Nano/Microfluidic BioMEMS Research

RLE Group
Micro / Nanofluidic BioMEMS Group

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Overview of group

Nanofluidic BioMEMS group in RLE (Han group) is exploring various ways that the micro/nanofabrication techniques can be used for advanced biomolecule manipulation and separation applications. It is now possible to reliably fabricate nanofluidic gaps and filters that have regular, controllable structures, with near-molecular dimensions (10 -100nm). One can take advantage of these nanofluidic structures for advanced separation and manipulation of various biomolecules and bioparticles, including cell, cellular organelles, DNA, protein, and carbohydrates. The research of Nanofluidic BioMEMS group is currently actively designing, fabricating and testing the new kinds of molecular sieves and filters that can be essential for the next-generation biomolecule assays in the new era of genomics, proteomics and glycomics. At the same time, the subject of molecular stochastic motion and molecular interaction with nanostructure is actively studied, in order to provide firm theoretical and scientific ground for the development of novel nanofluidic molecular filters.

1. Free-Flow Zone Electrophoresis of Peptides and Proteins in PDMS Microchip for Narrow Isoelectric Point (pI) Range Sample Prefractionation Coupled with Mass Spectrometry

Sponsors
NIH R21 EB008177
KIST-Intelligent Microsystems Center of Korea
NIEHS P30-ES002109

Project Staff
Yong-Ak Song

Isoelectric point (pI)-based fractionation is ideally suited for the first-dimensional separation because the pI value of any peptide or protein can be simply estimated from the sequence information. Therefore, the pI-based fractionation techniques can be highly specific to target peptides and proteins. Due to this benefit, there have been previous efforts to integrate isoelectric focusing (IEF) into mass spectrometry (MS)-based proteome analysis processes [1-4]. While the physical coupling between capillary IEF and ESI-MS is straightforward, the buffer systems for IEF separation (carrier ampholytes, a complex mixture of amphoteric small molecules) have low compatibility with electrospray (ESI)-MS interfaces. In view of this current deficit, we have developed an ampholyte-free, two-step cascaded microfluidic sorting technique based on free-flow zone electrophoresis that isolates the molecules of interest from a small sample volume of 100 μL within narrow and freely adjustable pI range (≤ 1 pH units), even below pH 3 and beyond pH 10 [5]. To create a salt bridge for free-flow electrophoresis in PDMS chips, we printed a submicron thick hydrophobic layer on a glass substrate and created an electrical junction gap for free-flow zone electrophoresis. With this sorting device, as shown in Figure 1, we demonstrated binary sorting of peptides and proteins in standard buffer systems, and validated the sorting result with liquid chromatography (LC)/MS. In Figure 2, the sorting result of the acidic peptides < pH 7 is shown exemplifically. Furthermore, we coupled two sorting steps via off-chip titration, and isolated peptides within specific pI ranges from sample mixtures, where the pI range was simply set by the pH values of the buffer solutions. This pI-based binary sorting device, with its simplicity of fabrication, and a sorting resolution of 0.5 pH unit, can potentially be a high-throughput sample fractionation tool for targeted proteomics using LC/MS.

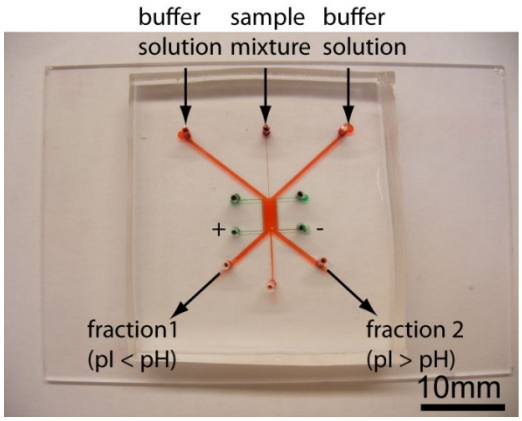

Figure 1: Free-Flow Zone Electrophoresis (FFZE) device in PDMS micro chip format. The sample is injected from the autosampler into the middle inlet. The width can be varied by adjusting the flow rates of the sheath buffer solutions. The separated sample fractions are collected from the three outlet channels.

