Modelling Cancer Cell Invasion of Tissue: Non-local Effects in the uPA System

Vivi Andasari and M.A.J. Chaplain

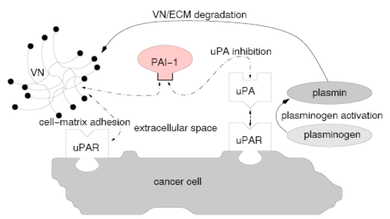
{vivi,chaplain}@maths.dundee.ac.uk

The Role of uPA

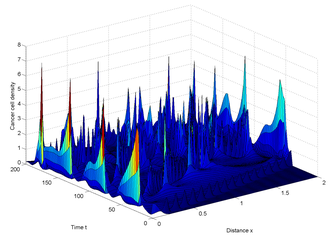
Urokinase-type Plasminogen Activator (uPA) is a proteolytic enzyme that can be found in the extracellular matrix (ECM). Over-expression of levels of uPA by cancer cells cause:

- activation of plasminogen then plasmin, and
- degradation of the ECM → cancer invasion

The activity of uPA is inhibited by PAI-1.



uPA Local Model



In this model, the motion of cancer cells is governed by (i) random motility, (ii) local flux terms for chemotaxis up gradients uPA & PAI-1 concentrations, and (iii) local flux term for haptotaxis up gradients ECM density, taking

$$\mathcal{A}\{u(t,\cdot)\} = \frac{\partial v}{\partial x} \tag{1}$$

The Equations

$$\text{cells}: \quad \frac{\partial c}{\partial t} = \underbrace{D_c \frac{\partial^2 c}{\partial x^2}}_{\text{random motion}} - \underbrace{\frac{\partial}{\partial x}\left(\chi_u(c,v)\frac{\partial u}{\partial x} + \chi_p(c,v)\frac{\partial p}{\partial x}\right)}_{\text{chemotaxis}} - \underbrace{\frac{\partial}{\partial x}\left(\chi_v(c,v)\mathcal{A}\{u(t,\cdot)\}\right)}_{\text{haptotaxis}} + \underbrace{\mu_c(c,v)}_{\text{proliferation}}$$

$$\text{VN}: \quad \frac{\partial v}{\partial t} = -\delta v m + \phi_{21} p u - \phi_{22} p v + \underbrace{\mu_v(c,v)}_{\text{proliferation}}$$

$$\text{uPA}: \quad \frac{\partial u}{\partial t} = D_u \frac{\partial^2 u}{\partial x^2} - \phi_{31} p u - \phi_{33} c u + \alpha_{31} c$$

$$\text{PAI-1}: \quad \frac{\partial p}{\partial t} = D_p \frac{\partial^2 p}{\partial x^2} - \phi_{41} p u - \phi_{42} p v + \alpha_{41} m$$

$$\text{plasmin}: \quad \frac{\partial m}{\partial t} = D_m \frac{\partial^2 m}{\partial x^2} + \phi_{52} p v + \phi_{53} c u - \phi_{54} m$$

Non-local Model

Here the local haptotaxis flux term (1) is replaced by non-local flux term modelling cell-cell and cell-matrix adhesion, in 1D:

$$\mathcal{A}\{u(t,\cdot)\} := \frac{1}{R}\int_0^R \sum_{j=0}^{1} \underline{\eta}(j)\cdot\Omega(r)g(\underline{u}(t,\underline{x}+r\underline{\eta}(j)))dr$$

referred to as the *adhesion velocity* of cells in the direction of forming the most bonds in the sensing region.

Non-local Effects in the uPA System

After expanding into a Taylor series, in the limit as $R \to 0$:

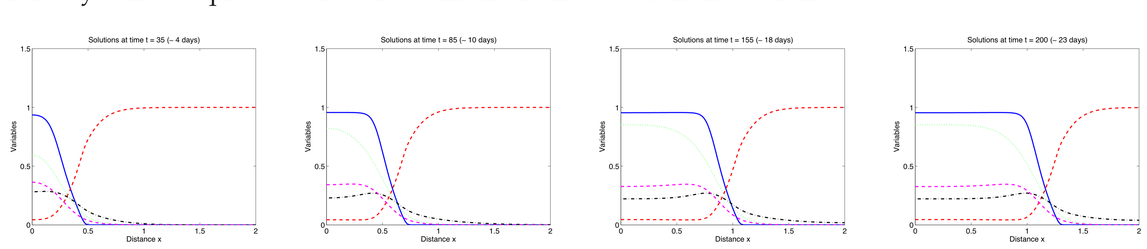
$$\mathcal{A}\{u(t,\cdot)\} \to A_1 \frac{d}{dx} g(\underline{u}(t,x)) = A_1 \nabla_{\underline{u}} g(\underline{u}(t,x)) \cdot \underline{u}_x(t,x)$$

We use overcrowding prevention (volume-filling) mechanism for

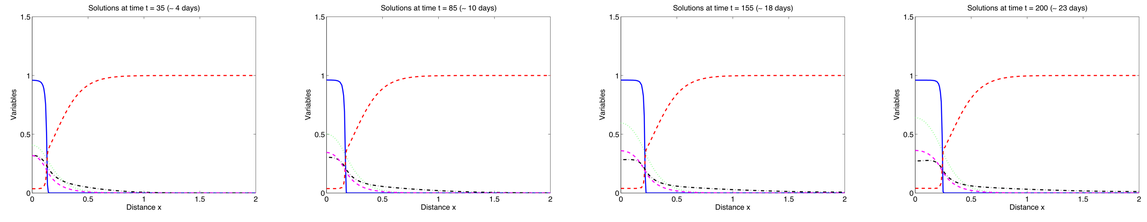
- chemotactic functions $\chi_u(c,v) = \chi_1 c(1-c-v)$ and $\chi_p(c,v) = \chi_2 c(1-c-v)$,
- proliferations $\mu_u(c,v) = \mu_1 c(1-c-v)$ and $\mu_v(c,v) = \mu_2 v(1-c-v)$,
- the function $g(\underline{u}) = (S_{cc}c + S_{cv}v)(1-c-v)$,

assuming $1-c-v \geq 0$.

S_{cc} is the cell-cell adhesion coefficient and S_{cv} is the cell-matrix adhesion coefficient. Invasion occurs if $S_{cc} < S_{cv}$. Linear stability analysis shows stability of the system of equations. For the numerical simulations in 1D, we impose zero-flux boundary conditions on a spatial domain $\Omega = (0,2)$. The maximum characteristic distance of invasion by the cancer cells $L = 0.1$cm.



a) Invasion ($S_{cc} < S_{cv}$)



b) No invasion ($S_{cc} > S_{cv}$)

Conclusions

We incorporated the non-local model accounting for cell-cell and cell-matrix adhesion into the uPA system considering prevention of overcrowding. The numerical simulations and analysis implied stability and traveling wave-like solutions of the cancer cells at the invasion stage.

References

[1] M.A.J. Chaplain and G. Lolas. Mathematical Modelling of Cancer Cell Invasion of Tissue: The Role of the Urokinase Plasminogen Activation System, *Mathematical Models and Methods in Applied Sciences*, vol. 15, (2005)

[2] A. Gerisch and M.A.J. Chaplain. Mathematical Modelling of Cancer Cell Invasion of Tissue: Local and Non-local Models and the Effect of Adhesion, *Journal of Theoretical Biology*, (2008)