Original Articles

Vol. 3 No. 2 (December 2019)
ISSN: 2532-5876

DOI: 10.13133/2532-5876/16448

Mathematical Modelling and Simulation of EMT/MET Biological Transitions

Corrado Mascia, [a] *Pierfrancesco Moschetta,* [a] *and Chiara Simeoni* [b]

[a] *Dipartimento di Matematica "Guido Castelnuovo", Sapienza University of Rome, Italy*

[b] *Laboratoire J.A. Dieudonné, Unicersity of Nice-Sophia Antopolis, France*

Corresponding author: Corrado Mascia, corrado.mascia@uniroma1.it

Abstract

The capability of cells to alter their phenotype in response to signals is crucial to the understanding of different morphogenetic pathways. We focus presently on the case of Epithelial-to-Mesenchynaml Transition (EMT) and its reverse Mesenchymal-to-Epithelial Transition (MET), which are considered as a plausible mechanism at the base of tumours onset and spread. We propose a simplified mathematical model, consisting of two coupled differential equations, aiming to describe the minimal dynamics of Epithelial and Mesenchymal cells. Differently from many previous models arising in various contexts, the basic assumption is the presence of a cooperative-like structure between the two families determined by the presence of a source term (possibly nonlinear) involving cells of the opposite compartment, in addition to an inherent apoptosis term. Finally, being the Mesenchymal phenotype characterised by high-level motility, the presence of motion is included into its dynamics by means of a diffusive-like term. In case the source term is truly nonlinear and, as a consequence, multiple equilibria may coexist, propagating fronts connecting such different states can be numerically observed. For different values of the parameters, specifically the relaxation times σ and τ, the measure of invasiveness λ and μ, together with functions f and g, the model is capable to describe various directions of propagation, also suggesting a possible simple mechanism responsible for tumour reversion.

Keywords: phase transitions, reaction-diffusion systems, propagating fronts, finite difference schemes, wave speed approximation

Citation: Mascia, C, Moschetta, P, Simeoni, C, 2019, "Mathematical Modelling and Simulations of EMT/MET biological transitions", *Organisms: Journal of Biological Sciences*, vol. 3, no. 2, pp. 65-74. DOI: 10.13133/2532-5876/16448

Introduction

In order to pursue investigation concerning cancer occurrence and development, mathematical modelling turns out to be a powerful tool of analysis experimental studies might rely on. Nowadays, indeed, trials in cancer research are one of the most challenging and interdisciplinary contexts, so that the possibility of improving strategies for approaching the subject to deliver better and faster results is imperative. A lot of effort is particularly made with the aim of developing suitable models that could account for the processes leading to tumour cells production and spreading. Although such techniques are typically bounded by limitations mathematical abstraction inevitably brings with it, the recognition of their relevance is increasingly perceptible inside scientific groups: the contribution in terms of predicting cells evolution, and potentially forecasting treatments, is remarkable, thus constituting an effective research path worth being deeply investigated.

Presently, we focus on the application to Epithelial-to-Mesenchymal Transition (EMT) and its reversal mechanism Mesenchymal-to-Epithelial Transition (MET). These are comprised among the experimental hallmar-

ks of cancer, as responsible also for the activation of invasion and metastasis (Hanahan and Weinberg, 2020, 2011; Magi et al., 2017; Thiery, 2006; Thiery and Sleeman, 2006; Thompson and Newgreen, 2005). Altogether, EMT and MET display dynamical behaviours which resemble those observed in physical systems during abrupt macroscopic changes between qualitatively separated stable states, also known as *phase transitions* (Davies et al., 2011). Also, such transitions are active in other important morphogenetic processes, such as early embryogenesis, tissue generation and wound healing (Kalluri and Weinberg, 2009).

More precisely, EMT is the process which allows a polarised epithelial cell, interacting with the basement membrane via its basal surface, to experience a phenotypical switch that permits it to acquire a mesenchymal phenotype. Such new epiphany is characterised by the loss of connectivity (usually as a consequence of down regulation of internal E-cadherin), improved migratory skills, enhanced invasiveness and elevated resistance to apoptosis. From a biomedical point of view, cells phenotypic differentiation turns out to be a crucial step for determining cancer onset and evolution. A characteristic element to be taken into consideration is that even gradual variation in a few control parameters and/or unknown densities can switch cells into distinct and specific phenotypes. The possibility of inducing MET, namely the reverse process of EMT, by means of some external stimuli, is giving rise to perform promising studies at the base of which lies the ultimate ambition to revert an apparently already sealed fate for cells having acquired malignant features.

Apparently, after some previous pioneering work, the first experimental studies showing the presence of a phenotypic transition have been published during the '80s (Greenburg and Hay, 1982). Nevertheless, the attention to this phenomenon has been limited until 2000, when the number of publications on these topics has drastically increased (Nieto, 2011). Since then, the exploration of the subject is considered as an emerging research front.

The most traditional approach is based on a bottom-up procedure, supposed to be predominant for describing how global structures are the result of underlying microscopic counterparts. Indeed, a large part of the literature is devoted to a detailed description of activators and inhibitors of the transitions as determined at molecular level, sometimes comparing an appropriately proposed mathematical model with experimental results. As an example, it is a well-known fact that transforming growth factor β (TGF-β) plays a pivotal role in EMT (Xu et al., 2009) and, thus, finding which elements could enhance its presence has been an issue in the last years (Snail, ZEB, Slug, Twist, ...). Correspondingly, up regulation of E-cadherin promotes the epithelial phenotype; thus, a big effort has been devoted to understand which are the specific ingredients (at the molecular scale) making its level growing (e.g. myo-inositol). In addition, the eventual appearance of an intermediate cells phenotype between the epithelial and mesenchymal ones has also been considered (Jolly et al., 2014).

