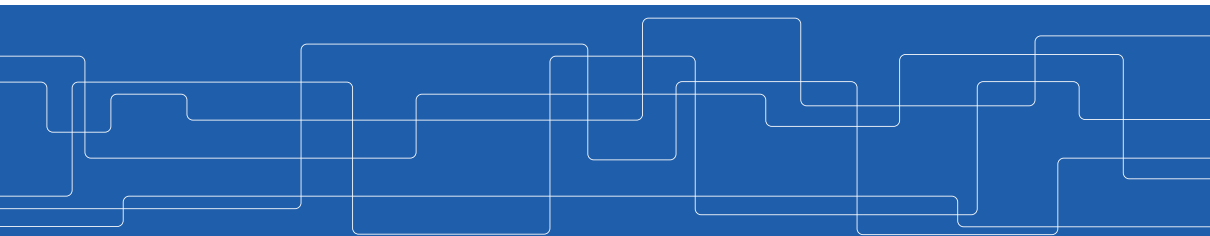# Modelling Pathogen Response of the Human Immune System in a Reduced State Space

Pouria Tajvar[†], Rikard Forlin[‡], Petter Brodin[‡], and Dimos V. Dimarogonas[†]
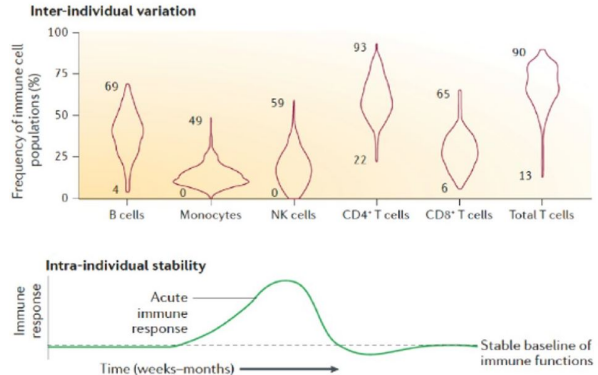
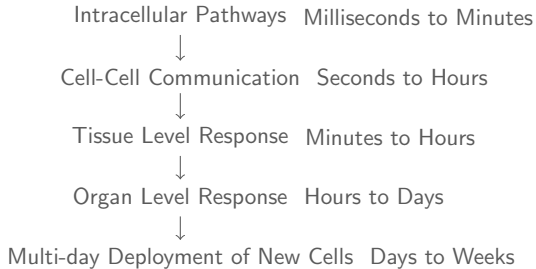[†]KTH Royal Institute of Technology
[‡]Karolinska Institute

Project Background

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

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[a]Kaczorowski, Kevin J., et al. "Continuous immunotypes describe human immune variation and predict diverse responses.", PNAS 2017

Inter-individual variation

Intra-individual stability

Time Scale Separation in the Immune Response

Intracellular Pathways   Milliseconds to Minutes
↓
Cell-Cell Communication   Seconds to Hours
↓
Tissue Level Response   Minutes to Hours
↓
Organ Level Response   Hours to Days
↓
Multi-day Deployment of New Cells   Days to Weeks

The immune system operates at multiple time scales, each affecting the dynamics at the next slower scale. [a]

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[a] 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 [a]

$$\frac{dM}{dt} = k_1 \cdot G - k_2 \cdot M$$

$$\frac{dP}{dt} = k_3 \cdot M - k_4 \cdot P$$

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[a]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 various signaling proteins, making it a function $k_1 = f(P)$ 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 Unchained

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

Control perspective
The irregular system excitation in such reactions can provide insights into:[a]

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

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[a]Consiglio, Camila Rosat, et al. "The immunology of multisystem inflammatory syndrome in children with COVID-19.", Cell 2020

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.[a]

