Solving problems

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The arguments for lab-on-a-chip (LoC) technology, and for applied microfluidics, are, to me, so strong as to be unarguable. Three strong ones are these: (i) Many analyses – especially biologically related analyses – *must* be carried out in solution, and thus must involve manipulating fluids. Medical and biological analyses, in particular, are often limited in the quantities of sample that are available, so "micro" is an essential part of any successful bioanalytical technology. (ii) The importance of streams of aqueous solutions – with dissolved biomolecules and suspended cells – moving in microchannels to understanding "life" is as great as is that of streams of electrons moving in semiconductors and metals to "information." Life and information are at the core of modern science and technology. (iii) Fluids moving in microchannels are vitally important in a legion of other areas, from food processing to enhanced oil recovery, and from water purification to the operation of fuel cells.

Stimulated, in the mid 1990s by a DARPA investment in a relatively routine (although technically difficult, and still largely unsolved) problem – the development of portable micro-analytical systems to protect military personnel from chemical and biological threats – LoC technology has developed remarkably rapidly. It has now, arguably, successfully reached the end of its first phase: the development of a science base, and of component prototypes, largely within academic laboratories. It has produced a range of successful, relatively low-cost, very flexible methods for manipulating fluids.

Many people, myself included, expected that the ability to manipulate fluid streams, in microchannels, easily, would result in a proliferation of commercial LoC systems, and that we would see applications of these devices proliferating throughout science. In fact, it has not (yet) happened. There are certainly important applications of microfluidics, and of some of the concepts of the LoC: fields that use microfluidic technology (whether originating in the new science of microfluidics, or in older areas of technology, is not important for this discussion) include gene sequencing, genomics and proteomics, high-throughput screening, capillary electrophoresis, systems for home health monitoring, CE-MS and other high-technology analytical methods, electrospinning, inkjet printing, and a number of others: all require controlling the flows of liquids in microchannels or microporous media. So, the technology is important and is spreading; but what it has not done is to produce the expected revolution in its applications.

Why not? And what of the future? I continue to think that the importance of "life" and "analysis" and "small volumes of fluids" are so great, and the potential of microfluidics to contribute to the science of life, and to the technologies of analysis, are so broad, that the overlapping fields of LoC and microfluidics will eventually become very important practically and commercially. I also think that based on commercial levels of investment—always *much* larger than academic levels—they will blossom into a major new technology. But why has it been slower than expected? What is missing?

I observe that microfluidics, to date, has been largely focused on the development of science and technology, and on scientific papers, rather than on the solution of problems. Developing a "real" technology – desk-top computation, commercial NMR spectroscopy, lasers, cardiac stents – is a very expensive process, and the resources (both human and financial) needed to do so (in a capitalist system) really only become available when it is clear that there is a market that will justify the investment of those resources in terms of return on investment. To say "market" in this context is not to refer to the many and important problems of manufacturing, distribution, and sales (although they are important) but only to the more limited activities required to connect a new technology to a recognizable problem for which that technology is uniquely the best solution.

One approach to helping microfluidics move to the second phase of its development – the phase in which it becomes an important commercial technology, rather than an area of academic research – requires understanding that to make contributions to solving commercially important problems, the field may require help (or even controlling direction) from disciplines that have little or nothing to do with microfluidics or LoC technology. Let me sketch four examples:

Biomedical analysis: Biomarkers of disease

The microfluidic science and microfabrication technology required to build simple systems to solve problems in bioanalysis is probably more than adequate now to produce at least working prototypes of commercial systems. What is almost completely missing is the biology that would make such systems valuable. The technologies for even routine colorimetric analyses, immunoassays, or simple nucleic acid-based analyses are not a routine part of LoC systems. There is no clear sense for what to do to make information produced in a LoC valuable to doctors or HMOs or insurers. And importantly from the vantage of the underlying science, the field of biomarkers – one of the fields commonly used to justify microfluidic systems in medicine – is currently in disarray. The LoC community must be able (alone, or more probably working with others) to identify *specific* bioassays (type, target, and use) that provide information that would be valuable in guiding diagnosis and treatment, that would benefit the patient, and that would also reduce the overall cost of the healthcare system. This specification of a problem is easy to state, but hard to solve, not because the LoC technology is inadequate, but because the biology and medicine are very difficult.

Organic synthesis

There is growing interest within the LoC community in developing microfluidic systems that are compatible with non-aqueous systems and harsh chemistry.

There may be important applications of such systems in the future: for exotic synthesis of the type required in PET analyses, or in working with small volumes of hazardous substances. But the assumption underlying the interest in this technology is that organic chemistry will continue to be focused on organic synthesis, and serve – primarily – the pharmaceutical industry. Chemistry has many important and interesting tasks in its future, but organic synthesis may, in fact, be much less important among them than it has been in its past.

Medicine

An assumption of the LoC community has been that an important customer for its products – perhaps the most important customer – would be the medical system, and the closely allied academic discipline of research biology. Medicine, as we know it in the developed world, is focused on end-of-life, high-technology, *very* expensive treatment of established disease. There are now enormous pressures to reduce the cost of this system, and substantial disagreement as to whether it is even correctly focused. "More analyses" is not emerging as the answer.

An alternative for the LoC community would be an alliance with the field of public health, where health-related information (and its cost), epidemiology, anticipatory and preventive medicine, environmental monitoring, and cost-effectiveness are key issues. These issues may be a better fit for LoC technology than curing cancer or limiting the effects of myocardial infarct, and in fact the largest number of bioassays performed in medicine are in managing a cost-sensitive, chronic disease: that is, measurement of blood glucose in diabetes.

And as for research biology, unless the LoC technology comes as a commercially standardized product, pre-sterilized in a bag, it is unlikely to be used by most biologists: the rigors of cell and organismic biology are such that it is implausible that research biologists will learn to design or fabricate their own microsystems.

Early-stage technologies

Imagination, and active exploration of new functions for microfluidic systems, has the potential to lead to unexpected new directions. We have found enormous interest in paper diagnostics for the developing world. Membranes for fuel cells, water purification, natural gas processing, and other applications in energy may benefit from the application of microfluidic technologies. The movement of oil and water through porous media is a classical problem in microfluidics, with many still unsolved problems. Emulsions and dispersions are critical to a surprising number of fields, and would benefit from microfluidics. All of the subjects in this list require a model for developing the relevant technology in which experts in microfluidics and LoC systems collaborate actively – and probably as followers rather than leaders – with experts in other fields. As an academic scientist/engineer, it is often more comfortable to work in isolation in developing technology and components, but lack of engagement with users will probably be the slow route to the point where microfluidics merits the investment required to produce a revolutionary technology.

But basically: if you simply build a better component for a microfluidic system now, chances are it will get lost. Building a better mousetrap requires knowing in detail what a mouse is and does, appreciating that people would like to trap them, and understanding how much they will pay to do so. The most elegant springs and frames – as components unconnected to products – will not make it. "Build it"—a complete system; one that successfully traps mice—and perhaps (or, optimistically, probably), "they will come."

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