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ON A BOUNDARY-VALUE PROBLEM POSED BY CANCER THERAPY WITH NEUTRON BEAMS

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Abstract

This paper contains a detailed formulation of advanced tumor therapy with neutron beams as a mixed boundary initial value problem for multigroup neutron diffusion in a composite 3D multiregional system. By applying a vector-matrix composite region finite-integral transformation we derive the principal operational solution to this problem as the group-regional neutron flux distribution inside the tumor 3D subregions. The principal solution is then converted into expressions of various order approximation, which may be directly programmed on a computer.

1. Introduction

Nuclear particle beam radiotherapy of certain tumors is currently a technologically advanced and effective means in the selective destruction of cancer cells.

Neutron therapy in particular could be more effective than radiation therapy with x-rays or charged particles for certain advanced, typically multi-regional 3D tumors because it has the propensity to kill tumor cells which are low in oxygen content and often become resistant to alternative forms of radiation [3, 10].

The (30–350) Mev cyclotrons commercially available nowadays which are dedicated to proton or neutron therapy are able to produce several beams that can rotate around the patient simultaneously. Proton or deuteron beams may, if required, be converted to neutron beams with space- $\mathbf{r}$, energy- E (or speed- v), and time- t dependent localized currents $J(\mathbf{r}, E, t)$ through, for example, bombarding various targets madeup of Be^9 or Li^7, say.

Such installations facilitate to a great extent 3D radiation therapy, image registration, 3D treatment plan optimization, radio-surgery and conformal radiotherapy with multileaf collimators [12].

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The present communication is arranged as follows. Cancer therapy with neutron beams is formulated as a neutronics boundary-value problem in the next section. Section 3 studies the structure of the analytic exact solution of this boundary-value problem. The final section, 4, is devoted to deriving various approximants to the exact operational solution of the boundary-value problem.

2. Boundary-value problem formulation

Neutron beams for cancer therapy can be obtained from a variety of origins including radio-isotopic and fission sources, nuclear reactors or various particle accelerators.

2.1. Neutron source Modern neutron therapy is conceived in association with high energy (30–350) Mev proton or deuteron bombardment of various targets including, in principle (but not in practice) some of the tumor tissues. The energy spectrum of emitted neutrons is fairly stable over a wide range of bombarding proton energies [2] because it is dominated by evaporative neutrons with energies typically below 20 Mev. Only forward anisotropy of neutron emission is increased by boosting the proton bombarding energy in a way leaving the energy spectrum virtually unaffected.

A group regional neutron source term $Q_{ik}(\mathbf{r}, t)$ in neutron therapeutic applications may be realised by, for example, a bombarding beam $I_i(\mathbf{r}, t)$ of high energy protons that is applied to the surface of the region R_i or perhaps by implanting an encapsulated C_f^{252} fission neutron source into the cancerous composite domain.

2.2. A composite domain Radiotherapy in general leads in many applications to an acute exposure of the patient to a large dose of radiation received over a short period of time.

Cancer therapy with neutrons invokes the problem of unsteady multigroup neutron diffusion inside a finite composite cancerous domain R bounded by a surface S_0 and divided into N finite subregions as illustrated in Figure 1. Each subregion, which may be of malignant or healthy tissues, is nonhomogeneous but isotropic in neutron scattering and may have a specific tolerance, Γ_i, for the maximum permissible absorbed dose of radiation.

The common interface $S_{ij} = S_{ji}$ of any two adjacent subregions R_i and R_j (with boundary surfaces S_i and S_j) is in perfect physical contact. In the event that S_i and S_j $(i \neq j)$ have no common interface, then we let $S_{ij} = 0$. If a subregion R_j is not in contact with the medium external to R then we let $S_{j0} = 0$.

Therefore the surface S_i of any subregion S_i may be given by

$$S_i = S_{i0} + \sum_{j=1}^{N} (1 - \delta_{ij}) S_{ij}, \tag{1}$$

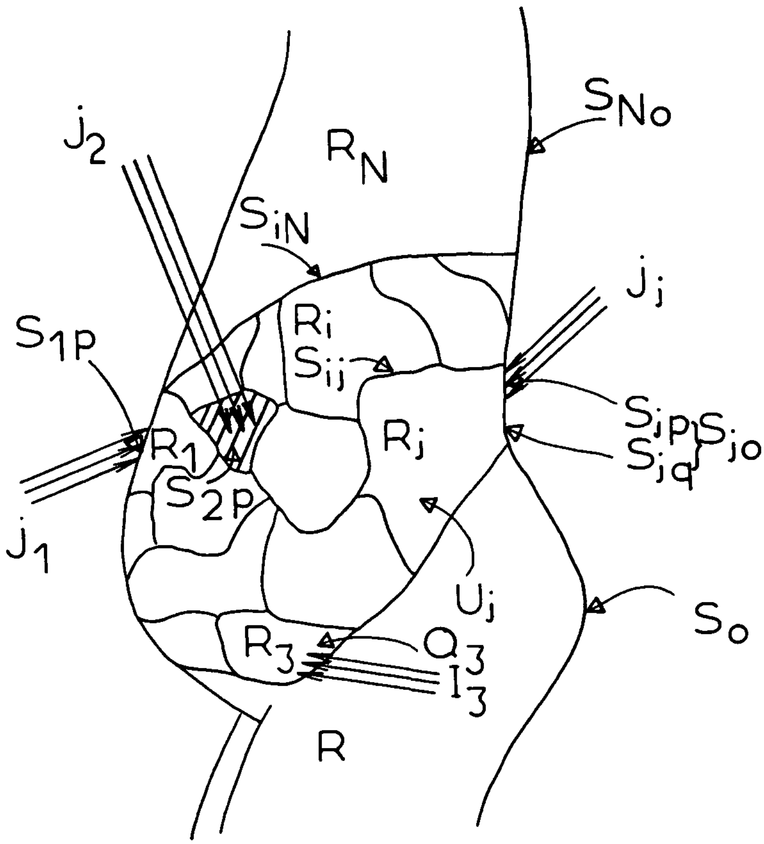

FIGURE 1. Sketch to illustrate the human body as a composite cancerous region that is irradiated by external neutron beams.

