Carnegie Mellon
ENGINEERING

# APPLICATIONS OF BEHAVIORAL MODELING AND SIMULATION ON LAB-ON-A-CHIP: MICRO-MIXER AND SEPARATION SYSTEM

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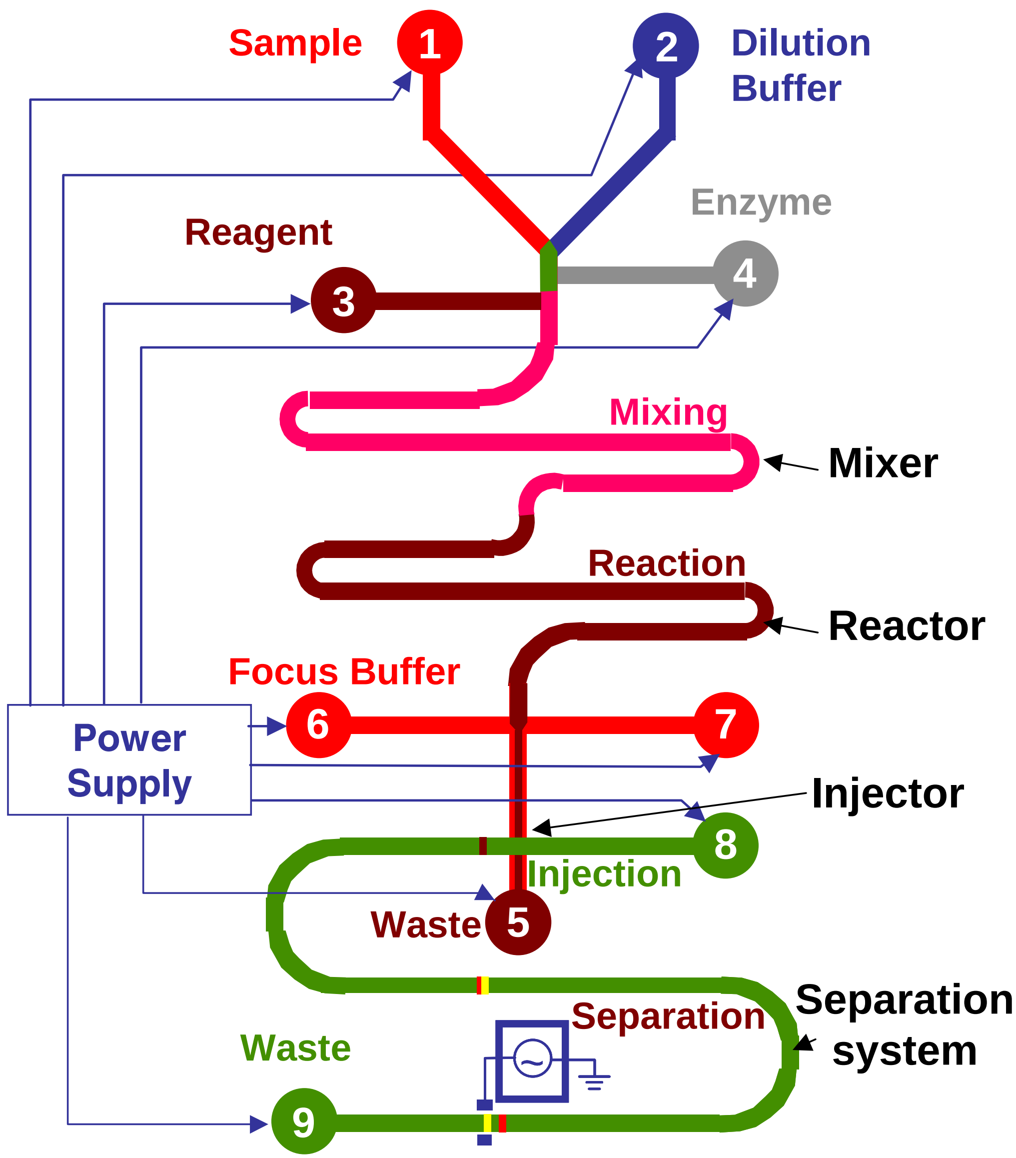
**http://www.ece.cmu.edu/~mems**

# Outline

- Introduction and Motivation
- Description of Model and Simulation Framework
- Composable System Simulation
- Summary

# Introduction: Biofluidic Lab-on-a-chip




- Biofluidic Lab-on-a-chip
  - Sample saving
  - Fast and parallel analysis
  - High integration and automation
- Four subsystems
  - Mixer
  - Reactor
  - Injector
  - separation system
- Electrokinetic driven flow
  - Voltage control

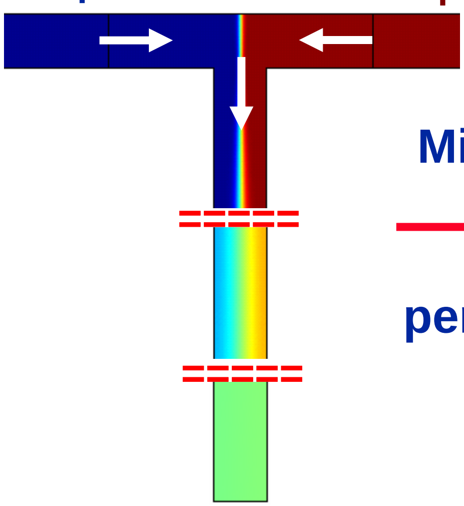
# Introduction: Electrokinetic Micromixers

- Mixing in Microscale
  - Low Reynolds number and laminar flow
  - Molecular diffusion dominant
  - Enhancing techniques
    - Focusing
    - Multi-lamination…

Long mixing channel
Long mixing time

Sample *b*

Sample *a*

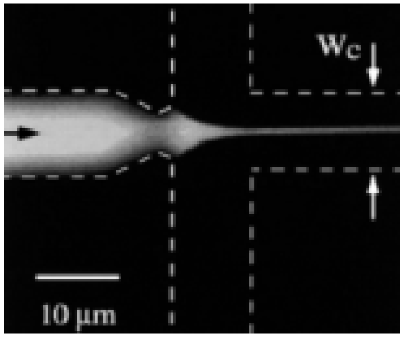


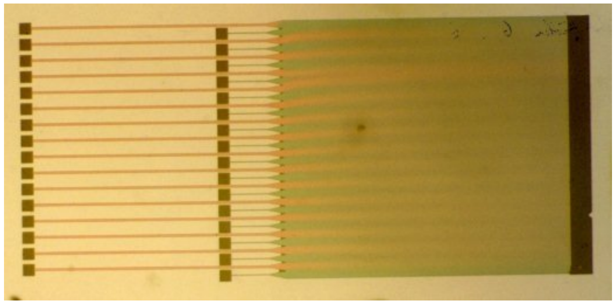
EK T-mixer

Minimized area

High performance

Focusing mixer
(Knight, J.B. et al.)



Multi-lamination mixer
(Koch, M. et al.)

Complex topology geometry/network

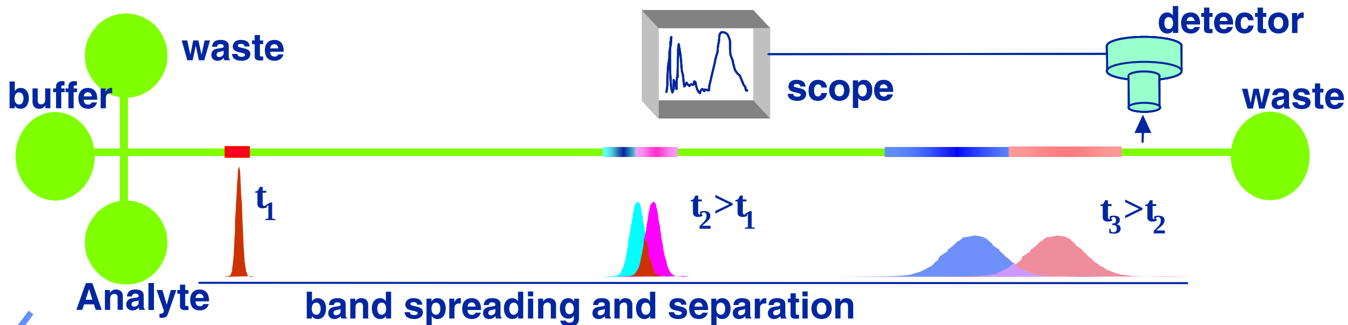
Extensive design space

Arbitrary flow ratio

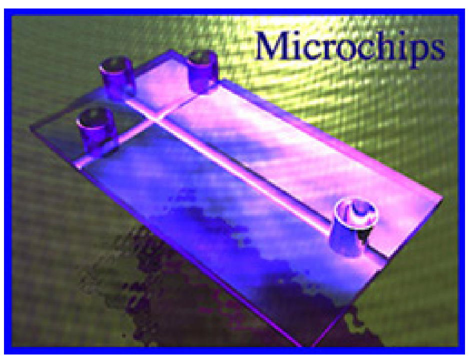
Arbitrary inlet concentration

# Introduction: Electrophoretic Separation

- An important subsystem of lab on a chip
  - Separation
  - Detection



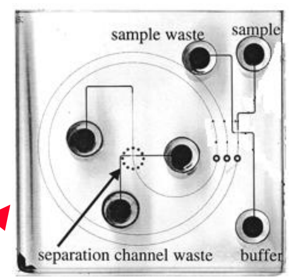

Straight Channel




CE chip (ORNL)

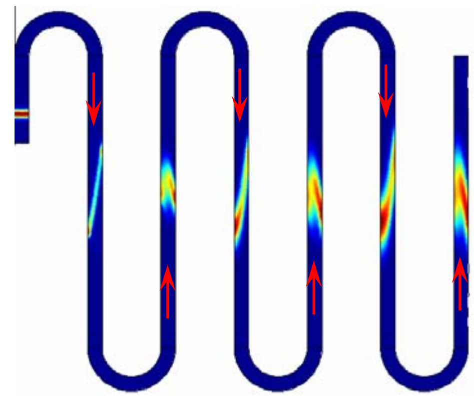
Minimized area

High performance




Spiral channel

Serpentine channel



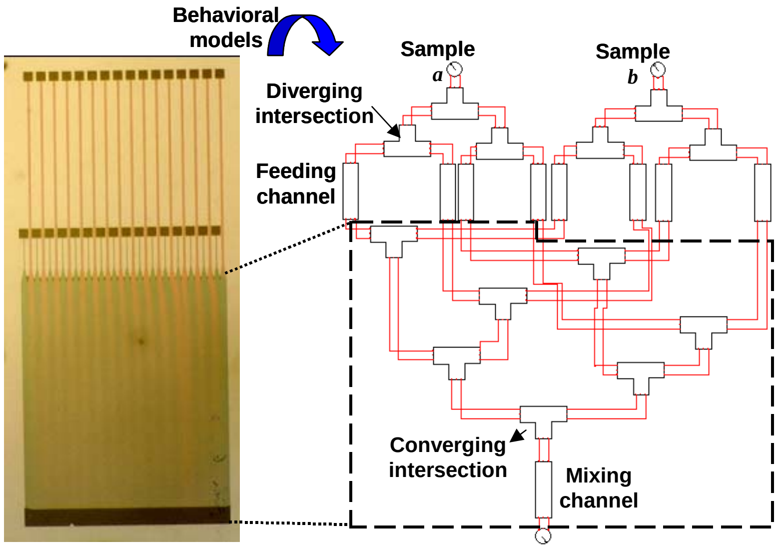
Band-broadening (dispersion)

Skew effect

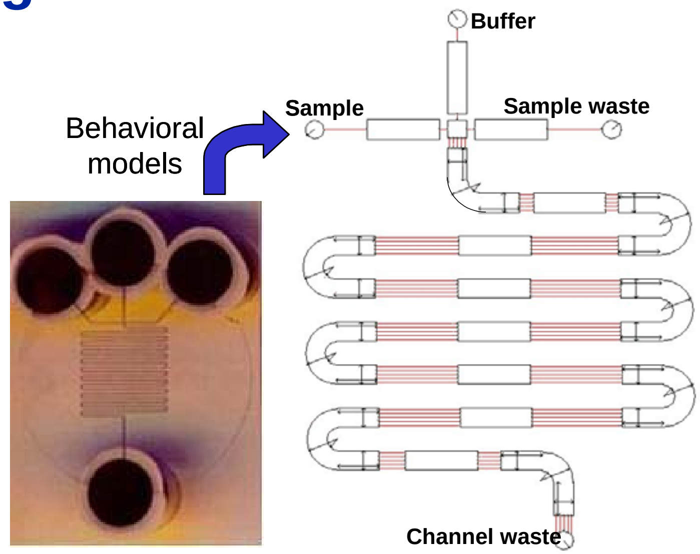
Interaction among channels

# Method of Composable System Simulation

- **A system decomposed into a set of behavioral models**
  - **Parameterized**
  - **Reusable**
- **Designs formed by interconnecting models**




**Multi-lamination mixer (Koch, M. et al.)**




**Serpentine separation chip (ORNL)**

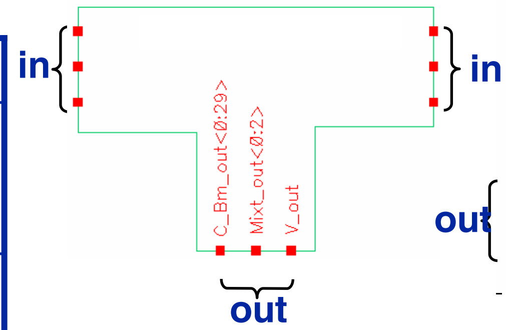
- **Top-down analysis and design methodology**
  - **Fast and computationally robust**
  - **Hierarchical system design**

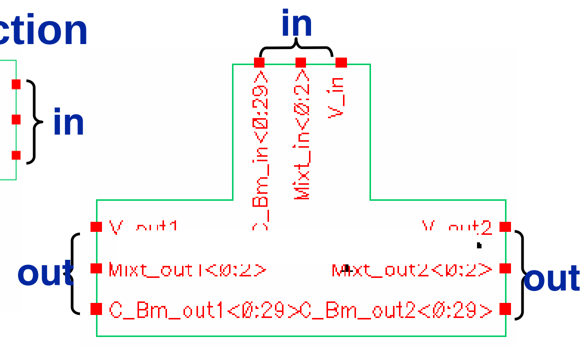
# Basic Element Models for Mixer

## ■ Basic element models

| Name | Description |
|---|---|
| Converging Intersection | Concentration merged and compressed<br>current converged |
| Diverging intersection | Concentration diverged, current diverged |
| Mixing straight Channel | Samples mixed along width-wise direction |
| Mixing turn | Elbow and U-turn of clockwise or counter-clockwise flow |

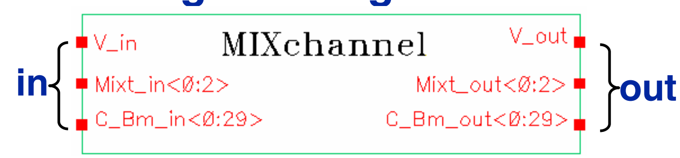
Converging intersection

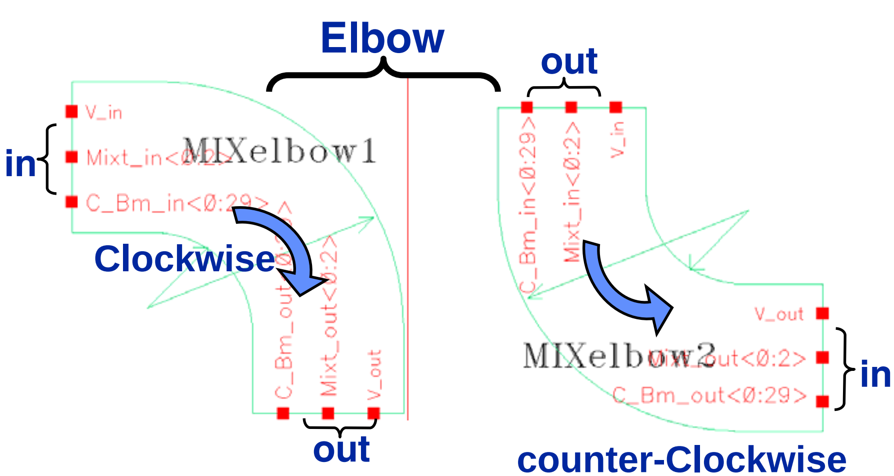


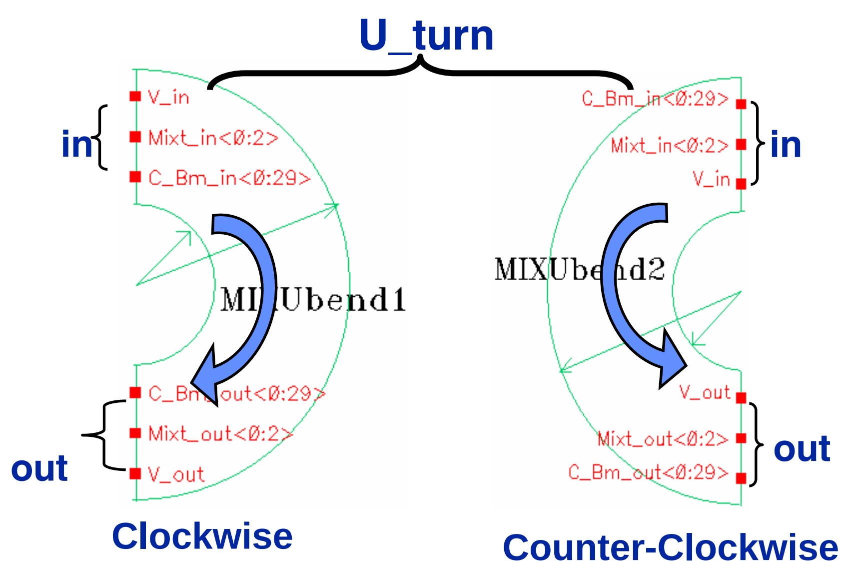




Diverging intersection

Straight Mixing Channel

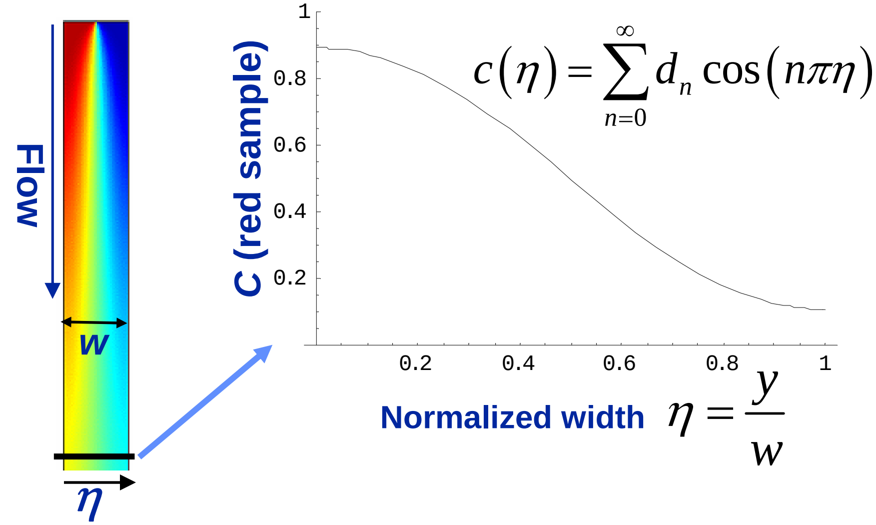


# Interface Parameters

- Interface parameters
  - Mixing time (*t*)
  - Conc. coeff. ($d_n$)
  - Voltage (*V*)

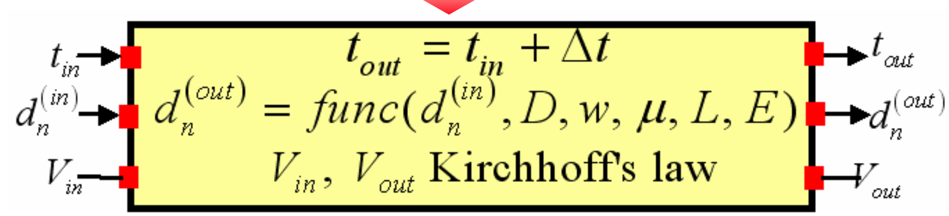



- Globally determined voltage
- Signal flow of fluidic interface parameters
- Starts from upstream-most sample reservoirs
- Simultaneous simulation of two or more samples in the buffer solvent

User input

**Component geometry (*w*, *h*, *L*)**

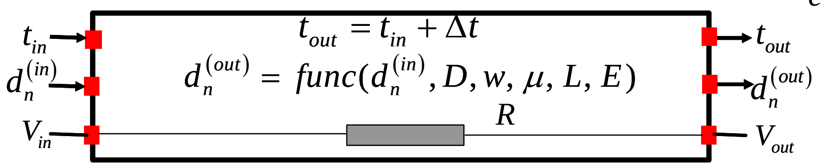
**mobility $\mu$ and diffusivity *D***



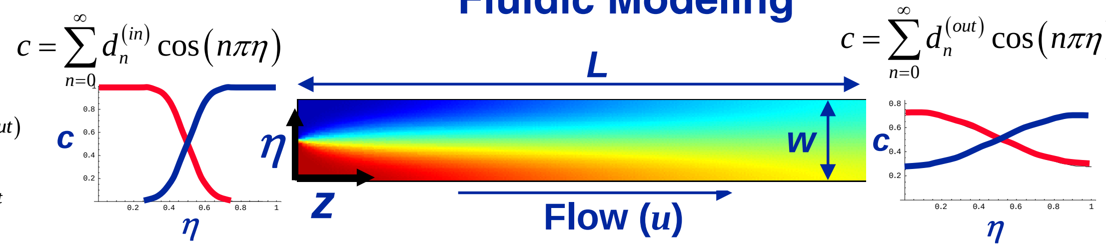

**Behavioral Model Structure of Mixing Channel**

# Model for Mixing Channels

### Model Structure




### Fluidic Modeling




- **Electric resistance and current**

E-conductivity

$$R = \frac{L\sigma}{wh} \;\Rightarrow\; I = \frac{\Delta V}{R}$$

Channel depth

- **Mixing Time**

$$\Delta t = L/u \qquad t_{out} = t_{in} + \Delta t$$

Sample electrokinetic velocity

- **Concentration coefficients**

$$d_n^{(out)} = d_n^{(in)} e^{-(n\pi)^2 \tau} \;\Rightarrow\; \tau = \Delta t \cdot D/w^2$$

Dimensionless diffusion time

Sample diffusivity

**Convection-diffusion equation**

$$u \frac{\partial c}{\partial z} = \frac{D}{w^2} \frac{\partial^2 c}{\partial \eta^2}$$

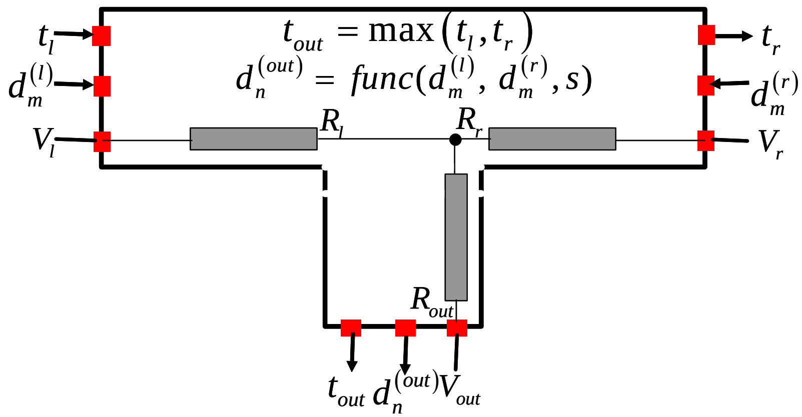
**Boundary conditions:**

$$\left.\frac{\partial c}{\partial \eta}\right|_{\eta=0,1} = 0$$

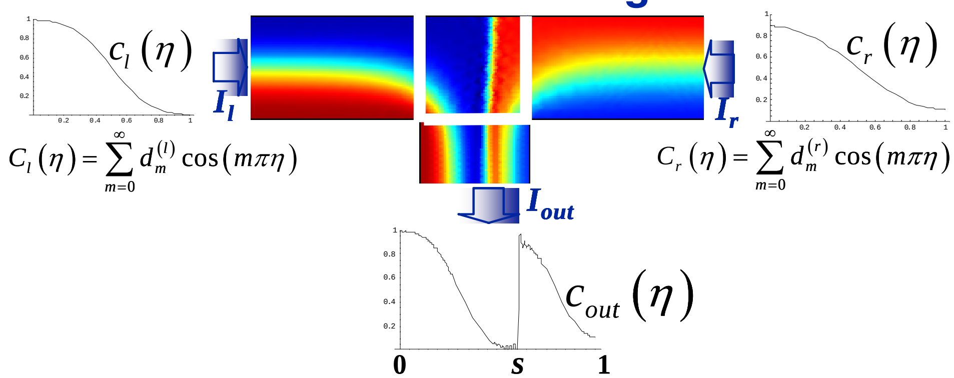
$$c\big|_{z=0} = \sum_{n=0}^{\infty} d_n^{(in)} \cos(n\pi\eta)$$

# Model for Converging Intersections

## Model Structure




## Fluidic Modeling




- **Electric resistance and current**

$$R_l = R_r = R_{out} = 0 \qquad I_{out} = I_l + I_r$$

- **Mixing Time**

$$\Delta t = 0 \;\Rightarrow\; t_{out} = \max\left(t_{in}^{(l)}, t_{in}^{(r)}\right)$$

$$C_{out}(\eta) = \begin{cases} \sum_{m=0}^{\infty} d_m^{(l)} \cdot \cos\left(\frac{m\pi\eta}{s}\right), & 0 \le \eta < s \\ \sum_{m=0}^{\infty} d_m^{(r)} \cdot \cos\left(\frac{m\pi(\eta - s)}{1-s}\right), & s \le \eta < 1 \end{cases}$$

**Interface position** $s = I_l / (I_l + I_r)$

- **Concentration coefficients**

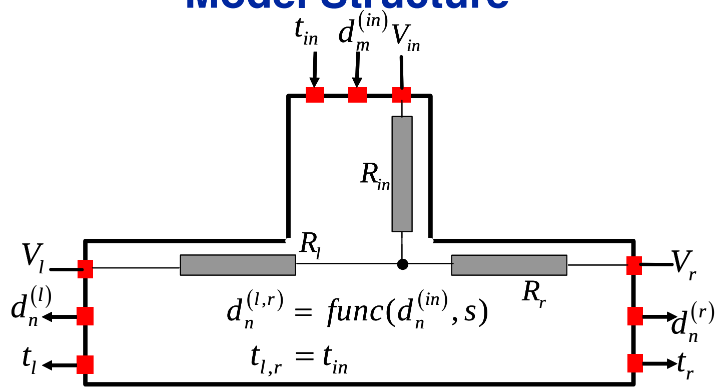
$$f_1 = (m - ns)\pi \qquad f_2 = (m + ns)\pi$$

$$F_1 = (m + n - ns)\pi \qquad F_2 = (m - n + ns)\pi$$

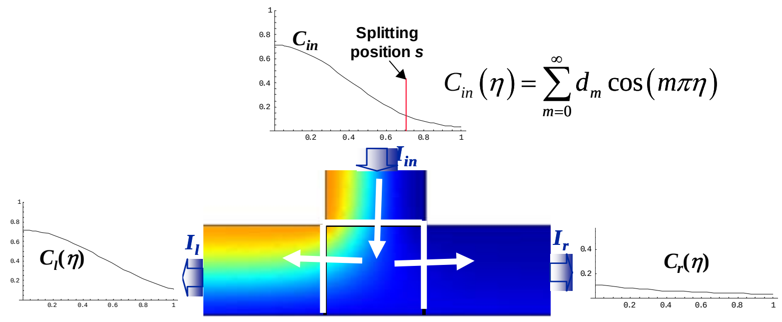
$$\begin{cases} d_0^{(out)} = d_0^{(l)} s + d_0^{(r)} (1-s) \\ d_{n\neq 0}^{(out)} = \sum_{m=0}^{m\neq ns} \Big\{ 2(-1)^n d_m^{(r)} (1-s)\big(\cos(F_2/2)\sin(F_1/2)/F_1 + \cos(F_1/2)\sin(F_2/2)/F_2\big) \\ \qquad + d_m^{(l)} s \big( f_1 \sin(f_2) + f_2 \sin(f_1) \big) / f_1 f_2 \Big\} + \sum_{m=0}^{m=ns} \left( d_m^{(l)} s + d_m^{(r)} (-1)^m (1-s) \right) \end{cases}$$

# Model for Diverging Intersections

## Model Structure




## Fluidic Modeling




$$C_l(\eta) = \sum_{m=0}^{\infty} d_m \cdot \cos(ms\pi\eta) \qquad c_r(\eta) = \sum_{m=0}^{\infty} d_m \cdot \cos\left(m\pi(1-s)\left(\eta + \frac{s}{1-s}\right)\right)$$

**Splitting position** $s = I_l / (I_l + I_r)$

- **Electric resistance and current**

$$R_l = R_r = R_{out} = 0 \qquad I_{in} = I_l + I_r$$

- **Mixing Time**

$$\Delta t = 0 \rightarrow t_l = t_r = t_{in}$$

- **Concentration coefficients**

$$f_1 = (m - ns)\pi \qquad f_2 = (m + ns)\pi$$
$$F_1 = (m + n - ns)\pi \qquad F_2 = (m - n + ns)\pi$$
$$\phi_1 = ms\pi \qquad \phi_2 = m(1-s)\pi$$

**Left stream**

$$\begin{cases} d_0^{(l)} = d_0^{(in)} + \sum_{m=1}^{\infty} d_m^{(in)} \sin(\phi_1)/\phi_1 \\ d_{n\neq 0}^{(l)} = 2 \sum_{m=0}^{m \neq n/s} d_m^{(in)} (-1)^{n+1} \phi_1 \sin(\phi_1) / f_1 f_2 \\ \qquad + \sum_{m=0}^{m=n/s} d_m^{(in)} \left(1 + \sin(2\phi_1)/(2\phi_1)\right) \end{cases}$$

**Right stream**

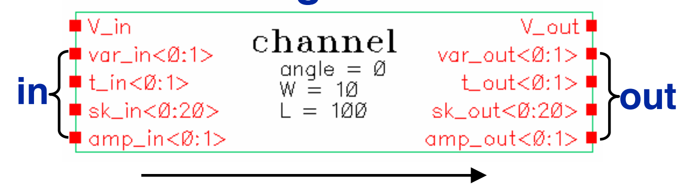
$$\begin{cases} d_0^{(r)} = d_0^{(in)} - \sum_{m=1}^{\infty} d_m^{(in)} \sin(\phi_1)/\phi_2 \\ d_{n\neq 0}^{(r)} = 2 \sum_{m=0}^{m \neq n/(1-s)} d_m^{(in)} \phi_2 \sin(\phi_1) / F_1 F_2 \\ \qquad + \sum_{m=0}^{m=n/(1-s)} d_m^{(in)} \left(\phi_2 \cos(\phi_1) - \sin(\phi_1)\right)/\phi_2 \end{cases}$$

# Basic Models for Separation System

## ■ Basic behavioral models

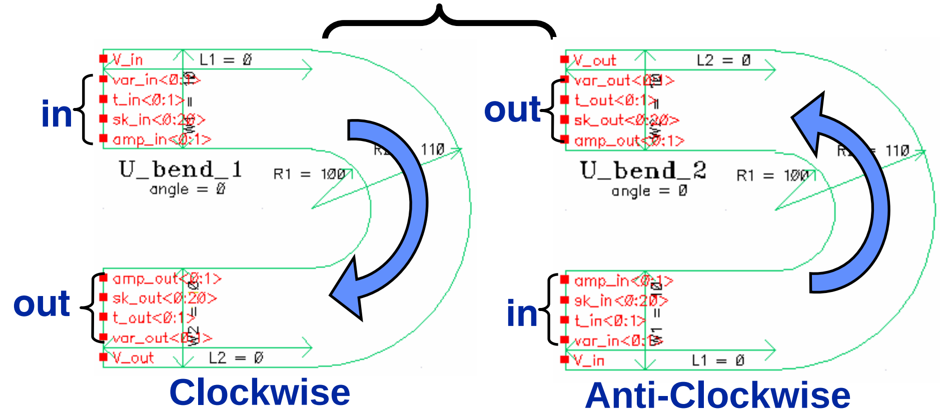
| Name | Description |
|---|---|
| Channel | Straight Channel |
| elbow_1 | Elbow of clockwise flow |
| elbow_2 | Elbow of anti-clockwise flow |
| U_turn_1 | Turn of clockwise flow |
| U_turn_2 | Turn of anti-clockwise flow |

**Straight channel**

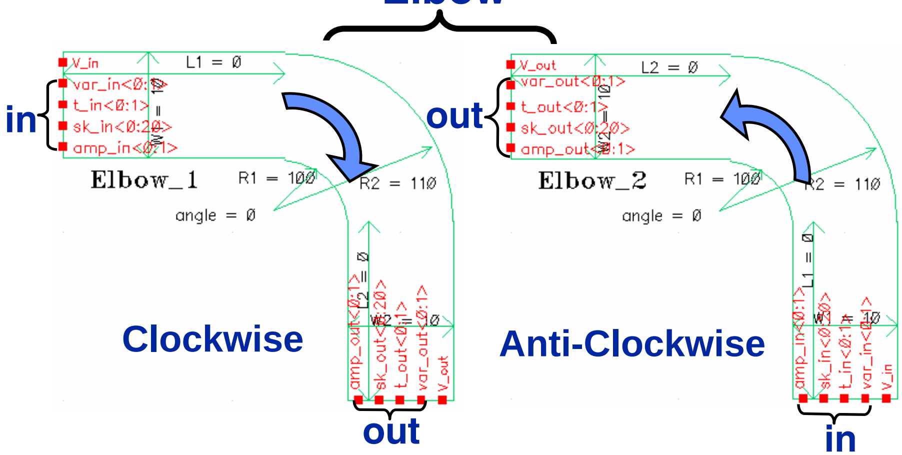



**Signal flow direction**

**U_turn**

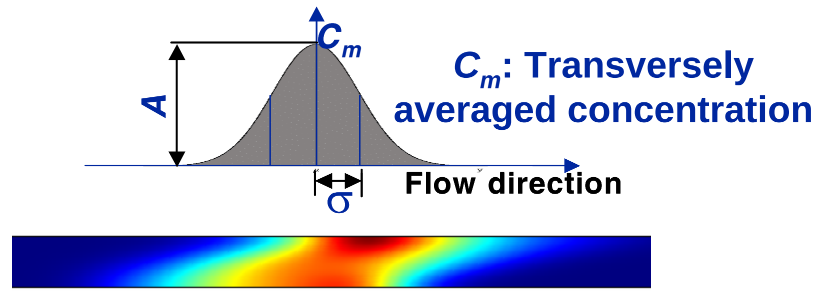



**Elbow**



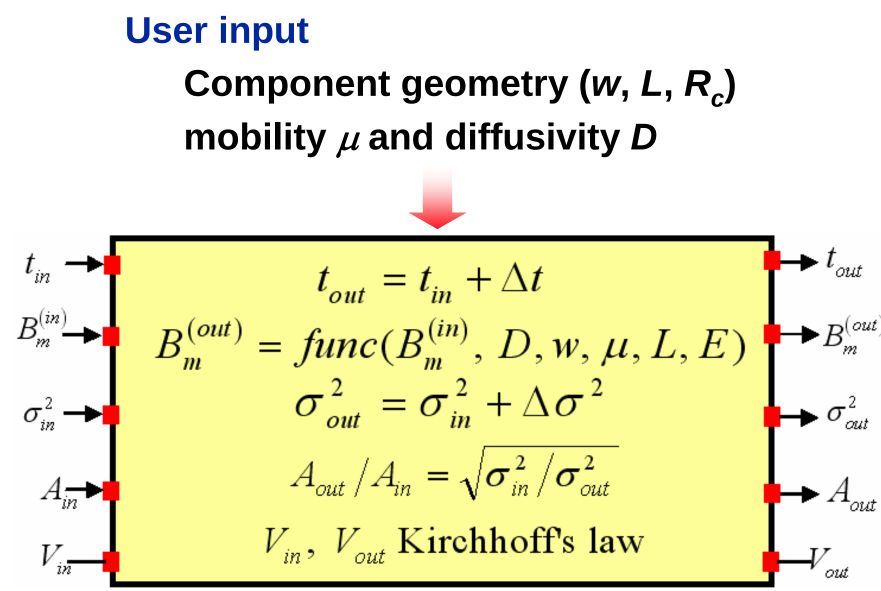
# Interface Parameters and Model Structure

- **Interface parameters**
  - **Variance ($\sigma^2$)**
  - **Separation time ($t$)**
  - **Skew coefficients ($B_m$)**
  - **Amplitude ($A$)**
  - **Voltage ($V$)**




Skew

- **Globally determined voltage**
- **Signal flow of fluidic interface parameters**
- **Starts from injector**
- **Simultaneous simulation of two or more species in the analyte**



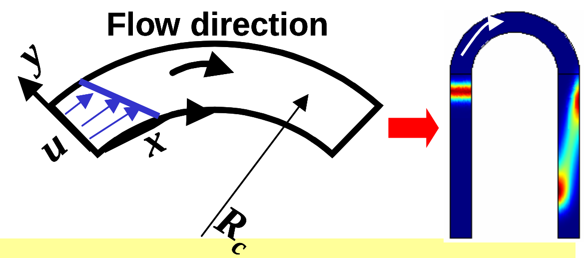

Behavioral Model Structure

# Model: Separation Channels of Turn Geometry

- **Electrophoretic velocity**

$$E = \Delta V / \theta R_c \;\rightarrow\; U = \mu E \;\rightarrow\; u \approx U \cdot \left(1 + \overbrace{\left(w - 2y\right)/R_c}^{\text{Non-uniform velocity}}\right)$$

Species mobility




- **Variance**

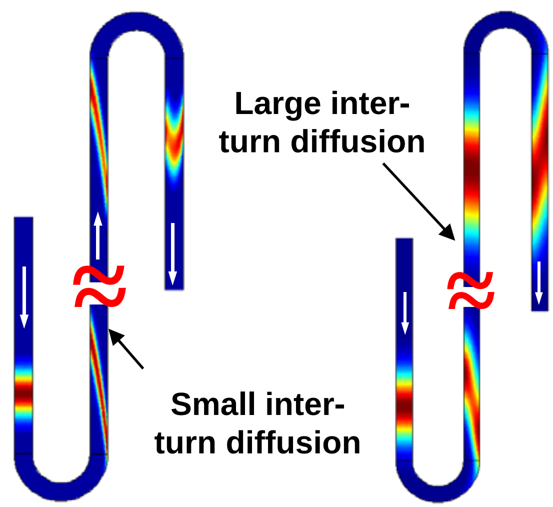
$$\Delta\sigma^2 = 2w^2\tau_t \pm Jw^2 \sum_{m=1,3,5...}^{\infty} \left( \overbrace{B_m^{(in)} \lambda_m \left(1 - e^{-\lambda_m \tau_t}\right)}^{\text{Input from upstream}} \pm J \left(\lambda_m \tau_t + e^{-\lambda_m \tau_t} - 1\right) / \lambda_m \right) / \lambda_m^3$$

- **Skew coefficients**

$$B_m^{(out)} = \pm J \left(1 - e^{-\lambda_m \tau_t}\right) / \lambda_m^2 + \overbrace{B_m^{(in)} \cdot e^{-\lambda_m \tau_t}}^{\text{Input from upstream}}$$

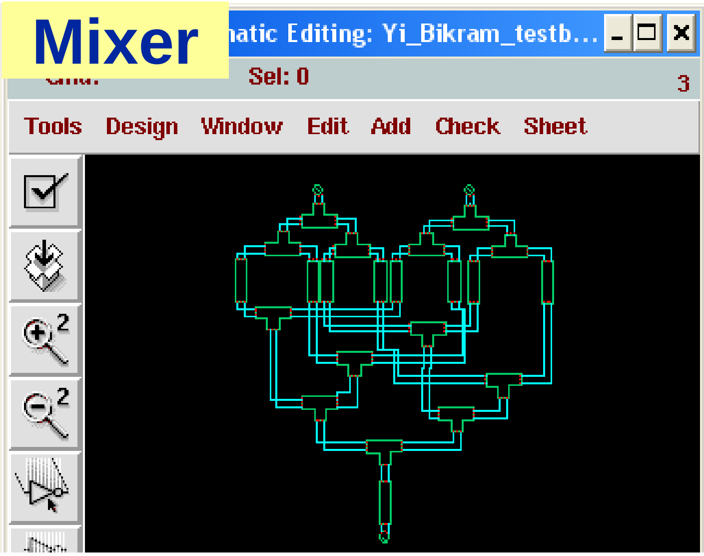
$$J = 8\theta / \tau_t \qquad \lambda_m = (m\pi)^2$$

$$t = \theta R_c / U \qquad \tau_t = t \cdot D / w^2$$



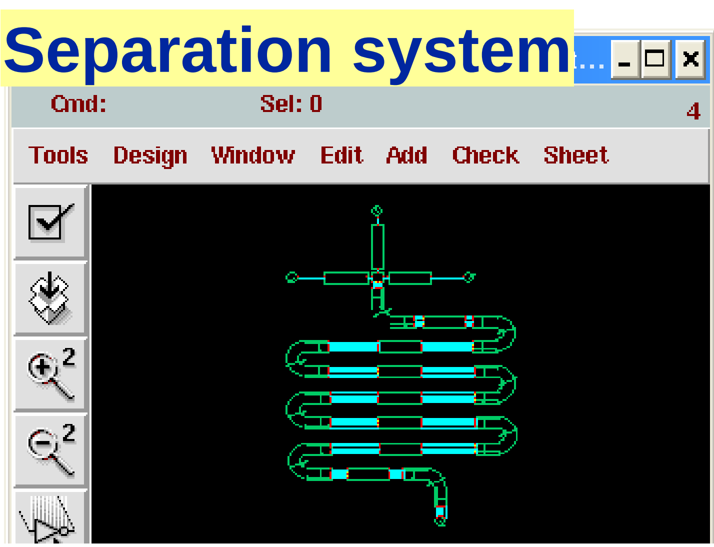
# System Simulations

**Mixer**

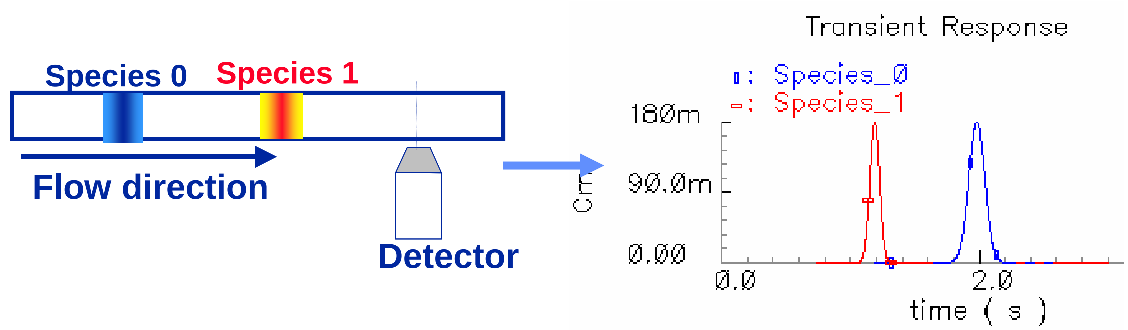



- **DC analysis**
  - Electric variable (voltage/current)
  - Microfluidic simulation
    - Mixing time ($t$)
    - Conc. profile ($d_n$)
    - Mixing performance

**Separation system**

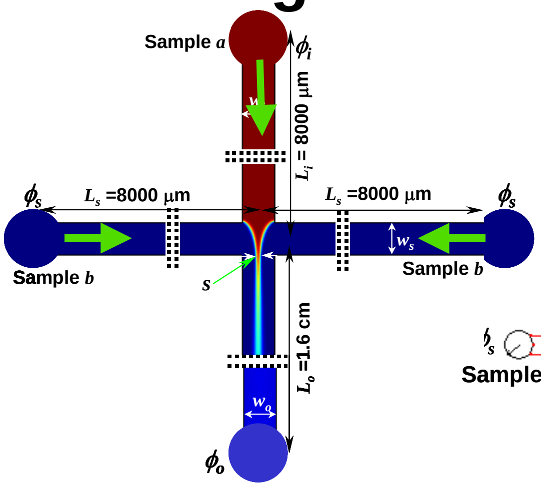


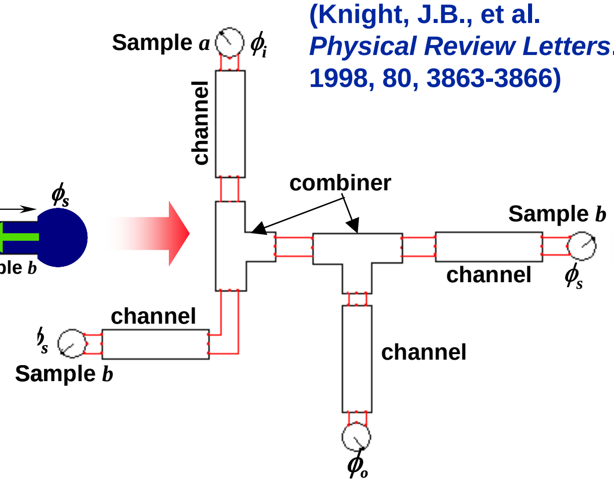

- **DC and Transient Analysis**
  - Resolution
  - Electropherogram



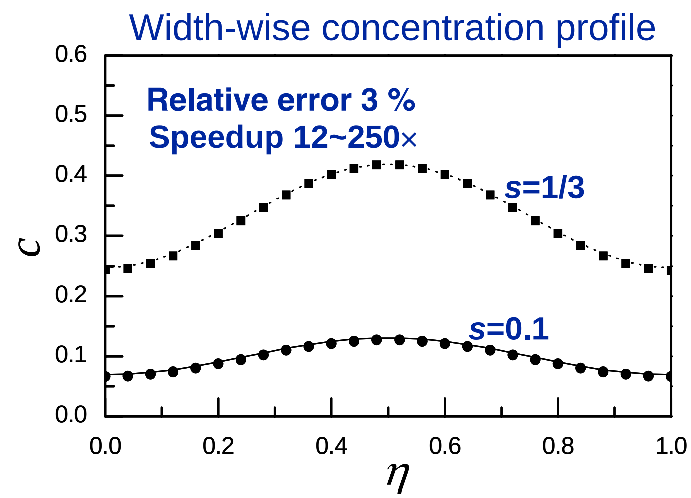
# Verification: Focusing and Multi-stream Mixers

## Focusing

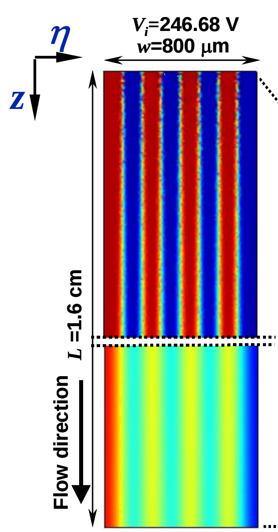


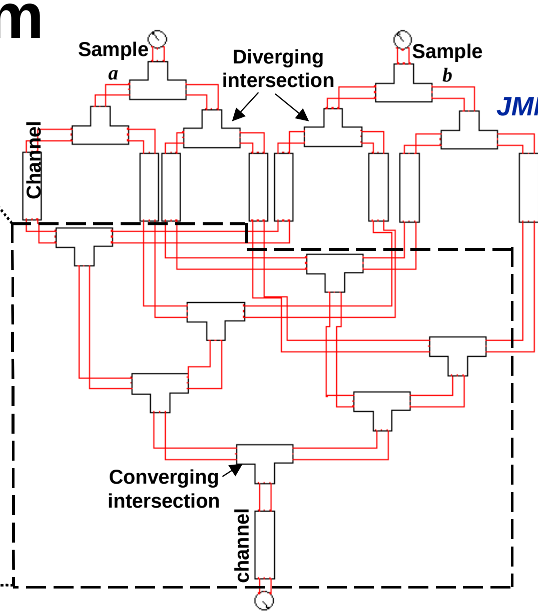




(Knight, J.B., et al. *Physical Review Letters*. 1998, 80, 3863-3866)

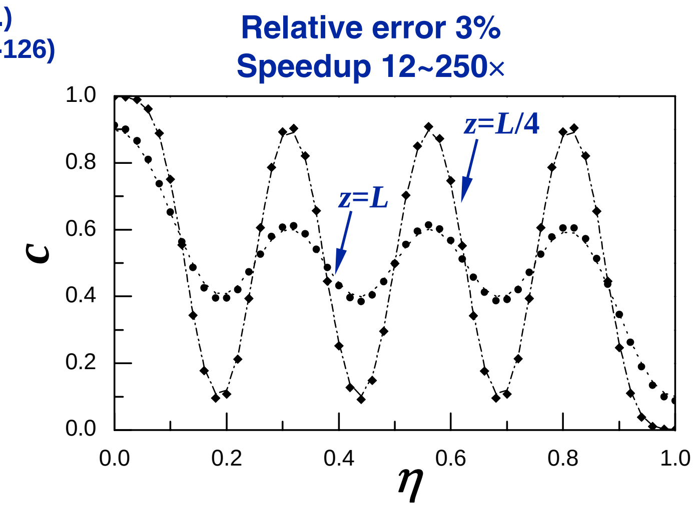



## Multi-stream




(Koch, M. et al.) *JMM*. 1998, 8, 123-126)

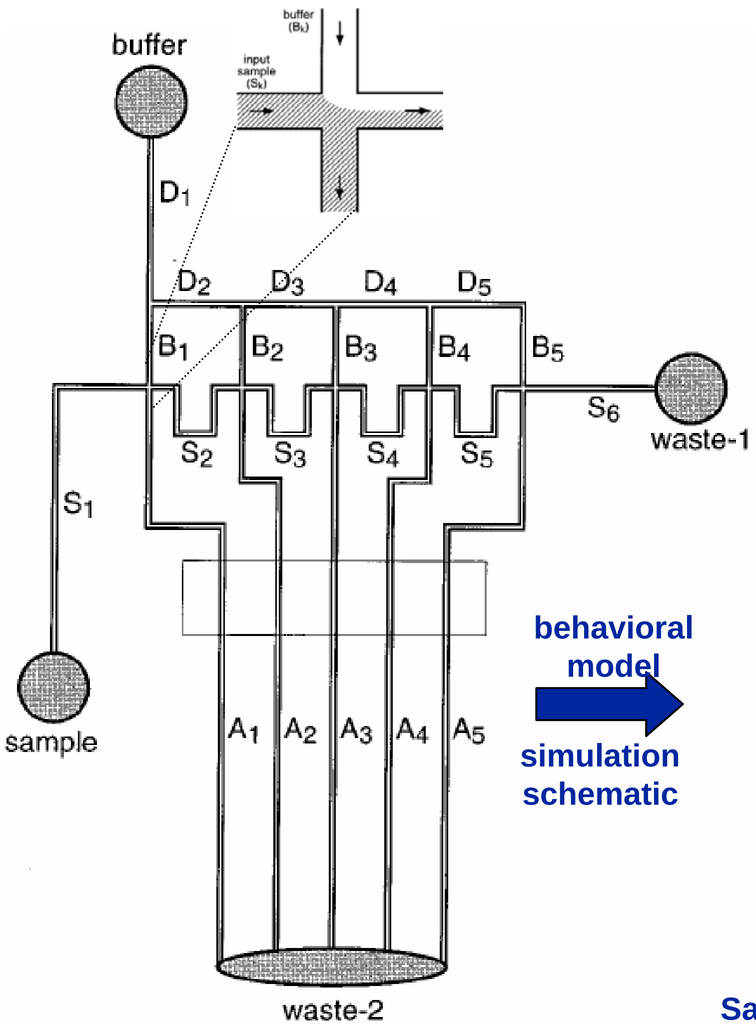


# Verification: Serial Mixing Network

## Concentration comparison

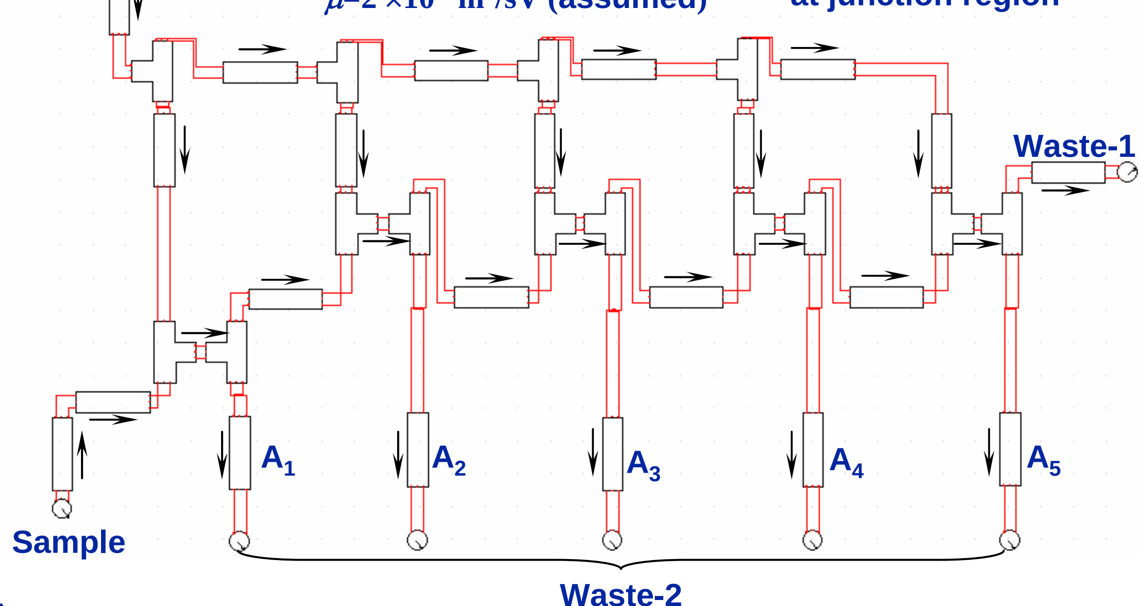
| Complete mixing | | | Partial Mixing | | |
|---|---|---|---|---|---|
| Channel | Sche. | Exper. | Sche. | Num. | Error |
| $A_1$ | 1.0 | 1.0 | 1.0 | 1.0 | |
| $A_2$ | 0.37 | 0.36 | 0.48 | 0.51 | 5.9% |
| $A_3$ | 0.22 | 0.21 | 0.186 | 0.195 | 4.6% |
| $A_4$ | 0.125 | 0.13 | 0.081 | 0.086 | 5.8% |
| $A_5$ | 0.052 | 0.059 | 0.029 | 0.0315 | 7.9% |

Caused by transitional field at junction region




behavioral model → simulation schematic

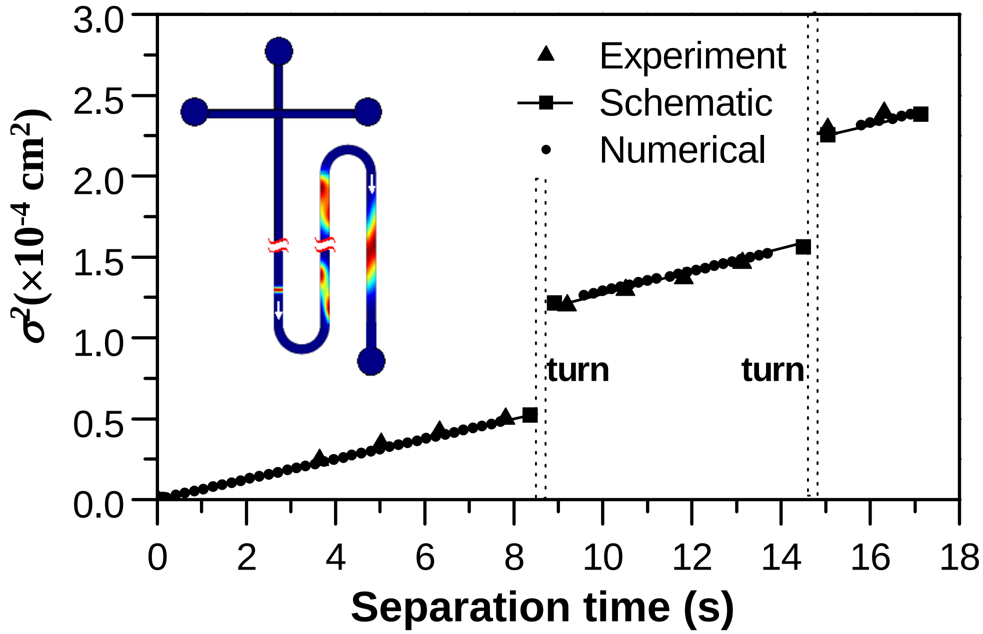
$D$=3.0×10$^{-10}$ m$^2$/s
$\mu$=2 ×10$^{-8}$ m$^2$/sV (assumed)



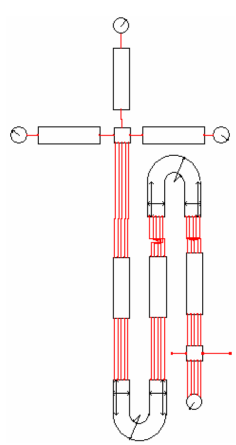

(Jacobson, S.C. et al. *Anal. Chem.* 1999, 71, 4455-4459)

# Verification: Double Complimentary Turns

**Worst relative error 5%** **Speedup 500~10,000×**

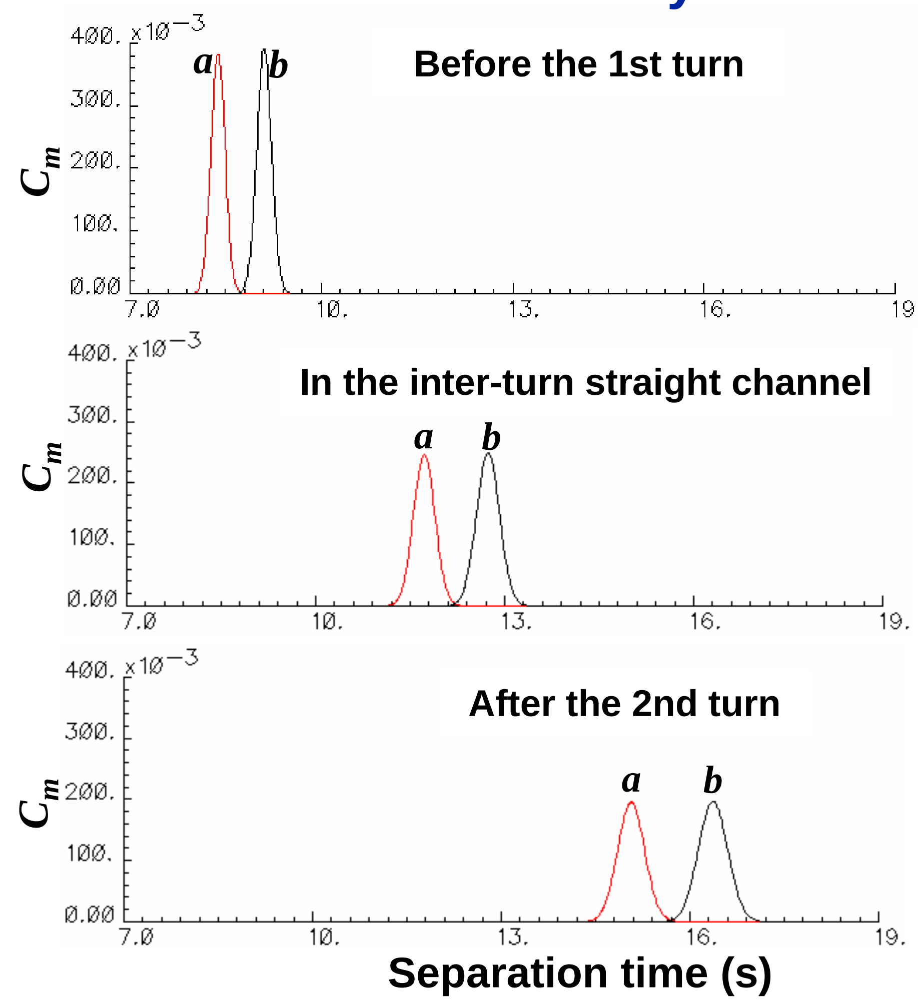



(C.T. Culbertson, S.C. Jacobson, J.M. Ramsey. *Anal. Chem.* 1998, 70, 3781-3789)



**Schematic simulations**

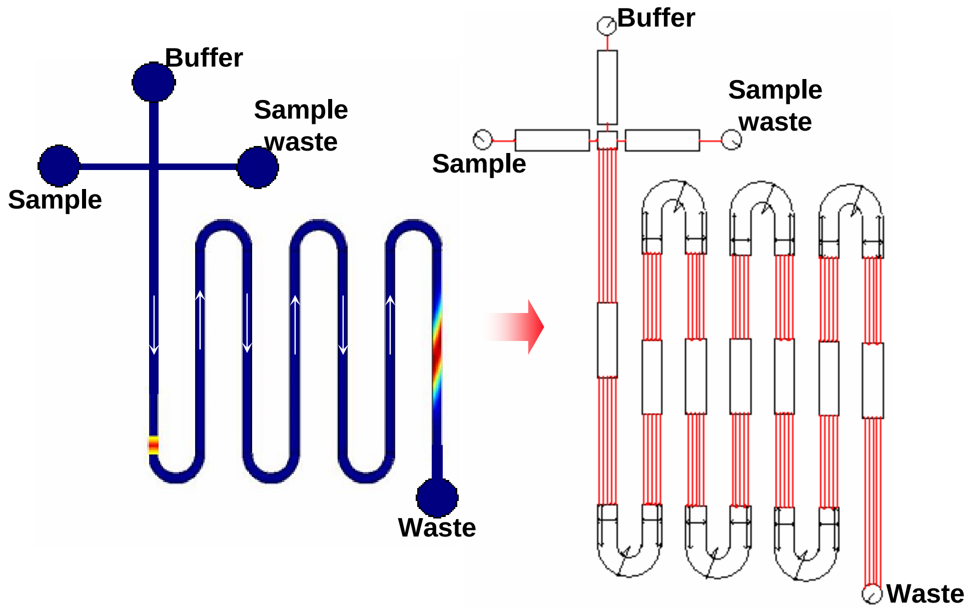
## Transient Analysis



# Verification: Multiple Turns

- Behavioral models used in complex EP system
- Good agreement and tremendous speedup

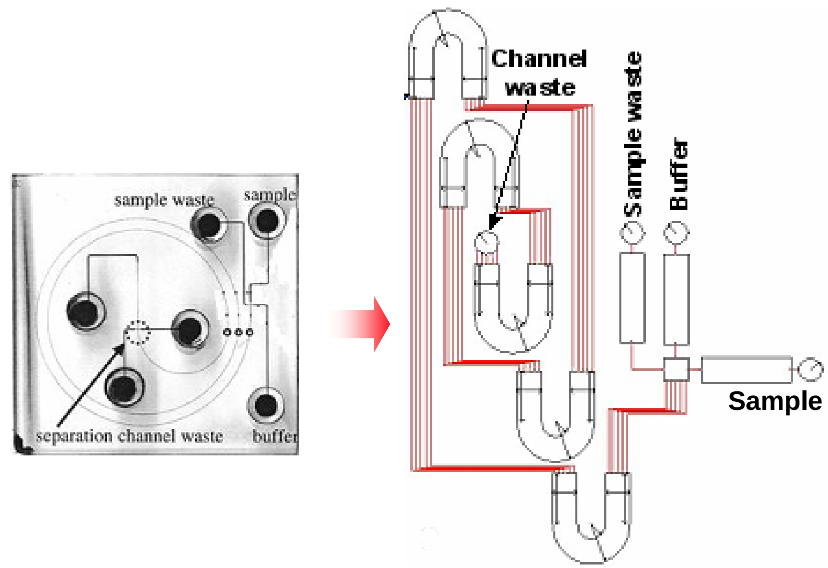
## Serpentine of six turns




**Worst relative error 9.5% compared with numerical simulation**

**Speedup 600~15,000×**

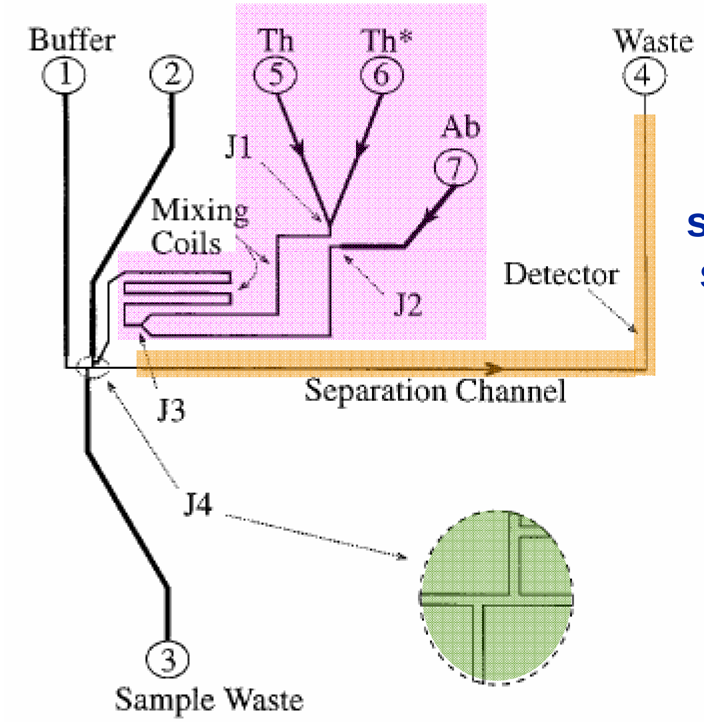
## Spiral of five turns




**Worst relative error 12% compared with experimental results**

(C.T. Culbertson, S.C. Jacobson, J.M. Ramsey. *Anal. Chem*. 2000, 72, 5814-5819)

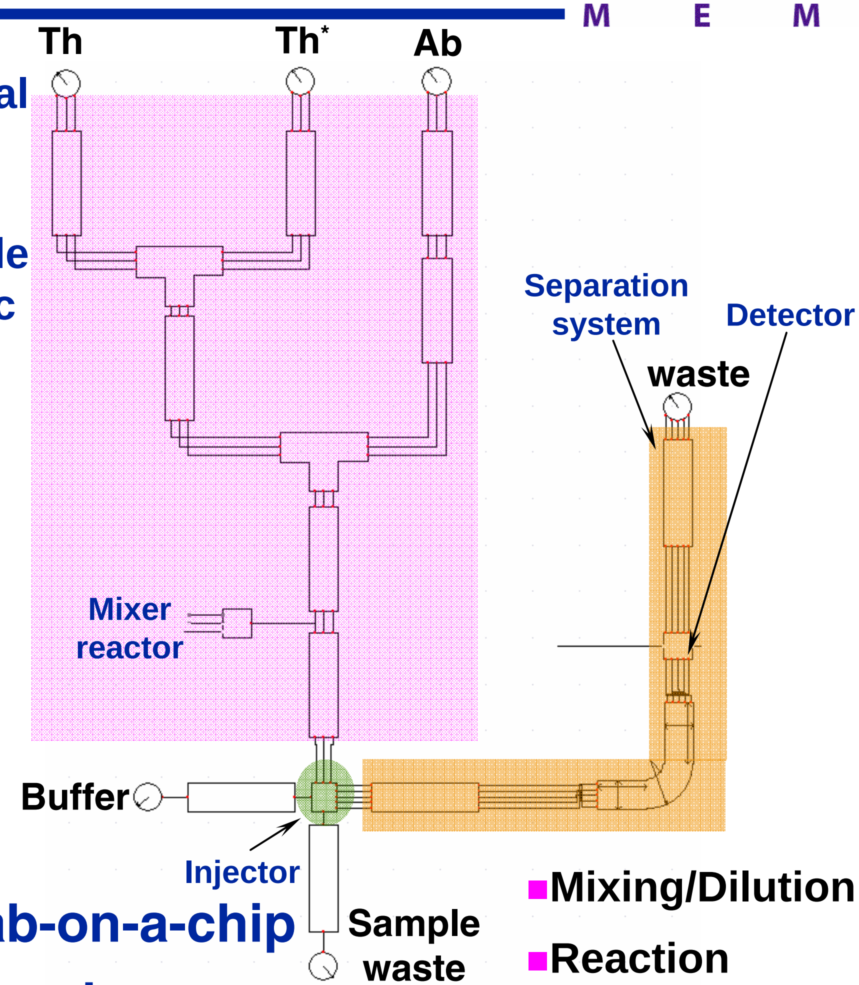
# Simulation Framework of Lab on a Chip




(Chiem, *Clin. Chem.*, 44, 591-598, 1998)

behavioral model

simulatable schematic




- First simulation on complete on Lab-on-a-chip
- Verilog-A simulated by Cadence/Spectre
- Two simulation phases
  - Loading (Mixing, reaction and injector loading)
  - Dispensing (injector dispensing, separation,detection)

- Mixing/Dilution
- Reaction
- Injection
- Separation
- Detection

# Conclusion

- A composable system simulation framework built for biofluidic lab-on-a-chip
- Behavioral Models implemented in analog hardware description language (Verilog-A)
- Simulation results verified numerically and experimentally (relative error ~< 10%)
- A tremendous speedup (10~15,000X) achieved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- DARPA
- NSF