Multiscale Flow Model for Simulation of Biofluidic Mixtures in Lab-Chip Devices

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***Abstract*—Diagnostic Lab-Chip devices contains multiphase and multicomponent biochemical mixtures. For its simulation we propose multiscale flow model, which consist of macro-, meso- and micro-scale submodels. Hybrid Galerkin FEM algorithm was used solving model equations and obtain simulation results.**

***Keywords*—Lab-chip; microfluidics; multiscale; flow; model; simulation; hybrid FEM; LBM; MDM**

I. INTRODUCTION

Microfluidic devices, like Lab-chips, μ-TAS and Bio-MEMS have achieved growing application in biochemical, biomedical and life-science domains. The basic and most important lab functions are biosensing and biodiagnosing of unknown biological markers in a fluidic sample. The main advantage of microfluidic devices is thousandfold reduction of sample consumption, leading to improved sensitivity and resolution of biomolecular detection. Besides, regular microfluidic device should be able to conduct all typical biochemical workbench processes, including: fluid handling, sample preparation, component transportation, mixing, reaction, separation, bio-target detection, transducer readout and many others in single device. In order to guarantee all typical laboratory functionalities, μFluidic devices should control fluid mixture parameters in each point of microchannel geometry. To do this, one have to describe and simulate the content and behavior of biofluidic mixture.

Most bio-fluidic mixtures are multicomponent and multiphase by its nature. It typically contain multiple constitutive components, which are completely or partially immiscible: viscoelastic liquids (water, oil, biological substances), bio-chemical colloidal solutions, solid particles, gases and others. Generally, multiphase flows appear when two or more immiscible fluids contact with each other. Such interaction results in various multi-phase effects, like suspended clusters, slugs, bubbles, droplets, etc. All these objects creates specific forces of viscous, inertial and interfacial nature, which significantly influence of fluid flow and components distribution over microfluidic channels. Particularly important role in multiphase flow plays partially immiscible fluid components and structure instabilities, which are able to form/vanish complex adhesive segments.

All above shows, that typical multiphase microfluidic systems rises mutual challenges for computer simulation procedures in common CFD tools. Despite progress in Lab-chip design automation, the issues for multiphase flow devices range from modeling and simulation-based verification to the structure synthesis and physical design [1].

II. PROBLEM STATEMENT

There is a wide area of microfluidic Lab-chip devices, which process flow mixtures with multiple fluid phases. Gas bubble and oil droplet dynamics and its interfacial behavior are crucial for the design of biochemical microreactors, drug-delivering chips, diagnostic chips, etc. Thus, the proper modeling and simulating of multiphase microfluidic flows is a crucial point, because its accuracy and consistency have a direct influence on the microchannel geometries and complete Lab-chip design process. Fluid flows in microchannels exploit two primary driving forces: pressure and electrokinetic forces. We focus our research mostly on pressure forces because programmable syringe pumps are the most popular drivers for incorporation and moving fluids in microchannels.

One of the best performing system available today for bio-cell detecting and sorting, is the "fluorescence activated" method [2, 3]. Mixing biofluid substance with fluorescent markers gives the ability to detect and sort individual particles by applying laser beam scattering and measuring fluorescent radiation. Another device category is microreactors, which concerns heterogeneous catalytic reactions, involving gas–liquid–solid or liquid–liquid–solid systems [4].

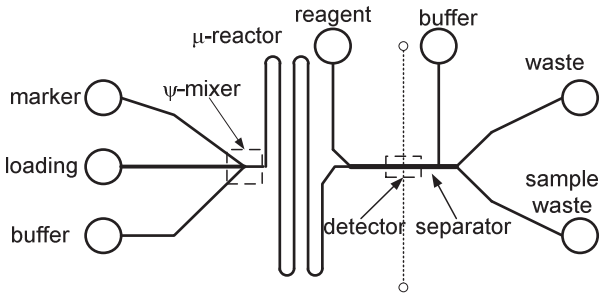

Fig. 1. The typical principle scheme of biofluid detecting and sorting Lab-chip device.

