Chapter 10

Estimation of TTFields Intensity and Anisotropy with Singular Value Decomposition: A New and Comprehensive Method for Dosimetry of TTFields

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10.1 Introduction

Tumor-treating fields (TTFields) are a new and effective treatment against glioblastoma (GBM) [1–3]. The treatment uses alternating fields (200 kHz for GBM) to inhibit cancer cell division and tumor growth. TTFields are induced by two electrical sources, each connected to its own pair of 3×3 transducer arrays, which are placed on the patient’s body surface in the vicinity of the tumor [4]. Recently, finite element (FE) methods have been used to calculate the distribution of TTFields in realistic human head models in efforts to estimate the treatment dose of TTFields [5–8]. This has provided important information about how the TTFields distribution is affected by human head morphology [9], tumor position [10, 11], tissue dielectric properties [9, 10, 12, 13], and transducer array layout [11, 14]. In addition, FE methods have been used to provide preclinical proof of concept for a new implementation of TTFields in which individual computational modeling is used to plan a surgical skull remodeling procedure that enhances the efficacy of TTFields by creating small holes in the skull at selected positions, facilitating current flow into the tumor [15, 16]. However, state-of-the-art approaches only use the intensity of TTFields as a surrogate “dose” estimate. This is motivated by in vitro studies showing that increasing TTFields intensity decreases tumor growth rate [17]. However, it is also known that the antitumor effects of TTFields depend on the treatment exposure time as well as the direction of the induced fields relative to the direction of cell division. Specifically, longer exposure time kills more cancer cells [18], and cells dividing along the direction of the active field are damaged to a greater extent than

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cells dividing perpendicularly to the field [17, 19]. This observation is supported by the fact that two sequential fields induced by layouts placed in orthogonal directions on the scalp enhance the efficacy of the treatment in vivo by approximately 20% compared to a single field [20]. This illustrates the notion that multidirectional TTFields are able to inhibit a larger fraction of cells in a volume because the effect is distributed more uniformly across cells dividing in random directions [20]. By a similar notion, TTFields are currently applied using two array pairs, which are activated in an even 50% duty cycle of 2-second duration (Optune®, Novocure, Ltd.). The arrays are positioned so that the field intensity in the tumor is maximized, while the arrays are maintained in approximately orthogonal orientations [4]. However, because of the complex conductivity distribution of the head and individual differences in anatomy and tumor morphology, the induced fields are not necessarily orthogonal throughout the exposed volume. This problem has not been addressed in TTFields modeling until now, which may give a biased or incomplete foundation for determining the actual efficacy of TTFields. This chapter presents a new method, which potentially resolves this limitation by quantifying both the average field intensity and the amount of unwanted spatial correlation between the induced fields. The chapter is based on results published by Korshoej et al. [21], and further elaborates on the underlying modeling methods. The new dosimetry approach is based on FE computations and principal component analysis (PCA). I will describe how significant field anisotropy can occur in GBM patients and how this potentially affects layout planning and clinical implementation. Finally, I will briefly discuss how unwanted field anisotropy can potentially be reduced using activation cycle optimization.

10.2 Preparation of Computational Models and Calculation of the Electrical Field

In the following sections, I will describe the methods used to perform FE calculations of the TTFields distribution in a realistic, patient-based head model. I will focus mainly on the basic physics of TTFields, as well as the general concept of FE computation.

10.2.1 *Laplace's Equation: The Electro-quasistatic Approximation of Maxwell's Equations*

The physical effects of TTFields are governed by Maxwell's equations of electrodynamics [22]. To describe the interaction of TTFields with a volume conductor, e.g., the human head or another body region, the goal is to approximate a solution to Maxwell's equations under a particular set of boundary conditions. These typically represent constraints applied to the functional values at particular regions of the

