Cell Therapy & Engineering Connect
ISSN: 3105-3866
2025, Vol. 1, Cite as: doi:10.x/journal.x.x.x

SCIFINITI PUBLISHING

OPEN ACCESS

Research Article

Characterizing Immunodeficiencies Using Entropy Phase Transitions as Signatures of the Status of the Immune System

Javier Burgos-Salcedo[1,2]

[1] Facultad de Ingeniería, Fundación Universitaria San Mateo; 111411 Bogotá, Colombia

[2]Research Department, Corporación para la investigación y la innovación-CIINAS, 251201 Bogotá, Colombia

Contact: jdariob@sanmateo.edu.co; jdburgoss@corporacionciinas.org

ORCID: **https://orcid.org/0000-0002-1257-4226.**

Abstract

Determining the fitness status of the immune system is one of the central challenges of modern biomedical sciences, due to the relationship it has with senescence processes and aging. Currently, there is no universally valid metric that allows establishment when an individual's immune system is competent and to what degree it is competent in each pathology. In the present study, a model of complex adaptive networks is developed, whose nodes are made up of the eleven central types of immune cells, focused on the phase transitions of entropy to distinguish the optimal functioning of the immune network in contrast to what occurs in cases of immunodeficiency states, both primary and secondary. The results of the dynamic simulation indicate the presence of differentiated profiles between the immunocompetence and immunodeficiency states of the immune system and provide evidence on the state of the complex immune network and its internal connectivity, suggesting the presence of aging patterns of the immune response effector networks. This entropy-based approach offers quantitative, holistic assessment of immune status with potential applications in AI-driven diagnostic systems, disease monitoring, and personalized immunomodulatory therapies.

Keywords: systems immunology; immune fitness; entropy phase transition; complex adaptive networks; Immunodeficiencies

Introduction

What characterizes an optimal immune response? The obvious answer is usually that it effectively controls an infection, that some type of cancer does not develop or that it does not generate a disease associated with hyperreactivity of the immune system such as allergies or autoimmune diseases, or on the contrary that some disease is generated due to the weakness or absence of the immune response capacity [1]. However, this response characterizes immunocompetence by its results even without understanding how it fully works.

On the other hand, the development and application of efficient vaccines allow us to understand that a protective immune response can be induced by biotechnological means [2], which although it is a considerable advance in terms of human well-being and health, still leads us to consider the action of the immune system from a totally empirical perspective [3]. Also, since the monitoring of the action of vaccines focuses on the measurement of cells and molecules that effector the immune response [4,5], a strategy that, although it has had a very positive impact, has contributed little to the understanding of the global mechanisms that give rise to a condition of immune fitness.

The theoretical approaches related to representing the immune system as a social network [6], as a complex adaptive system [7] or as an information transmission network [8], have allowed, being based on the use of mathematical models of finite graphs [9,10], the application of basic notions of information theory to the study of biological networks [11], in particular the concept of entropy, which is shown as a possible indicator of health status in humans [12], suggesting the presence of immune disorders [13], the progression of a disease [14], or the prediction of one [15].

The determination of the total mass, number and distribution of the eleven central cell types that make up the human immune system [16] generates essential information to carry out new quantitative models of the dynamics of immune networks as complex adaptive networks, as is the case of this work in which the basic immune network is represented as a connected graph of eleven nodes whose evolution is modeled by a system of differential equations ordinary and system dynamics [17].

Finally, considering, first, the useful background of the notion of entropy in the characterization of the state of a biological network, second, its illuminating applications in ecology [18,19], where phase transitions of entropy detect critical changes in natural ecosystems [19], and third, the availability of general methods for the detection of phase transitions in complex evolutionary networks [20,21], We propose a way to characterize and measure the transition dynamics of the entropy phase associated with an optimal immune system and also associated, in contrast, with primary and secondary immunodeficiency states, supporting the usefulness of this theoretical approach has been shown to have in biomedicine [22, 23] and the use of information theory to characterize complex networks [24].

Through systematic simulation of primary immunodeficiencies (genetic defects affecting specific immune components) and secondary immunodeficiencies (acquired conditions compromising immune function), we aim to demonstrate that entropy phase transitions can serve as distinctive signatures for various immunological states, establishing a quantitative framework that could integrates artificial intelligence systems with automated immune repertoire analysis, advancing our capacity to assess and manage immunological health in clinical settings.

Methods

Complex Adaptive Network Model

Based on the premise that the immune system is a complex network, we develop a computational model incorporating the eleven known major human immune cells [16], including eleven major cell types: T lymphocytes, B lymphocytes, natural killer cells, basophils, eosinophils, neutrophils, mast cells, macrophages, monocytes, plasma cells, and dendritic cells. The model was structured following Treur's formalism for network analysis [17], with each cell type represented as a node in the network (See Supplementary Data **Table 1** for details.) The key assumptions of our model include: The model of the healthy immune system is based on the optimal state of immune fitness characterized by the dynamics of eleven major immune cell types of populations conforming to a fully connected network under normal physiological conditions, assuming:

1. The immune network is fully connected in its optimal state, with each cell population potentially interacting with all the others.