Another important multiphase fluid flow task, related to studying formation of a thrombus (clots) in blood vessels [5]. Its specifics lays in the necessity to incorporate all cell types in single flow model to obtain thrombus development model.

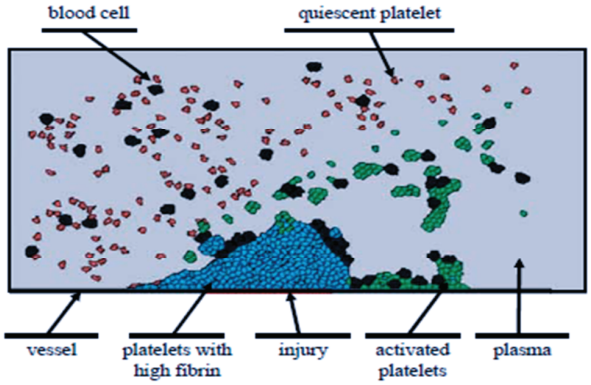

Fig. 2. Different types of cells in the model of thrombus development [5].

Since the beginning of microfluidics era, the simulation of all microfluidic flows have been conducted by computational fluid dynamic tools. Such simulation usually provides detailed insight of flow at the device geometry level, but is impractical for studying multiphase biofluidic transformations. To simulate the mentioned biofluid mixture flows, one have to model the behavior of viscous and incompressible bio particles, their adsorption and coalescence, activation and reaction of chemical components, effects on microchannel walls and their interactions.

Thus, successful design of Lab-chip devices requires new accurate, reliable flow models, numerical methods and software tools which can simulate various effects in complex multiphase mixtures. The most promising is a multi-scale modeling approach, which recently have been intensively developing [6]. The objective of actual research is to choose correct flow models for macro/meso/micro scales and to combine them in single multiscale model. Next, the algorithm for 3D numerical solution of multiscale model are developed, applied and tested for one microfluidic Lab-chip prototype.

III. Multiscale Flow Model

All multiphase flows in microchannels are exposed to the predominant influence of the interfacial effects.

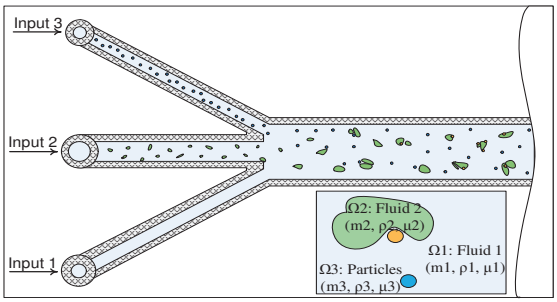

Fig. 3. Principle of multiphase input mixer: 1) buffer solution; 2) bio-substance; 3) fluorescent bio-markers.

General purpose of multiscale modeling of multiphase mixtures flow is to connect: molecular dynamics model at microscale, coarse-grained 'effective molecules' model at mesoscale, and continuous hydrodynamic model at macroscale.

The continuum model has a form of the Navier–Stokes equations, and it is able to describe the microfluidic flow where the channel sizes are in the micrometer range. As the length scale decreases, the continuum approach breaks down and molecular models should be applied to the discrete particles. Molecular models can't simulate the whole systems due to its prohibitive computational cost. At the same time, Navier–Stokes models cannot describe the Lab-Chip details in all cases. These limitations in simulation of microfluidic mechanics have stimulated CFD scientists to conduct research on multiscale simulation techniques. The multiscale simulation technique allows user to couple both models. One of two coupling schemes can be usually used: direct flux exchange or domain decomposition method.

A. Macroscale Model

At macroscale, fluid parameters are continuous functions of coordinates and time. The microfluidic flow model is simplified to Stokes formulation and consist of basic conservation equations with appropriate boundary conditions.

