NUMERICAL MODELING OF CAPILLARY ELECTROPHORESIS: ELECTROSPRAY MASS SPECTROMETRY INTERFACE DESIGN

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Capillary[Q3] electrophoresis hyphenated with electrospray mass spectrometry (CE-ESI-MS) has emerged in the past decade as one of the most powerful bioanalytical techniques. As the sensitivity and efficiency of new CE-ESI-MS interface designs are continuously improving, numerical modeling can play important role during their development. In this review, different aspects of computer modeling and simulation of CE-ESI-MS interfaces are comprehensively discussed. Relevant essentials of hydrodynamics as well as state-of-the-art modeling techniques are critically evaluated. Sheath liquid-, sheathless-, and liquid-junction interfaces are reviewed from the viewpoint of multidisciplinary numerical modeling along with details of single and multiphase models together with electric field mediated flows, electrohydrodynamics, and free fluid-surface methods. Practical examples are given to help non-specialists to understand the basic principles and applications. Finally, alternative approaches like air amplifiers are also included. © 2014 Wiley Periodicals, Inc. Mass Spec Rev 9999:1–12, 2014

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I. INTRODUCTION

Capillary electrophoresis (CE) coupled with electrospray mass spectrometry (ESI-MS) has recently received great interest in the field of the analysis of large biomolecules (Barry et al., 1996[Q4]; Krenkova & Foret, 2012). Hyphenation of CE with mass spectrometry (MS) offers a very effective combination of a high-resolution separation method with a unique detection technique, providing excellent selectivity and high sensitivity. CE-ESI-MS is widely used in these days for DNA adducts analysis (Barry et al., 1996[Q5]; Ding & Vouros, 1997), drug discovery analysis (Kohler, Schappler, & Rudaz, 2013), proteomics (Stalmach et al., 2013), glycomics (Yamada &

Kakehi, 2011), and biomarker discovery (Mischak et al., 2009) just to list a few important ones. Publications by Vouros and coworkers (Ding et al., 1997; Gennaro et al., 2004) are the outstanding work among the earlier articles applying CE-ESI-MS technique for the analysis of an environmental polycyclic aromatic hydrocarbon.

In capillary electrophoresis, charged compounds are separated in a liquid phase on the basis of their charge-to-size, or rather charge-to-hydrodynamic volume ratio, under the influence of an external electrical field. CE is a highly selective separation method, which requires small sample volumes and offers short analysis times with high efficiency and relatively low running cost. The numerous operation modes of CE have been summarized in the recent article of Bonvin, Schappler, and Rudaz (2012). The most commonly used detection modes in CE are UV/VIS absorbance and Laser-Induced Fluorescence (LIF); however, MS detection has provided some extra benefits in the past decade such as enhanced sensitivity and ability to identify unknown structures (Bonvin, Schappler, & Rudaz, 2012). In CE-MS coupling, the mass spectrometer is actually more than just a detection device. It rather provides a second dimensional separation that further fractionates the incoming sample by their mass-to-charge ratio in the gas phase. However, the hyphenation of CE with MS is not straightforward due to their different current levels (Hau & Roberts, 1999). Whereas some of the electrokinetic phenomena occurring at the exit of the separation capillary due to differences in the composition of the background electrolyte and the sheath (spray) liquid can often be directly calculated (Foret et al., 1994), computer programs for numerical simulations can also be readily used (see http://web.natur.cuni.cz/~gas/, last visit: October 20, 2013).

ESI interfaces in CE-MS play various roles: (i) physically position the CE capillary close to the MS orifice, (ii) close the electrical circuit for both the CE and ESI sides and (iii) support the proper droplet formation required for creation of free, gas phase ions. To this end, numerous tools have been developed during the past decade aiming to achieve high selectivity and sensitivity at a simple and low cost way. To speed up this endeavor various modeling techniques have been critically reviewed in this article.

Computational fluid dynamics (CFD) is a modeling tool to help quickly achieve an optimal design at low cost with a minimum number of actual experiments. It is well accepted in a wide range, from cardiovascular flow modeling (Johnston et al., 2004) via investigation of phase change (Al-abidi et al., 2013) to simulation of conventional mechanical

engineering problems (Aslam Bhutta et al., 2012). Albeit, modeling and simulation are primarily considered as design tools, they can also be used to support experimental data interpretation. Furthermore, modeling holds the promise for custom-made application-specific solutions, which could significantly speed-up the development processes. Whereas numerous review articles have been published in the last years summarizing the recent developments in CE-MS coupling (Ahmed, 2009; Yamada & Kakehi, 2011; Bonvin, Schappler, & Rudaz, 2012), only a restricted number of articles deal with CFD modeling probably due to the interdisciplinary nature of the field. In this article, we focus on the applicability of computational fluid dynamics based simulations to the most important CE-MS interfaces and critically review these modeling efforts. Since CE-ESI-MS coupling is a very challenging computer simulation task, we applied a multidisciplinary point of view to make this article more informative for a wider audience. In the following sections the fundamental steps of the CE-ESI-MS process are briefly outlined as well as different scales of modeling, including details of the incoming liquid flow, spray formation and the transport of the evaporated particles. We also report on the simulation results with the use of alternative approaches using the modeling apparatus detailed earlier. Finally a brief conclusion and future prospective are presented.

II. ENGINEERING ASPECTS OF CE-ESI DESIGN AND MODELING

Among the numerous ionization techniques reported on CE MS hyphenation (Hommerson et al., 2011), the most widely used is electrospray ionization (ESI) (Bonvin, Schappler, & Rudaz, 2012). The overall ESI coupling performance is a function of numerous effects such as fluid properties, emitter material and design, applied electric field distribution and control among others. The coupling efficiency could be further improved by having a deeper understanding and optimization of the fundamental aspects of the CE-ESI process and/or by using multi-emitter setting.

A. Fundamental Steps of CE-ESI Process

Although recent reviews (Pantuckova et al., 2011; Bonvin, Schappler, & Rudaz, 2012) were published on CE-MS technology and interface designs, we also present here the basic fundamentals with emphasis on mathematical formulizations. The overall electrospray process of the CE-ESI-MS hyphenation can be decoupled into three main parts: (i) establishment of the cone-jet, (ii) droplet evolution, and (iii) the formation of gas phase ions.

