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High-resolution dynamic computer simulation of electrophoresis using a multiphysics software platform☆

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ABSTRACT

The modeling and simulation software COMSOL Multiphysics® was recently extended with an electrophoretic transport interface. Its performance was investigated by comparison to results obtained using the 1D dynamic electrophoresis simulators GENTRANS and SIMUL5. Simulations of zone electrophoresis, isotachophoresis, isoelectric focusing and of an oscillating electrolyte system were performed. Smooth profiles were essentially identical indicating that the COMSOL electrophoretic transport interface is able to reproduce results of the 1D simulators. Differences in the way the respective numerical schemes handle steep concentration gradients and associated instabilities were observed. The COMSOL electrophoretic transport interface is expected to be useful as a general model for simulations in 1D, 2D or 3D geometries, as well as for simulations combining electrophoresis with other physical phenomena.

1. Introduction

Electrophoresis is concerned with the migration of charged species in solution under application of a uniform electric field. For exploring the fundamentals of electrophoretic systems, or for predicting the outcome of a given separation prior to any laboratory experiments, numerical treatment utilizing computer simulation is a valuable tool [1]. The three 1D dynamic electrophoresis simulators GENTRANS [2], SIMUL5 [3] and SPRESSO [4] are well-characterized and have been shown to produce identical results given the same input parameters [5]. These models are based on the principles of electroneutrality and conservation of mass and charge, and are composed of a set of coupled nonlinear partial differential equations (PDE) together with equations describing protolysis. Varying the initial component distribution and boundary conditions allows simulating all common modes of electrophoresis including zone electrophoresis (ZE), isoelectric focusing (IEF) and isotachophoresis (ITP). By providing input information about the component's mobilities and pK_a values, output in the form of concentration, pH and conductivity distributions at specified time points and the temporal behavior of the current density is obtained. Recently, GENTRANS and SIMUL5 were extended with algorithms that describe 1:1 chemical equilibria between solutes and a buffer additive, such as those associated with chiral separations [6–8].

1D models are useful for simulation of electrophoretic methods commonly used in the laboratory, including those performed in fused-silica capillaries or in straight microfluidic channels. However, to simulate 2D or 3D phenomena, e.g. potential dispersion effects across channel crossings or turns in microfluidic devices, multidimensional simulation software is required. This was realized for example by Shim et al. who developed a 2D model for simulation of IEF in microchannels [9] as well as by Chatterjee whose 3D model was designed for simulation of various phenomena, including electrophoresis, in microfluidics applications [10]. Electrophoresis simulation models have been created also in COMSOL Multiphysics® (COMSOL AB, Stockholm, Sweden) referred to as COMSOL in this paper. COMSOL is a commercial multipurpose software package for modeling and simulating a diversity of physics-based phenomena that can be described with PDEs [11]. The complete software platform is composed of a set of modules, which include pre-built computational packages (so called "physics

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interfaces") of equations and boundary conditions for setting up and coupling models. For simulations including electrophoresis, COMSOL models have been created e.g. to simulate electrokinetic sample stacking [12,13], and ITP in 1D [14,15], 2D [16,17] and 3D [18] geometries.

To increase the accessibility of general multidimensional and multiphysics electrophoresis simulations, COMSOL was recently extended by an electrophoretic transport interface. During the development of this interface, data obtained with benchmark simulation examples found in the literature were used to identify weaknesses of initially implemented algorithms and provided the basis for their optimization. The performance of the optimized and released interface in COMSOL version 5.3 has herein been evaluated by comparing the results to those obtained using GENTRANS and SIMUL5. The examples investigated include configurations of ZE, ITP and IEF and an oscillating electrolyte system with complex eigenmobilities. They represent tests for prediction of steep boundaries, treatment of the diffusion current, handling of species mobilities and application of boundary conditions at the ends of the column.

2. Materials and methods

2.1. Main features of the simulators

The 1D simulator GENTRANS is based on the model originally developed by Bier et al. [2] and later modified by Mosher et al. [19–21], and has been described in detail before [22]. SIMUL5, developed by Hruška et al. [3], is a comparable 1D simulator that features a comfortable Windows environment for data input, data evaluation, visual control of the ongoing simulation and visualization of a completed simulation in a movie format. A comparison of GENTRANS and SIMUL5 is given in [5]. A detailed description of and user guide to COMSOL in general, and the electrophoretic transport interface in particular, are included in the product documentation. Herein, only a brief description of all simulators, highlighting their differences, is provided.

