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Abstract

The immune system is a complex biological micro-ecosystem, adaptive, highly diversified, self-organized and cognitive network of cells and molecular entities with degeneracy properties. The adaptive immune system has evolved into a complex system of billions of highly diversified lymphocytes all interacting as a connective dynamic multi-scale organised and distributed system, in order to collectively insure body identity and integrity. This complex system insures species preservation of symbiotic and poly-genomic organisms. The immune system is characterized by complexity at many different levels; network organisation during the development, through fluid cell populations with inter- and intra-cell signalling, an extraordinary lymphocyte somatic receptor diversity, lymphocyte clonotype selection and competition at cell level, migration and interaction inside the immunological tissues and fluid dissemination through the organism, homeostatic regulation, while rapid adaptation to a changing environment. Lymphocytes are the key actors of the immune system of vertebrates, in the middle of a multi-scale biological organization “from molecule to organism”, and at the confluence with other different biological systems and the environment. The perception of antigens induces a network of immuno-receptors that could be viewed as an internal representation of antigens. Fluctuations, variability and diversity are key factor for the immune system to adapt perturbations and aging and to be or not resilient. Theoretical approaches of this complex system and multi-scale dynamic modeling are a challenge in the domain of complex systems. Theoretical, mathematics and computer models developed to improve our understanding of the multi-scale complexity of the immune system should be developed.

Introduction

The immune system is a complex biological micro-ecosystem, adaptive, highly diversified, self-organized cognitive network of cells and molecular entities with degeneracy properties, allowing in healthy individuals for a robust and resilient system with emergent properties such as anamnestic responses and regulations. The adaptive immune system has evolved into a complex system of billions of highly diversified lymphocytes all interacting as a connective dynamic multi-scale organised and distributed system, in order to collectively insure body identity and integrity, and species preservation of symbiotic organisms exposing polygenomic antigens. The immune system is characterized by complexity at different levels: network organisation through fluid cell populations with inter- and intra-cell signalling, an extraordinary lymphocyte receptor diversity, cell clonotype selection and competition at cell level, migration and interaction inside the immunological tissues and fluid dissemination through the organism, homeostatic regulation while rapid adaptation to a changing environment. Lymphocytes are the key actors of the immune system of vertebrates, in the middle of a multi-scale biological organization “from molecule to organism”, and at the confluence with other different biological systems and the environment. The perception of antigens induces a network of immuno-receptors that could be viewed as an internal representation of antigens. Fluctuations and variability are key factor for the immune system to adapt perturbations and aging.

A deeper understanding of T-cell differentiation, diversity, dynamics, repertoires selection and regulation processes is key for fundamental research, medical advancement and drug discovery. Moreover the immune system represents a complex system sharing some transversal properties with other complex systems (organisation as dynamical properties, resilience to perturbations …).

Crossing interdisciplinary transversal questions from other complex systems to study the complexity of the immune system

Understanding the organization and the regulation of the complex immune system refers to transversal questions already mentioned for other "live" complex systems such as other biological, social or ecological macro systems, with some peculiarities specific to the immune system. Thus, the immune system can be observed and modelled from different point of view with the theoretical and methodological approaches shared by other inter-disciplinary domains using biological, physical, philosophical, mathematical, statistical, and computer approaches. Some examples of the cross-fertilization required to solve open questions concerning specifically the immune system are proposed in Table 1.

Transversal questions commons to other complex systems	Questions specific to the immune system
Study and modeling of adaptive multi-scale system	The adaptive immune system
Integration of high-throughput multi-scale and multi-parametric data and metadata and sharing	Biological generic data from transcriptome, proteome, but also cytome, repertome…
Computer or mathematical tools for exploration and formalization	Supervised and non supervised statistical modeling, mechanistic reconstruction of immune system and lymphocyte behaviour
Theoretical reconstruction	Multi-scale analysis, representation of heterogeneous data, organisation of knowledge's database describing the immune system around the lymphocyte level, from molecule to organism, for data-driven and hypothesis-driven reconstruction
Metamodels, multi-formalism for reconstruction and visualization of dynamics, differentiation, and behaviour	Mathematical & computer modelling for lymphocyte cell population dynamics, activation, regulation and selection processes; use of oriented object, graphical languages, SMA, ontologies, for modeling the multi-scale entities of the immune system…
Fluctuations, stability, variability, regulations at multi-scale levels	Multi-level/Multi-scale: organism, lymphoid tissues, lymphocyte populations, cellular and molecular lymphoid repertoires
Robustness/resilience and relation to organization	Behavior of immune system from development to aging; resilience to perturbations, transition to immunopathologies (infection, autoimmunity, cancer…); immunotherapy/vaccination
Model the relationships between biodiversity, functioning and dynamics of the (eco)systems	Diversity, stability/perturbation of immune repertoires and lymphocyte populations
Self organization, simulation of virtual landscapes	Auto-organization of cells in lymphoid organs and development, cell network and immune repertoire
Data mining, extraction, visualization of data and semantic and syntactic analysis of scientific literature requires artificial intelligence and automatic learning approaches	Information extraction and visualization of immune literature with concepts specific to immune system

Table 1: Crossing transversal questions identified for the investigation of the complex systems[1] with the questions specific to the immune system.

