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Microfluidics and Nanofluidics: Science, Fabrication Technology (From Cleanrooms to 3D Printing) and Their Application to Chemical Analysis by Battery-Operated Microplasmas-On-Chips

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Additional information is available at the end of the chapter

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Abstract

The science and phenomena that become important when fluid-flow is confined in microfluidic channels are initially discussed. Then, technologies for channel fabrication (ranging from photolithography and chemical etching, to imprinting, and to 3D-printing) are reviewed. The reference list is extensive and (within each topic) it is arranged chronologically. Examples (with emphasis on those from the authors' laboratory) are highlighted. Among them, they involve plasma miniaturization via microplasma formation inside micro-fluidic (and in some cases millifluidic) channels fabricated on 2D and 3D-chips. Questions addressed include: How small plasmas can be made? What defines their fundamental size-limit? How small analytical plasmas should be made? And what is their ignition voltage? The discussion then continues with the science, technology and applications of nanofluidics. The conclusions include predictions on potential future development of portable instruments employing either micro or nanofluidic channels. Such portable (or mobile) instruments are expected to be controlled by a smartphone; to have (some) energy autonomy; to employ Artificial Intelligence and Deep Learning, and to have wireless connectivity for their inclusion in the Internet-of-Things (IoT). In essence, those that can be used for chemical analysis in the field for *"bringing part of the lab to the sample"* types of applications.

Keywords: microfluidics, nanofluidics, wet chemical etching, embossing, polymeric substrates, 3D printing, rapid prototyping, microplasmas, portability, postage stamp sized 2D-chips, 3D-chips, Lab-on-a-chip, MEMS, NEMS

1. Science, technology and advantages of microfluidics

As is the case in many fields of scientific research, the field of microfluidics has three main components: a science, a technology and an applications component.

For microfluidics, a common thread between all of these components is that they are micro-sized, so size will be briefly discussed first. The dimensions shown in **Figure 1** are approximate because size of naturally-occurring objects (and of some manufactured-things) varies, for example the diameter of a human hair is between 50 and 100 μm ; the diameter of the tip of a rollerball pen is between fine, medium and bold (e.g., between 0.5 and 0.7 mm); and of a 1 cent coin with its diameter varying slightly depending on the jurisdiction the penny was minted (typically around 20 mm or somewhat more).

1.1. Microfluidics as a science

Microfluidics has been defined [1–17] as the study of the behavior of fluids (or whatever is in them, e.g., colloids, discrete nanoparticles or individual cells), **in micro or in sub-millimeter channels** or around microstructures. Although microchannels can be relatively long (e.g., several 10's of mm), they are still called microchannels as long as one **critical dimension** (e.g., channel-width or channel-depth or tube radius) is in the micro scale. Microfluidic channels can be used for example to confine or to guide or to mix or to manipulate fluids.

- **The science of scaling as applied to microfluidics:** a number of physical properties of fluids change as size gets smaller [1–47], to quote “*smaller brings new capability*” [31]. These changes are often non-linear and have been discussed in books [1–17] and in journal papers [18–29]. A non-exhaustive list of size-dependent phenomena and effects is outlined below.

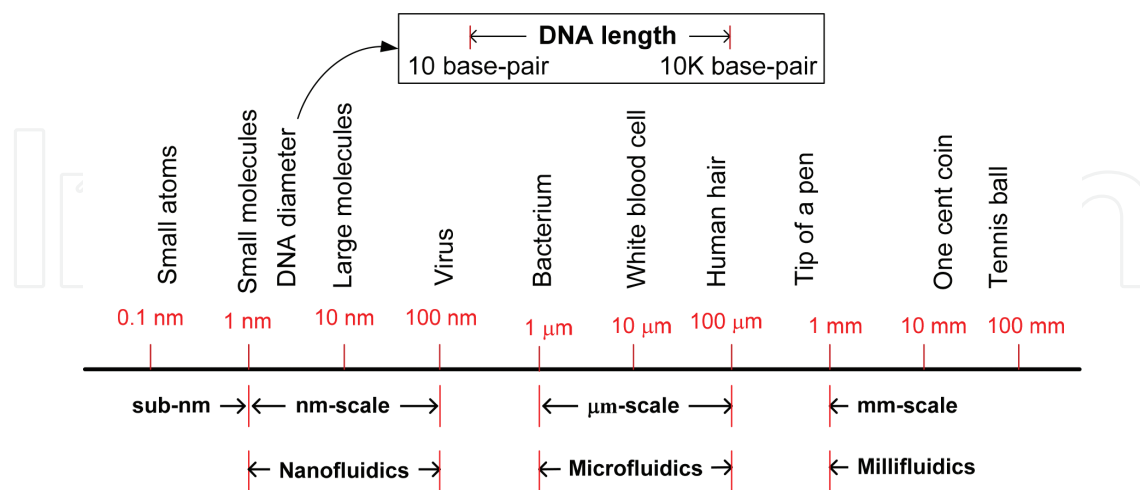


Figure 1. Examples of an approximate scale of things. The boundaries between micro and nanofluidics and between micro and millifluidics are fuzzy. In many cases, the strict definition adopted by the National Science Foundation (NSF) of the US for nano as anything with one critical dimension ≤ 100 nm is not strictly adhered to, thus there is a gap between 100 nm and 1 μm . Similar arguments apply to the NSF definition for micro (defined as one with a critical dimension between 1 and 100 μm). In many cases, the micro-scale is arbitrarily widened to ~ 1 mm and sometimes slightly more. The term millifluidics has recently been used for channels (or structures) with one critical dimension of a few mm.

- **The length-cube relationship:** the geometrical scale of length varies linearly but volume varies as length-to-the-power-of-three. As a consequence, volume changes rapidly as length decreases. Typical volumes of fluids in microfluidic channels range between nano-liter (nL) and femtoliter (fL). At the μm -scale, some properties of fluids change (as compared to a **mesoscale**, arbitrarily defined as the intermediate scale between the micro-scale and the macro-scale). Example properties that dominate at a micro-scale and that are different than those observed at the meso and macroscales include dominance of laminar-flow, diffusion-dominated mixing and capillary action. To highlight one such effect, a counter-intuitive example (from an every-day scale point of view) involves two parallel-flowing fluid-streams that come into contact in a microchannel. Since there are no eddy currents or turbulence (due to laminar flow), the only mixing that occurs is a result of slow-occurring diffusion at the interface between the two fluid-flows. Since there is no bulk mixing, mixture-separations in microchannels are faster and have shorter separation times.
- **The square-cube law:** states that volume increases faster than surface area. In microfluidics, fluid-flows in microchannels are influenced or controlled or are a function of surface area (e.g., surface tension) while others (e.g., weight) are a function of volume. Typically, in microfluidics there are no gravity effects but dominance of surface tension and of interface effects.
- **Examples of other phenomena influenced by size and expressed by dimensionless numbers:** these include laminar flow expressed by the Reynolds number; surface tension expressed by the Bond number; transient thermal effects expressed by the Fourier number; viscous heating by the Brinkman number; and fluid compressibility by the Mach number.
- As a result of channel-size, microfluidics enables one to probe individually whatever it is in a fluid constrained in a microchannel (e.g., a single cell), thus providing additional avenues for scientific inquiry and discovery (important especially in the bio-analytical sciences).

Overall, the relevant literature [1–47] describes efforts at exploring and understanding the Physics of flow-related phenomena. Developments enabled by microfluidics will be highlighted in this chapter, with emphasis on ionized gases (e.g., Paschen's law for electrical gas breakdown; plasma sheaths and the Debye length) as applied to microplasmas formed inside fluidic channels.

