BITS :: Call for Abstracts 2022 - Oral communication

Type	Oral communication
Session	Personal medicine
Title	GreatNector: a new perspective on personalized drug therapy for MS patients
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Motivation

Computational models have gained importance in the study of complex diseases, such as Multiple Sclerosis (MS), where the development and response of the immune system (IS) is driven by individual variability and cannot be fully captured due to a lack of disease information or to unpredictable environmental events.
Available therapies for MS modify the course of the disease slowing its progression. The choice of the drug mostly relies on the judgment and experience of the neurologist and depends primarily on the patient's clinical status, coexisting comorbidities and also on patients' preferences on administration methods. Alemtuzumab is classified as an immune reconstitution therapy with high efficacy. It depletes circulating T and B cells believed to be responsible for the inflammatory process typical of MS, by binding to the CD52 protein present on their surface. Lymphocytes depletion is followed by a reconstitution of the IS that is fundamental for the long-term persistence of clinical efficacy. Drug response differs in patients: the majority of them do not display any relapses for at least six years; others relapse already within two years and require further drug administrations. In this context, the integration of patient-derived data into a mechanistic model can provide an invaluable tool for the definition of (i) a patient-specific personalized drug administration schedule, and (ii) for the prediction of therapy efficacy based on the patient’s peculiar immunological structure at the time of the onset of the disease or therapy.

Methods

In this work, we considered data from a six-year follow-up of 29 MS patients treated with alemtuzumab [1]. Data consisted of immunophenotyping of CD4+ T cells, Th1, Th17, and Treg cells measured at regular time steps coupled with the Expanded Disability Status Scale (EDSS) score as a clinical measure of disability at every time point.
We developed a workflow, GreatNector, for data integration defined by the communication between two tools: CONNECTOR (https://qbioturin.github.io/connector) and GreatMod (https://qbioturin.github.io/epimod), as shown in the figure. The former is an R package encoding the Functional Clustering Model approach [2] that allows us to cluster time course data with similar behavior in an unsupervised manner to extrapolate useful insights and hypotheses. The latter is a general modeling framework that exploits a high-level graphical formalism to simplify the design and description of the system and allows the automatic derivation of the mathematical processes characterizing the system dynamics.

Results

CONNECTOR was exploited to cluster 29 patients that share similar clinical data about CD4+ T cell reconstitution and EDSS scores. The resulting clusters were able to distinguish groups characterized by patients with more than one relapse and patients without relapses. Then, the clusters information was integrated and exploited to calibrate the unknown parameters of an modified version of the MS model proposed in [3]. In detail, for each cluster of patients, we identified a specific parameter configuration, which was used 1) to simulate the model, capturing the variability characterizing the clusters, and 2) to study the individual IS response to alemtuzumab treatment. Therefore, in an era where therapies are focused on personalization, GreatNector aims to predict the evolution of MS and the response to treatments in specific patients, based on similar immunological structure (based on the clustering) at the time of the onset of the disease or therapy. Indeed, this workflow can lead to significant benefits for patients and improvements in their life conditions, that can be applied to other therapies different from the alemtuzumab treatment. Moreover, optimized therapies also mean more cost-effective therapies, since unnecessary and ineffective treatments will be reduced, with positive economic consequences.

Info

[1] Rolla S, De Mercanti SF, Bardina V, Maglione A, Taverna D, Novelli F, Cocco E, Vladic A, Habek M, Adamec I, Annovazzi POL, Horakova D, Clerico M. Long-Term Effects of Alemtuzumab on CD4+ Lymphocytes in Multiple Sclerosis Patients: A 72-Month Follow-Up. Front Immunol. (2022)
[2] James, Gareth M., and Catherine A. Sugar. Clustering for sparsely sampled functional data. Journal of the American Statistical Association (2003)
[3] S. Pernice, L. Follia, A. Maglione, M. Pennisi, F. Pappalardo, F. Novelli, M. Clerico, M. Beccuti, F. Cordero, S. Rolla. Computational modeling of the immune response in multiple sclerosis using epimod framework. BMC Bioinformatics (2020).

filename	GREATNECTOR.png

Figure

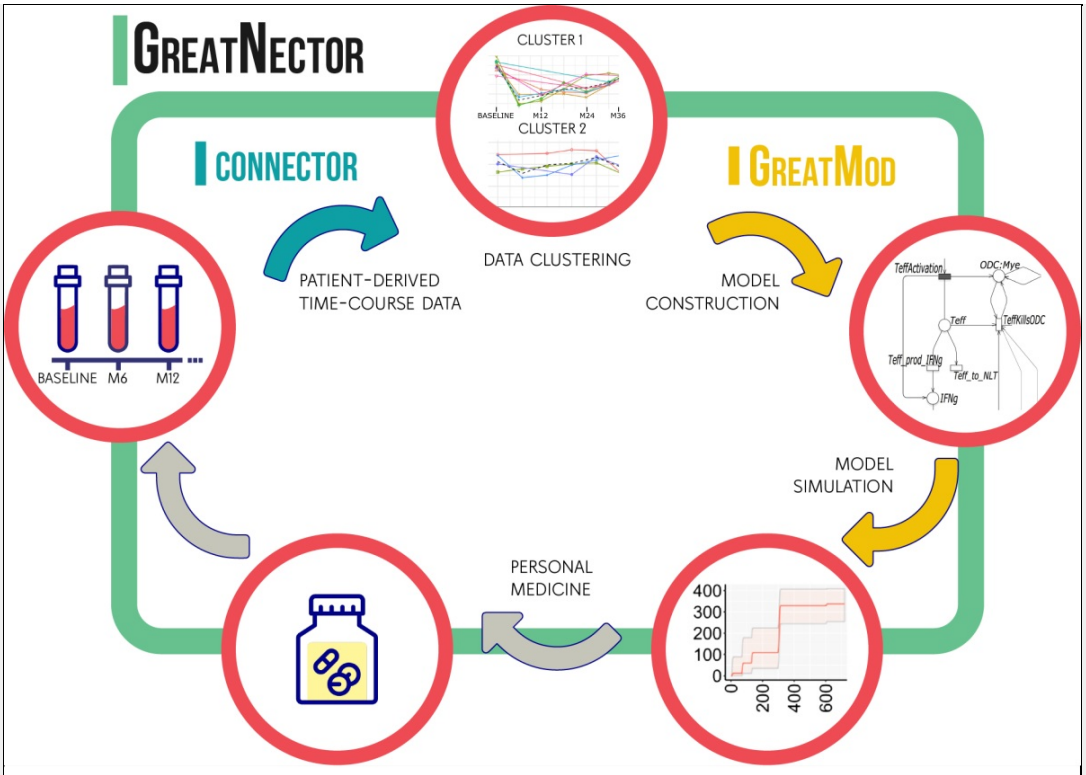

Figure. GreatNector represents a new workflow of analysis based on two tools: 1) the R package Connector and 2) the general modeling framework GreatMod. In particular, the time course clinical data obtained from in vivo experiments are analysed and clustered by Connector, grouping patients with similar characteristics. Successively, the obtained clusters are exploited to parameterize and define the MS computational model studied using the GreatMod framework. Thus, the model can be simulated under different scenarios and conditions to investigate in silico how the patients belonging to the same clusters response to the treatment, leading to new optimized therapies.

Availability	https://drive.google.com/file/d/1I4TAxwHebkC0o-c7eKYsZNgnc_IfFY0V/view?usp=sharing

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