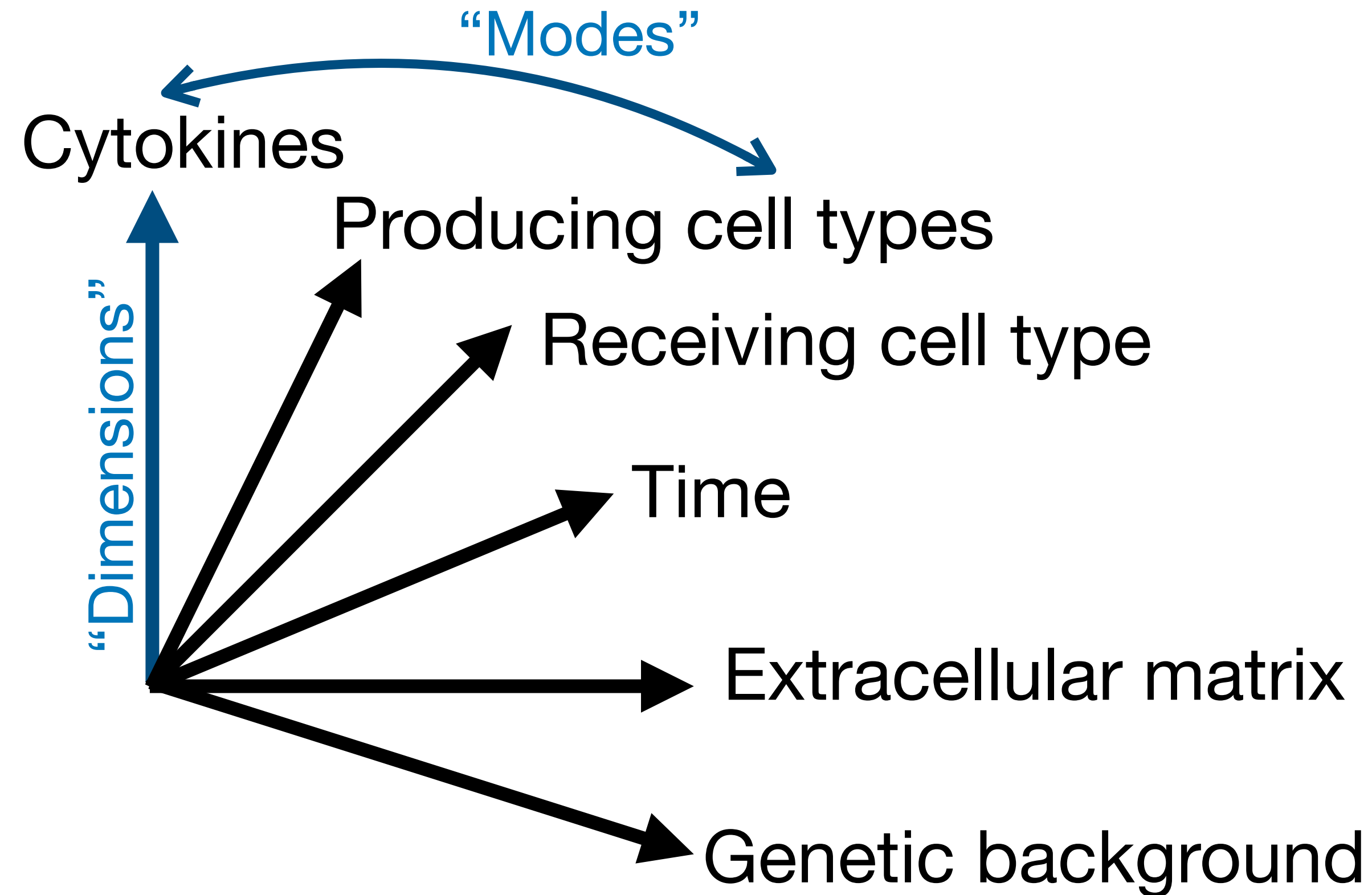


Mechanistic and data-driven dissection of cell communication through tensor methods

SIAM Mathematics of Data Science

Aaron Meyer — University of California, Los Angeles — September 27, 2022

Cell responses to their environment are highly multimodal

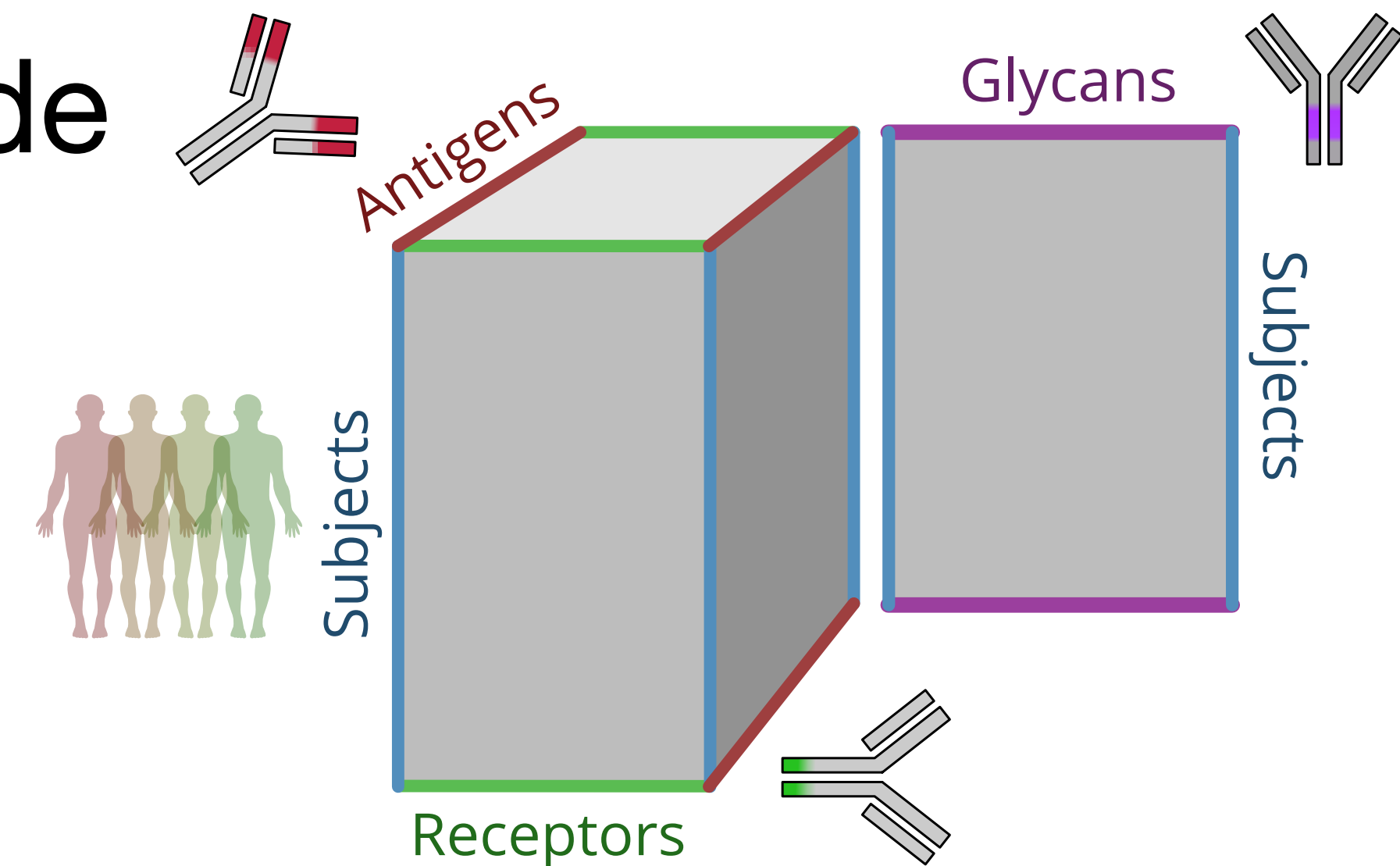


10 values for each → 1,000,000 combinations!

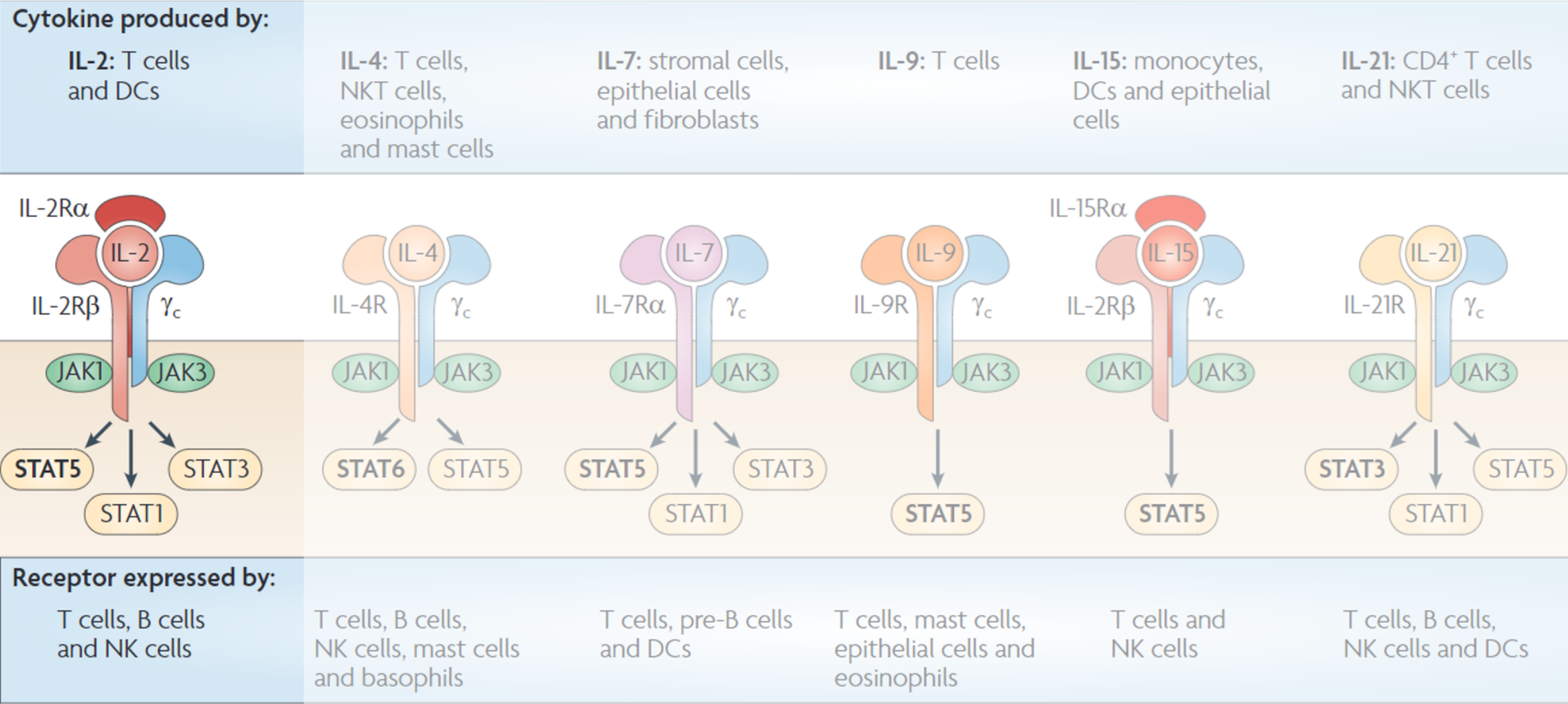
Three big, unique benefits of tensor methods

1. More extensive data reduction
2. Clear how patterns relate to each mode
3. Second property enables data integration

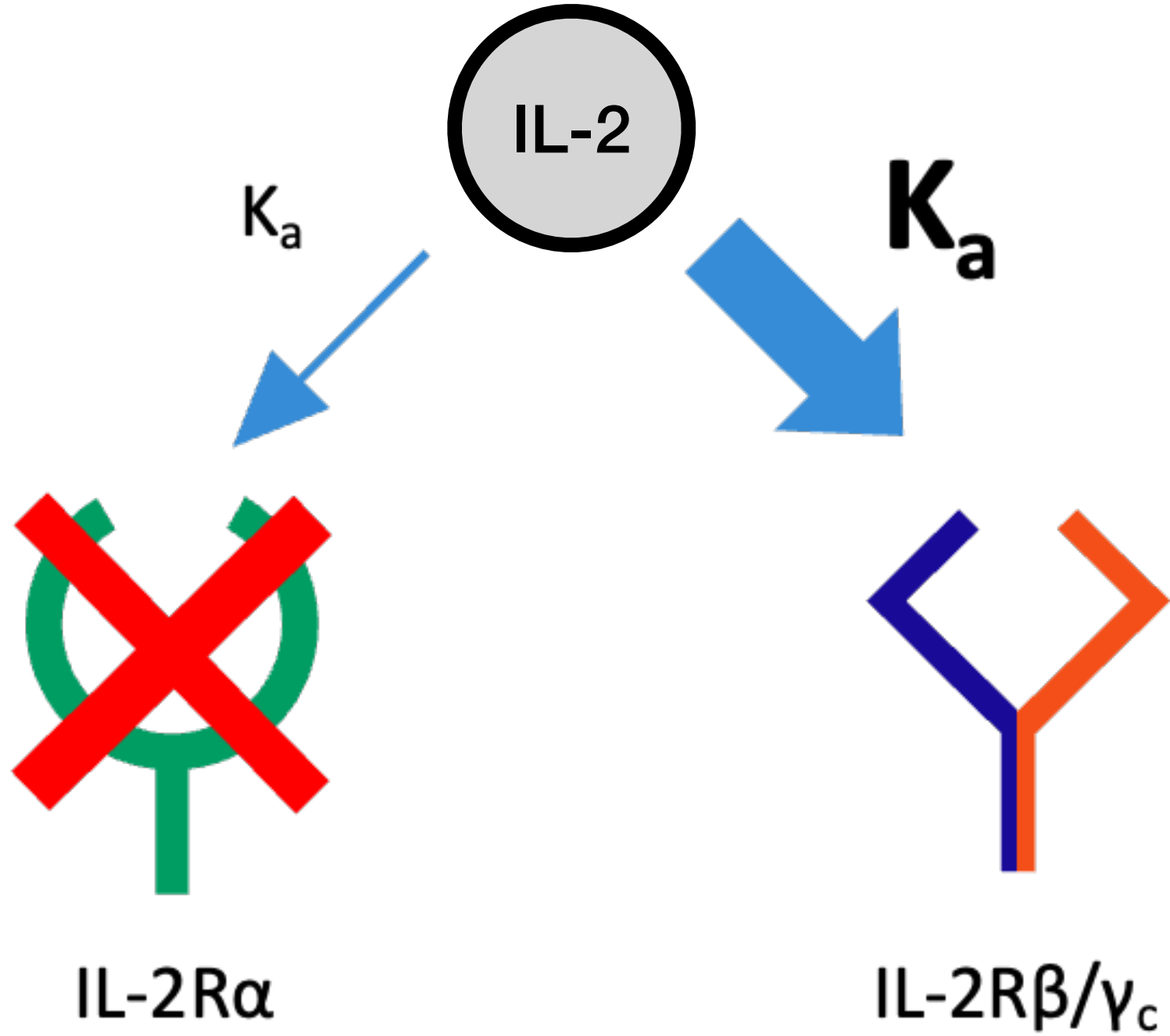
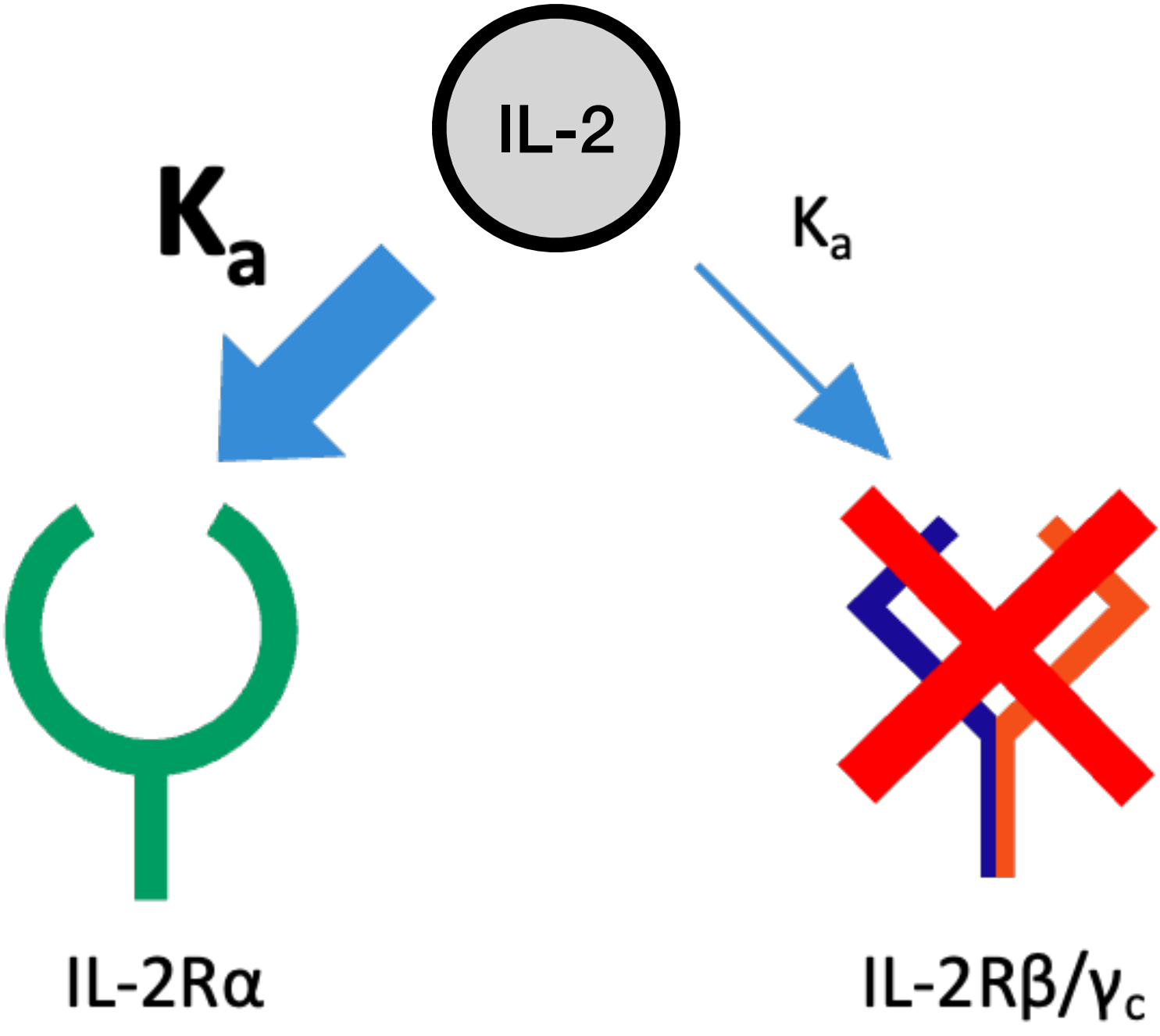
Not automatically better! Most effective when there are mode-specific effects.



