International Journal of Theoretical Physics, Vol. 41, No. 1, January 2002 (© 2002)

Composite Surface Integral Transforms in Neutron Therapy of Cancer

Nassar H. S. Haidar[1]

Received January 8, 2001

Composite surface finite integral transforms are applied to formulate the optimal ballistic property for a temporally tuned multibeam neutron cancer 3D therapy as a single-valued dynamical system. By invoking Pontryagin's maximum principle, with the operation functions of the beams constituting the control vector, it is proved, in an inverse problem formulation, that for every spatial configuration of the neutron beams, there exists an optimal temporal control vector satisfying an a priori system of linear homogeneous Volterra integral equations of the first kind and convolution type. A version of this newly advanced, temporally optimalized, multibeam 3D irradiation therapy, with a linearized ballistic property, is shown to result from a shooting-type solution to a related, semihomogeneous dual system of linear integral equations of the first kind. A criterion for the controllability of this optimization problem has also been established.

1. INTRODUCTION

Among the variety of possible radiations usable these days in cancer therapy, namely x rays, γ rays, electrons, protons, neutrons, heavy ions, π mesons, it is generally agreed that high energy protons exhibit the best ballistic index, i.e. the best ratio of the dose delivered to the tumor, compared with the dose delivered to the neighboring tissues.

However the effectivity of proton therapy appears to weaken for certain advanced irresectable tumors (Mills *et al.*, 1992), whereas neutron therapy happens to be more effective than other forms of radiation, because it has the propensity to kill advanced tumor cells low in oxygen content. Despite their relatively low ballistic index, neutrons are established to be primarily indicated for a well-defined subset of tumors that are mainly locally advanced and irresectable. The locally advanced tumor part of these cancers is often globally surrounded by the younger

[1] Department of Mathematics & Computer Science, Suffolk University, Boston, MA, USA, and Center for Advanced Mathematical Sciences, American University of Beirut, P.O. Box 11-0236, Beirut, Lebanon; e-mail: nshaidar@cartan.cas.suffolk.edu.

0020-7748/02/0100-0109/0 © 2002 Plenum Publishing Corporation

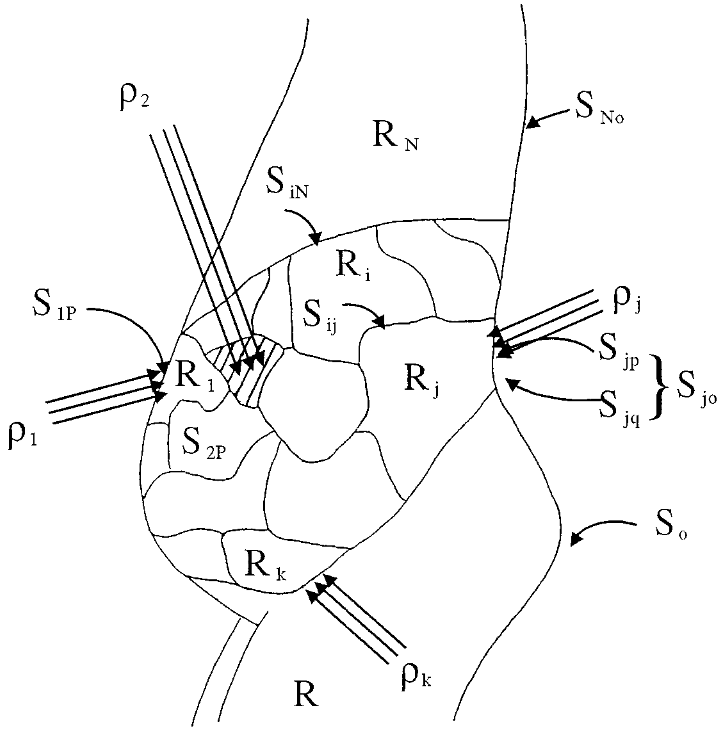

Fig. 1. Sketch to illustrate the human body as a composite cancerous region that is irradiated by temporally tuned external neutron beams.

tumor tissues that may not require neutron therapy or can tolerate only a fraction of the neutron dose admissible by the advanced disease parts.

It is widely known that temporal changes are practically of no interest in γ ray and charged particle treatment, because their relaxation times inside the tumor could be in orders of magnitude shorter than the practicable switching times of their beams. Distinctively, neutron transport in multiregional hydrogenous domains has a stronger response to temporal changes. In fact neutronic relaxation lengths are comparable (Haidar, 1982) to the sizes of some subdomains, and neutronic relaxation times may be comparable (Fujino and Sumita, 1970) to the switching times of modern cyclotrons.

The transient diffusion of slow neutrons during therapy in a finite composite region, like that of an advanced cancer (sketched in Fig. 1) has a complex physical model. It is formulated as a mixed boundary initial value problem in the energy multigroup G approximation as

$$A_R[\vec{\phi}] = \left[\nabla \cdot \mathbf{D}(\mathbf{r})\,\nabla + \sum(\mathbf{r})\right] \vec{\phi}(\mathbf{r}, t) = \hat{\mathbf{V}}^{-1}\,\frac{\partial}{\partial t}\vec{\phi}(\mathbf{r}, t), \qquad (1.1)$$

$$\Lambda_{S_c}[\vec{\phi}] = \left[\vec{\phi}(\mathbf{r}, t)|_{S_c^+} - \vec{\phi}(\mathbf{r}, t)|_{S_c^-}\right] = \mathbf{0}, \tag{1.2}$$

$$\Pi_{S_c}[\vec{\phi}] = \left[\mathbf{D}(\mathbf{r})\nabla\vec{\phi}(\mathbf{r}, t)|_{S_c^+} - \mathbf{D}(\mathbf{r})\nabla\vec{\phi}(\mathbf{r}, t)|_{S_c^-}\right] = \mathbf{0}, \tag{1.3}$$

$$C_{S_p}[\vec{\phi}] = \left[\mathbf{D}(\mathbf{r})\nabla\vec{\phi}(\mathbf{r}, t)|_{S_p} \pm \gamma_0\vec{\phi}(\mathbf{r}, t)|_{S_p}\right] = \vec{\rho}(\mathbf{r}, t), \tag{1.4}$$

$$E_{S_q}[\vec{\phi}] = \left[\mathbf{D}(\mathbf{r})\nabla\vec{\phi}(\mathbf{r}, t)|_{S_q} \pm \gamma_0\vec{\phi}(\mathbf{r}, t)|_{S_q}\right] = \mathbf{0}, \tag{1.5}$$

$$T_R[\vec{\phi}] = \vec{\phi}(\mathbf{r}, 0) - \vec{\chi}(\mathbf{r}) = \mathbf{0}. \tag{1.6}$$

The usual notation is used and is close to the one established in (Haidar, 1983, 1997) but the formulation is meant to be not only internal-source–free but also with a zero internal control matrix and a time-independent total-cross-section square matrix $\sum(\mathbf{r})$ of *GN* dimension. Obviously A_R represents the stationary diffusion operator in the composite domain R of N subregions with an outer surface S_o. Λ_{S_c} and Π_{S_c} are respectively the flux and current continuity operators on the common interfaces S_c, with S_c^+ and S_c^- representing the two different faces of the same S_c of dimension N' not equal to N. E_{S_q} is the extrapolated boundary operator on the composite outer surface $S_q \subset S$ of dimension M' less than N, i.e. $\cup_{r=1}^{M'} S_{rq} = S_q$, while C_{S_p} is the external beam boundary initial operator acting on $S_p \subset S$ of dimension M not equal to M', i.e. $\cup_{k=1}^{M} S_{kp} = S_p$. It is also assumed here that

$$\mathbf{V} = \mathrm{diag}\,[\nu_1\ \nu_2\ \nu_3 \cdot \cdots \cdot \nu_G]$$

and

$$\hat{\mathbf{V}} = \mathrm{diag}\,[\mathbf{V}\ \mathbf{V}\ \mathbf{V} \cdot \cdots \cdot \mathbf{V}]$$

of *GN* dimension. If $\mathbf{J}(\mathbf{r}, t)$ is the outward pointing to S_o neutron current, then T_R is the initial operator acting in R and is stimulated by the time-dependent (and possibly time-discontinuous) incoming external beam

$$\vec{\rho}(\mathbf{r}, t) = -\mathbf{J}(\mathbf{r}, t).$$

The $\pm$ sign in C_{S_p} and E_{S_q} means $+$ or $-$ when to an observer located inside S_{kp} or S_{rq} the outward normal to S_{kp} or S_{rq} points to the left-hand-side or to the right-hand-side respectively.

