Signatures of functional responses to acute and chronic COVID-19

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Introduction

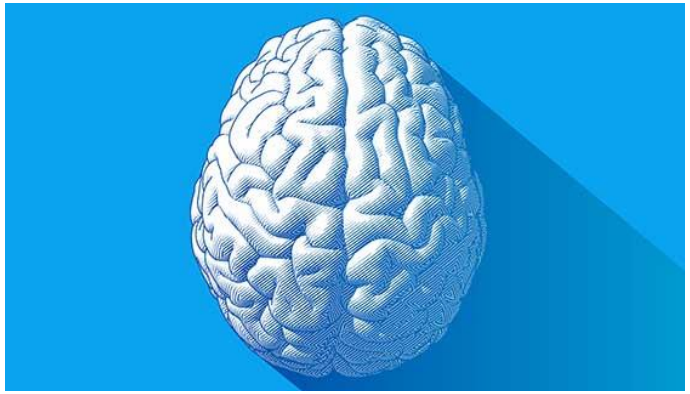
PASC, the immune system, and our data

PASC (Long Covid)

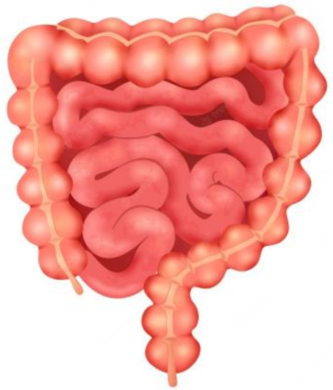
Long COVID Has Forced a Reckoning for One of Medicine's Most Neglected Diseases

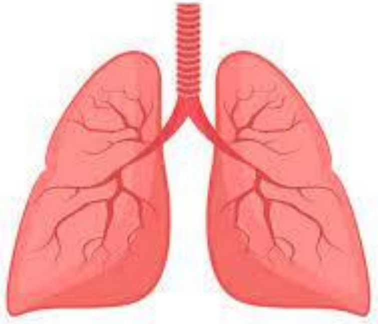
Only a couple dozen doctors specialize in chronic fatigue syndrome (ME/CFS). Now their knowledge could be crucial to treating millions more patients.

ED YONG SEPTEMBER 26, 2022



The data is clear: long Covid is devastating people's lives and livelihoods





31-69%

The number of people who go on to develop PASC after having COVID-19

Headlines: *The Atlantic*, *The Guardian*
PASC data: Su et al, *Cell,* 2022*;* Thaweethai et al, *JAMA*, 2023

PASC (Long Covid)

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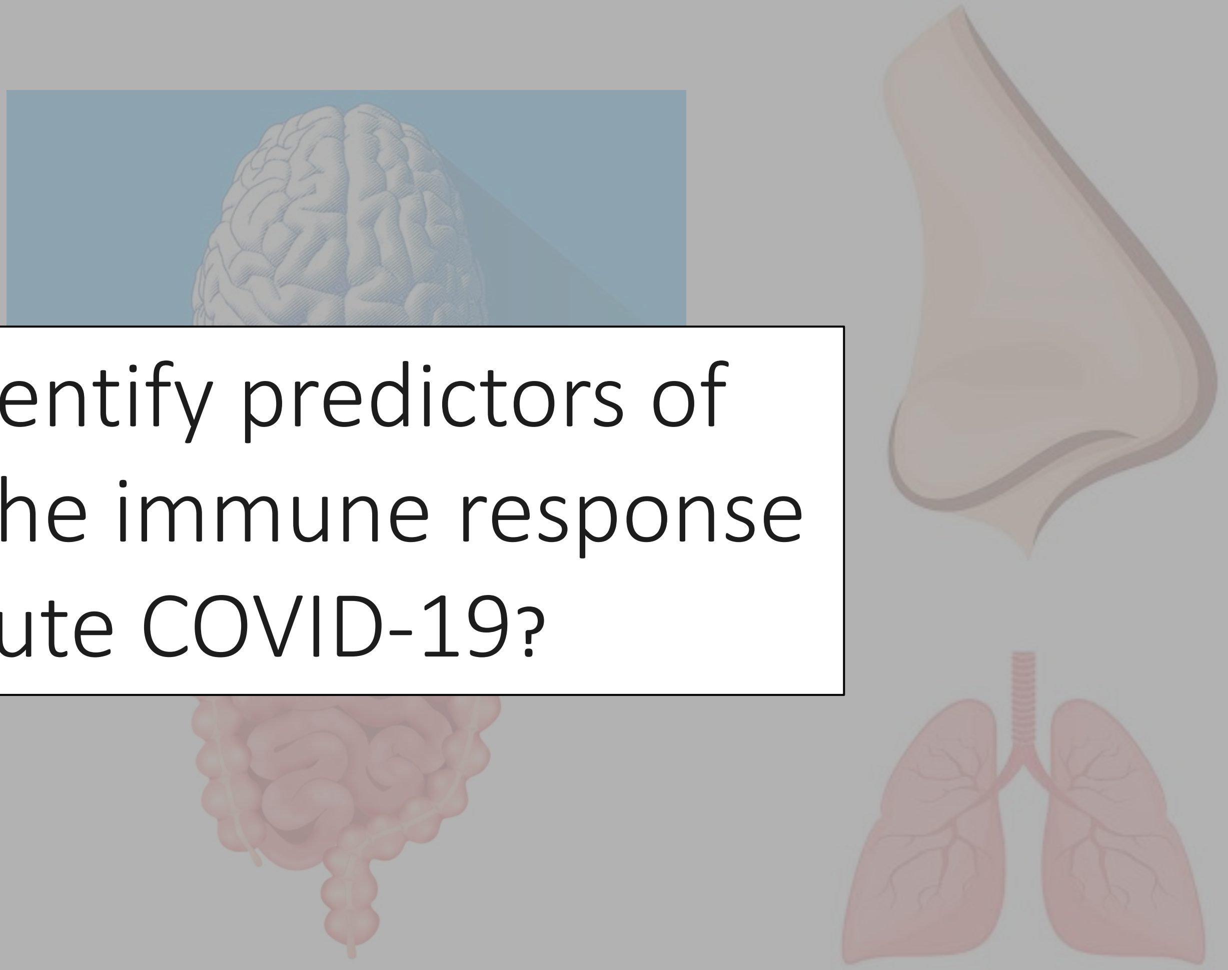


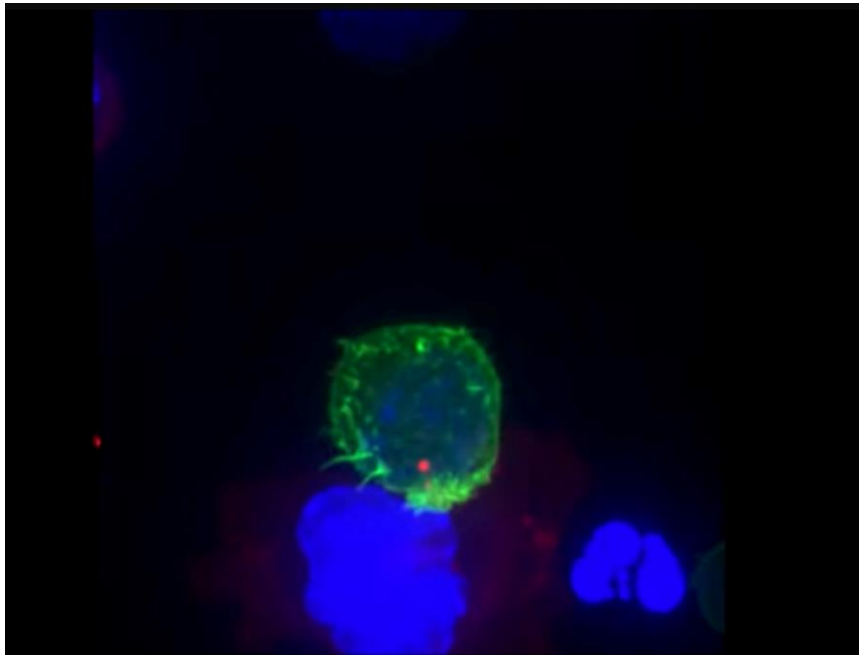
Can we identify predictors of PASC from the immune response to acute COVID-19?

