Optimization and Numerical Modeling in Irreversible Electroporation Treatment Planning

Anže Županič and Damijan Miklavčič*

Faculty of Electrical Engineering, University of Ljubljana, Ljubljana, SI-1000, Slovenia
* Corresponding author E-mail: damijan.miklavcic@fe.uni-lj.si

Introduction

When you overhear someone mention treatment planning, you can bet the conversation is about one of the forms of radiation therapy (RT). In the 1960s, when high powered x-ray delivery systems were readily available to radiation oncologists, the biggest challenge remained to improve the accuracy in locating the tumor and in directing the beams of charged particles. This changed when the first computed tomography (CT) scanners were invented (Lampert et al, 1974). Availability of 3D anatomical data and ever increasing computer processing power gave rise to numerical treatment planning. Together with improved beam generation and delivery technology, treatment planning has enabled RT to better target the tumor and to reduce adverse effects on vital organs (Jaffray et al, 2007). This is exactly what researchers would also like to achieve with irreversible electroporation (IRE): ablate the target tissue and spare as much healthy tissue as possible. Just as treatment planning in RT provides radiation oncologist with the radiation beam intensities and directions that cover the tumor without causing extensive damage to healthy tissue, so can treatment planning in IRE provide physicians with electrode configurations and amplitudes of electric pulses that result in adequate electric field distribution in and around the target tissue.

It might seem a bit early to talk about treatment planning for IRE as it is still in the phase of clinical experimentation. However, RT has been around for more than fifty years and has only become one of the most successful cancer treatments after treatment planning procedures were implemented. And while in RT one had to wait for medical imaging and powerful computers to appear, everything is readily available for IRE. There is also no need to wait for IRE to become a recognized and widely implemented ablation technique, treatment planning is just as important in the experimental stage, as experiences from electrochemotherapy, an application of reversible electroporation that has already made it to the clinic, have shown (Miklavcic et al, 1998; Miklavcic et al, 2000; Semrov & Miklavcic, 1998). Careful experiment planning not only increases the reproducibility of experiments, it also lowers the number of needed experimental animals, and thus improves the overall quality of research.

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In this chapter we compare features of external beam radiation therapy (and brachytherapy, when probe/electrode insertion questions are analyzed) with IRE features, which are relevant for the treatment planning procedure. By careful analysis we try to determine which features of RT treatment planning can be applied directly to IRE, which could be applied after adjustments and which cannot be applied due to overly different natures of both therapies. At the end we present our recent work in electroporation numerical modeling and genetic algorithm optimization in two illustrative (but hypothetical) examples of treatment planning of tumor ablation by IRE.

A Brief Overview of Irreversible Electroporation Basics

Cell membranes can be permeabilized by exposing them to a high enough electric field, a phenomenon termed electroporation (Neumann et al, 1982). The nature of electrically-induced membrane permeabilization can be predominantly controlled by the amplitude of local electric field. Permeabilization can be either reversible – the membrane stays permeabilized for up to minutes, allowing entrance of molecules that do not normally cross the membrane, and later recovers (Orlowski et al, 1988); or, if electric field strength is increased, irreversible – membranes do not recover and the cells die (Rubinsky et al, 2007). In biomedical research reversible electroporation has become widely used in the last decade, e.g. for electrochemotherapy (Belehradek et al, 1991; Heller et al, 1999; Mir et al, 1998; Serša et al, 2006), gene electrotransfer (Golzio et al, 2004; Hojman et al, 2007; Mir et al, 1999), transdermal drug delivery (Denet et al, 2004; Prausnitz, 1999) and electrofusion of cells (Scott-Taylor et al, 2000; Trontelj et al, 2008), while IRE has gained momentum in the last few years, since Davalos et al showed it can be used to kill cells without considerable thermal effects (Davalos et al, 2005). Further studies on ablation capacity of IRE have confirmed the absence of significant resistive heating during IRE (Al-Sakere et al, 2007; Edd et al, 2006; Miller et al, 2005) and have also demonstrated some additional advantages IRE has over more conventional thermal and chemical ablation techniques. These advantages include: 1) IRE is a non-thermal physical ablation modality, therefore not affected by blood flow (Miller et al, 2005); 2) delineation between treated (ablated) and untreated tissue after IRE is very sharp – only a few cells thick (Lee et al, 2007); 3) IRE affects only cell membranes and leaves extracellular structures intact – preservation of microvasculature is possible (Lee et al, 2007; Maor et al, 2007; Onik et al, 2007); 4) IRE elicits no immune response and can thus be used for treatment of patients with immune system deficiency (Al-Sakere et al, 2007); 5) the procedure is relatively fast compared to other ablation techniques (Lee et al, 2007); 6) IRE allows rapid regeneration of ablated tissue with healthy tissue (Rubinsky et al, 2007); 7) IRE can be accurately numerically modeled – numerical models of reversible electroporation that have been around for quite some time can be easily modified and implemented for IRE modeling (Corovic et al, 2007; Edd & Davalos, 2007; Pavselj & Miklavcic, 2008a).

