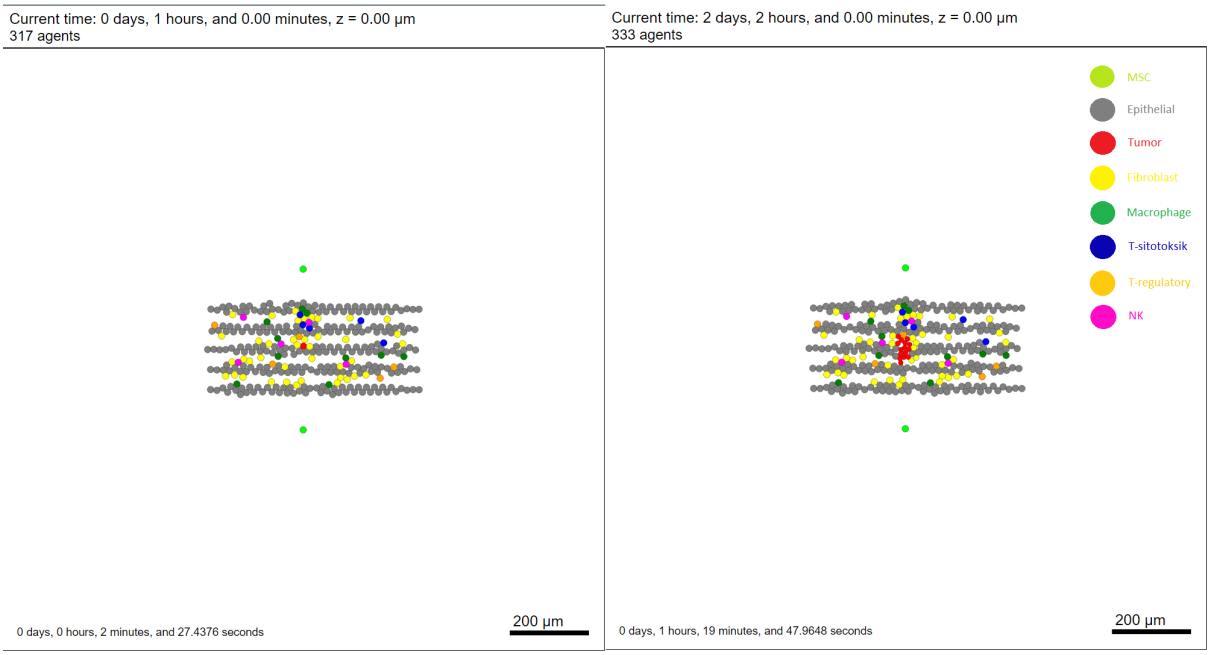
Investigation of Effects of Microenvironment and Immune Cells on Tumor Growth by Agent Based Modeling

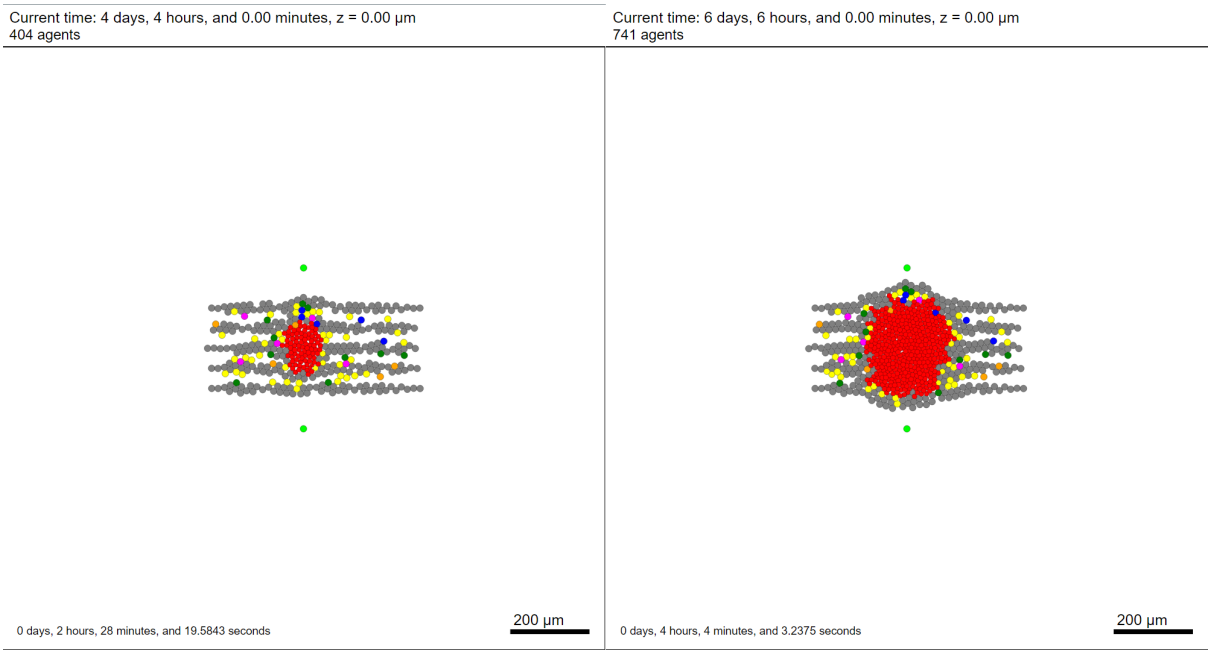
Cancer is one of the diseases that humanity suffered for a long time. We understand many aspects of this disease, but there is still much to learn. Because it is a complex disease that affects many processes, organs, cell types, and so on. We need to investigate cellular components, interactions and processes that are related to cancer as a whole to understand its structure. In this scope, investigating the microenvironment of tumors and interactions in it can reveal fundamental features of cancer.