2. Each cell population grows logistically once stimulated by an antigen.

3. Growth parameters are based on physiological carrying capacities derived from empirical data on human immune cell proportions.

4. Mortality rates vary between cell populations based on known lifespans.

It is important to note that the current model does not explicitly distinguish between naive and antigen-induced (activated) immune cells, we acknowledge that entropy values may vary depending on the state of activation. This distinction represents an important direction for future refinement of the model.

Currently, there are theoretical tools that measure the entropy of complex networks [24], and there are also models that enable their numerical representation and dynamic simulation using role matrices and differential equations [17]. Since the immune system is a complex network [6], and that, for the first time, there is a rigorous quantification of the eleven major types of cell populations that make up the immune system [16], a complex adaptive network model is developed following Treur's formalism (See Supplementary Data Figure 1 for details), and assuming that it is a connected network in which each type of cell population

grows logistically once they are stimulated by any antigen (See Supplementary Data **Table 2** for details). The Function Parameters Carrying capacity (*K*) and Mortality rate (*MR*) were obtained respectively from [16] and [25] respectively. Interaction strength (W_{int}) was derived from [26].

Dynamic simulation of the immune network is made using the following combination function (CF):

$$\frac{dX_i}{dt} = W_{int} * X_i \left(\frac{1 - X_i}{K}\right) - MR * X_i$$

Entropy calculation

We calculated network entropy (S) using Shannon's information entropy formula,

$$S = -k \sum_{i=1}^{n} p(X_i) \log\left(p(X_i)\right)$$

Network Density Analysis

To measure the **link density** (edge density) of a network, we calculate the ratio of existing links *(m)* to the total number of possible links. For a network of *N* nodes, the network link density is

$$D = \frac{m}{0.5 * N * (N - 1)}$$

The (maximal) link density *D* of a completely connected network is 1.

Simulating Immunodeficiencies

To model primary and secondary immunodeficiencies, we systematically modified the network structure by eliminating nodes (X_i) and reducing their connections as described in (supplementary Data **Table 3)** following the well-known clinical processes involved in these diseases [27-30].

Results

The results of this work include the determination of the entropy phase transition for the state of immunocompetence, and in primary and secondary immunodeficiencies.

Immune fitness

The study begins by simulating the optimal immune network, modeling the interactions of eleven key immune cell populations, such as T lymphocytes, B lymphocytes, and natural killer cells. Our study performs the dynamic simulation of an optimal immune network in which the eleven main cell populations of the immune system exhibit a logistic growth whose K and MR parameters take values considered typical of normal patterns of immune response in healthy individuals. The resulting pattern can be seen in **Figure 1A**. The entropy phase change associated with the optimal immune response state is presented in **Figure 1B** and can be characterized as a three-phase pattern as described below:

Stage 1: Network Activation ($0 \leq t \leq t_1$)

- Rapid entropy increasing
- Resource allocation and path development
- Network startup or traffic surge response

Stage 2: Coordination ($t_1 \leq t \leq t_2$)

- Entropy decreases as optimal flows established
- Route convergence and load balancing
- Efficient resource utilization patterns emerge

Stage 3: Stabilization ($t \geq t_2$)

- Stable entropy representing steady-state operation
- Established traffic patterns and resource allocation
- Network maintains responsiveness to changes

This entropy signature encapsulates the dynamic interplay of activation, regulation or coordination, and stabilization memory consolidation in a healthy immune system.

Immunodeficiencies

The behavior of phase transitions of entropy in primary and secondary immunodeficiencies and the connectivity condition is presented respectively in **Figure 2** and **Figure 3**. Our results indicate the sensitivity of entropy analysis to detect immune dysfunctions linking changes in entropy dynamics with changes in immune network connectivity.

2025, Vol. 1
doi:10.x/journal.x.x.x

Figure 1. Behavior of an immune system under optimal conditions.

