Bartosz SAWICKI, Artur KRUPA

Warsaw University of Technology

doi:10.15199/48.2016.07.18

Experiments with models of variability for biological tissues

***Abstract**. Properties of biological tissues are a subject of variability. Stochastic variable approach described using probability density function (PDF) allows to build more realistic models of human body comparing to the classical, deterministic models. In this paper two variability factors are investigated. One related with a shape of random distribution of parameter inside the organ, and the second related with the size of the variability grain. Based on experiments for simple current field model, it is shown that shape of PDF for tissue conductivity has important impact of distribution of results.*

***Streszczenie.** Właściwości tkanek biologicznych podlegają zmienności. Wykorzystanie zmiennych losowych opisywanych poprzez funkcje gęstości prawdopodobieństwa pozwala na tworzenie bardziej realistycznych modeli ludzkiego ciała niż klasyczne podejście deterministyczne. W artykule zostały przeanalizowane dwa parametry zmienności. Jeden związany z kształtem funkcji gęstości prawdopodobieństwa, a drugi zależny od rozmiaru elementarnego ziarna zmienności. Eksperymenty przeprowadzone dla prostego modelu pola przepływowego pokazują, że kształt zmienności konduktywności ma istotne znaczenie na rozrzut wyników. (**Eksperymenty z modelami zmienności tkanek biologicznych**)*

Keywords: Bioelectromagnetics, Random variable, Monte Carlo method.
Słowa kluczowe: Bioelektromagnetyzm, zmienna losowa, metoda Monte Carlo.

Introduction

Numerical modelling is an important tool used by modern bioelectromagnetics. Typical approach is based on deterministic models which are based on assumption that parameters of living organism are known and constant. In reality, for many applications, this is not a case: the parameters are uncertain and variable at the same time. This is due to fact that organs of the living body are not homogeneous and are sensitive to external condition and the passage of the time.

In previous works authors identified different sources of uncertainty in bioelectromagnetic problems [6]. It was shown that they can be epistemic (caused by lack of knowledge), and aleatory (inherent variations). Tissue properties has been identified as a major source of irreducible uncertainty.

Although stochastic, fuzzy methods are studied for nearly 100 years, its applications in real problems described by partially differential equations are still far from popularity. Science of the solid mechanics developed theory of Fuzzy Finite Elements [4] to describe imprecisely defined mechanical systems. Another examples of popular applications are connected with models with biological origin. Thermal analysis for food processing [2] are this kind of problem. There are modern studies [8] dealing with uncertainties of the properties the human body deteriorating accuracy of brain models.

Preliminary results presented in this paper were discussed during CPEE conference [10]. They were extended for different classes of probability density function (PDF). Moreover, higher number of simulations were performed to obtain better quality histograms and more reliable conclusions.

Tissue variability

Measurements of parameters of living tissues has been a subject of scientific interest since early beginning of bioelectromagnetics. Hundreds of scientific papers contains results of the measurements. Meta-analysis articles combine those values [7] and show variation of measurements over the years.

For purpose of this study we took measurements recently published by Gabriel et al. [1]. Those values were taken from 'in vivo' experiments conducted using animals. Chosen values presented in Table 1 shows large dispersion, reaching up to over 100%, what is typical for biological tissues.

Table 1. Low frequency conductivities for chosen tissues, values measured 'in vivo' on animals [1].

Tissue	*[S/m]*
Muscle	0.15 ± 0.01
Heart	0.48 ± 0.13
Skull	0.32 ± 0.38
Fat	0.078 ± 0.019
Blood	0.60 ± 0.21

We can distinguish two types of conductivity variability. The first one is related with inhomogeneity of tissue, and the second with variations between different patients with assumption that tissue is homogeneous. In real live those two types are overlapping, so total variation has to be treated as a combination of above two.

Simple, linear and homogeneous models can be analysed by scaling one of solutions. Variability of such results are simply related with variability of input parameter, so we don't devote much of an attention to this problem. The main focus of this paper is placed on inhomogeneous tissues variability.