However, more recently, such point of view has been widely disputed, leaving the space to different approaches based on special types of modelling programmes (Bertolaso, 2016). Actually, it has been proposed that critical events are the result of emerging properties at a scale that is larger than the microscopic ones, according to the influence of external constraints. Therefore, a novel strategy should be applied, grounded on what it is nowadays a well-established discipline, the so-called *Systems Biology approach* (Bizzarri et al., 2008; Bizzarri et al., 2013; Hornberg et al., 2006). More specifically, instead of focusing on the role of individual genes, proteins or other local pathways in biological phenomena, a pertinent alternative is to characterise the ways molecular parts adopt for interacting with each other to determine the collective dynamics of the system as a whole.

Therefore, following the same philosophy, we concentrate on the mechanisms emerging from a cumulative account of the different elements contributing to EMT and MET. Indeed, the main idea underlying the Systems Biology approach is to replace the reductionist paradigm by describing biological systems as a whole, through an holistic view by virtue of which the biomedical processes cannot be exhausted considering the system as the mere sum of its components; that is why, instead of focusing on the role of individual agents, the purpose is to define how essential components interact to characterise the collective dynamics.

In this direction, we propose a simplified mathematical model, which does not pretend to provide any quantitative description of the phenomenon under scrutiny, but only to attempt a qualitative analysis. Such a model considers a very limited number of unknowns —one for the epithelial and one for the mesenchymal

phenotype— and also a minimal set of parameters, then concentrating on the presence of *propagating fronts* which typically correspond to the invasion of one state into the other. We stress that the inclusion of a nonlinear term is crucial for the dynamics, since it guarantees the existence of fronts through the emergence of several discrete stationary states (we shall introduce the definition of these mathematical objects later on).

The majority of mathematical models relevant to the description of EMT/MET is based on *ordinary differential equations*, i.e. systems where the unknowns are considered as functions solely of the time variable. The resulting models are usually rather entangled, often consisting of very large systems, with each unknown variable possessing a stringent biological meaning (Bocci et al., 2018; Gasior et al., 2017; Guerra et al., 2018; Laise et al., 2012; MacLean et al., 2014; Turner and Kohandel, 2010).

Regrettably, the absence of physical space dependency limits dramatically their range of application, together with the capability of catching the correct and complete biological behaviour. As a matter of fact, cells migration requires some (spatial) destination. Thus, more recently, attention has been paid to a different type of modelling based on *partial differential equations* (Hellmann et al., 2016; Sfakianakis et al., 2018). In such an extended framework, as a consequence of the presence of a single (and simple) term accounting for the motility of cells with mesenchymal phenotype, propagation fronts take place and such appearance participate to the investigation in a crucial way.

In this article, EMT/MET analysis is carried out by exploiting a simplified one-dimensional hyperbolic-parabolic partial differential system. Specifically, the densities of epithelial and mesenchymal phenotypes are the unknown variables, and the main purpose consists in establishing the existence of traveling waves by means of numerical simulations. A reliable approximation of the propagating fronts speed is provided by the so-called *LeVeque-Yee formula* (LeVeque and Yee, 1990). One of the most interesting results arising from the model currently under investigation lies in the possibility of reproducing the property of being/not being invasive, according to the dependence on a reduced number of control parameters. Numerical simulations are based on *finite difference schemes* and carried out by employing an Implicit-Explicit strategy (Quarteroni, 2017).

1. A simple mathematical model

Following Simeoni et al., 2018, we propose a prototypical model which consists of two coupled differential equations aiming to reproduce the EMT/MET dynamics. The first is an ordinary differential equation for the nonnegative density $u = u(t,x)$ and it illustrates the time variation $\frac{\partial u}{\partial t}$ of the amount of cells displaying the epithelial phenotype. The second is a partial differential equation of reaction-diffusion type for the time variation $\frac{\partial v}{\partial t}$ of mesenchymal cells, with density denoted by $v = v(t,x)$. After rescaling the variables, the system reads as

$$(1)\quad \begin{cases} \sigma \dfrac{\partial u}{\partial t} = -u + \lambda f(v) \\ \tau \dfrac{\partial v}{\partial t} = -v + \mu g(u) + \dfrac{\partial^2 v}{\partial x^2} \end{cases}$$

for some given positive parameters σ, τ, λ, μ and functions f and g.

The two equations of system (1) have a strong similarity in their structure, guaranteeing a sort of symmetry of the underlying physical mechanisms. However, there are two crucial differences. Firstly, the presence of the parameters σ and τ is needed to incorporate different time-scales in the phenomena, often required when dealing with non-equilibrium thermodynamics. We focus mostly on the choice of values $\sigma = \tau = 1$, corresponding to the case of same time-scale for both the unknowns, although individual choices could be more appropriate, depending on the context. Secondly, the last term in the equation for v, which represents a motility given by the second order space derivative $\frac{\partial^2 v}{\partial x^2}$ of the unknown, is expressed as a diffusive term, which, on its turn, is the macroscopic appearance of an underlying *brownian random walk* (Taylor, 1920). Such term is mandatory, since one hallmark of the mesenchymal phenotype is its high degree of motility. Possible alternatives of modelling could also be considered, essentially corresponding to different types of random walk, such as the *correlated random walk* (Zauderer, 1983). Let us stress that modelling motility terms is one of the major issues in order to obtain a reliable model, but we made the choice of the above form to keep the presentation as simple as possible.

The unknowns u and v are interpreted as the amount of cells having epithelial and mesenchymal phenotype, respectively, inside some tissue under observation. The choice of the functions f and g is also crucial, and it con-

stitutes one of the points where the interaction between applied mathematicians and theoretical biologists is pivotal, as mentioned in the introduction. We assume that both functions f and g are nonnegative and monotone increasing, according to the modelling assumption that the system (1) is cooperative, i.e. a higher presence of epithelial phenotype determines a higher production of mesenchymal phenotype and viceversa.