where δ_{ij} is Kronecker's delta. The cancerous composite system geometry is arbitrary but for the restriction that the shape of the outer surface of each individual subregion S_{i0} as well as the overall outer surface of the system

$$S_0 = \sum_{j=1}^{N} S_{i0} \tag{2}$$

should be non-re-entrant to neutrons.

It is not unreasonable to assume further that the cancer growth time, which is comparable to the latent period characteristic of biological radiation exposure, is much longer than the radiation therapy time, so the composite region geometry is time independent.

2.3. Linearity In practical therapy with neutron beams some subdomains in the cancerous composite domain may have to contain certain burnable isotopes like, for example, B^{10}. The rate of elimination of neutrons of the k-th energy group [9] by such isotopes inside the i-th region, is representable by

$$\Sigma_{ik}^{b}(\mathbf{r},t)\varphi_{ik}(\mathbf{r},t), \tag{3}$$

where

$$\Sigma_{ik}^{b}(\mathbf{r},t) = N_i^b(\mathbf{r},t)\sigma_{ik}^{b} \tag{4}$$

and

$$\Sigma_{ik}^{b}(\mathbf{r}) = N_i^b(\mathbf{r},0)\sigma_{ik}^{b} \tag{5}$$

is the total macroscopic cross section of the burnable isotope, σ_{ik}^{b} being the microscopic total cross section of this isotope and $N_i^b(\mathbf{r})$ is its space-time dependent regional density. Here $\varphi_{ik}(\mathbf{r})$ is the group regional neutron flux.

The kinetics of this isotope density are governed by the differential equation

$$\frac{\partial}{\partial t}N_i^b(\mathbf{r},t) = -\sigma_{ik}^{b}\varphi_{ik}(\mathbf{r},t)N_i^b(\mathbf{r},t) \tag{6}$$

whose solution is

$$N_i^b(\mathbf{r},t) = N_i^b(\mathbf{r},0)\exp\left[-\sigma_{ik}^{b}\int_0^t \varphi_{ik}(\mathbf{r},\tau)d\tau\right]. \tag{7}$$

By virtue of (3)–(5) the last relation leads to

$$\Sigma_{ik}^{b}(\mathbf{r},t)\varphi_{ik}(\mathbf{r},t) = \Sigma_{ik}^{b}(\mathbf{r})\exp\left[-\sigma_{ik}^{b}\int_0^t \varphi_{ik}(\mathbf{r},\tau)d\tau\right]\varphi_{ik}(\mathbf{r},t). \tag{8}$$

This nonlinear rate (in the regional group flux) may be linearized however only when

$$\int_0^t \varphi_{ik}(\mathbf{r},\tau)d\tau \ll 1/\sigma_{ik}^{b}, \tag{9}$$

to permit

$$\Sigma_{ik}^{b}(\mathbf{r},t)\varphi_{ik}(\mathbf{r},t) \approx \Sigma_{ik}^{b}(\mathbf{r})\varphi_{ik}(\mathbf{r},t). \tag{10}$$

In the general case when (9) applies we shall adopt the notation

$$\Sigma_{ik}^{a}(\mathbf{r}) + \Sigma_{ik}^{b}(\mathbf{r}) = \Sigma_{ik}^{t}(\mathbf{r}) \tag{11}$$

in which $\Sigma_{ik}^{t}(\mathbf{r})$ denotes the group total macroscopic cross section and $\Sigma_{ik}^{a}(\mathbf{r})$ is the group regional total absorption cross section of non-burnable isotopes.

2.4. Regional therapy control Alternative methods for cancer radiotherapy which include therapy with selectively accumulating radioisotopes [8] such as J^{131} and Tc^{99}, injected colloidal radioactive metals like Au^{198} or Zn^{63} or artificially radioactive suspensions containing Y^{90} or Lu^{177}, say, have long been in practice [4]. A common problem with all alternatives has been in their nonuniformity of distribution inside some kinds of cancers.

The effectiveness of neutron therapy may also be intensified regionally by injecting a suspension that contains a biologically acceptable strong neutron absorber like B^{10} whose absorption *viz.* $B^{10}(n, \alpha)Li^7$ is accompanied by the emission of ionising α particles.

The rate of group regional depletion or multiplication of neutrons as a result of applying such alternative therapeutic techniques is

$$U_{ik}(\mathbf{r}, t)\varphi_{ik}(\mathbf{r}, t). \tag{12}$$

Here the space-time dependent arbitrary sign regional therapy control function $U_{ik}(\mathbf{r}, t)$ arises from the fact that the distribution of radioactive nucleide in a human being is a space-time dependent process with complex kinematics and dynamics [6].

The function $U_{ik}(\mathbf{r}, t)$ could moreover represent a regional accumulation, assimilation or elimination of certain neutron scattering or absorbing isotopes through injection or effluxion. Relation (12) may moreover in some situations simulate the function of hormones or drugs administered to stimulate the function of certain organisms in the human body during radiotherapy.

