Modelling Solid Tumour Growth
Lecture 4: Angiogenesis Models

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Prevalance of Angiogenesis

Angiogenesis as pathology

Diabetic retinopathy can cause blindness

Tumour angiogenesis step in tumour progression

It is estimated that by 2006, the market for all products that play a role in angiogenesis is likely to reach $1.75 billion.
Impact of Tumour Angiogenesis

Small tumour (1-2 mm)
- avascular
- dormant

Larger tumour
- vascular
- metastatic potential

Angiogenic switch
Results in overexpression of pro-angiogenic signals, such as VEGF
Outline

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

References

Background Biology: Angiogenesis

Schematic diagram of angiogenesis
Background Biology

Description of Angiogenesis

- Acquisition of host blood supply
- Capillary growth rate $\sim 0.2 - 0.6$ mm 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

\[ x \equiv 0 \Leftrightarrow \text{tumour} \quad x \equiv 1 \Leftrightarrow \text{limbus} \]

- **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 \( \sigma = \alpha_0 cb + \alpha_1 H(c - \hat{c})nc - \beta nb \)

- **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 $b$

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

- 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 ... (exercise sheet 4) ...
**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

\[ e.g., \text{with } \alpha_0 = 0, \text{angiogenesis fails if } \exp \left\{ \frac{\alpha_1}{2\chi} (1 - \varepsilon^2) \right\} < 1 + \frac{\beta x^*}{\gamma} \]

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

- **Note:** supporting examples in exercise sheet 4
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 ⇒ 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

Immunotherapy for Treating Cancer

- This group project relates to some of the work covered in this lecture i.e. using chemotaxis to direct engineered macrophages to tumour regions that are difficult to treat with standard therapies
- More details in tomorrow’s lecture!
Angiogenesis: Future/Ongoing Work

- Mechanisms for anastomosis and branching
- Formation of circulating blood flow
- Growth of blood vessels into tumour ⇒ 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)
Effective anti-angiogenic therapies will need to account for recruitment of EC stem cells to tumour sites.