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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.

Keywords
Biological phase transition
Entropy production rate
Epithelial-mesenchymal transition
Tumor-microenvironment cross-talk
Phenotypic transitions in cancer cell evolution

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, 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.

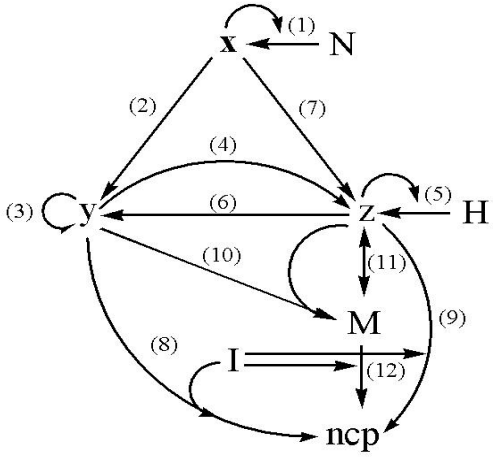

Fig. 1. The network model of epithelial-to-mesenchymal transition.

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 and 11 are related to the EMT. Step 10 represents an intermediate, preparatory step of epithelial cell before its transition to mesenchymal phenotype [20].

The constants for the model proposed (see Fig. 1) were chosen empirically [4] trying to have a greater generality and simplicity as possible, so we have: $k_1 = 2$ ml/(mmol s), $k_2 = 0.5$ ml/(mmol s), $k_3 = 4$ 1/s, $k_4 = 0.07$ ml/(mmol s), $k_5 = 0.5$ ml^2/(mmol^2 s), $k_6 = 0.001$ ml/(mmol s), $k_7 = 1$ ml^2/(mmol^2 s), $k_8 = k_9 = 1$ ml/(mmol s), $k_{10} = k_{12} = 0.1$ ml^2/(mmol^2 s) and for the step 11 $k_{11} = (0.3 - 0.001)$ mmol/(ml s) is the constant flux of EMT [9]. Sensitivity analysis were done [21] and quantitative investigation of the behavior of the output variables when the parameters change. Across the network model (Fig.1), key steps – in increasing order – are as follows: 5, 9, 12, and 11 respectively. It should be outlined that steps entailing both metastatic cells (5, 9) and EMT (12, 11) have a pivotal position in our model.

3. Mathematical model, stability analysis and numerical simulations

Mathematical models represent a suitable way for formalizing the knowledge of living systems obtained through a Systems Biology approach [22]. Mathematical modeling of tumor growth makes possible the description of its most important regularities and it is useful in providing effective guidelines for cancer therapy, drug development, and clinical decision-making [23, 24].

Although the role of the EMT are well documented in literature [25], there are just few reports dealing with EMT dynamics [26, 27]. Indeed, most of the computational dynamic and statistical models of EMT focus on genetic and biophysical changes associated with EMT [22].

The network model (Fig. 1) we propose is a qualitative representation of the population tumor cells growth, based on the experimental evidences already available. The three reactions corresponding to EMT transition are included. We used the mathematical methods of chemical kinetics in order to reduce the network to a system of ordinary differential equations (in this methods, the cell populations are equivalent to the chemical species concentrations). This system (eqs, 3.1) describes the avascular, vascular, and metastatic phases, as well as EMT in tumor dynamics:

$$\begin{aligned}
\frac{dx}{dt} &= x(2N - x) - Hxz \\
\frac{dy}{dt} &= y(4 - 0.14y) + 0.5x^2 - Iy - yz(0.1 + 0.5H) + 0.001z^2 \\
\frac{dz}{dt} &= -Iz + 0.07y^2 + yz(0.1 + 0.5H) - k_{11} - 0.002z^2 \\
\frac{dM}{dt} &= 0.1(yz - IM) + k_{11}
\end{aligned} \tag{3.1}$$

Quantitative value for each constant has been empirically obtained. Fixed points, stable states and bifurcations were calculated using the standard procedure [28-30]. Control parameters were represented by the population of immune cells I (lymphocytes T (CTL) and natural killers (NK) [18]).

In order to simplify, for this model it is assumed that the metastatic cells *z* (the epithelial cells) can be transformed in mesenchymal cells *M* at a constant rate. The vascular cells *y* and the metastatic *z* can

interact to produce *M* cells, but *y* population alone cannot produce *M* cells, neither *M* cells can be transformed in vascular cells *y*. These assumptions, although based on mere convenience, are within the bounds of what is reasonable.

