2018-00372 - PhD - Mechanistic modeling and optimization of vaccine response in HIV and Ebola

Niveau de diplôme exigé : Bac + 5 ou équivalent  
Fonction : Doctorant

The challenge is to analyze these BIG DATA to answer clinical and biological questions by using appropriate statistical methods. With data on the machinery of a cell to the clinical status of individuals in any circumstances including in clinical trials, new tools are needed to translate information obtained from complex systems into knowledge. This has led to the field of « systems biology » and « systems medicine » by extension, which naturally takes place in the context of translational medicine that links clinical and biological research. The statistical analysis of these data is facing several issues:

- There are more parameters (p) to estimate than individuals (n)
- The types/nature of data are various
- The relationship between variables is often complex (e.g. non-linear) and can change over time to tackle these issues we are developing specific approaches for these questions, often related to immunology.

The methods are mainly based on either mechanistic modeling using differential equation systems or on statistical learning methods. The general paradigm of our approach is to include as much information as available to answer a given question. This information comes from the available data but also from prior biological information available defining the structure of the model or restricting the space of the parameter values. We develop and apply our methods mainly for applications belonging to clinical research especially HIV immunology. For instance, several projects are devoted to the modelling of the response to antiretroviral treatments, immune interventions or vaccine in HIV infected patients.

Applications are provided by the Vaccine Research Institute (VRI), other teams in the research centre and the Bordeaux Hospital Clinical Trial Unit (CTU).

Contexte et atouts du poste

Scientific priorities: This PhD project is integrated in the Inria scientific strategy as it fits the “multiscale everywhere” topic and the “human-centered digital world” topic. It focusses on “predictive system immunology” (Challenge 13) regarding the methods that we plan to develop and it focusses on “integrative computational medicine” (Challenge 16) regarding the application toward personalized medicine.

Scientific Research context: Today vaccination strategies against HIV or Ebola consist in prime-boost schemes of two injections with same or different viral vectors. Optimal vector choice and timing between prime and boost injections have never been statistically investigated. Because all strategies cannot be explored in clinical trials as it would be expensive and time consuming, it is needed to develop in silico trials to evaluate alternative strategies based on computer simulations. In particular, we will develop methods to accelerate development of vaccine and define individualized strategies of vaccination for individuals or groups of bad responders. We propose to use available data to help answering these questions using an integrative system vaccinology approach based on mathematical modeling and control theory [1,2,3]. All methods developed will be applied to question arising in real trials with available data investigated by the Inria SISTM team. In particular, it will be applied to Ebola vaccine trials through the EBOVAC1,2,3 European project and in HIV vaccine trials through the Vaccine research institute. The methods will be applied to several available trials for which the dataset is already available. Especially, the EBL1001, EBL1003 and EBL1404 trials compare four prime boost strategies based on Ad26/MVA and MVA/Ad26 vectors against EBOVLA virus with multiple boosting times and the VIR01 trial which is Phase I/II open-label randomized multicenter trial to assess immunogenicity and safety of 4 prime-boost combinations (MVA/LIP0-5, LIP0-5/MVA, GTU-MultiHIV/LIP0-5, GTU-MultiHIV/MVA) of HIV vaccine candidates in healthy volunteers at low risk of HIV infection.

Mission confiée

We propose to combine exploratory analysis, dimension reduction methods for high dimensional data, mathematical dynamical modeling and optimal control theory to answer these questions.
Principales activités

Based on this general objective description, we expect to organize the work in three different tasks:

1/ Develop methods for integration and exploitation of heterogeneous data acquired on a patient and on a population. We will assimilate data from multiple sources using lasso-type methods to further understand what can be seen as a correlate of efficacy. In particular, we will be interested in identification and validation of an early correlate of late antibody response. It would allow early prediction of whether an individual, or group of individuals is likely to be a good or poor immunological responder [5]. Methods based on joint non-linear mixed models and sparse PCA will be investigated,

2/ Extend existing methods to estimate parameters in mechanistic models by using assimilation approaches based on filtering methods and compare them with penalized maximum likelihood as implemented in NIMROD [4]. In particular, we believe that these filter methods, which jointly estimate state and parameters, can help addressing the fact that biomarkers can sometimes not be observed but are only deduced from surrogate information. A particular example lies in gene expression information which may carry cells count information if proper deconvolution is used.

3/ Develop an optimal protocol to individualize and optimally choose a vaccination strategy using machine learning and particularly neural network approaches. The idea is that it is possible to build synthetic data with annotated optimal choice from the mechanistic model by using computer based simulation and that these datasets can be used as learning examples for neural network approaches.

We will compare this approach with existing approaches developed in the team such as Bayesian predictions and dynamic programming based on Markov impulse theory.

These methods will be illustrated on available clinical data, and particularly on the EBL1001+EBL1003+EBL1004 and VR101 trials described in the previous section for which we have measurement of humoral response, cellular response and transcriptomic data in respectively 216 and 92 individuals. More than eight longitudinal follow-up up guaranty good quantity of dynamic information. Moreover, these studies enable us to investigate the same viral vector (MVA) for different infectious diseases. We expect to publish the results in journals both theoretical and more applied to clinical practices. Finally, we expect that a software for joint analysis of multiple sources data in immunological studies will be developed and disseminated.

Keywords : Applied mathematics, Simulation and calculus, Biostatistics, Mixed effects dynamical models, control theory, vaccination

References :


Compétences

Required Knowledge and background : We seek for a very good master-level student (possibly from a French engineer school or foreign universities) with strong background in mathematics and/or statistics. We request good programming skills in any language, and a good knowledge of R. Proficient written and spoken English is needed. Previous experience in research, possibly working with differential equations or immunology, will be seen as a very competitive advantage.

Avantages sociaux

- Subsidised catering service
- Partially-reimbursed public transport

Rémunération

1982€ / month (before taxes) during the first 2 years, 2085€ / month (before taxes) during the third year