

## NUMERICAL SIMULATION OF ANTIBODY PENETRATION IN A SOLID TUMOR NODULE USING FINITE ELEMENT METHOD

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### ABSTRACT

The high binding specificity that monoclonal antibodies exhibit has led to great interest in using them to target tumor-associated antigens. The antibody may be coupled to a radionuclide or cytotoxic drug to create a tumor-targeted reagent that can be used to identify sites of metastatic disease and/or deliver a lethal substance to the tumor cells. However, successful application of these compounds in a clinical setting has been hindered by a poor understanding of the factors that govern antibody accumulation in a tumor. We have used a finite element method to develop a pharmacokinetic model describing the uptake of systemically-administered antibody in an early, prevascular spherical tumor nodule embedded in normal tissue. The model incorporates such processes as plasma kinetics, transcapillary transport, interstitial diffusion, binding reactions, lymphatic clearance, and antigen internalization.

### INTRODUCTION

Previously published papers by van Osdol et al. (1993) and Sung and van Osdol (1995) utilized a finite difference technique to generate simulations of the antibody uptake process. This technique was capable of describing the antibody concentration profiles in one region—the tumor nodule. An assumption was made that the normal tissue surrounding the tumor and the plasma are well-mixed compartments. The concentration of free antibody was equated across the tumor-normal tissue interface (Dirichlet boundary condition). Alternatively, one can specify a time-dependent flux across the tumor interface which derives from the assumption of pseudo-steady-state diffusion within the normal tissue. The magnitude of the flux is a function of the properties of the normal tissue. A rigorous test of this flux boundary condition, however, can only be obtained by solving the diffusion-reaction equations in both the tumor and normal tissue regions. FIDAP, with its finite-element capabilities, allows solution of the equations in both regions and, hence, examination of the spatial and temporal profiles in tumor and normal tissue.

### METHODS

Nondimensionalized partial differential equations representing diffusion of antibody in tumor embedded in normal tissue are incorporated in the finite element analysis.

#### Equations in Tumor

Free antibody equation showing diffusion and reaction:

$$\frac{\partial \hat{u}_1}{\partial \tau} = D_{str1} \cdot \nabla_{\epsilon}^2 \hat{u}_1 - (\gamma_1 \text{ratio}_1 \bar{k}_{str1}) \cdot \hat{u}_1 \cdot \hat{u}_2 + (\gamma_1 \text{ratio}_1) \cdot \hat{u}_3$$

Free antigen equation shows immobility,  $n=2$  for antibody binding:

$$\frac{\partial \hat{u}_2}{\partial \tau} = (-n\gamma_1 \bar{k}_{str1}) \cdot \hat{u}_1 \cdot \hat{u}_2 + n(\gamma_1 + \gamma_m) \cdot \hat{u}_3$$

Antibody-Antigen complex showing immobile complex:

$$\frac{\partial \hat{u}_3}{\partial \tau} = (\gamma_1 \bar{k}_{str1}) \cdot \hat{u}_1 \cdot \hat{u}_2 - (\gamma_1 + \gamma_m) \cdot \hat{u}_3$$

#### Equation in Normal Tissue Surrounding Tumor

Antibody equation showing diffusion, distributed sources and sinks. There is no reaction in normal tissue because antigen is absent.

$$\frac{\partial \hat{u}_e}{\partial \tau} = D_{e,str1} \cdot \nabla_{\epsilon}^2 \hat{u}_e + \hat{\beta}_1 \phi_e \cdot u_p(\tau) - (\hat{\beta}_1 + \hat{\beta}_2) \cdot \hat{u}_e$$

Antibody equation in Plasma Compartment:

$$u_p(\tau) = (\alpha_1 e^{-\Lambda_1 \tau} + \alpha_2 e^{-\Lambda_2 \tau})$$

#### Boundary Conditions

No flux across center of sphere and outer surface of normal tissue:

$$\frac{\partial \hat{u}_1(0, \tau)}{\partial \varepsilon} = 0; \quad \frac{\partial \hat{u}_e(\Gamma, \tau)}{\partial \varepsilon} = 0$$

Matched flux of diffusible species at interface between tumor and normal tissue:

$$D_{str1} \frac{\partial \hat{u}_1(1, \tau)}{\partial \varepsilon} = D_{e,str1} \frac{\partial \hat{u}_e(1, \tau)}{\partial \varepsilon}$$

No flux of immobile species at interface between tumor and normal tissue (boundary is impermeable to these species):

$$\frac{\partial \hat{u}_2(1, \tau)}{\partial \varepsilon} = 0 \quad \text{and} \quad \frac{\partial \hat{u}_3(1, \tau)}{\partial \varepsilon} = 0$$

