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**Diploma thesis**  
**for a bachelor's degree**

In the specialty 163 « Biomedical engineering »  
(code and name)

Topic: “Methods of electroporation and electric welding -principles and directions of development”

Completed: 4th year student, group BM-73i  
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“     ”                      2021

**TASK**

**For student`s bachelor thesis**

Haro Valenzuela Domenica Anahi

(Full Name)

1. Topic      Methods of electroporation and electric welding – principles and directions of development

scientific supervisor of the  
dissertation

Assoc. prof. Lebedev A.V

(last name, first name, patronymic, academic degree, academic title)

approved by the order of the university №257 / 19-si from 11/18/2021

2. The deadline for students to submit a dissertation 05.12.2021

3. The object of study is electroporation and electric welding.

4. the subject of research is principles and directions of development

5. List of tasks to be developed

- to describe the principle of electroporation

- to analyze the methods of electroporation

-to analyze the areas of application

-to develop a virtual device in the LabView and SolidWorks environments

-to understand the use of electric welding

- to design a living tissue welding simulation

6. Approximate list of graphic material 24 tables, 27 figures

7. Approximate list of publications: the bachelor thesis protection

8. Final deadline 07.06.2021

### SCHEDULE

| №  | Name of stages of execution<br>diploma thesis                                 | Deadline for stages<br>diploma thesis | Note |
|----|-------------------------------------------------------------------------------|---------------------------------------|------|
| 1  | Analysis of scientific literature and<br>patent databases on a given topic    | 10.11.2020                            |      |
| 2  | Development of the content and<br>structure of bachelor thesis                | 26.02.2021                            |      |
| 3  | Investigation of structures of methods<br>and optimization of electroporation | 12.03.2021                            |      |
| 4  | Development of applications of electric<br>welding                            | 26.03.2021                            |      |
| 5  | Experimental testing of electroporation<br>in COMSOL environment.             | 24.04.2021                            |      |
| 6  | Built of electric welding in SolidWorks<br>environment.                       | 24.05.2021                            |      |
| 7  | Registration of bachelor thesis                                               | 01.06.2021                            |      |
| 8  | Getting a review and feedback                                                 | 04.06.2021                            |      |
| 9  | Passing norm control                                                          | 07.06.2021                            |      |
| 10 | The bachelor thesis protection                                                |                                       |      |

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## **ABSTRACT**

Theme of work: “ Methods of electroporation and electric welding - principles and directions of development”.

The volume of work is 59 pages, contains 35 figures, 4 tables. In general, 69 sources were processed.

In every sector, simulation is one of the most important phases in developing the final product. Based on the model, the parameters that will be needed to further create the layout of the instrument for laboratory testing will be selected.

The aim of this project is to confirm the efficacy of electroporation and electric welding on a computer model of tissue in SOLID WORKS and COMSOL and refine the parameters of the layout components in order to demonstrate the process in laboratory tests.

To achieve the goal were set the following objectives:

- To analyze knowledge and patent references in order to potentially support the use of the electroporation process and electric welding in various fields.
- To investigate literary sources and build a virtual device.
- To model physiological processes in tissues during electroporation on the model in COMSOL.
- To identify the appropriate parameters from the model and optimize them for further reproduction on the layout.
- To design a living tissue welding simulation on the model SolidWorks

The object of research is electroporation and electric welding.

The subject of research is biological tissue characteristics, physical models created in SOLID WORKS and COMSOL.

The project confirmed the efficacy of electroporation and electric welding.

Keywords: electroporation, welding, parameter optimization, electrodes, electric pulse, transfer, block diagram.

## РЕФЕРАТ

Тема роботи: “Методи електропорації та електрозварювання - принципи та напрямки розвитку”.

Обсяг дипломної роботи складає 59 сторінки, кількість ілюстрацій – 35, таблиць – 4, джерел за переліком посилань – 69.

У кожному секторі моделювання є однією з найважливіших фаз у розробці кінцевого продукту. На основі моделі будуть обрані параметри, які будуть потрібні для подальшого створення схеми приладу для лабораторних випробувань.

Метою цього проекту є підтвердження ефективності електропорації та електрозварювання на комп'ютерній моделі тканини в системі SOLID WORKS та COMSOL та уточнення параметрів компонування компонування для демонстрації процесу в лабораторних випробуваннях.

Для досягнення мети були поставлені наступні завдання:

- Проаналізувати знання та посилання на патенти, щоб потенційно підтримати використання процесу електропорації та електрозварювання в різних областях.
  - Дослідити літературні джерела та побудувати віртуальний пристрій.
  - Моделювати фізіологічні процеси в тканинах під час електропорації на моделі в COMSOL.
  - Визначити відповідні параметри з моделі та оптимізувати їх для подальшого відтворення на макеті.
  - Розробити моделювання зварювання живої тканини на моделі SolidWorks
- Об'єктом дослідження є електропорація та електрозварювання.

Предметом дослідження є характеристики біологічних тканин, фізичні моделі, створені в SOLID WORKS та COMSOL.

Проект підтвердив ефективність електропорації та електрозварювання.

Ключові слова: електропорація, зварювання, оптимізація параметрів, електроди, електричний імпульс, передача, блок-схема.

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## LIST OF SYMBOLS, UNITS, ABBREVIATIONS AND TERMS

|     |   |                      |
|-----|---|----------------------|
| DC  | – | Direct current       |
| GET | – | Gene electrotransfer |
| ECT | – | Electrochemotherapy  |
| ENT | – | Otorhinolaryngology  |

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## INTRODUCTION

Nowadays, electroporation and welding are a new efficient method that are used in many areas because it is characterized by speed, efficiency, convenience and low cost. This directly applies to surgery, where the above qualities are the key to successful implementation of the planned goals.

This paper work presents the first step towards the development of a new therapeutic approach that can expand the use of electroporation and welding methods. Despite the high invasive therapy, in contrast to the trend towards minimally invasive approaches, this technique may offer a new opportunity for current incurable cases where there are several tumor nodules.

Modeling is one of the main stages in the creation of the final product in any industry. By designing the processes that are the basis for electroporation, it will be possible to assess the effectiveness of drugs directly to the tumor, without introducing these drugs through the body. Based on the model, the parameters necessary for further creation of the model of the device for laboratory research will be selected.

The aim of the work is to confirm the efficiency of electroporation on a computer model of tumor tissue in COMSOL environment and the design of a welding tweezers in SolidWorks, creating a simulation of living tissue, thus testing its use and effectiveness.

To achieve this goal, it is necessary to solve the following tasks:

1. Review the literature on the topic of the work.
2. Formulate medical and technical requirements.
3. Develop a structural and electrical schematic diagram of the device.
4. Design a prototype.
5. Compare test and simulation results.

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# CHAPTER 1

## FEATURES OF ELECTROPORATION

### 1.1 General description of electroporation

Electroporation (EP), also known as electropermeabilization, is a physical method of introducing polar molecules such as DNA into eukaryotic cells through the cell membrane by exposing cells to electric pulses. Neumann described the technique in 1982, and it is based on the earlier observation that biomembranes can be made transiently permeable by applying short electric impulses. [1].

Electroporation is based on a concise procedure. In a conductive solution, host cells and preferred molecules are suspended, and an electrical circuit is formed around the combination. The cell suspension is discharged with an electrical pulse of optimized voltage and period of a few microseconds to a millisecond. This disrupts the membrane's phospholipid bilayer, resulting in the formation of temporary pores. Similar to electrophoresis, the electrical potential across the cell membrane increases simultaneously, allowing charged molecules such as DNA to be propelled into the membrane through the pores [2].

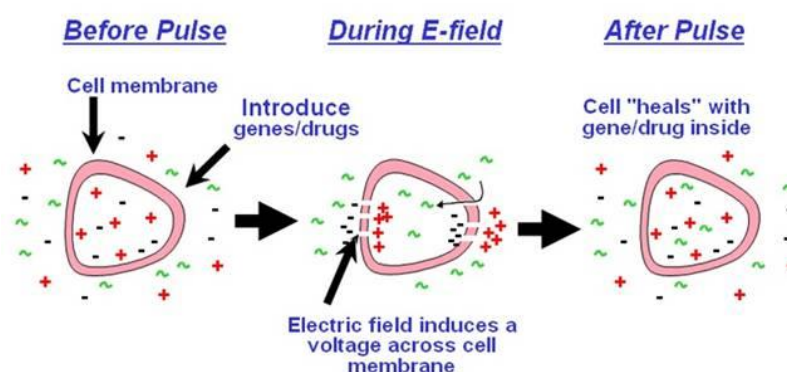


Fig.1.1 – How electroporation Works

The biggest advantage of electroporation is that it can be used for both transient and stable transfections of all cell types. As well, because electroporation is simple and quick, it can transfect a considerable number of cells in a short period of time once the optimal electroporation conditions are established. The main disadvantage of electroporation is that it causes significant cell death due to high voltage pulses and only partially successful membrane repair, necessitating the use of more cells than chemical transfection [2].

Depending on the number of pulses, their magnitude and duration, the permeabilization of the membrane induced by electroporation can be temporary or permanent.

Reversible electroporation forms the basis of electrogenic therapy, which facilitates the introduction of genes into cells by electrical pulses. In contrast, permanent electroporation forms the basis of the new heatless tissue ablation method, the so-called non-thermal irreversible electroporation, which is used to destroy solid tumors. While reversible electroporation does not compromise cell viability, permanent electroporation alters the homeostasis of the cell, thus inducing its death [3].

### 1.1.1 General optimization guide for Electroporation

Controlled direct current (DC) electrical pulses are applied to living cells and tissues for a short period of time during electroporation. The pulse produces transmembrane potential, which generates the reversible breakdown of the cellular membrane. The cellular uptake of the molecules continues during this process until the pores close, which can take milliseconds to minutes. Several factors go into optimizing the electroporation process; selecting the best wave form, determining field strength, and modifying pulse length are just a few examples. Cell diameter, DNA

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concentrations, temperature, and electroporation buffer are other criteria to consider when optimizing [4].

### Wave Forms

**Square wave pulse:** The voltage distributed, the pulse duration, the quantity of pulses, and the pulse interval length are all characteristics of this wave pulse. All of these parameters can be set using many conventional electroporators. By using a square wave system in in vivo and ex vivo tissues, embryos, cell junctions and plant protoplast applications, better results are obtained compared to an exponential decay wave system [5].

**Exponential decay wave pulse:** By allowing a capacitor to completely discharge, exponential decay waves generate an electrical pulse. When a pulse is discharged into a sample, the voltage fastly increases to the peak voltage array and then tends to fall over time. The impactful exponential decay wave pulse is commonly used to transform yeast, gram-negative and gram-positive bacteria, insect cells, plant tissues, and some mammalian cells [5].

**Time Constant:** A constant pulse is applied for a set period of time at a set voltage.

### Field Strength

The field strength is defined as kV/cm and is calculated as the voltage delivered across an electrode gap. Field strength is important for exceeding the electrical potential of the cell membrane and getting temporary reversible permeation or "pore formation" in the cell membrane to result. Cuvette gap size, cell diameter and temperature are three factors considered for optimizing field strength [4].

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Table 1.1 Field strength ranges according with the cell type

| Cell Types     | Field Strength Ranges |
|----------------|-----------------------|
| Bacteria/Yeast | 3-24 kV/cm            |
| Mammalian      | 0.25-3 kV/cm          |
| Plant          | 3-12 kV/cm            |

- Cuvette Gap Size

When optimizing an electroporation experiment, the distance between electrodes, or "gap size," is critical. Voltage divided by gap size is used to measure field strength.

