Brazilian Journal
of Chemical
Engineering

ISSN 0104-6632
Printed in Brazil
www.abeq.org.br/bjche

Vol. 33, No. 01, pp. 123 - 131, January - March, 2016
dx.doi.org/10.1590/0104-6632.20160331s20150032

CHOOSING THE OPTIMAL GEL MORPHOLOGY IN ELECTROPHORESIS SEPARATION BY A DIFFERENTIAL EVOLUTION APPROACH (DEA)

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(Submitted: January 19, 2015 ; Revised: June 30, 2015 ; Accepted: July 14, 2015)

Abstract - This paper introduces an effective optimization approach to investigate the morphological effects of nanocomposite gel electrophoresis and operational parameters (see below) by integrating the numerical simulations based on finite element method and population-based search algorithm such as *differential evolution*. Simulations are performed to study the solute transport by Convection-Diffusion-Electromigration in a microvoid with axially varying cross-section. Morphological parameters such as channel shape and size, as well as operational parameters such as pressure gradient in the axial direction, and electric field in the orthogonal direction were considered and found to have considerable effects on the separation resolution in electrophoresis. Key observations on the most favorable hydrogel morphology for an efficient electrophoresis separation are presented.
Keywords: Gel-Electrophoresis; Differential Evolution; Optimal Separation; Hydrogel Morphology Design; Electrophoretic Transport; Axially-Diverging Pores.

INTRODUCTION

The global market for commercial biotechnology based separation systems reached $14.6 billion in 2011, and it will further grow to $26.7 billion at an estimated compound annual growth rate (CAGR) of 12.8% by 2016. Specifically, the electrophoresis based separations market is set to reach US $1.6 billion by the end of 2013 (Research, 2011). Traditionally, two-dimensional gel electrophoresis (2DE) have been used for proteomic analyses which separate proteins according to two distinct protein characteristics, size and charge (Kolch *et al*., 2005). The ongoing challenge, for proteome analysis by 2DE, is the reproducible separation of complex protein mixtures with a high degree of resolution and to retain native state of the protein during the separation (Hortin *et al*., 2006). Improvements in gel electrophoresis will facilitate important advances in cancer diagnosis (Zhang *et al*., 2010), personalized medicine (Weston and Hood, 2004), and environmental proteomics (Keller and Hettich, 2009) to name just a few cases.

Gel morphology and charge effects have traditionally been manipulated by varying the copolymer composition (Stellawagen, 2009; Stellawagen and Stellawagen, 2009; Simhadri *et al*., 2010), but recent reports show that novel morphological changes can also lead to unique separations. Morphological changes can be induced in the gel using templating methods (Rill *et al*., 1996) and nanoparticle addition (Schexnailder and Schmidt, 2009). Of these various approaches to the hydrogel modification, the presence of nanoparticles can bring a significant change to the chemical physics of the gel morphology, and provide enhancements to other important properties

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(Simhadri *et al*., 2010). Nanocomposite (NCG) gels (i.e., nanoparticles embed into the polymer gel matrix) have been recently considered to have a beneficial effect to increase the efficiency in separations technologies for biomolecules. The particle surface and the particle shape as well as orientation of the nanoparticles - ceramic, metallic, polymeric - inside the gels can assist to improve separation by modifying both the effective mobility and the effective diffusivity of the solute, see Oyanader and Arce (2005). Procedures for the manufacturing of the nanocomposite gels have been reviewed by Simhradri *et al*. (2010) and Thompson *et al*. (2012). Several aspects related to the manufacturing and characteristics of these novel nanocomposite gels for protein separations has been reviewed by Simhadri *et al*. (2010); experimental observations on enhancements of protein electrophoretic mobilities have also been reported (Huang *et al*., 2006; Thompson *et al*., 2010; Thompson *et al*., 2012).