At the macro level, the fluid is considered as continuum substance. All fluid parameters, like pressure, velocity, density, temperature, concentration, etc. have certain values at each environmental point, that are continuous functions of coordinates and time. Then, taking into account the low Reynolds number, the microfluidic flow model is simplified according to the Stokes equation. So, it should consist of basic conservation laws (continuity, momentum, energy and mass):

$$\begin{cases} div(\vec{v}) = 0 \\ \rho \dfrac{\partial \vec{v}}{\partial t} = -\nabla p + \mu \nabla^2 \vec{v} + \rho g + f \\ \rho c \left(\dfrac{\partial T}{\partial t} + \vec{v} \nabla T \right) = \nabla \cdot (\lambda \nabla T) + q_v + \mu \Phi - p \nabla (\vec{v}) \\ \dfrac{\partial c_i}{\partial t} + \nabla \cdot (D_i \nabla c_i) - \nabla \cdot (\vec{v} c_i) = \Re_i \end{cases} \quad (1)$$

here v - velocity vector; ρ - density, μ - viscosity, f - external forces; c - specific heat, T - temperature; t - time, c_i - species concentration; D_i - diffusion coefficient ; R_i - generation or consumption rate of specie i; x - coordinates in $x \in \Omega$ - computation domain.

B. Mesoscale Model

At mesoscale, multiple phases and immiscible components coalesce and detach in all directions of biofluidic mixture. Flow model for this level should be able to describe: the formation/vanish of hetero clusters and phase transformations (Cahn-Hillard model), and the motion of biochemical components in microfluidic flow (Langevin model).

Convective Cahn–Hilliard equation with periodic boundary conditions allows to obtain thin and well-defined interfaces between immiscible fluid components :

$$\frac{\partial c_i}{\partial t} = D_i \nabla^2 \left({c_i}^3 - c_i - \gamma \nabla^2 c_i \right), \quad (3)$$

here D_i - diffusion coefficient of phase component i; $\sqrt{\gamma}$ - the length of the transition region between the phase domains; ∇^2 - n-dimension Laplacian; and value $\left(c_i^3 - c_i - \gamma\nabla^2 c_i\right)$ - represents the chemical potential.

Langevin equation was used to describe complex biological or biochemical motion of mesoscale particles in a mixture. It allows to describe the interaction of the bioparticles with the complex molecular fluid structures, causes random fluctuations of the submerged particles. Here mesoscale particles are the collection of biomolecules and bioparticles, which interacts through conservative, dissipative and stochastic forces:

$$\begin{cases} m\dfrac{d^2x}{dt^2} = -\lambda\dfrac{dx}{dt} + \eta(t) \\ ma = m\dfrac{dv}{dt} = \Phi(x) - \gamma v + \eta(t) \end{cases} \quad (2)$$

here x - mesoparticle position; m - mesoparticle mass; $\eta(t)$ - random force or noise term; $\Phi(x)$ - systematic force, that occurs at the intra- and inter- molecular interactions.

C. Microscale Model

At microscale, the atomistic modeling describe biochemical reactions and bio-molecule interactions in the local volume at an interacting point. Here, according to Newton's law of motion, it is determined dynamically by vectors of positions $\mathbf{r_i}=(x_i, y_i, z_i)$ & velocities $\mathbf{v}_i=(v_{x,i}, v_{y,i}, v_{z,i})$. The Lennard–Jones (12-6) potential is typically used in MD simulations:

$$\begin{cases} \phi_i(r) = \sum_{j=1}^{N_i} \phi_{ij}(r_{ij}) \\ \phi_{ij}(r_{ij}) = \sum_{j=1}^{N_i} 4\varepsilon_0 \left[\left(\dfrac{\sigma}{r_{ij}}\right)^{12} - \left(\dfrac{\sigma}{r_{ij}}\right)^{6} \right] \end{cases} \quad (4)$$

here r_{ij} is the distance between atoms i and j, ε- is the energy scale, and σ - is the Lennard–Jones diameter.