- Cell Diameter

Smaller cell dimensions generally demand higher voltages, whereas larger cell diameters probably require lower voltages for successful cell membrane permeation.

- Temperature

Over several factors, the temperature at which cells are maintained during electroporation affects electroporation efficiency. The vast majority of mammalian cell lines can be electroporated at room temperature. Samples that are generated at high voltages or involved to multiple pulses with long pulse durations can heats. These conditions promote cell death and reduce transfection efficiency. Lowering the temperature of the sample can reduce the heating effects on cell viability and efficiency. Because electroporation induces the transient formation of pores, maintaining the cells at a lower temperature after the pulse may allow the pores to remain open longer, allowing for more exogenous molecule uptake. To effectively penetrate the cell membrane during electroporation, the standard pulse voltage used for cells at room temperature should be risen at 4 ° C [4].

### Pulse Length

The pulse length is the amount of time that the sample is exposed to the pulse. This is defined in microseconds to milliseconds. This parameter's adjustment is dependent on whether the pulse generator is using a square wave or an exponential decay wave. In a square wave system, the pulse length can be directly entered. In an exponential decay wave system, the pulse length is referred to as the "time constant," and it is defined as the rate at which the pulsed energy (e) or voltage decays to 1/3 of the original set voltage. Time constant calculation

$$T = RC \quad (1.1)$$

where T denotes time, R denotes resistance, and C denotes capacitance

The pulse length, in conjunction with the field strength, indirectly increases pore formation and thus target molecule uptake [4].

Table 1.2 shows the parameters of the pulses for the electroporation procedure in different areas [3].

Table 1.2 Pulse parameters for different applications for electroporation

| Application                 | Amplitude   | Duration    |
|-----------------------------|-------------|-------------|
| Electrochemotherapy         | ~ 1 kV      | 1 $\mu$ s   |
| Electrical installation     | <1 kV       | 1 ms- 1 s   |
| Transdermal drug delivery   | <1 kV       | 1 ms        |
| Electrofusion               | ~ 1 kV      | 1 $\mu$ s   |
| Pasteurization              | >> 1 kV     | 1 $\mu$ s   |
| Tissue ablation             | > 1 kV      | 1 ms - 1 ms |
| Unicellular electroporation | > 1 mV      | 1 $\mu$ s   |
| Electroporation research    | 1 mV - 1 kV | 1 ns - 1 s  |
| Gene electrotherapy         | ~ 1 kV      | 1 ms - 1 ms |

According to yesthem are given in Table 1.2, it can be seen that on average for the electroporation procedure it is necessary to apply a pulse with an amplitude of 1 kV, duration 1  $\mu$ s.

## Electroporation Buffer

Depending on the cell type, different buffers are used for electroporation. Many systems employ highly conductive buffers which including PBS (30 ohms) and HBSS (30 ohms) or standard culture media that may involve serum. Hypoosmolar buffers, in which cells absorb water shortly before a pulse, are also recommended. This swelling of the cells lowers the optimum permeation voltage, making the membrane more permeable for certain cells but potentially harmful for others. To reduce the risk of arcing, the cells must be properly prepared and washed to remove excess salt ions [4].

### 1.1.2 Procedures of electroporation and electrofusion

The equipment required for electroporating cells is relatively simple, mainly consisting of an electrical pulse generator and a cell chamber (Fig.1.2). The major function of the pulse generator is to provide a high-voltage pulse with a large current output [6].

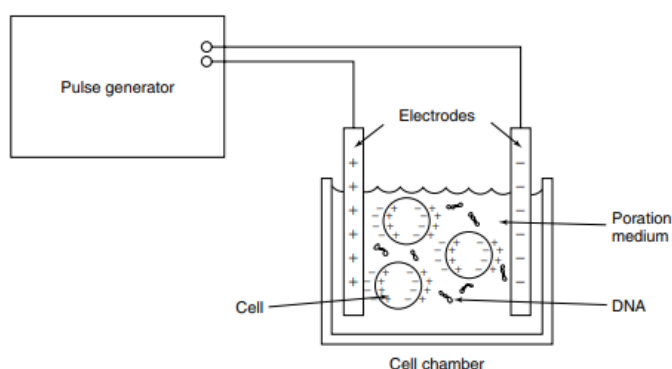


Fig.1.2 - A schematic diagram showing the basic device required for electroporation

Since the cell sample may have a very low resistance, this is needed. The sample chamber houses the cell sample as well as a pair of electrodes for applying the electric field. The electrodes are usually two parallel metal plates made of platinum, stainless steel, or aluminum separated by 0.1 to 0.4 cm; the procedure of electroporation is also very simple to introduce some substance into a cultured cell line.

- When the cells are growing in the mid-log phase, harvest them using the standard cell-detach treatment.
- Resuspend the cells in poration medium (PM) after washing them with it at least once. PM is essentially an isotonic buffer in which nonelectrolytes such as sucrose or mannitol substitute the majority of the salt.
- Load the cell sample into the chamber.
- Apply the electrical pulse to the sample.
- Transfer the cells from the sample chamber into the culture plate and culture them in their normal conditions.
- After the cells have been cultured for a long enough period of time, they can be tested for transfected gene expression or subjected to a selection
- process.

Electrofusion procedures are similar to electroporation procedures, with the exception that cells must be in contact with their fusion partners before the strong electric field is applied. Cells may be brought together using a variety of methods, including mechanical, chemical, and electrical means, depending on the goal of the fusion. The electrofusion buffer, known as fusion medium (FM), is similar to the PM used in electroporation, with the exception that FM must have very little salt [6].

## 1.2 Electroporation applications

### 1.2.1 Application of electroporation in mesotherapy

Electroporation is considered a non-invasive alternative to conventional Mesotherapy, since it has the advantage of not using needles (painless procedure) and allows the introduction of drugs in a localized way. For this reason, it is called Virtual Mesotherapy [7].

By emitting an alternating current of low frequency (10-60 Hz), the electroporation equipment opens very fine channels through the lipids of the intercellular space, and due to the peculiarity that its current permanently changes

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direction, the desired Continuous rearrangement that generates new pores and channels while the treatment is carried out. By means of electroporation, it is possible to introduce micro and macromolecules, even those of more than 800,000 Dalton, as in the case of hyaluronic, or of more than 500,000 Dalton, as with collagen [7].

The passage of substances through the skin requires crossing the stratum corneum and the dermis to reach the dermal vascular plexus or dermal papilla. This transmission is carried out through the cells themselves through pores formed in the cell membranes or through the intercellular space, crossing the lipids that cover them [7].

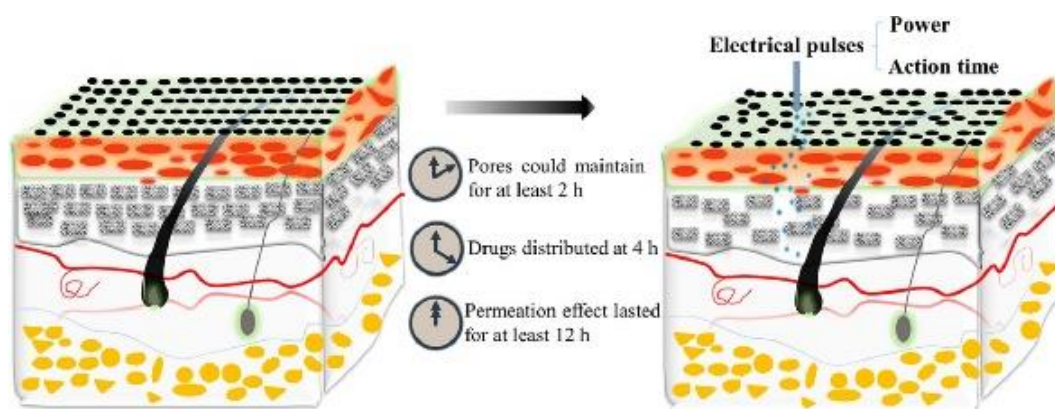


Fig.1.3 - Electroporation process in mesotherapy

The electroporator is an emitter of currents that generate electromagnetic waves of modulated hectometric frequencies. When undergoing the action of these currents, the cell membranes alter their physicochemical properties, creating difference in cellular potential, and modify the orientation of their transmembrane proteins, creating channels. It is an athermic process (without an increase in temperature) at the level of the cell membrane. The lipids of the cell membrane bilayer undergo a process of electrotation, causing the opening of the pore, the cell is thus subjected to a biological stress, which increases its permeability facilitating the penetration of substances by passive diffusion. Subsequently, the cell recovers its integrity and potential, that is, the cell normalizes [7].

### 1.2.2 Use of electroporation in eletrochemotherapy

Electroporation is a technique that uses electric pulses to increase cell membrane permeability. In human and veterinary medicine, electrochemotherapy (ECT), the most well-known application of electroporation, is a highly effective local treatment for tumors of any histology. ECT is a cancer treatment that involves using an electric field to raise cell membrane permeability along with the application of cisplatin, bleomycin or calcium [8].

In a standard ECT session, the patient arrives and the anesthetic procedure is performed; intravenous or intratumoral Bleomycin (BLM) is administered, followed by the application of electric pulses locally delivered to the target tumor via suitable sets of electrodes. Charges on the cell membrane begin to move when external electric charges are applied to the cells. The transmembrane voltage gradually rises as a result of this. An adequate and strong electric field is established through the cell membrane, where transmembrane voltage goes over the limit of a particular voltage; this leads to the establishment of a passage (pore) for water, charged and larger molecules to go across the cell membrane, they are created rapidly and disappear within a few seconds to several minutes after exposure to the electric field. BLM is the preferred drug, but also cisplatin (CDDP) can be used.

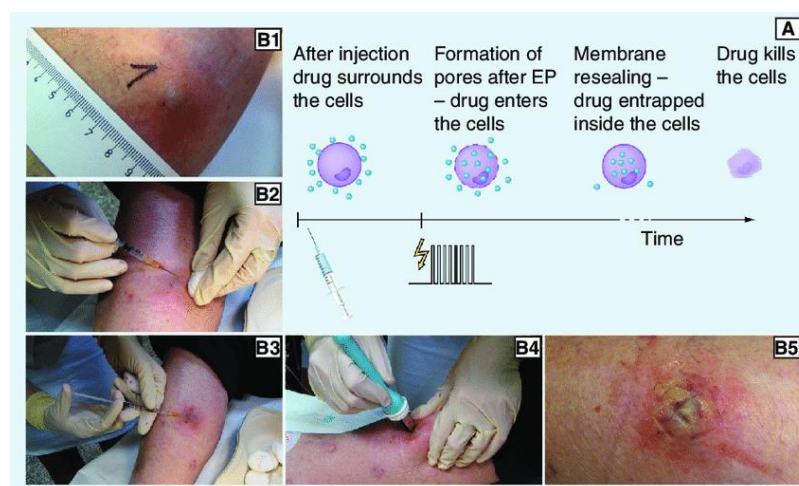


Fig.1.4 - Basic steps in electrochemotherapy treatment: B1) tumor before therapy; B2) local anesthesia; B3) drug injection; B4) application of electric pulses; B5) tumor after therapy

All biomedical applications of cell electroporation use direct currents with short and intense pulses. Amplitude of the pulses depends on the tissues and on the shape and position of the electrodes, but, in vivo, in the case of the tumors, the amplitude of the electric pulses has to be high enough to establish an electrical field of 400 V/cm in the area of tumor (8 pulses with duration of 100 microseconds). The duration of pulses is usually one hundred microseconds. In early experiments, pulses were delivered with period of 1 second (i.e. at a repetition frequency of 1 Hz); today, pulses are delivered in a much shorter time period, at a repetition frequency of 5000 Hz, resulting in a much less discomfort for the patient and in the shorter duration of treatment [8].

