The Transport of Specific Monoclonal Antibodies in Tumour Cords

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1 Introduction

Blood flow in tumour vasculature carries oxygen and nutrients necessary for cell life and proliferation, and allows delivery of therapeutic agents within the tumour. To reach their target cells, these agents must extravasate and be transported by diffusion and by the convection associated to the movement of extracellular fluid. Convective transport may become important for therapeutic agents with large molecular weight or size, such as the monoclonal antibodies or the viruses used as vectors in gene therapy [11]. The high interstitial fluid pressure, exhibited by most solid tumors, is thought to be a barrier for fluid extravasation and efficient convective transport.

Monoclonal antibodies, able to bind specifically to antigens located on tumour cell membrane, have been proposed for cancer therapy, either because of their possible direct cytotoxicity or because antibodies can be conjugated to radionuclides or toxins [2]. A mathematical model that describes the transport of monoclonal antibodies by diffusion and convection in spherical tumors, under the assumption of a continuous distribution of fluid and solute sources in the tumor mass, was proposed in [1]. Fujimori et al. [9], studied the transport of antibodies in a cylinder of tumour tissue around a central blood vessel. In that paper, convection was modelled in a very simplified way, but the binding of antibodies to cell membrane antigen was taken into account.

In the present work, we analyse the transport of antibodies within a cylindrical arrangement of tumour cells around a blood vessel and surrounded by necrosis (tumour cord, see [13, 10, 12]). We describe in more detail the diffusive and convective transport and the binding of bivalent (IgG) antibodies to

cell membrane molecules. For the fluid motion and the interstitial pressure, we use the model previously proposed [5, 6], with some refinements in the description of the necrotic region.

2 The Mathematical Model of Tumour Cords

In this section we summarize the tumor cord model proposed in [5, 6], and give an refined description of the necrotic region. We consider an ideal regular array of parallel and identical tumor cords inside the tumor mass (a geometry similar to the Krogh model of microcirculation), each cord being separated from others by a region of necrosis. We assume cylindrical symmetry around the axis of the central blood vessel, the radial coordinate r varying between the radius r_0 of the vessel and the outer boundary B of the necrotic region that surrounds each cord. The radius of the interface between cord and necrosis is denoted by ρ_N. Because of the radial symmetry of the system of cords, no exchange of matter occurs through the boundary $r = B$. This boundary is mobile since blood vessels are assumed to be displaced as the tumor mass is growing or regressing. The axial coordinate z will range in the interval $[-H, H]$. All the quantities involved depend at most on r, z, and the time t. Only one species of nutrient is considered, and we identify this critical nutrient with oxygen, denoting by σ its local concentration.

2.1 The Cord

In the general case of treated tumours, three components are present in the cord : 1) viable cells, which are subdivided into proliferating (P) and quiescent cells (Q); 2) dead (apoptotic) cells produced by treatment; 3) extracellular fluids that fill the interstitial space. We will denote the fractions of volume occupied locally by these components by ν_P, ν_Q, ν_A, and ν_E, respectively. Supposing no voids, we have

$$\nu_P + \nu_Q + \nu_A + \nu_E = 1\,.$$

As in [3, 4], it is assumed that (i) the volume fraction of extracellular fluid in the cord is constant; (ii) dead cells move at the same velocity as living cells; (iii) cell velocity is radial; (iv) σ, ν_P, ν_Q, ν_A, and the velocity $\mathbf{u}$ of the cellular component do not depend on z; (v) all cells die if σ reaches a death threshold σ_N. In view of assumptions (iii) and (iv), we have $\mathbf{u} = (u(r,t),\, 0)$. The velocity of the fluid component is denoted by $\mathbf{v} = (v_r(r,z,t),\, v_z(r,z,t))$.

