

Digital Bone Metastasis: an AI-based Organ-on-chip Platform for Modeling Breast Cancer Bone Metastasis

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Summary:

We present an integrated microfluidic and AI-based platform to model breast cancer (BC) bone metastasis on chip. We investigated how human bone marrow stromal cells (HBMSCs) influence BC cell motility, morphodynamics, and doxorubicin resistance. Our system captures rare motility phenotypes and increased invasion depth driven by stromal interactions. To decipher these behaviors, we developed the first agent-based model that reproduces the observed cellular dynamics, providing mechanistic insights into the metastatic process, ultimately bridging experimental and computational approaches.

Keywords: artificial intelligence, agent-based modeling, time-lapse microscopy, organ-on-chip, bone metastasis

Background, Motivation and Objective

Bone metastasis represents a major cause of morbidity and mortality in breast cancer (BC), largely due to microenvironment-mediated resistance to chemotherapy [1]. The bone niche provides biochemical and biomechanical cues that reprogram cancer cell phenotypes, promoting invasion and survival under treatment [2]. Conventional 2D cultures and animal models fail to capture the human-specific, dynamic interactions between BC cells and bone stromal cells that drive metastatic progression and drug resistance [3]. Organ-on-chip technologies offer a promising route to reproduce these interactions under controlled conditions [4], but quantitative, single-cell-resolved, and mechanistically interpretable frameworks are still lacking. Here we present an integrated bone-on-chip platform combined with artificial intelligence (AI) and agent-based modeling (ABM) to dissect stromal-driven chemoresistance in BC bone metastasis.

Description of the New Method or System

We engineered a microfluidic device hosting two adjacent compartments. Primary human bone marrow stromal cells (HBMSCs) were encapsulated in a 3D gelatin methacryloyl (GelMA)-Laponite® matrix. BC cells were seeded in an adjacent GelMA-coated chamber. Following BC cells invasion into the bone-like matrix, cultures were exposed to clinically relevant concentrations of

doxorubicin and monitored for three days using confocal time-lapse microscopy (Fig. 1a). To quantitatively analyze cell motility and morphodynamics, we applied AI-based automated cell detection, tracking (Fig. 1b), and deep-learning-driven morphodynamic (Fig. 1c) and kinematic (Fig. 1d) cell profiling [5]. Finally, we developed an agent-based model (ABM) of breast-to-bone metastasis calibrated on experimental organ-on-chip data.

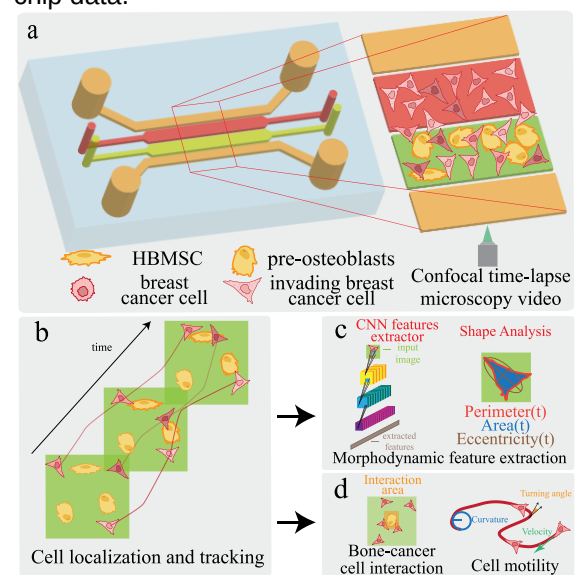


Fig. 1. (a) Schematic of the organ-on-chip model of the breast cancer bone metastasis. (b) Breast cancer cell localization and tracking. (c) Morphodynamic features extraction. (d) Kinematic features extraction.

