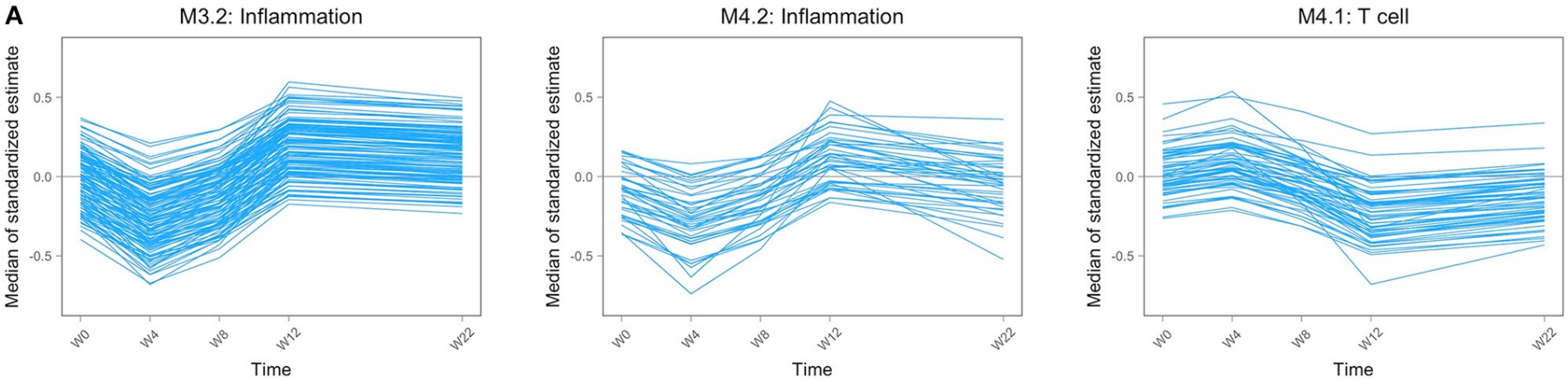


Capitaine et al. https://arxiv.org/abs/1906.01741

Frechforest

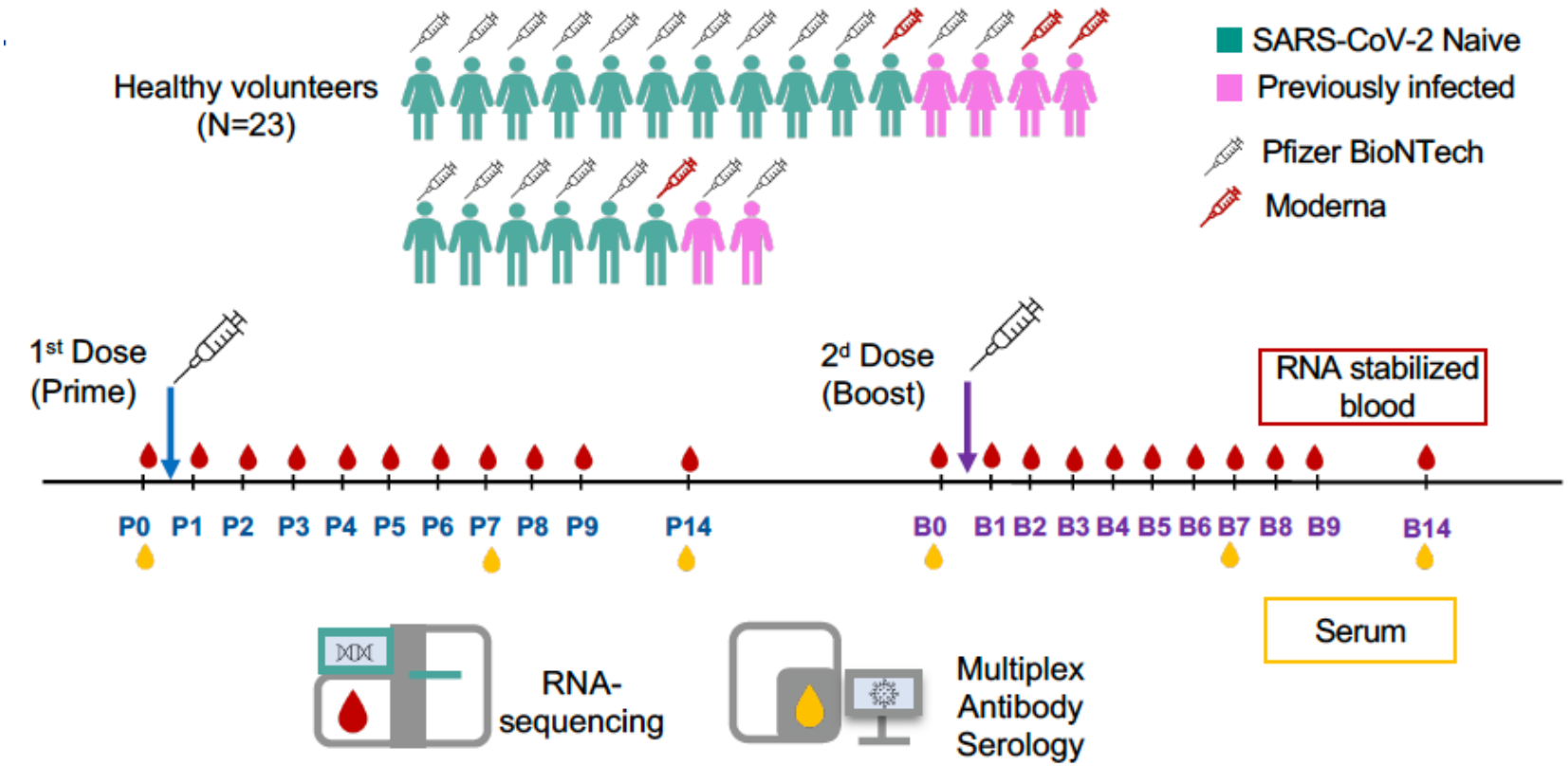
