CONSTRUCTING VERIFIABLE MODELS FOR RF ABLATION SIMULATION

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Abstract: Modeling the process of radiofrequency ablation (RFA) to support pre-interventional prediction of the treatment result has been desired for more than one decade by now. Still a correct description is mathematically demanding and needs further investigation into medical facts. The process is highly dependent on the patient specific anatomy and physiology. Descriptions from an engineering perspective explain many details, but are rarely integrated into one all encompassing model. None of the models dealing with realistic predictions has been verified. Therefore, none of them is suitable for use in clinical practice. This paper describes the details of the RFA process from an engineering perspective and presents the state of the art in computational prediction for the intervention. An approach towards verifiable models and which tasks have to be solved to gain them is discussed, and difficulties on the way pointed out.

1. Introduction

Radiofrequency ablation is a minimally invasive therapy for malignancies in the liver and other organs. Patients treated with percutaneous RFA stay in hospital for two days only and not more than one week as in the classical therapy form of liver resection. Advantages are obvious: less risk for the patient as in laparotomy, a shorter stay in hospital and therefore lower costs, and more over it is sometimes the only alternative. Still RFA is not the first choice for treatment, as the result of the procedure is hard to predict and therefore results in a high number of local recurrences. Furthermore, the result is hard to image during the intervention. A computational prediction of the result for treatment planning purposes would therefore be most desired.

For a model to be usable in clinical practice it has to have a high predictive power and it needs to be validated. To achieve this validation results from an intervention need to be compared to a computational prediction for different situations. In this paper the RFA process is described from an engineering perspective, state-of-the-art in modeling is described and a roadmap towards a verifiable computational model for the RFA process is lined out.

2. Overview over the current procedure

The RFA treatment is performed by placing a needle electrode inside the tumor to be destroyed. Using a preoperative CT or MRI scan the optimum path for placing the needle is decided based on the doctor's personal experience. The needle should be in a position which allows destruction of the tumor and a safety margin of healthy tissue without damaging vessels or important organs (heart, stomach, etc.). Once the needle is placed the RF generator is switched on and surrounding tissue heats up. Cells that reach approximately 50-55 Celsius degrees or more are destroyed.

Several patient specific factors determine the exact heating up and heat transportation process. Most important is the blood perfusion by nearby vessels, as this cools down the tissue and prevents cells from heating up. Occlusion of blood vessels is sometimes an alternative but may lead to other complications (like thrombosis). The overall course is highly patient specific and controlled by measurements of the RF generator as well as the ablation protocol.

Watching an ongoing ablation process is unreliable using Ultrasound and impossible using MRI. An early assessment after the intervention can be made using Ultrasound or CT, but this gives only limited information on the final result, as the shape of the necrosis zone changes during the next couple of weeks. Assessment of the procedures success is done by follow-up scans. If those don't show a local recurrence the tumor was destroyed successfully. Depending on the performing surgeon, the tumor location as well as other factors the rate for local recurrences reported in studies

varies between 10%-60%. A more detailed description of the procedure in clinical practice can be found in [1].

3. State of the art in RFA modeling

The first prediction of the RFA treatment result [2] modeled the shape of the necrosis zone as an ellipse (as inspired by [3]) with cut outs for blood vessels [4]. The respective treatment planning tool RF-Sim [5] provided an extensive planning environment showing a virtual presentation of the liver and the surrounding anatomical structures, was able to compute the optimum position for needle placement [6], and gave haptic feedback in intervention simulation.

Modeling the necrosis zone as an ellipsoid was reused in the RFAST project by the National Institute of Health, USA. This project led to a planning tool for RFA that incorporates image processing tools [7], but – as it was still based on the coarse shape estimation for the necrosis zone – still holds the same limitations as the RF-Sim approach.

Physically based 3D models to simulate RFA have been developed by [8]. Another model was created by [9]. Neither of these account for changes in cell metabolism. Kroeger models biochemical reaction rates based on reaction time for sugar and acids [10]. This model has been used for planning the optimum needle position [11] and for workflow oriented treatment planning [12].

The material constants in the bio-heat equation (specific heat capacity, specific electrical conductivity, etc.) are in fact patient specific parameters which change their properties within the process [13], [14]. Measuring these parameters is possible, but only using tissue samples.

The influence of the needle geometry has been widely researched. Ablation electrodes as used today in clinical practice are rarely simple mono-polar or bipolar electrodes but rather extendable umbrella shaped electrode arrays (like Rita StarBurst). In homogeneous media those produce sphere shaped large coagulations (up to 5cm). These electrode arrays are therefore better suited to treat tumors of relevant size (up to 3cm). A comparison of different needle geometries can be found in [15].

