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Modeling Approaches for Fluidic Mass Transport in Next Generation Micro and Nano Biomedical Sensors

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ABSTRACT

This review discusses on current methodologies and trends in modeling fluidic mass transport phenomena in micro and nano scale biomedical devices. We have presented the governing equations for species transport in micro and nano scales and provided analytical as well as computational approaches that can aid in obtaining solutions for complex flow problems. We have also reviewed novel methodologies that modern research community utilized for simulating species transport in micro and nano biomedical sensing devices.

Keywords: Analytical modeling, Bio sensors, Computational modeling, Microfluidics, Nanofluidics.

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I. Introduction

Micro and nanoscale devices have contributed tremendously to the fields of engineering, biomedical sciences, applied/natural sciences, health care, instrumentation and many more [1]. The significance of microelectromechanical systems (MEMS) origins due to the change in properties of atomic and molecular systems that to the classical understanding at such small length scales, and have contributed tremendously to modern research community and industry in many positive aspects [2]–[5]. The change in properties has resulted in enhanced resolution power and sensitivity of a microdevice to a device working at macro-scales [6].

While moving from macro to micro/nano scales, characteristic dimensions of a general system become comparable to the mean free paths of atoms and molecules, ultimately deviating from the description of the system from a classical perspective [6]. The behavior of systems at these scales demonstrated many enhanced functional properties [6], [7] such as thermal conductivity, optical properties, electrical conductivity and many more [7]. Such enhanced behavior has been used in many industrial, health care and technological applications to facilitate, enhanced heat transfer [8], [9], cancer cell detection [1], [2], advanced characterization [10], non-Newtonian fluid flow [11] and functional materials development [12], [13], etc.

Micro and nanodevices can be introduced as a marvel in engineering that utilizes small length scale behavior to fulfil many needs of the society [3]. MEMS devices can be entirely based on solid state, solid-liquid state as well as solid-gas conditions [2], [14], [15]. Depending on the application, in solid-liquid and solid-gas MEMS devices, fluid flow, heat transfer and mass transfer can take a significant role in the required process [1], [1], [3]. Therefore, to develop, model and prototype such devices, a broad understanding of fluid flow and mass transfer phenomena is needed. Through this work, we have given an attempt to present modeling processes of mass transfer phenomena in micro/nanodevices from analytical and computational approaches.

To extract few past work done based on mass transfer in micro devices, Gajasinghe *et al*. [2], [4] performed research on microfluidic bio sensors on detection of cancer cells in human blood cultures. They made a microchannel to achieve micro confinement of human cancer cell cultures and used electrical impedance spectroscopy to label the cells based on the change of impedance of the microchannel. Psaltis *et al*. [16] discussed the optical advantages of microfluidics in their review. As they have presented, microfluidics facilitated a branch referred to as optofluidics that can contribute to microscopic optical characterization. Terrey *et al*. [17] introduced microfluidic flow control by introducing control of colloidal particles in the fluid. Smart manipulation of colloidal particles benefitted smart microfluidic valves and micrometer-scale fluid pumps. Yildirim *et al*. [14] developed surface acoustic wave viscosity and density sensor integrating with microfluidics. Similar to the work done by Gajasinghe *et al*. [2], [4], they used electrical impedance spectroscopy to

perform desired measurements. Finally, Paprotny *et al.* [10] developed a microfluidic sensor to monitor the airborne particulate matter. They have used the principle of acoustic resonation to evaluate particulate matter concentration based on a change in resonant frequency. All such works demonstrate the advantages of microfluidics to industry and society due to the expanded reach for collecting information using such small length scales.

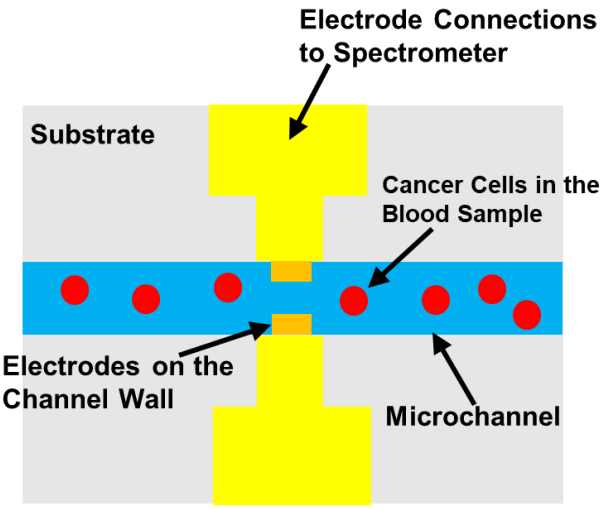

Fig. 1. Immobilization free microfluidic biosensor developed by Gajasinghe *et al.* [2].