[1] http://roadmap.csregistry.org/tiki-index.php?page=French+Roadmap
This live roadmap can be edited with new questions

Open question and challenges related to the complexity of the immune system

More than transversal questions common to other complex systems, the immune system present some peculiarities that require particular investigations and modelling and this represents new challenges to overcome.

Objective identification of immune system cell populations

Innate and adaptive immune system subpopulations are currently defined on the basis of the revelation of a combination of cell surface or intracellular/nuclear molecules that the researcher has to define to explore the phenotype and functionality of cells. Thus, the cell populations revealed by cell staining are largely dependant on the mixture and the number of chosen parameters (n) that will drive the number of subpopulations (2n). Techniques like Flow cytometry analysis allow quantification of several parameters from individual cells allowing characterizing cell size, structure, specific phenotype and function of millions of cells in a multi-dimensional way. However, current analyses performed by manual gating inspect parameters 2 by 2 and do not reveal the complexity of the lymphocyte subpopulations that co express several parameters.

The challenge is developing methods and software tools for current immunological analysis and automatic identification of cell subsets. This allows objective investigation and identification of cells subpopulations that have certainly been ignored by immunologists, to identify variability/stability, resilience or perturbations among development/aging, through genetic backgrounds, and during the course of perturbations as immunopathologies or immunotherapies.

Lymphocyte population dynamics & repertoire selection: Integration of multi-level/multi-scale data and reconstruction of dynamic interactions

The most important feature of the immune system is the availability of a diverse cell repertoire and its selection constraints. Lymphocytes are produced in primary lymphoid organs from precursors that differentiate and somatically rearrange DNA variable genes independently, leading to the expression of unique type of immunoreceptor in each lymphocyte. T or B cell repertoires are thus collections of lymphocytes, each characterized by its antigen-specific receptor produced by random somatic rearrangements of V(D)J gene segments during lymphocyte differentiation. The potential repertoire of 10^{15}TCR/Ig receptors is far beyond the lymphocyte count in a single individual. Then, process of lymphocyte selection with high cell death or amplification of particular antigen specific clones represent a network of dynamical interactions conferring tolerance to avoid autoimmunity though retaining the potential to respond to a very large collection of antigens. Thus, the dynamics of cell fluxes and turnover, cell selection through division and cell death is able to adapt a dynamic equilibrium according to the internal genetic variability but also external antigen challenges in various lymphoid populations. The rules governing the clonal selection processes and cell population dynamics stability or disturbance in immune pathologies and aging are far to be fully understood. Integration of high-throughput data describing qualitatively and quantitatively cell populations, repertoire diversity and gene expression should allow data mining, signature discovery and reconstruction of dynamics behaviours.

The challenge is the integration of multi-scale data and metadata describing cell populations, cellular and molecular lymphocyte repertoires, gene expression and proteome across time, lymphoid organs, and genetic background, in various conditions describing physiological or pathological states or treatments. Organization of knowledge's using standardized database with ontologies and state transition diagrams should improve organization of data for data mining and

dynamic computational modeling. Object-oriented computer modeling taking into account the levels of the "organism", the "organs", the "cell" and the "molecule" through various time scales, should improve the interoperability of mathematical and computer models already developed in the field, allowing also the direct intervention of the biologist to implement the models and suggest new experiments or treatments.

Understanding resilience or instabilities to perturbations, immune dysfunction in order to improve immuno-intervention strategies

Internal cell instability or external cell perturbations can impact the stability and reactivity of the immune system at various biological levels (from molecules to organism). Thus physiological aging and immunopathologies like infectious, autoimmune or inflammatory diseases, and cancer but also immunotherapies or preventive immuno-intervention like vaccination can perturb the system. Genetic or environmental component alterations (antigens, infections, chemicals, nutriments…) or other biological instabilities (as in nervous, hormonal, metabolic systems…) can affect the organisation of immune system, its dynamics and lymphocyte repertoires and turn the physiologic equilibrium to immuno-pathologies. The identification and quantification of variability and perturbations at these different levels and through time should allow understanding the resilience or instability of the system. Conversely, improving knowledge on the physiological or pathological dynamic behaviour of the immune system should also reveal keys for immuno-interventions.

The challenge is to connect and better integrate knowledge's, as a result of data mining, with dynamic computer modeling and simulations to be able to understand the system behavior under such perturbations. The resilience and homeostatic regulation of the system (steady state dynamic equilibrium) but also variability/fluctuation (according to genetic background, physiological development and aging) to pathological perturbations of the immune system should thus be investigated by multi-disciplinary approaches. This requires the development of original biological,

mathematical and computer modeling tools. This might allow assessing the quantity/quality of small perturbations, at various scale levels, that can impact and/or dys-balance the whole immune system equilibrium with the search of threshold effects. On the opposite it might allow estimating the maximal variability the system can endure without global perturbations at the organism level.