IRE was tested as an ablation modality in various medical applications, such as ablation of cancer (Onik et al, 2007; Rubinsky et al, 2008), epicardial ablation (Lavee et al, 2007) and prevention of restenosis after angioplasty (Maor et al, 2008). After encouraging primary results of these studies, researchers expressed the need for accurate experimental planning that would: 1) guarantee that thermal effects are indeed negligible; 2) take advantage of the sharp physical delineation between treated and untreated tissue to enable surgically precise ablation and 3) make experimental (and later medical) procedures more reproducible.

Before setting guidelines for proper treatment planning, it seems appropriate to check whether sophisticated and time consuming numerical treatment planning procedures are necessary in all biomedical applications of IRE. If, for example, IRE takes place in homogeneous and isotropic tissues with no vital organ in the vicinity of the treated area, then a simple look-up database of appropriate treatment parameters calculated by simple numerical models validated by experiments would suffice. The same can be said for more complex tissue geometries that do not change much from patient to patient, as is the case in restenosis prevention where electric pulses are applied to blood vessel walls. The look-up database should include electric field distributions generated by the use of different electrode geometries, different electrode configurations and a range of electrical input parameters. Such databases can be constructed using numerical modeling alone, without optimization, and have to provide enough information for the treating physician to choose the proper set of electrodes and electric parameters for each treatment. Optimization becomes important in more complex situations, when the target tissue is located near a vital organ whose function should not be compromised by the treatment. In such situations it is of vital importance to control the magnitude and distribution of the electric field so that as little as possible critical tissue (organ at risk) is compromised by the treatment. This can be effectively accomplished by numerical modeling of IRE and optimization based on anatomical medical imaging, as has been demonstrated recently for electrochemotherapy (Corovic et al, 2008; Zupanic et al, 2008). Numerical modeling may also be necessary for treatment planning in tissues with highly anisotropic properties and highly non-homogeneous tissues, where electric field distribution is otherwise difficult to predict (Pavselj & Miklavcic, 2008b). In all such cases the treatment planning procedure will have to be applied individually for each patient and the electric field distribution will have to be sculpted carefully to ablate all of the target tissue and preserve as much of the critical tissue as possible.

Radiation Therapy vs. Irreversible Electroporation Procedure

Over the past decades progress in imaging technology and computer processors have modernized RT through use of more accurate radiation dose calculation algorithms, more complex dose delivery techniques and modern imaging

modalities (Dawson & Sharpe, 2006; Jaffray et al, 2007). Modern radiation therapy techniques, such as 3D conformal RT (Purdy & Starkschall, 1999) and intensity-modulated RT (Boyer et al, 2001) are completely image-guided and computerized, which has enabled more accurate sculpting of radiation doses to clinical volumes (target volumes and critical volumes). RT treatment planning procedure has accordingly become extremely sophisticated, which makes it an ideal benchmark for treatment planning of other biomedical application based on physical agents. A typical RT treatment today generally consists of five major phases: simulation, treatment planning, set-up verification, dose delivery and response assessment (Lecchi et al, 2008). In the simulation phase, data on patients' anatomy are acquired via modern 3D imaging devices. In treatment planning, clinical volumes are first delineated, dose constraints are defined and the treatment plan is determined. Before treatment, imaging is again utilized for control of the clinical set-up. After the radiation dose is delivered the treatment success is periodically evaluated by following tumor response. In this chapter we analyze the first three phases with emphasis on the treatment planning phase.

Similar major phases as for RT can also be defined for IRE treatment: simulation, treatment planning, set-up verification, electric pulse delivery and response assessment. Simulation is probably not necessary in all biomedical applications of IRE; however, it is necessary in all situations that require numerical treatment planning. Treatment planning is currently limited to experienced researchers that are able to "predict" the appropriate electrode configuration and electric pulse amplitude, whether from experience alone or with help of modeling. The appropriate positioning of electrodes can be controlled by real time ultrasound measurements (Lee et al, 2007). Electric pulses are delivered by a clinical electroporator (Bertacchini et al, 2007) and evaluation of treatment success depends on individual IRE application, e.g. when using IRE for tumor ablation, tumor size is periodically measured.

Medical Imaging

The first phase in RT is medical imaging of the whole region surrounding the target tumor tissue. This is usually accomplished with computer tomography (CT), although, if necessary, other imaging modalities, such as magnetic resonance imaging (MRI) and positron emission tomography (PET) are also used as they can provide additional anatomical and physiological information (Lecchi et al, 2008; Newbold et al, 2006; Vanuytsel et al, 2000). If MRI or PET are used, their images are later aligned to the CT images using image-fusion algorithms (Skerl et al, 2007; Slomka, 2004). It is vital for the success of the therapy that the patient's position during imaging is as close as possible to the actual treatment position. In external beam RT this is usually achieved with laser positioning control and patient immobilization (Heinzerling et al, 2008). In brachytherapy, on the other hand, it is very important that imaging is done with probes already implanted inside the body, as their insertion can significantly change the internal organ

positions (Potter et al, 2008a; Potter et al, 2008b). During treatment, ultrasound can be used to control internal organ movement (Chandra et al, 2003).