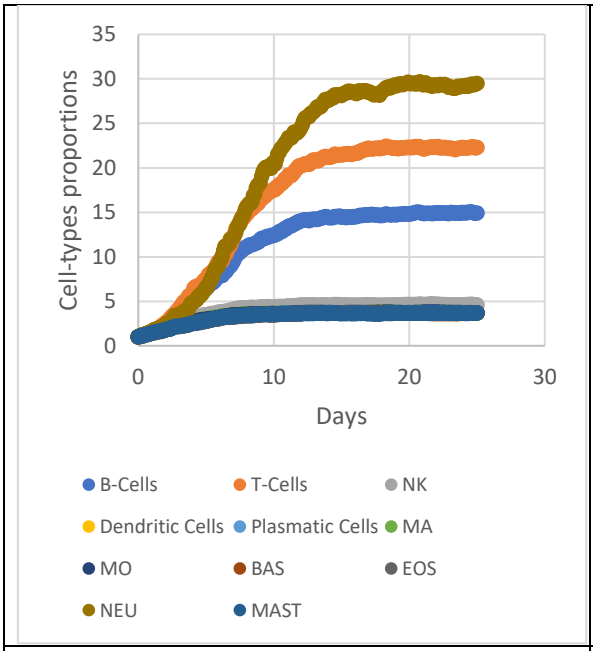


Figure 1A. Dynamic simulation for logistic combination functions for the immune effector cell types considered under optimal conditions

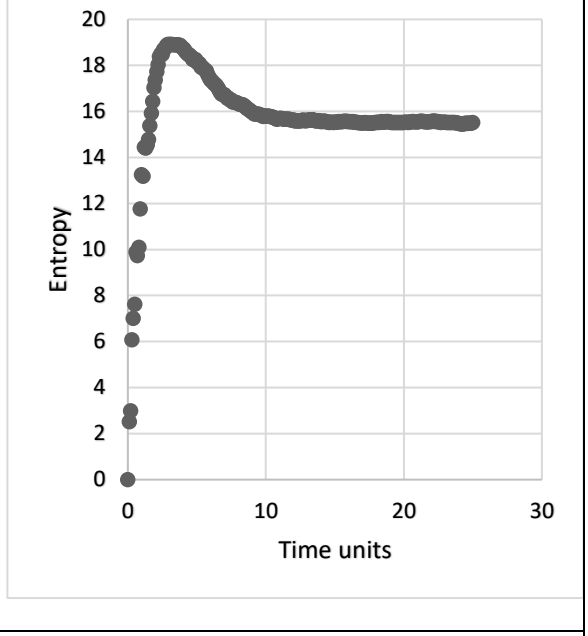


Figure 1B. Phase entropy transition for optimal immune fitness

Figure 2. Entropy transitions for primary immunodeficiencies.

