

MASS TRANSPORT IN SOLID TUMORS (II) —DRUG DELIVERY

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Abstract

Based on the flow field solution of the three-porous-medium model for tumor microcirculation, the diffusion-convection equations are solved with various initial and boundary conditions using finite element method. The concentration profile of two therapeutic agents: immunoglobulin G (IgG) and its antigen-binding fragment (Fab) in blood, lymph and interstitial fluid are obtained for normal-tissue-surrounded tumor. The effect of tumor microvasculature, lymph function, drug injection mode, the molecular weight and binding kinetics of the drug on the distribution in tumors are also considered.

Key words three-porous-medium model, solid tumor, drug delivery, diffusion-convection equations

I. Introduction

In Part (I), the three-porous-medium model is developed to simulate the fluid dynamic problem of tumor microcirculation. The pressure and velocity profile of blood, lymph and interstitial fluid are obtained. Based on these solutions, the transport process of immunoglobulin G (IgG) and its antigen-binding fragment (Fab) in the normal-tissue-surrounded tumor are analyzed in this paper. The finite element method is used to solve the diffusion-convection equations to get the concentration profile of IgG and Fab in blood, lymph and interstitial fluid. With various initial and boundary conditions, the effect of repeated injection (or continuous perfusion) and bolus injection, tumor necrosis and functional lymph are discussed. Furthermore, these equations are coupled with the first order binding kinetic equation for association-dissociation balance between the antibody (IgG or Fab) and antigens on tumor cell surface, to consider the possible effect of antibody-antigen binding and antibody metabolism.

II. Boundary Value Problem and Solution

The transport process of macromolecules in blood, lymph and interstitial fluid obeys the following diffusion-convection equations,

$$\partial C_i / \partial t + \nabla \cdot (\gamma_F \vec{u}_i C_i) = \nabla \cdot (D_i \nabla C_i) + \phi_i \quad (2.1)$$

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where C_i , u_i , D_i and ϕ_i ($i = 1, 2, 3$) represent the concentration of the antibody, flow velocity, diffusion coefficient and the antibody source in blood, lymph and interstitial fluid respectively. γ_{Fi} is the ratio of solute velocity to solvent velocity and it is assumed to be 1 in the following calculation.

The macromolecules transport from blood to interstitial fluid through diffusion driven by the concentration gradient and cross blood vessel wall convection driven by pressure difference. From the Kedem-Katchalsky formula in Ref. [1]

$$\phi_1 = -p_n(C_1 - C_3) - (1 - \sigma_D)((C_1 + C_2)/2)l_{13}n_1[(p_1 - p_3) - \sigma_T(\pi_1 - \pi_3)] \quad (2.2)$$

The lymphatics collect antibody from the tissue space mainly through the cross wall convection, that is,

$$\phi_2 = l_{23}n_2(p_3 - p_2)C_3 \quad (2.3)$$

In the tissue space, the concentration profile are mainly determined by the exchange between blood-interstitial fluid and lymph-interstitial fluid plus antibody binding and metabolism

$$\phi_3 = -\phi_1 - \phi_2 - \phi_R \quad (2.4)$$

$$\phi_R = k_f(B_{\max} - B)C_3 - k_rB \quad (2.5)$$

where the ϕ_R represents the clearance due to antibody-antigen binding and antibody metabolism ($\phi_R = 0$, no consideration of binding and metabolism). B is the concentration of the associated antibody-antigen in the interstitial fluid. Assuming this association/dissociation process is first order and reversible, then

$$\frac{\partial B}{\partial t} = k_f(B_{\max} - B)C_3 - k_rB - k_eB \quad (2.6)$$

For other undifined parameters in equations (2.2)~(2.6), please refer to table 1 and table 2.

The initial conditions for equations (2.1) assum there are no antibodies before injection

$$C_i|_{t=0} = 0 \quad (i = 1, 2, 3) \quad (2.7)$$

and the associated antibody-antigen concentration is also set to zero,

$$B|_{t=0} = 0 \quad (2.8)$$

The concentration and the flux at the boundary of different zone are continuous,

$$\left. \begin{aligned} C_i|_{r=r_j^-} &= C_i|_{r=r_j^+} \\ (u_iC_i - D_i\partial C_i/\partial r)|_{r=r_j^-} &= (u_iC_i - D_i\partial C_i/\partial r)|_{r=r_j^+} \end{aligned} \right\} \quad (i = 1, 2, 3) \quad (2.9)$$

r_j is r_T (radius of the solid tumor) for the homogeneous tumor and r_n (radius of the necrotic zone), r_s (radius of the semi-necrotic zone), r_T (radius of the growth zone) respectively. In which, $r_s = r_n + 0.5 \times (r_T - r_n)$.

