

# Numerical Investigation of Electric field, Ion Transport and pH damage during Electrochemical Treatment of Tumors: Effects of Physicochemical Reactions and Chlorine Bleaching

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## 1 ABSTRACT

Electrochemical therapy (EChT) is a promising alternative to conventional tumor treatment due to its relatively high efficiency, flexibility, reduced side effects and versatility. Tumor electrolysis, a form of EChT, utilizes low-level direct electric current (DEC). Electrolysis creates acidic and alkaline zones around anodic and cathodic implant electrodes that contribute to tissue necrosis. In this presentation we introduce two different numerical models of EChT, sodium chloride and bicarbonate buffered models. We demonstrate the models for a configuration of positive and negative straight and opposing electrodes in tumor tissue. The tumor is considered as an aqueous sodium chloride solution with or without bicarbonate buffer constituents. Our simulations predict that an initial condition with a homogeneous and almost neutral pH becomes extremely acidic (pH 2–3) and extremely basic (pH 10–12) in proximity to the anode and cathode, respectively. Concentration profiles of sodium, chloride, bicarbonate, carbonate, after 15 minutes of the EChT and the electrolyte potential distribution, as a function of time, are calculated. This approach and results open a promising area of research that may help in the interpretation of the real consequences of an EChT applied to tumor tissues.

**Keywords:** Electrochemical therapy (EChT), Tumor electrolysis, tumor destruction, mathematical modelling, non-buffered and buffered models, Nernst-Planck equations.

## 2 INTRODUCTION

Electrochemotherapy (EChT) of tumors consists in the passage of a direct electric current through electrodes inserted locally in the tissue, mainly causing its necrosis. This kind of treatment has been specially applied to more than 10,000 patients in China for the last decade with good clinical results (a total effective rate [complete response + partial response] of 71.8% and five-year survival rate of 47%) [1]. EChT is reported to be a simple, safe, less traumatic, quick recovery and low-cost technique for eliminating tumors. The therapy is especially indicated for patients with tumors that are unsuitable for surgery, radiotherapy or chemotherapy. It has even been suggested

that EChT improves the benefits and minimize the side effects of the above mentioned therapies. Determining the optimum current density distribution to apply when using different electrode arrays is one of the most important challenges to improve the efficacy of EChT. While the development of EChTs has been an active research area for the last three decades, relatively few rigorous process models exist and rational design is lacking.

Tumor electrolysis, a form of EChT, utilizes low-level direct electric current (DEC). Electrolysis creates acidic and alkaline zones around anodic and cathodic implant electrodes that contribute to tissue necrosis. During the treatment, the anodic electrochemical reactions mainly consist water decomposition and chloride oxidation, while protons, oxygen and chlorine are released. On the other hand, the cathodic reactions consist of production of hydroxide ions and hydrogen gas[2]. Ionic species present at the electrode boundary are transported through the medium by diffusion, migration and convection. This results in a strong anodic acidification and cathodic alkalization, as well as a net movement of fluid from anode to cathode [3]. Part of the gases released at the electrodes remain present in the medium and participate in other chemical reactions with organic and inorganic components of the tissue [4]. These further reactions can induce the production of new toxic products and local pH changes. It has been proposed that these extreme pH changes are the main cause of tumor destruction observed after the treatment and that they can reliably predict the extent of the tumor necrotic area.

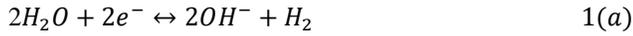
Specifically, in this paper we introduce two different numerical models of EChT, non-buffered and buffered models, both based on transport equations of ionic species in dilute solutions and on electrode kinetics. We solved the models for a configuration of positive and negative straight and opposing electrodes in tumor tissue, which is modeled as an aqueous solution of saline with or without bicarbonate buffer system. In this work we extend the results by comparing simulations with data obtained from non-buffered and buffered models. The model simulates the EChT process in a two-dimensional (2D) axisymmetric environment. A finite element analysis (FEA) package, COMSOL Multiphysics 5.3® was used for solving Tertiary Current Distribution, Nernst-Planck equations.