Disregarding the coupling term f, the density u of the epithelial phenotype is destined, asymptotically in time, to the extinction (due to the apoptosis-like term $-u$ in the first equation), that suggests a stabilisation towards the equilibrium point with an exponential decay rate (as characteristic for solutions to linear equations). A similar fate is expected for the other unknown v when neglecting the coupling term g, thus providing convergence —again, with an exponential decay rate— to its asymptotic equilibrium.

Examples for f and g, being considered in the forthcoming discussion, are

$$(2)\quad f(v) = v \quad \text{and} \quad g(u) = \frac{u^p}{1+u^p},$$

for some p > 1. The former is a standard linear function, while the latter is an S-shaped function, as for the classical saturating Hill form (Gesztelyi et al., 2012; Weiss, 1997). Such choice is motivated by the assumption that the default state of mesenchymal cells is prone to become motile without any limitation. On the contrary, epithelial cells have an inherent tendency to generate mesenchymal cells with an asymptotic bounded range of availability. Different choices can be easily implemented without specific and/or additional difficulty.

The presence of the coupling terms f and g determines the possible existence of a second stable equilibrium point with larger coordinates (u,v). The parameters λ and μ are interpreted, respectively, as a factor enhancing cell-cell adhesion (hence, structural stability typical of epithelial phenotype) and an inflammatory factor, inducing the transition towards a motile mesenchymal phenotype.

A reaction-diffusion system similar to (1) has already been discussed in Capasso and Maddalena, 1981. In that (epidemiological) context, the meaning of the variables u and v is different: the unknown u represents the average concentration of bacteria and v the infective human population inside an urban community; moreover, attention is drawn to convergence towards constant equilibrium states. Presently, we concentrate on the existence of propagating fronts, which are interpreted as epiphanies of EMT and/or MET, depending on the sign of the propagation speed.

In Section 1.1, we preliminarily consider basic properties of the ordinary differential equations obtained by disregarding the second order spatial derivatives. Then, we move to the case where space dependency is taken into account, hence leading, in particular, to the emergence of propagating fronts for describing invasion of one-state into another. Depending on the values λ and μ, invasion can be modulated and also reverted, thus corresponding to a possible tumour reversion scenario. Of course, the present model is too simple to be capable of providing quantitative predictions of such phenomenon, but is regarded as an attempt at a qualitative description of the basic elements at the core of tumour reversion.

1.1 Space independent solutions

Neglecting the space dependency, system (1) reduces to standard ordinary differential equations, usually describing the dynamics of a *well-stirred mixture*, that is

$$(3)\quad \begin{cases} \sigma \dfrac{du}{dt} = -u + \lambda f(v) \\ \tau \dfrac{dv}{dt} = -v + \mu g(u) \end{cases}$$

Analogous models are already present in the literature since decades. Among others, we quote Green and Sleeman, 1974 and its descendants, where the FitzHugh-Nagumo system is proposed in the context of axon signalling, with variables u and v denoting approximately the potential of nerve axons and a (qualitative) feature of the ionic channels opening/closure mechanism, respectively. The effect of the variable u inside the equation for v is completely different with respect to the model (3) presently considered: indeed, we attempt at simulating a particular type of cellular mechanism, distinguished by a cooperative-type coupling, for which each variable positively contributes to the increase of the other. Finally, in Jones et al., 2004, a system with analogous cooperative structure —arising in the context of wound healing experiments (Barriere et al., 2015)— is proposed, but with a mixed product $u \cdot v$ as consequence of the mass action law assumption, with the variables u and v describing the area of dead tissue and the

spatially-evolving section of the wound, respectively.

A standard procedure for analysing differential equations consists in evaluating constant steady states, i.e. special constant solutions which are preserved by the dynamics. For system (3), these are given by

$$\sigma \frac{du}{dt} = 0 \quad \text{and} \quad \tau \frac{dv}{dt} = 0$$

which correspond to the request that

(4) $u = \lambda f(v)$ and $v = \mu g(u)$.

As an example, we consider the functions in (2) with $p = 2$, for some parameters $\lambda, \mu > 0$. In such a case, the modelling function g is said to have a Holling type III response form (Holling, 1959). Substituting into (4), we deduce the polynomial equation

$$(1 - \lambda\mu \cdot u + u^2)u = 0,$$

which admits one, two or three solutions depending on the value of the product $\lambda\mu$. Indeed, for $0 < \lambda\mu < 2$ we compute a single (physically meaningful) solution u_0, for $\lambda\mu = 2$ two solutions $u_- = u_+$ and, finally, for $\lambda\mu > 2$ three solutions always with coordinates

$$u = u_0 = 0,\ u = u_-,\ u = u_+,$$

where

$$u_- := \frac{1}{2}\left(\lambda\mu - \sqrt{(\lambda\mu)^2 - 4}\right)$$

and

$$u_+ := \frac{1}{2}\left(\lambda\mu + \sqrt{(\lambda\mu)^2 - 4}\right).$$

In the latter case, the constant solutions $u_0 = 0$ and u_+ are shown to be asymptotically stable equilibria of the system (3), while the intermediate state u_- is unstable. In the present context, *stability* is referred to the behaviour of small perturbations to the corresponding state: stability being a (local) synonym of attractive, and instability of repulsive dynamics, respectively.

