ID de Contribution: **12** Type: **Non spécifié**

High-dimension Mechanistic Model Building using LASSO Approaches : Application to Ebola Vaccination

vendredi 17 novembre 2023 11:45 (25 minutes)

Constructing non-linear mixed-effects models (NLMEM) deepens our comprehension of biological processes. Specifically, NLMEM facilitates the incorporation of inter-individual variability by parameterizing models at the individual level within a population framework. To do so, parameters combine fixed effects, capturing population-level relationships with covariates, and random effects, accounting for individual deviations. Estimation in NLMEM is achievable through maximum likelihood methods, such as the Stochastic Approximation Expectation-Maximization (SAEM-Dempster, 1977; Kuhn & Lavielle, 2005) algorithm. However, this approach is computationally intensive, and selecting covariates that define individual-level parameters cannot be done by comparing all possible models.

For the optimized construction of NLMEM, traditional methodologies rely on modified stepwise approaches (SCM-Jonsson, 1998; COSSAC-Ayral, 2021). Alternatively, the Stochastic Approximation for Model Building Algorithm (SAMBA-Prague & Lavielle, 2022) builds the covariate model on the posterior realization of the parameters. Within a low-dimensional context, SAMBA efficiently and more rapidly constructs models by minimizing an information criterion. However, we aim to extend it for high-dimensional settings—such as those involving transcriptomic data. Initially, SAMBA employs a stepwise AIC algorithm for covariate selection. Our proposal integrates a multivariate LASSO approach, offering a more nuanced treatment of parameter correlations. This methodology incorporates a whitening step (Perrot-Dockès, 2018) and a stability selection process (Meinshausen & Bühlmann, 2010).

We validated our approach through simulations imitating the dynamics of the humoral immune response to an Ebola vaccine (Pasin, 2019). These simulations were replicated 100 times, each involving 100 individuals and 200 covariates. Remarkably, the False Discovery Rate for the proposed method was reduced by a factor of 10, while maintaining a similar False Negative Rate. This indicates enhanced control over the False Positive Rate. We applied our method using data from the Prevac/Prevac-UP trial (Prevac-UP Team, 2022), which compares two licensed vaccines for Ebola in Africa.

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Classification de Session: Apprentissage statistique et grande dimension