Ablation protocols have not been widely researched. Looking at efficiency and deposited energy [16] gives some insight. The electrode extension algorithm for the RITA system has been researched in medical experiments [17] but is not part of any simulation or planning application.

The anatomical effects of blood perfusion and tissue inhomogeneity on RFA treatment results have been observed many times in medical experiments (e.g. [18]) as well as in patient treatment. Mathematically most advanced predictions on the influence of perfusion have been carried out in [19]. The model shows in great detail the cooling effect and the effect of moving the hotspot in direction to the vessel. Recent advances show the effects of tumors as inhomogeneity factor [20]. Findings in medical studies show changes in the form of the necrosis zone after the treatment. Therefore, early detection of local recurrence is performed by analyzing 3D shapes in follow up scans [21], [22]. First steps to prediction of treatment results based on interventional MRI scans were taken in [23] and [24].

4. Radiofrequency ablation from a physical, biological and chemical perspective

The process of RFA begins with placing a needle into a tumor. Most important is here to hit the target exactly as planned. RFA coagulations created by expandable electrodes, as used in clinical practice, range up to 5 cm. This restriction leads to a maximum treatable tumor size of 3cm, given a desired safety margin of 1cm around the tumor. Treatment of bigger tumors demands either the infusion of saline to create a bigger necrosis from one needle, or else the placement of several needles. In any case, hitting the target not in the center means destruction of more than necessary healthy tissue on one side and possible survival of tumor cells on the other. Navigation aids for needle placement are a research topic of its own.

After the needle is placed in the correct position the RF generator is switched on. From here measurements performed by the generator and the ablation protocol determine the progress of the procedure. First, effects are determined physically. Later biochemistry determines the final result.

4.1. Heat propagation in the tissue

When switched on the RF generator creates an electromagnetic field. The needle electrode thereby plays the role of an antenna sending electromagnetic waves into the tissue. As in any electromagnetic field the energy density decreases with the distance to the needle with $1/r^4$. Ions are electrically charged atoms or

molecules and part of tissue and fluids. They move with the induced alternating electromagnetic field causing friction along their way. This friction generates heat in the target region. Understanding this mechanism leads to two important findings with direct consequences for the procedure and its result. First, the heat is generated in the tissue. It is flowing from the tissue to the needle and not vice versa. Measuring the needle temperature directly only gives hints on tissue temperature. Heating the needle in a different media leads to incomparable results that do not allow drawing conclusions on heating tissue. Second, hot spots in the tissue exist and depend on the tissue parameters. Obviously, those regions in the tissue that react strongest to the ion friction are heated most, not those closest to the needle. Modeling these effects correctly is currently part of any physically based simulation of the RFA process.

The created heat is conducted to surrounding tissue. The exact dimensions of heat flow depend on the material parameters (specific heat capacity). These material parameters are patient specific and even for one patient change with tissue type. The most dominating effect here is the cooling by perfusion. Blood in nearby vessels with diameter above 3mm is heated up, but then through blood flow carried away, taking a quantity of heat with it. It is replaced with new, cold fluid. This effect has often been watched in medical studies and determines size and shape of the coagulation visibly. Besides this, cooling in form of micro-perfusion also influences the size of the necrosis. Even at distance from big blood vessels RFA applied with the same outer parameters creates smaller coagulations in perfused tissue than in unperfused tissue.

The herein described effects are modeled in physical equations and influence the procedure and result in the organ on a ‘whole liver’ macroscopic scale. The electrophysiological principles for the described mechanism are explained in detail in [25].

4.2. Biological and chemical reactions

When the tissue is heating up the cell fluid starts boiling. As effect micro-bubbles are created. They are visible in ultrasound images during the procedure and mainly responsible for the low benefit of intra-operational ultrasound. Furthermore, the tissue coagulates and if heated up too high or too fast carbonizes.

Cell chemistry changes during the heating process. From a biochemistry point of view tissue coagulation happens as cell proteins denature. So by applying energy in the form of heat the protein molecules’ structures in space change. Chemical reactions of enzymes are hindered or impeded. Biological structures in the cell are destroyed. Most visible (under the microscope) is the destruction of the cell’s nucleus. Furthermore the mitochondria (responsible for the cell’s energy metabolism) are destroyed. Finally, the cell enters a metabolic cycle that leads to its death in near future [26].