In this model we have, on the one hand, the transient neutron population, described by the neutron flux *GN*-dimensional vector $\vec{\phi}(\mathbf{r}, t)$, in the cold part of the spectrum of thermal neutrons exhibiting a waveform-collective behavior that reflects and refracts from subdomain boundaries S_c. On the other hand, the transient neutron population in the hot part of the spectrum can leak out preferentially from various parts of the composite outer surface S_o of the irradiated body. Moreover the entire spectrum of thermal neutrons exhibit rethermalization (Haidar, 1982) across boundaries of substantially different regions in the tumor.

Modern optimal control single-valued theory has witnessed an intensive application over the last two decades in defining optimal regimens for the treatment of cancer (Nicolini, 1984; Zeitz and Nicolini, 1979)—where the state equations are ordinary differential equations that constrain a single performance criterion. With a vector of performance criteria, the techniques of vector optimization and Pareto control have been employed (Zeitz and Nicolini, 1979), e.g. in the search for optimal protocols in chemotherapy.

Optimization in neutron therapy of advanced cancers can be formulated with the (1.1)–(1.6) partial differential constraints that contain some nonhomogeneous initial boundary conditions. Solution of such problems calls for multivalued optimization techniques (Evans and Lions, 1980) like the penalized control (Lions, 1971) and penalized Pareto control (Lions, 1986).

Our purpose in this work is to analyze the naturally low ballistic index of slow neutrons in therapeutic environments by single-valued optimization techniques. So composite surface and composite region finite integral transforms (Haidar, 1997) are applied in Section 2 to map the linear BVP (1.1)–(1.6) to an equivalent linear IVP. This is subsequently employed in a dynamical system representation for the ballistic index, and the latter is then optimized by means of Pontryagin's maximum principle. The resulting inverse problem formulation is designed to be capable of indicating ways for a possible controllable improvement of this index through a temporally tuned $\mathbf{b}(t)$ multibeam irradiation,

$$\vec{\rho}(\mathbf{r}, t) = \hat{\mu}(\mathbf{r})\,\mathbf{b}(t), \tag{1.7}$$

of a certain part S_{p} of the composite outer surface S_{o} of locally advanced tumors.

In this representation of $\vec{\rho}(\mathbf{r}, t)$ there is an $M \times G$ matrix,

$$\hat{\mu}(\mathbf{r}) = [\vec{\mu}_1(\mathbf{r})\,\vec{\mu}_2(\mathbf{r})\,\vec{\mu}_3(\mathbf{r}) \cdots \vec{\mu}_k(\mathbf{r}) \cdots \vec{\mu}_M(\mathbf{r})]^T, \tag{1.8}$$

and a temporal control vector $\mathbf{b}(t)$ that is common for all neutron energy groups of the G-dimensional $\vec{\mu}_k(\mathbf{r})$ vectors. It is implicitly assumed in this model that each of these $\vec{\mu}_k(\mathbf{r})$ neutron beam vectors are falling normally on the corresponding $S_{k\mathrm{p}}$ subsurface. Therefore $\hat{\mu}(\mathbf{r})$ represents a beam system spatial configuration matrix that defines not only the position of the individual neutron beams but, in some way, also their orientation with respect to the irradiated composite domain as a whole.

The main result of this work is Theorem 2.2, stating that for every spatial configuration function $\hat{\mu}(\mathbf{r})$ there exists, in an inverse problem formulation, an optimal temporal control vector $\mathbf{b}^{\mathrm{o}}(t)$ satisfying an a priori system of linear homogeneous Volterra integral equations of the first kind and convolution type. In Section 3 we show that a version of this newly advanced, temporally optimalized, multibeam 3D irradiation therapy, with a linearized ballistic index, can result from a shooting-type solution to a related semihomogeneous dual system of linear integral equations of the first kind. Section 4 deals with demonstrating the complete state controllability of the addressed optimization problem and establishing a criterion for the regional flux controllability of therapeutic neutrons.

2. BALLISTIC INDEX OF NEUTRONS

The objective in slow neutron cancer therapy is to maximize the weighted seminorm (in an L^1 setting) representing the regional neutron flux ($\vec{\phi}_j(\mathbf{r}, t)$) reaction rate,

$$\|\vec{\phi}_j(t)\|_{G,1;\sum_j} = \sum_{g=1}^{G} \int_{R_j} \sum\nolimits_j^g(\mathbf{r})\vec{\phi}_j(\mathbf{r}, t)\, dR, \tag{2.1}$$

in an advanced tumor subdomain R_j over the irradiation period T, while minimizing it simultaneously over the surrounding young-tumor composite domain $\cup_{\substack{i=1\\i\neq j}}^{N} \mathbf{R}_i$, which is not supposed to require neutron therapy. Here $\sum_j^g(\mathbf{r})$ is the total macroscopic absorption cross-section of the neutrons of the gth energy group in the jth region of the cancerous domain.

As for the dynamic control of irradiation, the tuned neutron beams on the same accelerator are functionally operated by the (1.7) separated variable principle

$$\vec{\rho}_k(\mathbf{r}, t) = \vec{\mu}_k(\mathbf{r})\, b_k(t) \quad k = 1, 2, 3, \ldots\ldots, M. \tag{2.2}$$

A reasonable ballistic index of neutrons for advanced cancer therapy appears to be one for which the ratio

$$\int_0^T \sum_{\substack{i=1\\i\neq j}}^{N} \|\vec{\phi}_i(t)\|_{G,1;\sum_i}\, dt \bigg/ \int_0^T \|\vec{\phi}_j(t)\|_{G,1;\sum_j}\, dt$$

is minimized. However, some of the mathematically feasible $\vec{\phi}(\mathbf{r}, t)$ solution vectors in a nonconstrained optimization process involving the above (weak) functional, subject to the (1.1)–(1.6) state equations, may allow for situations where for short intervals of T inadmissible dose exposures may possibly be reached in some subdomains of the composite system. Avoidance of such medically unacceptable situations invokes the definition that follows for a rather safer (stronger) ballistic index for these neutrons.

Definition 2.1. The dynamic ballistic index of slow neutrons in cancer therapy is

$$\beta(\mathbf{b}) = \frac{1}{T}\int_0^T \left\{ \sum_{\substack{i=1\\i\neq j}}^{N} \|\vec{\phi}_i(t)\|_{G,1;\sum_i} \bigg/ \|\vec{\phi}_j(t)\|_{G,1;\sum_j} \right\} dt. \tag{2.3}$$

Obviously this index, which is explicitly independent of the set of tuned controls $\{b_k(t)\}_{k=1}^{M}$, must be minimized to improve the ballistic property of neutrons by an optimal control vector $\mathbf{b}^{\circ}(t)$. Furthermore, for a nontuned steady state irradiation of the same cancer with the same neutronic multibeam configuration, $\{\vec{\boldsymbol{\mu}}_k(\mathbf{r})\}_{k=1}^{M}$, we have $b_k(t) = 1, \forall\, k$ and $\vec{\phi}_i(\mathbf{r}, t) \to \vec{\phi}_i(\mathbf{r})\ \forall\, i$. Hence

$$\beta(\mathbf{1}) = \sum_{\substack{i=1\\ i\neq j}}^{N} \|\vec{\phi}_i\|_{G,1;\sum_i} \Big/ \|\vec{\phi}_j\|_{G,1;\sum_j} \tag{2.4}$$

represents the pertinent static ballistic index.