model. For TTFields, we may assume the electrodynamic behavior to be quasistationary, which simplifies the problem [23, 24]. Quasistationary systems satisfy particular conditions regarding the frequency of the current/field, the dielectric properties of the system materials, and the size of the system. Specifically, quasistationarity requires that the magnetic permeabilities and inductive effects are negligible. Furthermore, we require the ratio $\varepsilon\omega/\sigma$ to be low, i.e., $\varepsilon\omega/\sigma \ll 1$, where ε is the real-valued permittivity of the system, ω the angular frequency of the field, and σ the real-valued conductivity, which implies that capacitive effects are also negligible. Therefore, the induced currents are mainly Ohmic. Magnetization currents and displacement currents do not contribute notably and so local changes in the field are propagated throughout the physical system without time delay and produce synchronous field variations in the system. TTFields satisfies these electro-quasistatic assumptions when applied to the head. This is because of the dielectric properties of biological tissues, the low/intermediate frequency (200 kHz) of TTFields, and the small dimension of the physical system, i.e., head (0.2 m). Furthermore, this implies that the electric potential φ can be approximated with Laplace's equation $\nabla \cdot (\sigma \nabla \varphi) = 0$, where σ is the real Ohmic conductivity [5, 22–25]. The requirement of $\varepsilon\omega/\sigma \ll 1$ is supported by Wenger et al. [12], who reported a low sensitivity of the TTFields towards permittivity variations. Similar results were obtained by Lok et al. [26], which further supports that the electro-quasistatic assumption is valid within the range of parameters relevant for TTFields. In the following sections, I will describe the basics of FE approximation to Laplace's equation.

10.2.2 The Finite Element Framework for TTFields

In the data presented here, we used finite element methods to solve Laplace's equation of the electrostatic potential, as defined in the previous section. We used Dirichlet boundary conditions given by the geometrical boundaries of the head surface and the desired choice of electrostatic potential at the electrode interface. The finite elements had tetrahedral geometry adapted in shape and size to approximate the individual volumes and surfaces of the patient's head. In addition to providing a close anatomical approximation, the mesh was dense enough to allow for detailed variations in dielectric properties. Using first-order finite elements, we formulated the electric potential at any point in the model as a linear function of the electric potentials at the nodes of the tetrahedron containing the point. These linear "basis" functions were then used to build a system of linear equations, which was solved using a conjugate gradient solver (GetDP, <http://getdp.info/>) with the residual tolerance set to $<1\text{E-}9$. Potentials were fixed at the top of the individual electrodes in an array. All electrodes belonging to one array were thereby set to a potential of 1 V and the electrodes of the corresponding array to -1 V. We then calculated the electric field as the numerical gradient of the electric potential. The current density vectors were calculated with Ohm's law and we then rescaled the potentials, fields, and

current densities to obtain a total current of 1.8 A through each array pair. This was computed as the numerical integral of current density components normal to the arrays over the entire transducer array area. This approach was chosen over Neumann boundary conditions because it enabled us to model the actual situation in which all of the nine transducers in an array were connected to the same current source and therefore had the same electric potential.

10.2.3 *Creation of Personalized Head Models*

A number of different approaches have been used to create computational head models for TTFields [7]. We created a patient-specific head model based on T1- and T2-weighted MRI sequences from a male patient with GBM in the left parietal region. The images were processed using SimNIBS (simnibs.org) to produce a 3D volume head mesh consisting of five tissue types, namely skin, skull, cerebrospinal fluid (CSF), gray matter (GM), and white matter (WM). A detailed description of the SimNIBS workflow is given in Windhoff et al. [27]. In summary, segmentation is based on the initial extraction of tissue boundary surfaces, which are then processed and tessellated to produce a tetrahedral volume mesh with variable resolution. Surface meshes from WM, GM, cerebellum, and the brain stem are extracted from the T1 MRI data using Freesurfer algorithms (<http://surfer.nmr.mgh.harvard.edu/>) [28], while skin, skull, and CSF boundaries are extracted from both T1 and T2 MRI data using the FSL toolbox (<https://fsl.fmrib.ox.ac.uk/fsl/>) [29]. The surface meshes are then postprocessed in MeshFix [30] to repair self-intersections, remove duplicate triangles, and enhance triangle uniformity and regularity. Surfaces are then decoupled to ensure that all tissues are nonoverlapping. The tumor region was outlined manually from a gadolinium-enhanced T1 MRI sequence, following the initial automated segmentation, shown in Fig. 10.1. The resulting binary volume mask was subsequently smoothed and transformed into a triangulated surface mesh using custom scripts based on MeshFix, FSL, and Freesurfer. The tumor surface mesh was then merged with the GM and WM surfaces so that the entire tumor was included in the GM volume. This procedure was conducted using Meshfix by joining the inner part of the tumor surface and the outer part of the white matter surface and equivalently joining the outer part of the tumor surface with the outer part of the GM surface. The surfaces were then re-optimized. Following surface optimization, individual tissue volumes were tessellated using Gmsh [31] (<http://gmsh.info>) to produce a tetrahedral finite element mesh with five tissue volumes (Fig. 10.1). The quality of the resulting mesh was optimized [32] and the anatomical accuracy of the final segmentation was evaluated by visually inspecting the overlay of the mesh on the structural MRI images. The cerebellum was included as WM volume and the ventricles in the CSF volume. The tumor volume was finally defined by selecting the tetrahedra in the GM volume, which also lay within the binary mask created by manual outlining of the tumor. A peritumoral border zone was defined by automatic selection of all GM and WM tetrahedra within 1 cm of the outermost tumor border.