We developed finite element model with statistically varying parameter in each cell. We choose parameters of a heart tissue (mean 0.48, standard deviation 0.13 [S/m]). Shape of probability function is subject of investigation since in the literature values are given only by mean and standard deviation. Some authors assume uniform distribution, other normal shape. To determine impact of such assumptions we decided to compare those two types of variability.

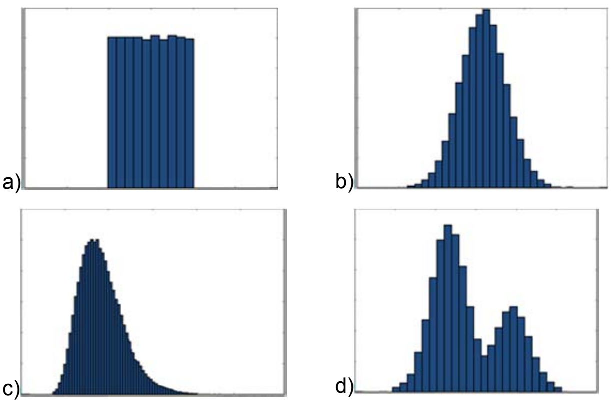


Fig. 1. Examples of different shapes of variability: a) uniform, b) normal, c) log-normal, d) mixture

Shapes of variability

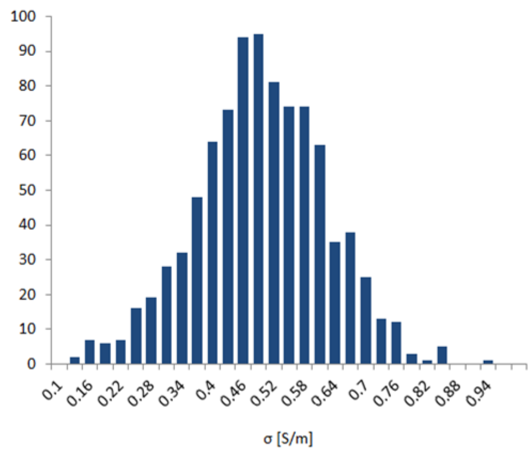
Determination of probability density function for stochastic parameters is often troublesome since access to the large number of measurements is limited. For that reason typical solution is to choose one of the popular shapes of variability. Below, we will introduce some basic PDF presented on Fig. 1.

Uniform distribution (Fig. 1a) is usually used when we have identical probability of data within declared range. This is correct shape, but practically we never have equal chances in multiple biological measurements to achieve the same results of each value.

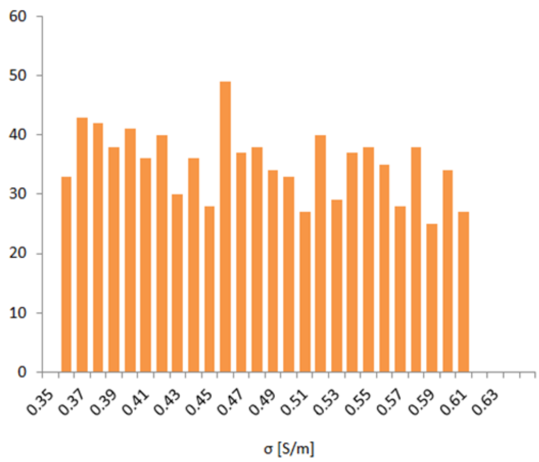
Normal distribution (Fig. 1b) is commonly used as a default shape of any numerical or statistical problems. It is usually correct, when we have multiple results within a declared range, but also derogations which can be covered by average deviation parameter. This shape is “universal” solution, but not covers the situation of non-symmetrical deviation.

Third shape is logarithmic normal distribution (Fig. 1c), which can help to describe a not symmetrical deviation other than in normal shape. Unfortunately this shape is only usable for one distribution only. When we have multiple similar size distributions – it is not applicable.