In the tumor center, from the non-permeable condition,

$$(u_iC_i - D_i\partial C_i/\partial r)|_{r=0} = 0 \quad (i = 1, 2, 3) \quad (2.10)$$

Assuming the concentration profile deep into the normal tissue has no effect on the transport process in tumor, it means,

$$(\partial C_i/\partial r)|_{r>r_T} = 0 \quad (i = 1, 2, 3) \quad (2.11)$$

Table 1 Parameters for mass transport***

(if there are two numbers in one space, the first is for IgG, the other Fab)

parameter	unit	data in tumor	data in normal tissue
hydraulic conductivity of the microvascular wall l_1	cm/mmHg-s	2.8×10^{-7}	0.36×10^{-7}
hydraulic conductivity of the lymphatic wall l_2		5.6×10^{-7}	1.98×10^{-6}
microvascular surface area per unit volume n_1	cm ⁻¹	200	70
lymphatic surface area per unit volume n_2		0.01	70
blood, lymph and interstitial osmotic pressure π_1, π_2, π_3	mmHg	20, 15, 15	20, 10, 10
osmotic reflection coefficient σ_T		0.82	0.91
diffusion coefficient D_1	10^{-8} cm ² /s	10^4	10^5
diffusion coefficient D_2		10	10^5
diffusion coefficient D_3		1.3, 4.4	0.048, 1.2
effective permeability coefficient P_{eff}	10^{-7} cm ² /s	5.73, 14.9	0.73, 19.1
average osmotic reflection coefficient σ_D		0.95	0.50
characteristic clearance time τ_p	h	103.8	3.0

* All values are based on Ref's. [2, 3] except l_2, n_2, D_1, D_2

** P_{eff} is based on experimental estimation which includes the contribution of both convection and diffusion. In general P/P_{eff} is in the range of 0~10%.

Table 2 Parameters for binding and metabolism*

(if there are two numbers in one space, the first is for IgG, the other Fab)

parameter	unit	data
saturation concentration of associated Antibody-antigen B_{max}	10^{-8} mol	1.175, 2.35
association rate constant k_f	10^{-6} mol ⁻¹ min ⁻¹	2.6, 0.8
dissociation rate constant k_r	min ⁻¹	0.0082, 0.0091
metabolism rate constant k_e	min ⁻¹	0.0, 0.0

* All values are based on Ref. [4] $C_p^0 = 1.0 \times 10^{-9}$ mol.

Considering two types of injection mode: (1) continuous perfusion or repeated injection. The antibody concentration in blood is assumed to be constant.

$$C_1|_{r>r_T} = C_p^0 \quad (2.12)$$

C_p^0 is the initial antibody concentration in blood; (2) bolus injection. The antibody concentration in blood is assumed to decrease exponentially

$$C_1(t)|_{r>r_T} = C_p^0 \exp(-t/\tau_p) \quad (2.13)$$

where τ_p is the clearance time of the antibody in blood.

Based on these conditions and the velocity u_i and pressure p_i obtained from Part (I), the equations (2.1) are solved using the finite element method.

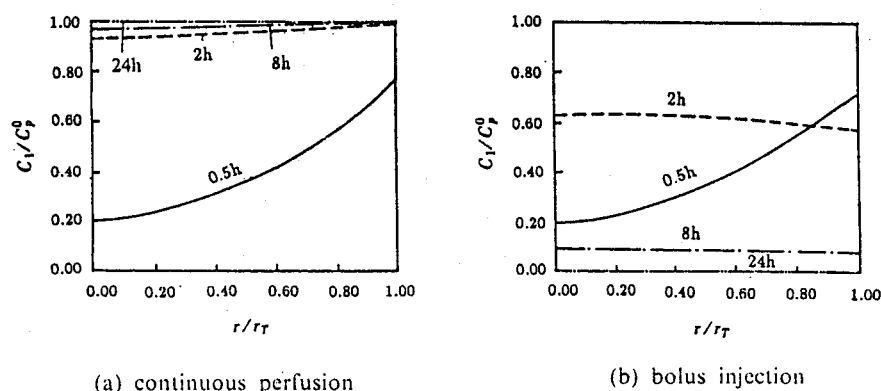


Fig. 1 Fab concentration in blood for $P/P_{eff} = 1\%$ in homogeneous and lymphatic tumor without consideration of binding and metabolism

