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Fluid flow electrophoresis model

Joseph D. Hickey*, Richard Gilbert

Department of Chemical Engineering, University of South Florida, 4202 E. Fowler Ave. ENB 118, Tampa, FL 33620, USA

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Abstract

Molecular delivery via electroporation is typically done via molecular diffusion and tissue perfusion. The inherent variability in those distribution methods limits the efficacy of this medical and laboratory technique. Electrophoresis has been shown to improve the distribution and placement of the molecule [Gene Therapy 9 (2002) 1286]. This paper presents a fluid flow model for electrophoresis in tissues. Parallel plate and four-needle needle array electrodes are the electrodes modeled as the delivery devices. The parallel plate electrode produces a homogeneous distribution of the analyte but the needle array electrode creates a peak where the electric field effects diminish.

Keywords: Fluid; Electrodes; Electrophoresis

1. Introduction

Electroporation molecule and gene delivery techniques have been used to treat cancer [2] and increase resistance to disease [3]. Current electroporation protocols for the delivery of chemotherapeutic agents and DNA plasmids require intravenous, IV, or intratumor, IT, injection and then waiting for the molecule to diffuse through the target tissue. An alternative option is an electrophoreticaly enhanced electroporation delivery system. This method uses an IT injection and electric fields to move ionized atoms and molecules.

Electrophoresis in tissues is a complex problem that has not currently been descriptively modeled. A descriptive electrophoresis tissue model will lead to improved electrode design and treatment molecule placement [1]. A descriptive model will also increase the understanding of the electrophoretic influence over the molecule being delivered. This paper will describe the governing principles and present the initial performance characterization of a fluid flow electrophoresis model.

Coulombic forces due to the applied electric field were the only driving forces considered. Model performance was evaluated using both parallel plate electrodes and a square, four-needle, needle array. Fluid flow values and travel directions were modeled as random decisions.

The model consisted of five elements. Element 1 is an odd number on a side, square element array. The second element is a series of randomly generated flow field values generated by a Park and Miller random number generator [4]. The third element is an initial concentration profile of the analyte studied. Element 4 is the tissue flow rules, and, finally, the fifth element is the effect and direction of the applied force. The synergy of these elements creates an infinitely scalable tissue model.

2. Fluid flow electrophoresis model elements

2.1. Lattice structure

The lattice model for this proof of principle evaluation was an 11×11-element-on-a-side structure, representing a

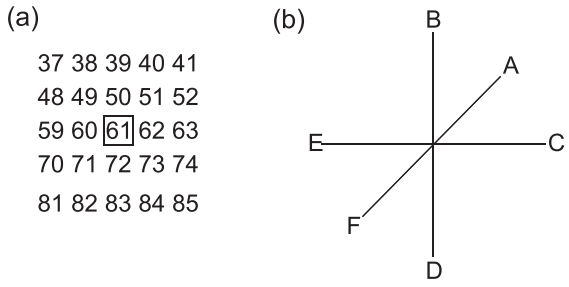

Fig. 1. Tissue lattice and fluid flow direction labels.

* Corresponding author. Tel.: +1-813-974-7477; fax: +1-813-974-3369.
E-mail address: hickey@eng.usf.edu (J.D. Hickey).

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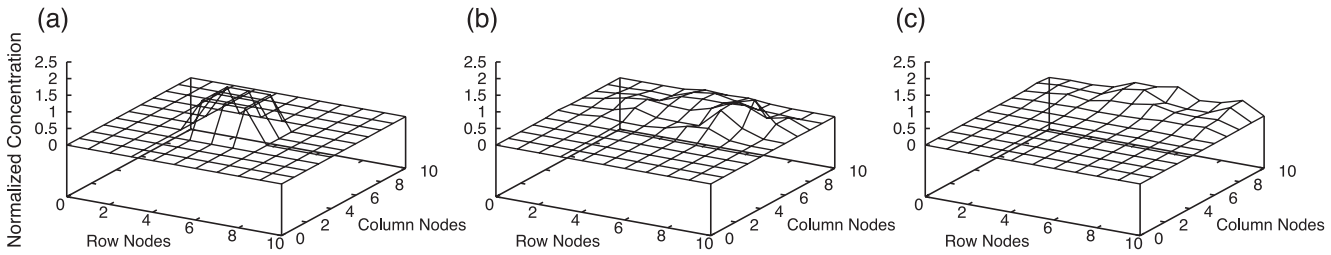

Fig. 2. Parallel plate electrode.

1-cm-on-a-side square. This size was selected because it scales conveniently to typical experimental conditions and a small array simplifies prototyping flow rules. An odd number array was selected because it has a definite center. A homogeneous tissue that had a random flow pattern between the different nodes was assumed as the preliminary model bed.

