Multigrid Accelerated Computation of Growth Factor-Receptor Binding and Dissociation under Flow Conditions *

Wensheng Shen†
Department of Computational Science,
SUNY Brockport,
Brockport, NY 14420, USA
Kimberly Forsten-Williams‡
Department of Chemical Engineering,
Virginia Polytechnic Institute & State University,
Blacksburg, VA 24061, USA
Michael Fannon§
Department of Ophthalmology and Visual Sciences,
University of Kentucky,
Lexington, KY 40506, USA
Changjiang Zhang¶ and Jun Zhang††
Laboratory for High Performance Scientific Computing and Computer Simulation,
Department of Computer Science, University of Kentucky,
Lexington, KY 40506 0046, USA

April 1, 2008

---

*Technical Report CMIDA-HFS/CCS 004-08, Department of Computer Science, University of Kentucky, Lexington, KY, 2008.
†Corresponding author. E-mail: wshen@brockport.edu. URL: http://www.cps.brockport.edu/~shen.
‡E-mail:kfw@vt.edu.
§E-mail: mwfann2@email.uky.edu.
¶E-mail: czhanb@csr.uky.edu.
††E-mail: jzhang@cs.uky.edu. URL: http://www.cs.uky.edu/~jzhang.
Abstract

This paper describes a multigrid finite volume method developed to speed up the solution process for simulating complex biological systems. The method is applied to a model system which includes flow through a cell lined cylindrical vessel and includes fibroblast growth factor-2 (FGF-2) within the fluid capable of binding to receptors and heparan sulfate proteoglycans (HSPGs) on the cell surface. The flow is assumed laminar and is simulated by the incompressible Navier-Stokes equations. FGF-2 transport is modeled by a convection-diffusion transport equation and interactions with cellular receptors and HSPGs are modeled through a series of biochemical reaction boundary conditions. For our simulations, the finite volume method was used to discretize the differential equations and the multigrid V-cycle algorithm was used to solve the discretized elliptical equations, which allows for non-uniform grid spacing and multiple levels of grids. Three iterative methods - Stone's SIP, BiCGSTAB, and GMRES - were used to solve the linear systems and their performance is compared. For the simple model system examined, the multigrid methods offered significant speed-up improvement over the single-grid method for all three solvers with all iterative methods yielding similar results. Our work indicates that a multigrid finite volume method may allow users to investigate complex biological systems currently intractable with single-grid methods.

Key words: Multigrid, Finite volume, Navier-Stokes equation, Fibroblast growth factor, Mass transport, Biological system.

1 Introduction

Communication between cells is achieved to a great extent by soluble molecules that are transported either by diffusion through extracellular matrices or through circulation of blood and lymph. The bioavailability of these molecules to cell surface is regulated by a number of factors. For example, a protein may have a unique family of cell surface receptors to which it binds. This binding will trigger a cascade of downstream signaling events in the cell. The efficiency of the binding events depends in part on the concentrations of both ligand and receptor, the intrinsic binding affinity of the molecules, and the presence of competing ligands and receptors.

Basic fibroblast growth factor (FGF-2) is the prototypical member of the family of fibroblast growth factors [13]. It has been demonstrated to be important in developmental processes, normal physiology, and pathologies such as cancer [7, 9]. In addition to its target cell surface tyrosine kinase receptor, FGF-2 also binds with high affinity to heparan sulfate proteoglycan (HSPG), which consists of a protein core with O-linked carbohydrate chains that are polymers of repeating disaccharides [5, 25]. HSPGs are present on almost all cell surfaces and generally in much higher numbers than FGF surface receptors. FGF-2 is present in circulation and its presence in elevated levels in blood is used in clinical settings as criteria for treatment strategies such as interferon alpha therapy for infantile hemangioma [4]. Although FGF-2 binding interactions have been the subject of a number of studies in static systems, far less is known about their behavior under flow.
The interaction between biochemical reaction and mass transfer is of particular interest for the real-time analysis of biomolecules in microfluid systems [11, 17]. Glaser [11] proposed a two-dimensional (2D) computer model, which was greatly simplified by assuming that the flow is parallel and the diffusion is perpendicular to the surface, to study antigen-antibody binding and mass transport in a microfluid chamber. Myszka et al. [17] used a computer model similar to that of Glaser [11] to simulate the binding between soluble ligands and surface-bound receptors in a diagnostic device, BIACORE, for both transport-influenced and transport-negligible binding kinetics. A 2D convection and diffusion equation was used by Chang and Hammer [3] to investigate the effect of relative motion between two surfaces on the binding of surface-tethered reactants. In this work, the binding of a cell-bound receptor and tethered ligand under fluid was considered mathematically similar to the binding of a free ligand and a cell-bound receptor in the presence of convective flow [3]. Model and Ommann [16] systematically analyzed the effect of mass transport rate, including diffusion and convection, on the kinetics of ligand binding. The quantitative relation between mass transport and ligand binding, however, was not established, and the convection diffusion equation was not actually solved. A theoretical investigation was conducted by Lagerholm and Thomson [15] to explain the possibility of ligand rebinding at cell membrane surfaces. Differential equations, including a Laplacian equation, of the probabilities were solved. Again, the effect of convection was not considered. The model presented in the current paper is more general than the previous studies. It is a multi-dimensional multi-component model, and multiple species can be added in the solution and on the surfaces. The two-dimensional concentration of ligand in solution, as well as the spatial and temporal concentration of cell surface components can be readily obtained.

