Modelling Solid Tumour Growth
Lecture 4: Angiogenesis Models

Helen Byrne

helen.byrne@nottingham.ac.uk

Centre for Mathematical Medicine, University of Nottingham

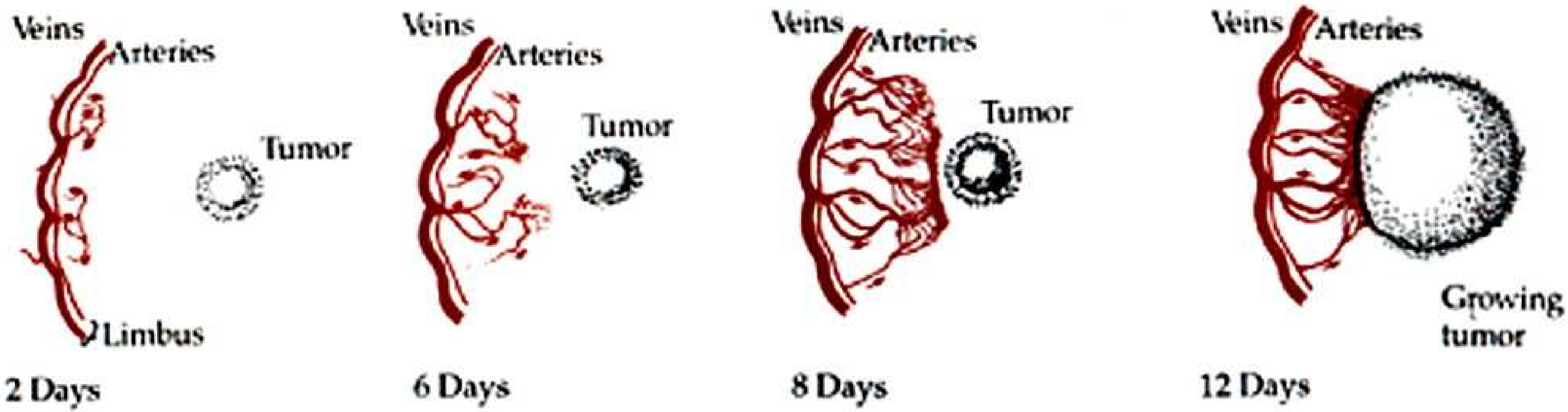
Outline

- Background Biology
- Deterministic (PDE) models
- Non-deterministic Models
- Discussion

References

- Balding and McElwain (1985) *J. theor. Biol.* **114**: 53-73
- Byrne and Chaplain (1995) *Bull. Math. Biol.* **57**: 461-486
- Anderson and Chaplain (1998) *Bull. Math. Biol* **60**:857-899
- T. Alarcon, H.M. Byrne and P.K. Maini (2003) *J. theor. Biol* **225**: 257-274

Background Biology: Angiogenesis



Schematic diagram of angiogenesis

Background Biology

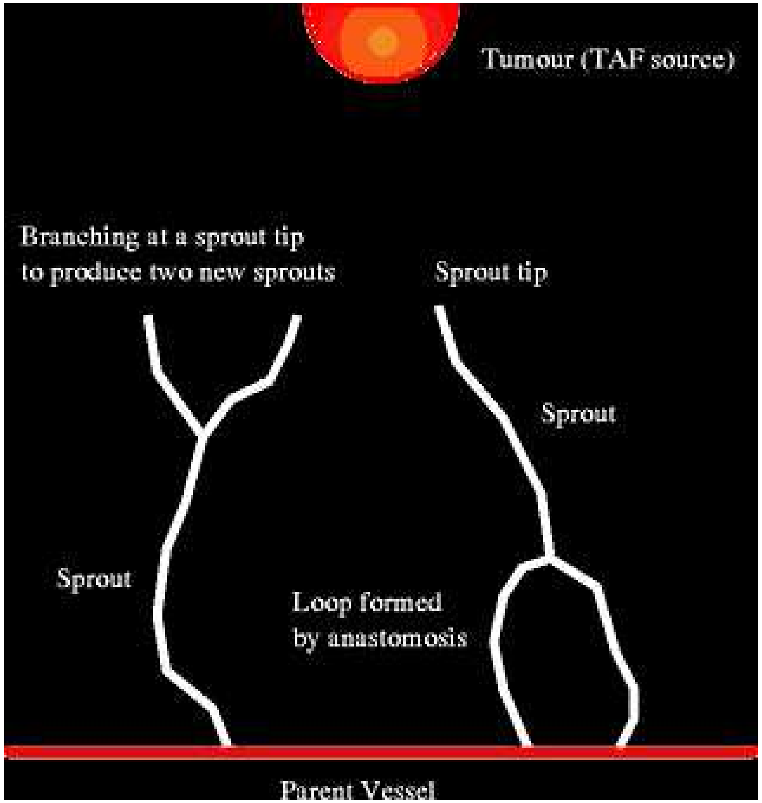
Description of Angiogenesis

- Acquisition of host blood supply
- Capillary growth rate $\sim$ 0.2 - 0.6mm per day
- Duration $\sim$ weeks
- Rapid vascular growth and metastasis ensue

Modelling Aims

- Reproduce qualitative features of angiogenesis
- Characterise extend of angiogenesis in terms of system parameters
- Highlight relative importance of physical processes

Background Biology: Angiogenesis



Schematic diagram of angiogenesis

Model Development

- Dependent Variables
  - Tumour-derived chemoattractant, $c(x,t)$
  - Capillary tip density, $n(x,t)$
  - Blood vessel density, $b(x,t)$

- Conservation Laws $\Rightarrow$ model equations

$$\frac{\partial}{\partial t}(\text{tips}) = \text{flux of tips} + \text{sources} - \text{sinks}$$

flux of tips = random motility + chemotaxis

Dimensionless Model Equations

$x \equiv 0 \Leftrightarrow$ tumour $\qquad x \equiv 1 \Leftrightarrow$ limbus

- TAF Concentration

$$\frac{\partial c}{\partial t} = \frac{\partial^2 c}{\partial x^2} - \lambda c$$

- Capillary Tip Density

$$\frac{\partial n}{\partial t} = -\frac{\partial J}{\partial x} + \sigma$$

where $J = -\mu \frac{\partial n}{\partial x} + \chi n \frac{\partial c}{\partial x}$ and $\sigma = \underbrace{\alpha_0 cb + \alpha_1 H(c - \hat{c})nc}_{\text{tip formation}} - \underbrace{\beta nb}_{\text{tip loss}}$

- Vessel Density

$$\frac{\partial b}{\partial t} = -J - \gamma b = \mu \frac{\partial n}{\partial x} - \chi n \frac{\partial c}{\partial x} - \gamma b$$

1D Numerical Results

- Successful angiogenesis
- Failed angiogenesis

1D Caricature Model

- Adopt quasi-steady approx for c and b

$$\frac{\partial c}{\partial t} = 0 = \frac{\partial b}{\partial t} \quad \Rightarrow c = c_0 \sinh \sqrt{\lambda}(1-x), \quad b = -\frac{\chi}{\gamma} n \frac{dc}{dx}$$

- Neglect random motion ($\mu = 0$)

$$\frac{\partial n}{\partial t} - \chi \frac{\partial c}{\partial x}\frac{\partial n}{\partial x} = n\left(-\chi \frac{d^2 c}{dx^2} + \alpha_1 c H(c - \hat{c}) + \frac{\beta\chi}{\gamma} n \frac{dc}{dx}\right)$$

- Example: $\lambda \ll 1$

$$c \sim 1 - x \quad \text{and} \quad b = \frac{\chi}{\gamma} n$$

$$\frac{\partial n}{\partial t} + \chi \frac{\partial n}{\partial x} = n\left(\alpha_1 (1-x) H(1 - x - \hat{c}) - \frac{\beta\chi}{\gamma} n\right)$$

- Method of Characteristics ...