(P/P_{eff} is the ration of vascular permeability coefficient to the efficiency permeability coefficient)

III. Results and Discussion

The baseline value for the parameters are listed in table 1 and table 2. All the results are for the normal-tissue-surrounded tumor. for a homogeneous and lymphatic tumor, the cross microvessel wall permeability coefficient P does not change the concentration profile in blood too much. As an example, blood Fab concentration for $P/P_{eff} = 1\%$ is shown in Fig. 1. It is found that early after the injection, the blood Fab concentration at the tumor edge is bigger than that of the tumor center, but in a very short time (about 2 hrs), the concentration is almost same elsewhere in tumor, which is close to C_p^0 for continuous perfusion. Due to the relatively small molecular weight of Fab, its clearance time is very short and its concentration in blood decrease rapidly becoming almost zero at 24 hrs after injection. Blood IgG concentration changes with time in a similar way, except that IgG enters tumor center and is cleared away from tumor at a slower rate due to its relatively large molecular weight.

Shown in Fig. 2~Fig. 5 are the antibody concentration in the interstitial fluid with $P/P_{eff} = 10\%, 1\%, 0$. When $P \neq 0$, the interstitial fluid antibody concentration early after the injection is similar to that in blood, with more antibody accumulate at the tumor edge than in the tumor center. After some time, the concentration profile will be relatively flattened inside tumor with possible drop at tumor edge due to the outward interstitial fluid flux, which is particularly evident for IgG. The permeability coefficient P is very important for the antibody distribution in interstitial fluid. For example, the dimensionless interstitial fluid antibody concentration at tumor center is close to 1 at 8 hrs after injection for $P/P_{eff} = 10\%$, while it is close to 1 at 24 hrs for $P/P_{eff} = 1\%$ with continuous perfusion. With bolus injection, the permeability coefficient P directly influence the highest concentration attainable in tumor. Furthermore, the interstitial fluid antibody concentration decreases earlier and more rapidly for a larger P . The IgG concentration for $P/P_{eff} = 1\%$ is less than one third of that for $P/P_{eff} = 10\%$ at 72 hrs after the continuous perfusion begins. Similar conclusion is true for Fab. For $P/P_{eff} = 10\%$, the interstitial fluid IgG concentration increases continuously only that the rate will decrease after some time, while this is not true for Fab. If $P/P_{eff} = 0$, the

antibody enters the tissue space mainly through diffusion, with the characteristic diffusion time $\tau^2/4D$. For Fab and IgG, the time diffuse a distance of 1mm may take about 16 hrs and 54 hrs respectively. There is almost no cross wall convection inside tumor except at the tumor edge and at the meanwhile, the antibody at the tumor edge may be brought out of tumor by the outward interstitial fluid flux, which results in a relatively low concentration at the edge and an almost zero concentration at the center. In conclusion, the molecular weight