Developing efficient solvers for nonlinear system of equations arising from fluid flow and mass transfer problems is of practical interest [8, 14]. When nonlinear partial differential equations are discretized in a particular spatial mesh, the result is a set of ordinary differential equations, with time as the independent variable,

$$\frac{df(\bar{u})}{dt} + \Phi(\bar{u}) = 0, \quad \bar{u} \in \mathbb{R}^n$$

where \(n\) is the number of control volumes in a finite volume method. The temporal terms may be further discretized using either an explicit or an implicit scheme. In an explicit method, a large number of independent equations, one for each control volume, have to be solved. In the case of an implicit discretization, we have to solve a large set of simultaneous equations,

$$F(\bar{u}) = \frac{f(\bar{u}) - f(\bar{u})^o}{\Delta t} + \Phi(\bar{u}) = 0$$

where \(f(\bar{u})^o\) is the value at the previous time step. If the number of components of \(\bar{u}\) is \(m\), the number of independent variables is \(mn\). Such large sets of nonlinear equations are generally solved by a variant of Newton’s method, where a sequence of linear systems are solved [8, 18]. The great advantage of the Newton iteration is its quadratic convergence. However, Newton iteration converges only if the initial guess is close to the solution. Instead, in this paper, the method of Picard iteration is applied, in which the nonlinear convective term and source term are linearized by using values from the previous outer iterations. This kind of linearization requires many more
iterations than a coupled technique such as Newton-like linearization, but an initial guess close to the solution is not critical for the convergence. The number of outer iterations, however, can be substantially reduced by using multigrid techniques.

2 Mathematical Model

A coupled nonlinear convection-diffusion-reaction model for simulating growth factor binding under flow conditions has recently been developed [10, 21] and is used here. This model provides the computational infrastructure needed to systematically study the effects of flow on growth factor binding within the bioreactor system, and to quantitatively evaluate the effect of cellular interactions on the distribution of growth factor in solution. The model could serve as a prototype for the more advanced simulation of growth factor binding dynamics in circulation. In this work, the model is used to predict the time-dependent distribution of FGF-2 in a capillary with complicated binding kinetics on the tube surface.

For simplicity, we consider a basic model, where FGF-2 is the only ligand in the solution, and cells which line the capillary express both FGF-2 receptors (FGFR) and HSPGs. As illustrated in Fig. 1, FGF-2 binds to FGFR and HSPG to form complexes of FGF-2-FGFR and FGF-2-HSPG. The resulting complexes may continue binding to produce either their dimers or FGF-2-FGFR-HSPG triads. The FGF-2-FGFR-HSPG triads may further bind to each other to generate bFGF-FGFR-HSPG dimers. Consequently, the concentration of FGF-2 in the solution is affected due to the molecular binding process.

![Figure 1: Sketch of growth factor binding to receptors and HSPGs and the formation of various compounds on the surface of a capillary. The symbols in the sketch are as follows: L=FGF-2, R=FGFR, P=HSPG, C= FGF-2-FGFR complex, G=FGF-2-HSPG complex, C2=FGF-2-FGFR dimer, G2=FGF-2-HSPG dimer, T=FGF-2-FGFR-HSPG complex, and T2=FGF-2-FGFR-HSPG dimer. The arrows represent velocity vectors, which are uniform in the entrance and evolve to parabolic later on.](image-url)
momentum, and protein transport in conservative form for incompressible flow can be written as:

\[
\frac{\partial \rho}{\partial t} + \frac{1}{r} \frac{\partial (\rho rv_r)}{\partial r} + \frac{\partial (\rho v_z)}{\partial z} = 0,
\]

(3)

\[
\frac{\partial (\rho v_r)}{\partial t} + \frac{1}{r} \frac{\partial (\rho rv_r v_r)}{\partial r} - \frac{1}{r} \frac{\partial}{\partial r} \left( r \mu \frac{\partial v_r}{\partial r} \right) + \frac{\partial (\rho v_r v_z)}{\partial z} - \frac{\partial}{\partial z} \left( \mu \frac{\partial v_r}{\partial z} \right) = -\frac{\partial p_r}{\partial r} - \frac{\mu_r}{r^2},
\]

(4)

\[
\frac{\partial (\rho v_z)}{\partial t} + \frac{1}{r} \frac{\partial (\rho rv_r v_z)}{\partial r} - \frac{1}{r} \frac{\partial}{\partial r} \left( r \mu \frac{\partial v_z}{\partial r} \right) + \frac{\partial (\rho v_z v_z)}{\partial z} - \frac{\partial}{\partial z} \left( \mu \frac{\partial v_z}{\partial z} \right) = -\frac{\partial p_z}{\partial z},
\]

(5)

\[
\frac{\partial \phi_i}{\partial t} + \frac{1}{r} \frac{\partial (ru \phi_i)}{\partial r} + \frac{\partial (v \phi_i)}{\partial x} = \frac{1}{r} \frac{\partial}{\partial r} \left( K_r r \frac{\partial \phi_i}{\partial r} \right) + \frac{\partial}{\partial x} \left( K_z \frac{\partial \phi_i}{\partial x} \right) + F_i(\phi_1...\phi_n), \quad 1 \leq i \leq n,
\]

(6)

where \( \rho \) is the density, \( \mu \) the dynamic viscosity, \( p \) the dynamic pressure, and \( v_r \) and \( v_z \) are velocity components in the radial and axial directions, respectively, \( \phi \) the concentration of protein, and \( S \) the source term. In the above equation set, the independent variables are time \( t \), radial coordinate \( r \), and axial coordinate \( z \).

