UNIVERSITY OF NEBRASKA AT OMAHA

Large Scale Dynamical Model of Macrophage/HIV Interactions

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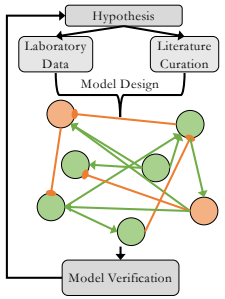
Introduction

- Large-scale, complex biological systems have been shown to display emergent properties—phenomena that arise out of network organization and dynamics that are not discernable at the individual gene or protein level.
- Here, we introduce a large-scale dynamical Boolean model of HIV/macrophage interaction. The model contains 714 components and 1584 edges and is simulatable in response to 38 different external inputs (growth factors, bacteria, viral soluble factors, etc.).
- The model was validated via reproduction of >50 different known phenomena, Determinative Power Analysis, and Biological Essentiality.
- The model reproduces data on proteins influenced by HIV infection.
- The completed model now provides a platform for the discovery and investigation of emergent properties of HIV-infected macrophages.



Methods

Model Creation: The Cell Collective[1] platform was used to create and simulate the model. Node and edge logic was designed using interaction data manually curated from the literature as reference; the dynamical nature of the interactions (e.g., positive or negative) and dominance among multiple interactions was inferred.

Model Description: The model contains 714 components and 1584 edges, and can be simulated in response to 35 different external inputs, including the following families:

| Growth Factors | Extracellular Matrix | Virus | Bacteria | Stress Factors | Ions | Interferons |

| HIV Soluble Factors | Immunoglobulins | Death Receptor Ligands |

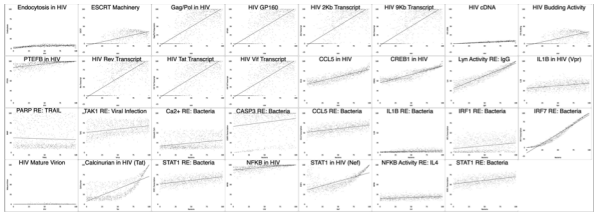
Model Validation: The model was validated using three different methods:

- **Phenomena Replication:** >50 canonical macrophage/HIV dynamical phenomena were found in the literature and verified using the Dose Response tool in Cell Collective, as explained in (1).
- **Determinative Power (DP):** DP of a particular component "X" in the network is the summation of all "information gain" that is received by all the downstream components regulated by X, obtained via the reduction of uncertainty of the state of the downstream components based on the knowledge of the state of "X," expressed as the classical *Shannon entropy*[2]. All components can then be ranked by DP, with the most powerful nodes having the highest DP values, representing network components whose states provide the most "information gain" in the network.
- **Biological Essentiality (BE):** The essentiality data for human proteins were obtained from the OGEE database V2[3]. All nodes were organized in descending order of DP values. To investigate the association of DP values with essentiality, we searched the proportion of essential nodes in the top 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% and across the whole network. Furthermore, within the top 10% (n=68) high DP nodes, we looked for essential nodes in the top 10, top 20, top 30, top 40 and top 50 nodes based on DP values. The proportion of essential nodes within groups was then compared across the whole network.
- **Confidence Interval Matching of Mass Spectrometry Data:**
  - Primary monocytes were collected from 7 healthy human donors, differentiated into macrophages (hMDMs), and then infected with HIV-1 or uninfected for control. Peptides were isolated from these samples and the subjected to mass spectrometry.
  - SWATH-MS was used to identify and quantify activity of 67 proteins from +/- HIV-infected hMDMs.
  - The model was simulated against two "environments" (the collection of activities for all input nodes) corresponding to +/- HIV infection. The results were assessed against the mass spectrometry data using a Python script for a variance-based confidence interval matching method to determine the biological relevance of our model.

(1) Helikar et al. (2008), Proc. Natl. Acad. Sci. 105 (6) 1913 (2) Pentzien et al. (2018) Front. Phys. (9) 1185; (3) Chen et al. (2017) Nucleic Acids Res. (45) D940

Results

Phenomena Replication: The model reproduces several canonical HIV-Macrophage interaction, immune signaling, and cellular signaling phenomena (31 shown):



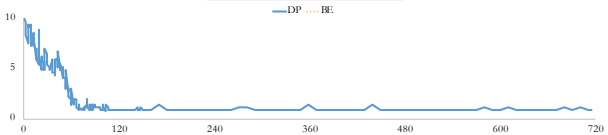
DP and BE Analyses

The 30 nodes with the highest DP along with their BE.

