Microwell Mixing with Surface Tension

Nick Cox

Supervised by Professor Bruce Finlayson

University of Washington

Department of Chemical Engineering

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Abstract

For many applications in the pharmaceutical industry, achieving the rapid, homogeneous mixing of very small volumes can have a dramatic impact on the success or failure of a process. One method of achieving a homogeneous mixture in a small volume (for instance, a 200 micro liter well in a in a 96-well plate) is the repetitive injection and subsequent aspiration of a concentrated liquid through an automatic pipette. Although the amount and speed of mixing has been measured experimentally using dyes and other methods, a theoretical/computational approach has not yet been developed. This report describes an investigation into the ability of computational methods to model microwell mixing. In particular, this report builds on previous work, attempting to include a model for the surface tension of the fluid inside a microwell.

Objectives

The primary objective for this project was to build on previous models of microwell mixing by adding in surface tension for the boundary which describes the fluid surface in the well.

Problem

The particular model in question involved the addition of 90 μL of a concentrated fluid through a pipette tip into a flat-bottomed cylindrical microwell containing 200 μL of stagnant liquid. This was to be followed by the removal of 90 μL through the same pipette tip (Fig 1).

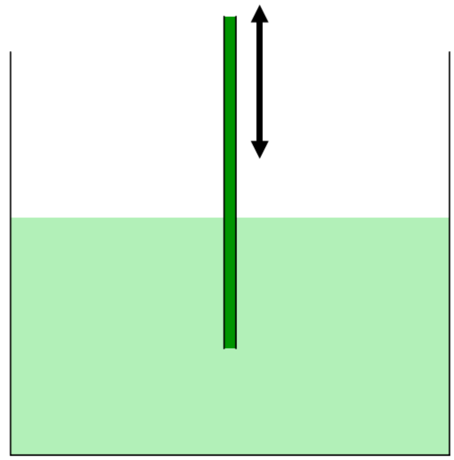

Figure 1: Diagram of microwell mixing problem (not-to-scale). 90 μL of high concentrated fluid is injected and then aspirated from a microwell initially containing 200 μL.

This problem proved to be difficult to solve not only because a convection/diffusion problem had to be evaluated simultaneously with a fluid dynamics problem, but also because the model had to account for a moving, deformed boundary at the surface of the fluid in the microwell.

Procedure

There are two primary equation systems that must be solved simultaneously in this problem. The first is a momentum balance represented by the incompressible Navier Stokes equation as shown in Eq. 1.

$$\rho \frac{Dv}{Dt} = \frac{\partial v}{\partial t} + (v \cdot \nabla)v = -\nabla p + \mu \nabla^2 + \rho g \qquad (1)$$

The second equation is a mass transfer equation accounting for convective and diffusive driving forces as shown in Eq. 2.

$$\frac{\partial c}{\partial t} + \nabla \cdot \left(- D \nabla c \right) = -v \nabla c \qquad (2)$$

These two equation systems would be evaluated using the Comsol Multiphysics package of Femlab.

In an attempt to build off of previous work, we added surface tension to the boundary describing the fluid surface in the well. In order to accomplish this, a "weak" term was add to the neutral equations for that surface, as shown below in Eq. 3.

$$\sigma\left[-n_r^2\varphi(vz) + n_r n_z(\varphi(uz) + \varphi(vr) - n_z^2\vartheta(ur)\right] \qquad (3)$$

In Eq. 3, σ represents the surface tension (in dimensionless terms), **n** represents the unit vector normal to the surface, *u* represents the fluid velocity in the radial direction, *v* represents the fluid velocity in the vertical (axial) direction, *r* and *z* are radial and axial distances, respectively, and φ represents the "test" function.

The parameters defining the fluid properties were approximated using common values for water at standard temperature and pressure. In particular, the model used a fluid density of 998 kg/m^3 and a dynamic viscosity of 0.001 Pa_s. The pipette has a diameter of 0.5 mm. The velocity in the pipette oscillates with a period of 8.3 seconds, and a peak average velocity of 0.23 m/s. This gives a Reynolds number of 116 based on the diameter of the pipette and the peak average velocity. A diffusivity of $5 \cdot 10^{-9}$ m^2/s is used, giving a Peclet number of 23,000 based on the peak average velocity and diameter of the pipette. The geometry of this problem was modeled in two dimensions, assuming symmetry about the center axis.

