What Comes Next?

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Reinvention

Every field must periodically reinvent itself to remain vital. Microfluidics, and the concept of the lab-on-a-chip (LoC), have had a spectacularly successful 15-year run of science and technology. The combination has achieved much more than one could have imagined at the beginning, but also less than one might have hoped for in the most expansive of visions. There are now two strategies—two paths—for it to follow in going forward: (i) It can gather up the technology that is now available, and develop it fully and completely. This strategy would focus on finding uses for what now exists, and motivate the development of downstream technologies—manufacturing at scale, quality control, standards, interfaces, regulatory clearance, and all the others—with those uses. The development of the downstream manufacturing technologies will be challenging, and absolutely necessary before laboratory prototypes become large-scale commercial realities. (ii) It can invent new things, and see if the momentum of new ideas will carry the field forward. This strategy does not necessarily directly result in products, but it demonstrates the components and options which would support *later* technologies. Sexy new ideas also build enthusiasm for the field, and demonstrate capabilities that—in an area that really *is* new—are *unique*, and that give rise to applications that pull the science into technology.

Both paths are important for LoC technology: It must, of course, push technology into products in order to have the impact that will sustain the field. Still, the period of highly productive invention and science in LoC systems and microfluidic technology is hardly over, so new ideas are also important.

Everyone active in the field could make up a list of exciting opportunities; the length of an aggregated list, and the diversity of the opportunities suggested, would provide one measure of its vitality. I would not presume to offer a canonical list, but I will summarize a few of my favorite topics, to give a sense for where I see attractive opportunities. Let me give you some of my favorites in both strategies: that is, in invention of new science and technology and in the development of existing technology.

1. Nanofluidics

Microfluidics is the study of fluids moving in micron-scale (usually, to be more accurate, 100-micron- or submillimeter-scale-) structures. There are many interesting characteristics of these now-familiar systems, of which perhaps the most different by comparison with macroscopic fluid flows, and thus, so far, the most useful, has turned out to be laminar, or low Reynolds-number, flow. The field of "microfluidics" has not yet made a concerted effort to understand true *nano*fluidics (which I will characterize as the behaviors of fluids in structures with dimensions from 1 to 100 nm). It is not quite clear why microfluidics has extended only slowly into nanofluidics, but one reason is probably that there are still no methods of fabrication that would make it easy to generate nanofluidic structures, or that would allow the behaviors of fluids in them to be easily characterized.

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And why would one care? What is interesting to me about nanofluidic systems, in principle, is that the behavior of fluids in nanochannels will probably be dominated by their proximity to the surfaces making up the walls of the channels (or other structures contacting the fluids). Nanofluidic systems will be, in other words, "all interface," and the study of nanofluidics may ultimately become more a branch of surface science than an extension of microfluidics. Regardless, one of the least understood, and most important, areas of science and technology is that of interfacial fluids. Storage of energy in capacitors and batteries, corrosion, lubrication, molecular recognition, sensing, adhesion, biocompatibility—all are intimately concerned with the properties of fluids (and, of course, of the molecules and ions in them) that are making the transition from a constrained environment (immediately adjacent to the surface) to the bulk fluid.

2. Digital microfluidics

The microfluidics/LoC community has begun actively to embrace the study of dispersed phases moving in microchannels. The invention of a number of simple structures (flow-focusing nozzles, T-junctions, and others) opened the door to this field by making it possible—for the first time—to generate monodisperse droplets or bubbles in virtually unlimited numbers, very rapidly (bubble generation rates now approach 100 kHz); microfluidic channels make it possible to manipulate and sort and combine these droplets with remarkable sophistication. Each of these droplets, in principle, is a micro-reactor, and the potential for using droplets for a wide range of applications—genomics, proteomics, single-cell analysis, cell selection, phage selection, many others—seems very large, albeit still at an early stage. "Digital PCR" (from which phrase I adapt "Digital Microfluidics") is developing rapidly, but other uses for these systems—in biology, in food science, in a wide variety of different types of analyses—coupled with the remarkable self-organizing properties of large numbers of droplets in microfluidic systems, makes this area, to me, extraordinarily attractive for exploratory research.

3. *Inside* biology

One of the long-term justifications for the relevance of microfluidics to biology has always been that it provides information concerning fluid flows in cells and organisms. Organisms with a circulatory system are, essentially, networks of pipes of various sizes which transport fluid among its various parts. Flows of fluids in biology range from turbulent in large pipes (*e.g.*, the aorta), to laminar in small ones (*e.g.*, capillaries); these flows can be either highly non-Newtonian (the contents of the bowel, the cytosol filling the interior of the cell) or Newtonian (normal urine); they can have multiple dispersed phases (cells or clots in blood or lymph, or pathogens in the circulation), or be (we think) homogeneous; the structures of the channels can range from simple tubes to complex, networked, gel-filled capillaries, and the immensely complex networks of structure and architecture constituting the human circulatory and lymphatic systems (which we barely understand). Most serious observations of fluidics in biology have discovered behaviors that are interesting and unexpected. Since almost everything in biology has layers of complexity that extend apparently without limit, if the first surveys of biological microfluidics have revealed as much of interest as they have, we can only begin to guess what more serious investigation will reveal.

