Integrating Evolutionary Game Theory of Propagation of Survival and Death Signals through Gap Junctions into an Agent-Based Model of Ductal Carcinoma in Situ

Abstract

There are many cells with various phenotypic behaviors in cancer. These cells with different phenotypic behaviors have interaction with each other. For example, an apoptotic cell may induce apoptosis to adjacent cells (called kiss of death or bystander effect). A living cell (i.e., a non-apoptotic and non-necrotic cell) can also protect cells from undergoing apoptosis and necrosis (called kiss of life or good Samaritan effect). These survival and death (i.e., apoptosis or necrosis) signals are propagated through some interaction ways between adjacent cells called gap junctions. The function of these signals depends on the cellular context of a receiver cell of signal. For instance, a receiver cell of signal with a low level of oxygen may interpret a received survival signal as an apoptosis signal.

We make an evolutionary game component to model the signal propagation through gap junctions. Each cancer cell is a player in this component. We consider four strategies (i.e., phenotypic behaviors) in the game: quiescence, proliferation, apoptosis, and necrosis and define game theory payoffs as a function of cellular context for the first time. The game theory component is integrated into an agent-based model to compose a new model. Finally, the new model is applied to ductal carcinoma in situ (DCIS) that is a type of early stage breast cancer. Different scenarios for the game theory component are explored to observe the impact of gap junction communication and parameters of the game theory component on cancer progression. We compare these scenarios with Wilcoxon signed-rank test to determine whether differences between these scenarios are significant or not. The model indicates gap junction communication and the value of the oxygen threshold at which survival signals turn into apoptosis can affect cancer progression significantly. This study illustrates the role of gap junction communication at early stage cancers like DCIS.

Keywords: Evolutionary game theory, Agent-based, Cancer modeling, Ductal carcinoma

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