چهارمین سمینار
پیل سوختی ایران
4 th Iranian Fuel cell seminar
سوم و چهارم آذر ماه ۱۳۸۹
November 24 & 25 ,2010
www.iranecs.ir/fuelcellseminar
دانشگاه تربیت دبیر شهید رجائی
دانشکده علوم پایه

Modeling of the Electrochemical Treatment of Tumors

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Abstract
The electrochemical treatment of cancer (ECHT) consists in the passage of a direct electric current through two or more electrodes inserted locally in the tumor tissue. The extreme PH changes induced have been proposed as the main tumor destruction mechanism. The studies presented in this research have given a strong indication of the destruction mechanism involved in ECHT. Mathematical models, describing the physicochemical reaction and transport processes of species dissolved in tissue surrounding platinum anodes and cathodes, during ECHT, are developed and visualized with COMSOL Multiphysics software in this study. The considered electrochemical reactions are oxygen and chlorine evolution, at the anode, and hydrogen evolution at the cathode. Concentration profiles of substances dissolved in tissue, and the potential profile within the tissue itself, are simulated as functions of time. Modeling work of the anode processes has explained the role of chlorine in the underlying destruction mechanism behind ECHT. It is found that the reactions of chlorine with tissue play important roles as generators of hydrogen ions. The contribution of these reactions to the acidification of tissue, surrounding the anode, is strongly dependent on the applied current density and increases with decreasing current density.

Keywords: Tumors, Mathematical Models, Electrochemical Treatment

1. Introduction
In electrochemical treatment (ECHT) therapy a direct electric current flows through the tumor cellular and interstitial compartments, the latter consisting mainly in a complex conglomerate of collagen, glycoproteins, proteoglycans and hyaluronic acid. Tissue destruction has been reported by this technique in a wide range of solid tumors, with greater efficacy observed in skin cancer, oral cavity and thyroid malignancies [1]. Although known since the end of the 19th century, Bjorn Nordenstrom, from Sweden, is considered to be a pioneer in the treatment of tumors with electric current and combination therapies in patients [2],[3]. In the late seventies, Nordenstrom treated primary lung cancers by applying current between two platinum wire electrodes and, in his book of 1983 [2], he reported results from the treatment

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of 26 lung tumors in 20 patients. Regression was obtained in 12 out of 26 tumors and no signs of regrowth were detected after a 2–5 year follow-up period. Following Nordenstrom works, Xin Yu-Ling and his group in China extended ECHT to the whole country (more than 15000 patients have been treated in the last 15 years) [4],[5]. Miklavcic and collaborators in Slovenia, in a series of papers starting in 1991, studied the effects of ECHT on tumors in mice [6–9].in particular, Sersa et al. [10] studied the potentiated effects of ECHT when combined with anticancer drugs such as bleomycin. More recently, von Euler et al. [11] presented results of cell proliferation and apoptosis in rat mammary cancer after ECHT treatment. At present, there are several groups working in Australia, Cuba, Japan, Sweden and the USA. a general review can be found in Nilsson et al. [1]. Some of the advantages of ECHT are its simplicity, effectiveness, low cost and negligible side effects. This therapy is specially indicated for superficial, not-operable or chemotherapy-resistant tumors. It has also been suggested that the ECHT would potentiate the anti neoplasic effects of radio and chemotherapy and minimize their side effects [3],[12–14]. The induced transmembrane voltage in a cell subject to an electric field results in an increase in membrane permeability thus allowing certain molecules to be transported into the cell [15]. This process is usually called electroporation or electropermeabilization and has been widely used in molecular biology and related fields. Electro chemotherapy (ECT) is a more recent technique based on cell electropermeabilization combined with the use of chemotherapy thus allowing greater therapy efficiency as much more drug can penetrate the cell (it is used specially with effective drugs such as bleomycin or cisplatin but with low membrane permeability). Pioneering studies of ECT were presented in 1991 by Mir et al. [16] from the Institute Gustave Roussy, Villejuif; their work stimulated other groups, among them, Miklavcic et al. [17] from the Institute of Oncology, Ljubljana, Slovenia. To date more than 200 patients with tumor nodules were treated with ECT using as anticancer drug bleomycin or cisplatin. The majority of patients had melanoma metastases, followed by patients with metastases of skin, head and neck, mammary, ovarian cancer, Kaposi's sarcoma and chondrosar coma.The results of the treatment showed good antitumor effectiveness, resulting in approximately 80% objective responses of the treated tumor nodules. In fact, ECT being an easy, highly effective and safe anticancer therapy is becoming a standard treatment for cutaneous and subcutaneous tumor nodules, mainly as a palliative, but further progress in the development of new electrodes will no doubt extend its use as an effective tumor ablation technique.

