tions are prone to exaggerated motion when non-adjacent beads approach each other. The bead-rod model attempts to account for the interaction by preventing the coarse-grained model of the chain from crossing itself. This approach can be relatively complex and a universally agreed upon approach has not been established.

Wall Interaction

Typically a wall is modeled with an image potential. In this case, a virtual particle that is located at the mirror location to the real particle provides an interaction potential. As such there is often an artificial buffer that prevents the bead from contacting the wall and migration away from surfaces is possible. Even though these interaction potentials have a short range, they can be strong to prevent beads from penetrating walls. As a result, time stepping becomes crucial, and too large of a time step can result in physically unrealistic motion. New methods to treat this artifact are needed to provide transport in confined channels.

DNA Hybridization

In the case of DNA transport, the researcher is often interested in hybridization, which is a reaction that changes the characteristics of the chain or causes additional forces. Motion in the presence of interaction particles is complex and has not received much attention.

Cross References

- ▶ AC Electro-Osmotic Flow
- ▶ Brownian Motion and Diffusion
- ▶ Dielectrophoretic Motion of Particles and Cells
- ▶ Dissipative Particle Dynamics
- ▶ Electrokinetic Flow and Ion Transport in Nanochannels
- ▶ Electroosmotic Flow (DC)
- ▶ Multiscale Modeling and Numerical Simulations
- ▶ Molecular Dynamics Simulation Method
- ▶ Polymer Synthesis Within Microfluidic Reactor
- ▶ Van der Waals Interaction Forces

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Single Cell Analysis in Microfluidic Devices

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Synonyms

Analysis of individual cell contents

Definition

▶ Chemical cytometry is a class of highly sensitive analytical techniques for the analysis of the chemical contents of single cells. These techniques enable the detection and identification of cell constituents including oligonucleotides, small molecules, and proteins, as well as providing means to monitor the effects of biochemical and enzymatic reactions.

▶ Capillary electrophoresis is an analytical technique used to separate chemicals in solution as a function of their charge and size. Samples are injected into a capillary, a high electric field is applied, and the analytes migrate to the end of the column, where they are detected.

Overview

The cell is a complex biochemical factory, capable of proliferation, differentiation and communication. The cell also interacts with its microenvironment, comprised of other cells, tissue matrix and interstitial vascular, lymphatic and non-biological compartments. Yet most of what is known about the correlation between behavior, function and genotype of biological cells comes from *average* measurements of cell populations. While useful, these studies are unfortunately incapable of assessing the response and interaction of individual cells within a heterogeneous population. As an illustration, a recent study [1] of hormone-induced maturation of unfertilized eggs (oocytes) as a function of enzyme activation was evaluated both based on populations and individual cells. The population data suggested a *graded* relationship between

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the hormone (progesterone) concentration and enzyme activation while the single cell data revealed a sharp *all-or-nothing* switch. The single cell analysis approach can in fact provide not only complementary information but rather reveal the actual functional interaction of biomolecules thus assisting in understanding complex biological systems on the cellular and tissue structural basis. This kind of biological insight is required to understand complex systems such as tissues, organs and even complete organisms. While it is obvious that this type of work is useful, single cell studies are much more complicated and time-consuming than their population counterparts; in fact, single cell analyses push the boundaries of conventional techniques.

Several single cell analysis techniques have been developed, which may be classified in terms of information content (# of elements capable of being studied simultaneously) and throughput (# of cells studied in a given time) – this is illustrated in Fig. 1. The simplest and most widely used forms of single cell analysis are fluorescence microscopy and flow cytometry. In microscopy, fluorescence from small molecule reporters, immunochemical labels, or transfected fluorescent proteins within cells is observed with subcellular localization. While this technique enables the measurement of time-dependent changes in response to stimuli of individual cells as well as cell-cell interaction studies, it is an inherently low-throughput method if used with high magnification. Conversely, flow cytometry is a high-throughput technique that can be used to analyze up to several tens of thousands of cells per second but is limited in the type of assays for which it can be used and does not provide subcellular resolution. Multiple wavelength analysis schemes have been developed, but the number of parameters which can be measured simultaneously is intrinsically limited by the finite spectral bandwidth of the detectors and the increasing complexity of using multiple fluorophores, excitation sources, and/or detectors. These two techniques therefore are classified in the region of low information content space in Fig. 1.

