Tumor-Stromal Interactions in Acid-Mediated Invasion

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Gatenby and Gawlinski (1996)

- Tumor cells produce excess acid, which diffuses into the surrounding tissue via mobile buffering species.
- Acidification of the environment causes normal cell death.
- Death of normal cells produces potential space into which the tumor cells may proliferate.

Martin et al. (2010)

- In order to invade, the tumor cells must kill normal cells (as before) and degrade the extra cellular matrix (ECM). Acidification of the environment causes normal cell death.
- The ECM is degraded by active matrix metalloproteinases (MMPs), which are formed at the interface between tumor and normal cells.

Mathematical Model

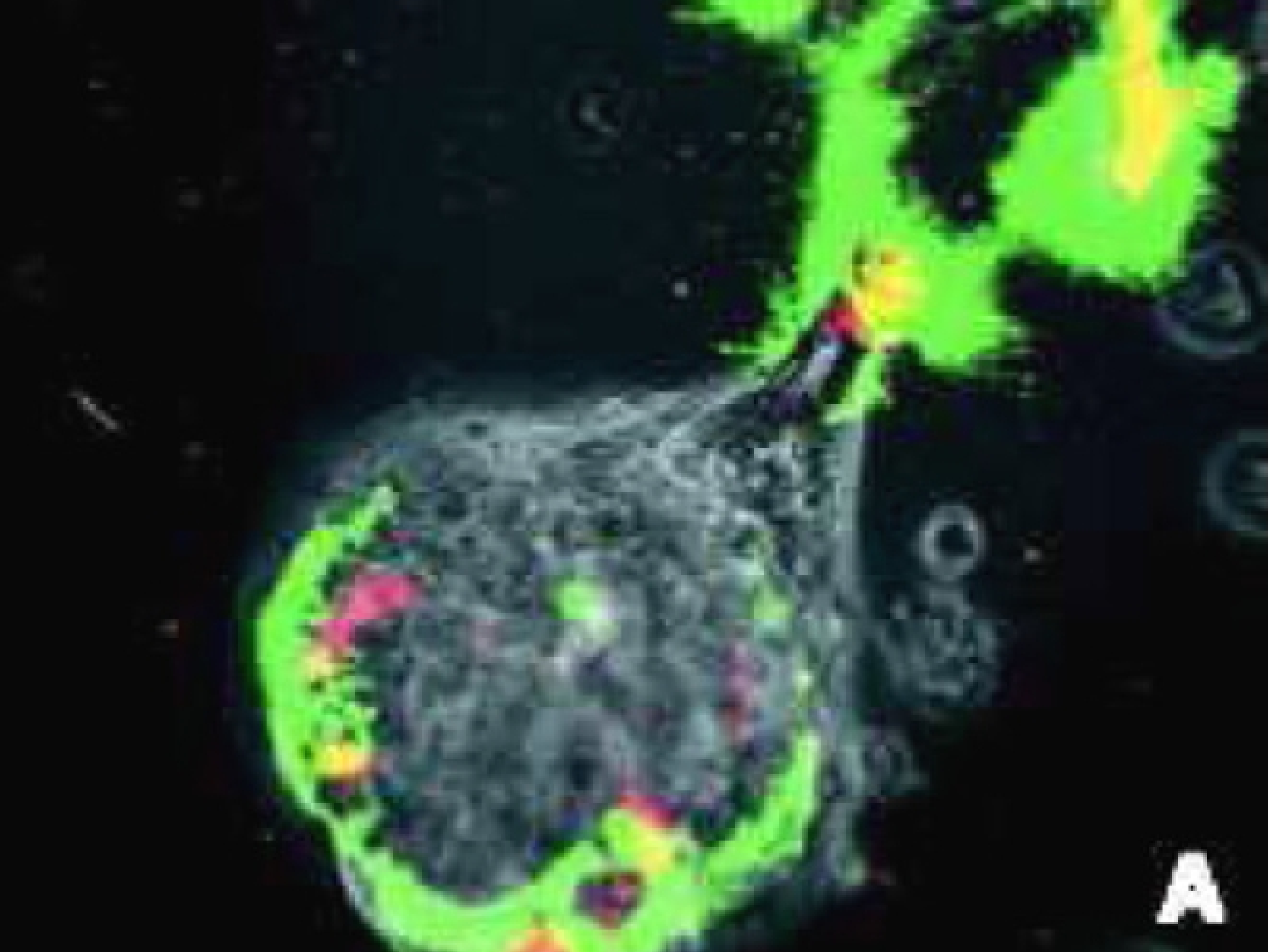
$$\frac{\partial N_1}{\partial t} = r_1 N_1 (1 - \frac{N_1}{K_1}) - d_1 L N_1$$

