Integrated Microscopic-Macroscopic Pharmacology of Monoclonal Antibody Radioconjugates: The Radiation Dose Distribution

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ABSTRACT

Accurate dosimetry is essential for the assessment of radioimmunotherapy. Most often studied to date has been the macroscopic dosimetry related to organ and tumor distribution of the radiolabeled antibody, but the question of microscopic dose heterogeneity is also important. To address the latter issue, we have taken an integrated approach to the pharmacology, taking into account whole-body distribution, transcapillary transport, percolation through the tumor interstitial space, antigen-antibody interaction, and antibody metabolism. The first step is to simulate the spatial antibody concentration profile in a tumor as a function of time after i.v. (e.g., bolus) injection, using reasonable values for the parameters involved. The second step is to calculate, also as a function of time, the absorbed radiation dose distribution resulting from each concentration profile.

Parameter values for IgG pharmacology and a radiation point source function for $^{131}$I are used to explore the effect of antibody distribution profiles on absorbed dose in the tumor. The geometry simulated corresponds to a spherical nodule of densely packed tumor cells. Absorbed doses are calculated for radiation from a single nodule (e.g., a micrometastasis or prevacular primary tumor) and for a cubic lattice of such nodules (e.g., corresponding to nodular lymphoma). As noted in our previous studies, there is a "binding site barrier." Binding to antigen retards antibody percolation into the nodules; high antibody affinity tends to decrease percolation and give a higher absorbed dose near the surface of each nodule. Heterogeneous antibody distribution results in a heterogeneous absorbed dose. This is more apparent in the case of radiation from a single nodule than it is for radiation from within an array of nodules. Dehalogenation results in a lower absorbed dose over time, and the effect is more apparent at later times after injection.

PERC-RAD, the computer program package developed for these analyses, provides a convenient and flexible way to assess the impact of macroscopic and microscopic parameters on the distribution of radioimmunoconjugates and on the consequent profile of absorbed radiation dose in tumors. This mathematical model and the general principles developed here can be applied as well to other radiolabeled biological ligands.

INTRODUCTION

MAbs have the potential to target tumor cells because of their affinity for tumor-associated antigens. Radiolabeled MAb should in principle be able to irradiate tumor cells with minimal radiation to normal tissues. Investigators have reported partial remissions for various tumors using $^{131}$I or $^{90}$Y-conjugated MAb (1-4).

Accurate dosimetry at the microscopic level is essential for assessment of the potential therapeutic effectiveness of radioimmunotherapy. Dosimetry performed in clinical studies is usually based on noninvasive imaging procedures including planar gamma camera imaging and/or single photon emission computed tomography. However, these methods do not provide enough information for microscopic dosimetry due to limited spatial resolution (5). Tumors are histologically heterogeneous, and penetration of a tumor by MAb after i.v. administration can also be heterogeneous, a complex function of time and position (6-10). Since the absorbed radiation dose distribution is directly related to the distribution of MAb, we must expect it to be heterogeneous as well (11, 12). Long-range $\beta$ emitters like $^{90}$Y will tend to give more homogeneous radiation dose distribution than will relatively short-range $\beta$ emitters like $^{131}$I. $\alpha$ emitters such as $^{211}$At will tend to result in heterogeneous radiation dose distribution because of several factors: the stochastic variations in track structure ionization; target size and position; relative specific ionization with distance traveled; and heterogeneous MAb distribution. Therefore, for both $\alpha$ and $\beta$ emitters we need to understand the heterogeneity of MAb distribution and its implications for radiation dosimetry in tumors. Here, we describe studies for the $\beta$ emitters; the more complex case of $\alpha$ emitters will be considered elsewhere.

We have developed the computer program package PERC for simulating MAb distribution in tumor nodules (13-15). PERC calculates MAb concentration in the tumor as a function of time and position based on: (a) molecular weight and valence of the antibody; (b) global pharmacokinetic profile (e.g., following i.v. bolus injection); (c) penetration through the vascular wall; (d) diffusive and convective transport through interstitial space in the tumor; (e) antigen-antibody interaction; (f) antibody metabolism. One prediction based on simulations using PERC is that antibodies (and other ligands) are prevented from penetrating tumors by the very fact of their successful binding to antigen. According to this "binding site barrier" hypothesis, high affinity and high antigen density can increase the heterogeneity of antibody distribution (13-15). Once PERC has been used to calculate the MAb concentration as a function of time and position in the tumor nodule, the radiation point source strength can also be calculated as a function of time and position.