Denote now the group-regional reduced current of applied static neutron beams as

$$\mathbf{Z}_i(\mathbf{r}) = \mathbf{V}\vec{\boldsymbol{\mu}}_i(\mathbf{r});\ \mathbf{r} \in S_{\mathrm{o}}. \tag{2.5}$$

Clearly, $\mathbf{Z}_i(\mathbf{r}) = \mathbf{0}$ when $\mathbf{r} \in S_{\mathrm{q}} \subset S_{\mathrm{o}}$. Next define the multigroup composite region finite integral transform,

$$H_N[\vec{\phi}_i(\mathbf{r}, t)] = \varphi_m(t) = \sum_{i=1}^{N} \int_{R_i} \Theta_{im}^T(\mathbf{r}) \cdot \mathbf{V}^{-1}\, \vec{\phi}_i(\mathbf{r}, t)\, dR, \tag{2.6}$$

and the multigroup composite boundary surface finite integral transform,

$$W_N[\mathbf{Z}_i(\mathbf{r})] = z_m = \sum_{i=1}^{M} \int_{S_{i\mathrm{p}}} \Theta_{im}^T(\mathbf{r}) \cdot \mathbf{V}^{-1}\, \mathbf{Z}_i(\mathbf{r})\, dS, \tag{2.7}$$

where $z_m = \sum_{i=1}^{M} z_{mi}$ and the associated

$$z_{mi} = \int_{S_{i\mathrm{p}}} \Theta_{im}^T(\mathbf{r}) \cdot \mathbf{V}^{-1}\, \mathbf{Z}_i(\mathbf{r})\, dS, \tag{2.8}$$

in all of which

$$\Theta_{im}(\mathbf{r}) = \mathbf{Y}_{im}(\mathbf{r}) / \|\mathbf{Y}_{im}\|_{N,2;V^{-1}} \tag{2.9}$$

and

$$\mathbf{Y}_{im}(\mathbf{r}) = [Y_{i1m}(\mathbf{r})\, Y_{i2m}(\mathbf{r})\, Y_{i3m}(\mathbf{r}) \cdots\cdots Y_{iGm}(\mathbf{r})]^T$$

are the functional eigenvectors of the auxiliary to the (1.1)–(1.6) vector matrix eigen boundary value problem (Ölçer, 1968; Haidar, 1983, 1997),

$$\nabla \cdot \mathbf{D}_i(\mathbf{r})\, \nabla \mathbf{Y}_{im}(\mathbf{r}) + \left[\sum\nolimits_i(\mathbf{r}) + \alpha_m \mathrm{V}^{-1}\right] \mathbf{Y}_{im}(\mathbf{r}) = \mathbf{0},$$
$$\mathbf{r} \text{ in } R_i,\ i = 1, 2, 3, \ldots\ldots, N; \tag{2.10}$$

$$\mathbf{Y}_{im}(\mathbf{r}) = \mathbf{Y}_{jm}(\mathbf{r}),$$
$$\mathbf{r} \text{ on } S_{ij},\ i, j = 1, 2, 3, \ldots\ldots, N;$$

$$\mathbf{D}_i(\mathbf{r})\frac{\partial}{\partial n_{ij}}\ \mathbf{Y}_{im}(\mathbf{r}) = \mathbf{D}_j(\mathbf{r})\frac{\partial}{\partial n_{ij}}\ \mathbf{Y}_{jm}(\mathbf{r}),$$
$$\mathbf{r} \text{ on } S_{ij},\ i,\ j = 1, 2, 3, \ldots\ldots, N; \tag{2.11}$$

$$\mathbf{D}_i(\mathbf{r})\frac{\partial}{\partial n_{i\mathrm{p}}}\ \mathbf{Y}_{im}(\mathbf{r}) \pm \gamma_{i\mathrm{p}}\ \mathbf{Y}_{im}(\mathbf{r}) = \mathbf{0},$$
$$\mathbf{r} \text{ on } S_{i\mathrm{p}},\ i = 1, 2, 3, \ldots\ldots, M < N; \tag{2.12}$$

$$\mathbf{D}_i(\mathbf{r})\frac{\partial}{\partial n_{i\mathrm{q}}}\ \mathbf{Y}_{im}(\mathbf{r}) \pm \gamma_{i\mathrm{q}}\ \mathbf{Y}_{im}(\mathbf{r}) = 0,$$
$$\mathbf{r} \text{ on } S_{i\mathrm{q}},\ i = 1, 2, 3, \ldots\ldots, < N. \tag{2.13}$$

The standing in (2.9)

$$\|\mathbf{Y}_{im}\|_{N,2;V^{-1}} = \left\{\sum_{i=1}^{N}\int_{R_i} \mathbf{Y}_{im}^{T}(\mathbf{r}) \cdot \mathbf{V}^{-1}\,\mathbf{Y}_{im}(\mathbf{r})\,dR\right\}^{\frac{1}{2}} \tag{2.14}$$

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

The composite region integral transforms $\varphi_m(t)$ and z_m have the following respective inversion formulae:

$$H_N^{-1}[\varphi_m(t)] = \vec{\phi}_i(\mathbf{r}, t) = \sum_{m=1}^{\infty} \varphi_m(t)\ \Theta_{im}(\mathbf{r}) \tag{2.15}$$

and

$$W_N^{-1}[z_m] = \mathbf{Z}_i(\mathbf{r}) = \sum_{m=1}^{\infty} z_m\ \Theta_{im}(\mathbf{r}). \tag{2.16}$$

After observing that the α_ms are independent of $\vec{\rho}_k(\mathbf{r}, t)$, and that

$$\varphi_m(0) = \xi_m(0) \tag{2.17}$$

and

$$\sum_{i=1}^{N}\int_{R_i} \Theta_{im}^{T}(\mathbf{r}) \cdot \mathbf{V}^{-1}\,\frac{d}{dt}\ \Theta_{in}(\mathbf{r})\,dR = 0, \tag{2.18}$$

by defining the mth harmonic $p_m(t)$ of the composite surface inverse transformed set of controls via

$$p_m(t) = \sum_{k=1}^{M} z_{mk}\ b_k(t), \tag{2.19}$$

we can state the theorem of Haidar (1997) in the following appropriately modified form.

Theorem 2.1 (Haidar, 1997). *The group-regional solution vector of the composite region internal-source–free BVP* (1.1)–(1.6) *is*

$$\vec{\phi}_i(\mathbf{r}, t) = \sum_{m=1}^{\infty} \varphi_m(t)\, \Theta_{im}(r), \tag{2.20}$$

with coefficients $\varphi_m(t)$ that satisfy the system ODE

$$\frac{d}{dt}\, \varphi_m(t) + \alpha_m\, \varphi_m(t) = p_m(t) \quad m = 1, 2, 3, \ldots\ldots, \infty, \tag{2.21}$$

subject to

$$\varphi_m(0) = \xi_m \quad m = 1, 2, 3, \ldots\ldots, \infty. \tag{2.22}$$

Direct solution of the uncoupled system IVP of the previous theorem for the $\varphi_m(t)$ transforms and consideration of the mth harmonic $q_m(t)$ of the exponentially convoluted composite surface inverse-transformed set of controls, defined viz

$$q_m(t) = \sum_{k=1}^{M} z_{mk} \int_0^t \exp[-\alpha_m(t-\tau)]\, b_k(\tau)\, d\tau, \tag{2.23}$$

leads to the lemma that follows.