The objective of this study is to develop mathematical models that are able to describe the concentration profiles of species, dissolved in tissue surrounding the electrodes, during the electrochemical treatment. The hypothesis is that these models will serve as useful tools in investigating the underlying destruction mechanisms behind ECHT, as well as in developing a dose planning strategy. For simplicity, the mathematical modeling is focused on treatments with spherical electrodes. The results from this study enable an investigation of the validity of the mathematical models, as well as of their applicability for dose planning.

2. Modeling

2.1 Destruction Mechanism

Several contributory factors seem to be involved in the tumor destruction, although their respective roles are not yet fully understood. However, the primary tissue destruction,

obtained in the electrodes' close vicinity, is most probably caused by the toxic species produced in the electrochemical reactions during electrolysis. The reaction products are toxic to both tumors and healthy tissue, although normal cells and tumor cells might show differences in their sensitivity to these species. The current yield of the different electrochemical reactions, occurring in the electrolysis of aqueous saline solutions, strongly depends on the choice of electrode material and operating conditions [18]. If the anode material is electrochemically soluble (e.g. copper), the major part of the anodic current will consist of metal dissolution. A small amount of the anodic current is transferred by the oxidation and reduction of certain species already dissolved in the tissue. Some dissolvable metals (e.g. silver) form a non conducting compound on the anode surface, which may cause current fluctuations. In cases where the anode material is made of a metal that can be passivated, such as platinum, metal dissolution is negligible. Passivity is caused by the formation of a thin, electron conducting, oxide film that acts as a barrier to the anodic metal dissolution reaction. The main reactions in these cases are the decomposition of water and oxidation of chloride ions:

$$2H_2O \Leftrightarrow O_2 + 4H^+ + 4e^- \quad (1)$$

$$2Cl^- \Leftrightarrow Cl_2 + 2e^- \quad (2)$$

The cathode material is protected against electrochemical dissolution by the applied cathodic current, and the major electrochemical reaction is, in all cases, the decomposition of water into molecular hydrogen and hydroxyl ions:

$$2H_2O + 2e^- \Leftrightarrow H_2 + 2OH^- \quad (3)$$

Since convective transport are obstructed by the dense structure of tissue, species produced at the anode and cathode are mainly transported to the surrounding tissue by diffusion, due to concentration gradients, and by migration (charged species), due to the potential gradient. The electrochemical reaction products may also react with organic and inorganic tissue constituents, to potentially form new toxic products. The presence of extreme local pH changes in tissue surrounding the electrodes, during and after ECHT treatment, has been confirmed in many studies [19],[20-21]. PH values down to 1 have been detected in tissue adjacent to the anode, while a pH as high as 13 has been measured near the cathode [20]. At these non-physiological conditions, vital proteins become denatured and precipitated [19],[21]. The extreme PH conditions in the vicinity of the electrodes have also been predicted in several theoretical studies. Cvirn et al. estimated the spreading of the alkaline zone around a spherical cathode while Berendson and colleagues [22],[23] studied the spreading of hydrogen ions and molecular chlorine around spherical and planar platinum anodes.

2.2 Model Definition

The transport equations of ionic species in dilute solutions [24] provide the basis for the analysis of the transport and reaction processes occurring in tissue during ECHT. In addition,

kinetic expressions for the electrochemical reactions are introduced at the electrode surface [24]. The implementation of electrode kinetics into the model makes it possible to estimate the anodic and cathodic over voltages, and, at the anode, the current yields of chlorine and oxygen evolution. The equations of electrode kinetics are based on reaction mechanisms proposed in the literature [25],[26]. In this section, a general description of the model equations used in the mathematical modeling is presented.

