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

Saara Mikkonen[a], Henrik Ekström[b,c], Wolfgang Thormann[a,*]

[a] Clinical Pharmacology Laboratory, Institute for Infectious Diseases, University of Bern, Bern, Switzerland
[b] COMSOL AB, Tegnérgatan 23, Stockholm, Sweden
[c] Department of Chemical Engineering, Applied Electrochemistry, KTH Royal Institute of Technology, Stockholm, Sweden

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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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* Corresponding author at: University of Bern, Clinical Pharmacology Laboratory, Murtenstrasse 35, 3008 Bern, Switzerland.
E-mail address: wolfgang.thormann@ifik.unibe.ch (W. Thormann).

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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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ferent computers were used. SIMUL5 can be executed under both formats.

3. Results and discussion

3.1. Zone electrophoresis

ZE is used to separate charged species based on differences in electrophoretic mobilities in a uniform background electrolyte. The ZE separation of the weak bases aniline and pyridine in an acetic acid/Tris buffer was previously used as benchmark simulation for evaluation of simulation models [1,4,5,24–27]. The profiles obtained using GENTRANS were published before [1,5] and found to be identical to those predicted by SIMUL5 [5]. Simulations presented here were performed in a 20 cm column divided into 16,000 segments ($\Delta x = 12.5\ \mu m$), at a constant current density of 2500 A/m^2. A sample, consisting of 1 mM each of aniline and pyridine, was initially applied at a position 2.5% from the anode, comprising a width of 2.5% of the total column length, and constant concentrations at the boundaries were applied. The concentration distributions of aniline and pyridine after 4 min of current application using GENTRANS and COMSOL are depicted in Fig. 1A and B, respectively. The profiles are very similar. Both simulators are able to correctly predict the triangular peak shapes with a sharp front and a broadening trailing boundary. Small differences were noted for the sharp front boundaries only. In case of aniline, a slightly broader boundary is predicted by COMSOL (Fig. 1C). This is due to the artificial diffusion used in the stabilizing methods. The same is true for pyridine. Furthermore, the pyridine boundary predicted by GENTRANS comprises a small distortion at the top (Fig. 1D). This is due to insufficient segmentation. With GENTRANS, the use of 32,000 instead of 16,000 segments has been previously shown to provide a smooth profile for this boundary [1]. This simulation example is available as a tutorial with step-by-step modeling instructions in version 5.3 of COMSOL.

For the ZE data presented in Fig. 1 using a four core i5 processor at 3.3 GHz and 4 GB RAM, COMSOL required 93.6 min for the simulation of the 4 min of electrophoresis time. Simulation of the same example with SIMUL5 on the same PC required 359 min. This simulation was executed with the entire calculation space and using the maximum relative error set to 10^{-11}. A larger error setting results in reduced simulation times. E.g., with an error setting to 10^{-4} as was employed in previous work and is used in GENTRANS [5], this simulation could be performed in 16.5 min and this without much loss in accuracy. SIMUL5 features the use of a reduced calculation space with moving borders that bracket the separation space with changing concentrations. For the two cases, activation of the moving walls reduced the simulation time intervals to 187.1 and 7.07 min, respectively. Comparable relationships were previously noted for the same example performed on a 32 bit PC [5]. GENTRANS executed on a four core i5 2.8 GHz processor with 4 GB RAM and with a maximum relative error of 10^{-4} required 8.6 min for that task. Running COMSOL on a faster PC with four Intel Xeon 3.7 GHz cores with 16 GB RAM revealed an execution time of 9.8 min which is comparable to that noted for GENTRANS.

