Chemical Mixing and Washing in Fluidic Diagnostic Systems

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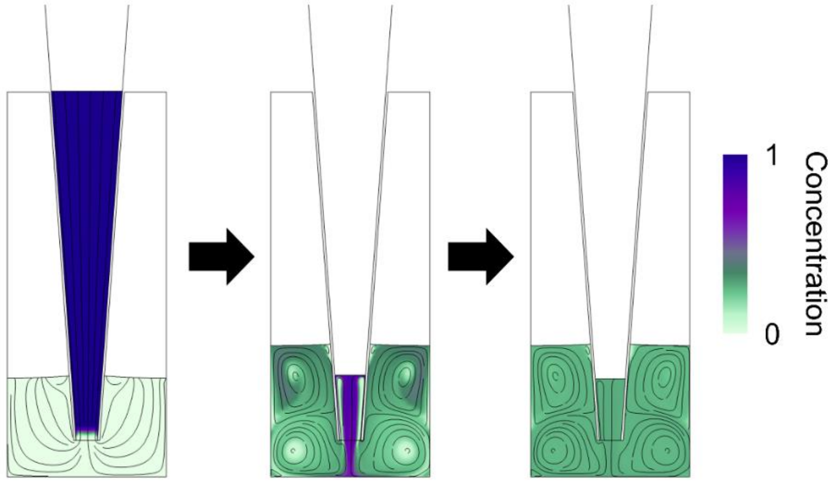
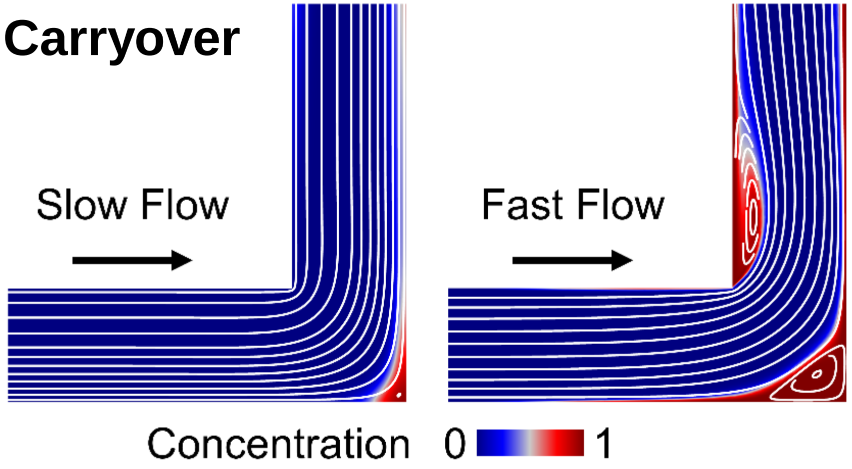
Introduction: Mixing and Carryover

- Modeling fluidic diagnostic systems requires setting up a multiphysics system with the following components:
  - Physics of fluid flow
  - Chemical concentration gradients
  - Heat transfer, if applicable
  - Problems with interfaces/wetting/bubbles
- We discuss two examples where COMSOL Multiphysics helps optimize mixing and cleaning protocols
  - Mixing in a microwell
  - Chemical carryover (cleaning between runs)