All these considerations must be decisive in defining the regional dosimetric levels

$$h_i = \sum_{k=1}^{G} \int_0^t \int_{R_i} \omega_{ik}(\mathbf{r}, t)\varphi_{ik}(\mathbf{r}, \tau) dR d\tau \leq \Gamma_i \tag{13}$$

in which $\omega_{ik}(\mathbf{r}, t)$ is the group regional biological effectiveness of the neutron radiation in the N-dimensional composite system.

2.5. Master PDEs The group neutronic properties of each subregion, whether healthy or malignant, are characterized by its space-dependent diffusion coefficient and macroscopic total and scattering cross sections $D_{ik}(\mathbf{r})$, $\Sigma_{ik}^t(\mathbf{r})$ and $\Sigma_i^{jk}(\mathbf{r})$ respectively.

The multigroup description of neutron diffusion in such systems poses [9, 6] the problem of solving the system of coupled PDEs

$$\begin{aligned} V_k^{-1}\frac{\partial}{\partial t}\varphi_{ik}(\mathbf{r}, t) &= \nabla\cdot[D_{ik}(\mathbf{r})\nabla\varphi_{ik}(\mathbf{r}, t)] - \Sigma_{ik}^t(\mathbf{r})\varphi_{ik}(\mathbf{r}, t) \\ &+ \sum_{j=1}^{G} \Sigma_i^{jk}(\mathbf{r})\varphi_{ij}(\mathbf{r}, t)U_{ik}(\mathbf{r}, t)\varphi_{ik}(\mathbf{r}, t) + Q_{ik}(\mathbf{r}, t), \\ i &= 1, 2, 3, \dots, N; \quad k, j = 1, 2, 3, \dots, G, \end{aligned} \tag{14}$$

where N and G stand respectively for the number of regions and neutron energy groups.

2.6. Boundary conditions Various boundary conditions of the third kind at all outer regional surfaces of the system are subject to the usual coupling conditions and to the initial conditions for the regional group neutron fluxes

$$\varphi_{ik}(\mathbf{r}, t) = F_{ik}(\mathbf{r}). \tag{15}$$

Note however that in almost all therapeutic situations

$$F_{ik}(\mathbf{r}) = 0, \quad \forall i, k.$$

The possible irradiation of a cancerous composite region by more than one group regional beam with a current $J_{ik}(\mathbf{r}, t)$, applied on S_{ip}, necessitates the imposition on the regional outer surface S_{i0} of the general nonhomogeneous radiative boundary condition

$$\begin{gathered} D_{ik}(\mathbf{r})\frac{\partial}{\partial n_{i0}}\varphi_{ik}(\mathbf{r}, t) \pm \gamma_{i0}\varphi_{ik}(\mathbf{r}, t) = -J_{ik}(\mathbf{r}, t) \quad \mathbf{r} \text{ on } S_{i0}, \\ i = 1, 2, 3, \ldots < N; \; k = 1, 2, 3, \ldots, G, \end{gathered} \tag{16}$$

with $J_{ik}(\mathbf{r}, t) \neq 0$ on S_{ip} and $J_{ik}(\mathbf{r}, t) = 0$ on S_{iq}.

Clearly $S_{i0} = S_{ip} + S_{iq}$ and $S_{ip} \neq 0$ only for a small number of subregions which are irradiated by a number $M < N$ of external neutron beams. One should also expect $S_{i0} = S_{iq}$ to hold for some regions; of course in fully internal regions $S_{i0} = 0$. Moreover, γ_{i0} is the transport theory corrected ratio of the diffusion coefficient to the extrapolation length, which is invariably equal to 0.47 for all i-regions and all energy groups, that is,

$$\gamma_{i0} = \begin{cases} 0, & \mathbf{r} \text{ on } S_{ip} \\ \gamma = 0.47, & \mathbf{r} \text{ on } S_{iq}. \end{cases} \tag{17}$$

Here $\frac{\partial}{\partial n_{i0}}$ denotes the normal derivative at the outer surface S_{i0} of the subregion R_i in the outward direction. The $+\gamma_{iq}$ and $-\gamma_{iq}$ in (16) are taken when this normal points respectively to the left and to the right side of an observer in R_i.

Therefore

$$\begin{gathered} D_{ik}\frac{\partial}{\partial n_{ip}}\varphi_{ik}(\mathbf{r}, t) \pm \gamma_{ip}\varphi_{ik}(\mathbf{r}, t) = -J_{ik}(\mathbf{r}, t), \quad \mathbf{r} \text{ on } S_{ip}, \\ i = 1, 2, 3, \ldots, M < N; \; k = 1, 2, 3, \ldots, G, \end{gathered} \tag{18}$$

$$\begin{gathered} D_{ik}\frac{\partial}{\partial n_{ip}}\varphi_{ik}(\mathbf{r}, t) \pm \gamma_{iq}\varphi_{ik}(\mathbf{r}, t) = 0, \quad \mathbf{r} \text{ on } S_{iq}, \\ i = 1, 2, 3, \ldots, < N; \; k = 1, 2, 3, \ldots, G. \end{gathered} \tag{19}$$