$$\frac{\partial N_2}{\partial t} = r_2 N_2 (1 - \frac{N_2}{K_2}) + \nabla_x \cdot \left[D_2 (1 - \frac{N_1}{K_1})(1 - \frac{N_3}{K_3}) \nabla_x N_2 \right]$$

$$\frac{\partial L}{\partial t} = r_3 N_2 - d_3 L + D_3 \nabla_x^2 L$$

$$\frac{\partial N_3}{\partial t} = -d_4 A N_3$$

$$\frac{\partial A}{\partial t} = r_5 N_1 N_2 - d_5 A + D_5 \nabla_x^2 A$$


A

Nondimensionalization

$$\eta_1 = N_1/K_1, \qquad \eta_2 = N_2/K_2, \qquad \eta_3 = N_3/K_3,$$

$$\Lambda = (d_3/r_3K_2)L, \qquad \xi = \sqrt{r_1/D_3}x, \qquad \Gamma = (d_4/r_1)A,$$

$$\tau = r_1 t.$$

New parameters: $\gamma_1 = d_1r_3K_2/d_3r_1,$

$$\delta_2 = r_2/r_1, \qquad \alpha_2 = D_2/D_3, \qquad \delta_3 = d_3/r_1,$$

$$\delta_5 = r_5K_1d_4/r_1^2, \qquad \gamma_5 = d_5/r_1, \qquad \alpha_5 = D_5/D_3.$$

Rescaled Model

$$\frac{\partial \eta_1}{\partial \tau} = \eta_1(1-\eta_1) - \gamma_1 \Lambda \eta_1$$

$$\frac{\partial \eta_2}{\partial \tau} = \delta_2 \eta_2 (1-\eta_2) + \nabla_\xi \cdot [\alpha_2 (1-\eta_1)(1-\eta_3) \nabla_\xi \eta_2]$$

$$\frac{\partial \Lambda}{\partial \tau} = \delta_3(\eta_2 - \Lambda) + \nabla_\xi^2 \Lambda$$

$$\frac{\partial \eta_3}{\partial \tau} = -\Gamma \eta_3$$

$$\frac{\partial \Gamma}{\partial \tau} = \delta_5 \eta_1 \eta_2 - \gamma_5 \Gamma + \alpha_5 \nabla_\xi^2 \Gamma$$

Steady States

1. $(\tilde{\eta}_{1,1}, \tilde{\eta}_{2,1}, \tilde{\Lambda}_1, \tilde{\eta}_{3,1}, \tilde{\Gamma}_1) = (0, 0, 0, \eta_3(0), 0)$

2. $(\tilde{\eta}_{1,2}, \tilde{\eta}_{2,2}, \tilde{\Lambda}_2, \tilde{\eta}_{3,2}, \tilde{\Gamma}_2) = (1, 0, 0, \eta_3(0), 0)$

3. $(\tilde{\eta}_{1,1}, \tilde{\eta}_{2,3}, \tilde{\Lambda}_3, \tilde{\eta}_{3,3}, \tilde{\Gamma}_3) = (1 - \gamma_1, 1, 1, 0, \delta_5(1 - \gamma_1)/\gamma_5)$

4. $(\tilde{\eta}_{1,1}, \tilde{\eta}_{2,4}, \tilde{\Lambda}_4, \tilde{\eta}_{3,4}, \tilde{\Gamma}_4) = (0, 1, 1, \eta_3(0), 0)$

Initial Conditions

$$\eta_1(0) = \begin{cases} 0.01 & \text{if } 0 \le \xi < 0.04 \\ 1 & \text{if } \xi \ge 0.04 \end{cases}$$

$$\eta_2(0) = \begin{cases} 1 & \text{if } 0 \le \xi < 0.04 \\ 0 & \text{if } \xi \ge 0.04 \end{cases}$$

$$\Lambda(0) = 0$$

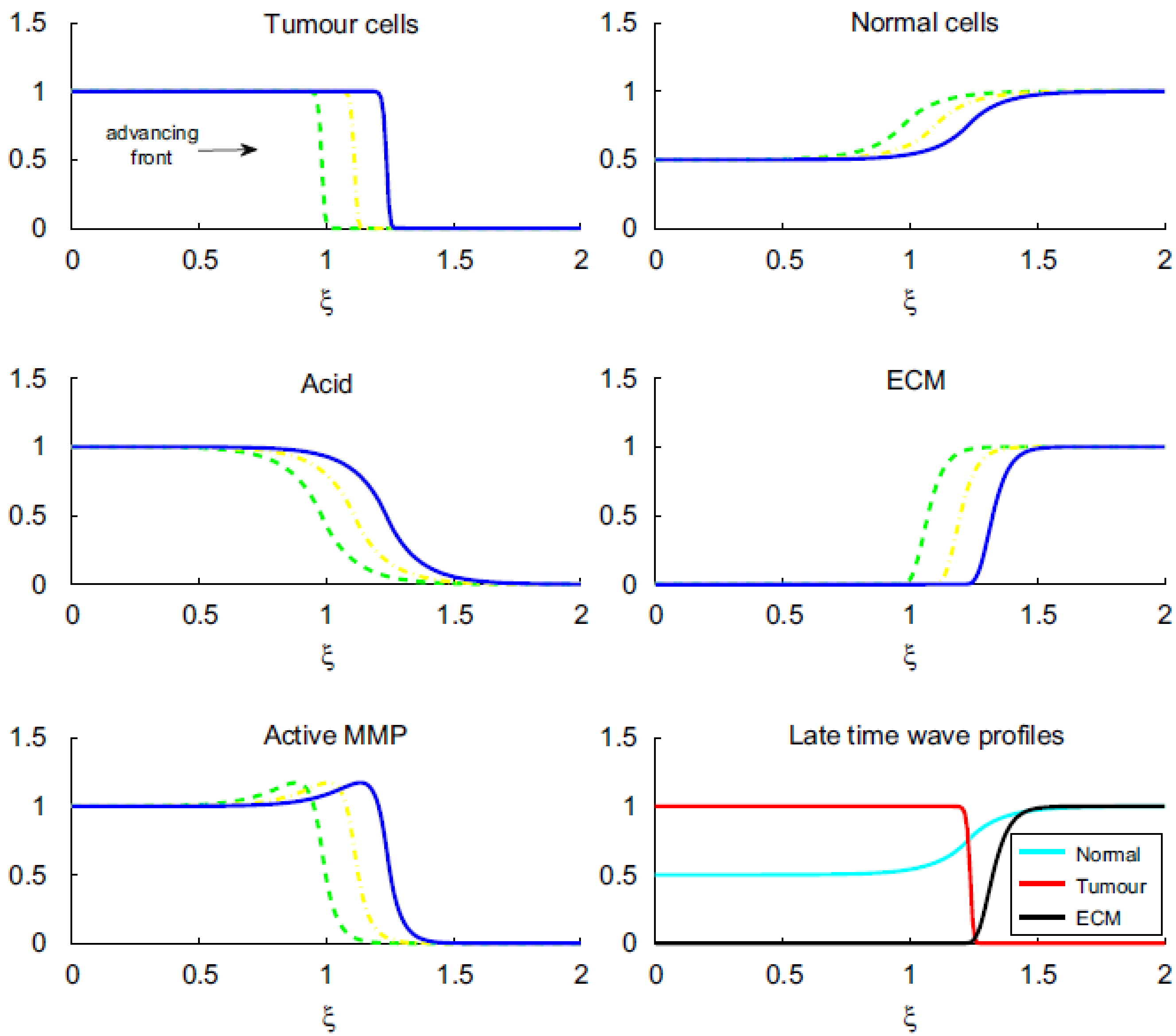
$$\eta_3(0) = 1$$

$$\Gamma(0) = 0.$$

Simulation Parameters

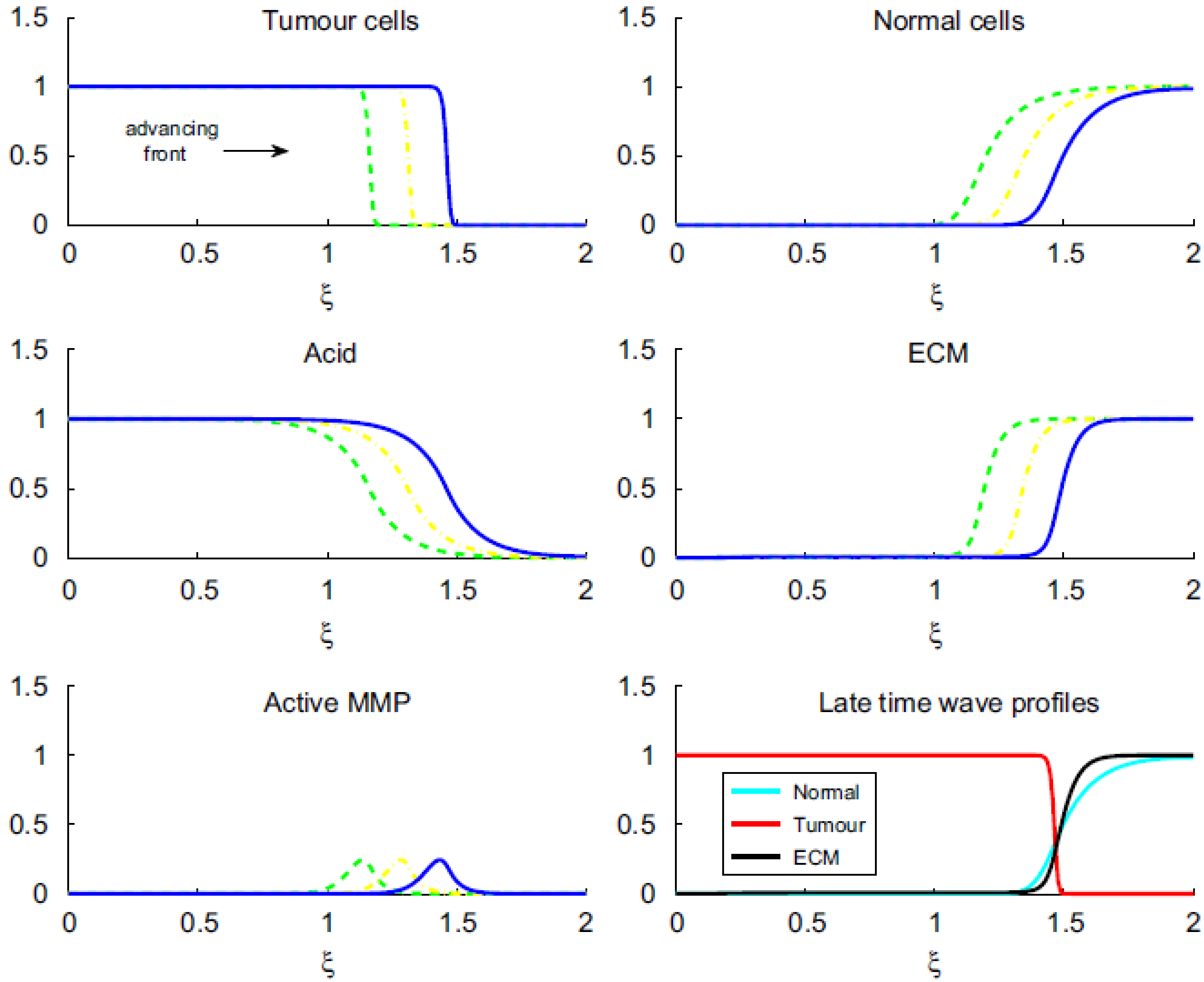
Parameter	Definition	Value
γ_1	$\frac{d_1 r_3 K_2}{d_3 r_1}$	1-100
δ_2	r_2/r_1	1
α_2	D_2/D_3	$4 \cdot 10^{-5}$
δ_3	d_3/r_1	70
δ_5	$\frac{r_5 K_1 K_2 d_4}{r_1^2}$	100
γ_5	d_5/r_1	50
α_5	D_5/D_3	0.1

