BITS :: Call for Abstracts 2022 - Oral communication

Type	Oral communication
Session	Systems Biology
Title	Simulate personalized tumor microenvironment evolution through a hybrid Multi-Agent Spatio-Temporal model informed by sequencing data
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Motivation

Recently, several computational modeling approaches, such as agent-based models (ABM), have been applied to study and simulate the interaction dynamics between immune and tumor cells. However, since each tumor is characterized by a specific and unique tumor microenvironment (TME), there is the unmet need for personalized simulations of specific cancer scenarios. In this context, the large amount of cancer sequencing data represents an unexploited goldmine of information to characterize TME-specific modeling.
Starting from a hybrid Multi-Agent Spatio-Temporal model (MAST) [1], we developed a framework able to simulate tumor-immune dynamics starting from specific TME subtypes characterized in the literature and that can be informed by high throughput sequencing (HTS) data such as bulk and single cell sequencing (e.g., bulk RNA-seq, DNA-seq and scRNA-seq).

Methods

MAST couples a discrete and stochastic ABM with a continuous and deterministic Partial Differential Equation (PDE)-based model to capture essential elements in the TME. Specifically, it allows to model: (1) spatio-temporal dynamics of cells in response to nutrient availability, (2) both innate and adaptive immune system (IS) response, and (3) immune escape mechanisms including: changes in proliferation/survival fitness [2]; loss/acquisition of antigenicity; loss of immunogenicity; and cancer cells ability to evade immune system by releasing signaling molecules that locally repel IS cells in order to shape an immunosuppressive microenvironment [3].
MAST simulation parameters can be informed using HTS data, yielding knowledge on i) acquisition rate of new mutations (through the computation of tumor mutational burden from DNA-seq data); ii) cell type composition and recruitment (through the analysis of cells proportions from deconvolution of bulk RNA-seq data or cell-type annotation of scRNA-seq data); iii) loss of immunogenicity (through the identification of upregulated inhibitory immune checkpoint genes from RNA-seq or scRNA-seq data).
To test the data-driven approach used to characterize MAST, we simulate tumor progression in four heterogenous colorectal cancer (CRC) subtypes, informing the model by coupling bulk sequencing data from TCGA database and scRNA-seq data from a publicly available dataset [4].

Results

Similarly to Kather et al. study [5], we validate the model outcomes using clinical data of the TCGA patient cohort and the available biological knowledge on CRC Consensus Molecular Subtypes (CMS): CMS1, characterized by hypermutated and strong immune infiltration; CMS2, which is immune-neglected; CMS3, which shows a metabolic dysregulation; CMS4, which induces an immunosuppressive TME [6].
The enclosed Figure shows how MAST can reproduce for each CMS its emergent biological properties and its tumor progression outcomes, defined hereby considering only the simulations that are not tumor-free (NTF) within a time-window. CMS1 and CMS4 subtypes result in high-proliferating tumors (NTF rate of 68% and 55%, respectively), compared to CMS2 and CMS3 subtypes (NTF rate of 38% and 50%, respectively). Simulated tumor progression outcomes' trend is in line with TCGA clinical data.
Consistently with literature, CMS1 shows strong immune response over time and tumor mass infiltration, whereas CMS4 tumors have the fastest growth rate of stromal component. In contrast, CMS2 and CMS3 subtypes have lower tumor progression outcomes, resulting from their immunogenic and metabolic properties, respectively.
We believe that MAST can be a useful tool to better understanding tumor-immune cells dynamics that drive tumor progression in specific and unique TMEs. We think that a data-driven approach to generate simulation settings could be a powerful tool in the way toward specialized and personalized studies of the TME. Ideally, the availability of patient-specific data and the ability to inform models from them pave the way towards the simulation of patient-specific tumor-immune system dynamics.