Studies showed that the main focus of the chemotherapeutic agents is on the actively dividing cancer cells and less on the nondividing population of normal cells in the surrounding tissue. When the tumor tissue is exposed to the electrical pulses, the tumor blood flow will reduce up to 80% and will come back to normal flow within 24 hours. In this way, the injected drug can stay in the tumor tissue for several hours which gives it more time to act [9].

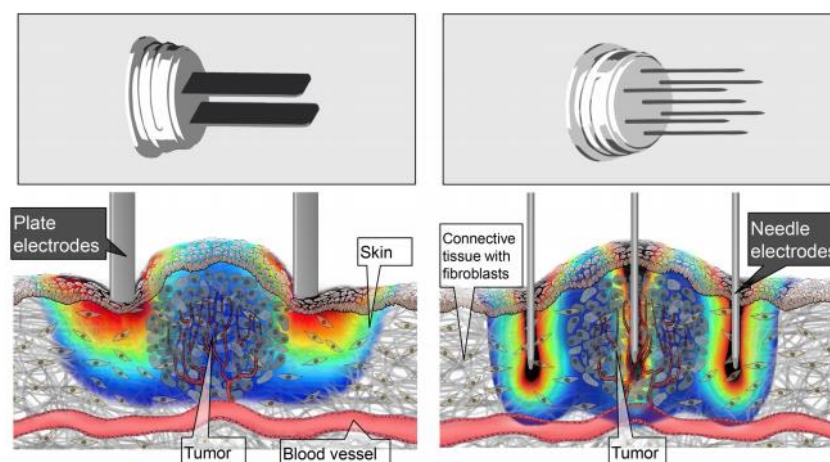


Fig.1.5 - Electric field distribution in and around tumor tissue throughout electric pulse application for plate (left) and hexagonal needle electrodes; cross section through the electrodes' mid-plane (right) [9].

### 1.2.3 Use of electroporation for gene electrotansfer

GET is a gene transfection delivery mechanism. It entails injecting plasmid DNA into the target tissue, followed by delivering electric pulses [8]. In contrast to ECT, pulsing parameters for GET include a wide range of options. One of the most commonly used protocols employs a combination of short, intense pulses followed by long, mild pulses.

In comparison to ECT, the pulsing parameters for GET provide a broad range of options. One of the most widely used protocols combines fast and intense pulses with long and gentle pulses. The first causes a brief permeabilization of the cell membrane, while the second causes DNA to move electrophoretically towards the electroporated cells. GET is a non-viral gene therapy technique that is one of the most successful. It has been shown to be effective in a variety of animal models using different tissue-specific protocols. GET can be used to reestablish normal functions in cells with faulty genes; it can be used to induce the development of immunogenic proteins in cancer cells. GET has advantages over viral-based gene therapy approaches in that large transgenes can be transferred into target cells, gene expression is transitory, and the risk of insertional mutations is low. These properties are useful for vaccination or immunostimulatory strategies based on the administration of genes encoding various cytokines. [8].

DNA vaccination protocols based on GET are typically applied to the skin or muscles. These sites contain antigen-presenting cells, such as dendritic cells, which are primarily involved in immune response activation. In contrast, giving GET to cancer cells results in transient expression because these cells divide quickly and gain the plasmid through dilution over cell divisions. Even so, this feature of tumor cell transfection is especially useful for the short-term production of immunostimulatory molecules such as anticancer cytokines, where the goal is to induce robust cell-mediated immunity to attack and destroy cancer cells bearing a specific antigen [8].

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However, choosing the correct plasmid isn't the only way to improve GET. Many efforts are being made to improve GET protocols through in vitro and in vivo studies in order to reduce tissue injury and increase gene transfection performance. Furthermore, the use of hyaluronidase, an enzyme capable of degrading hyaluronic acid, a part of the extracellular matrix, is a promising strategy for the DNA uptake and expression. This helps the plasmid to approach the cell membrane more closely. As a result, DNA is more readily available for internalization after the pulse has been delivered.

Table 1.3 Main characteristics of Electrochemotherapy (ECT) and Gene Electrotransfer (GET)

|                                    | ECT                                           | GET                            |
|------------------------------------|-----------------------------------------------|--------------------------------|
| Spares non-dividing cells          | Yes                                           | No                             |
| Drugs used                         | Bleomycin/cisplatin                           | Plasmids                       |
| Electrical parameters              | $8 \times 1000 \text{ V/cm } 100 \mu\text{s}$ | Varies                         |
| Thermal effect                     | No                                            | No                             |
| Regular use in human medicine      | Yes                                           | No                             |
| Regular use in veterinary medicine | Yes                                           | No                             |
| Uses                               | cancer                                        | cancer, vaccines, gene therapy |

## Conclusions to Chapter 1

Electroporation has become a field of interest and development due to its efficacy in the treatment of some diseases. There are key factors for the electroporation process to be successful, allowing you to choose the correct electrode and voltage, it is characterized in which areas the phenomenon of electroporation is applied. There has been a significant amount of research into how cell electroporation affects tissue and, as a result, drug and gene electrotransfer. Despite the fact that the exact mechanisms involved in cell and tissue electroporation at the molecular level are not completely known, a collection of electrical parameters can be determined, resulting in a safe and efficient technique for in vivo applications that could be converted into clinical use.

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## CHAPTER 2

### ELECTROPORATION SIMULATION

#### 2.1 Modeling methods

The model-based treatment planning procedure consists of: imaging, image segmentation, 3d reconstruction of the patient's anatomy, insertion of electrodes and calculation of the electric field and / or its optimization. At the stage of image segmentation, the target tissue (tumor) and the surrounding tissue must be correctly identified, because they differ significantly in their dielectric properties. Electrodes are often inserted around the tumor, which also has the added benefit of treating possible microscopic tumor growths that cannot be detected by imaging [10,11].

The electrodes position in relation to the structures of interest is critical for obtaining good or truly detrimental effects. It is more necessary in some tissues than others, but in general, precise positioning is needed.

##### 2.1.1 Numerical simulation using plate electrodes

Numerical simulations were performed using a geometric model (Fig. 2.1), which is a cylindrical part of the liver (radius 15 mm and height 30 mm), in which three tumor nodes are represented as a sphere (radius 3 mm) [12]. High voltage (0 V to 3000 V) was applied between parallel plates located in the upper and lower part of the liver.

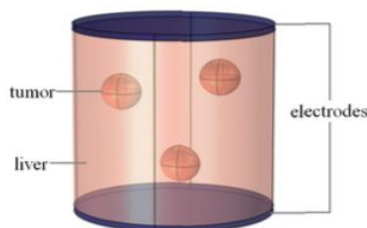


Fig. 2.1 - Geometric model used in the numerical study, containing: tumor - tumor; liver - liver; electrodes - electrodes [12]

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The recorded healthy conductivity of the liver to the study is from 0.03 C/m to 0.12 C/m [13]. These values can be used to calculate the distribution of the electric field within the model when a certain electric potential is applied between the two electrodes.

Changes in electrical conductivity were monitored in real time by installing two electrodes: 2 printed circuit boards with round gold electrodes (radius 10 mm), which are mounted on the pliers. The following parameters of electrical conductivity were used to build the theoretical model: electrodes -  $7.4 \cdot 10^6$  C / m; liver - 0.12; tumor - 0.27; liver after studies (in vivo) - 0.3. Resistance was measured using a sinusoid of amplitude 1 V at an excitation signal of 5 kHz [13].

### 2.1.2 Numerical simulation using needle electrodes

One pair of electrodes was used - modeled as cylinders with a diameter of 1.2 mm and a length of 4 cm - inserted at a distance of 1, 2 and 3 mm from the tumor surface [14]. The installation of the model is shown in Figure 2.2

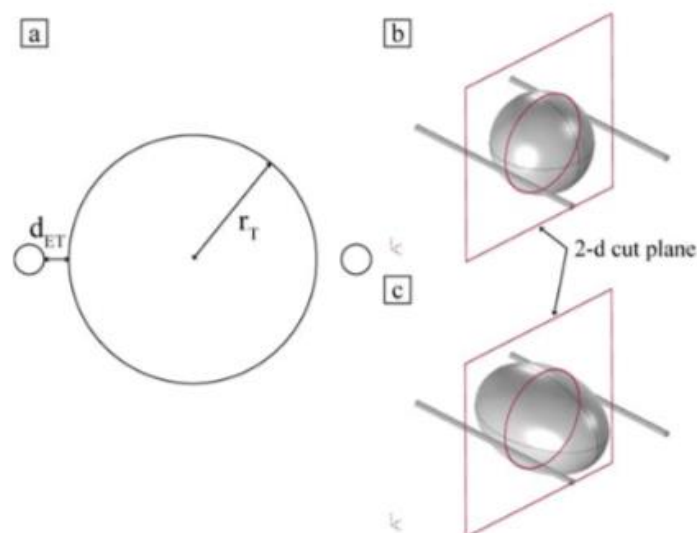


Fig.2.2 - Model installation:

a) 2d section with tumor radius  $r_T$  and distance from the electrode to the tumor  $d_{ET}$ ; b) spherical 3d model; c) elongated spheroidal model [14].

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The peculiarities of the study were that the conductivity of the surrounding tissue -  $\sigma_S$  and the conductivity of tumor tissue -  $\sigma_T$  were changed [18]. The lower threshold for increasing conductivity was 400 V / cm for tumor tissue and 300 V / cm for surrounding tissue. Ranges of values of conductivity and radii of a tumor are given in Table 2.1 [15].

Table 2.1 - Ranges of model parameters.

| Parameters                                                                 | The minimum value | Maximum value |
|----------------------------------------------------------------------------|-------------------|---------------|
| Tumor radius $r_T$                                                         | 4 mm              | 10 mm         |
| Tumor conduction $\sigma_T$                                                | 0.08 S / m        | 0.5 S / m     |
| Conductivity of surrounding tissues $\sigma_S$                             | 0.02 S / m        | 0.1 S / m     |
| The distance between the tumor and the electrode (from surface to surface) | 1 mm              | 3 mm          |

The problem was solved by optimizing the field coverage by using the Comsol optimization module on the 2nd model.

## 2.2 Analysis of irreversible electroporation

Irreversible electroporation is described by the death of the affected cell as a result of a constant disruption of the cell membrane or a substantial loss of intracellular components. Therefore, to study this phenomenon, the relationship between the time component (given only one pulse with a duration of 1  $\mu$ s) and the propagation of the electric field (V / m) was derived.

From the obtained data it can be seen that during the electroporation procedure with a given pulse duration of 1  $\mu$ s and constant frequency response (1 kV, 2.5 kHz) - the threshold value of the electric field reaches the set critical for this tissue (for the

liver 500 V / cm) [16]. Therefore, it can be argued that there is an irreversible process of cell destruction.

Similar to the case when irreversible electroporation was studied: according to Figure 2.10 it can be seen that temperature destruction does not occur. Heating of the fabric and surrounding elements does not exceed 36.6 0C.