1.2. Microfluidics as a technology

Microfluidics refers to a variety of approaches that enable exploitation of the phenomena mentioned above by fabricating microfluidic channels on a variety of substrates. For instance, on crystalline Silicon (of c-Si) wafers, on amorphous glass or on polymeric substrates. Due to the advantages of confining flow in microfluidic channels, several fabrication technologies have been developed and tested and will be briefly reviewed. These technologies are often collectively called micro Total Analysis Systems (μTAS) or Lab-on-a-Chip (LoC) or Micro Electro Mechanical Systems (MEMS). Microfluidics or whatever acronym is used to describe it, has attracted significant attention in books [1–17] and in journals [18–29]. While in the topic of publications, older references have been purposely included in this chapter followed by some recent publications. Where possible, the citations in the reference list have been grouped either according

to fabrication technology or according to the type of substrate used (e.g., c-Si, amorphous, polymeric) or according to application. Within each technology, the reference list has been sorted out chronologically to help interested readers follow the origin and evolution of ideas and technologies. Despite of the relatively large number of references included, this is not a comprehensive review. The reference list simply offers starting points. Getting back to the main theme, the question still remains: why does microfluidics continue to receive increased attention? What are the advantages of using microfluidics, especially for chemical analysis applications?

1.3. Advantages and selected applications of microfluidics

The science and technology mentioned above are widely exploited and applied to give microfluidics a host of advantages. A brief list includes use of small volumes of sample and reagents (thus reducing cost per analysis and minimizing waste disposal); rapid sample processing; potential for automation (thus reducing cost); reduced risk of contamination; short analysis time (e.g., by increasing speed of separations); small footprint and light-weight thus enabling development of future portable microfluidic-based, portable micro-instruments that can be employed *on-site* or for personal use or for personal dosimetry; potential for massive parallelism (for high sample throughput); and overall, lower ownership and operating costs (*vis-à-vis* conventional, lab-sized systems). Application areas (to name but a few), include analytical chemistry, synthetic chemistry (including nanomaterials synthesis), microbiology, biotechnology, point-of-care diagnostics, drug delivery, immunoassays and medicine, health-monitoring and health-diagnostics, agriculture, food safety and environmental monitoring [30–47].

2. Technology for fabrication of microfluidic channels

2.1. Fabrication using either crystalline Si (c-Si) or other substrates

Microchannel fabrication technology has been borrowed from the semiconductor industry. Initially, *bulk micromachining* [1–17, 48–51] was employed on crystalline Si (c-Si) substrates and on amorphous glass. To use it, a photolithographically patterned wafer was dipped into a chemical etching solution to etch-away (or subtract) material from the substrate, thus forming microchannels of desired geometry. This method is often referred to as *wet chemical etching* [48–51]. Inadequate control of channel depth (resulting unevenly etched channels) due to spatial etch-rate variations and to pyramid formation when crystalline-Si (c-Si) substrates and deep microchannels were etched are two key disadvantages. In contrast, *surface micromachining* [52–54] involves repetitive patterning, thin layer deposition and selective etching of sacrificial layers. The challenge here stems from the many photolithography steps involved and from the precautions required so that previously deposited layers are not damaged.

We used (as far back as the 1990's) cleanroom-based photolithography, bulk micromachining and **wet chemical etching** [48–51] to fabricate shallow-depth microchannels (with relatively low width-to-depth **aspect ratio**). This approach is often referred to as 2D sculpting of Manhattan-like structures and it offers a planar, 2D- rather than a 3D-perspective. Some examples will be briefly discussed later.

For completeness, other methods of microchannel fabrication on inorganic substrates (either crystalline or amorphous) have been described. A short list includes **laser machining** [55–58]; lithographie galvanoformung adformung (LIGA) or lithography electroplating molding [59–61] which is well suited for fabrication of high aspect ratio channels; deep reactive ion etching (DRIE) [62–65] often used for fabrication of microchannels with a high aspect ratio; and, **SU-8** (an epoxy-based negative photoresist) and its variants such as SU-8 series 2000 and SU-8 Series 3000) [66–68].

Technologies involving polymeric substrates [69–83] include replication via **imprinting** [69–73] or **embossing** [74–76]. Polymeric substrates are selected due to their bio-compatibility or to reduce cost of ownership. Examples will be shown later. The terms disposable or recyclable microfluidic devices is often used for microfluidic channels on polymeric substrates. **Soft lithography** [77–83] (defined as a collection of fabrication techniques for replication of microchannels) is a technology that does not require access to a clean room. It is called soft because it uses soft and flexible (primarily) elastomeric materials such as poly di methyl siloxane (PDMS) and often cyclic olefin copolymer (COC).

There are other techniques that are rather difficult to classify either according to fabrication technology or according substrate. Despite of being brief, the list includes **droplet microfluidics** [84–89], in which discrete droplets or small volumes of immiscible liquids are guided through microchannels. In the early literature, this approach was often called digital microfluidics. As it is known now, **digital microfluidics** [90–95] is an outgrowth of electrowetting [90, 92] and it involves use of discrete droplets on arrays of electrodes, with individual droplets manipulated by electrical means. The list also includes **centrifugal microfluidics** [96–101], a technique that enables micro-flow manipulation by using rotational forces (e.g., Coriolis) obtained by spinning a CD on top of which there are microfluidic channels. This technique is often called “*lab on a CD*”. It also includes **paper microfluidics** [102–108], a technique that uses paper for development of microfluidic approaches intended for use in resource limited situations (e.g., remote geographical areas or resource-limited locations).

Rapid prototyping via 3D-printing [109–122] involves both a technology (e.g., a 3D printer) and a materials platform (e.g., a polymer) for formation (primarily) of mill-sized fluidic (and recently) micro-sized channels [115, 117, 120]. An example of 3D printing will be discussed later in this chapter.

2.2. Fabrication technology examples

To highlight substrate-dependence of fabrication, the fabrication steps required for microchannels on c-Si and on amorphous glass or quartz substrates are compared and contrasted in **Figure 2**. It should be noted that depending on crystallographic orientation of the substrate and of the chemical cocktail used in the etching solution, isotropic or anisotropic etching may be obtained [48–51].

Example 1: Planar 2D-chips and wet chemical etching for fabrication of microchannels on crystalline and amorphous substrates (Figure 2).