The cone-jet, also referred to as Taylor cone, is established when the fluid at the end of the separation capillary is exposed to an electric field with sufficient strength. As a first approximation, it is assumed that in positive ESI mode, the applied field passes through the gas–liquid surface and interacts with the positive ions. This causes destabilization and distortion of the surface shape of the liquid at the interface. Assuming the fluid as a perfect conductor or dielectric, the induced electric stress is normal to the interface (Sen et al., 2006). If the liquid is treated as leaky-dielectric fluid, which is apparently the most accepted approach, the interfacial charges distort the electric field and viscous flow is developed to balance the force emerged due to

the tangential components of the field acting on the interface. The acting forces of the leaky-dielectric model (LDM) are visualized in Figure 1 as originally proposed by Melcher and Taylor (1969), and later discussed by Saville (1997).

When the electric stress overcomes the surface tension force and a fine jet emerges from the cone a potential emerges called onset or threshold potential. When the electric stress is sufficiently higher than the adhesion forces (surface tension and viscosity), the jet bursts into smaller droplets. The droplets are charged since LDM assumes the existence of charges only at the liquid surface and not in the bulk phase. Whereas there are numerous spraying modes, only the cone-jet model allows the description of the formation of small, and monodisperse droplets (Bonvin, Schappler, & Rudaz, 2012). The required onset potential can be estimated using Equation (1) (Kebarle & Verkerk, 2010):

$$V_{\mathrm{on}} = 2 \times 10^5 (\gamma r_{\mathrm{c}})^{1/2} \ln\left(\frac{4d}{r_{\mathrm{c}}}\right) \qquad (1)$$

where V_{on} is the onset potential, γ is the surface tension of the fluid, d is the distance between the end of CE capillary and the MS orifice (counter electrode) and r_{c} is the outer radius of the CE capillary. The effect of the applied potential is well predictable using numerical modeling (Wu, Oleschuk, & Cann, 2012).

The droplet evolution, that is, the evaporation of emitted droplets into small ones is the next step after Taylor cone formation. The droplets are flying towards the MS orifice due to their positive charge (in positive ESI mode). Whereas evaporation continuously decreases their radius, their net charge remains the same increasing in this way the charge density.

FIGURE 1. Force balance on a vertically arranged liquid cone-jet based on the leaky dielectric model of electrohydrodynamics.

Computational modeling of the multicomponent, non-ideal, and non-equilibrium spray evaporation process is extremely challenging. Whereas the dynamics of the spray process is thoroughly discussed in the literature, the comprehensive work on Eulerian and Lagrangian approaches of Sirignano (2005) should be highlighted.

When the charge density of the evaporating droplet exceeds a critical value, referred to as the Rayleigh limit, the Coulombic repulsion forces between the ions overcome the cohesive forces. The consequent instability causes Coulombic fission of the droplets. The limit of instability is expressed by Rayleigh's equation:

$$q_{Ra} = 8\pi(\varepsilon_0 \gamma R_{Ra}^3)^{1/2} \tag{2}$$

where q_{Ra} is the critical charge of the droplet, ε_0 is the permittivity of the vacuum, γ is the surface tension of the liquid, and R_{Ra} is the critical radius of the droplet.

The evaporation process continues until the droplets reach the size that is required for the formation of gas-phase ions, which is the third step of the overall electrospray process. There are two widely accepted models describing it. The first one was introduced by Dole et al. (1968) and called charge residue model (CRM). According to their model the evaporation process continues until the formation of an ultimate droplet, which contains only one molecule of solute. The molecule retains the charge of the original parent droplet and becomes a free gas-phase ion. This model is applicable for large biomolecules like proteins due to their relatively large size and the presence of polar side chains. The second model, called ion evaporation model (IEM) (Iribarne & Thomson, 1976; Thomson & Iribarne, 1979) suggests that a direct emission of the solute ions could occur when the evaporation process has sufficiently reduced the radius of the charged droplet. The pioneer publication on theoretical description of the electrostatic dispersion in nanospray (electrospray at flow rate less than 1,000 nL/min), is presented by Wilm and Mann (1994). In addition to these two models, some recent work (Hogan et al., 2009; Bichoutskaia et al., 2010) were reported on the investigation and theory of the evaporation behavior of charged particles. Despite of the fact that several publications dealt with the deeper theory of the suggested mechanism, the dynamics of molecules in ESI droplets are still not well understood (Hogan & Biswas, 2008).

B. Macro-, Meso-, and Micro-Scale Simulations

For the time being, different kinds of computational modeling are considered as important design tools and also be used to support experimental data interpretation (Chovan & Guttman, 2002). Modeling efforts can be classified at three levels: macro, meso and micro-scale. Macro level simulations based on the continuum approximation and usually referred to as CFD, which is thoroughly discussed in this article, because it is assumed to be the best choice for modeling and simulating the CE-ESI-MS process. Particle-based meso-scale methods are not widely accepted, but have growing interest in recent years since they can serve as intermediate stage between molecular and continuum descriptions. Mills, Mao, and Alexeev (2013) published a comprehensive review on the topic of complex physiological flows in biology and biotechnology (fluid flow in

living organisms) applying meso-scale models. The authors concluded that meso-scale modeling technique has increasing role, but their general application domain still not defined with proper scientific elaboration. In contrast, molecular or micro-scale simulation techniques, such as molecular dynamics (MD) and Monte Carlo (MC) simulations, are based on the exact track of the individual particle motion and allow precise description of the molecular environment of the system in question. However, in spite of the availability of appropriate computational capacity, those methods are not feasible when one attempts to simulate a system at the application scale level. Hogan and Biswas (2008) developed a model to predict the efficiency of electrospray ionization for macromolecules. In their work, the efficiency of electrospray ionization for macromolecules, that is the number of macromolecular ions produced by ionization per macromolecules electrosprayed ratio, can be calculated, but unfortunately the effect of macromolecular environment, for example, the geometric and flow dynamic characteristic of the domain of interest was not taken into account. The situation is the same for MD simulations, that is, only a part of the whole ESI process can be described, for example the final phase of ionization (Daub & Cann, 2011). Recently published results using this approach deal with just around thousands of molecules in the spray (Longhi et al., 2013).