In gel electrophoresis, the gel matrix has pores of different sizes, geometries and morphologies (shapes) which may act as a sieve for a molecule by providing the "fabric" for allowing the differentiation of motion of the different molecules that (ultimately) leads to separation. Experimental evidences (Thompson *et al*., 2010; Thompson *et al*., 2012) have shown that this "fabric" displays a tortuous network of paths through which the solute migrates in the presence of, for example, an electric field. In this network (or fabric) the movement of the biomolecule is affected by several "external" parameters (related to the applied field), and "internal" or, alternatively, material characteristics of the gel including porosity, orientation of pores, geometry of pores, etc (the TEM images of nanocomposite hydrogels obtained recently clearly indicate a network of a porous or cell-like structure in the gels, see Thompson *et al*, 2012). The presence of nanoparticles in these gels adds a significant change to the chemical physics of the gel morphology, in addition to expanding the multiscale nature of the material (Simhadri *et al*., 2010). As illustrated in Figure 1, NCG's may be described as "porous media" having microchannels or microvoids with (possibly) different geometries, length, sizes, shapes, etc. Therefore, the solute transport may be studied by using capillary-based models of porous media employed by researchers in other fields (Adler, 1992; Sahimi, 2011). Because the morphology of the gels in these nanocomposite materials may be altered by modifying the cross-linker density, the geometrical characteristics of nanoparticles, and the orientation of the particles or microvoids these capillary microvoid domains are useful model systems for exploring the morphological effects of the NCG on electrophoretic separations.

This contribution deals with two important aspects of gel electrophoresis, i.e. 1- Porous media and its capillary view for describing gel morphology and 2- Optimization methodologies in designing new morphological structures. In the paragraphs below, we will review relevant work pertaining these two aspects.

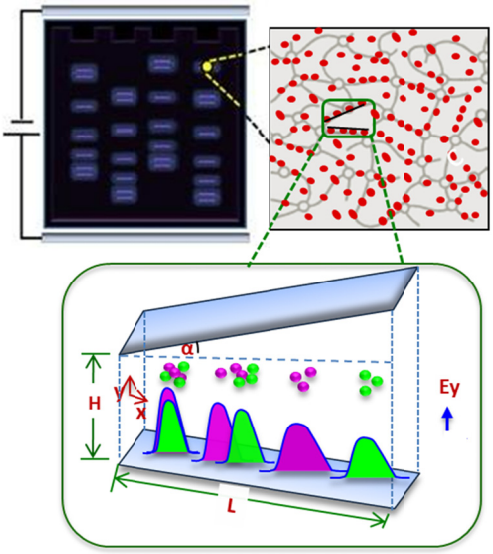

Figure 1: Schematic of the microvoid domain showing the different scales involved in the system.

Porous Media and its Capillary View for Describing Gel Morphology

The approach of describing electrophoretic transport in gels based on a "porous medium" view of the gels follows previous successful studies (Oyanader and Arce 2005; Sauer *et al*., 1995; Trinh *et al*., 1999) in analyzing the role of scaling and electric field orientation in electrophoresis. As such, a single microvoid domain of idealized geometry i.e., rectangular shape is utilized to demonstrate the potential role of the morphology on electrophoretic separation of point Brownian particles. This single domain may be viewed as a member of a massively arrayed micro/nanovoid (MAN) collection that could be viewed as a representation of the microvoids realistically present in a NCG. Understanding the role of the morphological characteristics (i.e., different shapes) of the microvoids of these NCG's on electrophoretic separations is an exciting prospect that could allow for the design of new micro/nanostructures with potential tunable sizes, shapes, and orientation. For example, Trinh *et al*. (1999) used a simple geometry of the capillary domain and found that a significant role

was played by geometrical parameters in the study of transport properties relevant for the separation of biomacromolecules. Ross *et al*. (2004) compared straight and diverging microchannels considering initial injection width of the dye as the primary factor for determining the best separation resolution. They found that diverging channels give the best resolution when the injection width is relatively wide. On the other hand, when the injection width is small, then straight channels gave the best resolutions. Dennison *et al*. (1982) found that (macroscopically) electrophoretic resolutions are higher in conical/wedge shaped polyacrylamide gels than the regular gels. Protein transport in pores of different sizes have also been studied in membrane-based separations (Yu *et al*., 2003). Berezhkovskii and Dagdug (2011) and Berezhkovskii *et al*. (2010) derived formulas to show the dependence of the transport coefficients i.e., effective mobility and diffusivity on driving force and geometric parameters of the capillary based on mapping the particle random walk. Their results showed the potential impact of axially-varying shapes within a microvoid and found qualitative differences in the dependence of effective mobility and diffusion coefficient on the driving force in capillary domains formed by cylindrical and spherical compartments. Li *et al*. (2011) modeled dispersion of anisotropic particles moving in nanofilters operating in Ogston regime. They compared these transport parameters obtained from the 1-D analytical model (based on macrotransport theory) to the ones obtained from 2-D numerical model. Model of a microfabricated device having repeated arrays of alternating deep wells and shallow slits is used for the analysis. Under experimentally relevant electric fields, the results show the field and size dependences of mobility and diffusivity with maximum difference on the order of 10%. Dutta *et al*. (Dutta *et al*., 2006) reviewed the effect of dispersion due to fluid shear in pressure-driven transport of fluid and solute on the channel geometry in microfluidic devices. They analyzed dispersion in rectangular, elliptical, trapezoidal, and isotropically etched designs and proposed optimum cross-sectional designs which have been shown to reduce the dispersion arising from the presence of channel walls.