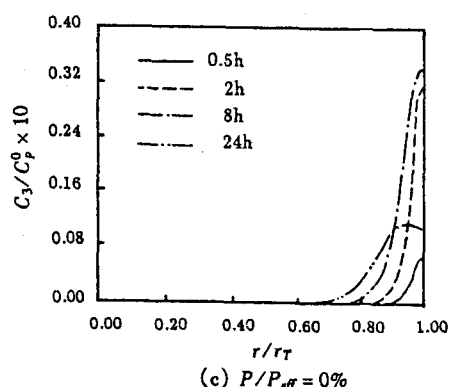
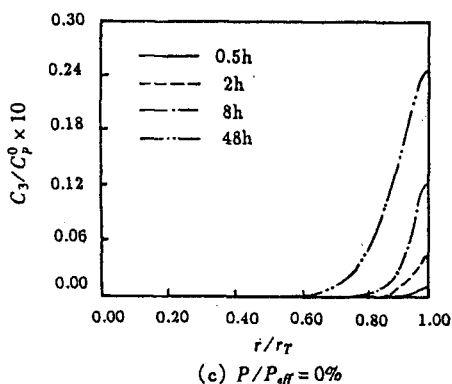
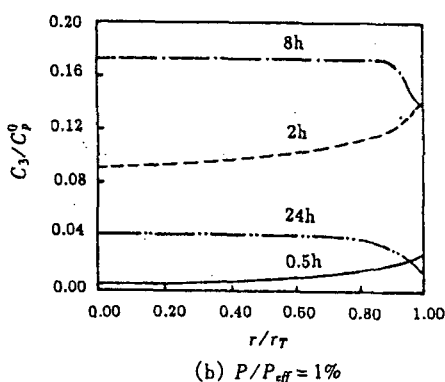
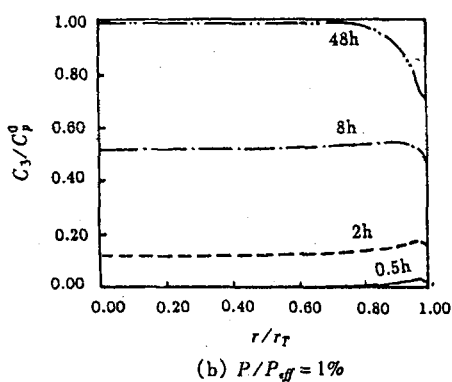
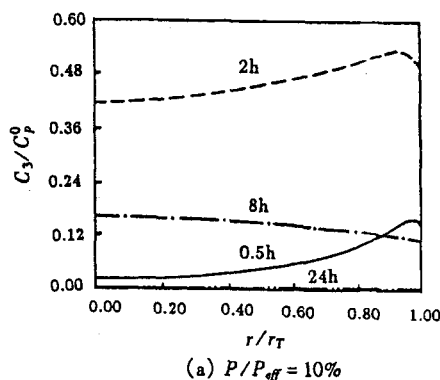
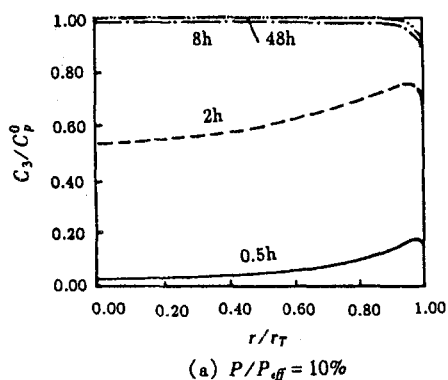
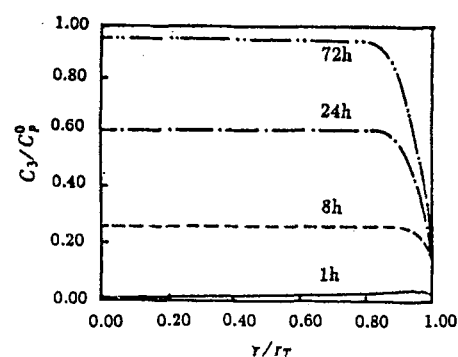


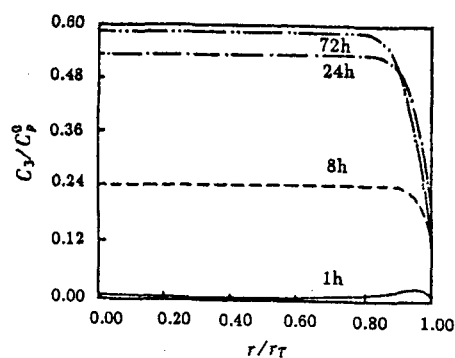
Fig. 2 Fab concentration in interstitial fluid for continuous perfusion in homogeneous and alymphatic tumor without consideration of binding and metabolism

Fig. 3 Fab concentration in interstitial fluid for bolus injection in homogeneous and alymphatic tumor without consideration of binding and metabolism

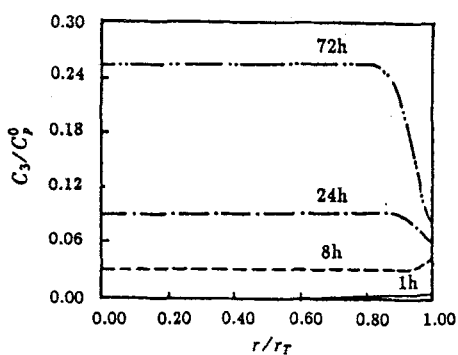
of the antibody play an important role in its transport process. Smaller molecule is easily diffused but is also cleared very rapidly, while larger molecule is just the opposite. Proper injection stragetes should consider the molecular weight of the antibodies to make their best use. Another critical factor is the permeability of the microvascular wall, which directly limits



