BITS :: Call for Abstracts 2019 - Oral communication

Type	Oral communication
Session	Translational Bioinformatics
Title	MAST: A MULTI-AGENT BASED SPATIO-TEMPORAL MODEL OF THE INTERACTION BETWEEN IMMUNE SYSTEM AND TUMOR GROWTH
All Authors	Baruzzo G(1), Finco G(1), Morandini F(1), Alotto P(2), Di Camillo B(1)

Affiliation

(1) Department of Information Engineering, University of Padova, Padova, Italy
(2) Department of Industrial Engineering, University of Padova, Padova, Italy

Motivation

In recent years, single-cell technologies have given the possibility to observe how tissues and organs are spatially and temporally organized as a system of multiple cells, able to communicate and interact with each other.
However, it is still unclear how cell communicate among them and with the environment and what new properties may result from collective cells behavior.
An interesting approach to study these properties are multi-agent based spatial models, which can be used to simulate complex systems of different cell types, interaction among cells and with the environment, stochastic behavior of cell responses and evolution in time. Moreover, if coupled with partial differential equations (PDE), dependency of cell behavior on concentration of communication molecules and nutrients can be also modeled.
In this context, a very interesting scenario is represented by tumor microenvironment, where many cells types are present and the tumor spatio-temporal evolution has a major role on patient's prognosis.
In this work we present MAST, a Multi-Agent base Spatio-Temporal model of the interaction between immune system and tumor growth.

Methods

MAST models different cell types such as CD8+ T, dendritic, natural killer, cancer, stroma and necrotic cells. Each type of cell is characterized by different possible actions and interactions with neighbor cells, namely: moving, dividing, dying, attacking, mutating. Starting from an initial state, the system evolves stochastically by selecting a possible action for each cell and consequently updating the communication molecules released in the neighborhood. The probability each cell has to fulfill a specific action depends on the cell type, on the type of surrounding cells and on the communication molecules in the neighborhood. For example, cancer cells can duplicate, mutate or die, either for lack of nutrients, which lead cells to necrosis, or for immune system attack. The probability of cells duplication depends, as necrosis, by available nutrients. Different kind of nutrients can be considered, each using partial differential equations (PDE) to model diffusion from their source (vessels) within the tissue. Genetic mutations of tumor cells are modeled as a probabilistic process that, with user specified rate, can give rise to i) new antigens; ii) ability to block the T-cells attack (like PDL-1+ mutation); ii) ability to release inhibitory molecules that would locally repel immune system cells. PDE are used to model nutrients diffusion from their source (vessels) within the tissue.
MAST is implemented in a Python program that records spatio-temporal information about the number of tumor and immune system cells, acquired genetic variation, providing a graphical 2D temporal evolution of tumor microenvironment. MAST is flexible, allowing to easily add new cell types and change simulation parameters in order to implement simulations that are specific for different tumor types. Remarkably, in the single cell sequencing era, model parameters' choice can be guided by patient-specific single-cell RNA-sequencing data.