In order to achieve a more comprehensive analysis of individual cells, methods that incorporate chemical separations have been developed to increase the number of parameters capable of being studied simultaneously. These techniques, termed *chemical cytometry* by Dovichi and coworkers [2] are used to detect and identify various components of single cells such as oligonucleotides, small molecules and proteins, as well as to monitor enzyme activity. Capillary electrophoresis (CE), laser-induced fluorescence (LIF), and electrochemistry are the tools which are used in chemical cytometry; this chapter deals with capillary electrophoresis implemented in microfluidic devices.
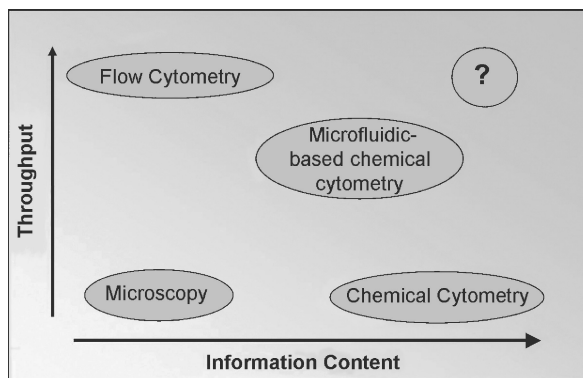
Single Cell Analysis in Microfluidic Devices, Figure 1   Chart comparing single cell bioanalytical techniques in terms of information content and throughput

CE-based chemical cytometry can be used to evaluate many cell constituents simultaneously, and is thus, as shown in Fig. 1, categorized as a high information content technique. This comes at a cost, however, as the cell injection schemes and use of a single capillary makes the technique extremely low-throughput. Ideally, the contents of hundreds of cells could be individually analyzed for statistical evaluation of the heterogeneity of a population; in practice, however, the arduous and time-consuming nature of chemical cytometry typically limits it to a few cells (i. e., < 10) per analysis.

In recent years, microfluidics has become a popular technology for applications in the life sciences. The continued development of new microfabrication techniques has permitted the integration and scaling down of several bioanalytical procedures into a single device, from which emerged the concept of Lab-on-a-Chip or micro total analysis system (µTAS). Microfluidic devices have several advantages over conventional bioanalytical techniques: low reagent and power consumption, low cost, and the potential for mass production and massively parallel scale analysis. As illustrated in Fig. 1, the application of microfluidics to chemical cytometry may result in a solution to the low-throughput problem of capillary-based chemical cytometry techniques, forming a new class of methods with high-throughput and information content. Several good reviews have been recently published covering the potential of microfluidics for applications involving cells [3, 4]. Microfluidics has been applied to microscopy, flow cytometry, and chemical cytometry, among others. As microscopy and flow cytometry are discussed in detail in other chapters in the *Encylopedia* (▶ flow cytometer lab-on-chip devices, ▶ detection using confocal microscopy), we focus here on chemical cytometry. In what follows, we discuss the state-of-the-field and

challenges remaining to be solved in the areas of fabrication, cell selection/transportation, cell lysis/treatment, and analysis, from the standpoint of microfluidic method development for high-throughput chemical cytometry.

Basic Methodology

Fabrication Considerations

There are many well-established microfabrication techniques which can be used to construct microfluidic devices (▶ microfabrication techniques). Each has strengths and weaknesses, but the choice of fabrication technique ultimately depends on cost, availability of the facility, and most importantly, on compatibility with the desired application. This is especially important for chemical cytometry, where the fabrication process must be versatile enough to form devices capable of implementing the many necessary functions. Key considerations for fabrication of chemical cytometry include material, integration, and macro-to-micro interface.

Material

The materials used for the fabrication of most microfluidic chips include glass, silicon, quartz, and plastics (▶ materials used in microfluidic devices) In addition to cost and optical, electrical and physical properties, careful consideration must be given to the surface chemistry of the material (▶ methods for surface modifications). In fact, surface chemistry plays a major role in chemical cytometry, as protein adsorption to the channel walls can degrade the separation performance and make the electroosmotic flow unreproducible.

Integration of Multiple Components

The functionality and versatility of microfluidic devices for chemical cytometry requires the combination of several cell manipulation, processing, and analysis steps. These techniques, discussed in detail in the next section, rely on device components such as microstructures, optical windows, electrodes, embedded waveguides, and valves and pumps; each of which must be miniaturized and integrated on a single microfluidic platform (please refer to the following chapters ▶ fabrication of 3D microfluidic structures, ▶ on-chip waveguide, ▶ pneumatic valves, ▶ thermomechanical valves, ▶ thermopneumatic valves). Integrating multiple components on a single device dramatically increases the complexity of the final product and introduces compatibility problems in the various integrated functions. For example, surfaces designed to promote or prevent cell adhesion (for cell manipulation) are often different than surfaces best suited for electrophoretic

separations. These engineering challenges are a bottleneck in the development of multifunctional microfluidic devices and must be addressed for the development of high-throughput chemical cytometry.

Macro-to-Micro Interface

A key concern for all microfluidic devices is the macro-to-micro interface. The complexity of the interface depends on the number of integrated functions (see ▶ packaging (including wire bonding)).

Cell Manipulation and Transportation

One of the most critical steps in single cell analysis is selection of predetermined individual cells and transportation through the device (▶ techniques for manipulating cells, ▶ microfluidic sample manipulation). The manipulation and transport techniques used for chemical cytometry should be multiplexed, have the potential for automation, and, depending on the assay, should have minimal biological or chemical impact on the cell(s) to be transported. Techniques fitting this description include cell sorting and integrated flow cytometry (▶ cell sorting, optophoresis for cell sorting, ▶ flow cytometer lab-on-chip devices). Several micromanipulation techniques based on mechanical, electrical and optical means have been developed for cell-based assays in microfluidic devices.

Mechanical Manipulation

While micromanipulators and micropipettes are routinely used for in vitro fertilization studies, they are bulky, suffer from low throughput and are not amenable to integration with a sealed microfluidic device. Other mechanical manipulation techniques include microfilters, dams, and *sandbag* structures. We note that these techniques are often used to capture, dock or sort many cells simultaneously without specificity and thus are limited in their use for single cell analysis where selecting a particular cell is a key goal.

Electrical Manipulation

The electric charge or polarity of cells (and cell contents) may also be used for manipulation and transportation within microfluidic devices. In contrast to mechanical methods, the use of electric field based approaches such as electrokinetics and dielectrophoresis are well-suited for microfluidics as they permit flexibility, controllability, automation and high-throughput capability. We note, however, that these kinds of techniques can produce undesired biological stress such as protein migration and clustering within the cells and in high fields, cells may even lyse

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(i. e., die). For more information, please refer to the following *Encyclopedia* chapters: ► dielectrophoretic motions of particles and cells, ► electrokinetic motion of cells and non-conductive particles, ► AC dielectrophoresis Lab-on-a-Chip devices.

Optical Manipulation

Optical micromanipulation techniques use lasers to apply piconewton forces on micron sized particles, and have been demonstrated to be useful for cell transportation in microchannels. One of the most popular optical techniques is ► optical *trapping* (or optical/laser tweezers), which is implemented by focusing a laser to a diffraction-limited spot by a high numerical aperture (N.A.) microscope objective. Although optical trapping can be used to select particular cells accurately, its slow translational speeds ($20-30\,\mu$m/sec) [5] makes it a low-throughput cell manipulation technique. We note that some have used diffractive optical elements (DOEs) and spatial light modulators to create multiple *optical traps* simultaneously, thus improving throughput [6]. These techniques are described further in ► optical tweezers for manipulating cells and particles. Another alternative in optical manipulation is laser-guided direct writing, in which a weakly collimated or converging beam pushes cells to desired locations [7]. This technique has been used to transport cells at $88\,\mu$m/s over several millimeters. A similar transportation technique was developed using evanescent waves from integrated waveguides to manipulate micron size particles [8]. While these two techniques suffer from lack of cell selectivity, they could potentially be automated to increase throughput in chemical cytometry by strategically positioning the integrated waveguides within the microfluidic device.

Cell Lysis/Treatment

In conventional population cell-based assays, sample preparation involves several steps, including lysis, filtration of non-solubilized cellular material, labeling of the analytes of interest, and sample purification. However, to prevent dilution of the extremely small samples in single cell analysis, filtration and purification are not typically integrated in chemical cytometry methods. This section briefly describes the various cell lysis techniques which have been implemented in microfluidics; for more detail, please see ► on-chip cell lysis.

In CE-based chemical cytometry, the quality of the information is ultimately determined by the manner in which the cells are lysed and their contents injected into the capillary. The technique employed to perform this task must be carefully designed to enable high quality, reproducible electrophoretic separations. Dilution of the contents of the cell prior to application of the electric field must be reduced to maximize sensitivity and resolution of the separated analytes. Lysis should occur in a manner such that the biochemical contents of the cell are not altered, for example, by the activity of proteases that are usually kept partitioned away from free cellular proteins. The technique must also address capillary clogging issues which result from the presence of insoluble cell debris. Finally, the lysis technique must be able to function in parallel for high-throughput applications. There are three categories of cell lysis techniques: electrical, mechanical and chemical lysis.

Electrical Lysis

When a large electric field is applied across a cell, the transmembrane potential is disrupted and pores are formed on the surface of the membrane. This phenomenon is called ► electroporation and is often used for gene transfection. As conventionally implemented, the process is reversible, and when the electric field is terminated, the pores close. The phenomenon can also be used to cause permanent disruption of the membrane, effectively lysing the cell. There have been several reports on the use of electrical lysis techniques in microfluidic devices [9–11]. Of particular interest, fast lysis of individual cells (~ 33 ms) by electrical pulses for chemical cytometry was demonstrated in a microfluidic platform [12]. These extremely rapid lysis methods which minimize unwanted effects of slow lysis (that may bias the results) make these techniques favorable for protein analysis when compared to chemical lysis techniques. One drawback of electrical lysis is that much of the cell membrane, subcellular structures and the nucleus may remain intact and thus can clog the channe or adhere to the surface, affecting the separation and limiting the capacity for re-use.

Mechanical Lysis

Typical lysis techniques based on mechanical forces such as sonication and bead milling are not amenable for integration in a microfluidic device; however, in recent work, cells were lysed in microchannels by mechanical shearing on nanostructured filter-like *nano-knives* [13]. This method had the additional advantage of aiding subsequent analysis steps by filtering out cellular debris thus preventing clogging and sample fouling.

Chemical Lysis

The most common macro-scale cell lysis methods make use of chemical agents; as a result, several research groups have used similar techniques to lyse cells in microfluidic

devices [14–16]. While detergents such as sodium dode-cyl sulfate (SDS) permit a greater number of proteins to be analyzed due to the capacity to solubilize membrane proteins and lipids, chemical lysis reaction times are relatively slow (tens of seconds). Therefore, this technique may not be ideal for applications in which desired biological events take place on time scales of seconds or less (e. g., metabolite concentrations can change by a factor of 10 within 1 s [17]) or when diffusion of the cellular content within the microfluidic chip structure can not be suppressed.

Analysis

While an array of analytical techniques has been developed to study various aspects of cells (please see ► cell assays in microfluidics), this chapter is focused on chemical cytometry. As mentioned above, chemical cytometry refers to methods in which intracellular constituents of a single cell are analyzed by means of a chemical separation. Such methods typically employ capillary electrophoresis for separations, combined with laser induced fluorescence (LIF) or amperometry for detection. We refer readers to other chapters for detailed descriptions of other methods used to evaluate contents of cells (► patch-clamp measurements on-chip, ► mass spectrometry on chip device).

In capillary-based chemical cytometry, a cell is injected into a capillary, where it is lysed, and then its contents are separated by electrophoresis. The separating contents are detected at or near the end of the capillary, as the analytes migrate past the detection zone. Microfluidic devices are well-suited to replace capillaries for chemical cytometry. The channel dimensions (5 – 100 µm) and planar geometry allow for very efficient dissipation of Joule heat produced from large electric field gradients. The capacity to apply high fields (e. g., 500 – 1000 V/cm) dramatically reduces separation time and minimizes band diffusion. Most importantly, the small channel dimensions can handle injection volumes ranging from nanoliters to hundreds of femtoliters [18], and thus results in minimal dilution of sample.

The level of expression of protein species within a single cell ranges between several millions to under 10 copies, requiring that extremely sensitive detection techniques be employed. LIF is particularly well suited for this task as it is capable of achieving mass concentration detection limits of a few tens of molecules and even single-molecule detection [19]. Amperometry has also been used frequently due to its high sensitivity. A more detailed look at these two techniques can be found elsewhere (► fluorescence measurements, ► amperometric techniques).

Key Research Findings

Over the past few years, several groups have attempted to integrate all of the critical processes for chemical cytometry on a single mirofluidic plattform. Various combinations of cell manipulation, cell lysis, and analysis strategies were used to obtain high content information with the goal of maintaining analysis in a high-throughput format. Some methods were optimized for analysis of small molecules and proteins, while others were developed for genetic assays, evaluating DNA or RNA content.

Protein or Small Molecule Analysis

Fang and coworkers [9] developed a glass microfluidic chemical cytometry device with a simple cross-shaped channel design. Derivatized glutathione (GSH) in single human erythrocyte cells was separated and detected by LIF. Cells were transported from the reservoir to the T-junction by hydrodynamic flow, which was controlled by adjusting the amount of liquid in the four reservoirs; fine positioning was performed by applying a series of voltages to *dock* the cell. Once positioned, each cell was electrokinetically lysed. This technique yielded a throughput of approximately 15 cells/h.

Hellmich et al. [20] designed a PDMS device comprising a cross-junction integrated with other micro-scale features as shown in Fig. 2a. GFP-transfected insect cells were selected and transported to the intersection using optical tweezers. After positioning, the cells were lysed with SDS; the microstructures acted as a physical cell trap, preventing the cell from moving away during the process. After each cell was lysed, fluorescently labeled contents (amino acids and proteins) were separated by electrophoresis and detected with LIF.

McClain et al. [12] also developed a microfluidic device that integrated cell handling, lysis and electrophoresis, as shown in Fig. 2b. The device was evaluated with T-cells loaded with fluorogenic dyes which were separated and detected by LIF. Cell transport and lysis were accomplished using electric fields. In order to reduce Joule heating, lysis was effected by superimposing AC fields on the DC fields used for separations. This technique enabled separation to be maintained throughout the process; lysis was completed within 33 ms and a throughput of 7 – 12 cells/min was achieved with a separation efficiency ranging from 2300 to 4000 theretical plates.

As an alternative to using AC fields, to prevent excessive Joule heating, Wang et al. [21] designed a microfluidic device with channels having variable cross-sections which modulated the local electric field strengths. Chinese hamster ovary cells labeled with calcein AM were used to

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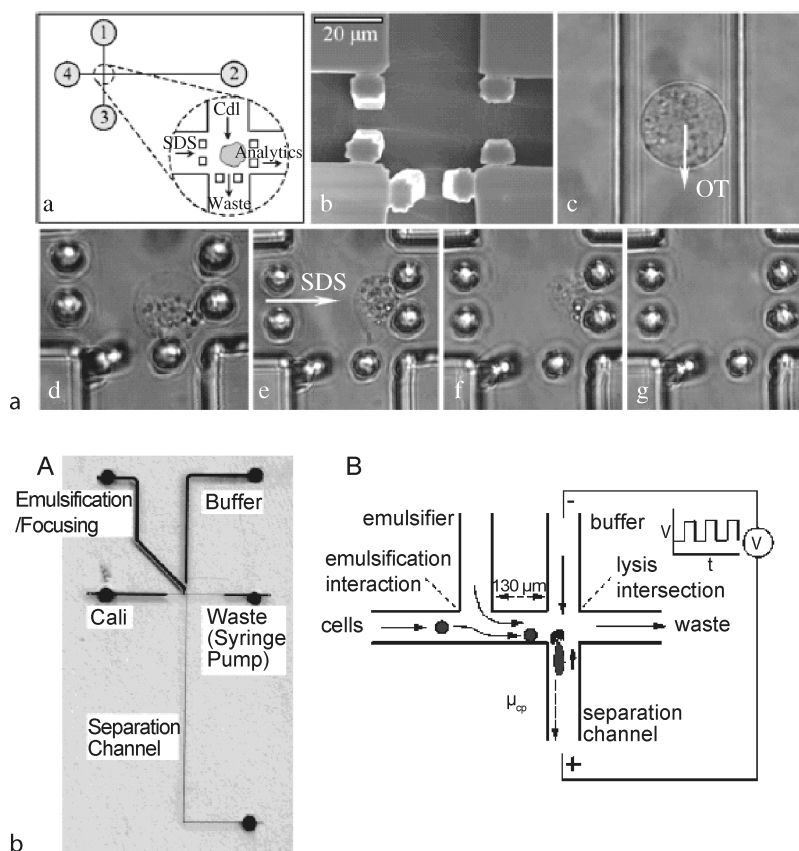
Single Cell Analysis in Microfluidic Devices, Figure 2   (**a**) PDMS single-cell microfluidic device with T-junction and integrated cell trap, formed from micron-sized posts. The cell is transported with optical tweezers (OT) to the intersection, followed by the delivery of the surfactant, SDS, to lyse the cell. (Image reproduced from [20].) (**b**) Design for high-throughput chemical cytometry; this method uses a combination of AC and DC electric fields for cell lysis and electrophoresis. (Image reproduced from [12])

test the device. The cells were driven to the T-junction by hydrodynamic flow generated by a syringe pump. Once at the junction, the cells were lysed and the contents were separated by electrophoresis and detected.

To increase throughput and eliminate sample cross-contamination, which is common when analyzing cells sequentially, Munce et al. [22] developed a microfluidic device with four parallel CE channels. Calcein-labeled acute myloid leukemia cells were selected and transported with optical tweezers to injector structures at the entrance of each channel, as shown in Fig. 3a. Once loaded, the cells were lysed by the combined action of an applied electric field and the reduction in channel cross-section (Fig. 3b). The injector design also enabled stepwise lysis of the cell, shown in Fig. 3c, where only the cyctoplasmic material (containing calcein AM in green) was injected into the capillary while the nucleus (stained blue with Hoechst 33342) remained in the injector structure. This selective lysis is especially useful to separate the cytoplasm from the nucleus and finally the membrane par-

ticularly if protein signalling is the focus of the application. The injector structures also prevented extracellular debris from entering the channels. Once loaded in the capillary, the analytes were separated and detected with LIF. The throughput was estimated to be 24 cells/h; however, this could be increased with additional separation channels.