31-69%

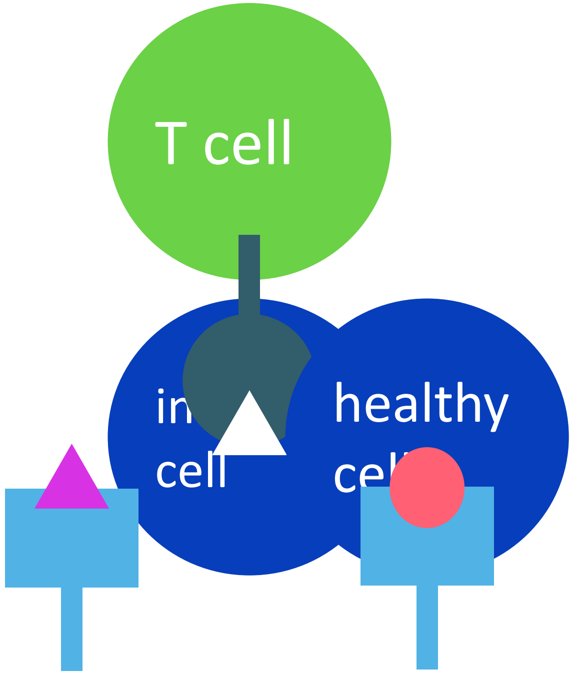
The number of people who go on to develop PASC after having COVID-19

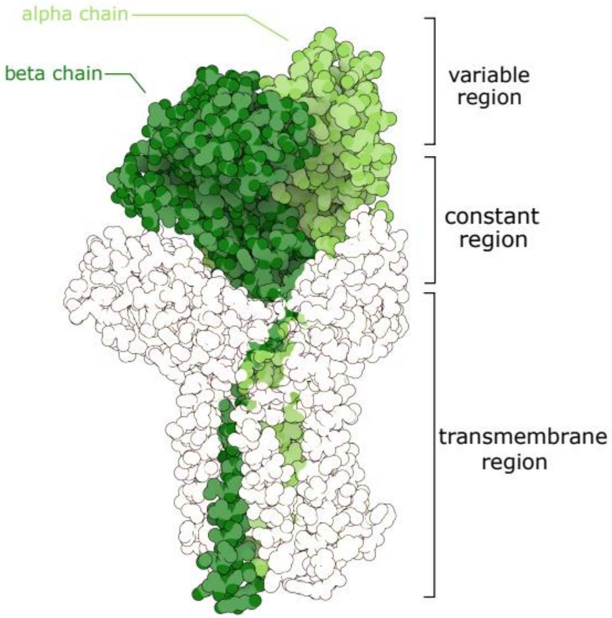
Headlines: *The Atlantic*, *The Guardian*
PASC data: Su et al, *Cell, 2022*

A brief overview of T-cell function



video: Griffiths lab, Cambridge Institute for Medical Research

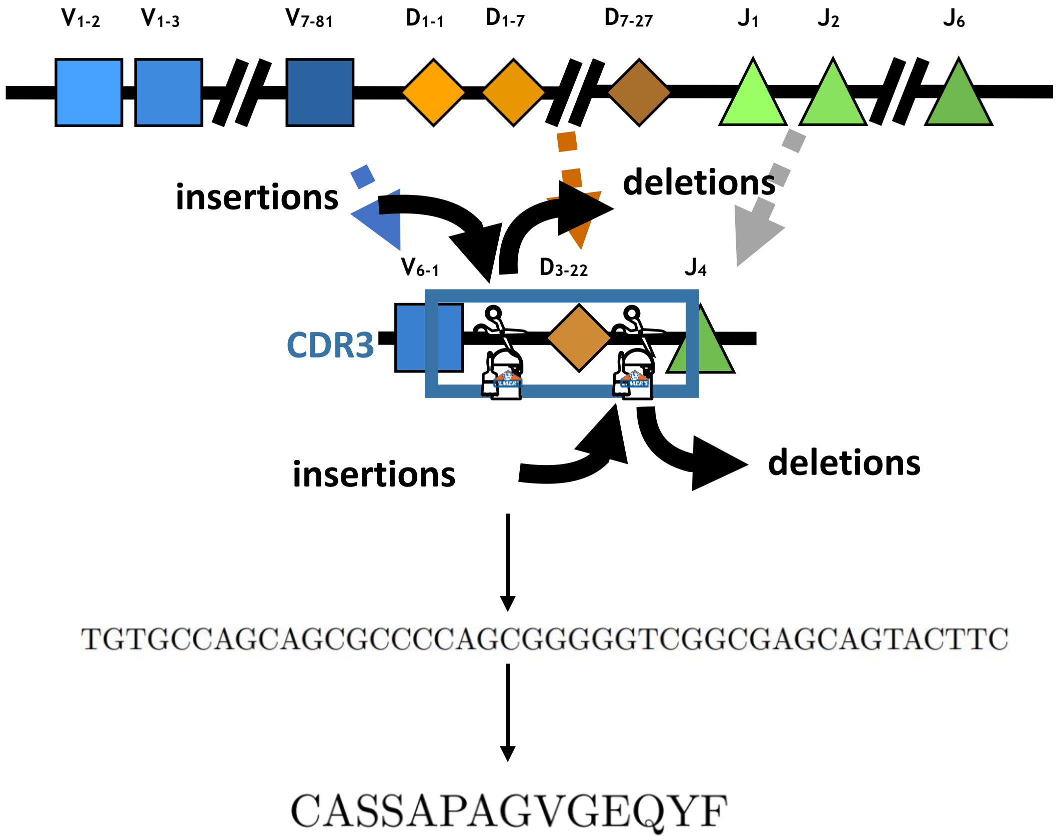




Pun, 2023

Generation of TCR diversity

VDJ recombination



TGTGCCAGCAGCGCCCCAGCGGGGTCGGCGAGCAGTACTTC

CASSAPAGVGEQYF

testing for functionality

~10^{18} potential TCRs
10^{12} in body
10^{6} in data – sampling variation!

