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57-59 rue Lhomond, F-75005, Paris- France
http://www.immunocomplexit.net/

Abstracts

Véronique Thomas-Vaslin
CNRS-UPMC UMR7211 « Integrative Immunology » team
Understanding the complexity of the immune system

The immune system that insures body organism and species preservation is a complex biological dynamic, adaptive, highly diversified, resilient system sensing the environment with emergent properties such as anamnestic responses and regulation. The immune system is characterized by complexity at different levels: network organization through fluid cell populations with inter- and intra-cell signaling, lymphocyte receptor diversity, clonotype selection and competition at cell level, migration and interaction inside the immunological tissues and dissemination through the organism, homeostatic regulation while rapid adaptation to a changing environment.

Understanding the multi-scale organization and regulation of this complex immune system refers to transversal questions mentioned for other complex systems such as other biological, social or ecological macro systems. Interdisciplinary approaches around the immune system, related to computer sciences, mathematics and philosophy help for a global understanding and evaluation of the system.

The ImmunoComplexiT network was initiated in 2011 with the objective to trigger new reflexions, views and approaches to improve global evaluation, data exploration and understanding of this complex biological system through interdisciplinarity. Our scientific motivations and challenges are described in the French roadmap of the Réseau National des Systèmes Complexes "from molecule to organism" in the section "complexity of the immune system".

THIEBAUT Rodolphe
INSERM U897
Integrative analysis of the immune response to a dendritic cell based HIV therapeutic vaccine

We present the integrative statistical analysis of the DALIA trial. Nineteen HIV infected patients with CD4 >500 cells/m3 and HIV RNA <50 cp/ml under HAART received at W0, 4, 8 and 12 ex-vivo generated IFN-α DC loaded with HIV-1 lipopeptides. Analytical treatment interruption (ATI) was conducted from W24. HIV-specific immunity was evaluated at baseline, W16, and W48 using: i) ex vivo IFN-γ ELISPOT; ii) intra cellular staining; iii) cytokine multiplex analysis for IL-2, IL-5, IL-10, IL-13, IL-17, IL-21, IFN-γ, TNF-α and IP10. PBMCs were stimulated with HIV peptide pools. Gene expression was repeatedly measured every 4 weeks with Illumina microarrays on whole blood.

Olivier Gandrillon
INRIA team Dracula
Predicting pathogen-specific CD8 T cell immune response from a modelling approach
Authors:
Fabien Crauste, Emmanuelle Terry, Isabelle Le Mercier, Julien Mafille, Sophia Djebali, Thibault Andrieu, Blandine Mercier, Gaël Kaneko, Christophe Arpin, Jacqueline Marvel and Olivier Gandrillon

The primary immune response mediated by CD8 T cells constitutes a major mechanism to fight an infection by intra-cellular pathogens. This response begins with an expansion phase through a fast increase of CD8 T cell count. Then most of the population dies by apoptosis in a contraction phase, followed by the generation of memory cells. These latter are specific of the antigen and will better control the pathogen in a subsequent infection.
We generated experimental data, consisting in CD8 T cell counts time evolution during the response to three different live intra-cellular pathogens, two viruses (influenza, vaccinia), and one bacteria (Listeria monocytogenes). These pathogens all harbour the same antigen, but differ in their interaction with the host, like the infection route.
We developed a mathematical model describing the evolution of CD8 T cell counts and pathogen amount during an immune response, characterized by 9 parameters and including feedback controls that regulate the response. We compared this model with the three data series and made an exhaustive estimation of the model parameter values. This provided distributions of the parameter values characterizing their ability to reproduce experimental data. Influence and relevance of each parameter value was investigated and showed that 2 to 5 parameters, related to the effector CD8 T cell mediated control of cell and pathogen death, and to a lesser extent to effector CD8 T cell proliferation and differentiation rates and to the pathogen natural elimination rate, mostly define the shape and strength of the CD8 T cell immune response and characterize the pathogen. This was obtained by focusing on the ability of the model first to reproduce the evolution of the total number of CD8 T cells over the course of the immune response, and second to display a crossing between effector and memory cell counts resulting in a larger amount of memory cells at the end of the response. Finally, the parameter associated with memory cell death was shown to play no role during the modeling of the main phase of the CD8 T cell response, yet it becomes essential when looking at the predictions of the model in terms of memory CD8 T cell counts several weeks or months after the infection.