Lemma 2.1. *The group-regional solution vector of the composite region internal-source–free BVP* (1.1)–(1.6) *is*

$$\vec{\phi}_i(\mathbf{r}, t) = \sum_{m=1}^{\infty} \Theta_{im}(\mathbf{r})\{\xi_m\ \exp[-\alpha_m t] + q_m(t)\}. \tag{2.24}$$

Proof: By direct integration of (2.21). □

Obviously at $t = 0$, $\mathbf{b}(0) = \mathbf{0}$ and $\vec{\rho}(\mathbf{r}, 0) = \mathbf{0}$. Therefore $\mathbf{\Phi}(\mathbf{r}, 0) = \mathbf{0}$ and it is possible to consider

$$\varphi_m(0) = \xi_m = 0, \forall\, m$$

in the previous lemma to establish the important relation between each regional $\varphi_m(t)$ and the entire set of surface z_{mk}s:

$$\varphi_m(t) = q_m(t), \forall\, m. \tag{2.25}$$

We may define now the weighted harmonic amplitudes,

$$w_{jm} = \|\boldsymbol{\Theta}_{jm}\|_{G,1;\sum_j} = \sum_{g=1}^{G} \int_{R_j} \sum\nolimits_j^g(\mathbf{r})\, \boldsymbol{\Theta}_{jm}(\mathbf{r})\, dR \quad m = 1, 2, 3, \ldots\ldots, l \to \infty, \tag{2.26}$$

the composite region transformed state vector,

$$\boldsymbol{\Phi}(t) = [\varphi_1(t)\ \varphi_2(t)\ \varphi_3(t) \cdots\cdot \varphi_m(t) \cdots\cdot \varphi_l(t)]^T,$$

and the vector of composite surface inverse transformed set of controls,

$$\mathbf{p}(t) = [p_1(t)\ p_2(t)\ p_3(t) \cdots\cdot p_m(t) \cdots\cdot p_l(t)]^T,$$

in (2.3) to rewrite the optimal control problem of slow neutron therapy as the following lth order dynamical system.

$$\min \beta(\mathbf{p}) = \frac{1}{T} \int_0^T \left\{ \left[\sum_{m=1}^{l} \sum_{\substack{i=1 \\ i \neq j}}^{N} w_{im}\, \varphi_m(t) \right] \Big/ \sum_{m=1}^{l} w_{jm}\, \varphi_m(t) \right\} dt,$$

subject to (2.21) and (2.22), as state equations, with

$$m = 1, 2, 3, \ldots\ldots, l \to \infty. \tag{2.27}$$

Further definition of the l-dimensional vector,

$$\mathbf{w}_j = [w_{j1}\ w_{j2}\ w_{j3} \cdots\cdot w_{jm} \cdots\cdot w_{jl}]^T,$$

and the associated homogeneous composite region transformed system spectral matrix,

$$\Lambda = \text{diag}[\alpha_1\ \alpha_2\ \alpha_3 \cdots\cdot \alpha_m \cdots\cdot \alpha_l], \tag{2.28}$$

allows representing (2.27) and (2.21) in vector matrix notation as

$$\min \beta(\mathbf{p}) = \int_0^T L(\boldsymbol{\Phi})\, dt = \int_0^T \frac{1}{T} \left[\sum_{\substack{i=1 \\ i \neq j}}^{N} \mathbf{w}_i^T \cdot \boldsymbol{\Phi}(t) \big/ \mathbf{w}_j^T \cdot \boldsymbol{\Phi}(t) \right] dt, \tag{2.29}$$

subject to

$$\dot{\boldsymbol{\Phi}}(t) = \mathbf{g}(\boldsymbol{\Phi}, \mathbf{p}) = -\boldsymbol{\Lambda}\boldsymbol{\Phi}(t) + \mathbf{p}(t) \tag{2.30}$$

and to

$$\boldsymbol{\Phi}(0) = \vec{\boldsymbol{\xi}} = \mathbf{0}. \tag{2.31}$$

The Lagrangian $L(\mathbf{\Phi})$ of this problem, which is a real function on $R_l \times [0, T]$ that is explicitly independent of $\mathbf{p}$, is further employed to construct its Hamiltonian $H(\mathbf{\Phi}, \mathbf{\Psi}, \mathbf{p})$,

$$H(\mathbf{\Phi}, \mathbf{\Psi}, \mathbf{p}) = L(\mathbf{\Phi}) + \langle \mathbf{\Psi}, \mathbf{g}(\mathbf{\Phi}, \mathbf{p}) \rangle, \tag{2.32}$$

in which $\mathbf{\Psi}(t)$ is a transform costate vector satisfying the terminal conditions

$$\mathbf{\Psi}(T) = \vec{\boldsymbol{\eta}} \tag{2.33}$$

and

$$\langle \mathbf{\Psi}, \mathbf{g}(\mathbf{\Phi}, \mathbf{p}) \rangle = \mathbf{\Psi}^T \cdot \mathbf{g}. \tag{2.34}$$

We need moreover to introduce the $M \times l$ rectangular coefficient matrix, $\mathbf{A} = \{a_{nm}\}$, of the following composite harmonic amplitudes as the entries

$$a_{nm} = \sum_{\substack{i=1 \\ i \neq j}}^{N} (w_{in}\, w_{jm} - w_{im}\, w_{jn}), \tag{2.35}$$

and the $l \times M$ rectangular functional matrix, $\mathbf{E}(t) = \mathbf{E}(t, \mathbf{Z}) = \{e_{mk}(t)\}$, with $\mathbf{Z}$ equal to $\{z_{mk}\}$ and the entries

$$e_{mk}(t) = z_{mk}\, \exp[-\alpha_m(t)] \tag{2.36}$$

to state the main result of this paper on optimal control vectors $\mathbf{b}^{\mathrm{o}}(t)$ for temporally tuned beaming by therapeutic neutrons.

Theorem 2.2. *For every spatial configuration matrix $\hat{\boldsymbol{\mu}}(\mathbf{r})$ of the neutron beams, the dynamic ballistic index $\beta(\mathbf{b})$ is minimized, subject to the satisfaction of* (1.1)–(1.6)*, by an associated optimal temporal control vector $\mathbf{b}^{\mathrm{o}}(t)$ satisfying the homogeneous linear system of the first kind, convolution-type Volterra integral equations*

$$\int_0^t \mathbf{A}\, \mathbf{E}(t-\tau)\, \mathbf{b}(\tau)\, d\tau = \mathbf{0}. \tag{2.37}$$

Proof: Applying Pontryagin's maximum principle (Kuo, 1980), based on the equivalence

$$\min_{\mathrm{p}} \langle -\mathbf{\Psi}(T), \mathbf{\Phi}(T) \rangle = \max_{\mathrm{p}} \langle \mathbf{\Psi}, \mathbf{g} \rangle,$$

to define the canonical system associated with (2.29)–(2.31), we have

$$\dot{\mathbf{\Phi}} = \frac{\partial}{\partial \mathbf{\Psi}} H(\mathbf{\Phi}, \mathbf{\Psi}, \mathbf{p}) = \mathbf{g}(\mathbf{\Phi}, \mathbf{p}) = -\mathbf{\Lambda}\mathbf{\Phi}(t) + \mathbf{p}(t) \tag{2.38}$$

and

$$\dot{\mathbf{\Psi}} = -\frac{\partial}{\partial \mathbf{\Phi}} H(\mathbf{\Phi}, \mathbf{\Psi}, \mathbf{p}) = -\left[\frac{\partial}{\partial \mathbf{\Phi}} \mathbf{g}(\mathbf{\Phi}, \mathbf{p})\right]^T \cdot \mathbf{\Psi} - \frac{\partial}{\partial \mathbf{\Phi}} L(\mathbf{\Phi}). \tag{2.39}$$