The limiting regime of system (3) as $\sigma \to 0^+$ is said to be a singular dynamics, since the first equation reduces to the algebraic identity $u + \lambda f(v) = 0$,which turns out to be a constraint for the overall dynamics. Correspondingly, there is no need of specifying an initial condition for the unknown u, thus being determined by the relation itself. In such regime, system (3) reduces to the first order differential equation

$$(5)\quad \tau \frac{dv}{dt} = -\frac{\partial H}{\partial v}(v;\lambda,\mu)$$

where

$$(6)\quad \frac{\partial H}{\partial v}(v;\lambda,\mu) = v - \mu g\big(\lambda f(v)\big).$$

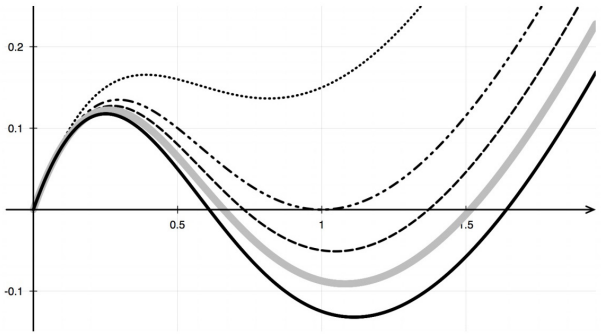

Figure 1. Graphs of the potential function H given in (7) for different values of the parameters.

Therefore, in the singular limit $\sigma \to 0^+$, the equation for v has a special form, which is usually called a *gradient-like structure*. Indeed, after multiplying both sides of (5) by $\frac{\partial v}{\partial t}$, we deduce the identity

$$\frac{d}{dt}H(v;\lambda,\mu) + \tau\left(\frac{dv}{dt}\right)^2 = 0,$$

which shows that the function H is dissipated (it has nonpositive variation) along trajectories of the variable v and thus, in principle, the solutions converge to its minima. In the specific case (2) with $p = 2$ and λ, μ appropriately chosen, the potential H has two distinct minima. Hence, H actually acts as a switch separating solutions which asymptotically converge to one of the two achievable phenotypes. Entering into details, for $f(v) = v$ and $g(u) = \frac{u^2}{1+u^2}$, from (6) there holds

$$(7)\quad \begin{aligned} H(v;\lambda,\mu) &= \frac{1}{2}v^2 - \frac{\mu}{\lambda}\int_0^{v/\lambda} g(\sigma)\,d\sigma \\ &= \frac{1}{2}v^2 + \frac{\mu}{\lambda}\Big(\arctan(\lambda v) - \lambda v\Big) \end{aligned},$$

by using the explicit form of the functions given in (2) with $p = 2$. For $\lambda\mu > 2$, the function H has the typical shape of a double-well potential with wells located at $u_0 = 0$ and u_+ defined above (see Figure 1). In particular, for a specific choice of the product $\lambda\mu$, the two wells have the same depth, with significant consequences in the space-dependent case of system (1), as we shall discuss in the following section.

1.2 Accounting for space dependency

The original model (1) is a simple instance within a wider class, usually referred to as *reaction-diffusion systems*, which very often support special solutions exhibiting a wave-like structure. Roughly speaking, the

interest in such mathematical objects is that they are designed to reproduce invasive patterns, which are a key-feature of many biological applications, properly starting from cancer modelling. A complete review on this issue and its ubiquity in biological modelling can be found in Volpert and Petrovskii, 2009.

As already mentioned in Section 1.1, the limit dynamics of system (1) as $\sigma \to 0^+$ is said to be singular since the mathematical object obtained by (formally) setting $\sigma = 0$ is not a differential equation, but rather an algebraic relation. This fact has a number of significant consequences, relatively to the number of initial/boundary conditions that can be imposed. In such regime, the system reduces to the identity $u = \lambda f(v)$ together with the scalar reaction-diffusion equation

$$(8)\quad \tau \frac{\partial v}{\partial t} = F(v) + \frac{\partial^2 v}{\partial x^2}$$

where $F(v) = -v + \mu g(\lambda f(v))$.Depending on the specific form of function F, the equation (8) may support special solutions of a traveling wave type, namely given by $v(x, t) = V(x - ct)$ for some profile V and *propagation speed* c (Volpert and Petrovskii, 2009). In addition, if the profile function V is such that there exists finite limits at $-\infty$ and $+\infty$, i.e.

$$\lim_{x\to-\infty} V(x) = v_- \quad \text{and} \quad \lim_{x\to+\infty} V(x) = v_+,$$

with $F(v_-) = F(v_+) = 0$, then the solution is said to be a *propagating front* with speed of propagation c. Let us stress that both the profile function V and the speed parameter c are unknown, and have to be determined by imposing that they satisfy the scalar reaction-diffusion equation (8) with boundary data v_- and v_+.

Inserting the above *ansatz* into equation (8) gives an ordinary differential equation for the profile V, parametrised by the speed value c, that is

$$(9)\quad \frac{d^2V}{dx^2} + \tau c \frac{dV}{dx} + F(v) = 0$$

which satisfies the boundary conditions $V(-\infty) = v_-$ and $V(+\infty) = v_+$. In mathematical terms, if $v_- \neq v_+$, we are looking for a so-called heteroclinic orbit (we note that, since the equation (9) is autonomous, the solutions are translationally invariant).

In the prototypical case (2) with $p = 2$, the reaction function becomes $F(v) = -v + \mu \dfrac{\lambda^2 v^2}{1 + \lambda^2 v^2}$,which has a bistable shape if $\lambda\mu > 2$, and then equation (8) supports propagating fronts. In general, the speed c in equation (9) does not have an explicit formula, nevertheless it can be approximated numerically, usually furnishing a value which depends on the parameter τ and the form of the function F.