### 3 COMPUTATIONAL MODELS

The modelling work is divided into two studies: one without the buffer and the other devoted to the buffer system. The first study treats a highly simplified model in which the tissue is treated as an aqueous solution of sodium chloride. A brief description of the development of the two models is given in this section. The analysis focuses on the physicochemical processes that occur in an aqueous ionic solution by applying a direct current between the two electrodes embedded in the tumor. The distance between the two electrodes is 12 mm.

#### *The sodium chloride model:*

In the sodium chloride model, tissue is approximated by an aqueous solution of 0.16 M sodium chloride at a pH of 7. The cathodic electrochemical reaction consists in the production of molecular hydrogen and hydroxide ions.



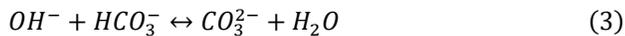
On the other hand, the anodic electrochemical reactions consist mainly of water decomposition and chloride oxidation, while protons, oxygen and chlorine are released.



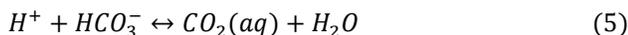
The solution near the electrode is assumed to be saturated with respect to oxygen and chlorine. Small gas bubbles, with an internal pressure of 1 atm containing either oxygen or chlorine, are assumed to be in equilibrium with the electrode surface[5].

#### *The bicarbonate buffer model:*

The sodium chloride model is subsequently extended to take into account the impact of a bicarbonate buffer on the spreading of hydroxyl and hydrogen ions, produced in the hydrogen evolution reaction and oxygen evolution reaction respectively. The bicarbonate buffer system around the cathode is modelled by the following reaction scheme[6]:



Acidification of tissue surrounding the anode is counteracted by the bicarbonate buffer system in accordance to the following reaction:



The bicarbonate concentration is set to 27 mM. The loss of  $CO_2(aq)$  is assumed to be negligible[4]. Finally, hydrogen and hydroxyl ions react through the water protolysis reaction:



#### **Model Equations:**

The solution domain to the problem is the electrolyte phase, where transport equations provide the basis for the analysis. At the electrode surface, both transport equations and electrode kinetics influence the concentration and potential fields. By assuming that transport equations in dilute solutions are applicable, a few principal expressions provide the basis for the analysis of the electrolyte phase. Electric current in the electrolyte is carried by ions. Transport of ionic species takes place by means of diffusion, stemming from concentration gradients, and migration, caused by the presence of potential gradients. The molar flux,  $N_i$ , of the ionic species  $i$  can be expressed as:

$$N_i = -D_i \nabla c_i - (z_i/|z_i|) u_i c_i \nabla \varphi \quad (7)$$

where  $D_i$  is the diffusion coefficient,  $u_i$  is the mobility and  $z_i$  is the number of charges carried by the ion  $i$ .  $c_i$  denotes the concentration of species  $i$  and  $\varphi$  is the potential field in the electrolyte.

A differential material balance for species  $i$  is given by

$$\partial C_i / \partial t = -\nabla \cdot N_i + R_i \quad (8)$$

where  $R_i$  represents the production of species  $i$  through homogeneous chemical reactions in the electrolyte and  $t$  is the time. The solution is electrically neutral, except for a very thin electrochemical double layer adjacent to the electrode. The condition of electro-neutrality states that:

$$\sum_{i=1}^7 z_i c_i = 0 \quad (9)$$

The three equations presented above provide a consistent description of transport processes in dilute electrolytic solutions. Multiplication of Eq. (8), by  $z_i F$ , and the addition of the species yields the following equation of charge conservation:

$$\nabla \cdot j = 0 \quad (10)$$

The model includes eight unknowns; namely, seven concentrations ( $Na^+$ ,  $H^+$ ,  $OH^-$ ,  $Cl^-$ ,  $HCO_3^-$ ,  $CO_2$ ,  $CO_3^{2-}$ ) and the potential field ( $\varphi$ ). Differential material balances are formulated for all seven species in the electrolyte domain:

$$\partial c_i / \partial t = D_i \nabla^2 c_i + (z_i / |z_i|) u_i \nabla \cdot (c_i \nabla \varphi) + R_i \quad (11)$$

For the species  $i = (\text{Na}^+, \text{H}^+, \text{OH}^-, \text{Cl}^-, \text{HCO}_3^-, \text{CO}_2, \text{CO}_3^{2-})$