IV. Methods for Numerical Solution

Regular computational fluid dynamics (CFD) still have difficulties to solve the full Navier-Stokes equations for multiphase mixtures with deforming interfaces. At microscale level the simulation of multiphase interactions in microchannels become more difficult due to the effects of large surface tension forces. Three main approaches were developed to predict the time evolution of interface shapes in multiphase and multicomponent flows [7]:

1) Moving mesh methods, where simulation of fluid flow is performed on a mesh, which is moving with the flow. There are two subgroups of this method - boundary fitted grid with each phase, and Lagrangian grid, which follows the fluid. The first group is suitable to study multiphase plug flow.

2) Interface tracking methods, which use virtual moving markers (Lagrangian particles) to track the phase interfaces according to the velocity field on a fixed computational grid. Most known are: marker and cell method (MAC), front-tracking method (FTM), immersed boundary method (IBM). These methods are more accurate at conserving the interface, but more complex in implementation and less accurate in the interface predictions. It is not suitable for phase breakup and coalescence, but can be used for simulating flow of particles.

3) Interface capturing methods: implicitly capture interface by a contour of a particular scalar function - (volume-of-fluid (VOF), level-set (LSM) and phase-field methods (PFM). The convection or diffusion of the particular order parameter is used to capture the interface. These methods are good for predicting interface, but does not conserve the interface and needed geometry reconstruction and reinitialization scheme. This class of methods was used in actual research.

V. Hybrid FEM for Simulation of Biofluidic Flow

High-level simulation of Lab-chip flow is not able to describe multiphase interactions and interface features. On the contrary, low-level simulation of whole Lab-chip requires high computational resources. Thus, multiscale modeling on base of hybrid FEM, allows to keep accuracy and minimize resources. A set of numerical procedures for scales connectivity and multiphase flows stabilization were developed and included in hybrid FEM algorithm.

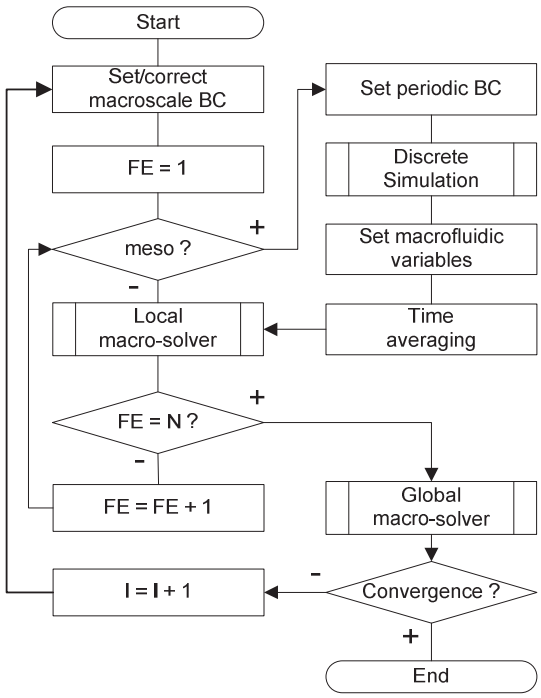

Fig. 4. Hybrid FEM algorithm for multiscale flow simulation.

The solution of Stokes equations system was obtained by classical Galerkin FEM method:

$$\begin{cases} \tilde{u}(t,x) = \sum_{j=1}^{N} a_j(t) N_j(x) \\ W_i(x) = N_i(x) + \sum_{k\in K_i} \alpha_{i,k} W_{(i,k)}(x) \end{cases} \quad (5)$$

where $\{N_j(x)\}$ – a set of continuous piecewise linear basis functions, W_i - a set of weight functions, Ki – the set of node numbers k , $a_{i,k}$ – numeric parameter, tuning curve shape, corresponding to the edge (i, k). This parameter allows to change the shape of the functions $W_i(x)$.

