Folding a drop of water solves a longstanding challenge in portable diagnostic devices

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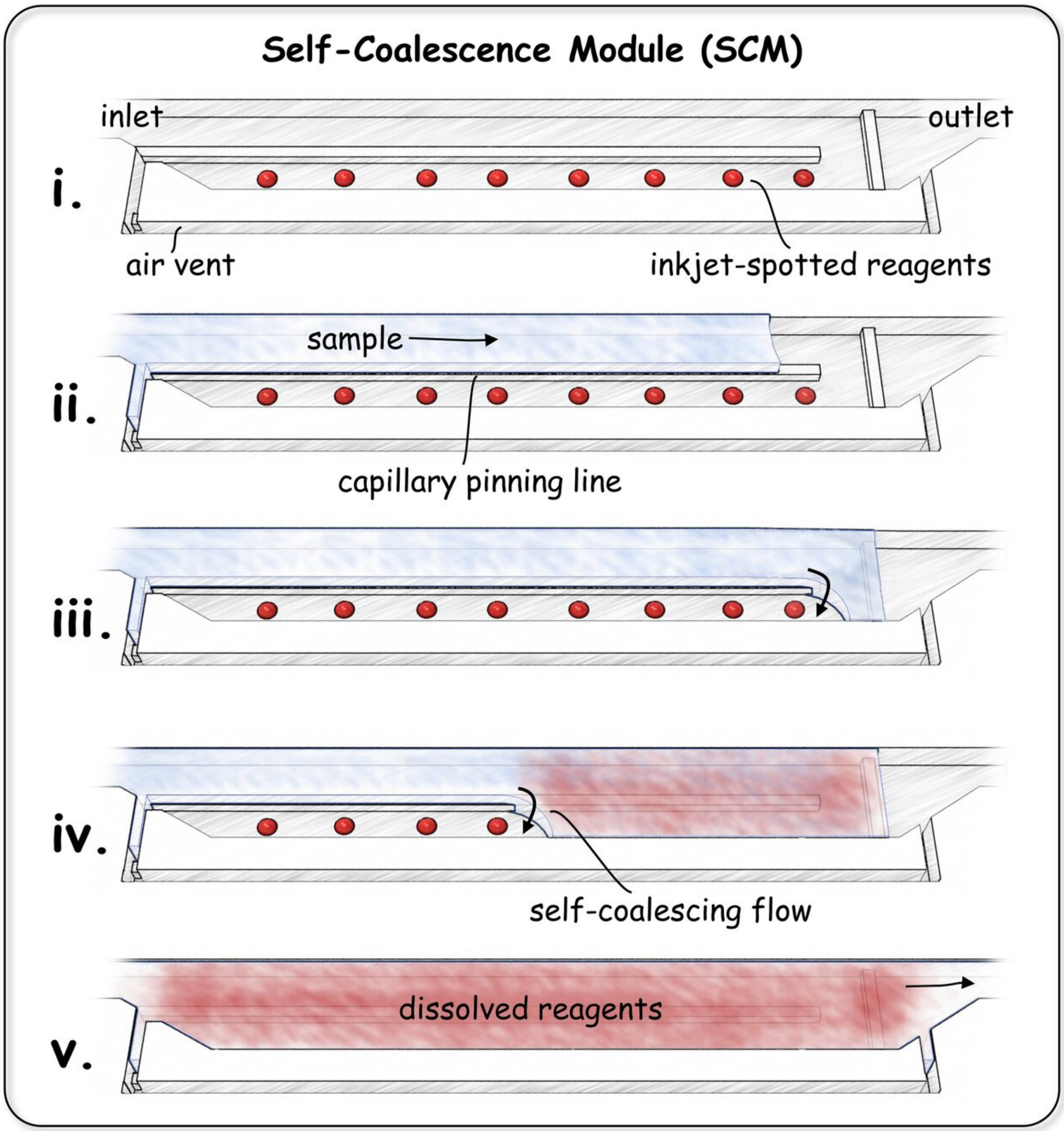

Artist's depiction of the process of self-coalescence in a microchannel. i) Picolitre-sized droplets of reagents are deposited by a process analogous to ink-jet printing into a microstructure, which is then sealed to form a microchannel a few tens of microns deep. ii) When the fluid sample is introduced, an air/water interface is created above the capillary pinning line at the middle of the channel. iii) The fluid is forced to make a U-turn and touch its own air/water interface, iv) causing it to "zip" along the interface, filling the channel perpendicularly to the general direction of the flow. v) In doing so, the reagents are reconstituted "on the spot" with minimal dispersion. Credit: Polytechnique Montreal and IBM Research Zurich

If you've ever stopped to watch rain falling on a windowpane, you've seen what happens when two drops of water touch and merge into one. The physics at work in this phenomenon could provide unlock a solution for the development of miniaturized personal biological analysis devices. An international team of scientists from IBM Research-Zurich and the Microfluidics for Oncology Laboratory at Polytechnique Montréal have reported this discovery in *Nature*.