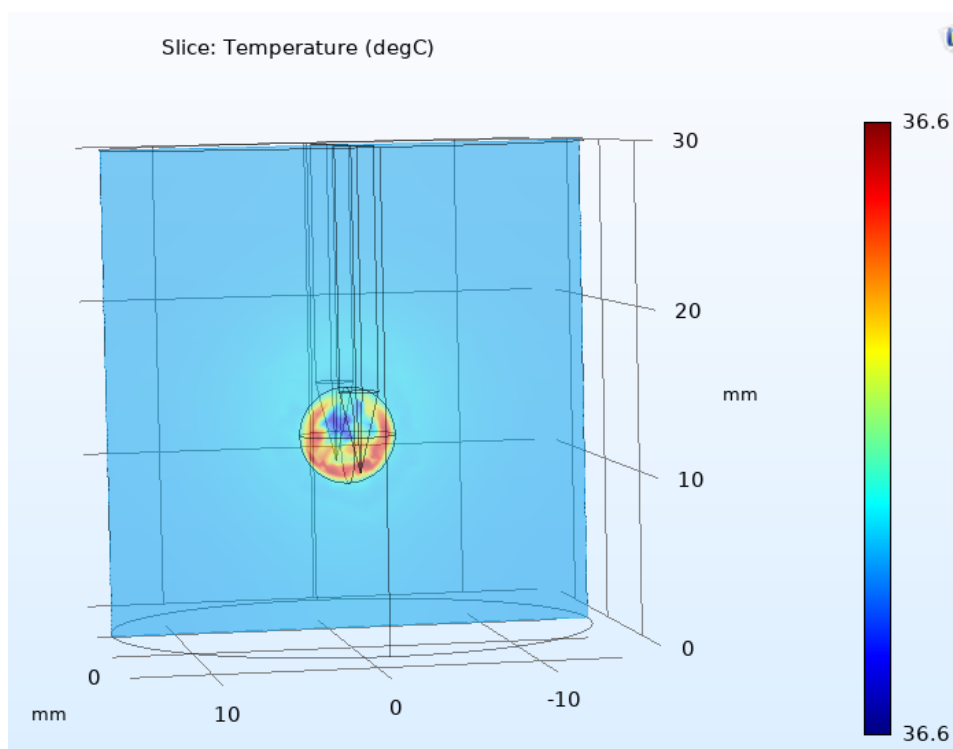


Fig.2.3 - Temperature distribution at 1 kV for 1  $\mu$ s.

The isothermal circuit method was used to demonstrate the destruction of tumor tissue and surrounding tissues. We establish the critical value of the electric field that can withstand liver tissue (500 V / cm) and conduct research.

After analyzing the results, it can be noted that to achieve the effect of irreversible electroporation (complete / partial death of the cell or its components) is sufficient that the amplitude of the pulse was 1 kV, the pulse does not need to be divided into a set of shorter duration (as in the case of reversible electroporation), and submit it once with a duration of 1  $\mu$ s.

## Conclusions to Chapter 2

A model for the study of electroporation environment is built and analyzed. Two cases are considered: the use of reversible and irreversible electroporation.

During the research, it was discovered that for an effective reversible electroporation there must be a relationship between the variable time portion and the constant frequency response of the pulse.

The following indicators were determined from the results: the total duration of electrical pulses (with a frequency of 2.5 kHz and an amplitude of 3 kV) is not more than 1  $\mu$ s. When the electric field reaches its highest permissible values between 0 and 1  $\mu$ s, the permeability of the tumor membrane correspondingly increases. With regard to irreversible electroporation, it can be noted that for a successful procedure it is sufficient that the amplitude of the applied pulse was 1 kV, and the pulse does not need to be divided into a set of shorter duration, as in reversible electroporation.

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## CHAPTER 3

### FEATURES OF WELDING

#### 3.1 Electric welding application of living tissue in surgery

Electric welding used in surgery for cutting, hemostasis and tissue joining. The tissue is compressed by electrodes and a high-frequency current is passed through it. Changes occur under the influence of temperature and electric field, which lead to the formation of a weld joint. In the place of welding, there is a close connection of bundles of elastic, collagen and smooth muscle fibers. The main mechanisms for the formation of a compound are fusion of muscle and collagen fibers, gluing with "DNA-protein-based bioadhesives" [17-20]. There are no such phenomena in conventional electrosurgery. At the E.O. Paton Electric Welding Institute of the National Academy of Sciences of Ukraine, this method began to be studied jointly with medical organizations since 1992. Patents from the USA, Russia and other countries were obtained [21-24]. The use of welding is indicated in the course of its introduction in the field of surgery.

#### 3.2 Welding applications

##### Urology operations

The use of welding in urology operations promising for: kidney resection, pyelolithotomy followed by plastic surgery of the renal pelvis by the method of electric welding, ureterolithotomy followed by restoration of the ureter integrity by applying a welded seam, imposition uretero-ureteroanastomosis end-to-end type, electric welding of longitudinal sections of the bladder wall, plastic surgery of the bladder with an ileal segment, adenomectomy [17, 56].

##### Organ transplant

Organ transplant welding reduces the likelihood of bleeding and lymphorrhea, less tissue injury better graft function is achieved [57].

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### Vascular surgery

In vascular surgery prevention of pulmonary embolism is carried out by closing the veins with a floating thrombus [17]. During operations in the mediastinum using welding, the likelihood of damage to vital organs is reduced. Welding bipolar probes are used for hemostasis after vein removal in the surgical treatment of varicose veins. Saline cooling facilitates instrument movement and reduces tissue damage.

### Hernias treatment

Welding the edges of the peritoneum over the mesh implant is a simple, reliable and safe method in which there is no need to additionally use suture and fixation material. Absent suppuration of the postoperative wound, smoke and unpleasant odor [17, 42, 58].

Laparoscopic operations are performed on a "dry" operating field. At the same time, the duration of the operation is reduced, its technique is greatly simplified [59].

### Veterinary

In veterinary medicine welding is used in general surgery, traumatology, for castration and sterilization of animals, reducing the operation time by 3-4 times, significantly reducing blood loss, pain syndrome.



Fig.3.1- Preparing for horse surgery

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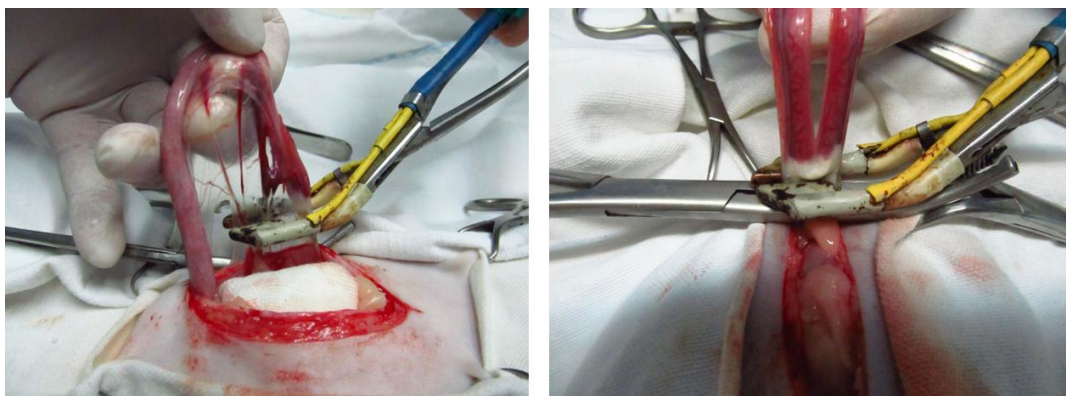


Fig.3.2- Sterilization of the dog by welding.

### Fallopian tubes restoration

Welding is used for restoration of the fallopian tubes patency in case of infertility or ectopic pregnancy. The operation contributes to the preservation of the patient's fertility and can be performed both openly and laparoscopically. Welding is effectively used for dissection of adhesions, removal of fibroids, artificial termination of pregnancy, open and vaginal hysterectomy [17]. Welding reduces blood loss by 70%, the probability of postoperative complications by 80%



Fig.3.3- Surgeon Anisimova L.P. with an assistant and surgical sister performs surgery to remove tumors and extirpation of the uterus [20].



Fig.3.4- The uterine ligaments are a welding clamp.

### 3.3 Welding application in hemostasis and tissue cutting

When welding vessels of small diameter, specialized tweezers are used, for larger ones - clamps (Fig.3.5).

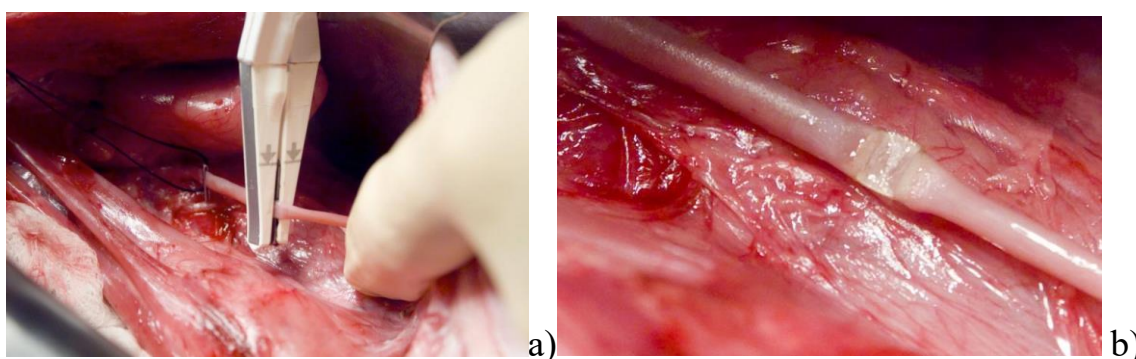


Fig.3.5 - a) Welding of an artery b) welded vessel.



Fig.3.6 - a) Appearance of a sealed artery of a pig with a diameter of 7 mm; b) Artery incision: 1- adventitia; 2 - media; 3 - intima. [25, 26, 27].

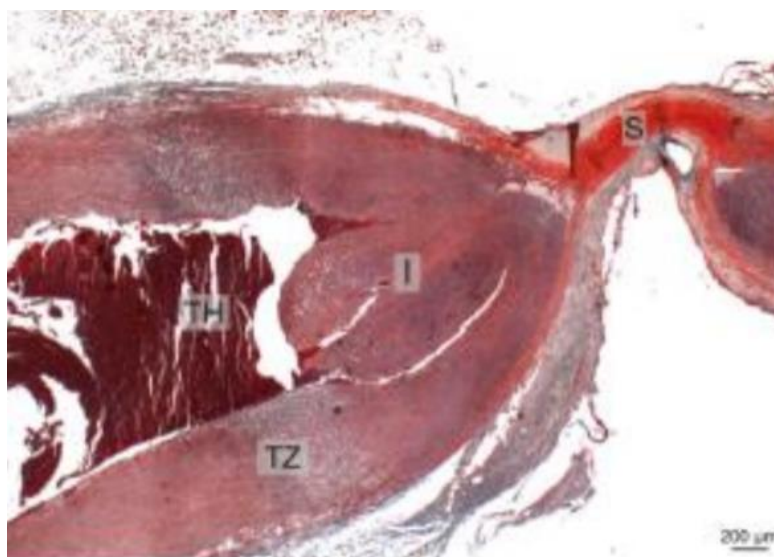


Fig.3.7 - Histology of the welded artery: S - suture; I - media; TH, thrombus; TZ - transition zone

With an increase in the frequency of the welding voltage, the effect of current displacement to the outer surface of the electrode begins to affect [28]. This phenomenon must be considered when developing new effective electrosurgical instruments.

In USA, an independent examination was carried out for welding arteries of pigs weighing 70 kg. Arteries with a diameter of 2 to 8 mm and aorta were welded with a diameter of 12 mm. The average bond strength is seven times normal systolic pressure and is 940 +/- 84 mm.