The transport equation for FGF-2 consists of two mechanisms, convection and dissipation. The convection term describes transport of local components along the streamlines of the flow, co-moving with the particles of the fluid. The velocity field of the flow is determined above. The dissipation term describes diffusive transport of components due to concentration gradient. The local concentration of a component changes with pressure difference, gravitational forces, and viscous dissipation. The mass of each species must be conserved. If binding or reactions occur within the fluid, the coupling of mass transport and chemical kinetics in a circular pipe can be described by the following equations:

\[
\frac{\partial \phi_i}{\partial t} + \frac{1}{r} \frac{\partial (ru \phi_i)}{\partial r} + \frac{\partial (v \phi_i)}{\partial x} = \frac{1}{r} \frac{\partial}{\partial r} \left( K_r r \frac{\partial \phi_i}{\partial r} \right) + \frac{\partial}{\partial x} \left( K_z \frac{\partial \phi_i}{\partial x} \right) + F_i(\phi_1...\phi_n), \quad 1 \leq i \leq n,
\]

(7)

where \( \phi_i \) is the concentration of species \( i \), \( u \) and \( v \) are the radial and longitudinal components of velocity, \( K_r \) and \( K_z \) the molecular diffusion coefficients, and \( F_i \) the rate of change due to kinetic transformations for each species \( i \). The basic model however has only FGF-2 within the fluid (\( \phi_i \) is simply FGF-2) and, thus, reactions (i.e., binding and dissociation) occur only on the capillary surface. That is to say that \( F_i \) is valid merely on the tube surface. The reactants and products involved in the chemical kinetics include FGF-2, FGFR, HSPG, FGF-FGFR complex and its dimer, FGF-HSPG complex and its dimer, FGF-HSPG-FGFR complex and its dimer, with a total of nine species (\( n = 9 \)) [10]. The boundary conditions of Eq. (7) are

\[
\frac{\partial \phi_i}{\partial r} = f_i(t, x, C_i) \quad \text{at} \quad r = R, \quad \frac{\partial \phi_i}{\partial r} = 0 \quad \text{at} \quad r = 0.
\]

(8)

The first boundary condition accounts for interactions at the vessel wall (\( R \) is the radius of the capillary and \( f_i \) the rate of binding to cells), while the second boundary condition reflects the axial symmetry.

3 Colocated Finite Volume Discretization

A cell-centered finite volume approach is applied to discretize the partial differential equations. The advantage of cell-centered arrangement is that second order accuracy is achieved, since nodal
value represents the mean over the control volume and the node is located at the centroid to the control volume.

Eqs. (3) ~ (7) can be expressed in the form of convection-diffusion equations. Two-dimensional convection-diffusion equation in cylindrical axisymmetric coordinates may be written as

$$\frac{\partial}{\partial t} (\rho \phi) + \frac{1}{y} \frac{\partial}{\partial y} \left( y \rho u \phi - y \Gamma \frac{\partial \phi}{\partial y} \right) + \frac{\partial}{\partial x} \left( \rho u \phi - \Gamma \frac{\partial \phi}{\partial x} \right) = S, \quad (9)$$

In the above expression, \( x \) and \( y \) are axial and radial coordinates, \( u \) and \( v \) are the velocity components in the axial and radial directions, respectively. The reason to write an equation in axisymmetric coordinates in such a way is to facilitate programming, i.e., to let the same computer program perform calculations in both 2D Cartesian coordinates and axisymmetric ones. For the momentum equation in radial direction, an extra term of \(-\frac{\Gamma \rho v}{y}\) should be added to the right-hand side of Eq. (9). It is worth noting that the mass conservation equation is a special case of Eq. (9) in which \( \phi, \Gamma, \) and \( S \) are taken as \( \phi = 1, \Gamma = 0, \) and \( S = 0. \)

To achieve higher order temporal accuracy, we use a quadratic backward approximation for the time derivative term. Such arrangement gives us second order temporal accuracy. Integrating Eq. (9), the corresponding finite volume equations can be derived. For the mass conservation equation, the finite volume counterpart reads,

$$\frac{3\rho_{p}^{n+1} - 4\rho_{p}^{n} + \rho_{p}^{n-1}}{\Delta t} + (F_{e} - F_{w}) + (F_{n} - F_{s}) = 0, \quad (10)$$

where \( F_{e, w, n, s} \) each represents the mass flux at each of the four interfaces of the control volume.

