

Modelling Solid Tumour Growth

Lecture 4: Angiogenesis Models

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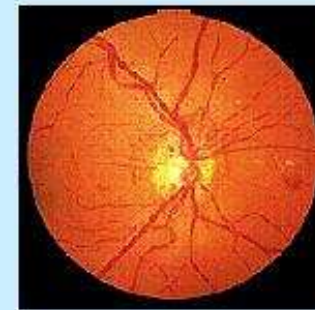
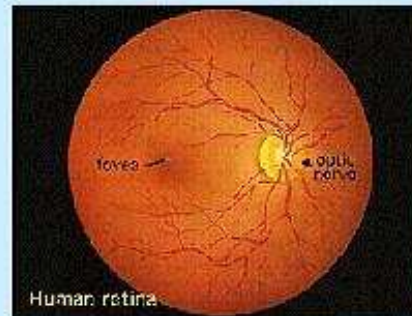
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Prevalance of Angiogenesis



Angiogenesis as pathology

Diabetic retinopathy
can cause blindness

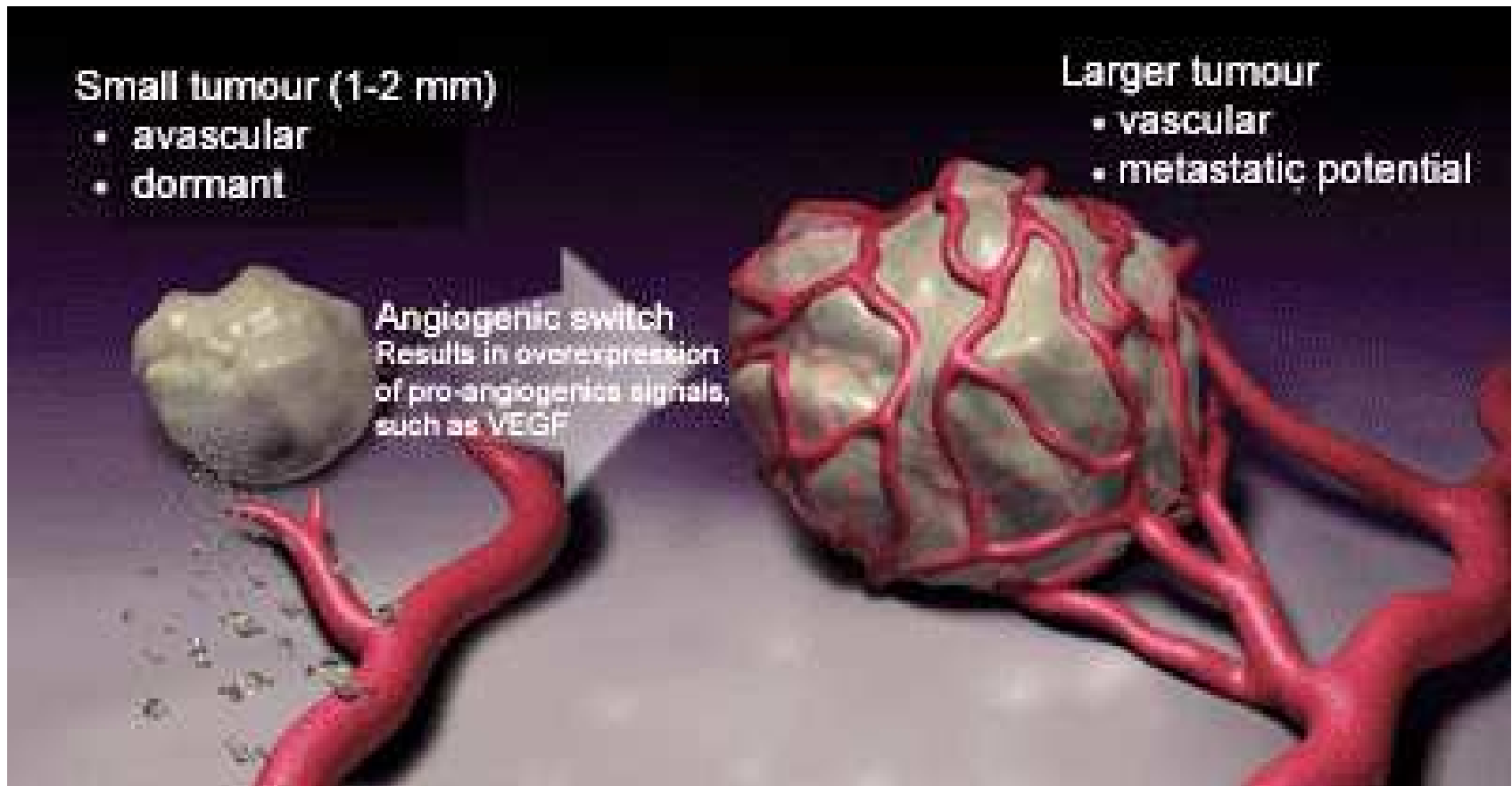


Tumour angiogenesis
step in
tumour progression



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