The last example of distribution shape is mixture (Fig. 1d). It should be used when several classes of objects with different PDF are mixed together with given ratio. This case is probably the most realistic in many biomedical cases, but proper definition of mixture is questionable.



a)



b)

Fig. 2. Histograms of conductivity distribution inside the model. Variability is equal to the heart tissue parameters (0.48 ± 0.13). a) normal distribution, b) uniform distribution

On Fig. 2. two exemplar histograms of variability of heart cells conductivity are presented. Both of them has the same mean value 0.48. The normal distribution has standard deviation equal to 0.13, while uniform distribution is whole contained between -0.13 and +0.13. Those distribution will be used in experiments described in the later sections.

To deal with probabilistic problem we choose Monte Carlo (MC) method. Another tool for fuzzy problems is interval analysis, which is known as a efficient solution for simple PDF. It was shown that results given by both of the methods are comparable [9]. Monte Carlo is especially attractive because it perfectly fits to modern computational systems that are often based on loosely connected nodes [5]. This architecture called cloud computing, gives economically attractive access to the huge computational resources. The most important is that MC gives complete statistical view of stochastic model. No simplifications and preliminary assumptions have to be made before analysis of the problem.

Numerical model

Study described in this paper is based on the simple model of stationary electrical current distribution inside rectangular shape specimen (as seen on Fig 3.). External voltage source (1 [V]) is connected to the left and right edge of the model, which dimensions are 3cm wide and 2cm height.

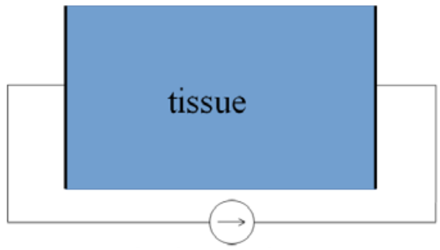


Fig. 3. Model of a direct electrical simulation used in experiment

This kind of the field problem could be described by basic Laplace equation using electric scalar potential φ

$$-\nabla \cdot \sigma \nabla \varphi = 0 \tag{1}$$

where σ is conductivity function. Two voltage sources placed on the sides of the model are modelled as Dirichlet boundary conditions:

$\varphi = 0$ on the left edge,

$\varphi = 1$ on the right edge.

Problem is solved with Finite Element Method implemented in self-developed solver based on FEniCS library [3].

For each simulation conductivity distribution was randomly generated according to the same probability density function. For that reason every result is unique, and to analyse them, statistical approach is required.

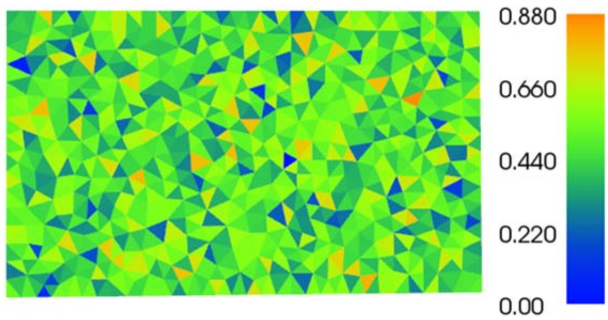


Fig. 4. Simple 2D rectangular model of random distribution of conductivity. Histograms of values are presented on Fig.2

Depending on chosen mesh resolution (see grain size experiments described in the second part of the paper) single simulation takes from 3 to 10 seconds. To obtain stable solution Monte Carlo algorithm requires large number of independent analysis. So this problem should be classified as computationally challenging, but easy to parallelize.

Different shapes of variability

The first set of experiments concerns answering the question how type of statistical variation of conductivity are changing results. Variability of heart tissue [1] was taken as an example, normal and uniform shapes of PDF were analysed.

Distribution of conductivity was generated randomly according to the given PDF (see Fig. 2), and then model was solved. This procedure was repeated 1000 times to obtain statistically significant set of results. Two types of solutions were analysed:

- global: total resistance of the model (R),
- local: maximal value of E field.

