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Phase transitions in tumor growth VI: Epithelial–Mesenchymal transition

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HIGHLIGHTS

- Cancer as an open, complex, self-organizing nonlinear dynamic system.
- The epithelial–mesenchymal transition appears as "first order" phase transition.
- EMT exhibit a Shilnikov's chaos.

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ABSTRACT

Herewith we discuss a network model of the epithelial–mesenchymal transition (EMT) based on our previous proposed framework. The EMT appears as a "first order" phase transition process, analogous to the transitions observed in the chemical–physical field. Chiefly, EMT should be considered a transition characterized by a supercritical Andronov–Hopf bifurcation, with the emergence of limit cycle and, consequently, a cascade of saddle-foci Shilnikov's bifurcations. We eventually show that the entropy production rate is an EMT-dependent function and, as such, its formalism reminds the van der Waals equation.

1. Introduction

Cancer is still a leading global health problem. It has been estimated that by 2025 there will be nearly 20 million new cancer cases diagnosed each year [1]. As reported previously, cancer can be viewed as a development 'gone awry', involving a network of interacting cells and their microenvironment, losing control over proliferation and cell-fate specification [2]. We posit that such process take place mostly through deregulation of critical events occurring during biological phase-transitions. Given that phenotypic differentiation and cancer transformation are both self-organized processes, ruled by non-equilibrium thermodynamics, fluctuations in the control parameters at the bifurcation point are of relevant value. Indeed,

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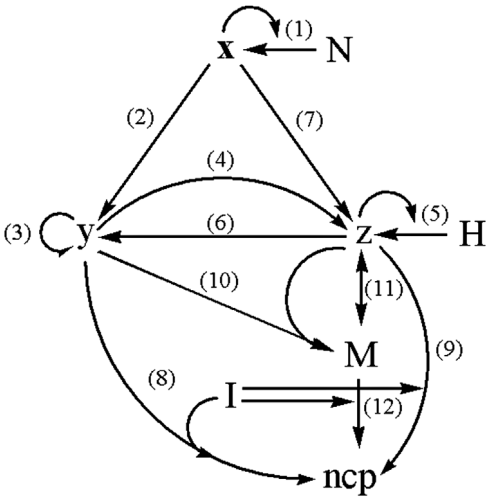

Fig. 1. The network model of epithelial-to-mesenchymal transition.

even subtle changes in some critical values may impair the self-organization process, leading to unexpected different states, exhibiting variable robustness and adaptability capability within the attractor landscape [3].

It is generally agreed that cancer evolves along three basic steps [4]: avascular, vascular and metastatic, all emerging downstream of biological phase transitions [5]. The metastatic process consists of sequential, interlinked, and selective steps [6], and many of these are prompted by a mandatory transition from a epithelial to a mesenchymal phenotype [7]. An epithelial–mesenchymal transition (EMT) is a biologic process that allows a polarized epithelial cell, which normally interacts with basement membrane via its basal surface, to undergo multiple biochemical changes that enable it to assume a mesenchymal cell phenotype, which includes enhanced migratory capacity, invasiveness, and increased resistance to apoptosis [8].

The current paradigm suggests that EMT drives metastasis by producing mesenchymal cells that escape the primary tumor and migrate to distant sites, whereby they can revert to an epithelial state through the mesenchymal–epithelial transition (MET). Moreover, depending on the relationships in between cells and their new microenvironment, the metastatic foci may either eventually spread to other organs and tissues, or enter into a state of dormancy [9].

We have previously proposed [5] an empirical model that qualitatively describes the general aspects of the evolution of a primary tumor from avascular to metastatic stage. The goal of this work is to generalize the previously proposed model for tumor growth [5] with the inclusion of the epithelial–mesenchymal transition. The manuscript is organized as follows: in Section 2 we propose a network model for epithelial–mesenchymal transition. Section 3 focuses into the analysis of the mathematical model derived from the mechanism previously proposed, including quantitative simulations and stability assay. Development of a thermodynamic framework, based on the entropy production rate is presented in Section 4. Finally, some concluding remarks are presented.

2. A network model of epithelial–mesenchymal transition

Tumor metastasis is a multi-step process by which tumor cells disseminate from their primary site and form secondary tumors at a distant site. Metastasis is the major cause of death in the vast majority of cancer patients [10–12]. However, the mechanisms underlying each step of this complex process remains obscure. EMT has been increasingly recognized to play pivotal and intricate roles in promoting carcinoma invasion and metastasis [13,14]. The EMT process has been observed in multiple epithelial tumors, including breast [15] prostate [16] and colorectal cancer [17].

Herewith, based on our previous discussed model, we proposed an integrated framework by including EMT, according to the network structure shown in Fig. 1.

In the model, N represents the population of normal cells exposed to the pro-carcinogenic stimulus; H the population of the host cells in the surrounding environment [18], comprising exclusively epithelial cells; I is the population of immune cells (T lymphocytes (CTL) and natural killer (NK)) [19], M is the population of mesenchymal cells. N and H are considered as constants (because these cell groups are much more numerous than cancer cells and for practical effects, their number does not change) and we posit I as the control parameter (because the population of immune cells may increase or decrease). Variables: x, y, z represent the population of epithelial tumor cells in an avascular, vascular and metastasis state, respectively. Finally, *ncp* represents a non-cancerous product due to the action of immune cells.

Steps 1, 3 and 2, 4, 6 are related to the process of mitosis and apoptosis of the proliferating tumor cells respectively; steps 5 and 7 correspond to the action of the host H [17]; steps 8, 9 and 12 show the action of immune cells I. Finally, steps 10