$$\gamma_1 = 0.5$$



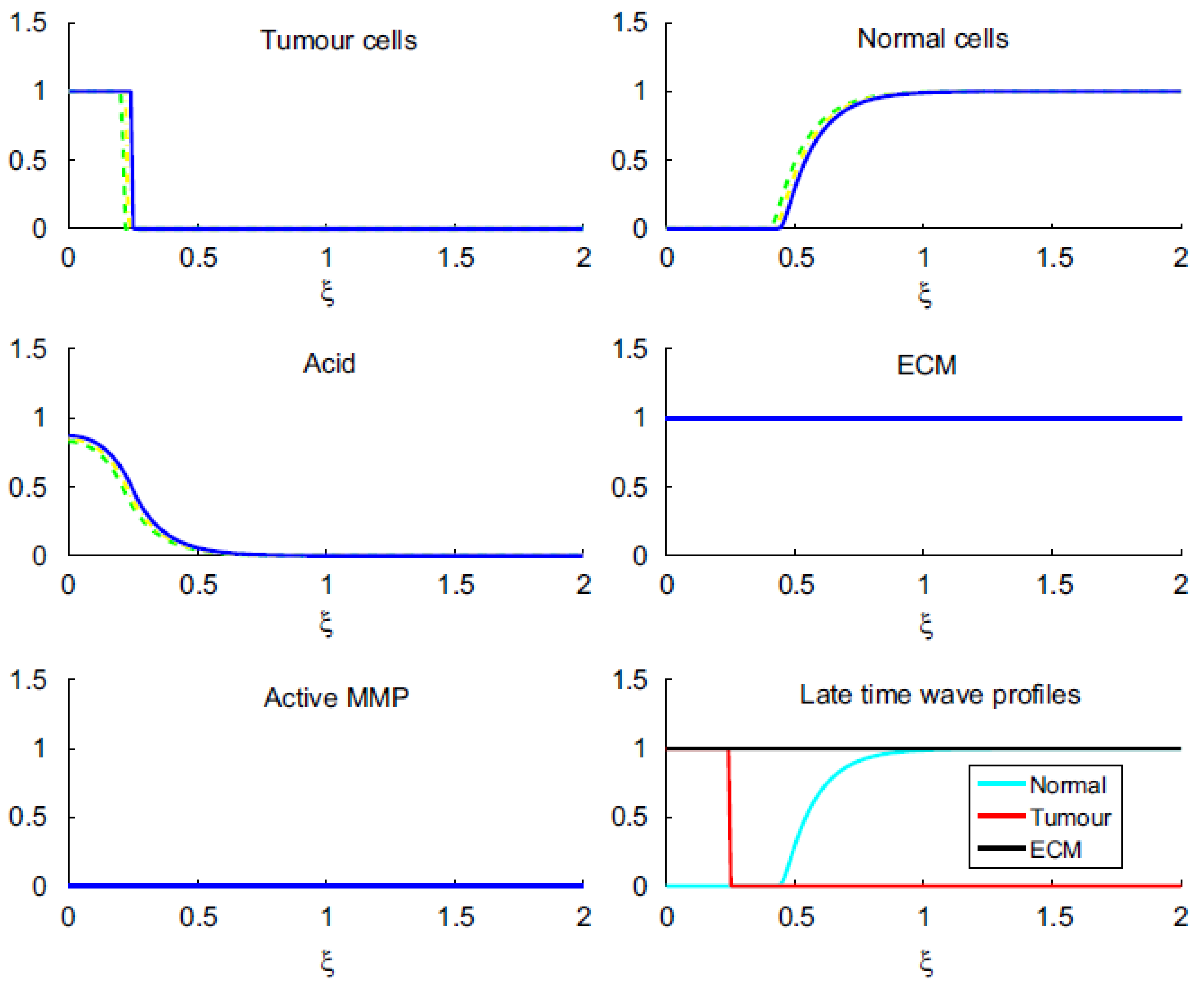
Tumour cells
advancing front
Normal cells
Acid
ECM
Active MMP
Late time wave profiles
Normal
Tumour
ECM
ξ

