

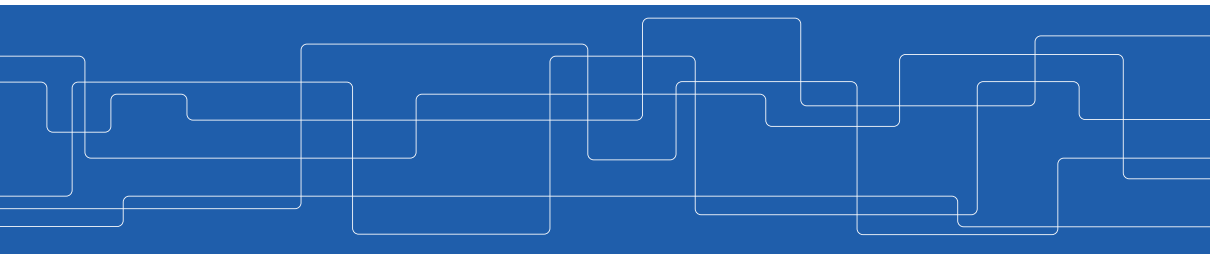


# Modelling Pathogen Response of the Human Immune System in a Reduced State Space

Pouria Tajvar<sup>†</sup>, Rikard Forlin<sup>‡</sup>, Petter Brodin<sup>‡</sup>, and Dimos V. Dimarogonas<sup>†</sup>

<sup>†</sup>KTH Royal Institute of Technology

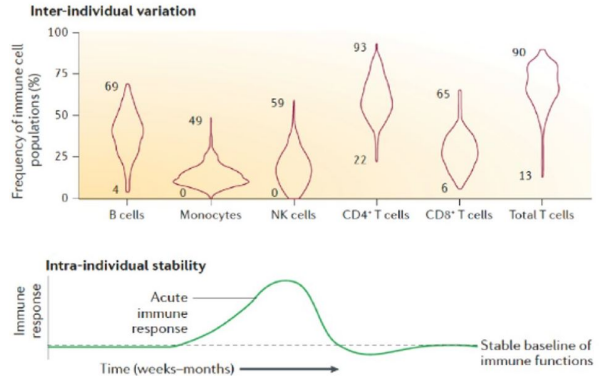
<sup>‡</sup>Karolinska Institute



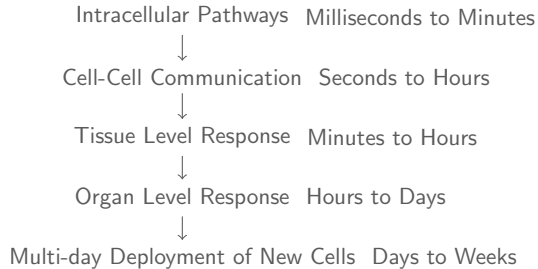
# Project Background

- ▶ Immune cell composition varies a lot between individuals.
- ▶ Cell composition is highly stable through life-time. (during health)
- ▶ Inter-personal differences can predict immune response differences. <sup>a</sup>

<sup>a</sup>Kaczorowski, Kevin J., et al.  
 "Continuous immunotypes describe human immune variation and predict diverse responses.", PNAS 2017



# Time Scale Separation in the Immune Response



The immune system operates at multiple time scales, each affecting the dynamics at the next slower scale. <sup>a</sup>

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<sup>a</sup>Moyles, Iain R., Chapin S. Korosec, and Jane M. Heffernan. "Determination of significant immunological timescales from mRNA-LNP-based vaccines in humans.", *Journal of Mathematical Biology* 2023

# Intra-cell dynamics example

## State-Space Equations <sup>a</sup>

$$\begin{aligned}\frac{dM}{dt} &= k_1 \cdot G - k_2 \cdot M \\ \frac{dP}{dt} &= k_3 \cdot M - k_4 \cdot P\end{aligned}$$

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<sup>a</sup>Lenstra, Tineke L., et al. "Transcription dynamics in living cells." , Annual review of biophysics 2016

## Parameters

$G$ : Gene concentration,  $M$ : mRNA concentration,  $P$ : Protein concentration



# Transcription Rate Modulation

## Dynamic Modulation of $k_1$

The transcription rate  $k_1$  can be influenced by the concentration of various signaling proteins, making it a dynamic function rather than a static constant.