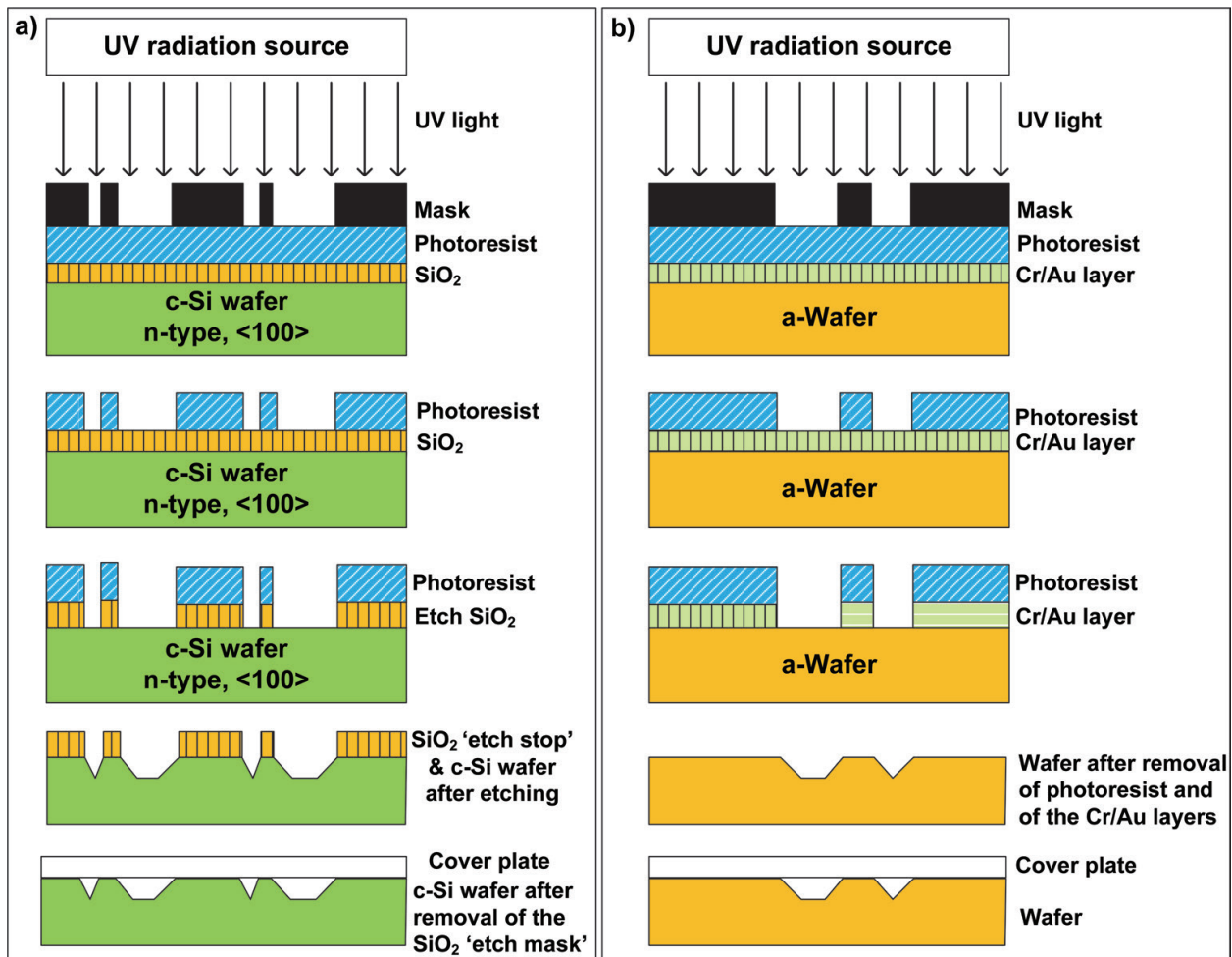


Figure 2. Simplified steps used for fabrication of microchannels on a) a c-Si wafer as a substrate and on b), a wafer made from an amorphous material (abbreviated as a-wafer-above, such as glass).

For completeness, an example of wet chemically etched microchannels on glass is shown in **Figure 3**.

The quality of the etched microchannels depended on the composition of the etching solution and on the geometric-primitives that were used to define the channels. To enclose the microchannel of **Figure 3**, a cover plate was used (but is not shown in **Figure 3**). Depending on the required optical transparency, a UV-transparent quartz cover plate was employed for most of the work described here. Furthermore, depending on the substrate (e.g., c-Si or glass), a variety of bonding methods can be employed [2–17].

Despite of the ability to fabricate low aspect ratio microchannels, wet chemical etching has shortcomings arising from costs, from limited access by many to photolithography and to cleanrooms, and from time-delays between mask-design (**Figure 3b**) and receipt of finished prototype (e.g., **Figure 3a**). At present, access to cleanrooms is not required because microfluidic chips can now be ordered from specialized foundries. In spite of this, there are still costs

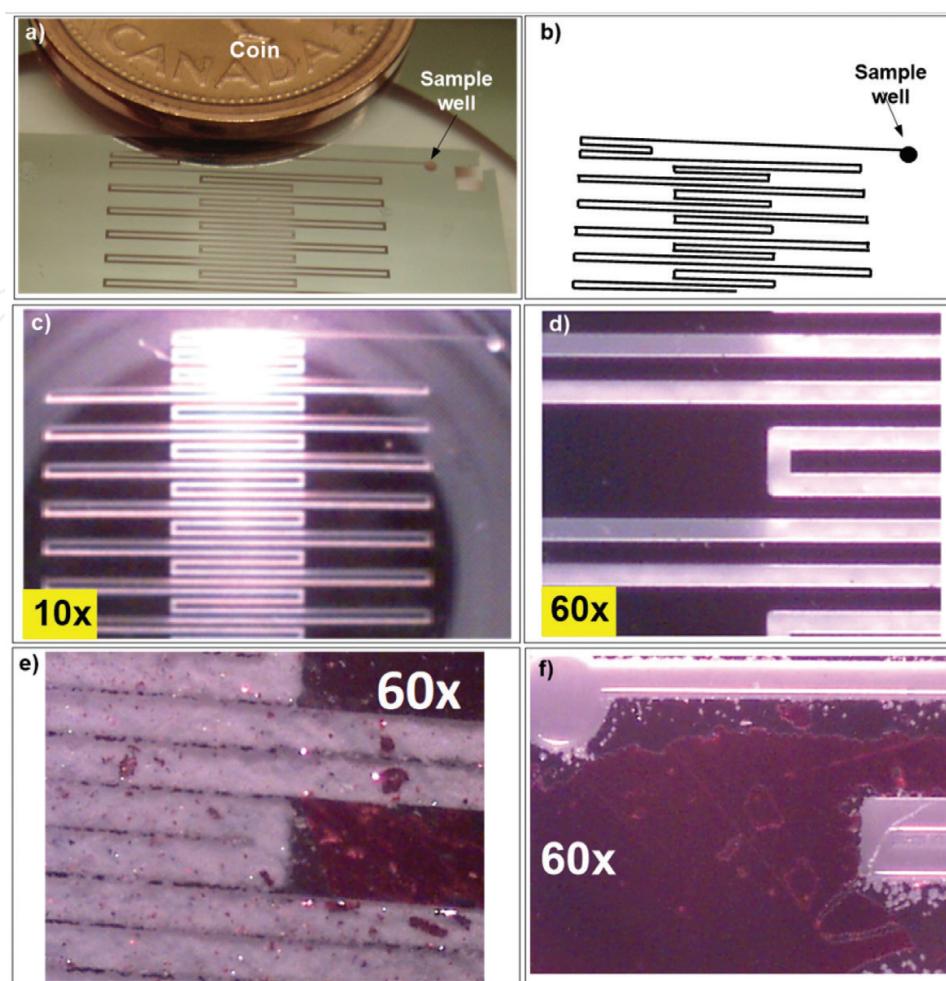


Figure 3. (a) Part of a 14.5 mm by 25.6 mm chip of an etched microfluidic channel on corning 7059 glass with the photoresist removed and (for clarity) without a cover plate. Also omitted are pipette-tips used as sample reservoirs that are attached to the sample well. A coin was included for size. (b) Part of a Mylar mask used for photo-lithography. (c) Part of a washed meandering microchannel shown under 10x magnification and (d) shown under 60-fold magnification. (e) an unwashed microchannel immediately after etching showing etching by-products inside the microchannels, thus requiring their removal. (f) a sample-well and a washed microchannel showing the quality of etching, in particular for the round sample-well. For (d), (e) and (f) the photoresist was not removed to provide contrast for the photographs.

and time-delays involved. There is another limitation if microchannels are to be used with biological samples, because many biosamples adhere to substrates. Thus, functionalized surfaces or microfluidic channels on polymeric substrates are preferred.

Example 2. Imprinting microchannels on planar polymeric 2D-chips. 2D-microchannel fabrication on polymeric substrates is one way of overcoming some of the limitations mentioned above. But polymers may contain additives, fillers or plasticizers that may contaminate the samples, and they may display auto-fluorescence. As for fabrication (**Figure 4**), it may be achieved by using Si-stamp imprinting (**Figure 4**) or by imprinting (by pressing) a wire on a substrate [69] (**Figure 5**). In the example shown in **Figure 4**, a c-Si stamp (or master or hard mold) was developed and was employed for replication by imprinting.