The microwell diameter as well as the pipette tip diameter were obtained from the Nealon article, allowing the calculation of the initial height of the domain representing the initial fluid in the microwell. The pipette tip geometry was extended well above the surface of the fluid in the microwell, allowing the flow within the tip to become fully developed by the time the fluid exits the pipette tip. It was assumed that the pipette tip extends 0.001 m below the surface of the liquid in the microwell. This geometry, as well as the corresponding finite-element mesh can be observed in Fig 2, where all given dimensions are in meters.

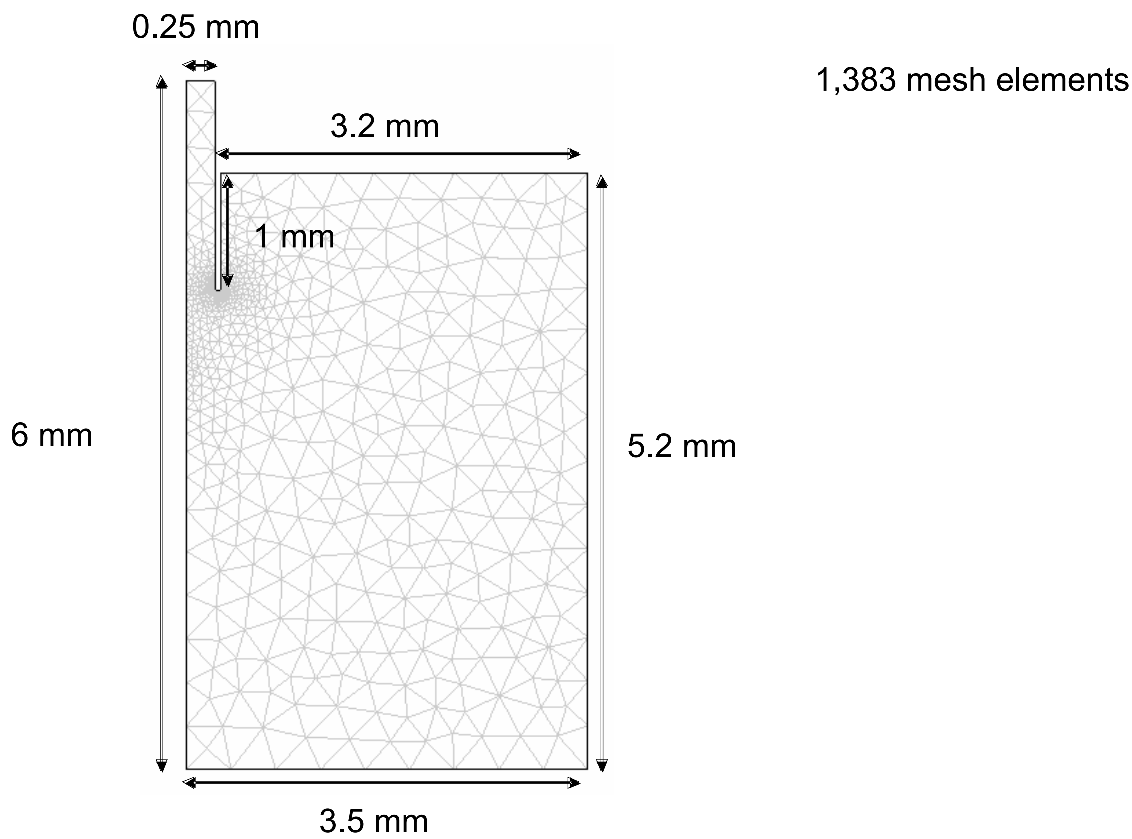

Figure 2: Domain geometry of the microwell mixing model. All dimensions are in meters. The domain is 2-dimensional and is axis-symmetric about R=0 m.