Maria Grazia Ruocco
Université Pierre et Marie Curie- Immunologie-Immunopathologie-Immunothérapie- CNRS UMR7211& INSERM U959
Visualizing tolerance induction: behavior and function of regulatory T cells during the establishment of materno/fetal tolerance
"Flash presentation" **"Poster"**
A fetus is inherently antigenic to its mother and yet is not rejected. Our understanding of the mechanisms that regulate materno/fetal tolerance is fragmentary, yet these mechanisms have important therapeutic implications in abnormal pregnancies, organ transplantation and autoimmune diseases.
Recently, regulatory T cells (Tregs) have been suggested to play a pivotal role in preventing the rejection of the fetus during pregnancy (Aluvihare, 2004; , Darrasse-Jeze, 2006, , Samstein, 2012), as ablation of Tregs results in increased resorption of the embryos in allogeneic matings in mice. Furthermore, women with repeated spontaneous abortions and preeclampsia were found to display decreased numbers of $CD25^{+}CD4^{+}$ Tregs (Arruvito, 2007).
We have undertaken a comprehensive analysis of the role, activation status and function of Tregs, their spatial and temporal distribution and their interactions with other immune system cells (DCs, Teffs and NK cells) during pregnancy. We found that embryo implantation triggers the early recruitment and proliferation of activated/memory Tregs in the uterine draining lymph nodes. Moreover, Treg proliferation is antigen-driven and self-specific. Finally, low-dose IL-2 treatment prevents abortion in an abortion prone model (Chen, in revision).

Cosma, Antonio
CEA, DSV / IMETI / SIV
Decrypting cell populations by Mass Cytometry

The advancement of high throughput technologies and the diversification of the immunological assays revealed the full complexity of the immune system. One recent innovative technology, the cytometry by time-of-flight (CyTOF), augmented the number of parameters analysed at the single cell level. The analysis of this increased number of parameters requires the use of new software solutions that integrate successive analysis steps (primary analysis, vector analysis and integrated analysis). It is evident that the analysis of this large amount of data is an important challenge. However, effective data analysis requires also optimal data storage and organization. In addition, metadata describing reagents, performances of the instruments and protocols need to be saved together with the dataset and eventually taken into account during analysis.

To fully address the challenge of the CyTOF technology and the integration with data and metadata, we created BATLab, a LIMS able to store, organize and visualize heterogeneous dataset together with the relative metadata. BATLab is powered by the commercial software Tableau Desktop that supports intuitive query and visualization analysis. All data and metadata generated in our laboratory can be searched and visualized by any member of the team with few clicks. BATLab allows the scientist to concentrate on the scientific questions instead of searching and preparing data for analysis. This innovative system found the basis for an integrated analysis of the immune system.

Ioannis, DRAKOS
Immunologie-Immunopathologie-Immunothérapie- CNRS UMR7211& INSERM U959
Data lifecycle management in systems immunology

Systems immunology, as any systemic scientific approach, is a field that incorporates big data diversity. Tracking, managing, comparing and analysing multidimensional data from multiple heterogeneous sources can become difficult without structured management protocols and tailor-made integration procedures.

Some researches may consider the time needed to design and implement structured data lifecycle management strategies as a luxury, but knowing the origin of a sample and its relation with the rest of the samples, being able to retrieve specific values from specific sub-populations, having the ability to compare values of different dimensions (e.g. the single numerical value of WBCC with the multi-dimensional matrix of values from a flow-cytometry measurement), feeling safe regarding the data security and confidentiality can only improve a researcher's pace.

Camilo LA ROTA
The CoSMo Company
Complex System's Modeling with CoSMo, application to the immune system

Biological systems show different levels of organization, they are formed by complex interaction networks, living at multiple spatial scales and acting at multiple time scales. The study of their emerging behaviour, robustness, regulation, and other important properties needs adequate methods and computational tools.

The CoSMo Company has developed a conceptual framework, a software platform and a methodology for the modeling of complex systems; the platform provides:

- a structured language to define multiscale complex systems
- tools to facilitate modeling authoring (graphical and application user interfaces)
- tools to simulate and analyze their behaviour (simulator generation in C++, high level languages wrappers for calibration and analysis protocol development, mechanisms to describe exogenous perturbations or alterations of the model during simulation (scenarios))
- tools to monitor and display simulation results
- mechanisms to test and validate model behavior.

