EXTENDED-NANOFLUIDIC SYSTEMS FOR CHEMISTRY AND BIOTECHNOLOGY

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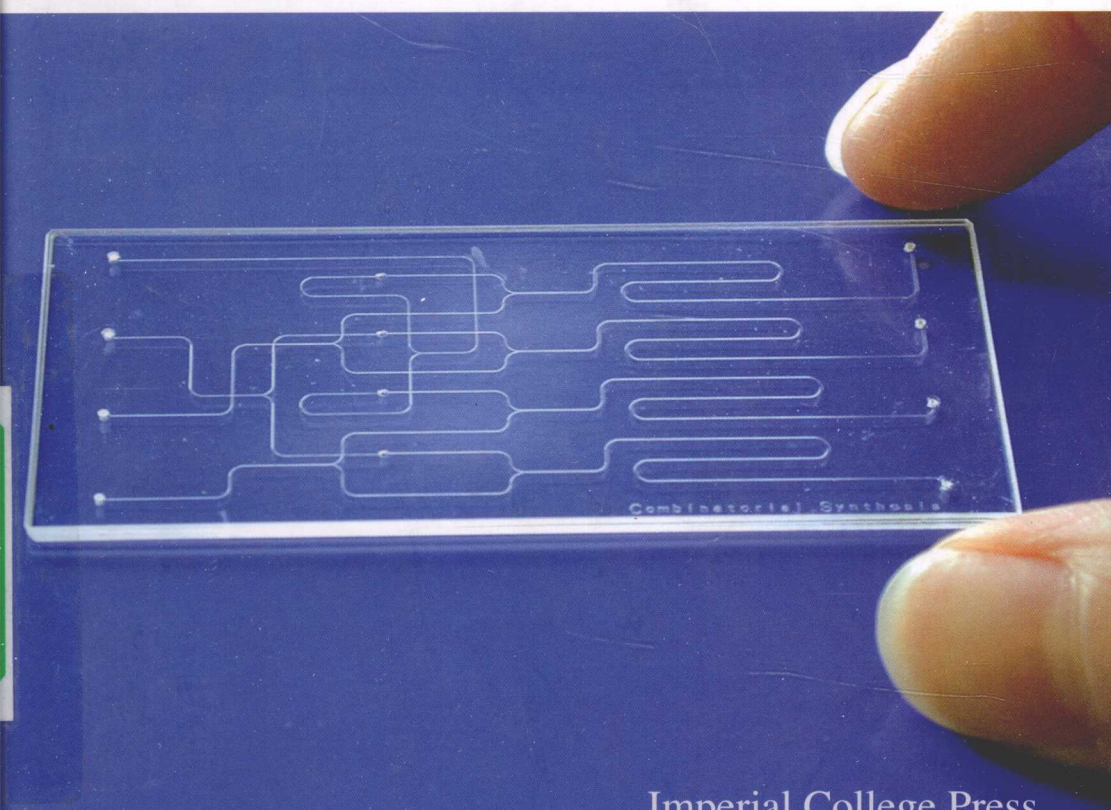

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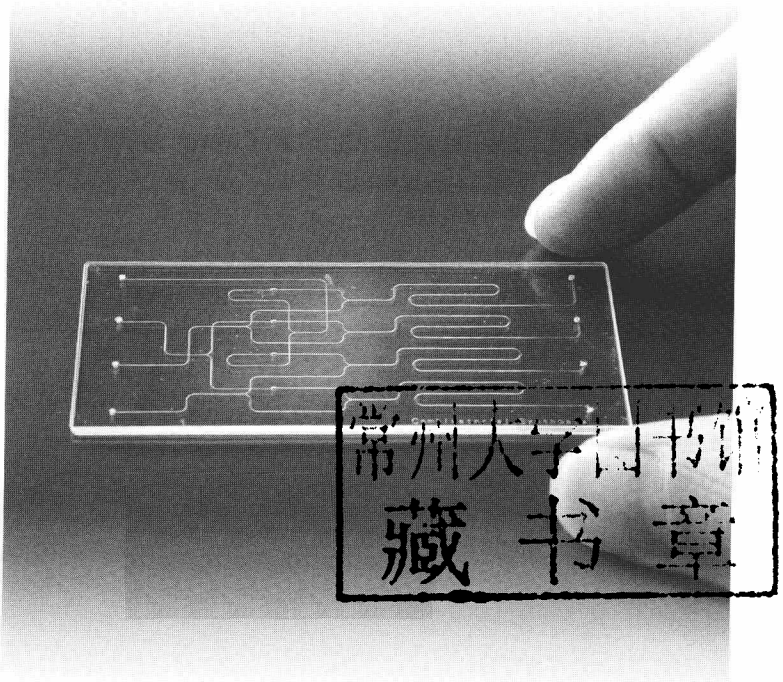