In order to solve this problem computationally, the domain is divided into several smaller geometries using a mesh. In this way, each mesh element is assumed to have uniform properties, including velocity, concentration, etc. Note that near the finer features of the domain geometry, mesh elements decrease substantially in size, and increase substantially in number. The mesh in this model contains 1,383 individual elements.

In addition to specifying the domain geometry and the appropriate fluid properties, we must also specify the boundary conditions for each equation model applied to the system. Although there are only two equation systems that we are solving for in this problem, there are really three different models applied to the system. For each boundary in the domain, we must specify conditions for the fluid dynamics model, the convection/diffusion model, and the moving-mesh model that allows for deformation and displacement of the free fluid surface (the surface at the top of the fluid in the microwell). Each boundary of the domain is assigned a number as shown in Fig 3. The specified conditions for each of these domains in each of the three models are described in Table 1.

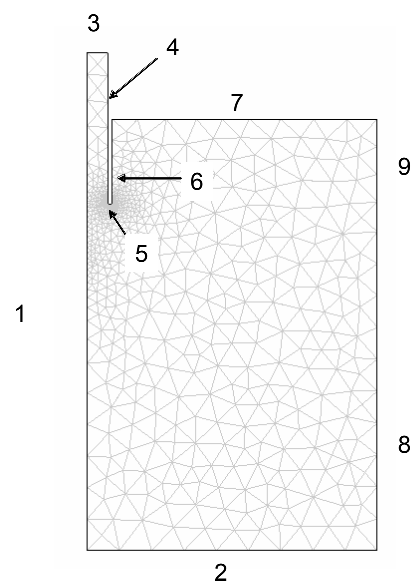

Figure 3: Boundary Labels

Table 1: Boundary conditions

#	Description	Fluid Dynamics	Conv/Diff	Moving Mesh
1	Center Axis	Axial Symmetry	Insulation	Displacement=0 m
2	Well Bottom	No Slip	Insulation	Displacement=0 m
3	Inlet	Inflow Velocity (max Re = 1000)	C= 1 mol/L	Displacement=0 m
4	Pipette Wall	No Slip	Insulation	Displacement=0 m
5	Pipette Edge	Slip Symmetry	Insulation	Displacement=0 m
6	Inner Well Wall (near surface)	Slip Symmetry	Insulation	Displacement=0 m
7	Fluid Surface	Neutral	Convective Flux	Velocity= u*nr+v*nz
8	Well Wall	No Slip	Insulation	Displacement=0 m
9	Outer Well Wall (near surface)	Slip Symmetry	Insulation	Displacement=0 m

Fluid Dynamics Boundaries

- No Slip: fluid touching the boundary does not move.
- Slip Symmetry: fluid is allowed to move along the boundary as though the boundary was a non-moving fluid.
- Axial Symmetry: fluid is allowed to move along the boundary as though the boundary were fluid moving at the same velocity.

Conv/Diff Boundaries

- Insulation: material can not diffuse into or out of the boundary.
- C = 1 mol/L: an arbitrary concentration set at the inlet. Initial concentration of the rest of the domain is at 0 mol/L.
- Convective Flux: material is allowed to diffuse into or out of the boundary.

Moving Mesh Boundaries

- Displacement = 0 m: the mesh boundary can not move.
- Velocity = u*nr+v*nz: allows the mesh along the boundary to move and deform according to the radial velocity of each element (u), the axial velocity of each element (v) and the respective vectors nr and nz.

The entrance velocity (velocity at boundary 3) is a key parameter for controlling the addition and subsequent removal of fluid from the microwell. It became necessary to control the velocity such that after 90 μL had been added, the inlet velocity changed sign such that fluid was removed. Although this could be done with a simple Boolean expression, such a discontinuous function generated serious complications when attempting to compute a solution. The way around this problem was to establish a continuous function of velocity over time, using a periodic function.