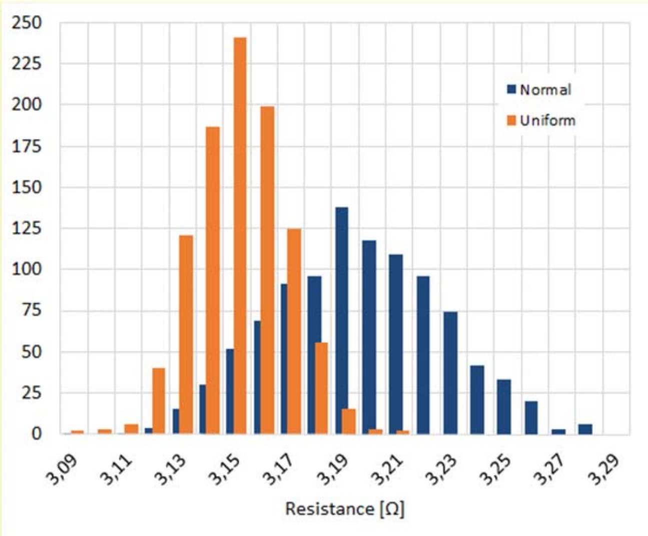


Fig. 5. Histograms of total resistance values for 1000 simulations based on stochastic model, for normal and uniform distributions of conductivity

Values of resistance results in the form of histogram are shown on Fig. 5. As seen, results for two cases are easily distinguishable. PDF for resistance based on uniform distribution is shifted to the left with smaller dispersion. Both solutions has Gaussian shape, what is natural since they are multiple combination of random variables.

Table 2. Numerical comparison of results for two different PDF shapes of input parameter (conductivity). Histograms are presented on Fig. 5 and 6

		mean	*std. dev.*
Normal PDF	R [Ω]	3.19	0.03
	E_{max} [V/m]	56.8	8.2
Uniform PDF	R [Ω]	3.15	0.02
	E_{max} [V/m]	41.6	1.1

Detailed values of statistical measures are contained in Table 2. Comparing mean values (3.15 and 3.19), difference is just above 1%. Similarly calculated relative variability for both cases is approx. 1%. It is important to note that it is much smaller that relative variability of input conductivity parameter (mean 0.48, standard deviation 0.13) which is 27%. This observation leads to conclusion that globally calculated results of simulations are nearly not sensitive to the inhomogeneity of the tissue, but impact of the shape of input PDF is observable.

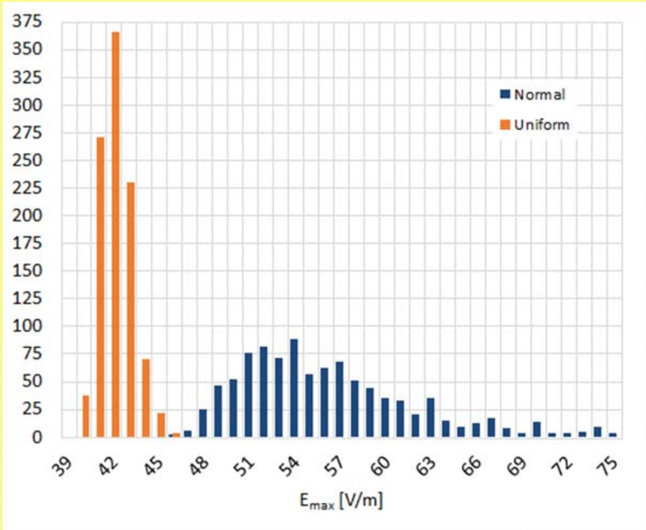


Fig. 6. Histograms of maximum values of electric field E for 1000 simulations

Much stronger difference is observed for locally defined results, such as maximal value of E field. Histograms are compared on Fig. 6. The mode of the 'normal distribution' case is shifted far to the right, what makes histograms nearly not overlapping. Values in the Table 2. show that mean value for normal PDF is 35% larger that for uniform distribution, what confirms importance of the assumption about the shape of density function of input parameter.