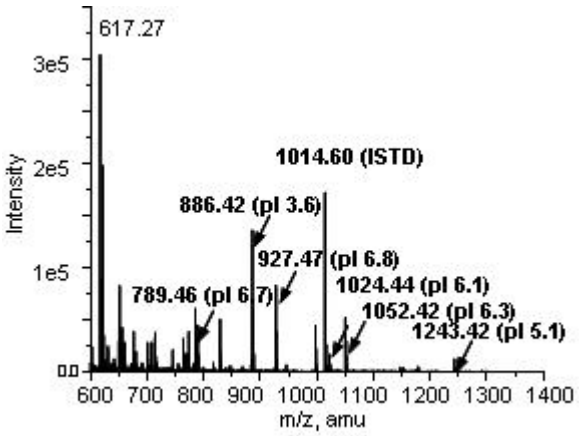

Figure 2: ESI-MS result of a single fractionation of 8 peptides (40 nM) at pH 7.0 with E=279V/cm and 0.5μL/min. From a mixture of 8 acidic and basic peptides, we could successfully fractionate acidic peptides with pI 3.6, 5.1, 6.1, 6.3, 6.7 and 6.8.

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2. Dispersive Transport of Biomolecules in Periodic Energy Landscapes with application to nanofilter Sieving Arrays

Sponsors
Singapore-MIT Alliance II

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Based on continuum transport model and the macrotransport theory, we derived the analytical solutions of asymptotic mobility and dispersivity of charged, isotropic or anisotropic biomolecules over nanofilter array comprising of alternating deep and shallow regions. The key principle involved in this theory is to transform the transient transport of molecules in a repeated pore/nanofilter structure into the steady state description of molecular transport in a single unit (c.f. Fig. 1). This formulation provides accurate asymptotic solutions for mobility and dispersivity, with significantly reduced numerical computations. More importantly, it enables us to derive explicit analytical solutions for the transport parameters without the need for solving partial differential equations numerically. Even though the explicit formulas are derived based on simplified energy landscape, the resulted mobility and dispersivity are about only ~10% higher than the *expected* results from 2D numerical simulation in the experiment relevant field strengths (c.f. Fig. 2). These models and solutions describe the effects of various control parameters clearly and provide important insights into the physical mechanism. This simplifies the design and optimization processes and reduces the cost significantly, because no extensive numerical simulation is required.

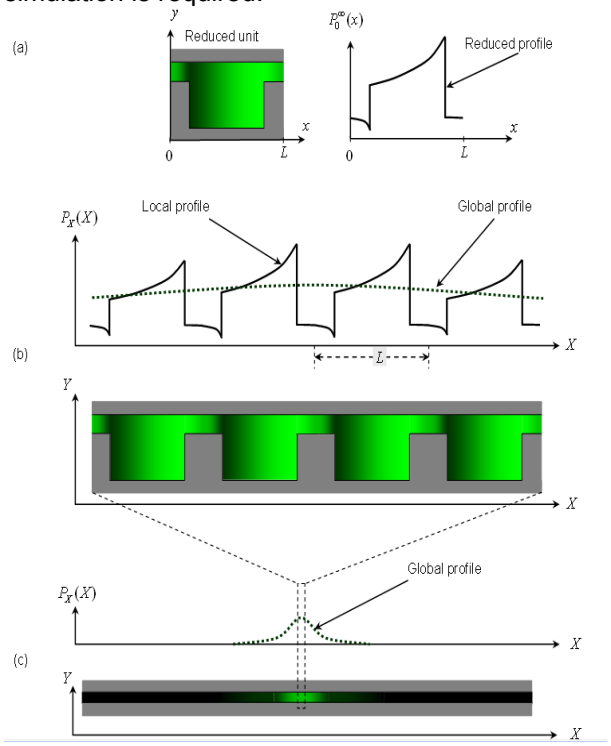

Figure 1. Global scale and local scale of the nanofilter array in the macrotransport model. (a) Geometry of the unit cell and the asymptotic reduced probability profile. (b) Local periodic units and transient probability profile. (c) Global structure and averaged global probability profile.

