Handheld Sample Preparation for Complex Samples

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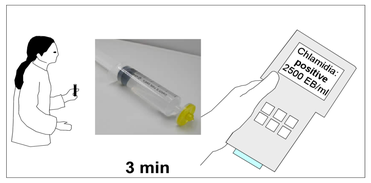
Overview

Micro-scale sample preparation technology is a critical component next generation biochemical assays.

Drastic scale-down of biochemical assays have several advantages over their bench top counterparts that they:

- Can be made into portable systems
- Require smaller sample size
- Have subsequent lower costs
- Provide scalable parallel detection and diagnostic solutions.

We are developing sample preparation technology that can be realized in a handheld device. This technology is capable of manipulating both biological and non-biological materials with micro-scale precision.



Handheld Detector Concept

Techniques: Electro-Osmotic Flow

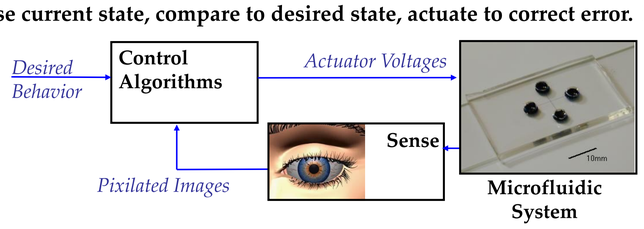
Principle of Operation:

- Particles suspended in liquid
- Applied electric field induces liquid motion
- Liquid pulls particles

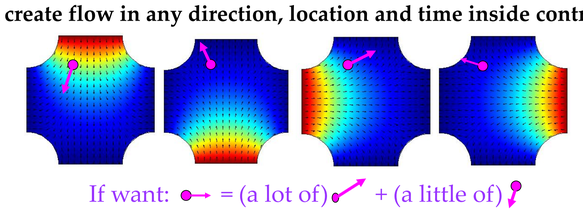
Advantages

- Self correcting. Any errors at current time fixed at next time.
- Feedback quickly forces system to desired behavior.

Sense current state, compare to desired state, actuate to correct error. Repeat.



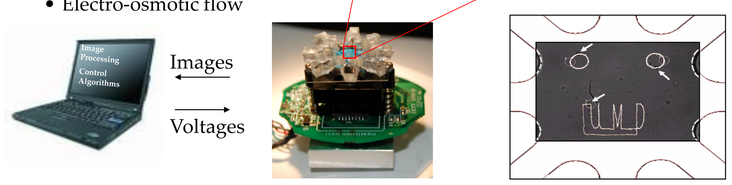
Can create flow in any direction, location and time inside control area.



Experimentally demonstrated steering of up to 4 particles simultaneously.

Handheld prototype

- 8 channels
- 7 degrees of freedom
- Electro-osmotic flow



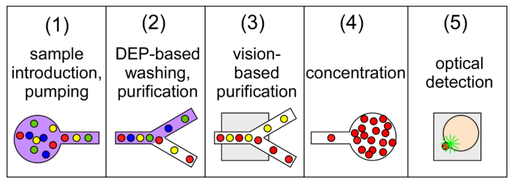
System Design

Principle of Operation

- Cascade various micro-scale stages to take an unknown sample and extract, concentrate, and detect properties of its important analytes

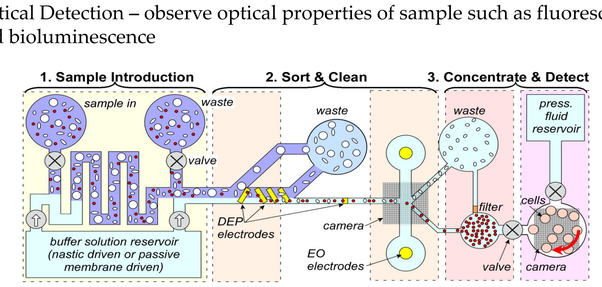
Advantages

- Each stage provides a specific function with minimal footprint
- Can fabricate all components simultaneously



The system requires five core components

- Sample introduction and pumping – performs pre-filtering and moves sample through system
- DEP-based washing and purification – coarse filtering of non-relevant material
- Vision based purification – precision sorting of individual cells
- Sample Concentration – concentrate relevant analyte to increase detection probability
- Optical Detection – observe optical properties of sample such as fluorescence, and bioluminescence



Schematic illustration (not to scale) of microfluidic system for sample cleaning, sorting, concentration, mixing, and detection. Sample preparation proceeds from strong and robust mechanical forces and initial particle extraction on the left to fine-scale control and single particle processing on the right. (Electrode connections to external electronics not shown.)