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4. New types of uses

Partially as a reflection of the history of its origin (and partly, probably, since it is where the money for start-up companies has largely been), developments in LoC technology have strongly emphasized bioanalysis, particularly bioanalysis relevant to human healthcare and to research biomedicine. This field is enormous and diverse, and these developments will certainly continue. The field should think about opportunities in other areas as well. In applied biology, there are a range of opportunities in plant and animal health, and largely untouched potential for use in public health (as opposed to high-technology medicine): vaccination status and nutritional status are two in which convenience and very low cost are especially important. Fluidic optics—the use of fluid-filled channels as optical waveguides and lasers, and of droplets for lasing, and for uses of lasing such as in-cavity detection—is attracting substantial interest. Systems of droplets or bubbles in complex microfluidic behaviors indicate massively parallel interactions among them, and suggest the possibility of use in new kinds of analog computation, and possibly in transmission of information. The use of microfluidic systems in organic synthesis is no longer a new idea, but applications successful enough to drive the field still remain to be developed. The uses of magnetic separations in all areas of microanalysis have just begun to be examined. Combinations of microfluidic systems, compressed gases, and liquid metals, offer potential routes to the solutions of problems in soft robotics. Most of the cards in the microfluidic deck have still not been revealed!

5. Cheap, interconnectable, stackable systems

One of the surprises of microfluidic systems is that although the technology has developed well, LoC systems are still not being used extensively. There are various arguments for what is now required to make the next step, but one guiding lesson from other fields of microscience is "cheap is good;" the second is "they should be easy to build with." Microelectronics has prospered because it learned (in fact, taught) both lessons; silicon MEMS, by contrast, has developed much more slowly, in part because "cheap" has been difficult. And even in microfluidics, polymers have essentially displaced silicon and glass, largely because of cost.

Although the field of microfluidics strives to draw analogies between LoC systems and integrated circuits, the analogy is fundamentally weak. The parallel fabrication, and ease of interconnection, available with silicon microelectronics simply, at present, has no parallel in LoC technology, and even inexpensive polymer systems are dramatically more expensive than microcircuits of comparable functionality and complexity. Taking microfluidics to a new plateau of cost and interconnectivity may not require fundamentally new science, but it will require a change in the objectives of the engineering: the rapid development of simple microfluidic systems based on patterned paper for applications in public health in developing countries provides an example of the power of "cheap" and "simple."

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6. New fluids, fluidics, and materials

The field of microfluidics has had a very restricted view of fluids and the materials used to contain them, and LoC technology has worn complementary blinders. Much of the work in microfluidic systems is implicitly focused on the objective of bioanalytical systems, and thus has found it quite satisfactory to use commercial polymers, and to assume water or an aqueous solution as the working fluid. What could be done with fundamentally different fluids, and what materials might be required to work with them? As one example, many inorganic materials (for example, glass, calcium phosphate, silicon) form low-viscosity fluids at sufficiently high temperatures. What could be done by manipulating such high-temperature fluids using microfluidic systems? What would be the behaviors of high-temperature melts of glasses or metals moving through appropriate systems? Could one make microelectronic systems, or silicon MEMS, by molding liquid semiconductors? Solar cells? LEDs? Could one assemble more complex systems using techniques related to cofabrication? What about the microfluidics of flames and plasmas? Most of these exploratory efforts would require new methods of fabricating microfluidic systems in unfamiliar materials (*e.g.* zirconium oxide, thorium oxide, graphite, and niobium have excellent high temperature properties, but how would one fabricate microsystems in them? Even more to the point, how would one characterize the movement of fluids in them?).

On a more mundane level, is it inconceivable to make microsystems fabricated in glass as inexpensive as those fabricated in polymers? To do so would certainly solve many of the problems that appear when using reactive solvents in polymer-based microfluidic systems.

7. Interfaces and standards

The subject of interfaces and standards might seem boring, but to a technologist they are not, they are essential parts of building any new technology. Think of what the simple USB connector has done for microelectronics. Think (or learn) about all of the standards that go into microelectronics, or components in automobiles, or open software, or household electrical systems. Complex technologies almost always have multiple parts, and the parts must connect with one another transparently and effortlessly, so that designers know that the component they are designing can be connected, and so that users know how to put components together (with the assurance that they will work once connected). The field of microfluidics is beginning to think about interfaces and standards, but there is still disagreement about whether the time is ripe for a serious effort to design and set standards. Setting standards is, in a sense, imposing a freeze on design, and one does not want to do it in a way that limits creativity and slows the development of new systems. Nonetheless, until there are standards, it is effectively impossible to build a technology of interconnected components, and the creativity of down-stream designers – the designers whose skill is to take existing components and put them together in creative new ways – is blocked without understood standards. There is also no free lunch, and building interfaces and standards requires work. It may, however, be appropriate, and necessary, now. Thinking through standards and interfaces, prototyping systems demonstrating them, and developing a technology for them for LoC systems will require great ingenuity, and will be *very* important for the field.

Lack of standards and interconnectivity poses a potential barrier to the creativity of designers.

These seven topics are purely personal choice: any reader could come up with an equally good list, and the list would probably be quite different. That fact—that there is a wide range of opportunities, and a wide range of opinions on what is more important and what is less important—gives a measure of the health of the field. So long as there are *lots* of opportunities, and *lots* of differences in opinion, the broad area encompassing LoC and microfluidic technology (and plausibly extending into a range of other subjects, from energy storage and robotics to low-cost MEMS) is in good shape. Disputation is good.

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