Mixing

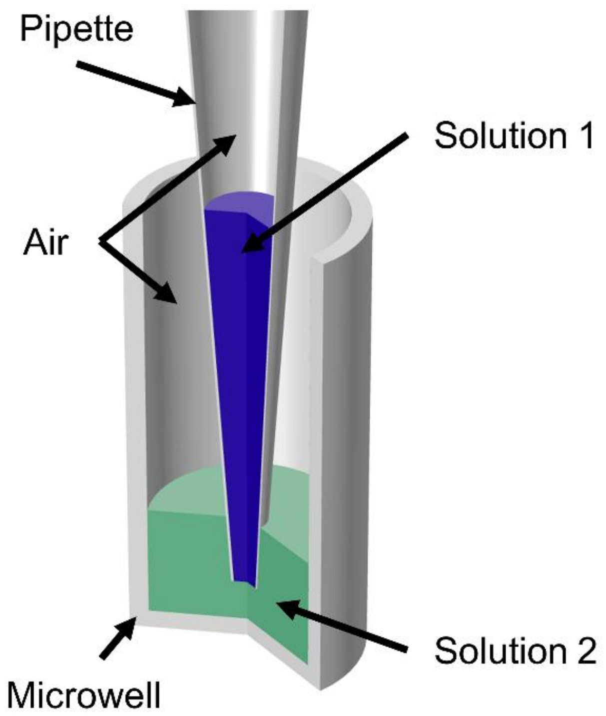


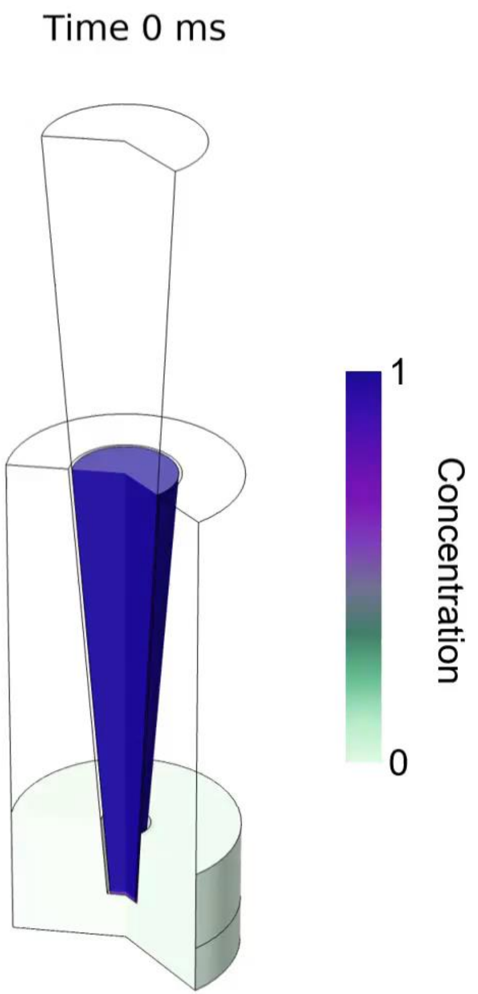
Carryover



Mixing in a Microwell by Repetitive Pipetting

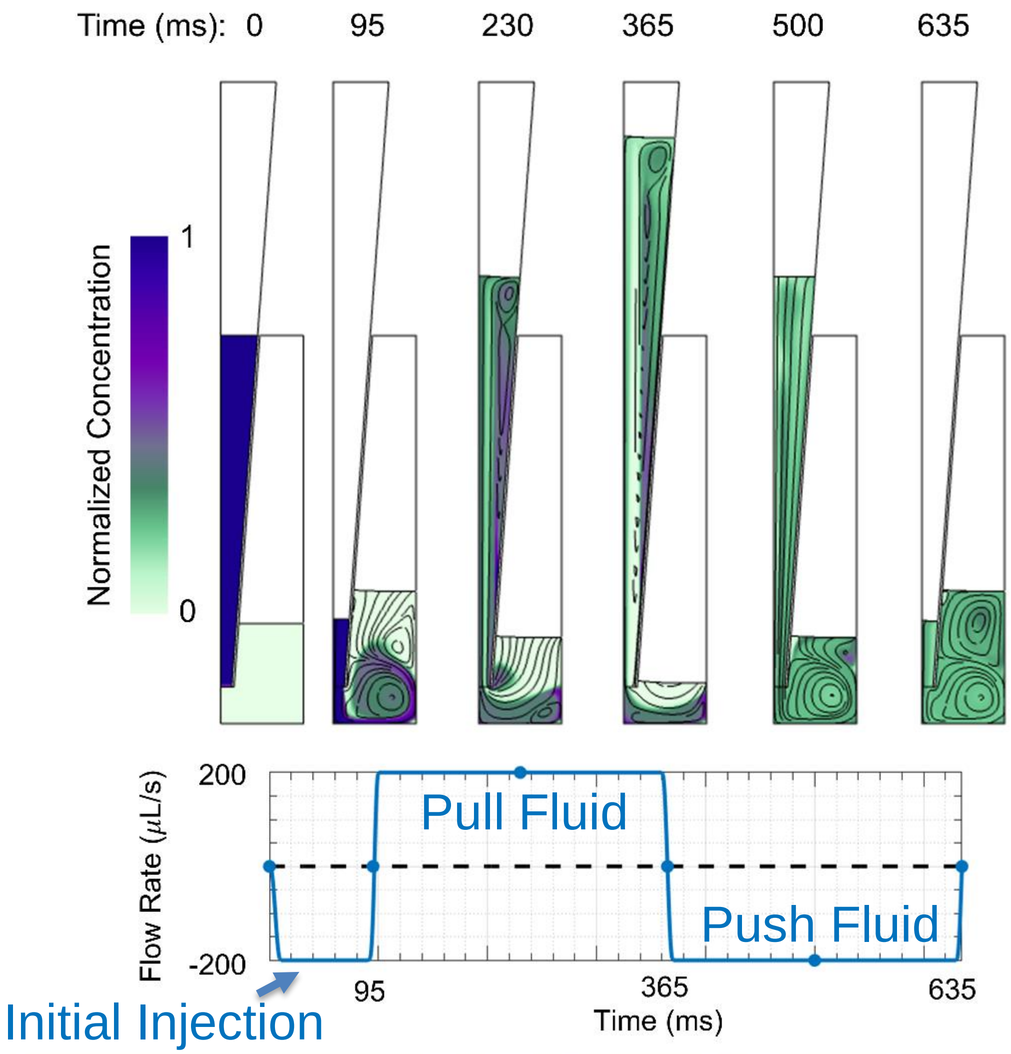
- We study the mixing of two fluids which are mixed by repeatedly moving fluid up and down in a pipette
- This is an advection-diffusion problem involving moving interfaces and chemical gradients
- A pipette containing 20 µL of a reagent is mixed into 60 µL of water
- Animation: The first 1.5 seconds of mixing using a fast flow rate (200 µL/s) and large cycled volume (55 µL)
- Concentrations are normalized by the initial concentration in the pipette tip