BE Abbreviations:
E = Essential;
NE = Not essential;
N/A = Not applicable
(e.g., a viral protein)

HIV-Tat-Nucleus (N/A)	**Nef Virion (N/A)**	**Pr55 Gag Cleavage (N/A)**
NFκβp150-RelAp65 (E)	**STAT1 (E)**	**Pak (E)**
IRF5-IRF5-Nucleus (NE)	**HIV 4kb mRNA (N/A)**	**CaM (E)**
IRF1 Nucleus (E)	**Rho A (E)**	**HIV PIC (N/A)**
Cytosolic Ca (N/A)	**HIV Endosome (N/A)**	**PIP245 (N/A)**
TP53 Nucleus (E)	**JNK (E)**	**HIV 2kb mRNA Cyt (N/A)**
PKA (E)	**P38 (E)**	**Endocytosis (N/A)**
CD4 (NE)	**PKC (E)**	**CCR5 (NE)**
CSF1-R (E)	**P60 Src (NE)**	**ISGF3 Nucleus (NE)**
p21 (Cip1) (NE)	**HIV 9kb mRNA (N/A)**	**Gαi (NE)**

Overlap of DP and BE Analyses

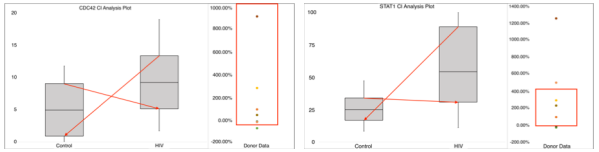


DP (blue) and BE (orange) ranked 0-10 (low to high) of all 714 model nodes. Nodes assigned number (X-axis) based on overlap between DP, BE, and out-links.

Confidence Interval Matching

All 67 laboratory identified proteins were contained in the model. The activity of 77% (at 95% CI) and 91% (at 99% CI) of the HIV +/- hMDM proteins were replicated by the model.

Examples of Confidence Interval Matching



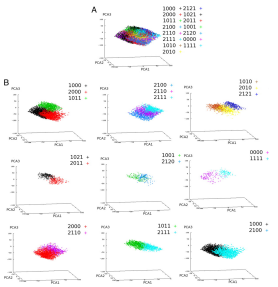
99% CI for CDC42. 6/7 (85.71%) match.

95% CI for STAT1. 3/7 (42.85%) match.

Summary: The model reproduces many canonical phenomena relevant to HIV infection pathology and immune signaling functions described in the literature. Non-HIV nodes with high determinative power correlate with critical components of many distinct signaling pathways.

Conclusions and Future Directions

- Emergent properties (EP) are "more than the sum its parts" phenomena that arise from the dynamics of a system.
- EP systems are by definition irreducible. Thus, they are difficult to understand as they must be studies as a whole.
- Using large-scale, dynamical modeling, our group published the first evidence of the emergent property of nontrivial information processing in cells (1). The current model can be evaluated for EP's in HIV infection.
- The model was validated via reproduction of >50 different known phenomena, Determinative Power Analysis, and Biological Essentiality, and reproduces data on proteins influenced by HIV infection.
- Modifications to the model necessary to emulate additional datasets may indicate potential drug targets.
- Determining how HIV affects the EP's of the system will indicate emergent effects of the virus using visual inference testing[2].
- Together, these results will be used to guide future hypothesis creation and testing in the laboratory.

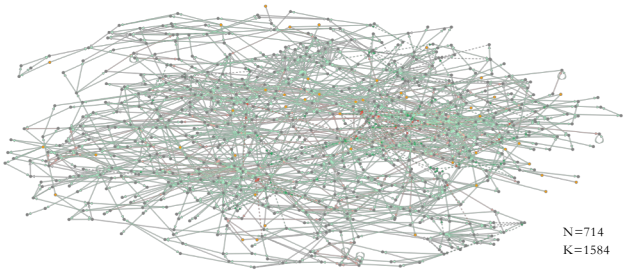


Evidence of pattern classification in cells, a nontrivial, emergent property

(1) Helikar et al. (2008) Proc. Natl. Acad. Sci. 105(6):1913;

(2) Majumder et al. (2013) JASA (108)942

The Macrophage Model



N=714
K=1584

Acknowledgements

Tomás Helikar designed, owns, and maintains the Cell Collective platform. Matthew Pelz, Trevor Pentzian, Bhanwar Puniya, and Michaela Matache designed the determinative power and bioessentiality analyses for Boolean models. The Pawel Ciborowski lab conducted all laboratory experiments. Wenxian Zhou designed the confidence interval matching analysis for which Sean Bresnahan designed the Python script. Oversight for all mathematical experiments was conducted by Jim Rogers and Mahbubul Majumder. Poster design by Sean Bresnahan and Matthew Froid. This project was funded by NIH DA043258; publication is in prep.

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