The finite volume expression of the momentum transport equations is written as

$$\frac{3(\rho \phi)^{p}_{n+1} - 4(\rho \phi)^{p}_{n} + (\rho \phi)^{p}_{n-1}}{\Delta t} + (J_{e} - J_{w}) + (J_{n} - J_{s}) = S_{C} + S_{P} \phi_{P} + S_{sym}, \quad (11)$$

where \( J_{e, w, n, s} \) is the convection-diffusion flux at each of the four interfaces of the control volume \( P, \) with \( J_{e, w} = F_{e, w} - D_{e, w}, J_{n, s} = F_{n, s} - D_{n, s}, S_{C} \) and \( S_{P} \) are the results of source term linearization, and \( S_{sym} \) is the contribution from axisymmetric coordinates, with \( S_{sym} = -\Gamma \frac{u}{y} \) for the momentum equation of \( v. \) The approximation of convective flux is critical for an accurate solution. Frequently used methods include first order upwind and second order central difference. Here, a so-called “deferral correction” technique is employed for higher-order flux approximation [8]. This technique calculate higher-order flux explicitly using values from the previous iteration. Using deferred correction [8], which is a combination of the first order upwind differencing and the second order central differencing, the convective flux is written as a mixture of upwind and central differences, \( F_{e, w} = \frac{F_{e, w}^{u}}{\lambda} + \frac{F_{e, w}^{c}}{\lambda}, \) where \( F_{e} = \max((\rho u) \Delta x_{j}, 0) \phi_{P} \min((\rho u) \Delta x_{j}, 0) \phi_{E}, F_{w}^{u} = \max((\rho u) \Delta x_{j}, 0) \phi_{W} \min((\rho u) \Delta x_{j}, 0) \phi_{P}, F_{w}^{c} = (\rho u) \Delta x_{j} (1 - \alpha_{E}) \phi_{P} + (\rho u) \Delta x_{j} \phi_{E}, \lambda \) is a parameter set as \( \lambda = 0 \sim 1, \) and the superscript \((\circ)\) indicates taking the value from the previous iteration, which will be taken to the right hand side and treated as a part of the source term. The same can be applied to convective flux in radial direction, \( F_{n, s} = \frac{F_{n, s}^{u}}{\lambda} + \frac{F_{n, s}^{c}}{\lambda}, \) where \( F_{n}^{u} = \max((\rho v) \Delta x_{i}, 0) \phi_{S} \min((\rho v) \Delta x_{i}, 0) \phi_{N}, F_{n}^{c} = (\rho v) \Delta x_{i} (1 - \alpha_{S}) \phi_{S} + (\rho v) \Delta x_{i} \phi_{N}, \) The interpolation factors are defined as \( \alpha_{E} = \frac{x_{e} - x_{P}}{x_{e} - x_{P}^{u}}, \)
\[ \alpha_w = \frac{x_p - x_w}{x_p x_w}, \quad \alpha_n = \frac{x_n - x_p}{x_n x_p}, \quad \text{and} \quad \alpha_s = \frac{x_p - x_s}{x_p x_s}. \] 

The diffusion fluxes are
\[ D_e = \frac{K_e y_e (\phi_e - \phi_p)}{x_p x_p}, \quad D_w = \frac{K_e y_e (\phi_e - \phi_w)}{x_p x_p}, \quad D_n = \frac{K_e x_n (\phi_e - \phi_p)}{x_n x_p}, \quad \text{and} \quad D_s = \frac{K_e x_s (\phi_e - \phi_p)}{x_s x_p}. \]

The notations of spatial discretization in Eq. (11) is illustrated in Fig. 2, where the uppercase letters indicate the center of the control volumes, and the lowercase letters indicate the interfaces between neighboring control volumes.

![Figure 2: Finite volume notation of control volumes in axisymmetric coordinates.](image)

Substituting into Eq. (11) and collecting terms, a set of algebraic equations are obtained, of the following form
\[ A_S \phi_S + A_w \phi_W + A_P \phi_P + A_E \phi_E + A_N \phi_N = b. \] (12)

The coefficients of Eq. (12) consist of a pentadiagonal matrix, and they are given by
\[ A_S = -\max((\rho u)_w \Delta x_i, 0.) - \frac{K_{e_x} \Delta x_i r_n}{x_p}, \quad A_W = -\max((\rho u)_w \Delta x_i, 0.) - \frac{K_{e_x} \Delta x_i r_p}{x_p}, \quad A_N = \min((\rho v)_n \Delta x_i, 0.) - \frac{K_{e_y} \Delta x_i r_n}{x_p}, \quad A_E = \min((\rho v)_n \Delta x_i, 0.) - \frac{K_{e_y} \Delta x_i r_p}{x_p}, \quad \text{and} \quad A_P = \frac{3 \rho_P \Delta x_i \Delta x_j}{2 \Delta t} - (A_W + A_S + A_E + A_N). \]

The right-hand side vector is given by
\[ b = \left( S_C + S_P \right) r_P \Delta x_i \Delta x_j + \left( \frac{4 \rho_P \rho_D \Delta t}{2 \Delta t} - \frac{\rho_D^2 \Delta t}{2 \Delta t} \right) r_P \Delta x_i \Delta x_j - \lambda \left( F_e - F_i - F_w + F_w + F_n - F_n - F_e - F_n \right). \]

The banded matrix equation is solved using an efficient linear system solver, which will be discussed later.