Montague, 2023
Janeway, 2001

PASC immune repertoire data

63

patients without PASC

61

patients with PASC

28

male

35

female

24

male

37

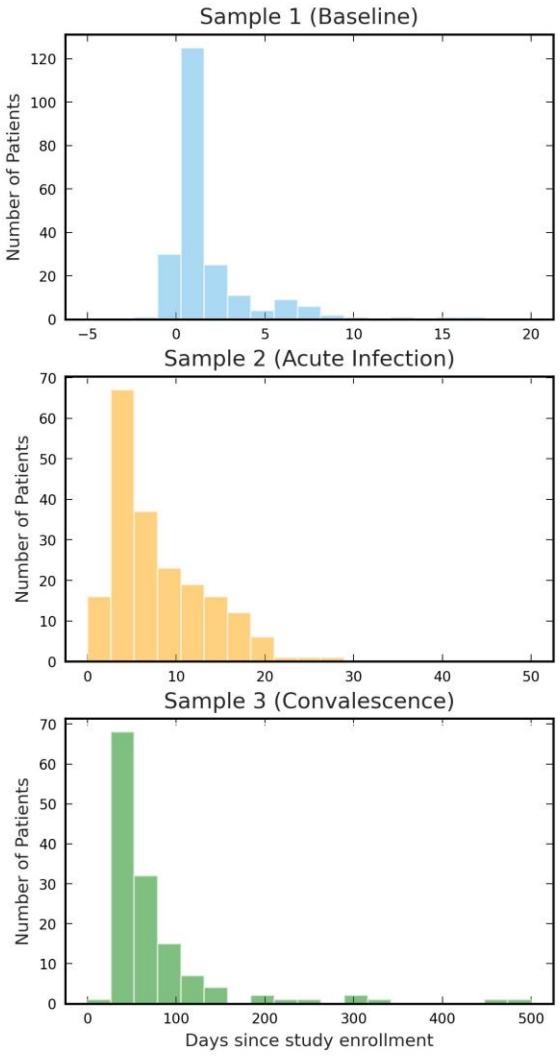
female

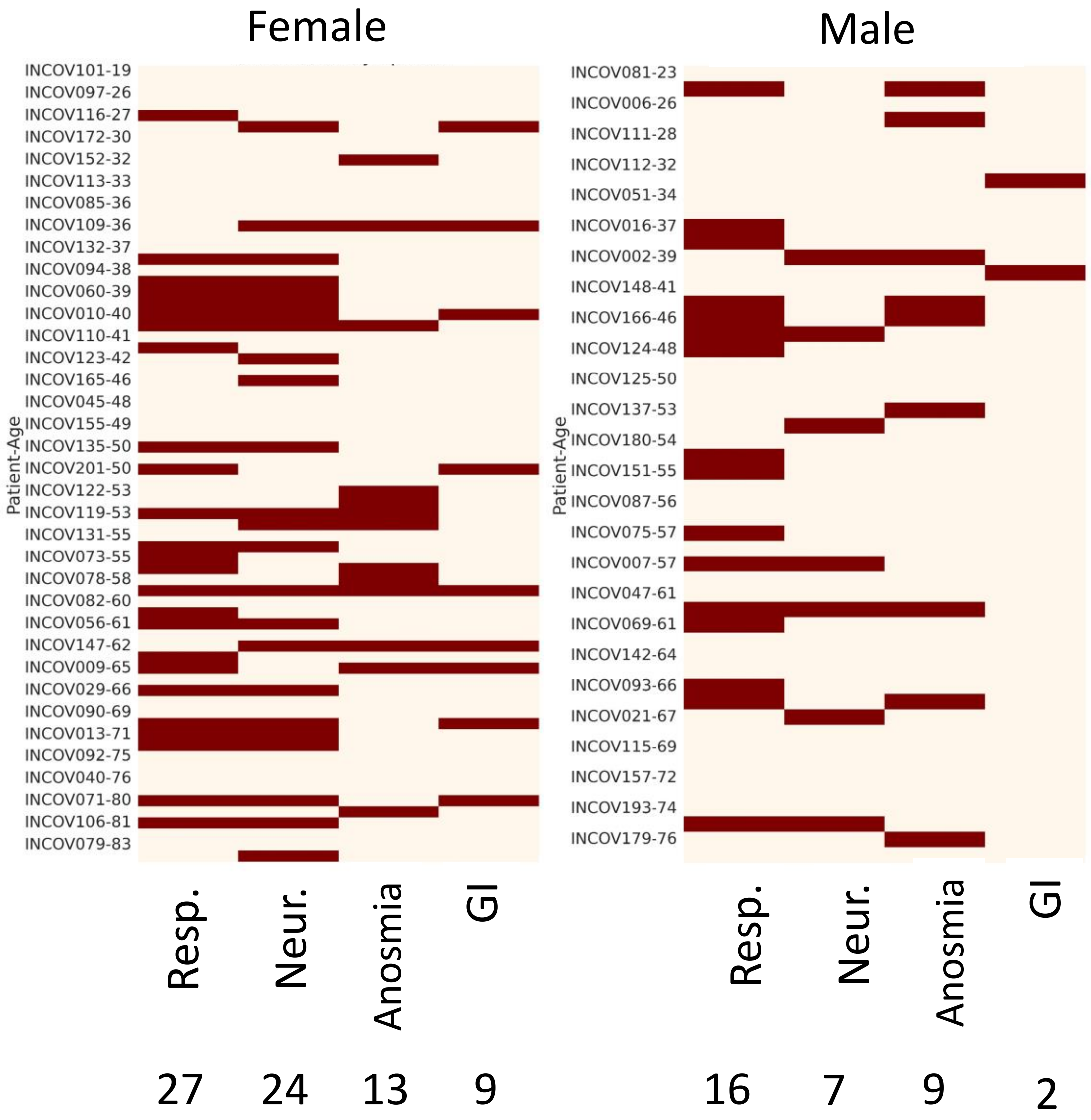
aged

19-86

274, 923

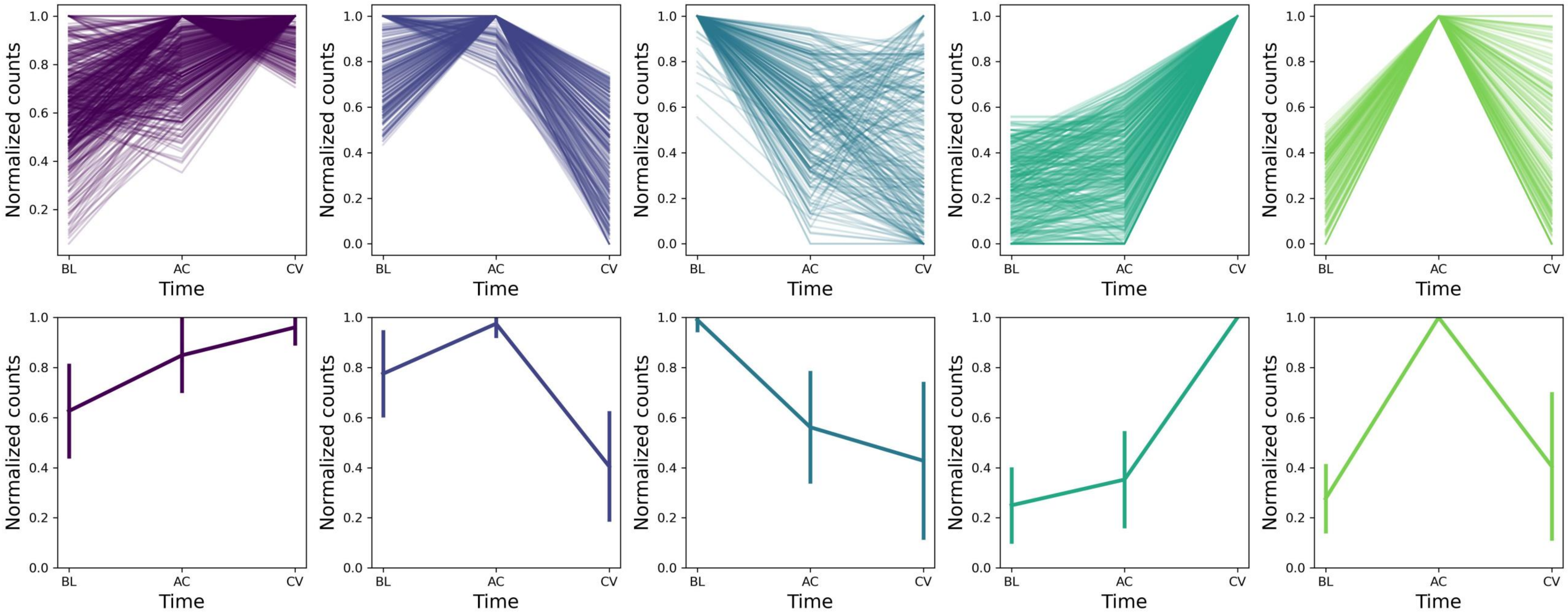
avg # of unique TCRs per patient



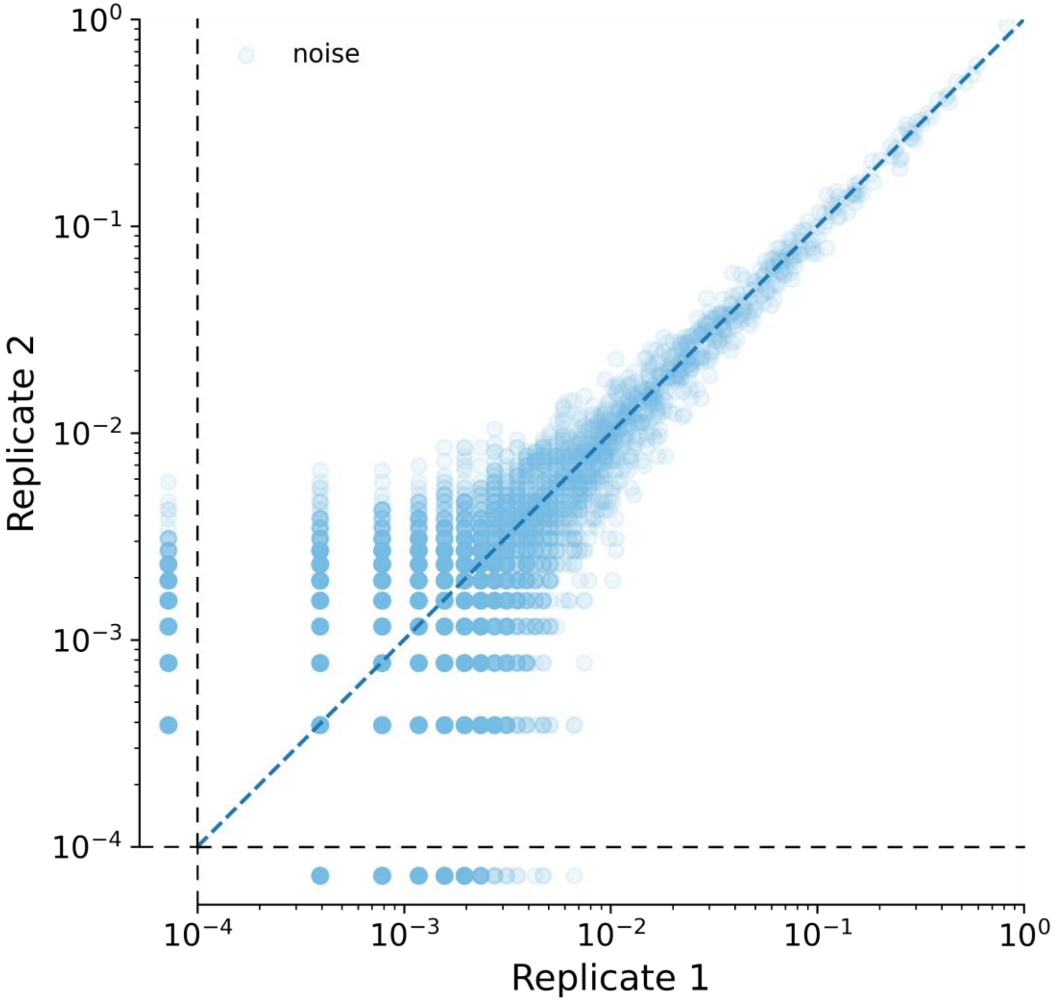