Optimization Methodologies in Designing New Morphological Structures

In order to design a new nanocomposite gel there will be several morphological-based possibilities as well as operational-based parameters that need to be considered. In such a multiparameter system, simultaneously changing all the parameter values increases the number of possibilities that can affect the electrophoresis separation efficiency. Therefore, *a systematic optimization-based approach is appealing* because an optimal separation of practical use can be achieved efficiently from a complete understanding of all possibilities. This (overall) morphology-based optimization could be helpful in assisting potential new designs that work towards systematically generating a multidimensional structure having broader tunability (Thompson *et al*., 2008) for a given type of molecule.

The concept of automation through optimization techniques with the objective of increasing the separation quality of biomolecules is becoming increasingly important in the field of electrophoresis. For example, McGuffin and Tavares (1997) developed a computer-based program for the systematic optimization of separations in capillary zone electrophoretic systems; this was accomplished based on a combination of regression and theoretical models which requires no experimental data for implementation. They calculated both the separation resolution between the adjacent species and the chromatographic resolution static (CRS), a response function used for the chromatographic separations to assess the overall quality of the separation. The main advantage of this optimization program is that by carefully adjusting the input parameters such as capillary dimensions, and buffer composition, the instrumental parameters for optimal experimental conditions can be predicted. Pfeiffer *et al*. (2004) implemented both heuristic and numerical optimization techniques for the design of microchip-based capillary electrophoresis systems which have greater system performance while simultaneously occupying less area. Buchholz *et al*. (2002) used capillary electrophoresis in combination with genetic algorithms with the application to increase the separation quality of nucleotide and nucleotide sugar separation. There are several optimization algorithms that have been applied to other electrophoresis (Buchholz *et al*., 2002; McGuffin and Tavares, 1997) techniques, but the application to gel electrophoresis seems to be missing. In this contribution, a systematic-optimization-based approach is introduced and its first successful application to study the effect of a rectangular and diverging microvoid (i.e., an axially varying cross section) on the separation performance of the material is presented.

Global optimization techniques can be classified as deterministic and stochastic methods. Deterministic methods require a first or second order derivative of the objective function to exist and also will increase the difficulty in searching optimum solution

(Rangaiah, 2010). Stochastic methods for global optimization rely, on the other hand, on probabilistic approaches. They are easy to implement and require no transformation of original problem (treated as a black box) so that it can be linked to any other software in which the dynamic model of the electrophoretic system has been implemented. One such stochastic method for global optimization of interest to the current work is the Differential Evolution (DE) method presented by Storn and Price (1997). It is a stochastic population-based optimization algorithm. Since its introduction, DE has been applied for the optimization of reactive distillation processes, thermal cracking operation, heat exchanger equipment design to name a few in the field of engineering (Babu and Sastry, 1999).

AN EFFECTIVE SOLUTION METHODOLOGY: BRIEF DESCRIPTION

The methodology described in this section will be used for the exploration of (optimal) potential morphological effects and favorable operation conditions applicable, potentially, to enhance electrophoresis-based species separations by using, for example, nanocomposite gels. The combination of the dynamic numerical model in COMSOL software with the Differential Evolution (DE) (Storn and Price, 1997)-one of the most robust population-based search algorithms available is proposed for the first time to study the species transport in electrophoretic systems. As known (COMSOL-Multiphysics, v3.5a), COMSOL is a software for the simulation of multiphysics problems and it is based on finite element method (FEM). The main advantage of the use of COMSOL lies in its capabilities to solve the potential highly nonlinear characteristics of physicochemical problems without over constraining their solution with simplifying assumptions. The modeling and analysis of the different model applications are conducted through modules within the COMSOL Multiphysics software interface. The module created in COMSOL, for handling electrophoretic transport problems such as the one of interest in this work is used. This module is efficient for formulating and solving the convection-electromigration-diffusion transport involved. In addition, Differential Evolution (Storn and Price, 1997) is comparatively a recent technique in the class of population based search heuristics and it has emerged as one of the most favored techniques by engineers for solving continuous optimization problems (Ali *et al*., 2009; Babu and Angira, 2003).

