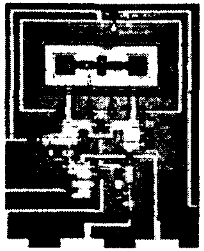
2005 유체기계 연구개발 발표회 논문집, pp. 94~101
창원대학교 국제교류센터 및 정보전산원 2005. 12. 1~2

Bio-MEMS/Medical applications in CFD-ACE+



First polysilicon surface micromachined MEMS device integrated with circuits (Resonant-microbridge vapor Sensor)
Howe R T and Muller R S, *IEEE Trans. Electron Devices (1986)*

Kyung Won Tech.
2005

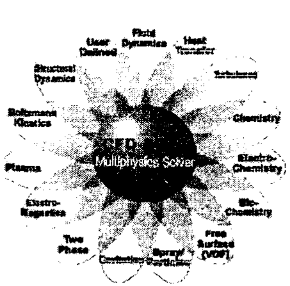
On the Leading Edge of CFD Technology

Contents

- Introduction
  - About CFD-ACE+
  - CFD-ACE+ for Bio-MEMS
- (Bio) MEMS
- Simulation Based Design
- Future Plan

On the Leading Edge of CFD Technology

About CFD-ACE+



- **Multiphysics simulations, linked in any combination**
- **All grid topologies, including unstructured, polyhedra grids**
- **Pre-processing (geometry / grid), Post-processing (visualization / animation), and Data analysis modules**
- ***Simulation Manager, facilitates* automatic parametric analyses and design optimization**

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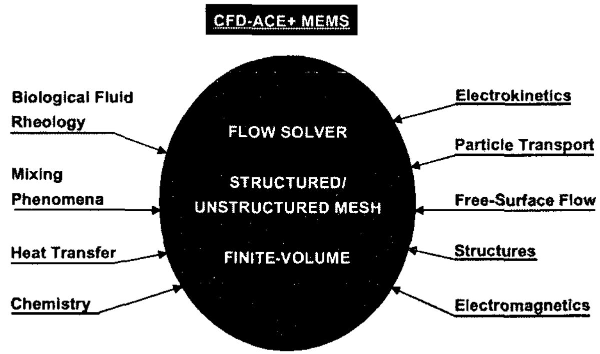
About CFD-ACE+



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CFD-ACE+ for Bio MEMS

- Multi-Disciplinary, Multi-Level (3D/2D/1D/circuit) CAD Environment for Design of Bio-Microfluidic Microsystems
  - automated model generation (CFD-Micromesh) starting from layouts and process to 3D geometry, meshes, and models (BCs, VCs, material properties,...)
  - multi-physics coupled field solvers: (CFD-ACE+) fluids, thermal, chemical, mechanical, electrostatics, electromagnetics, controls, bio-electrochemistry, ...
  - focus on bio-fluidics, bio-chemistry, bio-electrochemistry, cell sensors, cell physiology, DNA electroelastodynamics, influence of external fields on DNA, bio-agents detection, etc.
- Funded by Corporate R&D, DARPA, US Dep. Of Commerce ATP proj.

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(Bio) MEMS

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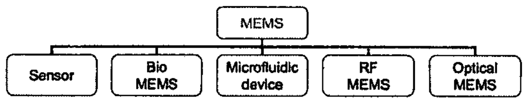
MEMS Classification

(By application)



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History

1500
Early lithographic processes for sub-mm features

1940s
The development of pure semiconductors (Ge and Si)

1960
Invention of the planar batch-fabrication process-the beginning of the IC industry
Invention of MOSFET

1964
Nathenson at westinghouse made the first engineered batch-fabricated MEMS device

1970
The development of the microprocessor

1970s, 1980s
MEMS commercialization was started for the automotive industry

1990s ~
A tremendous increase in the number of devices, technologies, and applications

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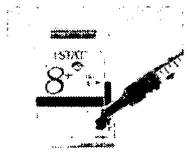
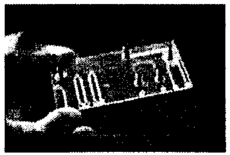
Bio-MEMS

- What's Bio-MEMS?
  One of MEMS (Micro Electro Mechanical Systems) applications to Bio-relating areas
- Characteristics of Bio-MEMS
  Unified Platform
  A microchannel network
  Characteristic dimension is in the micron range
  Miniaturization of various techniques
- Applications
  Bio-diagnostics, Genomics/Proteomics, Genetic identification, High throughput screeening, Drug delivery, Immunoassay, Environmental, Industrial, Defense, ...



i-STAT clinical analyzer



Siemens industrial seawater analyzer

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Applicability of N-S equation

Knudsen Number, Kn = Mean Free Path / Characteristic length = λ/L

$Kn \le 0.01$: Continuum
NS equation with conventional no-slip condition
$0.01 \le Kn \le 0.1$: Slip Flow Regime
NS with slip-velocity BC
$0.1 \le Kn \le 3$: Transitional Regime
Continuum assumption breaks down
$3 < Kn$: Continuum assumption approach breaks down completely
Free Molecular Regime

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Applicability of N-S equation

- Gas phase:

$$\lambda = \frac{RT}{\sqrt{2}\pi\sigma^2 P N_{av}} = \frac{kT}{\sqrt{2}\pi\sigma^2 P}$$

σ : collision diameter of molecule
N_{av} : avogardro's number
P : local pressure

Gas	σ_c(m)
Air	3.66X10^{-10}
Ar	3.58X10^{-10}
CO_2	4.53X10^{-10}
H_2	2.71X10^{-10}
He	2.15X10^{-10}
Kr	4.08X10^{-10}
N_2	3.70X10^{-10}
NH_3	4.32X10^{-10}
Ne	2.54X10^{-10}
O_2	3.55X10^{-10}
Xe	4.78X10^{-10}

From CRC handbook

1μm채널, 표준상태에서(충돌직경 약 3.66X10^{-10}m)의

$$\lambda = \frac{1.38\times10^{-23}\times298}{\sqrt{2}\times3.14\times(3.66\times10^{-10})^2\times100000} = 0.0691\mu m$$

$$Kn = \frac{\lambda}{L} = \frac{0.0691\mu m}{1\mu m} = 0.0691 \longrightarrow \text{Slip flow regime}$$

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Applicability of N-S equation

- Liquid phase:

$\lambda \approx 1 \sim 10nm$

1μm채널, 표준상태에서

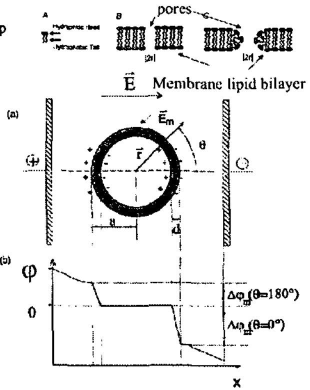
$$Kn = \frac{\lambda}{L} = \frac{1\sim10nm}{1\mu m} = 0.001\sim0.01 \longrightarrow \text{Continuum regime}$$

On the Leading Edge of CFD Technology

Simulation Based Design

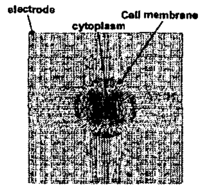
Modeling of Cell Electroporation & Lysis

- Cell membrane electroporation (CME) opens up lipid-protein membranes.
- Can be controlled by an AC E-field
- Can be used for LYSIS to extract intracellular components including DNA.
- Can be used to implant foreign genes, deliver drugs, in-vivo PCR, in-vivo chemotherapy,...

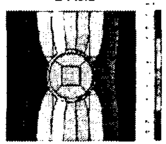


Modeling of Cell Electroporation & Lysis

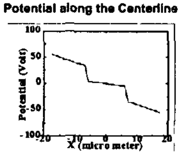
- MicroCell Lysis Device could Utilize AC Electric Field to Electroporate Cell Membrane Walls
- CFD-ACE+ Model of Cell Lysis in E-Field
  - convection, diffusion, and drift of neutrals and charged ions
  - energy equation to model heat absorption
  - cell membrane model for shape and pore density



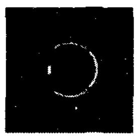
E-Field



Potential along the Centerline

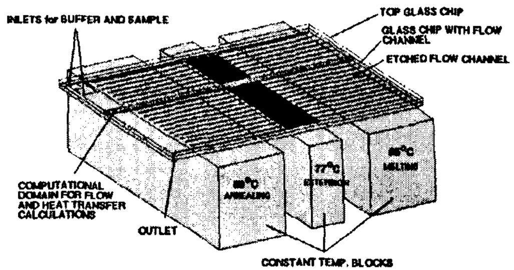


Concentration of Negative Ions

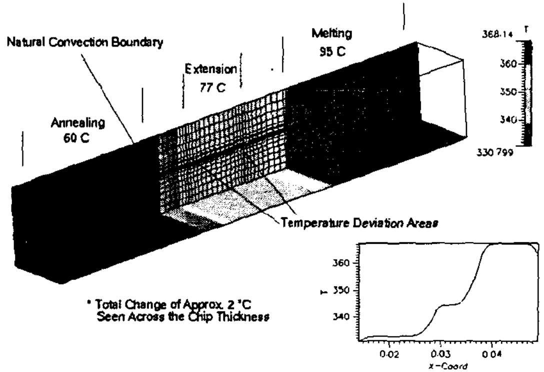


Continuous Flow PCR Model

- Design by Kopp, Mello and Manz (Science, 1998)
  Single Loop Selected for High-Fidelity Simulations
- Flow Domain: One Cycle (Full Chip has 20 Cycles, 120K Grid)
- Model: Flow and Conjugate Heat Transfer



Continuous Flow PCR Model



* Total Change of Approx. 2 °C Seen Across the Chip Thickness

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PCR Microreactor Prototyping

- **PCR Microreactors**
  - small sample sizes: afford fast cycle times ~ seconds/cycle
  - fast heating/cooling rates: temperature uniformity essential
  - feed-forward controllers essential *for accurate control of* heater/cooler elements to avoid temp over/under shoots
  - thermal inertia of the system can make control problem *more difficult*

- **Virtual Prototyping Environment**
  - use CFD-ACE+ as the virtual reactor
  - allows exact definition of the *reactor*, including heaters, and natural and active cooling
  - couple with LQC controllers in SABER for control of *active heater and cooler elements*
  - parallel execution of CFD-ACE+, *controlled by* SABER

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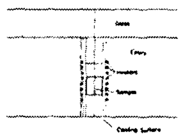
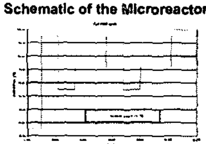
PCR Microreactor Prototyping

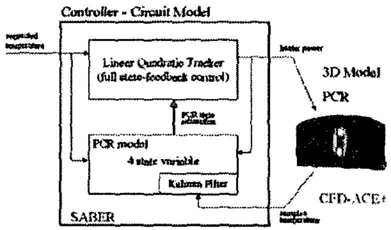
- Generic Microreactor with Cylindrical Well (courtesy Motorola)
- A Sample Thermal Cycling Schedule shown



Schematic of the Microreactor



Temperature - Time Profile



Description of the Controller and Link with the Microreactor

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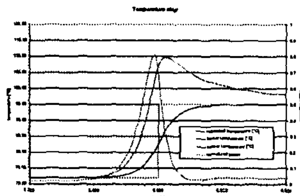
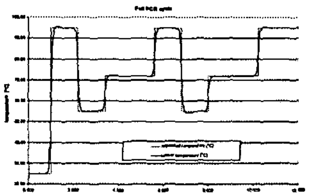
PCR Microreactor Prototyping



Power Input and System Response During a Step Increase in Temperature Only Heater Element Turned On

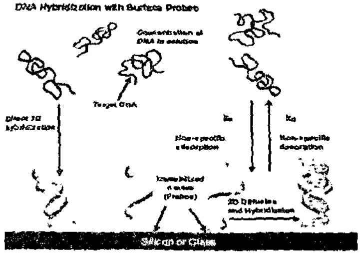


System Temperature Response During a Full PCR Cycle with Both Heater and Cooler Turned On

On the Leading Edge of CFD Technology

Heterogeneous DNA Hybridization Model

- Hybridization of target DNA from solution to immobilized DNA probes on an array of specific microspots.
- Unknown (target) DNA can be determined by detecting patterns of hybridized molecules (e.g. by photoluminescence)
- Brownian Dynamics model of Axelrod (1994) adapted to model ligand-receptor binding (implemented in CFD-ACE+ surface chemistry module).



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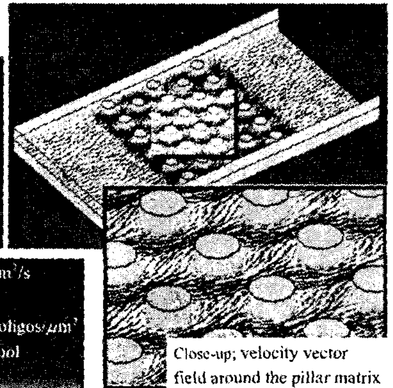
Heterogeneous DNA Hybridization Model

Channel with pillar arrays with immobilized DNA probes

- Diffusivity of DNA: $D = 2.2\times10^{-11}$ m^2/s
- Inlet Concentration: $C_0 = 3\ \mu$Mol
- Density of Surface Probe: $P_s = 8498$ oligos/μm^2
- Molecular Weight: $M = 6415$ Kg/Kmol
- Inject Velocity: $V = 1\sim10$ mm/s



Close-up; velocity vector field around the pillar matrix

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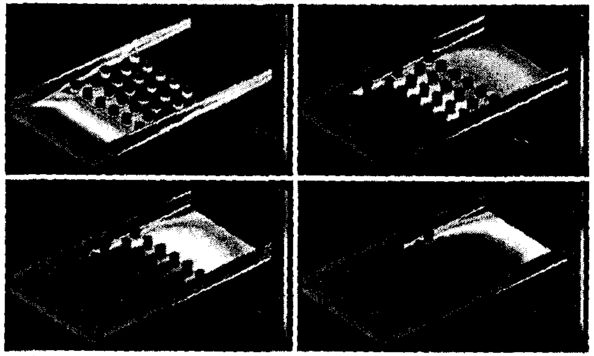
Heterogeneous DNA Hybridization Model

Normalized DNA Concentration ($C/2C_0$) in solution near Lower Channel Wall and Pillars



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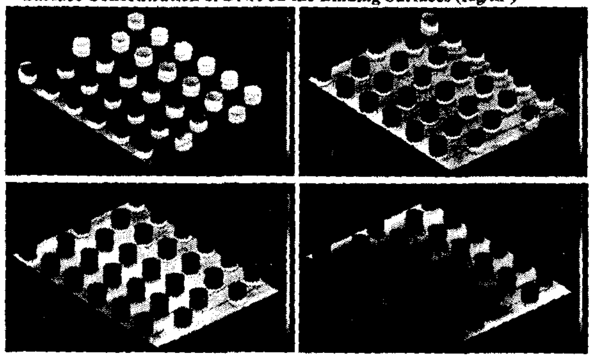
Heterogeneous DNA Hybridization Model

Surface Concentration of DNA on the Binding Surfaces (Kg/m^2)



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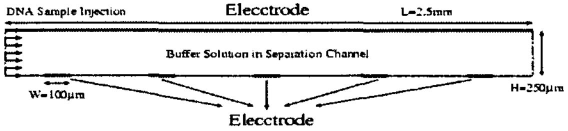
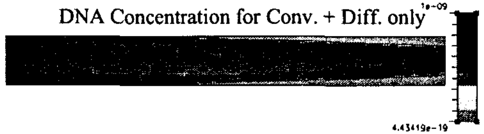
DNA Electrokinetic Transport and Binding

- CFD-ACE+ used for DNA transport, and site specific binding on electrodes.
- Investigate influence of: diffusion, convection, electrophoresis, and electroosmosis.



DNA Concentration for Conv. + Diff. only



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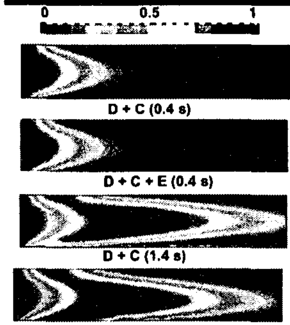
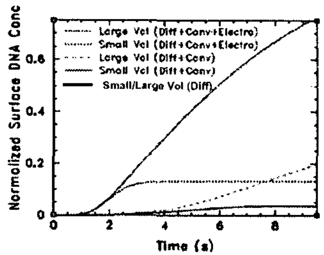
DNA Electrokinetic Transport and Binding



Normalized DNA Concentration Contours in Flow Domain



Effect of Transport Mechanism and Sample Volume on Hybridization Process (Sample Plug Length for Small Volume = 1 cm, Large Volume >> 1 cm)

Demonstrates Hybridization Speed-up Due to Electrophoresis

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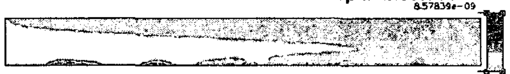
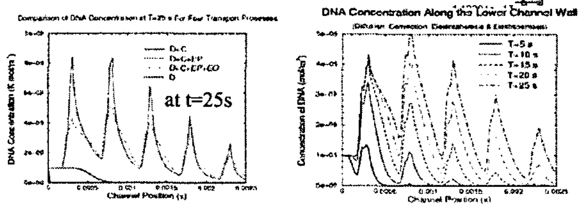
DNA Electrokinetic Transport and Binding

Electric Field Potential

DNA Concentration for Conv.+Diff+Electoph.+Electoosm.



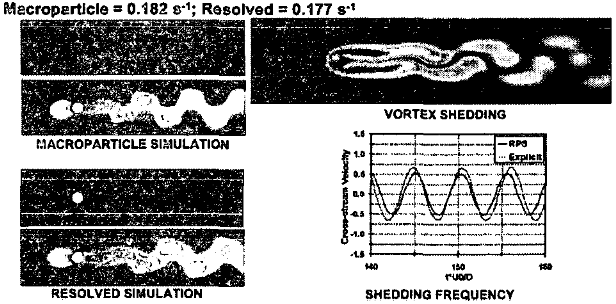


On the Leading Edge of CFD Technology

Macro Particle

FLOW OVER A CYLINDER

- Both macroparticle and resolved simulations (Re = 100)
- Shedding frequency to within 3% of theoretical shedding frequency (0.17 s^{-1}) Macroparticle = 0.182 s^{-1}; Resolved = 0.177 s^{-1}



Good Agreement With Resolved Simulation & Analytical Solution

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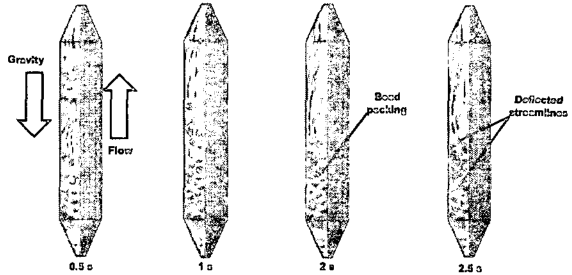
Macro Particle

HINDERED SETTLING



- Settling of "fully resolved" large beads (3 mm beads, 16 mm dia. chamber)
- Beads tracked subject to drag, bead-bead interactions and gravity
- Bead motion coupled with analyte transport and surface biochemistry
- Bead collisions resolved at near close packed state
- Fluid streamlines deflected around the beads

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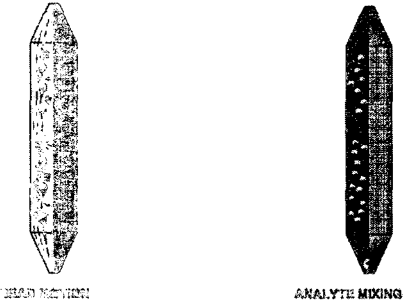
Macro Particle

HINDERED SETTLING

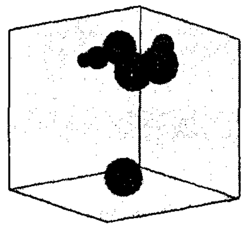


- Surface coverage non-uniformities captured
- Analyte stream has to bend around the beads
- *Bead surface exposed to higher analyte concentration exhibits high surface coverage*

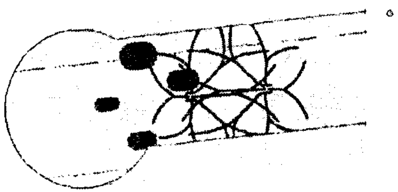
On the Leading Edge of CFD Technology

Macro Particle

Macro Particle Application Example



Multi-Sized Particles Falling Under Gravity in a Box With Fluid



Filter Simulation

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Future CFD-ACE+ for BIO-MEMS

- **The Electrochemistry module in ACE+ is being extended to Bio-Electrochemistry: models for surface (wall, cell) binding, multistep kinetics of PCR, Ag-Ab binding, ...**
- **Accurate modeling of large macromolecules (e.g. DNA) in 3D fields will be facilitated using the Filament model in ACE+**
- **Mixed-level simulation of entire fluidic bio-MEMS with 3D high fidelity models used for key devices and network models used for all other parts ("plumbing", interconnects,control,..).**
- **A PHYSIOLOGICAL CELL MODEL will be developed in ACE+. Detailed models of cell membranes (lipid bilayer), cytoskeleton, nucleus, membrane proteins, channels, metabolism chemistry, ... will be implemented.**

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