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Mathematical modeling: a valuable training aid for new medical devices

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Abstract

Este artículo trata sobre la modelización biomédica en general y cómo las técnicas de modelización pueden ayudar para mejorar la práctica clínica en el uso de nuevos dispositivos médicos en particular. La ecuación "Bioheat" o de difusión del calor en tejido biológico se utiliza como ejemplo para mostrar como, incluso en el caso en que los modelos matemáticos estén basados en ecuaciones complejas, los términos de dichas ecuaciones representan fenómenos que pueden ser entendidos de forma intuitiva. El artículo también presenta ejemplos en los cuales el modelado matemático se usa para estudiar la adecuación de los dispositivos médicos, especialmente aquellos relacionados con la ablación por radiofrecuencia.

The paper deals with biomedical modeling in general and in particular how modeling techniques can be used to improve the training of clinical practitioners in the use of new medical devices. The Bioheat Equation is given as an example to show how, even though mathematical models are based on complex equations, the terms of the equations represent phenomena which can be intuitively understood. The paper also describes examples in which mathematical modeling was used to study the performance of medical devices, especially those related with radiofrequency ablation.

Keywords: Biomedical Engineering, Clinical Applications, Finite Element Method, Mathematical Modeling.

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1 Introduction

The paper deals with biomedical modeling in general and in particular how modeling techniques can be used to improve the training of clinical staff in the use of new medical devices. It is also necessary to emphasize the importance of modeling techniques for postgraduate students in biophysics and biomathematics. First of all, it should be made clear that mathematical models are not only used to create mathematical games or to publish scientific papers in specific journals. Some maintain that mathematical models are too simple to be useful and that the real world is more complex. Two examples can be given to show that this is not true. The first is not concerned with biomedicine: Imagine you have a solid wooden table that you want to protect by means of a glass top (Figure 6.1). The glazier asks for the required dimensions. Most people would choose to measure the diameter, or maybe the circumference. What have they done? Of course, they have modeled the circular surface of the table. Everybody knows that circular tables are not exactly circular, but this approximation is usually enough.

Figure 6.1: Measuring the diameter of the surface of the table shown above is implicitly assuming that we are modeling the surface as a circle, that is, as a geometrical shape.

Likewise, a number of surgeons and physicians, fortunately only a minority, criticize mathematical models as being too simple. They maintain that mathematical models cannot possible reproduce the complex human behavior they had to study at medical school for many years. This again is not true. When physicians diagnose an illness, they obtain information on a system before deciding on a treatment, which is an input into the system. In this case the system involved is the human body. The physician has a patient in mind, but even so he/she has to consider the body as a model, with inputs and outputs. In fact, the physiological performance of the body cannot be understood without either mathematical or conceptual models.

2 Creating a model

To create a model, one has to complete the following steps:

1. Analyze the physical situation.

2. Simplify the real situation (which means considering only certain variables and hence ignoring other factors).
3. Define the relationships between variables.
4. Define the model (equations, conditions, restrictions, etc.).
5. Implement (e.g. by means of a computer).
6. Use (or enjoy) it.
7. Finally, validate it by some means.

However, in this list we have deliberately omitted the most important step, which should always be the first: we have not mentioned the objective for which the model was built. In fact, by keeping to the objective we will be able to discard a number of variables and so simplify the model. In modeling, the simpler the better.

3 Example: The Bioheat Equation

We will use the example of medical devices for the heating of biological tissue by means of electrical currents (especially radiofrequency currents). The theoretical models used to study temperature distributions in biological tissue when heated by various types of energy are based on differential equations which describe physical phenomena [1]. To be more precise, two equations have to be solved. First, the Laplace Equation has to be solved in order to obtain the spatial and time distribution of voltage, current density and electric field in the tissue. We then have to solve the thermal problem by means of the Bioheat Equation by using the electrical power density absorbed by the tissue, which is obtained from the electrical problem. This equation governs thermal conduction in biological tissue and although it is a differential equation with many terms, I will show that each term represents a certain phenomenon.