Frechet random forest





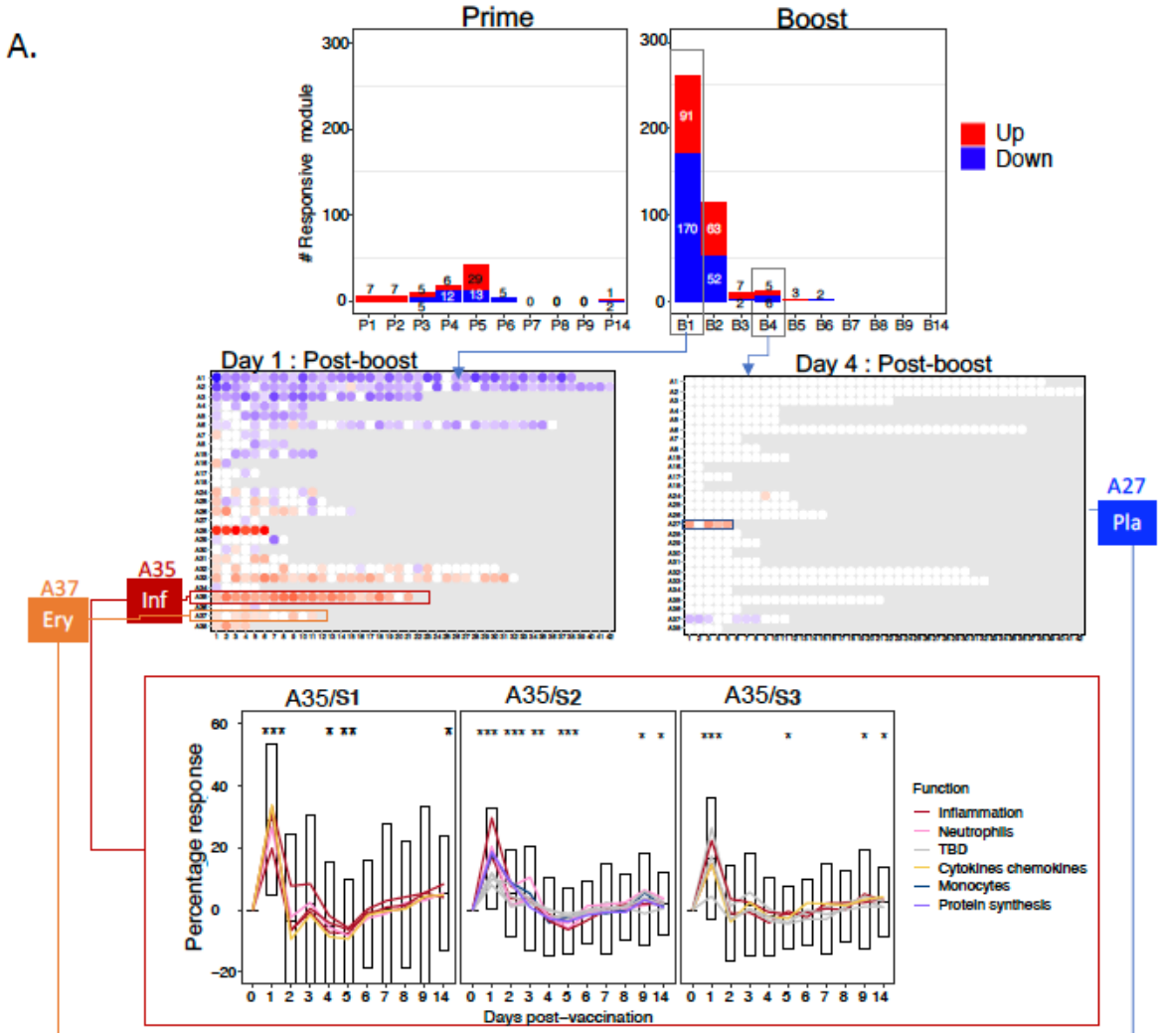
Capitaine et al. https://arxiv.org/abs/1906.01741