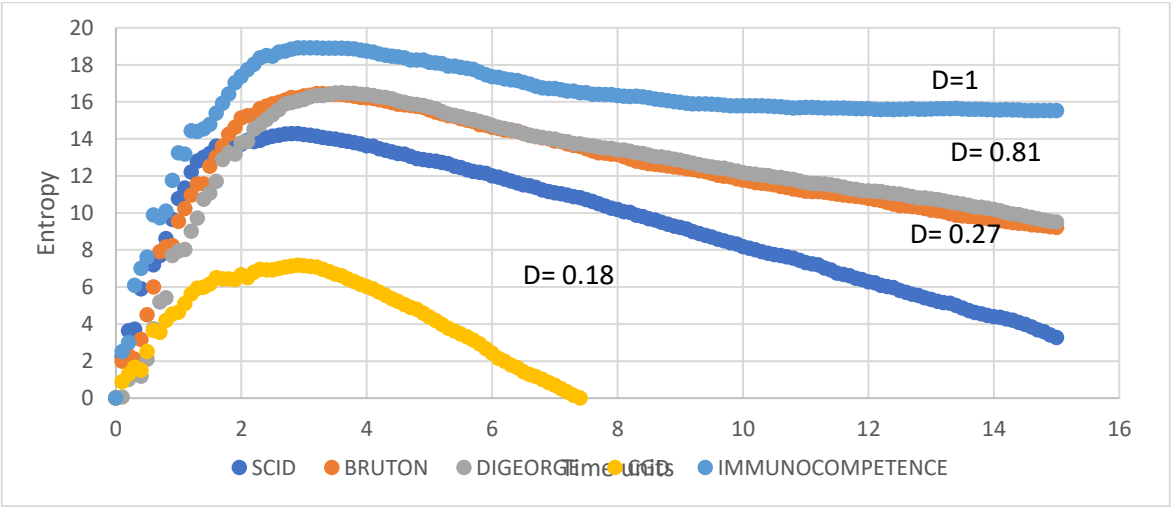
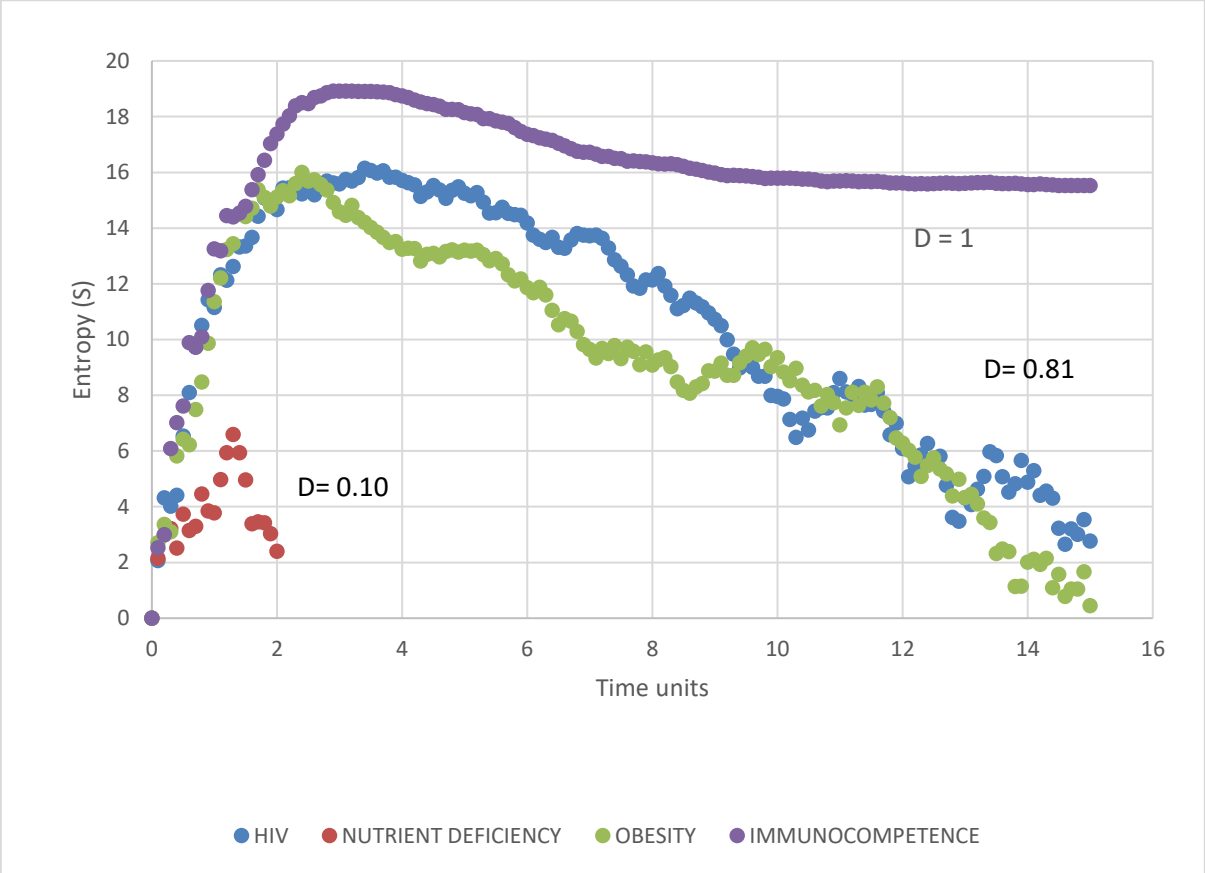


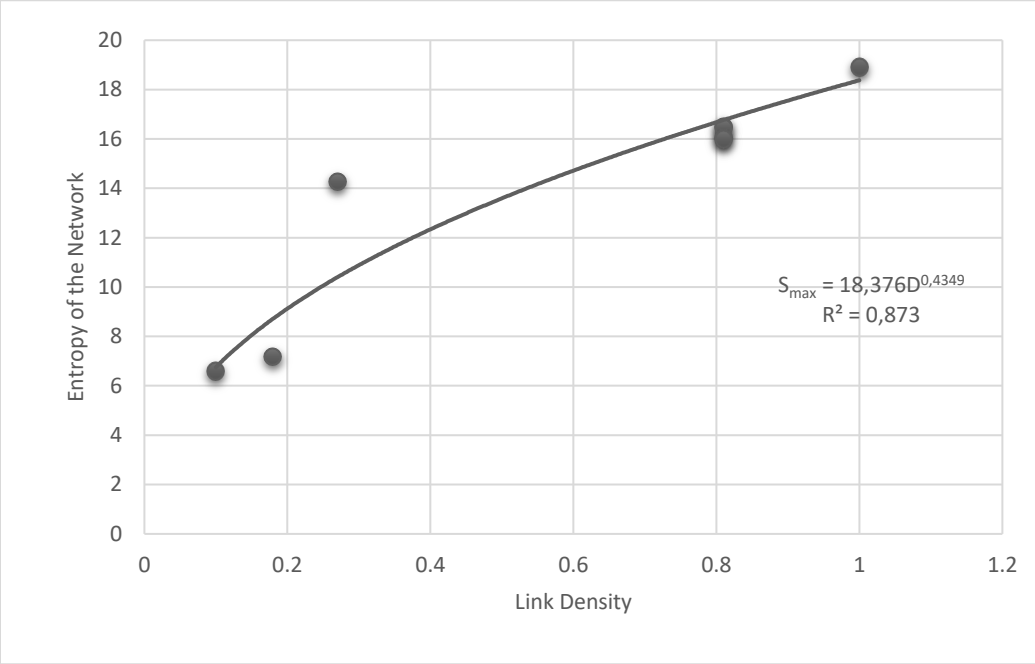
Figure 3. Entropy transitions for secondary immunodeficiencies.