T Cell Population Dynamics Analysis

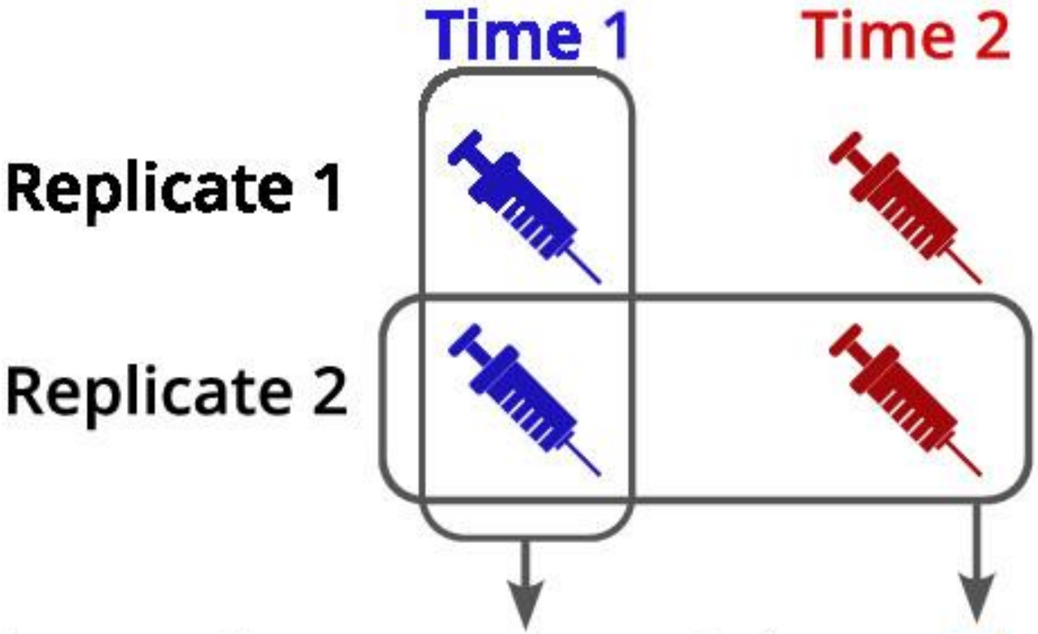
Clone Read Trajectories

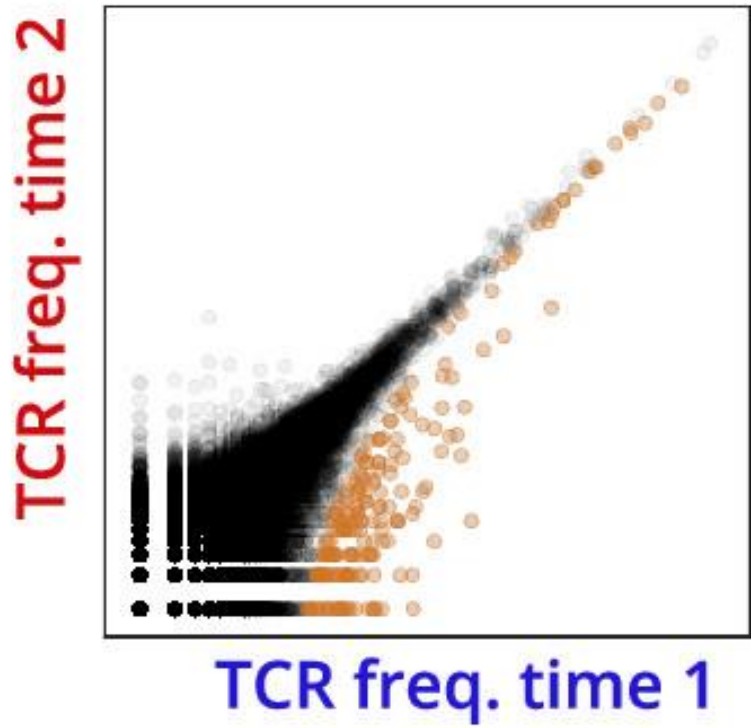


Undersampling leads to variation in TCR reads



NoisET

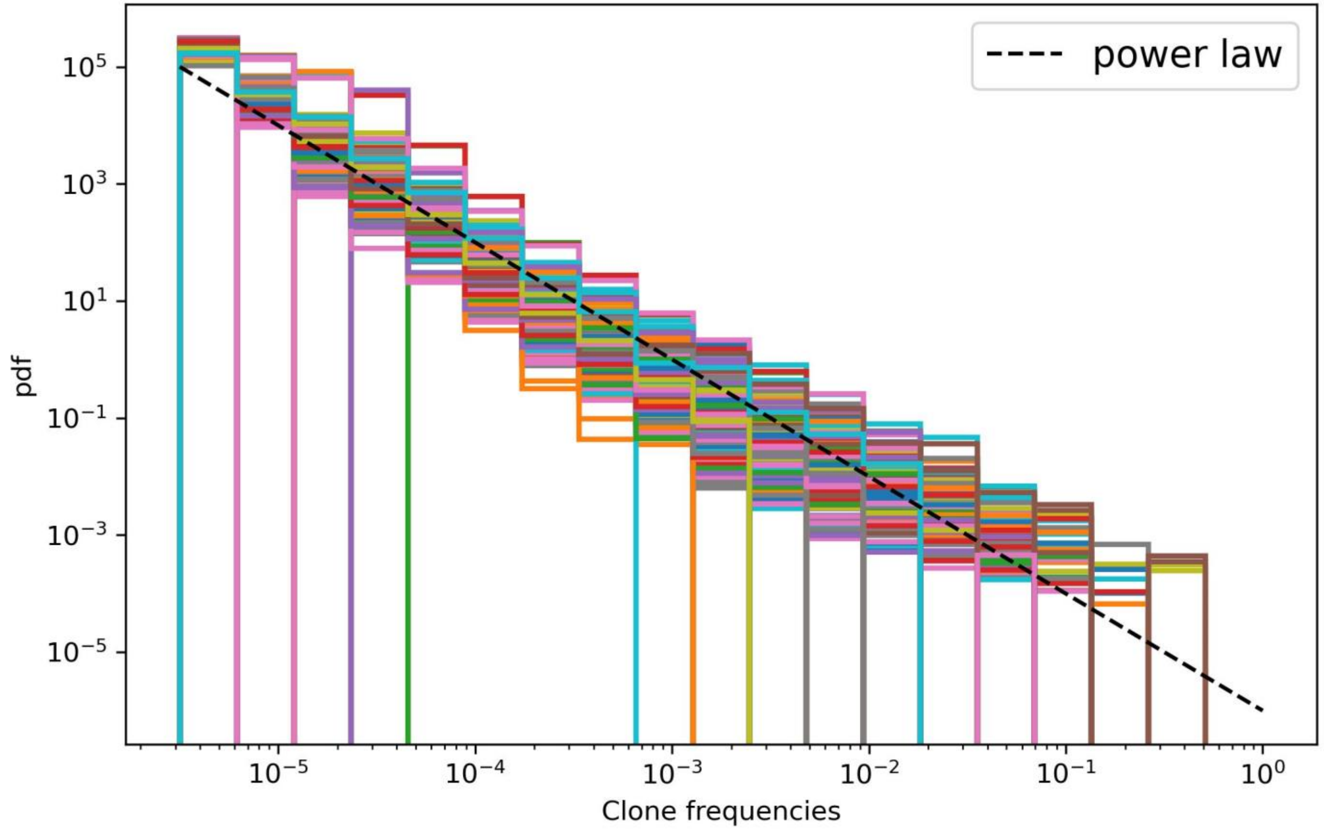




Learn the experimental noise with two replicates → **Identify significantly contracted T-cell receptors**