#### Boundary and initial conditions:

Charge transfer and mass transport at the anode surface proceed at the same rate for all species involved in the electrode reactions. Thus:

$$\begin{aligned} -D_i (\nabla c_i \cdot n) - \\ (z_i / |z_i|) u_i c_i (\nabla \varphi \cdot n) = (v_{i,j} i_j) / (n_j F) \end{aligned} \quad (12)$$

where  $n$  is the outward unit normal vector,  $n_j$  the number of electrons transferred in the electrochemical reaction  $j$ ,  $v_{i,j}$  the stoichiometric coefficient.  $i_j$  denotes the current density contributed by the electrochemical reaction  $j$ . For the other species, the zero flux condition applies.

The anode and cathode current densities, are a result of oxygen, chlorine and hydrogen evolution reactions, respectively. All of these surface electrochemical reactions follow the general Butler-Volmer equation as follows:

$$i_{loc} = i_0 (c_{red} \exp(\alpha_a F \eta / RT) - c_{ox} \exp(-\alpha_c F \eta / RT)) \quad (13)$$

Where  $i_0$ ,  $\alpha$ ,  $\eta$  are exchange current density, transfer coefficients and overpotential respectively.

At the outer boundary, concentration and electric potential gradients are given by:

$$\nabla c_i \cdot n = 0 \quad (14)$$

$$(i \cdot n) / F + \sum_i |z_i| u_i c_i (\nabla \varphi \cdot n) = 0 \quad (15)$$

## 4 RESULTS & DISCUSSION

Calculations have been performed in order to investigate the potential and concentration profiles, as a function of duration of treatment. Simulations have been run using a total electrolyte current density of  $100 \text{ mA/cm}^2$ . The changes of the potential field, with respect to time and distance from the electrodes, have been examined. The electrolyte potential and current density of the domain are presented in Fig.1 and Fig.2 after 1000s of electrolysis. In order to make an

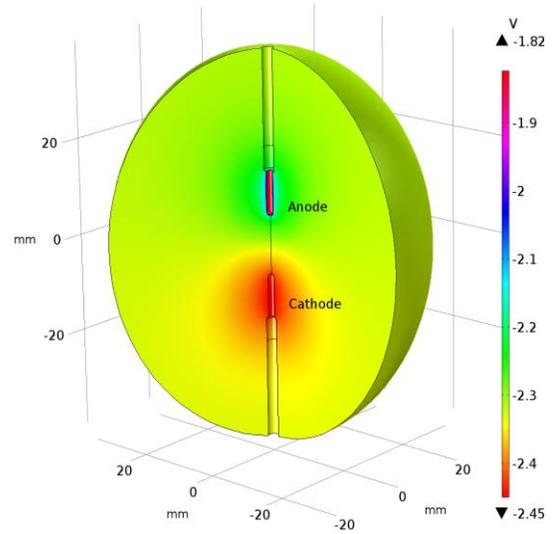


Figure 1: Electrolyte potential obtained from the buffered model, after 1000s of electrolysis.

adequate evaluation of the calculated potential field, the equations for the potential gradient have to be discussed. The relationship between the potential and concentration gradients for the participating species, is given by:

$$\nabla \varphi = -j / \kappa - (F / \kappa) \sum_{i=1}^7 z_i D_i \nabla c_i \quad (16)$$

Where

$$\kappa = F \sum_{i=1}^7 |z_i| u_i c_i \quad (17)$$

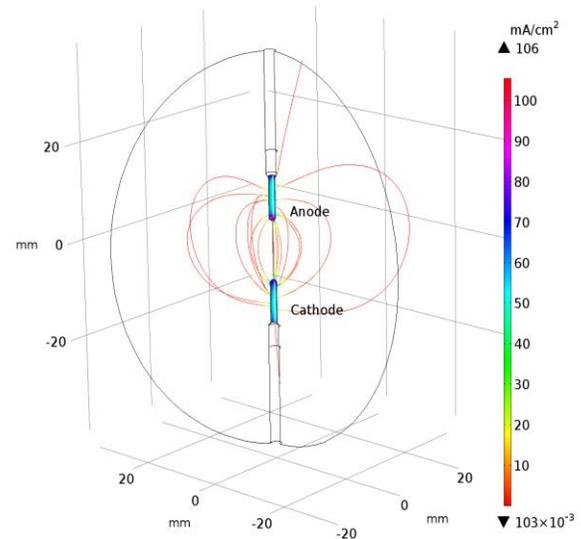


Figure 2: Simulated Electrolyte current density vector obtained from the buffered model, after 1000s of electrolysis.