The *LZ* complexity [31, 32], was calculated using the proposed algorithm by Lempel & Ziv. Lyapunov exponents were calculated using the Wolf algorithm in Fortran language [33]. Lyapunov dimension D_L, also known as Kaplan–Yorke dimension [24], was evaluated across the spectrum of Lyapunov exponents λ_j as:

$$D_L = j + \frac{\sum_{i=1}^{j} \lambda_i}{\left|\lambda_{j+1}\right|} \tag{3.2}$$

where *j* is the largest integer number for which $\lambda_1 + \lambda_2 + ... + \lambda_j \geq 0$.

For modeling network model, COPASI v. 4.6.32 software was used. However, numerical integration was performed on the system of ODEs Eq. (3.1) through implementation of Gear algorithm for stiff equations, in Fortran with double precision and tolerance of 10^{-8} [34]. For the construction of the bifurcation diagram, correlation dimension and power spectrum, the package TISEAN 3.01 was used [35]. The results are summarized in Table 1.

Table 1**.** Stability, and complexity for the system of ODEs (3.1) for different values of the control parameter I ($N = 5,\ H = 3,\ k_{11} = 0.3$).

I	Eigenvalues of the Jacobian matrix	Lyapunov Exponents λ_j	*LZ* complexity	D_L
4 ss_s stable focus	-1.261418e-1 -5.375474i -1.261418e-1 +5.375474i -4.000000e-1 -8.012672	-0.126027 -0.127308 -0.403574 -8.00536	-	0
3 Limit cycle	1.031544e-1 -4.859511i 1.031544e-1 +4.859511i -3.000000e-1 -6.764248	~0.00 -0.173849 -0.303749 -6.27233	0.01000	1
1 saddle-foci	4.581987 9.124765e-3 -1.851758i 9.124765e-3 +1.851758i -1.000000e-1	~0.00 -0.103604 -0.690052 -1.93351	0.01429	1
0.4 Shilnikov's chaos	3.325962 2.969116e-2 -1.382981i 2.969116e-2 +1.382981i -4.000000e-2	0.0740662 ~0.00 –0.0516013 –1.9353	0.02388	2.03

In table 1 we show the dynamical behavior of the proposed ODEs (3.1) for different values of the control parameter I. At I = 4, there is a stationary state. As I is decreasing, the stationary state changes

only in its values. Yet, at the critical point I = 3.76, a supercritical Andronov–Hopf bifurcation takes place [36], giving rise to a limit cycle. Thus, the dynamical behavior turns oscillatory.

As I further decreases, reaching $I \approx 0.65$, a new qualitative change occurs: the limit cycle undergoes a distortion. Two maxima for the values of each the oscillating variables (x, y, z, M) were recorded, thus achieving a period duplication bifurcation type saddle-focus, as previously described by Shilnikov [37]. Therefore, a cascade of bifurcations is triggered downstream. The model shows, for lower critical value of the control parameter (when $I \approx 0.53$ (see Table 1 for $I = 0.4$ and Fig. 2), that tumor cells exhibit "apparently random behavior" (as Shilnikov's chaos [34, 36, 37]) when challenged by immune system activation. That hypothesis has been vindicated by a recent study, demonstrating that a mesenchymal phenotype correlates with immune evasion via reduced expression of the immunoproteasome, underlying mechanism of immunoproteasome regulation that involved STAT3, STAT1 and miR-200s [38].

Concomitantly with the reduction in I values, the overall dynamics of the process increases in complexity, as witnessed by the upraised values in LZ. This leads to a parallel increase in the robustness of the EMT process.

In Fig. 2 is shown the dynamic behavior EMT during the metastatic process.

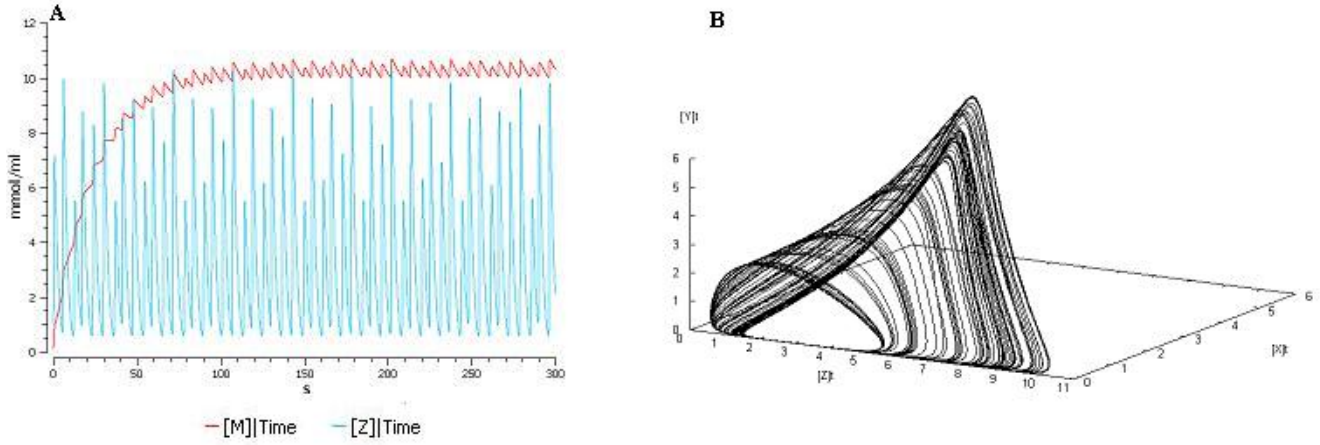

Fig. 2 **A.** EMT dynamics for the proposed model (3.1), control parameter values: $I = 0.4$, time series; epithelial cells z (light blue, large variations) and mesenchymal cells M (red, small variations); **B**. Chaotic attractor.

This behavior has important biological implications. On the one hand, the high sensitivity of the system to initial conditions makes unfeasible long-term predictions regarding EMT evolution, *i.e.* the end forecasts are improbable (uncertain prognosis).

Furthermore, the system displays a high degree of robustness [39, 40]. This implies cancer cells are resilient in respect to pharmacological treatment, thus leading to a low response rate, namely when cancer is at the metastatic state [41].

The drug-resistance mechanisms developed during the multiple transition affecting cancer development are still in place even after successful primary chemotherapy intervention and sustain high clinical recurrence rate [42, 43].

4. Thermodynamics framework

The thermodynamics formalism of irreversible processes [44-47], systems biology [48] and complex systems theory [49], offer a theoretical framework appropriate for the characterization of the emergence and evolution of tumor growth. The seminal work of Posch–Hoover [34] and more recently Gaspard [35] have shown that the production of entropy per unit of time S_i it is related to the spectrum of Lyapunov exponents λ_j through the relationship

$$\frac{dS_i}{dt} \equiv \dot{S}_i \approx -\sum_j \lambda_j > 0 \qquad (4.1)$$

where λ_j are the spectrum of Lyapunov exponents.

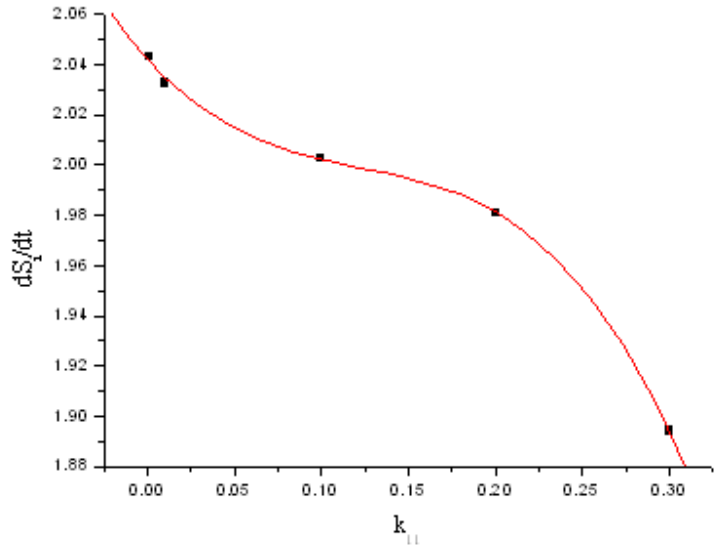

Fig. 3 Dependence of the rate of entropy production $\dot{S}_i$ as a function of the constant flux of the EMT, k_{11}, keeping the constant control parameter I ($I = 0.4$).

Through Eq. (4.1) the rate of entropy production was evaluated as a function of the constant flux of the EMT k_{11}, keeping the control parameter I constant ($I = 0.4$), as shown in figure 3. This constant was moved in the positive range (*M* cells cannot be transformed in *z* cell in this range). Accordingly to our model, sensitivity analysis reveals that the constant flux of the EMT process (step 11, Fig.1) is among those that exhibit greater Sensitivity Coefficient changes. Moreover, changes in the frequency of EMT dramatically alter population dynamics towards exponential growth.

Based on empirical data (see table 2), through Eq. (4.1) the polynomial regression the rate of entropy production $\dot{S}_i$ is obtained as a function of the constant flux of the EMT, k_{11} as

$$\dot{S}_i = a + b\Omega + c\Omega^2 + d\Omega^3; \qquad (4.2)$$

where Ω represent the constant flux k_{11} of the EMT, and the constants of Eq. (4.2) are: ($a = 2.042 \pm 0.002$, $b = -0.8 \pm 0.1$, $c = 5.0 \pm 1.0$, $d = -14.0 \pm 2.0$; R-square=0.99938, SD=0.00296, P<0.03182). The polynomial regression, Eq. (4.2), reminds the van der Waals equation, which it is useful to describe the first order phase transitions.

The critical point is determined through the Eq. (4.2) as: $\frac{\partial^2 \dot{S}_i}{\partial \Omega^2} = 0$; we calculated consequently that $\Omega_{crit} \equiv k_{11}^{crit} = 0.11905$. For values of the constant flux k_{11} greater than the critical value ($\Omega > \Omega_{crit}$) it is concluded that: $\frac{\partial^2 \dot{S}_i}{\partial \Omega^2} < 0$; On the contrary, if $\Omega < \Omega_{crit}$ it can be verified that: $\frac{\partial^2 \dot{S}_i}{\partial \Omega^2} > 0$, that is, the rate of entropy production $\dot{S}_i$ exhibits a minimum.

The Fig. 4, shows the time series of the proposed model (3.1) for different values of the constant flux k_{11} for EMT.

