In silico control and optimization of Natural Killer cell activation

Natural killer (NK) cells are part of the innate immune system and are capable of killing diseased cells. As a result, NK cells are being used for adoptive cell therapies for cancer patients. The activation of NK cell stimulatory receptors leads to a cascade of intracellular phosphorylation reactions, which activates key signaling species that facilitate the secretion of cytolytic molecules required for cell killing. Strategies that maximize the activation of such intracellular species can increase the likelihood of NK cell killing upon contact with a cancer cell and thereby improve efficacy of NK cell-based therapies. However, NK cell exhaustion, a phenotype characterized by reduced effector functionality, can limit the NK cell's capacity for cell lysis. Due to the complexity of intracellular signaling, it is difficult to deduce a priori which strategies can enhance species activation.

To aid in the development of strategies to enhance NK cell activation and limit the NK cell exhaustion, we constructed a mechanistic model of the signaling pathways activated by stimulatory receptors in NK cells. We then extended the model to describe the dynamics of the cytolytic molecules granzyme B (GZMB) and perforin-1 (PRF1). We implemented an information-theoretic approach to perform a global sensitivity analysis and optimal control theory to investigate strategies to enhance intracellular signaling and maximize GZMB and PRF1 secretion. In total, we developed a theoretical framework that provides actionable insight into engineering robust NK cells for clinical applications.

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