DRUG DELIVERY

# Controlling the flow

**One of the challenges facing drug delivery is to achieve a constant, steady dose of a drug instead of the large, sudden doses generated with pills. New silicone rubber devices with specially shaped microscopic channels could open up new possibilities for medicine-delivering implants, according to Stephen Quake and colleagues in the 9 May issue of *Science*. The researchers created two miniature fluid devices, one to control the liquid-flow rate and the other for fluidic memory, both of which rely on the special behaviour of polymer liquids to function.**

**In a throw back from the 1960s and 1970s when fluidic circuit research was overtaken by silicon-based electronics, in part because fluidic circuits could not be miniaturized easily, amazing advances in microfluidics now present the possibilities of giant robotic biochemical workstations being replaced by an entire lab-on-a-chip.**

**The flow control device is called a flux stabilizer, which is analogous to an electronic constant-current source, and it can deliver a constant rate of liquid discharge despite changing driving pressure. The dissolved polymer molecules make the liquid thick and resistant to movement above a particular flow rate, thereby stabilizing the flow output at a well-defined value. The present experiments used polyacrylamide, but the use of other polymers, such as DNA, should have the same result. Groisman *et al.* also used the nonlinear properties of polymers and an innovative fluid chamber design to construct a fluidic memory device called a flip-flop, which is analogous to a digital flip-flop memory. The tiny fluid gadget can maintain a 'high' or 'low' state of either pressure or flow rate, storing information as ones and zeroes, as in electronic memory.**

**Although only pilot devices have been built so far, one can imagine an implanted pill or a miniature intravenous drip with an inflatable chamber to hold a drug. If this reservoir was connected to the microfluidic flux stabilizer, a relatively constant flow of medicine could be achieved despite decreases in driving pressure as the chamber empties.**

*Melanie Brazil*


**References and links**

**ORIGINAL RESEARCH PAPER** Groisman, A., Enzelberger, M. & Quake, S. R. Microfluidic memory and control devices. *Science* **300**, 955–958 (2003)


DRUG RESISTANCE

# Pumping stations


Most cells are protected by efflux pumps that actively expel toxic compounds. However, this evolutionarily conserved survival mechanism is also responsible for bacterial resistance to some antibiotics, and can greatly reduce the effectiveness of cytotoxic anticancer drugs. Efforts to combat these problems have been hampered by the fact that the structural basis of the interaction between efflux pumps and drugs has not been determined. This hurdle has now been overcome with the publication in *Science* of high-resolution X-ray crystallographic structures of complexes between the prototypical efflux pump *Escherichia coli* AcrB and four structurally diverse ligands.

Energized by proton motive force, AcrB facilitates the efflux of a wide range of substrates, including most of the antibiotics used at present. It is a homotrimer of ~110-kDa subunits, in which three periplasmic domains form a central 'funnel' and a connected pore. From the pore, three vestibules open into the periplasm, and three transmembrane domains form a large central cavity that extends into the cytoplasm.

Yu and colleagues have shown that four ligands — the dyes rhodamine and ethidium, the disinfectant dequalinium, and the antimicrobial ciprofloxacin — each use a different subset of amino-acid residues to bind at various positions within wild-type AcrB, a characteristic that greatly increases the range of potential drug–protein interactions. Complexes are stabilized by interactions between bound ligands, three of which bind simultaneously to the 5,000 Å$^3$ central cavity, primarily by aromatic stacking, and through van der Waals and hydrophobic forces. Ligand binding also induces rotational movements in AcrB subunits that enlarge its periplasmic domain, possibly triggering the interaction between AcrB and the periplasmic protein AcrA that is essential to the efflux mechanism. These findings should facilitate the development of strategies to overcome drug resistance.

*Suzanne Farley*


**References and links**

**ORIGINAL RESEARCH PAPER** Yu, E. W. *et al.* Structural basis of multiple drug-binding capacity of the AcrB multidrug efflux pump. *Science* **300**, 976–980 (2003)

**FURTHER READING** Coates, A. *et al.* The future challenges facing the development of new antimicrobial drugs. *Nature Rev. Drug Disc.* **1**, 895–910 (2002)

**WEB SITE**

**Encyclopedia of Life Sciences:** http://www.els.net/ Bacterial antibiotic resistance | bacterial membrane transport: superfamilies of transport proteins