2.2.1 Domain Equations

This model uses the Nernst-Planck application mode to predict the transport and reaction in the electrolysis of tumor tissue in a liver. A needle electrode is placed in the tumor, and transport is assumed to take place radially to and from this electrode. Because we can assume rotational symmetry, the computational domain reduces to a line (r_a, r_r) where r_a is 1 mm and r_r is 6 cm that shown in a figure (1).

The species we consider in the model are the protons, chloride, and sodium. At the surface of the anode we account for the chlorine and oxygen evolution reactions.

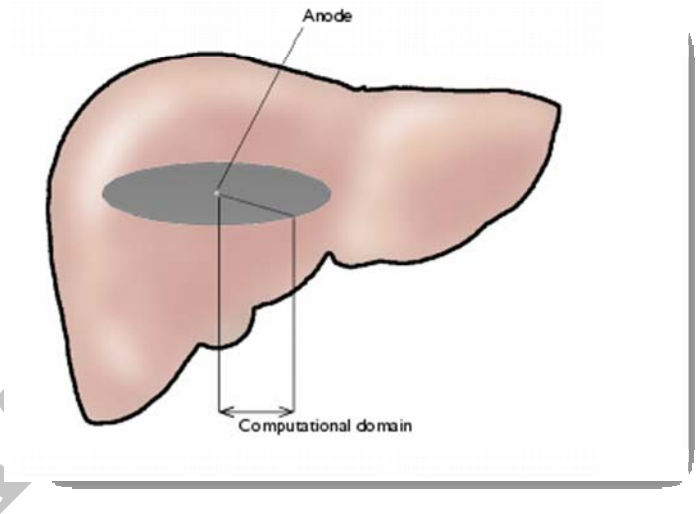

Figure 1: Diagram of the Cylindrical Modeling Domain inside a Tumor

The governing equations include differential material balances for all species considered in the solution domain, Ω:

$$\frac{\partial C_i}{\partial t} = -\nabla . N_i + R_i \qquad (4)$$

Here, C_i denotes the concentration, t the time, N_i the molar flux and R_i represents the production of species i through homogeneous chemical reactions. The molar flux vector is expressed as:

$$N_i = -D_i \nabla C_i - \frac{Z_i}{|Z_i|} U_i C_i \nabla \Phi \qquad (5)$$

Where D_i is the diffusion coefficient, Z_i the number of charges carried by the ion i, U_i the ionic mobility and Φ the potential field in the electrolyte. The production term in equation (4), R_i, is directly related to the kinetics of the chemical reactions that occur in the electrolyte domain. For example, the production term of hydroxyl ions, in the anode modeling, is expressed as:

$$R_{OH^-} = -k_f C_{H^+} C_{OH^-} + k_b C_{H_2O} \qquad (6)$$

Where k_f and k_b denote the forward and backward rate constants of the water proteolysis reaction (7), respectively:

$$H^+ + OH^- \Leftrightarrow H_2O \qquad (7)$$

The condition of electro neutrality forms the remaining model equation in the electrolyte domain:

$$\sum_i Z_i C_i = 0 \qquad (8)$$

2.2.2 Boundary and Initial Conditions

Mass transport of species i across the electrode surface, $\partial\Omega_e$ is either nonexistent or equal to the charge transfer, present through virtue of the electrochemical reactions.

$$-D_i(\nabla C_i.n) - \frac{Z_i}{|Z_i|} U_i C_i (\nabla \Phi.n) = \frac{v_{ij} i_j}{n_j F} \qquad (9)$$

Where n the outward unit is normal vector, n_j the number of electrons transferred in the electrochemical reaction j, v_{ij} the stoichiometric coefficient and F is Faraday's constant. i_j Denotes the current density contributed by the electrochemical reaction j.