Relative variabilities is 14% for normal, and 3% for uniform distribution. What is higher comparing with variability of the global results (resistance, approx. 1%), but still below variability of input parameter (conductivity, approx. 27%).

It should also be noted that plots are clearly non-symmetrical. Steep curve at the begging and flat tail of the histogram is characteristic for a log-normal distribution (compare with Fig. 1c). This type of variability has wide range of applications where extreme values are analysed.

Different grains of variability

Shape of probability is important parameter of the stochastic spatial function, but variability related with distribution in the space shouldn't be ignored. That's why in the second part of the study, influence of conductivity grain size on results variation will be presented.

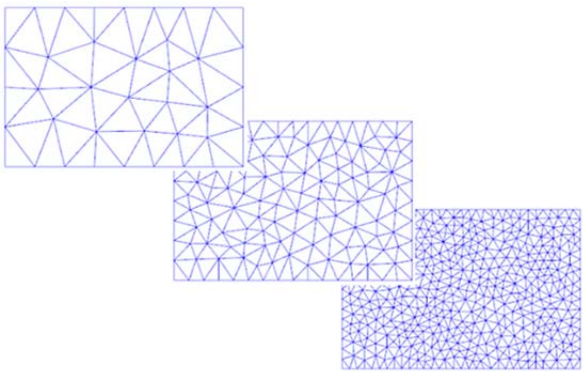


Fig. 7. Different grain size of piecewise homogeneity modelled as FEM different mesh resolution

Fig. 7 is an illustration how changing resolution of the mesh can be interpreted as a change in conductivity grain size. Natural assumption for Finite Element Method is that value of material parameters is piecewise constant on the elements. We have connected those two factors. Low resolution means large grains, while higher resolution leads into smaller mesh element and conductivity grains. Side effect of this approach is that models with smaller grains has more elements so a computation process is longer comparing with models with larger grains.

To preserve statistical properties of the results six sets of 100 simulations have been solved for different grains of conductivity. Results on Fig. 8 na 9 refers to the relative grain of conductivity which is defined as a ratio between average size of the element and size of the whole model.

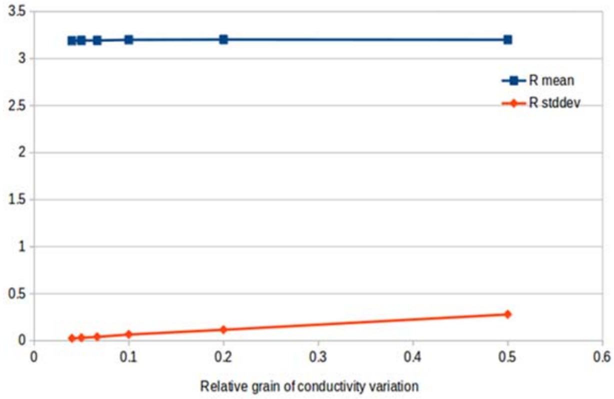


Fig. 8. Mean and standard deviation of total resistance as a function of relative size of grain variation

Line for mean resistance is nearly flat (see Fig. 8), what means that this value is not dependent on the size of the grain of conductivity inhomogeneity. It is worth to note that value 3.125 is equal to homogeneous solution for the mean value of conductivity. Values for Emax is not stable for small variability grains (see Fig. 9), and asymptotically goes to 33 which is homogeneous solution.

Standard deviations demonstrate different behaviour. For resistance, rapidly changing conductivity (small grain) gives nearly zero stddev. However for Emax low deviation is observed for large grain of conductivities.

To overcome shortcomings related with direct mapping of mesh size into conductivity grain size, and to be able to analyse smooth transitions in conductivity distribution more advanced model has to be developed. In the future works authors plan to create independent spatially variable function of conductivity that will be discretized before applying FEM.