Under the assumption that all the components have the same constant mass density, the mass balance equations, for $r_0 < r < \rho_N(t)$, can be written as follows:

$$\frac{\partial \nu_P}{\partial t} + \nabla \cdot (\nu_P\, \mathbf{u}) = \chi \nu_P + \gamma(\sigma)\nu_Q - \lambda(\sigma)\nu_P - \mu_P(r,t)\nu_P\,, \qquad (1)$$

$$\frac{\partial \nu_Q}{\partial t} + \nabla \cdot (\nu_Q \, \mathbf{u}) = -\gamma(\sigma)\nu_Q + \lambda(\sigma)\nu_P - \mu_Q(r,t)\nu_Q \,, \tag{2}$$

$$\frac{\partial \nu_A}{\partial t} + \nabla \cdot (\nu_A \, \mathbf{u}) = \mu_P(r,t)\nu_P + \mu_Q(r,t)\nu_Q - \mu_A \nu_A \,, \tag{3}$$

$$\nu_E \nabla \cdot \mathbf{v} = \mu_A \nu_A - \chi \nu_P \,. \tag{4}$$

In (1)–(4), χ is the rate of volume increment due to cell proliferation; $\gamma(\sigma)$ and $\lambda(\sigma)$ are the rates of the transitions $Q \to P$ and $P \to Q$, respectively, assumed as in [8] to be regulated by the oxygen concentration; μ_P and μ_Q are death rates representing the killing effects of treatment by drugs or radiation; μ_A is the rate of volume loss due to degradation of apoptotic bodies to a liquid waste. According to the experimental evidence, the function $\lambda(\sigma)$ will be nonincreasing and $\gamma(\sigma)$ nondecreasing. In particular, we assign two threshold values for σ, $\sigma_Q < \sigma_P$, and we assume $\lambda = \lambda_{max}$ and $\gamma = \gamma_{min}$ for $\sigma \leq \sigma_Q$, $\lambda = \lambda_{min}$ and $\gamma = \gamma_{max}$ for $\sigma \geq \sigma_P$, with $\lambda_{max} > \lambda_{min} \geq 0$ and $\gamma_{max} > \gamma_{min} \geq 0$. In the interval (σ_Q, σ_P), $\lambda(\sigma)$ decreases linearly and $\gamma(\sigma)$ increases linearly.

We set $\nu^\star = \nu_P + \nu_Q + \nu_A = 1 - \nu_E$, where $\nu^\star$ is constant in view of assumption (i), and we derive the equation for the composite velocity by summing (1)–(4),

$$\nabla \cdot (\nu^\star \mathbf{u} + (1 - \nu^\star)\mathbf{v}) = 0 \,. \tag{5}$$

By summing (1)–(3), we obtain the equation for $u(r,t)$,

$$\nu^\star \frac{1}{r} \frac{\partial}{\partial r}(ru) = \chi \nu_P - \mu_A(\nu^\star - \nu_P - \nu_Q) \,. \tag{6}$$

Equation (6) is complemented by the boundary condition

$$u(r_0, t) = 0 \,.$$

This equality implies that no boundary condition is required for (1)–(3).

We assume that diffusion in a quasi-stationary regime is the dominant transport mechanism for oxygen, because of the high oxygen diffusivity [13]. Thus we have the following equation for σ:

$$\Delta\sigma = f_P(\sigma)\nu_P + f_Q(\sigma)\nu_Q \,,$$

with the boundary conditions

$$\sigma(r_0, t) = \sigma_b \,,$$

$$\left.\frac{\partial \sigma}{\partial r}\right|_{r=\rho_N(t)} = 0 \,,$$

where $f_P(\sigma)$, $f_Q(\sigma)$ denote the ratio between the consumption rate per unit volume of P and Q cells, respectively, and the diffusion coefficient. We set $f_P(\sigma) \geq f_Q(\sigma)$ and require $f_Q(\sigma_N) > 0$. At the inner boundary $r = r_0$, we

prescribe the (constant) oxygen blood concentration $\sigma_b > \sigma_P$, although a more realistic flux condition might be imposed.

To determine the interface $r = \rho_N(t)$, we recall that necrotic material cannot be converted back to live cells and that assumption (v) precludes to have live cells when σ is smaller than σ_N. Thus the following inequalities must be satisfied:

$$u(\rho_N, t) - \dot{\rho}_N \geq 0\,,$$
$$\sigma(\rho_N, t) \geq \sigma_N\,.$$

As pointed out in [5], two regimes are possible, one with $u(\rho_N, t) - \dot{\rho}_N > 0$ and the other with $u(\rho_N, t) - \dot{\rho}_N = 0$, that must satisfy the constraint

$$\big(u(\rho_N, t) - \dot{\rho}_N\big)\,\big(\sigma(\rho_N, t) - \sigma_N\big) = 0\,.$$

Switching between the two regimes is possible during the evolution of the cord that follows the treatment.