Cytokines are potent immune modulators with pleiotropic effects

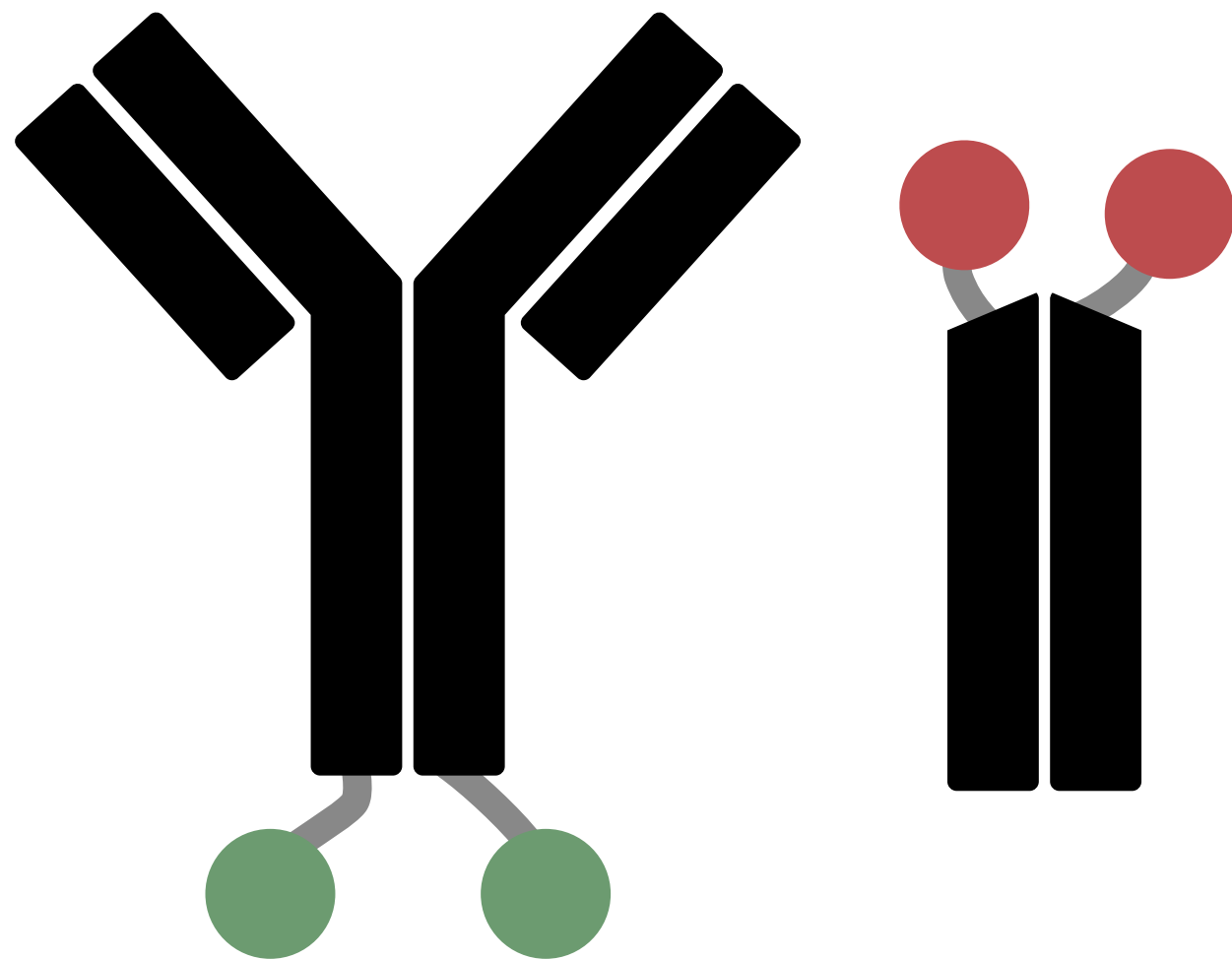


Simple Example Goal: A T_{reg} selective, Fc-fused IL-2

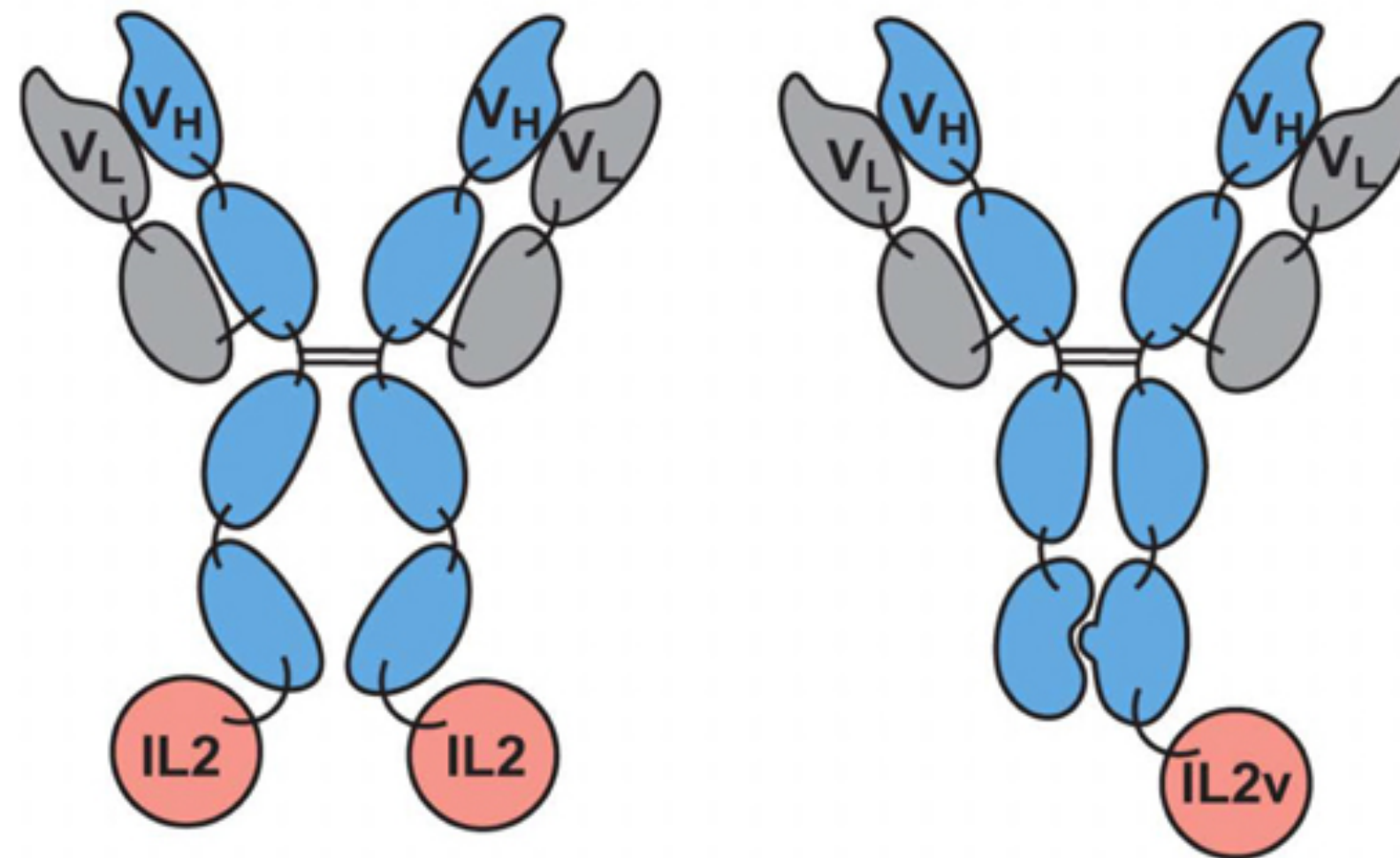
	 IL-2Rα IL-2Rβ/γ_c	 IL-2Rα IL-2Rβ/γ_c
Cell targets	Selective expansion of CD8 ⁺ , NK, T _{helpers}	Selective expansion of T _{reg} s
Intended effect	Immunostimulatory: treatment for metastatic melanoma, anti-tumor therapies, etc.	Immunosuppressive: treatment for autoimmune diseases, host vs. graft disease etc.

How can we do better? Unbiased profiling across a wide panel of Fc fusions

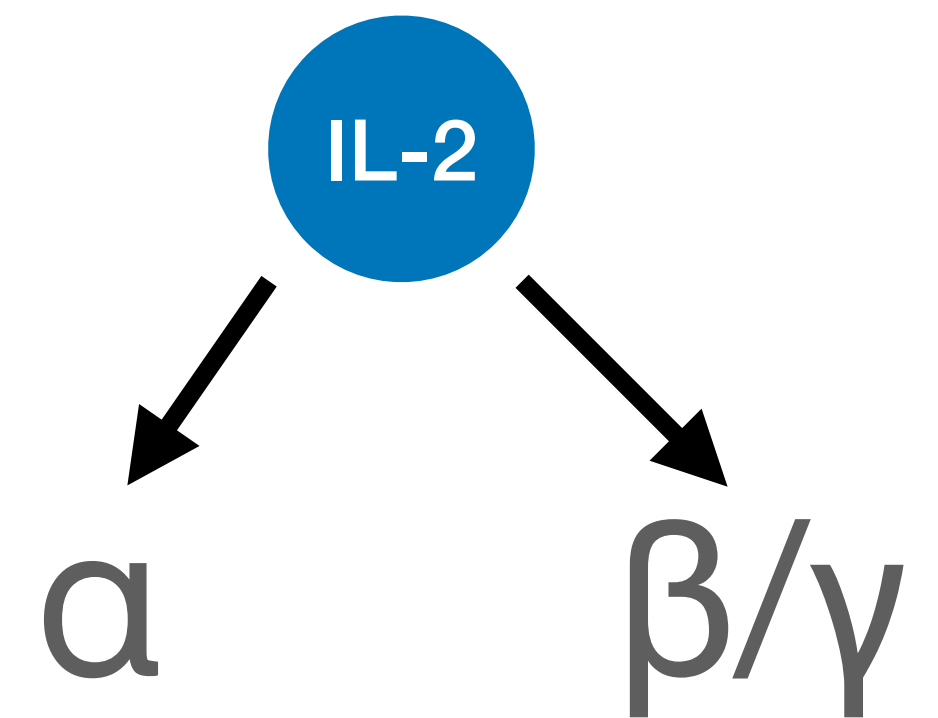
Fc fusion orientation



Valency

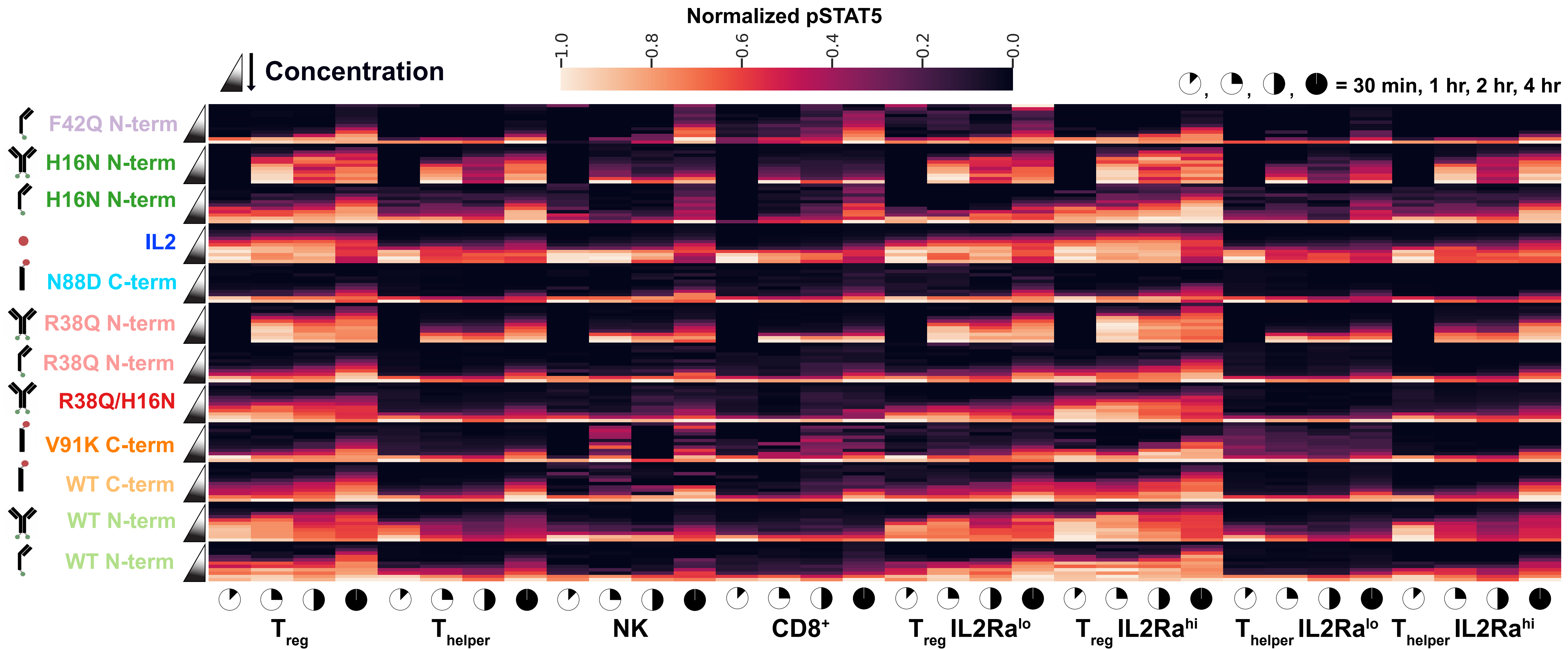


Receptor affinities



13 molecules profiled across 12 concentrations, 5 timepoints, 8 cell types

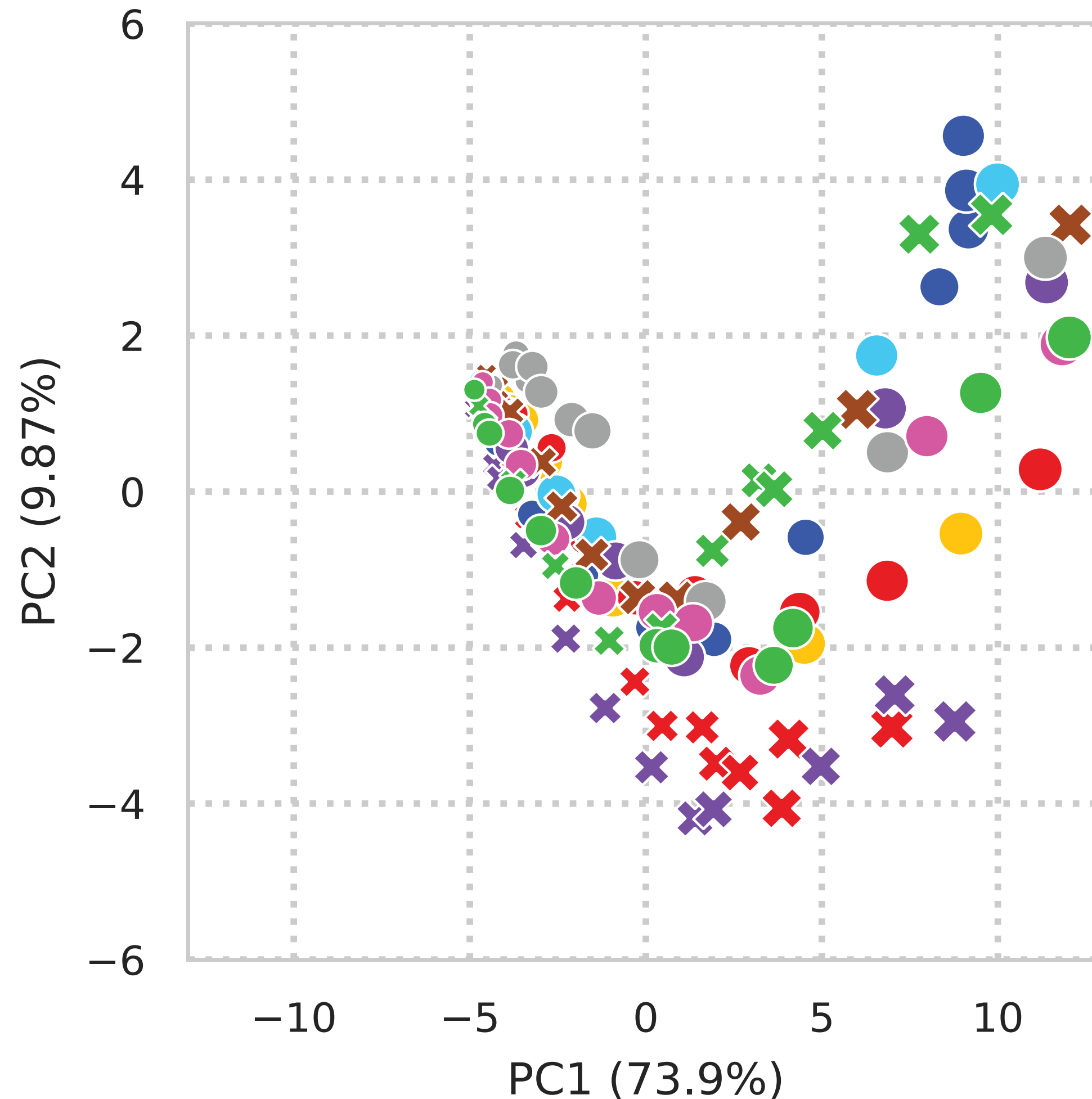
Unbiased profiling across a wide panel of Fc fusions



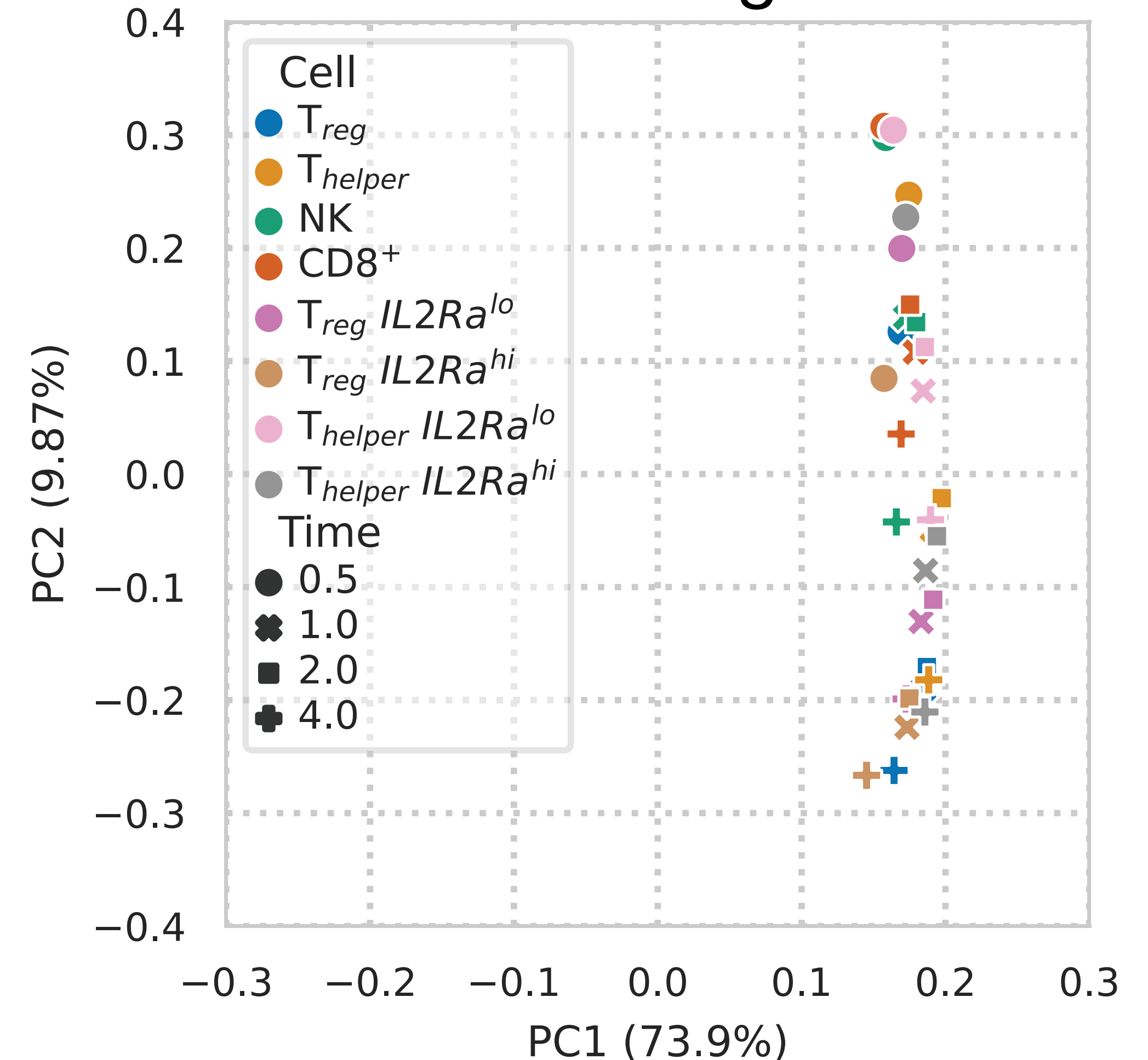
What if we use PCA to visualize the data?