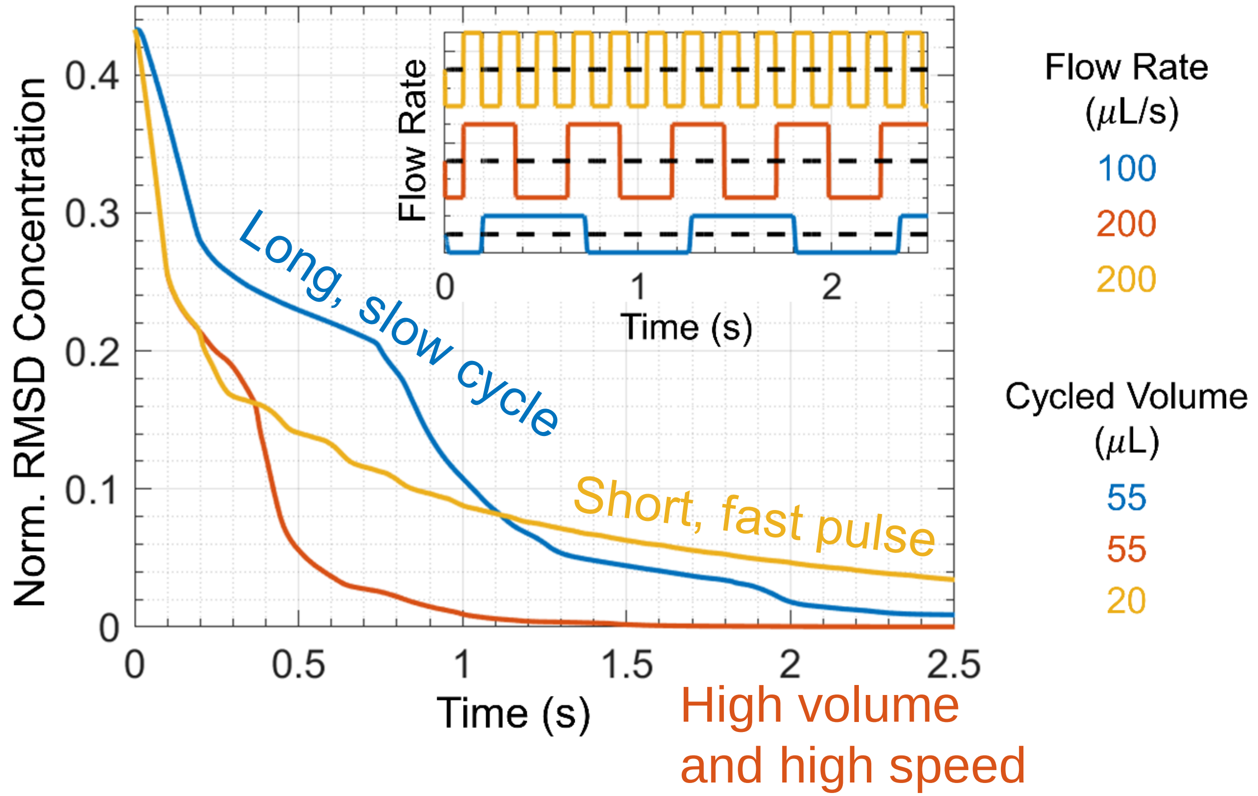
Snapshots of a Mixing Cycle

- Mixture concentration (color) normalized by initial pipette concentration and streamlines (black lines) at different times within the first mixing cycle for a mixing protocol with fast flow rate (200 µL/s) and large cycled volume (55 µL)
- Flow rate profile is shown at bottom with time points corresponding to images above



Effect of Flow Rate and Cycled Volume

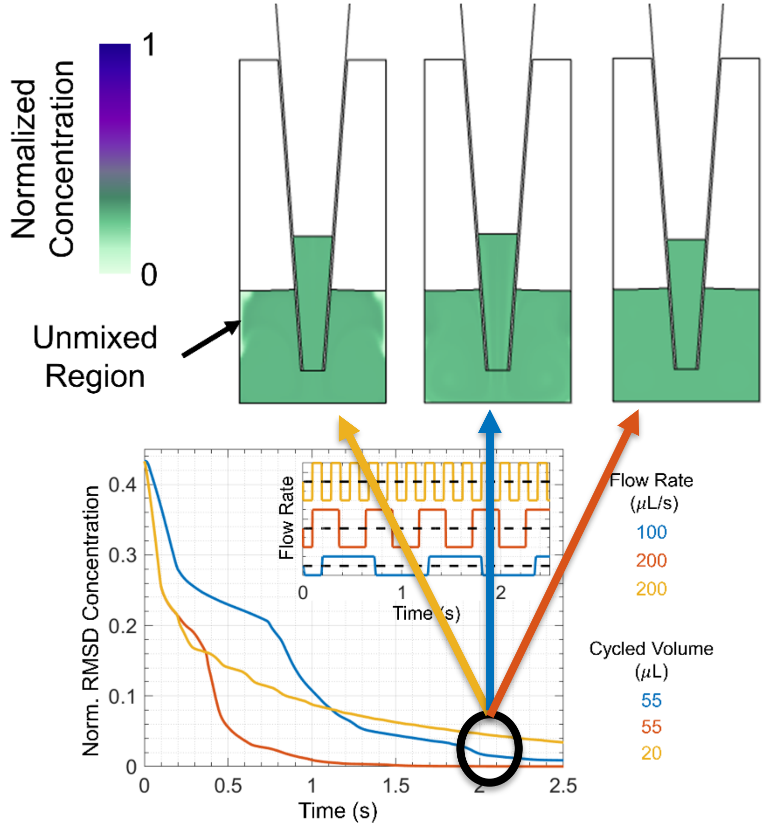
- Root-mean-square deviation (RMSD) of mixture concentration normalized by initial pipette concentration vs. time for multiple cycles of three mixing protocols
- The inset shows the flow rate profile associated with each RMSD curve
- We compare three strategies showing different cycle speeds and volumes
  - Increasing flow velocity improves mixing for the same cycled volume
  - Pulsating short, small-volume cycles is not an effective mixing strategy