Application for COVID19 vaccine



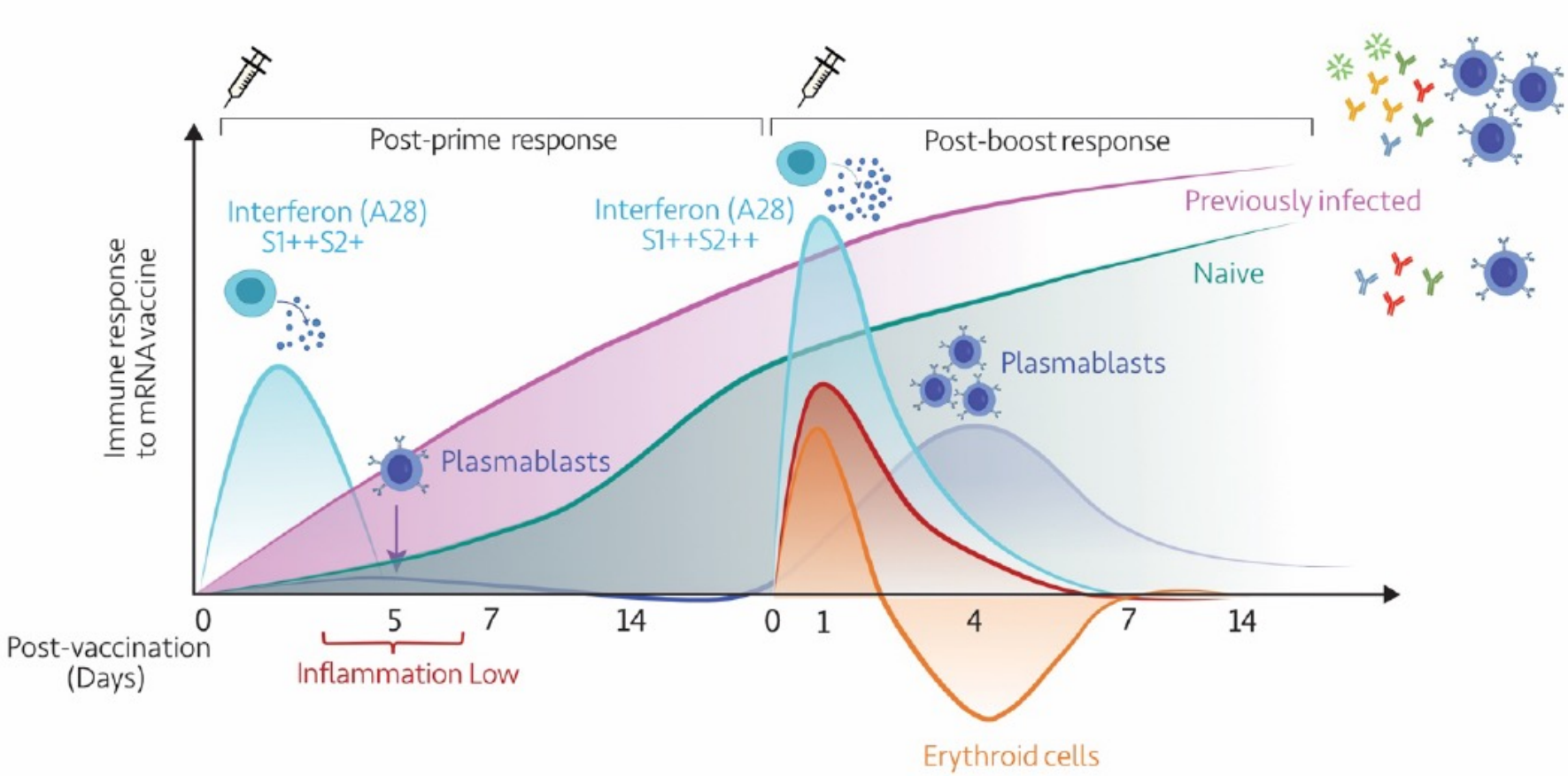
Chaussabel et al. https://www.biorxiv.org/content/10.1101/2021.12.12.472257v2