Fig. 10.1 *Top row*, gadolinium-enhanced T1 MRI from a GBM patient. *Bottom row*, the resulting volume segmentation based on the MRI data shown above and the SimNIBS software. The model is composed of skin, skull, CSF, GM, WM, tumor (yellow), and peritumoral volumes (magenta)

The final mesh consisted of seven tissue volumes and provided an accurate morphological representation based on 4,014,379 tetrahedra with a mean volume of 0.80 mm^3 .

10.2.4 Placement of Transducer Arrays

To place the arrays in the model, we defined appropriate centers and orientations of each array using the SimNIBS graphical user interface and the specific head model. The orientation was given as a unit vector along the short axis of the array. The central transducer of the array was placed at the defined array center. We then constructed a longitudinal orthonormal vector as the cross product of the directional vector and the unit vector normal to the skin surface at the defined center. Two points were then defined at 45 mm and -45 mm from the center of the transducer along the line of the longitudinal vector, respectively. Each point was projected onto the closest triangle of the skin surface, which was then defined as the center of the middle transducer of the corresponding column in the array. In this way, all three transducers of the longitudinal center row were placed. A similar approach was adopted to place the transducers of the first and third row in the array. However, in this case, the originally defined directional vector of the short axis was used to

Fig. 10.2 Surface representation of the head model after placement of transducer arrays. The layout shown here corresponds to the layout proposed by the NovoTAL® algorithm used for clinical treatment. (Courtesy of Novocure, Ltd.)

define points at 22 mm and -22 mm distances from the centers of each transducer in the middle row. Using this approach, it was possible to place all transducers automatically and without significant undesirable overlap. Four different, clinically relevant layouts were tested. The procedure was implemented in a custom MATLAB script (Mathworks, Inc.). Figure 10.2 shows an example array layout.

10.2.5 Assignment of Tissue Conductivity

For the skin, skull, and CSF volumes, uniform and isotropic scalar conductivity values were assigned to all nodes belonging to the corresponding tissue volume in the mesh. Values were taken from the literature and based on in vitro and in vivo measurements at comparable frequencies (skin 0.25 S/m; bone 0.010 S/m; and CSF 1.654 S/m [33–39]). Electrodes were modeled with a 0.5 mm layer of conductive gel (1.0 S/m conductivity) between the electrode and the scalp. For GM, WM, and tumor tissues, we used an individualized anisotropic conductivity estimation technique, *direct conductivity mapping*, based on diffusion MRI (dMRI) data [40, 41]. The technique is based on the cross-property relation between general classes of transport tensors, e.g., diffusion and conductivity tensors, and the underlying microstructure of the transport medium. The general principle is that different “transport processes” will share the same eigenvectors of the corresponding transport tensors when taking place in the same medium. This allows for a simplified representation of the transport process through calculation of the eigenvalues specific for the given process. In the case of conductivity and diffusion, these eigenvalues are approximately linearly related so that the anisotropic conductivity tensor, required for accurate approximation of a solution to Laplace’s equation, can be directly inferred from