The exact same imaging procedures as in RT can also be used in IRE; however, since IRE is a local treatment, less extensive imaging is necessary. Ultrasound imaging can be very useful in IRE, e.g. for real-time ultrasound guidance of electrode insertion and real-time ablation zone monitoring (Lee et al, 2007). Electrical impedance imaging has also been suggested as a real-time electroporation monitoring modality (Davalos et al, 2004; Davalos et al, 2002; Granot & Rubinsky, 2007; Ivorra & Rubinsky, 2007), as has been current and voltage measurement during pulse delivery (Cukjati et al, 2007). As precise positions of electrodes for IRE are only available after the treatment planning procedure, it would be no use to insert them prior to imaging. Instead, ultrasound imaging will probably have to be relied upon to assure adequate positioning of the electrodes with respect to the target volume and critical volumes.

Delineation of Clinical Volumes and Definition of Dose Constraints

Oncology experts examine the acquired medical images slice by slice and delineate the target volumes and critical volumes for the treatment as defined by the International commission on radiation units and measurements (ICRU) reports 50 and 62 (ICRU-50, 1993; ICRU-62, 1999). If the location of the target tissue is such that target and critical volumes coincide, the expert has to use his/her experience and adjust the volumes with respect to the patient's best interest. Dose constraints for each critical volume and target dose are also defined according to the same ICRU reports. In RT there is no threshold effect: lower doses already cause tissue damage and by increasing the dose the damage increases up to the point where the dose necessary to kill all cancer cells is achieved.

The ICRU reports define clinical volumes mainly according to the probability of error in accurate delineation, according to the probability of microscopic spread of tumor cells outside the main tumor mass and accordingly to the set-up and delivery errors, which were all evaluated by a vast collection of clinically acquired data. As only the set-up and delivery error are radiation specific and are analyzed separately, tumor volumes treated by IRE can also be defined using ICRU reports. In IRE electric field strength is believed to be the main factor controlling the treatment outcome. IRE is apparently, contrary to RT, a threshold phenomenon. Electric fields below the irreversible threshold permeabilize cells reversibly, but do not kill them, while electric fields over the threshold irreversibly permeabilize cells and thus destroy them. This effectively means that tissue damage can theoretically be sculpted to the target tissue and around all critical tissues with great accuracy. IRE thresholds have, however, been found to be tissue specific. Furthermore, several electric pulse parameters affect the threshold values: pulse duration, number of pulses and to some extent also pulse repetition frequency (Edd & Davalos, 2007; Miklavcic & Kotnik, 2004). Prior to any treatment planning, data on thresholds for all target tissues and all critical tissues should be available for a range of electroporation parameters.

Tissue Properties

For radiation therapy data on tissue properties is readily available directly through CT imaging. Namely, CT values correlate well with electron density, the main tissue property used in computation of Compton scattering, which is the most probable interaction of high energy X rays with atomic nuclei in living beings. It is also considered that electron density remains the same during the entire treatment (Ruchala et al, 2000).

Data on human tissue electrical properties (electrical conductivity and electrical permittivity) are harder to come by. Although several reports have been published (Gabriel et al, 1996a; Gabriel et al, 1996b; Miklavcic et al, 2006b; Polk & Postow, 1996), the data between individual studies differ by a factor of 2 or more. A database of electrical properties is desperately needed, preferably with additional data on electrical property variation with age, gender and pathological changes (e.g. different tumors or scarred tissues). Furthermore, because electric tissue properties change dramatically during electroporation (Pavlin & Miklavcic, 2008; Pliquett & Weaver, 1996), these data should be available not only for pre-electroporation, but also for permeabilized tissues. Models of electroporation that take this dynamic change in tissue properties into account, provide us with much more detailed description of electroporation and can describe in vivo phenomena that cannot be explained with models that use constant tissue properties. Data on electrical tissue properties after electroporation are, however, very scarce, although they may prove crucial for accurate treatment planning.

Dose Calculation Algorithms

In modern radiation therapy two main calculation methods are used: convolution-superposition, where the patients dose is computed and lateral transport of radiation, beam energy, beam modifiers and electron density distribution are accounted for (Mackie et al, 1985; Sharpe & Battista, 1993); and Monte-Carlo where the dose is computed directly from first principles (Reynaert et al, 2007). While convolution-superposition is faster, Monte-Carlo is more accurate. Medical physicists in oncology usually choose the method according to necessity (and availability); when time is very important and many calculations are needed, convolution-superposition is used, and when high accuracy is needed, Monte-Carlo based methods are used.

In tissue electroporation modeling several algorithms are used, mostly utilizing the finite element method (for details on finite element modeling in electroporation based applications consult *Finite element modeling of in vivo electroporation* by Pavselj and Miklavcic). The difference between individual models is mostly whether they take into account the changes in tissue electrical properties during electroporation or not. Steady-state models calculate the electric field distribution without incorporating changes in tissue properties. These models give reasonably good results, if the tissues modeled are homogeneous and isotropic. (Edd & Davalos, 2007; Miklavcic et al, 2006a; Miklavcic et al, 2000). When this is not the case, sequential models can be used. These models approximate changes in electrical properties as a function of the magnitude of

electric field and thus approximately describe the time course of conductivity increase during electroporation (Sel et al, 2005). Further improvements in accuracy can be achieved by taking into account a certain time-dependency of changes in electrical properties (Pucihar et al, 2008), or even by multiscale modeling that combines single cell electroporation into the bulk tissue models (Esser et al, 2007; Smith & Weaver, 2008; Weaver, 2003). Each of these improvements is computationally more intensive than the previous one, thus taking more time. For treatment planning purposes it is necessary to choose the model that takes the least time to compute, while at the same time maintains an adequate level of accuracy. Since steady-state models cannot accurately simulate IRE in complex anatomies, and multiscale models are so computer intensive that so far they have only been used in 2D, currently the only achievable options are sequential models.