2.7. The boundary-value problem Now consider the matrix relation

$$\hat{\Sigma}_i(\mathbf{r},t) = \hat{U}_i(\mathbf{r},t) + \hat{\Sigma}_i^s(\mathbf{r}) - \hat{\Sigma}_i^t(\mathbf{r}) \tag{20}$$

in which

$$\hat{\Sigma}_i^s(\mathbf{r}) = \left\{\Sigma_i^{jk}(\mathbf{r})\right\}, \quad k, j = 1, 2, 3, \dots, G$$

is the matrix of regional intergroup scattering cross section and

$$\hat{U}_i(\mathbf{r},t) = \mathrm{Diag}[U_{i1}(\mathbf{r},t)U_{i2}(\mathbf{r},t)\cdots U_{iG}(\mathbf{r},t)]$$

is the diagonal matrix of group regional control functions. In association with (14) we write the multiregional neutronics boundary-value problem in the multigroup vector-matrix form

$$\hat{V}^{-1}\frac{\partial}{\partial t}\varphi_i(\mathbf{r},t) = [\nabla\cdot\hat{D}_i(\mathbf{r})\nabla + \hat{\Sigma}_i(\mathbf{r},t)]\varphi_i(\mathbf{r},t) + \mathbf{Q}_i(\mathbf{r},t),$$
$$i = 1, 2, 3, \dots, N, \tag{21}$$

$$\varphi_i(\mathbf{r},t) = \varphi_j(\mathbf{r},t), \quad \mathbf{r} \text{ on } S_{ij},\ i, j = 1, 2, 3, \dots, N,\ t > 0, \tag{22}$$

$$\hat{D}_i(\mathbf{r})\frac{\partial}{\partial n_{ij}}\varphi_i(\mathbf{r},t) = \hat{D}_j(\mathbf{r})\frac{\partial}{\partial n_{ij}}\varphi_i(\mathbf{r},t), \quad \mathbf{r} \text{ on } S_{ij},$$
$$i, j = 1, 2, 3, \dots, N,\ t > 0, \tag{23}$$

$$\hat{D}_i(\mathbf{r})\frac{\partial}{\partial n_{ip}}\varphi_i(\mathbf{r},t) \pm \gamma_{ip}\varphi_i(\mathbf{r},t) = -\mathbf{J}_i(\mathbf{r},t), \quad \mathbf{r} \text{ on } S_{ip},\ i = 1, 2, 3, \dots, M < N, \tag{24}$$

$$\hat{D}_i(\mathbf{r})\frac{\partial}{\partial n_{iq}}\varphi_i(\mathbf{r},t) \pm \gamma_{iq}\varphi_i(\mathbf{r},t) = 0, \quad \mathbf{r} \text{ on } S_{iq},\ j = 1, 2, 3, \dots, < N, \tag{25}$$

$$\varphi_i(\mathbf{r},0) = F_i(\mathbf{r}), \quad i = 1, 2, 3, \dots, N, \tag{26}$$

involving the column vectors

$$\begin{aligned}
\varphi_i(\mathbf{r},t) &= [\varphi_{i1}(\mathbf{r},t)\varphi_{i2}(\mathbf{r},t)\dots\varphi_{iG}(\mathbf{r},t)]^T,\\
\mathbf{F}(\mathbf{r}) &= [F_{i1}(\mathbf{r})F_{i2}(\mathbf{r})\dots F_{iG}(\mathbf{r})]^T,\\
\mathbf{Q}_i(\mathbf{r},t) &= [Q_{i1}(\mathbf{r},t)Q_{i2}(\mathbf{r},t)\dots Q_{iG}(\mathbf{r},t)]^T,\\
\mathbf{J}_i(\mathbf{r},t) &= [J_{i1}(\mathbf{r},t)J_{i2}(\mathbf{r},t)\dots J_{iG}(\mathbf{r},t)]^T,
\end{aligned} \tag{27}$$

and the diagonal matrices

$$\begin{aligned}
\hat{D}_i(r) &= \mathrm{Diag}[D_{i1}(\mathbf{r})D_{i2}(\mathbf{r})\dots D_{iG}(\mathbf{r})],\\
\hat{\Sigma}_j^t(r) &= \mathrm{Diag}[\Sigma_{i1}^t(\mathbf{r})\Sigma_{i2}^t(\mathbf{r})\dots\Sigma_{iG}^t(\mathbf{r})],\\
\hat{V}^{-1} &= \mathrm{Diag}[V_1^{-1}V_2^{-1}\dots V_G^{-1}].
\end{aligned} \tag{28}$$

Obviously $\partial/\partial n_{ij}$ denotes the normal derivative at interfaces S_{ij} between subregions R_i and R_j in the same sense from R_i to R_j.

3. Operational analysis

It should be observed that the variable coefficient boundary-value problem (21)–(28) is nonhomogeneous both in its differential equation (due to the $\mathbf{Q}_i(\mathbf{r}, t)$ term) and in its boundary conditions (due to the $\mathbf{J}_i(\mathbf{r}, t)$ term). Moreover, both of these terms are in principle space-time dependent.

Such a boundary initial value problem may have closed-form solution in terms of its Green's function [1] only for a single-region system. The construction of Green's functions for multiregional composite systems of arbitrary geometry is well-known to be formidably difficult, if not a practically impossible task. Moreover, even for the simplest case of a single-region system, the solution of such boundary initial non-homogeneous boundary-value problems is not amenable to standard eigenfunction expansions. Indeed if a single-region finite integral transform [5] is applied to solve such a single-region problem, the transformation of the partial differential equation (21) into an ordinary differential equation will not be possible because the eigenfunctions and eigenvalues of the corresponding eigenvalue problem would depend on both $\mathbf{r}$ and t, with a necessary continuum [7] in the eigenvalue spectrum. Certainly composite-region boundary-value problems require the application of composite-region finite integral transforms [11] for their solution.