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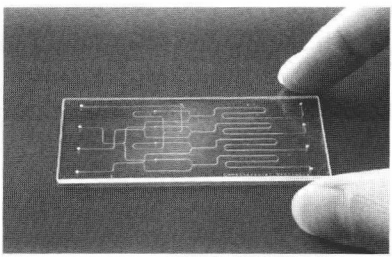

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Chapter 1

INTRODUCTION

Integrated microchemical systems on chips (microchemical chips) are recognized as one of the key technologies for future progress in chemical and biochemical technologies. The advantages of this miniaturization include compact, high speed, and functional instrumentation for analysis and synthesis in bio and related sciences and technologies. In 1979, Terry *et al.* first reported a chemical chip in which a gas chromatography column was fabricated on a silicon wafer; there had not been any reports on microintegration for a decade at that time.[1] In the 1990s, Manz and coworkers pioneered the lab-on-a-chip, or microchip, concept and illustrated its usefulness. Manz's group integrated the function of capillary electrophoresis on a single glass chip. Along with the requirement for fast DNA analysis of a small sample with small reagent volume, the microchip has been recognized as a promising technology, mainly for the separation of DNA and proteins. The technologies utilized were primarily electroosmotic flow (EOF), electrophoretic separation, and laser-induced fluorescence (LIF) detection.[2,3] At that time, these microchips were referred to as micro total analysis systems (μTAS). However, other analytical and synthesis methods were required for wide application in more general, analytical, combinatorial, physical, and bio-related chemistries that included complicated chemical processes, organic solvents, neutral species, and non-fluorescent molecule detection. From this point of view, general microintegration methods on microchips were quite important for wide application.

For these purposes, general concepts were proposed to achieve general microintegration on a chip, which was called a lab-on-a-chip, or microchemical chip. Many bulk scale unit operations such as

mixing, extraction, phase separation, and other unit operations of chemical processes are integrated as microscale chemical components and named as micro unit operations (MUOs). The MUOs can be combined in parallel and in series, like an electric circuit, through continuous flow chemical processing (CFCP). The microchemical chip also has a functional chemical central processing unit (CCPU). This combination has enabled a variety of analyses, syntheses, and biochemical systems to be integrated on microchips, and has been proven to be an effective general methodology for microintegration (Figure 1.1). As a result, superior performance has been demonstrated in a shorter processing time (from days or hours to minutes or seconds), smaller sample or reagent volume (diagnosis with one drop of blood), with easier operation (from professional to personal), and in smaller systems (from 10 m scale chemical plants to desktop plants, and desktop systems to mobile systems) than conventional analysis, diagnosis, and chemical synthesis systems. Practical prototype systems have also been realized in environmental analysis, clinical diagnosis, cell analysis, gas analysis, medicine synthesis, microparticle synthesis, and so on. The general concept has allowed the establishment of "chemical devices" for the first time.

In order to realize these basic concepts, fundamental technologies are essential. These technologies include: pressure-driven microfluidics

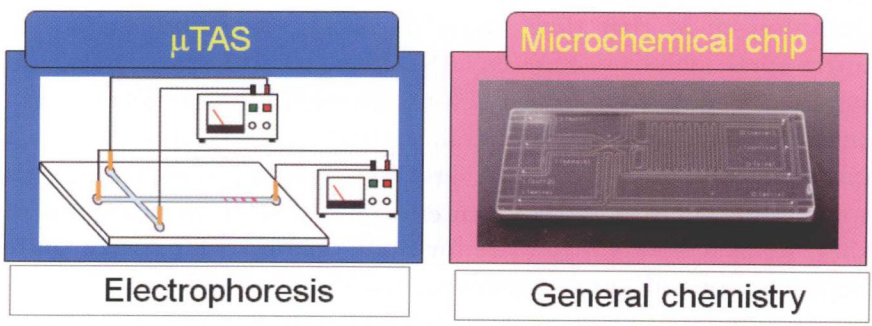

Figure 1.1. Transition from electrophoresis to general chemistry by microchemical chip or lab-on-a-chip.