For a researcher who is motivated in developing smart microfluidic device, modeling is a crucial need before moving to prototyping. In general, we can characterize main areas of interest in microfluidics as mechanical, fluid flow, thermal, electrical, and mass transport. Mass transfer in microfluidics has tremendously contributed to many biological applications [2] and also mechanical, thermal, heat transfer aspects as discussed in the previous paragraph. To adhere to the scope of this review, herewith we introduced an overview of modeling methods in microfluidic mass transport starting from governing equations for microflows.

We have presented analytical and numerical approaches that have gained popularity in microfluidic research community and are accepted as standards in understanding micro/nano flows. All solutions as similar to the classical approaches, based on solving fundamental governing equations pertaining to a specific transport phenomenon. We will notice that after manipulating through the small length and time scales, will still recover classical definitions of transport phenomena. Therefore, to develop a bridge between continuum (classical) and non-continuum (micro/nano) description, we initially present classical governing equations and solutions to mass transport problems. And the relation between classical and non-continuum laws is subsequently discussed in this article.

II. Continuum Modeling Approaches for Mass Transport

A. Analytical Approaches

In continuum-based solutions for mass transport, we pre-assume that molecular mean free paths of the species are many orders of magnitude smaller compared to the flow domain. In addition to this assumption, we also consider carrier fluid medium, or the bulk medium has a mean free path that is much smaller than the species [18]. Due to this assumption, we can define the transport properties of the system in a bulk approach which can be considered independent of the effect of the spatial domain.

B. Brownian Motion

Brownian motion can be considered the simplest mass transport process. The species in a bulk medium diffuse in space due to intermolecular collisions (atomic/molecular vibrations) and can be mainly attributed to concentration gradient-driven transport. We can mainly describe continuum Brownian motion from Fick's first diffusion law by defining bulk diffusion coefficient (D) and local concentration (c) of the species [19], [20]. Therefore, mass flux of the species (J), by Fick's first law for fully concentration gradient driven transport can be given as [19]:

$$J = -D\,\nabla.c \tag{1}$$

where ∇ can be subsequently written as, $\frac{\partial}{\partial x}+\frac{\partial}{\partial y}+\frac{\partial}{\partial z}$ to represent three dimensions in the cartesian coordinate system. The definition for diffusion coefficient can be different based on the criteria of the system, however, for a most general case for the diffusion of spherical particles with an average diameter d_p, we can write an expression for d_p using Stokes-Einstein relationship as:

$$D = \frac{k_B.T}{6\pi\eta d_p} \tag{2}$$

where k_B is the Boltzmann constant ($k_B = 1.38 \times 10^{-23} J/K$) and T is the absolute temperature. And η is the bulk fluid viscosity. In most cases, Fick's first law becomes a qualitative comparison tool for mass transport. However, Fick's second law provides temporal evolution characteristics of transport and many analytical solutions become possible to resolve the process. Therefore, Fick's second law can be given as:

$$\frac{\partial c}{\partial t} = D\,\nabla^2.c + \omega_0 \tag{3}$$

where t is the time in real space and $\nabla^2 = \frac{\partial^2}{\partial x^2}+\frac{\partial^2}{\partial y^2}+\frac{\partial^2}{\partial z^2}$ and ω_0 is mass source or sink term in the system. Analytical approaches can be presented for (3) for many flow arrangements based on the feasibility of developing an analytical solution [21].

C. Advection with Fick's Diffusion

So far, Brownian motion considered diffusion of species in a stationary medium. For transport in a moving medium, Fick's second law can be modified by accounting advection effects. Therefore, Fick's second law with advection effects can be given as [18]:

$$\frac{\partial c}{\partial t} = u\,\nabla.c\; + D\,\nabla^2.c + S \tag{4}$$

where u is the velocity profile of the carrier medium and can be written for three dimensions, $u = i.u_x + j.u_y + k.u_z$, with i, j and k are unit vectors in x,y and z coordinates. And S is the source or sink term.

The initial step for seeking a solution to any advection-diffusion problem is to resolve the velocity profile in the transport domain. Herewith we assume that species concentration is dilute enough therefore, it will not influence bulk fluid flow. The most general approach is to obtain velocity distribution by solving momentum equations to obtain velocity distribution and subsequently solving advection-diffusion equation in case of a steady flow problem. For a transient problem, a coupled analytical solution is needed to study the process [22].