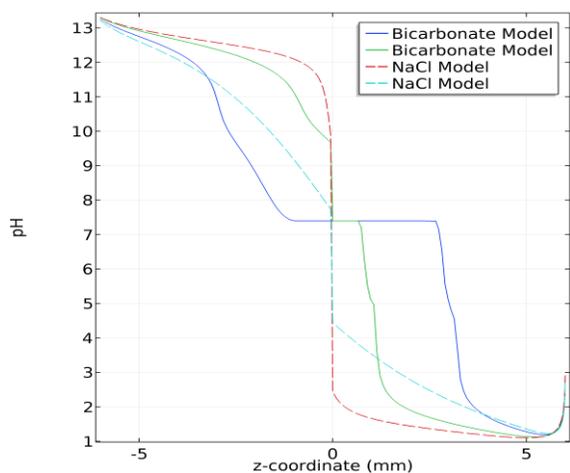


Figure 3: Comparison between simulated pH profiles, obtained from the NaCl and Bicarbonate models.

Fig.3 shows the comparison between the simulated pH profiles around the electrodes, obtained from the sodium chloride model and bicarbonate model at different times. The extension of the destruction zone is considerably impeded by the bicarbonate buffer system. Moreover, the pH profiles predicted by the bicarbonate buffer model are steeper than those obtained by the sodium chloride model.

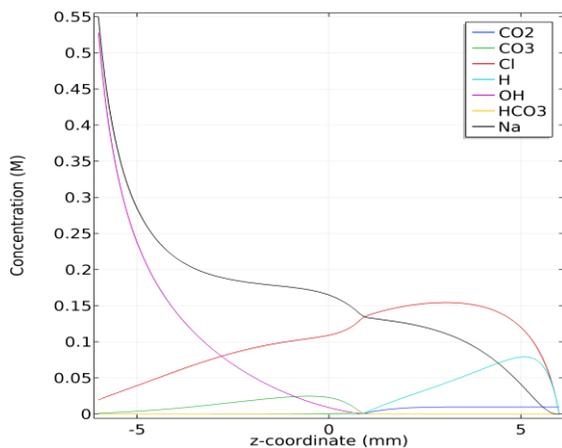


Figure 4: Concentration profiles of sodium, chloride, hydroxyl, bicarbonate and carbonate ions, after 1000s of electrolysis.

Fig.4 shows the simulated concentration profiles of sodium, hydrogen, chloride and bicarbonate ions at the end of this electrolysis. The concentration profiles of the sodium and chloride ions closely resemble those obtained by the sodium chloride model, except from the fact that the bulk concentration of chloride is lower in the bicarbonate buffer model. The spreading of hydrogen ions is counteracted by bicarbonate buffer capacity. The spreading of hydroxyl ions is also, counteracted by their reaction with the bicarbonate and carbon dioxide. Chloride is consumed in the chlorine evolution reaction, which results in depletion of chloride ions adjacent the anode. The sodium ions are transported away

from the anode by means of migration. The concentration profiles of all ions are closely related through the electro-neutrality condition.

## 5 CONCLUSION

In this work we have demonstrated two numerical models of EChT (non-buffered and buffered models) that predict electrolyte diffusive and migratory transport near the anode and cathode in a diluted solution, with the presence of buffer in the medium. The system is solved, for each time step, by a finite elements technique in a fixed domain and with a variable mesh that allows greater accuracy near the anodic and cathodic boundary region. The purpose of this work is to describe the pH distribution near the electrodes inserted in the tumor tissue.

The main goal of this paper is to make explicit numerical resolution of Nilsson's models. We introduced both electrodes and higher dimensions to the model which makes it more reliable than the previous one dimensional and single electrode models. We detailed the parameter values and the discretization method that make the models function better. This approach opens a promising area of research that may help in the interpretation of the real consequences of an EChT applied to tumor tissues. We believe this could have significant implications in the future design of optimal operative conditions and dose planning of this kind of therapy.

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