Results and Discussion

Unfortunately, a working solution past the time point where the velocity at the inlet reverses could not be found. There are many difficulties in trying to arrive at a convergent solution for a model such as this. In the first place, this is a transient problem, and in order to overcome this, several technical barriers must be breeched. Based on the scope of this project, simulations were performed on ordinary modern day desktop computers, which often ran into physical memory limitations preventing the use of very fine meshes, and smaller timesteps (two things that aid in circumventing difficult problems). In the second place, we are dealing with a moving, deformed finite element mesh. After several timesteps, the mesh becomes very distorted, resulting in inverted elements (which, in this model, typically occurred around the very small boundary corresponding to the edge of the pipette tip) and non-convergent solutions. Typically, in order to get around this, one simply has to run the simulation for shorter periods of time, re-mesh, and continue the solution. While this enabled us to find solutions for time points much further than what was accomplished at the outset, we were not able to achieve a solution beyond 0.125 seconds.

However, although our initial objective was not accomplished over the course of this project, we do have partial solutions. In Fig. 4, we can see the concentration gradient (and mesh displacement) at 0.125 seconds.

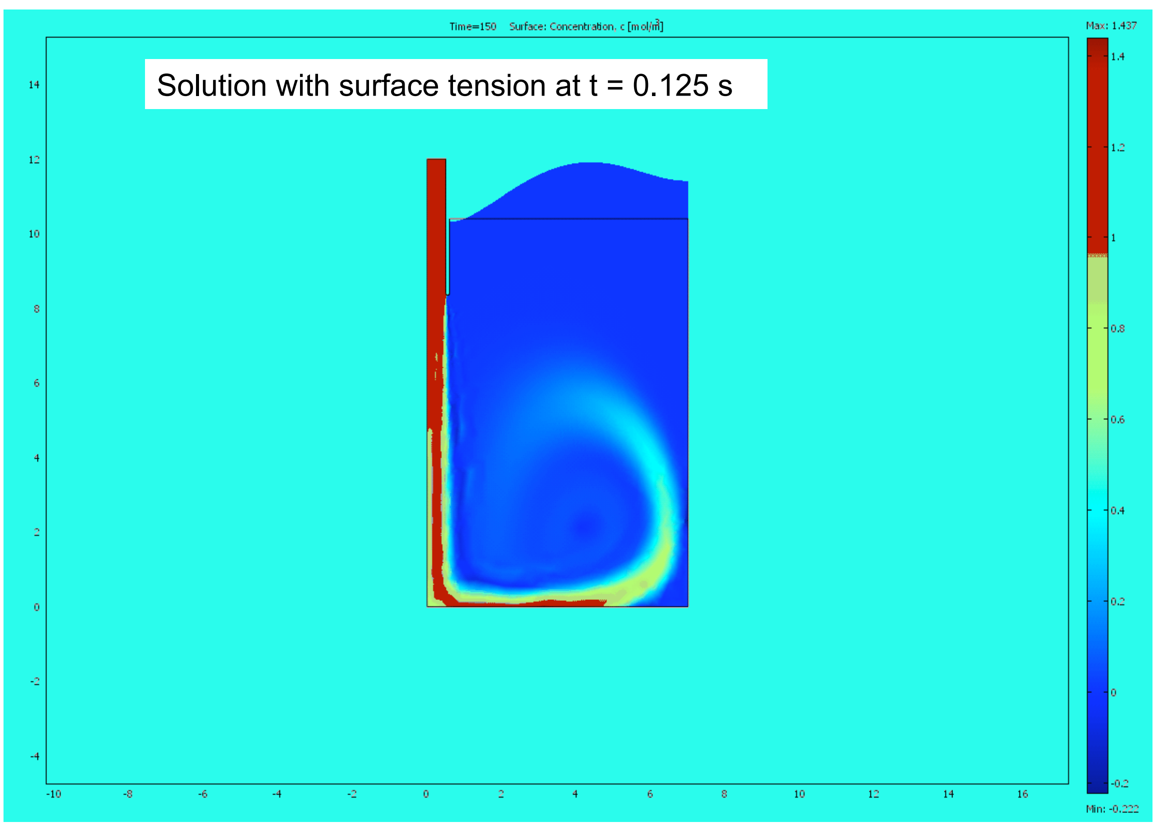

Figure 4: concentration gradient at t = 0.125 s for model with surface tension.

We note from Fig. 4 that the majority of the fluid remains at a concentration of 0, except for the jet of fluid having a concentration of nearly 1 which runs down the center axis of the well, hits the well bottom, and begins curving up and out. This is behavior that we would expect under these conditions from a qualitative standpoint.