Fig. 10.3 Coronal views of the mean conductivity and FA of the conductivity tensor obtained using direct conductivity mapping. Significant conductivity variations occur in the tumor and peritumoral regions. WM tissue is highly anisotropic and FA values also vary within the region of the tumor. (Adapted from Wenger et al. [26])

diffusion MRI data using the same diffusion tensor eigenvectors and linearly scaled eigenvalues. Specifically, conductivity eigenvalues were calculated by fitting a linear relation with no intercept to the mean of diffusion eigenvalues, thereby ensuring that the distribution of the geometrical mean of conductivities (scaled eigenvalues) was centered at the in vivo mean estimates for the corresponding tissue in a least squares sense [41, 42]. The linear relationship was given by $\sigma_v = s \cdot d_v$, where σ_v is the conductivity along a given eigenvector v , d_v are the diffusion eigenvalues in the same direction, and s is a linear scale factor given by $s = (\overline{d_{WM}} \sigma_{WM}^{iso} + \overline{d_{GM}} \sigma_{GM}^{iso}) / (\overline{d_{WM}}^2 + \overline{d_{GM}}^2)$. In the latter expression, σ_{WM}^{iso} and σ_{GM}^{iso} are the uniform isotropic conductivity values (in vivo mean) of WM and GM, respectively, and $\overline{d_{WM/GM}} = \sqrt[3]{\sum_N d_1 \cdot d_2 \cdot d_3 / N}$ represent the “average” value over N voxels in the corresponding tissues (GM and WM separately) of the geometric mean of the diffusion eigenvalues [42].

The scale factor was fitted using diffusion data within the GM and WM tissues of the healthy right hemisphere, and the scale factor was then applied to the entire diffusion tensor to extrapolate the conductivity estimates for the GM, WM, and tumor region in both the left and right hemispheres. The calculated voxel conductivities were assigned to mesh nodes of the corresponding tissue using nearest-neighbor interpolation [42]. The direct mapping procedure was implemented using the *dwi2cond* algorithm in SimNIBS. The resulting conductivity tensor is shown in Fig. 10.3 along with a topographical map of the fractional anisotropy.

10.3 Dosimetry of TTFields

10.3.1 The Problem

As described previously, Optune® therapy (TTFields) is performed by sequential activation of two electrode array pairs. This means that the field distribution throughout an activation cycle is composed of two consecutive fields, which are active for

Fig. 10.4 Topographical field distribution for the left-right (L/R, left panel) and anterior-posterior (A/P, right panel) array pairs. The middle panel shows an enlarged schematic view of the two sequential field vectors in a small subvolume of the tumor. The illustration shows that the two fields are not entirely orthogonal and that they do not have equal magnitude

an equal amount of time (1 s). In the present context, the objective is to quantify the average effect of TTFields based on all sequential fields in the duty cycle. Previously, studies have presented the field distributions induced by each active pair, as originally described by Miranda et al. [5]. This approach is demonstrated in Fig. 10.4.

Although illustrative for many purposes, this approach does not account for spatial field correlation. This unwanted correlation causes the average antitumor effect to vary between cells depending on their direction of cell division, as previously explained. Figure 10.4 illustrates schematically how the induced sequential field vectors of each electrode pair are not orthogonal but rather have a variable extent of spatial correlation. In addition, fields may be orthogonal, but have different magnitude and so the average efficacy will still be biased and have variable antitumor activity towards cells dividing in different directions. In the following sections, I will describe a method for estimating the strength of the *uncorrelated* field components in any small tissue region and over one entire activation cycle of TTFields. The method provides individual measures of [1] the mean field intensity experienced by a cell dividing in any random direction in a local volume and [2] of the directional preference of efficacy caused by spatial field correlation. The calculations are based on the field distributions obtained using the FE methods described above.

10.3.2 The Basic Framework

First, we will consider TTFields at a specified point in the head model. We can assume that the fields are constant within a small volume surrounding the point. Although Optune® therapy is currently applied using two array pairs, TTFields can

potentially be applied using any number $n \in N$ of pairs. We will denote the field vector generated by the i th array pair as $\mathbf{E}_i$ ($i = 1, 2, \dots, n$) and define $\boldsymbol{\varepsilon}$ to be the *field matrix* with transposed sequential field vectors $\mathbf{E}_i$ in each row, i.e.,

$$\boldsymbol{\varepsilon} = \begin{bmatrix} \mathbf{E}_1^T \\ \vdots \\ \mathbf{E}_n^T \end{bmatrix} \in \mathbb{R}^{n \times 3} \quad (10.1)$$