Cutting the tissue with simultaneous brewing of vessels can be done in two ways. In the first case, with clamps or tweezers for welding, an array of tissue is first boiled, and then cut. In the second case, specialized tweezers and clamps are used, which simultaneously cut and make hemostasis [29].

Hemostasis is carried out due to the formation in the zone of the welding joint of sticky-like biomass, vasospasm and the presence of thrombotic masses.

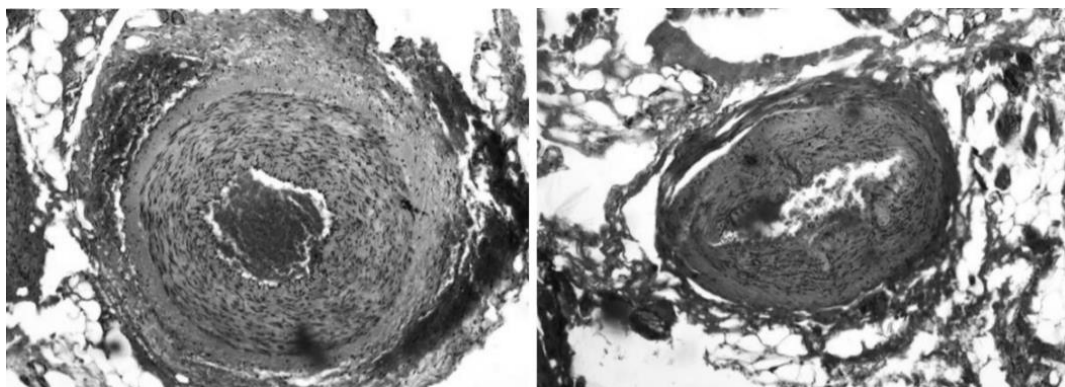


Fig.3.8 - Changes in muscle type arteries when using IES LMT; a) - the membranes are preserved, a mixed thrombus in the lumen; b) - in the muscular membrane coagulation of protein masses. Staining with hematoxylin and eosin. Magnification  $\times 200$  [8]. [3-4].

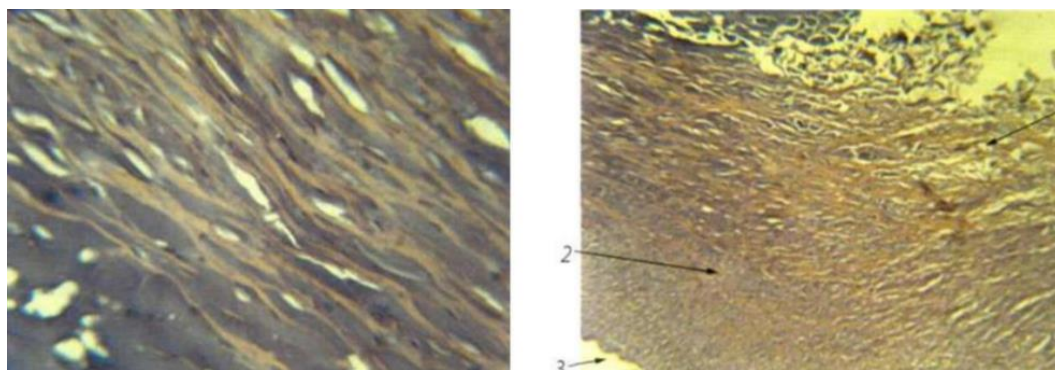


Fig.3.9 - Perifocal zone of the welded artery a) - collagen fibers and smooth muscle cells ( $\times 400$ ); b) 1 - adventitia, 2 - media, 3 - intima ( $\times 100$ ) [1].

There is no necrosis in the section, the pink muscles remain viable [17]. Cutting tools have narrower electrodes [30].

For hemostasis of parenchymal organs and stopping capillary bleeding, instruments with two fixed electrodes, separated by an insulating pad, are used. A current flow through the tissue between the electrodes, coagulating blood and brewing vessels [31].

With a decrease in the thickness of the pad, the temperature of the tissue increases, which facilitates its cutting with simultaneous hemostasis [32].

Bipolar instruments with flexible wires are used in endoscopic operations to stop gastrointestinal bleeding.

### 3.4 Welding application in oncological operations

Tumors are intensively supplied with blood. It is necessary to close the vessels without causing the spread of tumor cells. Due to rapid hemostasis, welding can significantly reduce the operation time, reduce blood loss, ensure non-septicity and sealing of the junction. The absence of suture material eliminates complications associated with the body's reaction to a foreign component [17, 19, 33].

Patients are admitted for surgery after courses of radiation and chemotherapy. This weakens the immune system and the body's ability to heal wounds. The use of thread sutures to connect the edges of wounds leads to purulent and inflammatory processes and the absence of tissue fusion. Welding immediately connects tissues, which has a beneficial effect on the postoperative period. When removing brain tumors, welding is used for hemostasis and implants that close defects in the dura mater.

### 3.5 Welding application in laparoscopic operations

For laparoscopic operations the tissues connection and the overlap of blood vessels and ducts use clips or brackets, which increases the cost of the operation, leaves foreign components in the body. Staple puncture sites do not provide a complete seal. The clips can slide off the blocked vessels and ducts, causing complications.

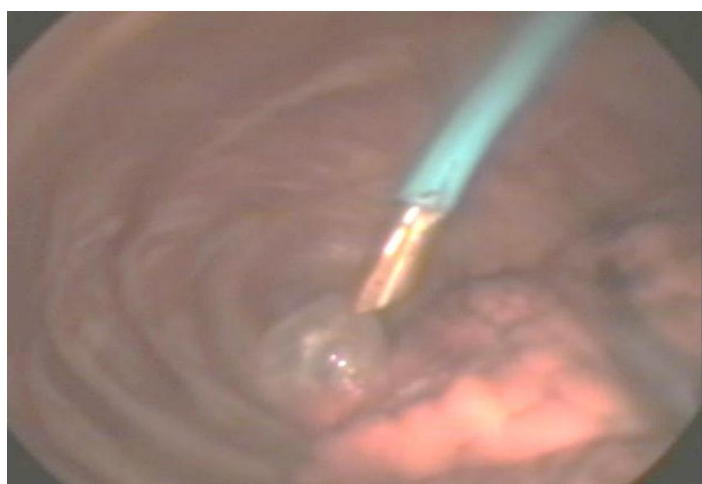


Fig.3.10 - Welding a bubble on the surface of the lung with a split electrode

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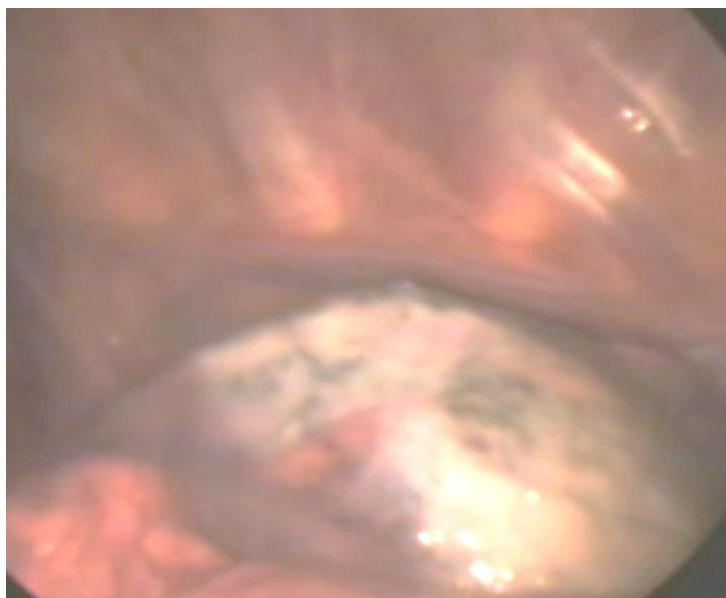


Fig.3.11 - Surface of the lung after welding

Welding ensures the tightness of the joint, the heat does not spread to the surrounding tissues. In the seam there are numerous tissue components, including intact cells, which creates the prerequisites for subsequent recovery [34].

Welding tools are used not only for welding, but also for mobilizing and manipulating organs, which is convenient for surgeon, especially when SILS operations (single incision laparoscopic surgery), performed through one puncture in the navel area [35].

When performing a cholecystectomy, a welding tool is used to isolate vessels and ducts with subsequent welding. Welding in the treatment of acute appendicitis eliminates the need for drainage, creates an antimicrobial effect at the suture site, hermetically closes the appendix lumen, reduces the likelihood of postoperative complications and the time spent in the hospital [17, 36].

A bipolar laparoscopic instrument is used to seal air bubbles (bulls) on the surface of the lung with a diameter of about 1 cm in the treatment of spontaneous pneumothorax. When welding, the bulla coagulates, shrinks, decreases in size and is firmly welded to the lung tissue. This allows you to avoid complex surgery for resection of the affected part of the lung [17, 31, 37].

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Laparoscopic welding is used for splenectomy, removal of tumors, adrenal glands, cysts, marginal resection of the liver and lung. Welding will be reliable and efficient if the recommendations are followed [38].

When welding, the specific pressure of the electrodes on the tissue should be 1.5-2 N / mm<sup>2</sup>. It is necessary to apply special measures to transfer increased forces to the electrodes [39, 40].

When cutting the parenchymal organs with a scalpel there is a greater loss of blood, sewing with threads or staples is inconvenient due to the low resistance of the tissue and the lack of tension. Resection of an organ with simultaneous hemostasis by means of welding gives a tight seam with a minimal heat-affected zone, significant savings in operating and suture materials, a decrease in the time of surgery and postoperative treatment. There is no lymphorrhea, necrosis, rejection when removing significant tissue and organs. [17, 41, 42].

For endovitreal operations in ophthalmology, a monopolar instrument is used for cutting, hemostasis, welding and manipulation, which allows to work without opening the eyeball (Fig.3.12). When removing melanomas and hemangiomas inside the eye, it is used to make reliable hemostasis, which provides ablative conditions with preservation of vision [43, 44, 45].

Compared with laser coagulation, welding of the retina to the choroid is less traumatic, faster, and the likelihood of complications decreases [46].

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Fig.3.12 - a) Monopolar instrument for operations inside the eye b) welding of the retina to the choroid of the eye.

Removal of the eyeball followed by welding of the conjunctiva is performed with special instruments without the use of suture material. In the place of welding, a conglomerate of destroyed tissue elements, denatured proteins, collagen fibrils, fine-fibrillar “felt-like” material is formed, which seals the wound surface [47, 48].

Welding is used for resections and removal of the adrenal glands, operations on the thyroid, pancreas and parotid glands. It reduces the duration of operations by 30%, blood loss by 20-50%, and the number of postoperative complications is significantly reduced [17, 42, 49, 50].

Bowel welding easier and faster than stitching. The absence of foreign material helps to reduce inflammation and the appearance of adhesions, even with diffuse peritonitis. Moderate collagen formation prevents excessive scarring [51].

Welding can be used to connect dissimilar organs: bile ducts, intestines and stomach [17, 52, 53].

The appendix welding technology seals reliably and tightly creating an antimicrobial effect [17, 36].

The E.O. Paton Electric Welding Institute has developed instruments for simultaneous bowel welding by open and laparoscopic methods. The staples do not

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remain in the body, the suture retains its tightness at higher pressure, the technology is simpler than the application of a thread suture [17, 24].