The extracellular fluid motion was described in [5, 6] by deriving an approximate equation for the longitudinal average of $v_r(r, z, t)$:

$$v(r, t) = \frac{1}{2H}\int_{-H}^{H} v_r(r, z, t)\, dz\,.$$

This was achieved by approximating the volumetric efflux of liquid from the cord ends according to

$$(1 - \nu^\star)[v_z(r, H, t) - v_z(r, -H, t)] = 2\zeta_{\text{out}}(p(r, t) - p_\infty)\,, \tag{7}$$

where ζ_{out} represents the conductivity of the tissues traversed by the outgoing flux, p_∞ is a "far field" pressure (identifiable with the pressure in the lymphatic vessels), and $p(r, t)$ is the longitudinal average of fluid pressure. Thus, starting from (5), the following equation for the average radial velocity $v(r, t)$ is obtained:

$$\frac{1}{r}\frac{\partial}{\partial r}(rv) = -\frac{1}{1-\nu^\star}\left[\chi\nu_P - \mu_A(\nu^\star - \nu_P - \nu_Q) + \frac{\zeta_{\text{out}}}{H}(p - p_\infty)\right]. \tag{8}$$

Assuming that extracellular fluid flow is governed by Darcy law, the longitudinal average of the radial component of Darcy equation,

$$(1 - \nu^\star)(v - u) = -\kappa\frac{\partial p}{\partial r}\,,$$

yields the following equation for p:

$$p(r, t) = p_0(t) - \frac{1-\nu^\star}{\kappa}\int_{r_0}^{r} [v(r', t) - u(r', t)]\, dr'\,, \tag{9}$$

with $p_0(t) = p(r_0^+, t)$. The pressure $p_0(t)$ is actually unknown, and (9) requires a condition at $r = \rho_N(t)$, which we will see below. Equation (8) is complemented by the boundary condition at the vessel wall,

$$(1 - \nu^\star) v(r_0, t) = \zeta_{\text{in}}(p_b - p_0(t)) ,$$

where ζ_{in} is the hydraulic conductivity of the wall and $p_b > p_\infty$ represents the longitudinal mean of hydraulic pressure in the blood, corrected with the jump of osmotic pressure.

2.2 The Necrotic Region

The necrotic region (N) is composed of dead cells and liquid, with volume fractions denoted by ν_N and ν_E ($\nu_N + \nu_E = 1$). Dead cells degrade to liquid with rate constant μ_N. Thus, for $\rho_N(t) < r < B(t)$, mass balance yields:

$$\frac{\partial \nu_N}{\partial t} + \nabla \cdot (\nu_N \, \mathbf{u}) = -\mu_N \nu_N , \tag{10}$$

$$\frac{\partial \nu_E}{\partial t} + \nabla \cdot (\nu_E \, \mathbf{v}) = \mu_N \nu_N , \tag{11}$$

where $\mathbf{u}$ and $\mathbf{v}$ still represent the velocities of the cellular and, respectively, of the liquid component. As above, $\mathbf{u} = (u(r,t), 0)$. Assumption (i) is relaxed, by allowing ν_E (and then ν_N) to change with time. We assume that the pressure of the liquid, p_N, is spatially uniform. From (10), we obtain

$$\frac{1}{r}\frac{\partial}{\partial r}(ru) = -\mu_N - \frac{\dot{\nu}_N}{\nu_N} , \tag{12}$$

and, since $\nabla \cdot (\nu_N \mathbf{u} + \nu_E \mathbf{v}) = 0$, we have

$$\nabla \cdot \mathbf{v} = \frac{\nu_N}{1 - \nu_N}\left(\mu_N + \frac{\dot{\nu}_N}{\nu_N}\right) . \tag{13}$$

We consider the longitudinal average, $v(r,t)$, of the radial component of $\mathbf{v}$ and make the following assumption (that paralleles (7))

$$(1 - \nu_N)[v_z(r, H, t) - v_z(r, -H, t)] = 2\zeta_{\text{out}}^N (p_N(t) - p_\infty) ,$$

where $\zeta_{\text{out}}^N \geq \zeta_{\text{out}}$ is the conductivity of the tissues traversed by the flux outgoing from necrotic region. Proceeding as above, from (13) we obtain

$$\frac{1}{r}\frac{\partial}{\partial r}(rv) = \frac{1}{1 - \nu_N}\left[\mu_N \nu_N + \dot{\nu}_N - \frac{\zeta_{\text{out}}^N}{H}(p_N - p_\infty)\right] . \tag{14}$$