(parallel multiphase flow or droplet-based multiphase flow), surface control methods (hydrophobic/hydrophilic, bio-molecule, cell, catalyst, etc.), detection methods (optical, electrochemical, and conventional analytical instruments by developing the interface), and fabrication methods (silicon, glass, polymer, ceramics, etc.). The device development of these methods is also an important issue because microchemical chips work as CCPUs and the peripheral devices are necessary to realize microchemical systems.

There are two directions for microtechnologies. One is to put these technologies to practical and commercial use for micrometer scale chemical systems on chips. For example, practical systems have been developed for clinical diagnosis, environmental analysis, food analysis, drug synthesis, basic research for biology, and pharmaceutical and tissue engineering. For these purposes, designing tools for microchemical processes and reliable fluidic devices will be important, in addition to reducing costs.[4]

The other direction is to extend the method to nanometer scale chemical experiments, which is opening new horizons for chemical research tools. Recently, microfluidic systems and detection devices were applied to 10^1–10^3 nm scale fluidic systems, which we call extended nanospace to distinguish it from the 10^0–10^1 nm scale space belonging to conventional nanotechnology. This extended nanospace bridges the gap between single molecules and normal, condensed phases (Figure 1.2), the liquid properties of which have not yet been properly explored. In order to understand these liquid properties, new fundamental technologies are required as basic research tools, since conventional technologies are difficult to apply due to the extremely small size of the extended nanospace. These technologies are those of fabrication, fluidic control, detection, and surface modification methods, with many challenges present due to the small and closed space. Great efforts have been made to develop these basic technologies in recent years, and the methodologies have revealed many unique liquid properties.[5,6] By utilizing these unique liquid properties, new chemical operations are increasingly reported, which are quite difficult to achieve using microtechnologies, and will be useful for future bio and analytical technologies

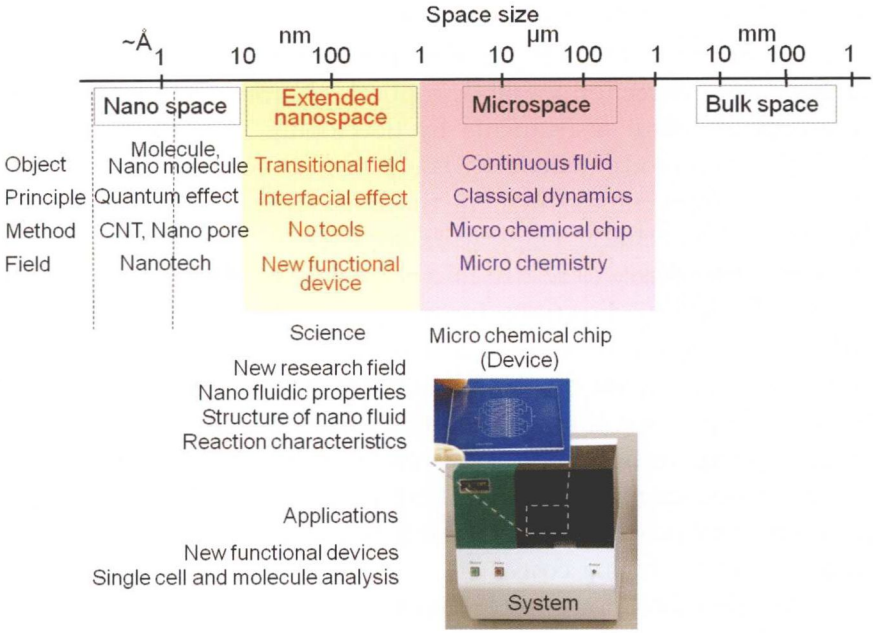

Figure 1.2. Size hierarchy and micro and extended nanospace.