D. Darcy's Model

Significance in Fick's diffusion is that mass transport is only controlled by either advection or concentration gradient. However, mass transport influenced by a pressure gradient is not addressed. In Darcy's model, mass transport velocity is successfully described using a pressure gradient and gained wide popularity in applying to porous media flow [20].

$$\frac{dp}{dx} = \frac{\mu v}{Pm_v} + \frac{\rho v^2}{Pm_I} \tag{5}$$

where, dp/dx is the pressure gradient and Pm_v and Pm_I are viscous and inertial permeabilities of the species respectively. These values can be found empirically for porous media. Finally, it is important to note that Darcy's model considers the diffusion medium as homogeneous, and velocity (v) provides the diffusion velocity of the species itself.

E. Numerical Approaches

Analytical solutions for transport problems are mostly possible when the geometry is not complex and can be successfully defined with a minimum number of variables that can facilitate an analytical solution. However, when the geometry is complex enough and the problem expands to multi-dimensions with complex boundary conditions, analytical solutions become infeasible. Therefore, as an alternative, computational modeling is necessary with valid approximations within an acceptable tolerance [23]. Computational fluid dynamics (CFD) as a modeling tool highly facilitated resolving transport problems in these aspects [24].

F. Species Transport

Objective of CFD approaches in species transport is to solve governing equations from a numerical approach. The most common methodology is to utilize finite volume (FVM) or finite difference method (FDM) depending on the complexity of the geometry. We can discretize the advection-diffusion equation ((4) using one dimensional explicit FDM only for x direction as [18]:

$$\frac{c_{i,j}^{n+1} - c_{i,j}^{n}}{\Delta t} = u_i\left(\frac{c_{i+1,j}^{n} - c_{i-1,j}^{n}}{\Delta x}\right) + D\left(\frac{c_{i,j}^{n} - 2c_{i,j}^{n} + c_{i-1,j}^{n}}{\Delta x^2}\right) + \emptyset \tag{6}$$

where $c_{i,j}^{n+1}$ and $c_{i,j}^{n}$ are concentration of the species at n+1 and nth time step. Δt is the time step size for each iteration and Δx is the grid spacing in x-dimension. For any source or sink of mass in the transport domain $\emptyset$ can be added as an additional variable. Similar to analytical solutions, equation (6) has to be solved coupled with momentum equations to obtain flow field information [18].

G. Multiphase Modeling Methods

Mass transport can also be modeled using pure computational techniques such as multiphase models. Most common multiphase models are discrete phase (DPM) and volume of fluid (VOF) modeling. In DPM, mass transport is modeled as individual particles that are not influencing the flow paths of bulk flow. Therefore, DPM is acceptable to dilute flows [25]. The general transport equation of DPM can be given as [26]:

$$\frac{\partial C_s}{\partial t} + u\,\nabla.C_s = D\,\nabla^2.C_s - u_1.\nabla C_s - u_r.\nabla C_s \tag{7}$$

where C_s is the discrete particle concentration, u is the local bulk fluid velocity, u_1 is the local lift velocity based local and average shear stresses. And u_r is local drift velocity which is impacted by fluid drag and buoyant forces.

Secondly, VOF model defines two phases in discrete way using an order parameter. Order parameter is usually a fraction between 0 and 1 (Referred as void fraction) which identifies the volume occupied by each phase in a discrete simulation volume [27]. Therefore, VOF solves two coupled conservation equations simultaneously for species transport and order parameter [28], [29]. The conservation equation to void fraction can be given as [29]:

$$\rho(\varphi)\left(\frac{\partial u}{\partial t} + u.\nabla u\right) = -\nabla p + \rho(\varphi).g + \nabla.[\mu(\varphi)(\nabla u)] \tag{8}$$

where, φ is the void fraction and $\rho(\varphi)$ is the density associated with the order parameter. And $\mu(\varphi)$ is the dynamic viscosity of the respective phase. Continuum Porous Media Modeling

Porous media becomes an important application when considering micro-nano scale transport. Application of porous media has benefited in many aspects in heat and mass transfer [18], [30]. Therefore, continuum scale porous media modeling is highly benefited modern research community. By considering a continuum overall diffusion coefficient species transport equations can be solved for porous media using methods introduced before. However, solving the velocity profile can be highly challenging in such domains. As a solution for this issue, a momentum sink term can be introduced to Navier-Stokes (momentum) equations to represent a virtual type of porous media to obtain the velocity profile as below [20].

$$\frac{\partial(\rho v)}{\partial t} + \nabla.(\rho \mathrm{v}.\mathrm{v}) = -\nabla.\mathrm{p} + \nabla.\tau - F \tag{9}$$

where F is the momentum sink term and τ is the viscous shear stress tensor. F can be modeled as [31]:

$$F = -\frac{\mu}{\alpha}.v + \frac{1}{2}.C_2\rho v.v \tag{10}$$

where, α is the bulk permeability of the porous media and C_2 is a model constant.