Koraichi et al, *J. Phys. Chem. A*, 2022

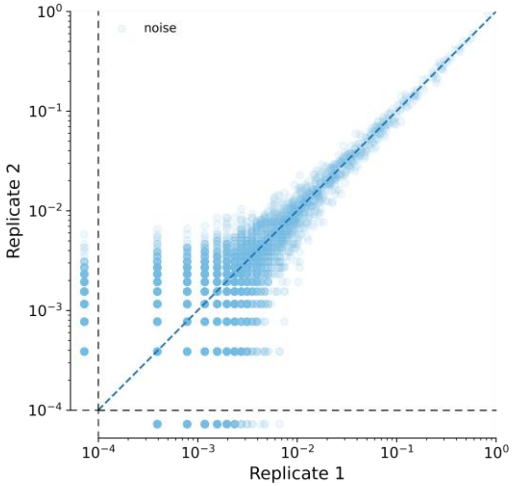
Clone size distributions follow a power law



$$\rho(f) = C f^{-2}$$

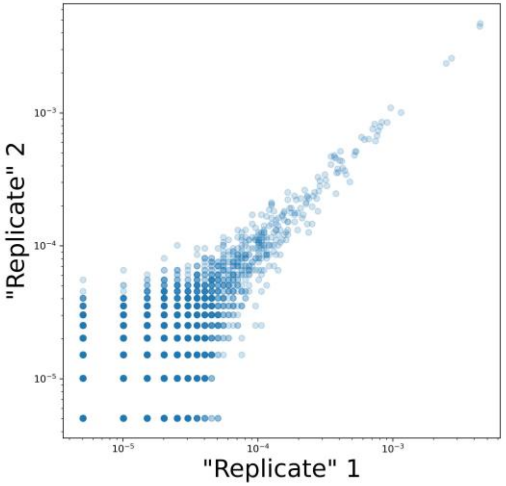
Koraichi et al, *J. Phys. Chem. A*, 2022

Data thinning in lieu of biological replicates



data thinning

$$X^{(1)} + X^{(2)} = X$$



Neufeld et al, preprint, 2023
Koraichi, NoisET tutorial, Github

Noise Model Choices

$$P(\hat{n}|f) = \mathrm{Pois}(f N_r)$$

$$P(\hat{n}|f) = \mathrm{NegBin}(\hat{n}; N_r f, N_r f + a(N_r f)^b)$$

Koraichi et al, *J. Phys. Chem. A*, 2022

Expansion Model

$$f(t_1) = f \longrightarrow f(t_2) = fe^s$$

$$P((\hat{n}_i(t_1) = \hat{n}_1, \hat{n}_i(t_2) = n_2)|\gamma, \bar{s}) =$$

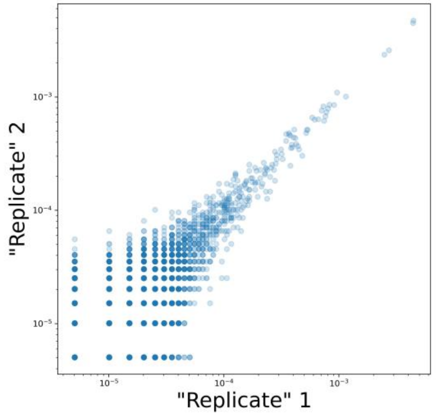
$$\iint df_1 \rho(f_1) ds P(s|\gamma, \bar{s}) P(n_1|f_1) P(n_2|fe^s)$$

$$P(s|\hat{n}_1, \hat{n}_2) = \frac{P(\hat{n}_1, \hat{n}_2|s, \gamma, \bar{s}) P(s|\gamma, \bar{s})}{P(\hat{n}_1, \hat{n}_2)}$$