Equations (12) and (14) are complemented by the following boundary conditions at $r = \rho_N$:

$$\nu_N(t)(u(\rho_N^+,t)-\dot\rho_N)=\nu^\star(u(\rho_N^-,t)-\dot\rho_N)\,,$$
$$(1-\nu_N(t))(v(\rho_N^+,t)-\dot\rho_N)=(1-\nu^\star)(v(\rho_N^-,t)-\dot\rho_N)\,.$$

The dynamics of ν_N, p_N, and B was derived in [6] on the basis of the following assumptions: 1) the cellular fraction cannot not exceed a maximal value smaller than one, since necrotic cells retain some structural integrity before degradation; 2) the fluid pressure cannot exceed a given increasing function of B, denoted by $\Psi(B)$, because of the elastic reaction to displacement of the tissues that surround the whole tumour; 3) when ν_N is strictly smaller than the maximal value (taken equal to $\nu^\star$), the reaction of surrounding tissues is supported by the liquid component and the pressure is equal to $\Psi(B)$. In summary:

$$\nu_N(t)\le\nu^\star\,,$$
$$p_N(t)\le\Psi(B(t))\,,$$
$$\big(\nu_N(t)-\nu^\star\big)\big(p_N(t)-\Psi(B(t))\big)=0\,.$$

As discussed in [6], two regimes are possible. In the first one we have $\nu_N(t)<\nu^\star$, $p_N(t)=\Psi(B(t))$ and

$$\frac{dB^2}{dt}=2\rho_N[(1-\nu^\star)v(\rho_N,t)+\nu^\star u(\rho_N,t)]-\frac{\zeta_{\rm out}^N}{H}\big(B^2-\rho_N^2\big)(p_N-p_\infty)\,, \quad (15)$$

$$\frac{d\nu_N}{dt}=\frac{1}{B^2-\rho_N^2}\Big[2\rho_N\nu^\star(u(\rho_N,t)-\dot\rho_N)-2\nu_N\big(B\dot B-\rho_N\dot\rho_N\big)\Big]-\mu_N\nu_N\,. \quad (16)$$

Taking into account that matter cannot cross the boundary $r=B(t)$, (15) can be derived from the mass balance of dead cells plus liquid in N, and (16) from the mass balance of dead cells, whose total volume is $2H\pi(B^2-\rho_N^2)\nu_N$. In the second regime we have instead $\nu_N(t)=\nu^\star$, $p_N(t)\le\Psi(B(t))$ and

$$p_N(t)=p_\infty+\frac{H}{\zeta_{\rm out}^N}\left[\frac{2\rho_N(1-\nu_N)[v(\rho_N,t)-u(\rho_N,t)]}{B^2-\rho_N^2}+\mu_N\right], \quad (17)$$

$$\frac{dB^2}{dt}=2\rho_N u(\rho_N,t)-\mu_N\big(B^2-\rho_N^2\big)\,. \quad (18)$$

Equation (18) is derived from the mass balance of dead cells, by taking into account that $\nu_N=\nu^\star$ in this case, whereas $p_N(t)$, according to (17), is such that the outgoing flux keeps the volume fraction of liquid at the value $1-\nu^\star$. During the evolution, switching between the above regimes may occur when one of the two constraints (on ν_N or on p_N) can no longer be satisfied.

2.3 The Steady State

In the absence of treatment ($\mu_P=\mu_Q=0$), the only cell populations present in the cord are the viable proliferating and quiescent subpopulations, and

$\nu_P + \nu_Q = 1$. In this condition, the model admits a stationary state defined by the constants $\rho_N, B, \nu_N, p_0, p_N$, and by the time-independent functions $\nu_P(r)$, $\sigma(r)$, $p(r)$, defined in the interval (r_0, ρ_N), and $u(r)$, $v(r)$ in (r_0, B). Existence and uniqueness of the stationary solution were proved in [5] for a simplified version of the model in which the whole necrotic region was treated as a liquid. The behaviour of the steady-state solutions was explored numerically in [6].