Radiation dose profiles from a point source have been determined by several investigators, using empirical and theoretical approaches (16-20). Splicing together information on microscopic MAB distribution and the point source function of ionizing radiation (radioisotope attached to MAb) enables us to predict the microscopic cumulative absorbed dose in tumor. We have combined PERC and the point source function in one program package and have termed it PERC-RAD. Solutions were generated on a CRAY X-MP 24 (Cray Research, Inc., Mendota Heights, MN).

The spirit of this analysis should be clearly understood at the outset. There are still many unanswered questions about the factors that determine antibody distribution. Also, configurations of tumor nodules and tumor capillaries are too complex and difficult to model completely. Hence, our aim is to provide an aid to concept development and a guide to further experimentation. A central consideration is that nonuniform MAb...
distribution in the tumor may result in heterogeneous absorbed dose distribution. $^{131}$I, the isotope most commonly used in early clinical studies, is used for this analysis. What is surprising to us is the degree of microscopic dose heterogeneity indicated by these calculations. Absorbed dose calculations have also been done to examine the effect of heterogeneous MAb distribution for other $\beta$ emitters.$^6$

### MATERIALS AND METHODS

MAb distribution in tumor nodules was simulated using the PERC program package (14, 15). PERC simulates MAb distribution in tumors by splicing together information on global pharmacokinetics, transport across the capillary wall, diffusive/convective penetration through the tumor interstitial space, antigen-antibody interaction, and metabolism (14, 15).

MAb concentration in a spherical nodule was simulated (15). A single such nodule (Fig. 1A) would correspond to an isolated microscopic metastasis. An array of such nodules would correspond in a general way to nests of tumor cells in a macroscopic tumor. More specifically, our calculations for an array (Fig. 1B) are based on the quite regular structure of nodular lymphoma, which consists of dense aggregates of cells several hundred $\mu m$ across. The interstices between nodules contain principally nontumor cells, stromal elements, and most of the blood vessels. Measurements and appropriate geometric calculations based on fixed sections of nodular lymphoma yielded an average nodule radius of 222 $\mu m$ and a center-to-center distance of 600 $\mu m$. These numbers were used in the calculations described here (Table 1), although the exact values are of only secondary importance. These nodules are of about the size to which tumor spheroids can grow without central necrosis.

For these calculations the global pharmacokinetics of IgG following i.v. injection were simulated using the same parameter values as those used in a previous study (15). These values were obtained by fitting biexponentials (Table 2) to measurements of plasma $^{111}$In-labeled 9.2.27 concentration in melanoma patients (21). Those parameter values were used for simulating the plasma MAb concentration ($c_p, M$) in blood capillaries, including those of the tumor. MAb transport ($J_n$) across the capillary wall is rendered here as

$$J_n \approx P_{ef}(c_p - c_l) \quad (A)$$

where $P_{ef}$ is the effective capillary permeation constant (cm/s) and $c_l$ is the free MAb concentration within the nodule at its surface (m). Since the nodule is radially symmetrical and there is no sink in the center, MAb is assumed to enter and leave through the nodule's surface. If, for example, the transcapillary transport is assumed to take place largely by convection (22), and return to the circulation is assumed to be via the lymphatics (23, 24), then a more appropriate (though still approximate) expression would be

$$J_n \approx P_{ef} c_p - L c_l \quad (B)$$

where $L$ is the elimination rate through the lymphatics. This would have the effect of adding one additional free parameter to the system. We chose to avoid this additional complication, which would not be expected to change the major conclusions here. Elsewhere, we include transcapillary convection and lymphatic efflux explicitly, using a nonequilibrium thermodynamic formulation.$^7$ The choice of efflux model will be more significant at late time points than at early ones. We have previously discussed the relationship of $P_{ef}$ to diffusive and convective transport (14, 15).