Denote the group regional reduced source vector by

$$\mathbf{E}_i(\mathbf{r}, t) = \hat{V}\mathbf{Q}_i(\mathbf{r}, t) \tag{29}$$

and the group regional reduced current of the applied neutron beam vector by

$$\mathbf{Z}_i(\mathbf{r}, t) = \hat{V}\mathbf{J}_i(\mathbf{r}, t). \tag{30}$$

Next define the multigroup composite-region finite integral transform

$$H_N[\varphi_i(\mathbf{r}, t)] = \tilde{\varphi}_m(t) = \sum_{i=1}^{N} \int_{R_i} \boldsymbol{\theta}_{im}^T(\mathbf{r}, t)\hat{V}^{-1}\varphi_i(\mathbf{r}, t)dR \tag{31}$$

and the multigroup composite-boundary finite integral transform

$$W_N[\mathbf{Z}_i(\mathbf{r}, t)] = Z_m^*(t) = \sum_{i=1}^{N} \int_{S_{i0}} \boldsymbol{\theta}_{im}^T(\mathbf{r}, t)\hat{V}^{-1}\mathbf{Z}_i(\mathbf{r}, t)dS \tag{32}$$

with

$$\boldsymbol{\theta}_{im}(\mathbf{r}, t) = \mathbf{Y}_{im}(\mathbf{r}, t)/\|\mathbf{Y}_{im}\|_N \tag{33}$$

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and $\mathbf{Y}_{im}(\mathbf{r}, t)$ being the functional eigenvectors of the vector matrix eigen boundary-value problem [6, 11] auxiliary to (21)–(26).

$$\nabla \cdot \hat{D}_i(\mathbf{r})\nabla \mathbf{Y}_{im}(\mathbf{r}, t) + \lfloor \hat{\Sigma}_i(\mathbf{r}, t) + \alpha_m(t)\hat{V}^{-1}\rfloor \mathbf{Y}_{im}(\mathbf{r}, t) = \mathbf{0}, \tag{34}$$

$$\mathbf{Y}_{im}(\mathbf{r}, t) = [Y_{i1m}(\mathbf{r}, t)Y_{i2m}(\mathbf{r}, t)\cdots Y_{iGm}(\mathbf{r}, t)]^T, \quad \mathbf{r} \text{ in } R_i;\ i = 1, 2, 3, \dots, N.$$

$$\mathbf{Y}_{im}(\mathbf{r}, t) = \mathbf{Y}_{jm}(\mathbf{r}, t),$$

$$\hat{D}_i(r)\frac{\partial}{\partial n_{ij}}\mathbf{Y}_{im}(\mathbf{r}, t) = \hat{D}_j(r)\frac{\partial}{\partial n_{ij}}\mathbf{Y}_{jm}(\mathbf{r}, t), \quad \mathbf{r} \text{ on } S_{ij};$$

$$i, j = 1, 2, 3, \dots, N,\ t > 0, \tag{35}$$

$$\hat{D}_i(r)\frac{\partial}{\partial n_{ip}}\mathbf{Y}_{im}(\mathbf{r}, t) \pm \gamma_{ip}\mathbf{Y}_{im}(\mathbf{r}, t) = 0, \quad \mathbf{r} \text{ on } S_{ip};\ i, j = 1, 2, 3, \dots, M < N, \tag{36}$$

$$\hat{D}_i(r)\frac{\partial}{\partial n_{ij}}\mathbf{Y}_{im}(\mathbf{r}, t) \pm \gamma_{iq}\mathbf{Y}_{im}(\mathbf{r}, t) = 0, \quad \mathbf{r} \text{ on } S_{iq};\ i, j = 1, 2, 3, \dots, < N. \tag{37}$$

Here

$$\|\mathbf{Y}_{im}\|_N = \left\{\sum_{i=1}^{N}\int_{R_i}\mathbf{Y}_{im}^T(\mathbf{r}, t)\hat{V}^{-1}\mathbf{Y}_{im}(\mathbf{r}, t)dR\right\}^{1/2} \tag{38}$$

is a composite-region weighted norm of the $\mathbf{Y}_{im}(\mathbf{r}, t)$ vector and $\alpha_m(t)$ is the eigenvalue associated with this eigenvector.

The composite-region integral transforms (31) and (32) have respective inversion formulae

$$H_N^{-1}[\tilde{\varphi}_m(t)] = \varphi_i(\mathbf{r}, t) = \sum_{m=1}^{\infty}\tilde{\varphi}_m(t)\boldsymbol{\theta}_{im}(\mathbf{r}, t), \tag{39}$$

$$W_N^{-1}[Z_m^*(t)] = \mathbf{Z}_i(\mathbf{r}, t) = \sum_{m=1}^{\infty}Z_m^*(t)\boldsymbol{\theta}_{im}(\mathbf{r}, t). \tag{40}$$

After observing that the $\alpha_m(t)$ are independent of both $\mathbf{Q}_i(\mathbf{r}, t)$ and $\mathbf{J}_i(\mathbf{r}, t)$, that

$$\tilde{\varphi}_m(0) = \tilde{F}_m(0) \tag{41}$$

and writing

$$G_{mn}(t) = \sum_{i=1}^{N}\int_{R_i}\boldsymbol{\theta}_{im}^T(\mathbf{r}, t)\hat{V}^{-1}\frac{\partial}{\partial t}\boldsymbol{\theta}_{in}(\mathbf{r}, t)dR, \tag{42}$$

we can state the main result of this paper.