Let us take as an example a fragment of tissue with a uniform temperature of 37°C. If we used an applicator to heat part of the tissue, we create a temperature gradient like that shown in Figure 6.2 A. We are only concerned with the temperature in such a small fragment of tissue that we can consider it to be a uniform 47°C (Figure 6.2 B). The Bioheat equation thus has to solve this distribution, i.e. it has to obtain the temperature value at each point (x, y, z) and time (t).

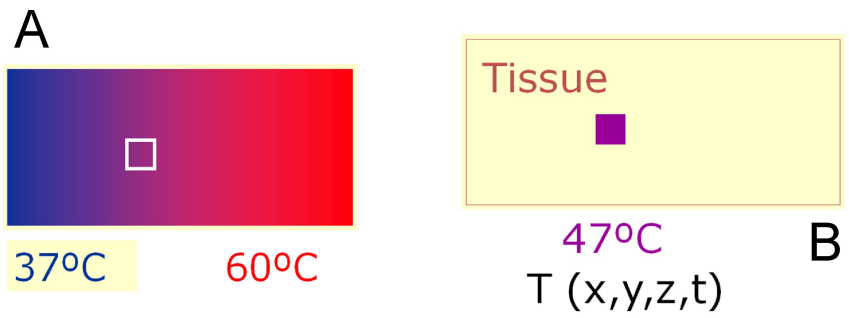

Figure 6.2: A: Large fragment of a tissue heated by any kind of energy. B: The problem of temperature distribution is simplified by only considering temperature in a very small fragment of tissue.

Let us now consider a tissue fragment with higher temperature, as shown in Figure 6.3 C. Heat will now flow towards the unheated part because there is a temperature difference or thermal gradient. This gradient is directly related (proportional) to the rate of temperature change at this point. This rate is mathematically represented as the first derivative of temperature versus time. Finally, the factor relating to the change rate and thermal gradient is a tissue characteristic known as *thermal conductivity* (k), which models the quantity of heat flowing between two points with different temperatures.

However, other factors are involved. If we touch with our hands two objects at 200°C, one a sponge and the other a brick, which will be more painful and why? Intuitively, we think that the brick will be more painful to the touch since a brick can store more heat than a sponge. This capability is modeled by two characteristics of the material, mass density and specific heat. These terms are inversely proportional to the temperature rate of change (Figure 6.3 A). Obviously, it is easier (faster) to heat a sponge with lower density and specific heat than a brick. Finally, temperature is scalar and its gradient is a vector. Since we have to use scalar terms on both sides of the equation, we therefore use divergence, which is an operator that measures the magnitude of the source of a vector field at a given point (Figure 6.3B).

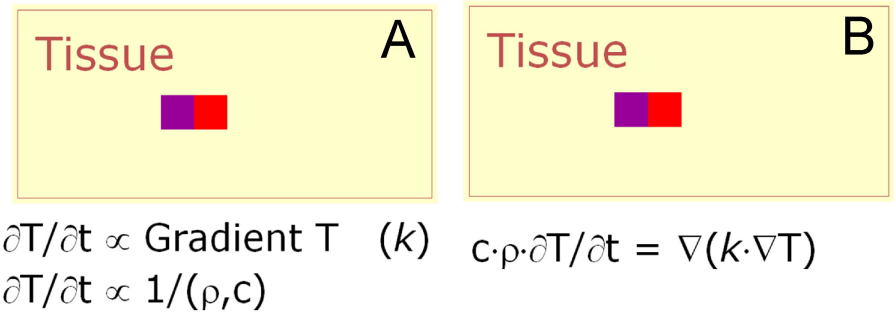

Figure 6.3: A: The rate of change of temperature in thermal conduction is directly proportional to thermal conductivity (k) and inversely proportional to the capacity for storing heat (ρ, c). B: Temperature divergence allows both sides of the equation to be expressed in scalar form.

However, other phenomena have to be considered. We have to remember that most tissues have small blood vessels called *capillaries* (responsible for blood perfusion) which transport blood at normal temperature (37°C) (see Figure 6.4 A). This blood flow removes the heat from this point. For this reason the Bioheat Equation includes a negative term on the right side, which is directly proportional to the capacity of the circulating blood to store heat (mass density and specific heat). It is also proportional to the blood flow and difference between temperature at that point and temperature blood. Another negligible term in RF heating of biological tissues is *metabolic heat* (see Figure 6.4 B), which represents the heat produced by the tissue itself due to its metabolism.