Aging property

In **Figure 4** we present a power law relationship between connection density (*D*) and maximum entropy (*Smax*), with an exponent of 0.4349**,** resembling what is known as "aging property," suggesting that immunodeficient networks lose their scale-free properties, becoming more homogeneous and less capable of forming preferential connections.

Figure 4. The power-law relationship between entropy and immune network connectivity



Discussion

Our results indicate that entropy phase transitions can differentiate between immunocompetence and immunodeficiency status of the immune network. The entropy patterns observed in optimal immune networks likely corresponds to key immunological events: initial activation and expansion, coordination of specific effector responses, and maintenance of memory, aligning with current understanding of immune response kinetics [31].

The ageing property provides insight into the structural basis of immune network dysfunction [32,33], explaining why immunodeficiencies often affect multiple immune functions beyond the primary defect: the network loses its ability to compensate through alternative pathways [34,35]. By contrast, the human immune system exhibits scale-free properties in their optimal state [36-40], showing highly connected "hub" nodes and many sparsely connected ones, a topology that confers robustness and efficiency [41]. The finding that immunodeficient networks lose these scale-free properties and become "more homogeneous" suggests a fundamental shift away from this optimal, robust architecture. Homogenization implies that the distinction between highly connected hubs and less connected nodes diminishes [42].

Our approach offers several advantages over traditional immunological assessments, like providing a holistic measure that integrates multiple immune parameters, capturing dynamic properties of the immune response rather than static measurements and establishing quantitative relationships between network structure and function.

Considering the limitations of our study, first, the model assumes logistic growth dynamics for all cell populations, oversimplifying the complex immune kinetics [43]. Second, the model does not account for spatial factors in immune cell interactions [44] nor for connection weights between cell types are not differentiated based on signaling strength or type. On the other hand, clinical validation is paramount from a translational perspective; without empirical data from human patients, the model remains a theoretical framework, emphasizing the crucial next step of bridging computational predictions with real-world clinical observations, which is essential for establishing diagnostic and prognostic utility and advancing computational biology into clinical practice. While the present study focuses on immunodeficiencies, we recognize the potential of entropy-based signatures to distinguish between types of infections.

Moreover, interindividual variability is a critical factor in immune system modeling. In future research, enabling the model to be more robust in capturing individualized immune dynamics, wherein advanced computing and AI tools such as deep learning, probabilistic, hybrid models, and the use of supercomputing resources to perform advanced simulations of biological systems can now be applied to demystify the complexity of the human immune system [45,46]. For instance, deep learning approaches must be used to estimate the parameter values for immune age, which are strongly correlated with multimorbidity, inflammatory markers, immune senescence, frailty, and cardiovascular aging..

Lastly, the ability to decode and harness the power of the human immune system is one of the great frontiers of biomedicine. The immune system represents a complex network of genes, proteins, cells, and tissues, a billion or more times larger than the entire human genome. It differs among individuals and changes over time because a wide range of factors, including age, genetic, and environmental factors influences it..

Conclusion

The present work models the complex network of interactions between the eleven central cell types that make up the human immune system using system dynamics and adaptive networks making use of entropy phase changes to determine how the state of optimal immune response or immunocompetence is characterized, finding a pattern of three states: activation, coordination and stabilization of the network. Next, the dynamics of the entropy phase change of the immune network under immunodeficiency scenarios, both primary and secondary, are estimated, finding entropy phase change patterns for each disease. The methodology presented here supports the search for a holistic understanding of the functioning of immune effector cell networks.

Abbreviations list

Abbreviation	Definition
AI	Artificial Intelligence
AIDS	Acquired Immune Deficiency Syndrome

BAS	Basophils
B-Cells	B-Lymphocytes (used in data tables)
Bruton	X-linked Agammaglobulinemia (Bruton Disease)
CGD	Chronic Granulomatous Disease
CF	Combination Function (model equation)
DC	Dendritic Cells
DiGeorge	DiGeorge Syndrome (Congenital Thymic Aplasia)
D	Link Density (network parameter)
EOS	Eosinophils
HIV	Human Immunodeficiency Virus
K	Carrying Capacity (model parameter)
MA	Macrophages
MAST	Mastocytes (Mast Cells)
MO	Monocytes
MR	Mortality Rate (model parameter)
NEU	Neutrophils
NK	Natural Killer Cells
PC	Plasmatic Cells (Plasma Cells)
S	Shannon's Entropy (network entropy)
Smax	Maximum Entropy
SCID	Severe Combined Immunodeficiency
T-Cells	T-Lymphocytes (used in data tables)
Wint	Interaction Strength (model parameter)
X1–X11	Model variables for immune cell populations (see supplementary Table 1)

Availability of Data and Materials: Data supporting the results of this study is available upon request from the corresponding author

Author Contributions: Author is a sole responsible for **c**onceptualization, methodology, software: validation, visualization, formal analysis, Investigation, resources, data curation, writing—original draft preparation—review and editing.