Interestingly, note that unlike the transform state equations, which are linear constant coefficient in both $\mathbf{\Phi}$ and $\mathbf{p}$, the transform costate equations,

$$\dot{\mathbf{\Psi}} = \mathbf{\Lambda\Psi} - \mathbf{A\Phi}/T\left(\mathbf{w}_j^T \cdot \mathbf{\Phi}\right)^2, \tag{2.40}$$

are explicitly independent of $\mathbf{p}$, while being nonlinearly dependent on $\mathbf{\Phi}$. Now to determine the form of the optimal control vector $\mathbf{p}^o(t)$ corresponding to a given $\hat{\boldsymbol{\mu}}(\mathbf{r})$, we differentiate $H(\mathbf{\Phi}, \mathbf{\Psi}, \mathbf{p})$ partially with respect to $p_m^o(t)$ setting $\frac{\partial}{\partial p_m^o} H = 0, \forall\, m$ to arrive at

$$\frac{\partial}{\partial \mathbf{p}^0} H = \mathbf{\Psi} = \mathbf{0}. \tag{2.41}$$

Upon substitution of this result in (2.40) we have

$$\mathbf{A\Phi} = \mathbf{0}. \tag{2.42}$$

Further consideration of (2.25) and (2.23) in (2.42) leads to

$$\sum_{m=1}^{l} a_{nm} \sum_{k=1}^{M} z_{mk} \int_0^t \exp[-\alpha_m(t-\tau)]\, b_k(\tau)\, d\tau = 0 \quad n = 1, 2, 3, \ldots\ldots, M, \tag{2.43}$$

which rewrites in vector matrix notation as (2.37). □

Despite the fact that the convolution Volterra system (2.37) appears to be well-posed, the problem of uniqueness of its solution cannot be expected to be a simple one. This claim can straightforwardly be illustrated via an operational solution of this system for optimal $\mathbf{b}(t)$s. Indeed if we define the Laplace transform pair

$$b_k(t) \leftrightarrow B_k(s), \tag{2.44}$$

we are able to represent the Laplace transformed (2.37) system as

$$\sum_{m=1}^{l} \frac{a_{nm}}{S + \alpha_m} \sum_{k=1}^{M} z_{mk} B_k(s) = 0 \quad n = 1, 2, 3, \ldots\ldots, M. \tag{2.45}$$

Let us introduce then the $M \times l$ functional matrix $\mathbf{F}(s)$ [equal to $\{f_{nm}(s)\}$] with the entries

$$f_{nm}(s) = \frac{a_{nm}}{s + \alpha_m} \tag{2.46}$$

and the $l \times M$ coefficient matrix

$$\mathbf{Z} = \{z_{mk}\} \tag{2.47}$$

to put the homogeneous system of functional equations (2.45) in the vector-matrix form,

$$\mathbf{F}(s)\ \mathbf{Z}\ \mathbf{B}(s) = \mathbf{0}. \tag{2.48}$$

Obviously a necessary and sufficient condition for (2.48) to accept nontrivial $\mathbf{B}(s)$ solutions would be

$$\det[\mathbf{F}(s)\ \mathbf{Z}] = 0, \forall\ s. \tag{2.49}$$

Moreover, satisfaction of (2.49) does not guarantee uniqueness of the optimal $\mathbf{B}(s)$ since it should still contain a number of free parameters (like $B_k(s) \leftrightarrow b_k(t)$) equalling to

$$M\text{-rank}\ [\mathbf{F}(s)\ \mathbf{Z}], \tag{2.50}$$

which varies with s and cannot be less than one.

Proposition 2.1. *For L^1-solvability of* (2.37) *the dual condition to* (2.49) *should be satisfied, i.e., a certain generalized* det **AE** *should not vanish.*

Proof: It is quite possible to effectively replace the condition (2.49), when the image $\mathbf{F}(s)\ \mathbf{Z}$ is regular enough, by some weak form in the s domain. Such a form would define a certain unique, but generalized, corresponding solution in the t domain. Actually, the pertaining uniqueness of solution to the scalar form of equations like (2.37) has previously been thoroughly investigated by Titchmarsh (Bukhgeim, 1999). For the case of square systems like (2.37), Asanov employed in 1998 the notions of convolution algebra to generalize the theorem of Titchmarsh to establish the necessary and sufficient conditions for the uniqueness of the solution on the commutative ring.

Following Asanov (1998), let $\mathbf{x}(t)$ be an m-dimensional vector function with the norm $\|\mathbf{x}\|$. Denote then by $C_m(I)$ the space of continuous vector functions $\mathbf{x}(t)$, defined on $I = [0, T]$ or $R^+ = [0, \infty]$, which is endowed with the norm

$$\|\mathbf{x}\|_C = \max_{t \in I} \|\mathbf{x}\|. \tag{2.51}$$

Moreover, for any two locally independent elements, $a(t), b(t) \in C_1(I) \cap L^1_{\text{loc}}(I)$, it is possible to define the convolution (con) multiplication

$$a(t) * b(t) = \int_0^t a(t-\tau)\, b(\tau)\, d\tau \quad t \in I.$$

Presumably, $L^1_{\text{loc}}(I)$ is a commutative ring relative to this multiplication.

Let also $C_{mn}(I)$ denote the set of all $m \times n$ matrices to invoke the con multiplication:

$$\mathbf{\Pi}(t) * \mathbf{U}(t) = \mathbf{V}(t)$$

for $(m \times l)$ by $(l \times n)$ matrices, yielding the $\mathbf{V}(t)$ [equal to $\{v_{ij}(t)\}$] matrix of $(m \times n)$ dimension with the elements

$$v_{ij}(t) = \sum_{k=1}^{l} \pi_{ik}(t) * u_{kj}(t).$$

In a similar fashion, the con determinant (con.det) is defined for a square matrix $\mathbf{U}$ equal to $\{u_{ij}(t)\}$ as

$$\text{con.det}\,\mathbf{U}(t) = \sum_{j=1}^{m} u_{ij}(t) * U_{ij}(t),$$

with $U_{ij}(t)$ (equal to $(-1)^{i+j} M_{ij}(t)$) and $M_{ij}(t)$ as respectively the con algebraic supplement and the con.minor of the element $u_{ij}(t)$ in any ith row.

By assuming the null space of $\mathbf{\Gamma}(t)$ (equal to $\mathbf{AE}(t)$) to be $\wp(\mathbf{\Gamma})$ and recognizing that

$$\mathbf{\Gamma}(t) \in C_{MM}(I),$$

it is possible now to state Asanov's theorem (Asanov, 1998) for the system (3.27).

The system

$$\mathbf{\Gamma}(t) * \mathbf{b}(t) = \mathbf{0}$$

has a unique solution in $\wp(\mathbf{\Gamma}) \cap \mathbf{L}^1_{\text{loc}}(I)$ iff $\exists$ no number $\delta \in I$ such that

$$\text{con.det}\,\Gamma(t) = 0 \quad t \in (0, \delta),$$

i.e. if the con.det $\Gamma(t) \in C_1(I)$ is a reversible element relative to the $*$ multiplication (1). □

The question about what $\hat{\boldsymbol{\mu}}(\mathbf{r})$ is to be considered in optimal therapy remains open but may also be resolved from an analysis of the corresponding static ballistic index. So if

$$c_m = \sum_{k=1}^{M} z_{mk} \tag{2.52}$$

and

$$\mathbf{c} = [c_1\ c_2\ c_3 \cdots c_m \cdots c_l]^T, \tag{2.53}$$

it is not difficult to illustrate that

$$\varphi_m(t) = q_m(t) \rightarrow \frac{c_m}{\alpha_m}\ \forall\ m. \tag{2.54}$$

By stationarizing (2.30) and considering (2.54), it is possible to write the following expression for $\beta(\mathbf{1})$, which corresponds to the same geometrical arrangement ($\hat{\boldsymbol{\mu}}(\mathbf{r})$) of the neutron beaming system addressed by (2.29)–(2.31):

$$\beta(\mathbf{1}) = \sum_{m=1}^{l} \sum_{\substack{i=1 \\ i \neq j}}^{N} \mathbf{w}_i^T \cdot \boldsymbol{\Lambda}^{-1} \mathbf{c} \Big/ \sum_{m=1}^{l} \mathbf{w}_j^T \cdot \boldsymbol{\Lambda}^{-1} \mathbf{c}. \tag{2.55}$$