(e.g. single cell and single molecule analysis). Now, microchip technologies are moving to the next generation by combining with extended nanospace.

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Chapter 2

MICROCHEMICAL SYSTEMS

Integrated microchemical systems have great potential for application in various fields. In order to realize the general analytical, combinatorial, physical, and biochemical applications, general integration methods on microchips are important. Conventional, macroscale chemical plants or analytical systems are constructed by combining unit operations, such as mixers, reactors, and separators. A similar methodology can be applied to microchemical systems. However, miniaturizing conventional unit operations is often ineffective and sometimes impossible, due to the many physical properties (e.g. heat and mass transfer efficiency, specific interfacial area, and gravitational force) and since the dominant factors for fluidics and chemistry are significantly different in microspace. Therefore, new MUOs taking these issues into account are required.

For this purpose, multiphase microflow is utilized. In conventional macroscale devices, the aqueous and organic phases are separated by gravity. In microspace, however, the fluid is greatly influenced by liquid/solid, liquid/gas, and liquid/liquid interfaces because of the large specific interfacial area. The main physical forces in the microchannels, including the viscous force, and the interfacial parameters can be analyzed using the dimensionless Reynolds (Re) and Bond (Bo) numbers, defined as the ratio of inertial-to-viscous forces and the ratio of gravity-to-tension, respectively. Bo is defined as $Bo = (\Delta\rho)gdh2/\gamma$, where $\Delta\rho$, γ, and dh are the density difference, the interfacial tension between the two phases, and the equivalent diameter, respectively, and where g is the gravitational acceleration (9.8 ms^{-2}). Therefore, multiphase microflows are generally considered to be laminar flows. Usually, multiphase microflows are divided into droplet flows and parallel flows, which have both advantages and disadvantages,

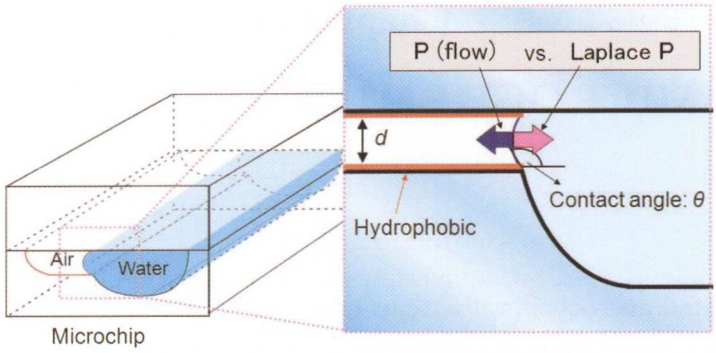

Figure 2.1. Laplace pressure for stabilizing the interface.

while parallel flows are used for the general integration of complicated chemical processes, controlled by pressure.[1] It is important to remember that the pressure driving the fluids decreases in the downstream part of the flow due to the fluids' viscosity. When two fluids in contact with one another have different viscosities, the pressure difference (ΔP_{Flow}) between the two phases is a function of the contact length and the flow velocity. Another important parameter is the Laplace pressure ($\Delta P_{\text{Laplace}}$) caused by the interfacial tension between two phases. The interface is fixed at a position in the microchannel determined by the balance established between $\Delta P_{\text{Laplace}}$ and ΔP_{Flow}. Figure 2.1 illustrates the pressure balance at the liquid/liquid interface of a two-phase microflow. With a glass surface, the liquid/liquid interface curves toward the organic phase because of the hydrophilicity of the glass, a substrate used for general chemistry. $\Delta P_{\text{Laplace}}$ is generated at the curved liquid/liquid interface. On the basis of the Young–Laplace equation, $\Delta P_{\text{Laplace}}$ is estimated as follows:

$$\Delta P_{\text{Laplace}} = \frac{\gamma}{R} = \frac{2\gamma \sin(\theta - 90^\circ)}{d}, \tag{1}$$

where R is the radius of curvature of the liquid/liquid interface, and θ is the contact angle. The contact angle is restricted to the set of values between the advancing contact angle of the aqueous phase, θ_{aq},

and that of the organic phase, θ_{org}. Therefore, $\Delta P_{Laplace}$ is restricted as follows:

$$\frac{2\gamma \sin(\theta_{aq} - 90^\circ)}{d} < \Delta P_{Laplace} < \frac{2\gamma \sin(\theta_{org} - 90^\circ)}{d}. \quad (2)$$