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THEOREM. *The group-regional solution vector of the composite-region boundary-value problem (21)–(28) is*

$$\varphi_i(\mathbf{r}, t) = \sum_{m=1}^{\infty} \tilde{\varphi}_m(t)\boldsymbol{\theta}_{im}(\mathbf{r}, t), \tag{43}$$

with coefficients $\tilde{\varphi}_m(t)$ that satisfy the system of ordinary differential equations

$$\begin{gathered}\frac{d}{dt}\tilde{\varphi}_m(t) + \alpha_m(t)\tilde{\varphi}_m(t) + \sum_{n=1}^{\infty} G_{mn}(t)\tilde{\varphi}_n(t) = \tilde{E}_m(t) - Z_m^*(t), \\ m = 1, 2, 3, \dots, \infty,\end{gathered} \tag{44}$$

subject to

$$\tilde{\varphi}_m(0) = \tilde{F}_m(0), \quad m = 1, 2, 3, \dots, \infty. \tag{45}$$

PROOF. Details of the proof of this theorem are given in the appendix.

Once a solution to (44)–(45) is found, the regional absorbed dose during cancer therapy with neutron beams is determined, *viz.*,

$$h_i = \sum_{m=1}^{\infty} \int_0^t \int_{R_i} \boldsymbol{\Omega}_i^T(\mathbf{r}, t)\tilde{\varphi}_m(t)\boldsymbol{\theta}_{im}(\mathbf{r}, t)\,dR\,d\tau, \tag{46}$$

where

$$\boldsymbol{\Omega}_i(\mathbf{r}, t) = [W_{i1}(\mathbf{r}, t)W_{i2}(\mathbf{r}, t)\cdots W_{iG}(\mathbf{r}, t)]^T. \tag{47}$$

4. Approximate solution

It is common knowledge that an exact solution to an infinite set of coupled differential equations like (44) is theoretically impossible. In practice, however, it is always possible to truncate the infinite sum in (44) leaving l terms and solve the [6] l-th order approximation,

$$\begin{gathered}\frac{d}{dt}\tilde{\varphi}_m(t) + \alpha_m(t)\tilde{\varphi}_m(t) + \sum_{n=1}^{l} G_{mn}(t)\tilde{\varphi}_m(t) = \tilde{E}_m(t) - Z_m^*(t), \\ m = 1, 2, 3, \dots, \infty,\end{gathered} \tag{48}$$

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subject to

$$\tilde{\varphi}_m(0) = \tilde{F}_m(0), \qquad m = 1, 2, 3, \ldots, \infty. \tag{49}$$

This is an initial-value problem also with an infinite system of ordinary differential equations but only the first l of which are coupled.

The first l-coupled equations of the system (48) may be written in vector-matrix form

$$\frac{d}{dt}\tilde{\varphi}(t) = \hat{A}(t)\tilde{\varphi}(t) + \tilde{\mathbf{E}}(t) + \tilde{\mathbf{Z}}(t), \tag{50}$$

subject to

$$\tilde{\varphi}(0) = \tilde{\mathbf{F}}(0), \tag{51}$$

with

$$\tilde{\varphi}(t) = [\tilde{\varphi}_1(t)\tilde{\varphi}_2(t)\cdots\tilde{\varphi}_l(t)]^T,$$
$$\tilde{\mathbf{F}}(0) = [\tilde{F}_1(0)\tilde{F}_2(0)\cdots\tilde{F}_n(0)]^T,$$

and $\hat{A}(t)$ an $l \times l$ matrix.

The solution of the nonhomogeneous differential system (50) is usually attempted by defining the associated disjoint equation

$$\frac{d}{dt}\mathbf{X}(t) = \hat{A}^*(t)\mathbf{X}(t) \tag{52}$$

and the $\hat{H}(t)$ matrix which is the transpose of the matrix of simple and generalized eigenvectors of $\hat{A}^*(t)$. The initial-value problem (50)–(51) admits the closed-form solution

$$\tilde{\varphi}(t) = \hat{H}^{-1}(t)\hat{H}(0)\tilde{\mathbf{F}}(0) + \hat{H}^{-1}(t)\int_0^t \hat{H}(\tau)[\tilde{\mathbf{E}}(\tau) + \mathbf{Z}^*(\tau)]d\tau. \tag{53}$$

For the uncoupled transforms $\tilde{\varphi}_m(t)$: $m = l+1, l+2, l+3, \ldots, \infty$, the initial-value problem (48)–(49) becomes

$$\frac{d}{dt}\tilde{\varphi}_m(t) + \alpha_m(t)\tilde{\varphi}_m(t) = f_m(t),$$
$$\tilde{\varphi}_m(0) = \tilde{F}_m(0), \quad m = l+1, l+2, l+3, \ldots, \infty, \tag{54}$$

with

$$f_m(t) = \tilde{E}_m(t) - Z_m^*(t) - \sum_{n=1}^{l} G_{mn}(t)\tilde{\varphi}_n(t) \tag{55}$$

considered known. Its solution is straightforward and can be written as

$$\tilde{\varphi}_m(t) = \tilde{F}_m(0)\exp\left\{-\int_0^t \alpha_m(\tau)d\tau\right\} + \int_0^t f_m(\tau)\exp\left\{-\int_\tau^t \alpha_m(u)du\right\}d\tau. \quad (56)$$

Ultimately the l-th order approximation to the solution vector $\varphi_i(\mathbf{r}, t)$ of the boundary-value problem (21)–(28) is determined by applying the inversion formula (39) to the l-th order approximation of the transform $\tilde{\varphi}_m(t)$ as defined by relations (53) and (56).