Wu et al. [23] designed a PDMS microfluidic device for chemical cytometry, consisting of integrated valves which formed a reaction chamber and a picopipette for reagent delivery. The system, depicted in Fig. 4a, allows for individual cells to first be isolated in a closed chamber, and then be combined with an aliquot of lysis and fluoresecent derivatization reagents, delivered by the picopipette. After lysis and derivatization, the valves are opened and voltage is applied to separate the derivatized amino acids. Figure 4b shows an electropherogram collected from a single Jurkat T cell compared to one generated from a population of cells with off-column lysis and derivatization. With the pneumatic valves, 70-picoliter reaction chamber, and
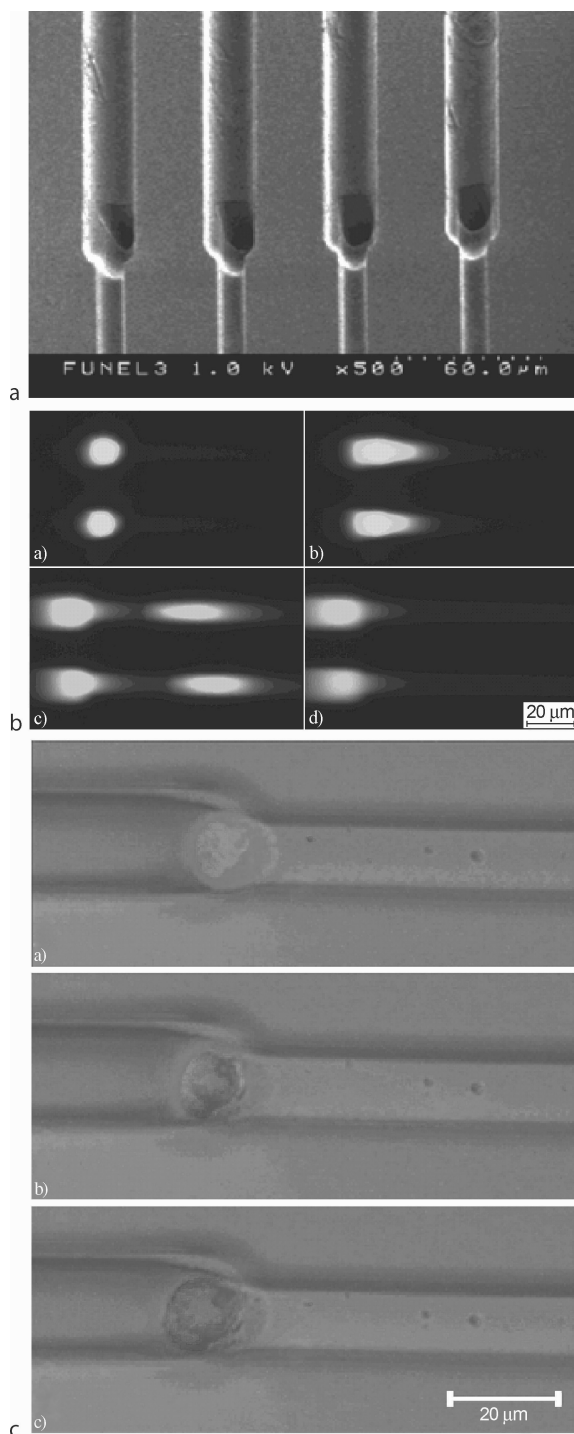
Single Cell Analysis in Microfluidic Devices, Figure 3 (**a**) Four parallel laser-etched injector structures in PMMA. (**b**) Sequence of fluorescent images of two calcein-labeled AML cells being lysed and injected into 2 separation channels. (**c**) Stepwise lysis of an AML cell. The cytoplasmic material (labeled in green) is loaded into the electrophoresis channel while the nucleus (labeled in blue) remains in the injector structure. (Images reproduced from [22])

picopipette, this device simultaneously addresses the problems of fluid control and reagent delivery without affecting sample dilution. This system could also be implemented in parallel to increase throughput.