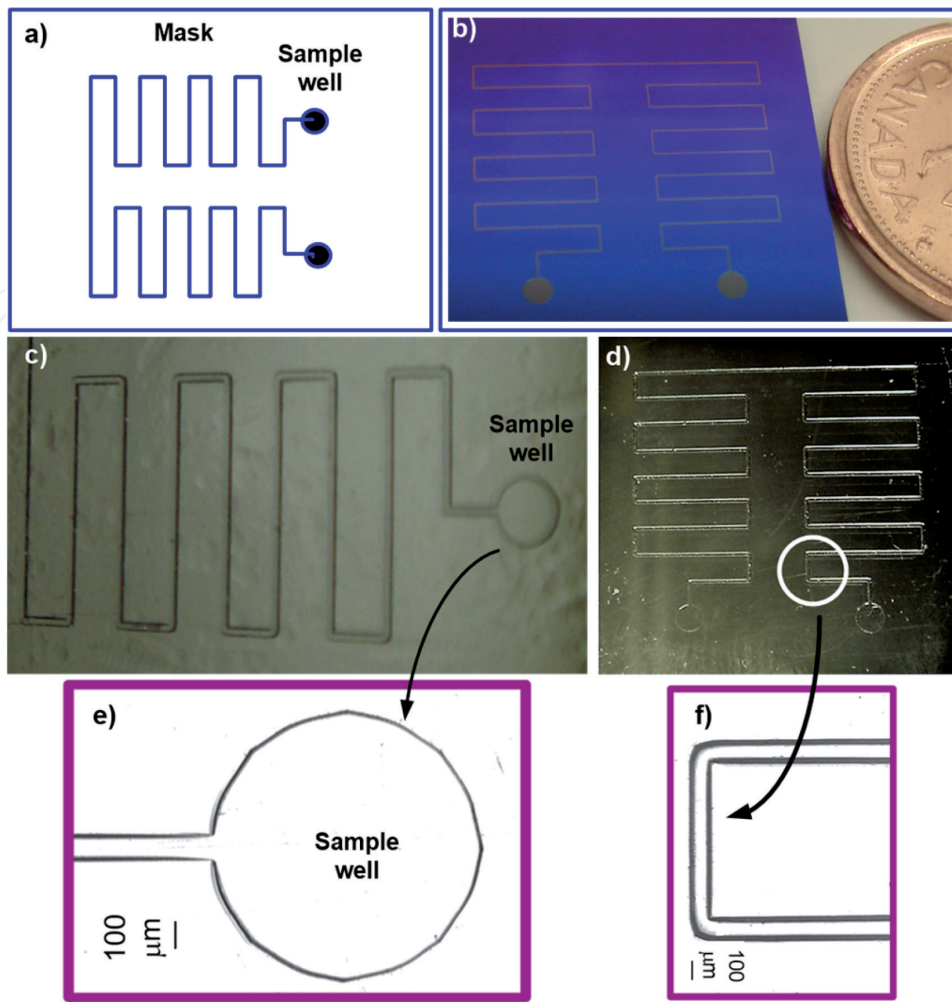


Figure 4. (a) Mask; (b) mask on c-Si chip, coin has been added for size; (c) chemically etched c-Si chip (serving as a stamp), the meandering pattern is protruding from the surface of the chip; (d) imprint generated by pressing the stamp and the polymeric chip together by placing them in a hydraulic press and by applying pressure at room temperature; (e) imprinted sample-well on a polymer chip shown under magnification; and (f), part of an imprinted meandering channel shown under magnification. For (d) and (e) and (f) different polymeric materials were used.

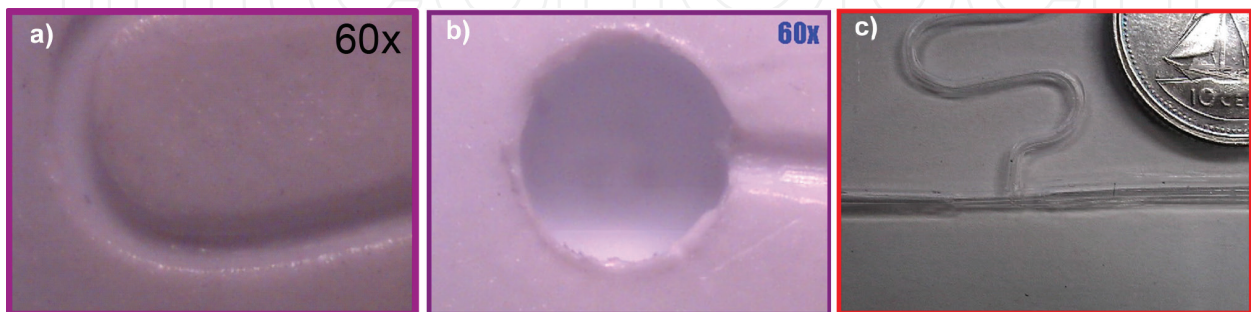


Figure 5. (a) Imprinted channel on a polymeric chip (60x magnification), (b) sample-well (60x magnification) and (c) Venturi micropump with no moving parts and no electrical power requirements fabricated by imprinting (coin included for size) [73].

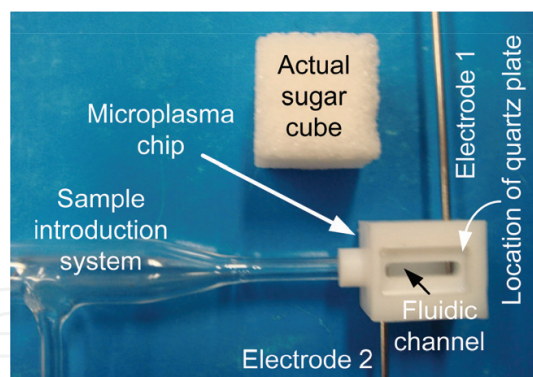


Figure 6. Sugar cube-sized, 3D-printed hybrid-chip with a millifluidic channel to be fitted with a quartz cover plate (selected for UV transparency). A sample introduction system is also shown and it has been included to provide an overall size for this “critical” component of a potential future micro-instrument. An actual sugar-cube (~1 cm by ~1 cm) has been included for scale comparisons.

Example 3: 3D-printed, milli-sized fluidic channels on polymeric materials for hybrid 3D chips. 3D printing technology [109–122] using polymeric materials is receiving attention for rapid prototyping [109] including fabrication of mm channels (often called **millifluidics**) and more recently for sub-mm channels (using specialized printers) [120, 121]. We used 3D-printing due to reduced fabrication and ownership costs and due to quick turn-around times (often from concept to prototype in hours). A simple, hybrid, 3D-printed 3D-chip containing a millifluidic channel is shown in **Figure 6**. The word *hybrid* was used because the two needle electrodes and the quartz cover plate were not 3D-printed.

In my laboratory, some of the fabrication technologies discussed thus far have been used to constrain plasmas in microfluidic or in millifluidic channels. But why plasmas and why microplasmas?

3. Why plasmas?

There are four states of matter: gases, liquids, solids and plasmas [123–131]. To generalize, atmospheric pressure plasmas are ionized gases that are either hot or cold (about room temperature or somewhat above it). Plasmas occur in nature, for example those found in inter-stellar space, in the ionosphere, in auroras and in lightening. There are also artificially-generated plasmas that are being used in many every-day-life applications. Neon signs and fluorescent lights in which low-pressure plasmas are formed either in Neon (Ne) gas or in Argon (Ar) gas) are two such examples. Other examples include plasmas employed for device fabrication by the semiconductor industry or for materials synthesis in nanoscience and nanotechnology [129–131]. **It has been estimated that over 50%** of whatever goes inside any electronic device (e.g., a tablet, a smartphone, TV) is fabricated using a low-pressure plasma.

Conventional-scale (or **lab-scale**) atmospheric pressure plasmas are widely used in **chemical analysis**, primarily in the form of atmospheric-pressure, **6000–10,000 K hot** Inductively Coupled Plasmas or ICPs [132]. Due to their size and weight (e.g., in the few 100's of pounds),

their gas consumption (e.g., ~20 L/min), their power usage (e.g., 1–2 kW) and their need for cooling, ICPs are primarily used in a lab.

3.1. Some fundamental aspects of plasma science

A plasma is an ionized gas [123–131]. The term *plasma* was coined by Langmuir in the 1920's and it is derived from the ancient Greek word $\pi\lambda\acute{\alpha}\sigma\mu\alpha$ (plasma), freely translated to something “moldable”. A plasma consists of ions (with ion number density n_i) and electrons (with an electron number density n_e), and on the average it is quasi-neutral, and for singly ionized gases $n_e \approx n_i$. Thus, a prerequisite for plasma formation is ionization. Singly-charge ionization (in the form of ion-electron pair formation) is done by detaching an electron from a neutral gaseous atom or molecule. Although there are other ways of detaching an electron (e.g., thermally), one way doing it is by placing a gas between two electrodes and by applying an electric field with a sufficiently field-strength to ionize the gas (**Figure 7**), thus forming an *electrical gas discharge*. Because neutral gaseous atoms or molecules (ordinarily insulators) become ion-electron pairs, they also become (partial) conductors. Partial because to an approximation, conductivity depends on the degree of ionization (this is important for weakly ionized plasmas).