Boundaries between the different methods are apparently symbolic, thus multi-scale approaches like smoothed dissipative particle dynamics model were developed (Kulkarni et al., 2013) to describe the fluid flow. Similarly, combined solutions can be applied in modeling CE-MS hyphenation. In the CE-MS process, the evaporation and pH characteristics of the background electrolyte could have important effects on the selectivity and sensitivity, as well as on the overall interface design. Properly chosen background electrolyte composition can lead to efficient separation. This so-called solvent property engineering, also known as wet chemistry of background electrolyte, can be assisted by micro-scale computational methods. COSMO-RS (Klamt, Eckert, & Arlt, 2010) is one of the most innovative ways to carry out such calculations at the molecular level applying *ab initio* quantum chemistry together with statistical thermodynamics. A brief description of the available modeling methods, their basic concepts, the areas of their applicability and some selected software tools are summarized in Table 1.

III. MODELING TECHNIQUES IN CONVENTIONAL COUPLINGS: SHEATH LIQUID AND SHEATHLESS INTERFACES

Basically, there are three different ways of CE-MS coupling namely the sheath-liquid, sheathless, and liquid-junction interfacing. The most frequently used is the sheath-liquid interface (Olivares et al., 1987; Kleparnik & Otevrel, 2010), in which case a sheath liquid is flowing in a coaxial tube around the separation capillary and mixing with the analyte molecules at the end of spray tip. In the sheathless arrangement (Klampfl, 2009) the ESI tip is an integral part of the separation capillary and the CE electric connection is achieved either via the metalized tip (Ding & Vouros, 1997), or, more recently, via a semipermeable porous junction (Hau & Roberts, 1999). Another type of interfaces is called liquid-junction interface, where the make-up liquid is delivered through a T-junction, which decouples the CE capillary and the ESI needle by a 25–50 μm gap (Hommerson

TABLE 1. A summary of the available computational modeling tools and some selected software packages

	Concept	Areas of applicability	Software implementation
Micro-scale	Molecular scale simulation on the level of Density Function Theory, Molecular Dynamics or Monte Carlo methods	Track the motion of individual atoms and molecules	Materials Studio, Turbomole, Gaussian, COSMOtherm
Meso-scale	Particle based method, which deals with clusters of molecules	Dynamics and equilibrium properties of complex fluids	MesoDyn, Fluidix, Mesocite, OCTA
Macro-scale	Simulation based on the solution of continuous transport equations (bulk phase)	Momentum, heat and component transport	Fluent, Ansys, CFD-ACE+, Flow3D, COMSOL Multiphysics

et al., 2011). Independently of the basic types of interface, CE-ESI-MS coupling is a very challenging task in computer modeling point of view, therefore, the selection of an appropriate modeling level is quite important. On one hand, over-detailed models have very high computational cost, whereas an over-simplified simulation could result in misleading data. For instance, when the question is the pressure drop at the output of the CE capillary, a single phase model together with the description of the electric field could be an optimal choice. However, a laminar two phase model augmented with the so-called free surface approach and coupled with electrostatic modeling is suggested for the simulation of ESI process (Sen et al., 2006; Sen, Darabi, & Knapp, 2007; Wu, Oleschuk, & Cann, 2012). The transport of the evaporated ions at high flow rate is typical in ESI-MS interfaces, which is truly a turbulency related problem. Considering the different levels in simulations, the applied methods are reviewed in this section. Multiphysics modeling, that is, the possibility of one or two ways coupling of different physical models is the feature of many CFD codes and allows applying modeling as daily routine.

In spite of the variety of the modeled interfaces and applied techniques the software implementations and the basic developing process is always the same, that is, design of geometry, definition of the governing equations, meshing, solving, and post-processing. First, the geometry design could be carried out by either applying built-in CFD program tools or any computer-aided design software, such as AutoCAD or Inventor. The next step is the specification of the governing equations by defining the form and associated coefficients in the governing partial differential equation, the boundary conditions and the initial values. Then meshing (also referred to grid generation or discretization) splits the complex geometry of the modeled domain into smaller, primitive sub-domains to solve the governing equations at each nodal point of the sub-domains. Solving uses different algorithms that are available in the function of the problem nature for steady-state or time dependent studies. Finally, post-processing is the step where the calculated data is visualized by graphs, plots, and animations according to the problem in hand.

Numerous commercially available software packages such as Fluent, Ansys, CFD-ACE+, Flow3D, COMSOL, and Multi-physics, as well as free codes like OpenFOAM or ADFC are suitable for modeling fluidic flows in CE-MS interfaces. Most of the problems, even in complex challenging geometries can be solved using CFD codes. However, no software could be considered as "black-box" tool, since solutions could converge into local minima showing unrealistic results, which could mislead an untrained user. To avoid such incorrect interpretations, simulations should be performed many times with different meshing methods and sizes to obtain grid-independent data (Supeene, Koch, & Bhattacharjee, 2008).

A. Flow Dynamics

In a simple case scenario, the modeled device is assumed to be a single-phase system, where a liquid is flowing in a capillary due to the electroosmotic flow generated by the applied electric field. This phenomenon can be modeled using the modified ($\rho_e E$ term is added to the RHS of the original equation) Navier–Stokes equation

$$\rho\left(\frac{\partial u}{\partial t} + (u \cdot \nabla)u\right) = \nabla(-pI + \eta(\nabla u + (\nabla u)^{\mathrm{T}})) + \rho_e E \quad (3)$$

of fluid motion that is generally using a continuum mechanics model to describe the flow of incompressible fluids. Equation (3) is usually coupled to the continuity equation of

$$\nabla \cdot u = 0 \quad (4)$$

where u is the linear velocity, ρ is the fluid density, η is the dynamic viscosity of the fluid, t is the time, E is the electric field, and p is the pressure. It is important to note, that Equation (3) describes the velocity flow field as a function of time, rather than the exact position of any part of it, that is, it treats the flow as a bulk. The calculated results can be visualized as particle trajectories of the bulk phase, which helps in the interpretation of the obtained results. The governing equations can be solved in both steady-state and dynamic cases by different solver algorithms.