For the current paper, the transport characteristics of solute are studied in an expanding (or diverging) domains by modeling the axially-expanding domain using convective-diffusive-electromigrative transport equations based on continuum mechanics. There are several parameters that need to be considered related to the study of the effect of the divergent angle, α, of the idealized microvoid domain shown in Figure 1. Indeed, several discrete combinations of morphological (such as height and length of the domain) and operational parameter (electric field, flow rate) values are possible if approached in an empirical manner. In order to reduce the time and cost necessary to potentially design the internal structure of gels for improving separation quality, optimization methods such as DE can be used as a tool to predict or suggest optimal design conditions that, in addition, will guide the selection of optimal conditions for the experimentalist. The flowchart shown in Figure 2 illustrates the steps carried out for the entire optimization procedure for its application to electrophoresis in nanocomposite gel used in this study. The functionality of COMSOL's integrating capabilities with MATLAB (MATLAB, 2008) (M) has been very advantageous for this work so that the COMSOL-generating M-file can be converted into a black box (optimization method guided by the value of the electrophoresis resolution) for executing the DE optimization algorithm. Application of DE in the optimization processes require electrophoretic spatial resolution values only and hence identification of parameters using this strategy is possible without a need for a mechanistic understanding of the discrete combinations of parameters (Price, 1999). The first step in the optimization is the generation of randomized set of parameter values of each design variable. The parameter values are given to the FEM package where the parametrically defined FEM model of the electrophoretic system is updated according to the parameter values set of the microvoid domain. Then the separation quality of the given sample mixture is judged by evaluating the objective function value (specified by electrophoretic resolution, see Equation (4)) of all the individuals of population (design parameter set) and finding out the best parameter values of the current generation in the computational iteration. The individual parameter values obtained from the first generation forms the basis set of parameter values for the next generation. The cycle of DE generating new values for the desired parameters to be optimized, and COMSOL simulating the electrophoresis model while keeping other parameters constant is repeated until a best separation criterion (as given by the electrophoresis resolution, Equation (4)) is

reached. This approach is well suitable for capturing the numerous aspects and parameters needed to modeling separation in gel-like materials.

One of the most important variables in electrophoresis used to measure the separation performance of the system, is the spatial resolution (R) (Giddings, 1991); mathematically defined as the ratio of distance between the two adjacent solute bands to the band dispersion (see Figure 3). By using a chromatographic-like analysis of resolution, the position of the peaks and the band dispersion can be calculated from the statistical moment analysis in the resolution step given in the flowchart (Giddings, 1991). Typical desirable resolution is 1.5 which corresponds to "baseline" resolution (Giddings, 1991). This is utilized as the objective function of the optimization problem.

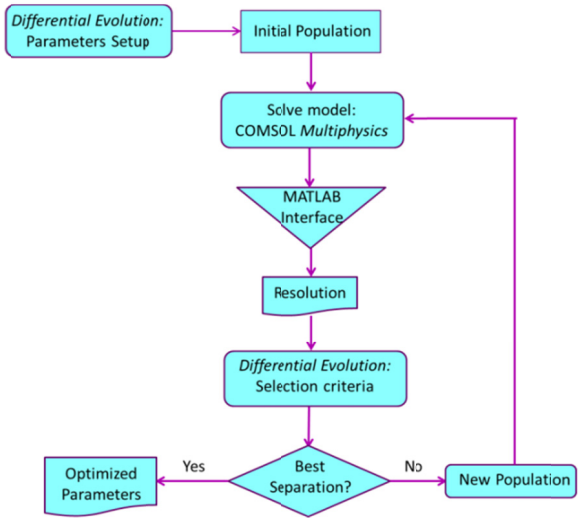

Figure 2: Novel exploration of morphological effects of nanocomposite gel electrophoresis by integrating the numerical simulations based on finite element method (COMSOL) and population-based search algorithm (Differential Evolution).