When the parameter σ is non zero, similar properties hold for the complete system (1). More precisely, a traveling wave solution is a special solution of the form

$$(10)\quad \begin{cases} u(x,t) = U(x - ct) \\ v(x,t) = V(x - ct) \end{cases}$$

And we notice that, by definition, both components are assumed to travel with the same propagation speed. The system of ordinary differential equations for U and V is obtained by substituting (10) into (1), so that

$$(11)\quad \begin{cases} \sigma c \dfrac{dU}{dx} + U - \lambda f(V) = 0 \\ \dfrac{d^2V}{dx^2} + \tau c \dfrac{dV}{dx} + V - \mu g(U) = 0 \end{cases}$$

As before, the solution is said to be a *propagating (or invasion) front* if it defines a heteroclinic orbit of the dynamical system (11) with constant (and different) boundary values

$$(12)\quad \lim_{x\to\pm\infty} U(x) = u_\pm \quad \text{and} \quad \lim_{x\to\pm\infty} V(x) = v_\pm,$$

where the asymptotic states $(u_\pm, v_\pm)$ are forced to be equilibria of system (1) as given by equations (4).

Incidentally, let us observe that being system (11) autonomous, the profile functions U and V, whenever they exist, are determined up to a translation of the independent variable, as for the scalar case (9).

The parameter c has to be appropriately tuned in order for the boundary conditions (12) to be satisfied. Determining the exact —or, at least, an approximate— value of the propagation speed c is crucial for the understanding of the EMT/MET phenomenon under investigation, since it provides the velocity of invasion of phenotype fronts. Actually, computing an exact solution for c is, in general, not possible; thus, it is crucial to develop a suitable algorithm producing a reliable numerical estimate of the speed (refer to Section 2.2).

1.3 A short overview of rigorous results

For the sake of simplicity in the presentation, we focus on the case of modelling functions (2) with $p = 2$.

In the singular limit $\sigma = 0$, the model system (1) reduces to the scalar reaction-diffusion equation

$$\frac{\partial v}{\partial t} = -\frac{\partial H}{\partial v}(v;\lambda,\mu) + \frac{\partial^2 v}{\partial x^2},$$

where the potential H is given in (7). Whenever the function H has two wells, there exists a propagating front connecting the two minima of this potential, with a unique propagation speed c, whose value is linked to the difference of depth of the potential wells. Moreover, its stability is rigorously established as in Fife and McLeod, 1977. An identity for the propagation speed is indeed available and it shows that, in the particular case of two wells of equal depth, the traveling wave is, in fact, a steady state ($c = 0$).

Similarly, for $\sigma > 0$,when H has the same properties as mentioned above, there exist positive values λ_0 and μ_0 such that system (1) possesses a standing wave with profiles $(U, V) = (U(x), V(x))$ corresponding to the speed $c = 0$. Such value separates positive and negative speeds of propagation, and it is determined by the requirements

$$H(v_0;\lambda_0,\mu_0) = \frac{1}{2}v_0^2 + \frac{\mu_0}{\lambda_0}\left(\arctan\left(\lambda_0 v_0\right) - \lambda_0 v_0\right) = 0$$

and

$$\frac{\partial H}{\partial v}(v_0;\lambda_0,\mu_0) = v_0 - \mu_0\frac{\lambda_0^2 v_0^2}{1+\lambda_0^2 v_0^2} = 0\,.$$

The first condition corresponds to the requisite that the two wells of H have same depth; the second one translates the fact that v_0 is a zero of the variation $\partial H/\partial v$ — hence a singular point of the potential $H(\cdot;\lambda,\mu)$— and consequently a candidate for the asymptotic state v_+. Together, they imply that the speed is zero and the wave is stationary.

Finally, in that framework, one can compute the stationary traveling fronts U and V by using the standard construction of a steady heteroclinic orbit for the double-well potential with wells of equal depth (Mascia et al., 2019). Incidentally, we recall that a rigorous proof of the existence of propagating fronts for the system (1) is an open problem in full generality.

2. Numerical simulations

In the mathematical literature, there is a number of numerical schemes of different types for approximating partial differential equations. The choice depends mainly on the dynamical features of the numerical solution one is interested in and, even within the same framework, various algorithms could be implemented (Quarteroni, 2017). As regards the numerical strategy to be applied to the model system (1), we have chosen to employ an implicit-explicit finite difference algorithm. Such a choice allows adopting larger time steps compared to fully explicit schemes, which are instead heavily conditioned by the restrictions that stability requires, thus leading to less computationally expensive simulations. As a matter of fact, our numerical algorithm discretises implicitly all the linear terms, whilst the nonlinear reaction functions f and g are treated explicitly.

We denote by dx and dt the space and time steps, respectively, and by $x_j = j\,\mathrm{dx}$, $j = 1,2,\ldots$, the discretisation points located on a uniform mesh, together with $t^n = n\,\mathrm{dt}$, $n = 1,2,\ldots$, the discrete times. Moreover, the symbols u_j^n and v_j^n indicate numerical approximations of the values $u(x_j, t^n)$ and $v(x_j, t^n)$, respectively. Then, the corresponding numerical scheme reads as

$$\begin{cases} \sigma\dfrac{u_j^{n+1}-u_j^n}{\mathrm{dt}} = -u_j^{n+1} + \lambda v_j^{n+1} \\ \tau\dfrac{v_j^{n+1}-v_j^n}{\mathrm{dt}} = -v_j^{n+1} + \mu g(u_j^n) + \dfrac{v_{j+1}^{n+1} - 2v_j^{n+1} + v_{j-1}^{n+1}}{\mathrm{dx}^2} \end{cases}$$

in the model case (2) with $p = 2$, since the function f is linear. After simple algebraic manipulations, the above algorithm becomes a linear system for the unknown couple (u_j^{n+1}, v_j^{n+1}) to be computed in term of the parameters $\sigma, \tau, \lambda, \mu$ and the (known) couple (u_j^n, v_j^n). By iterations, one ends up with an explicit approximation for the unknown variables at time t^{n+1} (for more details, see Mascia et al., 2019). In the general case of a nonlinear function f, the same implicit-explicit strategy would have suggested the modified scheme

$$\begin{cases} \sigma\dfrac{u_j^{n+1}-u_j^n}{\mathrm{dt}} = -u_j^{n+1} + \lambda f(v_j^n) \\ \tau\dfrac{v_j^{n+1}-v_j^n}{\mathrm{dt}} = -v_j^{n+1} + \mu g(u_j^n) + \dfrac{v_{j+1}^{n+1} - 2v_j^{n+1} + v_{j-1}^{n+1}}{\mathrm{dx}^2} \end{cases}$$