2.2. Tissue flow field values

The Park and Miller randomly generated flow values ranged from 0 to 1 whereby a value of 0 was a completely obstructed flow and a value of 1 approximated completely unobstructed flow. The forward or A direction (see Fig. 1b) was always the first flow value chosen. The second flow out of a node was then randomly directed either right, C, or left, E. The direction and residual flow percentage was chosen by the Park and Miller random number generator. The third direction received the remaining fraction of the analyte. The other three directions, B, D and F were excluded from this first analysis. The F direction was excluded because the ionic drift was chosen to only be generally forward. This model can easily be altered to include the B and D directions through the adaptation of the flow rules to a three-dimensional system.

2.3. Initial concentration profile

The initial concentration profile was mapped onto a three-node on a side square of normalized value (see Fig. 2a). This profile can easily be changed depending on the shape required. A circular initial concentration distribution with tapering values the further from the center is close to experimental, but it requires a larger lattice structure. This will be included in the next iteration of this tissue flow model.

2.4. Tissue flow rules

The simulation starts with an initial amount of an analyte in a given node (see node 61 in Fig. 1a). The amount of the analyte changes in node 61 and the surrounding nodes, e.g., nodes 60, 62 and 50, as the analyte is moved to and from the individual nodes as a function of electric field, fluid viscosity, flow obstruction, flow direction and time. The flow is driven by the electrophoresis force applied to the analyte by the electric field. Reverse flow was eliminated from the flow rules because the positive electric field was applied into the page for Fig. 1b. The three flows out of a node are in the A, C and E directions (Fig. 1b). Flow out of and into each node was a function of the initial state of that node and the surrounding nodes, the flow pattern of that node and the surrounding nodes and the force of the electric field on the analyte in that node.

2.5. Effect of electric field on flow pattern

The electric field force is a scaler that is calculated from the sum of the driving Coulombic and retarding frictional forces. For the parallel plate model, this value was chosen to be identical everywhere but for the needle electrode, the values vary as a function of location to the opposing electrode pairs [5]. The individual node voltage values were calculated using an electric field tissue map and the voltages were then converted into force values.

3. Results

The motion of potassium ions was followed in both the parallel plate electrode and the needle electrode submodels. Each image in Figs. 2 and 3 is 350 ms apart. The parallel plate

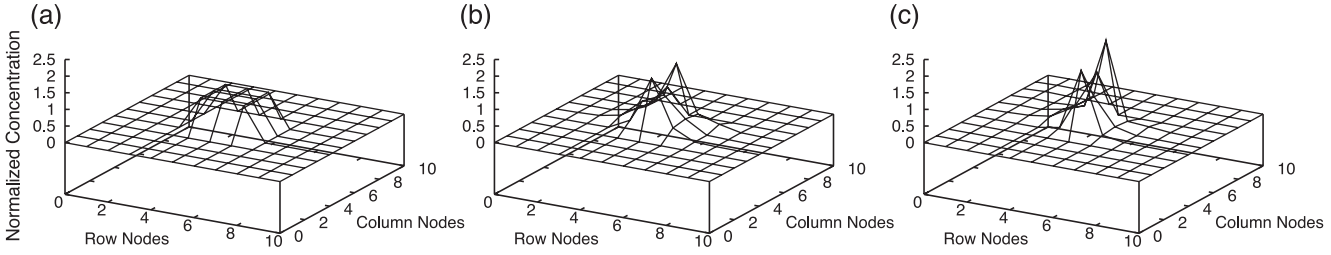

Fig. 3. Needle electrode.

electrode seen in Fig. 2 forced the analyte away from the anode and toward the cathode. The needle electrode forces the ion away from the anode and toward the cathode but due to anisotropy of the electric field, the analyte is piled into a peak (see Fig. 3). This concentrated area of ions will diffuse over time as a function of Coulombic interaction and diffusion but at a much slower rate than graphically examined [6].

References

[1] D.A. Zahroff, R.C. Barr, C.-Y. Li, F. Yuan, Electromobility of plasmid dna in tumor tissues during electric field-mediate gene delivery, Gene Therapy 9 (2002) 1286–1290.

[2] M.J. Jaroszeski, D. Coppola, C. Pottinger, K. Benson, R.A. Gilbert, R. Heller, Treatment of hepatocellular carcinoma in a rat model using electrochemotherapy, European Journal of Cancer 37 (2001) 422–430.

[3] M.L. Lucas, R. Heller, Immunomodulation by electrically enhanced delivery of plasmid DNA encoding IL-12 to murine skeletal muscle, Molecular Therapy 3 (2001) 47–53.

[4] W.H. Press, S.A. Teukolsky, W.T. Vetterline, B.P. Flannery, Numerical Recipies in C, 2nd ed., Cambridge Univ. Press, Cambridge, UK, 1992.

[5] D. Miklavčič, D. Šemrov, H. Mekid, L.M. Mir, A validated model of in vivo electric field distribution in tissues for electrochemotherapy and for DNA electrotransfer for gene therapy, Biochimica et Biophysica Acta 1523 (2000) 73–83.

[6] J.D. Hickey, Modelling the motion of ions and molecules in electroporation and electrophoresis field conditions, University of South Florida, College of Arts and Sciences, Department of Physics, Tampa, Florida, 2003.