

Figure 2 | Tentative interpretation of geological and climatic influences on valley spacing. According to theory, valley spacing in low-relief, soil-mantled landscapes is set by the ratio between hillslope transport (soil creep) intensity and channel incision intensity⁴⁻⁷. Perron and colleagues⁷ provide a successful test of theory, and their data contain further hints about the underlying controls exercised by the substrate and climate: weaker rocks and (less certainly) drier climates seem to lead to a dominance of channel-incision processes and more closely spaced valleys.

is associated with a change from semi-arid grassland to oak savannah. Could these small differences be sufficient to explain the five-fold difference in valley spacing, or are other factors at play?

Much remains unknown about the complex controls on the intensity of soil creep and channel incision. But the work by Perron and colleagues⁷ will encourage further investigation because their ratio seems to set the fundamental length scale in landscapes, and also suggests a method for quantifying rate constants for both creep and incision. The analysis has limitations, as the authors acknowledge. It is restricted to low-relief, soil-mantled landscapes, where landslides, earth flows and debris flows do not occur; it does not account for a threshold for channel incision^{4,5}; and it is applicable only to quasi-steady-state conditions, in which erosion rate is approximately constant in space and time. Other considerations that merit attention are how temporal variations in rock uplift or climate change, over millennial to 100,000-year scales, may influence either topographic estimates of D/K or the relationship between D/K and valley spacing.

Despite these limitations, Perron *et al.*⁷ have provided a powerful tool for further exploration. It promises to help deliver additional discoveries about the complex interactions between the physical, chemical and biological processes acting on the land surface.

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- Rodríguez-Iturbe, I. & Rinaldo, A. *Fractal River Basins: Chance and Self-Organization* (Cambridge Univ. Press, 2001).
- Perron, J. T., Kirchner, J. W. & Dietrich, W. E.

J. Geophys. Res. doi:10.1029/2007JF000866 (2008).

- Smith, T. R. & Bretherton, F. P. *Wat. Resour. Res.* **8**, 1506-1529 (1972).
- Howard, A. D. *Earth Surf. Process. Landf.* **22**, 211-227 (1997).
- Tucker, G. E. & Bras, R. L. *Wat. Resour. Res.* **34**, 2751-2764 (1998).
- Perron, J. T., Dietrich, W. E. & Kirchner, J. W.

J. Geophys. Res. doi:10.1029/2007JF000977 (2008).

- Perron, J. T., Kirchner, J. W. & Dietrich, W. E. *Nature* **460**, 502-505 (2009).
- National Center for Airborne Laser Mapping. www.ncalm.org.
- Fernandes, N. F. & Dietrich, W. E. *Wat. Resour. Res.* **33**, 1307-1318 (1997).

BIOENGINEERING

Cellular control in two clicks

Jason A. Burdick

If complex tissues are to be engineered, synthetic materials will be needed that provide cells with precisely located molecular cues. A method that attaches such cues to specific areas of a gel could be the answer.

Contrary to popular belief, George Washington's dentures weren't made of wood — they were actually made of ivory and gold. As with many other materials that have been used in biological systems, ivory and gold are relatively inert, and simply provided mechanical support for their intended application. Although giving biomaterials only a supporting role restricts their applications, it has nevertheless led to the development of a range of clinically useful materials (such as bone cements) and implantable devices (such as fixation plates for holding fractured bones in place). But what is really needed are biologically active materials that interact with and signal to surrounding cells and tissues.

Of particular interest are materials that can both track and manipulate the local three-dimensional arrangement of cells. Such an achievement would have been unimaginable

just a few years ago, yet it is exactly what has been reported by DeForest *et al.*¹ in *Nature Materials*. Using cell-compatible reactions², the authors first encapsulate cells in hydrogels — water-swollen polymer networks — and then introduce precisely targeted molecules into the gels to either monitor or alter the cells' behaviour. Hydrogels are especially attractive as media for cell culture because they provide a tissue-like, three-dimensional environment in which cells can flourish³.