Application for COVID19 vaccine



Chaussabel et al. https://www.biorxiv.org/content/10.1101/2021.12.12.472257v2

Application for COVID19 vaccine



Chaussabel et al. https://www.biorxiv.org/content/10.1101/2021.12.12.472257v2

Acknowledgments

SISTM team and other collaborators

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The sparse Partial Least Squares method

Number of predictors (genes) > number of patients:

PLS + LASSO

Regression method

- Independent linear combinations of predictors, ie **genes**
- Independent linear combinations of explaining variables, ie **immunological measures**
- Components **maximize their covariance**

Penalization method

- Select only a few predictors, i.e. **genes**
- **Sparse**: all non selected predictor Coefficients are estimated **as exactly 0**

*Each **sPLS** component is **sparse:** only a few variables contributes to each components*

Refs: Esposito Vinzi *et al.* (2010), *Handbook of Partial Least Squares* ;
Tibshirani (1996), Regression shrinkage and selection via the lasso. *JRSS-B* ;
Lê Cao,K.-A. *et al.* (2008), A sparse PLS for variable selection when integrating omics data. *Stat. App. In Gen. & Mol. Biol.*

- Aims:
  1. Symmetric situation. Analysis the associations between two blocks of information, analysis focuses on shared information.
  2. Asymmetric situation. **X** matrix= predictors and **Y** matrix= responses variables, analysis focuses on prediction.

- Partial Least Square Family: dimension reduction approaches
  - PLS find pairs of latent vectors $\mathbf{C_X} = \mathbf{Xu}$, $\mathbf{C_Y} = \mathbf{Yv}$ with maximal covariance.

$$e.g., \quad \mathbf{C_X} = u_1 \times SNP_1 + u_2 \times SNP_2 + \ldots + u_p \times SNP_p$$

  - Symmetric situation and Asymmetric situation.
  - Successive matrix decomposition of **X** and **Y** into new latent variables.