The anode current densities, contributed by oxygen and chlorine evolution, respectively, are given by:

$$i_{O_2} = i_{0,O_2} \left\{ \exp\{-\frac{F(\Phi + E^{ref}_{eq,O_2})}{2RT}\} - (P_{O_2})^{\frac{1}{4}} C_{H^+} \exp\{\frac{F(\Phi + E^{ref}_{eq,O_2})}{2RT}\} \right\} \qquad (10)$$

$$i_{cl_2} = i_{0,cl_2}\left\{C_{cl^-}\exp\{-\frac{F(\Phi+E^{ref}_{eq,cl_2})}{2RT}\}-(C_{cl_2(aq)})^{\frac{1}{2}}\exp\{\frac{F(\Phi+E^{ref}_{eq,cl_2})}{2RT}\}\right\} \quad (11)$$

While the analogous expression for the current density, contributed by hydrogen evolution reaction at the cathode, is:

$$i_{H_2} = i_{0,H_2}\left\{(C_{OH^-})^2 P_{H_2}\exp\{-\frac{3F(\Phi+E^{ref}_{eq,H_2})}{2RT}\}-\exp\{\frac{F(\Phi+E^{ref}_{eq,H_2})}{2RT}\}\right\} \quad (12)$$

Where, $C=\frac{C_i}{C_i^{ref}}$ and $P=\frac{p_i}{p_i^{ref}}$, with p denoting the partial pressure and ref a reference state. E^{ref}_{eq}, is the potential difference between the solid and liquid phases, at equilibrium conditions and relative to a reference, and is found through Nernst's equation. i_0, denotes the exchange current density, T the absolute temperature and R the universal gas constant. In addition to equation (9), formulated for the involved species, the boundary conditions at the electrode include the condition of electroneutrality (8).

The concentration gradients are equal to zero at the outer boundary surface, $\partial\Omega_r$:

$$\nabla C_i.n = 0 \quad (13)$$

The potential gradient, at the outer boundary surface, is obtained through substituting the molar migration flux vector into Faraday's law:

$$\frac{1}{F}(i.n)+\sum|Z_i|U_iC_i(\nabla\Phi.n)=0 \quad (14)$$

Where i is the current density Vector.

Initially, there are no concentration gradients throughout the electrolyte, and the concentrations are given by the initial condition below:

$$C_i(r,0)=C_i^0 \quad (15)$$

The initial potential at the electrode, Φ_e^0 is solved from the given current density, applied at the electrode, and its respective contributions obtained from equations (10),(12). The initial potential profile throughout the solution domain, is obtained by integrating equation (14) using the boundary $\Phi^0(r_e,0)=\Phi_e^0$.

2.2.3. Input Data

The amount of parameter that used in a equations for describing ECHT process and inserted in COMSOL Multiphysics software are shown in a table (1) .

Table 1: Amount of Parameter that use in a Model

Parameter	Value	Description	Parameter	Value	Description
D_{Na}	$1.33 \cdot 10^{-9}$ m^2/s	Diffusion coefficient, Na^+	$j_{I,0}$	10^{-6} A/m^2	Exchange current density, reaction I
D_H	$9.31 \cdot 10^{-9}$ m^2/s	Diffusion coefficient, H^+	$j_{II,0}$	10 A/m^2	Exchange current density, reaction II
D_{Cl}	$2.03 \cdot 10^{-9}$ m^2/s	Diffusion coefficient, Cl^-	$V_{ra,0}$	-1.4787 V	Initial anode potential
$c_{Na,0}$	0.16 mol/liter	Inlet concentration, Na^+	$E_{eq,I}$	1.23 V	Equilibrium potential, reaction I
$c_{H,0}$	10^{-7} mol/liter	Inlet concentration, H^+	$E_{eq,II}$	1.36 V	Equilibrium potential, reaction II
$c_{Cl,0}$	0.16 mol/liter	Inlet concentration, Cl^-	T	298 K	Temperature
j_0	100 A/m^2	Initial current density	p_{O2}	1 atm	pressure
p_{Cl2}	1 atm	pressure			

3. Results

The general behavior of the anodic sodium chloride model is visualized and discussed in this section. The physicochemical input parameters used in these simulations are those valid at 37°C. The anode radius is set to 1 mm and the anode current density is 100 A/m2. Figure (2) shows the concentration profiles of sodium, hydrogen and chloride ions, obtained from the sodium chloride model in a different time step of electrolysis. Hydrogen ions, produced in the oxygen evolution reaction, form an acidic zone around the anode. Chloride is consumed in the chlorine evolution reaction, which results in the depletion of chloride ions close to the anode. The sodium ions are transported away from the anode by means of migration. The concentration profiles of all the ions are closely related through the condition of electroneutrality. The depletion of chloride ions and the fact that the electroneutrality condition has to be maintained give rise to a depletion of hydrogen ions, close to the anode, and a maximum in hydrogen ion concentration further out in the electrolyte. The mobility of the hydrogen ion is 7 times larger than that of the sodium ion, and about 5 times larger than the mobility of the chloride ion. This, together with the condition of electroneutrality, leads to a situation where the spreading rate of hydrogen ions, away from the anode, is limited by the transport of sodium and chloride ions away and towards the anode, respectively. The corresponding H^+ profile in figure (2-a) shows that the concentration maximum is not at the anode surface. This result arises because the current density is not constant over time. At high current densities, large amounts of protons are produced and this front moves inwards in the domain as the current density is lowered.