From the viewpoint of hydrodynamics modeling, flow characteristic can be laminar or turbulent. In laminar flow, the

trajectory of any particle, which is part of the continuum, is not randomly dependent of the time element; therefore, the trace can be calculated if the boundary conditions are known. The dimensionless parameter called Reynolds number, representing the ratio of viscous and inertial forces and most often defined as:

$$Re = \frac{\rho l v}{\eta} \qquad (5)$$

where ρ is the density (kg/m³), l is the characteristic linear dimension (m), v is the mean velocity (m/sec), and η is the dynamic viscosity (Pa sec) of the fluid. Flows tend to be turbulent around $Re > 2,000$, but in certain instances it could be laminar even at much higher Re numbers (Brody et al., 1996). Flows, characterized by Reynolds number in the range from 100 to 2,000, called transient flow and the streaming nature depends on additional factors. In CE, the characteristic inner diameter of the capillary tubes is ~20 to 100 µm, whereas the typical flow rate is usually between 20 and 100 nL/min (Ramautar et al., 2012) resulting in $Re \ll 1$, assuming the flow of water at 20°C. At such low Re numbers, flow fields could be simulated using the laminar form of Navier–Stokes equation and the results are quite reliable.

Wojcik et al. (2010) published an interesting work where a one phase laminar CFD model was used to optimize and understand the electrokinetic transport in a newly developed sheathflow interface. By means of a multiphysics model, coupling electric, electroosmotic, and mass conservation functions, the authors investigated the effect of spacing between the separation capillary tip and the emitter tip. Furthermore, different tip sizes, buffer viscosity, relative conductivity of the separation buffer and sheath liquid were examined. They concluded that the optimal spacing was 1 mm with a 2 µm diameter emitter tip size, which was also validated by experimental work. In the article of Kler et al. (2013) a very intuitive modeling strategy was reported. They dealt with capillary isotachophoresis and mass spectrometric simulation in 3D taking the fluid flow and electrophoretic transport into account. Since 3D simulations are time consuming and costly, the fluid flow model was solved as steady state in the whole domain of interest, whereas the electric field mediated transport was solved time-dependently only in 1D using extracted flow velocity data from the 3D solution. This strategy could be very efficient in solving complex problems like CE ESI-MS coupling. It is well illustrated in Kleparnik and Otevrel (2010), where the authors applied axially symmetrical arrangement to simplify the 3D model to 2D. The long transfer distance of ions from the ionization source into the MS orifice (remote ionization) could be an interesting way of developments. Others (Garimella et al., 2012) applied laminar flow models to demonstrate that laminar flow can transfer ions over long distance up to 6 m in a cylindrical tube. A rather complex two-step simulation utilizing, among others, a laminar fluid flow model is published by Grym, Otevrel, and Foret (2006). The authors developed a microfabricated interface without electrospray tips, and as a first step optimized the aerodynamic flow profile by CFD inside the focusing chamber of the device. In the next step, the behavior of an ion cloud was simulated with a set of identically charged spheres representing the electrosprayed droplets. It was concluded that the air flow had a major influence on the transport of the electrosprayed droplets.

On the contrary, the turbulent fluid flow is chaotic and its trajectory is nearly unpredictable. The flow characteristic is determined by inertial forces. Commonly applied approaches take the kinetic energy dissipation into account like k–ε, k–ω, and Shear Stress Transport (SST; a common form of k–ω model) for the turbulent models. A detailed description of these models is beyond the scope of this review but readers are referred to Rogallo and Moin (1984) for the fundamentals of turbulence. In commercial as well as in free CFD codes more turbulent models are implemented; however, their accuracy and robustness are still questionable. An especially interesting research article was published by Poehler et al. (2011)[Q6], dealing with numerical simulation of the gas flow within a multi-purpose ion source. A time-averaged velocity and turbulent kinetic energy distributions model, SST, and its validation were given. Using CFD simulation, two operating points, which differ in gas volume flow, were investigated. Figure 2 shows the calculated flow field, where streamline density is proportional to the magnitude of fluid flow, whereas the heat-map illustration denotes the relative analyte concentration (the warmer the color the higher the concentration).

Based on their simulation results, the authors concluded that for ion transport into the MS ion transfer capillary, electromagnetic forces are at least as important as fluid dynamic forces. Their conclusion properly illustrated the usefulness of multiphysics CFD models for the deeper understanding of complex physical phenomenon.

