

Viewpoint on “Dissolvable fluidic time delays for programming multi-step assays in instrument-free paper diagnostics”

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Simplicity in diagnostics

Medical diagnostics must function in a wide range of environments: from urban hospitals in developed countries (where cost and simplicity are presently not crucial objectives) to remote settings in developing economies, where little is available in terms of infrastructure (and where low cost and great simplicity are everything). The “developing economy” challenge is one that is now being embraced by the microfluidics community: exactly how *does* one provide biomedical information when there is no electricity, refrigeration, clean water, or trained medical personnel?

Although the challenges of inexpensive, self-contained medical diagnostics are often phrased in terms of medical needs encountered in, say, the rural villages and large urban slums of Africa, practical solutions to these challenges would also be widely useful in many other circumstances: examples of other types of applications that share at least some technical requirements include medical diagnosis in military field operations, detection of diseases of animals and plants, verification of food and water safety, environmental monitoring, analyses for homeland security, and chronic and point-of-care health monitoring. In each area, specific applications require some combination of simplicity, robustness, and low cost. New methods applicable to one have the potential to be applicable to others.

Making diagnostics reliable without the infrastructure usually available in a well-supported academic laboratory (where much of the LoC technology has originated) is more difficult than it seems. The characteristics that must be built into a successful system make a long list, and sometimes seem incompatible; for example: how can *unskilled* personnel accurately measure the intensity of color in a colorimetric assay? How can one use the reliable, workhorse reagents (*e.g.*, common enzymes and antibodies) of bioanalysis if they are unstable in the environments in which they must be used? Because the list is so long, there will probably be no single, best solution, but rather ingenious solutions for each problem

that will then be combined in packages tailored to specific applications.

Passive delays

Of the myriad of problems, a recent *Lab on a Chip* paper, *Dissolvable fluidic time delays for programming multi-step assays in instrument-free paper diagnostics* by Lutz and co-workers,¹ takes on an important one that is general to many procedures, and offers an ingenious approach to a solution. Most biochemical analyses require a sequence of steps: collection and manipulation of the sample, preparation of the sample for analysis, introduction of the sample into the analytical system, addition of reagents (often complicated by episodes of washing and/or incubation), readout of the results, and so on. This sequence of steps, in turn, often has the common problem of *timing*. How does one make sure that the steps occur in the correct order, and follow the protocols required for their successful operation, when they must proceed with minimal or no human involvement (either because there are no trained personnel, or because the personnel are occupied by other jobs)?

Lutz *et al.*¹ demonstrate that it is possible to achieve controllably variable timing in paper microfluidic systems by using solid sugars deposited in the channels to provide time delays; they further show that this type of system provides the basis for the timed addition of reagents and washes required in a protocol modeled on the familiar lateral flow immunoassay. A number of methods of controlling the valving of flows through channels have been demonstrated in the past. In particular, Paul Yager² showed that sugars provided the basis for valving in paper microchannels, and Scott Phillips *et al.*^{3,4} offered an alternative method based on the use of wax to tailor the hydrophilic/hydrophobic balance of the channels, and thus the flow through them. The paper by Lutz¹ carries this approach further, and places it on a more quantitative engineering footing, in two steps: (i) They analyze the characteristics of the flows through channels in which movement of a capillarity-driven liquid front was accompanied by

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solution of solid sugar deposited on the paper, and demonstrate that the success of the sugar-based “delay lines” depend primarily on the viscosity of the solution moving through them (highly concentrated, viscous solutions of sugars move more slowly; less concentrated, less viscous solutions move more rapidly). (ii) They design (using their understanding of these flow characteristics) an ingenious gold-amplified immunoassay, in which the timing of the addition of samples, washes, and reagents is controlled by the amount of sugar deposited on the paper in the channels. It is an elegant idea, and one that fits naturally into facts that suggest it has characteristics required of a technique that is to become a component of the technology of paper diagnostics: in particular, it is inexpensive and simple, and sugars are already commonly used as additives to stabilize proteins against degradation and loss of activity upon storage in the dry state.

Next steps

As with any new technology, this one will require further development before it is ready for routine use. Some obvious problems probably have solutions that can be accomplished through good engineering (for example, evaporation of water from channels has the potential to change concentrations, and

thus rates of flow, but should be controlled through careful packaging); some will be more difficult (the flows of liquids observed show non-uniform profiles (for example, “fingering”) across the channels—a type of behavior that is frustratingly familiar from experience with the use of water flooding in enhanced recovery of oil from petroleum reservoirs). These issues aside, the spirit of this demonstration—to replace mechanical valves and electrical controllers with physically based processes that take place autonomously—is exactly the correct one, and this work—together with other, ideologically related solutions to other problems—will ultimately combine into the technology base that will support some of the lowest-cost, most robust, and most fieldable of the diagnostic systems that will develop as this type of academic technology matures into practical products accepted by users.

References

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