Cell-Based Models of Tumour Angiogenesis

Michael John Plank

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Department of Applied Mathematics.

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Abstract

It is now accepted that a tumour must induce the growth of new blood vessels, a process called angiogenesis, in order to grow beyond a diameter of approximately 2 mm. Knowledge of angiogenesis has increased massively over the last 30 years, enabling mathematical models of the process to be constructed and analysed. Initially, modelling was done at the continuum (i.e. cell density) level but, more recently, the appreciation that angiogenesis is an inherently discrete process has led to increasing research using individual cell-based models.

In this thesis, tumour angiogenesis is modelled at the individual cell level, using techniques based on the theory of reinforced random walks, and cell-based simulations are carried out. The purpose of this work is to develop the modelling techniques, to improve understanding of angiogenesis and to highlight potential strategies for therapeutic intervention.

Chapters 1 and 2 contain an introduction to the relevant biological and mathematical literature respectively. In chapter 3, the theory of reinforced random walks is introduced. A result regarding the large time behaviour of one of the key governing equations is proved and a generalisation of the basic random walk model is presented, allowing a wider range of biological scenarios to be modelled.

In chapter 4, the basic model for cell movement is developed in close conjunction with experimental data. Chemokinesis, chemotaxis, haptotaxis are included and their relative contributions to cell movement discussed. In chapter 5, a model of tumour angiogenesis is formulated and used to simulate the growth of capillary networks. The model is also used to assess the potential of anti-angiogenic strategies. Chapter 6 develops a new model that includes the role of the angiopoietins, a recently discovered family of growth factors which have emerged as critical regulators of angiogenesis. In chapter 7, a model that frees the cells from geometric constraints (a non-lattice model) is developed, and critically compared to existing lattice-based models.

The material in chapters 4 and 5 has been accepted for publication [126, 127].

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List of Abbreviations

AMP	Adenosine monophosphate
Ang	Angiopoietin
bFGF	Basic fibroblast growth factor
Da	Dalton (unit of molecular weight)
DNA	Deoxyribonucleic acid
EC	Endothelial cell(s)
ECM	Extracellular matrix
M	Molar (1 mol/l)
MMP	Matrix metalloprotease
mRNA	Messenger ribonucleic acid
ODE	Ordinary differential equation
PA	Plasminogen activator
PAI	Plasminogen activator inhibitor
PDE	Partial differential equation
PDGF	Platelet-derived growth factor
TAF	Tumour angiogenesis factor
TGF	Transforming growth factor
TIMP	Tissue inhibitor of metalloproteases
VEGF	Vascular endothelial growth factor

Notation

$\mathbb{Z}$, $\mathbb{R}$ and $\mathbb{C}$ respectively denote the sets of integer, real and complex numbers. For $N \in \mathbb{Z}$, $\mathbb{R}^N$ denotes the N-dimensional set $\{(x_1, \ldots, x_N) : x_i \in \mathbb{R}, i = 1, \ldots, N\}$.

For $a, b \in \mathbb{R}$, $[a, b) \subseteq \mathbb{R}$ is used to denote the interval of the real line, $\{x \in \mathbb{R} : a \leq x < b\}$. The only possible ambiguity is (a, b), which is also used to denote a member of $\mathbb{R}^2$, but the intended meaning will always be made clear from the context.

For two sets, A and B, $A \times B$ denotes the set of pairs of elements of A and B, $\{(a, b) : a \in A, b \in B\}$. For $m \in \mathbb{R}$, $A^{\geq m}$ denotes the set $\{a \in A : a \geq m\}$. $f : A \to B$ denotes a function with domain A and range B.

For $\Omega \subset \mathbb{R}^N$, the boundary of Ω is denoted by $\partial\Omega$, the set of $x \in \mathbb{R}^N$ satisfying: (i) $\exists x_1, x_2, \ldots \in \Omega$ such that $\lim_{n\to\infty} x_n = x$; (ii) $\forall \epsilon > 0, \exists y \notin \Omega$ such that $|x - y| < \epsilon$.

For $n \in \mathbb{Z}$ and $A \subseteq \mathbb{C}$, $C^n(A)$ is used to denote the set of n times continuously differentiable functions, $f : A \to \mathbb{C}$. Unless stated otherwise, the symbol $'$ denotes differentiation of a function $f : A \to \mathbb{C}$ with respect to its argument.

The gradient operator is denoted by $\nabla = \left(\frac{\partial}{\partial x}, \frac{\partial}{\partial y}, \frac{\partial}{\partial z}\right)$; the divergence of a vector field, $F : \mathbb{R}^3 \to \mathbb{R}^3$, is denoted by $\nabla.F$; the Laplacian operator is denoted by $\nabla^2 \equiv \nabla.\nabla$.

For $n \in \mathbb{Z}$, $J_n : \mathbb{C} \to \mathbb{C}$ and $I_n : \mathbb{C} \to \mathbb{C}$ respectively represent the Bessel function and the modified Bessel function of the first kind and n^{th} order.

For $N \in \mathbb{Z}^{>0}$, $I^{[N]}$ denotes the $N \times N$ identity matrix, defined by $I^{[N]}_{ij} = \left\{ \begin{array}{ll} 1, & i = j \\ 0, & i \neq j \end{array} \right\}$ for $i, j = 1, \ldots, N$.

$\delta : \mathbb{R} \to \mathbb{R}$ denotes the Dirac delta function, defined by $\delta(x) = 0$ for $x \neq 0$ and $\int_{-\infty}^{\infty} \delta(x) f(x)\, dx = f(0)$ for any function $f \in C^0(\mathbb{R})$. $H : \mathbb{R} \to \mathbb{R}$ denotes the Heaviside step function, defined by $H' = \delta$ and $H(x) = 1$ for $x > 0$.

$P(\cdot) \in [0, 1]$ is the standard probability measure function and $P(A|B)$ denotes the conditional probability of A occurring given that B has occurred. $E(X)$ and $\mathrm{Var}(X)$ respectively denote the expected value and the variance of the random variable, X.