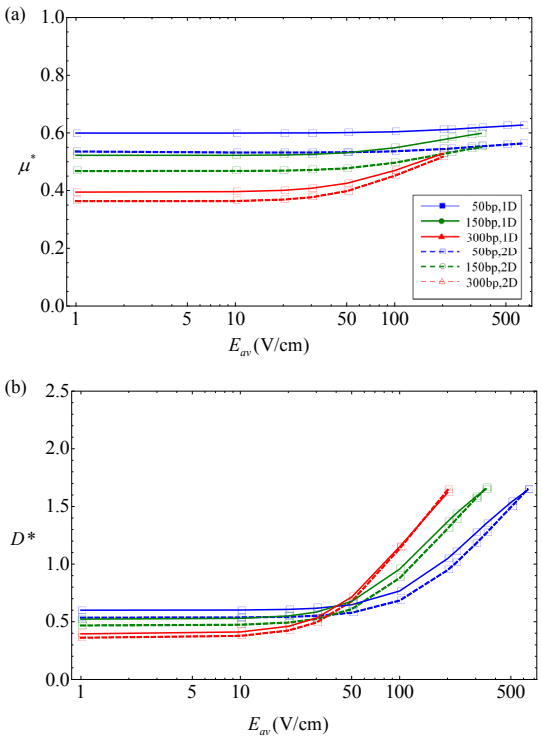

Figure 2. Comparison of relative mobility (a) and relative diffusivity (b) of 50bp, 150bp and 300bp DNA molecules calculated from 1D and 2D models. It is found that the explicit formulas from 1D model overestimate the transport parameters by ~10%.

3. Direct Seawater Desalination using Ion Concentration Polarization

Sponsors
National Science Foundation
SMART Innovation Center

Project Staff
Dr. Sung Jae Kim
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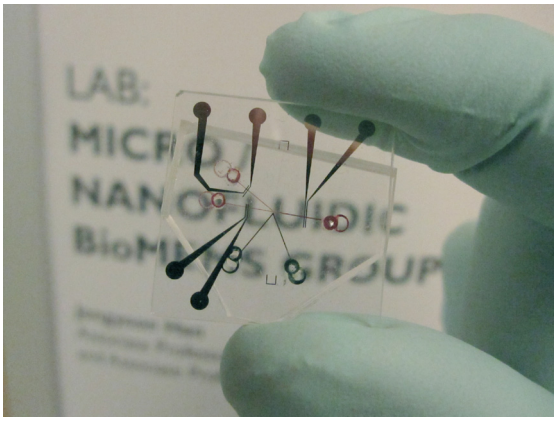
Katherine Zhu
Bumjoo Kim (POSTECH)

Due to an explosive growth of population along with industrial/agricultural activities, the shortage of fresh water is one of the acute challenges that the world is facing now. Thus, converting abundant seawater into fresh water can provide substantial solution to this worldwide water crisis. Much research for energy efficient desalination has been done over the last few decades, for example, on reverse osmosis, electro-dialysis and thermal distillation. However, current desalination methods requires high power consumption and large scale infrastructures, which do not make them as the appropriate choice for resource-limited settings such as underdeveloped countries or disaster-stricken area.