Results

HBMSCs were found to induce heterogeneity in BC cell motility (Fig. 2a), characterized by the emergence of rare, highly motile “leader-like” cells that drive tissue penetration. Motility distributions were extracted from single-cell tracking on confocal time-lapse acquisitions and compared across conditions. Importantly, these extreme motility phenotypes persisted under doxorubicin treatment in the presence of HBMSCs, whereas chemotherapy significantly suppressed the highly motile BC cell population in their absence. This BC cell motility behavior was successfully qualitatively reproduced by the ABM model (Fig. 2b). Deep learning (DL)-based morphodynamic profiling, extracting time-resolved shape descriptors from segmented cell sequences, revealed that HBMSC interaction drives a distinct cancer cell state (Fig. 3a), largely insensitive to drug-induced morphological perturbations (Fig. 3b). On the contrary in the absence of HBMSCs a doxorubicin-induced switch in morphodynamic features was observed (Fig. 3c). We found doxorubicin significantly reduces BC cell interactions with HBMSCs measured in terms of interaction commitment (defined as the ratio between the interaction area and the total area of the cell) (Fig. 4a). This behavior was qualitatively reproduced by the *in silico* model (Fig. 4b).

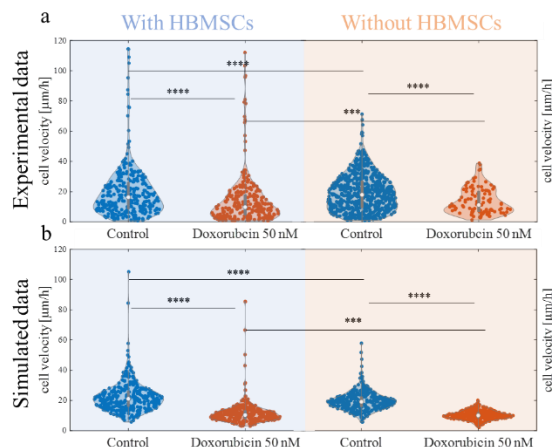


Fig. 2. Average cell velocity with (left-blue panel) and without (right-red panel) in experimental (a) and simulated (b) data.

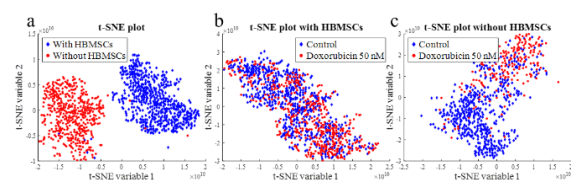


Fig. 3. t-SNE scatter plot of BC cell morphodynamic descriptors. With vs without HBMSC (a), Control vs Doxorubicin 50 nM with (b) and without (c) HBMSCs.

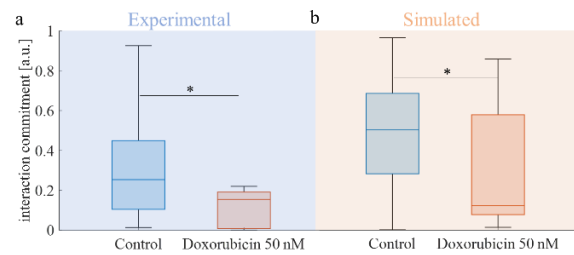


Fig. 4. Box-plot of BC cells-HBMSCs interaction commitment in control and Doxorubicin 50 nM treated scenarios in real (a) and simulated (b) data.

Direct quantification of cancer–stroma interactions demonstrated that interaction with HBMSCs significantly triggers a motility switch toward faster and more directed migration, as well as cell elongation and a change in DL-based morphodynamic descriptors (results will be presented at the conference). Viability assays confirmed that HBMSCs provide a protective niche, significantly attenuating doxorubicin-induced cytotoxicity (results will be presented at the conference), in agreement with previous reports on mesenchymal stromal cell-mediated drug resistance [6]. By explicitly incorporating cell–cell attraction, repulsion, matrix-dependent friction, and nutrient gradients, the ABM model identified intercellular interaction strength and chemotactic sensitivity as key regulators. This study demonstrates how advanced organ-on-chip biomaterials, AI-powered single-cell analytics, and mechanistic *in silico* modeling can be integrated into a predictive platform for metastatic disease. This approach will help link simplified *in vitro* models to complex physiological conditions observed *in vivo*, increasing the translational relevance of the obtained results.

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