We will now define the relative activation time α_i of $\mathbf{E}_i$ as

$$0 < \alpha_i = \frac{t_i}{\sum_{j=1}^n t_j} < 1, \quad (10.2)$$

where $t_i \geq 0$ is the absolute “on-time” of $\mathbf{E}_i$ during an activation cycle. We see that $\alpha_1 = \alpha_2 = \frac{1}{2}$ for Optune®, corresponding to a 50% duty cycle. If we denote $\mathbf{A} \in \mathbb{R}^{n \times n}$ as the diagonal *activation time matrix* with entries $a_{ii} = \sqrt{\alpha_i}$ for all i , then the matrix

$$\mathbf{P} = \mathbf{A}\boldsymbol{\varepsilon} \in \mathbb{R}^{n \times 3} \quad (10.3)$$

defines an “activation-time-weighted” field matrix. We now want to quantify the activation-time-weighted field intensities and evaluate whether they are distributed isotropically over the three directions in space. This can be estimated using principal component analysis of $\mathbf{P}$ to represent this matrix by up to three orthonormal basis vectors (principal components) collected in a matrix $\mathbf{W} \in \mathbb{R}^{3 \times 3}$, and these will be uncorrelated over the dataset:

$$\mathbf{T} = \mathbf{P}\mathbf{W} \in \mathbb{R}^{n \times 3}. \quad (10.4)$$

The matrix $\mathbf{T}$ is equivalent to $\mathbf{P}$ after a change of basis has been performed. Estimating $\mathbf{W}$ is equivalent to fitting an ellipsoid to the data, and the axes of the ellipsoid are defined by the principal components (see Fig. 10.5).

There are a number of ways to estimate the principal components. Here we use the singular value decomposition (SVD)

$$\mathbf{P} = \mathbf{U}\boldsymbol{\Sigma}\mathbf{W}^T \in \mathbb{R}^{n \times 3}. \quad (10.5)$$

The matrix $\mathbf{W}$ contains the orthonormal right singular basis vectors and the matrix $\boldsymbol{\Sigma} \in \mathbb{R}^{n \times 3}$ contains the singular values σ_k , $k \leq 3$, which correspond to the lengths of the semiaxes of the fitted ellipsoid. This gives us the opportunity to estimate the average intensity of TTFields and the local field correlation for arbitrary configurations with n array pairs.

Fig. 10.5 Geometrical interpretation of the singular value decomposition. $\mathbf{E}_1$ and $\mathbf{E}_2$ are the two sequential field vectors, and the corresponding duty cycle is shown on the left. The parameters $\sigma_{\min}$ and $\sigma_{\max}$ are the minimum and maximum nonzero principal components corresponding to the semiaxes of best ellipsoid fit to the field data

10.3.3 Estimation of the TTFields Intensity

In light of the above derivations, we can express the average field intensity using singular value notation. First, we will define the average field intensity E_{avr} as the Frobenius norm of $\mathbf{P}$:

$$E_{\text{avr}} = \mathbf{P}_F = \sqrt{\sum_{i=1}^n \alpha_i E_i^2} = \sqrt{\sum_{k=1}^3 \sigma_k^2} \quad (10.6)$$

We see that E_{avr} is the square root of the activation-time-weighted contributions of energy from each sequential field in the activation cycle. This definition is convenient because it is linked with both the decorrelated principal components and the actual applied fields, i.e., it can be calculated from both parameters and it has a direct physical interpretation. We note that σ_k is the magnitude of the average field vector in the direction of the corresponding principal component. Since $\text{rank}(\mathbf{P}) = 2$ for the current Optune™ device, this configuration can induce a maximum of two nonzero principal components because it uses only two field directions. So, at least one singular value of $\mathbf{P}$ will be zero. This implies that the cells dividing in the direction of any zero eigenvector will likely experience little or no inhibiting effect of TTFields. Also, cells dividing at a positive angle to the plane of the induced fields will experience reduced average effects proportional to the projection of the field onto the subspace of nonzero principal components. Based on this notion, it would be necessary to alternate between at least three linearly independent field vectors throughout the activation cycle and thereby use at least three sets of electrode pairs in order to avoid this problem and induce inhibitory effects on all cells in the volume. It is also notable that the maximum average field intensity will be equal to the largest singular value and the minimum average field intensity equal to the minimum

singular value. The directions in which these extreme values occur are given by the corresponding right-singular vectors. This further prompts the consideration that optimization of the activation cycle and the current settings may be employed to induce a more effective field distribution created as a linear combination of the sequential fields. This topic is briefly described below in this chapter.

