CFCAM Discussion Meeting

ImmunoComplexiT network

http://www.immunocomplexit.net/

Previsional discussion meeting in March 2013

Institut des Systèmes Complexes-Paris Ile de France (ISC-PIF)

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1. Proposal

1.1. Introduction and motivation

Face to the complexity of the biological immune system, the ImmunoComplexiT network was initiated in 2011 by V. Thomas-Vaslin with the objective to trigger new reflexions, views and approaches of this complex biological system through multidisciplinary interactions. Our scientific motivations and challenges are described in the French roadmap of the Réseau National des Sytèmes Complexes "from molecule to organism" in the section "complexity of the immune system". Main of these points are described here:

The immune system is a complex biological adaptive, highly diversified, robust and resilient system with emergent properties such as anamnestic responses and regulation. The adaptive immune system has evolved into a complex system of millions of highly diversified lymphocytes all interacting as a connective, dynamic, anamestic, multiscale organised and distributed system, in order to collectively insure body and species preservation.
The immune system is characterized by complexity at different levels: network organisation through fluid cell populations with inter- and intra-cell signalling, 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.
A deeper understanding of T cell differentiation, diversity, dynamics, and repertoires selection 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 …) that leads to interdisciplinar interactions through theoretical and methodological approach as mathematical, statistical, computer and text mining approaches.
Understanding the organization and regulation of this complex immune system refers to transversal questions already mentioned for other complex systems such as other biological, social or ecological macro systems, with some peculiarities specific to the immune system as summarized below.

Transversal questions commons to other complex systems (*specific to immune system*):

-study and modelling of adaptive multiscale system (*the adaptive immune system*)
-integration of high-throughput multiscale and multiparametric data and metadata and sharing (data from transcriptome, proteome, but also *cytome, repertome…*)
-Computer or mathematical tools for exploration and formalisation *(supervised and non supervised statistical modeling, mechanistic reconstruction of immune system behaviour)*
-Theoretical reconstruction *(data mining, multiscale analysis, representation of heterogeneous data, organisation of knowledge's database describing the immune system around the lymphocyte level, from molecule to organism, data-driven and hypothesis-driven reconstruction*

-Metamodels, multiformalism 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, UML, SMA, ontologies, for modelling the immune system…)*
-Fluctuations, stability, variability, regulations at multiscale levels (Multilevel/Multiscale: organism, *lymphoid tissues, lymphocyte populations, cellular and molecular lymphoid repertoires*)
-Robustness/resilience and relation to organisation (*analyse behaviour 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-organisation 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*)

1.2 State of the art

It is now recognized that, in addition to looking to individual elements, it is necessary to integrate information and devise global analysis solutions and modelling). It is particularly true of the immune system : multicellular, spatio-temporal, multilevel diversity, intricate selection and regulatory processes… Therefore, we believe that it is necessary to complement “traditional” reductionism-based approaches by a more global Systems Biology and complex systems approach. Systems Biology consists in viewing complex multi-level biological systems as a whole in order to infer mathematical models through iterative analysis (.

This coincides with the strong development of transdisciplinary research networks for the study of complex systems in general (e.g. Complex Systems Society, Institut des Systèmes Complexes in France). Recommendations of the European Science Foundation on the systems biology medical applications[1] are related to integration of data, mathematical and dynamic modelling of biological processes and diseases involving the immune system, simulations and theoretical thinking. Several studies around the world have been conducted to model biological systems especially in immunology (Rangel, Angus et al. 2004 ; Braga-Neto and Marques 2006 ; Morel, Ta'asan et al. 2006 ; Petrovsky and Brusic 2006 ; Borghans and de Boer 2007 ; Chan and Kepler 2007 ; Cohn and Mata 2007 ; Flower and Timmis 2007 ; Germain, Meier-Schellersheim et al. 2011), and on the T cells dynamics (Callard, Stark et al. 2003 ; Callard and Yates 2005 ; Callard and Hodgkin 2007 ; Efroni, Harel et al. 2007 ; Ribeiro and Perelson 2007 ; Thomas-Vaslin, Altes et al. 2008; Asquith, Borghans et al. 2009; Souza-e-Silva, Savino et al. 2009). Analysis of repertoire immune receptors has also been developed (Boudinot, Marriotti-Ferrandiz et al. 2008; Pham, Manuel et al. 2011). In parallel, specialized journal, as well as trans-disciplinary research network on complex systems (Complex Systems Society ; Institut des Systèmes Complexes in France) and

1 www.esf.org/publications.html SPB35 SysBioMed.pdf

artificial **life (ICARIS**[2] **Workshop « Qualitative Langages for Immune Modelling ») (**McEwan, Bersini et al. 2011**;** McEwan, Bersini et al. 2011**) have developed with the incitation for biologist to use state transition diagrams (**Bersini, Klatzmann et al. 2012**). The international database IMGT is a good example of the system immunology here in France (**Pappalardo, Lefranc et al. 2010**). Integration of data in knowledge base that collects data and metadata (hypothesis, technology, results) covering the major fields of biology, for standardized data integration of flow cytometry (**Sansone, Rocca-Serra et al. 2012**) is also a challenge.**

Systems biology focuses on tackling complexity, based on analysing large data sets with unsupervised learning methods regardless of pre-conceived hypotheses . International initiatives such as ImMunoGeneTics (**www.imgt.org**), European Immunogrid (**www.immunogrid.org**), American Immunological Genome project (**www.immgen.org**), Stanford's proteomics centre (**proteomics.stanford.edu**) Biomodels (**www.biomodels.net**) or InSilico DB (**http://insilico.ulb.ac.be**) are established to provide standardized immune databases. However, these databases fail to describe the population dynamics, differentiation, migration, repertoire selection, proliferation and death of T cells during their journey in the thymus, and peripheral lymphoid tissues. Data mining that has been employed in various domains to extract information and create databases has never been used to explore the immune literature. Data mining has shown to be very handful for extracting information about protein-protein interaction (**Abi-Haidar, Kaur et al. 2008**) and drug interaction (Wang et al 2009).