The corresponding plot for chloride figure (2-c) shows a continuous decrease of chloride concentration close to the anode surface. This in turn decreases the production of chlorine and increases oxygen evolution.

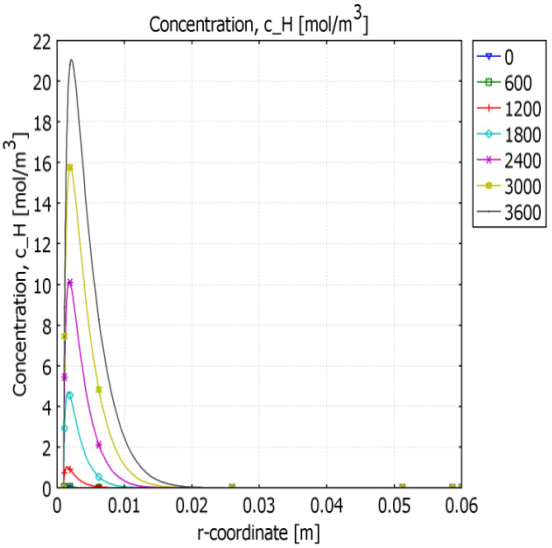

Figure 2(a): H^+ Concentration Profile.

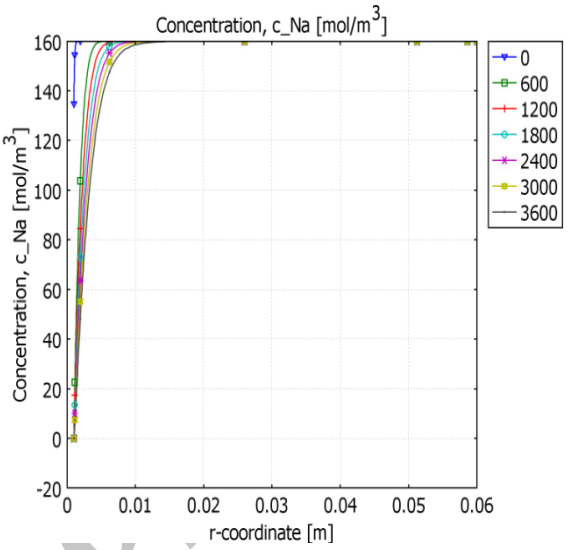

Figure 2(b): Na^+ Concentration Profile.

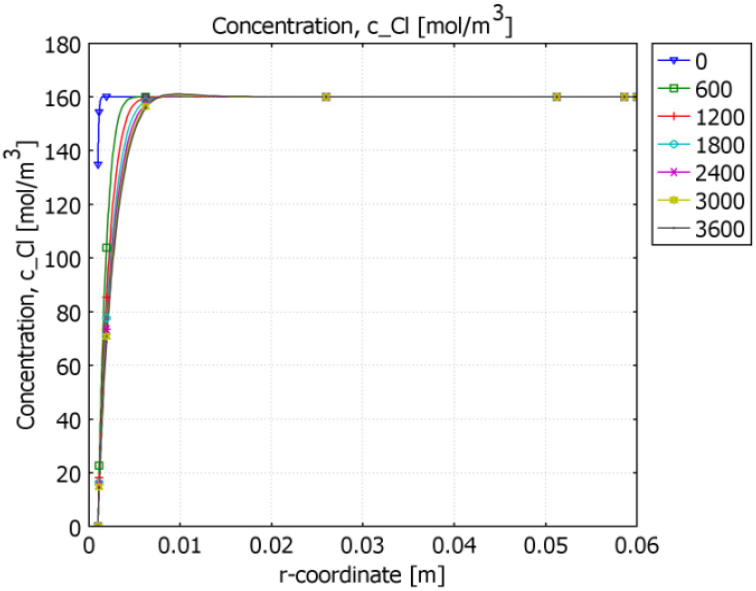

Figure 2(c): Cl^- Concentration Profile.