To obtain electrical gas breakdown, the dielectric strength of the gas must be exceeded. The dielectric strength is the maximum electric field-strength (in V/m) an insulating gas can endure without breaking down into ions and electrons. If there is a sufficiently large field-strength, breakdown of the dielectric strength will cause formation of (typically) a low-current **spark** (i.e., a momentary electrical discharge, an example is electrostatic discharge from static electricity), or formation of a continuous electric-**arc** requiring continuous application of an electric field from an external power supply (**Figure 7**) capable of providing high-current (often in the Amp range). Arcs find applicability in welding of metals.

Conditions for sustaining continuous plasma operation: Following gas breakdown, there must be continuous application of external power to sustain a plasma. Other criteria include an electrode distance d that must be $\gg \lambda_D$ and that $n_e \lambda_D^3$ must be $\gg 1$ (this is easy to satisfy

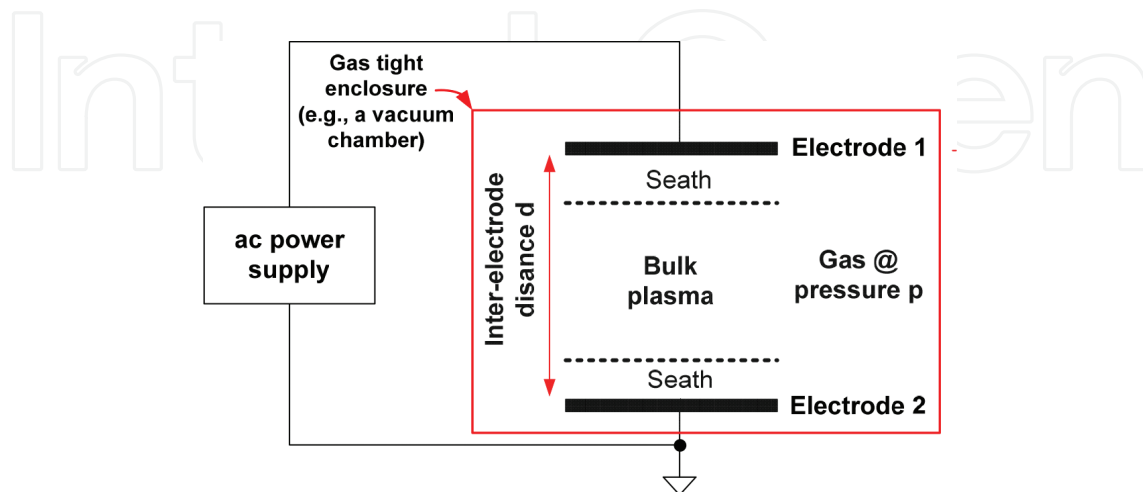


Figure 7. Ideal plasma formed in a gas-tight and pressure-controlled enclosure. The plasma is formed between two conducting plates or electrodes positioned at a distance (or gap) d from each other. For dc operation, pertinent literature should be consulted [124].

for the plasmas of interest to this work), where λ_D is the Debye length [133–137]. These will be briefly discussed later in this section.

For microplasmas formed inside fluidic microchannels, in addition to gas breakdown and to continuous application of power, a microplasma must be formed in a constrained microchannel.

3.2. Scaling of lab-size, ambient-pressure plasmas to microplasmas

Arbitrarily defined, microplasmas are those with **one critical dimension** in the micro-meter (μm) or in the sub-milli-meter regime [138, 139]. The words “*critical dimension*” (i.e., one dimension such as channel depth or width or radius) are important here: an **atmospheric** pressure microplasma in a microfluidic channel can range in length from μm to a 10's of mm, as long as its critical dimension fits the definition above. But as the critical dimension is reduced to sub-mm and depending on operating conditions, atmospheric pressure plasmas transition from **thermal and 10,000°C hot** (e.g., lab-scale ICP [132]) to **non-thermal and cold** [133–139] (e.g., microplasmas). They also transition from equilibrium to non-equilibrium (to an approximation, to those with gas temperature $T_g \ll T_e$ (electron T)). There are scientific implications due to these transitions (e.g., for nanomaterials synthesis) and for excitation mechanisms (e.g., for chemical analysis). In terms of technology-implications, cold plasmas enable use of inexpensive polymeric substrates that do not melt because microplasmas are cold and they do not require cooling; and they allow use of inexpensive 3D printing technology for fabrication.

Why miniaturize atmospheric-pressure plasmas? Operation at (or near) atmospheric-pressure is preferred because it obviates the need for heavy-weight and power-consuming vacuum pumps. By reducing weight and power consumption, atmospheric-pressure operation enables microplasma portability for chemical analysis *on-site* (i.e., in the field). By bringing a microplasma-based instrument to the field, microplasmas are expected to cause a paradigm shift in classical chemical analysis in which samples are collected in the field and are brought to a lab for analysis [140–148].

Due to plasma miniaturization, a number of questions arise. For example, how small **can** microplasmas be made? And, how small **analytical** microplasmas **should** be made? From a technology perspective, what is the minimum voltage required to ignite and sustain a microplasma? Would substrates tolerate the required high voltage? And, what is the preferred fabrication technology?

3.3. How small atmospheric-pressure microplasmas can be made?

A plasma (**Figure 7**, regardless of its size) consists of two plasma sheaths (located in the vicinity of two electrodes bathed in a gas-of-interest in a gas-tight container) and a bulk plasma [133–137]. Shielding (or damping or screening) of the electric field arises from the presence of charged species in the plasma and from the unequal mobility of ions and electrons in the vicinity of the electrodes. Inside the plasma sheath, macroscopic electrical neutrality is likely not maintained. But outside of it (labeled bulk plasma in **Figure 7**), macroscopic neutrality is maintained and (time-averaged) electron and ion fluxes are roughly equal. Thus (on a time-average and per unit-volume), $n_e \approx n_i$ (for singly charged species). The distance (or thickness) a sheath screens electric fields is called the *Debye length* (λ_D), given by Eq. 1.

$$\lambda_D = \left[\frac{\epsilon_0 kT}{n_e e^2} \right]^{1/2} \quad (1)$$

where k is the Boltzmann constant, T is the electron temperature, ϵ_0 is the permeability in vacuum, n_e is the electron number density and e is the charge of an electron.

To generalize, a key assumption is that sheath thickness is about the same magnitude as the Debye length. A few, what-if type thought-experiments will be used to obtain an indication on how λ_D changes as T and n_e vary. For example, for an atmospheric pressure plasma when $T = 10,000$ K (with 1 eV = $11,600$ K) and $n_e = 10^{16} \text{ m}^{-3}$, then $\lambda_D = 110 \text{ }\mu\text{m}$. But when $T = 5000$ K and assuming that there is no thermal ionization (thus the degree of ionization is constant and the same as in the example above) with $n_e = 10^{16} \text{ m}^{-3}$, then $\lambda_D = 80 \text{ }\mu\text{m}$. For less than atmospheric pressure operation and assuming that $n_e = 5 \times 10^{14} \text{ m}^{-3}$ and (for simplicity, assuming that the degree of ionization is unchanged) and that $T = 5000$ K, then $\lambda_D = 350 \text{ }\mu\text{m}$. Because plasmas cannot be made smaller than their boundary layers (per conditions outlined in Section 3.1), plasma sheaths (and Debye length) set a **fundamental limit** as to how small the inter-electrode distance d (**Figure 7**) can become, in other words, **how small a microplasma can be made**.

Since inter-electrode distance d must be $\gg \lambda_D$, and for the example with $\lambda_D = 110 \text{ }\mu\text{m}$ and for a two-electrode operation, then the microplasma must be larger (or much larger) than 2 times λ_D or (for this example) it must be $\gg 220 \text{ }\mu\text{m}$. As d becomes ~ 2 times the length of the sheath, the sheath-bulk plasma structure must disappear and thus the plasma must become devoid of a bulk plasma (**Figure 7**), that is to become a sheath-only plasma. But in a strict interpretation of the definition of a plasma, can such an ionized gas still be called a “*plasma*” [134]? There are published reports of microplasmas formed in constrained cavities that are smaller than $10 \text{ }\mu\text{m}$ by $10 \text{ }\mu\text{m}$ [133–137]. This has been explained by considering that sheath-thickness scales as inter-electrode distance decreases. Several open-ended questions in this research area still remain unanswered for instance, would microplasmas the size of 10’s of μm be useful for chemical analysis? To obtain insights, perhaps this question must be re-phrased to read “*how small analytical, atmospheric pressure microplasmas should be made*”?