Also, it is important to note that experimental data shows that there is a nonlinear dependence between the antitumor effects of TTFields and the Euclidean magnitude of the field. Specifically, low effects occur when the field is below a threshold [17]. Compared to a linear weighting of individual field strengths, the above definition of average field intensity accounts for circumstance to some extent by assigning higher weight to stronger fields. However, alternative definitions can also be used and additional studies are needed to determine which norm best represents the efficacy of TTFields. Recently, the local minimum field intensity (LMiFI, V/cm) and the local minimum power density (LMiPD) were proposed as appropriate dose estimates. The LMiFI is the lower of the two sequential field intensities delivered at a given point in the model. The LMiPD is the lower of the two power densities delivered at a given point in the model (mW/cm^3), where the power density is calculated as $P = 1/2(\sigma E^2)$. The authors found that both estimates correlated with clinical outcome [43, 44], such that patients who had a high LMiFI and LMiPD during the course of treatment (when accounting for the average device on-time, compliance) lived longer. Although promising, this approach is also based on field intensity estimates alone, and does not account for activation cycle variations or spatial field correlations, so it should be explored in similar studies as to whether these parameters represent independent predictors of treatment efficacy.

10.3.4 *Estimating the Spatial Correlation of TTFields Using the Fractional Anisotropy (FA) Measure*

Having characterized the average field intensity, the next objective is to define a measure of field correlation, which generalizes to multiple field directions. To do this, we will adopt the FA estimate, which has been used extensively in diffusion tensor imaging [45]:

$$\text{FA} = \sqrt{1/2} \frac{\sqrt{(\sigma_1 - \sigma_2)^2 + (\sigma_2 - \sigma_3)^2 + (\sigma_3 - \sigma_1)^2}}{\sqrt{\sigma_1^2 + \sigma_2^2 + \sigma_3^2}}. \quad (10.7)$$

FA is calculated from the singular values, and it estimates the fractional deviation of $\mathbf{P}$ from the condition in which all principal components have equal magnitude, i.e., the time-averaged field over an activation cycle is the same in all directions and therefore the same for all cells in the small volume of interest. For implementations of TTFields with less than three singular values, such as the current Optune®

technology, the missing values are assigned a value of zero. FA can generally take values between zero and one, where higher values represent a higher degree of unwanted spatial field correlation and lower values the opposite. Since two pairs of arrays can induce a maximum of two linearly independent fields, and therefore a maximum of two nonzero principal components, the lowest value of FA which can be achieved with Optune® is $\frac{1}{\sqrt{2}} \oplus 0.71$. Lower values of FA would require that at least three field components (i.e., three array pairs) be used, as described above.

It must be noted that other generalized measures on spatial correlation may also be used, e.g., relative anisotropy, volume ratio, etc. [45]. Furthermore, simpler measures such as the scalar product, cross product, or angle between field vectors can be used, but these measures are only well defined for configurations with exactly two field directions.

10.3.5 Step-by-Step Framework for Calculation of FA and E_{avr}

In this section, I will briefly recapitulate the framework for estimation of FA and E_{avr} .

Step 1: Calculate the field distribution for each array layout. This is done using the methods described in Sect. 10.2, although alternative approaches may also be used [7]. Here, we calculated the field distributions for two different scenarios, namely before and after resection of the tumor in a realistic GBM head model. Resection was modeled by assigning isotropic CSF conductivity to the tumor volume, which is equivalent to a realistic resection cavity.

Step 2: Build the field matrix for each element in the model. Each matrix is composed of the calculated field vectors for the element, and the collection of matrices defines a tensor field equivalent for the computational model.

Step 3: Define the diagonal activation time matrix describing the relative activation times given by the TTFields activation cycle. In the case of Optune®, this will be a 2x2 matrix with the diagonal entries given by 0.5.

Step 4: Calculate the activation-time-weighted field matrix $\mathbf{P}$ as the product of the field matrix and activation-time matrix for each element in the model.

Step 5: Calculate the singular value decomposition of $\mathbf{P}$ for all elements in the model. This yields tensor fields for the left-singular matrices, the singular value matrices, and the right-singular matrices.

Step 6: For all elements, calculate FA and E_{avr} , as given by Eqs. (10.6) and (10.7), to obtain scalar fields of these estimates in all compartments of interest in the model.

Step 7: Postprocess the estimates of FA and E_{avr} , e.g., to visualize the data, obtain average estimates, distribution functions, or other outputs of interest.

