

# Stochastic modeling of CAR T cell therapy with in silicon clinical trials

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**Abstract:** Chimeric antigen receptor (CAR) T cell immunotherapy has been regarded as a major advance in the fight against cancers, especially those associated with the hematopoietic system. This is a special adoptive cellular therapy in that T lymphocytes are taken from the patient's blood, genetically modified to recognize specific antigens expressed by the tumor, expanded in vitro, and infused into the patient. Due to its verified success in eliminating or relieving endurable types of lymphomas and leukemia, in 2017, the Food and Drug Administration (FDA) approved the commercialization of two therapies with CAR-T cells for the treatment of CD19+ B cell malignancies. However, temporal reductions in tumor burdens have been observed in patients treated with CAR T cells although overall response rate and complete response rate are high in many CAR T cell drug clinical trials. This requires a complete understanding of the treatment process after CAR T cell infusion. In particular, the dynamics of CAR T cells after infusion, and the interactions among CAR T cells, cancer cells, and other relevant cells. It is an opportunity for mathematical analysis and in silicon simulations to make contributions in the CAR T cell therapy.

Based on a deterministic and stochastic process hybrid model for CAR T cell therapy, we introduce patient variabilities as noises and construct a stochastic model in terms of Ito stochastic differential equations for the treatment. The stochastic model has three ergodic invariant measures which correspond to three unstable equilibrium solutions of the deterministic system, while the ergodic invariant measures are attractors under conditions for tumor growth. As the stable dynamics of the stochastic system reflects long-term outcomes of the therapy, the transient dynamics provide chances of cure in short-term. Two stopping times, the time to cure and time to progress, allow us to conduct in silicon clinical trials with three different protocols of CAR T cell treatment through the transient dynamics. The probability distributions of the time to cure and time to progress present outcome details of different protocols, which are significant for clinical study.