Analytical Results

- Acceleration of vascular front
- Brush-border effect
- Max tips density precedes max vessel density
- Bounds on n when vascular front reaches tumour
- Criteria for successful angiogenesis

e.g., with $\alpha_0 = 0$, angiogenesis fails if

$$\exp\left\{\frac{\alpha_1}{2\chi}(1-\hat{c}^2)\right\} < 1 + \frac{\beta x^*}{\gamma}$$

where $x^* \in (0,1)$ denotes initial support of vessels

Alternative Approaches

- 2D PDE models – see OHPs
- Discrete models – see OHPs

Model Extensions

- Distinguish between anastomosis and tip death
- Changes in vascular network eg branch thickening
- Distinguish different angiogenic factors

Conclusions

PDE Models

- Good qualitative agreement with experiments
- Predict conditions under which angiogenesis occurs
- Caricature model $\Rightarrow$ analytical solutions
- Extension to 2D demonstrated

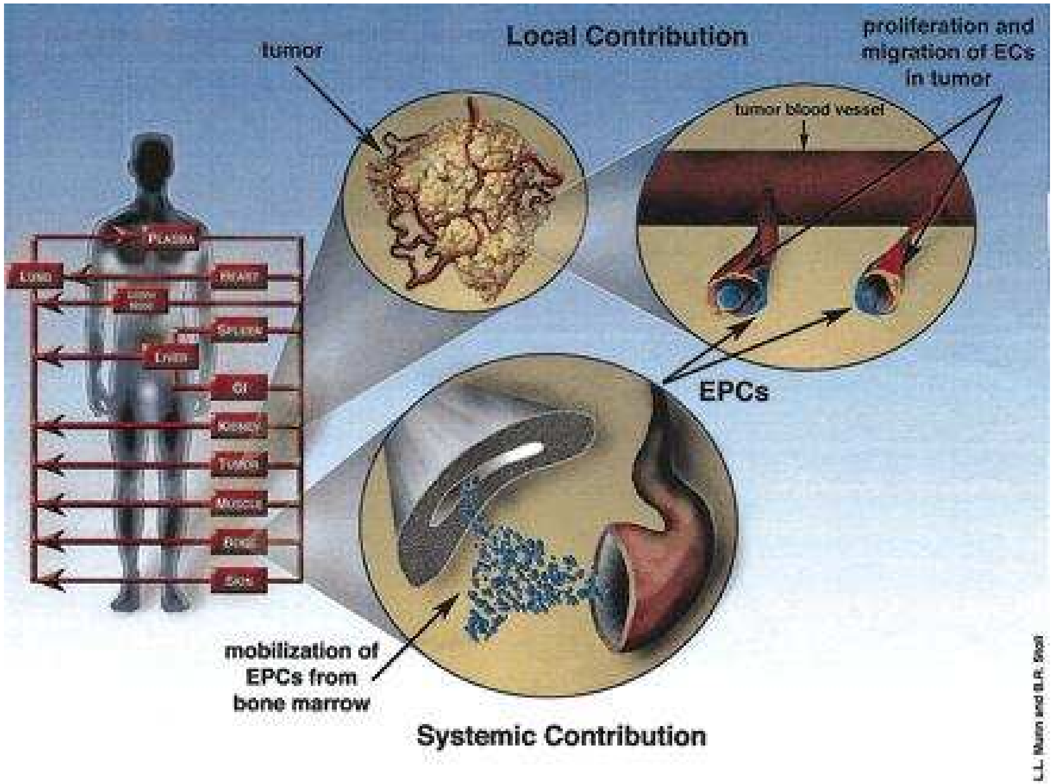
Stochastic Models

- Excellent qualitative agreement with experiments
- Simple to extend to 2D and 3D
- Difficult to obtain analytical insight

Angiogenesis: Future/Ongoing Work

- Mechanisms for anastomosis and branching
- Formation of circulating blood flow
- Growth of blood vessels into tumour $\Rightarrow$ VASCULAR TUMOUR GROWTH
- Anti-angiogenic strategies (McDougall et al)
- Interactions with the extracellular matrix (Levine, Sleeman et al)
- Remodelling of blood vessels (Alarcon et al)
- Interactions with tumour cells - nutrient/oxygen delivery by blood vessels (Alarcon et al)

Angiogenesis: Future/Ongoing Work



Effective anti-angiogenic therapies will need to account for recruitment of EC stem cells to tumour sites.