The spherical nodule of radius $R = 222 \mu m$ is divided into $N$ (set as $N = 30$ in this study) thin concentric spherical shells, each at radial position $r_i$ (for $i = 1, \ldots, N$). The nodule is taken to be radially symmetrical, and there is assumed to be no convection within it, although there may be convection in the surrounding region. Radially symmetric diffusion in a sphere is governed by the following differential equation for free MAb at position $r$:

$$\frac{\partial c_i}{\partial t} = D \left( \frac{\partial^2 c_i}{\partial r^2} - \frac{2 \partial c_i}{\partial r} \right) - k_i c_i + k_{ei} \quad (C)$$

and free antigen concentration is governed by

$$\frac{\partial c_l}{\partial t} = -n_k c_l + n_k c_{ei} \quad (D)$$

where $c_{ei}$ is the initial MAb concentration.

#### Table 1 Parameter values used for the baseline calculation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline value</th>
</tr>
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<tbody>
<tr>
<td>$R$</td>
<td>Radius of nodule</td>
</tr>
<tr>
<td>$X_L$</td>
<td>Intermodular distance</td>
</tr>
<tr>
<td>$D$</td>
<td>Effective interstitial diffusion coefficient</td>
</tr>
<tr>
<td>$P_{ef}$</td>
<td>Effective capillary permeation constant</td>
</tr>
<tr>
<td>$c_p$</td>
<td>Initial MAb concentration in plasma</td>
</tr>
<tr>
<td>$s$</td>
<td>Total antigen concentration in tumor</td>
</tr>
<tr>
<td>$n$</td>
<td>Valence of the MAb</td>
</tr>
<tr>
<td>$A_0$</td>
<td>Initial specific activity of MAb</td>
</tr>
<tr>
<td>$\lambda$</td>
<td>Decay constant of $^{131}$I</td>
</tr>
</tbody>
</table>

$^a$ Based on Ref. 10.  
$^b$ Approximately calculated by taking into account measured microvascular surface areas per unit volume, microvascular permeabilities, and nodule volumes (32–34).  
$^c$ Based on Ref. 15.

#### Table 2 Parameter values for plasma MAb pharmacokinetics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>$c_p$</td>
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</tr>
<tr>
<td>$c_l$</td>
<td>$1.9 \times 10^{-4}$</td>
</tr>
<tr>
<td>$c_0$</td>
<td>0.73</td>
</tr>
<tr>
<td>$c_1$</td>
<td>$7.4 \times 10^{-4}$</td>
</tr>
</tbody>
</table>

$^c$ Biexponential fit:

$$c_p = c_0(e^{-\alpha_1 t} + \alpha_2 e^{-\alpha_3 t})$$

where $c_0$ is the initial MAb concentration.
where \(c_0\) is the concentration of free MAb (M); \(s_i\) is the concentration of free antigen (M); \(c_{b,i}\) is the concentration of bound MAb (M); \(c_{mb,i}\) is the concentration of total MAb (M); \(k_f\) is the forward rate constant for specific binding (M\(^{-1}\)s\(^{-1}\)); \(k_r\) is the corresponding reverse rate constant (s\(^{-1}\)); \(n\) is the valence of antibody; \(D\) is the effective interstitial diffusion coefficient (cm\(^2\)/s); and \(r_i\) is the radial distance from the center of the nodule (µm). Note that the sign convention has been changed from that in Ref. 15. In this study, \(D\) was taken as 1.3 \times 10^{-4} \text{cm}^2/\text{s} (15), and \(P_{n,e}\) was taken as 8.18 \times 10^{-8} \text{cm/s} . Antigen concentration in the nodule (expressed in terms of interstitial volume) was taken as 1.0 µM. These parameter values were fixed for this study (as summarized in Table 1). \(k_f\) and \(k_r\) were varied to test the effect of MAb distribution on the absorbed radiation dose profiles.

The antibody molecules can be considered as single-emission point sources of radiation. The theoretical isotropic point-source energy distribution can be characterized for each \(\beta\)-emitting radionuclide. This distribution describes the theoretical absorbed dose from a point source as a function of distance (the “point source function”). Point source functions for some of the isotopes used in radioimmunoa therapy are available in analytical form (18-20). Combining MAb concentration profiles in the tumor nodules with this function, we can calculate absorbed dose as a function of time and position for the surrounding region. For simplicity, MAb concentration in the extranodular space was assumed to be zero for the purpose of integrating the point source function. This assumption will be quite reasonable when selective uptake of antibody dominates over concentrations in plasma and in interstitial spaces between nodules. This is more likely to be the case at later time points after injection.