B. Free-Surface Modeling

Both in sheath liquid and sheathless interface models, including setups where an additional gas flow is applied for enhancing the spray formation, at least two phases are incorporated where the shape of the phase interface is continually changing making numerical modeling very complicated. The highly dynamic changes can result in coalescence of heterogenic systems or breakdown of the continuous phase. Basically, there are two types of widely accepted methods to describe the evolution of interfaces, namely interface capturing and interface tracking methods. In capturing, an implicit function is used to determine the surface, whereas the tracking methods solve the interface evolution equation in Lagrangian way (Hieber & Koumoutsakos, 2005). The level set (LS) and volume of fluid (VOF) methods, which are the most commonly used, belong to the first one. LS is originally introduced by Osher and Sethian (1988) and suitable for viscous, laminar flows where interfaces have significant topological changes. It is applied in the fields from fluid mechanics to image processing. Level set method defines the interface by a certain contour of a smooth continuous function usually denoted by Φ, which is time and space dependent. In the computational domain, Φ could vary between 0 and 1 and the interface is represented by the 0.5 contour. The advantage of the method is that it can accurately determine the position of the interface, but on the other hand it suffers from inaccuracy in mass conservation. A modified LS method, called reinitialized level set method can be used to avoid such drawbacks (Min, 2010). The VOF method was also developed (Hirt & Nichols, 1981) and achieved remarkable success in simulations of free surface and multiphase flows. The VOF method uses a discontinuous function, F, in each discretized unit (also referred to grid cell), which is zero in one phase and one in
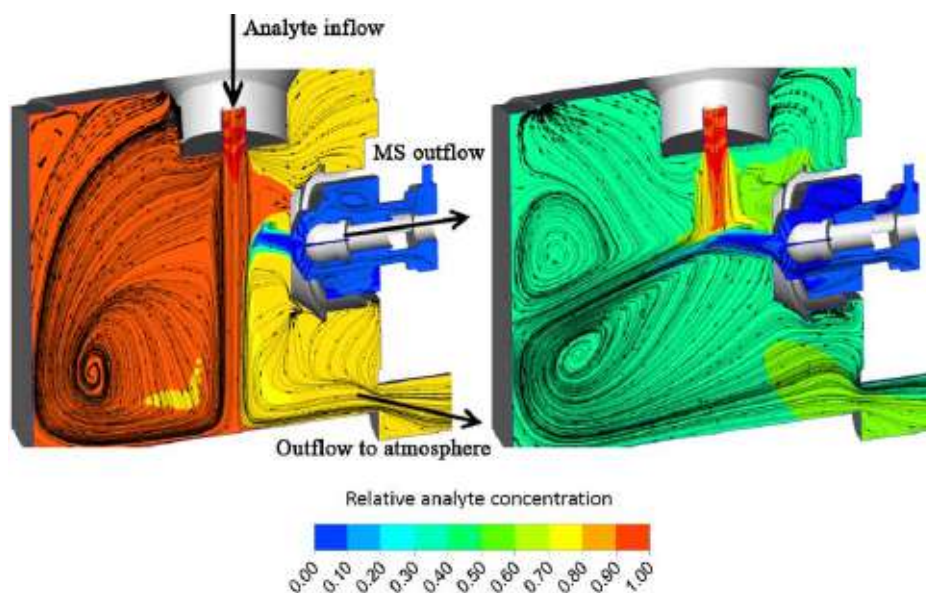
FIGURE 2. Simulated flow field distribution and analyte concentrations in a multi-purpose ion source using Shear Stress Transport turbulent model. Two diverse (left is the higher) gas flow rates were compared based on the calculated relative analyte concentration. The colored areas of the figure are the domain of calculation, whereas gray parts represent boundaries. The original graphic work is labeled, with permission[Q7] from [...]hler et al. (2011)[Q8].

the other. Due to the discontinuity, VOF methods cannot determine the exact position of the interface. In VOF technique, the kinematic condition at the interface is represented by Equation (6):

$$\frac{\mathrm{d}F}{\mathrm{d}t} + \vec{u}\,\nabla F = 0 \qquad (6)$$

where u is the velocity vector of the fluid (Sen, Darabi, & Knapp, 2007) and F is a discontinuous fraction function. Similar to the LS method, exact surface characterization inevitably requires finer meshing.

Recently, to achieve the desired resolution in surface interface calculation, different alterations and combinations of the LS and VOF methods were developed. These combinations were motivated by the demand of obtaining information in the dense zone of the different sprays, where nearly no experimental data are available (Lebas et al., 2009). Using the combination of Level Set/VOF/Ghost Fluid methods a 3D simulation of the primary atomization zone of a turbulent liquid jet is reported (Ménard, Tanguy, & Berlemont, 2007) and the results are shown in Figure 3.

Although the obtained results are very attractive, the model has some handicap from practical engineering point of view. First and most importantly, by defining the mesh resolution, the minimum droplet diameter was determined, which contradicted physical reality. Furthermore, no secondary break up was taken into account. As another approach, novel particle level set method was reported by Hieber and Koumoutsakos (2005) where the LS equation was solved in a Lagrangian fashion. The authors claimed their model to be suitable for real time simulations. As an alternative to LS, VOF, and those combinations, Phase Field method took the chemical potential into account to represent a diffuse interface, which separates the two phases. This approach was based on the Cahn–Hilliard equation, see the corresponding comprehensive work in (Badalassi, Ceniceros, & Banerjee, 2003).

CE-MS interfaces have been made of various materials such as plastic, glass, and metal. The bulk phase material properties, for example thermal conductivity, could be included into the models by simply using literature data or built-in libraries. On the other hand, handling the effect of liquid–solid interplay is a more difficult task. Surface tension and wall adhesive forces are both governing the nature of interaction. Surface tension is a unique property of a given liquid and, among others, depends on temperature and composition if the solvent is not pure. The ratio of liquid–liquid and liquid–solid molecular interactions could be taken into account using the contact angle of liquid–solid system. This feature could be particularly useful since it allows using a given contact angle according to the design criteria or engineering intuition, which could lead to the discovery of new structural materials.

