Latent space modelling of high dimensional cytokine dynamics

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Context

- Immunotherapies are being developed [1]: engineered T cells, cancer vaccines, etc.
- New experimental and modelling tools are needed to assess and improve them.
- Success of immunotherapy treatments depend on **antigen quality** (potency) [2].
- Immune cells produce different **cytokine** response for antigens of different qualities.
- We lack quantitative principles to interpret high dimensional cytokine dynamics [3].

Data: cytokine time series

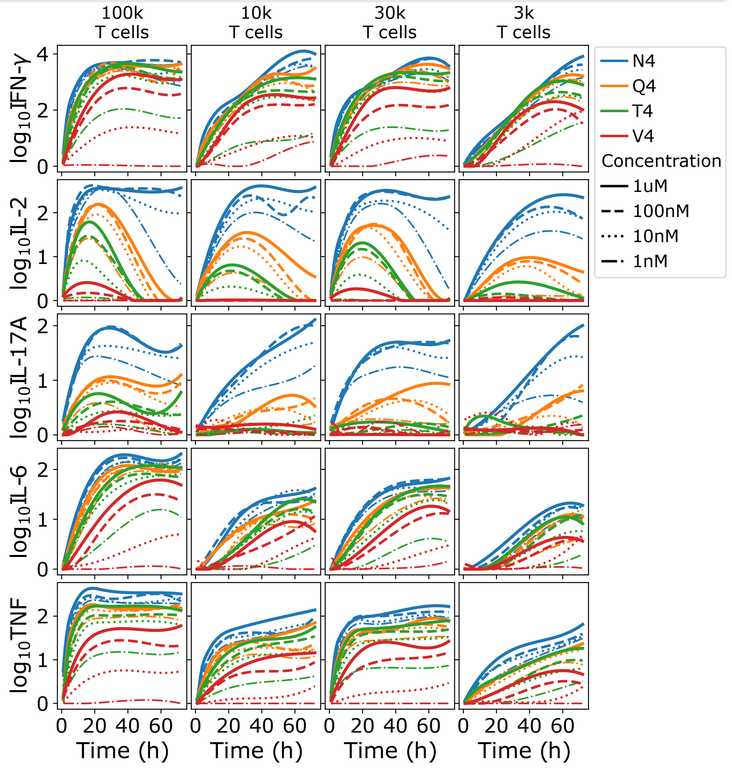

Figure 1: Using a robotic platform, we can track over time the concentration of many cytokines (5 shown) produced by T cells responding *ex vivo* to various antigens. Different antigen qualities trigger different kinds of cytokine time series.

Glossary

- **Antigen**: molecule (peptide) that can be detected by the immune system.
- **Quality**: potency, capacity of an antigen to trigger a response when detected.
- **Cytokines**: extracellular messaging molecules produced and consumed by immune cells.

Antigen encoding in latent space

Goal: find a low-dimensional representation in which cytokine dynamics can be modelled and classified according to antigen quality.

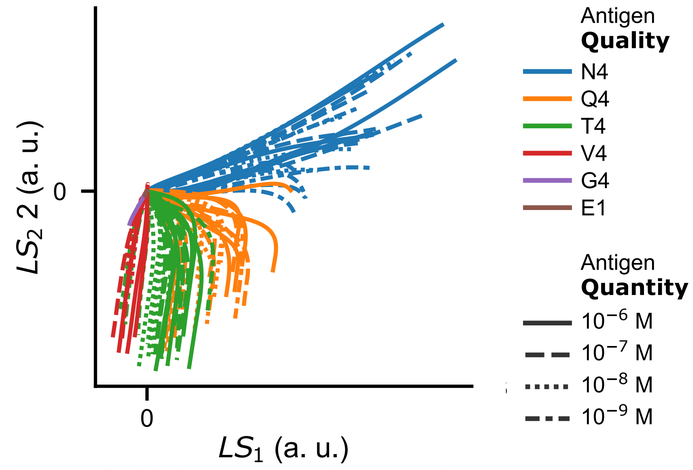

Figure 2: Using a small neural network, we found that time integrals of the logs of cytokines can be projected to a 2D space in which trajectories are separated according to antigen quality. We term this structure **"antigen encoding"**.