When ΔP_{Flow} exceeds the maximum value of $\Delta P_{Laplace}$, the organic phase flows toward the aqueous phase. When ΔP_{Flow} is lower than the minimum value of $\Delta P_{Laplace}$, the aqueous phase flows toward the organic phase. When the ratio of flow rates is changed, the pressure balance is maintained through changing the position of the liquid/liquid interface. This model indicates that the important parameters for microfluid control are the interfacial tension, the dynamic contact angle, and the depth of the microchannel. This model can also be applied to gas/liquid microflows. In order to stabilize the interface, $\Delta P_{Laplace}$ should be maximized by controlling channel size, shape, and surface hydrophobicity. This strategy allows various multiphase parallel flows.

Using these methods, bulk scale unit operations can be integrated as MUOs, as shown in Figure 2.2. By combining MUOs with different functions in series and in parallel, various chemical processes can be integrated into microchips through the use of a multiphase microflow network, CFCP, as shown in Figure 2.3.[2] Many MUOs have been developed for wide application, such as mixing and reaction,[3,4] phase confluence and separation,[5–16] solvent extraction,[17] gas/liquid extraction,[18–21] solid-phase extraction and reaction on surfaces,[22–33] heating,[34–38] and cell culture.[39–43] These methodologies allow for the general integration of chemical processes. Finally, the microchip is installed in a microsystem and works as a CCPU. Several microsystems have been realized for practical applications (Figure 2.4).

Designing microchips is an important issue and an example of designing a microcobalt, wet analysis is illustrated in Figure 2.5. Conventional analytical procedures in bulk scale analysis consist of a chelating reaction, solvent extraction of the complex, and the decomposition and removal of the co-existing metal complex. These

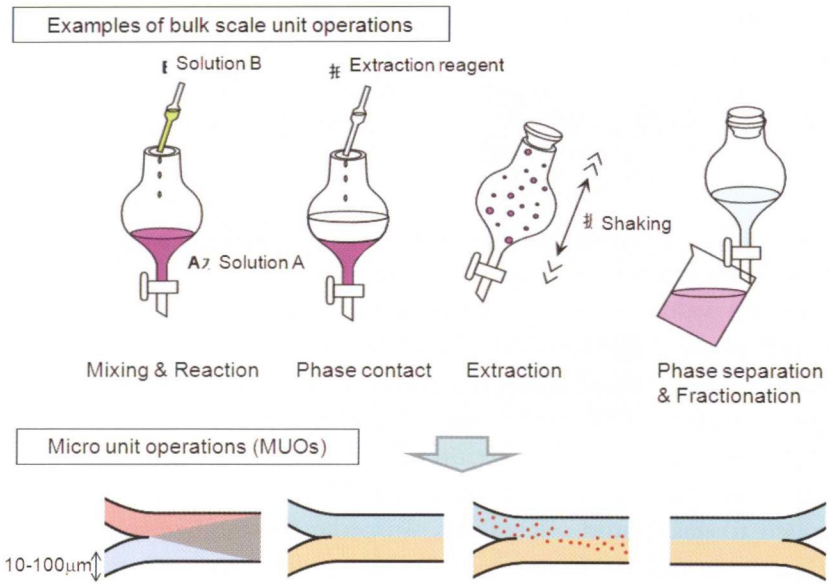

Figure 2.2. Conversion of bulk scale and MUOs.