Multiphysics (Applicable to Irreversible Electroporation Only)

One of the main advantages of irreversible electroporation is its non-thermal ablation capacity. When electric pulses are applied to biological tissue, heat is generated in the form of resistive heating and the temperature increases. In order to guarantee non-thermal ablation IRE treatment planning must involve a control for the heat generated by electric pulses. Coupling of electrical and thermal phenomena can provide an estimate of temperature rise and distribution due to IRE (Davalos & Rubinsky, 2008; Edd & Davalos, 2007; Pliquett, 2003); thus it can be used to calculate temperature increases for each individual application of IRE or to generate a conservative range of electric pulse parameters (pulse duration, number of pulses, pulse repetition frequency) that do not elevate tissue temperatures excessively. When the electric field distribution is highly non-homogeneous, with high local peaks, calculation of resistive heating should be included in the treatment planning process.

Forward and Inverse Treatment Planning Procedure

Forward planning is a technique used in RT to produce a treatment plan that consists of a set of physically deliverable modulated beam fluence profiles, which in practice means that, for each beam, a direction, duration and modulated intensity have to be chosen. In forward planning, an initial plan is made by a treatment planner (usually a medical physicist) who uses his/her experience to produce a set of treatment parameters that can deliver sufficient radiation to a tumor while sparing vital organs and also minimizing the dose to other healthy tissues. The treatment dose is then calculated and evaluated by an oncology expert. If necessary, improvements to the plan are made and radiation doses are recalculated. This cycle is repeated until a satisfactory plan is produced. Forward planning is used for the majority of RT treatments.

In more complex cases, when vital organs are near the target volume or the target volume is of complex shape, inverse planning produces better results (Ezzell et al, 2003; Galvin et al, 2004; Lindegaard et al, 2008; Webb, 2003). In inverse planning, which is used in intensity-modulated radiation therapy, a desired dose

distribution (dose constraints) in and around the target volume is defined. Then a computer optimization technique is used together with the dose calculation algorithm to determine the optimal set of treatment parameters resulting in a dose distribution that most closely matches the desired one. The optimization algorithm compares the quality of different treatment plans according to an objective function that incorporates dose constraints defined earlier. The constraints are usually implemented using dose-volume criteria: how much target volume and critical volume is covered by the appropriate dose; how much is overdosed and how much underdosed. Biological effects models, such as tumor control probability and normal tissue complication probability are also used: what are the biological consequences of covering a certain volume of the tumor and of critical tissues with a certain dose (Bortfeld, 1999; Lyman & Wolbarst, 1987). Currently, gradient based optimization algorithms and stochastic optimization algorithms are used in radiation therapy (Bortfeld, 2006; Ezzell, 1996). Gradient algorithms are faster, but require a good initial guess to reach a satisfactory solution, while stochastic algorithms, such as simulated annealing and genetic algorithms are slower, but do not require an initial guess.

In IRE, a treatment plan should consist of appropriate electric pulse parameters, i.e. pulse duration, number of pulses, pulse repetition frequency and pulse amplitude, and of appropriate electrode parameters, i.e. electrode geometry, configuration of electrode arrays and sequence of electrode activation in cases when multiple pulses (that would induce different electric field distributions) would have to be delivered. The effect of number of pulses, their duration and repetition frequency to treatment success can be substantial; increasing the number of pulses or pulse duration increases electroporation efficiency, increasing repetition frequency decreases efficiency. Increasing any of the three increases tissue temperature (Macek-Lebar et al, 2002; Pucihar et al, 2002). Since the sequential models cannot currently evaluate the effect of these parameters on electroporation efficiency, all three parameters have to be chosen according to the experimental results and the non-thermal criteria. Numerical treatment planning procedure should therefore only deal with pulse amplitude and electrode related parameters, unless appropriate biological effects models are included.

Forward planning in IRE is possible, but probably not sensible, since inverse planning is not much more time consuming and produces better results. The choice between gradient and stochastic methods is less straight-forward. Gradient methods are faster and more accurate, if a good initial guess is available and if the number of parameters optimized for is not too large. Increasing the number of parameters can result in gradient optimization methods becoming stuck in one of the local optimums a long way away from the global optimum. In such a case, stochastic methods, such as genetic algorithm and simulated annealing, are much more likely to come close to the global optimum (since the methods are stochastic, the probability of reaching the global optimum in a reasonable amount of time are slim, however, they do find an acceptably good solution in a fixed amount of time). An additional advantage of genetic algorithm optimization is its ability to return more than one high-quality suggestion for the optimal parameters, thus giving the treatment planner more than one option of similar quality into consideration. No matter which methods (gradient

or stochastic) are used, the IRE treatment planning procedure should follow the RT procedure closely. Target volumes, critical volumes and the appropriate electric field distributions should be defined. Optimization algorithm should then compare the quality of different treatment plans according to an objective function that takes into account that the electric field must be over the IRE threshold in all the target tissue and under the IRE threshold in vital organs and as low as possible elsewhere. If biological effect models ever become available for IRE, they should also be included in the objective function.

