From gene regulatory network inference to multiscale modeling: understanding the crosstalk between immune and cancer cells in Chronic Lymphocytic Leukemia

Malvina Marku, Hugo Chenel, Julie Bordenave, Nina Verstraete, Flavien Raynal, Leila Khajavi and Vera Pancaldi

The tumor microenvironment (TME) can be seen as a complex system containing multiple cell types interacting through contact and cytokine exchanges. In particular, immune cells play a major role in cancer development and their characterization allows a better understanding of the TME. In this context, transcriptomics time courses allow studying the gene regulatory networks and interactions between myeloid immune and cancer cells to obtain relevant information about the biology behind them, and to identify novel molecular interactions and potential drug targets.
In this project, we aim to characterize the formation of Nurse Like Cells (NLC), a type of tumour associated macrophages found in lymph nodes of Chronic Lymphocytic Leukemia (CLL) patients, and to investigate their crosstalk with cancer cells from a network perspective. To this end, building on in-vitro experiments of macrophage-CLL co-culture, we use multi-scale approaches to study the system at the molecular and cellular scale. *Firstly*, we built a gene regulatory network of macrophage polarization with a literature-based approach, identifying the main molecular regulators defining the macrophage phenotype in the presence of different extracellular stimuli, including CLL secreted cytokines. Additionally, we performed inference of regulatory networks in the CLL cells, using several inference methods on RNAseq time-series from CLLs isolated from a 13-days co-culture with macrophages. Furthermore, we applied TF activity analysis to reveal the processes taking place inside the CLL cells as they interact with the macrophages.
Secondly, to study the cell population spatio-temporal dynamics, we built an agent-based model of the co-culture, thus identifying important cellular processes as well as patient features determining the system's longitudinal behavior. We aim to integrate these two approaches in a multi-scale dynamical model, in which cell behavior is determined both by cells' interactions and by intra-cellular molecular regulation. With this multi-level approach we aim to recapitulate the processes that lead to the formation of tumour protective macrophages, specifically highlighting their effect ontemporal dynamics of the CLL cell population. Finally, we hope to identify novel molecular targets to disrupt this interaction, which can strongly increase resistance to therapies in CLL and other cancers.

Key words: *gene regulatory networks, Boolean models, agent-based modeling, time series transcriptomics, Nurse Like cells, Chronic Lymphocytic Leukemia*