All models are based on mass and charge conservation and the assumption of local electroneutrality. Relationships between the different species of a component (e.g. the neutral and dissociated species of a monovalent weak acid) are described by algebraic association/dissociation equilibria with associated equilibrium constants, and component fluxes by electromigration, diffusion and convection are calculated using the Nernst–Planck continuity equation for molecular transport in aqueous solution [2–4]. The mass and charge conservation relations are PDEs in space and time, and discretization of the spatial derivatives allows approximating the PDEs as ordinary differential equations in time. In GENTRANS and SIMUL5 this is performed using the finite difference method. For this method, potential spurious oscillations can generally be eliminated by refining the mesh, which, however, also increases the computation time. To speed up a simulation, GENTRANS includes an optional feature of data smoothing by removal of negative concentrations [5]. This approach may, however, result in prediction of non-physical phenomena, and should thus be used with caution. With SIMUL5 the computational time interval can be decreased when it is operated with a reduced calculation space that features moving borders [3,5]. GENTRANS and SIMUL5 do not include the dynamic adaptive grid approach used to speed up simulations in SPRESSO [4,5]. COMSOL is based on the finite elements method, which allows non-isotropic computational meshes, and is therefore generally more versatile for simulations in complex geometries [23], especially in 2D and 3D. To facilitate the numerical convergence, in-built stabilization schemes, which introduce artificial diffusion, can be employed. The two consistent stabilization methods streamline and crosswind diffusion operate by adding a term to the transport equations in such a way that its magnitude decreases upon approaching the solution. Thus, the solution obtained using these stabilization techniques is a solution also to the original differential equation. Stabilization methods adding artificial diffusion are not used in GENTRANS and SIMUL5.

Table 1
Input parameters for all components included in the simulations.

Component	pK_a	Mobility $\times 10^{-8}$ [m^2/Vs]
Aniline	4.80	3.25
Pyridine	5.18	3.00
Acetic acid	4.76	4.24
Tris	8.30	2.41
β-alanine	3.60, 10.19	3.63[a]
Sodium	–	5.19
Lithium	–	4.10
Potassium	–	7.62
Carrier ampholytes	ΔpK_a 2 (p*I* 3.1–9.9)	3.00[a]
Sebacic acid	4.53, 5.38	2.07, 4.49
Imidazole	7.15	5.20

[a] The same mobility value was used for both charged species.

SIMUL5 is based on a single set of PDEs for computation of all components, whereas GENTRANS and COMSOL support different ways of defining the fluxes of different types of components such as biprotic ampholytes, different types of monovalent and multivalent components, and proteins [5]. All programs require input information about mobility (or diffusivity) and pK_a values. In GENTRANS, the mobility is considered to be independent of the ionic strength for small, monovalent components, whereas COMSOL and SIMUL5 have the optional feature of applying ionic strength corrections. GENTRANS includes a specific module for the treatment of proteins [19–21], which requires a diffusion coefficient and a pH vs. net charge table as input, and the relation between ionic strength and mobility is accounted for via the Linderström-Lang approximation. This treatment of proteins has been incorporated also into the COMSOL electrophoretic transport interface.

GENTRANS and SIMUL5 are 1D simulators and run on a uniform grid. COMSOL allows 1D, 2D, 3D or axisymmetric 1D and 2D geometries. The mesh for computation can be non-isotropic with different resolution in different parts of the geometry, and can either be set by the user or automatically generated. For all programs, input information about initial concentrations and distributions in the separation space of all components needs to be provided together with boundary conditions at the ends of the domain.

2.2. Computer simulations

To compare the output of the simulators, simulations of ZE, ITP, IEF and an oscillating electrolyte system were performed using model systems taken from the literature. Input parameters used in the simulations are given in Table 1. For all included examples, experimental validation of the simulated behavior had been previously performed in various laboratories. For the ZE, ITP and IEF examples, also the dynamics were investigated in detail before [1,4,5,24–30]. Thus, for these cases, data for specific time points are shown only whereas the dynamics are depicted for the oscillating electrolyte system. All the presented examples were performed in 1D using a uniform mesh and without application of convective flow. If not otherwise stated, the GENTRANS results were obtained without smoothing, and streamline and crosswind diffusion were enabled in the COMSOL simulations. COMSOL version 5.3 was used for the COMSOL simulations, and the SIMUL5 simulations were performed using the software version released in 2007 (downloaded from http://www.natur.cuni.cz/Gas). Simulations were performed on Windows 7 based PCs. Since COMSOL version 5.3 requires a 64 bit and GENTRANS only runs on a 32 bit Windows environment, dif-

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