Finally, we have the energy delivered by an applicator (RF currents, microwaves, ultrasound, laser, etc.). This is modeled by means of a term q which produces the increase in temperature (Figure 6.5 A).

We now have to consider the temperature value of every small piece of tissue (see Figure 6.5 B). Our research group used the Finite Element Method to solve these problems by numerical techniques. This method consists of breaking down the model into small fragments (finite elements) to solve the equations for each fragment. To achieve a single solution we have to set thermal and electrical boundary conditions. This is because solving differential equations

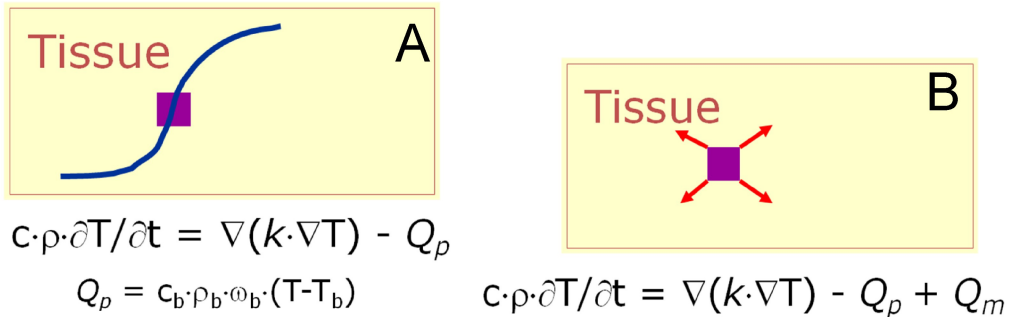

Figure 6.4: A: The small blood vessels transport blood at normal temperature and reduce temperature. B: The metabolic heat term is usually negligible in RF heating of biological tissue.

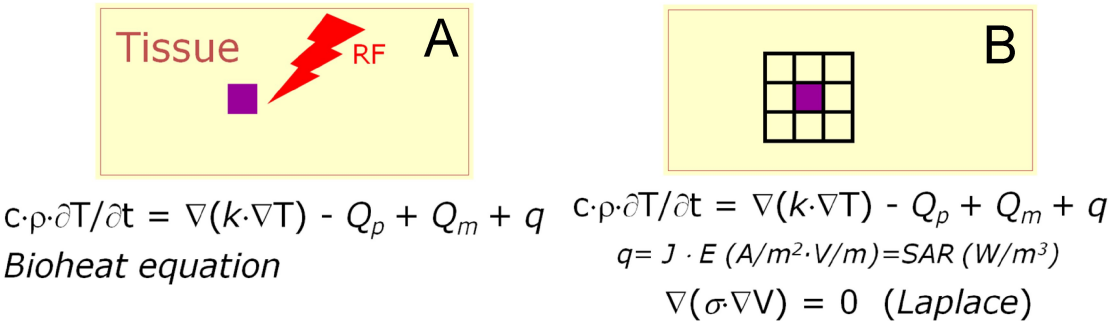

Figure 6.5: The Bioheat Equation includes the term q, which models the external source of power. B: This term is obtained by means of the Laplace equation and Ohm's law.

involves integrals.

We finally obtain the temperature at each point and time ($T(t)$). However, temperature alone does not represent thermal injury in the tissue: Note that 43°C on our skin is negligible for 10 seconds, but unbearable after two hours. Time is therefore also important and has to be allowed for in thermal injury. Thermal damage functions have been proposed to model this phenomenon ([1]).

4 Clinical application of the mathematical models: Example of radiofrequency cardiac ablation

Radiofrequency (RF) cardiac ablation is used to eliminate a fragment of heart tissue which has caused an arrhythmia[2], a heart-rhythm disorder. In this procedure a catheter including an electrode at the tip is applied to the tissue. Once the target has been located, RF currents are applied between the electrode and a dispersive electrode placed on the patient's back (see Figure 6.6). The tissue in contact with the electrode receives the maximum current density and thus experiences the maximum temperature rise.