Ethics Committee Approval and Consent to Participate:

Ethical committee approval was not required for this work because it involves a theoretical and computational immune network model developed using parameters derived from previously published literature, without the use of human or animal subjects, identifiable data, or clinical samples.

Conflicts of interest: The author declares no conflicts of interest.

Funding: No external funding was received for this research.

Acknowledgements: The author acknowledges Corporación CIINAS and Fundación Universitaria San Mateo for providing their research facilities and resources. Claude ai was

employed solely to carry out stylistic corrections in the text. The graphical abstract was generated using Copilot.

Supplementary Material:

Supplementary material associated with this article has been published online and is available at: Link to the DOI

References

1. Vester, J. C.; Kraneveld, A. D.; Garssen, J. The assessment of Immune Fitness. *Journal of Clinical Medicine* **2023**, *12* (1), 22. https://doi.org/10.3390/jcm12010022.
2. Laupèze, B.; Del Giudice, G.; Doherty, M. T.; et al. Vaccination as a preventative measure contributing to immune fitness. *npj Vaccines* **2021**, *6*, 93. https://doi.org/10.1038/s41541-021-00354-z.
3. Stroncek, D. F.; Butterfield, L. H.; Cannarile, M. A.; et al. Systematic evaluation of immune regulation and modulation. *J. Immunother. Cancer* **2017**, *5*, 21. https://doi.org/10.1186/s40425-017-0223-8.
4. Kohrt, H. E.; Nouri, N.; Nowels, K.; Johnson, D.; Holmes, S.; Lee, P. P. Profile of immune cells in axillary lymph nodes predicts disease-free survival in breast cancer. *PLoS Med.* **2005**, *2*, e284.
5. Tvedt, T. H.; Rye, K. P.; Reikvam, H.; Brenner, A. K.; Bruserud, O. The importance of sample collection when using single cytokine levels and systemic cytokine profiles as biomarkers--a comparative study of serum versus plasma samples. *J. Immunol. Methods* **2015**, *418*, 19–28.
6. Rieckmann, J. C.; Geiger, R.; Hornburg, D.; Wolf, T.; Kveler, K.; Jarrossay, D.; Sallusto, F.; Shen-Orr, S. S.; Lanzavecchia, A.; Mann, M.; Meissner, F. Social network architecture of human immune cells unveiled by quantitative proteomics. *Nature Immunology* **2017**, *18* (5), 583–593. https://doi.org/10.1038/ni.3693.
7. Burgos-Salcedo, J. A Memory Evolutive System-Model of Immunocompetence with Applications to SARS-CoV-2. *Sch Acad. J. Biosci.* **2022**, *10* (4), 77–84.
8. Burgos-Salcedo, J. Immune network operations in COVID-19. *Explor Immunol.* **2022**, *2*, 572–580. https://doi.org/10.37349/ei.2022.00068.
9. Yue, X.; Wang, Z.; Huang, J.; Parthasarathy, S.; Moosavinasab, S.; Huang, Y.; Lin, S. M.; Zhang, W.; Zhang, P.; Sun, H. Graph embedding on biomedical networks: methods, applications and evaluations. *Bioinformatics* **2020**, *36* (4), 1241–1251. https://doi.org/10.1093/bioinformatics/btz718.
10. Bergthaler, A.; Menche, J. The immune system as a social network. *Nat Immunol* **2017**, *18*, 481–482. https://doi.org/10.1038/ni.3727.
11. Hong, R.; Tong, Y.; Liu, H.; et al. Edge-based relative entropy as a sensitive indicator

of critical transitions in biological systems. *J Transl Med* **2024**, *22*, 333. https://doi.org/10.1186/s12967-024-05145-3.