Effect of Flow Rate and Cycled Volume

- To visualize mixing, we show snapshots at right of mixture concentration normalized by initial pipette concentration after similar elapsed times
- Three mixing protocols are shown with different combinations of flow rate and cycled volume
- Unmixed regions are noticeable in the leftmost snapshot and a jet-shaped distortion can be seen in the middle snapshot in the full resolution image
- RMSD concentration chart offers a more accurate comparison, showing the quantitative differences
- In general, outer edges and top surface of fluid in microwell are the least mixed

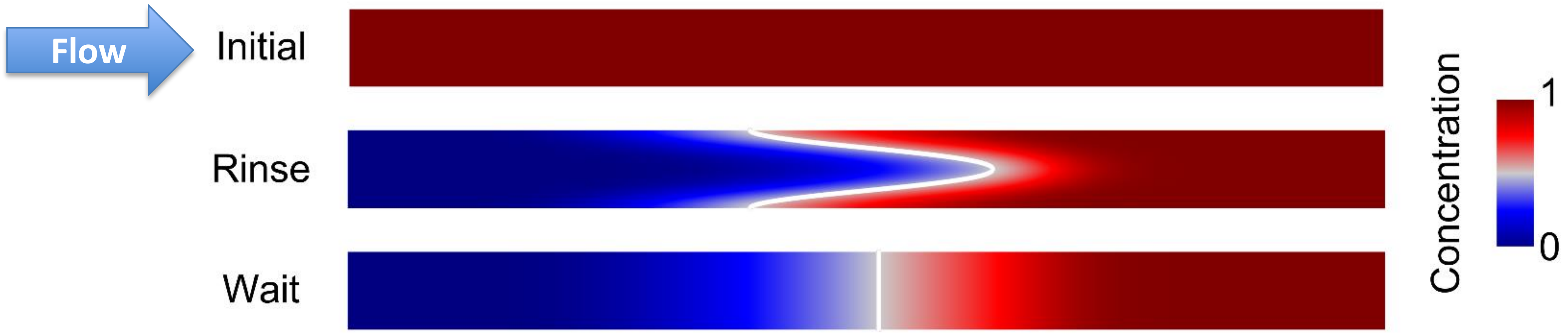
Flow Rate (μL/s)	200	100	200
Cycled Volume (μL)	20	55	55
Elapsed Time (s)	2.17	2.33	2.24



Part 2: Chemical Carryover

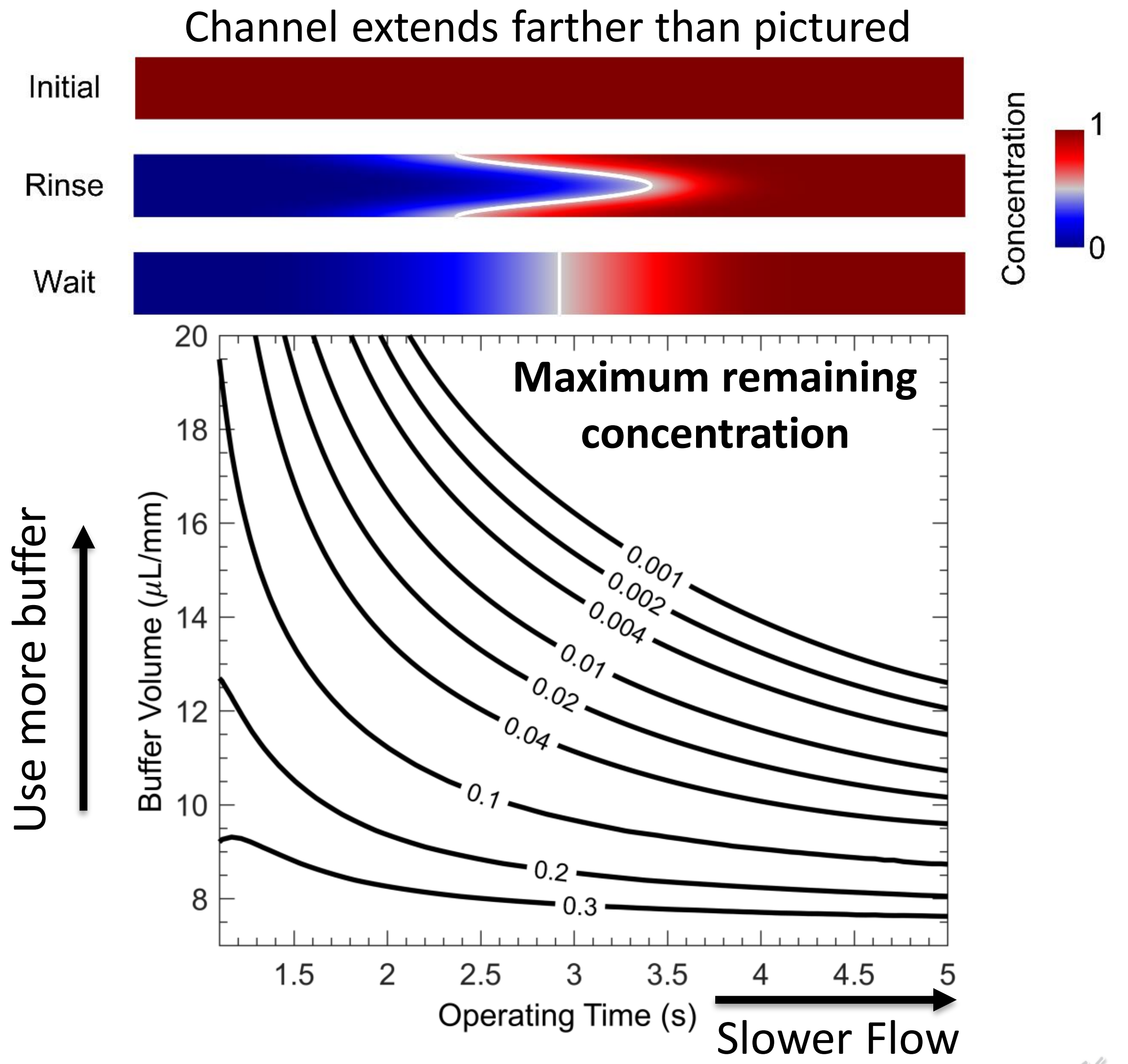
Setup for Chemical Carryover Simulation

- Problem: How best to wash a microchannel between runs, in terms of wash volume and flow speed?
- Microfluidic channel is initially filled with a chemical sample or reagent (top)
- Wash buffer is introduced at the left inlet, flushing out chemical and creating a vertically and horizontally varying chemical concentration (middle)
- Vertical concentration gradients equilibrated after a few seconds of chemical diffusion (bottom)
- Channel has 0.1 mm height and extends much farther than pictured (actual aspect ratio 700:1)



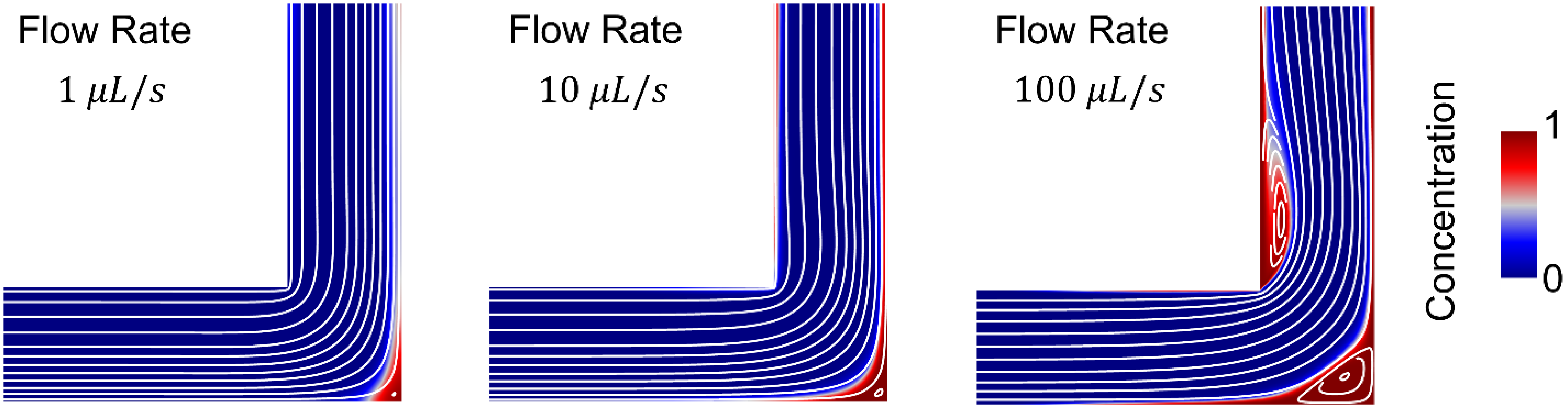
Tradeoffs in Clear Time, Buffer Volume, and Efficacy

- To remove more of the red reagent, one can either pump more buffer through the system or pump the same volume of buffer at a slower rate to allow diffusion to smooth out the parabolic flow profile
- Plot shows contours of maximum carryover concentration relative to initial sample or reagent concentration for a straight microfluidic channel
- For interpreting the y-axis, total channel volume is 7 µL per mm channel depth (into page)



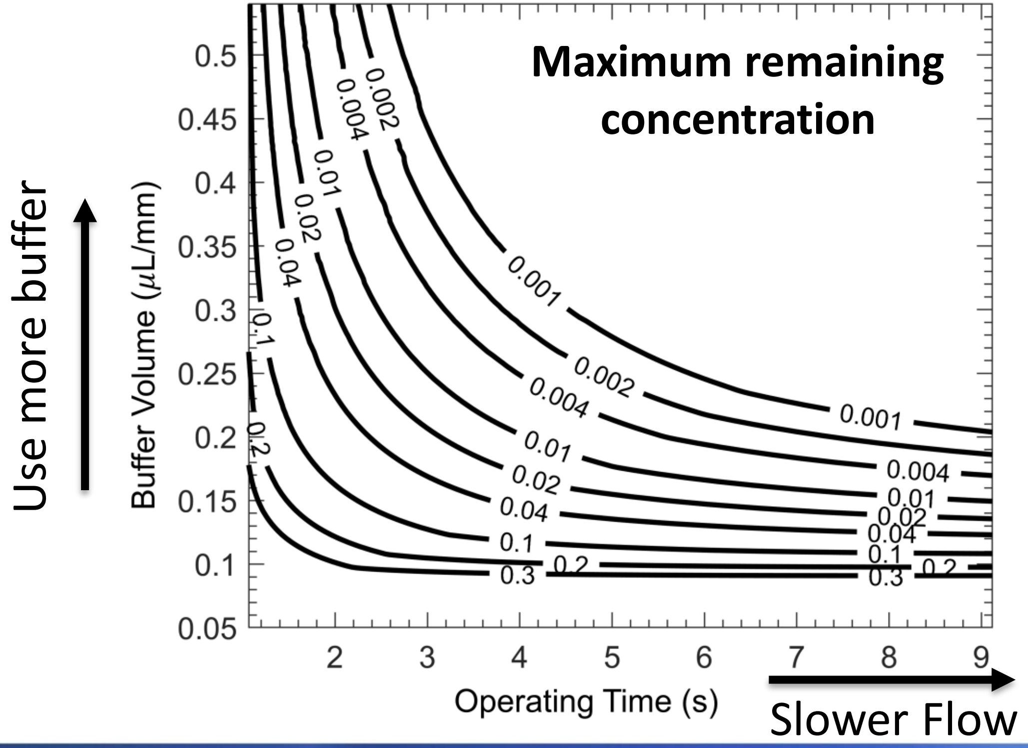
Carryover in a Corner

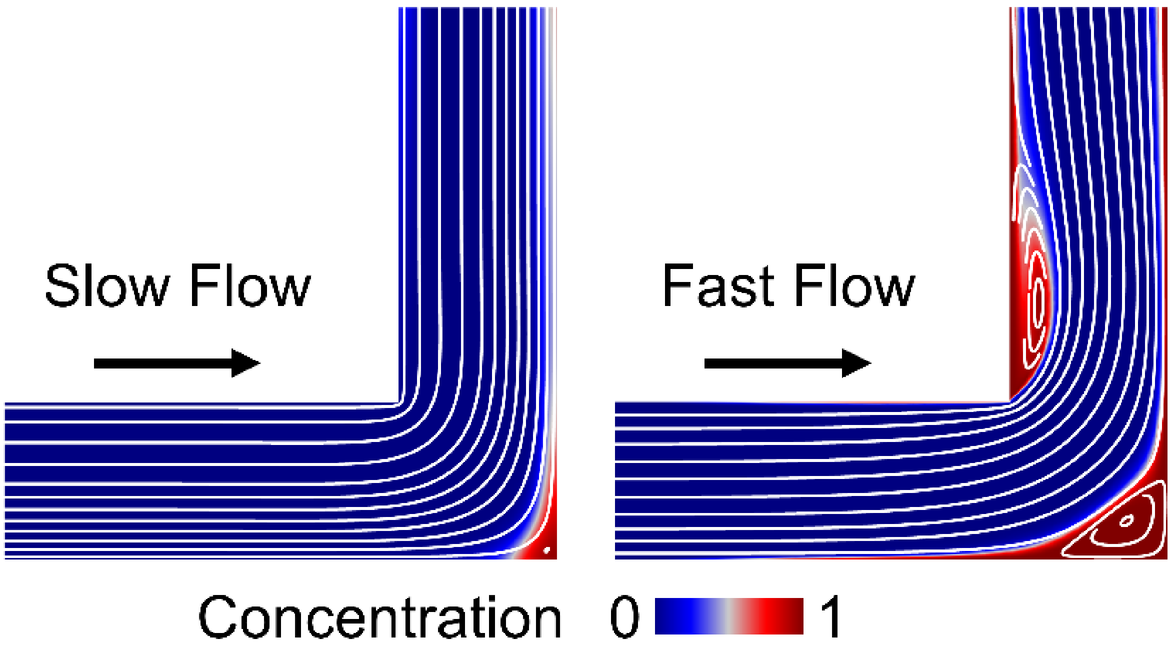
- Carryover concentration relative to initial sample or reagent concentration (color) and flow field streamlines (white) for three different flow rates in an L-shaped channel
- Channel height 0.1 mm, depth (into page) 1 mm, length 0.6 mm. In each case, the same buffer volume is pumped through the channel
- Recirculation zones develop and increase in size as the flow rate and Reynolds number increase



Tradeoffs in an L-Shaped Turn

- Turns and corners add recirculation regions which can trap old reagent
- Brute force approach of simply flowing faster has diminishing returns
- Buffer volume units are not directly comparable to previous graph since L-turn channel volume is 0.06 µL per mm channel depth (into page) instead of 7 µL





Conclusions

- Mixing in a microwell:
  - COMSOL Multiphysics® gracefully handles moving interface, laminar flow, and species transport
  - Model shows that optimal mixing occurs when the largest volumes of fluid are moved with the highest velocity

- Chemical carryover:
  - Wash cycles for microfluidic devices involve tradeoffs between wash buffer volume and wash time
  - Turns and corners require different strategies to flush out reagents