The naive way of colocated arrangement makes the solution of Navier-Stokes equations not very pleasant due to the checkboard pressure distribution. Therefore staggered grid was once considered as a standard way for the calculation of incompressible flow [12, 18]. A remedy was proposed by van der Wijngaart [24] to deal with the pressure-velocity coupling on colocated grids by eliminating the oscillations in the pressure field [8]. Our work uses a colocated grid and adopts the remedy to filter out the oscillations. A colocated arrangement is attractive when using a non-orthogonal grid, complex geometry, and multigrid methods.

## 4 Multigrid Methods

The initial guess in an iterative method is usually far from the converged solution and, very frequently, a initial guess of zero is used. It therefore makes sense to solve the equation first on a very coarse grid and use that solution to provide a better guess for the initial guess on the next finer grid [14]. In this way, by the time the finest grid is reached, a good starting solution has been generated. Some iterative methods produce errors that are smooth functions of the spatial
coordinates. In such methods, after a few iterations, the rapidly changing components of the error have been removed and the error becomes a smooth function of the spatial coordinates. If the error is smooth, the update can be computed on a coarser grid [1]. Furthermore, iterative methods converge much faster on coarser grids. This suggests that much of the work can be done on a coarser grid. To do this the relationship between a fine grid and a coarse one has to be determined, which can be done by intergrid transfer operations called restriction and prolongation [1]. Restriction is to project the residual from the fine grid to the coarse one. Prolongation is to interpolate the updates or corrections from the coarse grid to the fine one.

The solution of Navier-Stokes equations consists of two loops. The inner iteration handles each of the individual equations of momentum, energy, and turbulent kinetics if necessary, and the outer iteration deals with the coupling and nonlinearity. For unsteady flow using implicit discretization, the linear equations need not be solved very accurately at each outer iteration. Usually a few iterations of a linear system solver is enough. More accurate solution will not reduce the number of outer iterations but may increase the computing time [26]. For steady flow calculation, the computation cost can be greatly saved by using the multigrid method.

In finite volume method on a structured grid, the multigrid version in 2D can be constructed such that each coarse grid control volume is composed of four control volumes of the next finer grid [8]. To do this, a grid generator that is able to generate multiple grids is used. The grid generator takes input of the number of grid levels, the number of lines along each boundary, the coordinates of starting and ending points for each line, the line type, etc., for the coarsest grid. The data of the rest levels of grids are computed automatically by subdividing each control volume in finer ones and saved as binary files to be loaded by the flow solver.

In the current work, we use a full multigrid procedure previously described by Schreck and Peric [19]. A coarse grid is chosen and a converged solution is obtained. This solution is interpolated to the next finer grid to obtain a starting solution. After performing a few outer iterations on the finer grid, the calculation is moved to the coarser grid, to start a V-cycle like computation.

The algebraic equation Eq. (12) can be written more abstractly as

$$A\phi = b,$$

where $A$ is a square matrix, $\phi$ the unknown vector, and $b$ the source vector. After the $k$th outer iterations on a grid with spacing $h$, the intermediate solution satisfies the following equation,

$$A_h^k \phi_h^k = b^k = r_h^k,$$

where $r_h^k$ is the residual vector after the $k$th iteration. Once the approximate solution at the $k$th iteration is obtained, we restrict the approximate solution as well as the residual to the the next coarse grid by the restriction operators $R_h^k$ and $\tilde{R}_h^k$. An approximate solution to the coarse grid problem can be found by solving the following system of equations,

$$A_{2h} \phi_{2h}^1 = A_{2h}(R_h^{2h}) - \tilde{R}_h^{2h} r_h^k.$$

After the solution on the coarse grid is obtained, the correction $\Delta \phi = \phi_{2h}^1 - \phi_{2h}^0$ is transferred to the fine grid by interpolation (prolongation), where $\phi_{2h}^0 = I_h^{2h} \phi_h^k$. The difference of $I_h^{2h}$ and $\tilde{R}_h^{2h}$ is
as follows, $I_{2h}^k$ takes the mean value of states in a set of cells, but $I_{2h}^k$ performs a summation of residuals over a set of cells. The value of $\phi_h^k$ is updated by

$$
\phi_h^{k+1} = \phi_h^k + I_{2h}^k \Delta \phi,
$$

(16)

where $I_{2h}^k$ is a prolongation operator. This procedure is repeated until the approximate solution on the finest grid converges using the multigrid V-cycle algorithm [19]. The relaxation technique used in the multigrid method is Stone’s strong implicit procedure (SIP), which is a modification from the standard ILU decomposition [22]. This paper has adapted the multigrid method for incompressible Navier-Stokes equations provided by Schreck [19] and extended it to include the mass transport. Since the concentration of ligand is very small, in the order of $10^{-11}$ to $10^{-10}$ M, we may assume that the momentum and mass transfer equations are independent to each other. Consequently, the momentum transfer equation can be solved first to obtain the velocity distribution, which is then put into the mass transfer equation. The modified multigrid algorithm for incompressible flow and mass transfer is presented in Algorithm 1.