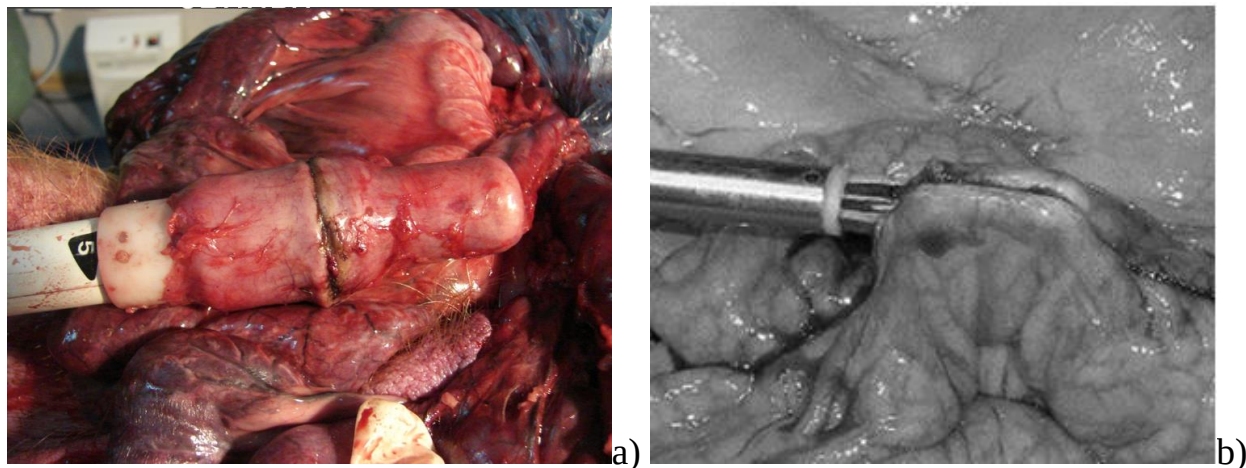


Fig.3.13- One-step welding of the intestine: a) - "end-to-end" welding seam; b) - welding with a laparoscopic instrument of the intestine "side to side"



Fig.3.14 -Intestinal Butt Weld Strength Test, USA, 2004

Patients with stage 3-4 laryngeal cancer undergo a course of radiation therapy before surgery, which weakens the immune status. Therefore, thread sutures cause disruption of blood supply, migration of microorganisms along the threads, which can lead to purulent complications, an allergic reaction of the body to a foreign material,

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the development of inflammatory and edematous tissue changes, and the appearance of fistulas. Welding tightly connects tissues, reduces pain and makes possible to create an artificial vocal cord (Fig.3.15) [33, 54].

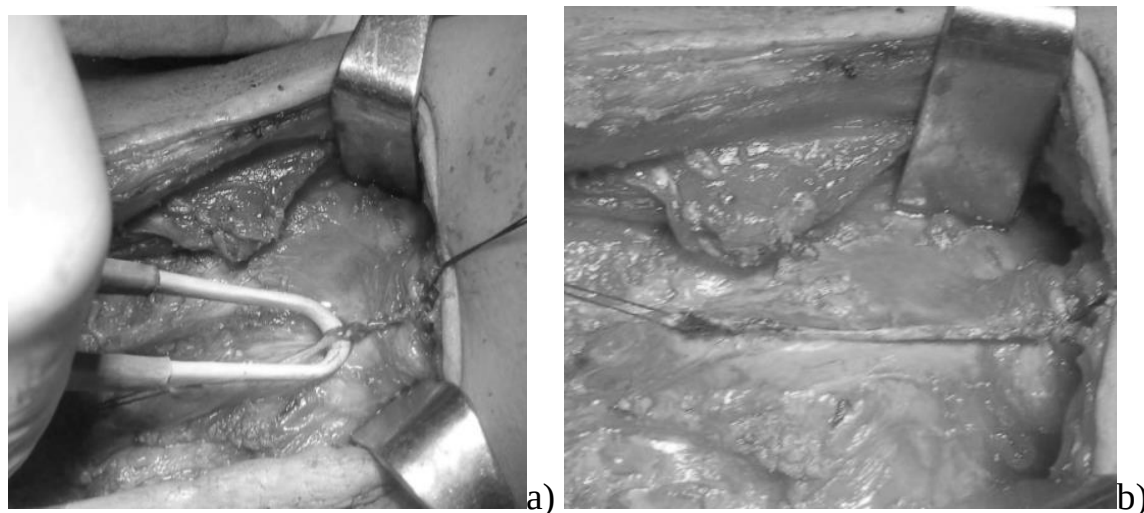


Fig.3.15 - a) Welding of the pharyngeal-esophageal junction b) after welding.

For ENT surgery, special instruments for bloodless cutting, coagulation and welding have been developed and patented. They contain two electrodes of different shapes, separated by an insulating baffle. The removal of papilloma, adenoids, tonsils or size reduction occurs with less blood loss, the operation time is reduced, there are no postoperative complications. In the treatment of curvature of the nasal septum, its mobilization is performed with a bipolar electrosurgical unit, welding is done with forceps [17, 32, 55].

### Conclusions to Chapter 3

Welding of living tissues shortens the operation time, blood loss, does not leave foreign material in the body. It is especially promising in those areas of surgery where it is inconvenient or impossible to apply thread sutures.

## CHAPTER 4

### WELDING SIMULATION

#### 4.1 Computer simulation of living tissue welding in surgery

Electric welding used in surgery for cutting, hemostasis and tissue joining. At the E.O. Paton Electric Welding Institute of the National Academy of Sciences of Ukraine, this method began to be studied jointly with medical organizations since 1992. The tissue is compressed by electrodes and a high-frequency current is passed through it. Changes occur under the influence of temperature and electric field, which lead to the formation of a weld joint. In the place of welding, a close connection, fusion of muscle and collagen fibers are observed. Bio-glue is formed, which increases the strength of the welding [60].

When studying welding and designing tools, it is necessary to know mechanical stresses, displacements, deformations, temperature, current density, and voltage gradient in tissue. It is difficult or impossible to experimentally determine these values due to the rapid course of the processes and the small volume of tissue. Therefore, the most convenient way is computer simulation. Simulation eliminates many experiments with experimental animals, which significantly saves time and money. The authors used the Abaqus and SolidWorks software to simulate, which enable collaborative simulations for the most complex linear and nonlinear engineering problems of mechanical, electrical, thermal, and other processes.

High-frequency electric welding of biological tissues is an effective method of treatment in ophthalmology. This method can be used to perform complex operations such as welding of the retina, resection of tumor tissue and many other operations. Optimal temperature, pressure force on the electrode, welding time and voltage were found using simulation in Abaqus.

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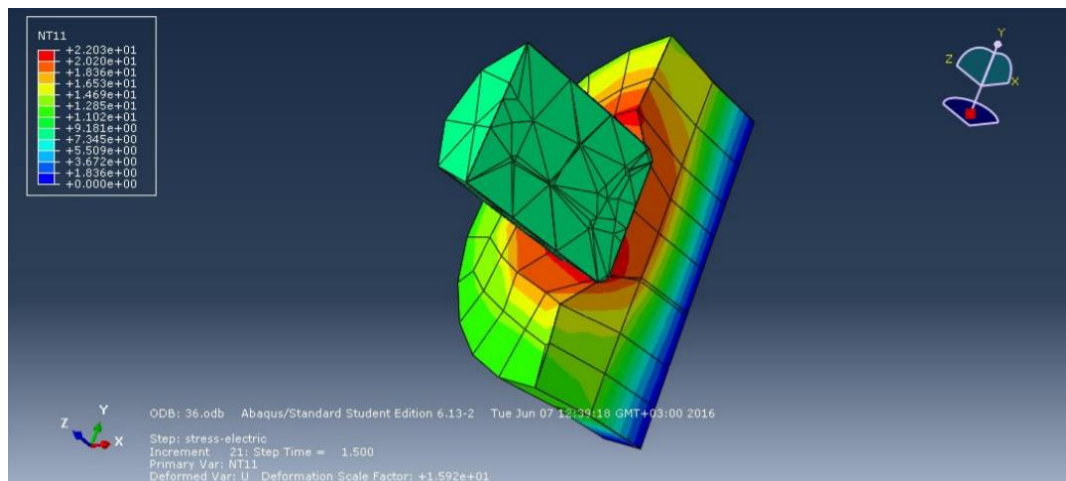


Fig.4.1-Temperature propagation over the model at an electric voltage of 20 V and a welding duration of 1.5 seconds [61].

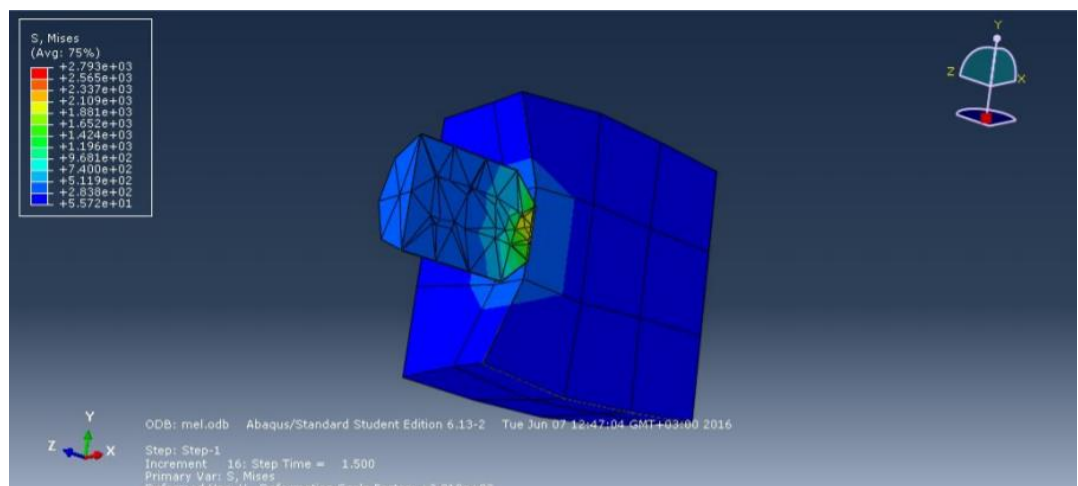


Fig.4.2- Distribution of mechanical load over the model at a voltage of 70 Volts and a welding duration of 1.5 seconds

Abaqus is a simplified built-in editor of 3D models, which are not suitable for use. Therefore, in many cases it is convenient to use SolidWorks. SolidWorks has a convenient graphical editor for 3D models and allows you to simulate mechanical processes, do thermal and frequency analysis, electrostatics, and jointly simulate electrical, electromagnetic and thermal processes.

Vascular occlusion is the most commonly used surgical procedure. The use of welding technology allows access and mobilization of organs with minimal blood loss.

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Operations are performed on a "dry" operating field. At the same time, the duration of the operation is reduced, its technique is simplified, suture material is not used, and the time of the operation and the recovery period is reduced. In the SolidWorks environment, the strength of the welded joint of blood vessels was investigated depending on the diameter of the vessel, its wall thickness, modulus of elasticity and Poisson's ratio.