In conclusion, most continuum approaches are satisfactorily valid for limited cases in microfluidic devices where associated transport is sufficiently dense therefore, rarefication effects can be neglected. However, using continuum methods is completely not valid for nanofluidics.

III. Non-Continuum Modeling Approaches

So far, we have considered continuum methods for simulating mass transport with assumptions based on small molecular mean free paths compared to dimensions of the flow domain. Because of this assumption, we were able to define the holistic flow and diffusion properties to arrive at a transport solution.

However, when characteristic dimensions of the domain at the order of the magnitude of the molecular mean free path, scattering of molecules with domain boundaries becomes significantly important similar (or greater) to intermolecular collisions. In classical laws, it is considered that scattering with domain boundaries is insignificant compared to intermolecular scattering. Due to this phenomenon, we observe a deviation of diffusion properties that to continuum assumptions in such length scales [6].

In addition to boundary scattering, due to rarefication, surface forces from the boundaries become a dominant driving force in fluid flow and mass transport. Secondly, because of the dominance of surface effects, no slip boundary condition arises at the surface invalidating zero flow velocities at the fluid-solid interface. Thirdly, non-Newtonian effects take place in fluid flow showing non-linear behavior in fluid shear stress at such length scales [6]. The objective of this section is to provide solution approaches for mass transport under rarefication effects and varying diffusion properties at micro-nano length scales.

A. Analytical Methods

Similar to continuum methods, analytical solutions are possible for specific flow cases in micro-nano scales where simple geometries are involved. Herewith we present the most common analytical solutions for microscale mass transport processes.

B. Capillary Transport

Capillary transport refers to the transport of fluids in channels without and external driving force. The transport occurs due to surface forces on liquid molecules and this effect becomes dominant in microdevices with characteristics length scales of the order of 10^{-6} m [32]. Though we have stated that capillary effects are due to surface forces, however, capillary effects can be boosted by controlling the surface forces using methods from thermal, chemical, electric fields, optics and hydrodynamic itself [6]. These effects can be used to further scale down the microdevices up to nanoscale by helping to develop more sophisticated devices [6].

The initial solution for capillary flow in microchannels starts with reduced order model to obtain velocity distribution in microchannels [6]. In the reduced-order model, capillary flow is attributed to a lumped system analysis. Therefore, the flow fields inside the microchannel are not explicitly solved rather than providing average values for velocity based on capillary dimensions.

Reduced order model stems from the momentum equations as discussed before. The most final form of reduced-order model with an added mass for a rectangular microchannel with width w and length l and height h_0, can be given as [6]:

$$\frac{d}{dt}\{(M_a + \rho h_0 lw)u_t\} = 2\sigma_{lg} hw[\frac{cos\theta}{h_0} + \frac{1}{w}] + F_m - F_D \tag{11}$$

where M_a is the added mass, θ is the dynamic contact angle, F_D is the drag force and F_m is any force that acts on the system apart from the drag force. The added mass is a virtual mass that has been introduced to remove inconsistency of the solution. Therefore, with $r_h = \frac{2wh_0}{2(w+h_0)}$, we can write an expression for M_a as [6]:

$$M_a = \frac{\rho\pi r_h^2 w}{8}, \tag{12}$$

To arrive at the complete solution of (11), definition of drag force F_D is necessary. F_D can be modeled for different flow systems as presented elsewhere [6].

We can solve for mass transport by reducing order velocity using (4). Using (4) does not account impact of rarefication on mass transport and results can be somewhat non-assuring. Therefore, to overcome such inaccuracies, the most valid approach is to utilize VOF full scale numerical model to resolve mass transport as presented in non-continuum computational methods section.

C. Electrokinetic Transport

Electrokinetic transport occurs in small length scales due to an applied electric field on the transport medium. Fluid flow is initiated due to the phenomenon called electric double layer formation (EDL) [6]. Capillary front can be stimulated by the effects of EDL to produce fluid flow [6].

Herewith we present a most common mass transport model under electrokinetic flow as presented by Chakraborty *et al*. [6] on the transport of macromolecules in the order of size of the flow domain in narrow confinements. Macromolecular transport analysis has been highly contributed to the separation of analytes in many microscale characterization processes [32].