5 Results and Discussion

The flow model in the current paper is the well-known incompressible Navier-Stokes equation, which has been widely used to solve low speed fluid mechanics problems. A convection-diffusion equation is applied to address the mass transport of growth factor in solution. A similar mass transport model has been used by Glaser [11] to describe the biological interaction of antigen and antibody, and by Myszka et al. [17] to investigate the interactions of a variety of biomolecules in BIACORE, where the flow cell was of rectangular geometry. However, to study the binding and dissociation of growth factor, its receptor, and HSPG in a capillary of a cylindrical geometry with the application of a 2D Navier-Stokes equation, as far as we know, has not been reported previously. The numerical procedure and simulation results for a single grid is presented elsewhere [21], while the main purpose of the current paper is to demonstrate a multigrid solution to the convection-diffusion-reaction model of mass transport and chemical kinetics of protein ligands.

The dimensions of the capillary under consideration were length $L = 0.1$ m and radius $R = 0.00035$ m, corresponding to that of a Cellmax Cartridge System bioreactor (FiberCell Systems, Inc., Frederick, MD, USA). The ratio of length over diameter is 286. To simulate the capillary flow, four types of boundary conditions are used in the numerical simulation: inlet boundary to the left-hand side, outlet boundary to the right-hand side, symmetry boundary at the bottom, and impermeable wall boundary at the top. For inlet boundary, all quantities are prescribed, and the incoming convective flux is calculated as well. For outlet boundary, zero gradient along the grid line is applied. A three-level multigrid method is considered, as shown in Fig. 3, and the number of control volumes are $40 \times 5, 80 \times 10$, and $160 \times 20$, respectively. First the coarsest grid is initialized, and each time the grid is refined, one control volume is divided into four smaller control volumes.

The ligand interactions within the capillary were modeled as a problem of mass transport with a reactive boundary condition. For the mass transport equation, the boundary conditions are: given concentration on the west, zero flux on the east, symmetrical condition on the south,
Algorithm 1 Multigrid Algorithm for Incompressible Flow and Mass Transfer.

1: while $\text{levelOfGrid} < \text{levelOfGrid}_{\text{max}}$ do
2:  Extrapolate from coarse to fine grid, $(u, v, p, \phi)^{\text{levelOfGrid}_{\text{max}}} \leftarrow (u, v, p, \phi)^{\text{levelOfGrid} - 1}$
3:  while $t < t_{\text{step}}$ do
4:    Save data at time $t - 2$, $(u, v, \phi)^t_{\text{2}} \leftarrow (u, v, \phi)^t_{\text{1}}$
5:    Save data at time $t - 1$, $(u, v, \phi)^t_{\text{1}} \leftarrow (u, v, \phi)^t$
6:    while outerIter < outIter$_{\text{max}}$ do
7:      solve for $u$
8:      solve for $v$
9:      solve for $p$
10:     residual = Max(residual$_u$, residual$_v$, residual$_p$)
11:    if residual > largeNumber then
12:      exit “Diverge”
13:    else if residual > convergenceCriteria then
14:      for $i = \text{levelOfGrid}; i > 1; i --$ do
15:        Restriction
16:      end for
17:      for $i = 1;i < \text{levelOfGrid} + +$ do
18:        Prolongation
19:      end for
20:    else
21:      Break
22:    end if
23:  end while
24:  solve for $\phi$
25:  if residual > largeNumber then
26:    exit “Diverge”
27:  else if residual < convergenceCriteria then
28:    for $i = \text{levelOfGrid}; i > 1; i --$ do
29:      Restriction
30:    end for
31:    for $i = 1;i < \text{levelOfGrid} + +$ do
32:      Prolongation
33:    end for
34:  else
35:    Break
36:  end if
37: end while
38: end while
Figure 3: Computational grids for capillary flow and protein transport. (a) First level grid. (b) Second level grid. (c) Third level grid.

and reaction boundary on the north. An existing model of biochemical reactions on the capillary surface from Försten-Williams et al. [10] is used in our simulations (illustrated in Fig. 1). The reaction rates for all species are represented by a set of ordinary differential equations (ODEs), as shown in Table 1, and the parameters are primarily determined by experiments [10]. The system of ordinary differential equations are solved by a variable-coefficient ODE solver VODE for stiff and nonstiff systems of initial value problems [2].

The code is developed to solve the time-dependent Navier-Stokes and convection-diffusion-reaction equations with a particular application in growth factor transport and binding. The computation is performed on a Sun-Blade-100 machine with a single 500 MHz SPARC processor and 2 GB memory. A typical numerical solution is plotted in Fig. 4, where the concentration distribution of fibroblast growth factor inside the capillary is shown at an instant time of \( t = 10 \text{ min} \). The solution in Fig. 4 corresponds to the finest grid arrangement in the multigrid system. Note that the ligand concentration in the figure is non-dimensionalized with respect to the inlet concentration on the west boundary. To demonstrate the impact of surface binding on ligand transport, two numerical experiments have been conducted, one without surface binding, Fig. 4(a), and the other with surface binding to receptors and heparan sulfate proteoglycans, Fig. 4(b). As expected, without surface binding, displayed in Fig. 4(a), the ligand moves with the flow by convection and diffusion, and its concentration has a uniform distribution along the radial direction in a portion of the capillary from \( x = 0 \) to roughly \( x = 0.05 \text{ m} \). One may further predict that a uniform concentration distribution in the whole capillary will be obtained after \( t = 20 \text{ min} \). It clearly shows in Fig. 4(b) that the concentration of ligand in the capillary is spatially reduced by a great margin down along the capillary as well as in the radial direction due to biochemical reactions on the surface.
Table 1: The rate of concentration change due to protein interactions (the initial concentration of surface variables are $R_0 = 1.6 \times 10^4$ receptors/cell and $R_0 = 3.36 \times 10^5$ sites/cell).