Koraichi et al, *J. Phys. Chem. A*, 2022

Algorithm

data thinning

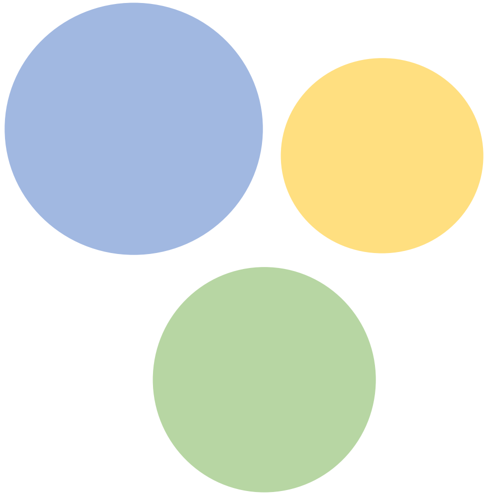


× 100

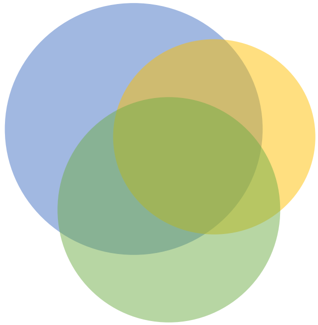
α, f_{min}

α, f_{min}

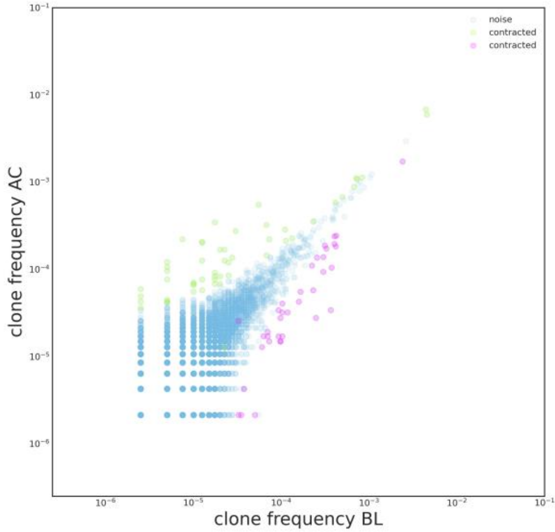
α, f_{min}



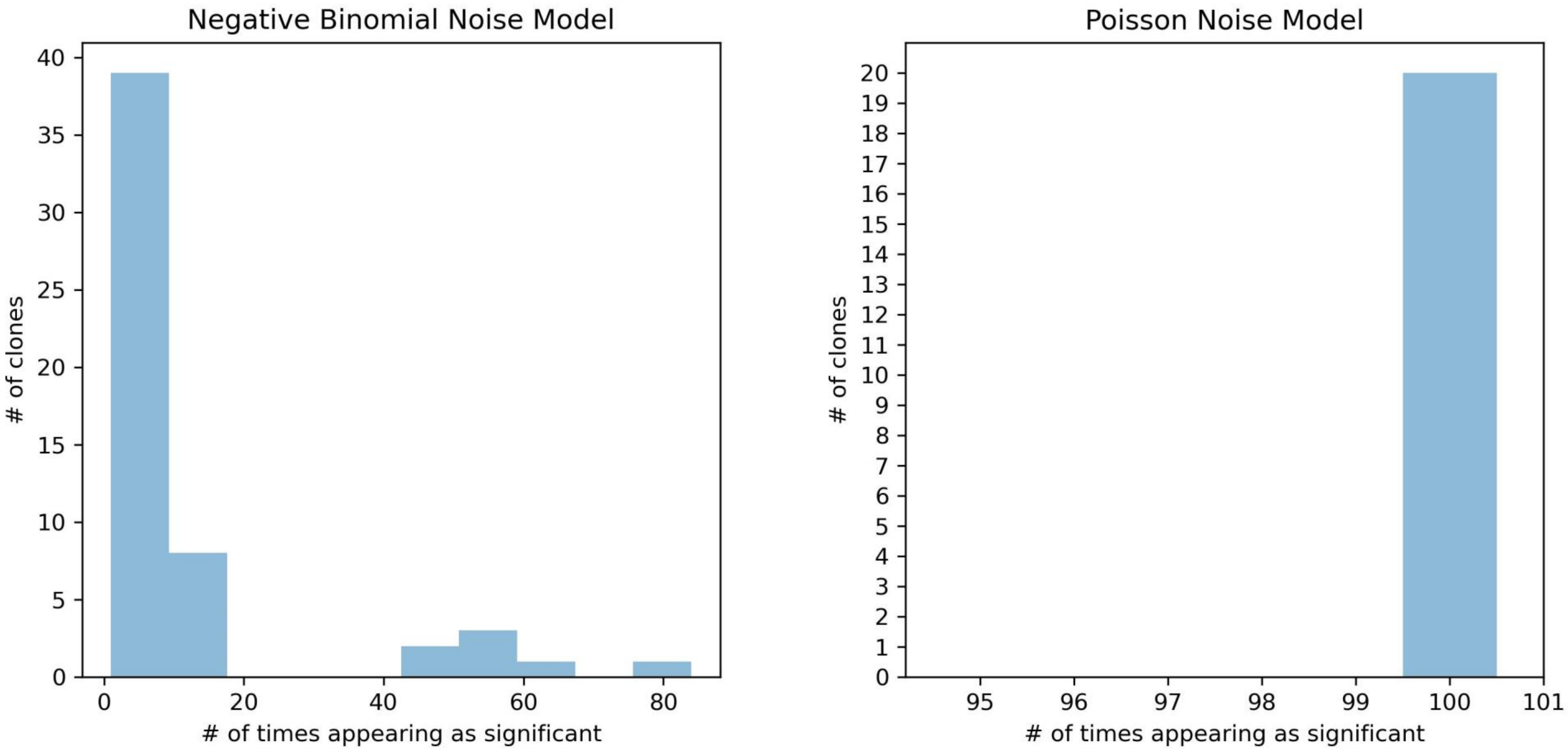
significant clones



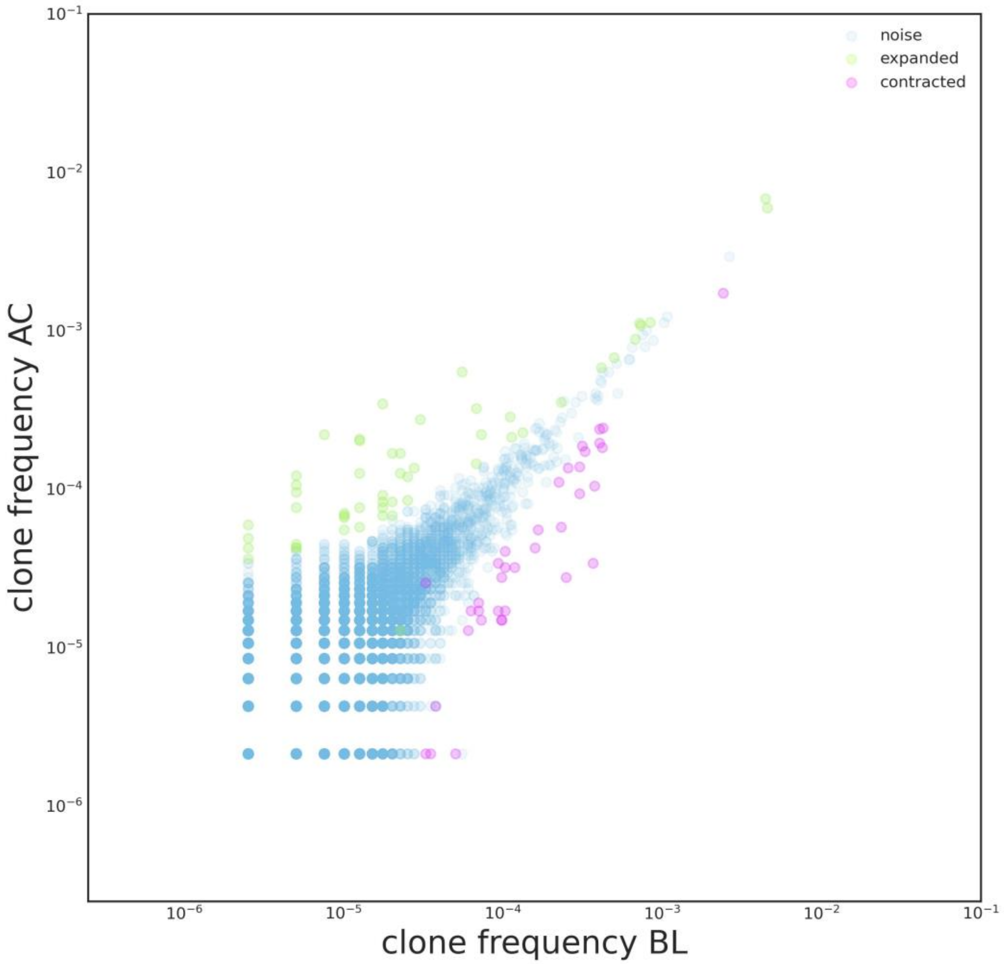
intersect significant clones



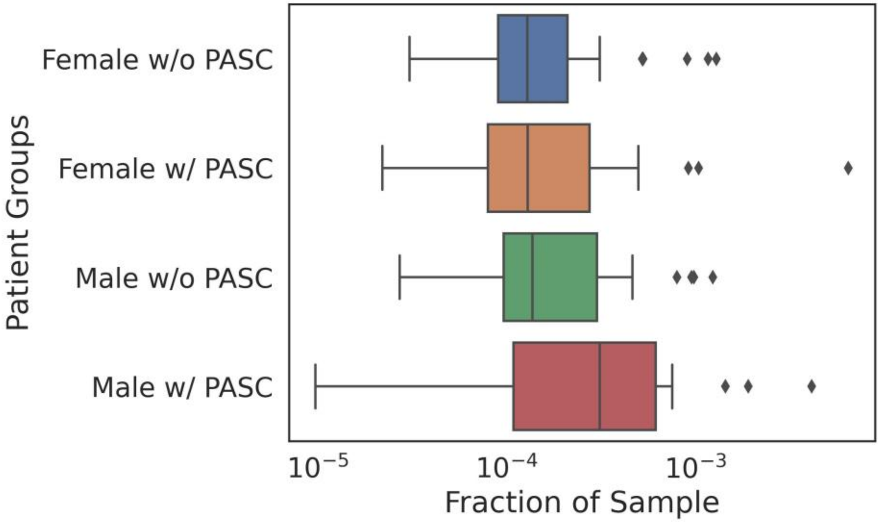
Choosing between noise models



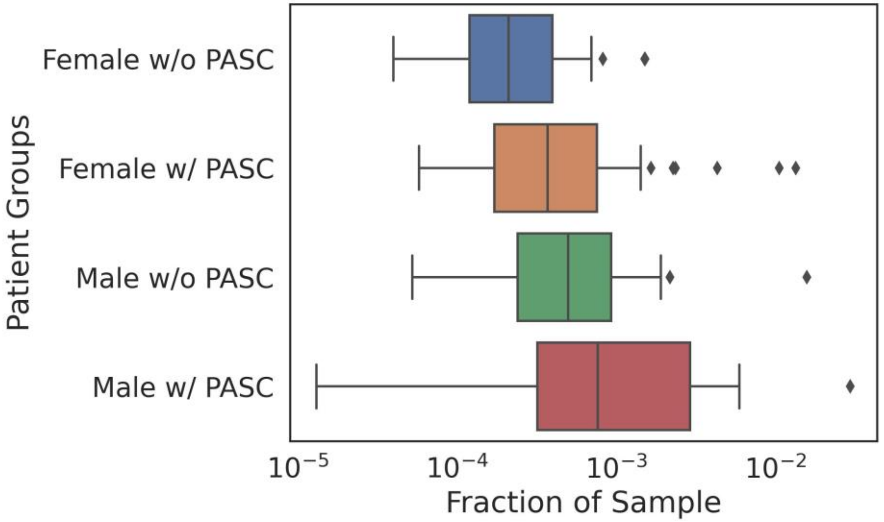
Detecting Expansions and Contractions



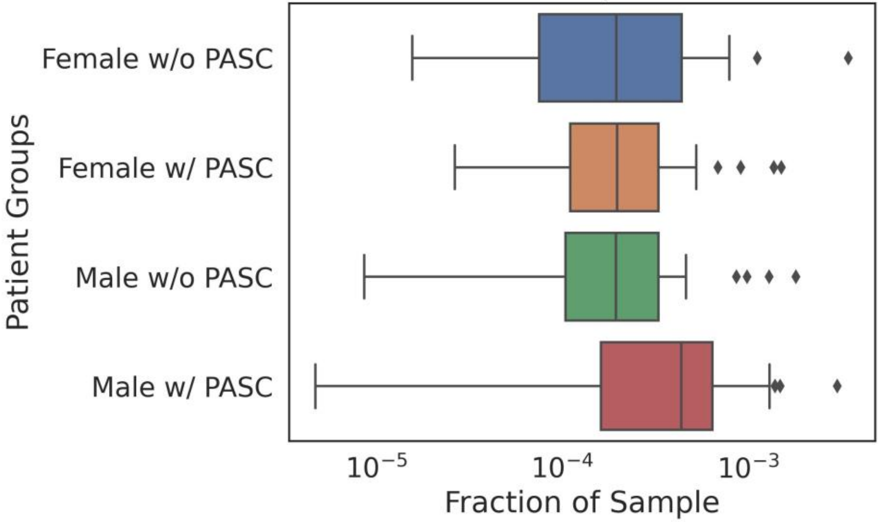
Fraction responding by demographic group