An approximated solution to system (1) is thus the result of time iterations starting from some spatially discretised initial datum which has to be furnished. Presently, we consider initial data of *Riemann type*, i.e. discontinuous profiles consisting of two different constant states at the left and the right of some given point, usually located at $x = 0$, namely

$$(13)\quad u(x,0) = \begin{cases} u_- & \text{for} \quad x < 0 \\ u_+ & \text{for} \quad x > 0 \end{cases}$$

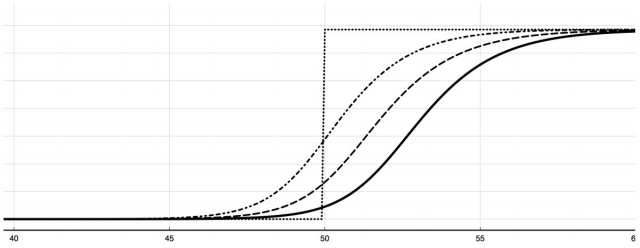

Figure 2. Graphic illustration of case 1 (propagation from right to left)

with the analogous definition for $v(x, 0)$, where $(u_{\pm}, v_{\pm})$ are constant steady states of system (1).

2.1. Computational results for EMT/MET

As mentioned in Section 1.2, in the singular regime $\sigma \to 0^{+}$, the system (1) reduces to a standard parabolic reaction-diffusion equation (8) for the mesenchymal phenotype. The behaviour of such a model is essentially well-known, separating EMT invasion and MET regression regimes by appropriately tuning the model parameters. The general case, for $\sigma > 0$, follows the same qualitative analysis with respect to the model parameters.

In particular, for the reaction functions given in (2) with $p = 2$ and $\mu = 1$, threshold values for the dynamics can be explicitly computed, which are

$0 < \lambda_{*} = 2.0 < \lambda_{0} = 2.175063$.

The analysis is straightforward for $0 < \lambda < \lambda_{*}$, since any positive initial datum generates a solution (u, v) which converges to $(0,0)$ as $t \to +\infty$ with exponential rate. Next, we concentrate on the regime $\lambda > \lambda_{*}$. The numerical results reported below illustrate only the profile for the component u, the profile of the component v being qualitatively very similar. We also limit the presentation to the dynamics exhibited by choosing an initial datum of Riemann type (13).

Case 1: $\lambda = 2.1 > \lambda_{*}$. For this choice of the parameter λ, numerical evidence of the existence of a traveling front is obtained. Moreover, being the stable state u_{+} closer to the critical state corresponding to the threshold value λ_{*}, the solution exhibits a regressive behaviour, namely the front travels towards the right-hand side with positive speed (see Figure 2).

Case 2: $\lambda = \lambda_{0}$. Since the two wells of the potential function H have the same depth for this value of λ, system (1) possesses a stationary solution with the required asymptotic behaviour for $\sigma = 0$. In particular, the dynamics is independent from the relaxation parameters σ and τ, and the existence of a traveling wave in the regime $\sigma > 0$ is a straightforward consequence of the observation that the fronts are actually steady states.

Case 3: $\lambda = 2.25 > \lambda_{0}$. Again, numerical evidence of the existence of propagating fronts emerges as the long-time behaviour of the solution to a Riemann problem (13). The traveling wave has positive speed, so that we are in a situation for which invasion is possible, corresponding to the typical EMT/MET phenomenon (see Figure 3). For more general initial data, competition between different branches of the solution starts playing a crucial role in featuring the large-time behaviour.

As far as λ increases, the numerically computed speed of the propagating fronts increases in absolute value and, thus, invasive EMT/MET regimes are more and more probable.

2.2. Approximation of the speed

Finding a reliable approximation for the velocity of propagating fronts when an explicit formula is not available is crucial for many theoretical reasons. In particular, the speed of propagation c provides an additional parameter which, in principle, could be used to calibrate the model in practical situations. The numerical approximation of the propagation speed relies on the approach originally proposed in LeVeque and Yee, 1990, and successfully applied to systems of reaction-diffusion equations in Lattanzio et al., 2019a, 2019b, Moschetta and Simeoni, 2019.

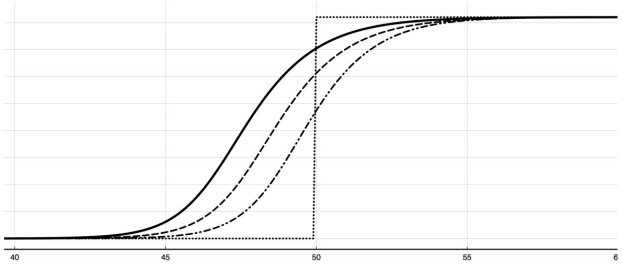

Figure 3. Graphic illustration of case 3 (propagation from left to right)

We provide a brief recasting of the basic idea behind such method: given a smooth function φ with asymptotic states $\varphi_{\pm} = \varphi(\pm\infty)$, there holds

$$\int_{\mathbb{R}} \left[\phi(x+h) - \phi(x)\right] dx = h \int_{\mathbb{R}} \int_{0}^{1} \frac{d\phi}{dx}(x + \theta h)\, d\theta\, dx = h\,[\phi]\,, \tag{14}$$

for any $h \in \mathbb{R}$, where $[\varphi] := \varphi_+ - \varphi_-$, this formula being obtained by interchanging the order of integration.