Figure 2: Species concentration in the domain at different time steps.

The pH profiles obtained by the sodium model after different times of electrolysis, is presented in Figure (3). The movement of the acidic zone, in the tissue surrounding the anode,

is considerably impeded by the sodium system. We can see that values below pH 2 are reached after 2160 seconds. At this pH, tumor destruction starts to occur very rapidly according to the theoretical.

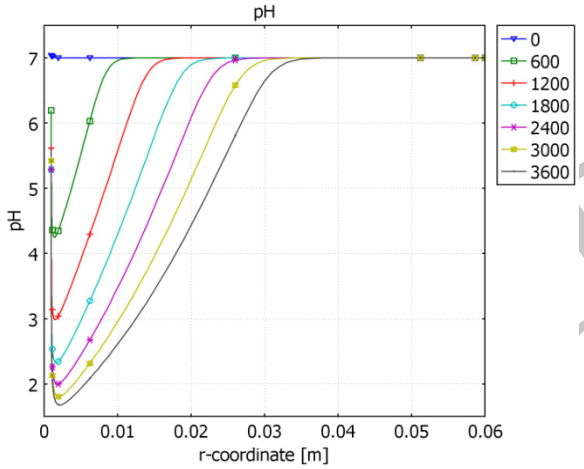

Figure 3: pH-profiles at different time steps during the treatment.

The current-density plot in figure (4) shows that the total current decreases rapidly as the concentration overvoltage for chlorine formation increases, due to lowered chloride concentration at the anode surface. The potential is then increased, which results in an increase in total current through increased oxygen evolution.

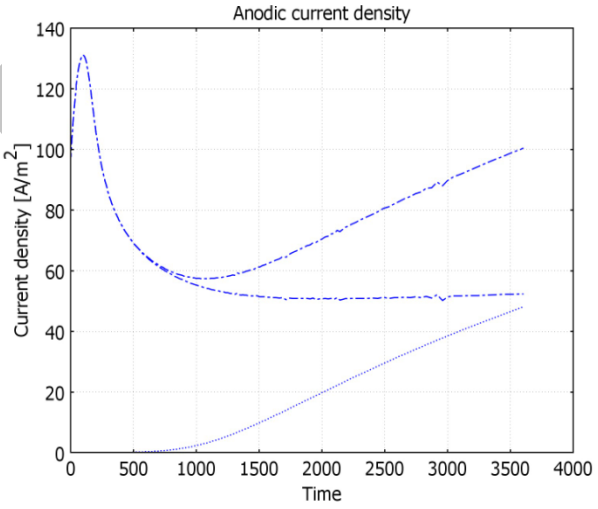

Figure 4: Total current density and current density for the competing reactions on the anode surface. Oxygen evolution is the lowest graph.

4. Conclusion

This study has given a strong indication of the destruction mechanism involved in ECHT. The mathematical model, developed in this article, is valuable tools in optimizing the operating conditions of ECHT. It is possible to extend the use of the models, to predict the effect of the treatment in clinical situations, using several electrodes. Predictions could be made for optimizing an appropriate number and the positions of electrodes in a tumor, and is not limited to the single electrode models treated here. Modeling of the anode processes has explained the role of chlorine in the underlying destruction mechanism behind ECHT. A considerable amount of the chlorine, produced at the anode, reacts with water to form hypochlorous acid. Chlorine and hypochlorous acid are potent chlorinating and oxidizing agents, with strongly toxic properties. Their impact in the overall destruction mechanism was, however, found to be very limited, since the acidic zone always reaches further out from the anode than the chlorinated zone does. Although chlorine and hypochlorous acid themselves are found to have limited roles in the destruction mechanism of ECHT, their secondary reactions with tissue are shown to be important sources of hydrogen ions. The contribution of these reactions, to the acidification of tissue surrounding the anode, is strongly dependent on the applied current density and increases with decreasing current density.

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