PLS

- Output of PLS: K pairs of latent variables $(\mathbf{C_X}^k, \mathbf{C_Y}^k)$, $k = 1, \ldots, K$ with $K << min(p, q)$.
- Reduction method but no variable selection for extracting the most relevant variables from each latent variables.

sparse PLS

- sparse PLS select the relevant SNPs
- Some coefficients u_l are equal to 0
  $C^k = u_1 \times SNP_1 + \underbrace{u_2}_{=0} \times SNP_2 + \underbrace{u_3}_{=0} \times SNP_3 + \ldots + u_p \times SNP_p$
- The sPLS components are linear combinations of the selected variables

Group PLS

Aim: Select group variables taking into account the data structures

- PLS components
  $C^k = u_1 \times X_1 + u_2 \times X_2 + u_3 \times X_3 + \ldots + u_p \times X_p$
- sparse PLS components (sPLS)
  $C^k = u_1 \times X_1 + \underbrace{u_2}_{=0} \times X_2 + \underbrace{u_3}_{=0} \times X_3 + \ldots + u_p \times X_p$
- group PLS components (gPLS)

$$C^k = \overbrace{\underbrace{u_1}_{=0} X_1 + \underbrace{u_2}_{=0} X_2}^{module_1} + \overbrace{\underbrace{u_3}_{\neq 0} X_3 + \underbrace{u_4}_{\neq 0} X_1 + \underbrace{u_5}_{\neq 0} X_5}^{module_2} \ldots \overbrace{\underbrace{u_{p-1}}_{=0} X_{p-1} + \underbrace{u_p}_{=0} X_p}^{module_K}$$

$\hookrightarrow$ select group of variables; all the variables within a group are selected otherwise none of them are selected

Sparse Group PLS

Aim: combine both sparsity of groups and within each group.
Example, $\boldsymbol{X}$ matrix= genes, we might be interested in identifying particularly important genes in pathways of interest.

- sparse PLS components (sPLS)

$$C^k = u_1 \times X_1 + \underbrace{u_2}_{=0} \times X_2 + \underbrace{u_3}_{=0} \times X_3 + \ldots + u_p \times X_p$$

- group PLS components (gPLS)

$$C^k = \overbrace{\underbrace{u_1}_{=0} X_1 + \underbrace{u_2}_{=0} X_2}^{module_1} + \overbrace{\underbrace{u_3}_{\neq 0} X_3 + \underbrace{u_4}_{\neq 0} X_1 + \underbrace{u_5}_{\neq 0} X_5}^{module_2} \ldots \overbrace{\underbrace{u_{p-1}}_{=0} X_{p-1} + \underbrace{u_p}_{=0} X_p}^{module_K}$$

- sparse group PLS components (sgPLS)

$$C^k = \overbrace{\underbrace{u_1}_{=0} X_1 + \underbrace{u_2}_{=0} X_2}^{module_1} + \overbrace{\underbrace{u_3}_{\neq 0} X_3 + \underbrace{u_4}_{=0} X_4 + \underbrace{u_5}_{=0} X_5}^{module_2} \ldots \overbrace{\underbrace{u_{p-1}}_{=0} X_{p-1} + \underbrace{u_p}_{=0} X_p}^{module_K}$$

Optimisation problem

- PLS

$$\min_{||\tilde{\boldsymbol{u}}||_2=1,\tilde{\boldsymbol{v}}} ||\boldsymbol{X}^{\mathrm{T}}\boldsymbol{Z} - \tilde{\boldsymbol{u}}\tilde{\boldsymbol{v}}^{\mathrm{T}}||_F^2 \qquad (\text{respectively}, \min_{\tilde{\boldsymbol{u}},||\tilde{\boldsymbol{v}}||_2=1} ||\boldsymbol{X}^{\mathrm{T}}\boldsymbol{Z} - \tilde{\boldsymbol{u}}\tilde{\boldsymbol{v}}^{\mathrm{T}}||_F^2)$$