3 Transport of Antibodies in the Cord at Steady State

Although the monoclonal antibodies (Ab) used for cancer therapy are usually conjugated to radionuclides or toxins, here we restrict to considering the transport and binding of antibodies (assumed to have negligible mass) deprived of cytotoxic action. The cord steady state will then be not perturbed. The transport of free Ab molecules occurs by diffusion and convection in the interstitial space only. We will consider IgG antibodies possessing two equivalent binding sites, and the antigen is assumed to be monovalent and able to diffuse on the cell membrane, so that antibodies can form single or double bonds.

Let us denote the extracellular free Ab concentration by c, and the surface concentrations of antibodies bound monovalently or bivalently by $\hat{b}_1$ and $\hat{b}_2$, respectively. Let $\hat{S}$ be the (constant) surface concentration of total antigen. Free and bound antigens in the extracellular fluid are disregarded (no antigen shedding). By writing the mass balance in the toroidal volume element $(r, r + dr) \times (z, z + dz)$ of the cord, we obtain

$$\frac{\partial}{\partial t}(c\nu_E) - \nu_E D \nabla c + \nabla \cdot (c\nu_E f \mathbf{v}) = -2k_a c \hat{s} \alpha^\star + k_d \hat{b}_1 \alpha^\star \,, \tag{19}$$

$$\frac{\partial}{\partial t}(\hat{b}_1 \alpha^\star) + \nabla \cdot (\hat{b}_1 \alpha^\star \mathbf{u}) = 2k_a c \hat{s} \alpha^\star - k_d \hat{b}_1 \alpha^\star - \hat{k}'_a \hat{s} \hat{b}_1 \alpha^\star + 2k_d \hat{b}_2 \alpha^\star \,, \tag{20}$$

$$\frac{\partial}{\partial t}(\hat{b}_2 \alpha^\star) + \nabla \cdot (\hat{b}_2 \alpha^\star \mathbf{u}) = \hat{k}'_a \hat{s} \hat{b}_1 \alpha^\star - 2k_d \hat{b}_2 \alpha^\star \,, \tag{21}$$

with

$$\hat{s} = \hat{S} - \hat{b}_1 - 2\hat{b}_2 \,. \tag{22}$$

In the above equations, D is the effective interstitial diffusivity, f is the retardation factor (i.e., the ratio of solute velocity to fluid velocity), $\alpha^\star$ is the area of cellular surface per unit volume, $2k_a$ is the rate constant for forming the first bond between the antibody molecule and the antigen, k_d is the dissociation rate constant of a bond (any bond is assumed to be independent), and $\hat{k}'_a$ is the rate constant for forming the second bond (see [7]). In the case of delivery of the antibody Fab fragment, which is monovalent, the equations have to be changed accordingly. We disregard the possible internalization of bound Ab, that however could be easily accounted for.

Consistently with assumption (iv), we assume that Ab concentration in the central vessel, c_b, is independent of z, and that also c, $\hat{b}_1$, $\hat{b}_2$ are independent of z. After defining the quantities

$$b_1 = \hat{b}_1 \frac{\alpha^\star}{\nu_E}\,, \quad b_2 = \hat{b}_2 \frac{\alpha^\star}{\nu_E}\,, \quad S = \hat{S}\frac{\alpha^\star}{\nu_E}\,, \quad k'_a = \hat{k}'_a \frac{\nu_E}{\alpha^\star}\,,$$

by taking (5) and (6) into account and performing the longitudinal mean over $(-H, H)$, (19)–(22) become

$$\frac{\partial c}{\partial t} - \frac{D}{r}\frac{\partial}{\partial r}(r\frac{\partial c}{\partial r}) + fv(r)\frac{\partial c}{\partial r} = f\chi\frac{\nu_P(r)}{1-\nu^\star}c - 2k_a cs + k_d b_1\,, \tag{23}$$

$$\frac{\partial b_1}{\partial t} + u(r)\frac{\partial b_1}{\partial r} = -\chi\frac{\nu_P(r)}{\nu^\star}b_1 + 2k_a cs - k_d b_1 - k'_a s b_1 + 2k_d b_2\,, \tag{24}$$

$$\frac{\partial b_2}{\partial t} + u(r)\frac{\partial b_2}{\partial r} = -\chi\frac{\nu_P(r)}{\nu^\star}b_2 + k'_a s b_1 - 2k_d b_2\,, \tag{25}$$

with

$$s = S - b_1 - 2b_2\,.$$

We recall that the functions $u(r)$, $v(r)$, and $\nu_P(r)$ are solutions of the model at the steady state.