Application domains presently include urban modeling (transport, water supply, waste treatment networks), biology (genetic networks, immunology, bioproduction) and epidemiology (disease propagation, pharmacoeconomics).

We currently work in the multiscale modeling and simulation of CD8 cells memory generation, within the framework of the PrediVac ANR project for vaccine efficacy prediction.

Encarnita Mariotti-Ferrandiz[1], Charles Plessy[2], Guanying Wang[1], Ryuji Iida[1], Osami Kanagawa[1], Teruhiko Wakayama[3], Ri-ichiroh Manabe[2], Shohei Hori[1]. [1]**RIKEN RCAI,** [2]**RIKEN OMICS Science Center,** [3]**RIKEN CDB, Japan.**

High-throughput sequencing provides quantitative evidence for distinct central and peripheral Tregs TCR repertoires

Foxp3-expression regulatory T cells (Treg) play a critical role in maintaining peripheral immunological self-tolerance and have been suggested to be generated as a distinct T cell lineage mainly in the thymus. Despite several studies, TCR diversity overlap with conventional $Foxp3^{-}CD4^{+}$ T cells (Tconv) and impact of selection events on actual Treg TCR repertoire remain unclear, primarily because classical TCR sequencing analysis methods are low-throughput and do not give sufficient depth to draw quantitative pictures. Taking advantage of recent advances in sequencing technologies, coupled with genomics and transcriptomics accurate sequences mapping as well as ecology-based statistics, we developed a robust method to quantitatively characterize TCR repertoires, and analyzed peripheral and thymic Treg and Tconv repertoires in mice. Our results confirmed qualitative, and revealed quantitative, differences between Treg and Tconv repertoires with a higher dissimilarity found in the periphery than in the thymus. Moreover, the similarity between peripheral and thymic Treg repertoires was lower than that between peripheral and thymic Tconv repertoires, suggesting extensive reshaping of the Treg repertoires in the periphery.

Aleksandra, Walczak
Ecole Normale Supérieure, Laboratoire de Physique Théorique

Quantifying immune receptor diversity

Recognition of pathogens relies on the diversity of immune receptor proteins. Recent experiments that sequence the entire immune cell repertoires provide a new opportunity for quantitative insight into naturally occurring diversity and how it is generated. The generation process is implemented via a series of stochastic molecular events involving gene choices and random nucleotide insertions between, and deletions from, genes. I will describe how we can attempt to quantify the diversity of the receptors formed in this complex process and point to the origins of diversity in these sequences.

Boudinot Pierre
INRA, Virologie et immunologie moléculaires, équipe infection et immunité des poissons

Teleost Fish Mount Complex Clonal IgM and IgT Responses in Spleen upon Systemic Viral Infection

Upon infection, B-lymphocytes expressing antibodies specific for the intruding pathogen develop clonal responses triggered by pathogen recognition via the B-cell receptor. The constant region of antibodies produced by such responding clones dictates their functional properties. In teleost fish, the clonal structure of B-cell responses and the respective contribution of the three isotypes IgM, IgD and IgT remain unknown. The expression of IgM and IgT are mutually exclusive, leading to the existence of two B-cell subsets expressing either both IgM and IgD or only IgT. Here, we undertook a comprehensive analysis of the variable heavy chain (VH) domain repertoires of the IgM, IgD and IgT in spleen of homozygous isogenic rainbow trout (Onchorhynchus mykiss) before, and after challenge with a rhabdovirus, the Viral Hemorrhagic Septicemia Virus (VHSV), using CDR3-length spectratyping and pyrosequencing of immunoglobulin (Ig) transcripts. In healthy fish, we observed distinct repertoires for IgM, IgD and IgT, respectively, with a few amplified m and t junctions, suggesting the presence of IgM- and IgT-secreting cells in the spleen. In infected animals, we detected complex and highly diverse IgM responses involving all VH subgroups, and dominated by a few large public and private clones. A lower number of robust clonal responses involving only a few VH were detected for the mucosal IgT, indicating that both IgM+ and IgT+ spleen B cells responded to systemic infection but at different degrees. In contrast, the IgD response to the infection was faint. Although fish IgD and IgT present different structural features and evolutionary origin compared to mammalian IgD and IgA, respectively, their implication in the B-cell response evokes these mouse and human counterparts. Thus, it appears that the general properties of antibody responses were already in place in common ancestors of fish and mammals, and were globally conserved during evolution with possible functional convergences.