For an analyte introduced for a microchannel with a mean velocity $\bar{u}$, we can write the species conservation equation for the concentration of the analyte (c) [6] as:

$$\frac{\partial c}{\partial t} + \frac{\partial}{\partial x}((u_p - \bar{u})\mathrm{c}) + \frac{\partial}{\partial y}(v_p \mathrm{c}) = \frac{\partial}{\partial x}(D_x \frac{\partial c}{\partial x}) + \frac{\partial}{\partial y}(D_y \frac{\partial c}{\partial y}) + \frac{\partial}{\partial x}(\mu_{ep} c \frac{\partial \Psi}{\partial x}) + \frac{\partial}{\partial y}(\mu_{ep} c \frac{\partial \Psi}{\partial y}) \tag{13}$$

where u_p and v_p are axial and transverse non-electrophoretic velocities respectively. And D_x and D_y axial and transverse diffusivities respectively. The parameter μ_{ep} is called electrophoretic mobility which is a parameter that takes into factors that are beyond concentration gradients (free energy potentials etc. [6]). And Ψ is the external electrostatic potential.

For fully developed flow in rectangular microchannel with appropriate boundary conditions, we can obtain axial and transverse diffusivities as [6],

$$D_x = D\frac{\int_{Ac}\frac{1}{\beta_1}exp(-\frac{\omega_w(y_{cp})}{k_BT})\,dA}{\int_{Ac}exp(-\frac{\omega_w(y_{cp})}{k_BT})\,dA} \quad (14)$$

$$D_y = D\frac{\int_{Ac}\frac{1}{\beta_2}exp(-\frac{\omega_w(y_{cp})}{k_BT})\,dA}{\int_{Ac}exp(-\frac{\omega_w(y_{cp})}{k_BT})\,dA} \quad (15)$$

where D is the classical diffusion coefficient of the analyte based on particle diameter R_p, and can be obtained using:

$$D = \frac{k_BT}{6\pi\eta R_p} \quad (16)$$

and β_1 and β_2 are drag enhancement factors of analytes in longitudinal and transverse directions and need to be evaluated separately based on imposed transport conditions [6].

In addition to the previous approach, as a more holistic solution for analyte flow, have presented by Chakraborty *et al*. [6] consider the transformation of advection-diffusion species transport to an equivalent dispersion equation using perturbation analysis, considering a dispersion coefficient (D^*) as [6]:

$$\frac{\partial\langle C\rangle}{\partial t} + \langle u\rangle\overline{U}\frac{\partial\langle C\rangle}{\partial x} = D_yD^*\frac{\partial^2\langle C\rangle}{\partial x^2} \quad (17)$$

where $\langle C\rangle$ is the average concentration by perturbation analysis and $\overline{U}$ is the band velocity with $\langle u\rangle$ as the average velocity in the channel. From this work, the time evolution of the concentration of analytes can be presented as [6]:

$$\langle C\rangle = \frac{n_0}{2c_0wH}\cdot\frac{1}{\sqrt{4\pi D_yD^*t}}exp[-\frac{(L-\langle u\rangle\overline{U}t)^2}{4D_yD^*t}] \quad (18)$$

where n_0 is the number of moles of analytes in the channel. w and H are channel width and height respectively with c_0 as the initial concentration of analytes introduced to the channel. Electrokinetic transport has been highly contributed to many biological microelectronic systems (BioMEMS) in evaluating invasion-free cancer cell detection, Immunology and many technological aspects [34].

D. Colloidal Transport

Another form of important micro and nanoscale transport process can be extracted as discrete particle transport or colloidal transport which contributed tremendously to BioMEMS applications [2]. Colloidal transport refers to the transport of micro and nanoscale particles or agglomerates in a bulk suspension. The recent motivations in such colloidal suspensions are due to the enhanced properties of the suspension than the base fluid [6]. The introduction of nanoparticles to a base fluid has resulted in increased functional properties such as thermal conductivity [7], [35]. Therefore, such composite fluids have aided to increase heat transfer efficiencies in many solid and liquid state heat transfers [37].

The solutions to transport properties in composite suspensions are highly challenging with analytical methods due to a large number of particles and associated degrees of freedom. Almost all colloidal transport models are solved using numerical approaches. However, we introduce a few colloidal masses transport models in this section, and solution methods will be introduced in the upcoming section.