One of the major fields to focus on when investigating tumor cell properties such as proliferation, immune evasion, immune cell controlling, angiogenesis, metastasis, cell type or cell feature differentiations, and dormancy is communication between cells and their microenvironment. Cancer initiation, progression, and patient prognosis are all influenced by interactions between tumor cells and their microenvironment. Cancer was previously thought to be a heterogeneous disease characterized by aberrant mutations in tumor cells; however, we now include microenvironmental composition and stromal cell proportions or activation states to define the diverse structure of cancer. We now know that the tumor microenvironment changes over time in response to normal or oncogenic tumor cell signals as well as micro or macro environmental conditions.

Homeostasis is the balance between cell proliferation and death processes. Tumors can shift this balance in favor of the proliferation, via regulating some of the immune system cells. For example, macrophages help tumors to suppress immune system activity by blocking immune system cells and prevent antigen presentation if their phenotype shifted from M1 to M2 phase. M2 phase macrophages are called Tumor-Associated Macrophages(TAM). Same transformation can apply to other stromal cells like fibroblasts. They induce tumor progression and invasion. These transformations are the result of signals transmitted by chemokines, cytokines and metabolites. Other microenvironmental cell types(MSCs, Tsit, Treg, NK etc.) are differentiated into cancer related ones upon receiving these signals. These cells can be re-educated to return back to their normal properties. With the help of modeling we can understand how these cells behave and discover more effective drug or treatment targets in the tumor microenvironment.

We use C++ based PhysiCell/BioFVM as the modeling environment. 2D or 3D agent based models of tissues can be constructed and simulated using this tool. The tool takes XML file and CPP file codes as inputs to construct the designed model. In intracellular models, FBA, Libroadrunner can be used to investigate intracellular dynamics. SBML files are used to establish cell features, secretions and reactions. In this work, we designed a tissue-like multicellular structure. In this structure, initially we have a single cancer cell in the middle of many epithelial cells. Fibroblast cells and macrophage cells are located around this core. Also, we have Tsit, Treg, NK and MSC cells. Distinct features of these cells lead them to behave differently in terms of growth rate, migration patterns, cellular interactions and metabolite/protein secretion. Tumor progression under different conditions was simulated using this model structure, four time points from a sample simulation are shown in the below figure.


Current time: 0 days, 1 hours, and 0.00 minutes, z = 0.00 µm
317 agents
Current time: 2 days, 2 hours, and 0.00 minutes, z = 0.00 µm
333 agents
MSC
Epithelial
Tumor
Fibroblast
Macrophage
T-sitotoksik
T-regulatory
NK
0 days, 0 hours, 2 minutes, and 27.4376 seconds
200 µm
0 days, 1 hours, 19 minutes, and 47.9648 seconds
200 µm


Current time: 4 days, 4 hours, and 0.00 minutes, z = 0.00 µm
404 agents
Current time: 6 days, 6 hours, and 0.00 minutes, z = 0.00 µm
741 agents
0 days, 2 hours, 28 minutes, and 19.5843 seconds
200 µm
0 days, 4 hours, 4 minutes, and 3.2375 seconds
200 µm