Techniques: Dielectrophoresis

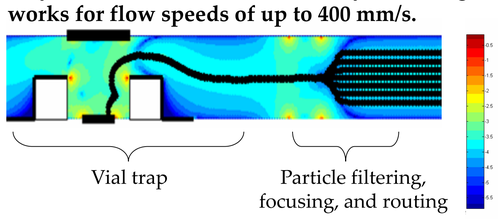
Principle of Operation

- Direction of force depends on dielectric constant relative to fluid.
- Dielectric constant varies with frequency.

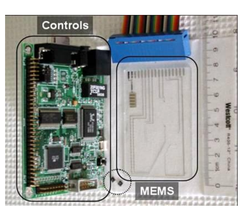
Advantages

- Can apply positive or negative DEP sequentially or simultaneously using multiple control frequencies.
- Parasitic traps are actively cancelled using negative DEP.

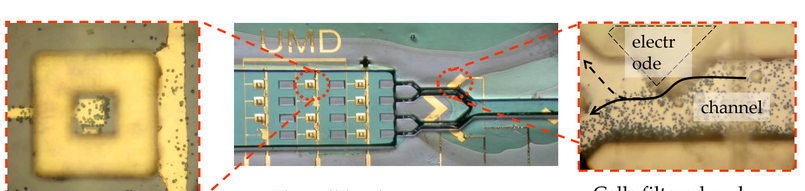
A system to load cells automatically was designed and modeled carefully. It works for flow speeds of up to 400 mm/s.



Vial trap | Particle filtering, focusing, and routing



Handheld prototype



Cells were loaded successfully into vials.

The cell loading system was fabricated and tested.

Cells filtered and routed by DEP electrodes

Techniques: Microscale Optics

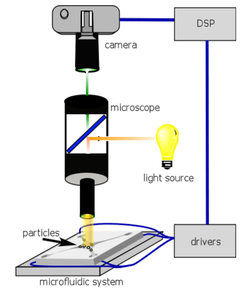
Principle of Operation

- Replace macro-scale optical systems with micro-scale imaging
- Particles coupled directly to surface of image sensor
- Particles either block light or emit light to produce images on camera

Advantages

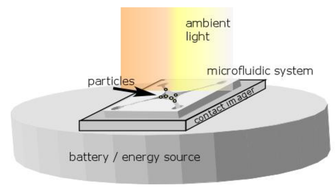
- Increase collection efficiency to ~50%
- No need for large, heavy optical components
- Simple on-chip pre-processing facilitates detection algorithms

Typical Particle Steering System



- System volume ~0.5 m^3, weight ~50 kg

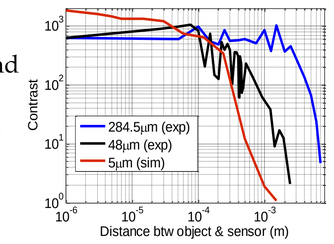
Micro-scale Particle Steering System

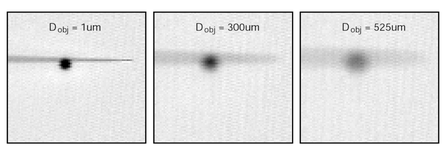


- System volume ~50 cm^3, weight ~300 g

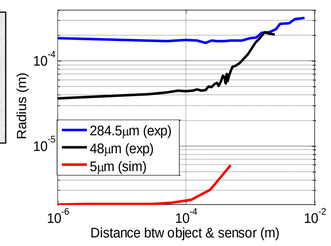
Resolution of contact imaging

- Investigated through simulations and experiments.
- Contrast decreases, radius increases with distance.

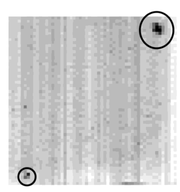




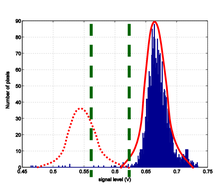
Contact images of 48.5 μm diameter polystyrene bead.



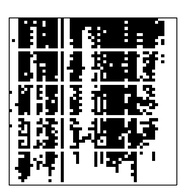
Choosing the correct threshold is critical!



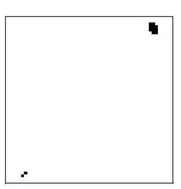
Contact image of cells



2 clusters of pixel intensities



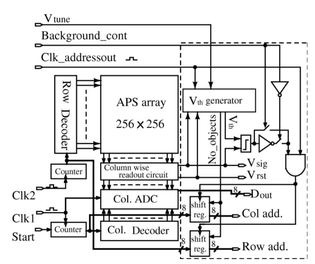
Wrong threshold



Correct threshold

Contact imager / cell detector

- 0.18 µm CMOS technology
- Novel 5 x 5 µm pixel with dark current suppression, high linearity
- 256 × 256 array
- On-chip threshold generation and binarization



System architecture

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