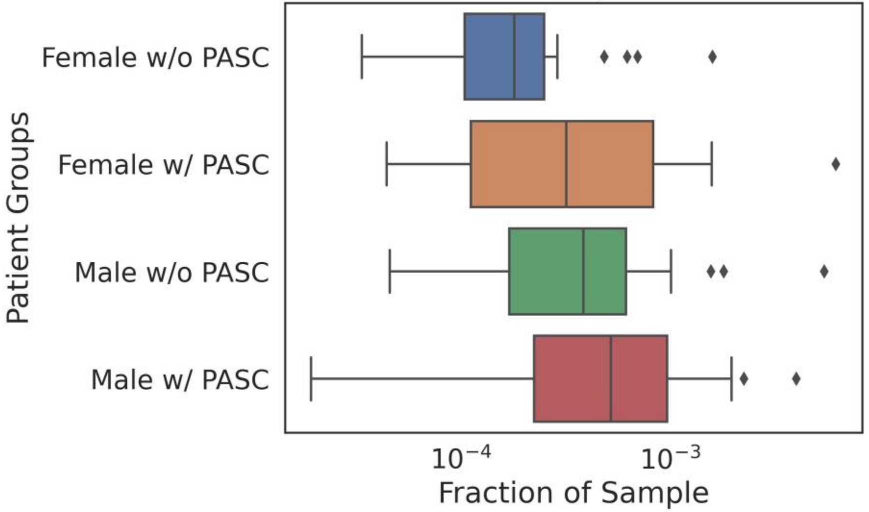
BL to AC Contractions



AC to CV Contractions



BL to AC Expansions

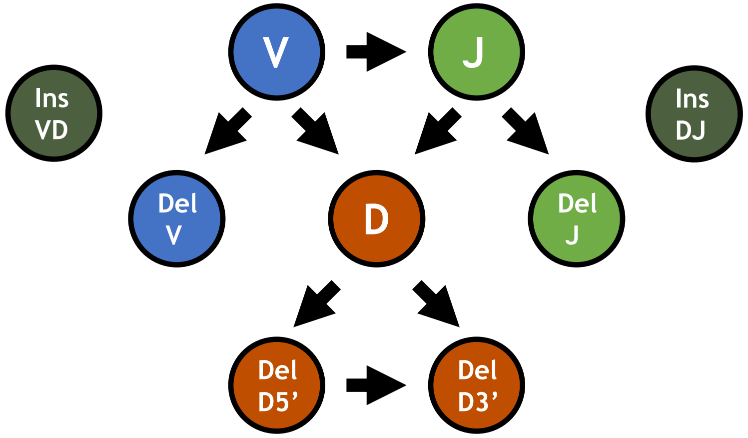


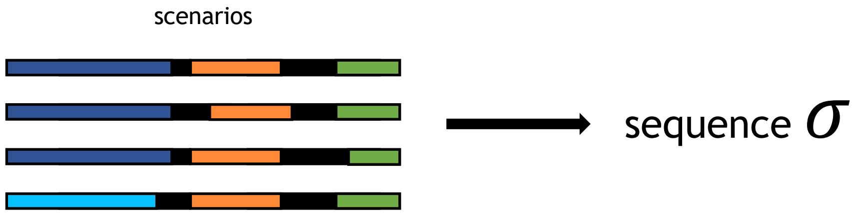
AC to CV Expansions

Generation and Selection Probability Analysis

Modeling generation and selection

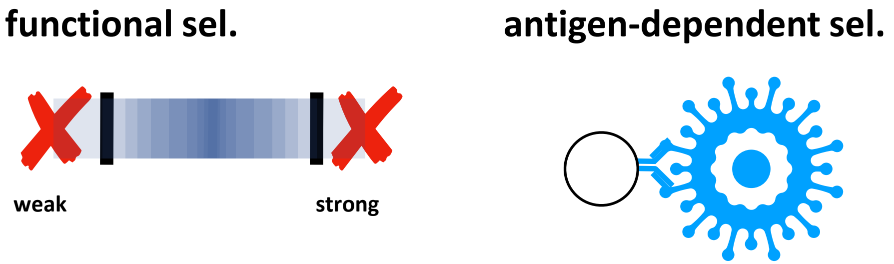
IGoR



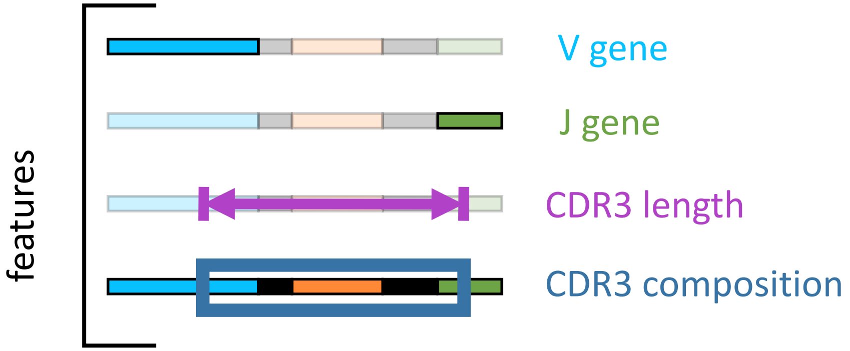


$$P_{gen}(\sigma) = \sum_{scenarios} P^{recomb}(scenario)$$

SONIA



$$P_{post}(\sigma) = P_{gen}(\sigma)e^{\sum_f \lambda_f}$$



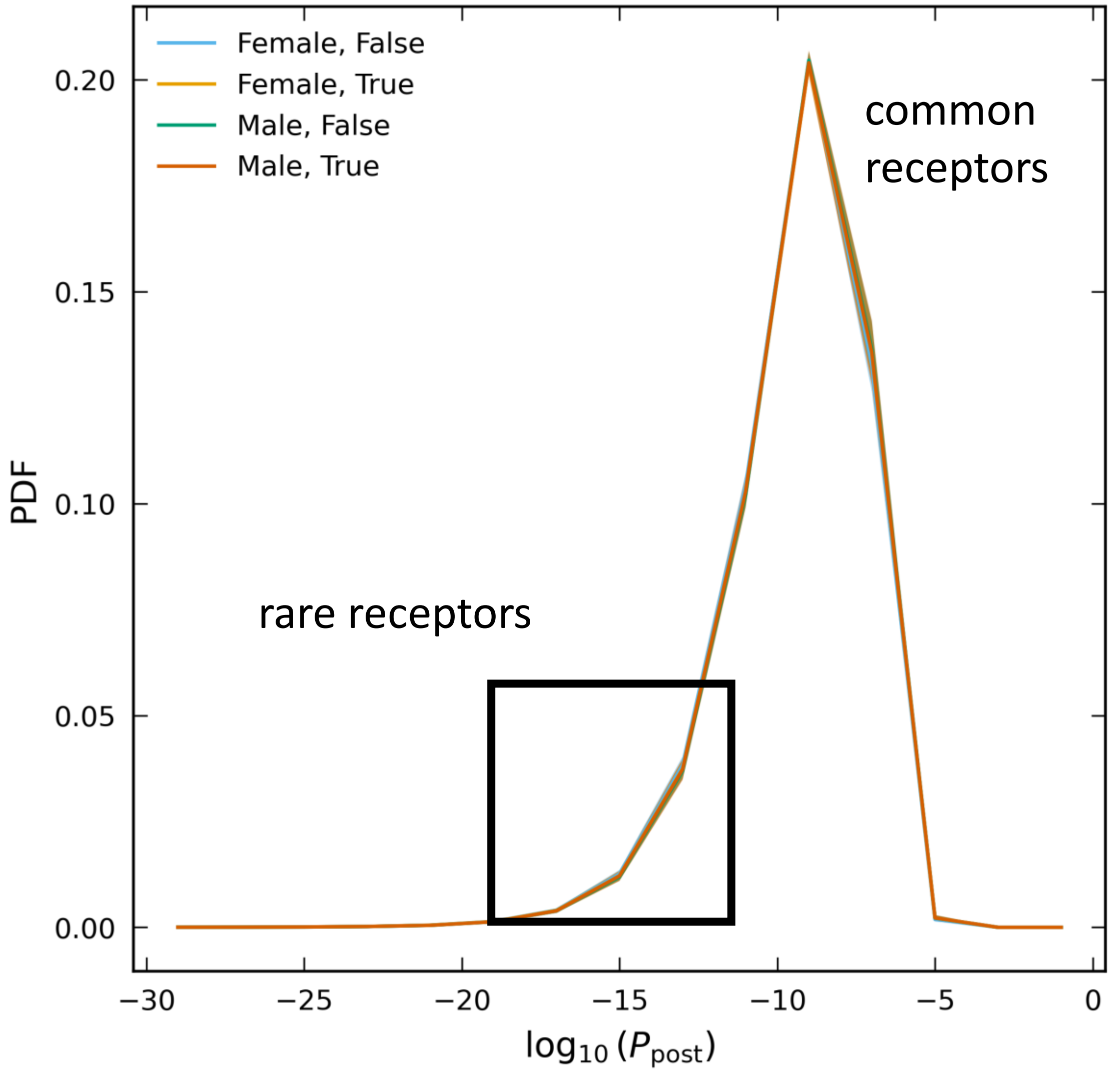
Sethna et al, *PLOS Comp Bio*, 2020
Montague, 2023