It's a mess!

“Scores”



“Loadings”

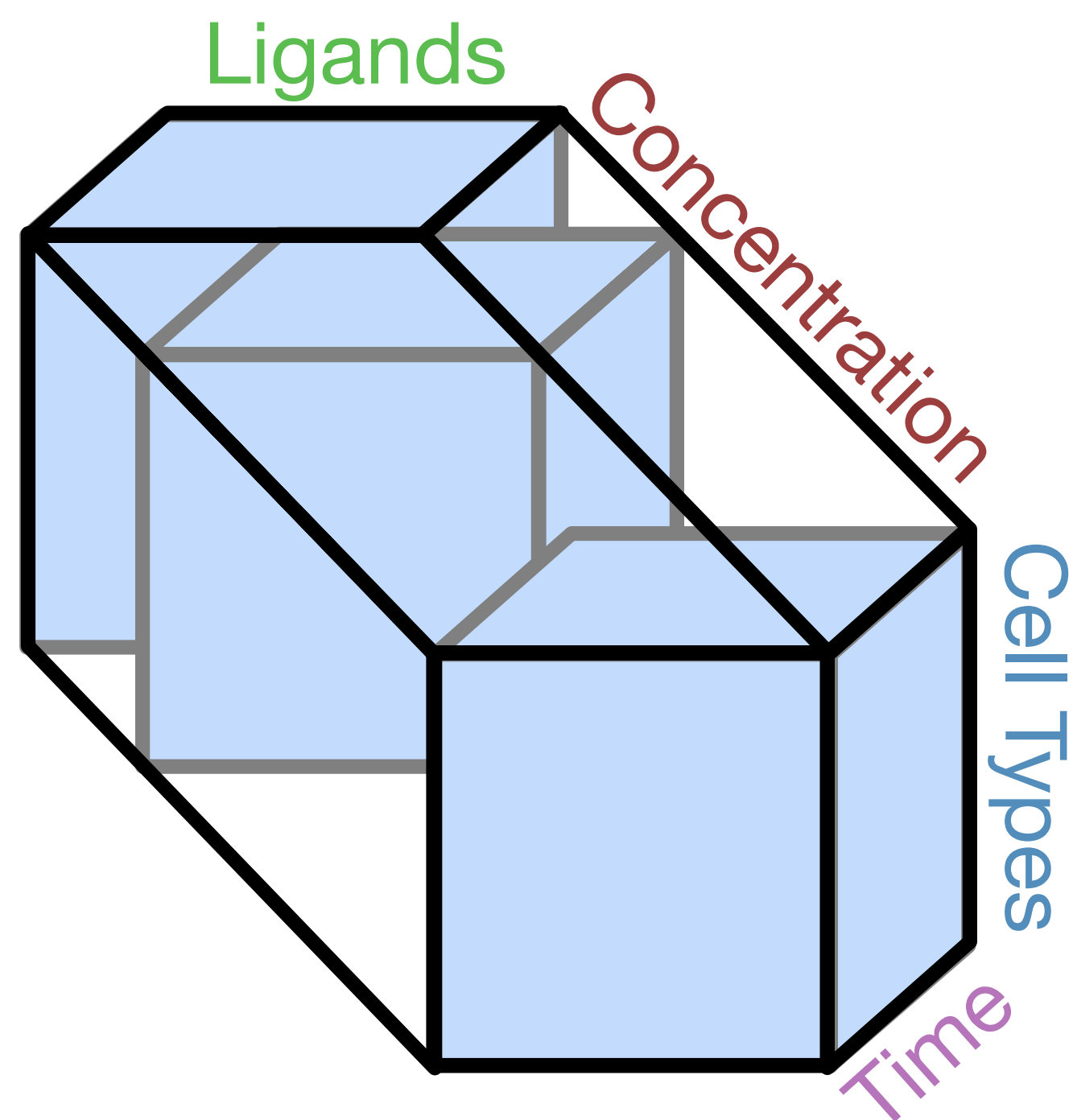


We don't study other things by flattening them!

Why do we do this to our data?

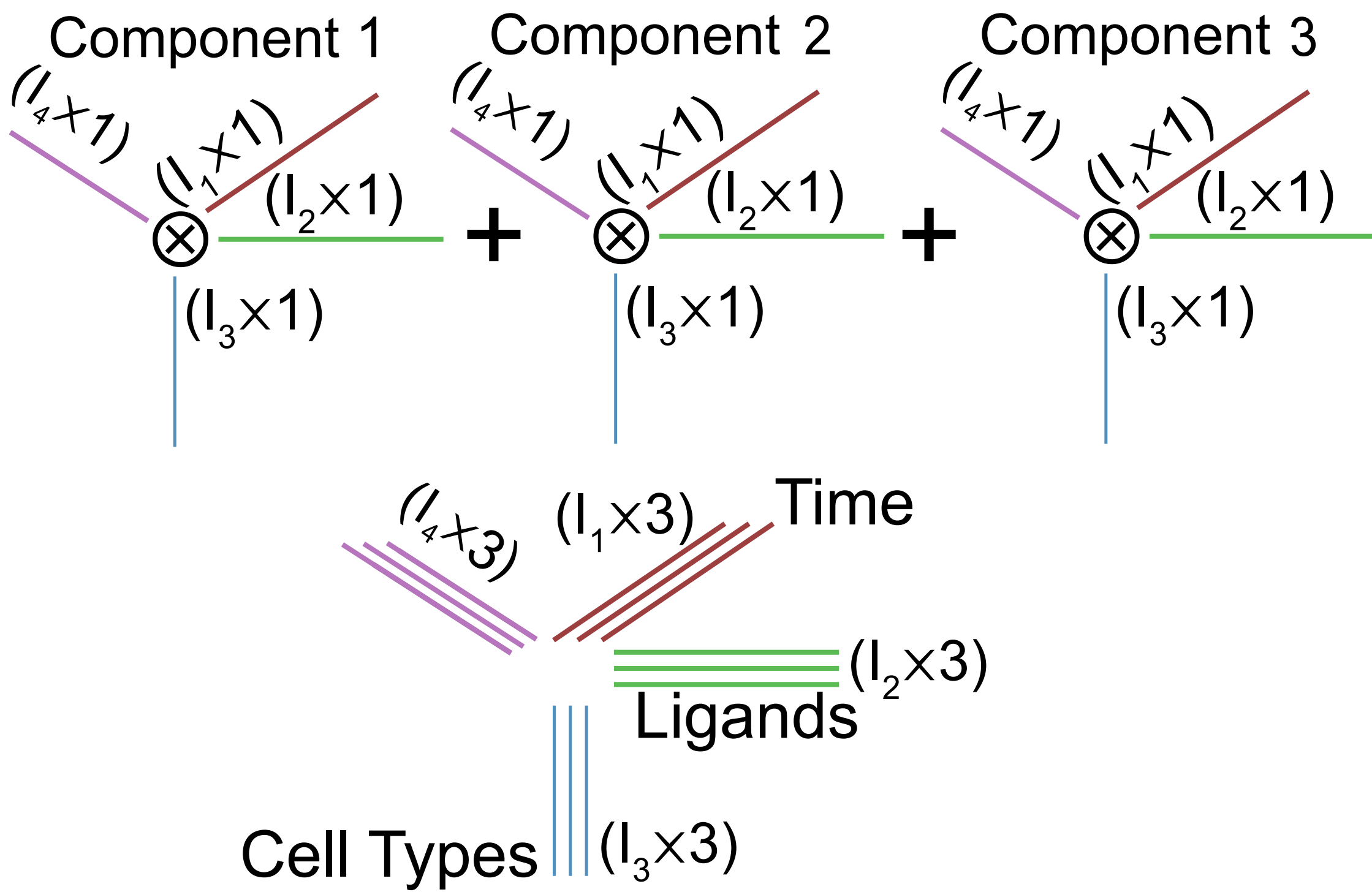


Cytokine profiling data can be efficiently arranged in tensor form



4368 measurements

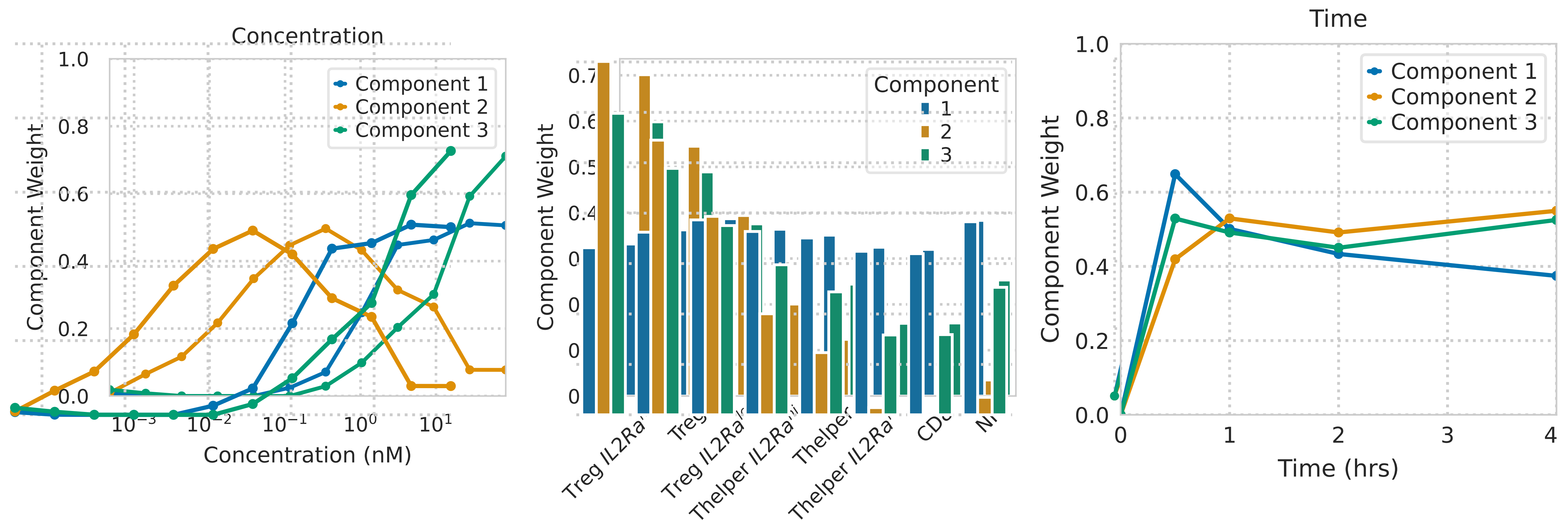
$\approx$



108 values
~90% of the variance

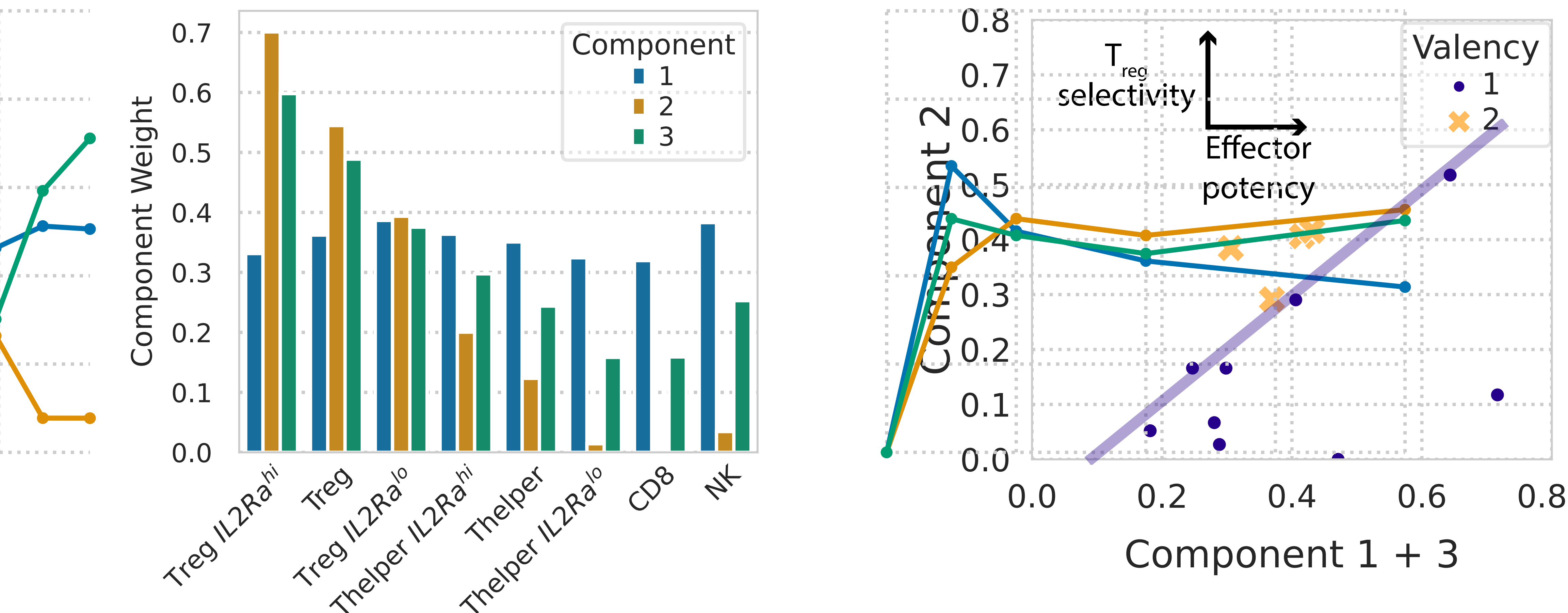
Components represent data patterns

Component 2 is uniquely T_{reg} specific with typical dynamics

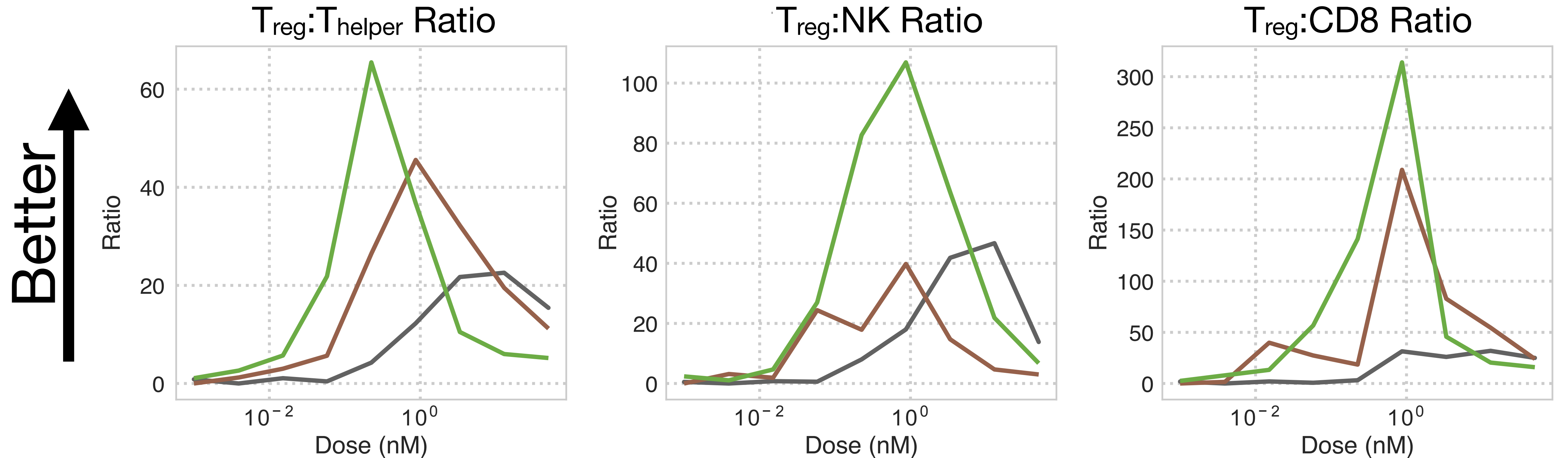
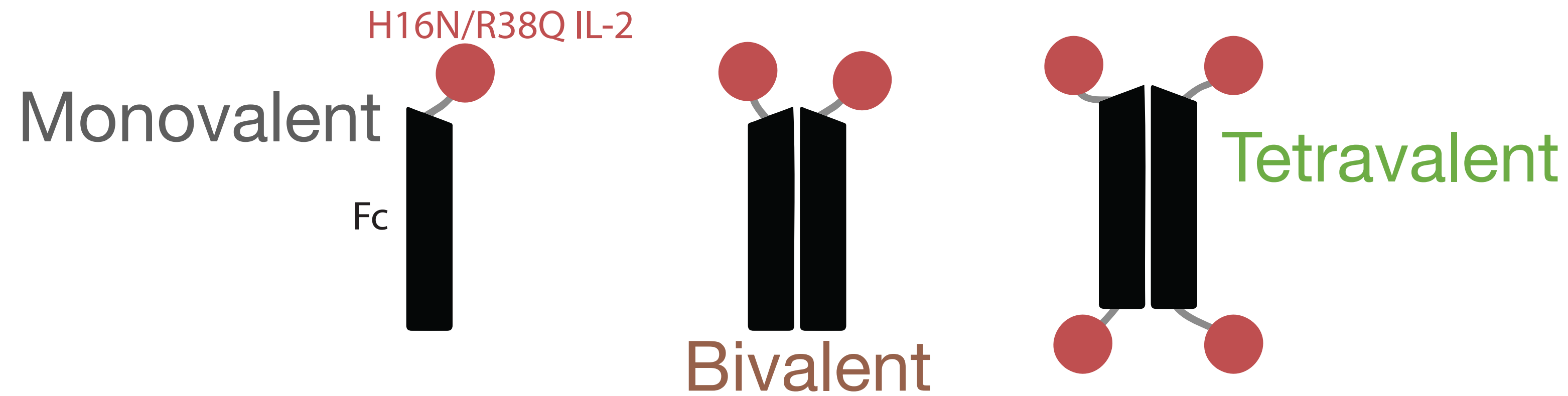