## Origin of Signaling Proteins

These proteins can:

- ▶ Be produced within the cell as a result of other pathways.
- ▶ Originate from external sources, such as soluble ligands produced by other cells.

This interplay leads to complex signaling pathways and underscores the importance of cell-cell communication.

## Challenge

The modulation dynamics is by design very robust, redundant, and adaptable.



# Cytokine Storm: A Biological System Uncontrolled

## Definition

A cytokine storm is an overproduction of immune response molecules (cytokines) leading to harmful levels of inflammation and potential multi-organ failure.

- ▶ Can be seen as "overcompensation" – a disproportionate reaction to an external input.
- ▶ Highlights the importance of balanced, regulated feedback to maintain system stability.

## Control perspective

The irregular system excitation in such reactions can provide insights into:

- ▶ How biological systems balance robustness and adaptability.
- ▶ Potential interventions to dampen or prevent such extreme reactions.

# Our Data: Annotated scRNA from PBMC Cells

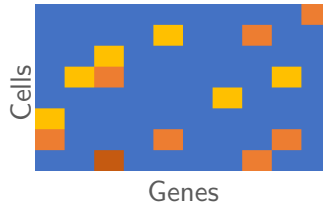
## Data Source

Single-cell RNA data: a snapshot of RNA molecules in individual cells.

- ▶ Samples taken from 120 healthy individuals.
- ▶ Exposed to three pathogens in-vitro.
- ▶ Measured in the untreated state as well as 3h and 24h after exposure.<sup>a</sup>

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<sup>a</sup>Oelen, Roy, et al. "Single-cell RNA-sequencing of peripheral blood mononuclear cells ... gene expression regulation upon pathogenic exposure.", Nature Communications 2022



## Function vs. Measurement

- ▶ Cellular function largely happens at the protein level.
- ▶ However, proteins are complex and harder to quantify at a single-cell level compared to RNA.

## Remarks

- ▶ While RNA data provides rich insights, the translation from RNA to protein and then function is nuanced and can introduce modeling challenges.
- ▶ The cells are destroyed during this measurement (i.e. the one-shot challenge)





# The One-Shot Challenge Across Domains

## Implications for Modeling Dynamics

- ▶ Tracking individual trajectories becomes impossible.
- ▶ Relies heavily on population-level or ensemble statistics.

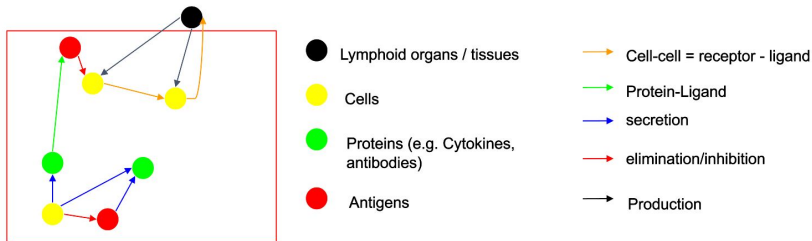
## Other Systems Facing Similar Challenges

- ▶ **Economic Systems:** One-time surveys or censuses provide static snapshots; dynamic behaviors inferred indirectly.
- ▶ **Social Systems:** Single interactions or events can have cascading effects; hard to trace back individual trajectories.

## Key Insight

Combining data-driven models with domain-specific insights, can help in tackling these challenges.

# Overview of Our Approach



## Approach Highlights

- ▶ Modelling each cell type as an agent.
- ▶ Challenge: high dimensionality of each agent's state (expression level of thousands of genes) and relatively few time points.
- ▶ Proposed approach: Discrete time model alternative in a low dimensional projection of the state space.