The instantaneous absorbed dose rate \(D_{a,i}(\text{Gy/h})\) at time \(t\) and position \(x,y,z\) (in either the nodule or the internodular space) from the single nodule (Fig. 1A) is governed by the expression

\[
D_{a,i}(x,y,z,t) = \int \int \int F(s) c_{b,i}(x',y',z',t) e^{-\frac{s_i}{D} (x-x')^2 (y-y')^2 (z-z')^2} \; dx'dy'dz' 
\]

where \(c_{b,i}(x',y',z',t)\) is total MAb concentration in the tumor nodule at the position \(x',y',z'\) (defined in Cartesian coordinates) at time \(t\); \(A_0\) is the initial specific activity of MAb (MBq/nmol); \(\lambda\) is the decay constant of the \(\beta\) emitter; \(s\) is the distance from the target; \(s_i\) is the initial distance from the target to the point source function; \(F(s)\) is the point source function for the particular isotope. For the present study, we have chosen the analytical representation of the \(^{131}\text{I}\) dose point kernel studied by Prestwich et al. (19) for the point source function \(F\). In Fig. 2 this function is compared with tabulated data from Berger (16), Cross et al. (17), and Fisher (a) using a method previously published by Traub et al. (25) for estimating \(\beta\) doses to skin surfaces. The results agree within a few percent.

Cumulative absorbed dose \(\bar{D}_{a,i}(\text{Gy})\) at time \(t\) and position \(x,y,z\) with relation to the single nodule is obtained from the expression

\[
\bar{D}_{a,i}(x,y,z,t) = \int_0^t D_{a,i}(x,y,z,t') dt 
\]

The instantaneous absorbed dose rate \(D_{a}\) from multiple nodules at time \(t\) at position \(x,y,z\) is calculated by summation of the absorbed dose from each nodule (obtained by Equation E) integrated over all nodules near enough to contribute (Fig. 1B)

\[
D_{a} = \sum_i \sum_y \sum_x \bar{D}_{a,i}(x,y,z,t) 
\]

The array size used for calculation was taken such that the distance from target to the most distant nodule is larger than the maximum range of the isotope. The range of the highest-energy \(\beta\) emission of \(^{131}\text{I}\) is 0.337 g/cm\(^2\), and the density of tumor is approximately 1.05 g/cm\(^3\). Hence, the maximum range is about 0.321 cm, and an array size of six on each side was therefore sufficient to model a tumor of infinite size.

Cumulative absorbed \(\beta\) dose at time \(t\) and position \(x,y,z\) resulting from isotope in the infinite array of nodules is governed by

\[
D_{a,m} = \int_0^t D_{a} dt 
\]

For the calculations here, the initial MAb concentration of plasma was taken as 100 nm, and the \(^{131}\text{I}\) specific activity of MAb was taken as 55.6 MBq/nmol (10 mCi/mg). These values were considered to be representative for \(\beta\)-emitting radioimmunoconjugates, although there is clearly considerable variation in the numbers pertinent to various clinical studies. For the standard 70-kg person with a plasma volume of 3 liters, this MAb concentration and the specific activity correspond to 45 mg IgG and 1.67 \times 10^4 MBq (450 mCi). Absorbed doses are calculated as a function of time and position for (a) the radiation from a single nodule and (b) the radiation from an indefinitely large cubic array of nodules. The former case represents an “inherent” absorbed dose profile for the single nodule; the latter includes the “mass” effect of multiple nodules and reflects absorbed dose in a larger tumor. The cubic array, rather than a hexagonal or random one, is used to represent multiple nodules in a tumor because it is easier to visualize. Previous studies show this assumption to be a good approximation, based on statistical analyses of stereographic histological images.\(^7\) The results are not expected to differ qualitatively from those for the other array types. Effects of the loss of activity due to dehalogenation of \(^{131}\text{I}\) are also examined.