3.4. How small analytical, ambient-pressure plasmas should be made?

There are two answers to this question. One is that microchannels can be 10’s of mm long ([48–51] and cited literature). Since there does not seem to be a fundamental reason why microplasmas should be constrained in μm -size cavities, microplasmas can occupy part of mm-long microchannels (**Figure 8**). Therefore, such microplasmas are not limited by Debye length or by plasma sheaths.

The other answer involves residence time of an analyte in a microplasma (**analyte = the chemical species of interest in a sample to be used for chemical analysis**). Residence time (important in elemental chemical analysis) is defined as the time an analyte resides in, or is in contact with or it interacts with a microplasma. In general, as microplasma length (dictated by the inter-electrode distance or gap) decreases, so does residence time. But as residence time decreases, so does signal intensity from an analyte introduced into a microplasma. This

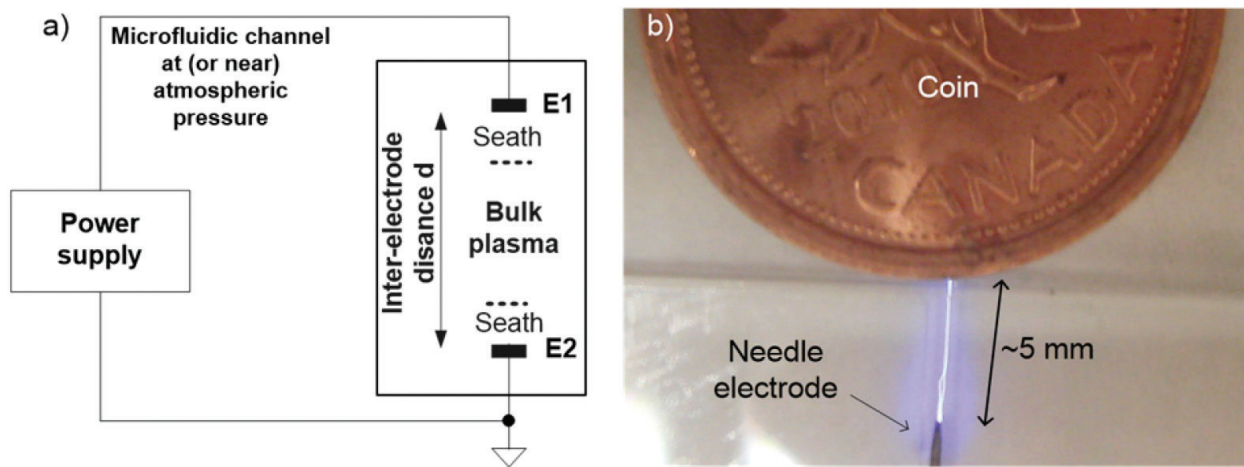


Figure 8. (a) Simplified diagram of a microplasma and (b) microplasma formed at the end of a needle electrode (OD: 470 μm , ID: 130 μm) inside a microfluidic channel on a microfluidic chip. A Canadian 1 cent coin (about the same diameter as that of a US one-cent coin, or UK's one-pence, or a one-cent euro) has been included for size.

is mainly due to a reduced interaction-time between an analyte and a microplasma. Thus, from an elemental analysis viewpoint, decreasing the length of a microplasma (e.g., by fabricating microplasmas in μm cavities) may not necessarily be beneficial in terms of signal intensity. This is significant because as signal intensity worsens, signal-to-noise ratio (SNR) degrades, thus degrading the detection limit (defined as the minimum amount or concentration that can be detected with a stated statistical confidence). The detection limit is a key figure of merit in chemical analysis. From the foregoing it can be concluded that mm-long microplasmas formed inside microfluidic channels (e.g., **Figure 8**) will likely be beneficial for elemental chemical analysis.

3.5. Igniting and sustaining a microplasma at atmospheric pressure

Conceptually, there are two steps involved in forming and sustaining a continuously-operated atmospheric-pressure microplasma. For instance, a microplasma must be first initiated (or “ignited”) and then it must be sustained. The minimum “ignition” (or sparking) voltage (V_b) for which the entire discharge gap is fully formed (often called “bridged”) when a uniform electric field is applied between two flat electrodes at a distance or gap (d) immersed in a gas of interest under pressure (p) can be determined using Paschen’s law (Eq. 2).

$$V_b = \frac{Bpd}{\ln\left[\frac{Apd}{\ln(1/\gamma)}\right]} \quad (2)$$

A and B are constants that depend on the properties of the gas in which the electrodes are immersed in (not accounting for any ionization due to background radiation). The values of A and B are either determined experimentally or they are calculated from literature values [139]. The coefficient γ (also known as Townsend’s coefficient) incorporates properties of the

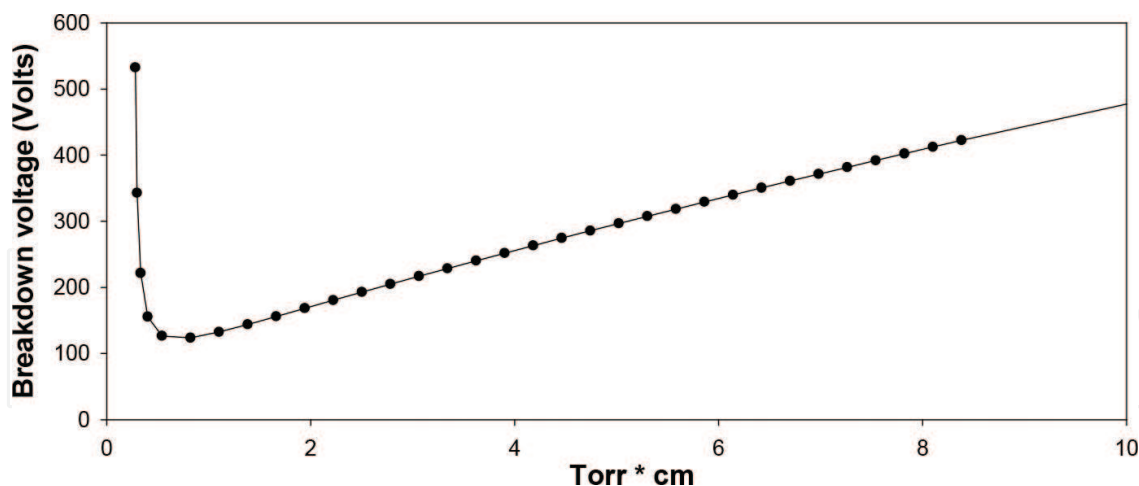


Figure 9. Paschen curve for argon gas and for a 2.8 mm inter-electrode gap (d) as a function of pd .

electrode material (e.g., work function) and it assumes that gas breakdown is predominantly a function of electron emission from the electrodes. In short, the two key variables in this equation are pressure (p) and inter-electrode distance (d). The product of p times d is often called “**pd scaling**.” An example of a Paschen curve is shown in **Figure 9**.

Paschen’s law applies to electrical discharges formed at low-pressures. In high-vacuum or at high pressures (e.g., atmospheric), Paschen’s law fails ([139] and references herein). There are also deviations from the behavior predicted by Eq. 2 when kHz or MHz ac voltages are used or when μm inter-electrode distances (or gaps d) are employed [139]. Undeniably, there are limits to applicability of Paschen’s law. Despite of these limitations, Paschen’s law (**presumably, the only choice**) can be used to obtain rough estimates of the magnitude of the voltage required to ignite (or initiate) an atmospheric pressure plasma. Thus it can be used as an aid in the design of appropriate power supplies. For instance, when the electrodes are made from Iron (Fe) and the inter-electrode distance d is 2.8 mm, and the discharge gas is Argon (Ar) at (or near) atmospheric pressure, the minimum voltage (V_b) required for gas breakdown (or for microplasma ignition) is about 6000 V. As the inter-electrode distance d decreases from 2.8 to 1 mm (and by keeping all else constant), V_b drops to about 2400 V, and when d further decreases to 0.5 mm, V_b drops to about 1400 V. It should be emphasized that gas breakdown at the minimum voltage V_b is not always necessary and that (once ignited), to sustain a microplasma lower voltages are typically required. An example is the ballast used in fluorescent lights.