As an alternative to LIF, Xia et al. [24] used amperometry to detect the contents of single wheat callus cells. In this work, cells were transported electrokinetically to a double T-junction, and docked, after which they were lysed by a DC electric field. Ascorbic acid and other analytes were separated by electrophoresis and detected by means of an amperometric detector.
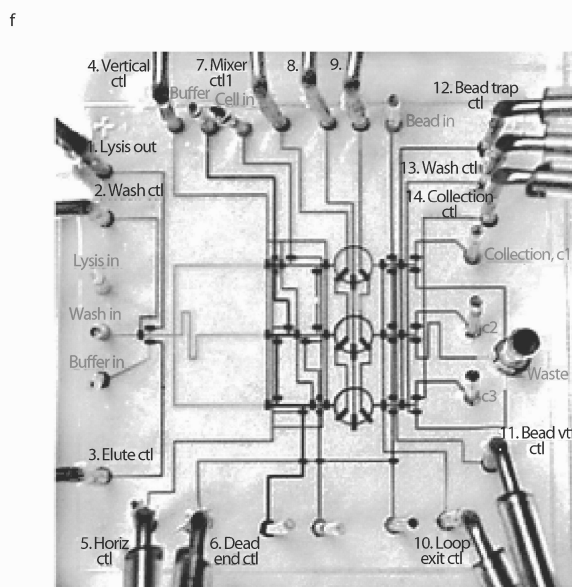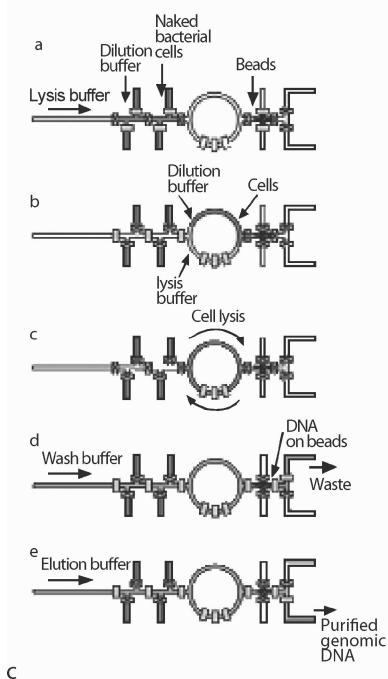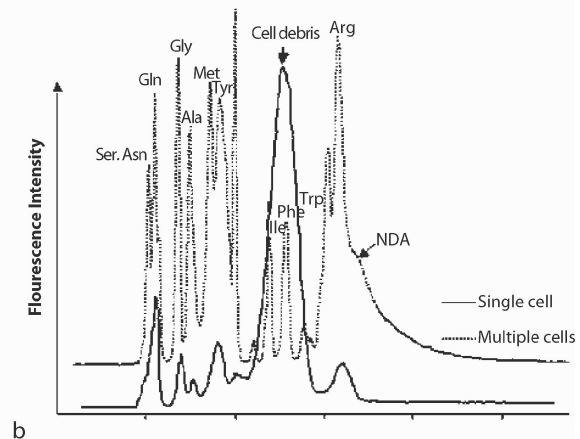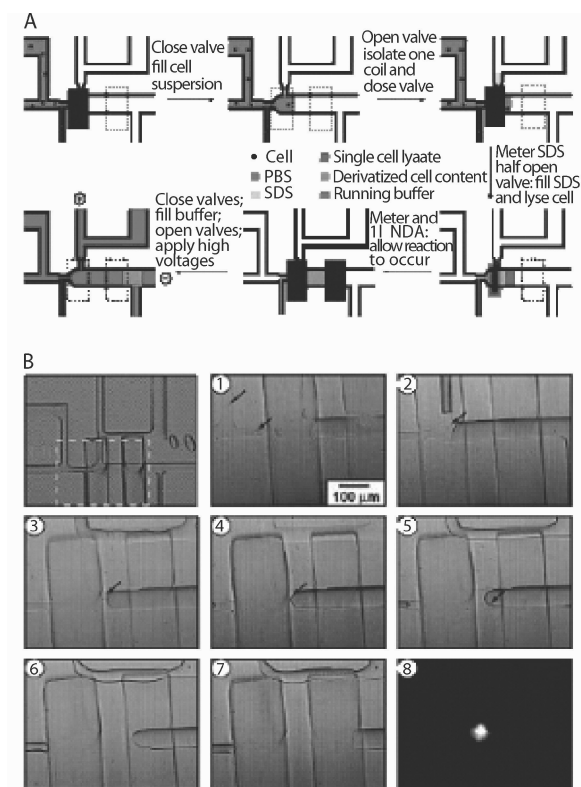
DNA Analysis

A study of doxorubicin-induced apoptosis (programmed cell death) in individual cardiomyoctes was performed using a microfluidic device created by Horky and coworkers [25]. Apoptotic DNA fragments from individual cells were electrophoretically separated and detected by LIF. The device consisted of a simple cross channel design; cells were injected into the device and transported by pressure-driven flow by application of a vacuum. Cell lysis was achieved by activating an electric field across the T-junction, which was filled with a 2% solution of linear polyacrylamide.

Quake and coworkers [16] developed a PDMS microfluidic device (shown in Fig. 4c) for nucleic acid purification from a small number of bacterial or mammalian cells. This multilayer device contained fluidic channels and a system of membrane-actuated pneumatic valves and pumps, which enabled precise control of buffers, lysis agents and cell solution, and also allowed for parallel processing. Bacterial cells, dilution buffer and lysis buffer are first introduced into the chip and then transferred into the rotary mixer. Once mixed, the lysate is flushed over a DNA affinity column and drained. The DNA is recovered from the chip with an elution buffer for further analysis. We note that this is the only microfluidic chemical cytometry device to use a separation method other than solution-phase electrophoresis (i. e., solid phase extraction).

Future Directions for Research

This chapter has outlined the challenges inherent in chemical cytometry, i. e., the separation and detection of the contents of a single cell. Microfluidics is a promising technology in the goal of developing high-throughput chemical cytometry techniques, which require robust and repeatable means for cell transportation, lysis and analysis applied in parallel (or very rapidly in series). The current methods have established proof-of-principle; however, much work remains to be done, especially related to scaling up for parallel analysis.

S

A

Close valve
fill cell
suspension

Open valve
isolate one
coil and
dose valve

Meter SDS
half open
valve: fill SDS
and lyse cell

- Cell
- PBS
- SDS
- Single cell lyaate
- Derivatized cell content
- Running buffer

Close valves;
fill buffer;
open valves;
apply high
voltages

Meter and
1 l NDA:
allow reaction
to occur

B

100 μm

Ser. Asn   Gln   Gly   Ala   Met   Tyr   Cell debris   Arg

Ile   Phe   Trp   NDA

Flourescence Intensity

—— Single cell
······ Multiple cells

a

b

a

Lysis buffer   Dilution buffer   Naked bacterial cells   Beads

b

Dilution buffer   Cells

lysis buffer

c

Cell lysis

d

Wash buffer   DNA on beads   Waste

e

Elution buffer   Purified genomic DNA

c

f

4. Vertical ctl   7. Mixer ctl1   8.   9.   12. Bead trap ctl

Buffer   Cell in   Bead in

1. Lysis out   13. Wash ctl

2. Wash ctl   14. Collection ctl

Lysis in   Collection, c1

Wash in   c2

Buffer in   Waste

c3

11. Bead vtf ctl

3. Elute ctl

5. Horiz ctl   6. Dead end ctl   10. Loop exit ctl

Single Cell Analysis in Microfluidic Devices, Figure 4 (**a**) 70-picoliter reaction chamber chemical for cytometry comprising a 3-state valve, a 2-state valve and a picopipette. The sequence illustrates the isolation and lysis of a single cell, as well as fluorescent derivatization of amino acids in the lysate. (**b**) Electropherogram collected from a single Jurkat T cell (solid line) generated in the microfludidic reaction chamber compared to one generated from a population of cells with off-column derivatization (doted line). (Images in (a) and (b) reproduced from [23].) (**c**) Multilayered PDMS microfluidic device with integrated pneumatic valves and pumps. The sequence illustrates the steps for cell isolation, lysis in a rotary mixer, and DNA purification and harvesting. (Image reproduced from [16]) (▶ Color Plate 17) ◀

Cross References

- ▶ Flow Cytometer Lab-on-Chip Devices
- ▶ Detection Using Confocal Microscopy
- ▶ Microfabrication Techniques
- ▶ Materials Used in Microfluidic Devices
- ▶ Methods for Surface Modifications
- ▶ Fabrication of 3D Microfluidic Structures
- ▶ On-Chip Waveguide
- ▶ Pneumatic Valves
- ▶ Thermomechanical Valves
- ▶ Thermopneumatic Vavles
- ▶ Packaging (Including Wire Bonding)
- ▶ Techniques for Manipulating Cells
- ▶ Microfluidic Sample Manipulation
- ▶ Cell Sorting
- ▶ Dielectrophoretic Motions of Particles and Cells
- ▶ Electrokinetic Motion of Cells and Non-Conductive Particles
- ▶ AC Dielectrophoresis Lab-on-a-Chip Devices
- ▶ Optical Tweezers for Manipulating Cells and Particles
- ▶ On-Chip Cell Lysis
- ▶ Cell Assays in Microfluidics
- ▶ Patch-Clamp Measurements On-Chip
- ▶ Mass Spectrometry On Chip Devices
- ▶ Fluorescence Measurements
- ▶ Amperometric Techniques
- ▶ Chemical Cytometry

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