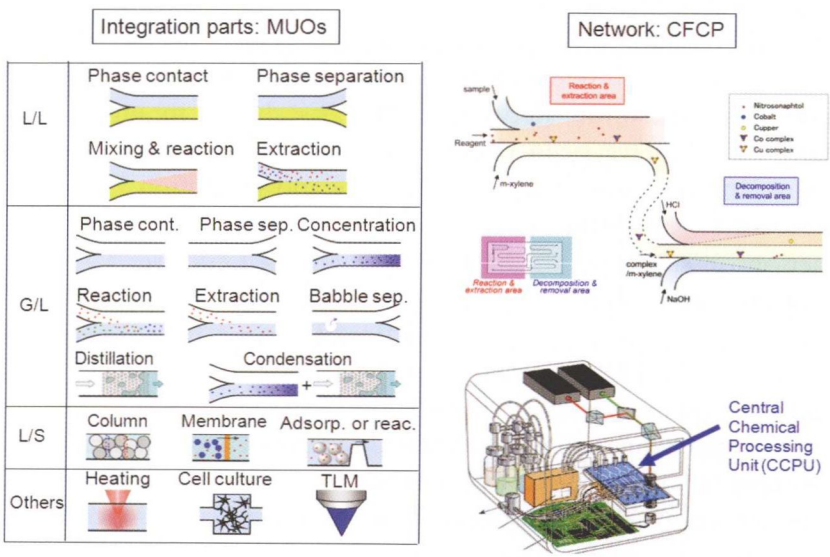

Figure 2.3. Realization of chemical processes on a microchip and in a microsystem.

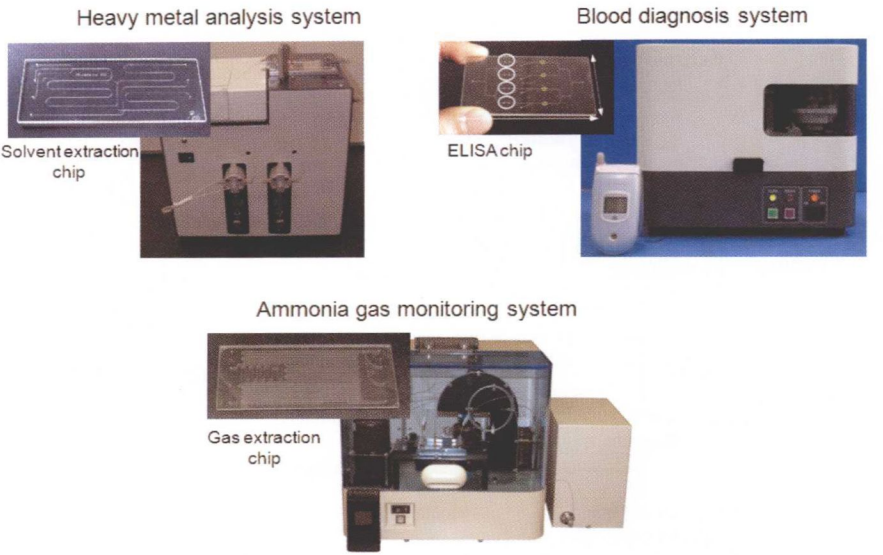

Figure 2.4. Examples of microchips and systems for real application.

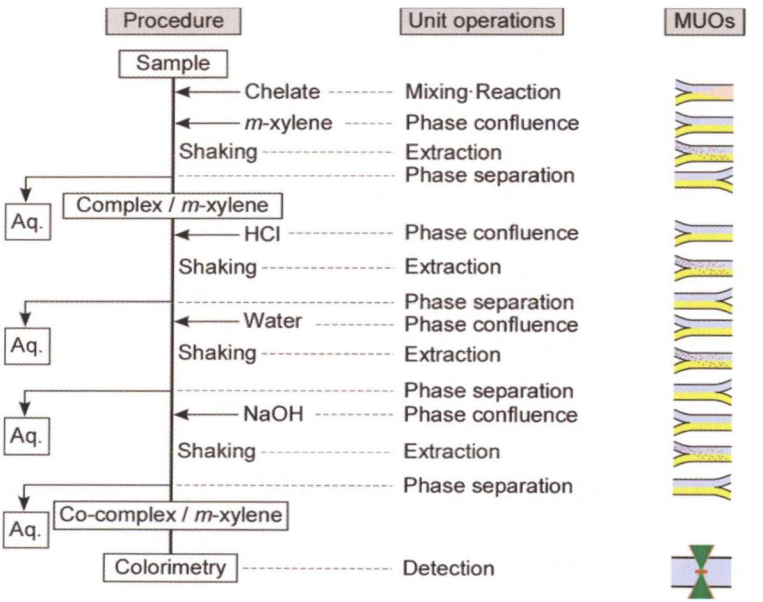

Figure 2.5. Examples of the design procedure for a micro wet analysis chip.