Modelling latent space dynamics

We found simple dynamical equations to describe trajectories in latent space.

$$\mathbf{r}(t) = \begin{cases} \mathbf{v}_0 t & t \leq t_0 \\ \frac{\mathbf{v}_0 - \mathbf{v}_t}{k}\left(1 - e^{-k(t-t_0)}\right) + \mathbf{v}_t(t - t_0) + \mathbf{v}_0 t_0 & t > t_0 \end{cases}$$

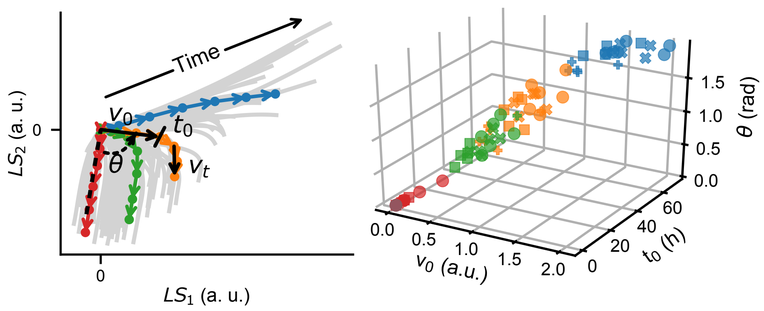

Figure 2: (Left) model parameterization of latent space curves. (Right) parameter values fitted on each curve reflect antigen quality (color of dots).

References

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Model-generated cytokine data

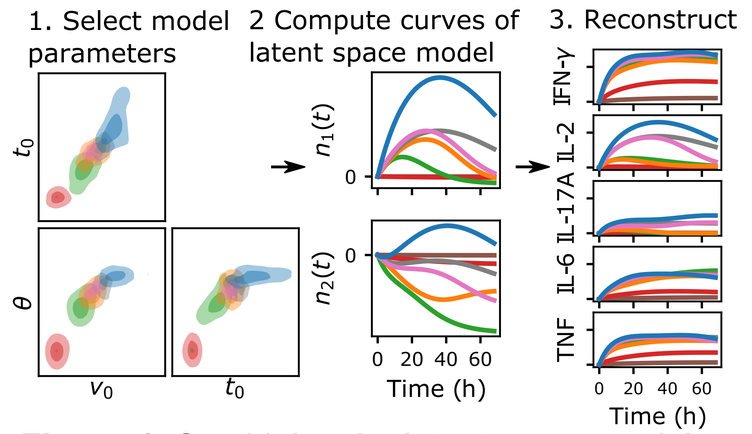

Figure 4: Combining the latent space model and a non-linear reconstruction method allows us to generate model-derived cytokine time series.

Application to engineered T cells

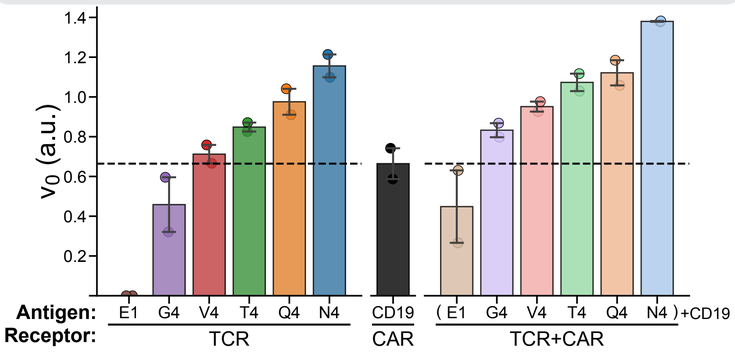

Figure 5: Values of model parameter v0 fitted on cytokine trajectories coming from anti-CD19 chimeric antigen receptor (CAR) T cells reveal sub-optimal activation those T cells by CD-19.

Conclusions

- Cytokine time series encode antigen quality in a 2D latent space.
- A simple dynamical model captures this dependency of the latent space on quality and can generate new cytokine time series.
- This model allows us to quantify the response of T cells engineered for therapy.

Acknowledgements

This work was also supported by a grant from the **Simons Foundation** to PF and an **NSERC-CREATE Graduate Award in Complex Dynamics** to FB. The Immunodynamics group is supported by the intramural research program of the **National Cancer Institute**.