Leveraging the Molecular Signatures of Cancer for Dynamic Network Modeling

Nurcan Tunçbağ	NTUNCBAG@ku.edu.tr	Turkey	Koç University
Enes Sefa Ayar	eayar15@ku.edu.tr	Turkey	Koç University

Molecular heterogeneity and resistance to the treatment are among the obstacles in developing treatment strategies in cancer. Therefore, transforming patient-specific molecular data into clinically interpretable knowledge is fundamental in personalized medicine. However, not all molecular alterations drive cancer. The distinction of drivers from latent drivers and passengers, their cooperativity and exclusivity, and the temporal order of accumulation of molecular alterations is a crucial yet daunting, unsolved task. Early alterations in temporal order can inform about network rewiring and direct the identification of drug targets. The challenge in temporal modelling of cancer and the respective elucidation of the chronological order of molecular alterations, especially in terms of the evolution of networks beyond the alterations, remains elusive. The focus of this study is directly devoted to address this challenge. We developed an integrative computational modeling approach to reveal the network-based history of tumor progression and to design personalized therapeutic strategies based on the validated models. The core method in this approach is the graph-based cellular automata (GCA), which is a discrete dynamic model. GCA model can simulate complex systems by considering local interaction rules, and it gives insights into the underlying mechanism of complex behavior. The reference graph is a tissue-specific interactome consisting of protein-protein interactions and regulatory interactions. Proteins are assumed to have a state of being for cancer-driving or neutral/against cancer progression. We applied this model to the cell line-dependent data in DepMap which consists of both molecular alterations (mutation transcriptomic and proteomic data) and drug response. As a result of a rigorous dynamic network comparison we constructed a network-based taxonomy of the tumors both within each cancer type and cross-cancer-types. We expect that this approach from molecular alterations to dynamic networks will transform the already available large datasets to gain new clinically relevant insights and improve personalized medicine.