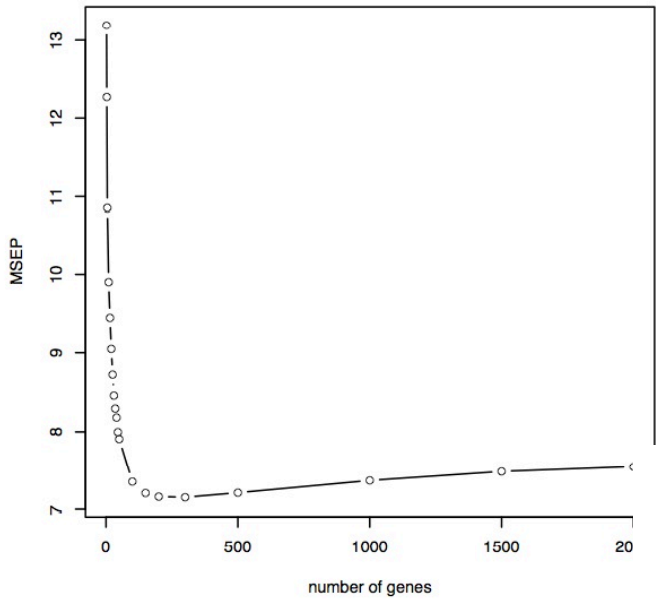
- sPLS

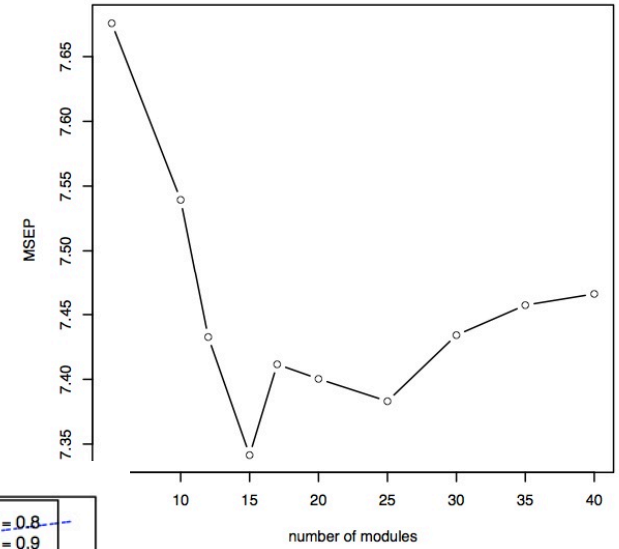
$$\min_{\boldsymbol{u}_h,\boldsymbol{v}_h} ||\boldsymbol{M}_h - \boldsymbol{u}_h\boldsymbol{v}_h^{\mathrm{T}}||_F^2 + P_{\lambda_{1,h}}(\boldsymbol{u}_h) + P_{\lambda_{2,h}}(\boldsymbol{v}_h)$$

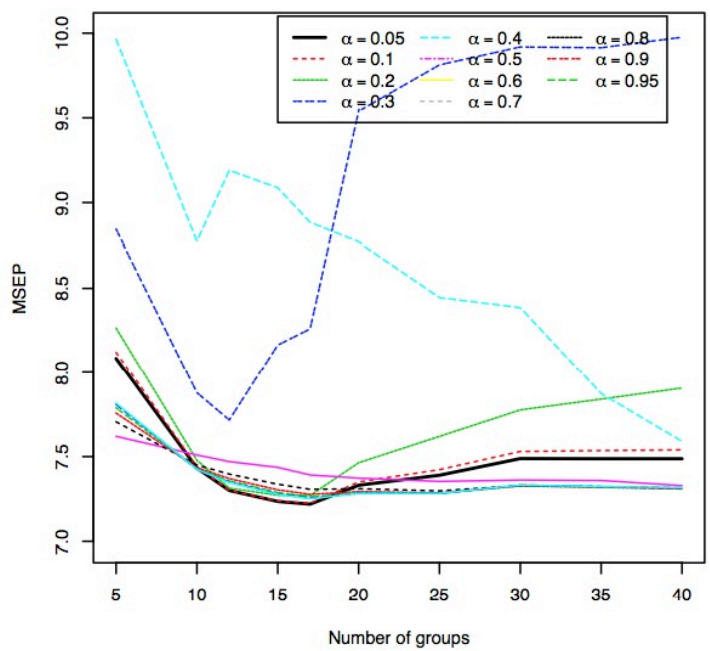
$$P_{\lambda_{1,h}}(\boldsymbol{u}_h) = \sum_{i=1}^{p} 2\lambda_1^h |u_{i,h}|$$

$$P_{\lambda_{2,h}}(\boldsymbol{v}_h) = \sum_{j=1}^{q} 2\lambda_2^h |v_{j,h}|$$

Choice of penalty by 5-fold cross validation of MSEP*







* MSEP: Mean Square Error of Prediction