Professor Jongyoon Han's research group recently published a ground-breaking publication (Kim et al. Nature Nanotech, 2010), which elucidates a novel process to convert seawater to fresh water by utilizing an electrokinetic phenomenon called ion concentration polarization. A continuous stream of seawater is divided into desalted and concentrated stream, which then is flown into different microchannels. The key distinct feature of this scheme is that both salts and larger particles (cells, viruses, and microorganisms) are pushed away from the membrane, in a continuous, steady-state flow operation, significantly reducing the possibility of membrane fouling and salt accumulation that plagues the reverse osmosis and other membrane filtration methods. Using the simple microfluidic unit device, we have demonstrated a continuous desalination of seawater (~99% salt rejection at 50+% recovery rates) at the power consumption less than 3.5Wh/L, which is comparable to the state of the art reverse osmosis desalination systems. Currently, we are pursuing to build a small-portable scale desalination/purification system which can supply enough amount of potable water to a family, with the possibility of battery-powered operation rather than competing with larger desalination plant. Eventually, we envision this technology as a high-efficiency alternative for current seawater desalination methods, when the necessary engineering and optimization of this process is accomplished.



A demonstrated unit microfluidic device for seawater desalination. Courtesy of Dr. Sung Jae Kim, RLE / MIT.

4. Margination-based malaria-infected Red Blood Cell sorting

Sponsors
SMART center

Project Staff
Han Wei Hou (National University of Singapore / SMART center)
Dr. Ali Bhagat (SMART center, Singapore)
Pan Mao
Prof. C. T. Lim (National University of Singapore)

In blood vessels with luminal diameter less than 300μm, red blood cells (RBCs) which are smaller in size and more deformable than leukocytes, migrate to the axial centre of the vessel due to flow velocity gradient within the vessels. This phenomenon displaces the leukocytes to the vessel wall and is aptly termed as margination. Here, we demonstrate using microfluidics that stiffer malaria infected RBCs (*i*RBCs) behave similar to leukocytes and undergo margination towards the sidewalls. This provides better understanding of the hemodynamic effects of *i*RBCs in microcirculation and its contribution to pathophysiological outcome relating to cytoadherence. In this work, cell margination is mimicked for the separation of *i*RBCs from whole blood based on their reduced deformability. The malaria infected sample was tested in a simple microfluidic device fabricated in polydimethylsiloxane. In these microchannels, cell margination was directed along the channel width with the *i*RBCs aligning near each sidewall and then subsequently removed using a 3-outlet system, achieving separation. Tests were conducted using ring stage and late trophozoite/schizont stage *i*RBCs. Device performance was quantified by analyzing the distribution of these *i*RBCs across the microchannel width at the outlet and also conducting flow cytometry (FACS) analysis. Results indicate recovery of ~75% for early stage *i*RBCs and >90% for late stage *i*RBCs at the side outlets. The simple and passive system operation makes this technique ideal for on-site *i*RBCs enrichment in resource-limited settings, and can be applied to other blood cell diseases, *e.g.* sickle cell anemia and leukemia, characterized by changes in cell stiffness.

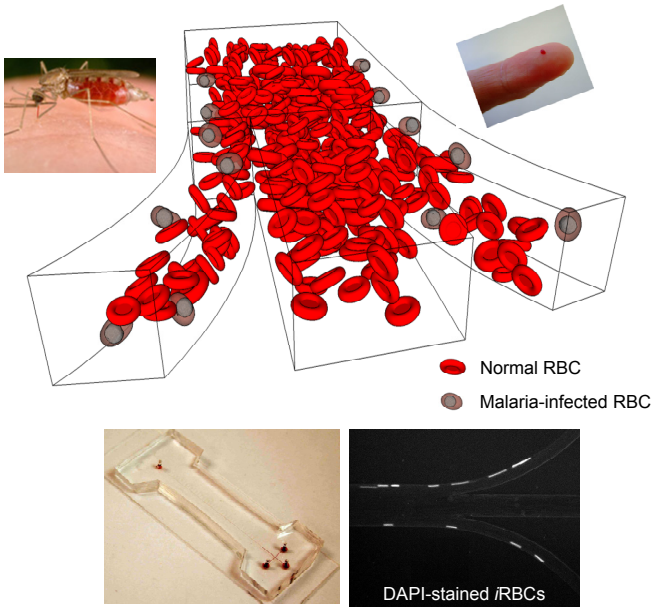


Figure adapted from Hou et al. Lab Chip (2010)

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