<table>
<thead>
<tr>
<th>Reaction rate</th>
<th>Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\frac{dL}{dt} = -k_f^L[R][R] + k_{in}[C] + k_{in}^T[T] - k_{out}[R][G]$</td>
<td>$k_f^L = 2.5 \times 10^8 \text{M}^{-1}\text{min}^{-1}$, $k_{in}^T = 0.001 \text{min}^{-1}$, $k_{out} = 0.001 \text{min}^{-1} \text{(#cell)}^{-1}$, $k_{int} = 0.005 \text{min}^{-1}$, $R = 80 \text{sites/min}$</td>
</tr>
<tr>
<td>$\frac{dP}{dt} = -k_f^P[L][G] + k_{in}^P[G] + k_{in}^T[T] - k_{out}^P[C][P]$</td>
<td>$k_f^P = 9 \times 10^8 \text{M}^{-1}\text{min}^{-1}$, $k_{in}^T = 0.001 \text{min}^{-1}$, $k_{out} = 0.001 \text{min}^{-1} \text{(#cell)}^{-1}$, $k_{int} = 0.005 \text{min}^{-1}$, $P = 1680 \text{sites/min}$</td>
</tr>
<tr>
<td>$\frac{d[P]}{dt} = -k_f^P[L][R] + k_{in}^P[C] + k_{in}^T[T] - k_{out}^P[L][P]$</td>
<td>$k_f^P = 2.5 \times 10^8 \text{M}^{-1}\text{min}^{-1}$, $k_{in}^T = 0.001 \text{min}^{-1}$, $k_{out} = 0.001 \text{min}^{-1} \text{(#cell)}^{-1}$, $k_{int} = 0.005 \text{min}^{-1}$</td>
</tr>
<tr>
<td>$\frac{dC}{dt} = k_{out}^T[C_2] + k_{in}^T[C]$</td>
<td>$k_{out}^T = 0.048 \text{min}^{-1}$, $k_{in} = 0.001 \text{min}^{-1}$, $k_{int} = 0.005 \text{min}^{-1}$</td>
</tr>
<tr>
<td>$\frac{dD}{dt} = \frac{1}{2}k_{out}[C_2] - k_{in}^T[C_2] - k_{int}^D[C_2]$</td>
<td>$k_{out} = 0.001 \text{min}^{-1} \text{(#cell)}^{-1}$, $k_{int} = 1 \text{min}^{-1}$</td>
</tr>
<tr>
<td>$\frac{dC}{dt} = -k_f^C[L][R] + k_{in}[C] + k_{in}^T[T] - k_{out}[R][G]$</td>
<td>$k_f^C = 2.5 \times 10^8 \text{M}^{-1}\text{min}^{-1}$, $k_{in}^T = 0.001 \text{min}^{-1}$, $k_{out} = 0.001 \text{min}^{-1} \text{(#cell)}^{-1}$, $k_{int} = 0.005 \text{min}^{-1}$</td>
</tr>
<tr>
<td>$\frac{dD}{dt} = \frac{1}{2}k_{out}^D[C_2] - k_{in}^D[C_2]$</td>
<td>$k_{out}^D = 0.001 \text{min}^{-1} \text{(#cell)}^{-1}$, $k_{int} = 1 \text{min}^{-1}$</td>
</tr>
<tr>
<td>$\frac{dG}{dt} = k_{out}[G] + k_{in}[C][P] - k_{out}^G[T][T] - k_{out}^G[T]$</td>
<td>$k_{out}^G = 0.001 \text{min}^{-1} \text{(#cell)}^{-1}$, $k_{out} = 0.001 \text{min}^{-1} \text{(#cell)}^{-1}$, $k_{int} = 0.005 \text{min}^{-1}$</td>
</tr>
<tr>
<td>$\frac{dD}{dt} = k_{out}[G] + k_{in}[G][P] - k_{out}^D[T][T]$</td>
<td>$k_{out}^D = 0.001 \text{min}^{-1} \text{(#cell)}^{-1}$, $k_{int} = 1 \text{min}^{-1}$</td>
</tr>
<tr>
<td>$\frac{dD}{dt} = \frac{1}{2}[T]^2 - k_{out}[T_2] - k_{in}^D[T_2]$</td>
<td>$k_{out}^D = 0.001 \text{min}^{-1} \text{(#cell)}^{-1}$, $k_{int} = 1 \text{min}^{-1}$</td>
</tr>
</tbody>
</table>
Figure 4: A snapshot of ligand concentration distribution at $t = 10$ min in the capillary at the temperature of $37^\circ C$ and the uniform inlet velocity of $u = 5.2$ mm/min. (a) Surface binding is not considered. (b) Ligands bind to receptors and HSPGs on the capillary surface.