In RF cardiac ablation the power of the RF generator is automatically modulated in order to keep the temperature in the electrode constant. This is done by means of a temperature sensor located at the tip (yellow circle in Figure 6.6). This temperature value is known as the *target temperature*. Increasing the temperature produces a heat flux towards the deeper tissue,

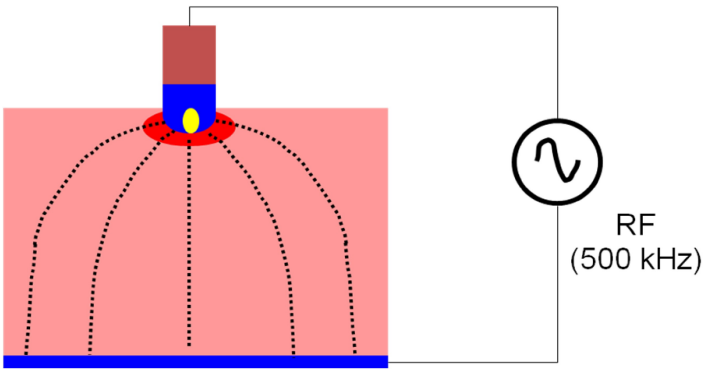

Figure 6.6: Model representing the RF cardiac ablation process.

although part of this heat moves towards the blood circulating in the cardiac chamber through the mass of the electrode. The lesion (assessed by the 50°C isotherm line) gradually expands (see Figure 6.7 A). This means that the hottest point is not located at the electrode, but $1-2$ mm away (see Figure 6.7 B). This was first demonstrated by mathematical models before being shown to be true in practical experiments. Notice that although the target temperature (measured by the sensor) is around 55°C, the maximum temperature could be much higher, as much as 100°C.

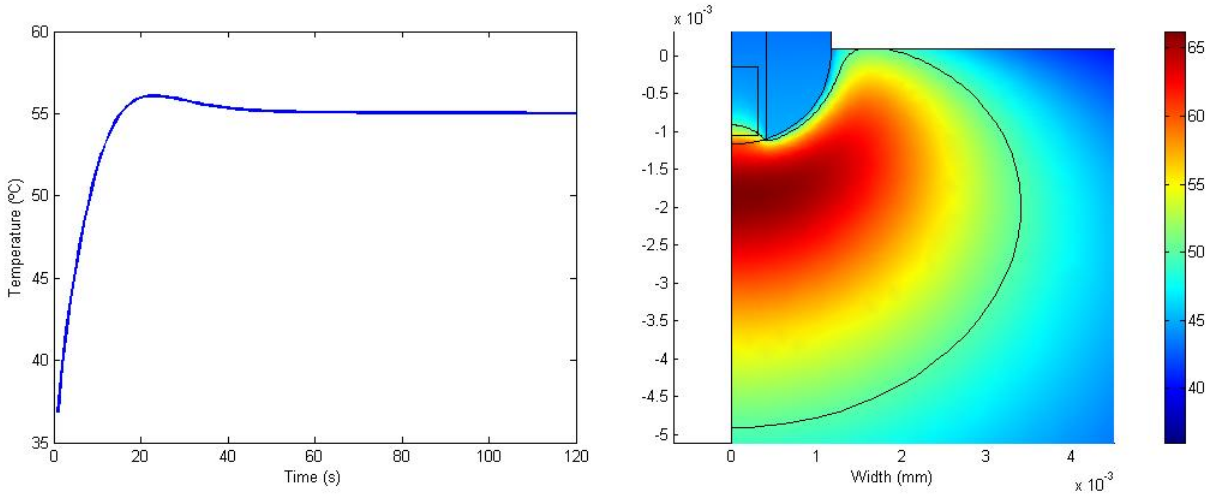

Figure 6.7: Right: Temperature is kept constant at the electrode by modulating the voltage applied. Left: The hottest point is not on the electrode surface but $1-2$ mm away.

Around five years ago, some patients died after RF cardiac ablation of the left atrium due to collateral thermal injury in the esophagus. This seemed obviously due to the short distance between the esophagus and atrium (see Figure 6.8). Under certain conditions, the atrium wall is only $1-2$ mm thick. Our research group thus decided to study the effect of different factors on injuries in the esophagus [3]. We used mathematical models as a hypothetical experimental or clinical study would have been impossible due to the excessive number of factors involved. This is a clear example where the simplification of the real physical situation is mandatory.