3. PROBLEM WITH LINEARIZED BALLISTIC INDEX

The abovementioned nonuniqueness of the optimal $\mathbf{B}(s)$ and the problem of existence of an analytic $\mathbf{B}^{\circ}(s)$ is expected to enhance any inherent instabilities in the solution to (2.37). This may also be attributed to the fact that both the costate equations (2.40) and the Hamiltonian

$$H(\boldsymbol{\Phi}, \boldsymbol{\Psi}, \mathbf{p}) = -\boldsymbol{\Psi}^T \cdot \boldsymbol{\Lambda} \boldsymbol{\Phi} + \boldsymbol{\Psi}^T \cdot \mathbf{p} + \sum_{\substack{i=1 \\ i \neq j}}^{N} \mathbf{w}_i^T \cdot \Phi \big/ T \mathbf{w}_j^T \cdot \Phi \tag{3.1}$$

are nonlinear in $\boldsymbol{\Phi}(t)$. As a linear function of $\mathbf{p}(t)$ this Hamiltonian has an absolute minimum along the optimal trajectories $\boldsymbol{\Phi}^{o}(t)$ no matter what the nature of the constraint set for $\mathbf{p}(t)$ may possibly be.

The fact that the state equations (2.30) are linear in both $\boldsymbol{\Phi}$ and $\mathbf{p}$ indicates that the above noted instabilities are not of neutron physical nature but are purely mathematical consequences of the nonlinear formulation (2.29) for the Lagrangian,

$$L(\boldsymbol{\Phi}) = \frac{1}{T} \sum_{\substack{i=1 \\ i \neq j}}^{N} \mathbf{w}_i^T \cdot \boldsymbol{\Phi}(t) \big/ \mathbf{w}_j^T \cdot \boldsymbol{\Phi}(t), \tag{3.2}$$

of the optimal control problem. All of this motivates us to try to relax the nonlinearity (Lee, 1966) in $L(\boldsymbol{\Phi})$ as a possible means for obtaining a unique optimal $\mathbf{b}^{\circ}(t)$ for every configuration matrix $\hat{\boldsymbol{\mu}}(\mathbf{r})$ of the irradiating beams. Such a motivation is enhanced further by observing the previous generic nonuniqueness of the solution to (2.48) and to its inverse Laplace-transformed system (2.37). Clearly by virtue of Lerch's lemma, for any assumed analytic $\mathbf{B}(s)$ image one can straightforwardly define a unique preimage $\mathbf{b}(t)$. Moreover, before stating the main result of this section, we introduce the following notation:

$$\int_0^T q_m(t)\, dt = \varepsilon_m \tag{3.3}$$

and

$$\int_0^T \mathbf{w}_i^T \cdot \boldsymbol{\Phi}(t)\, dt = T \mathbf{w}_i^T \cdot \int_0^T \boldsymbol{\Phi}(t)\, dt = T \mathbf{w}_i^T \cdot \bar{\boldsymbol{\Phi}} = h_i, \tag{3.4}$$

where h_i^* is the value of h_i that corresponds to a certain optimal trajectory $\mathbf{\Phi}^*(t)$.

Theorem 3.1. *The linearized dynamic ballistic index* $\beta(\mathbf{b})$ *is minimized for a given* $\hat{\boldsymbol{\mu}}(\mathbf{r})$ *by an optimal temporal* $\mathbf{b}^*(t)$ *vector satisfying the dual system of linear integral equations*

$$\int_0^t \mathbf{A}\,\mathbf{E}(t-\tau)\,\mathbf{b}(\tau)\,d\tau = \mathbf{0} \tag{3.5}$$

$$\int_0^T \int_0^t \mathbf{E}(t-\tau)\,\mathbf{b}(\tau)\,d\tau\;dt = \vec{\varepsilon}, \tag{3.6}$$

in which $\vec{\varepsilon}$ *is the solution vector to the linear programming problem*

$$\max\zeta = \sum_{m=1}^{l}\left[w_{jm} - \sum_{\substack{i=1\\ i\neq j}}^{N} w_{im}\right]\varepsilon_m \tag{3.7}$$

subject to

$$\sum_{m=1}^{l} w_{im}\varepsilon_m = h_i^{(0)} \leq \mathit{or} \geq h_i^* \quad i = 1, 2, 3, \ldots\ldots \leq N;\, i \neq j. \tag{3.8}$$

Proof: Reconsider $\beta(\mathbf{b})$ in the form

$$\min\beta(\mathbf{p}) = 1 - \frac{1}{T}\int_0^T \left\{\left[\mathbf{w}_j^T\cdot\mathbf{\Phi}(t) - \sum_{\substack{i=1\\ i\neq j}}^{N}\mathbf{w}_i^T\cdot\mathbf{\Phi}(t)\right]\Big/\,\mathbf{w}_j^T\cdot\mathbf{\Phi}(t)\right\} dt,$$

subject to (2.30) and (2.31).

Assume then the existence of a certain optimal control vector $\mathbf{b}^{(0)}(t) \leftrightarrow \mathbf{B}^{(0)}(s)$ derivable from (2.48) when

$$\|\det[\mathbf{F}(s)\mathbf{Z}]\| \leq \left\|\vec{\boldsymbol{\delta}}^{(k)}\right\| \tag{3.9}$$

via a system-conditioning scheme as, e.g.

$$\mathbf{B}^{(1)}(s) = \mathbf{Z}^{-1}\,\mathbf{F}^{-1}(s)\,\vec{\boldsymbol{\delta}}^{(1)}$$

and

$$\mathbf{B}^{(2)}(s) = \mathbf{Z}^{-1}\,\mathbf{F}^{-1}(s)\,\vec{\boldsymbol{\delta}}^{(2)},$$

with $\delta_k^{(2)} \neq \delta_k^{(1)}$, $\forall\, k$. The entries $B_k^{(0)}(s)$ are determined as the linear Richardson extrapolation-like limits

$$B_k^{(0)}(s) = \left[B_k^{(1)}(s)\delta_k^{(2)} - B_k^{(2)}(s)\delta_k^{(1)}\right]\Big/\left[\delta_k^{(2)} - \delta_k^{(1)}\right]. \tag{3.10}$$

Defining then the averaged numeric vector $\bar{\mathbf{\Phi}}^{(0)}$ to approximate $\beta(\mathbf{b})$, with $\beta(\mathbf{p})$, we have

$$\beta(\mathbf{p}) \approx 1 - \frac{1}{T}\int_0^T \left[\mathbf{w}_j^T \cdot \mathbf{\Phi}^{(0)}(t) - \sum_{\substack{i=1\\ i\neq j}}^{N} \mathbf{w}_i^T \cdot \mathbf{\Phi}^{(0)}(t)\right] dt/T\mathbf{w}_j^T \cdot \bar{\mathbf{\Phi}}^{(0)}. \quad (3.11)$$

Clearly then the minimization of $\beta(\mathbf{b})$ in the context of (2.29)–(2.31) is according to (3.11) and (2.25), identical to

$$\max \zeta = \sum_{m=1}^{l}\left[w_{jm} - \sum_{\substack{i=1\\ i\neq j}}^{N} w_{im}\right]\int_0^T q_m^{(0)}(t)\, dt \quad (3.12)$$

subject to

$$\sum_{m=1}^{l} w_{im}\int_0^T q_m^{(0)}(t)\, dt = h_i^{(0)} \quad i = 1, 2, 3, \ldots\ldots, N. \quad (3.13)$$

The h_i^* of (3.8) can be taken either equal to $h_i^{(0)}$ or from the satisfaction of

$$h_i^* = T\mathbf{w}_i^T \cdot \mathbf{\Lambda}^{-1}\mathbf{c}, \quad (3.14)$$

pertinent in $\beta(\mathbf{1})$ associated with the same geometrical $\hat{\boldsymbol{\mu}}(\mathbf{r})$ setting of the beams. Replacement of (3.12) and (3.13) by (3.7) and (3.8) will always be valid for a $\mathbf{q}^*(t)$ vector that is close to $\mathbf{q}^{(0)}(t)$. □

4. BALLISTIC INDEX CONTROLLABILITY

The term controllability means the possibility of driving any regional neutron flux inside the tumor back to its initial value in some finite time. Therefore establishment of the controllability of the ballistic index considered above is a further proof that therapeutic neutrons are superior to γ rays or charged particles in their response to temporal changes of their external beams.