3.2. Isotachophoresis

In ITP a sample becomes sandwiched between a leading electrolyte with a coion of higher mobility and a terminating electrolyte comprising a coion of lower mobility. Upon application of an electric field, a steady-state configuration of consecutive, self-sharpening zones, ordered by electrophoretic mobility and migrating at the same velocity, is formed. The formation of sharp boundaries and the associated steep property changes poses challenges for the numerical prediction of the established zone boundaries [1,5]. A cationic ITP system of 10 mM potassium acetate (leader) and 10 mM lithium acetate (applied terminator) and having a sample composed of 10 mM sodium acetate was previously investigated [28–30]. In this configuration, acetic acid acts as counter component and the entire dynamics of this system predicted by GENTRANS are presented in [30]. Herein, this simulation was performed in a 1 cm column divided into 4000 segments ($\Delta x = 2.5\ \mu m$), under application of a constant 2000 A/m^2. The sample was applied between 0.05 and 0.10 cm of the column length and the concentrations at the columns ends were kept constant. Computer predicted profiles for the established sodium ITP zone between the leader and the adjusted terminator after 0.08 min (4.8 s) of current application are shown in Fig. 2. These data illustrate the sharp transitions formed in the system and that both simulations can handle them without the occurrence of numerical oscillations. Furthermore, this example illustrates that the current carried by diffusion is included in the calculations. It has previously been shown that without proper handling of the diffusion current in the transport equations, non-physical spikes are predicted in the zone boundaries of the pH profiles [29,30]. This is illustrated with the dotted line in the GENTRANS profiles in Fig. 2A. In comparison, when the diffusion current is considered, sharp transitions in pH are obtained (Fig. 2). The overlaid profiles reveal small differences in the boundary shapes, as is illustrated with the pH profiles depicted for the transition between sodium and lithium (Fig. 2C) and between potassium and sodium (Fig. 2D). The COMSOL profiles are somewhat broader which is due to the artificial diffusion introduced in the stabilizing methods. Otherwise no differences in the data of the two simulators were observed. Execution time intervals with GENTRANS (four core i5 processor at 2.8 GHz) and COMSOL (four Intel Xeon 3.7 GHz cores) were 1.85 and 2.33 min, respectively.

3.3. Isoelectric focusing

In IEF, amphoteric species are separated based on differences in isoelectric points (pI) in a pH gradient increasing from anode to cathode. Since the pH gradient is commonly formed using a mixture of carrier ampholytes, simulation of typical IEF experiments requires handling of a large number of components. The formation of a wide range pH gradient was studied with 35 hypothetical carrier ampholytes with pI values between 3.1 and 9.9 (ΔpI 0.2) and ΔpK_a of 2 for each component. The dynamics of this system were previously investigated using GENTRANS [1]. The ampholytes were initially uniformly distributed along the separation column at a concentration of 1 mM each. Initial pH and conductivity were calculated as 6.5 and 0.072 S/m, respectively. Simulations were performed in a 5 cm column divided into 10 000 segments ($\Delta x = 5\ \mu m$) applying a constant 300 V/cm and closed boundary conditions at the column ends. The resulting concentration, pH and conductivity distributions predicted by GENTRANS and COMSOL after 10 min application of voltage are shown in panels A and B of Fig. 3, respectively. The time point depicted in Fig. 3 represents the distribution after separation of the 35 carrier components [1]. The overall profiles predicted by the two simulators (Fig. 3A and B) are again very similar. There are small differences in the overlaid conductivity profiles at the boundary locations between adjacent ampholyte zones as is seen in Fig. 3C. The conductivity peaks predicted with COMSOL are broader. This is a result of artificial diffusion introduced for stabilization. Execution time intervals with GENTRANS (four core i5 processor at 2.8 GHz, without smoothing) and COMSOL (four Intel Xeon 3.7 GHz cores) were 748 and 647 min, respectively. Using 2000 segments and data smoothing, GENTRANS required 34 min for

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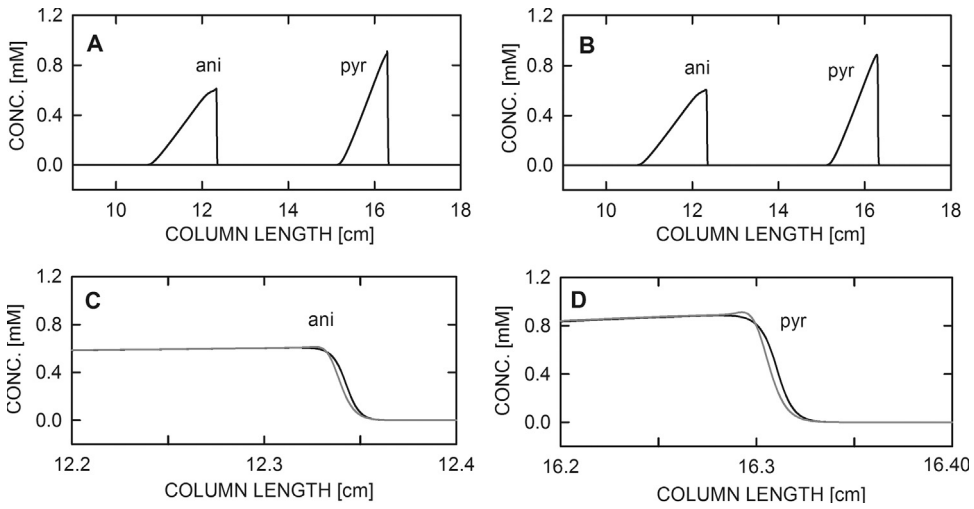

