Master 2 Internship in Bayesian Inference for Viral Dynamics Models with PDEs and Mixed Effects

Context

Within-host models of infectious disease dynamics describe the interactions between infectious agents, target cells and the immune response. Mixed-effects models combine a shared mechanistic structure with individual parameters to quantify variability between individuals.

Partial differential equations (PDEs) extend models based on systems of ordinary differential equations (ODEs) by introducing an additional variable. They can represent heterogeneity among cells according to their age of infection, linking intracellular and extracellular dynamics in viral hepatitis [1,2]; the distribution of infected cells according to their viral RNA content in hepatitis C [3]; or the spatial spread of infection and transport of viral particles through the respiratory tract during influenza infection [4]. These models help interpret biological measurements and treatment responses when assumptions of homogeneous compartments are insufficient.

However, inferring parameters and their variability between individuals remains challenging. In a Bayesian framework in particular, estimation requires numerous model evaluations to explore the posterior distribution of population parameters and random effects. When each evaluation requires solving a PDE for every individual, the computational cost becomes a major obstacle. Observations, which are often partial or aggregated, may also limit parameter identifiability.

In recent work by our team (Hozé et al., in preparation), we developed and implemented in Stan [5] a method based on polynomial chaos expansions (PCE) [6,7] to accelerate Bayesian inference in mixed-effects ODE models. It approximates the dependence of model outputs on random effects using a limited number of numerical solutions shared across all individuals. Individual trajectories are then reconstructed from this approximation. By avoiding many redundant ODE solves, this approach substantially reduces computation time, particularly when the number of individuals is large.

Objective

The main objective of this internship is to extend this method to mixed-effects PDE models, making Bayesian inference of population parameters, interindividual variability and individual random effects more accessible. The work will combine methodological development with validation using simulated data and two published within-host models. The resulting R code will be made available to the community.

Proposed work

- Extend the PCE method to mixed-effects PDE models and clarify how it integrates with Bayesian inference.
- Conduct simulation studies to assess the performance of the PCE approximation in terms of parameter estimation and computation time.
- Implement the two published models described below.
- Develop a tool, potentially in R, to facilitate inference and diagnostics.

Two models of infection within the host

The first application will focus on the multiscale hepatitis B virus (HBV) model of Iyaniwura et al. [1], which extends the work of Gonçalves et al. [2]. This model links intracellular dynamics to circulating HBV DNA and RNA concentrations. We will implement its formulation structured by the age of infection of cells and retain the mixed-effects structure used in the paper.

The second application will focus on the hepatitis C model of Woot de Trixhe et al. [3], structured by intracellular viral RNA content. It describes heterogeneity among infected cells according to their physiological state and links this distribution to measurements of viral RNA in plasma and liver. Random effects are assigned to viral clearance and the loss rate of infected cells.

The two models differ notably in their structuring variable: age of infection for HBV and intracellular state for HCV. They will allow the method to be evaluated in two complementary biological and mathematical settings. In the published studies, simplifying assumptions allow the models to be reduced to ODEs for estimation; we will use these reductions as benchmarks for the PCE–PDE solution.

Candidate profile

Applicants should be in the second year of a master's degree or the final year of a French engineering degree, with a background in mathematics, physics, biostatistics or biomathematics. Proficiency in R is required. Experience with numerical PDE solvers or Stan would be an advantage. Candidates should be rigorous, able to work independently and interested in biological modelling.

Research environment and supervision

The internship will be hosted by the MOCLID team at Inserm UMR 1137 IAME, on the Bichat Hospital campus in Paris. A stipend will be provided in accordance with Inserm regulations.

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References

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