12. Wang, L.; Whittemore, K.; Johnston, S. A.; Stafford, P. Entropy is a Simple Measure for the Antibody Profile and is an Indicator of Health Status: A proof of concept. *Scientific Reports* **2017**, *7*, 18060. https://doi.org/10.1038/s41598-017-18469-6.
13. Melis, M.; Littera, R.; Cocco, E.; Frau, J.; Lai, S.; Congeddu, E.; Ragatzu, P.; Serra, M.; Loi, V.; Maddi, R.; Pitzalis, R.; Orrù, S.; Chessa, L.; Perra, A.; Carcassi, C. Entropy of human leukocyte antigen and killer-cell immunoglobulin-like receptor systems in immune-mediated disorders: A pilot study on multiple sclerosis. *PLoS One* **2019**, *14* (12), e0226615. https://doi.org/10.1371/journal.pone.0226615.
14. Zhong, J.; Tang, H.; Huang, Z.; Chai, H.; Ling, F.; Chen, P.; Liu, R. Uncovering the Pre-Deterioration State during Disease Progression Based on Sample-Specific Causality Network Entropy (SCNE). *Research (Wash D C)* **2024**, *7*, 0368. https://doi.org/10.34133/research.0368.
15. Yan, J.; Li, P.; Li, Y.; Gao, R.; Bi, C.; Chen, L. Disease prediction by network information gain on a single sample basis. *Fundam Res.* **2023**, *5* (1), 215–227. https://doi.org/10.1016/j.fmre.2023.01.009.
16. Sender, R.; Weiss, Y.; Navon, Y.; Milo, I.; Azulay, N.; Keren, L.; Fuchs, S.; Ben-Zvi, D.; Noor, E.; Milo, R. The total mass, number, and distribution of immune cells in the human body. *Proceedings of the National Academy of Sciences* **2023**, *120* (44), e2308511120. https://doi.org/10.1073/pnas.2308511120.
17. Treur, J. Analysis of a network's asymptotic behavior via its structure involving its strongly connected components. *Network Science* **2020**, *8* (S1), S82–S109. https://doi.org/10.1017/nws.2019.24.
18. del Jesus, M.; Foti, R.; Rinaldo, A.; Rodriguez-Iturbe, I. Maximum entropy production, carbon assimilation, and the spatial organization of vegetation in river basins. *Proc. Natl. Acad. Sci. U.S.A.* **2012**, *109* (51), 20837–20841. https://doi.org/10.1073/pnas.1218636109.
19. Tirabassi, G.; Masoller, C. Entropy-based early detection of critical transitions in spatial vegetation fields. *Proc. Natl. Acad. Sci. U.S.A.* **2023**, *120* (1), e2215667120. https://doi.org/10.1073/pnas.2215667120.
20. Znaidi, M. R.; Sia, J.; Ronquist, S.; et al. A unified approach of detecting phase transition in time-varying complex networks. *Sci Rep* **2023**, *13*, 17948. https://doi.org/10.1038/s41598-023-44791-3.
21. Dorogovtsev, S.; Mendes, J. F. Evolution of networks. *Advances In Physics* **2002**, *51*, 1079–1187. https://doi.org/10.1080/00018730110112519.
22. Wu, J. W.; Patterson-Lomba, O.; Novitsky, V.; Pagano, M. A Generalized Entropy Measure of Within-Host Viral Diversity for Identifying Recent HIV-1 Infections. *Medicine (Baltimore)* **2015**, *94* (42), e1865. https://doi.org/10.1097/MD.0000000000001865.