1.3 Objectives

The ImmunoComplexiT network : Understanding the complexity of the Immune system

Created in 2011, the interdisciplinary ImmunoComplexiT network has received the label from RNSC as a thematic network, involved in understanding and modeling the immune system.

Considering the immune system as a complex system that requires global approaches is new and we are the first in the domain of complex systems and immunology to introduce these concepts and challenges.

The researchers from the **ImmunoComplexiT network** are involved in the production and integration of multi-parameter immunological data at multiscale level and in statistical, mathematical and computer modeling and in theoretical approach of complex systems. Thus, assessment of variability, diversity, perturbation, robustness and resilience of the immune system through aging and perturbations is key to understand its complex dynamics behaviour, emergence, immergence, regulation, memory…
Development of mathematical models and graphical formalism allows us to describe immunological objects and behaviour at different granularity to provide visual modeling and simulations of physiology or perturbations related to immunopathologies or treatments. Semantic interoperable computational approach should lead a better understanding of the complexity of the immuno-physiome.

2 "http://www.artificial-immune-systems.org/icaris/2010/programme.html

Some of these aspects were recently discussed in a meeting with 5 presentation in a half-day, organized by V Thomas-Vaslin at ISC-PIF with 45 participants.

Objectives of the discussions/meeting

The objectives of the meeting are to invite speakers and other participants to discuss 2 themes per day of meeting with presentation of the problematics and discuss potential approaches.
These discussions should help to

reinforce the visibility of the ImmunoComplexiT network

to propose some collaborative applications to national or international finantial supports.

To propose an international meeting in 2 years

We have already initiated a similar half-day meeting on 23th Octber with 45 participants
http://immunocomplexit.wordpress.com/events/

We have delineated 5 challenges related to the complexity of the immune system

More than transversal question common to other complex systems, the immune system present some peculiarities that require particular investigations and modeling and represent new challenges to overcome.

1. **Objective identification of immune system cell populations**
2. **Lymphocyte population dynamics & repertoire selection: Integration of multilevel/ multiscale data and dynamic modeling**
3. **Understanding resilience or instabilities to perturbations, immune dysfunction in order to improve immuno-intervention strategies**
4. **Extract, visualize and organise immunological knowledge from scientific immune literature**
5. **Contribute to global evaluation of complex systems and risk issue**

1. Objective identification of immune system cell populations,
Innate and adaptive immune system subpopulations are currently defined based on the revelation of a combination of cell surface or intracellular/nuclear molecules that the researcher has to define. 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 (2^n). 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.

2. Lymphocyte population dynamics & repertoire selection: Integration of multilevel/ multiscale 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 from precursors in primary lymphoid organs that differentiate and somatically rearrange DNA variable genes composing a particular repertoire. 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, producing a potential repertoire of 10^{15}-10^{18} TCR/Ig receptors 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 process through division and cell death constraint the immune system to adapt a dynamic equilibrium according to programmed genetic variability's and permanent antigen challenge. 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 multiscale data and metadata describing cell populations, cellular and molecular repertoires and gene expression across time, lymphoid organs and genetic background or various conditions describing physiological or pathological states or treatments. Organisation of knowledge's using standardised database with ontologies and state transition UML diagram should improve organisation of data for data mining and dynamic computational modelling. Object-oriented computer modelling 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.

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

Aging, immunopathologies as infectious, autoimmune or inflammatory diseases, cancer as well as immunotherapies, vaccination represent either internal instability or external aggressions that impact the stability and reactivity of the immune system at various biological levels (from molecules to organism). 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 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 and dynamic computer modelling and simulations of 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 multidisciplinary approaches. This requires the development of original biological, mathematical and computer modelling tools. This might allow to assess the quantity /quality of small perturbations at various scale levels that can impact /dys-balance the whole immune system equilibrium or on the contrary to estimate the maximal variability the system can endure without global perturbations at the organism level.

4. 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.

5. 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 to understand the robustness and degree of resilience of systems selected on the basis of their organisation and risk of changes in the dynamic equilibrium. The notion of emergence and immergence have to be analysed to understand whether aging and evolution of a system and threshold effects are involved in the resilience of systems or could induce their disorganisation.

Responding to these challenges will improve global data exploration and understanding of the immune system linked to other biological systems (see Physiome project initiative) or to macro ecological/biosphere systems.

1.4 Potential list of Speakers

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2. Financial Support

To organise a whole day of discussion meeting with 20 to 45 participants a finantial support from the CFCAM of 1000 euros should allow to invite speakers outside from Ile de France (travel and 1 night hotel) and to provide a local buffet lunch to pursue convivial discussions.

A 2000 euros support has also been requested to RNSC to organize other similar meeting for 2 others days on the other challenges and to invite international speakers (under evaluation).

This seminar will benefit to Institutions that organizers are supported from at local Ile de France level (UPMC, ISC-PIF) with the contribution of a DIM post-doctoral fellowship to Alaa Abi-Haidar (in 2011-2012), National Institutions (CNRS, RNSC), and International support from PHC-Egide allowing to invite our European collaborators.

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