Fig. 1. GENTRANS (A) and COMSOL (B) simulated concentration profiles for cationic ZE of 1 mM each of aniline (ani) and pyridine (pyr) in 20 mM acetic acid and 12 mM tris. The overlaid concentration profiles (grey: GENTRANS, black: COMSOL) at the sample peak positions are shown in panels C and D. Simulation conditions: 16,000 segments ($\Delta x = 12.5\ \mu m$), 2500 A/m^2 applied for 4 min. The anode is on the left.

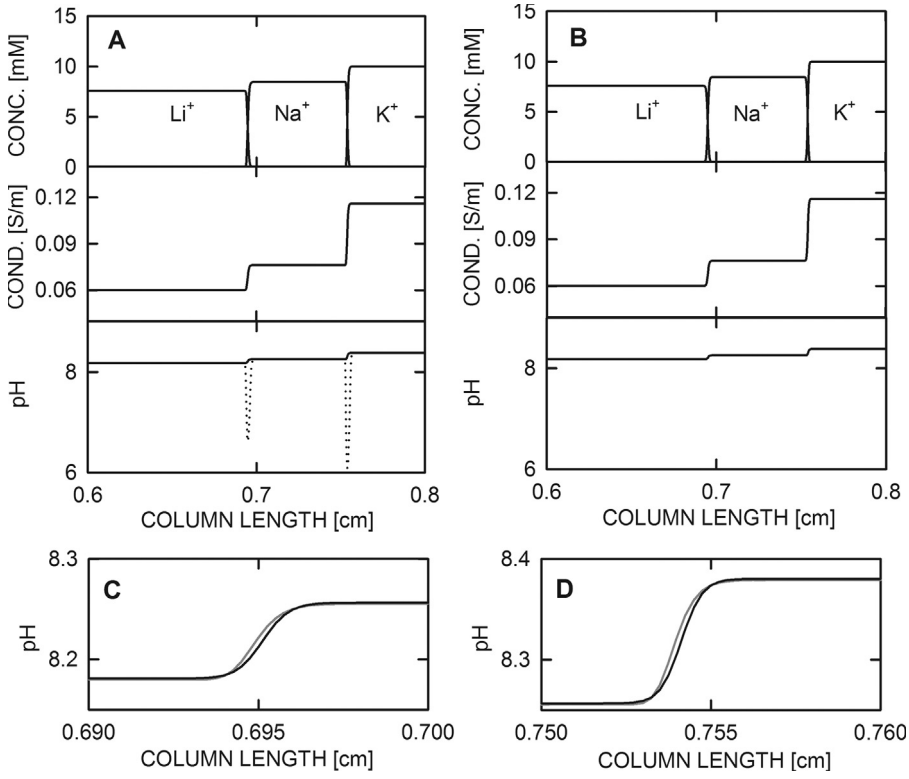

Fig. 2. GENTRANS (A) and COMSOL (B) simulated concentration, conductivity and pH distributions for cationic ITP of Na^+ (sample) between K^+ (leading component) and Li^+ (terminating component). Data of the counter component (acetic acid) are not shown. The dotted line graph in panel A depicts the pH profile using GENTRANS without inclusion of the diffusion current in the transport equations. The overlaid pH profiles (grey line: GENTRANS) at the two boundaries are shown in panels C (transition between Na^+ and Li^+) and D (transition between K^+ and Na^+). Simulation conditions: 4000 segments ($\Delta x = 2.5\ \mu m$), 2000 A/m^2 applied for 0.08 min. The anode is on the left.

the same simulation but revealed slightly distorted boundaries (for use of smoothing refer to Ref. [5]).