Choosing the shift value $h = -cdt$ we infer that

$$c = \frac{1}{[\phi]\,\mathrm{dt}} \int_{\mathbb{R}} \left[\phi(x) - \phi(x - c\,t)\right] dx \ .$$

Denoting by φ_j^n the approximation of $\varphi\,(x_j - ct^n)$, the numerical counterpart of identity (14) is given by

$$(15) \quad c^n := \frac{\mathrm{dx}}{\mathrm{dt}} \sum_j \frac{\phi_j^n - \phi_j^{n+1}}{[\phi]} \ .$$

The approximation (15) is indeed exact whenever φ_j^n is related to a traveling wave solution with constant speed c and asymptotic states $\varphi_\pm$. In general, the value c^n can be regarded as a space-averaged propagation speed, which is suppose to stabilise towards the correct speed c when φ_j^n converges to the traveling profile.

Because the model system (1) has two dynamical variables u and v, the respective speed values can be computed through the LeVeque-Yee formula (15) by applying it either to u_j^n or to v_j^n. Actually, for large n, the two numerically estimated values appear to be close one to the other, as expected from the theoretical analysis (refer to Section 2.2).

Conclusions

In the recent years, EMT and MET have been considered as an important emerging research subject, constituting a crucial event in cancer onset and spread, also strictly related with invasive features and linked to the consequent formation of metastasis. We have proposed a simplified mathematical model, consisting of a system of coupled partial differential equations for two variables, describing, in principle, two different cells phenotypes, namely epithelial and mesenchymal. The model system is of reaction-diffusion type and often supports the emergence of propagating fronts under minimal assumptions on the physical parameters. Of course, the presence of a space-dependent diffusion term is crucial, together with a little amount of nonlinearity. We also illustrated a numerical algorithm able to furnish reliable approximations for the propagation speeds, which could be useful to calibrate the model with respect to experimental data and realistic situations.

Acknowledgments

The research presented in this article has been motivated by the fruitful discussions with the researchers of the Systems Biology Group Lab — www.sbglab.org — settled at the Department of Experimental Medicine, Sapienza University of Rome (Italy) and, in particular, with M. Bizzarri and S. Dinicola.

This project is partially supported by the French government, managed by the ANR under the UCA JEDI Investments for the Future project, reference No. ANR-15-IDEX-01.

References

Barriere, G, Fici, P, Gallerani, G, Fabbri, F & Rigaud, M 2015, "Epithelial mesenchymal transition: a double-edged sword", *Clinical and Translational Medicine*, vol. 4, no. 14, pp. 1-6.

Bertolaso, M 2016, *Philosophy of cancer. A dynamic and relational view*. History, Philosophy and Theory of the Life Sciences 18, Springer Netherlands.

Bizzarri, M, Cucina, A, Conti, F & D'Anselmi, F 2008, "Beyond the oncogene paradigm: understanding complexity in carcinogenesis", *Acta Biotheoretica*, vol. 56, no. 3, pp. 173-196.

Bizzarri, M, Palombo, A & Cucina, A 2013, "Theoretical aspects of Systems Biology", *Progress in Biophysics and Molecular Biology*, vol. 112, no. 1-2, 33-43.

Bocci, F, Jolly, MK, George, JT, Levine, H & Onuchic, JN 2018, "A mechanism-based computational model to capture the interconnections among epithelial-mesenchymal transition, cancer stem cells and Notch-Jagged signalling", *Oncotarget*, vol. 9, no. 52, pp. 29906-29920.

Capasso, V & Maddalena, L 1981, "Convergence to equilibrium states for a reaction-diffusion system modelling the spatial spread of a class of bacterial and viral diseases", *Journal of Mathematical Biology*, vol. 13, pp. 173-184.

Davies, P, Demetrius, L & Tuszynki, J 2011, "Cancer as dynamical phase transition", *Theoretical Biology and Medical Modelling*, vol. 8, pp. 1-30.

Fife, P & McLeod, J 1977, "The approach of solutions of nonlinear diffusion equations to travelling front solutions", *Archive for Rational Mechanics and Analysis*, vol. 65, pp. 335-361.

Gasior, K, Hauck, M, Wilson, A & Bhattacharaya, S 2017, "A theoretical model of the Wnt signaling pathway in the epithelial mesenchymal transition", *Theoretical Biology and Medical Modelling*, vol. 14, no. 20, pp. 1-20.

Gesztelyi, R, Zsuga, J, Kemeny-Beke, A, Varga, B, Juhasz, B & Tosaki, A 2012, "The Hill equation and the origin of quantitative pharmacology", *Archive for History of Exact Sciences*, vol. 66, pp. 427-438.

Green, M & Sleeman, B 1974, "On FitzHugh's nerve axon equations", *Journal of Mathematical Biology*, vol. 1, pp. 153-163.

Greenburg, G & Hay, ED 1982, "Epithelial suspended in collagen gels lose polarity and express characteristics of migra-

ting mesenchymal cells", *Journal of Cell Biology*, vol. 95, no. 1, pp. 333-339.

Guerra, A, Rodriguez, DJ, Montero S, Betancourt-Mar, JA, Martin, RR, Silva, E, Bizzarri, M, Cocho, G, Mansilla, R & Nieto-Villar, JM 2018, "Phase transitions in tumour growth VI: Epithelial-Mesenchymal transition", *Physica A*, vol. 499, pp. 208-215.

Hanahan, D & Weinberg, RA 2011, "Hallmarks of cancer: the next generation", *Cell*, vol. 144, no. 5, pp. 646-674.

Hanahan, D & Weinberg, RA 2000, "The hallmarks of cancer", *Cell*, vol. 100, no. 1, pp. 57-70.