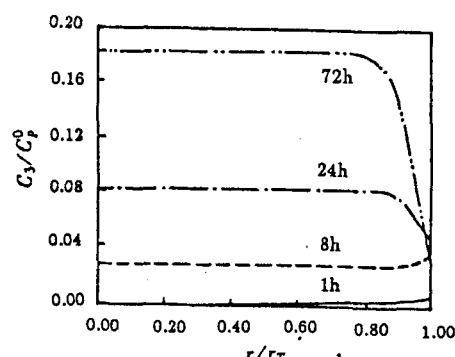
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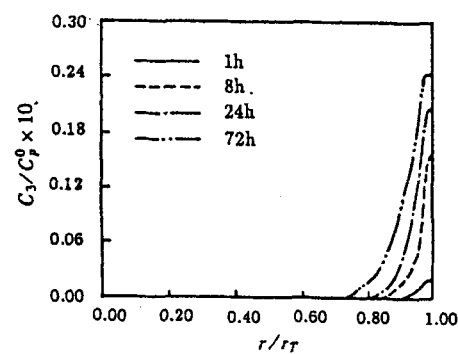
(a) $P/P_{eff} = 10\%$



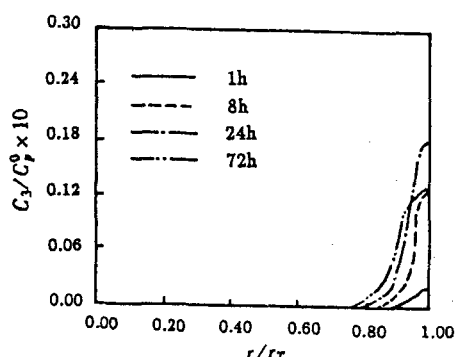
(b) $P/P_{eff} = 1\%$



(b) $P/P_{eff} = 1\%$



(c) $P/P_{eff} = 0\%$



(c) $P/P_{eff} = 0\%$

Fig. 4 IgG concentration in interstitial fluid for continuous perfusion in homogeneous and alymphatic tumor without consideration of binding and metabolism

Fig. 5 IgG concentration in interstitial fluid for bolus injection in homogeneous and alymphatic tumor without consideration of binding and metabolism

the transport efficiency from blood to tissue space.

In the following discussion, P/P_{eff} is always equal to 1%, so other factors can be considered.

(1) Effect of necrosis

For the tumor with a necrotic core, it is divided into necrotic zone, semi-necrotic zone and growth zone from the tumor center to the edge. From the flow field solutions in Part (I), the characteristics of necrosis are known to be dramatically increased resistance to flow and severely hindered exchange between blood and tissue space. Therefore, the values of l_{13} , D_1 for necrotic zone and semi-necrotic zone are 1/10000 and 1/100 of the values for growth zone (which are listed in table 1). Assuming the radius of the necrotic core is 0.5cm, the IgG concentration in blood and interstitial fluid are shown in Fig. 6 (continuous perfusion) and Fig. 7 (bolus injection). Limited by the space, the results for Fab and $r_n=0.95$ cm are not listed here, which also have similar trends. It is found out that the distribution of antibody in blood directly influences its distribution in interstitial fluid. Early after the injection, IgG penetrates only into the growth zone, then gradually it makes its way into semi-necrotic zone

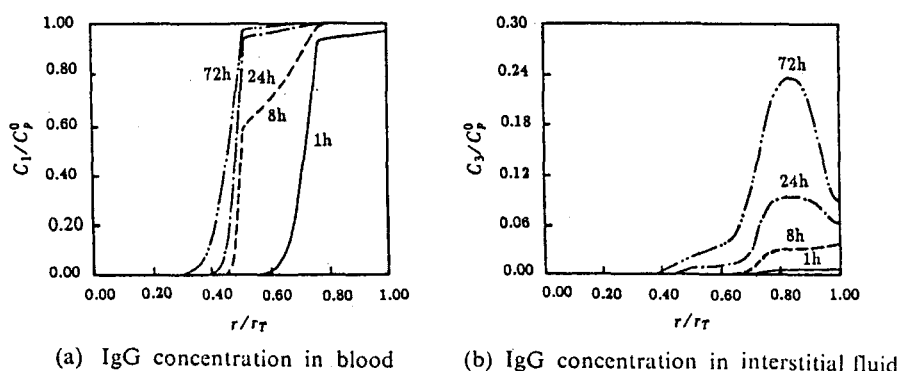


Fig. 6 IgG concentration for continuous perfusion in heterogeneous and alymphatic tumor without consideration of binding and metabolism $P/P_{eff}=1\%$, $r_n=0.5$ cm