Components represent data patterns

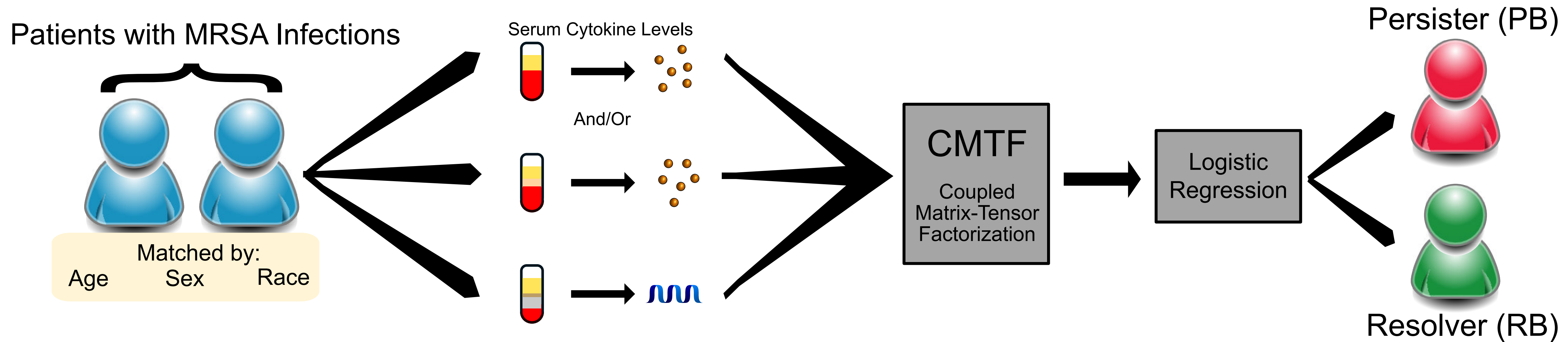
Component 2 is a T_{reg} specific pattern induced by bivalency



Tetravalent IL-2 more selectively activates T_{reg}S



Immune response measures can predict outcome of MRSA bacteria infection



Clinical cohort studies take a large team

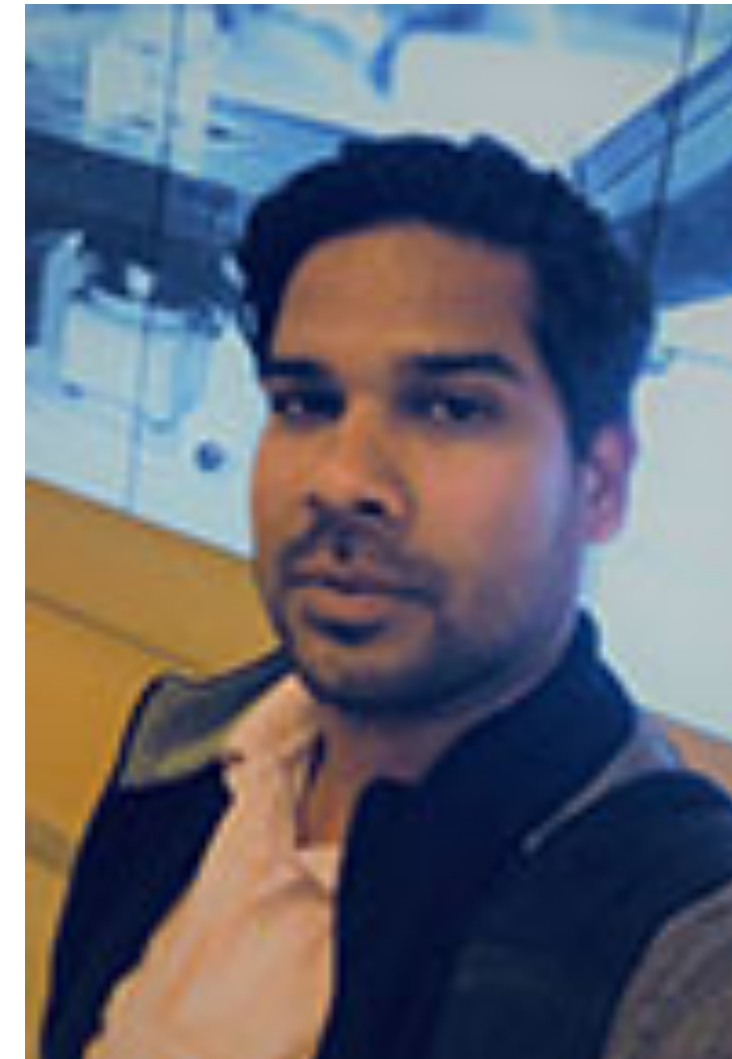
UCLA



Prof. Elaine Reed



Prof. David Gjertson



Dr. Rajesh Parmar



Dr. Richard Ahn

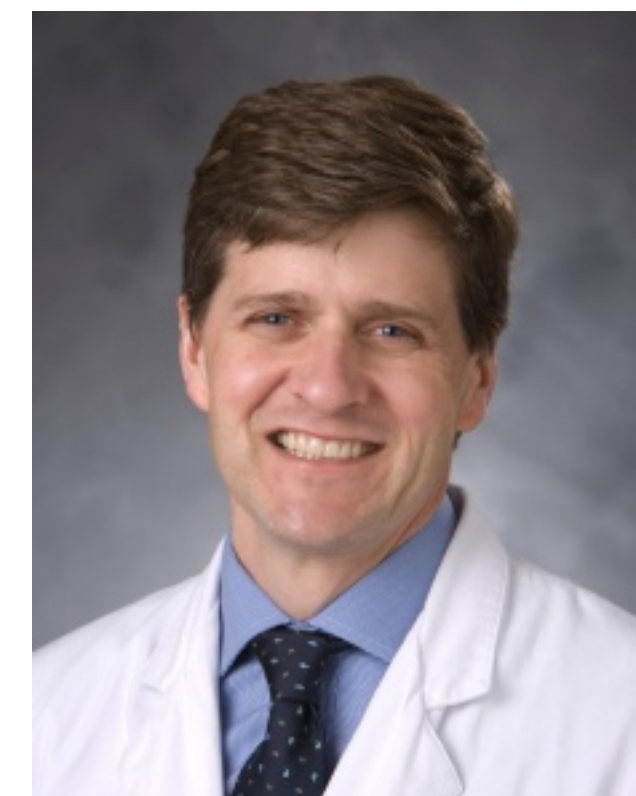


Prof. Michael Yeaman

Duke

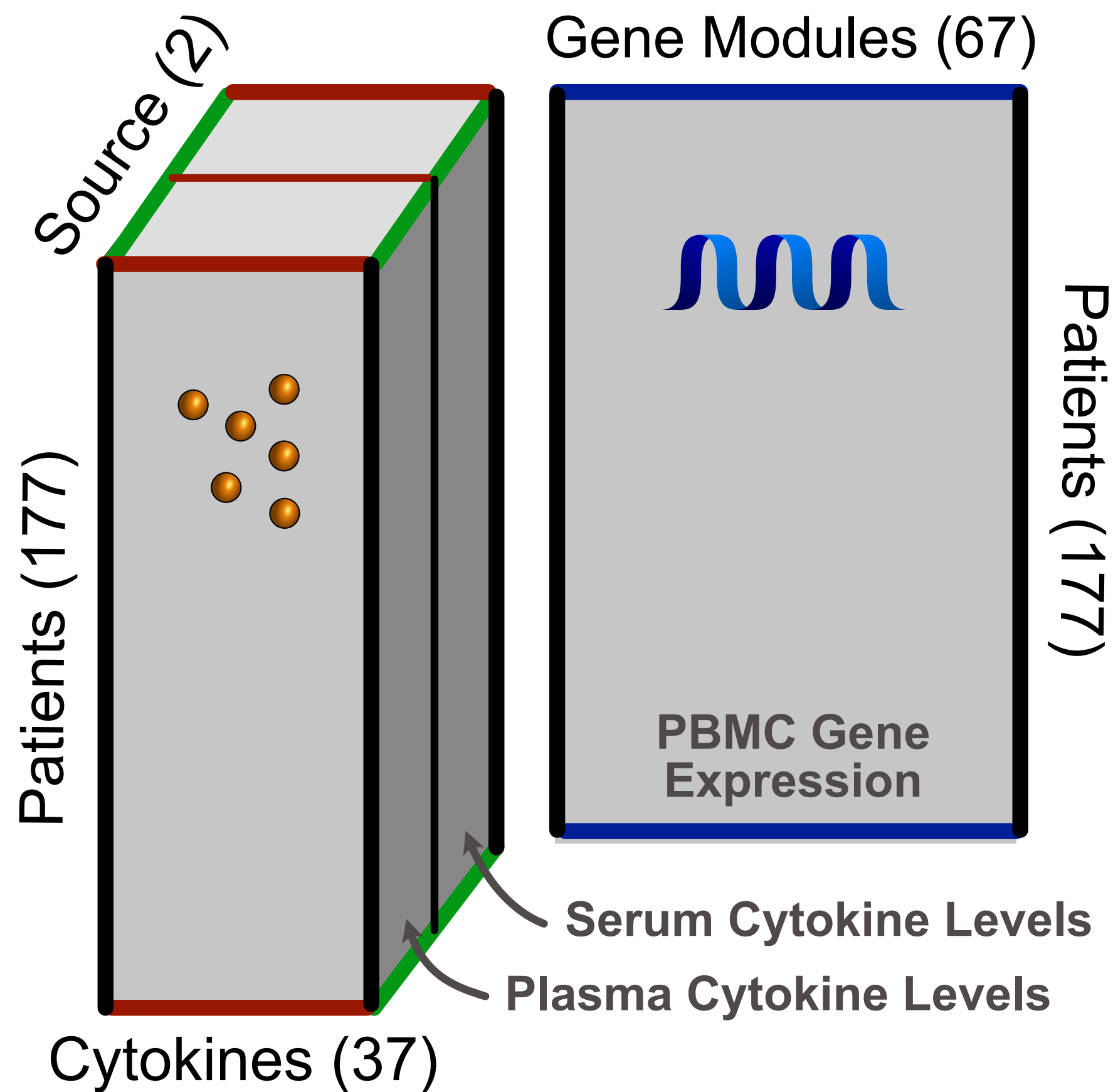


Felicia Ruffin

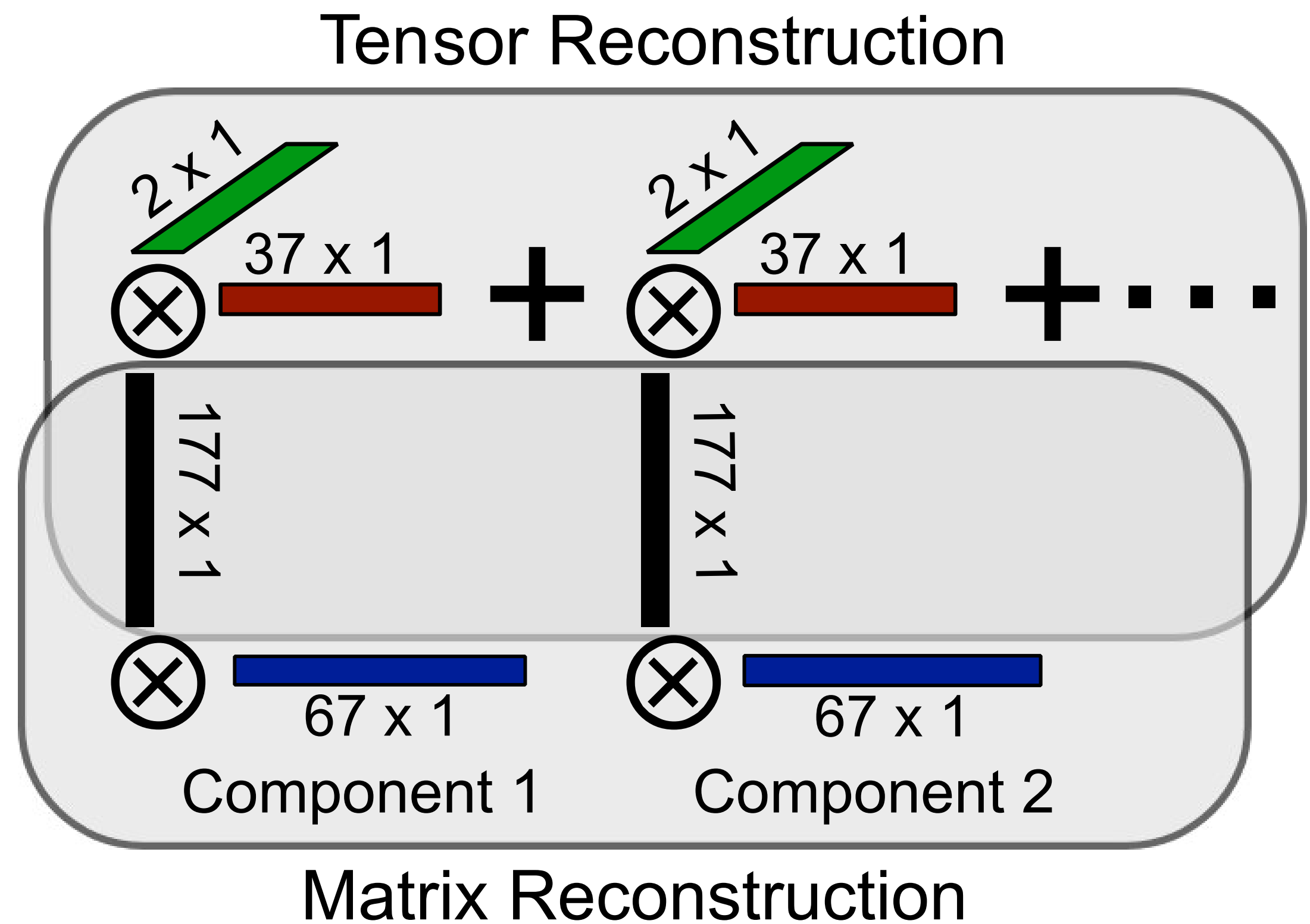


Prof. Vance Fowler

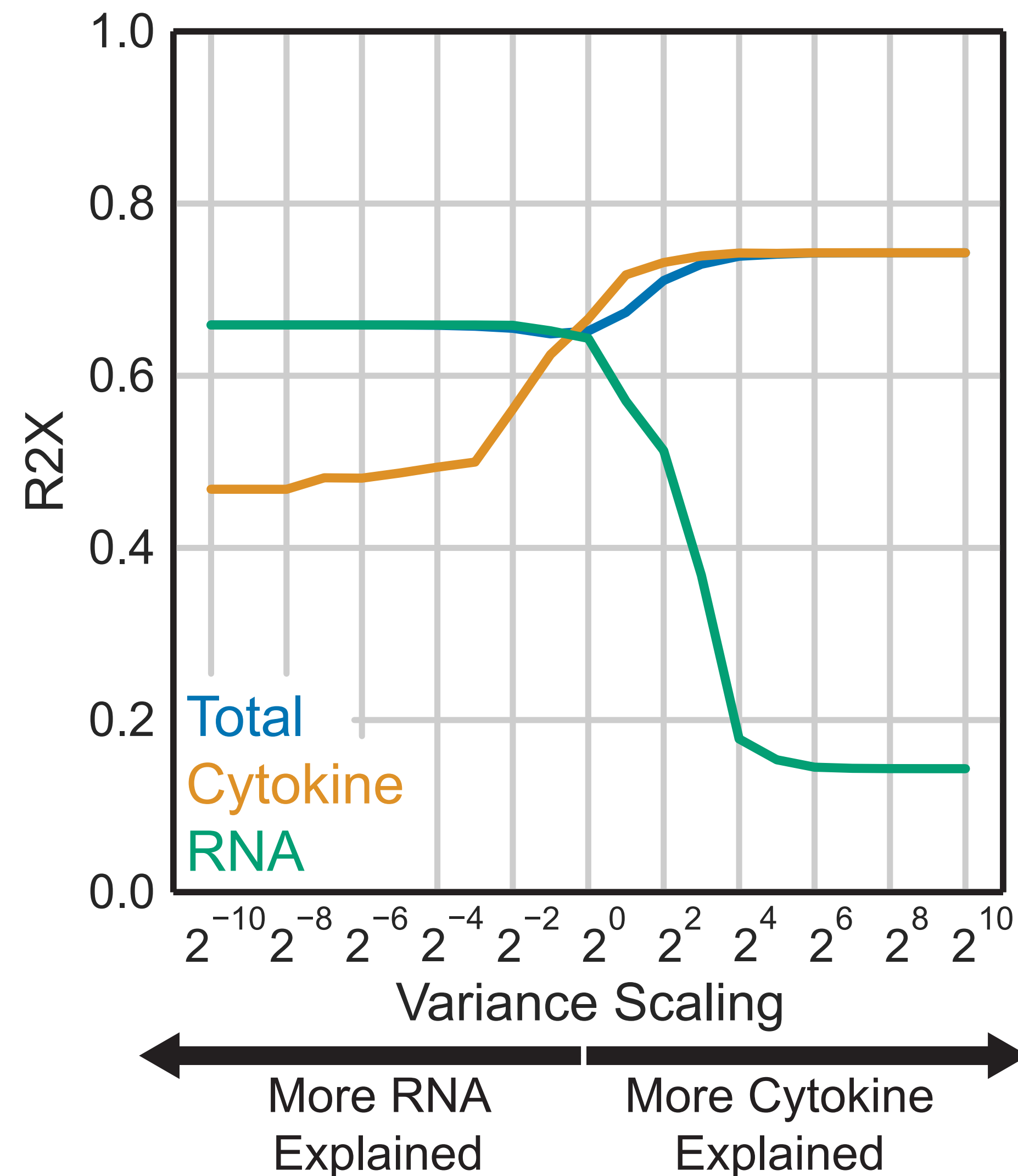
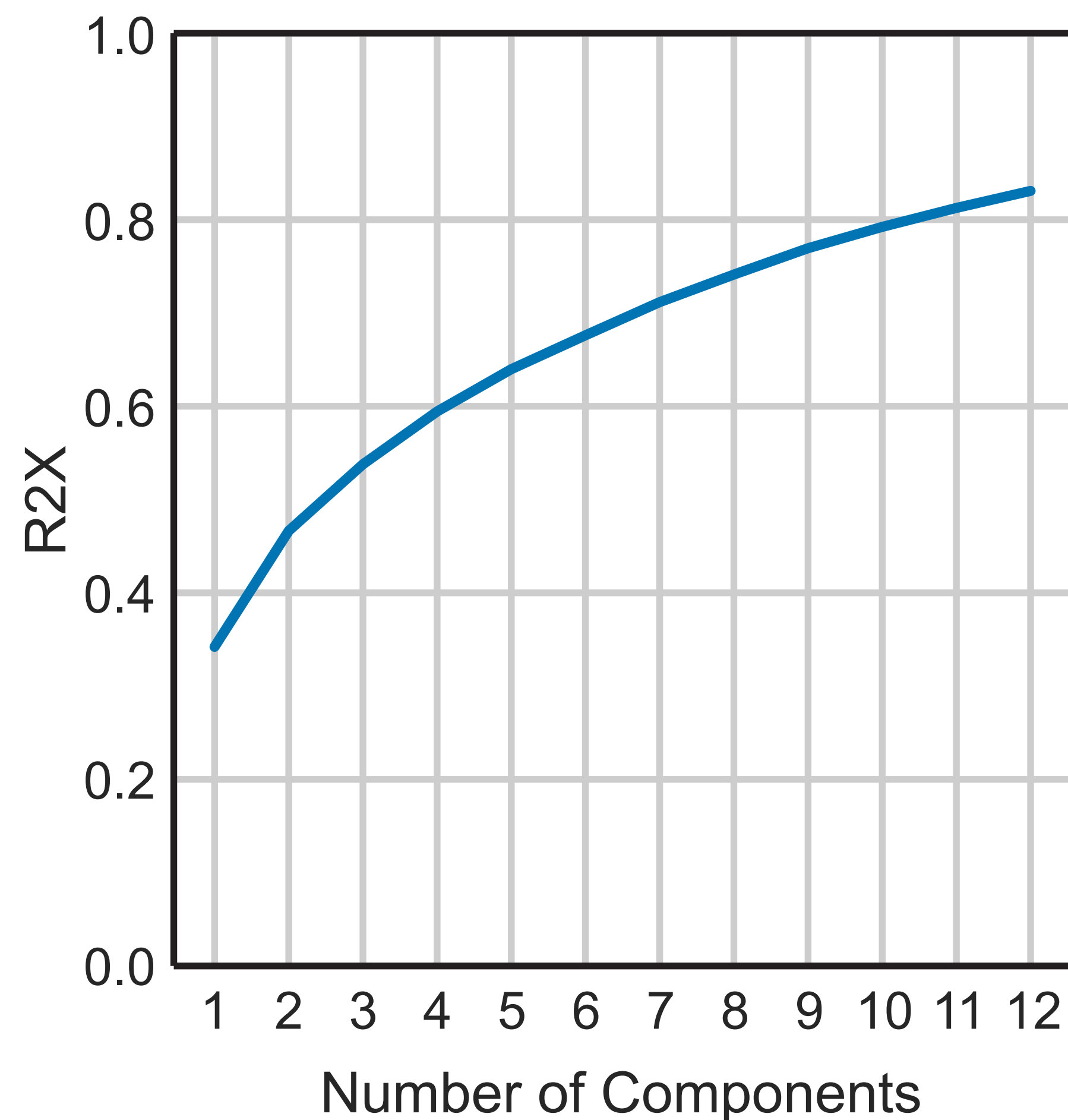
An important benefit of tensor-based decomposition is separation of mode contributions