**RESULTS**

Figs. 3, 4, and 5 show the \(^{131}\text{I}\)-IgG concentration profiles and instantaneous absorbed dose rate profiles from a single nodule and an indefinitely large array of nodules. Results are shown for \(^{131}\text{I}\)-IgG for different affinities (\(K_a = 1.0 \times 10^6, 1.0 \times 10^9, 1.0 \times 10^{10} \text{M}^{-1}\)) and times after i.v. injection (48 and 144 h). Higher MAb affinity results in more heterogeneous MAb distribution as noted previously (14). Lower affinity leads to lower MAb concentrations near the surface of a nodule and higher concentrations near the center than those calculated for higher affinity. Higher MAb affinity results in a higher concentration at the surface of a nodule (at 222 µm) and a higher instantaneous absorbed dose (i.e., a higher “ridge” in the figure).

\(^7\) D. R. Fisher, personal communication.

\(^8\) Hui and D. R. Fisher, Battelle Laboratories, unpublished observations.
Fig. 3. MAb concentration (A, D), instantaneous absorbed dose from a single nodule (B, E), and instantaneous dose from multiple nodules (C, F) of $^{131}$I-MAb ($K_a = 10^9$ M$^{-1}$) at 48 h (A–C) and 144 h (D–F) after i.v. injection. In each panel there is a profile on the x-y plane out to 300 µm (half of the internodular distance) from the center of the nodule, z-axes (vertical axes), MAb concentration (nM; A and D) and absorbed dose (mGy/h; B, C, E, and F). A “ridge” can be seen at about 222 µm (the surface of the nodule) in each case.

at this radial distance from the center. Even though MAb concentration near the center of the nodule is nearly zero for higher-affinity MAb, absorbed doses there are higher than those for lower-affinity MAb.

Fig. 6 compares contour maps of MAb concentration profiles with the cumulative absorbed doses for a single nodule and for multiple nodules through 144 h after i.v. injection. Results are shown for different affinities ($K_a = 1.0 \times 10^8, 1.0 \times 10^9,$ and $1.0 \times 10^{10}$ M$^{-1}$). Higher affinity results in higher concentration at the surface of the nodule (at 222 µm), and MAb penetration toward the inside of the nodule (Fig. 6, left-hand panels) is retarded compared with that for lower affinity. As a result, MAb concentration in the deep sites of the nodule is higher for lower-affinity MAb. Cumulative absorbed doses both from a single nodule and from multiple nodules show a peak near the surface of the nodule through 144 h. Higher affinity leads to higher cumulative absorbed dose near the surface. Cumulative absorbed doses are more heterogeneous over space for higher affinity, and this is more apparent for the case of radiation from a single nodule.

In this particular parameter set, the radiation dose to deep sites in the nodule shows an interesting behavior as a function of MAb affinity. In the case of radiation from a single nodule, lower affinity does not necessarily show a lower cumulative absorbed dose near the center of the nodule than that for higher-affinity MAb (Fig. 7A). When radiation comes from multiple nodules, higher affinity results in a higher absorbed dose, but lower affinity leads to a more homogeneous dose distribution (Fig. 7B). When the absorbed radiation dose is expressed as the average over the entire tumor mass, as is the case in most clinical studies, affinity also has a greater effect on the average cumulative radiation dose in the multiple-nodule case. In contrast, it has only a small effect on the average area under the curve of MAb concentration and the average cumulative dose in the single-nodule case with parameter values used in this study (Table 3).

The effect of dehalogenation on absorbed doses is shown in Fig. 8. Rates of dehalogenation were chosen as 0%, 10%, and 20%/day. $^{131}$I released from the antibody was assumed to disappear quickly from the system and have no effect on irradiation to tumor. Dehalogenation lowers the cumulative absorbed dose. This effect is more apparent at later times, and the cumulative absorbed dose for 20%/day dehalogenation is about half of that for no dehalogenation at 144 h in this calculation.

**DISCUSSION**

The principal purpose of this study was to predict the spatial and temporal profiles of absorbed radiation dose in a tumor nodule after injection of radiolabeled MAb. A first obvious limitation of the analysis is that tumors are histologically heterogeneous, and we do not expect simulated dose calculations to correspond with those in any actual tumor. However, simulations such as these can help to sort out concepts and provide
INTEGRATED PHARMACOLOGY OF RADIOLABELED MAb AND RADIATION DOSE

MAb concentration (144 hours)

Fig. 5. As in Fig. 2 but for \( K_a = 10^{10} \text{ M}^{-1} \).

a guide to further experimentation when the system is complex.