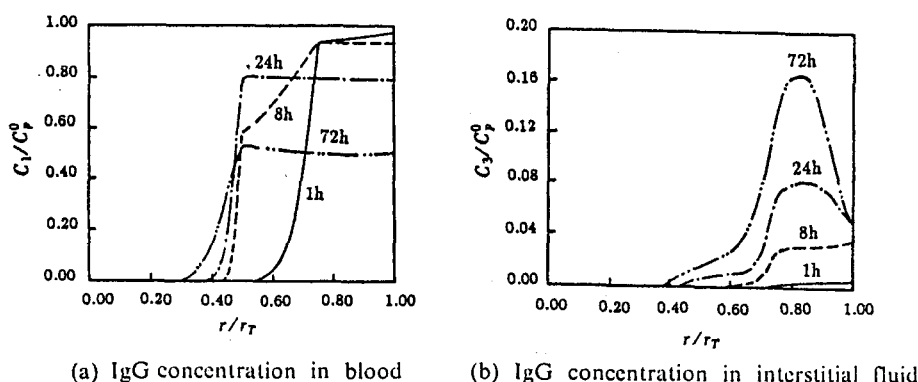


Fig. 7 IgG concentration for bolus injection in heterogeneous and alymphatic tumor without consideration of binding and metabolism $P/P_{eff}=1\%$, $r_n=0.5$ cm

(about 8hrs). For continuous perfusion, IgG will eventually enter the edge of the necrotic zone. For bolus injection, it may accumulate more in the semi-necrotic zone than in growth zone, the so-called reservoir effect. The IgG concentration in both blood and interstitial fluid are very low in the necrotic core. While the concentration in interstitial fluid is much lower than that in blood in semi-necrotic zone and the necrotic zone edge, indicating that it is more difficult for antibody to penetrate into tumor in tissue space than in microvasculature. In summary, necrosis can greatly hinder the drug delivery into tumor with the situation becoming worse as necrosis further develops. The antibody cannot make its expected success because it is limited in semi-necrotic zone and growth zone other than the antigen-abundant necrotic core.

(2) Effect of lymphatic function

Shown in Fig. 8 are the antibody concentration in lymph assuming there are functional lymph inside tumor. Comparing with those alymphatic tumor, Fab concentration is almost the

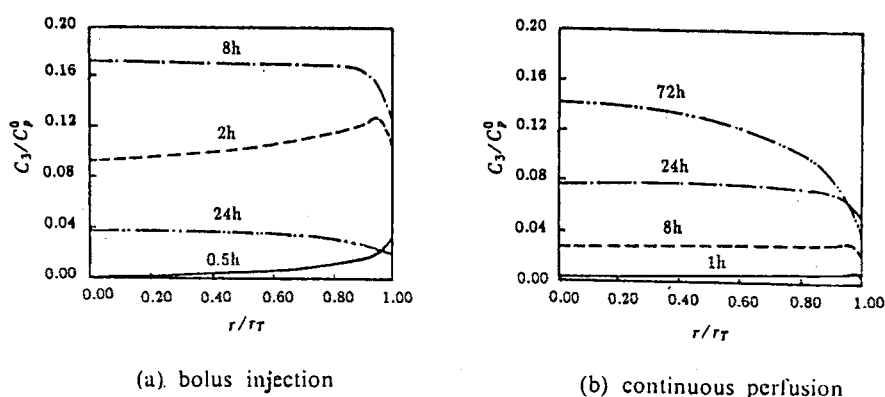


Fig. 8 Antibody concentration in interstitial fluid for homogeneous tumor with functional lymphatics, $P/P_{eff} = 1\%$