Finite elements, which has multiple phases, require the interface-capturing equation. So, motion of (diffusive) phase interface was obtained from convective Cahn-Hilliard equation by using Lattice Boltzmann method (LBM). We used D2Q9 distribution functions f_i. and the most widely used Bhatnagar-Gross-Krook (BGK) collision operator [8]:

$$f_i^{\phi}\left(x+e_i\delta_t,t+\delta_t\right)-f_i^{\phi}\left(x,t\right)=\left(1-q\right)\cdot$$
$$\left[f_i^{\phi}\left(x+e_i\delta_t,t\right)-f_i^{\phi}\left(x,t\right)\right]+\frac{1}{\tau^{\phi}}\left[f_i^{\phi\,eq}\left(x,t\right)-f_i^{\phi}\left(x,t\right)\right] \quad (6)$$

where τ^{φ} - dimensionless single relaxation time for species ϕ (usually $\tau^{\varphi}=0{,}7$); q - constant (when $q=1$, above LBE receives conventional form); e_i - discrete velocities. Here $f_i^{\phi\,eq}$ is the equilibrium distribution function, which depends on the local density, the local velocity relaxation parameter for ϕ.

For the D2Q9 model, they are given as:

$$e_i=\begin{cases}(0;0) & i=0\\ (\pm1;0)c \quad (0;\pm1)c & i=1,2,3,4\\ (\pm1;\pm1)c \quad (\pm1;\pm1)c & i=5,6,7,8\end{cases}, \quad (7)$$
$$w_i=\begin{cases}4/9 & i=0\\ 1/9 & i=1,2,3,4\\ 1/36 & i=5,6,7,8\end{cases}$$

where $c=\delta x/\delta t$. The macroscopic variables are evaluated as:

$$\rho=\sum_i f_i;\quad \rho v=\sum_i f_i e_i .$$

The following equilibrium distribution functions were used:

$$f_i^{\phi eq}=\rho w_i\left(r_i+3e_i v+\frac{9}{2}\left(e_i v\right)^2-\frac{3}{2}v^2\right) \quad (8)$$

For this Boltzmann equation, the distribution function at any location is defined as a dependent variable, instead of velocity and pressure. Then, surface tension on the phases interface can be easily obtained using the gradient of the chemical potential.

For unknown mesoscopic parameters, microscale molecular dynamic simulation procedure (MD) may be conducted to recalculate and return required microfluidic parameters.

VI. Conclusions

The developed multiscale microfluidic flow model allows to clarify multiphase processes and to design microfluidic Lab-chip devices for various biofluidic mixtures. The solution was based on combination of Galerkin FEM, discrete LBM and MD in extra cases. The calculated density distribution of microfluidic mixture across the channel (pic.5) gives correct sharp difference between two phases.

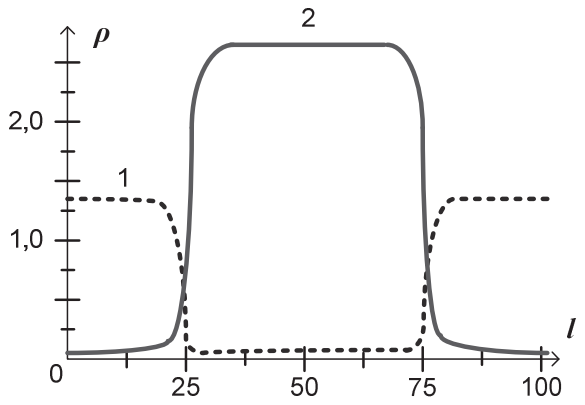

Fig. 5. Density distribution across the microchannel: 1) fluid; 2) bio-object.

It was shown, that the flow characteristics continuously change as the simulation continues, until a steady state is reached. such parameters, as interface position, mean viscosity and mean density in each phase component. The phase interface moves because of the applied interaction forces. The mean density and viscosity differs from the initial parameters, because the two phases are not 100% immiscible.

Actual work bridge models and methods from three different scales by means of hybrid Galerkin FEM. It demonstrate that careful fluid simulation with multiscale model allows to predict multiphase interactions and design valuable microfluidic devices. The behavior of multiphase flows of scalable multiphase systems are also discussed. The details of implementation and results of microfluidic flow simulation together with model verification is shown in presentation.

VII. Acknowledgement

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