C. Multi-Emitters and Complex Models

Traditional electrospray emitters are single-channeled, either with or without a taper. However, there is a clear drive toward the development of emitters that produce multiple sprays (Gibson, Mugo, & Oleschuk, 2009). Many groups focus on the development of multi-emitters, but for the time being only just a few publications are available where numerical modeling is applied. It is crucial that the individual spraying channels (also referred to as emitter holes), should be independent of each other. Recently, a comprehensive CFD study (Wu, Oleschuk, & Cann, 2012) was published on various multi-emitter designs. The developed model was rather complex, applying two phase flow laminar fluid dynamic simulation combined with electrostatics (together referred to as electrohydrodynamics) and free
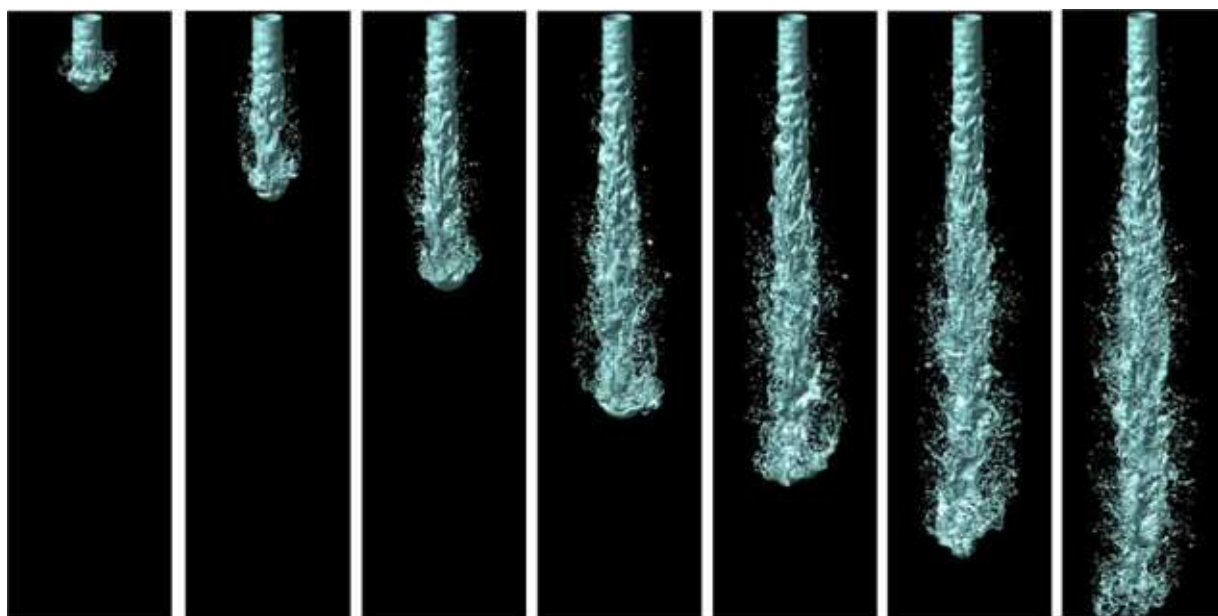
FIGURE 3. 3D simulation results of the evolution of a liquid jet using the combination of Level Set/VOF/Ghost Fluid methods. With permission[Q9] from Ménard, Tanguy, and Berlemont (2007).

surface approach. However, the droplet formation and the consequent charged particle transport were not included into the model. The authors used numerical simulations to optimize the emitting hole layout in linear and triangular arrangements. A feasible validation method using the calculated spray current was reported as well. Furthermore, the effects of spray voltage, flow rate, emitter tapering, surface hydrophobicity, and fluid conductivity were investigated on spray performance. As an example, the simulated effect of sprayer voltage on a two-hole emitter is illustrated in Figure 4.

An analogous numerical modeling work was published by Sen et al. (2006), with simulations carried out to develop a novel carbon nanofiber (CNF) emitter for ESI-MS instrumentation. The electrospray ionization process was simulated using a CFD model utilizing the LDM and VOF methods, which were both discussed previously. The point of their work was based on the observation that an array of carbon nanofibers at the end of a micro-scale emitting capillary could establish individual spray-jets. First the developed multi-emitter model was validated for a conventional multiple electrospray emitter, then used to investigate the CNF emitter. Their simulation results indicated that the emitter could generate steady state cone-jets from individual nanofibers forming an array of electrosprays. By the time of simulations, the fabrication of the CNF emitter was underway, which well emphasizes the role of numerical modeling in the development process as an important part of designing new CE-ESI-MS interfaces.

D. Description of the Electric Field Distribution

One of the most important factors in ESI-MS sampling efficiency is the electric field distribution in the ion source, since it governs the movement of charged particles. The experimental analysis of field strength distribution is difficult in such small and complex devices. The differential equation that describes

the potential of the electrostatic field, which is irrotational and divergence-free, is:

$$\nabla \varepsilon \nabla V = -\rho_v \tag{7}$$

where ε is the permittivity of the dielectric, V is the voltage, and ρ_v is the charge density. Eliminating the charge, Equation (7) becomes the Laplace equation:

$$\nabla^2 V = 0 \tag{8}$$

Analytical solutions of Equation (8) could exist but can be derived just in some special cases (simple geometry with ideal boundary conditions). Numerical simulation plays an important role in the investigation of static electric fields (Zhao, Zhong, & Chen, 2012) as the electric field interacts with charged particles. Basically, two different kinds of forces are taken into account, one is the Columbic force and the other is the polarization stress. Both can be summarized as an additional source term (electromechanical force) in the Navier–Stokes equation (Melcher, 1981):

$$\vec{f}_e = q\vec{E} - \frac{1}{2}\vec{E}\vec{E}\nabla\varepsilon \tag{9}$$

where f_e is the electromechanical force, q is the free charge density, E is the electric field, and ε is the permittivity. When fluid dynamics is coupled to electrostatic effects the resulted phenomena is usually referred to as electrohydrodynamics.

Zhong et al. (2009) reported on CFD simulations to assess the effect of electric field strength in an electrospray ionization source under various conditions and the influence of an atmospheric pressure ion lens, as well. The authors compared their numerical results with analytical solution based on the
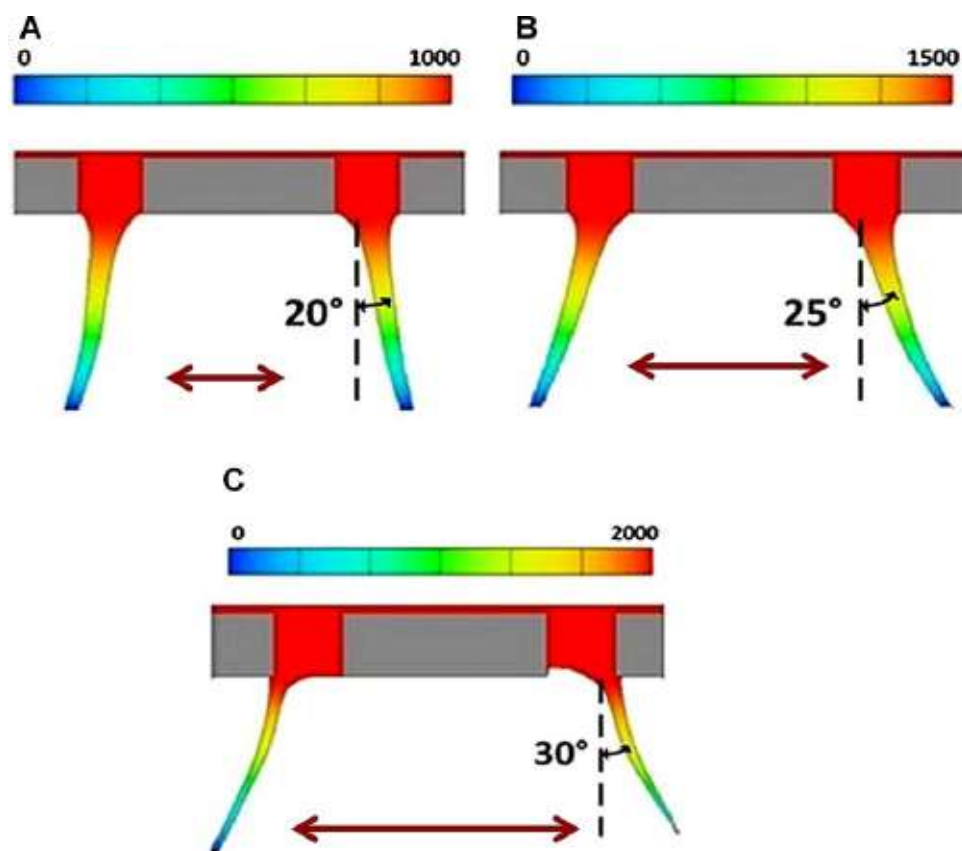
FIGURE 4. Simulated repulsion effect between the jets in the function of voltage in case of two-hole emitter designs. The inflow velocity was 0.09 m/sec, whereas the applied voltages were 1,000 V (**A**), 1,500 V (**B**), and 2,000 V (**C**), respectively. With permission[Q10] from Wu, Oleschuk, and Cann (2012).