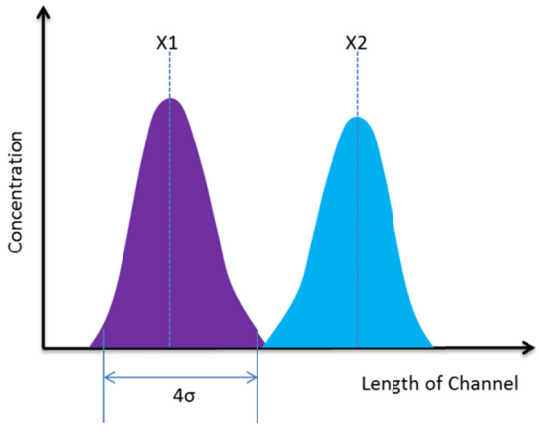

Figure 3: Resolution of two peaks represented as Gaussian distributions.

MODEL SYSTEM DESCRIPTION

In order to determine possible optimal parameter values, the optimization-based approach sketched in Figure 2 is applied to the diverging microvoid domain as shown in Figure 1. This particular capillary's geometry is described in Cartesian coordinates with length, L and height, H, and with an axially-varying cross section (i.e., a diverging domain), that is controlled by the inclination angle, α. An electrical field is applied in the orthogonal direction denoted by the non-dimensional parameter Ω (Sauer *et al.*, 1995); and a pressure gradient in the axial direction. The key assumptions for conducting this analysis are as follows: (i) No significant charges are present on the walls of the microdomain (i.e., this is an electrophoretic process only and with negligible electro osmotic flow); (ii) Electroneutrality condition is valid at all times (iii) Joule heating is neglected, and (iv) Assume that by system symmetry, the concentration variations of the sample species are not present in the direction perpendicular to the xy-plane, which reduces a 3-D model to a 2-D problem.

Each charged species in the buffer housed in the microvoid moves or transports by diffusion, convection, and electromigration since there is pressure gradient applied, and orthogonal electric field. The molar species continuity equation of transported species in the dilute solution limit, with the molar flux is given by the species-continuity (Masliyah and Bhattacharjee, 2006) equation

$$\frac{\partial C_i}{\partial t}+v_x\left(\frac{\partial C_i}{\partial x}+\frac{\partial C_i}{\partial y}\right)+v_y\left(\frac{\partial C_i}{\partial x}+\frac{\partial C_i}{\partial y}\right)= \frac{\partial}{\partial x}\left(\mu_i F z_i c_i \frac{\partial \phi}{\partial x}\right)+\frac{\partial}{\partial y}\left(\mu_i F z_i c_i \frac{\partial \phi}{\partial y}\right) +\frac{\partial}{\partial x}\left(D_i \frac{\partial C_i}{\partial x}\right)+\frac{\partial}{\partial y}\left(D_i \frac{\partial C_i}{\partial y}\right) \quad (1)$$

where, c_i is the concentration of species i, F is the Faraday constant, z_i is the charge of species i, μ_i is the electrophoretic mobility, ϕ is the electric potential, D_i is the diffusion coefficient of species i. For the case under study, a Gaussian profile of solute mixture is injected into the microvoid domain at time t=0 at the center of the microdomain.

The applied electric potential ϕ, can be calculated by solving the Laplace equation for electric potential equation with constant conductivity and having a fixed potential k_2 applied in orthogonal directions on the boundary (Oyanader and Arce, 2005;

Sauer *et al*., 1995). The hydrodynamic velocity of the solvent of the system is determined by using the Navier-Stokes equation with suitable boundary conditions.

Initial and Boundary Conditions

A mixture of two sample test solutes A and B (point particles), each having a fixed valence (z), mobility, diffusivity, and a total initial concentration are injected at the center of the inlet wall of microvoid. The mathematical representation of initial and boundary conditions are given below.