It is well known that stability and controllability of the system of state equations (2.30) is closely tied to the nature of the α_m elements in its $\mathbf{\Lambda}$ matrix. We emphasize here that our $\{\alpha_m\}_{m=1}^{l}$ set represents the eigenvalue spectrum of a composite region BVP (2.10)–(2.13), which is after all a system Sturm Liouville 3D problem. As such these eigenvalues should satisfy the condition

$$\alpha_m \geq 0, \forall\, m. \quad (4.1)$$

However, the 3D dimensionality of the BVP for these α_ms is supposed to cause possible degeneracies (Knoble and McLaughlin, 1994) in some of these eigenvalues.

Moreover, the satisfaction of (4.1) by the $\{\alpha_m\}_{m=1}^{l}$ set happens to guarantee a stability, in the sense of Lyaponov (Kalman, 1964), for the solution to the (2.30) system of transformed neutronic state equations. Therefore any emerging instabilities during the course of finding the optimal control vector to the dynamical system (2.29)–(2.31) should not be traced back to the pertinent transformed neutronic state equations.

Furthermore, regardless of the nonuniqueness of the local (and even the quasi-global) optimal control vector to the dynamical system (2.29)–(2.31), its state controllability turns out to be independent of the nature of the $\{\alpha_m\}_{m=1}^{l}$ eigenvalue spectrum. The controllability of the ballistic index $\beta(\mathbf{b})$ directly follows the controllability of regional flux vector, which is the controllability of practical interest, and this may differ from the rather abstract state controllability.

Definition 4.1 (Kuo, 1980). The dynamical system defined by (2.30) and (2.31) is completely state controllable if ∃ is a piecewise continuous $\mathbf{p}(t)$ defined over the interval $t_i < t < t_f$ that transforms the neutron diffusion process from an initial state $\mathbf{\Phi}(t_i)$ to a final state $\mathbf{\Phi}(t_f)$ in the interval $t_f - t_i$.

Lemma 4.1. *For the system defined by* (2.30) *and* (2.31) *to be completely state controllable it is sufficient (but not necessary) that the spectrum of eigenvalues of the homogeneous BVP* (2.10)–(2.13) *is nondegenerate.*

Proof: By observing that the necessary and sufficient condition for complete controllability [19] of (2.30) and (2.31),

$$\mathrm{rank}\{\hat{\mathbf{1}} \vdots -\mathbf{\Lambda} \vdots \mathbf{\Lambda}^2 \vdots \cdots\cdots \vdots (-1)^m \mathbf{\Lambda}^m \vdots \cdots\cdots \vdots (-1)^{l-1}\mathbf{\Lambda}^{l-1}\} = l,$$

can always be satisfied and even for $\mathbf{\Lambda}$ matrices with repeated diagonal elements. □

Theorem 4.1. *For the system defined by* (2.30) *and* (2.31) *to be regional flux controllable it is sufficient (but not necessary) that the spectrum of eigenvalues of the homogeneous BVP* (2.10)–(2.13) *is nondegenerate.*

Proof: Consider the regional flux expansion (2.15) and define the regional matrix

$$\mathbf{\Xi}_i = (\mathbf{\Theta}_{i1}(\mathbf{r})\,\mathbf{\Theta}_{i2}(\mathbf{r})\,\mathbf{\Theta}_{i3}(\mathbf{r}) \cdots\cdots \mathbf{\Theta}_{im}(\mathbf{r}) \cdots\cdots \mathbf{\Theta}_{il}(\mathbf{r})).$$

Obviously the nondegeneracy of the eigenvalues mentioned in the theorem guarantees linear independence of the column vectors of Ξ_i in a sufficient but not necessary sense, $\forall i$. The necessary and sufficient condition for complete regional flux controllability of (2.30) and (2.31),

$$\text{rank}\{\Xi_i \vdots -\Xi_i \boldsymbol{\Lambda} \vdots \Xi_i \boldsymbol{\Lambda}^2 \vdots \cdots\cdots \vdots (-1)^m \Xi_i \boldsymbol{\Lambda}^m \vdots \cdots\cdots \vdots (-1)^{l-1} \Xi_i \boldsymbol{\Lambda}^{l-1}\} = l,$$

can then always be satisfied. □

Clearly the satisfaction of the conditions of this theorem can serve as an analytical and computational sufficiency criterion for the regional flux controllability of therapeutic neutrons.

5. CONCLUSION

Optimalized neutron therapy of advanced cancers calls for extremizing their ballistic index subject to the satisfaction of the associated mixed initial boundary value problem of multigroup neutron diffusion. In this work, composite surface integral transforms were demonstrated so as to enable reducing this optimization problem to a dynamical system that is optimally controlled (with temporally tuned external neutron beams) by means of Pontryagin's maximum principle.

As for practicability of this rather novel modality for neutron therapy, the more versatile is the composition of the tumor subdomains the less likely that the associated $\{\boldsymbol{\Theta}_{im}(\mathbf{r})\}_{m=1}^{l}$ set of vectors, $\forall i$, may become linearly dependent. The advanced criterion for controllability indicates remarkably that for such tumors the ballistic index of therapeutic neutrons should be expected to be more controllable; given of course that the configurations of the irradiating neutron beams are the same.

APPENDIX: PRELIMINARIES ON NEUTRON THERAPY

In therapy with neutrons, protons, or heavy ions, a specific problem requires to be taken into account because of the fact that their relative biological effectiveness (RBE) is significantly different and not unity. The RBE of fast neutrons varies within wide limits, depending on the neutron energy spectrum, dose, biological system, and endpoint. For proton beams, the RBE ranges within smaller limits, (about 1.0–1.2). Furthermore, large variations of intrinsic radiosensitivities among patients with identical tumor type make it quite difficult to select and classify patients for specific radiotherapy schedules and protocols. This is basically because cells in the different stages of the cell cycle in a tumor differ in radiosensitivity with S-phase cells (the most radioresistant) and G2/M cells (most radiosensitive), and the DNA content of the cells in these different stages also differ. DNA content and cellular proliferation kinetics could actually have an influence on intrinsic radiosensitivity and could serve as predictors of radiation response. This response is found by radiotherapy experience to depend more on tumor histology and stage than on site of origin.

High energy proton beam radiotherapy of certain tumors is nowadays a technologically advanced and effective means in the selective destruction of cancer cells. Its rational can be traced back to a paper published in 1946 by R. Wilson (1946) who recognized that protons, with their well-defined range limited scattering potential, could be an ideal radiation modality for improving the physical dose localization to a tumor target.

The main advantage of using proton beams in radiation therapy over x rays, γ rays, electrons, or neutrons is the pertinent ability to use their sharp distal falloff and lateral penumbra to shape the dose distribution very precisely to the tumor volume, thereby sparing adjacent normal sensitive structures. However results of Mills *et al.* (1992) and Larsson (1995) indicate that patients with small disease, either unsuitable for or remaining after surgery, are the ones that will benefit most from neutron therapy. Neutron therapy seem fortunately to be an effective treatment for these negatively selected patients, and it remains the treatment of choice (Stannard *et al.*, 1995) for patients with advanced irresectable salivary gland tumors and for those with macroscopic residual or questionable resectable tumors. They can also be used for the treatment of technically resectable tumors of head and neck, for cosmetic and logistic considerations, and for some metastatic neutron-responsive tumors.