For example, the zero order ($l = 0$) solution vector $\varphi_i^0(\mathbf{r}, t)$ of the above-mentioned boundary-value problem is

$$\varphi_i^0(\mathbf{r}, t) = \sum_{m=1}^{\infty}\left[\tilde{F}_m(0)\exp\left\{-\int_0^t \alpha_m(\tau)d\tau\right\}\right.$$
$$\left. + \int_0^t [\tilde{E}_m(\tau) + Z_m^*(\tau)]\exp\left\{-\int_\tau^t \alpha_m(\tau)d\tau\right\}d\tau\right]\boldsymbol{\theta}_{im}(\mathbf{r}, t).$$

The first order ($l = 1$) solution vector $\varphi_i^1(\mathbf{r}, t)$ is given by

$$\varphi_i^1(\mathbf{r}, t) = \varphi_i^0(\mathbf{r}, t) + \sum_{m=2}^{\infty}\left[\int_0^t G_{mi}(\tau)\tilde{\varphi}_1(\tau)\exp\left\{-\int_\tau^t \alpha_m(u)du\right\}d\tau\right]\boldsymbol{\theta}_{im}(\mathbf{r}, t),$$

where

$$\tilde{\varphi}_1(t) = \tilde{F}_1(0)\exp\left\{-\int_0^t \alpha_1(\tau)d\tau\right\} + \int_0^t [\tilde{E}_1(\tau) + Z_1^*(\tau)]\exp\left\{-\int_\tau^t \alpha_1(u)du\right\}d\tau$$

and so on.

In conclusion, it should be noted that these approximations to the solution of the boundary-value problem can be directly programmed on a computer.

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Appendix. Proof of the theorem

Expand $\varphi_i(\mathbf{r}, t)$ in terms of the eigenfunctions of (34)–(37) over the subregion R_i as

$$\varphi_i(\mathbf{r}, t) = \sum_{m=1}^{\infty} C_m(t)\mathbf{Y}_{im}(\mathbf{r}, t). \quad (A.1)$$

In order to define $C_m(t)$ it is necessary to derive a composite-region multigroup orthogonality relation. We do that by studying equations (34) for two distinct eigenvalues $\alpha_m(t)$ and $\alpha_n(t)$. Multiplication of the first by $\mathbf{Y}_{in}^T(\mathbf{r}, t)$ and the second by $\mathbf{Y}_{im}^T(\mathbf{r}, t)$ and dropping out the independent variable to simplify the notation leads to

$$\nabla \cdot \hat{D}_i(\mathbf{Y}_{in}^T \nabla \mathbf{Y}_{im} - \mathbf{Y}_{im}^T \nabla \mathbf{Y}_{in}) + (\alpha_m - \alpha_n)\mathbf{Y}_{in}^T \hat{V}^{-1}\mathbf{Y}_{im} = 0. \tag{A.2}$$

Let us integrate (A.2) over the spatial variables in the corresponding subregion and add similar terms for all subregions.

$$(\alpha_m - \alpha_n)\sum_{i=1}^{N}\int_{R_i} \mathbf{Y}_{in}^T \hat{V}^{-1}\mathbf{Y}_{im} dR = \sum_{i=1}^{N}\int_{R_i} \nabla \cdot \hat{D}_i(\mathbf{Y}_{in}^T \nabla \mathbf{Y}_{im} - \mathbf{Y}_{im}^T \nabla \mathbf{Y}_{in}) dR. \tag{A.3}$$

We then apply the Gauss divergence theorem to transform (A.3) into

$$(\alpha_m - \alpha_n)\sum_{i=1}^{N}\int_{R_i} \mathbf{Y}_{in}^T \hat{V}^{-1}\mathbf{Y}_{im} dR = \sum_{i=1}^{N}\int_{S_i} \begin{vmatrix} \mathbf{Y}_{in}^T \hat{D}_i \frac{\partial}{\partial n_{ij}} \mathbf{Y}_{in} \\ \mathbf{Y}_{im}^T \hat{D}_i \frac{\partial}{\partial n_{ij}} \mathbf{Y}_{im} \end{vmatrix} dS, \tag{A.4}$$

with the vertical bars denoting determinant, and consider the boundary conditions (35)–(37) together with (33) to arrive at the composite-region orthonormality property

$$\sum_{i=1}^{N}\int_{R_i} \boldsymbol{\theta}_{in}^T(\mathbf{r}, t)\hat{V}^{-1}\boldsymbol{\theta}_{im}(\mathbf{r}, t) dR = \delta_{mn}. \tag{A.5}$$

The boundary-value problem (21)–(28) may be solved operationally by application of the H-transform. This is actually done by multiplying equation (21) by $\boldsymbol{\theta}_{in}^T(\mathbf{r}, t)$ and integrating over the R_i subregion to obtain

$$\int_{R_i} \boldsymbol{\theta}_{im}^T \hat{V}^{-1}\frac{\partial}{\partial t}\boldsymbol{\varphi}_i dR = \int_{R_i} \boldsymbol{\theta}_{im}^T \nabla \cdot \hat{D}_i \nabla \boldsymbol{\varphi}_i dR + \int_{R_i} \boldsymbol{\theta}_{im}^T \hat{\Sigma}_i \boldsymbol{\varphi}_i dR + \int_{R_i} \boldsymbol{\theta}_{im}^T \mathbf{Q}_i dR. \tag{A.6}$$