The model proposed by us was three-dimensional and included the atrial wall, an epicardial fat layer, the esophagus, and other more distant organs such as the aorta, lung and associated

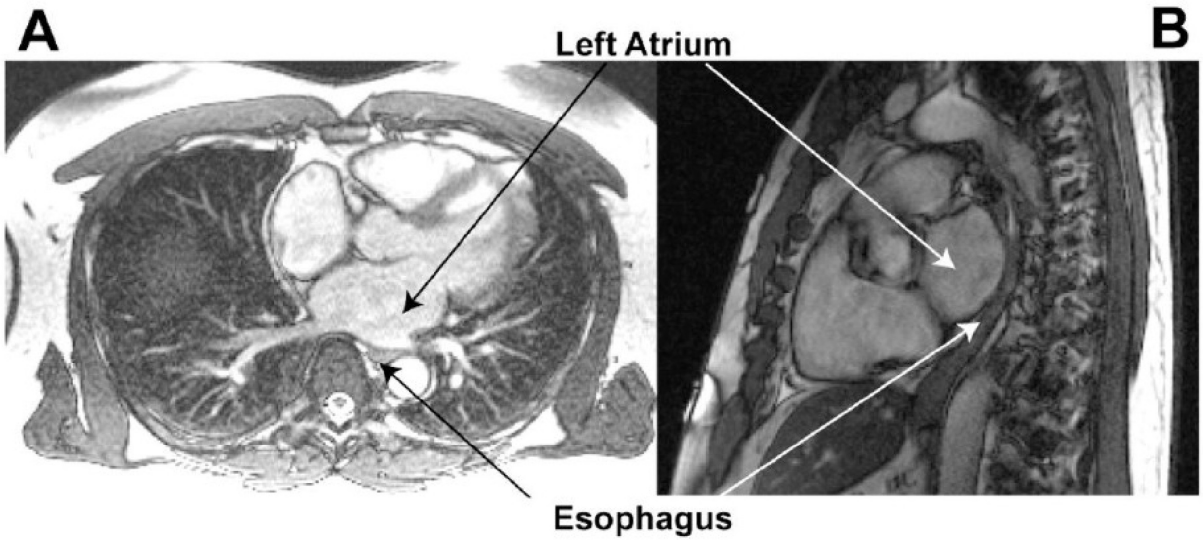

Figure 6.8: A: Sagital view. B: Transversal view. Relative position between left atrium and esophagus.

connective tissue (see Figure 6.9 A). The electrode included a temperature sensor located at the point of maximum temperature. Thanks to the two symmetry planes, the computational model only included one quadrant. Figure 6.9 B represents the theoretical model built using the software for Finite Element Analysis (ANSYS) and shows an image of the meshing of the small elements. Greater detail is shown in the zone around the electrode with highest gradient.