Extract, visualize and organise immunological knowledge from scientific immune literature

The complexity of the immune system, related to biological multi-scale levels, but also of the data generated by multiple technologies, published in the form of unstructured text requires the development of innovative techniques of data and literature mining to enhance information retrieval, visualization of enormous quantities of data and organisation of knowledge.

The challenge is to develop data mining and machine learning methods to have a better understanding of the complexity of the immuno-physiome. Innovative data mining, semantic and syntactic analytical approaches should help define the concepts that have to be extracted and algorithms to automatically extracts the data with a maximum of accuracy.

Contribute to global evaluation of complex systems and risk issue

A global evaluation of the behaviour of complex systems should be undertaken under philosophical and scientific aspects. The behaviour of complex systems is related to their multi-scale organisation. While the immune system is related to micro-levels from molecule to organism, the biosphere is related to macro-levels from organisms to global environment, though social interactions, migration, ecosystems, climate and biosphere. Indeed data, simulations and predictions are difficult to establish for some systems. Organisation of systems results from the selection among diversities of only a small fraction of all potential possibilities, with an infinite combination of parameters. This contributes to selected dynamic equilibrium allowing the systems to resist time and perturbations unless the resilience is disrupted.

The challenge is to provide a global analysis of common properties of complex multi-scale systems in order to understand the robustness and the degree of resilience of systems selected on the basis of their organization and risk of changes in the dynamic equilibrium under various perturbations. The notion of emergence and immergence have to be analyzed in order to understand whether or not the aging and evolution of a system and the threshold effects are involved in the resilience of systems or could induce their disorganization and fragility.

The human perspective: revisiting the "immune system", limits, definition, characteristics, functions and stability

Complex systems are often viewed as multi-scale, self-assembly, adaptive dynamic and cognitive networks of diverse interacting agents capable of sensing patterns with degenerative properties. In biology, links between entities are processes that occur at various scales. At the macroscopic level, the nervous system insures the cognition, perception and memory of "self", through mental links and related relations to macroscopic external environment, allowing to define ego as well as physical/somatic identity based on consciousness, memory and social interactions. Similarly, at the microscopic level, the immune system as a cognitive, diverse, dynamic, fluid and anamnestic system, sense the quality and quantity of microscopic patterns, either from body or environment. The immune system is thus at the interface of the dynamic symbiotic organisation of the individual (composed in adults of 10 times more prokaryotic than eukaryotic cells) and constantly senses its environment, and its own components (idiotopes). This leads to individual cell signalling up to collective decision-making allowing for discrimination and memory of microscopic entities in a systemic way.

Biological and philosophical conceptual questions remain about the notion of organization, organism, immune system, the perception of self, identity, memory, tolerance and resilience.

- *Are there limits between the immune system, the organism and the environment?*
- *Has the immune system a role to define the identity of an organism?*

- *What are the major characteristics of an organisation and an organism?*
- *How do cognition, diversity, selection, memory and dominant tolerance contribute to the dynamic stability of the system and the resilience of the organism?*
- *How can we define the immune system? Is the term "immune", with its etymologic origin meaning "exempt", adequate according to current knowledge?*

Bio-inspired and artificial immune systems

Knowledge's assembled to understand, reconstruct, simulate and predict the complex multi-scale behaviour and resilience of the immune system dynamics in health, aging, diseases or treatments could be useful for the design of innovative artificial immune systems reproducing or inspired from the behaviour of the natural immune system. Thus, understanding this natural organisation, selected during the evolution of species and cells in organism, can help to design innovative evolutive artificial immune systems, and referring to the "war" metaphor to design the best "immuno-logistic" optimization. This could help understanding the characteristics of an organisation as a process and as a result, from organisms to societies and for the design of regulatory processes and security purposes.

The challenge is to overcome the conceptual and technical limitations to design self-organized artificial immune systems resilient to perturbations and able to preserve the identity and integrity of the organism or societies.

Conclusions

Identifying theoretical and methodological questions related to the complexity of the natural and artificial immune systems will help to structure new ideas and collaborative work across complex systems. Responding to these challenges will improve the global data exploration, the emergence

of new concepts and understanding of the immune system linked to other biological systems or to macro ecological/biosphere systems.

Biography of the author

PhD in Immunology at University Pierre et Marie Curie, researcher at CNRS, Véronique Thomas-Vaslin has founded and directed the Integrative Immunology: Differentiation, Diversity, Dynamics team (https://www.i3-immuno.fr/en/#People/VTV). As a member of "Réseau National des Systèmes Complexes" she has founded the ImmunoComplexiT network (http://www.immunocomplexit.net/) and is in the steering committee of Institut des Systèmes Complexes -Paris Ile-de-France (http://iscpif.fr/).
Her research focuses on lymphocyte population dynamics, diversity, selection of repertoires, studying the physiology of the immune system, tolerance, and the regulation of immune responses in health and diseases. Her current aim is the integration of the complexity of the immune system as an ecosystem, responding to perturbations and aging. Computational model are designed to reconstruct the multi-scale T-cell dynamics, from their generation in thymus to the control of immune responses.

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