4. Microplasma formation inside fluidic channels

The key idea behind microplasma miniaturization [138] is to obtain analytical performance about equal to that of lab-scale ICP-optical emission spectrometry (ICP-OES) systems [132] but by using self-igniting, low-power, low-cost, small-size, light-weight, continuous-flow and low gas-consumption (e.g., 250 mL/min) atmospheric-pressure microplasmas. The expectation is that such microplasmas can be used for “*taking part of the lab to the sample*” types of applications [140–142].

Based on these ideas, we fabricated and tested a variety of battery-operated, atmospheric pressure, self-igniting, mm-length microplasmas in fluidic channels [143–156]. Due to their mm-length, plasma sheath and Debye length are not of a concern. In addition to being “cold”, their high surface area-to-volume ratio further facilitates heat dissipation, thus facilitating use of polymeric substrates and 3D-printing fabrication methods. Example microplasmas fabricated in a variety of substrates will be discussed next.

4.1. Microplasmas in fluidic channels on amorphous substrates

For microplasmas formed inside a **microfluidic channel on a chip**, a dual substrate approach was used (**Figure 10**). Briefly, cleanroom-technologies (**Figure 2**) were employed to define and to sputter-deposit Au electrodes E1 and E2 (**Figure 10a**). Holes were drilled for the inlet and the outlet. On the bottom wafer, a chemically etched microchannel was formed. The top and bottom wafers (**Figure 10a and b**) were aligned so that the central part of the etched channel matched the protruding part of electrodes E1 and E2. Then the wafers were bonded together (**Figure 10c**) [143] and glass-tubes were affixed to the inlet and outlet holes (**Figure 10d**). The inlet was connected to a gas-supply (Ar-3\%H_2) that was used as the microplasma gas and as the sample-introduction carrier-gas. Upon application of electrical power, the microplasma self-ignited, it was formed between electrodes E1 and E2 and was sustained by continuous application of electrical power (~ 10 W). To avoid electrode breakage, a high-voltage ac [143] was used.

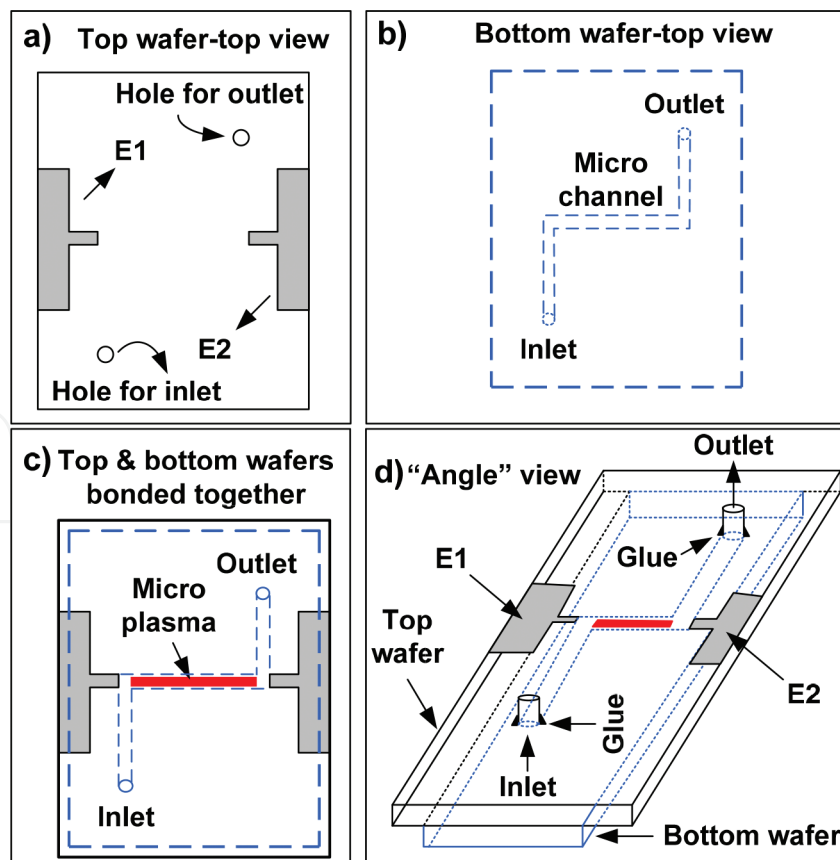


Figure 10. (a) Top chip showing electrodes E1 and E2, (b) bottom chip showing the etched microchannel, (c) the top and bottom chips bonded together (the microplasma was formed between electrodes E1 and E2, and (d) an “angle” view of the two bonded chips.

4.2. Postage stamp-sized microplasmas on polymeric substrates

To reduce ownership, operation and fabrication costs, we developed and evaluated a variety of microplasmas on polymeric substrates (e.g., **Figures 11** and **12**) [144–146]. Although a critical microplasma dimension was in μm -meter regime (**Figure 11**), these microplasmas were formed inside **millifluidic channels** (e.g., ~ 2 mm wide). This was done for rapid prototyping [109] and to avoid accidental contact of the microplasma with the channel-walls

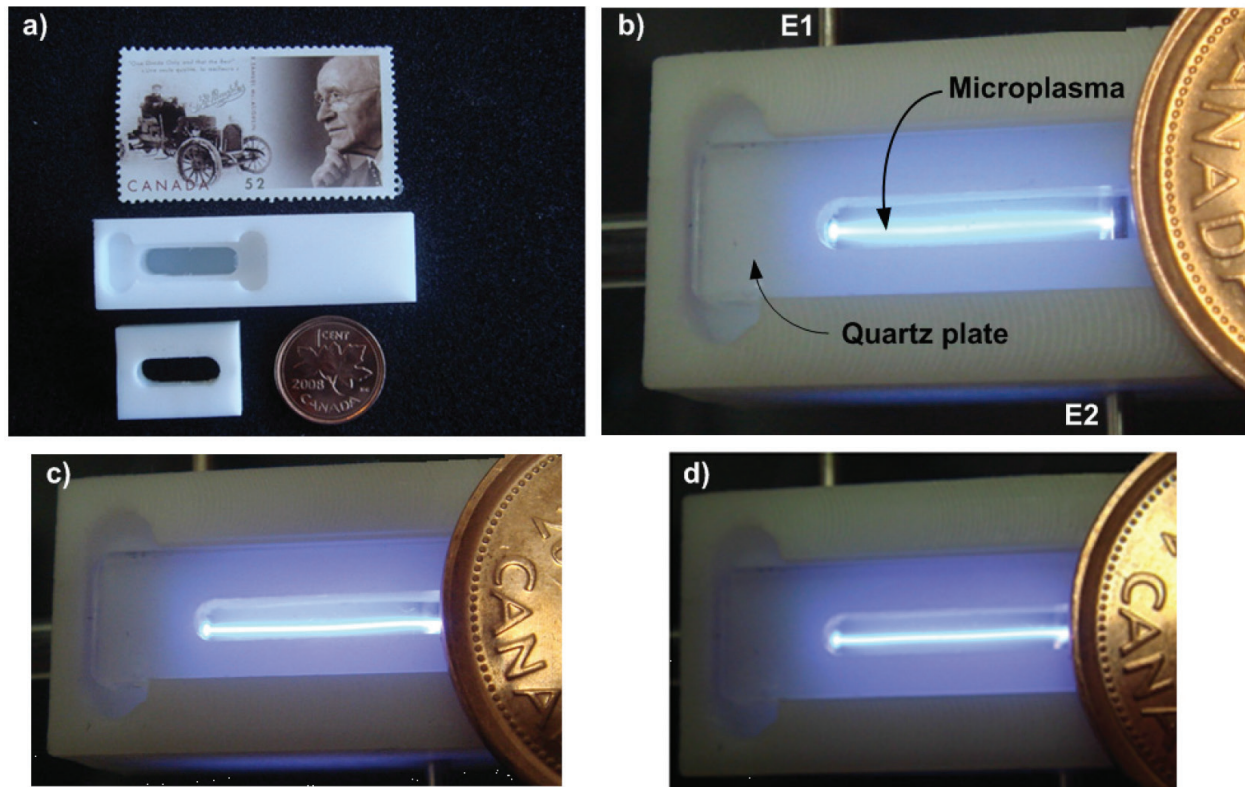


Figure 11. (a) Postage stamp-sized polymeric 3D-chips and (b) microplasma formed between electrodes E1 and E2. Depending on operating conditions, microplasmas with diameters of (b) ~ 750 μm , (c) ~ 400 μm and (d) ~ 200 μm were formed. A 1 cent coin was included for size, the microplasma fit inside the letter a of the coin.