The walls of the microvoid are assumed to be impermeable to the solute transport, and thus the no-flux boundary condition is applied and is given as

$$\left.\begin{aligned} D_i \left.\frac{\partial C_i}{\partial y}\right|_{y=-h(x)} + v_y C_i\Big|_{y=-h(x)} + \mu_i C_i \left.\frac{\partial \phi}{\partial y}\right|_{y=-h(x)} &= 0 \\ D_i \left.\frac{\partial C_i}{\partial y}\right|_{y=h(x)} + v_y C_i\Big|_{y=h(x)} + \mu_i C_i \left.\frac{\partial \phi}{\partial y}\right|_{y=h(x)} &= 0 \end{aligned}\right\} \quad (2)$$

At the initial time, t=0 a Gaussian plug of solute is injected at the center of the microvoid that is mathematically given by,

$$C_i(x,y,t=0) = \frac{C_0}{\sigma_0\sqrt{2\pi}} e^{-\left(\frac{x^2+y^2}{2\sigma_0^2}\right)} \quad (3)$$

where, σ_0 is the initial injection standard deviation, and C_0 is the initial concentration of solute.

Resolution

The most important parameter that measures the performance of the system is the resolution; this parameter helps to understand how the solute bands are separated sufficiently so that separation can take place. Giddings (1991) mathematically defined the resolution as a ratio of distance between the two adjacent solute bands to the function of band dispersion as

$$R = \frac{x_2 - x_1}{4\sigma_{avg}} \quad (4)$$

In the above equation x_1 and x_2 can be obtained from the first moments whereas the average standard deviation of the two bands can be calculated from the second moments for the solute bands approximated as Gaussian distributions (Giddings, 1991). Typical desirable resolution is 1.5 which corresponds to "baseline" resolution. The resolution can be impeded due to dispersion in the microvoid which is a result of diffusion, microvoid geometry, and flow conditions, among other parameters.

Numerical illustration of this model to show the optimized parameters for separation will be discussed in the next section.

ILLUSTRATIVE RESULTS AND DISCUSSION

This section includes graphical illustrations showing the numerical results obtained from the simulation of rectangular diverging microvoid domain (as sketched in Figure 1) of a single microcavity in, for example, a nanocomposite gel material.

The numerical approach is incorporated into the optimization routine as shown in Figure 2. In total five parameters i.e., microvoid size (L/H), shape (given by inclination angle α), dimensionless orthogonal potential (Ω), flow rate of the buffer (given by Pe) and mobility ratio of two species were considered to study the influence on the separation quality and the selected parameter values are motivated by the analysis of electric field effects given in Oyanader and Arce (2005). Even though numerous parameters are available the strategy of optimizing the effect of microvoid shape (α), and operational parameters (Ω, Pe) is utilized while fixing the other parameters.

The selected parameters, their ranges and resulting optimized parameters are shown Table 1 and Table 2 for aspect ratios of 9 and 15, respectively. Overall, from both the tables it can be observed that microdomains which have smaller values of the divergent angle are able to produce high separation resolution compared to higher angle values. As the species band travels down the axially varying cross section, it broadens or disperses and this dispersion can be attributed to an increase of diffusion over convection and microvoid morphology. This increased dispersion (over convection) smears the species bands, leading to a lower separation efficiency of the electrophoresis separation; this result is clearly due to changing the competition between diffusive-transport with respect to the convective-transport. As the mobility ratio increases the optimized values of the operational parameter i.e., Ω values are lower than for the case of lower mobility even though the resolutions are similar in values for example, for fixed Pe=2, α=0°, L/H=9 the highest resolution of 2 is obtained at Ω=4.8 when μ_b/μ_a=2, but the same resolution value is obtained when Ω=3.9 for a

μ_b/μ_a=5. From this it can thus be said that it appears to require a smaller magnitude of orthogonal electric field when the difference in species mobility becomes higher. However, as the Pe is increased (for the fixed L/H, and model solution run time) the resolution appears to decrease and also it requires higher values of orthogonal electric field. For example, for a fixed time, α=0°, μ_b/μ_a=2, L/H=9 when Pe=2 the resolution is 2.0 when Ω=4.8, but the resolution reduced is to 1.6 for Pe=6, and further reduced to 1.2 for Pe=10 and also the values of orthogonal field needed are also higher as the Pe increases. Similar trends are observed for an aspect ratio of L/H=15 but however the values of resolution and Ω are different from those of the L/H=9 case which means that the change in the size parameter of the microvoid has an important effect on the separation efficiency.

Table 1: Optimized values of selected parameters and their effect on electrophoresis separation resolution for L/H=9.