At $r = r_0$, we impose for c the following boundary condition that accounts for both diffusive and convective extravasation:

$$-D\frac{\partial c}{\partial r}\bigg|_{r=r_0} + fv(r_0)c(r_0,t) = \frac{P}{\nu_E}(c_b(t) - c(r_0,t))\frac{\mathrm{Pe}}{\mathrm{e}^{\mathrm{Pe}}-1} + v(r_0)(1-\sigma_f)c_b(t)\,,$$

where Pe (Peclet number) is given by

$$\mathrm{Pe} = \nu_E v(r_0)(1-\sigma_f)/P\,,$$

P is the permeability of the vessel wall, and σ_f is the filtration reflection coefficient. The second boundary condition for c requires the description of the antibody transport in the necrotic region.

We assume that antibodies in the region N can bind to the surface of dead cells with the same binding constants as in the living cord. Moreover, we assume that antigen and bound antibodies are destroyed upon the degradation of the cell, which is consistent with the assumption of neglecting free and bound antigen in the extracellular fluid. Proceeding as above, and using (12), the following equations are obtained for $r \in (\rho_N, B)$:

$$\frac{\partial c}{\partial t} - \frac{D}{r}\frac{\partial}{\partial r}(r\frac{\partial c}{\partial r}) + fv(r)\frac{\partial c}{\partial r} = -f\mu_N\frac{\nu_N}{1-\nu_N}c - 2k_a c\tilde{s} + k_d\tilde{b}_1\,, \tag{26}$$

$$\frac{\partial \tilde{b}_1}{\partial t} + u(r)\frac{\partial \tilde{b}_1}{\partial r} = 2k_a c\tilde{s} - k_d\tilde{b}_1 - \tilde{k}'_a\tilde{s}\tilde{b}_1 + 2k_d\tilde{b}_2\,, \tag{27}$$

$$\frac{\partial \tilde{b}_2}{\partial t} + u(r)\frac{\partial \tilde{b}_2}{\partial r} = \tilde{k}'_a\tilde{s}\tilde{b}_1 - 2k_d\tilde{b}_2\,, \tag{28}$$

with $\tilde{s}=\tilde{S}-\tilde{b}_1-2\tilde{b}_2$ and having defined:

$$\tilde{b}_1=\hat{b}_1\frac{\alpha_N}{1-\nu_N}\,,\quad \tilde{b}_2=\hat{b}_2\frac{\alpha_N}{1-\nu_N}\,,\quad \tilde{S}=\hat{S}\frac{\alpha_N}{1-\nu_N}\,,\quad \tilde{k}'_a=\hat{k}'_a\frac{1-\nu_N}{\alpha_N}\,.$$

In the above definitions, α_N denotes the area of cellular surface per unit volume in the N region. Taking $\alpha_N/\alpha^\star=\nu_N/\nu^\star$, we have

$$\tilde{S}=\frac{\nu_N}{\nu^\star}\frac{1-\nu^\star}{1-\nu_N}S\,,\quad \tilde{k}'_a=\frac{\nu^\star}{\nu_N}\frac{1-\nu_N}{1-\nu^\star}k'_a\,.$$

At $r=\rho_N$, we impose

$$c(\rho_N^+)=c(\rho_N^-)\,,$$

that, from the continuity of the flux of free antibodies and the assumption that retardation factor is equal in the cord and in the region N, implies

$$(1-\nu_N)\frac{\partial c}{\partial r}\bigg|_{r=\rho_N^+}=(1-\nu^\star)\frac{\partial c}{\partial r}\bigg|_{r=\rho_N^-}\,.$$

Furthermore, we have

$$\tilde{b}_i(\rho_N^+,t)=\frac{\nu_N}{\nu^\star}\frac{1-\nu^\star}{1-\nu_N}b_i(\rho_N^-,t)\,,\quad i=1,2\,.$$

Finally, at $r=B$, we impose

$$\frac{\partial c}{\partial r}\bigg|_{r=B}=0\,.$$

4 Nondimensional Variables and Parameters

In the numerical solution, we use the following nondimensional variables:

$$t'=t\chi\,,\qquad r'=\frac{r}{r_0}\,,\qquad z'=\frac{z}{H}\,,$$

$$u'=\frac{u}{\chi r_0}\,,\qquad v'=\frac{v}{\chi r_0}\,,\qquad p'=\frac{p-p_\infty}{p_b-p_\infty}\,,\qquad \sigma'=\frac{\sigma}{\sigma_b}\,.$$