Installing a lab on a chip: a longstanding challenge

For the past two decades, research conducted around the world into so-called lab-on-a-chip devices has shown promise for portable tools requiring only a small sample of bodily fluid (e.g., blood, saliva, urine) to screen for diseases or measure biological data. These kinds of miniature systems already exist for simple measurements made with few reagents: glucose meters and pregnancy tests are two examples. But more complex analyses, which require mixing a single sample with a series of reagents in precise quantities in a specific order, have proven more difficult to develop.

One of the most promising approaches for integrating multiple reagents into one testing device is to deposit picolitre-sized droplets (a few billionths of a millilitre) into a microsystem using a technique analogous to inkjet printing, and then sealing the device. On contact with air, the tiny quantities of liquid evaporate instantly, leaving a very precise sequence of dried reagents, which can be rehydrated when the fluid sample is added at the time of the test. A major difficulty has persisted, however: When the fluid moves across the dried reagents, it disperses them, "scrambling the signal," and preventing execution of delicate diagnostic steps that involve precise biochemical measurements.

To attack the dispersion problem, Onur Gökçe, Yuksel Temiz and Emmanuel Delamarche of IBM Research-Zurich hit upon the idea of stretching a water droplet into a long ribbon-like shape in a microchannel the width of a human hair, and forcing the liquid to fold over onto itself. In doing so, the water sample closes up in a manner similar to a zipper being fastened.

"This very intriguing process allows us to reduce, to the minimum, the flow rate of the liquid locally, where the dried reagents are, so that when the reagents are rehydrated, they no longer disperse," explains Emmanuel Delamarche, manager of the Precision Diagnostics group at IBM Research-Zurich.

While the results observed were conclusive, the team studied the fluid dynamics phenomenon at work so that it could be exploited as part of a reliable process. Professor Thomas Gervais, head of the Microfluidics for Oncology Laboratory at Polytechnique, tackled that part of the project.

From experimentation to modeling

By further studying the behaviour of the water drop, the researchers concluded that it was related to the phenomenon of coalescence, one example of which is seen in the spontaneous merging of two drops of a liquid that come into contact with each other. In physics terms, coalescence originates from the strong affinity between water molecules, the effect of which is to reduce the surface of water exposed to the air to a minimum. That's why tiny water drops are spherical: of all geometric shapes, the sphere has the smallest surface area for a given volume.

"In this case, however, we had to study what happens when a water droplet distorted in a microchannel coalesces with another part of itself," Professor Gervais explains. "Our goal was to understand the phenomenon and control it, so that we could force the liquid to stagnate at the precise spot where it meets a reagent inside the device."

modeling of the phenomenon, which the team dubbed "self-coalescence," was based on a mathematical approach developed in the 1950s to study unbounded two-dimensional viscous flows. The work was performed using calculation techniques developed by Samuel Castonguay, who is completing his Ph.D. in engineering physics at Polytechnique under Professor Gervais's direction. To harmonize the modeling results with the experimental results, Mr. Castonguay went to Zurich, working for a few months with the IBM researchers.

"Not only have our models enabled us to master this new type of flow, but we can also very precisely program spatial and temporal configurations of chemical signals using a combination of reagents, with minimal dispersion, and with no need for user intervention," Professor Gervais notes. "The partnership between our two teams has therefore given birth to a novel, particularly flexible and precise biochemical testing architecture, which preserves the usage sequence of dozens of reagents simultaneously during a test."

Toward targeted mobile diagnostic tools

The IBM team also demonstrated that this type of architecture could be used to measure enzymatic reactions, with an eye to detecting various diseases (genetic illnesses, for example). It also showed a proof-of-concept for a method of DNA amplification, a reaction used to produce copies of a specific DNA segment from a sample, at ambient temperature. The method eliminates the need for a technician to perform repeated heating and cooling cycles on the sample. A single sample droplet is inserted into the device, and analysis is performed automatically. This experiment shows potential for future use of the process to perform DNA sequencing of genes associated with pathologies such as cancer, and to detect certain viruses.

"Our hope is that our process will enable lab-on-a-chip manufacturers to achieve unprecedented diagnostic performance, with products that are as simple to use as today's glucose meters," Dr. Delamarche says.

Lastly, given that the biochemical signals recorded by this type of test could likely be read by a smartphone and transmitted to a centralized databank, the tests could also play an important future role in monitoring the spread of epidemics in remote regions far from medical centres, and in national- and international-level screening for various diseases.

More information: Self-coalescing flows in microfluidics for pulse-shaped delivery of reagents, *Nature* (2019). DOI: 10.1038/s41586-019-1635-z , nature.com/articles/s41586-019-1635-z

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