The effects of boiling cell fluid and coagulating tissue not only deduct energy (i.e. heat) from the process serving as a tiny heat sink, but they also have direct influence on the tissues material parameters: the local efficiency of radiation conduction, heat conduction and ion friction change with tissue heat. The respective physical equations therefore do not rely on constants for the material properties but on parameters that couple the result back to the source. At the same time changes in cell metabolism are responsible for ongoing cell death after switching off the RF generator and removing the needle. The final necrosis changes size and shape for a couple of days after the intervention.

4. Mathematically modeling the RFA process

To predict the outcome of the intervention mathematical modeling of all the above described effects is necessary. The main governing equation is the Bioheat equation [27]. This mathematical description allows computing the heat transfer in biological tissue. Modifications for this equation exist, for example to model micro-perfusion [28]. These equations allow modeling of the heat transfer induced by radiation, the cooling effect by vessels as well as the heat conduction in the tissue. They are in nature coupled partial differential equations in three dimensions and cannot be solved analytically. To solve them numerically Finite Differences or Finite Element Method (FEM) have to be applied, where FEM is the method of choice in literature. In any case a numerical solution to the problem is demanding in computation time [8].

Effects of changes on cell level are mathematically not well modeled yet. As explained above boiling cell fluid as well as changes in chemistry, i.e. tissue coagulation and carbonization, change the electrical and heat conduction properties in the tissue [13]. Still the Bioheat equation assumes thermal and electrical properties of tissue to be constant. Furthermore, the material parameters depend on the tissue type as well as patient specific characteristics [20], [29]. A numerical solution therefore has to take the changes in material properties into account.

Models for ongoing cell death after ending a thermal ablation have been proposed in [24], [23]. These models start with measuring the thermal history for the regions. By relating the thermal dose taken by a cell during the ablation they predict cell death according to phenomenological descriptions. Measurements for heat distribution are acquired using intera-operative MRI scans and compared to histological findings to gain validation hints. As the models are based on phenomenological observations further research to understand cell changes and theoretically model mechanisms on cell level is still needed.

To compute a real setting all model parameters and their changes over time need to be known. Of course this also holds for treatment method and parameters. The needle geometry determines size and shape of the coagulation widely. An example of computing the coagulation for an expandable needle, as used in clinical practice today, can be found in [19]. The mathematical model describes an evolving heat distribution for an expanded array electrode, resulting in a spherical shape. Another external parameter is the ablation protocol. Clearly the information how much power is applied for how long influences the outcome of the treatment. Combining this information with the mathematical models discussed above leads to a complete mathematical description for a realistic ablation scenario.

A constructed model has to be validated before applied in clinical practice. Validation of the model requires comparison of treatment results with computational predictions. As the procedure applied for patients in clinical practice holds a lot of overlaying effects, treatment results from patients cannot be used for validation purposes [1]. Furthermore, the final result is hard to image and only visible in histological examinations. Therefore, animal studies have to be performed for experimental validations.

5. Validating a computational model for RFA

To predict treatment results patient specifically or to validate the result in an animal study, the above described mathematical equations have to be applied to treatment specific properties. As the equations are solved numerically using FEM, the geometrical setting determining the Finite Elements first has to be constructed. Furthermore, the material parameters entering the Bioheat equations need to be determined.

5.1. Geometry for the FEM model

To construct the individual geometry for the simulation the subject's anatomy as well as the exact position of the needle electrode have to be determined. The geometrical model entering the numerical computations should include:

- The liver: As the region relevant for the computations cannot easily be clipped, imaging the whole liver is necessary to base computational predictions on.
- The vessel trees: The most dominant effect in liver tissue is the heat sink effect due to blood perfusion in large vessels. The liver hosts three vessel trees (artery, hepatic vein, and portal vein). All three contribute to possible heat sink effects and should therefore be included in the model.
- Bile ducts: Though bile ducts go through the whole liver, they contain non-moving fluid and therefore do not contribute to the heat sink effect. Still they build inhomogeneities which could influence heat distribution, though in a much smaller extension than the heat sink effect.
- The tumor: As the tumor marks the region that is targeted for destruction in this intervention, knowing its size and location is very important. Furthermore, as tumor tissue heats different from other tissue, the tumor region has to be equipped with different material parameters for the numerical computation.
- The needle probe: The needle probe's tip is the source of the RF waves starting the ablation process. Its exact shape and location is therefore very important. For treatment prediction possible treatment results for given needle positions can be computed and eventually the optimum position suggested. For validation purposes, the needle position in the computation has to be set analog to its position in the experiment.