### Initial Conditions

$$\hat{u}_1(\varepsilon, 0) = 0 \quad \text{for} \quad 0 \leq \varepsilon \leq 0; \quad \hat{u}_2(\varepsilon, 0) = 1 \quad \text{for} \quad 0 \leq \varepsilon \leq 1$$

$$\hat{u}_3(\varepsilon, 0) = 0 \quad \text{for} \quad 0 \leq \varepsilon \leq 1; \quad \hat{u}_e(\varepsilon, 0) = 0 \quad \text{for} \quad 1 < \varepsilon \leq \Gamma$$

With the nondimensionalization, the finite element mesh is scaled such that the tumor has nondimensional radius 1 and the normal tissue surrounding the tumor has nondimensional radius 10. Mesh is graded finer towards the tumor and normal tissue interface.

### RESULTS AND DISCUSSION

Values of calculated antibody concentrations in normal tissue and in tumor nodule along the radial direction for different time steps are shown in Fig. 1. Figure 2 and 3 shows spatial and temporal dependent free antigen and antigen-antibody complex concentrations, respectively, in the tumor nodule. All above figures are complimentary to each other.

From Fig. 1 and 3, about 60% penetration of antibody is observed in the tumor nodule after 16 hours of treatment. Arrow #1 in Fig. 1 shows increase in antibody concentration with time in the tumor nodule whereas in Fig. 2 it shows decrease in antigen concentration level from an initial nondimensional value of 1 at  $t = 0$ . Arrow #1 in Fig. 3 indicates increase in antigen-antibody complex concentration with time. Arrow #2 in Fig. 1 indicates the increase in antibody concentration with time. Far away from the tumor nodule, the antibody concentration is essentially a representation of the source and sink terms present in the antibody governing equation in normal tissue.

The initial finite element calculations are indicative of a correct trend. However, further numerical and experimental research are needed to accurately quantify the parameters, governing equations, boundary and initial conditions.

### REFERENCES

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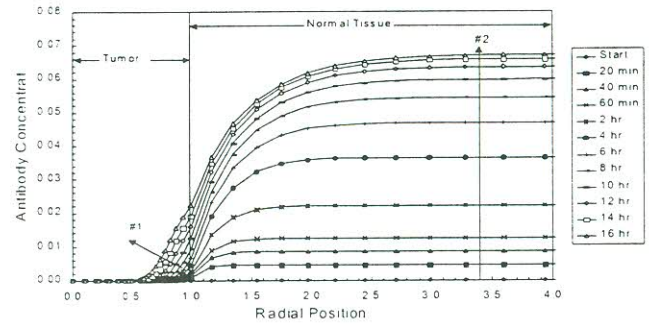


Fig. 1 Free antibody concentration (nondimensional form) in normal tissue and in tumor nodule.

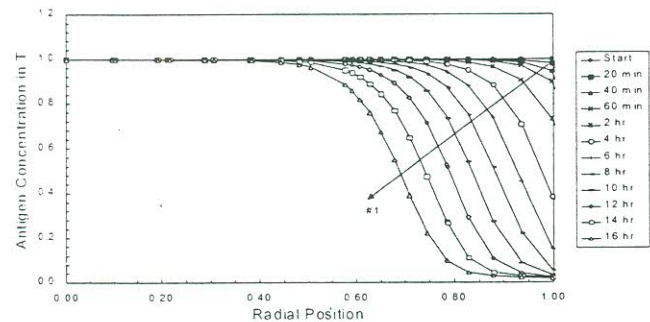


Fig. 2 Free antigen concentration (nondimensional form) in tumor nodule.

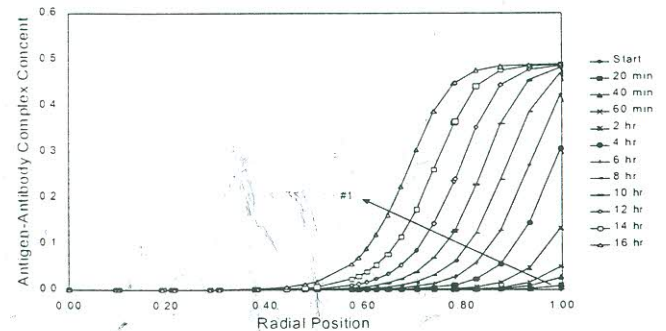


Fig. 3 Antigen-Antibody Complex concentration (nondimensional form) in tumor nodule.