MAb distribution in a tumor can be heterogeneous for many histological, physiological, and physical reasons (26–30). Accurate microscopic dosimetry must take account of the consequent heterogeneous radioactivity distribution. Howell and Rao (11) have studied macroscopic dosimetry for various isotopes with linearly or exponentially radial concentration gradient in a spherical model. Humm and Cobb (12) have also studied nonuniformity of tumor dose in a random distribution of cells at the microscopic level. Fisher (31) studied the microdosimetry of \( \alpha \) emitters in radioimmunotherapy applications and described the dose distributions in statistical terms using the “probability density” of specific energy. These studies, however, did not take account of MAb transport in tumors and assumed that MAb concentration was fixed over time.

PERC-RAD integrates major factors from macroscopic and microscopic MAb kinetics (as presented in PERC) with radiation point-source functions to examine the heterogeneity of radiation dose distribution. MAb concentration in the tumor is simulated as a function of time and position. Among many factors in the system which could have been explored, we chose to examine the effect of MAb affinity for the purposes of this presentation.

Antibodies against tumor-associated antigens have the advantage of selective binding to specific tumor sites. Antigen-antibody binding in the tumor node is predicted to impose a “binding site barrier” that retards MAb percolation and causes a heterogeneous distribution (13–15).

Lower doses at the center of a nodule may be a disadvantage if the aim is to irradiate all tumor cells, including those distant from the vascular supply. Microscopic cumulative doses are predicted to be more heterogeneous for higher-affinity MAb. For \( K_a = 10^{10} \text{ M}^{-1} \), cumulative doses at the center of a nodule (the lowest doses) at 144 h after i.v. injection are 150.1 and 334.3 cGy. Those at the surface of the nodule (the highest dose) are 308.7 and 522.1 cGy for the single- and multiple-nodule cases, respectively. The ratios of the highest to lowest dose are 2.06 for the single-nodule and 1.56 for the multiple-nodule array. Thus, increasing affinity is predicted to result in more heterogeneous dose distribution. And in certain time ranges and when penetration of the capillary wall is rate limiting, higher affinity may even decrease slightly the average dose to a small tumor (Fig. 7A). The reason is that some of the \( \beta \)-radiation dose from antibody near the edge of a nodule will be deposited outside of the nodule. Even in a large tumor, increasing affinity is predicted to result in more heterogeneous dose distribution, although it will generally increase the average dose.

If a long-range \( \beta \) emitter (e.g., yttrium-90) is used for radioim-
Table 3 The volume-averaged ratio of specific MAb to nonspecific MAb at 144 h

<table>
<thead>
<tr>
<th>Affinity of MAb (K_a, M⁻¹)</th>
<th>AUC of MAb concentration</th>
<th>Cumulative dose (single nodule)</th>
<th>Cumulative dose (multiple nodules)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10⁻⁴</td>
<td>4.41</td>
<td>4.82</td>
<td>5.45</td>
</tr>
<tr>
<td>10⁻⁵</td>
<td>4.60</td>
<td>4.14</td>
<td>5.92</td>
</tr>
<tr>
<td>10⁻⁶</td>
<td>4.67</td>
<td>5.12</td>
<td>8.02</td>
</tr>
</tbody>
</table>

* Value for specific MAb; value for nonspecific MAb.
* AUC: area under the curve.
* Average in the nodule.

Fig. 8. The effect of dehalogenation of the MAb. Cumulative absorbed dose from multiple nodules with no dehalogenation (---), 10% dehalogenation/day (-----), and 20% dehalogenation/day (- - - -) at 48 h (A) and 144 h (B) after i.v. injection. K_a = 10⁻⁴ M⁻¹. Abscissa, distance from the center of the nodule (0 µm) to 300 µm (half of the internodular distance) on the axis of Fig. 1.

REFERENCES


15. Fujimori, R., Covell, D. G., Fletcher, J. E., and Weinstein, J. N. A modeling...
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