derived function of Eyring, Mackeown, and Millikan (1928). They concluded that the numerically obtained electric field intensity (8.446E6 V/m) at the end of the sprayer tip was quite close to the analytical solution (8.766E6 V/m), which validated the approach. Another comprehensive work was published by Wissdorf et al. (2013), where simulations were applied to investigate the three-dimensionally resolved ion trajectory in an atmospheric pressure ion source. They assumed that the motion of highly diluted ions had no effect on the dynamics of the bulk gas flow. Therefore, it was possible to decouple the transport simulation of the sheath flow from the migration of ions. SIMION, a special software package (Dahl, 2013) along with the statistical diffusion simulation (SDS) algorithm were used to numerically describe the migration of ions under the electric field. As an intuitive point of the development, an external automation script was written in Python environment for the systematic alteration of voltages on the spray shield and capillary cap electrodes for automation purposes. Their CFD model was tested against experimental fluid dynamic measurements using particle image velocimetry technique (Oehler et al., 2011[Q11]). The very good overall agreement between the experimental and numerical results reliably validated their model, even in complex cases. Others (Geerlings et al., 2012) published a simplified mode to represent the interaction between the applied electric forces and mechanical momentum in the electrospray process. Unfortunately, their model was limited

just for a given range, restricting the usefulness of their efforts. In contrary, the publication of Sen et al. (2006) especially detailed from the viewpoint of electrostatic field modeling and simulation. The authors expanded Equation (9) with the divergence of the electrostrictive pressure, p_{st}:

$$p_{st} = \frac{1}{2}(\varepsilon - \varepsilon_0)|\vec{E}|^2 \qquad (10)$$

where ε and ε_0 are the permittivity of the liquid and vacuum, respectively. This new term represented the electromechanical force density due to the non-uniformity of the applied electric field. The model was validated against experimental data (Hartman et al., 1999), using the length of the Taylor cone. The simulated and measured length were approximately the same, therefore, the model could be reliably used to investigate the effect of flow rate, potential difference and liquid properties, such as conductivity, viscosity, and surface tension.

IV. ALTERNATIVE APPROACHES

The use of alternative approaches in CE-ESI-MS hyphenation originates from the typical low ion transmission efficiency. Whereas the ionization efficiency is quite high, the transmission efficiency is very low due to the space/charge repulsion that

occurs during the transport of ions. Zhou et al. (2003) suggested the use of a Venturi device, a commercial air amplifier based on Coanda effect (Gregory-Smith & Senior, 1994), to focus the electrospray ion beam toward the sampling orifice of the mass spectrometer. An interesting work was published by Robichaud et al. (2011) on the improvement of detection limits for biomolecules using such air amplifier and ESI-MS. It is important to note that inside such devices the air flow is strongly turbulent, which effect could not be neglected. Therefore, a k–ω turbulent model was implemented in their in-house developed CFD code using central differences as discretization method. Numerical modeling was used to evaluate the new design, including the simulation of electrospray in each iteration step during the development process. Later, computational results were confirmed by experimental pressure profile measurements.

By means of an air amplifier, a 34-fold improvements was reported in the signal level comparing to a similar experimental setup without using the air amplifier.