The identity

$$\boldsymbol{\theta}_{im}^T \nabla \cdot \hat{D}_i \nabla \boldsymbol{\varphi}_i = \nabla \cdot (\boldsymbol{\theta}_{im}^T \hat{D}_i \nabla \boldsymbol{\varphi}_i - \boldsymbol{\varphi}_i^T \hat{D}_i \nabla \boldsymbol{\theta}_{im}) + \boldsymbol{\varphi}_i^T \nabla \cdot \hat{D}_i \boldsymbol{\theta}_{im}, \tag{A.7}$$

together with the Gauss divergence theorem enable us to write the first integral to the right-hand side of (A.6) as

$$\int_{R_i} \boldsymbol{\theta}_{im}^T \nabla \cdot \hat{D}_i \nabla \boldsymbol{\varphi}_i dR = \int_{R_i} \boldsymbol{\varphi}_i^T \nabla \cdot \hat{D}_i \nabla \boldsymbol{\theta}_{im} dR + \int_{S_i} \begin{vmatrix} \boldsymbol{\theta}_{im}^T \hat{D}_i \frac{\partial}{\partial n_{ij}} \boldsymbol{\theta}_{im} \\ \boldsymbol{\varphi}_i^T \hat{D}_i \frac{\partial}{\partial n_{ij}} \boldsymbol{\varphi}_i \end{vmatrix} dS. \tag{A.8}$$

Replace $\mathbf{Y}_{im}^T(\mathbf{r}, t)$ by $\boldsymbol{\theta}_{im}(\mathbf{r}, t)$ in (34) and multiply throughout by $\boldsymbol{\varphi}_i^T(\mathbf{r}, t)$ to get

$$\boldsymbol{\varphi}_i^T \nabla \cdot \hat{D}_i \nabla \boldsymbol{\theta}_{im} = -\boldsymbol{\varphi}_i^T[\hat{\Sigma}_i + \alpha_m \hat{V}^{-1}]\boldsymbol{\theta}_{im}. \tag{A.9}$$

Substitute (A.9) into (A.8) and the resultant relation into (A.6) to obtain

$$\int_{R_i} \boldsymbol{\theta}_{im}^T \hat{V}^{-1} \frac{\partial}{\partial t} \boldsymbol{\varphi}_i dR = -\alpha_m \int_{R_i} \boldsymbol{\theta}_{im}^T \hat{V}^{-1} \boldsymbol{\varphi}_i dR + \int_{S_i} \begin{vmatrix} \boldsymbol{\theta}_{im}^T \hat{D}_i \frac{\partial}{\partial n_{ij}} \boldsymbol{\theta}_{im} \\ \boldsymbol{\varphi}_i^T \hat{D}_i \frac{\partial}{\partial n_{ij}} \boldsymbol{\varphi}_i \end{vmatrix} dS + \int_{R_i} \boldsymbol{\theta}_{im}^T \hat{V}^{-1} \mathbf{E}_i dR, \tag{A.10}$$

In view of definition (31), summation of (A.10) over $i = 1, 2, 3, \dots, N$ yields

$$\sum_{i=1}^{N} \int_{R_i} \boldsymbol{\theta}_{im}^T \hat{V}^{-1} \frac{\partial}{\partial t} \boldsymbol{\varphi}_i dR = -\alpha_m \tilde{\varphi}_m(t) + \tilde{E}_m(t) + \sum_{i=1}^{N} \int_{S_i} \begin{vmatrix} \boldsymbol{\theta}_{im}^T \hat{D}_i \frac{\partial}{\partial n_{ij}} \boldsymbol{\theta}_{im}^T \\ \boldsymbol{\varphi}_i^T \hat{D}_i \frac{\partial}{\partial n_{ij}} \boldsymbol{\varphi}_i^T \end{vmatrix} dS. \tag{A.11}$$

On following a similar procedure that takes into consideration the boundary conditions (22)–(25) and (35)–(37), we see that

$$\sum_{i=1}^{N} \int_{S_i} \begin{vmatrix} \boldsymbol{\theta}_{im}^T \hat{D}_i \frac{\partial}{\partial n_{ij}} \boldsymbol{\theta}_{im}^T \\ \boldsymbol{\varphi}_i^T \hat{D}_i \frac{\partial}{\partial n_{ij}} \boldsymbol{\varphi}_i^T \end{vmatrix} dS = -\sum_{i=1}^{M} \int_{S_{ip}} \boldsymbol{\theta}_{im}^T \hat{V}^{-1} \mathbf{Z}_i dS. \tag{A.12}$$

Therefore

$$\sum_{i=1}^{N} \int_{R_i} \boldsymbol{\theta}_{im}^T \hat{V}^{-1} \frac{\partial}{\partial t} \boldsymbol{\varphi}_i dR = -\alpha_m \tilde{\varphi}_m(t) + \tilde{E}_m(t) - Z_m^*(t). \tag{A.13}$$

Differentiate (43) with respect to time and substitute the resulting equation into (A.13). We obtain

$$\sum_{i=1}^{N} \int_{R_i} \boldsymbol{\theta}_{im}^T \hat{V}^{-1} \left\{ \sum_{n=1}^{\infty} \boldsymbol{\theta}_{in} \frac{\partial}{\partial t} \tilde{\varphi}_n(t) \right\} dR + \sum_{i=1}^{N} \int_{R_i} \boldsymbol{\theta}_{im}^T \hat{V}^{-1} \left\{ \sum_{n=1}^{\infty} \tilde{\varphi}_n(t) \frac{\partial}{\partial t} \boldsymbol{\theta}_{in} \right\} - \alpha_m \tilde{\varphi}_m(t) + \tilde{E}_m(t) - Z_m^*(t). \tag{A.14}$$

The orthonormality property (A.5) together with (42) yield the required result.

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