Tumor Ablation with Irreversible Electroporation Treatment Planning Examples

We present two examples of treatment planning of ablation by IRE using numerical modeling and a genetic optimization algorithm. In both examples we try to determine the best possible configuration and electric potentials of six electrodes surrounding a subcutaneous tumor - the target tissue. Our goal is to irreversibly electroporate ($E > E_{irr}$) the entire tumor volume, while sparing as much as possible of the hypothetical spherical organ at risk, situated next to the tumor (Figure 1).

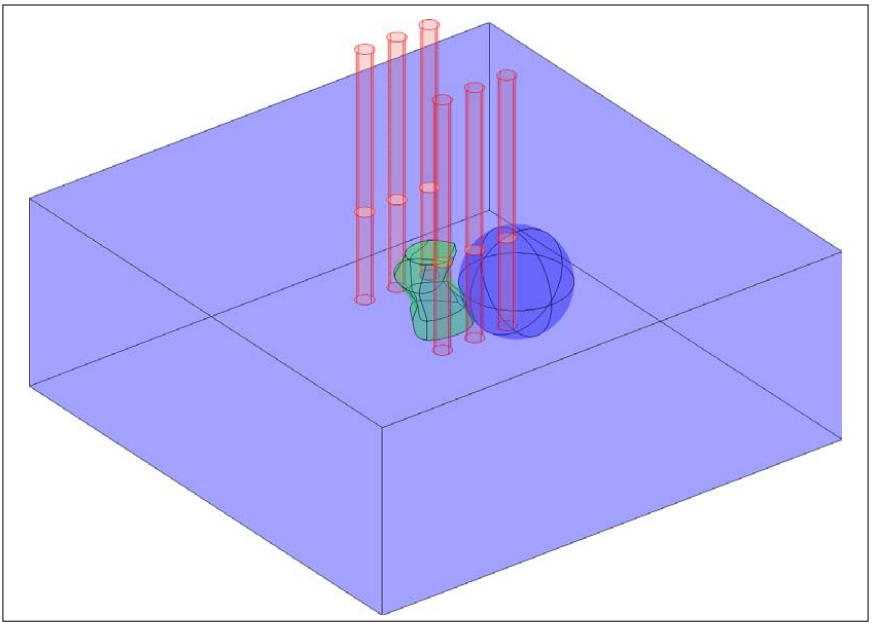

Fig. 1. Model geometry: biological tissue (light blue); tumor (green) – geometry taken from (Sel et al, 2007); organ at risk (dark blue). Needle electrodes (pink – two rows of needle electrodes as in example 1) are inserted into the tissue and appropriate electric potentials are assigned to each electrode so that the entire tumor volume and the least possible volume of the organ at risk is irreversibly electroporated.

In both examples we use the same steady-state numerical model of electroporation; i.e. electric field distribution in the tissue caused by an electric pulse is determined by solving the Laplace equation for static electric currents. All tissues are considered isotropic and homogeneous, the assigned conductivity values being 0.4 S/m for the tumor and 0.2 S/m for healthy tissue and for organ at risk (Cukjati et al, 2007; Pavselj et al, 2005). The IRE threshold is taken to be 800 V/cm, which is the average threshold reported in literature (Davalos et al, 2005). However, this value is only used for demonstration purposes, as the exact threshold is tissue dependent and also depends on electric pulse duration and number.

The genetic algorithm (Holland, 1992) was written in Matlab and was run together with the numerical calculation using the link between Matlab and COMSOL Multiphysics, a finite element software. In both examples the initial population of chromosomes is generated randomly, taking into account the following model constraints: range of distances between electrodes, range of depth of electrode insertion into the tissue and range of electric potential values on individual electrodes. Chromosomes for reproduction are selected proportionally to their fitness, according to the fitness function:

$$F = 10000 \cdot V_{Tir} - 200 \cdot V_{OARir} - 2 \cdot V_{HTir},$$

where F stands for fitness, V_{Tir} stands for fraction of tumor volume subjected to local electric field above irreversible threshold ($E > E_{irrev}$), V_{OARir} stands for fraction of volume of organ at risk subjected to $E > E_{irrev}$ and V_{HTir} stands for volume of healthy tissue subjected to $E > E_{irrev}$. The weights in the fitness function are set arbitrarily, but with respect to the importance of the individual parameters for efficient IRE. Namely, V_{Tir} is crucial for efficient IRE of the target tissue, therefore its weight is largest (10000) than the weight of V_{OARir} (-200), which is in turn larger than the weight of $V_{HTir,}$ because the organ at risk needs to be preserved, if possible.

Example 1. – two rows of three needle electrodes.