For comparison with previous results, Fig. 5 is provided, which depicts a similar model during the injection phase. This comparison is purely qualitative in nature, and shows how the fluid surface for the case without surface tension forms sharp "peaks" – behavior that we would not expect to see from a qualitative standpoint.

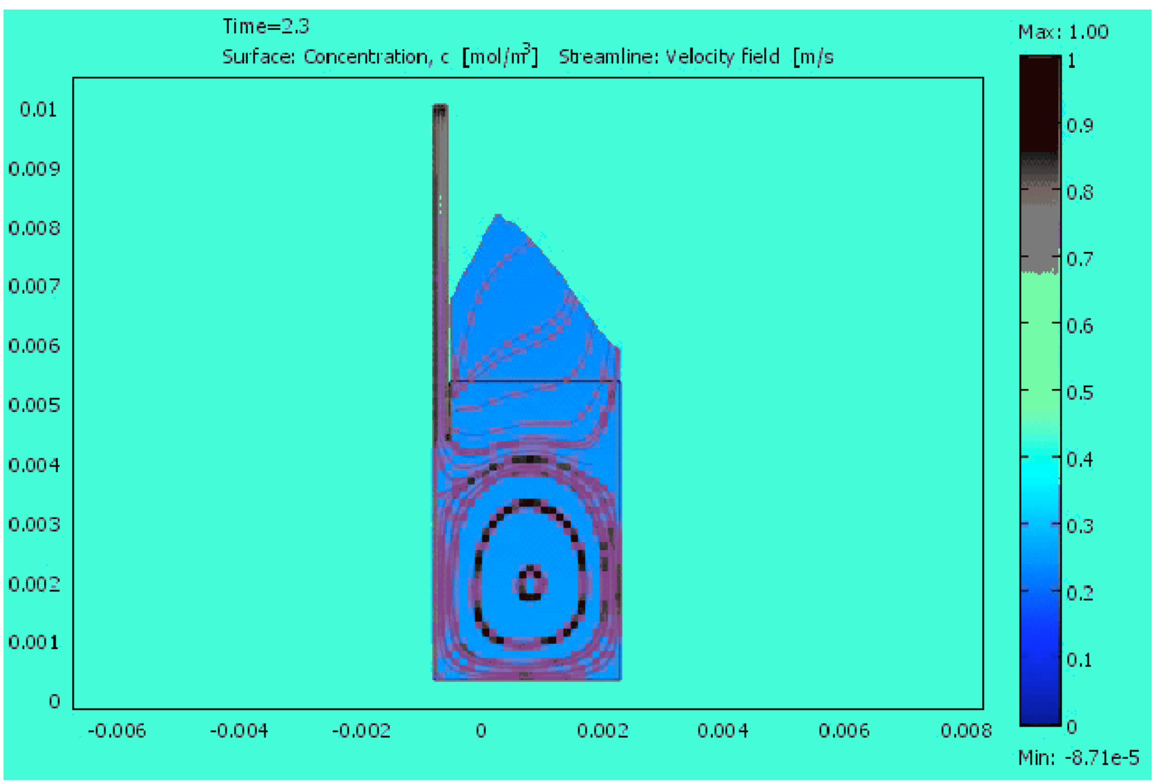

Figure 5: solution during injection phase at t = 2.3 s for case without surface tension.

From Figs. 4-5, we note that there is a distinct difference in the cases with and without surface tension, but because of the limited results which we were able to obtain for the case with surface tension, more direct, quantitative comparisons are not possible.

Conclusions

This project had very specific goals, but from an objective standpoint it served as an investigation into the ability of computational methods to solve a complicated fluid dynamics problem. Transient problems involving moving meshes in addition to fluctuating boundary conditions present many opportunities for failure when applying computational approaches. We can conclude that while these sorts of problems can be exceedingly difficult and challenging, they are certainly not impossible. Further complicating matters, we have no existing literature with which to compare our results – therefore, this report should be seen as purely a theoretical exercise into the abilities of Comsol© to solve these sorts of problems.