

ANALYTICAL CHEMISTRY

Do-it-yourself microfluidics

Derek Bruzewicz and his colleagues have found a new application for the desktop plotter. They have used it to create an impressively simple microfluidics device that can be produced without a clean room or photolithographic equipment.

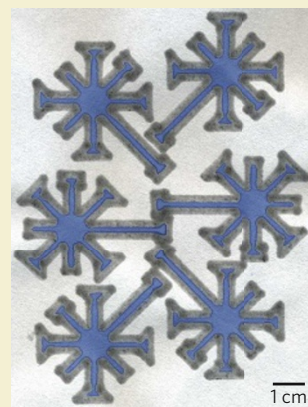
According to Bruzewicz and colleagues, second-hand desktop plotters can be had for as little as \$50. Other simple components of their device are paper and the commonly used organic polymer poly(dimethylsiloxane), or PDMS, which is cheap, can be diluted in hexane solvent and is flexible when cured. The team's study is described in *Analytical Chemistry*

(D. A. Bruzewicz *et al.* *Anal. Chem.* 10.1021/ac702605a; 2008).

The system works like this. By replica moulding, the pens of the plotter are replaced with PDMS versions that can deliver various types of 'ink'. The purpose of the ink, when cured, is to create channels in a filter-paper substrate, and after experimenting with the possibilities Bruzewicz *et al.* found that a syrupy mixture of 3:1 PDMS:hexane did just fine. Having chosen the appropriate paper, the trick then is to use the plotter to draw channel shapes, with the PDMS syrup penetrating the full depth of the paper to create water-tight chambers in various patterns.

One form the device takes is what the authors call a "dip star". Filter paper is patterned with eight PDMS channels radiating out from the centre; in principle, each of these channels can be loaded with a different chemical indicator. The flexibility of the channels means that the paper can be folded, with the centre becoming one corner that can be dipped into the fluid to be assayed. The channels are at least 1 millimetre wide. In keeping with the guiding principle of the system, the readout equipment is similarly widely available: the human eye.

The authors have tested different types of the device with well-tried colorimetric assays for identifying excess protein and glucose in urine, and found they performed well, with no cross-contamination between channels.



Another pattern, shown here, is a variant on the dip star. It shows that channels can be printed over a large area of paper, and can be designed for loading by multipipette rather than dipping.

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are activated by glutamate and are named after their chemical agonist NMDA. These findings are consistent with the emerging concept that voltage-gated ion channels, as well as voltage-sensitive NMDA receptors, are crucial to the integrative function of dendrites⁵. In addition, they suggest that each dendritic branch could generate a unitary (all-or-none) output in the form of a localized dendritic spike; this conclusion has fuelled emerging theories that treat dendritic branches as the functional units of neurons^{6,7}.

In their latest work², Losonczy *et al.* ask how dendritic spikes could be shaped by experience, in the form of repeated stimulation under conditions that are known to facilitate functional plasticity. They studied pyramidal neurons, which are the principal type of neuron in the brain's cortex, the region that contributes to higher cognitive functions.

They find that, when groups of spines are repeatedly activated so that they produce a spike in a dendritic branch, an increase in the size of the spike (from about 1 millivolt before to roughly 5 millivolts after repeated stimulation) is observed at the cell body. They call this change in response 'branch-spike plasticity'. Furthermore, they find that, even before repeated activation, some branches show a weak response and others a stronger one; this observation is consistent with the view that such branch-spike plasticity occurs spontaneously *in vivo*, and may therefore genuinely reflect a natural process, not just an experimental phenomenon.

Because of the structural properties of branching dendrites, and the types of ion channel in their membranes, spikes do not propagate well in dendrites⁸. The amplitude of the spike reaching the cell body depends on these same factors. But Losonczy and colleagues find that branch-spike plasticity results in a several-fold increase in voltage at the cell

body, compared with the voltage normally produced by a single branch. This increase, which results from enhanced propagation of the spike along the dendritic branch, seems to be due to a downregulation of the Kv4.2 voltage-gated potassium channels, which otherwise limit the excitability of the branch.

Are these observations surprising? Although the synapse has been considered to be the main functional unit of plasticity in neurons mediating learning, forms of plasticity involving voltage-gated ion channels have been described before, and it has been suggested that different types of plasticity cooperate to form the set of neuronal changes that collectively underlie learning⁹. But the argument against plasticity of voltage-gated ion channels as a mechanism for learning is that it is less specific than synaptic plasticity, and thus could potentially shift the minimal unit of plasticity from the synapse to the whole neuron. This problem is mitigated by the finding¹⁰ that these channels could mediate plasticity in restricted portions of the dendritic tree.

Losonczy and colleagues' finding² — that such localized plasticity might even be restricted to individual dendritic branches — supports the notion that regulation of voltage-gated channels can cause changes that are specific to small groups of synapses rather than to the whole neuron or large parts of it. Together with the recently described spread of communicative signals among adjacent spines on a single dendritic branch¹¹, the emphasis seems to be shifting from individual spines to groups of spines and dendritic branches as the functional units of plasticity underlying information storage and memory formation. By restricting changes to a limited number of spatially localized and temporally coactivated synapses, experience may be able to 'tune' neurons to respond to several different spatio-temporal patterns of synaptic input.

As is always the case, several questions remain. First, Kv4.2 potassium channels are probably not the only player in this story. The authors observe considerable variability in the size of dendritic spikes, as measured in the cell body, even in animals lacking Kv4.2, which indicates that other channels also regulate the excitability of dendritic branches. Second, for practical reasons, the authors restricted their study to dendritic branches quite close to the cell body. Does branch-spike plasticity also occur in more distant branches? Does the influence of a branch on the cell body depend on the distance between them?

The broader functional relevance of branch-spike plasticity must also be explored. Does branch-spike plasticity occur in other types of neuron? Is it something that happens in intact animals, and, if so, is it required for learning? Answering these questions will be challenging, but will be essential for a better understanding of the neural basis of learning and memory. ■

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