## Mathematical modeling of CLL dynamics in patients under Ibrutinib treatment

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Chronic Lymphocytic Leukemia (CLL) is a widespread form of cancer affecting B lymphocytes. The treatment of this disease has been recently revolutionized by the replacement of immunechemotherapies by targeted therapies. The Btk inhibitor ibrutinib has recently been approved as a monotherapy in relapsed/refractory CLL. It impairs B-cell receptor signaling, survival, and homing of leukemic cells, it purges these cells from the lymphoid organs and induces cell death. However, important inter-patient variability in the redistribution of the leukemic cells, the rate of leukemic cell elimination and the disparity of relapses calls for an analysis of biological parameters influencing the dynamical behavior of the leukemic cell population in individual patients.

This work is based on real medical data (CompuTreatCLL cohort), before and during treatment cell counts were obtained from peripheral blood (leukemic B cells, CD4<sup>+</sup> T cells, Treg cells, CD8<sup>+</sup> T cells, NK cells) and with imaging techniques from lymph nodes (leukemic B cells). Based on blood leukemic B cells counts after 3 months of treatment, patients were split into 2 groups and these groups were associated with therapy outcomes. We proposed to characterized the two groups of patients with a mathematical model accounting for the physical and biological evolution of CLL leukemic cells during ibrutinib therapy. We aim with this model at getting insight into inter-patient variability as well as at confirming the biological parameters associated with the two groups.

We introduce an ordinary differential equation-based model of leukemic B cell and T cell dynamics in CLL patients treated with ibrutinib. In order to account for inter-patient variability in cell count dynamics, parameter estimation will be performed with nonlinear mixed effect models, using Monolix software [1,2]. The idea is to characterize the average behavior and to extract the patient-specific dynamics from this behavior. The nonlinear mixed effect model was constructed with an automatic model building method, SAMBA [3], that facilitates decision-making and allows to optimally include correlation, covariates, and random effects. We will show that our approach manages to discriminate the different responses to treatment based on three parameters of the mathematical model, and allows to characterize patient-specific responses. In addition, the mathematical parameters discriminating the different responses to treatment are in agreement with the biological parameters associated with a better outcome: a larger lymph node exiting rate of leukemic B cell, a reduced production rate of the leukemic B cells and a higher death rate of CD4<sup>+</sup> T cells.

[1] M. Lavielle M, Mixed effects models for the population approach. Models, Tasks, Methods and Tools. Chapmann and Hall/CRC, 383p, 2014.

[2] Monolix version 2021R1. Antony, France: Lixoft SAS, 2021.

[3] M. Prague and M. Lavielle, SAMBA: a Novel Method for Fast Automatic Model Building in Nonlinear Mixed-Effects Models, CPT Pharmacometrics Syst Pharmacol, 11: 161- 172, 2022.