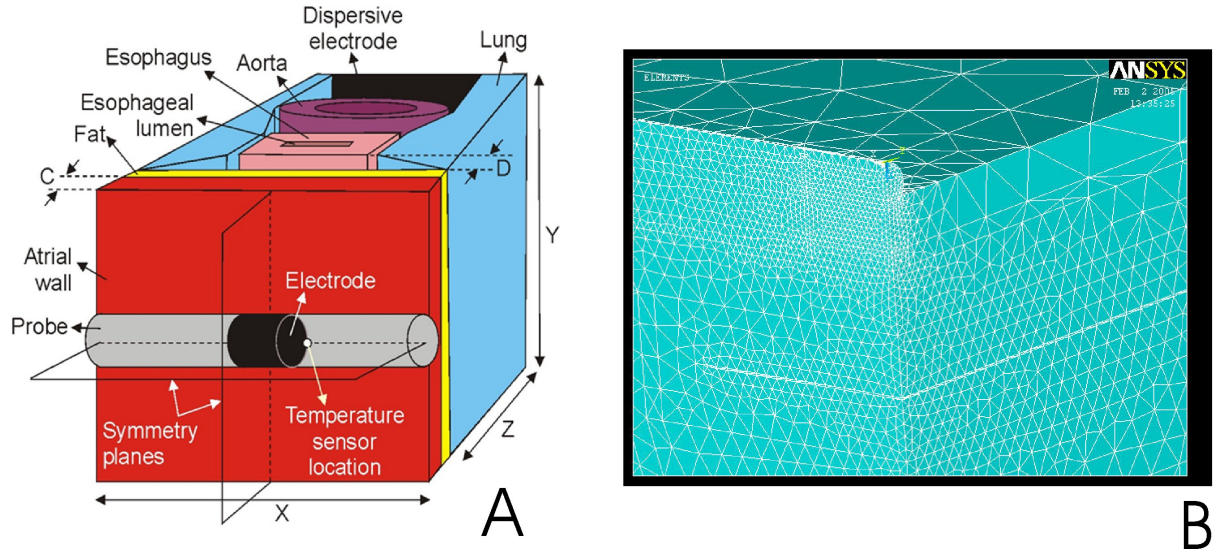

Figure 6.9: A: Theoretical model to study temperature distributions in the esophagus during RF cardiac ablation. B: Detail of the meshing near the electrode.

The effect of different factors was studied with this model. Figure 6.10 gives the power density distribution and shows how electrical power is absorbed into the tissue. Notice that almost 100% of the power is distributed within 1 mm of the electrode. Some surgeons have claimed that thermal injury to the esophagus can be caused by the electrical power it absorbs, however, our computer results show that this is not true.

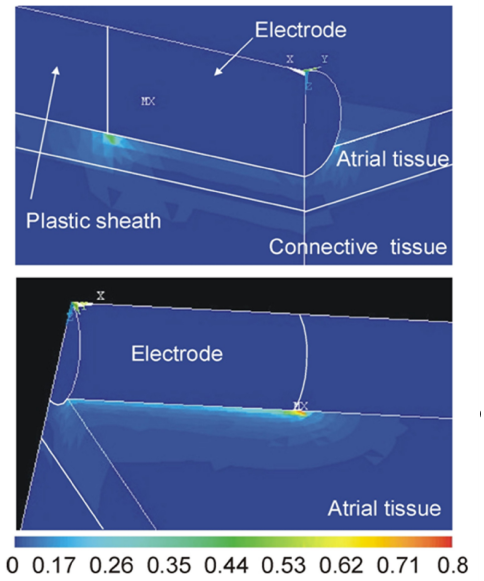

Figure 6.10: Since almost 100% of the electrical power was deposited within 1 mm of the electrode, this suggested that thermal lesions in the esophagus were due exclusively to thermal conduction and not to the deposited electrical power (units in 10^9 W/m^3).

As a solution we came up with an original idea: a cooled balloon introduced into the esophagus via the mouth to protect it during RF ablation. Before spending time and money building prototypes and conducting experiments, we decided to conduct a proof-of-concept by means of mathematical models [4]. We modified our previous model to include a balloon in the lumen and the results suggested that the device could provide a workable solution (see Figure 6.11). From the results obtained from the mathematical models a clinical group in Japan [5] planned a clinical trial with patients in a practical test.

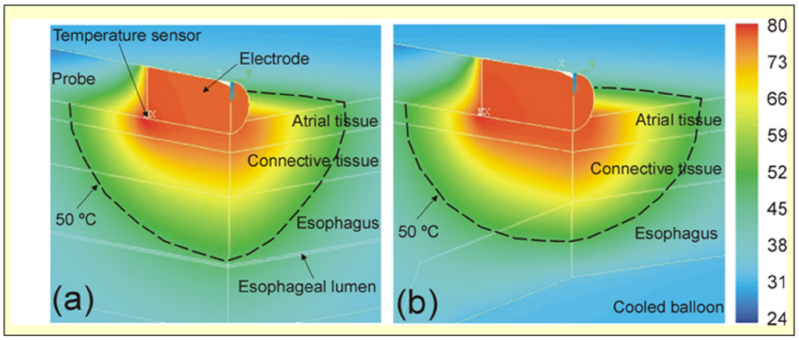

Figure 6.11: Temperature distribution in the esophagus without (a) and with a cooled balloon (b).