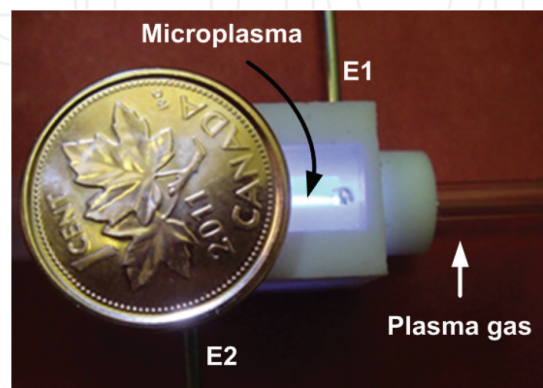


Figure 12. 3D printed microplasma on a hybrid 3D-chip formed between electrodes E1 and E2 (coin has been included for size, the microplasma fit inside the letter a of the 1 cent coin).

(important during testing). Once prototypes were produced, channel width was never revisited. Although polymeric substrates have high dielectric strength, to address poor transmission of polymers in the UV, the channels were fitted with a quartz plate (**Figure 11b**).

4.3. Millifluidic channels in 3D-printed chips for microplasma

3D-printing [109–122] was accomplished using a 3D-printer (~\$1000) to rapidly prototype 3D-chips in a few hours (or less), thus obviating the need for cleanrooms and lithography. We used 3D-printing to fabricate hybrid chips (fitted with a quartz plate and needle electrodes) for microplasma formation in millifluidic channels [146, 147, 149]. An example is shown in **Figure 12**.

5. Nanofluidics

The nanoscale [157–194] is a natural extension of the microscale (**Figure 1**) and it is defined as the science, technology and application of transport phenomena and of fluid-flow in channels ≤ 100 nm or around nano-size objects [158, 170]. This is not universally accepted, many consider nano-size as anything with one critical dimension ≤ 1 μm . The range between 100 nm and 1 μm is sometimes referred to as “*extended nanofluidics*” [181]. Nanofluidics is not new, although the name is [159, 160].

5.1. The science of nanofluidics

In nanofluidics, size (or scale) is important, likely more so than in microfluidics. For instance, at the nano-scale many dimensions of molecules are of similar size as the nano-fluidic channels that constrain them (**Figure 1**). A few scientific questions that being addressed include: How do properties of individual atoms, ions or molecules, manifest themselves as they are confined in spaces (roughly) of their own size? Would quantum effects become important [173]? Since pressure is not used to force fluids through nanochannels, should electrokinetic flow be preferred? And, as surface-to-volume ratio increases significantly (over microchannels), what is the effect of surface-charge on ions or molecules confined in nanochannels? What is the effect of surface roughness on fluid-flow? And, how do surfaces interact with ions or molecules so close to them? What are the best surface modification approaches? What is the effect of van der Waals forces and of the electric double layer (EDL) at the nm-scale? Some questions arising from technology include: how would one introduce very small volumes of analytical samples into nanofluidic channels? To facilitate discussion, assume a cylindrical nanochannel with 100 nm diameter and 1 μm length. In this case, the volume is 100 atto Liter (aL). How would one introduce an aL volume sample into a nanochannel without evaporation of some of the analyte or of the solvent? Due to the infinitesimal volumes used, would single atom, ion or molecule measurement techniques be essential? In support of this, it has been estimated that in a liquid the volume of a cube with dimensions 100 nm by 100 nm by 100 nm, there are only ~ 6 analytes when the concentration of the analyte is 1 μm [160]. Would sample separation, pre-concentration and use of highly-sensitive detection techniques (e.g., laser induced fluorescence or LIF) become essential?

5.2. Technology for fabrication of nanofluidic channels

According to the National Science Foundation (NSF) in the US and its National Nanotechnology Initiative (NNI), nanotechnology involves “*the application of scientific knowledge to manipulate and control matter in the nanoscale*” [158, 170], more or less arbitrarily defined at ≤ 100 nm [158, 170]. Nanofluidics often falls under nano electro mechanical systems (NEMS) [164, 177–179, 184] typically fabricated using complementary metal oxide semiconductor (CMOS) technology [177, 178].

For nanofabrication, many technologies have been described [159–162, 165, 166, 169, 171, 172, 180]. Some of them are nano-specific [159, 169] for example, scanning probe lithography (SPL) [161], etching using a focused ion beam (FIB) [171] and nanoimprinting [159]. In many cases use of a cross-sectional area of a nanochannel is preferred (e.g., 10 nm by 10 nm) rather than aspect ratio. Nanofluidic channels can be nanofabricated using either top-down or bottom-up approaches.

Top down methods of fabrication of nanochannels: By analogy to micromachining, these fabrication methods include bulk nanomachining; surface nanomachining; and, imprinting (as is typical of soft-lithography) [159, 161–165, 169]. A top plate is typically used to cover nanochannels but due the nanosize of the channels and unless precautions are taken, channels may plug-up during bonding.

Bottom up methods of nanostructure formation: in some cases molecules can be “convinced” to self-assemble into nanostructures by controlling chemical conditions [160, 162].

Associated nanofabrication technologies include scanning probe lithography (SPL) [161], electron beam lithography (EBL) [159] and dip-pen nanolithography [185]. Such approaches are typically used to bypass the diffraction-limit of photolithography or to provide new capabilities.

5.3. Applications of nanofluidics

In addition to enabling fundamental studies of fluid-flow and of transport phenomena (with many studies aimed at the study of naturally occurring processes in biological nanochannels), many applications are aimed at bio-sciences, bio-nano-technology and bio-analytical chemistry where applications exist in abundance [166–169]. Applications outside of classical nano-fluidics include nano-pores (e.g., for bio-applications and DNA sequencing) [186–192] and even for the study of fluid-flow in nano-porous media [193, 194]. For chemical analysis, NEMS have been developed for single protein mass spectrometry [174] and for airborne nanoparticle detection [176]. From this short list it can be concluded that nanofluidics has the potential to become a disruptive technology worthy of further investigation.

6. Conclusions

Microfluidics continues to receive attention in science and technology due to its many applications. And as shown, it has the potential to find applicability in constraining atmospheric-pressure microplasmas in 2D-microfluidic channels (**Figures 8 and 10**) or in 3D-millifluidic

chips (**Figures 11** and **12**). Future developments include coupling of standard CMOS fabrication technology [179, 183, 184, 195–197] with microfluidics or millifluidics, thus allowing integration of fluidics with electronics. Microinstruments are those with at least one critical (or essential) component operating in the micro-regime. For nanofluidics as may be applied to chemical analysis, it appears that it will be best if nanofluidic channels was packaged alongside microfluidic channels.

It is envisioned that future fluidics (**Figure 1**) will be embedded within portable micro- or nano-instruments for measurements *on-site* (i.e., in the field). Such instruments will have (some) energy autonomy [198–200], will incorporate some “smarts” [201] (e.g., based on Artificial Intelligence and Deep Learning) and will have wireless capability [202] so that they can become a part of the Internet of Things (IoT) [200–203]. Clearly, fluidics (e.g., milli-, micro- or nano-) have the potential to become critical components of mobile (or even wearable) instruments that are “cheap, smart and under wireless control” [139].

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