To reconstruct the subject's geometry demands imaging of the structures mentioned above. For patients imaging possibilities are limited due to medical and ethical reasons. Available images depend on the diagnostic process. In an animal study performed to verify a computational model imaging modalities can be chosen more liberally as best suited for the verification process. The aim in imaging is here to generate datasets that show all desired information, have adequate resolution, and are easy to process for reconstruction purposes. Choosing the best suited image modality and the best acquisition parameters is a complicated task and demands a radiologist's skill combined with input from computer vision and modeling experts.

As FEM computation demands a volume reconstruction with clear boundaries in between structures, the main task for computer vision is to segment the image correctly. As the intervention result cannot be imaged in any radiological modality, images from histology have to be fused with the radiological acquired ones. Obviously these histological images if acquired originate in animal studies. Limiting factors in this approach rely in both imaging technology and computer vision methodology. Low errors in reconstruction demand image modalities to show anatomy as clearly as possible in 3D datasets with overlapping pixels so there is no space between the acquired image planes. Not every imaging modality shows every desired structure. For example imaging the bile ducts requires MRCP (an imaging technique based on MRI) and is not possible using CT scans. The needle probe has to be compliant with the used imaging technology and might create artifacts in some images. High contrast is achieved using contrast agents, but these are also not visible at all time. Furthermore, contrast agents demand blood flow and therefore in-vivo studies.

Single images that are perfect for segmentation of one of the desired structures might not be ideal for imaging the other geometric information. Therefore, combinations of different image modalities or else different images acquired in the same modality but at different times might be a better solution than one image showing everything - or sometimes even the only possibility. But with every additional image acquisition the two images have to be registered onto each other. As in-vivo studies require the subject to breathe in between and the liver deforms with every breath and every heart beat, a non-rigid registration between the different images is necessary. This approach is demanding in computer vision skills, as the registration of deforming non-rigid structures is and unsolved scientific problem. Last but not least images taken from histology are very hard to register to a radiological image. Not only does the liver deform when removed from the animal, but slicing the liver into small portions leads to further deformation in the cutting process. Reconstructing a volume out of histological data is in itself a demanding computer vision topic. Registering those images to radiological ones is performed rarely. A first approach was taken in [30].

5.2. Material parameters

Besides efforts to reconstruct the right geometry, an FEM model also needs the parameters contained in the equations that have to be solved numerically. As explained above these parameters are subject specific material parameters. Physically measuring their values demands the examination of tissue samples in a laboratory. Measurement techniques are described in detail for example in [29].

While [29] concludes, that the differences in material properties are negligible, [13] shows the differences in material properties for heating tissue. Nevertheless, for patients taking tissue samples is impossible. But for constructing a verifiable model with an animal study opens this opportunity. Still measuring these values is not easily done. Therefore, they could also be taken from literature, for example from [13] or [31]. In the end a prediction for these values based on easily acquirable patient data and properties is needed. But this is a medical task to solve.

Another needed parameter is the current blood flow through vessels in the liver. Here it is obvious, that the amount of cooling fluid varies with cross section as well as pressure. While the vessels diameter (cross section) can be reconstructed from images, the blood pressure cannot easily be deducted. Measuring the pressure at the entry to the liver seems a possibility to attack this challenge.

6. Discussion and Conclusion

Many approaches have been taken to predict the result of a RFA intervention. Modeling the typical result has been performed in the past using models like ellipsoids. This modeling unfortunately only predicts typical cases, which can be predicted by medical doctors without the modeling effort. More complex situations do not end in typical shapes. Physiological models have been developed for less typical and more realistic situations. To validate the predictive power of a model, comparison to experimental results is needed. So far no realistic model has been experimentally validated. Patient data is not sufficient to generate this validation. Therefore, data has to be collected in animal studies.

The direct approach to data collection would then be to build an as accurate as possible virtual model of the respective liver. The geometry needed for the respective FEM model – the anatomy of the subject – has to be reconstructed from radiological images. Images thereby need to be acquired according to the needs of the modeling and taking into account difficulties from image processing. Therefore, specifications for imaging procedures demand a radiologist’s skill as well as knowledge in computer vision and biomedical engineering. Tissue properties can either be collected from tissue samples (for animals) or taken from books.

The question of how to determine the properties patient specifically without tissue samples is a task to be researched by medical doctors.

The next steps towards a verifiable model for the RFA process is the definition of an exact procedure to be used in an animal study. Then the development of suitable image processing and geometry reconstruction tools can be attacked. Finally, the comparison of existing models and variations of these models will lead to new insights and a verifiable model for the RFA process.

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