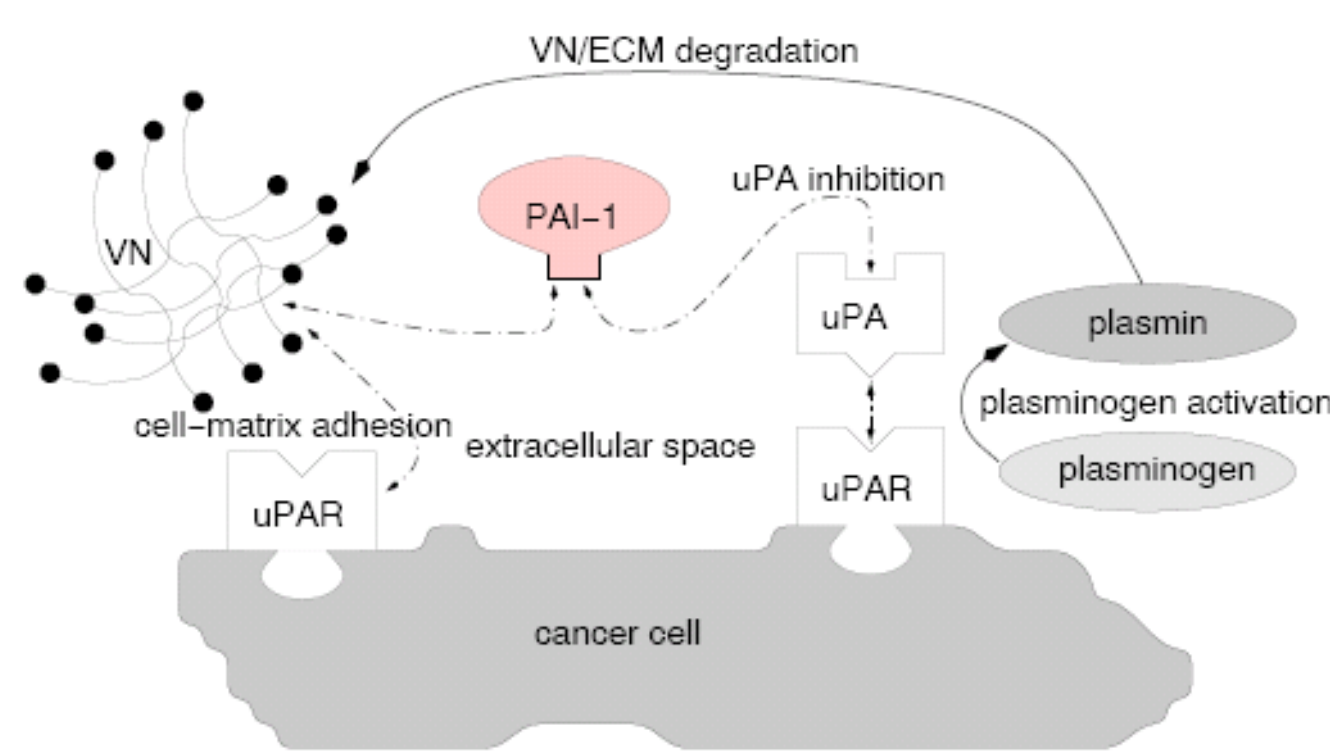


The Role of uPA

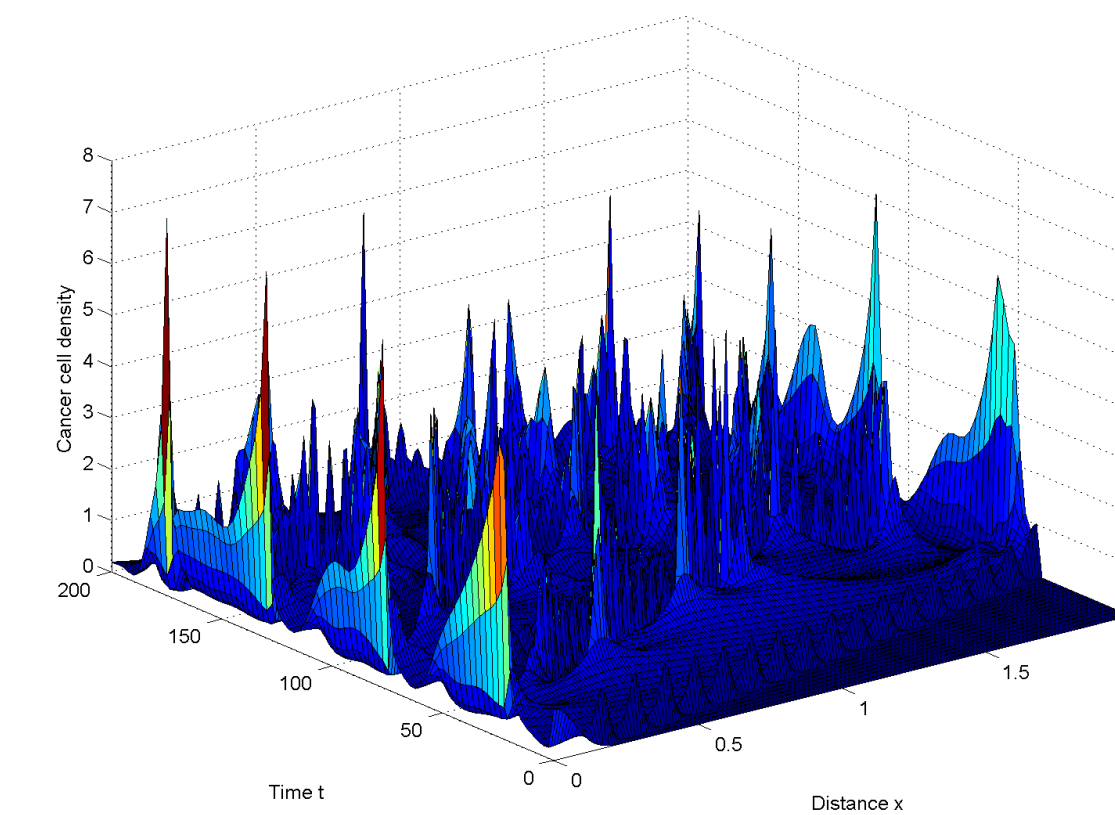
Urokinase-type Plasminogen Activator (uPA) is a proteolytic enzyme that can be found in the extracellular matrix (ECM). Over-expression of levels of uPA by cancer cells cause:

- 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

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

Non-local Effects in the uPA System

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

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

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 sim-

ulations 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 $L = 0.1\text{cm}$.

The Equations

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

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

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

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

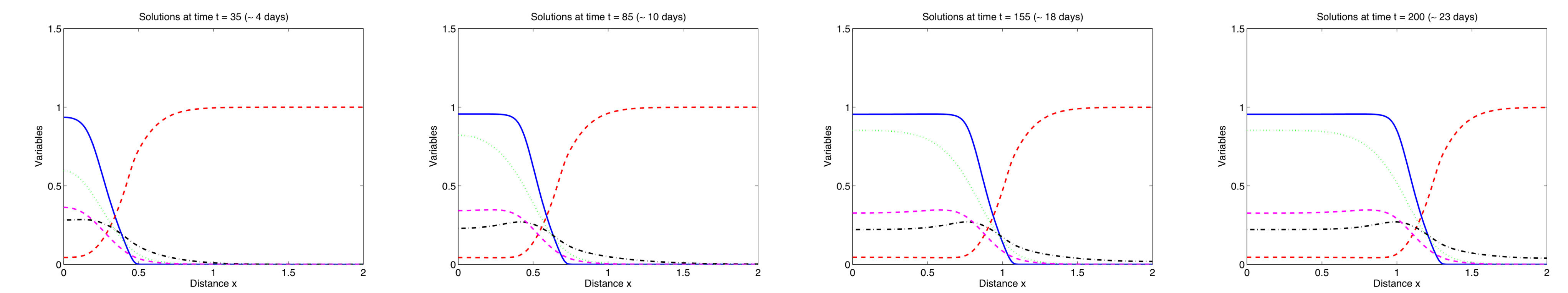
$$\text{plasmin : } \frac{\partial m}{\partial t} = D_m \frac{\partial^2 m}{\partial x^2} + \phi_{52} p v + \phi_{53} c u - \phi_{54} m$$

Non-local Model

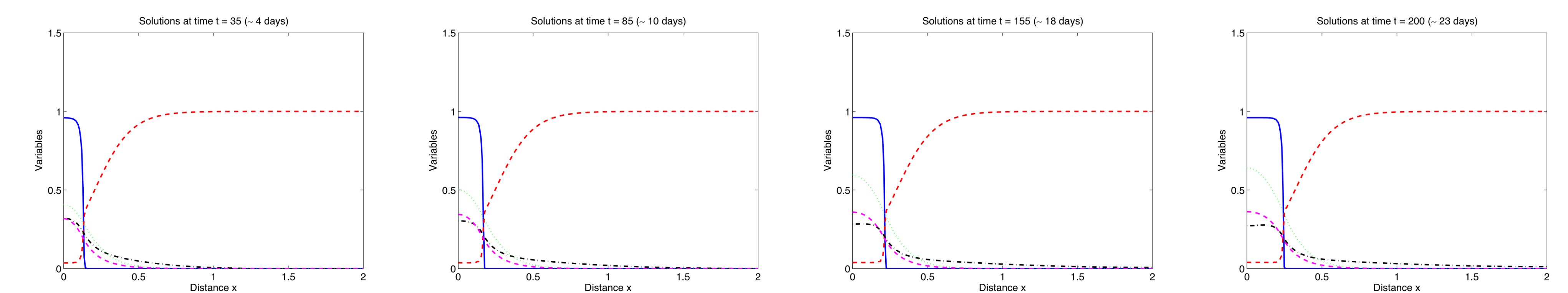
Here the local **haptotaxis** flux term (1) is replaced by non-local flux term modelling cell-cell and cell-matrix adhesion, in 1D:

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

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



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)