The past couple of decades have seen an explosion of work in which engineers and biologists have collaborated to find ways of assembling cells, molecules and scaffold materials, with the ultimate goal of growing biological tissues⁴. These efforts are leading to new therapies, but progress has been slow, especially in producing tissues that consist of several cell types or that lack the capacity to

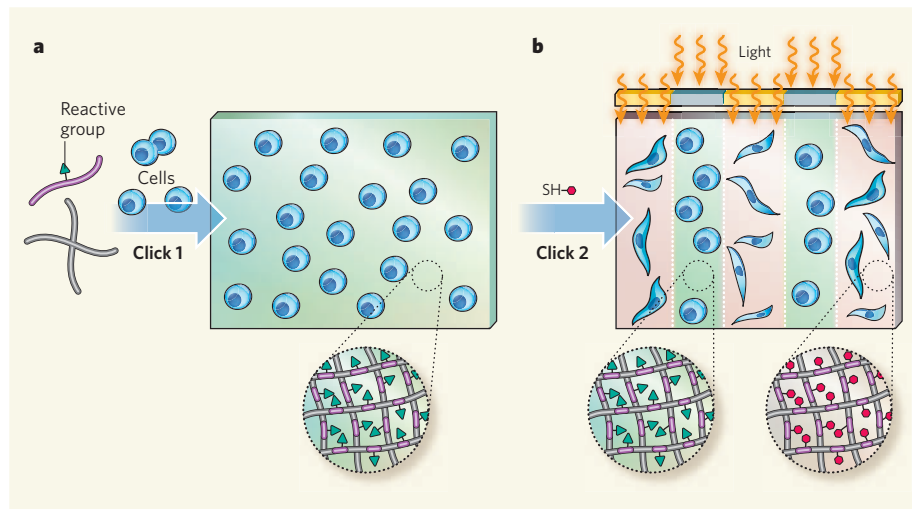


Figure 1 | Clicking into place. DeForest *et al.*¹ have developed a method for monitoring or controlling the behaviour of cells at user-defined sites within a hydrogel (a water-swollen, polymeric network). **a**, The gel is prepared from its monomers in the presence of cells using a 'click' reaction, so that the cells become encapsulated in the gel. The crosslinks of the polymer network incorporate a reactive chemical group. **b**, When irradiated with light, the chemical group reacts in a second click reaction with molecules that contain thiol (SH) groups; these molecules act as signals that monitor or dictate the behaviour of the encapsulated cells. In the example shown, light is shone through a mask, so that only groups in the illuminated regions react. Once incorporated into the gel, the signal molecules cause the cells to change shape.

regenerate after damage. The problems might stem from the lack of materials that provide appropriate biological signals for cells. *In vivo*, cells receive many cues from their surroundings⁵. Factors such as the topography of the local environment, its chemical and mechanical properties, and the availability of soluble molecules can combine to instruct cells to migrate, proliferate or — especially for stem cells — turn into another type of cell. Materials that can be manipulated in both time and space to provide such cues might be the only option if complex tissues such as heart muscle or brain tissue are to be engineered.

Some materials that can control the arrangement of cells have already been reported. Most of these use light to trigger the control processes because high spatial resolution can be obtained using laser beams or by shining light through masks. For example, materials have been made⁶ that contain chemical groups that decompose when irradiated with light, thus exposing molecules that react with cell-binding peptides. This approach enabled neural cells to grow into a hydrogel at defined locations, but has limited potential for direct cell encapsulation because the process produces potentially toxic side products. More recently, another hydrogel system was described⁷ in which distinct regions were created that either permit or inhibit the spread of cells, depending on the degree and type of crosslinking in the material. This process produces no toxic side products, but it is not compatible with many biological cues, and it also causes structural changes in the material — which can lead to inadvertent signalling to cells.

DeForest *et al.*¹ report the first biologically compatible system for encapsulating cells in hydrogels that have spatially defined cues, and in which the cues are introduced without affecting the molecular structure of the polymer network. In their approach, the authors first form a uniform hydrogel in the presence of cells, using a 'click' reaction — a specially designed reaction in which two small chemical groups combine quickly and reliably. They thus obtain a material that is highly swollen with water and has tissue-like properties (Fig. 1).

In the second step of the process, the authors use a different click reaction to incorporate biologically active molecules into the material. This reaction proceeds only where light is shone, so that molecules can be incorporated at specific regions with micrometre precision, using a laser or a mask. A wide range of molecules that act as biological cues can be incorporated in this way, as long as they contain an appropriate reactive group. For example, any peptides that contain a cysteine amino acid fall into this category, because cysteine contains a reactive thiol (SH) group.

To illustrate the general applicability of their technology, DeForest *et al.* incorporated two different molecules into their hydrogel network. The first was a peptide that fluoresces after it is cleaved by enzymes secreted by the

cells. The authors thus showed that their method can be used in real time to image the enzymatic behaviour of cells in regions of the gel that can be defined by the user. The second molecule was a peptide that acts as a cellular adhesion site. It is known that, when included in synthetic networks containing adhesion sites and appropriate enzyme-degradable crosslinks, cells can spread and remodel their surroundings⁸. Using their click reaction to control the location of adhesion sites, DeForest *et al.* were able to exert spatial control of cell spreading in their gels.