A nanoparticle motion in a suspension can be initially described using Newton's second law of motion [6],

$$m.\frac{dv_p}{dt} = \vec{F} \quad (19)$$

where m is the particle mass, v_p is the particle velocity and $\vec{F}$ is the total force acting on the particle. The complete form of this equation can be given considering all force effects on nanoparticles based on Stokes drag, Basset History, virtual mass, acceleration of undisturbed fluid and body forces as respectively following the addition terms [6]:

$$m.\frac{dv_p}{dt} = 6\pi\mu r_p(v_l - v_p) + 6\mu r_p^2\sqrt{\frac{\rho\pi}{\mu}}\int_0^t\frac{d(v_l-v_p)}{dt}.\frac{d\tau}{\sqrt{t-\tau}} + \frac{2}{3}\pi\rho r_p^3(\frac{Dv_l}{Dt} - \frac{dv_p}{dt}) + \frac{4}{3}\pi\rho_l r_p^3\frac{Dv_l}{Dt} + \frac{4}{3}\pi r_p^3(\rho_p - \rho_l)g \quad (20)$$

where τ is the relaxation time.

By knowing this information, we can study the evolution of a particle using the relation [6]:

$$r_{p,i}(t+\Delta t) = r_{p,i}(t) + \int(\int F_i dt)dt + \sum_j\frac{\partial D_{ij}(t)}{\partial r_{p,j}}\Delta t + \sum_j\frac{D_{ij}F_j(t)}{K_BT}\Delta t + R_i(\Delta t) \quad (21)$$

where $r_{p,i}$ represents the position of i[th] particle with respect to time t. F_i is the force on i[th] particle as described from (20). D_{ij} is the diffusion tensor and has to be obtained based on a specific system. Finally, $R_i(\Delta t)$embed the random nature of displacement with Gaussian variance $2D_{ij}\Delta t$.

In addition to single-particle motion, motion of particle agglomerates is also ubiquitous in colloidal suspensions. Particle agglomerates form due to enhanced interparticle forces due to increased surface area to volume ratios on nano scale [6].

Herewith we end the discussion on colloidal suspensions by introducing the composite particle agglomerate and breakup rate model in colloidal suspensions. Under association with the composite agglomerate model and solving for time evolution as in (21), we can extract the most complete information on the colloidal transport [6] problem.

$$\frac{\partial n_k(t)}{\partial t} = \frac{1}{2}\sum_{i+j=k}K_{ij}^An_i(t)n_j(t) - n_k(t)\sum_{i=1}^{\infty}K_{ik}^An_i(t) + \sum_{m=k+1}^{\infty}\frac{k_m^Bn_m(t)}{m} - \frac{k-1}{k}.K_k^Bn_k(t) \quad (22)$$

where $n_k(t)$ is the equilibrium aggregate number density at specific time t. K^A and K^B are aggregate agglomeration and breakage parameters respectively.

IV. Computational Methods

A. Full-scale Volume of Fluid Model for Capillary Transport

Full-scale VOF model can be presented as the most complete solution method for capillary flows. Parallel to the continuum CFD VOF approach we can provide the governing equations of VOF as follows [6], [38].

$$\frac{\partial}{\partial t}(\alpha_j \rho_j) + \nabla.(\alpha_j \rho_j v_j) = 0 \tag{23}$$

where α_j is the volume fraction of phase j and ρ_j and v_j are density and velocity of phase j respectively. The bulk fluid in the capillary is considered the primary phase and any species are considered secondary phases [6].

The conservation of the volume fraction can be written as [6]:

$$\sum_j \alpha_i = 1 \tag{24}$$

The general Navier-Stokes (NS) equation can be presented as [21]:

$$\frac{\partial}{\partial t}(\rho v) + \nabla.(\rho v v) = -\nabla p + \nabla.\tau + F \tag{25}$$

Together with VOF conservation equations, NS equations can be solved for capillary flow with my modeling source term *F* in (5) to account for surface tension effects as [6]:

$$F = \sigma_{ij} \frac{\rho k_i \nabla \alpha_j}{(\rho_j + \rho_i)/2} \tag{26}$$

Due to its straightforward VOF capillary fluid modeling approach is a versatile and time-saving tool to simulate mass transport in microchannels.

B. Molecular Dynamics

Molecular dynamics (MD) as a computational approach has been highly aided research community in simulating micro/nanoscale transport. Even with non-continuum approaches to developing solutions, certain assumptions have to be made by reducing the accuracy of the solution to some factor. However, MD allows simulating individual atoms or molecules in a transport system on a more sophisticated basis. In MD, a large number of atoms are simulated with multiple degrees of freedom which requires large computational power. Due to this bottleneck, MD simulations are limited to simulating transport in small length scales where scalable number of atoms can be included. This restricts MD to micro and nano length scales producing challenges to expand it to larger length scales [6].