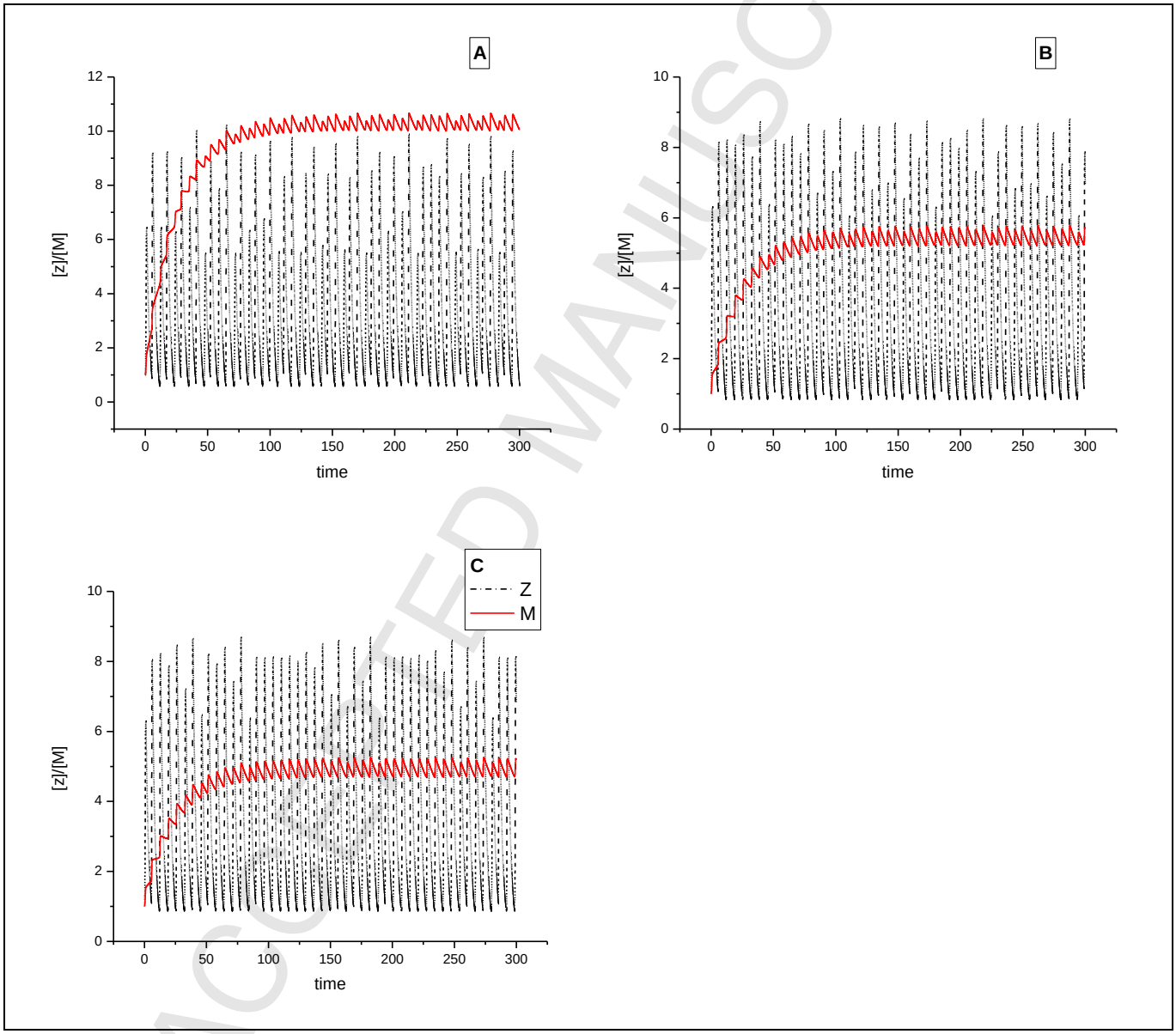

Fig. 4 Time series of the proposed model (3.1) for different values of the constant flux k_{11} for EMT ($N = 5,\ H = 3,\ I = 0.4$); epithelial cells z (dash dot, black) and mesenchymal cells M (solid, red): **A**. $k_{11} = 0.3$, **B**. $k_{11}^{crit} = 0.11905$, **C**. $k_{11} = 0.1$.

Dynamics (see Fig.4) of the two phenotypic populations: mesenchymal *versus* epithelial, highlights that, for $k_{11} > k_{11}^{crit}$, dominates the density phenotypic populations of the M cell; below that value, for a discrete range of $k_{11} \le k_{11}^{crit}$ values, the systems display a hybrid epithelial-mesenchymal configuration, thus supporting previous reported experimental data suggesting that EMT is rarely an "all-or-none" phenomenon [21] and exhibit a minimum entropy production rate [50]. Yet, a threshold value of k_{11} can be recognized at which the transition from the epithelial to the mesenchymal phenotype emerge abruptly, like a "first order" phase transitions.

Table 2**.** Stability, and complexity for the system of ODEs (3.1) for different values of the constant flux k_{11} for EMT ($N = 5,\ H = 3,\ I = 0.4$).

k_{11}	Eigenvalues of the Jacobian matrix	$\lambda_{\max}$	LZ complexity
$k_{11} = 0.3$	3.325962 2.969116e-2 -1.382981i 2.969116e-2 +1.382981i -4.000000e-2	0.0740662	0.02388
$k_{11}^{crit} = 0.11905$	3.306470 -7.598350e-3 -1.276400i -7.598350e-3 +1.276400i -4.000000e-2	0.0464444	0.01785
$k_{11} = 0.1$	3.304328 -1.154246e-2 -1.264596i -1.154246e-002 +1.264596i -4.000000e-2	0.0514299	0.02231

Indeed, complexity (*LZ*) (see Table 2) increases for k_{11} values both higher and lower than the critical value $k_{11}^{crit} = 0.11905$, this probably means that 'true' epithelial and mesenchymal phenotypes display greater complexity than the mixed phenotype (E/M). However, it is verified that for values $k_{11} \le k_{11}^{crit}$ the entropy production rate exhibit a minimum, which indicates the directional nature of the EMT process [50].

5. Conclusions and remarks

The proposed network model generalized, almost qualitatively, the main features of the metastasis processes associates with epithelial-mesenchymal transition. In summary, in this paper we have found that:

- The metastasis state and the EMT exhibit Shilnikov's chaos dynamical behavior. The transition is tightly influenced by the control parameter *I*, representing by the microenvironment-based immune surveillance. This result outlines the pivotal role that cell-microenvironment dynamical interactions, namely those involving the participation of the immune system, is

likely to play in ruling tumor evolution and the commitment of cancer cells towards distinct fates.

- The EMT appear as type "first order" phase transitions, even if for a range of discrete values of the order parameter *S* a continuum spectrum of transitions from one phenotype to the other can be recognized both from the model and the experimental data. Appraisal of EMT as a process featured by criticality and threshold values may help in finding treatment strategies aimed at modifying the overall process by targeting the singularities. This approach would probably focus on reverting the cancer phenotype instead of merely killing cancer cells, an aim hardly achieved with the current chemotherapy regimens [51] We hope that the theoretical framework herewith described may help in establishing critical experiments that would improve our understanding of the cancer evolution process as well as finding optimal pathways for future treatments.

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Phase transitions in tumor growth VI: Epithelial-Mesenchymal transition

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.