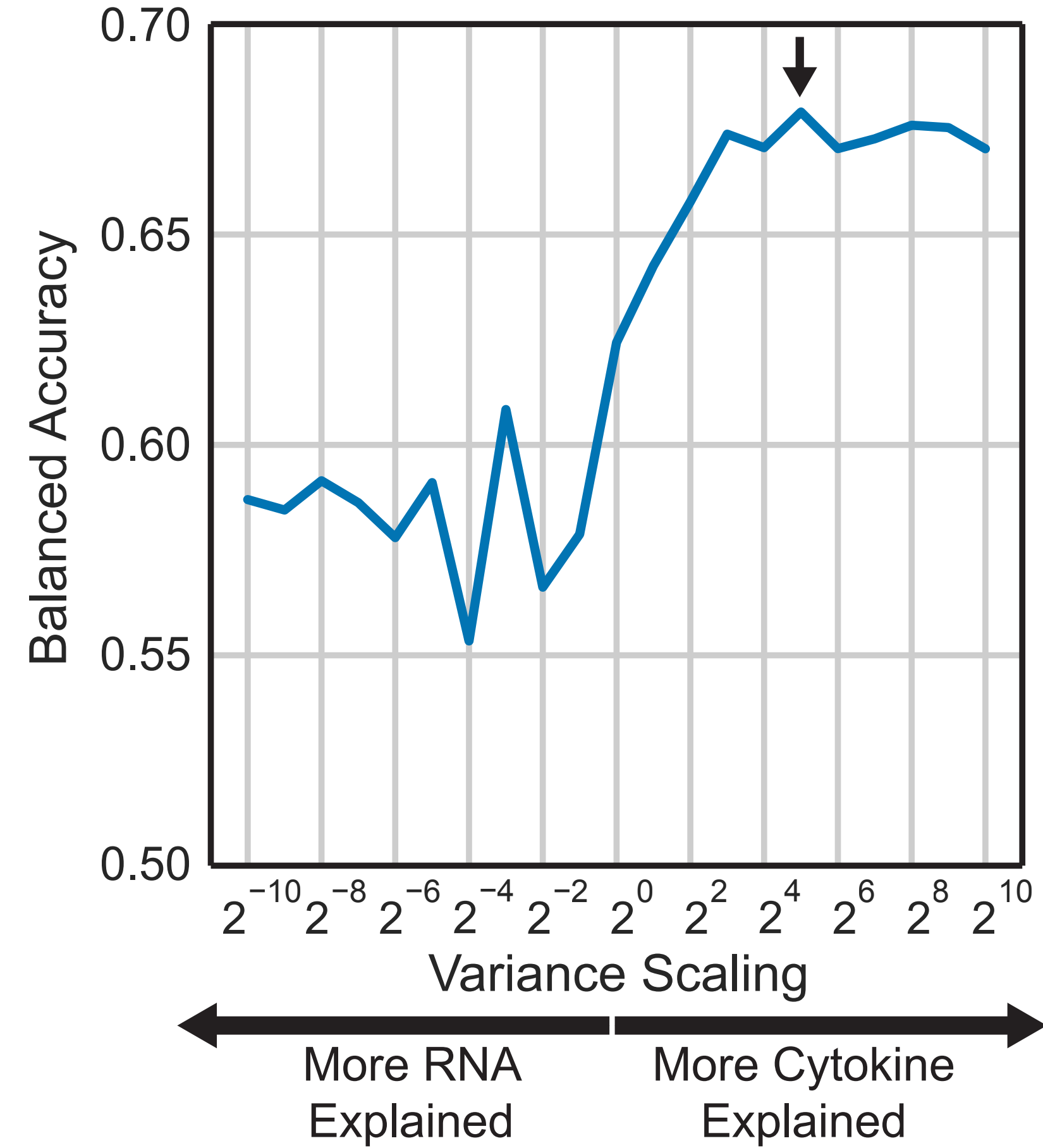
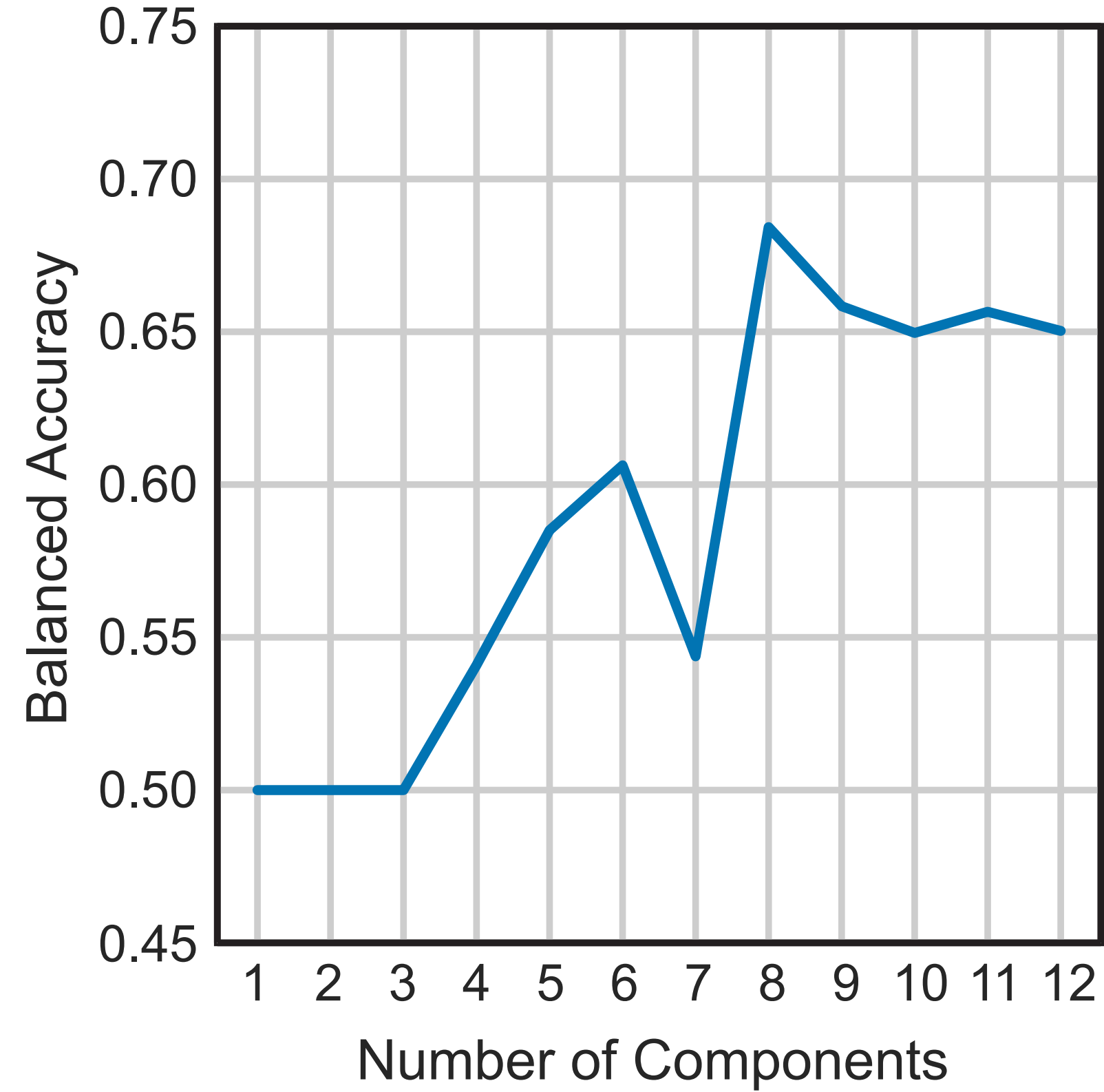
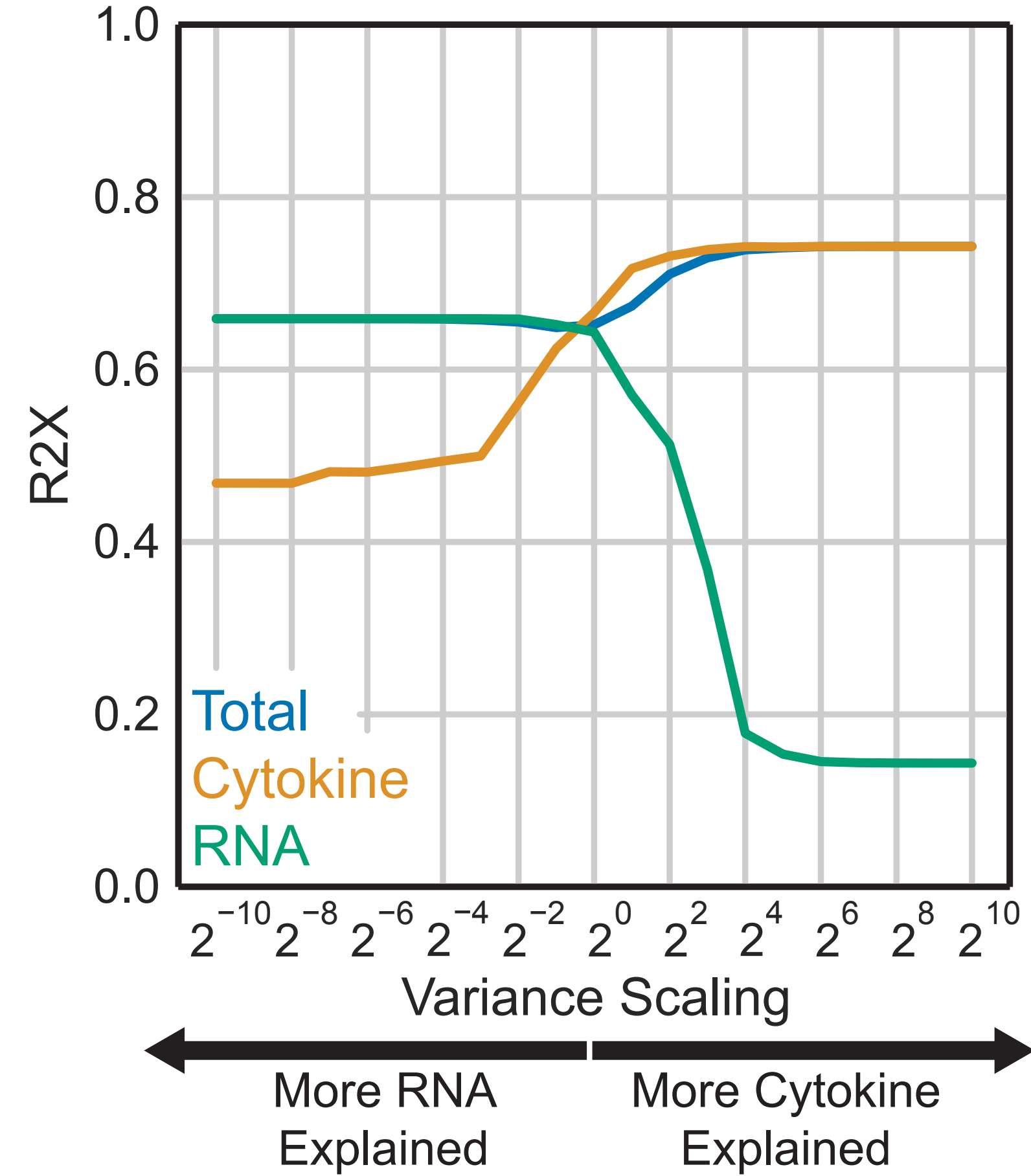
$\approx$



Factorization tuned for predicting MRSA persistence

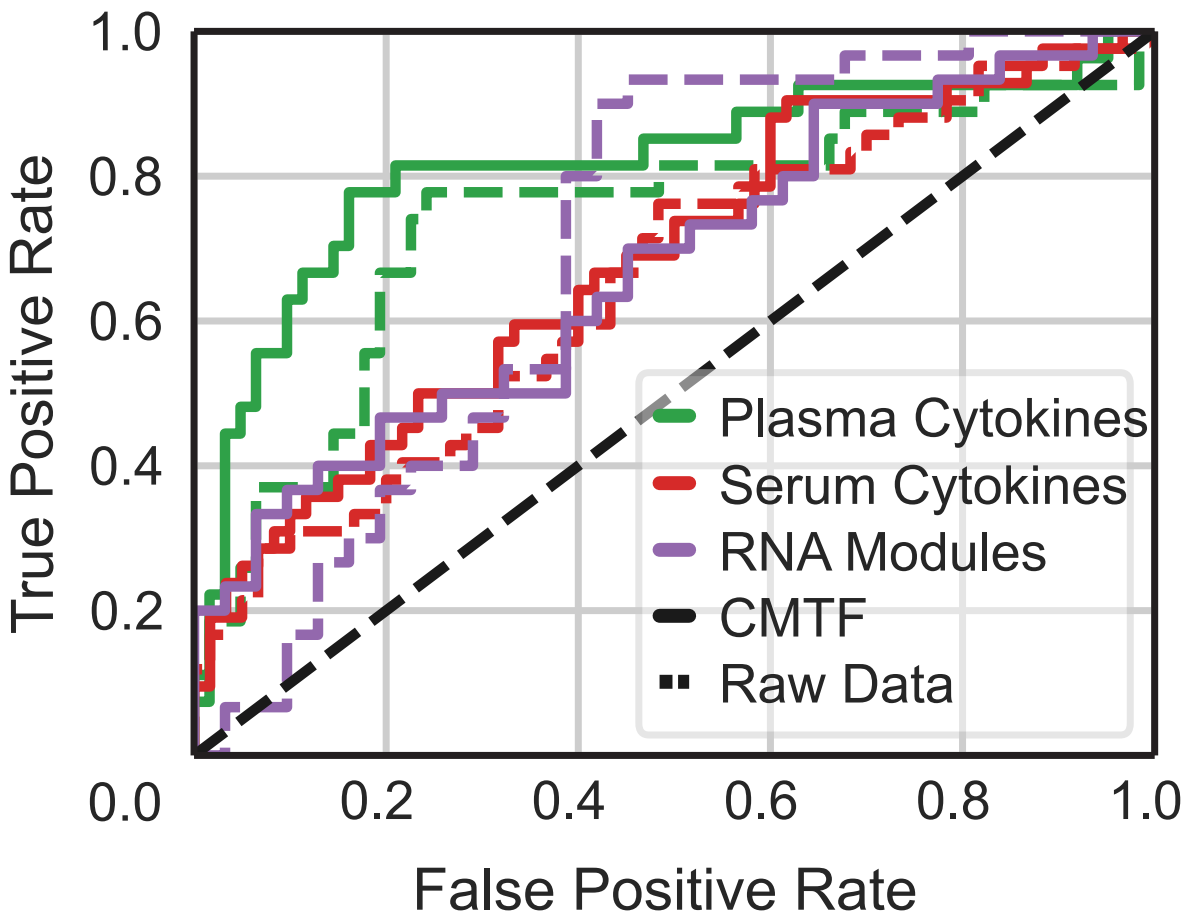
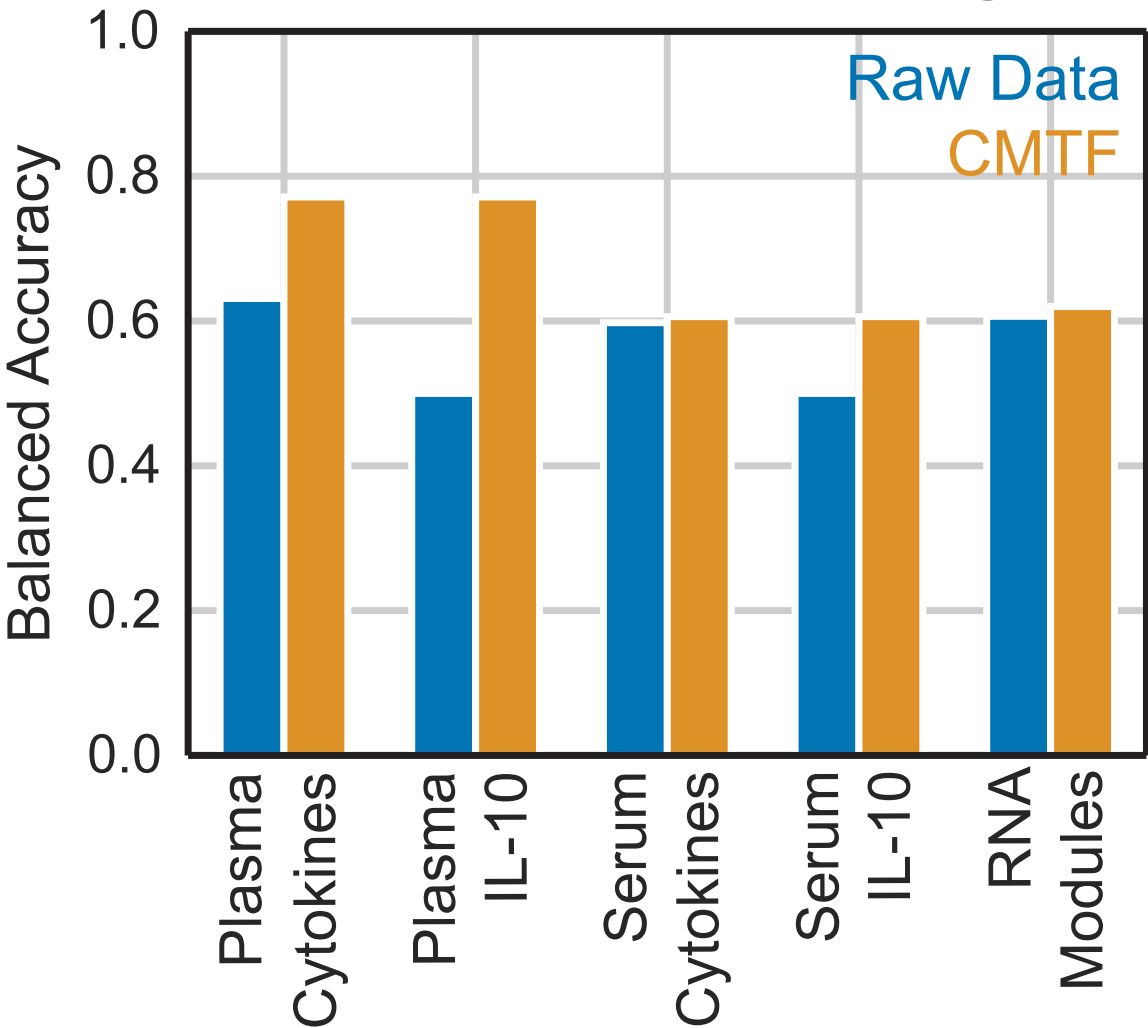