23. Asti, L.; Uguzzoni, G.; Marcatili, P.; Pagnani, A. Maximum-Entropy Models of Sequenced Immune Repertoires Predict Antigen-Antibody Affinity. *PLoS Comput Biol* **2016**, *12* (4), e1004870. https://doi.org/10.1371/journal.pcbi.1004870.
24. Freitas, C. G. S.; Aquino, A. L. L.; Ramos, H. S.; et al. A detailed characterization of complex networks using Information Theory. *Scientific Reports* **2019**, *9*, 16689. https://doi.org/10.1038/s41598-019-53167-5.
25. Yanes, R. E.; Gustafson, C. E.; Weyand, C. M.; Goronzy, J. J. Lymphocyte generation and population homeostasis throughout life. *Semin. Hematol.* **2017**, *54* (1), 33–38.
26. Subramanian, N.; Torabi-Parizi, P.; Gottschalk, R. A.; Germain, R. N.; Dutta, B. Network representations of immune system complexity. *Wiley Interdisciplinary Reviews: Systems Biology and Medicine* **2015**, *7* (1), 13–38.
27. Ballow, M.; Sánchez-Ramón, S.; Walter, J. E. Secondary Immune Deficiency and Primary Immune Deficiency Crossovers: Hematological Malignancies and Autoimmune Diseases. *Front Immunol.* **2022**, *13*, 928062. https://doi.org/10.3389/fimmu.2022.928062.
28. Tangye, S. G.; Al-Herz, W.; Bousfiha, A.; Chatila, T.; Cunningham-Rundles, C.; Etzioni, A.; Franco, J. L.; Holland, S. M.; Klein, C.; Morio, T.; Ochs, H. D.; Oksenhendler, E.; Picard, C.; Puck, J.; Torgerson, T. R.; Casanova, J. L.; Sullivan, K. E. Human Inborn Errors of Immunity: 2019 Update on the Classification from the International Union of Immunological Societies Expert Committee. *J Clin Immunol.* **2020**, *40* (1), 24–64. https://doi.org/10.1007/s10875-019-00737-x.
29. Amaya-Uribe, L.; Rojas, M.; Azizi, G.; Anaya, J. M.; Gershwin, M. E. Primary immunodeficiency and autoimmunity: A comprehensive review. *J Autoimmun.* **2019**, *99*, 52–72. https://doi.org/10.1016/j.jaut.2019.01.011.
30. Justiz Vaillant, A. A.; Qurie, A. Immunodeficiency. In *StatPearls*; StatPearls Publishing: Treasure Island (FL), 2025. https://www.ncbi.nlm.nih.gov/books/NBK500027/.
31. Roach, T. N. F. Use and Abuse of Entropy in Biology: A Case for Caliber. *Entropy* **2020**, *22* (12), 1335. https://doi.org/10.3390/e22121335.
32. Sherwin, W. B. Entropy, or Information, Unifies Ecology and Evolution and Beyond. *Entropy (Basel)* **2018**, *20* (10), 727. https://doi.org/10.3390/e20100727.
33. Paredes, O.; Farfán-Ugalde, E.; Gómez-Márquez, C.; Borrayo, E.; Mendizabal, A. P.; Morales, A. The calculus of codes - From entropy, complexity, and information to life. *Biosystems* **2024**, *236*, 105099.
34. McCusker, C.; Upton, J.; Warrington, R. Primary immunodeficiency. *Allergy Asthma Clin Immunol.* **2018**, *14* (Suppl 2), 61. https://doi.org/10.1186/s13223-018-0290-5.
35. Lehman, H. K. Autoimmunity and Immune Dysregulation in Primary Immune Deficiency Disorders. *Curr Allergy Asthma Rep.* **2015**, *15* (9), 53. https://doi.org/10.1007/s11882-015-0553-x.
36. Assogba, Y. P.; Adechina, A. P.; Tchiakpe, E.; et al. Advanced in immunological

monitoring of HIV infection: profile of immune cells and cytokines in people living with HIV-1 in Benin. *BMC Immunol* **2024**, *25*, 22. https://doi.org/10.1186/s12865-024-00615-1.

37. Vassilopoulou, E.; Venter, C.; Roth-Walter, F. Malnutrition and Allergies: Tipping the Immune Balance towards Health. *Journal of Clinical Medicine* **2024**, *13* (16), 4713. https://doi.org/10.3390/jcm13164713.
38. Szasz, A.; Szigeti, G. Exploring Biocomplexity in Cancer: A Comprehensive Review. *Open Journal of Biophysics* **2024**, *14*, 154–238. https://doi.org/10.4236/ojbiphy.2024.142009.
39. Gubela, N.; von Kleist, M. Efficient and accurate simulation of infectious diseases on adaptive networks. *PLOS Complex Syst* **2025**, *2* (6), e0000049. https://doi.org/10.1371/journal.pcsy.0000049.
40. McMillen, P.; Levin, M. Collective intelligence: A unifying concept for integrating biology across scales and substrates. *Commun Biol* **2024**, *7*, 378. https://doi.org/10.1038/s42003-024-06037-4.
41. Müller, L.; Di Benedetto, S.; Müller, V. From Homeostasis to Neuroinflammation: Insights into Cellular and Molecular Interactions and Network Dynamics. *Cells* **2025**, *14* (1), 54. https://doi.org/10.3390/cells14010054.
42. Liu, X.; Li, D.; Ma, M.; Szymanski, B. K.; Stanley, H. E.; Gao, J. Network resilience. *Physics Reports* **2022**, *971*, 1–108.
43. Pham, D.; Tan, X.; Balderson, B.; et al. Robust mapping of spatiotemporal trajectories and cell–cell interactions in healthy and diseased tissues. *Nat Commun* **2023**, *14*, 7739. https://doi.org/10.1038/s41467-023-43120-6.
44. Fu, T.; Dai, L. J.; Wu, S. Y.; et al. Spatial architecture of the immune microenvironment orchestrates tumor immunity and therapeutic response. *J Hematol Oncol* **2021**, *14*, 98. https://doi.org/10.1186/s13045-021-01103-4.
45. Singh, B.; Jevnikar, A. M.; Desjardins, E. Artificial Intelligence, Big Data, and Regulation of Immunity: Challenges and Opportunities. *Archivum Immunologiae et Therapiae Experimentalis* **2024**, *72* (1).
46. Niarakis, A.; Laubenbacher, R.; An, G.; Ilan, Y.; Fisher, J.; Flobak, Å.; Glazier, J. A. Immune digital twins for complex human pathologies: applications, limitations, and challenges. *NPJ Syst. Biol. Appl.* **2024**, *10* (1), 141.