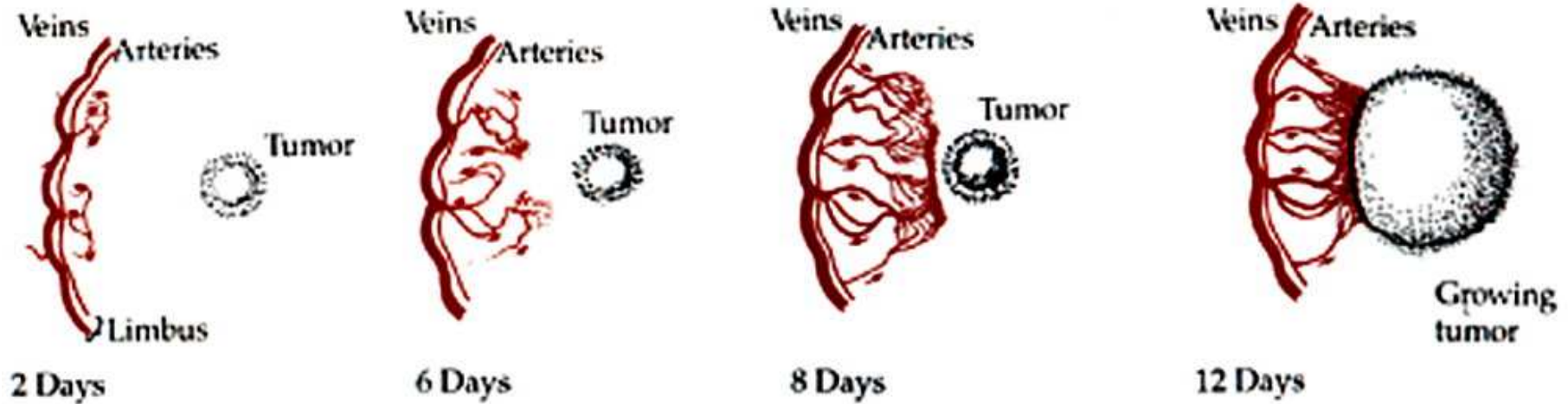
Outline

- 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

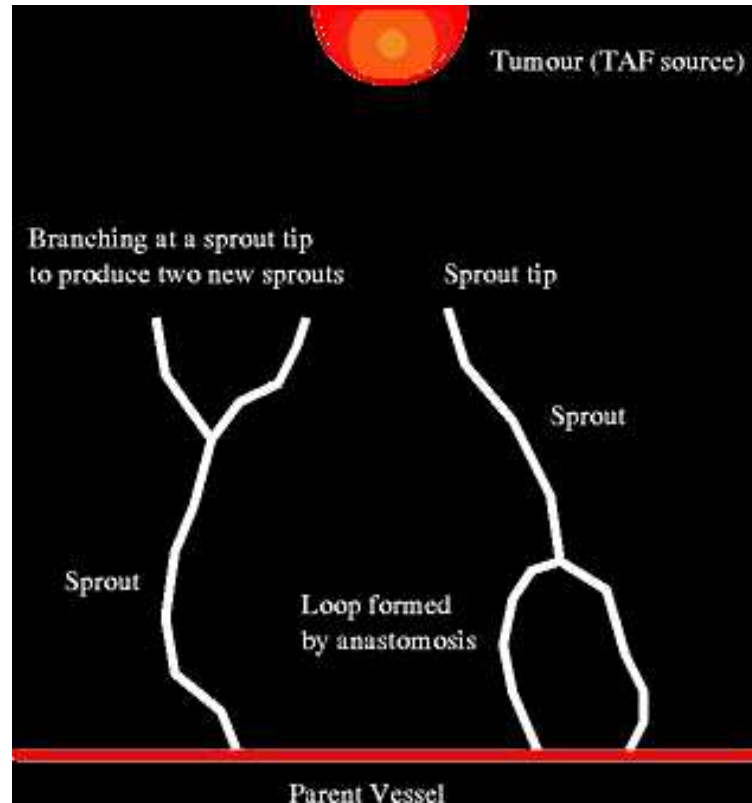
Description of Angiogenesis

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

Modelling Aims

- Reproduce qualitative features of angiogenesis
- Characterise extent 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

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

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

- 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