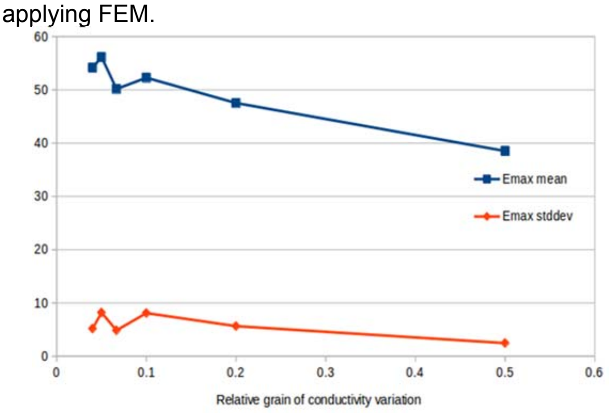


Fig. 9. Mean and standard deviation of max. value of electric field as a function of relative size of grain variation

Conclusions

Two shapes of variability of the tissue parameter have been investigated. Numerical experiments for created models of inhomogeneous organs have shown that global result values has very different characteristic that local values. It was shown that the latter one is especially sensitive to the shape of probability density function of input parameter.

In future works more efforts should be placed on development of statistical models of tissues and computational techniques designed for dealing with high number of simulations.

***Authors**: dr hab. inż. Bartosz Sawicki, Politechnika Warszawska, Instytut Elektroenergetyki Teoretycznej i Systemów Informacyjno-Pomiarowych, ul. Koszykowa 75, 00-662 Warszawa, E-mail: Bartosz.Sawicki@ee.pw.edu.pl; mgr inż. Artur Krupa, j.w., E-mail: Artur.Krupa@ee.pw.edu.pl*

REFERENCES

[1] Gabriel C.,Peyman A., Grant E. H., Electrical conductivity of tissue at frequencies below 1 MHz, *Phys. Med. Biol.*, vol. 54 (2009), pp.4862-4878
[2] Nicolai Bart M., Egea J. A., Scheerlinck N., Bagna J. R., Datta A. K., Fuzzy finite element analysis of heat conduction problems with uncertain parameters, *Journal of Food Engineering*, vol 103 (2011), pp. 38-46
[3] Logg A., Mardal K.-A., Wells G. N. et al., Automated Solution of Differential Equations by the Finite Element Method, *Springer*, 2012
[4] Rao S., Sawyer J. P., Fuzzy finite element approach for analysis of imprecisely defined systems, *AIAA Journal*, Vol. 33, No. 12 (1995), pp. 2364-2370
[5] Cunha A. Jr., Nasser R., Sampaio R., Lopes H., Breitman K., Uncertainty quantification through the Monte Carlo method in a cloud computing setting, *Computer Physics Communications*, vol. 185 (2014), pp. 1355-1363
[6] Sawicki B., Uncertainty of numerical simulations in bioelectromagnetic problems, *Przeglad Elektrotechniczny*, vol. 91, no. 7, pp 49-51, 2015
[7] Hasgall P. A., Neufeld E., Gosselin M. C., Klingenböck A., Kuster N., IT'IS Database for thermal and electromagnetic parameters of biological tissues, *Version 2.5*, August 1st, 2014
[8] Schmidt C., Grant P., Lowery M., van Rienen U., Influence of Uncertainties in the Material Properties of Brain Tissue on the Probabilistic Volume Tissue Activated, *IEEE Transactions on Biomedical Engineering*, vol. 60, no. 5, May 2013
[9] Abebe A.J., Guinot V., Solomatine D.P., Fuzzy alpha-cut vs. Monte Carlo techniques in assessing uncertainty in model parameters, *Proc. 4-th International Conference on Hydroinformatics*, Iowa City, USA, July 2000
[10] Sawicki B., Krupa A., Study of biological tissues variability modeling, *Proc. of Computational Problems of Electrocal Engineering 2015*, Lviv, Ukraine, September 2015

.