Info

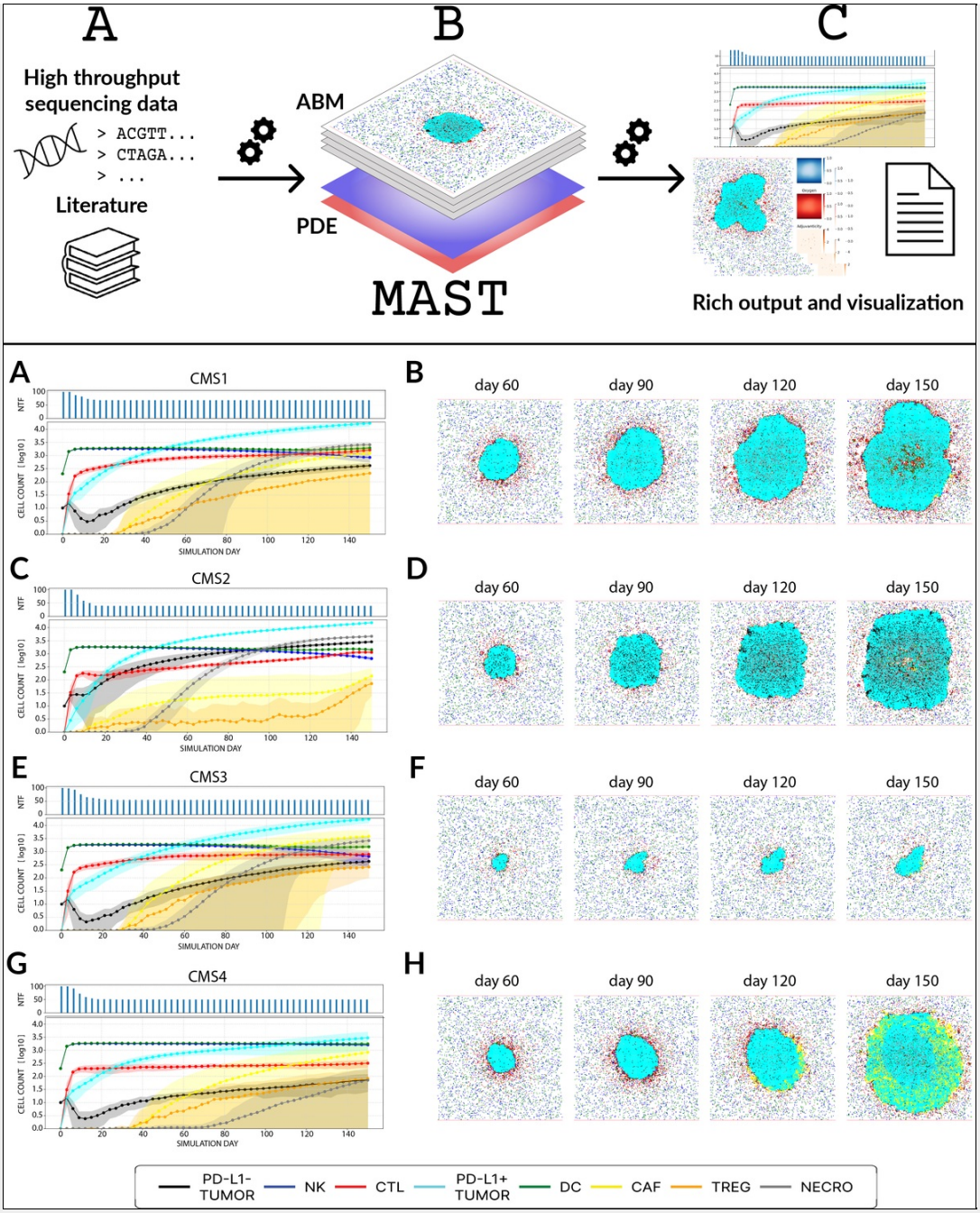
References

[1] G. Baruzzo, G. Finco, F. Morandini, P. Alotto, B. Di Camillo, “MAST: a Multi-Agent based Spatio-Temporal model of the interaction between immune system and tumor growth”, Annual Meeting of the Bioinformatics Italian Society (BITS) 2019
[2] A. Vicens and D. Posada, “Selective Pressures on Human Cancer Genes along the Evolution of Mammals,” Genes (Basel), vol. 9, no. 12, Dec. 2018, doi: 10.3390/GENES9120582.
[3] G. L. Beatty and W. L. Gladney, “Immune escape mechanisms as a guide for cancer immunotherapy,” Clinical Cancer Research, vol. 21, no. 4, pp. 687–692, Feb. 2015, doi: 10.1158/1078-0432.CCR-14-1860/270283/AM/IMMUNE-ESCAPE-MECHANISMS-AS-A-GUIDE-FOR-CANCER.
[4] H. O. Lee et al., “Lineage-dependent gene expression programs influence the immune landscape of colorectal cancer,” Nat Genet, vol. 52, no. 6, pp. 594–603, Jun. 2020, doi: 10.1038/S41588-020-0636-Z.
[5] J. N. Kather et al., “In silico modeling of immunotherapy and stroma-targeting therapies in human colorectal cancer,” Cancer Research, vol. 77, no. 22, pp. 6442–6452, Nov. 2017, doi: 10.1158/0008-5472.CAN-17-2006/653067/AM/IN-SILICO-MODELING-OF-IMMUNOTHERAPY-AND-STROMA.
[6] J. Guinney et al., “The consensus molecular subtypes of colorectal cancer,” Nature Medicine 2015 21:11, vol. 21, no. 11, pp. 1350–1356, Oct. 2015, doi: 10.1038/nm.3967.

Figure Caption

The upper panel shows in its subpanels how MAST (A) can be informed through a data-driven approach using several sources of information to model unique characteristics of the TME in a tumor, (B) couples a discrete agent-based model (ABM), which simulate tumor-immune system dynamics in the TME, and a continuous partial differential equations (PDE)-based model to simulate nutrient diffusion from vessels and (C) provides tabular and graphical outputs in order to analyze spatio-temporal evolution of in silico tumor growth simulation.
The lower panel shows for each CMS information on the temporal evolution of 100 simulations (left panels A, C, E, and G) and information on the spatio-temporal evolution of one simulation of interest (right panels B, D, F, and H).
In particular, a single left panel shows in the upper subgraph, the number of not completely tumor-free (NTF) simulations in a determined instant (day), i.e., simulations having at least one cancer agent in the domain, and in the below subgraph, the time course of agent counts across not completely tumor-free simulations in log10-scale: continuous line represents the average count, and the shaded area represents its variability (± standard deviation).
Moreover, for each CMS the right panels represent tumor progression on days 60, 90, 120, and 150. Legend represents color-agent association related to the above representations. All graphical representations are generated using MAST.

filename	MAST_figure.png
Figure	



Availability	https://gitlab.com/sysbiobig/mast

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Submitted on	29.04.2022