10.4 Results from Example Calculations

In this section, I will present the results obtained using the proposed approach and the patient-based GBM head model prepared as described in Sect. 10.2.

10.4.1 Topographical Distributions of FA and E_{avr}

Figure 10.6 (middle panels) shows the distribution of the maximum and minimum singular values given in a particular sequence of field distributions (shown in Fig. 10.6, left panels).

The field distribution in each finite element is anisotropic with a notable difference between the two principle components throughout the brain. This notion is further illustrated in the right-most lower panel of Fig. 10.6, which shows the topographical map of FA. Although FA was reasonably low in the tumor region, it was considerable in the peritumoral border zone. We see that the use of two field directions was not entirely able to distribute the inhibiting fields equally among the different directions in the plane of the two fields, as was in fact intended.

Following resection, the observed field anisotropy was significantly more pronounced (Fig. 10.7). The two array pairs induced high field intensities in different areas of the brain and resection border (Fig. 10.7, left). This caused significant differences between the principal components (i.e., $\sigma_{max} \gg \sigma_{min}$, Fig. 10.7 middle

Fig. 10.6 The left panels show the field intensity distributions induced by the L/R and A/P array pairs. The tumor is outlined by the solid line. The middle panels show the corresponding distribution of minimum (bottom) and maximum (top) singular values. The right panels show the efficacy parameters E_{avr} (top) and FA (bottom). (Adapted from Korshoej et al. [21])

Fig. 10.7 The left panels show the field intensity distributions induced by the L/R and A/P array pairs after tumor resection. The resection cavity is indicated. The middle panels show the corresponding distribution of minimum (bottom) and maximum (top) singular values. The right panels show the efficacy parameters E_{avr} (top) and FA (bottom). (Adapted from Korshoej et al. [21])

Fig. 10.8 Scatterplot of the corresponding minimum (*ordinate*) and maximum (*abscissa*) non-zero singular values (V/m) in the peritumoral region. The identity line (solid black) represents field isotropy. (Figure adapted from Korshoej et al. [21])

panels) and pronounced FA (Fig. 10.7, right bottom panel) in these regions. Specifically, FA was high in the region surrounding the resection cavity, though E_{avr} was also high in this region (Fig. 10.7, right top panel).

Figure 10.8 illustrates the extent of anisotropy as a scatterplot of paired singular values from elements in the peritumoral region around the resection cavity. The maximum achievable extent of isotropy using two array pairs would imply that both nonzero singular values were the same. However, as evident from Fig. 10.8, a large number of elements show considerable deviation from this condition.

The field redistribution observed following resection was caused by increased shunting of current through the CSF-filled resection cavity, which further caused high field strengths in the regions where the resection border was perpendicular to current and the applied field [6, 10]. In this case, the use of two field directions arguably served the purpose of distributing the field across the whole region, rather than inducing inhibiting fields in multiple directions. With this in mind, it is worth

considering if highly anisotropic cases would be treated more efficiently with TTFields configurations designed to induce a high average field intensity and satisfactory pathology coverage, albeit at high anisotropy. Such implementations may be exemplified by “single-field” configurations. Alternatively, configurations may potentially be optimized to maintain an acceptable coverage and field intensity, albeit at a lower extent of anisotropy. The latter topic is highly interesting from a duty cycle optimization perspective, as discussed below.

10.4.2 Variations in FA and E_{avr} for Different Array Layouts

To examine a clinically relevant aspect of TTFields dosimetry, we investigated the field decomposition of four different layouts (Fig. 10.9).

Without tumor resection, E_{avr} indicated the following order of layout performance: Layout 4 > 3 > 2 > 1 (Fig. 10.10a, c). The FA estimate, however, indicated a reverse order (Fig. 10.10b, d), which raises questions about the true efficacy of the layouts. The median FA in the tumor and the peritumoral regions were 0.715 and

Fig. 10.9 Surface plot of four different array layouts tested. Gray and blue represent one pair and orange and white another. (Adapted from Korshoej et al. [21])

Fig. 10.10 Cumulative probability density functions of the mean intensity E_{avr} (left column) and FA (right column). The graphs show the percentage of elements in the selected volume that are equal to or higher than the corresponding value on the *abscissa*. Panels **a** and **b** represent values from the tumor volume before resection, panels **c** and **d** represent values from the peritumoral border zone before resection, and panels **e** and **f** represent the peritumoral region after resection

0.73, respectively. Resection caused a significant increase in FA for all layouts (median FA >0.82, Fig. 10.10f). Contrarily, resection reduced the median field intensity E_{avr} from ~120–150 V/m to ~100–110 V/m (Fig. 10.10c, e), and the distributions of FA and E_{avr} were close to identical for all layouts (Fig. 10.10e, f). This indicates that the positioning of arrays may be less important in some resected cases.