Alaa, Abi-Haidar
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What can Immunologists learn from data mining?

We aim to develop a new and automatic approach to improve our knowledge of the immune system in general and of T cell differentiation, diversity and dynamics specifically. The goal is to use cutting-edge techniques from data mining and machine learning to automatically extract the necessary parameters and values with the best accuracy possible from thousands of published articles.

Researchers from both disciplines of immunology and computer science aim to collaborate to offer solutions from bio-literature mining techniques. Text mining is capable of identifying concepts and extracting valuable information at semantic and syntactic levels. The former can be achieved by frequency and co-occurrence of terms in text while the latter can provide more accurate information, using natural language processing (NLP) to identify sentence structure and understand the relation between the terms. Moreover, text mining can benefit from immunology specific dictionaries and ontologies to identify terms of interest (and possible synonyms), and relate them to each other.

Moreover, the algorithmic development for immune literature mining can be generalized to analyse and understand other complex systems, in particular ecological or social systems also involved with populations dynamics and selection purposes.

Jean-Gabriel Ganascia
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Connecting Memory Extensions to Internal Memory

With the considerable improvement of sensors, storage devices and communication techniques, the quantity of everywhere-and-anytime-available information reaches a point unheard of. Everybody has access, day and night, to the content of the major libraries in the world, including the Library of Congress, the British Library, etc. It also becomes possible for anyone to record almost all the important events of his/her life with devices like the Steve Mann's EyeTap or the Google Glass, and then to build his/her personal individual archives. However, with the considerable augmentation of external storage devices, it becomes more and more difficult to retrieve personal information: we need to remember our remembering, to be able to access it. With the notion of "Memory Islands", we propose here to help us find our way in our remembering by automatically generating artificial cartographies of our memories. This approach is based on the old "arts of memory" that were practiced in the Antiquity and the Middle Age to enhances individual memory by the placement of things to memorize in architectural spaces. Nevertheless, "Memory Islands" make also use of modern knowledge representation and cartographic techniques, which allows navigating through artificial landscape of our imagination. As this is done, we claim that users let connect the electronic storage devices, which constitute external memory extensions, to our own internal memories. We use the memory island to visualize a complex system in order to simplify it. For example, we apply the memory island on the minimum spanning tree of a co-authorship network in the field of T cell regulation extracted from the bibliography of a review article by Rudensky.

Luis M. Rocha
Indiana University, USA and Instituto Gulbenkian de Ciencia, Portugal

Turing's Tape and Immunocomplexity

Many have argued that life and open-ended evolution depend on a semiotic closure, or a complex interplay, between separated symbolic information and molecular dynamics components. Alan Turing also showed that the separation between data and program is essential to achieve universal computation. Many, at least since John Von Neumann, have argued that this separation between information/data and dynamics/program is an evolutionary system that is more general than computation, and indeed defines life as we know it. In this talk I will review this idea and suggest that vertebrate Immunocomplexity is based on yet another biological re-discovery of this evolutionary principle of organization. I will also discuss what does this mean for our modelling of the adaptive immune system.

Frédéric Jacquemart
GIET (Groupe International d'Etudes Transdisciplinaires)

"Un enjeu capital pour le monde moderne: l'évaluation globale"

L'humanité est à un tournant de son histoire. La destruction du monde vivant que le développement de la techno-science engendre met en cause la pérennité de l'espèce humaine.
Face à ce défi majeur (et passionnant!) de nouveaux outils d'aide à la decision sont nécessaire, qui peuvent prendre en compte le fonctionnement global de la biogée.
Le système immunitaire, en tant que système complexe abordable expérimentalement (contrairement à la biogée!) devrait permettre de valider ou non, expérimentalement ou par modélisation, des principes généraux concernant l'évaluation globale des systèmes.

Cet exposé est un appel à la mobilistation des cerveaux et des bonnes volontés pour la realisation de cet objectif, qui se décline actuellement dans le programme d'Etat "EvaGlo", mené en partenariat avec le department de philosophie de l'INSA de Lyon.