TRAVELLING WAVES IN TWO MECHANOCHEMICAL MODELS OF TUMOR ANGIOGENESIS

K. Piechór

Institute of Fundamental Technological Research, Warszawa, Poland

1. Introduction

At the early stages of its formation the tumor secrets some chemical signals, called Tumor Angiogenic Factors, into the neighbouring extracellular matrix (ECM) to stimulate sprouting new blood vessels from the existing vascular system. This process is an example of the phenomenon called angiogenesis. The TAF when reach a blood vessel make the cells forming the outer layer, the endothelium, to move via chemotaxis into the direction of the tumor. The travelling endothelial cells cause some traction within the tissue inducing some deformations of it and changing its density, what in turn influences the motion of the endothelial cells themselves..

2. The model

In the mathematical model only four field velocities are taken into account. They are:

- $\mathbf{u}(t,\mathbf{x})$ - the displacement at time *t* of a point of ECM being initially at the position **x**,
- $N(t,\mathbf{x})$ - the density of ECM at time *t* and position **x**,
- $n(t,\mathbf{x})$ - the density of the endothelial cells at time *t* and position **x,**
- $r(t,\mathbf{x})$ - the concentration of TAF at time *t* and position **x.**

The ECM is modelled as a visco-elastic continuum It is assumed that the Reynolds number is small, consequently, the inertial terms are ignored. The body force balances the elastic force, the viscous force, and the cell traction within the ECM. The force balance equation reads

$$\nabla\cdot\left\{\overbrace{\left[\frac{1-2\nu}{1-\nu}\varepsilon-\beta_1\nabla^2\varepsilon+\left(\frac{\nu}{1-2\nu}\theta-\beta_2\nabla^2\theta\right)\mathbf{I}\right]}^{\text{elastic force}}+\overbrace{\mu_1\frac{\partial\varepsilon}{\partial t}+\mu_2\frac{\partial\theta}{\partial t}\mathbf{I}}^{\text{viscous force}}+\overbrace{\tau s\mathbf{I}}^{\text{traction}}\right\}=\overbrace{\rho\frac{\partial\mathbf{u}}{\partial t}}^{\text{body force}}, \tag{1}$$

$s=s(n)$ is the traction stress, ν is the constant Poisson ratio, μ_1,μ_2 are the constant shear and bulk viscosities, β_1,β_2 are positive constants, $\mathbf{I}$ is the unit matrix, and τ is a positive parameter characterising the strength of the traction τs, and ρ is a positive constant , $\varepsilon=\frac{1}{2}\left(\nabla\mathbf{u}+\nabla\mathbf{u}^{\mathrm{T}}\right)$ is the strain tensor, where $^{\mathrm{T}}$ denotes the transpose, and $\theta=\nabla\cdot\mathbf{u}$ is the dilatation

The cells of ECM move only due to convection. Hence this equation is of the form

$$\frac{\partial N}{\partial t}+\overbrace{\nabla\cdot\left(N\frac{\partial\mathbf{u}}{\partial t}\right)}^{\text{convection}}=0. \tag{2}$$

The EC cell density changes due passive convection, random diffusion, chemotaxis and haptotaxis. Due to the deformations of the ECM the diffusive flux is biased. Simply, scalar coefficient of diffusion is replaced by a tensor depending on the strain in the ECM. In our model we assumed for sake of some mathematical simplicity that the chemotactic flux is also biased by the same tensor. This assumption can be removed at the expense of more complicated formulae.. The equation of the EC density reads

$$\frac{\partial n}{\partial t}+\overbrace{\nabla\cdot\left(n\frac{\partial \mathbf{u}}{\partial t}\right)}^{\text{conection}}=\nabla\cdot\left[\overbrace{D\left(\mathbf{I}+\vartheta-\frac{\theta}{2}\mathbf{I}\right)\cdot\left(\nabla n-\alpha\frac{n}{r}\nabla r\right)}^{\text{biased diffusion and chemotaxis}}-\overbrace{n\nabla\gamma(N)}^{\text{haptotaxis}}\right], \tag{3}$$

where D, α are positive constants, and $\gamma(N)$ is the haptotactic function describing the adhesion of the endothelial cells to the ECM.

Finally, we assume that the TAF concentration changes in time due to diffusion and degradation, i.e. "consumption" by EC. The equation reads

$$\frac{\partial r}{\partial t}=\overbrace{d\nabla^2 r}^{\text{diffusion}}-\overbrace{F(n,r)}^{\text{degradation}}. \tag{4}$$

To close the system (1) – (4) we need to know the functional form of $s(n)$, $\gamma(N)$, and $F(n,r)$. We use the following models

$$s(n)=\frac{P_s n}{1+k_s n^2},\quad \gamma(N)=\frac{P_\gamma N}{1+k_\gamma N},$$

and two models of the degradation function

$$F_I=knr \quad \text{and} \quad F_{II}=kn, \tag{5}$$

where $P_s, k_s, P_\gamma, k_\gamma, k$ are positive constants. The reason of considering two models given by F_I and F_{II} is that the "equations of state" like $s(n)$, $\gamma(N)$, etc. are known only in a very rough approximation. Frequently they are they chosen for simplicity. We show that despite the small difference between F_I and F_{II} the corresponding travelling waves differ significantly.

We look for solutions of the system (1) – (4) in the form of travelling waves, i. e. the field quantities $\mathbf{u}, N, n, r$ are assumed to be functions of one independent variable $\xi=\mathbf{k}\cdot\mathbf{x}-\sigma t$, where $\mathbf{k}$ is a given constant vector, and σ is a positive constant, interpreted as the wave speed.

We prove that the wave propagates only in the direction of the vector **k.** The main result of the paper is

Theorem *The endothelial cell density n and the TAF concentration r are well defined function on the real axis* $(-\infty,\infty)$. *They are positive, and for positive wave speed* σ, $r(\xi)$ *it is monotonically increasing in its domain. Moreover, they satisfy: for Model I*

$$n(\xi)=\begin{cases} n_- + o(1) & as \quad \xi\to-\infty \\ O\left(e^{-\sigma\xi}\right) & as \quad \xi\to+\infty \end{cases} \qquad r(\xi)=\begin{cases} O\left(\exp\left(\frac{\sigma}{\alpha}\xi\right)\right) & as \quad \xi\to-\infty \\ r_+ + o(1) & as \quad \xi\to+\infty \end{cases}$$

and for Model II

$$n(\xi)=\begin{cases} O\left(\exp\left(\frac{\sigma}{\alpha}-1\right)\right) & as \quad \xi\to-\infty \\ O\left(e^{-\sigma\xi}\right) & as \quad \xi\to+\infty \end{cases} \qquad r(\xi)=\begin{cases} O\left(\exp\left(\frac{\sigma}{\alpha-1}\xi\right)\right) & as \quad \xi\to-\infty \\ r_+ + o(1) & as \quad \xi\to+\infty. \end{cases}$$

Hence, in the case of Model I the EC density has the form of a kink, whereas in the Model II its profile has the form of an impulse and vanishes at both ends. Therefore, such a wave cannot be accepted as a solution of the tumor angiogenesis problem; rather it corresponds to an *in vitro* vasculogenesis

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