Results

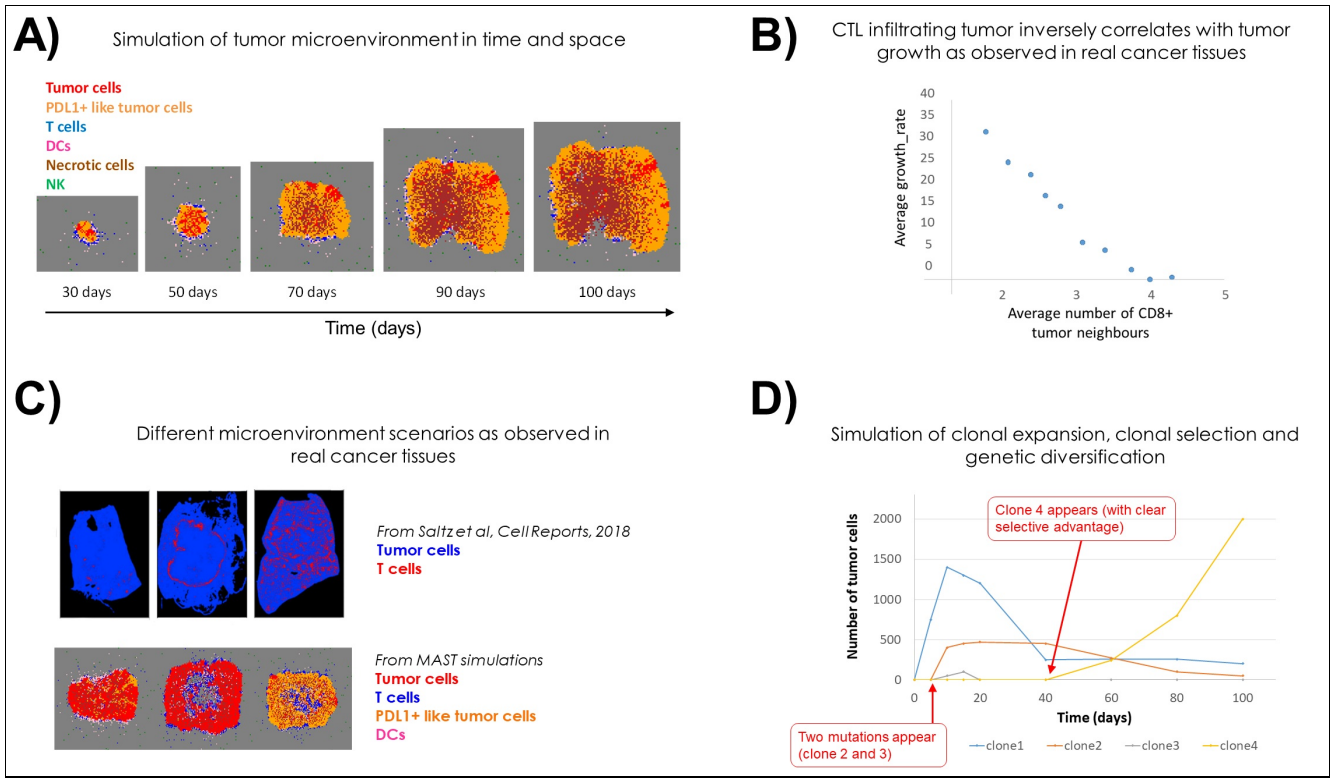
MAST is able to reproduce key aspects of tumor microenvironment such as infiltration of immune cells in tumor tissue and its inverse correlation with tumor growth rate (Figure 1B). Other examples of MAST simulations in terms of spatio-temporal tumor evolution, ability to recreate different microenvironment scenarios observed in real data and cell mutations are shown in Figure 1A, 1C and 1D, respectively.
In terms of developing personalized medicine strategies, the final goal is to use MAST to mimic different clusters of patients with specific mutation rate, tumor immuno-editing, and presence/absence of stroma, so to study the macro-characteristic of tumor evolution in several scenarios.

Info

Figure 1. Examples of MAST simulation results. A) Spatio-temporal simulation of tumor microenvironment. Five time steps from a 100 days simulation are reported. Pixel colors encode for cell types: red (tumor cells),

yellow (PDL1+ cells), blue (T cells), pink (dendritic cells DC)), brown (necrotic cells) and green (natural killer cells). B) Resulting relation between the infiltration of cytotoxic T cell (CTL) in the tumor and tumor growth rate. The two quantities show the same trend observed in real cancer tissues. C) Different simulated tumor microenvironments resembling the characteristic of real cancer tissues. Three images from Saltz et al. (tumor cells in blue, T cells in red) are compared to three images from MAST simulation (tumor cells in red, T cells in blue, PDL1+ cells in yellow, dendritic cells in pink). Please note that the color scheme adopted to identify the cell types is different across Saltz et al. images and MAST images. D) Relation between tumor growth over time and the different tumor cell clones in the tissue.

Figure



Availability	-

Corresponding Author

Name, Surname	Barbara, Di Camillo
Email	barbara.dicamillo@unipd.it
Submitted on	24.04.2019