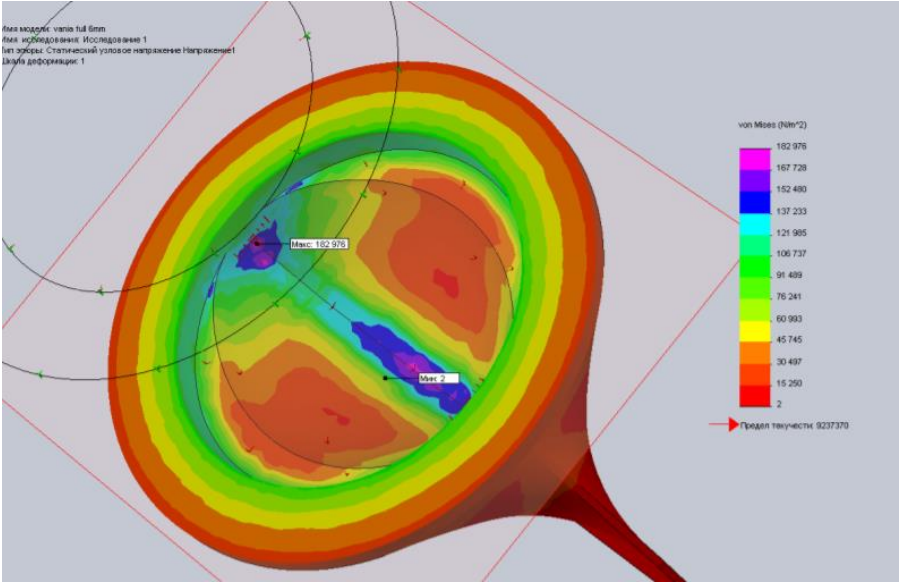


Fig.4.3- The tension in an artery with a diameter of 6 mm, a wall thickness of 1 mm, E = 0.5 mPa. The maximum stress on the weld surface is 184 976

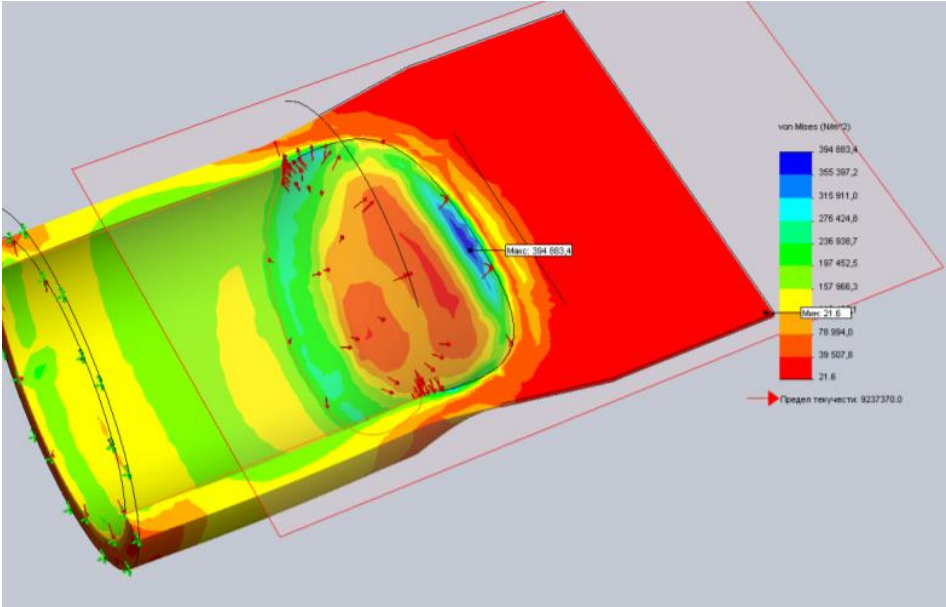


Fig.4.4 -Stress in an artery with a diameter of 6 mm, a wall thickness of 0.5 mm at a modulus of elasticity of 5 MPa. Maximum voltage 384 883 Pa. [62].

It is shown that the greatest influence on the mechanical stresses in the weld is exerted by its diameter and wall thickness. An increase in the diameter of the vessel and a decrease in the wall thickness lead to an increase in mechanical stresses in the weld.

#### 4.2 design of electric welding tweezers

During operations, electric welding tweezers are often used. The mechanical stresses, deformations and displacements in the vessel to be welded and tweezers have been investigated. The design of the tweezers is made so that the electrodes, at the beginning of the tissue grasping, are located at an angle. This improves tissue fixation, but leads to uneven compression, which can affect the quality of welding

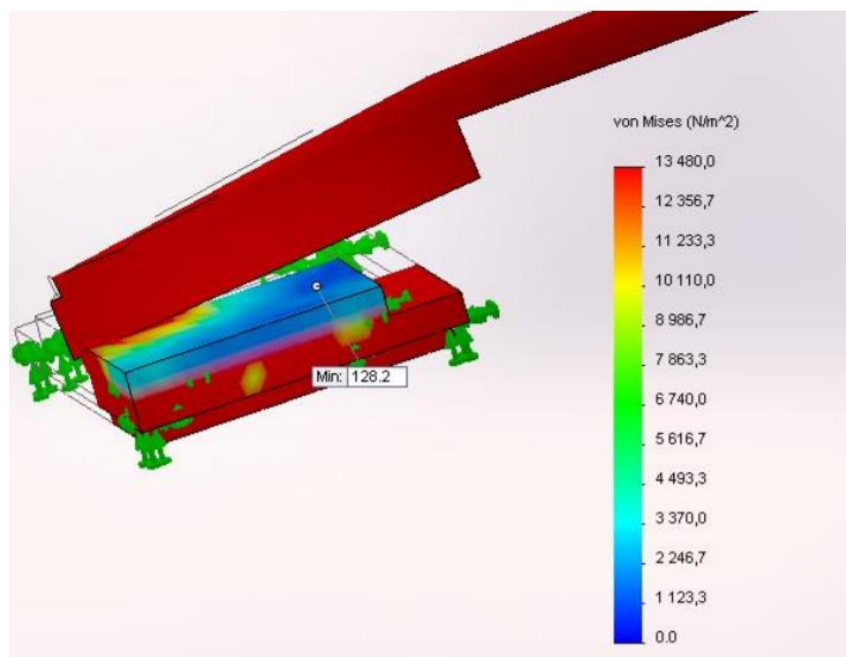


Fig.4.5- Mechanical stresses at a jaw compression force of 2 N and Young's modulus of  $7 \cdot 105 \text{ Pa}$ . [63].

Thermal processes during welding with tweezers were investigated [64]. It is shown that the temperature of the tissue in the center of the electrode can be more than the temperature at the edges, which can lead to defects in the welded joint.

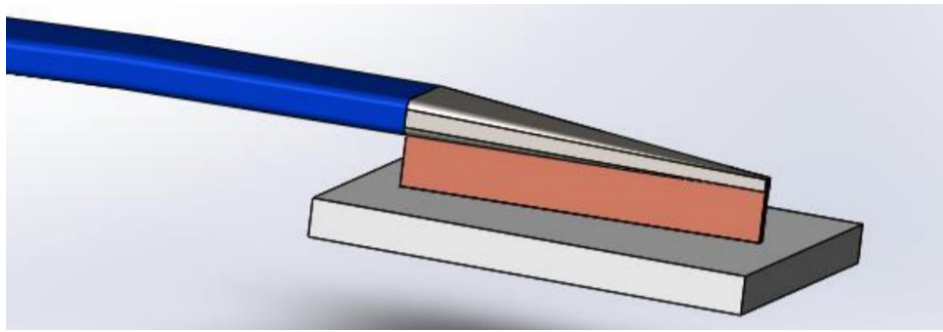


Fig.4.6- Biological tissue forceps branch

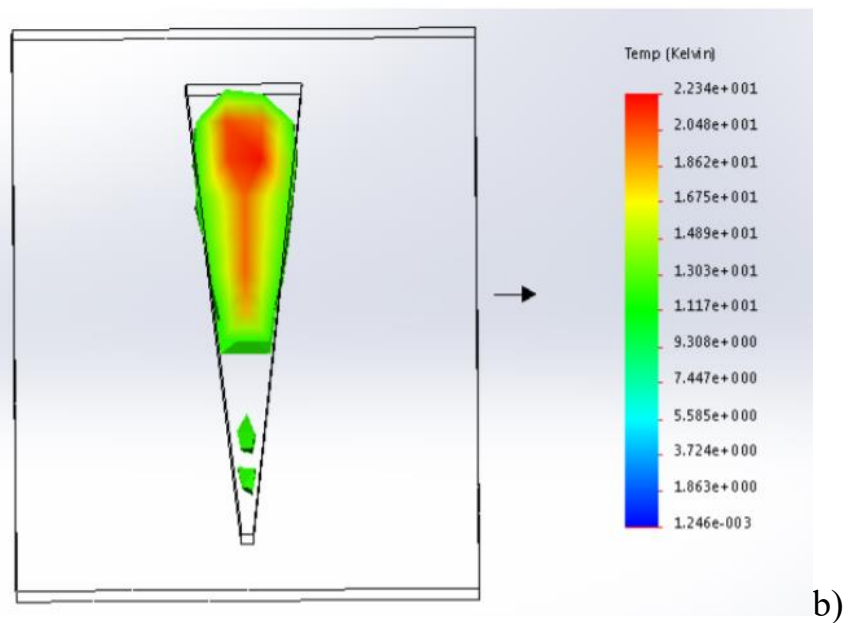
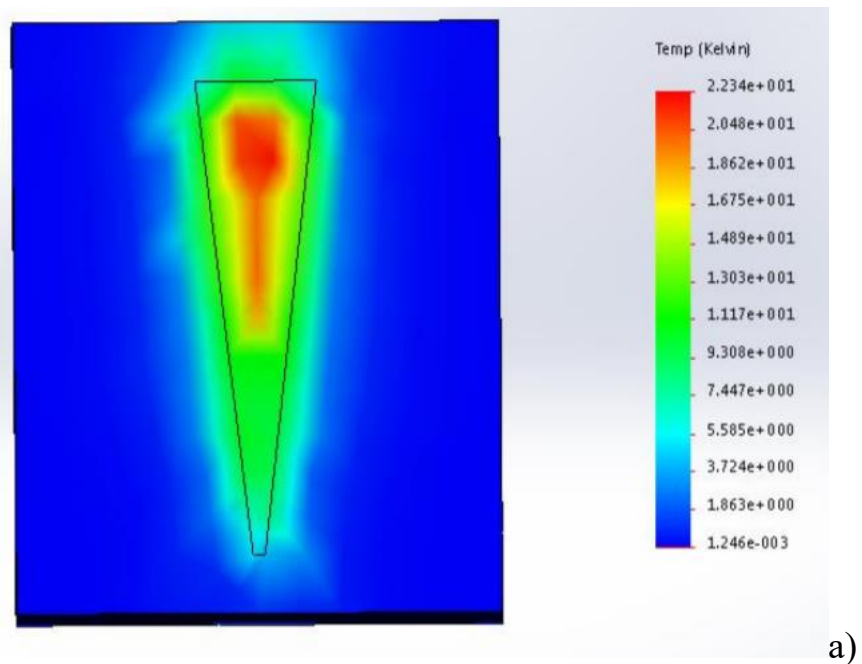


Fig.4.7- Temperature distribution: a) general, b) area with the highest temperature

SolidWorks is used in the design of laparoscopic instruments. To obtain a high-quality weld, it is necessary to ensure the pressure of the electrodes on the tissue of approximately  $2\text{N/mm}^2$ . Due to the transfer of the compression force from the handle along the long, thin tube, there is a decrease in the compression force of the tissue, which is unacceptable when welding large arrays, where an increased compression force is required

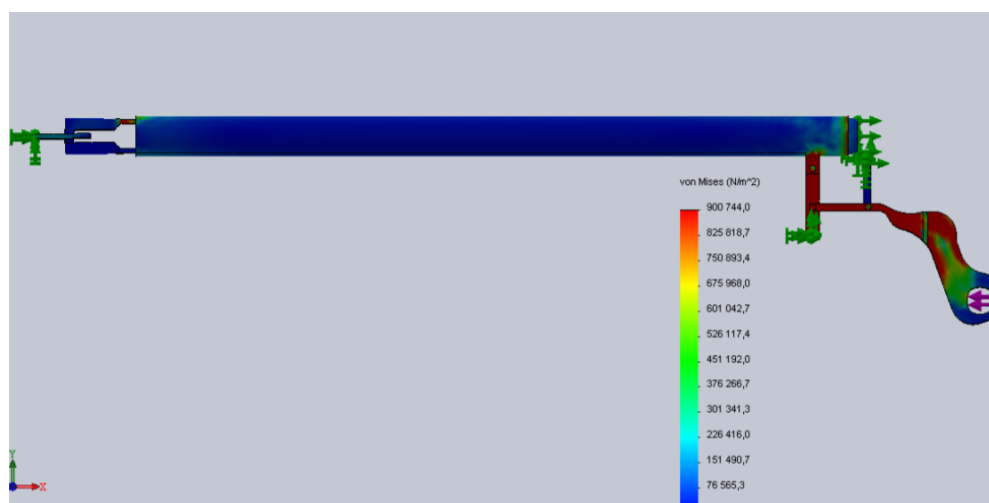


Fig.4.8 - Distribution of stress in the mechanism model [65,66].