All the Ab concentrations are rescaled by S. All the rate costants, χ, γ, λ, μ_N, k_d are rescaled by χ. The association rate constants are rescaled by χ/S. For the other parameters we have

$$\kappa'=\kappa\frac{p_b-p_\infty}{\chi r_0^2}\,,\quad \zeta'_{\rm in}=\zeta_{\rm in}\frac{p_b-p_\infty}{\chi r_0}\,,\quad \zeta'_{\rm out}=\zeta_{\rm out}\frac{p_b-p_\infty}{\chi H}\,,$$

$$D'=\frac{D}{\chi r_0^2}\,,\quad P'=\frac{P}{\chi r_0}\,.$$

For the sake of simplicity, the primes will be omitted and we will use the same symbols for the nondimensional and the dimensional quantities.

5 Numerical Results

In this section we give examples of the distribution of bound antibody computed according to the proposed model. For the numerical solution of the steady state of the tumour cord, we refer to [6]. To approximate the nonlinear elasticity of biological tissues, the function $\Psi(B)$ was chosen as $\Psi(B)=e(B-1)^2$ in the nondimensional form, with e a given elasticity coefficient. As in [6], the nondimensional values of the cord parameters were chosen, whenever possible, according to dimensional values available in the literature. Concerning the parameters of Ab transport, the values of diffusivity and vessel permeability were chosen according to the following dimensional values: $D=1.3\times10^{-8}\,\mathrm{cm}^2/\mathrm{s}$ and $P/\nu_E=5.7\times10^{-7}\,\mathrm{cm/s}$ [9]. Moreover, $f=0.75$ and $\sigma_f=0.8$ [1]. For the time course of Ab concentration in plasma, we have set

$$c_b(t)=c_{b0}\left(m\mathrm{e}^{-t/\tau_1}+(1-m)\mathrm{e}^{-t/\tau_2}\right),$$

with values of m, τ_1 and τ_2 as in [9]. Equations (23)–(25) and (26)–(28) were solved by means of a finite difference method that combines a modified Crank-Nicholson scheme for c with the solution of the equations for the bound concentration over the characteristic lines. Zero initial conditions were assumed.

Figure 1, upper left panel, shows the distributions of bound (b_1+b_2) and free Ab in a high-affinity case with $K=k_a/k_d=50$ (the corresponding dimensional value is $5\times10^7\,\mathrm{M}^{-1}$ if $S=10^{-6}\,\mathrm{M}$). In this case, antibodies in the cord are mainly in the bound state and their concentration declines with r. The lower left panel shows the time course of b_1 and b_2 at $r=r_0$ and $r=\rho_N$. The doubly bound Ab largely prevails, expecially at the cord periphery where the free Ab concentration is very small. Note the marked time delay of the maximal bound concentration at the periphery with respect to the inner region of the cord. The panels on the right of Fig. 1 depict the case of a reduced affinity, with $K=2$. The bound Ab is much smaller, but more uniform with r. Since the free Ab concentration is higher, b_1 is close to b_2 (lower panel). The delay of the maximum of bound Ab at the periphery is decreased, highlighting the role of binding in reducing the velocity of Ab penetration.

In the above simulations, taken as the reference cases, the cord steady state had $\rho_N=6.23$, $B=9.42$, $\nu_N=0.315$, $p_0=0.86$, and the mean interstitial fluid velocity was 90.93. Because of the high value of Darcy's constant κ, it is $p_0\simeq p_N$, so the fluid pressure is fairly uniform throughout the system. The computation of the diffusive and convective terms revealed a rather significant contribution of convection to the transport. To test the influence of a reduced convection, we decreased $\zeta_{\mathrm{out}}=\zeta_{\mathrm{out}}^N$ from 0.5 to 0.065 and increased e from 12×10^{-3} to 14×10^{-3}. In this way we had $p_0=0.98$ and a quite small interstitial fluid velocity (mean value equal to 7.02), while the radius B was almost unchanged ($B=9.36$). In the high-affinity case, the maximum of bound Ab at $r=r_0$ is only slightly reduced (88% of the reference value), whereas the reduction is greater at the cord periphery (26%). In the low-affinity case, the