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

- 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., 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

- **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 \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

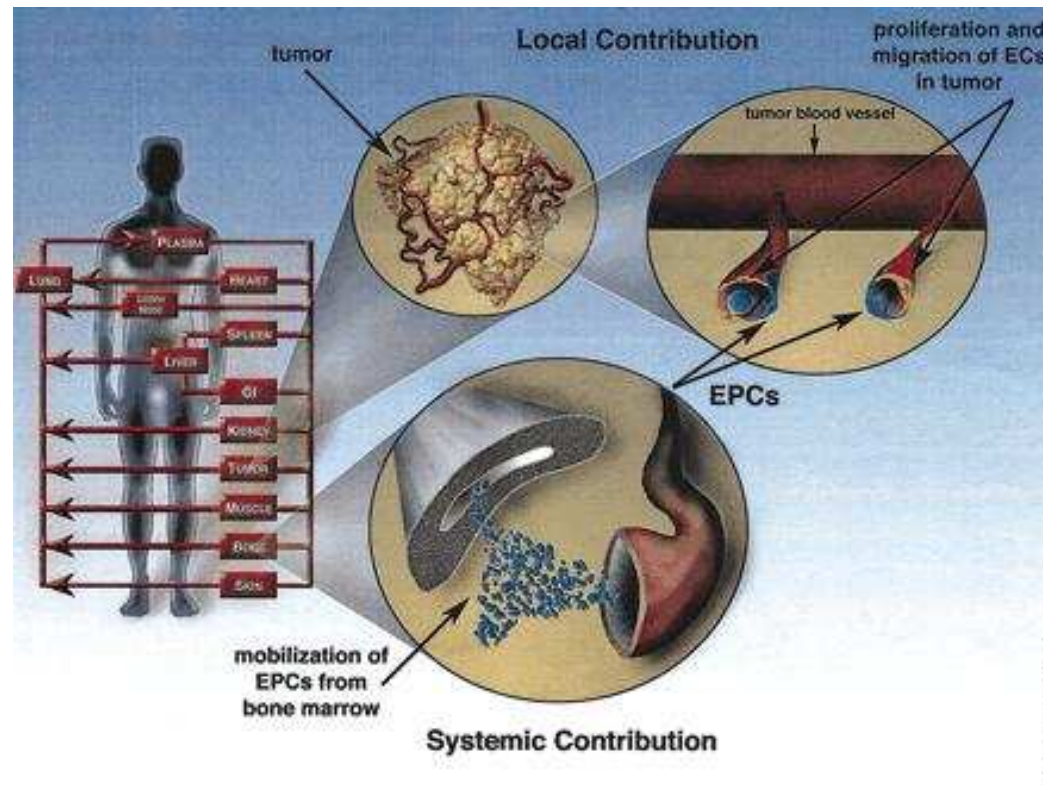
Immunotherapy for Treating Cancer

- 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)

Angiogenesis: Future/Ongoing Work



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