Pe=2, μ_b/μ_a =2						**Pe=2, μ_b/μ_a =5**				
α	0°	0.5°	1°	2°	3°	0°	0.5°	1°	2°	3°
Ω	4.8	5.0	5.1	6.1	6.4	3.9	4.0	4.2	4.1	2.9
R	2.0	1.5	1.1	0.72	0.49	2.0	1.5	1.1	0.74	0.47
Pe=6, μ_b/μ_a =2						**Pe=6, μ_b/μ_a =5**				
α	0°	0.5°	1°	2°	3°	0°	0.5°	1°	2°	3°
Ω	5.8	6.0	6.0	6.9	7.1	4.0	4.1	5.3	4.3	5.0
R	1.6	1.1	0.91	0.46	0.28	1.6	1.1	0.82	0.46	0.28
Pe=10, μ_b/μ_a =2						**Pe=10, μ_b/μ_a =5**				
α	0°	0.5°	1°	2°	3°	0°	0.5°	1°	2°	3°
Ω	7.0	7.2	7.1	8.0	8.3	3.9	5.0	5.1	4.9	5.2
R	1.2	0.81	0.55	0.29	0.16	1.2	0.8	0.55	0.29	0.16

Table 2: Optimized values of selected parameters and their effect on electrophoresis separation resolution for L/H=15.

Pe=2, μ_b/μ_a =2						**Pe=2, μ_b/μ_a =5**				
α	0°	0.5°	1°	2°	3°	0°	0.5°	1°	2°	3°
Ω	4.9	5.2	6.0	6.2	6.3	4.0	3.9	4.1	4.3	4.3
R	2.0	1.2	0.83	0.44	0.26	2.0	1.3	0.85	0.45	0.30
Pe=6, μ_b/μ_a =2						**Pe=6, μ_b/μ_a =5**				
α	0°	0.5°	1°	2°	3°	0°	0.5°	1°	2°	3°
Ω	5.1	5.0	6.2	7.2	8.1	3.8	4.0	4.0	5.0	5.1
R	1.6	0.92	0.56	0.24	0.12	1.6	0.91	0.55	0.24	0.15
Pe=10, μ_b/μ_a =2						**Pe=10, μ_b/μ_a =5**				
α	0°	0.5°	1°	2°	3°	0°	0.5°	1°	2°	3°
Ω	6.9	7.0	7.4	8.1	10.0	4.0	5.3	5.3	5.5	6.2
R	1.2	0.62	0.35	0.14	0.064	1.2	0.65	0.35	0.14	0.07

SUMMARY AND CONCLUDING REMARKS

In this contribution, an effective differential evolution approach (DEA) is introduced and implemented to obtain the optimal morphological and values of the operational parameters describing gel electrophoresis separation. The hydrogel's structure is described by using a capillary model and, in particular, a rectangular geometry of their microvoid is used. The parameters considered include the microvoid size, L/H and the microvoid shape, *α* (morphological); the flow rate of the buffer given by the Pe and the dimensionless orthogonal electric field, Ω (operational); and the mobility ratio of species (transport). From the analysis, we can infer the following key observations: 1-All the parameters mentioned above had an effect on the separation resolution for electrophoresis; however, the DEA does an excellent performance in handling the multiparameter space to suggest optimal values; 2- The highest possible separation resolution can be obtained when the angle of deviation of the microvoid domain is relatively small; and 3- Imperfections in microvoids, i.e. deviations from an ideal type of geometry such as rectilinear channels or cells (obtained by a magnetic orientation of the nanoparticle in the gels, see Thompson *et al*., 2012) should be avoided in order to increase separation efficiency.

In particular, and as an overall conclusion, this study suggests that the magnetic alignment of nanoparticles within the gels achieved by Thompson *et al*. (2012) and that showed potential for improving separation has now a *possibly fundamental explanation based on the study reported here*. This study also suggests (for the first time and to the best of our knowledge) a possible useful approach to choose both a favorable hydrogel morphology as well as optimal values of the operating parameters for a given type of separation medium The use of nanoparticles (Thompson *et al*., 2010; Thompson *et al*., 2012) such as ceramic, metallic or polymer types might be an excellent way to achieve this objective by orienting them during the gels manufacture with the use of magnetic fields, for example.

ACKNOWLEDGMENTS

Dr. J. Simhadri is grateful to research assistanceships provided by the Center for Manufacturing Research (CMR) and the Center for the Management, Utilization and Protection of Water Resources from Tennessee Technological University, Cookeville, Tennessee-USA.

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