Factorization tuned for predicting MRSA persistence

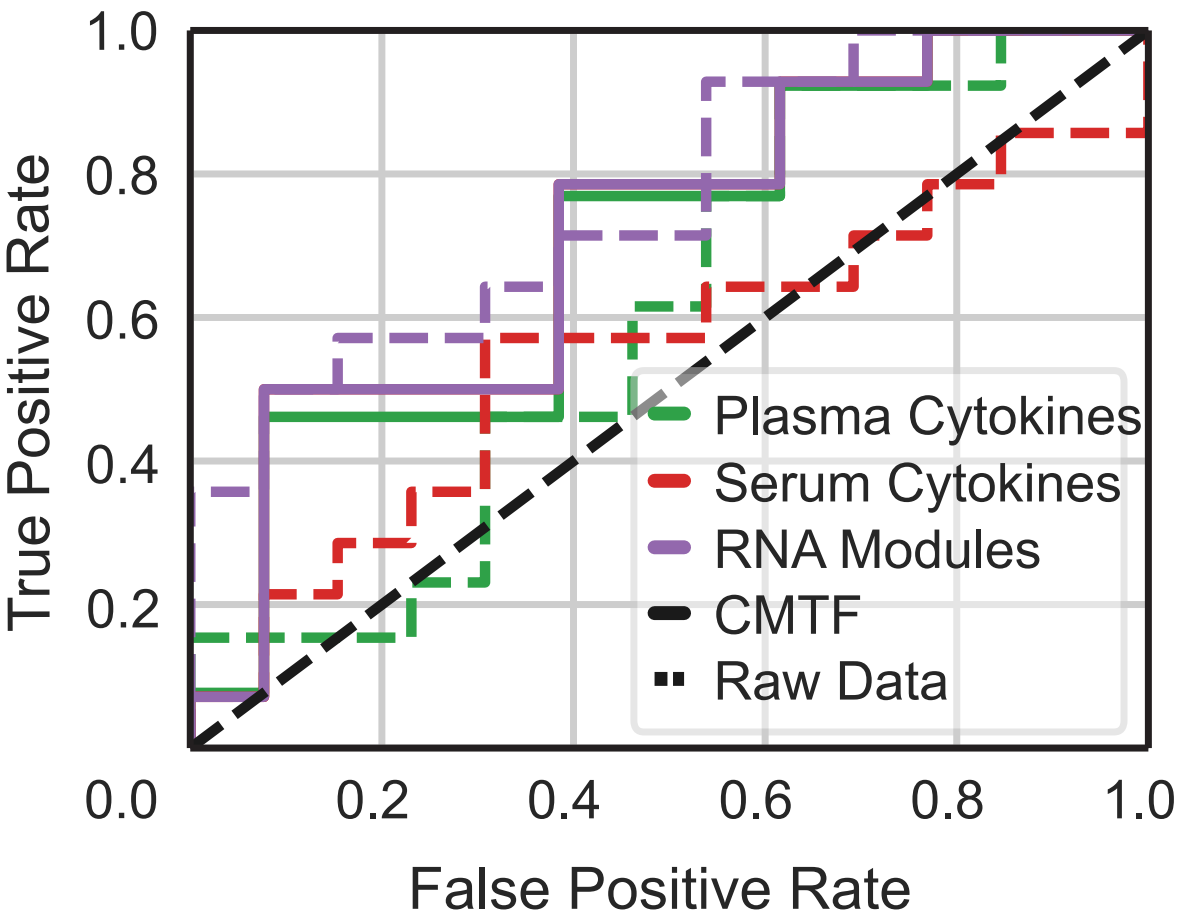
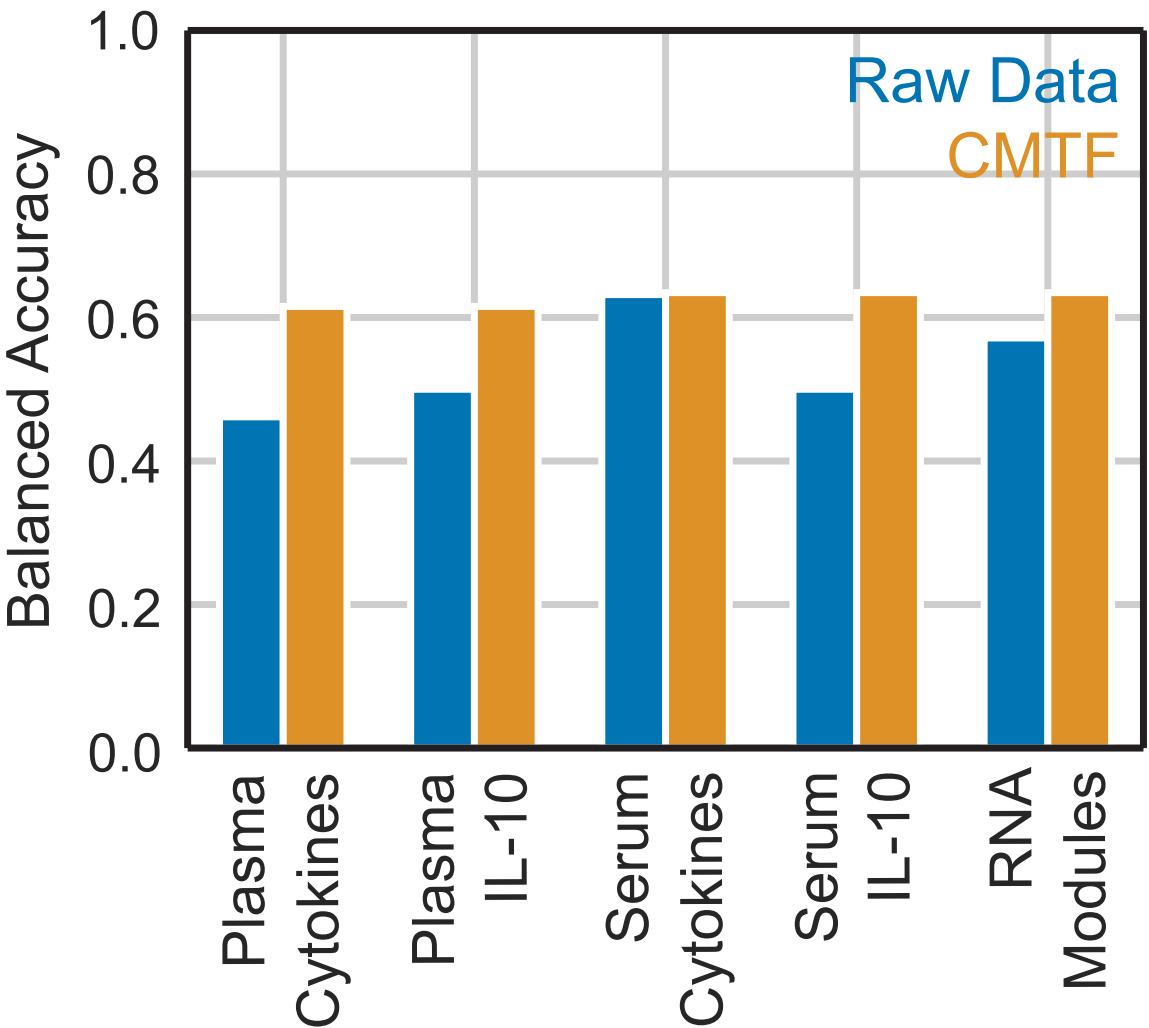


Data integration improves prediction of MRSA persistence

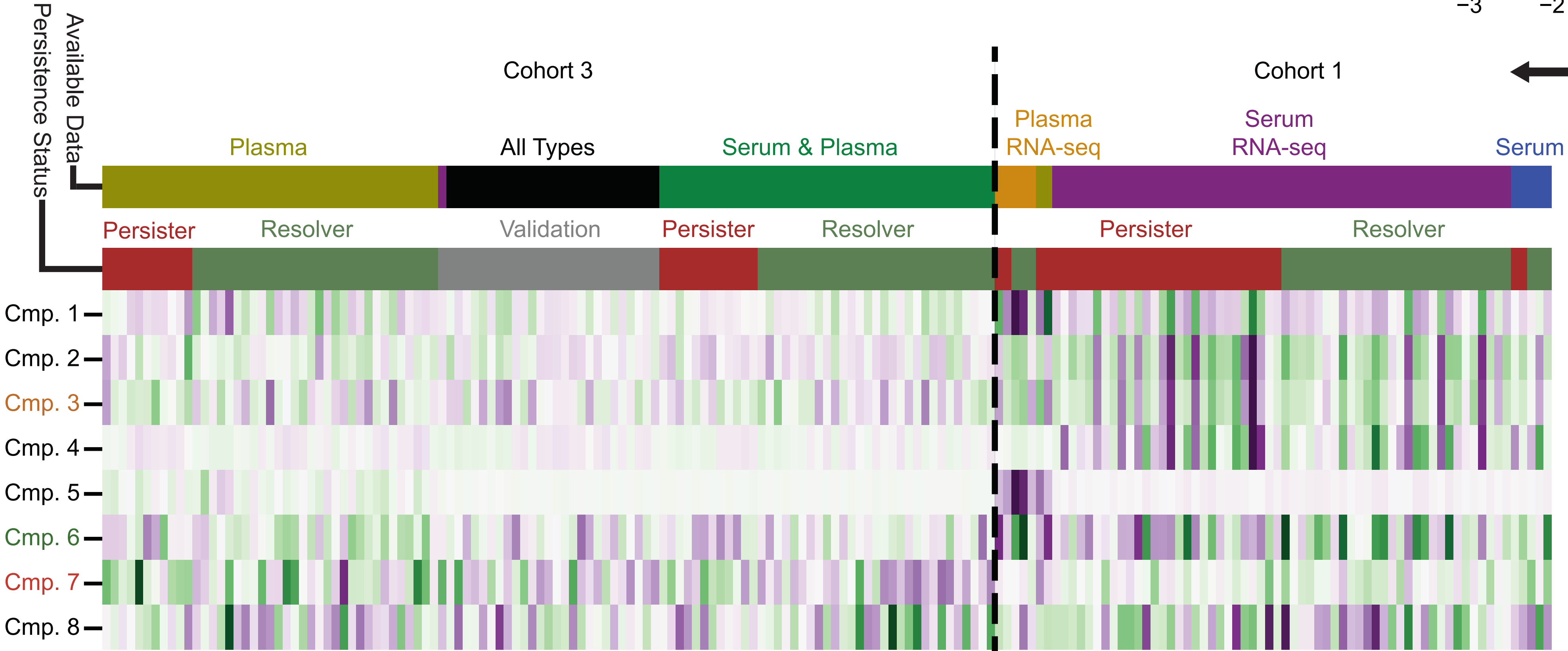
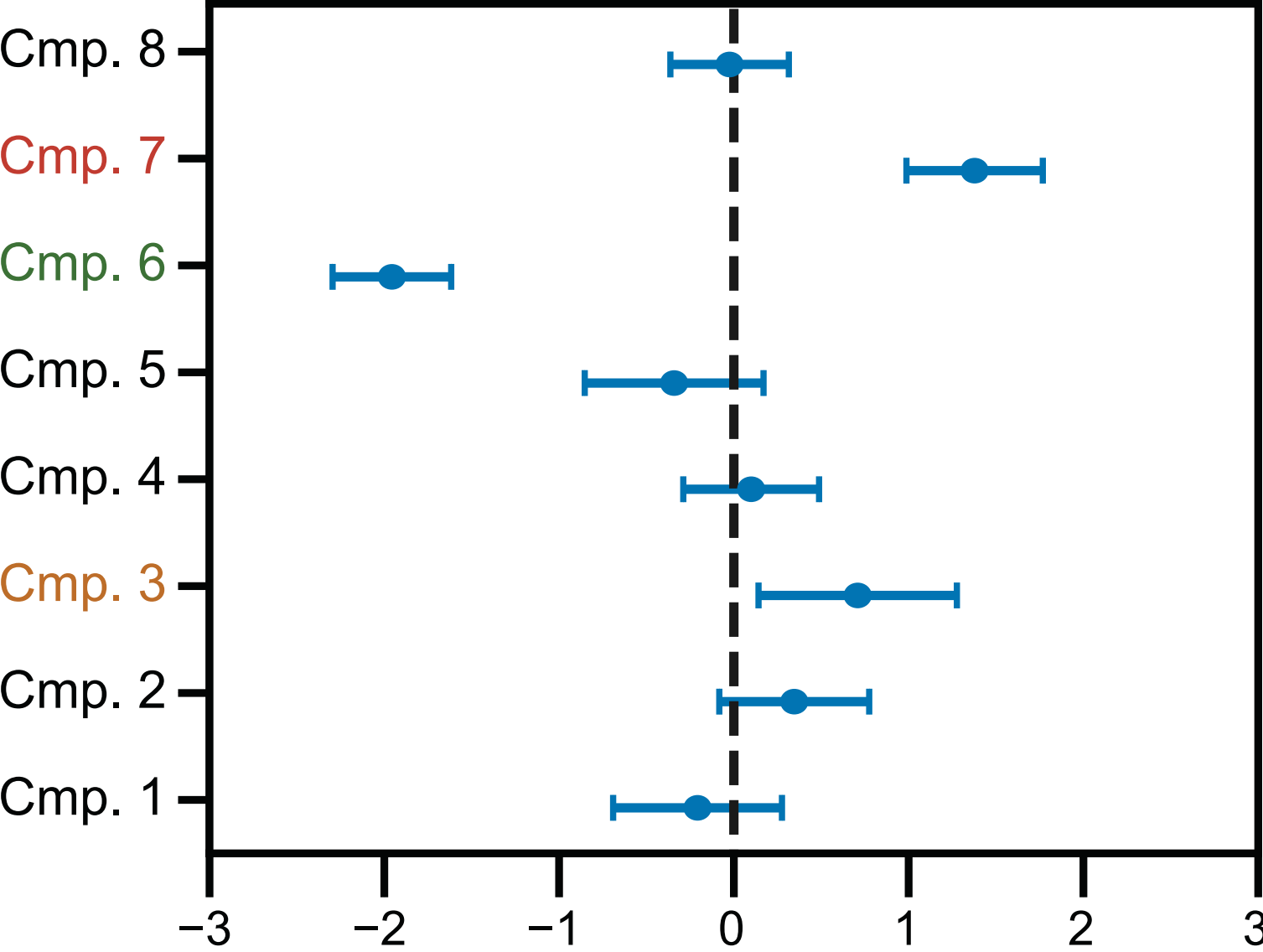
Training Cohort Cross-Validation