Hellmann, N, Kolbe, N & Sfakianakis, N 2016, "A mathematical insight in the epithelial-mesenchymal-like transition in cancer cells and its effect in the invasion of the extracellular matrix", *Bulletin of the Brazilian Mathematical Society*, vol. 47, no. 1, pp. 397-412.

Holling, C 1959, "Some characteristics of simple types of predation and parasitism", *The Canadian Entomologist*, vol. 91, no. 7, pp. 385-398.

Hornberg, JJ, Bruggeman, FJ, Westerhoff, HV & Lankelma, J 2006, "Cancer: A Systems Biology disease", *Biosystems*, vol. 83, no. 2-3, 81-90.

Jolly, MK, Huang, B, Lu, M, Mani, SA, Levine, H & Ben-Jacob, E 2014, "Towards elucidating the connection between epithelial-mesenchymal transitions and stemness", *Journal of the Royal Society Interface*, vol. 11, no. 101, 20140962.

Jones, M, Song, B & Thomas, D 2004, "Controling wound healing through debridement", *Mathematical and Computer Modelling*, vol. 40, pp. 1057-1064.

Kalluri, R & Weinberg, RA 2009, "The basics of epithelial-mesenchymal transition", *Journal of Clinical Investigation*, vol. 116, no. 6, pp. 1420-1428.

Laise, P, Fanelli, D, Lio', P & Arcangeli, A 2012, "Modeling TGF-β signaling pathway in epithelial-mesenchymal transition", *AIP Advances*, vol. 2, 011201, pp. 1-11.

Lattanzio, C, Mascia, C, Plaza, RG & Simeoni, C 2019a, "Analysis and numerics of the propagation speed for hyperbolic reaction-diffusion models", in preparation.

Lattanzio, C, Mascia, C, Plaza, RG & Simeoni, C 2019b, "Kinetic schemes for assessing stability of traveling fronts for the Allen-Cahn equation with relaxation", *Applied Numerical Mathematics*, vol. 141, pp. 234-247, 2019.

LeVeque, R & Yee, H 1990, "A study of numerical methods for hyperbolic conservation laws with stiff source terms", *Journal of Computational Physics*, vol. 86, no. 1, pp. 187-210, 1990.

MacLean, AL, Harrington HA, Stumpf, MPH & Hansen, MDH 2014, "Epithelial-Mesenchymal transition in metastatic cancercell populations affects tumor dormancy in a simple mathematical model", *Biomedicines*, vol. 2, no. 4, 384-402.

Magi, S, Iwamoto, K & Okada-Hatakeyama, M, 2017, "Current status of mathematical modeling of cancer - From the viewpoint of cancer hallmarks", *Current Status in Systems Biology*, vol. 2, pp. 39-48.

Mascia, C, Moschetta, P & Simeoni, C 2019, "Phase transitions of biological phenotypes by means of a prototypical PDE model", *Communications in Applied and Industrial Mathematics*, vol. 10, no. 1, pp. 1-17.

Moschetta, P & Simeoni, C 2019, "Numerical investigation of the Gatenby-Gawlinski model for acid mediated tumour invasion", *Rendiconti di Matematica e delle sue Applicazioni*, vol. 7, pp. 1-31, online first.

Nieto, MA 2011, "The ins and outs of the epithelial to mesenchymal transition in health and disease", *Annual Review of Cell and Developmental Biology*, vol. 27, pp. 347-376.

Quarteroni, A 2017, *Numerical models for differential problems*. Third edition. Modeling, Simulation and Applications 16, Springer, Cham.

Sfakianakis, N, Kolbe, N, Hellmann, N & Lukacova-Medvidova, M 2017, "A multiscale approach to the migration of cancer stem cells: mathematical modelling and simulations", *Bulletin of Mathematical Biology*, vol. 79, no. 1, 209-235.

Simeoni, C, Dinicola, S, Cucina, A, Mascia, C & Bizzarri, M 2018, "Systems biology approach and mathematical modeling for analyzing phase-space switch during epithelial-mesenchymal transition", in M Bizzarri (ed) *Systems Biology*, pp. 95-123, Methods in Molecular Biology 1702, Springer Protocols + Business Media LLC.

Taylor, GI 1920, "Diffusion by continuous movements", *Proceedings of the London Mathematical Society*, vol. 20, pp. 196-212.

Thiery, J 2006, "Epithelial-Mesenchymal transitions in tumour progression", *Nature Reviews Cancer*, vol. 2, no. 6, pp.442-454.

Thiery, J & Sleeman, J 2006, "Complex networks orchestrate epithelial-mesenchymal transitions", *Nature Reviews Molecular Cell Biology*, vol. 7, no. 2, pp. 131-142.

Thompson, EW & Newgreen, DF 2005, "Carcinoma invasion and metastasis: A role for epithelial-mesenchymal transition?", *Cancer Research*, vol. 65, no. 14, pp. 5991-5995.

Turner, C & Kohandel, M 2010, "Investigating the link between epithelial-mesenchymal transition and the cancer stem cell phenotype: A mathematical approach", *Journal of Theoretical Biology*, vol. 265, no. 3, pp. 329-335.

Volpert, V & Petrovskii, S 2009, "Reaction-diffusion waves in biology", *Physics of Life Reviews*, vol. 6, no. 4, pp. 267-310.

Weiss, J 1997, "The Hill equation revisited: uses and misuses", *The FASEB Journal*, vol. 11, no. 11, pp. 835-841.

Xu, J, Lamouille, S & Derynck, R 2009, "Tgf-β-induced epithelial to mesenchymal transition", *Cell Research*, vol. 19, no. 2, pp. 156-172.

Zauderer, E 1983, *Partial Differential equations of applied mathematics*, Wiley, New York.