In our first example we optimize the positions of two rows of three needle electrodes, which is a needle electrode array often used in electrochemotherapy (Gilbert et al, 1997; Puc et al, 2004). The optimized parameters are: distance between rows of electrodes, distance between electrodes in a row, depth of electrode insertion, x and y coordinates of the electrode array central point and the voltage between rows of electrodes; altogether six parameters.

The final treatment plan is presented in Figures 2 and 3. We can see that the electric field distribution is rather homogeneous; the field is very high only very close to the electrodes and just above the E_{irr} inside the tumor. Electric field is quite high in the organ at risk closest to the tumor as well – all in all E_{irr} is exceeded in 2.43 % of the organ at risk (Table 1).

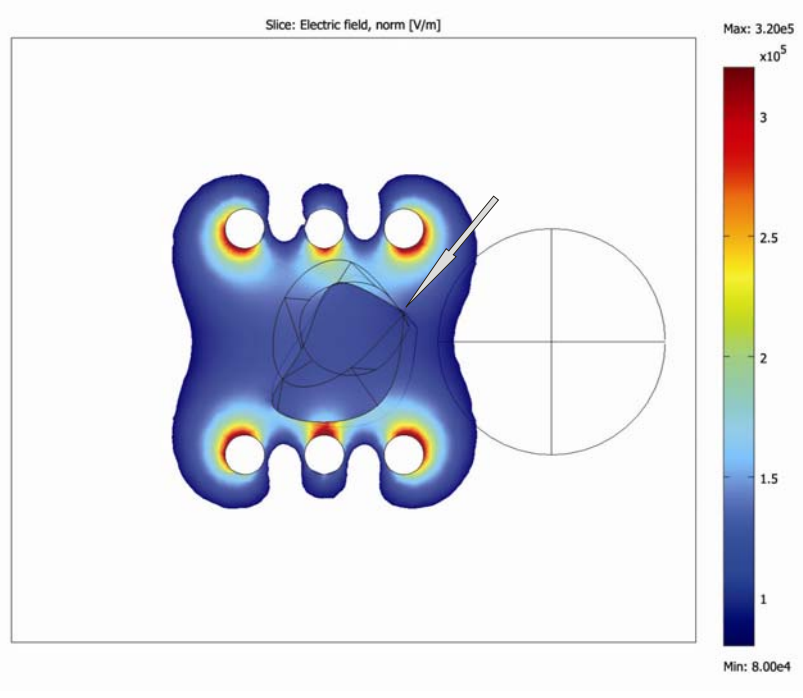

Fig. 2. Local electric field distribution for treatment plan 1 is shown in the XY plane through the center of the tumor. White arrow marks part of the tumor, where electric field is barely over IRE threshold (800 V/cm).

At a first glance it seems that the electric field exceeds E_{irr} in a large volume outside the target tissue and that the treatment planning algorithm should give better results. The obvious change to improve the result would be to put the electrodes more to the left, so that less of the organ at risk gets affected, or perhaps to use only four electrodes instead of six. Actually, none of these two obvious improvements work (data not shown). Moving the electrodes further left causes the electric field on the edge of the tumor (Figure 2) to fall below E_{irr} – as a result the potential on the electrodes has to increase so that the whole tumor volume is covered and this in turn increases the affected volume of organ at risk. Using only four electrodes leads to a similar result.

Example 2. – six needle electrodes.

In our second example we optimize the positions of six individual needle electrodes. Optimized parameters are: x and y coordinates of each of the electrodes separately, electric potential of each electrode and depth of electrode insertion (the same for all electrodes); altogether 19 parameters.