Constructive methods of obtaining the required pressure on the tissue for high-quality welding are shown.

Specialized electric welding clamps are used for welding large tissue masses, for example, lungs, liver [67]. If the width of the electrodes is reduced, the clamp can be used to cut tissue with simultaneous hemostasis.



Fig.4.9 - Dissection of muscles with electro-surgical scissors with simultaneous hemostasis. [68].

In the SolidWorks environment, a 3-D model of a bipolar forceps for welding and cutting tissue was created. The cutting of muscle tissue with a thickness of 5 mm and an electrode width of 2 mm were simulated (Fig.4.10).



Fig.4.10 - 3D model of bipolar forceps for bloodless cutting of living tissue

The greatest mechanical stresses occur in the branches, the stresses in the tissue are much less [69]. The elastic deformation of the jaws stabilizes the pressure of the electrodes as the tissue thickness decreases during the cutting process. The greatest deformation of the tissue occurs in a perpendicular plane to the compressive force, contributing to its separation. To study electrical and thermal processes, the ElectroMagneticWorks (EMW) is used, which allows to simulate processes with direct and alternating currents. The built-in material library contains electrical and thermal parameters of the main human organs at various frequencies. The use of EMW showed that at a voltage of 200 V after 0.5 s, the tissue heats up under the electrodes to 100 ° C. In the middle of the tissue, the temperature is even higher; when the compression force of the jaws is weakened, the pressure decreases.

Considering a clamp welding simulation. The model consists of two layers of muscle tissue with a thickness of 0.75 mm and two electrodes 25 mm long with cross-sections: 5 \* 4 and 2.5 \* 2 mm (Fig.4.11).

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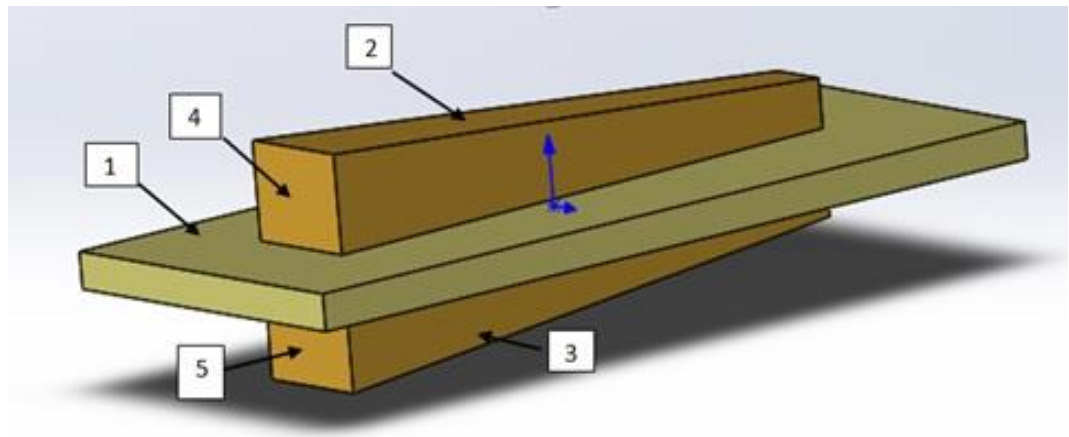
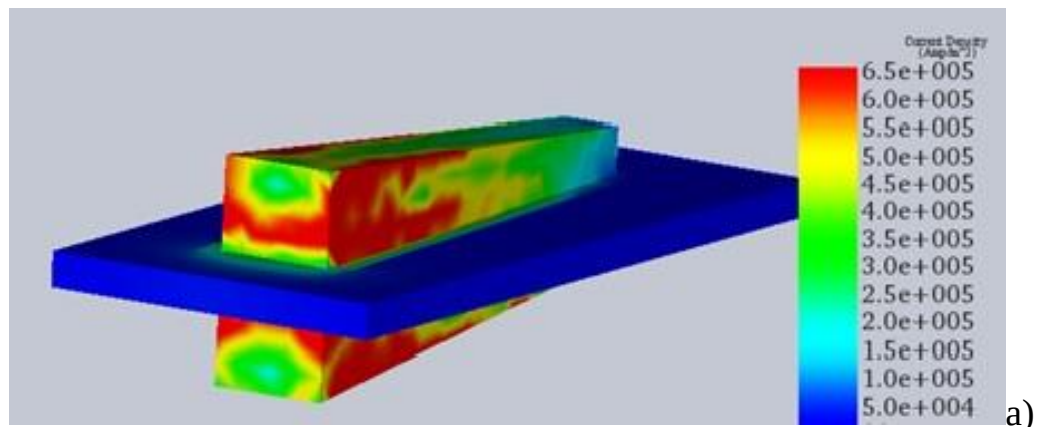
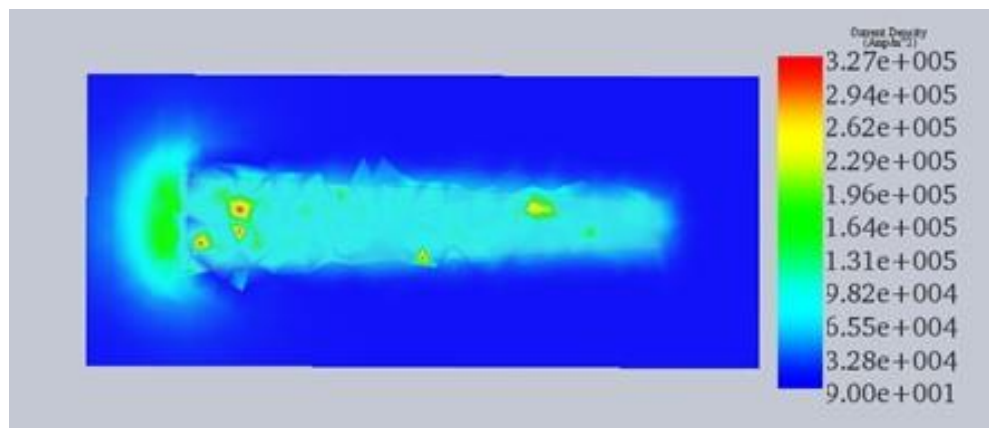


Fig.4.11 - Welding model of living tissues: 1 - two layers of tissue, 2 and 3 - electrodes, 4 and 5 - alternating voltage is applied to the edges of electrodes.

Living tissue consists of cells surrounded by membranes that create capacitors. Therefore, the impedance of the tissue has an active-capacitive character. The cable connecting the welding tool to the power source has an inductive reactance. Since a sufficiently high frequency is used, in the branches and electrodes of the instrument, the current is displaced to the surface and the current in the electrodes converge, which adds the inductance of the secondary circuit and losses in the electrodes. EMW can simulate AC, DC and electromagnetic processes. DC simulation allows to determine resistance, loss, heating, and current distribution in electrodes and tissue. AC simulation determines the capacitance and inductance of the loop, calculates the current density. Electromagnetic simulation calculates current density taking into account the surface effect and proximity effect, temperature. Due to the influence of magnetic fields, the current is displaced to the edges and bases of the electrodes (Fig. 4.12a). The tissue conductivity is much lower than that of the electrodes. Therefore, there is no surface effect and the current density is the same over the entire tissue section (Fig.4.12b).



a)



b)

Fig.4.12 - Current density a) on the surface of the model; b) in the middle of the tissue at a welding voltage of 40V and a frequency of 500 kHz.

After 3 seconds of welding, the temperature inside the tissue reaches 1500 C. The electrode removes heat from the tissue and heats up to 70 C. In places where the electrode does not cool the tissue, it heats up to a higher temperature.

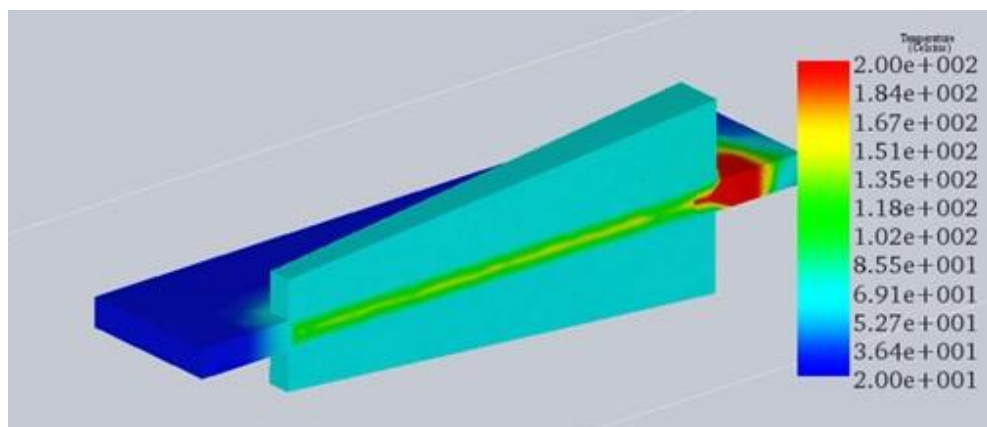


Fig.4.13 -Temperature in the longitudinal section of the model at a voltage of 40V, a frequency of 500 kHz, and a welding duration of 3s.

### Conclusions to Chapter 4

Computer simulations are used to study welding and equipment design in many areas of surgery. With the help of modeling, it is possible to obtain information that is extremely difficult or impossible to obtain by experimental methods, to speed up and reduce the cost of research.

## CONCLUSIONS

After analyzing the electroporation area, it was discovered that in order to optimize it, many factors must be considered, including the type of current, pulses, and buffers, depending on the field in which it is used. This new approach has received a positive response in a variety of different sectors, especially in medicine, where significant progress has been made. One of the most notorious applications is electrotherapy, which has shown promising results in the treatment of tumor lesions located in the skin or subcutaneous tissue, both primary and metastatic, regardless of the histological type of the tumor or previous treatments

Welding is used in many areas of surgery. Operation time, blood loss, and the likelihood of postoperative complications decrease. It is convenient to use it where it is difficult or impossible to use threads, clips, staples. Computer simulation allows abandoning experiments on animals and accelerates research and equipment design in many cases.

With the results obtained, it can be concluded that electroporation and welding are accepted method for the application both in laboratory research and in the treatment of diseases, directly and at a lower cost. With the current advances in knowledges, these methods will grow, thus having a better quality of life for human beings.

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