Other methods that include therapy with selectively accumulating radioisotopes (Haidar, 1992) such as ^{131}I and ^{99}Tc, injected colloidal radioactive metals like ^{198}Au and ^{63}Zn, or artificially radioactive suspensions containing e.g. ^{90}Y or ^{177}Lu have long been in practice (Hahn and Sheppard, 1948). A common problem among all of these alternative methods has been in their nonuniformity of distribution inside some kinds of cancers. Such nonuniformity results with overdosage in certain regions of the tumor and negligibly low doses in others. Neutron therapy is expected to be more effective in such situations and could in principle be carried out simultaneously with one or more of these alternatives, whose implementation may affect the established neutron flux inside the tumor in various ways (Haidar, 1997).

Effectiveness of neutron therapy may also be intensified regionally by uptaking in the tumor a biologically acceptable strong neutron absorber like ^{10}B, which has a cross-section of 3840 barns for thermal neutron capture $^{10}B(n, \alpha)^{7}Li$. The reaction releases 2.8 MeV, including a 0.5 MeV γ ray. The ranges of the α and ^{7}Li are 9 and 5 μm respectively, about the size of the biological cell. It was suggested as early as 1936 that if a tumor could be loaded with ^{10}B and irradiated with thermal neutrons, energy would be released in the tumor cells. Three problems of conventional radiotherapy would then be solved by this BNCT (boron neutron capture therapy): attacking the tumor precisely, even on a microscopic scale, conforming the dose to tumor cells; and treating metastases. It is well documented (see e.g., Hart and Fidler, 1981) that one of the most formidable obstacles to the successful treatment of metastatic diseases is the fact that cells of a tumor are biologically heterogeneous.

Most neutron production methods generate high-energy neutrons, which, not being captured by ^{10}B, irradiate indiscriminately; but thermal neutrons cause skin damage, and penetrate only a few cms in tissues. The best compromise energy is 0.1–10 keV. Such neutrons penetrate with little damage, and are thermalized in tissue. High enough fluxes of such filtered slow neutron beams have become available for therapeutic use only during the last decade; in a way widening the horizons for this unique kind of radiotherapy. This situation, and important recent chemical and biological developments, contribute to the renewed interest (McMichael *et al.*, 1995) in the classical idea of BNCT. This modality, evidently dependent on the ability of used boron compounds to penetrate in tumor tissue, is very likely to be more useful for treatment of small local metastases and infiltrating tumor cells than in radiotherapy for solid tumors. There has thus been a need for development of improved boron-carriers, and important progress is being made (Larsson, 1995).

In order to improve uptake and specificity of boron in tumor cells, some new approaches in synthesizing boron containing compounds, like some nido derivatives of DL-4-carboranyl phenylalnine, have been followed. Another strategy has been to couple the boron containing compound to a tumor-affine protein (antibody, receptor ligand, liposomes etc.). Furthermore, boron can be localized in the DNA of target cells, when coupled to a pyrimidine derivative or to a DNA dye, respectively. Many other compounds have been synthesized, each using a different approach in binding the tumor cells with ^{10}B. From the chemistry point of view, BNCT is not yet optimized, and progress and success of this therapy mode depends strongly on the progress in different fields in biology, physics, chemistry medicine and mathematical modelling.

ACKNOWLEDGMENTS

This work was supported in part by the Lebanese National Council For Scientific Research, Beirut, Lebanon.

REFERENCES

Asanov, A. (1998). Regularization, Uniqueness and Existence of Solutions of Volterra Equations of the First Kind. Inverse and Ill-Posed Problems Series, VSP, Utrecht.

Bukhgeim, A. L. (1999). Volterra Equations and Inverse Problems. Inverse and Ill-Posed Problems Series, VSP, Utrecht.

Evans, L. C. and Lions P. L. (1980). Resolution des équations de Hamilton-Jacobi-Bellman pour des opérateurs uniformement elliptiques. *Comptes Rendus de l'Academie des Sciences* **260**, 1049–1052.

Fujino, M. and Sumita, K. (1970). Measurements of neutron thermalization time constant of light water by pulsed neutron method. *Journal of Nuclear Science and Technology* **7**, 277–284.

Hahn, P. F. and Sheppard, C. W. (1948). The therapeutic use of radioactive elements in maliganacy. *Annals of Internal Medicine* **28**, 598.

Haidar, N. H. S. (1982). New singular integral equations in experimental neutron rethermalization. *Nuclear Science and Engineering* **80**, 113–123.

Haidar, N. H. S. (1983). Operational analysis of multiregional nuclear reactor kinetics. *Institute of Mathematics and its Applications Journal of Applied Mathematics* **30**, 247–267.

Haidar, N. H. S. (1992). A phenomenological model for radioactive poisoning by a human body. *Revue de Bio-Mathematique* **120**, 21–47.

Haidar, N. H. S. (1997). On a boundary value problem posed by cancer therapy with neutron beams. *Journal of the Australian Mathematical Society, Series B* **39**, 46–60.

Hart, J. and Fidler, I. J. (1981). The implications of tumor heterogeneity for studies on biology and therapy of cancer metastasis. *Biochimica et Biophysica Acta, Reviews on Cancer* **651**, 37–50.

Kalman, R. E. (1964). When is a linear control system optimal? *Journal of Basic Engineering (Transactions of the American Society of Mechanical Engineers, Section D)* **86**, 51.

Knoble, R. and McLaughlin, J. R. (1994). A reconstruction method for a Two-dimensional inverse eigenvalue problem. *Journal of Applied Mathematics and Physics (ZAMP)* **5**, 794–826.

Kuo, B. C. (1980). *Digital Control Systems*, Holt-Saunders, Tokyo.

Larsson, B. (1995). Neutron capture therapy: Status and prospects. In *Neutron Therapy Symposium*, Cape Town, South Africa, Oct. 16, 1995, unpublished.

Lee, E. S. (1966). Quazi-linearization, nonlinear boundary value problems and optimization. *Chemical Engineering and Science* **21**, 183–194.

Lions, J. L. (1971). Optimal Control of Systems Governed by Partial Differential Equations, Springer, Berlin.

Lions, J. L. (1986). Contrôle de Pareto de systèmes distribués. Le cas stationaire. *Comptes Rendus de l'Academic des Sciences* **302**, 223–228.

McMichael, G. E., Yule, T. J., and Zhou, X. L. (1995). *The Argonne ACWL a potential accelerator-based neutron source for BNCT. Nuclear Instruments and Methods in Physics Research, Section B* **99**, 847–850.

Mills, E. E., Stannard, C., Levin, V., Vernimmen, F. J., and Wilson, J. (1992). Neutron therapy improves control of malignant salivary gland tumor. *South African Medical Journal* **82**(2), 121.

Nicolini, C. (1984). Modeling and Analysis in Biomedicine, World Scientific, Singapore.

Ölçer, N. Y. (1968). A general class of unsteady heat flow problems in a finite composite hollow circular cylinder. *Quarterly of Applied Mathematics* **26**, 355–371.

Stannard, C., Vernimmen, F. J., Jones, D. T., Van Wijk, A. L., Brennan, S. M., Visser, A. M., Johnson, C. A., Wilson, J. A., Murray, E. A., Levin, C. V., Mills, E. E., Alberts, A., Werner, I. D., Smith, B. J., and Schmitt, G. (1996). The neutron therapy clinical programme at the National Accelerator Centre (NAC). *Bulletin of Cancer Radiotherapy* **83**, 87s–92s.

Wilson, R. R. (1946). Radiological use of fast neutrons. *Radiology* **47**, 487.

Zeitz S. and Nicolini, C. (1979). Mathematical approaches to optimization of cancer chemotherapy. *Bulletin of Mathemaical Biology* **41**, 305–324.