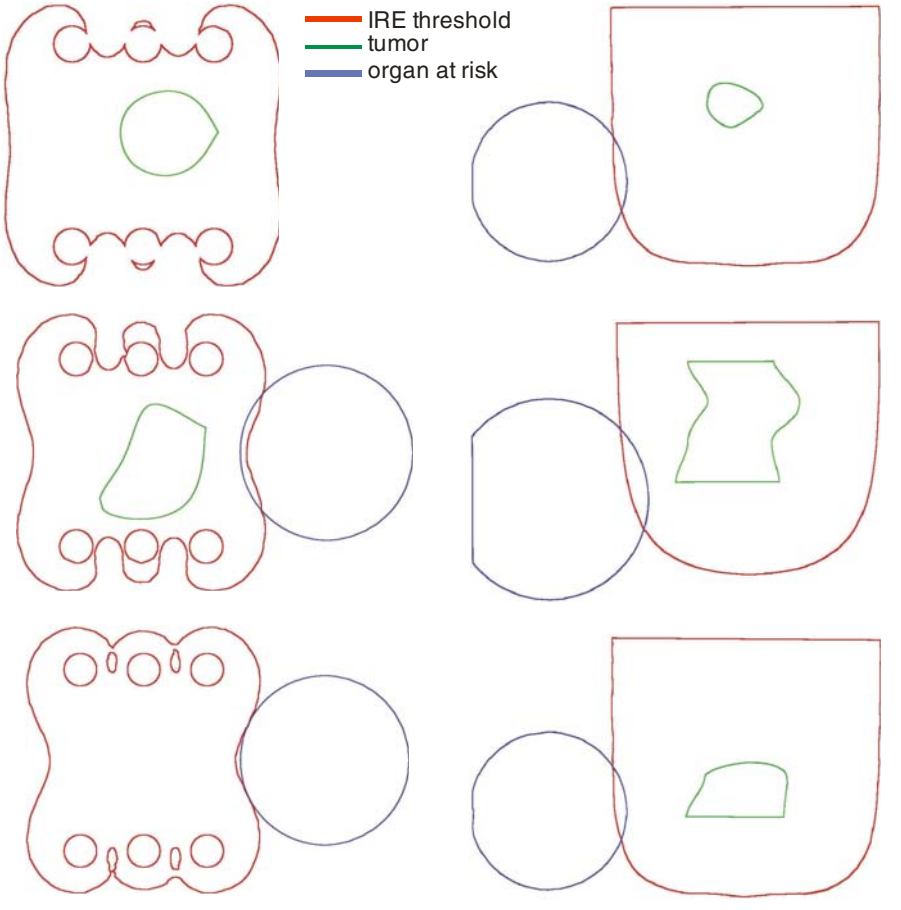

Fig. 3. Target tissue, organ at risk and IRE are presented as contours in the XY plane (left) at three different depths (top: 8 mm; middle: 23 mm; bottom: 38 mm) and in the XZ plane (right) at three different cross-sections (middle: tumor center; top and bottom: 1.2 mm from tumor center).

Table 1. Quality of treatment planning parameters V_{Tir}, V_{OARir}, V_{HT} and treatment planning (computational) time. V_{Tir} and V_{OARir} are normalized by their tissues' respective volumes, V_T and V_{OAR}. All values were calculated using the optimal parameters acquired by the optimization procedure.

	F	V_{Tir}/V_T [%]	V_{OARir}/V_{OAR} [%]	V_{HTir} [mm^3]	No. of parameters	Calculation time [h]
Example 1	9995.0	100	2.4	89	6	1.5
Example 2	9998.1	100	0.8	149	19	4.2

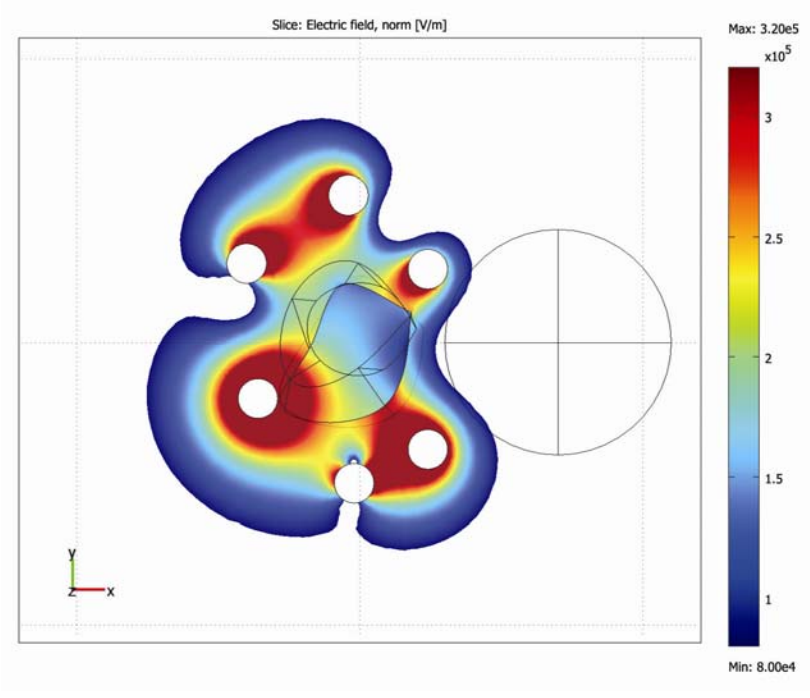

Fig. 4. Electric field distribution for the treatment plan 2 is shown in the XY plane through the center of the tumor. For better comparison, the same color legend (800 V/cm – 3200 V/cm) as in Figure 2 is used. Values over 3200 V/cm are shown in dark red.

The final treatment plan is presented in figures 4 and 5. We can see that the electric field distribution in this case is not at all homogeneous; the field around the electrodes and also in the tumor is much higher than in example 1. Nevertheless, only 0.8 % of the organ at risk is affected (Table 1). We can clearly see that the irregular positioning of the electrodes and different potentials on each electrode result in an electric field distribution "avoiding" high electric fields in the organ at risk on the expense of higher electric field elsewhere.

Both treatment plans provide the treating physician with a set of treatment parameters that successfully ablate the entire target tissue. The treatment plan 2 causes less damage to the organ at risk, however, it takes longer to calculate and causes more damage to the non-critical healthy tissue (Table 1). According to our fitness function F, treatment plan 2 is in fact better than treatment plan 1. However, in the clinical environment, the treating physician has control over the fitness function weights, which can be chosen according to expert knowledge and the choice may well be significantly different from ours, which may result in treatment plan 1 winning out over treatment plan 2.