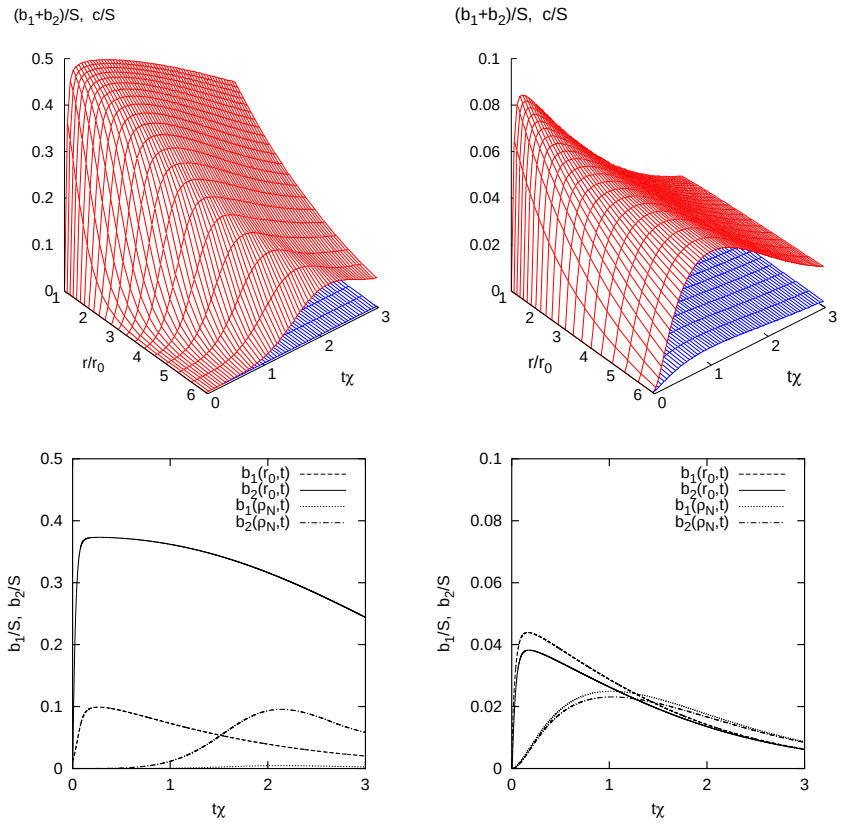

Fig. 1. Distribution of bound and free Ab (upper panels, in both panels the lower surface represents free Ab); time course of b_1 and b_2 at $r = r_0$ and $r = \rho_N$ (lower panels). Left panels: $k_a = k'_a = 1000$, $k_d = 20$. Right panels: $k_a = k'_a = 100$, $k_d = 50$. Other parameters: $\zeta_{\text{in}} = 400$, $\zeta_{\text{out}} = \zeta^N_{\text{out}} = 0.5$, $\kappa = 10000$, $e = 12 \times 10^{-3}$, $\mu_N = 1$, $D = 400$, $P = 5$, $c_{b0} = 0.1$.

reduction of the maximum is more uniform with r, in particular it is 70% at $r = r_0$ and 65% at $r = \rho_N$. By contrast, an increased convection was obtained lowering p_0 to 0.52, by setting $\zeta_{\text{out}} = \zeta^N_{\text{out}} = 3$ and $e = 7 \times 10^{-3}$ (mean value of v equal to 324.8 and $B = 9.36$). In the high-affinity case, the maximum of bound Ab at $r = r_0$ is slightly increased (110% of the reference value), whereas the increment is very marked at the cord periphery (344%). We note that in the inner cord the increment is not so large because the binding sites are almost saturated. In the low-affinity case, the increment of the maximum is still more uniform, in particular 131% at $r = r_0$ and 158% at $r = \rho_N$.

As a concluding remark, we observe that the high binding to cell surface antigens results in a "barrier" to Ab penetration, generating a more hetero-

geneous Ab distribution, since the binding in the inner region of the cord produces a marked decrease of free Ab concentration as r increases (see also [9]). In our simulations, convective transport appears to be significant especially at the periphery of the cord, although, even at very high interstitial pressures, the overall transport is not suppressed. However, further investigations that explore other parameter combinations are necessary to elucidate the importance of this phenomenon on Ab transport.

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