$$\gamma_1 = 1.5$$



Tumour cells
advancing front
Normal cells
Acid
ECM
Active MMP
Late time wave profiles
Normal
Tumour
ECM
ξ
0
0.5
1
1.5
2

$$\gamma_1 = 12.5$$



Tumour cells
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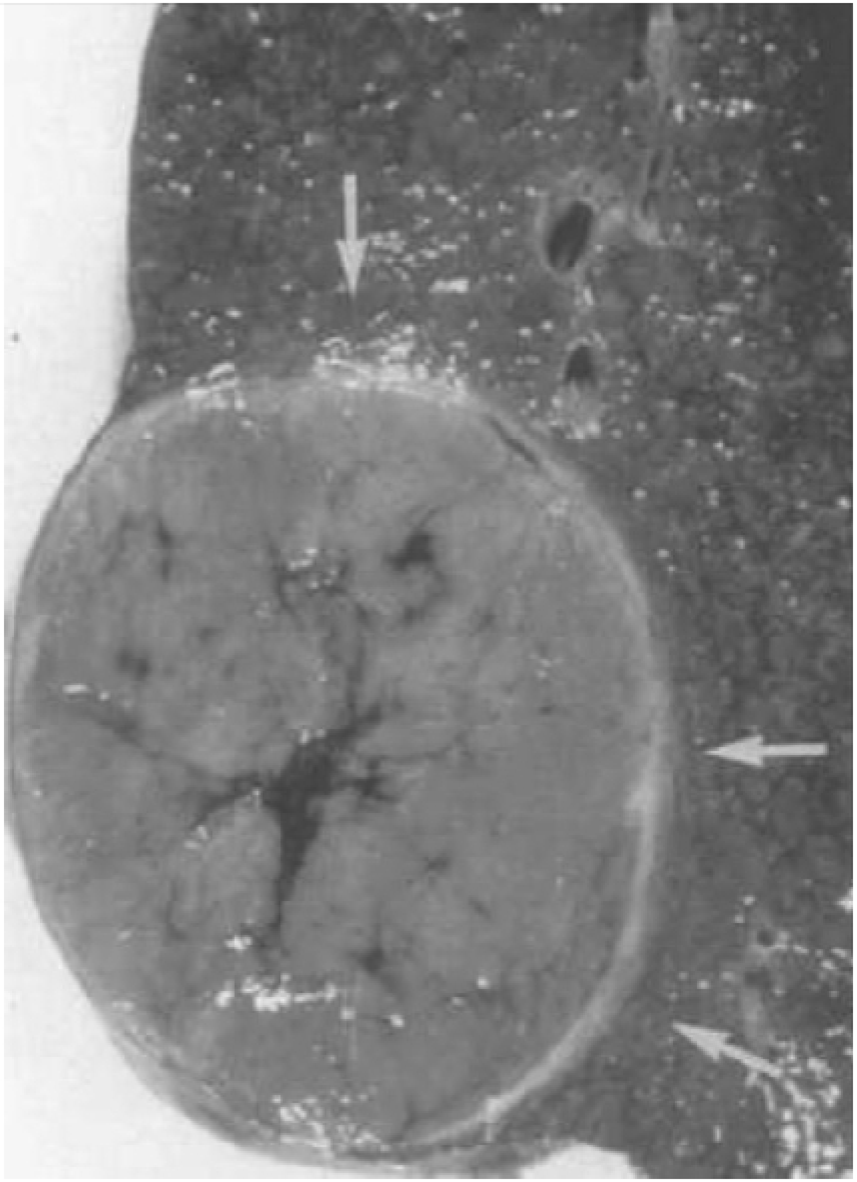
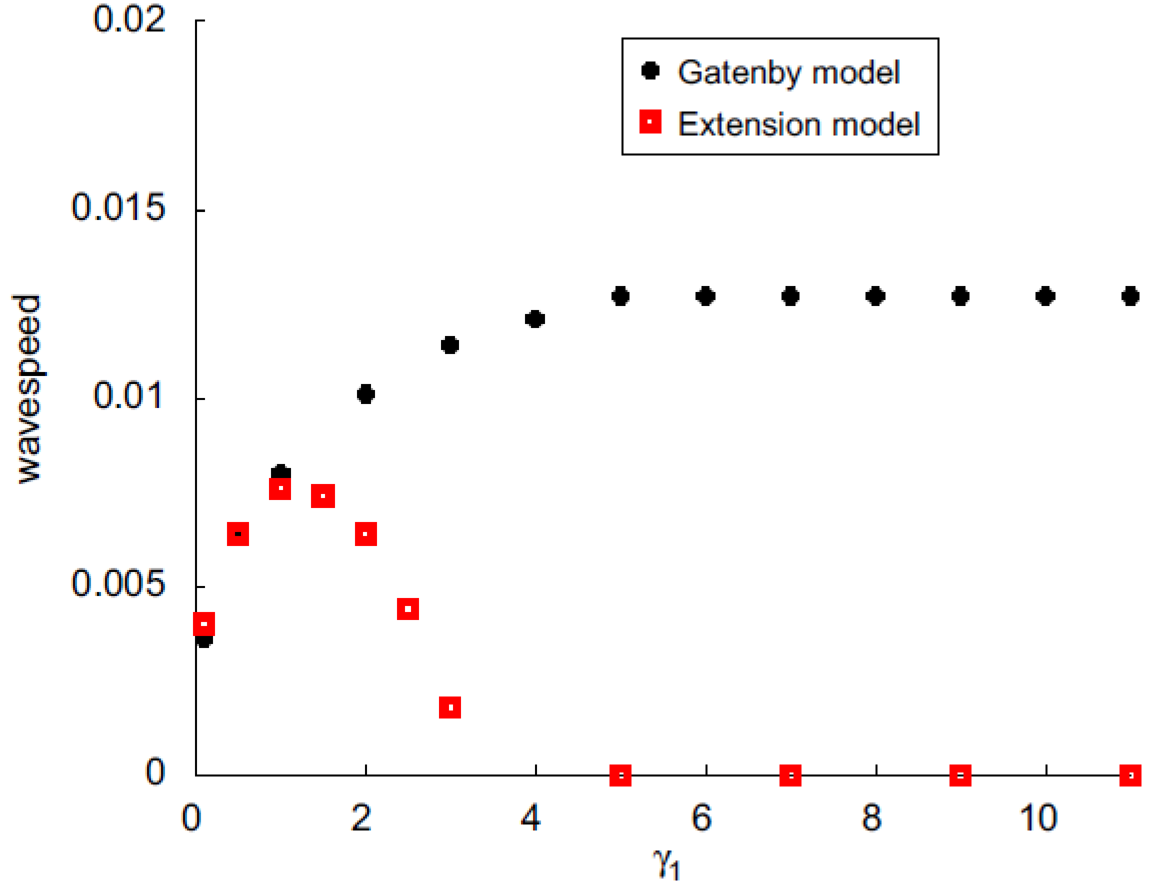
2





0.02
0.015
0.01
0.005
0
wavespeed
Gatenby model
Extension model
0
2
4
6
8
10
γ1

Conclusion

- Incorporating the production of proteases and the degradation of the extracellular matrix into the model qualitatively alters tumor invasion dynamics.
- Invasion speed is slow for both small and large values of the tumor acid aggression parameter.
- Large values of the acid aggression parameter allow for encapsulated