10.4.3 Optimization of the TTFields Activation Cycle to Reduce Unwanted Field Anisotropy

Given the possibility of quantifying FA, it is natural to consider whether TTFields therapy can be optimized to reduce this unwanted parameter. For instance, it might be desirable to plan the treatment array layout to maximize field intensity in the

tumor, while simultaneously reducing FA. However, this may not always be possible, as some high-field configurations also produce high FA and vice versa. Recently, we proposed an approach in which FA can be reduced for an arbitrary layout without compromising the field intensity. The principle is based on individualizing the activation cycle of TTFields for each patient and each given array layout, rather than using a standard even 50% cycle. Specifically, the activation cycle is altered such that both pairs are activated simultaneously with a balanced intensity, so that the two fields are combined linearly to produce two resulting sequential fields, which are minimally anisotropic on average (in the volume of interest). Throughout the volume of interest, the field will thus be relatively orthogonal and have approximately equal magnitude. The factors determining the balance can be considered as linear gain factors to be applied to the standard current settings of each source in the system. In an alternative embodiment, the derived scale factors are used to modify the on-time of the given source. Although promising, the proposed activation cycle procedure is not currently supported by the Optune® device. Furthermore, it is important to note that reduced FA comes at the expense of increased total current density if the average field intensity is maintained. If FA is reduced at unchanged total current settings, then the mean field intensity will be reduced. So in all cases, there will be a trade-off, which highlights the importance of clarifying which efficacy parameters are more significant. For further details, the reader is kindly referred to Korshoej et al. [46].

10.5 Summary

In this chapter, I have described an extended framework to estimate the antitumor “dose” of TTFields. The approach is based on principal component decomposition of average field vectors induced over an activation cycle, and it quantifies both the mean intensity (E_{avr}) and unwanted spatial correlation (FA) of TTFields. These measures have a physical interpretation and generalize to an arbitrary number of array pairs. Furthermore, they account for all factors known to affect TTFields efficacy and provide a more comprehensive method for dose estimation than the current art. Computations show that significant unwanted FA occurs in the entire brain and tumor, which potentially affects the treatment effect as well as the approach to treatment planning. Without resection of the tumor, we found that E_{avr} and FA varied significantly for different layouts. Layouts that induced a high mean intensity also caused considerable unwanted anisotropy of the average field components. This effect may influence the overall efficacy, and therefore it should be incorporated in future dose estimation methods to improve accuracy. As a general observation, FA could only be reduced at the expense of reduced E_{avr} . Future experiments are necessary to determine the optimal balance between E_{avr} and FA, and the two measures may potentially be combined into a single measure of clinical efficacy. When characterizing the effect of tumor resection on the TTFields dose, we found that resection changes the topographical distribution of E_{avr} and FA. Furthermore, it almost

nullified the differences in field distribution that we observed before resection for different array layouts. This suggests that accurate positioning may be less important after tumor resection. Resection also increased FA significantly, particularly at the resection border. This implies that multiple fields may not always be able to distribute the effect of TTFields sufficiently to target cells dividing in different directions, which is otherwise the intended purpose of using sequential and orthogonal fields. Instead, multiple fields may serve the main purpose of ensuring that all tumor-infiltrated regions are exposed to high mean field values. This suggests that it may be better to plan the array layout in such a way that good pathology coverage is obtained, even if the macroscopic orientation of the layout is not orthogonal. It is clear that the use of only one electrode pair that induces the highest average field intensity in the tumor will maximize E_{avr} across the activation cycle. Such configurations could be used if good field coverage of the tumor can be obtained, as it would be expected for smaller lesions or resections. Finally, the singular value decomposition approach allows for a direct linear optimization of the activation cycle for each patient and each layout, with the objective of reducing FA while maintaining high field intensities in the tumor.

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