This study¹ represents a giant leap towards the goal of controlling and monitoring cells in three-dimensional environments. But there is still much to be done to exploit such control for reconstructing multicellular tissues that will have functional properties. One limitation is that the synthetic schemes required are currently quite complex, which might curb the immediate widespread use of the technology.

Nevertheless, the authors' technique will be particularly useful for investigating how cells interact with their environment, and could one day form the basis of a method for manipulating cells for regenerative medicine. ■

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1. DeForest, C. A., Polizzotti, B. D. & Anseth, K. S. *Nature Mater.* doi:10.1038/nmat2473 (2009).
2. Baskin, J. M. *et al.* *Proc. Natl Acad. Sci. USA* **104**, 16793–16797 (2007).
3. Cushing, M. C. & Anseth, K. S. *Science* **316**, 1133–1134 (2007).
4. Khademhosseini, A., Vacanti, J. P. & Langer, R. *Sci. Am.* **300** (5), 64–71 (2009).
5. Burdick, J. A. & Vunjak-Novakovic, G. *Tissue Eng. A* **15**, 205–219 (2009).
6. Luo, Y. & Shoichet, M. S. *Nature Mater.* **3**, 249–253 (2004).
7. Khetan, S., Katz, J. S. & Burdick, J. A. *Soft Matter* **5**, 1601–1606 (2009).
8. Lutolf, M. P. & Hubbell, J. A. *Nature Biotechnol.* **23**, 47–55 (2005).

INFECTIOUS DISEASES

An ill wind for wild chimps?

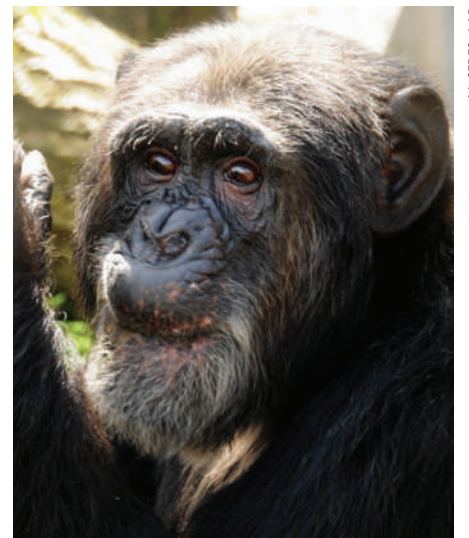
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Simian immunodeficiency virus is associated with increased mortality in a subspecies of chimpanzee living under natural conditions in East Africa. This is worrying news for the chimpanzee populations involved.

Today's pandemic strain of HIV-1 crossed the species barrier from chimpanzees (*Pan troglodytes*) to humans less than 100 years ago. Until now, it has been widely assumed that the precursor of HIV-1, chimpanzee simian immunodeficiency virus (SIVcpz), causes little, if any, illness in its animal host. On page 515 of this issue, however, Keele and colleagues¹ show that small groups of wild chimpanzees naturally infected with SIVcpz do develop hallmarks of AIDS. Careful monitoring for almost a decade has revealed that SIV-infected animals of the eastern subspecies of chimpanzee (*Pan troglodytes schweinfurthii*) in the Gombe National Park in Tanzania have a markedly higher death rate than non-infected animals.

Chimpanzees — humans' closest living relative — are not only genetically similar to humans but also share susceptibility to some infectious diseases. For instance, outbreaks of haemorrhagic fever caused by relatives of Ebola virus in chimpanzees and gorillas have resulted in marked mortality in wild populations². However, subtle chronic diseases like those caused by lentiviruses such as SIV/HIV are more difficult to document in wild non-human primates than are acute diseases with high mortality rates.

More than 40 strains of SIV are known to cause natural infection in African non-human primates³, but few cases of AIDS have



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Figure 1 | Survivor. Noah, the first *Pan troglodytes schweinfurthii* to be identified with naturally acquired SIVcpz infection, is alive and well almost 20 years later. By contrast, a number of SIVcpz-infected chimpanzees in the wild seem to develop an AIDS-like illness.

been recorded, and progression to illness after viral infection is thought to be rare. This lack of disease has been well documented in African green monkeys and sooty mangabeys⁴. In addition, a captive *P. t. schweinfurthii* is in good