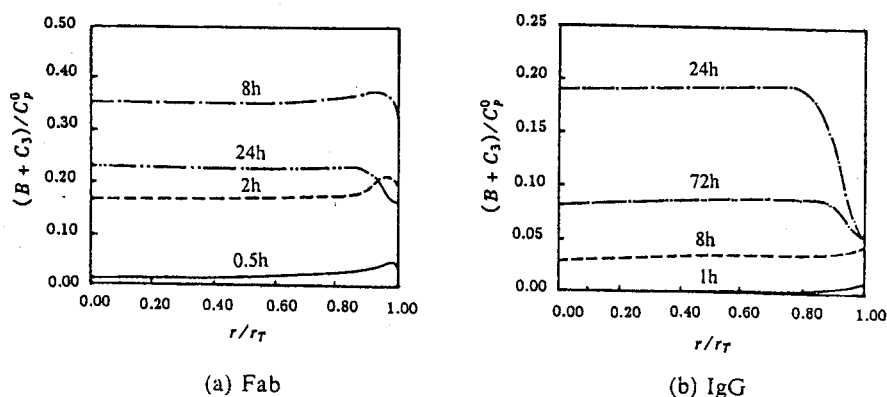
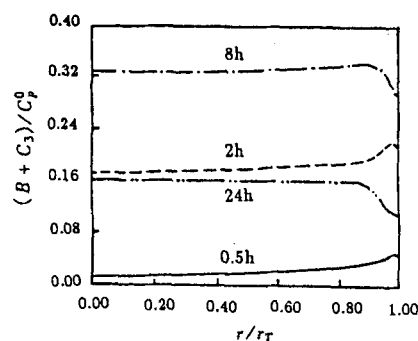


Fig. 9 Antibody concentration in interstitial fluid with binding and metabolism for bolus injection (parameters are the baseline value listed in table 2)

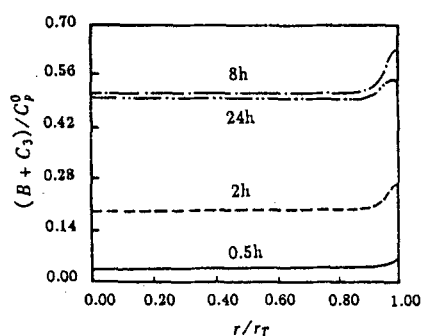
same, while IgG concentration is considerably lower. The possible explanation lies in the fact that functional lymph reduces the high interstitial pressure which may favor the penetration of antibodies into tumor and at the same time, and they also may bring them out of tumor by collecting them from the tissue space. While both Fab and IgG will be brought out of tumor, it is more difficult for IgG to get into tumor even for the reduced interstitial pressure.

(3) Effect of antibody binding

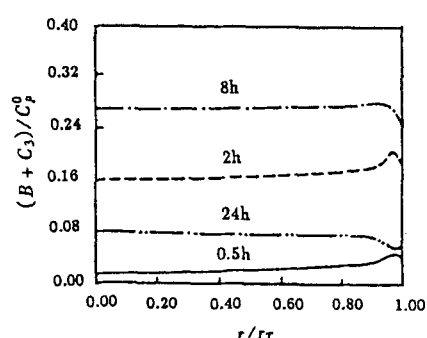
The total antibody concentration (associated and free antibody) in interstitial fluid is shown in Fig. 9 with the parameters taking the values listed in table 2. Fab concentration increases dramatically while IgG concentration only increases a little as compared with those assuming there is no binding. This is more evident long time after injection begins for bolus injection than continuous perfusion (not listed here). The concentration profiles for changing several parameters are listed in Fig. 10. It is found that antibody concentration in interstitial fluid will increase as the amount of the bolus injection increases. For larger association rate constant, the antibody can reach higher concentration in tumor and for Fab, the rate of concentration decrease may also be slower. If $k_e \neq 0$, more antibody may be cleared in tissue space and the clearance increases with time. In a word, the binding and metabolism of antibodies are very important for their distribution in tumor. The influence will be bigger for small molecules than large ones. For example, bolus injection of Fab with a large association rate constant may help more Fab to penetrate into tumor and stay there. It is shown that the extensive sensitive analysis is helpful for understanding and designing drug-delivery strategies.



(a) $C_p^0 = 100 \times$ the baseline value



(b) $k_f = 10 \times$ the baseline value



(c) $k_r = 0.0013 \text{ min}^{-1}$

Fig. 10 Fab concentration in interstitial fluid with binding and metabolism for bolus injection (parameters are the baseline value listed in table 2 except otherwise indicated)

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