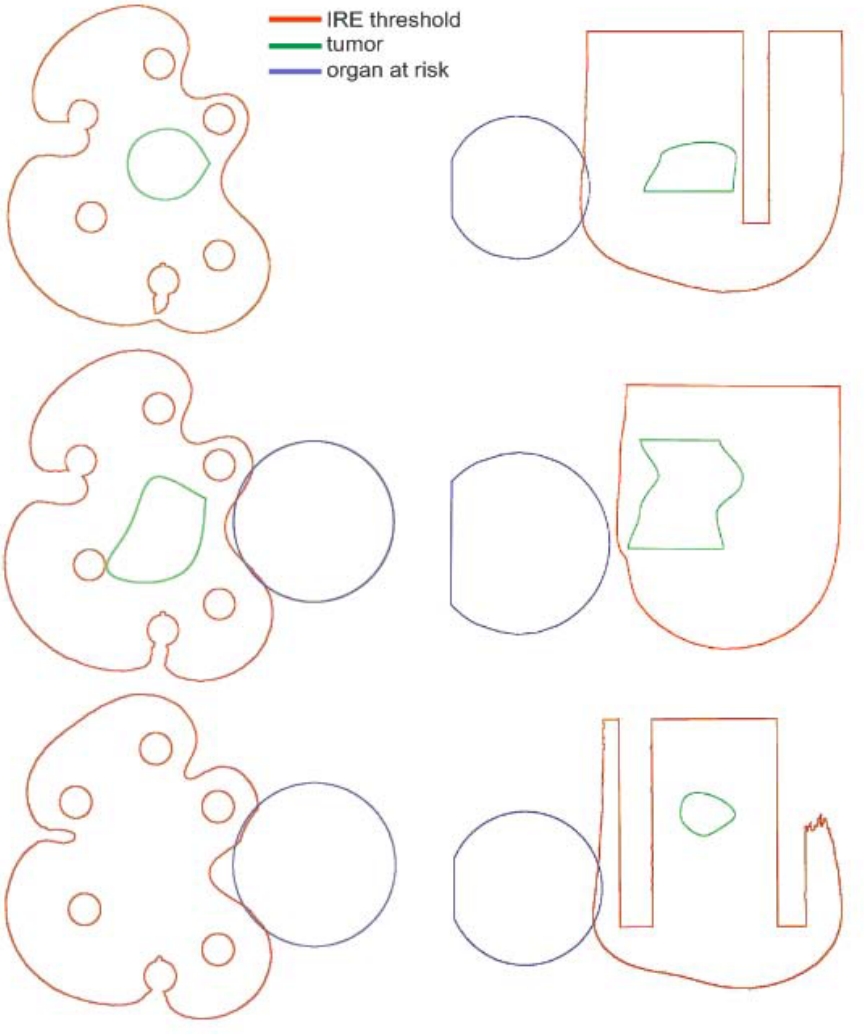

Fig. 5. Target tissue, organ at risk and IRE are presented as contours in the XY plane (left) at three different depths (top: 8 mm; middle: 23 mm; bottom: 38 mm) and in the XZ plane (right) at three different cross-sections (middle: tumor center; top and bottom: 1.2 mm from tumor center)

Conclusions

There are many similarities between radiation therapy and irreversible electroporation. Both treatments depend on the knowledge of the treated anatomy and on medical imaging. Both treatments are based on harmful effects of a

physical agent, which can be efficiently and accurately numerically modeled. Both treatments are local – they target a certain volume of tissue and try not to affect the rest. That is why the RT treatment planning methodology can at least partially be translated to IRE treatment planning, while keeping in mind the relevant differences between the two treatments.

RT and IRE treatment planning both rely on medical imaging to provide patient anatomical data. RT also relies on imaging to provide patient tissue properties, while IRE relies on average electrical properties of excised human tissue measured by different researchers. While tissue properties do not change significantly during RT, they do during IRE. Tissue properties and tissue specific IRE thresholds seems to be the biggest challenge that IRE planning has still to address. Before IRE treatment planning takes off, additional research will have to be performed on human tissue electrical properties, before, during and after electroporation. More data on tissue specific IRE thresholds are also needed, at the very least for all target tissues and critical tissues. At the moment IRE thresholds are only available for few tissue types and limited pulse parameters (Miklavcic et al, 2000; Pavselj et al, 2005). Only after these crucial parameters are available will it become possible to accurately model IRE and provide high accuracy treatment plans.

Choosing the appropriate mathematical model and the appropriate optimization algorithm are also very important steps in treatment planning, as is the decisions, which parameters should the algorithm optimize. Currently, the most viable option seems to be the sequential model of electroporation in combination with one of the stochastic optimization algorithms, which generally provide the best results for higher numbers of optimized parameters (Corovic et al, 2008; Sel et al, 2007; Zupanic et al, 2008). When non-homogeneous electric field distributions are expected, electroporation models should also include modeling of the thermal effects to guarantee non-thermal ablation of target tissue (Davalos & Rubinsky, 2008; Edd & Davalos, 2007).

The presented (hypothetical) IRE treatment planning procedure used the steady-state electroporation model, i.e. no changes in tissue conductivity due to electroporation is taken into consideration, and the genetic optimization algorithm to plan IRE treatment of a subcutaneous tumor. Two different numbers of optimized parameters were chosen and two completely different treatment plans resulted in completely covering the tumor with sufficiently high electric field and only minimally affecting the organ at risk. The presented approach represents the basis for developing future IRE treatment planning algorithms.

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