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

scRNA data remarks

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
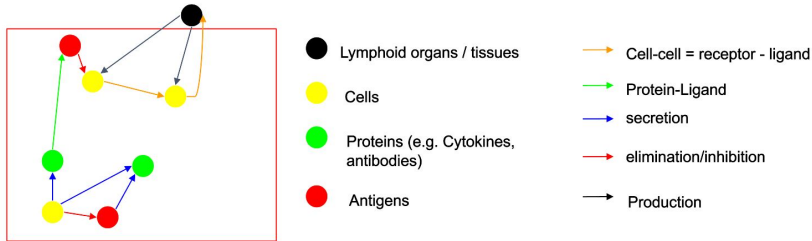
Implications for Modeling Dynamics

- ▶ 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

Legend:
- ● Lymphoid organs / tissues
- ● Cells
- ● Proteins (e.g. Cytokines, antibodies)
- ● Antigens

- → Cell-cell = receptor - ligand
- → Protein-Ligand
- → secretion
- → elimination/inhibition
- → Production

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
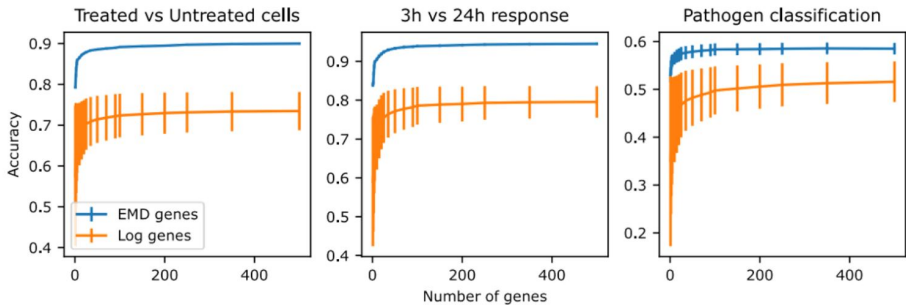
Addressing the Dimensionality Challenge

- ▶ 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.

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

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.

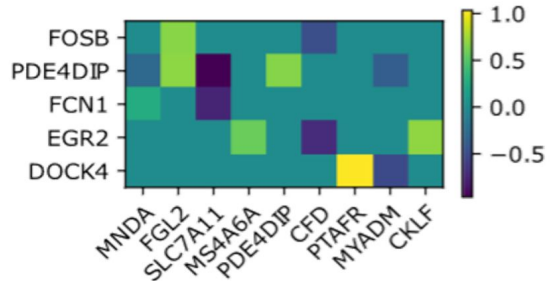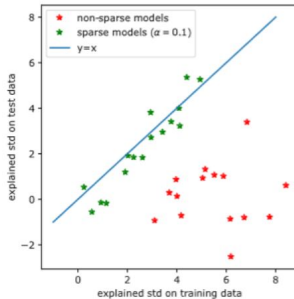Classifying cells from different samples based on their gene expressions

- Identifying 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.
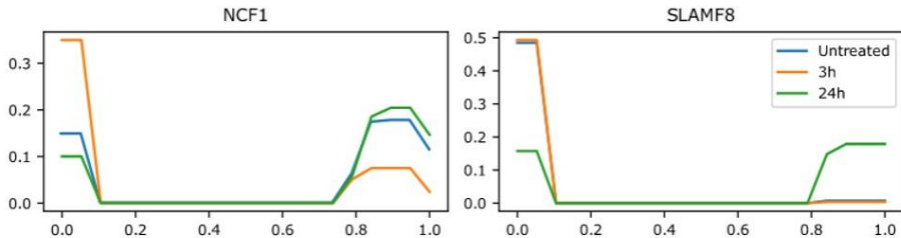
- Constructing a linear model of the transcription dynamics $k_1 = AP$.
- We can compute linear dynamics as a solution to an optimization problem to penalize non-zero elements for enforcing sparsity.

- Preliminary solution: Incorporating known gene interaction pairs and determining their presence in high-EMD gene list.
- Compute a communication score to construct an initial estimate of the network topology:

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: