Design Optimization of an Electrowetting Cell Sorter Chip Platform

B. Goellner[1], D. Kerkhoff[1], U. Michelsen[1], M. Padberg[1], F. Schreiber[2], D. Erni[2]

[1] Bartels Mikrotechnik GmbH, D-44227 Dortmund, Germany, goellner@bartels-mikrotechnik.de
[2] Universität Duisburg-Essen, Allgemeine und Theoretische Elektrotechnik (ATE), and CENIDE – Center for Nanointegration Duisburg-Essen, D-47057 Duisburg, Germany.

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Main Topics

- Cell sorting by electrowetting
- First design studies for an efficient cell sorter platform based on simulations of different generic sorter topologies
- First prototypes for proof of concept of neccessary sorting operations

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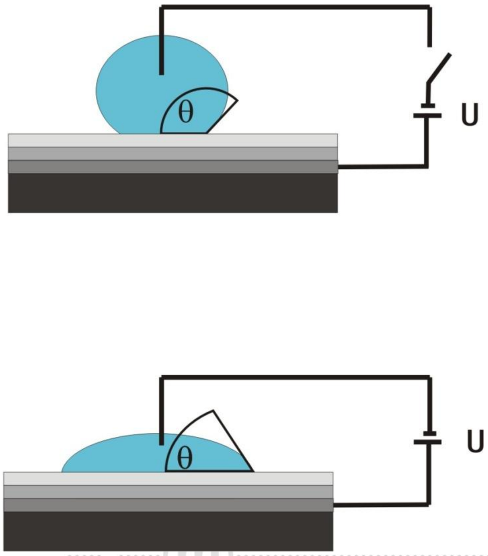
Electrowetting Principle

Lippmann-Young Equation

$$\cos\theta = \cos\theta_0 + \frac{\varepsilon_0 \varepsilon_r U^2}{2\,\gamma_{LG}\, d}$$

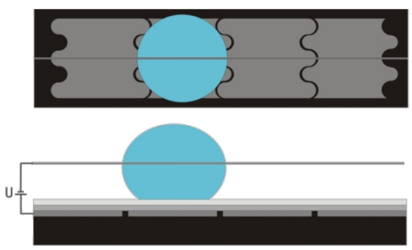
θ Contact Angle
ε_r Dielectric Constant
γ_{LG} Surface Tension
d Thickness of Dielectric
U Voltage



Change of contact angles when a voltage is applied

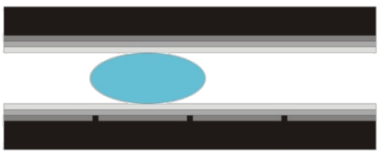
Electrowetting Principle

a)

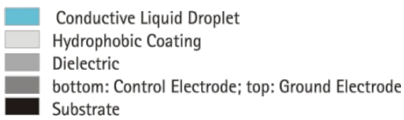


Open electrowetting system

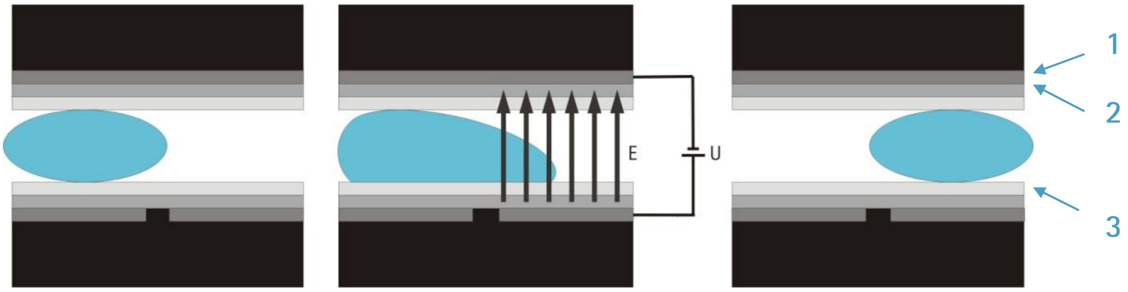
b)



Closed electrowetting system
with filler fluid



Electrowetting Principle

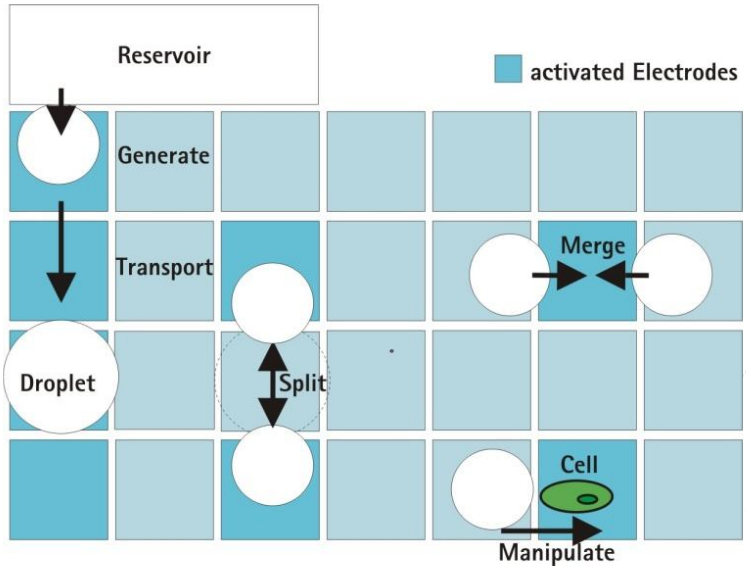


- Moving of a droplet by selected switching an electrode array
- Top and Bottom substrate coated with electrodes (1), dielectric (2) and hydrophobic layer (3)

Typical Characteristics of Electrowetting

System type	steady state or bistable movement of droplets, either in an open or closed (covered) system
Fluids	liquid/liquid or liquid/gas
System architecture	2D or 3D; rigid or flexible
Functionality	droplet generation, moving, merging, mixing and splitting of droplets
Droplet size	0,3 mm – 10 mm
Droplet speed	0.3 Hz – 200 Hz
Operation voltage	typ. 15-50 VAC
Actuation modes	single droplet, multiple droplets simultaneous or multiple droplets separately

Operations for Cell Sorting



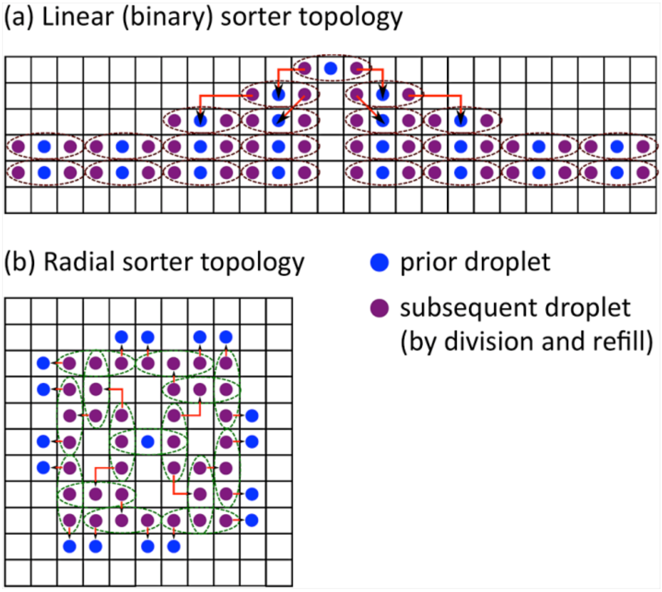
- Generation of Droplets from cell suspension
- Sorting of labelled cells
- Reduction of cell load in droplet by successive splitting and diluting
- Optical inspection of cell load and ratio of labelled cells

Methods

- **Modeling physical sorting algorithms**
  Droplet chains are conceptualized as clocked data streams with a datum information of droplet volume, total number and number of labeled cells. With a data matrix, corresponding to the electrode matrix, the three main operators (transport, merging, splitting) can be simulated. Idealized models can provide qualitative estimates on performance, scaling behavior and potential bottlenecks.

- **Electrowetting test chips**
  Verification of sorting operations on test chip designs and feedback information for simulation.
  Optimization of chip design for parallelization of droplet handling and increasing sorting speed.

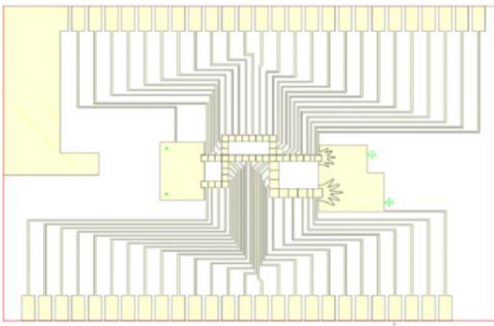
Two Generic Sorter Topologies



- High-volume cell sorting needs algorithm as simple as possible
- Throughput of labeled cells in (a) depends on horizontal extent of electrode array and composition of the suspension in start droplet
- Radial sorter topology (b) combines 4 linear sorters through a center region
- First simulations show a 1.3-fold speed up
- Simulation is simplified (boundaries)

Chip Designs 1

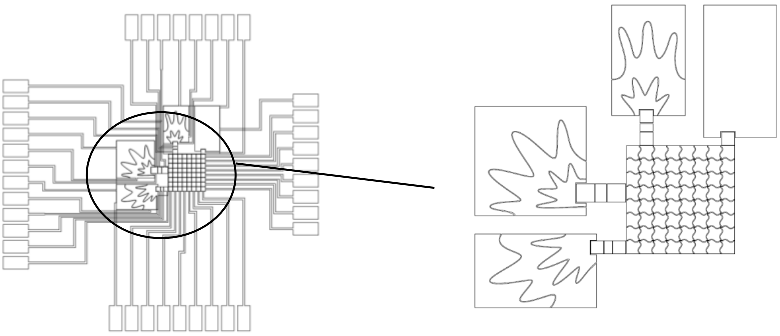
Single electrode activation design



- Number of electrodes limited due to circuit lines
- Principal fluidic operations evaluated with PBS and silcone oil
- Droplet generation 3s, transportation 2,5 mm/s and splitting 2s
- Bottle neck: mixing with 5 to 10 s depending on mixing strategy

Chip Designs 2

Matrix design

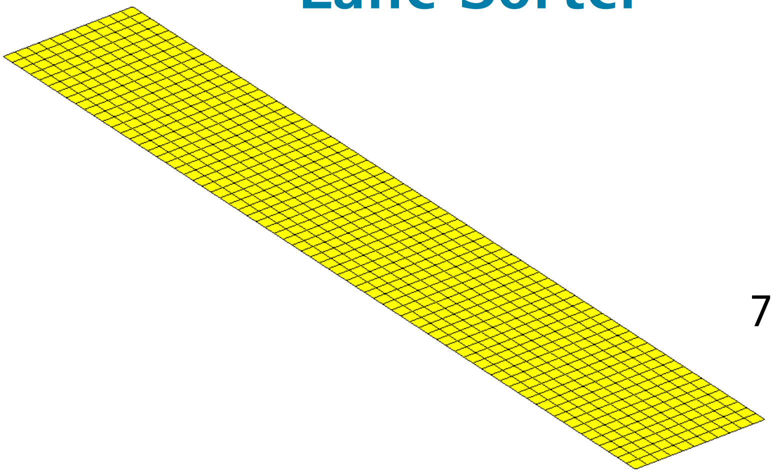


- Matrix approach offers more flexibility on droplet processing and less electrode tracks and allows equal timing
- Parallelization of handling and controlling of droplets offers possibility to verify the theoretically modeled sorting routines
- Electrodes with spline geometry

Realistic Sorter Topologies

- Throughput of a realistic sorter topology was expected to significantly drop compared to first theoretical attempts
- Main reason is that the PBS supply and the removal of end products have to be arranged around the main droplet flows
- First realistic topology named *lane sorter* considers boundary conditions of electrowetting and provides a counterbalance to these bottlenecks
- Second topology named *circulation sorter* is an improvement of the first approach and was inspired by the concepts of distribution network topologies

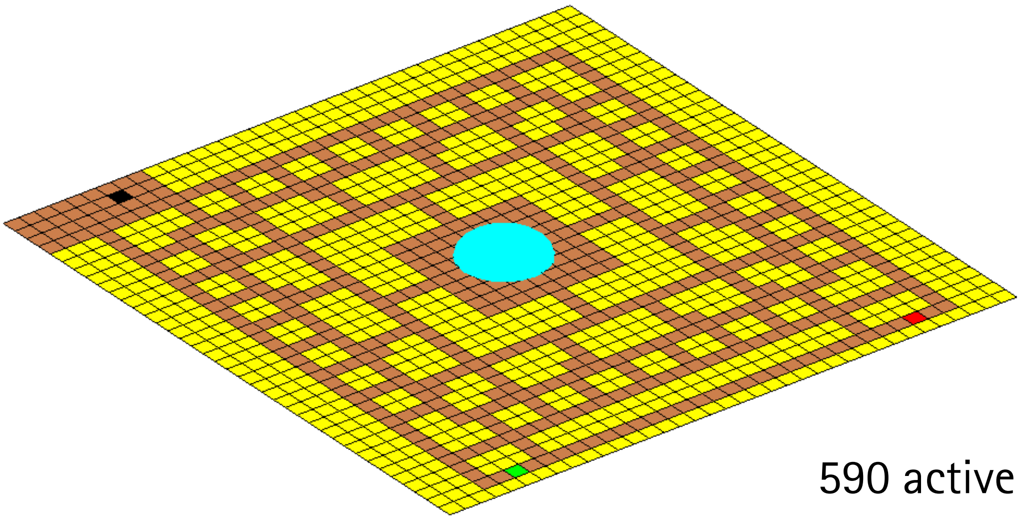
Lane Sorter



700 active electrodes

- Schematic of the scalable lane sorter unit with the cell suspension (black), PBS supply (blue), and end products with labeled cells (green) and residual cells (red)
- Mixing operations reduce overall performance by 33%
- End products are removed laterally in output pathways which yields in the order of 0.2 cells/clock and scales worse with increasing path length

Circulation Sorter



590 active electrodes

- Schematic of the circulation sorter with the suspension reservoir (A) and circulating channel (B), central PBS supply (C), end products (D) and output buffers (E)
- Throughput increases to 0.4 cells/clock

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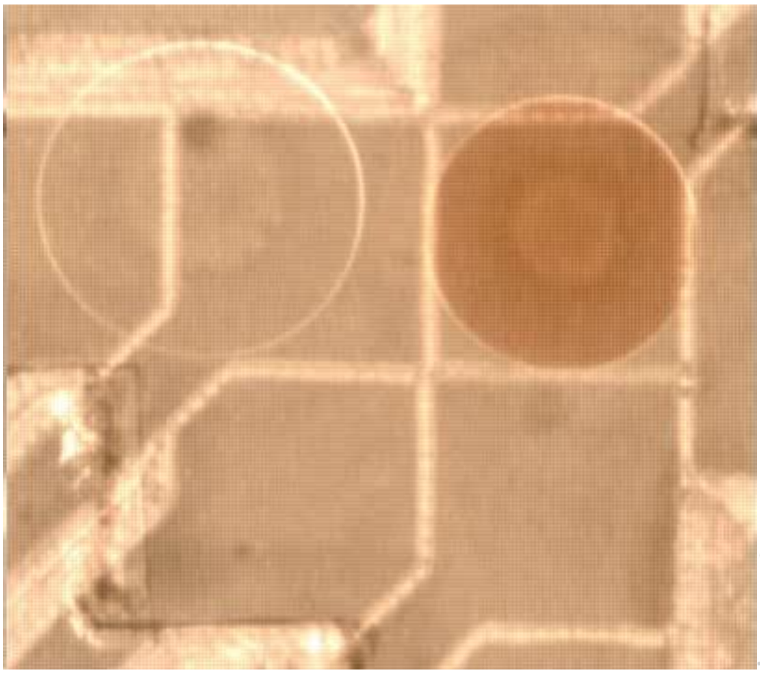
Video Mixing



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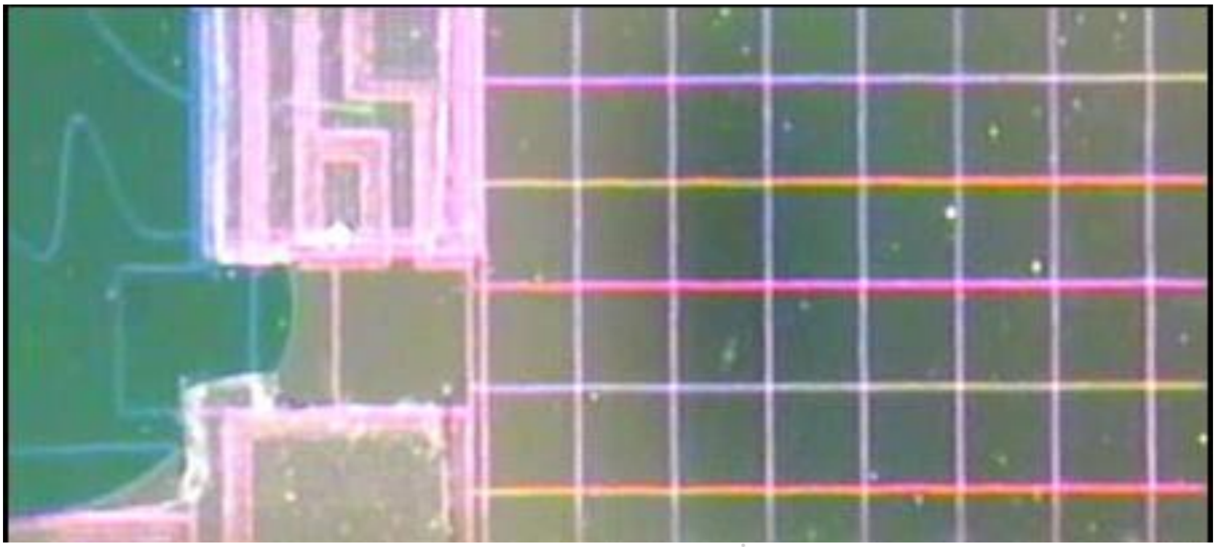
Video Matrix Chip



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Conclusions

- Theoretical considerations have led to promising topologies for general cell sorting process.
- Tests on ewet-chips confirmed modeled process steps and timing required.
- Two opposing goals, high-volume throughput and high sorting efficiency, were identified.
- The maximization of the sorting efficiency was chosen as entry point for the presented design studies .
- It seems that "smart" sorting has to be traded against "fast" sorting, but the focus on smart sorting can be eased by proper spatial scaling (i.e. parallelization).

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Bartels Mikrotechnik GmbH

Emil – Figge - Straße 76 A

44227 Dortmund

Tel.: +49(0)231 / 9742 – 500

Fax.: +49(0)231 / 9742 – 501

www.bartels-mikrotechnik.de

company@bartels-mikrotechnik.de

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