In Figure 4, the front of ligand transport is dissipative, which may be explained by the relative importance between convection and diffusion. The Peclet number is defined as the ratio of convective transport to diffusive transport, $Pe = uL/D$, where $u$ is the velocity, $L$ is the characteristic length, and $D$ is the diffusion coefficient. The characteristic length can have a significant impact on the value of $Pe$. Under current simulation, the velocity is $u = 0.0867$ mm/s, the diffusion coefficient is $D = 9.2 \times 10^{-7}$ cm$^2$/s. Using the capillary radius as the characteristic length, the resulting Peclet number is $Pe = 330$. This value indicates a convective dominated process however the value is somewhat intermediate indicating diffusion does make a not insignificant contribution to the overall process.

Figure 5(a) displays the convergence history for capillary flow in a single grid with the finest grid spacing. In the current calculation, the energy equation is not considered. The results clearly show that the residuals are reduced effectively in the first 200 outer iterations, and after that, they cannot be further eliminated no matter how many more outer iterations are performed. The results also indicate that the pressure equation has a relatively large residual (Fig. 5(a)).

A comparison was then made between the single-grid and multigrid computations, shown in Fig. 5(b), where the number of iterations means the number of outer iterations on the finest grid ($160 \times 20$). Only the residual from the pressure equation is shown as it had the largest value for the single-grid (Fig. 5(a)), but similar differences were found for the other residuals (data not
Figure 5: Comparison of convergence history between single-grid and multigrid computations. (a) Residuals of pressure and velocities in single-grid computation. (b) Comparison of pressure residuals between single-grid and multigrid computation with different linear system solvers.

shown). In single-grid computation, the pressure residual can only be reduced to the order of $10^{-3}$ while in the case of the three-level multigrid computation, it can be reduced to the order of $10^{-5}$ within less than 100 outer iterations. Table 2 lists the number of outer iterations, CPU-time, and speed-up ratio for the capillary flow with various mesh size and different linear system solvers. In Table 2, the recorded CPU-time for multigrid is the total computing time for all levels of grids that are involved. For all three solvers studied (SIP, BiCGSTAB, and GMRES) the CPU time in going to a finer grid was significantly less than the time taken with a single-grid. For example, the CPU time needed for a $160 \times 20$ grid using the SIP method was 176.45 seconds for the single-grid and 5.39 for the multigrid. This difference in time was due to the significant difference in the number of outer iterations required which was 6000 for the single-grid and only 54 for the multigrid. This can result in a speed-up ratio for the capillary flow of over 30 for the finest grid. Three iterative solvers, SIP [22], BiCGSTAB [23] and GMRES [20] are used to solve the inner linear system and their performance are compared. In this particular case with a five diagonal coefficient matrix, BiCGSTAB and GMRES solvers do not have obvious advantages over SIP in reducing the number of outer iterations of Navier-Stokes equations in the multigrid computation.

6 Conclusion

This paper presents a multigrid computation strategy for the numerical solution of ligand transport and cellular binding within a capillary (i.e., cylindrical geometry). The capillary flow is predicted using the incompressible Navier-Stokes equations by the finite volume method with colocated mesh arrangement with the assumption that the capillary is a circular pipe. To reduce the computation
Table 2: Performance comparison of multigrid method with different linear system solvers.

<table>
<thead>
<tr>
<th>Solver</th>
<th>Mesh</th>
<th>No. Outer Iterations</th>
<th>CPU-Time (s)</th>
<th>Speed-up Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Single-grid</td>
<td>Multigrid</td>
<td>Single-grid</td>
</tr>
<tr>
<td>SIP</td>
<td>40 x 5</td>
<td>234</td>
<td>234</td>
<td>0.41</td>
</tr>
<tr>
<td></td>
<td>80 x 10</td>
<td>898</td>
<td>28</td>
<td>6.87</td>
</tr>
<tr>
<td></td>
<td>160 x 20</td>
<td>6000</td>
<td>54</td>
<td>176.45</td>
</tr>
<tr>
<td>BICGSTAB</td>
<td>40 x 5</td>
<td>114</td>
<td>114</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td>80 x 10</td>
<td>432</td>
<td>26</td>
<td>5.24</td>
</tr>
<tr>
<td></td>
<td>160 x 20</td>
<td>6000</td>
<td>50</td>
<td>174.66</td>
</tr>
<tr>
<td>GMRES</td>
<td>40 x 5</td>
<td>101</td>
<td>101</td>
<td>0.22</td>
</tr>
<tr>
<td></td>
<td>80 x 10</td>
<td>389</td>
<td>23</td>
<td>5.43</td>
</tr>
<tr>
<td></td>
<td>160 x 20</td>
<td>6000</td>
<td>52</td>
<td>186.75</td>
</tr>
</tbody>
</table>

cost, a multigrid V-cycle technique is applied for the nonlinear Navier-Stokes equations, which includes restriction and prolongation to restrict fine grid solution to coarse grid, and to interpolate coarse grid solution to fine grid. The multigrid method is extended to solve the mass transport equation. Computational results indicate that the multigrid method can reduce CPU time substantially. The computed profile of ligand distribution in the capillary is presented for one set of conditions and no advantage with regard to CPU time or residual size was noted between the three linear system solvers used.

Acknowledgment
This research work is supported in part by NIH under grant 1R01 HL086644-01, in part by NSF under grants CCF-0727600 and CCF0527967.

References