3.4. Oscillating system

In electrolyte systems with complex eigenmobilities, current passage can lead to periodic chemical oscillations [31,32]. An example of such a system is the electrolyte composed of 0.210 mM of the divalent acid sebacic acid together with 0.323 mM of the weak base imidazole [31]. This system was simulated using GENTRANS, SIMUL5 and COMSOL in a 1 cm column divided into 2000 segments ($\Delta x = 5\ \mu m$), applying a constant 1000 V/cm. At the channel center a concentration increase of 0.001 mM imidazole (peak concentration of 0.324 mM) comprising a width of 2% of the column was applied (dotted line in the bottom graphs of Fig. 4). Constant concentrations of both components at the boundaries were used.

In Fig. 4, GENTRANS (Fig. 4A), SIMUL5 (Fig. 4B) and COMSOL (Fig. 4C) predicted imidazole concentration profiles after 0, 3, 6, 9, 12 and 15 s of voltage application are shown together with sebacic acid concentration, pH and conductivity profiles for the 15 s time

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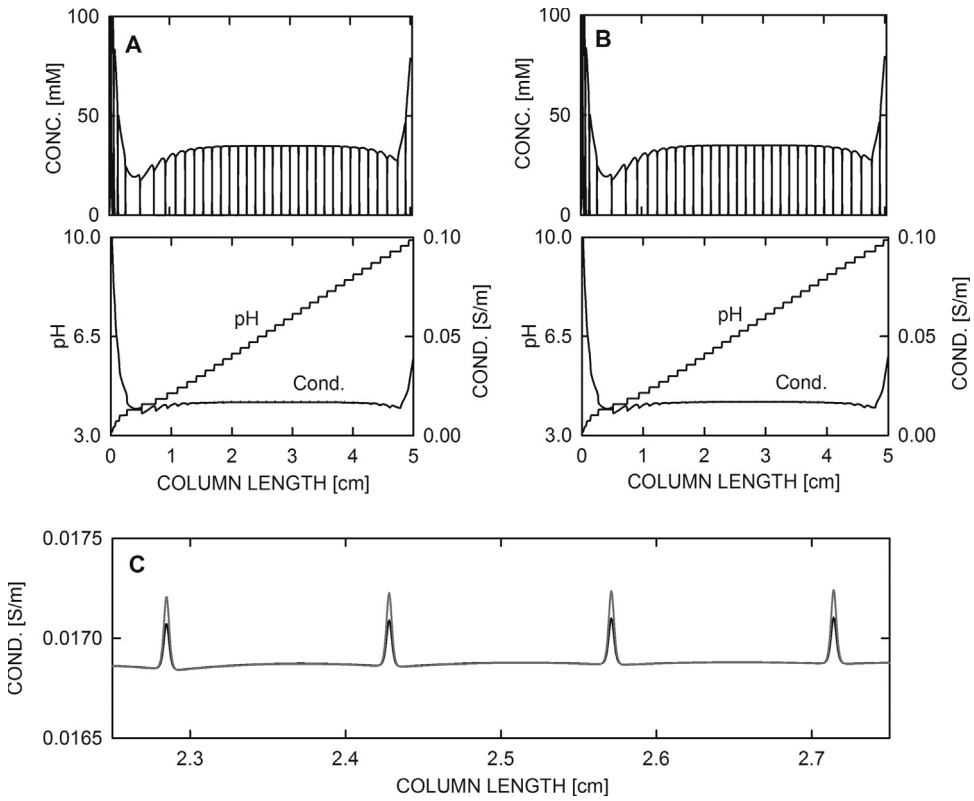

Fig. 3. GENTRANS (A) and COMSOL (B) simulated concentration, pH and conductivity profiles for IEF of 1 mM each of 35 hypothetical carrier ampholytes (uniform initial distribution) with p*I* 3.1–9.9 ($\Delta pI = 0.2$) and $\Delta pK_a = 2$. The overlaid conductivity profiles at the channel center are shown in panel C (the grey line: GENTRANS). Simulation conditions: 10,000 segments ($\Delta x = 5\ \mu m$), 300 V/cm applied for 10 min. The anode is on the left.

