Instantiation of patient-specific network-based logical models with multi-omics data allows clinical stratification of patients

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We present here a novel framework to tailor logical models to a particular biological sample like a patient's tumor. This methodology permits to compare the model simulations to individual clinical data, such as drug response and survival time. Our approach focuses on integrating mutation data, copy number alterations (CNA), and expression data (transcriptomics or proteomics) to logical models. These data need first to be binarized or set between 0 and 1, and can then be incorporated in the logical model by modifying the activity of the node, the initial conditions or the transition rates. The use of MaBoSS, a tool that uses Monte-Carlo kinetic algorithm to perform stochastic simulations on logical models and obtain model state probabilities, allows for a semi-quantitative study of the model's phenotypes and perturbations.

As a proof of concept, we use a published generic model of a cancer network and molecular data from 1904 METABRIC breast cancer patients. For this example, we test several combinations of data incorporation and discuss that the most comprehensive METABRIC patient-specific cancer models are obtained by modifying the activity of the nodes of the logical model with mutation and CNA data and altering the transition rates with RNA expression. We conclude that these models' simulations show good results when compared to the clinical data such as patients' Nottingham prognostic index (NPI) subgrouping and survival time. We observe that two highly relevant cancer phenotypes, Proliferation and Apoptosis, exhibit different simulated probabilities across NPI subgroups: patients with low survival show highly proliferative and low apoptotic probabilities, in accordance with biological expectations. Our approach aims to combine the mechanistic insights of logical modeling with multi-omics data integration to provide patient-relevant models. This work leads to the use of logical modeling for precision medicine and will eventually facilitate the choice of patient-specific drug treatments by physicians.