As the main starting point, MD simulates the evolution of a system of particles confined in space. Evolution of velocities and positions are tracked for individual particles using Newton's second law of motion. For MD, Newton's second law can be given as [6], [37]:

$$m_j \frac{\partial v_j}{\partial t} = \sum_{i \neq j} \nabla V(r_{ji}) \tag{27}$$

and

$$\frac{\partial r_j}{\partial t} = v_j(t) \tag{28}$$

where $V(r_{ji})$ is the interaction potential between atoms and molecules. The most common method to model the interaction potential is the Lennard-Jones potential given by [6],

$$V(r_{ji}) = 4\epsilon\{(\frac{\sigma}{r_{ji}})^{12} - (\frac{\sigma}{r_{ji}})^{6}\} \tag{29}$$

where σ is the Lennard-Jones diameter and ϵ is the energy parameter.

C. Boltzmann Transport and Lattice Boltzmann Method

Molecular dynamics approach as a simulation method is highly convenient when simulating very narrow flow domains (~nm scale geometries) [6]. To simulate a complete microfluidics system under multiple lengths scales molecular dynamics becomes computationally intensive and somewhat becomes infeasible. Lattice Boltzmann method (LBM) can be given as a solution to such bottlenecks in MD by facilitating effective coupling between micro and macro scales. Therefore, LBM can be considered a mesoscale approach [38].

In MD, microstate of each induvial atom or molecule is considered while simulating a large number of atoms/molecules. In LBM, ensembles of atoms which has the same microstates are considered, and their evolution is modeled. Ensembles of microstates are defined using distribution functions specific to the system conditions (Temperature, macroscopic velocity etc.) [38]. And by studying the evolution of the distribution function from its equilibrium distribution function, microscopic properties and, as well as governing equations of fluid flow and mass transfer can be recovered [38]. By this approach, the number of variables to be solved is reduced but still preserving the details of microscale behavior.

The time-dependent behavior of the distribution function (f) is described by Boltzmann transport equation (BTE):

$$\frac{\partial f}{\partial t} + c_i.\nabla f = \Omega(f) \tag{27}$$

where f is the temporal distribution function, c_i is the microscopic velocity and $\Omega(f)$ is the collision term [6].

The foundation to simulate any system using BTE is to accurately define the collision term. However, it has been a great challenge to define exact collision terms due to complexity of the system. However, as a crude definition for $\Omega(f)$, a relaxation time approximation is generally used [38].

Analytical solutions to BTE are available for many solid-state transport problems [39]. However, analytical solutions to BTE for fluid flow and mass transport become highly challenging. Therefore, as a remedy, LBM as a numerical approach can be introduced to obtain solutions to BTE. LBM stems initially from the Bhatnagar-Gross-Crook (BGK)

approximation to collision operator where a single relaxation time (τ) is assumed as [38]:

$$f_i(c + c_i\Delta t, t + \Delta t) - f_i(x,t) = \frac{f_i(x,t) - f_i^{eq}(x,t)}{\tau} \quad (28)$$

where c_i is the microscopic velocity. After rigorous mathematical manipulations (discretizing Maxwell-Boltzmann distribution function), $f_i^{eq}(x,t)$ can be written as,

$$f_i^{eq}(x,t) = \rho w_i[1 + \frac{u.c_i}{c_s^2} + \frac{1}{2}(\frac{u.c_i}{c_s^2})^2 + \frac{u.u}{2c_s^2}] \quad (29)$$

where ρ and u are macroscopic density and velocity and can be simply obtained from:

$$\rho = \sum_i f_i(x,t) \quad (30)$$

and

$$\rho u = \sum_i f_i(x,t)c_i \quad (31)$$

where c_s is referred to as lattice sound speed and w_i is a weight factor assigned based on discretization approach.

For a two dimensional flow domain, the most common approach of D2Q9 [38], c_s can be obtained from the characteristic microscopic length and time scales as:

$$c_s^2 = \frac{\Delta x^2}{3\Delta t^2} \quad (32)$$

Equation (32) can be presented as one of the noteworthy point where the mesoscopic bridge has been made. The continuum level NS equations can be obtained from this point onwards using a mathematical manipulation referred to as Chapmen-Enskog expansion [38].

