Modelling Cancer Cell Invasion: The Roles of Cell-cell & Cell-matrix Adhesion

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Introduction

Cancer cell invasion of tissue is a multistep process that involves, in general:

- Over-expression of proteolytic enzyme activity, leading to matrix degradation
- Alterations in adhesive interactions between cell-cell and cell-matrix

The aim here is to develop a model that couples the processes. A mathematical model for the first part has been developed [1] and analysed [2]. For the latter we use cell-cell adhesion model [4], [3].

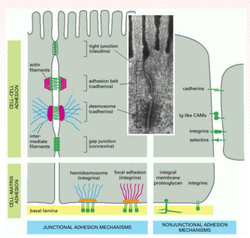
uPA Model

The uPA model [1], [2] describes interactions between cancer cells, host tissue, urokinase-type Plasminogen Activator (uPA), uPA inhibitors (PAI-1), and plasmin. The migratory properties of cancer cells are modelled through random motility, chemotaxis and haptotaxis.

Key processes in cancer invasion

Adhesion

To incorporate adhesion, the local haptotaxis term is replaced with a non-local term describing adhesive interactions between cells S_{cc} and cell-matrix S_{cv}. Invasion occurs when $S_{cc} < S_{cv}$, otherwise the cancer remains localised.



Key adhesive process between cells and matrix. Figure from "Molecular Biology of The Cell", Alberts et.al.

The Equations

$$\text{cells}: \quad \frac{\partial c}{\partial t} = \underbrace{D_c \nabla^2 c}_{\text{random motion}} - \underbrace{\nabla \cdot \left[c \, \frac{1}{R} \int_{-R}^{R} g(S_{cc}, S_{cv}, c, v)\, \Omega(r)\, dr \right]}_{\text{adhesions}}$$

$$- \underbrace{\nabla \cdot (\chi_u c(1-c-v)\nabla u + \chi_p c(1-c-v)\nabla p)}_{\text{chemotaxis}} + \underbrace{\mu_c c(1-c-v)}_{\text{proliferation}}$$

$$\text{VN}: \quad \frac{\partial v}{\partial t} = -\delta v m + \phi_{21} p u - \phi_{22} p v + \mu_v v(1-c-v)$$

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

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

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

Dispersal Curves

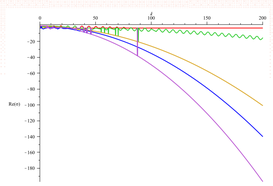
Global steady states give one point, taking from $1 - c^* - v^* = 0$, that is at $(c^*, v^*, u^*, p^*, m^*) \approx (1,\ 0,\ 0.205,\ 1,\ 0.307)$ by using parameters given in [1]. Linear stability analysis confirms that this equilibrium is stable. Two qualitative terms for radial dependency $\Omega(r)$ [3], for 1D

$$\Omega_{1D}(r) = \begin{cases} \frac{1}{2R} & \text{for constant} \\ \frac{1}{R}\left(1 - \frac{r}{R}\right) & \text{for linearly decay}, \end{cases}$$

and for 2D

$$\Omega_{2D}(r) = \begin{cases} \frac{1}{\pi R^2} & \text{for constant} \\ \frac{3}{\pi R^2}\left(1 - \frac{r}{R}\right) & \text{for linearly decay}. \end{cases}$$

Dispersal curves from linear stability analysis,



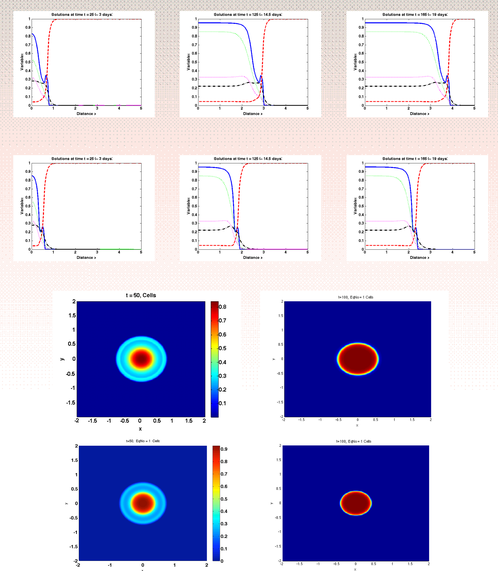
showing that real part of eigenvalues are negative.

Numerical Simulations

Simulations are performed using Plasmin Code implemented in a Fortran subroutine and called from Matlab®. For g we use

$$g(S_{cc}, S_{cv}, c, v) = (S_{cc}c + S_{cv}v)(1-c-v)$$

where S_{cc} and S_{cv} are for now set constants. Below are results for $\Omega(r)$ is constant and $r-$dependent.



Adhesive Pathways

To make our model more realistic, we will consider S_{cc} and S_{cv} to be functions of other variables and not just constants. This is to be our future work. The cadherin pathway for individual cells has been modelled [5] in a system of ODEs. The model considers interactions between E-cadherin, $\beta-$catenin, complex E-cadherin-$\beta-$catenin, and proteasome.

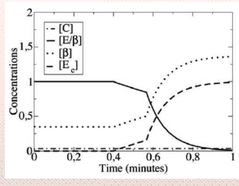


Figure [5] shows loss of cell bonds with the neighbour, that is when S_{cc} is down-regulated, and hence potential invasion.

Future Work

The complex interactions of cells with extracellular matrix involve transmembrane integrin receptors. It will be our future work to model integrin pathway and combine it with cadherin to develop our model.

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References

[1] M.A.J. Chaplain, 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* (2005) 15

[2] M.A.J. Chaplain, A. Gerisch, G. Lolas. A Mathematical and Computational Analysis of a Model of Cancer Cell Invasion of Tissue *Journal of Mathematical Biology* (in revision)

[3] A. Gerisch, 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* (2007) 250

[4] N.J. Armstrong, K.J. Painter, J.A. Sherratt. A Continuum Approach to Modelling Cell-cell Aadhesion *Journal of Theoretical Biology* (2006) 243

[5] I. Ramis-Conde, D. Drasdo, A.R.A. Anderson, M.A.J. Chaplain. Modelling the influence of the E-Cadherin-β-Catenin pathway in cancer cell invasion: A multi-scale approach *Biophysical Journal* (2008) 95