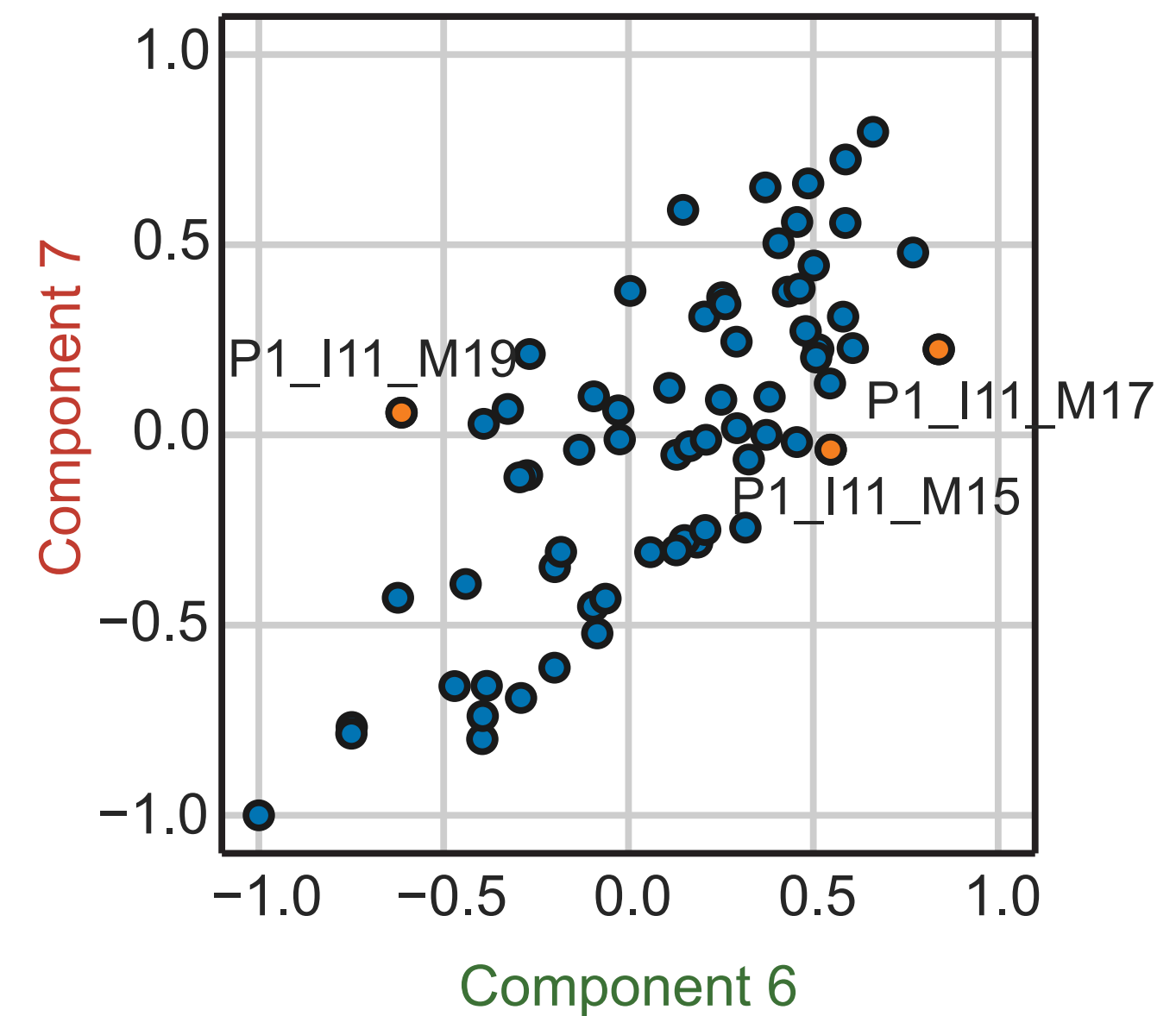
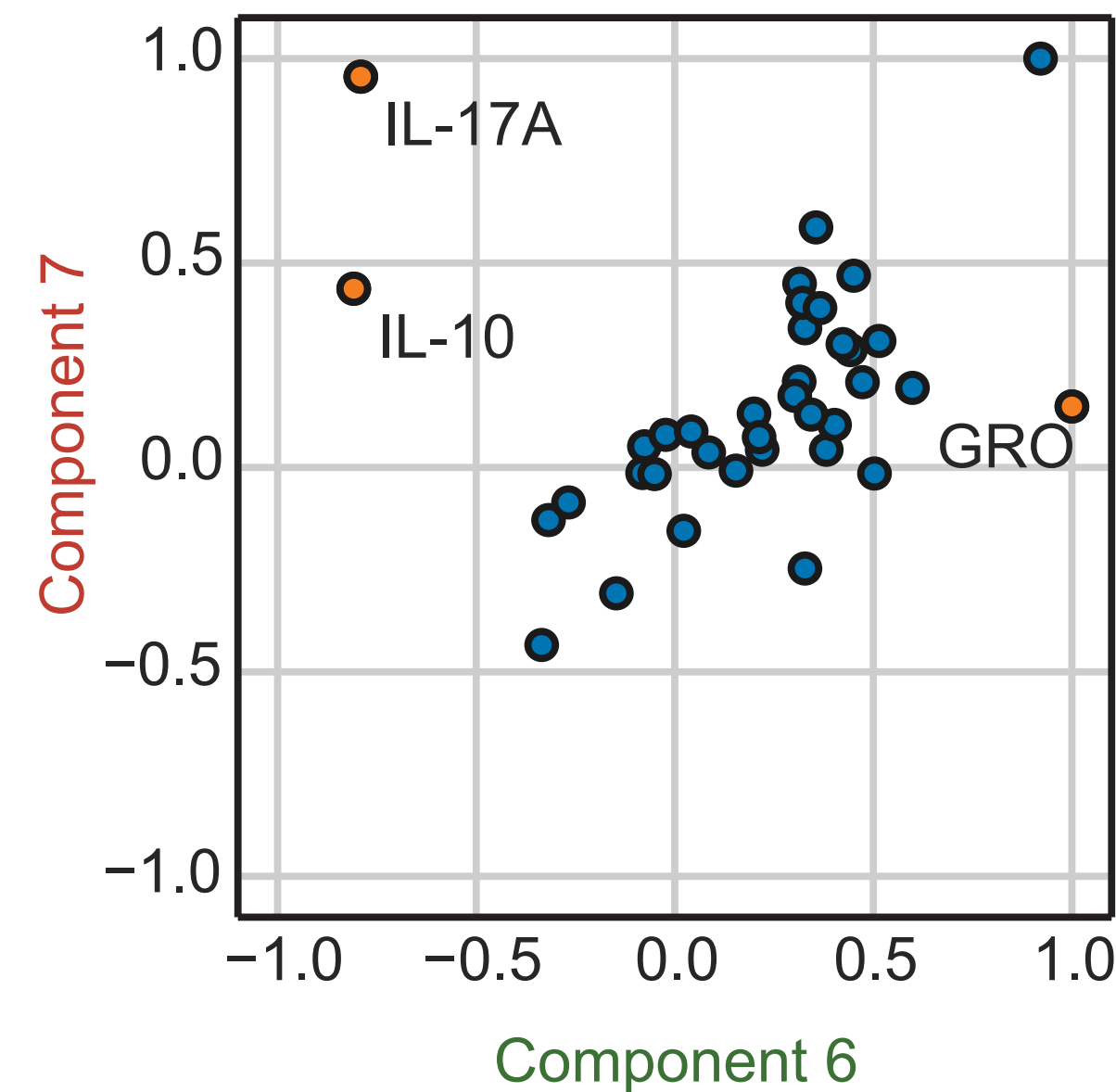
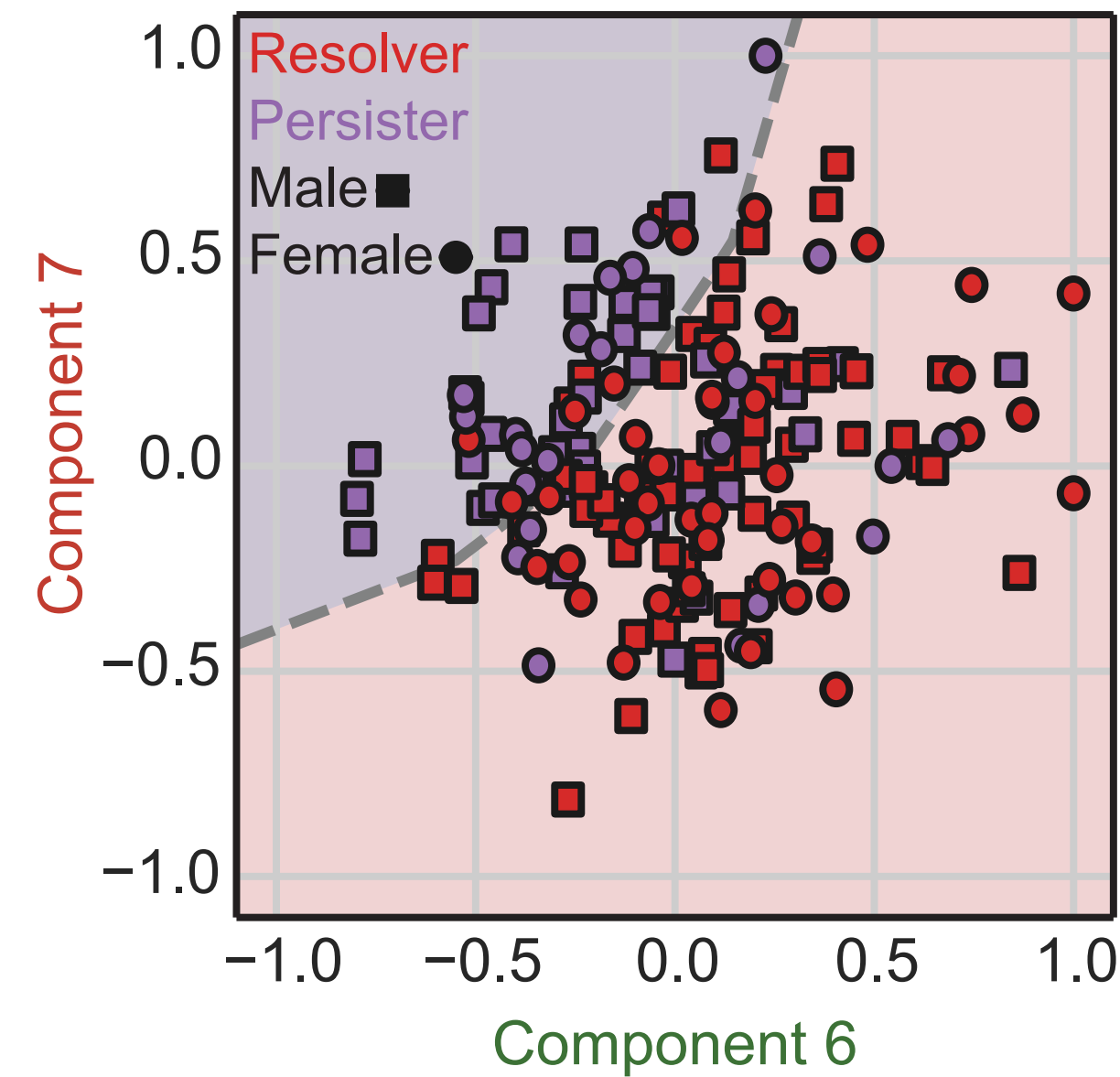
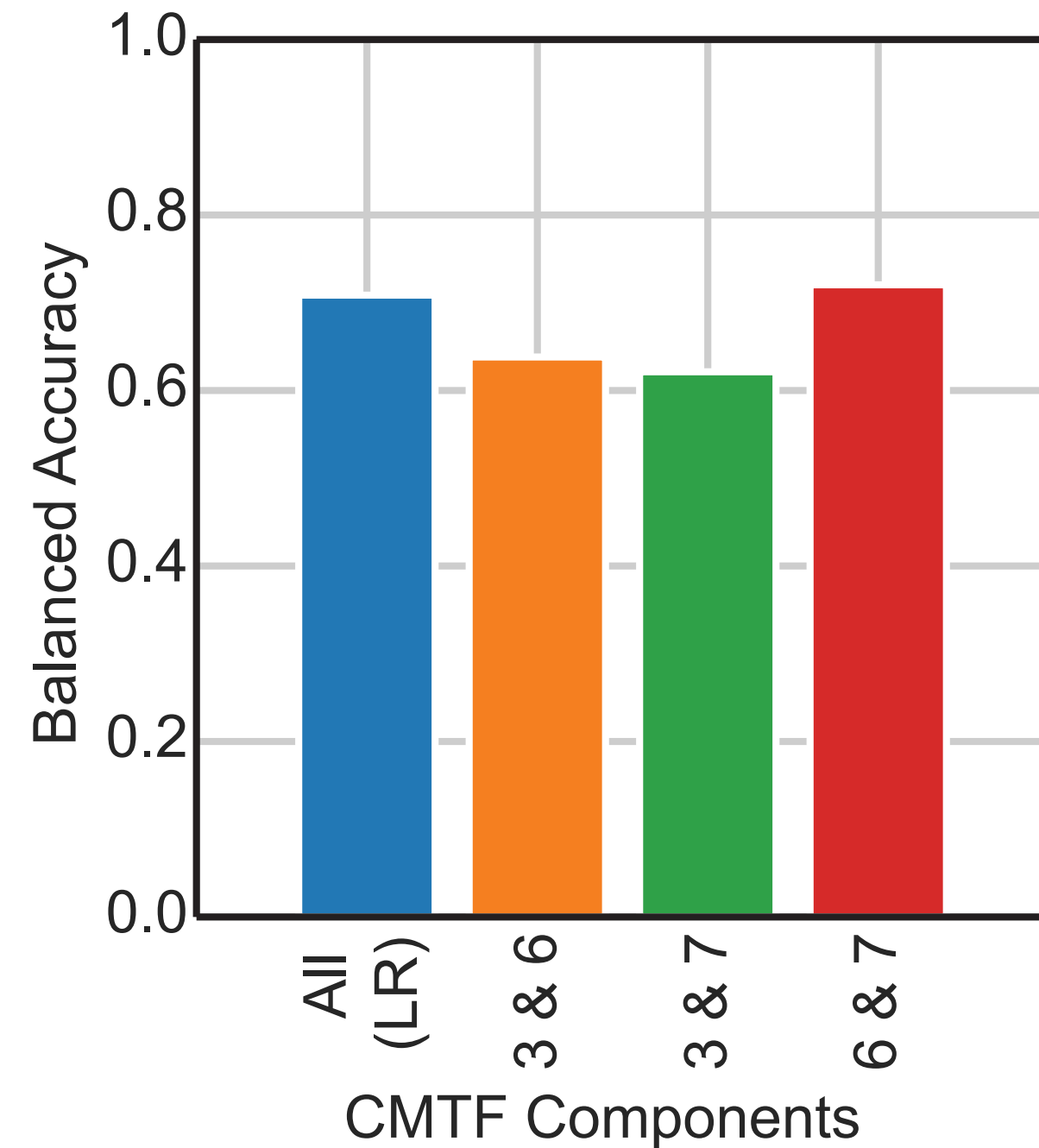
Validation Cohort



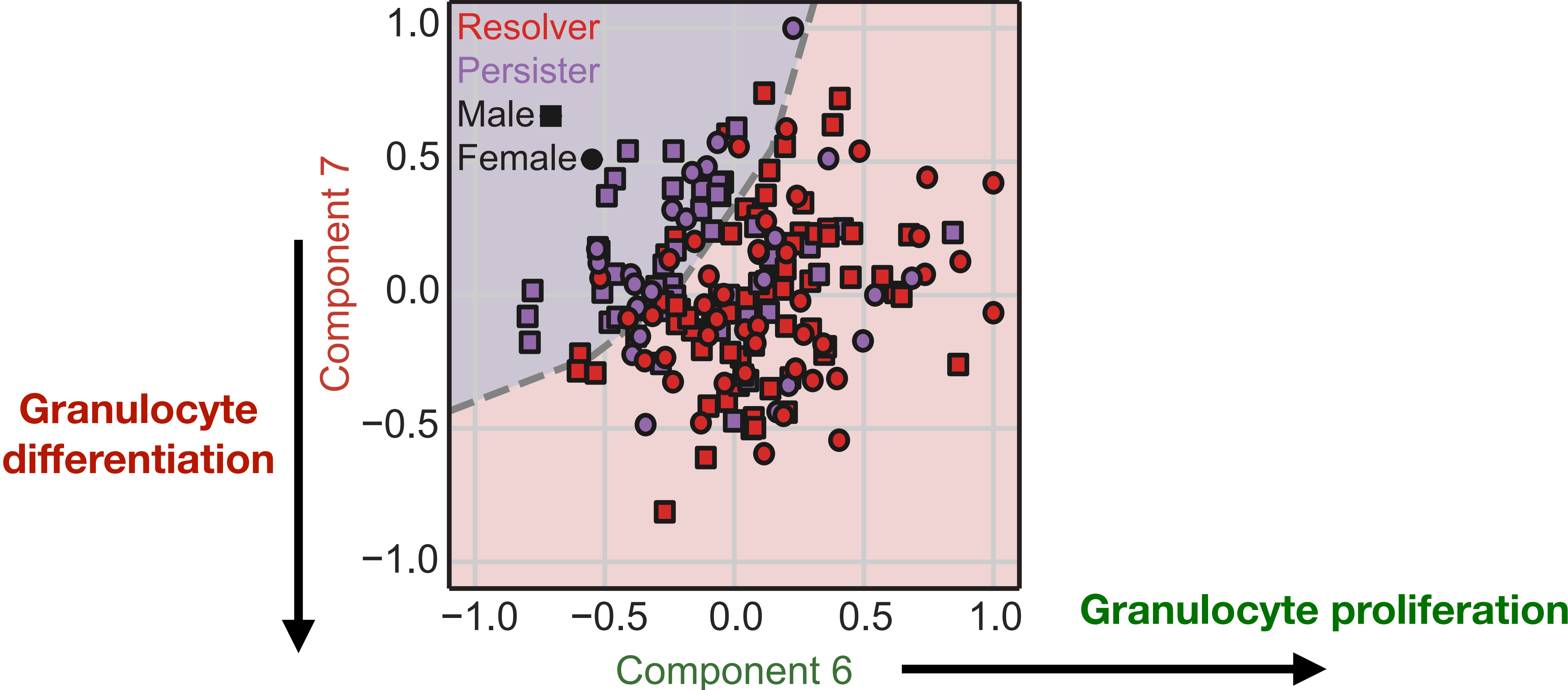
Factors collapse patterns that are shared or measurement-specific



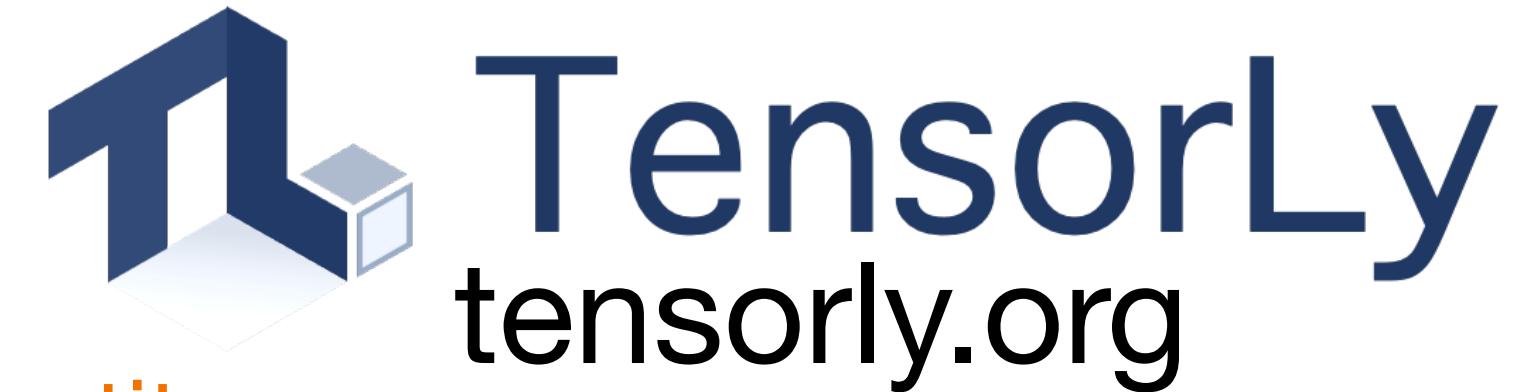
Opposing components 6 & 7 are independently predictive



Predictive factors identify subgroups of patients with either suppressed granulopoiesis or granulocyte differentiation

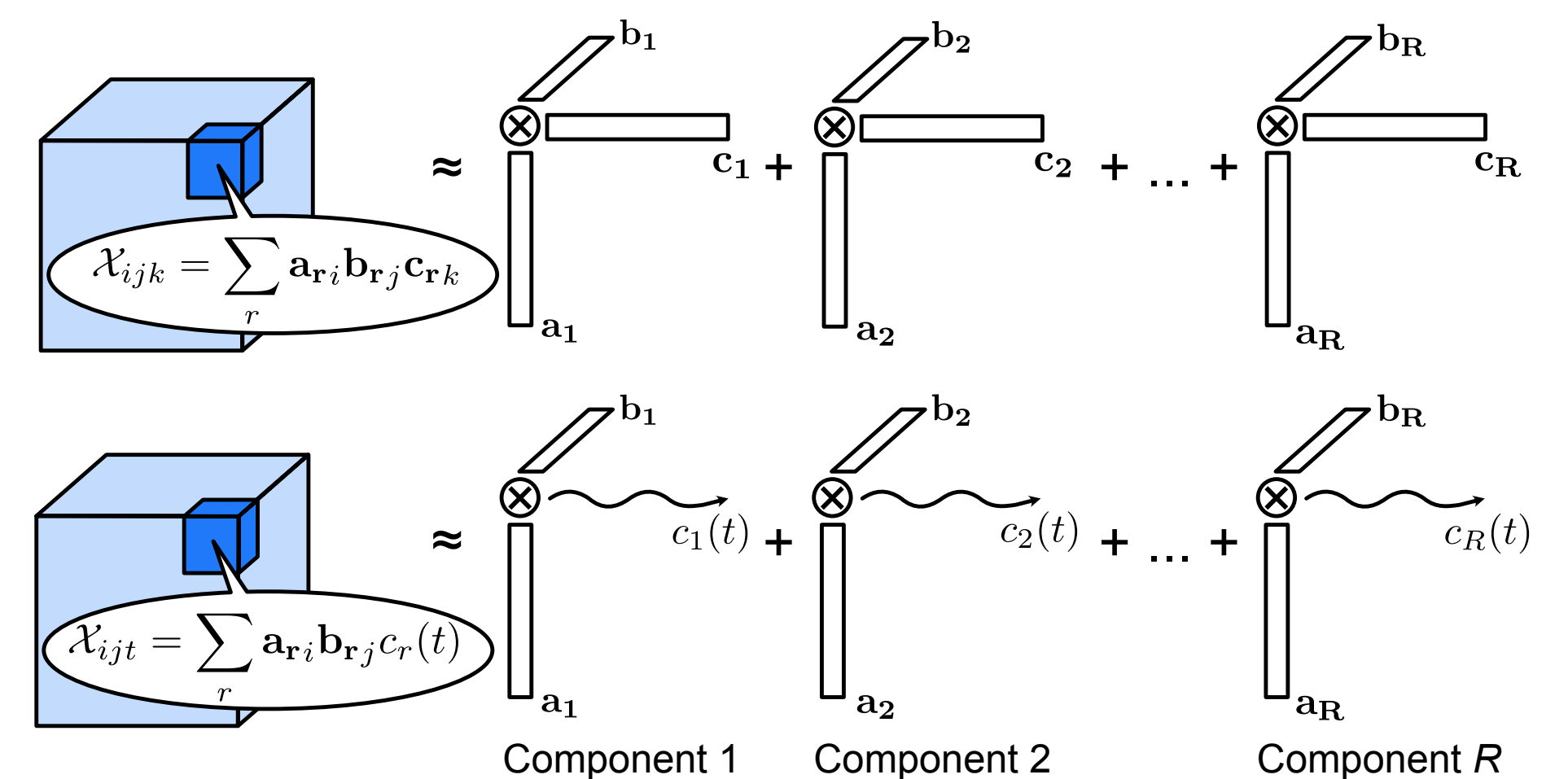
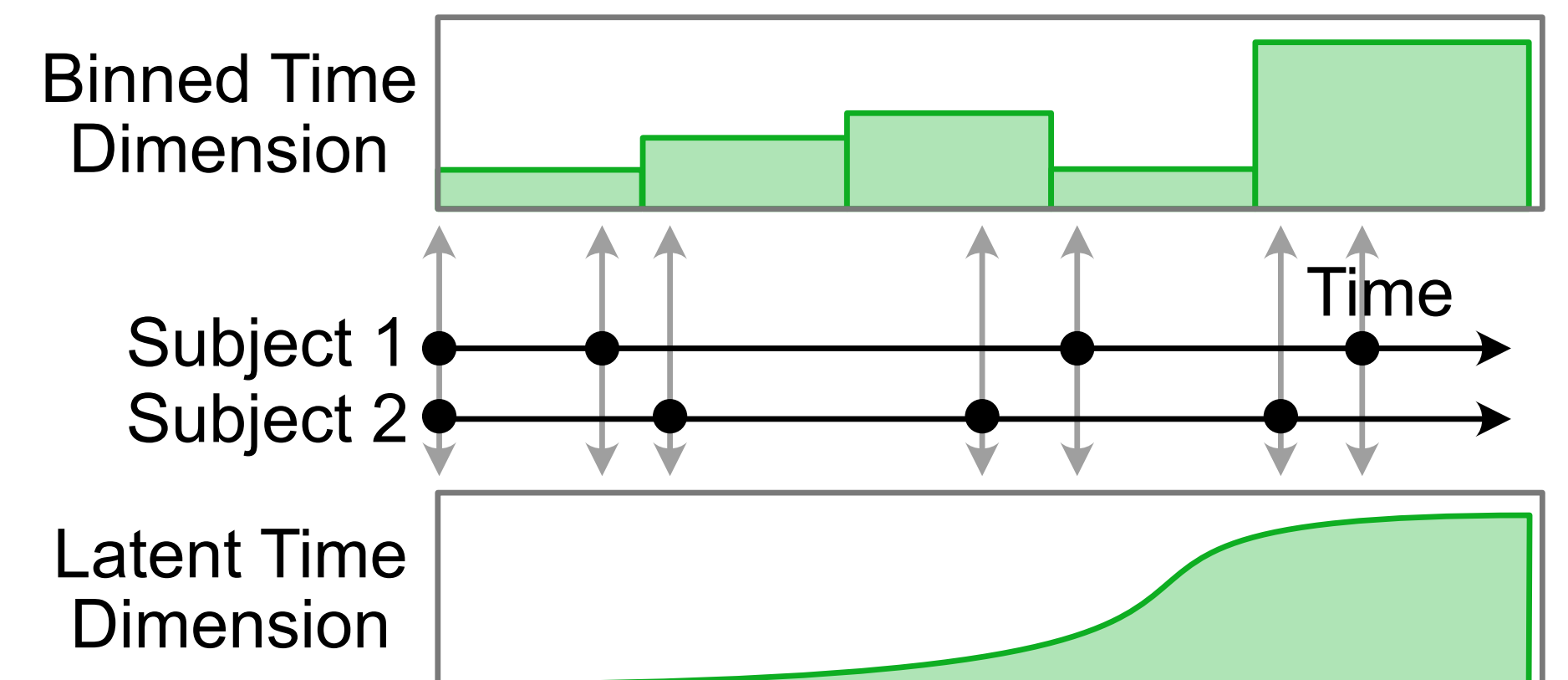
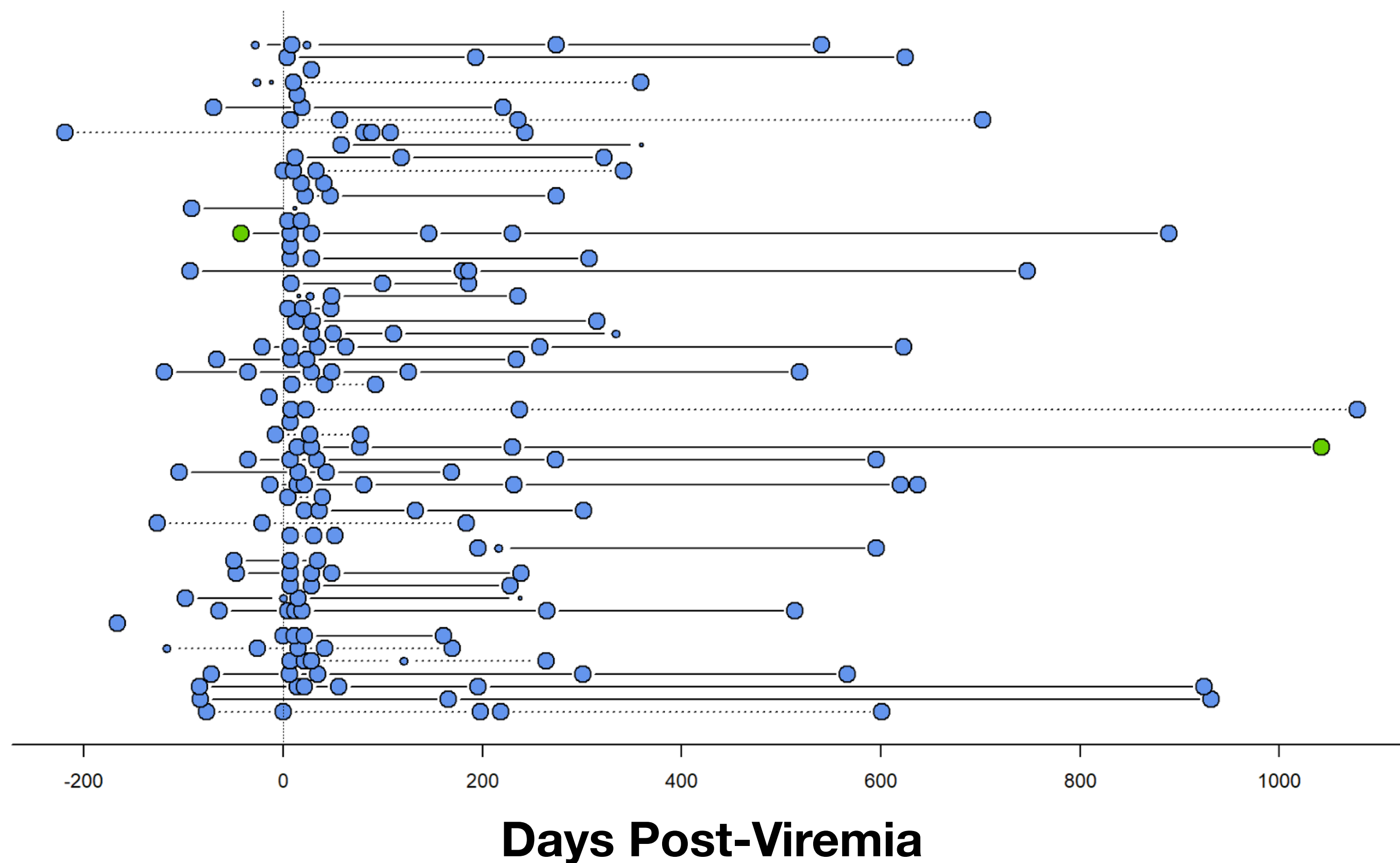


Why *aren't* you using tensor decomposition?

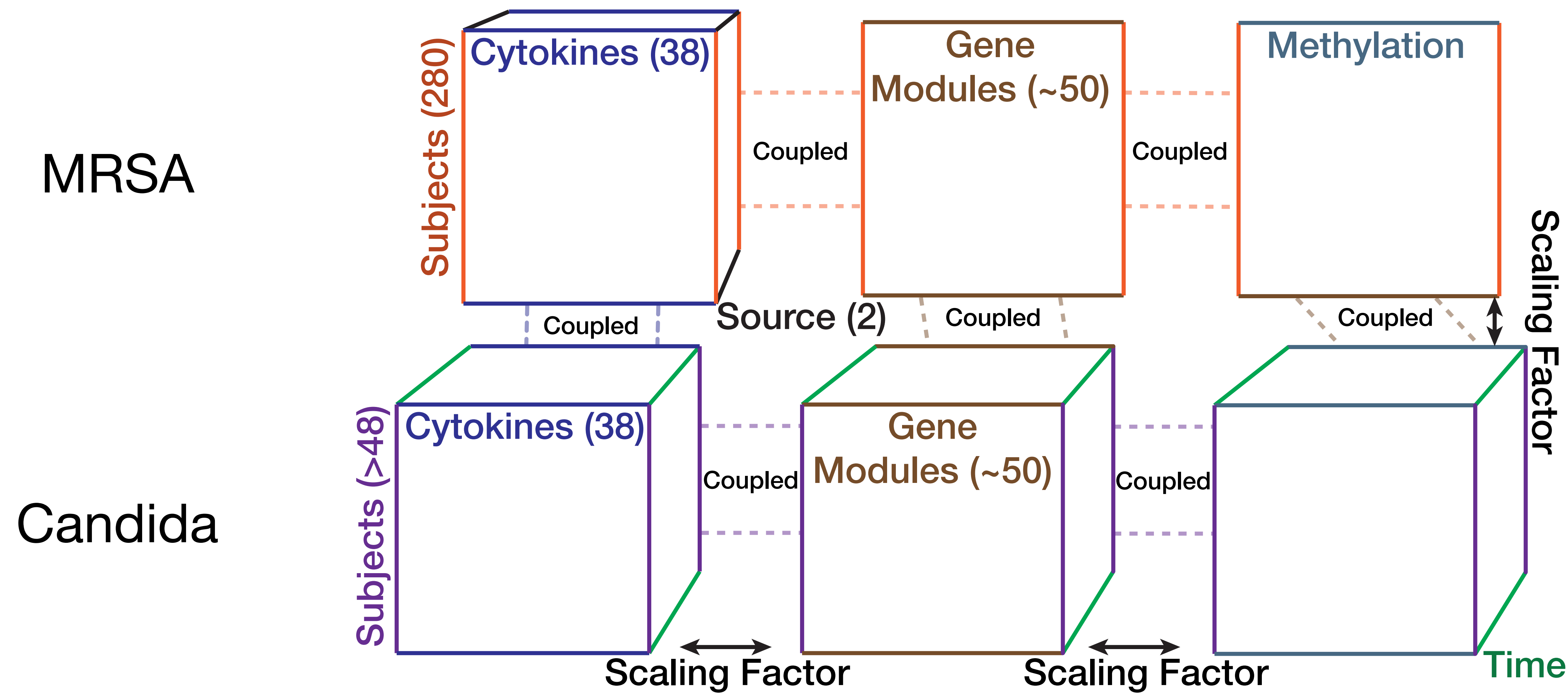


- **Engineered ECM:** stiffness × adhesion × porosity
- **ECM microarrays:** ECM × cell line × drug treatment × measured quantity
Mohammadi *et al*, In preparation
- **Serology:** antigen specificity × immune receptor binding × subject
Tan... Meyer, *Mol Sys Biol*, 2021
- **Immunology:** cytokines × subjects × time × measurement × cell types
Orcutt-Jahns *et al*, In preparation
- **Cell signaling:** ligand × cell type × concentration × time
Farhat... Meyer, *Cell Reports*, 2021; Orcutt-Jahns *et al*, *bioRxiv*, 2022
- **Multi-omic studies:** subjects × timepoints × genes × measurement (CNV/methylation/RNA)
Chin *et al*, In preparation
- **Cell Communication:** sender cell × receiver cell × condition × ligand-receptor pair
Armingol *et al*, *Nature Communications*, 2022

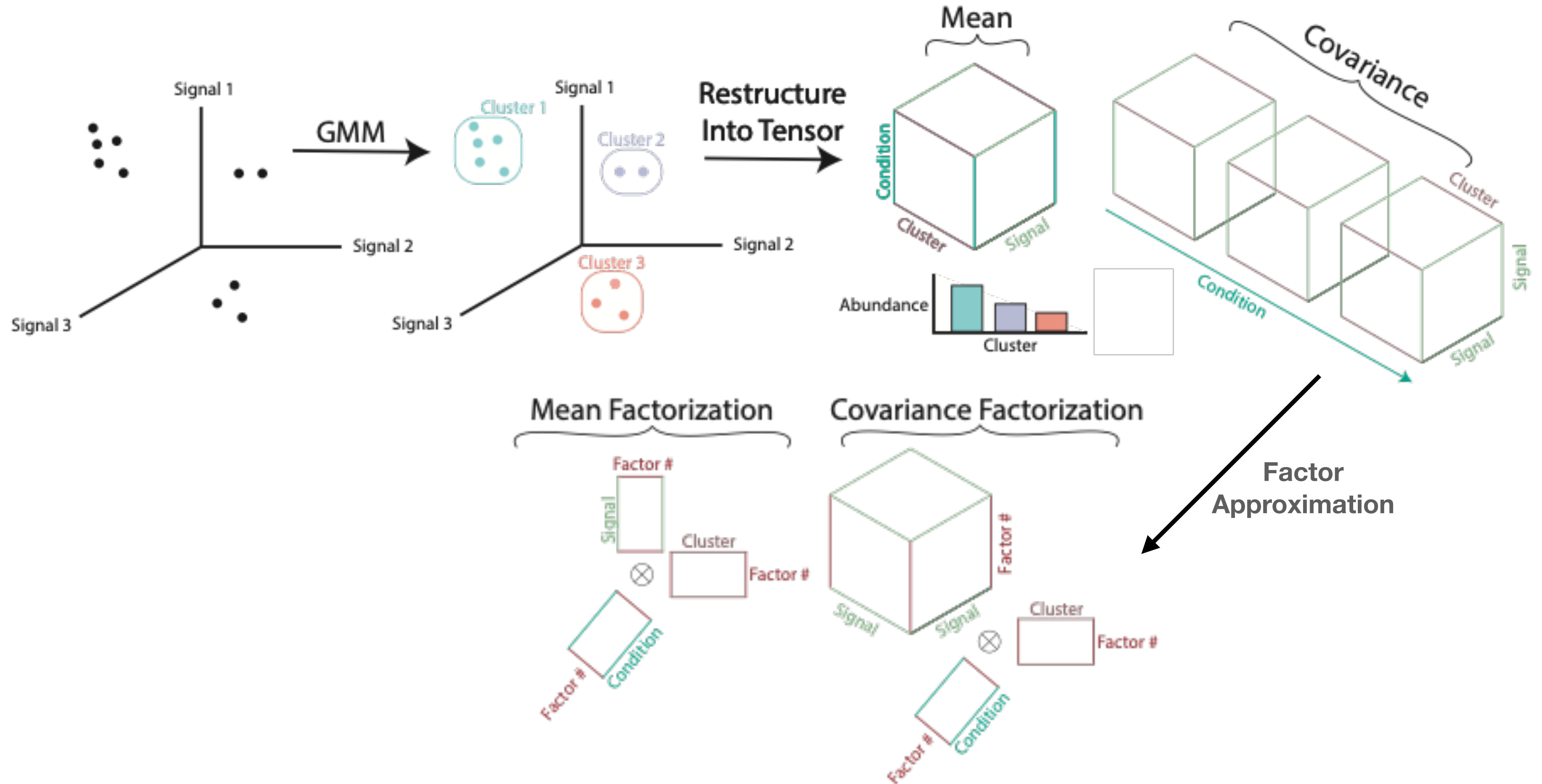
Methodological improvements in tensor decomposition will improve their scope and capabilities



Flexible decomposition coupling will enable more widespread data integration



Tensor tools for single cell data



Acknowledgements

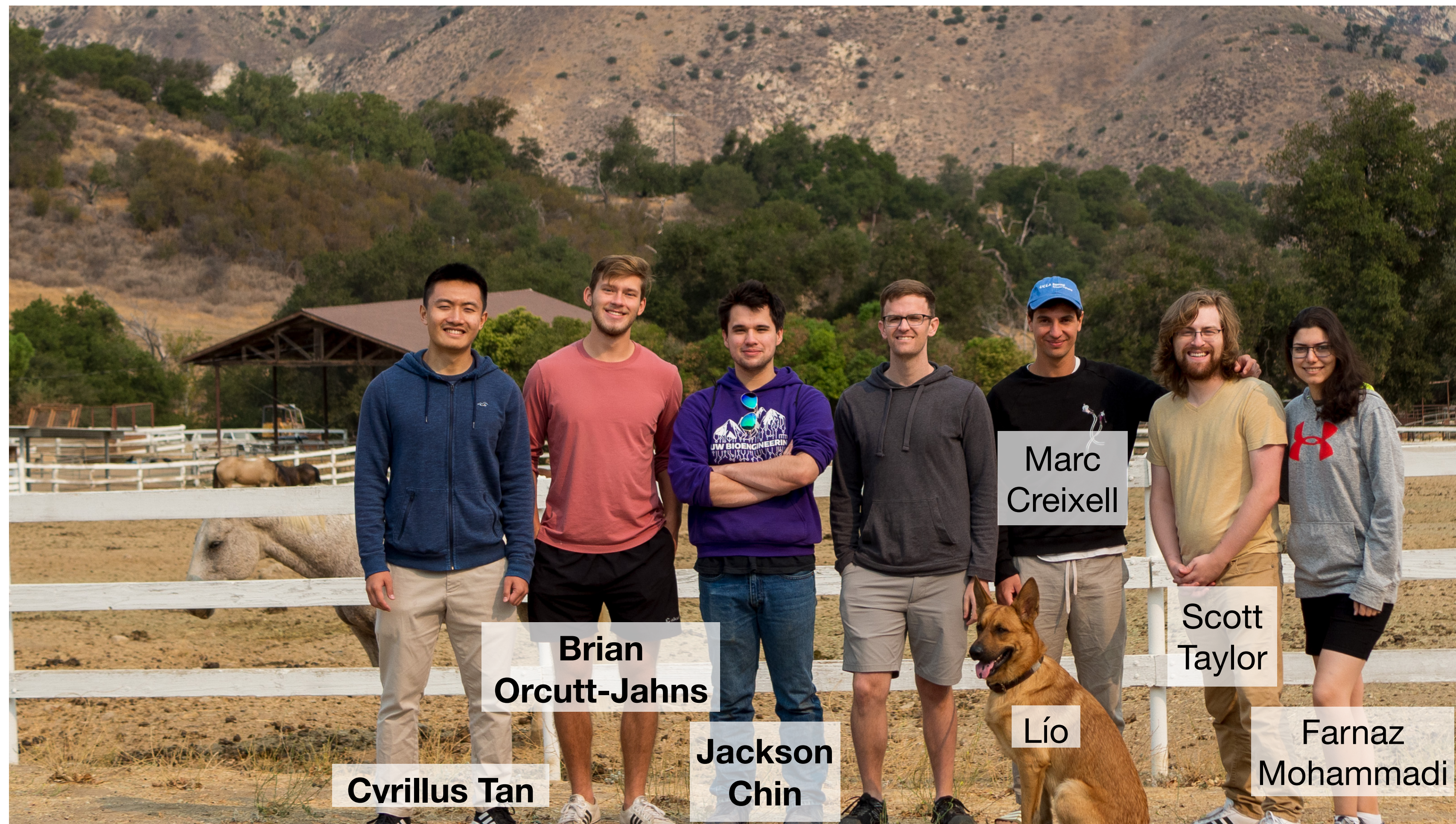


Madeleine Murphy

Andrew Ramirez



Michelle Loui



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