Air amplifier can be used at microscale dimensions as well. Jurcicek, Zou, and Gao (2013) reviewed real life examples to illustrate how modeling an help to optimize different design concepts. In a microelectromechanical system (MEMS) based air amplifier device, as well as in commercial ones, the width of the nitrogen input gap is a crucial engineering criterion. Simulations were used to optimize the geometry and to meet performance requirements. Their models were focused on the hydrodynamics of the supporting nitrogen and induced air flow. Unfortunately, simulation details were not published, but Figure 5 clearly shows how numerical modeling can predict gas flow behavior.
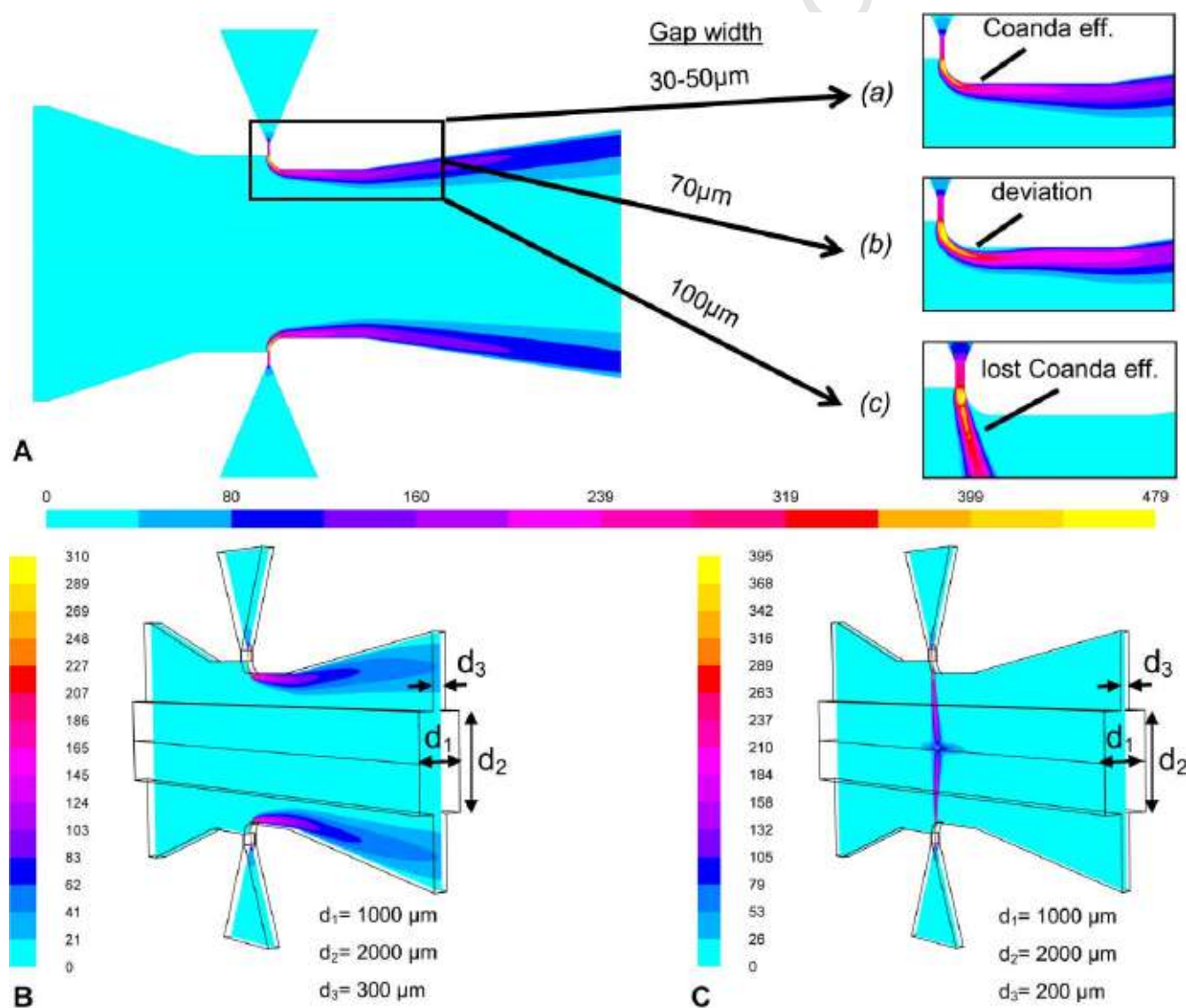

FIGURE 5. Simulation results of the interior flow field inside a MEMS based air amplifier. The inserted views show the nitrogen gas flow velocity contours in the near-wall region with different gap widths of 30–50, 70, and 100 μm, respectively. With permission[Q12] from Jurcicek, Zou, and Gao (2013).

V. CONCLUSION AND FUTURE PROSPECTIVE

Computational fluid dynamic simulation of CE-ESI-MS interfaces utilizes a wide range of frequently used current state of the art modeling techniques. Modeling and simulation of CE-ESI-MS are in their emerging phase, but for the time being the entire process is not fully covered in an original research study, thus a comprehensive work will be needed to describe the whole hyphenation emphasizing novel computational capabilities. The specific fabrication and working conditions require both numerical modeling in design and interpretation of experimental findings. Deeper understanding of various physical phenomena by means of CFD may lead to implementation of more efficient couplings. In addition to clearly speeding up the development process of CE-ESI-MS interface design, modeling and simulation also reduces their cost. For instance, modeling the influence of the raw materials used to fabricate the spraying devices on ionization efficiency via surface hydrophobicity is possible by including the contact angle of the flowing fluid into the model. Furthermore, it could boost the development of specific surface coatings to reduce non-specific binding. It is expected that in the near future, CE-ESI-MS couplings developed by the help of computation modeling and design will open up new horizons in genomics, proteomics, metabolomics, lipidomics and glycomics studies, just to list a few important ones.

Validation requirement against experimental results is a common issue in all modeling and simulation approaches as the obtained data may not always be reliable. Accuracy of simulation results is mostly the question of the purpose of the modeling work (properly selected simulation level) and the convergence of solution as well. In CE-ESI-MS coupling the applied models usually describe multiphysics based physical phenomena, therefore, meshing (discretization) should be handled with care even in case of simple geometry domains. Fortunately, good examples are reported, which can help readers to avoid using unconverged solutions.

Computational modeling of rapidly changing phenomena such as ion formation and dynamically controlled effects are of particular interest and impose further challenges. In conclusion, we envision that comprehensive computational fluid dynamics modeling of CE-ESI-MS interface design will play a significant role in the future providing a particularly important toolset for cross-disciplinary research teams in various sections of the bioanalytical field.

VI. ABBREVIATIONS

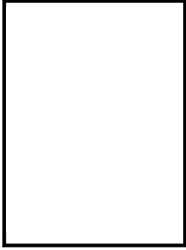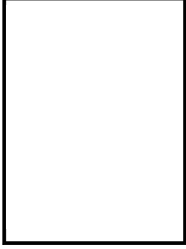|	
CE	capillary electrophoresis
CFD	computational fluid dynamics
CNF	carbon nano fiber
CRM	charge residue model
ESI-MS	electrospray ionization mass spectrometry
IEM	ion evaporation model
LDM	leaky-dielectric model
LIF	laser induced fluorescence
LS	level set
MC	Monte Carlo
MD	molecular dynamics
MEMS	micro electro mechanical system
MS	mass spectrometry
SST	shear stress transport
VOF	volume of fluid
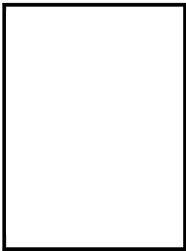
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