Marcou et al, *Nat. Commun.*, 2018

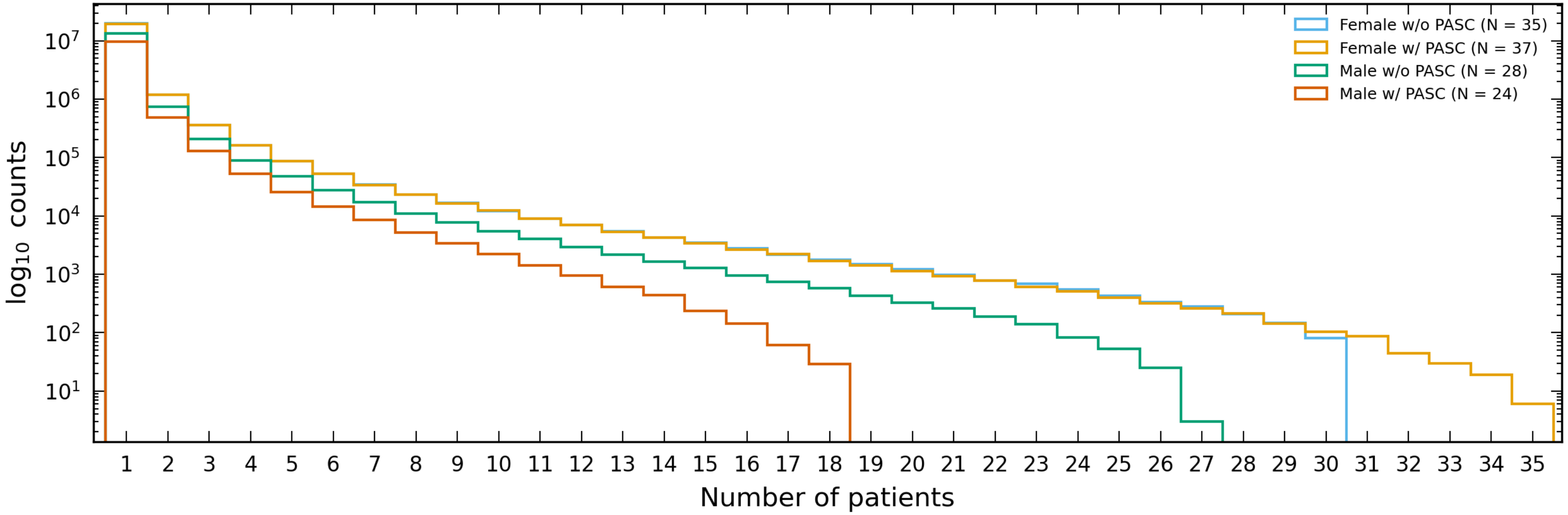
P_{post} distributions

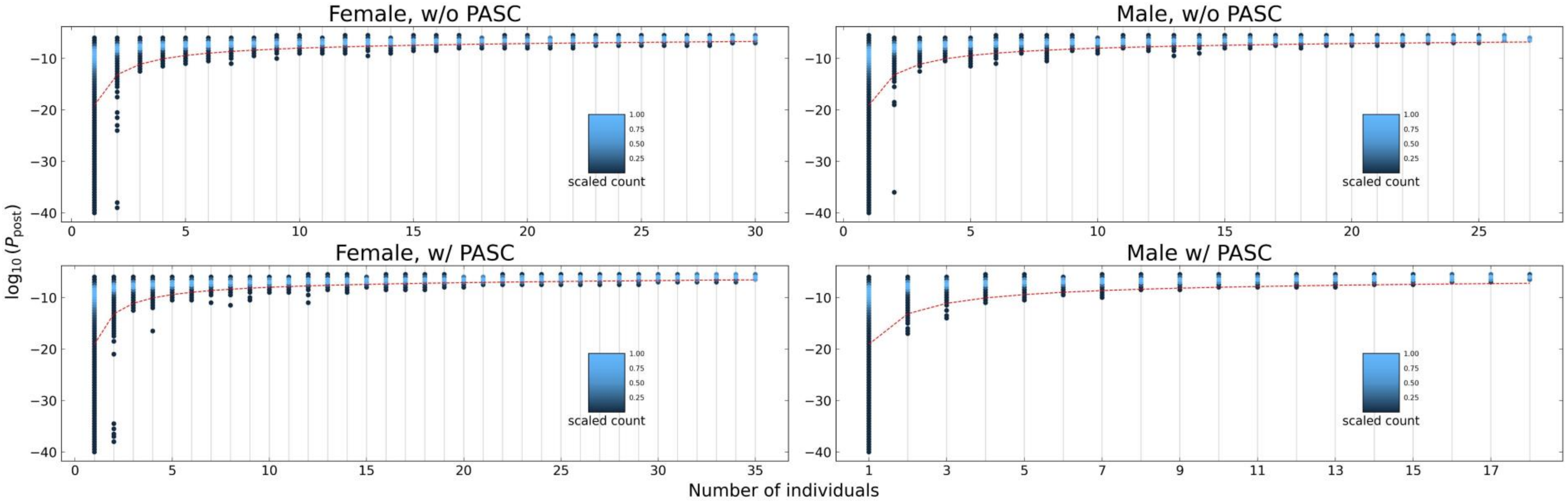
Why might individuals share clones?

- Convergent recombination
- Experimental biases
- Exposure history



Clone sharing and P_{post} in shared clones

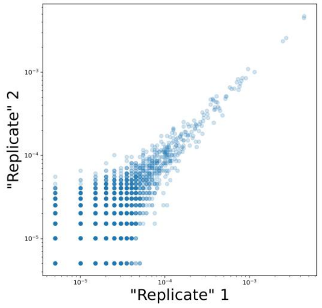




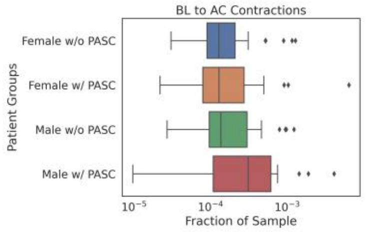
Discussion

Project Summary

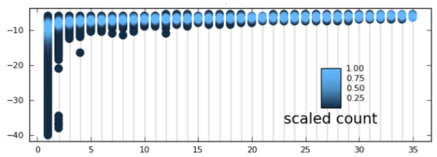
- Developed data thinning method for expansion analysis



- Detected expanding and contracting clones



- Identified rare, shared clones



Future Outlook

- Compare receptor distributions using information theoretic measures
- Refine data thinning technique
- Network analysis of responding clone sequences
- Integrate analysis with electronic health record data

Acknowledgements

Thank you to my mentors for the summer, Zach Montague and Armita Nourmohammad, the Nourmohammad lab, and the UW Physics REU program.

This work was supported by the National Science Foundation.