# Using Earth Mover's Distance (EMD) for Dimension Reduction

## Addressing the Dimensionality Challenge

- ▶ We need to find a low-dimensional projection of the state space.
- ▶ We use Earth mover's distance (EMD) that is a measure of the distance between two probability distributions.

$$DE_g^{EMD}(L^{(1)}, L^{(2)}) = \int_0^\infty \left| \int_0^v (\mathbb{P}(\mathbf{x}_g = v' \mid L^{(1)}) - \mathbb{P}(\mathbf{x}_g = v' \mid L^{(2)})) dv' \right| dv$$

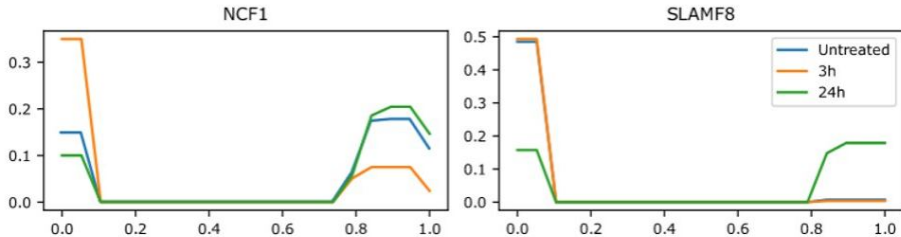
## EMD in Our Context

- ▶ We have shown that EMD is a robust measure to identify important states in response to an input. (Compared to the standard alternative in gene expression i.e. logarithm difference).
- ▶ The selected genes (i.e. states) are also shown to be informative in response detection.

## Classifying cells from different samples based on their gene expressions

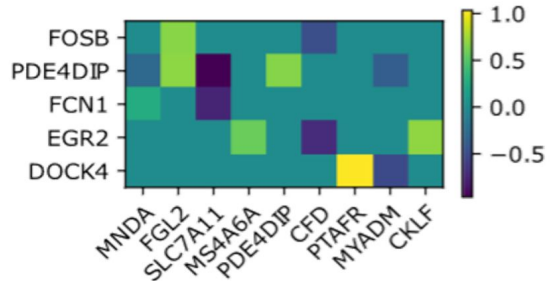
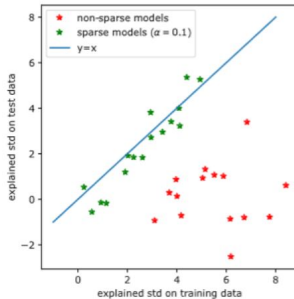
## Identifying fast vs. slow responding genes

- ▶ Identifying 3h vs 24h genes enables distinguishing fast and slow responding genes.
- ▶ Fast-responding genes are likely to be in the upstream of the signalling pathway.



# Response analysis

- ▶ Constructing a linear model of the internal dynamics.
- ▶ We can compute linear dynamics as a solution to an optimization problem to penalize non-zero elements for enforcing sparsity.



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- A network diagram illustrating interactions between various cell types. The nodes are represented by blue circles with labels: megakaryocyte, CD8T, NK, monocyte, CD4T, DC, hematopoietic, B, plasma B, and DNT. The edges represent interactions between these cell types. The network shows a central cluster of interactions involving CD8T, NK, monocyte, CD4T, and DC, with additional connections to megakaryocyte, hematopoietic, B, plasma B, and DNT.



# Summary

## EMD in Dimensionality Reduction

- ▶ EMD is a robust metric for identifying significant dimensions in the cell state space in the immune response.

## Cell-Cell Communication Dynamics

- ▶ Cell-cell communication dynamics includes fast-changing and slow-changing dimensions that can potentially be incorporated with multi-step models.

## Future Work

- ▶ Adapt the continuous time network topology identification method to our irregular, discrete time points.





# Thank You!

The Git repository containing the source code for our paper, along with these presentation slides, can be accessed at the following link:

**<https://github.com/KTH-DHSG/immune-system-pathogen-response>**

Alternatively, scan the QR code below to directly access the resources:

