Using Molecular Communication in Anticancer Intervention

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I. Background

Coupling the molecular communication (MC) paradigm with the computational biology approach could provide detailed platforms of health problem functioning. This could potentially facilitate the prototyping for novel, more precise theranostic solutions.

Here we focus on the MC system based on the transfer of biological signaling macromolecules called extracellular vesicles (EVs), which are membrane vesicles ranging from 100 nm to 5000 nm with different biophysical and biochemical properties [1], [2]. EVs are secreted by cells of different histotypes through various biogenesis pathways into the circulation [1], [2]. Several hypotheses suggest that EVs may represent a vehicle for intercellular communication where they may deliver lipids, proteins, soluble factors, RNA, and microRNAs which modulate the protein expression of recipient cells [3]. Although very promising in biotherapeutics [4], EVs are also promoters of tumors since they may create an immuno-privileged environment within the tumors [3], thus facilitating tumorigenesis by regulating different processes, including tumor growth, immune modulation, metastatic spread, and metastasis formation [1]. Given this, *terminating the EV-mediated intercellular traffic* in the tumor microenvironment (TME) is an act of a potential anticancer treatment.

The TME is acidic and does not allow the survival of healthy cells. Instead, such conditions are preferable by malignant tumor cells [3]. The survival characteristic of malignant tumor cells is due to the buffering capacity of the cell and membrane-based ion transporters [5]. They do not permit the acidification of the cellular cytosol, thus maintaining a high intracellular pH (pHi) and low extracellular pH (pHe) levels [5]. A few important cell membrane ion transporters are the Na^+/H^+ (NHE(1)), Na^+-independent and Na^+-dependent $HCO3^-/Cl^-$ (THCO3), and H^+/lactate co-transporter [5]. Specific inhibition of H^+ release induces acidification of the intracellular space [6] and potentially tumor cell death (apoptosis) [7], therefore exerting an anticancer effect.

Here we computationally explore the possibility to affect the EV-mediated intercellular traffic by modulating the levels of cell acidity within the cell, i.e. pHi levels. One possibility to modulate pHi and subsequently induce tumor cell apoptosis is to utilize membrane-based ion transporter inhibitors, for example, NHE and THCO3 inhibitors. Cell apoptosis would eventually lead to the terminated release of EVs, because a dead cell is not functionally active, and thus terminated tumorigenesis by EVs.

To do so, we couple the *biophysical model of tumor cell pH regulation* functioning [8] with the *computational cell proliferation model* [9] and our previously developed *pHe-dependent EV release MC model* [10]. The biophysical model of tumor cell pH regulation mechanism increases understanding of the complex dynamics of cellular functions involving biochemical, mechanical, and biophysical factors [8]. It models the dynamic interplay between glucose and O_2 consumption with lactate and CO_2 production and links these processes to H^+ and HCO_3^- fluxes inside and outside cells [8]. The influence of medium toxicity on the cell proliferation patterns incorporates the nutrient content and the pH variations of the cell culture medium [9] through which we discover the tendency of the EV release and pHi during the tumor cell cycle over the behavior of pHe. Coupling both models with the MC-inspired model of the pHe-dependent EV release dynamics [10], here extended with a velocity drift and natural EV degradation effect, enables us to study the spatiotemporal evolution of the EV dynamics during a tumor cycle. We report the initial numerical results in Section II.

II. Initial Results

We run numerical simulations in MATLAB for a time period of 14 days and space interval of $\sim$6300 $\mu\mathrm{m}$. Normalized tumor cell density (inset in Fig. 1) defines size of the tumor sphere presented with the 3D spherical coordinates with radial symmetry. Experiments show that apoptosis of a tumor cell occurs in an acidic TME when pHi is $6.7 - -6.9$ [5], [11]. Given this, we set the simulated tumor cell apoptosis threshold to the pHi level of 6.7. The inhibition of NHE and THCO3 depends on the inhibitor concentration and is implemented by fitting the inhibition factors to the experimental data [12], [13] and incorporating them into tumor cell pH regulator model [8]. We apply inhibition at day 8 in acidic TME (pHe$<$7.2).

Fig. 1 shows the behavior of the EV release (orange solid line), pHi (blue dashed line) and normalized tumor cell density (inset) during the tumor cycle based on the medium acidity (blue solid line) and apoptosis pHi threshold. Figures 2a-2c depict the spatiotemporal EV biodistribution in the TME and the behavior of pHe, pHi and tumor cell density with the different NHE inhibitor factors: 0, 0.4453 (20 $\mu\mathrm{M}$ inhibitor concentration), and 1. We notice that the application of the NHE inhibitor accelerates the tumor cell apoptosis and produces fewer EVs (noticed in the colorbar values) in the same time-space domain. This is expected to reduce the probability of tumorigenesis.

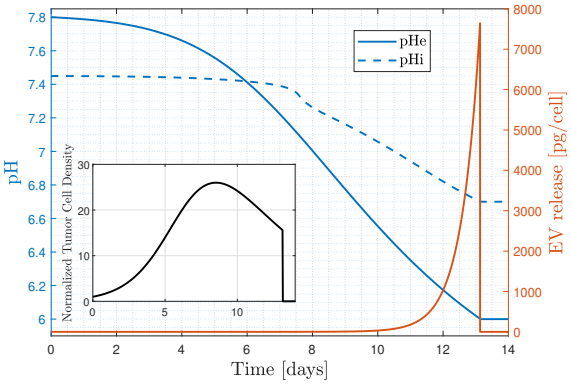
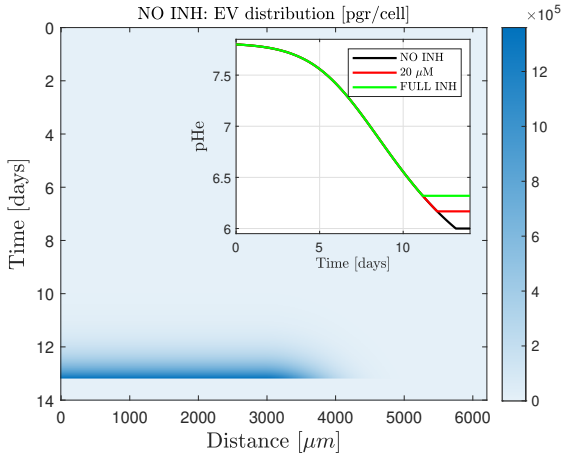
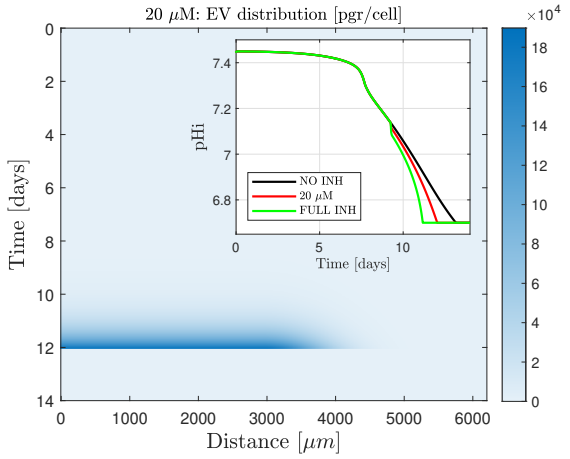


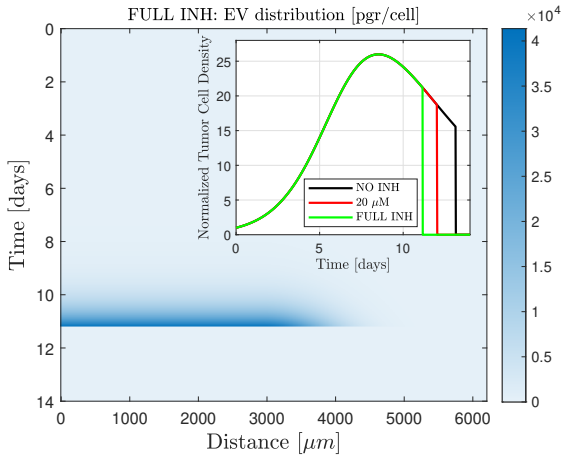
Fig. 1: Plots of pHe (blue solid line), pHi (blue dashed line), EV release (orange solid line) and tumor cell density (inset) during 14 days of the tumor cycle based on [8]–[10].



(a) No inhibition.



(b) NHE inhibition with 20 μM drug dose.



(c) Full NHE inhibition.

Fig. 2: EV biodistribution profiles and pHe, pHi and normalized tumor cell density curves for NHE scenarios: (a) no inhibition, (b) 20 μM inhibitor concentration, (c) full inhibition.

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