**Multi-Scale Modeling of T Cell and Antigen Presenting Cell Interaction in the Tumor Microenvironment**

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**Introduction:** The impact cancer has on the world today is very significant and costly. In 2016, an estimated 1,685,210 new cases of cancer will be diagnosed in the United States and 595,690 people will die from the disease with national expenditures for cancer care possibly reaching $156 billion in 2020 (National Institute of Cancer, NCI). Out of the current treatments for cancer one of particular promise is immunotherapy. Cancer is a systemic disease that influences and is influenced by the immune system. Immunotherapy is a type of cancer treatment that helps the immune system fight cancer. (NCI). T Cell immunotherapy in particular has seen recent development and promising success. One form of this therapy is checkpoint-blocking. Immune checkpoint molecules are used by tumors to suppress and evade attacks from the immune system. Checkpoint blocking therapies seek to prevent this suppression of immune activity. However, a large fraction of cancer patients is still unresponsive to immunotherapies. This is partly due to the fact that every patient is different and tumor microenvironments are very diverse. There is therefore a need for predictive tools suitable for adjusting treatments to individual patient’s microenvironments. To this end we implement a computational model of immune cell interactions including cell types and molecular processes relevant for cancer immunotherapy. The model allows to simulate biological and chemical processes within the tumor microenvironment. Ultimately, the model will enable clinicians to test therapies and dosages to define optimal treatment plans for individual patients.

**Materials and Methods:** We developed a multi-scale model comprising extracellular and intracellular processes. The model includes inter-cellular interactions between T Cells and Antigen Presenting Cells in the tumor microenvironment. These were simulated using an agent-based approach based on a Cellular Potts Model. For this purpose, CompuCell3D (CC3D), a modeling environment for developing and running agent based multi-scale cell simulations, was used. We modeled the movement of cells in 3D space as pseudorandom (Naïve T Cells were attracted to APCs). T Cells move at a rate of ~0.75um/min while APCs move at ~0.1um/min and interact upon contact by pre-stipulated rules that contemplate the complement of surface molecules present on each cell. Intracellular processes were simulated as systems of coupled Ordinary Differential Equations (ODEs) representing biochemical interactions. Specifically, BioNetGen was used to create a rule-based biochemical system representing the intracellular events resulting from Naïve T Cell co-activation by APCs. In particular, we focus on the CTLA-4 recycling process as this co-receptor is a key player in checkpoint blockade therapies. The co-activation model also included the interactions between T-Cell receptors TCR, CD28, CTLA-4, and APC ligands Peptide-MHC, CD80, and CD86. Both Regulatory T Cells (Tregs) and Conventional T Cells (Tconvs) were simulated with the Tregs having both CD28 and CTLA-4 surface expression while the Tconvs only expressing surface CTLA-4 when activated. Both inter- and intra-cellular models were run sequentially, with the biochemical model being updated every XXXX Monte Carlo step. Simulations were typically run for XXX model hours.

**Results and Discussion:** The model successfully recapitulated the movement of cells and the ligand competition between the CTLA-4 and CD28 receptors in the various T cell cohorts. There was a 70% selection rate of CTLA-4 over CD28. T Cell activation requires two signals which was successfully simulated with the receptor-ligand T Cell co-activation process implemented in the biochemical system.

**Conclusions:** Our multi-scale model successfully integrates the intracellular process of CTLA-4 recycling as well as cell movement and T Cell co-activation through cell-cell interaction. However, more complex intracellular and extracellular processes must still be added in order for the model to become a predictive tool for personalized immunotherapy design. At the current stage, the model includes the basic processes relevant for checkpoint-blockade immunotherapies, setting a basis for subsequent development.