So far, we have introduced the basics of resolving the flow field using LBM. To adhere to the scope of this paper, we will present the mass transfer modeling capabilities of LBM. After resolving the microscopic flow field, governing equation for the convection diffusion process (equation (4)), can be recovered using LBM approach [38] as:

$$j_i(x + c_i\Delta t, t + \Delta t) - j_i(x,t) = -\frac{j_i(x,t) - j_i^{eq}(x,t)}{\tau_c} + \Delta t S_i + \frac{\Delta t^2}{2} D_i S_i \quad (33)$$

where j_i is the new distribution function attributed for mass transfer. And D_i is the new diffusion coefficient due to impact from the microscale and it is related to relaxation time τ_c by:

$$D_i = \frac{2\tau_c - 1}{2}\Delta t c_s^2 \quad (34)$$

Similarly, the source term, S_i can be expressed according to LBM method as:

$$S_i = (1 + \frac{2\tau_c - c_i.u}{2\tau_c - \theta c_s^2})w_i S \quad (35)$$

where we can express the local concentration using:

$$c = \sum_i j_i \quad (36)$$

And new equilibrium distribution function can be obtained from:

$$j_i^{eq} = w_i c \quad (37)$$

Similar to before, Chapmen-Enskog analysis can be used to recover the macroscopic governing equation of mass transport [39].

V. Examples in Practical Implementation

Herewith we present a few works that have been performed on simulating mass transfer in micro and nanodevices. Kumar *et al*. [39] modeled mass transfer in Magentofluidic micro mixer using COMSOL software. Their simulations are based on solving continuum scale NS equations using shallow channel approximation. They have validated the numerical model with experimental data for microfluidic mass transfer only using a classical approach. Gajasinghe *et al*. [2] performed continuum scale multiphysics simulations to obtain impedance flux behavior when an alien cell is introduced to a microchannel filled with a regular blood culture using COMSOL software. The modeling results helped and motivated them to implement practical MEMS biosensors for cancer cell detection. Farsani *et al*. [5] modeled mass transfer in stirred microbial reactors using continuum approach. They have shown great success in simulating reaction phenomena by modeling source and sink term in continuum level species conservation equations. As a breakthrough study, Hernando *et al*. [40] modeled human living cell transport in micro confinements using lattice gas automata (LGA) methods. The approach is mostly parallel to LBM simulations since LBM stems from LGA concepts. Chevalier *et al*. [32] presented semi-analytical modeling of mass transfer in microfluidic electrochemical chips. They are approached by, starting from NS equations, solutions to flow fields accounting microfluidic effect are obtained initially. Secondly, they implemented Lèvêque approximation to model reactant diffusion from electrodes to the center of the microfluidic channel. Chevalier *et al*.'s [32] work is a sound example of utilizing both analytical as well as numerical methods to simulate mass transfer in microchannels.

VI. Conclusion and Future Implications

In this review, we introduced the multiscale modeling approaches in microfluidic mass transport. Transport behavior at micro/nano length scales can be highly deviant from classical definition due to rarefaction. Effects that showed negligible impact on macro scales showed dominance in many microfluidic applications (surface and charge effects). Analytical solutions are possible for many general transport cases. However, numerical approaches provide great flexibility in studying complex transport problems. Molecular dynamics has shown great potential in resolving the transport up to molecular scale but limiting the size of the simulation domain due to large associated

computational costs. Lattice Boltzmann method bridges the gap between macroscopic and microscopic scales and allows the researcher to simulate complex domains within a reasonable computational cost.

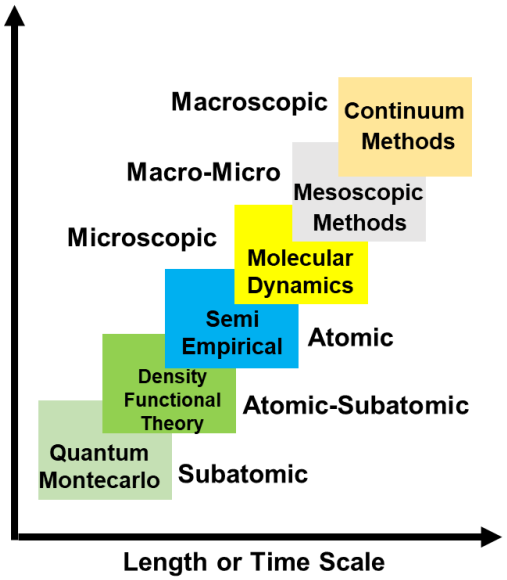

Fig. 2. Time and length scales of solution methods starting from macroscopic Sizes [7].

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CONFLICT OF INTEREST

The authors declare that they do not have any conflict of interest.

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