point. The data in Fig. 4 show that all three simulators are able to predict the oscillating behavior of this electrolyte system. The oscillations originate from the concentration increase in the channel center, and the predicted profiles are initially very similar (compare the 3 s time point). Thereafter, differences in the evolvement of the oscillation pattern occur. The oscillations predicted by GENTRANS are developing faster and with larger amplitudes, and the smoother parts surrounding the original perturbation zone in the channel center are predicted to be broader in the SIMUL5 and COMSOL simulations compared to the GENTRANS results. Parameters like time stepping, error limits and boundary conditions at the column ends are known to have an impact on the magnitudes of the oscillations and could thus be responsible for the encountered differences. It is interesting to note that all three programs revealed the existence of small oscillations in the seemingly flat parts in Fig. 4. Furthermore, the time intervals employed for the simulations with COMSOL and SIMUL5 on the same PC (four core i5 processor at 3.3 GHz; 10^{-11} error setting for SIMUL5) were 25.6 and 4.9 min, respectively. It was interesting to find that this example with a divalent weak acid was faster executed by SIMUL5. Reasons for this behavior were not evaluated. Execution with GENTRANS (four core i5 processor at 2.8 GHz) required 0.58 min.

For the sebacic acid-imidazole system, the mobilities of the divalent and univalent form of sebacic acid, u_2 and u_1, respectively, must fulfill $u_2/u_1 > 2.12$ for oscillations to occur [31]. In Fig. 5A and B, imidazole and sebacic acid concentration profiles after 15 s of voltage application for the same configuration as in Fig. 4 but with $u_2 = 4.14^{*}10^{-8}$ ($u_2/u_1 = 2.0$) are shown. These data do not reveal any oscillations. Two migrating system peaks which move in opposite direction, originating from the initial imidazole perturbation at the channel center, are formed instead. These peaks can be seen also in the pH and conductivity profiles (data not shown). The simulation data in Fig. 5 are overlaid GENTRANS, SIMUL5 and COMSOL profiles, showing that all simulators are able to correctly differentiate the oscillating from the non-oscillating behavior.

4. Conclusions

The performance of the new electrophoretic transport interface in COMSOL Multiphysics was investigated by comparison to results obtained with the 1D dynamic electrophoresis simulators GENTRANS and SIMUL5. Smooth profiles were essentially identical, whereas the ways the respective algorithms handle numerical instabilities resulted in small differences in steeper profiles. Data produced by GENTRANS and SIMUL5 could be reproduced by COMSOL, which confirms that the algorithms incorporated into COMSOL are able to correctly describe the dynamics of electrophoretic processes. The assembly and solver routines used by COMSOL are multithreaded. Using fast multicore PCs, the time intervals required for the simulation of the investigated examples were found to be comparable to those with GENTRANS. The COMSOL electrophoretic transport interface can be expected to be useful as a general model for investigation of electrophoretic phenomena in 1D, 2D and 3D, and the complete software package further provides a suitable environment for creating models combining electrophoresis with other physical phenomena. Among the simulators used, setting up and following a simulation is easiest with SIMUL5. This simulator is free of charge, limited to 1D and well suited for simple investigations to evaluate the behavior of buffer systems, the formation of boundaries and sample application under the influence of the applied electric field.