Other groups had other ideas, for example, measuring the temperature in the lumen with a temperature probe, and switching off the RF power if it is too high. The temperature sensor is simply a plastic probe with a thermistor at the tip. It seems a reasonable idea, but what will happen if the thermistor is not placed near the ablation electrode? The sensor will probably underestimate the maximal temperature reached in the esophagus, but by how much? The mathematical models also produced answers to this question. Using the model shown in Figure 6.9 A, we obtained the results given in Figure 6.12 [6] after comparing the maximal temperature

reached at Point A in the lumen to temperatures measured at other possible locations. Our results suggested that if the thermistor was placed almost 2 cm away from the transversal plane including the electrode (point C3) the underestimation was very high.

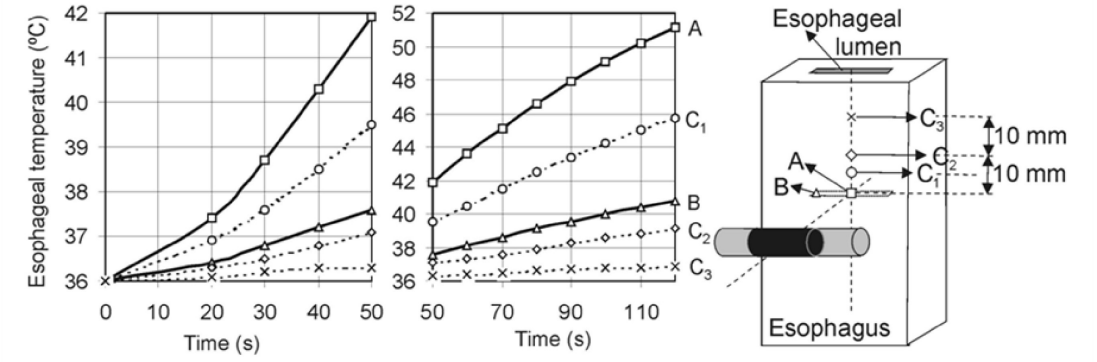

Figure 6.12: Left: temperature evolution at different locations inside the esophagus. Right: Model geometry and nomenclature of the locations.

From our research with mathematical models in RF cardiac ablation, we concluded that the mathematical models make it possible:

1. To observe variables that cannot be measured experimentally (e.g. current density) and also their evolution with time.
2. To study rapidly and cheaply the effect of electrode geometries, energy-delivering protocols and the effects of different types of biological tissue.
3. To study random phenomena or hazards in conditions which are difficult or almost impossible to reproduce with experimental models.

5 Communicating the results

Finally, and by no means the least important factor, the results obtained from the mathematical models have to be transmitted to those involved in clinical practice. For this, communications skills are crucial. Unfortunately, after seeing the results of simulation, many physicians ask question like: do these results demonstrate that if I set 50 V for 60 seconds the temperature in that zone will reach 70°C? The answer is always somewhat complicated. It is important to point out that the results are always qualitative, not quantitative, since we use generic tissue characteristics and not the characteristics of an actual patient. In fact, the current limitations of these models are not related to computer shortcomings, but rather to the accurate reproduction of tissue characteristics. It is not an easy task to explain simulation results to clinical surgeons. On one occasion I was told: "A mathematical model is a thing nobody believes except the model's creator; an experimental model is something everybody believes, except the model's creator".

In spite of this limitation, our experience of mathematical models and transmitting the results to clinical practitioners has convinced us that mathematical models are valuable tools in studying the performance of a medical device. This is easy to explain with an example: if a surgeon

observes the time evolution of a temperature distribution in a computer simulation derived from a mathematical model (e.g. Figure 6.11), he/she will know the exact thermal performance of the device and will be able to predict the consequences in thermal behavior if a parameter changes, such as a rise in the pressure between electrode and tissue, or a change in the target temperature. This means that surgical devices can be used with better information and improved safely.

6 Conclusions

Everybody uses a type of model to understand reality, from a baby to an experienced medical practitioner. Mathematical models are a powerful, fast and cheap tool to achieve in-depth knowledge of the performance of a medical device. This, in turn, allows safer use. Finally, although mathematical models are based on complex equations, their terms represent natural phenomena which can be intuitively understood.

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