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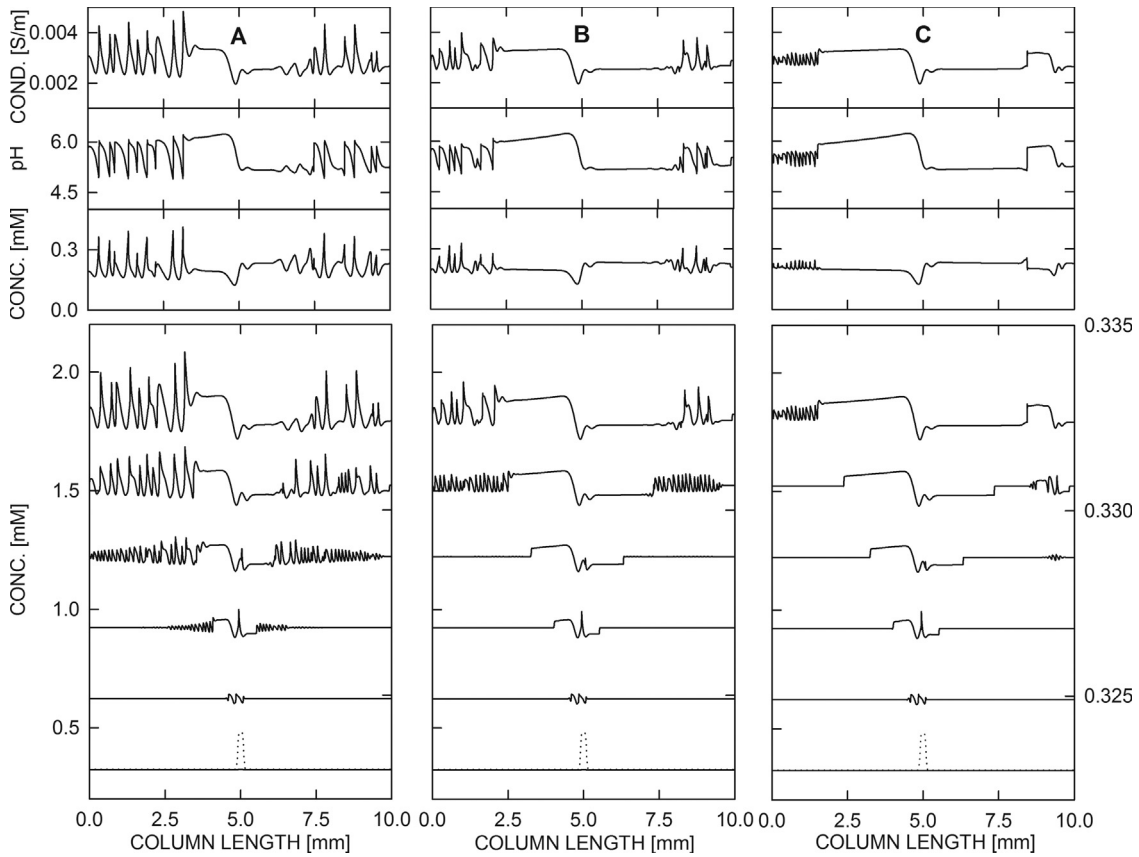

Fig. 4. GENTRANS (A), SIMUL5 (B) and COMSOL (C) simulated imidazole concentration profiles after 0, 3, 6, 9, 12 and 15 s of current passage (from bottom to top) in an electrolyte system composed of 0.21 mM sebacic acid and 0.323 mM imidazole with a 0.001 mM concentration increase of imidazole at the channel center. The concentration profiles are displayed with an offset of 0.3 mM, and the initial imidazole concentration is shown as a dotted line with the axis on the right hand side. The profiles shown at the top represent sebacic acid concentration, pH and conductivity for the 15 s time point. Simulation conditions: 2000 segments ($\Delta x = 5\ \mu m$), 1000 V/cm applied, no numerical stabilization. The anode is on the left.

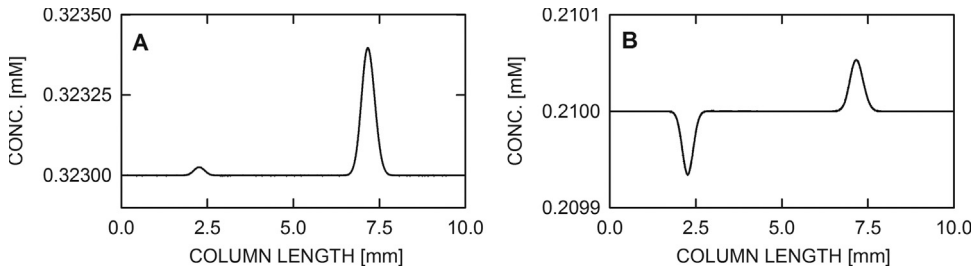

Fig. 5. Imidazole (A) and sebacic acid (B) concentration profiles at 15 s simulated with GENTRANS, SIMUL5 and COMSOL (overlaid) for the electrolyte system in Fig. 4 using $2.07*10^{-8}$ m^2/Vs and $4.14*10^{-8}$ m^2/Vs as mobility input for sebacic acid. Further explanations are given in the text. The simulation conditions are the same as for Fig. 4.

Conflict of interests

The authors have declared no conflict of interests.

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