amniotes rapidly diversifed this to support a great variety of drought-adapted bodies as they were racing to conquer habitats on dry land.

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Engineering

Mass production of 3D microcomponents

Christoph A. Spiegel & Eva Blasco

Combining a high-throughput technique with 3D printing offers a way of fabricating micrometre-sized particles for use in electronics and biotechnology. The versatile method can produce one million intricate shapes in a single day. **See p.306**

Micrometre-sized particles are key elements of several technologies ranging from drug-delivery vehicles to microelectronics, which makes optimizing the fabrication of these particles big business. One production strategy involves a bottom-up approach[1–3], in which particles come together from smaller components, through self-assembly, for example. Although bottom-up techniques enable high-throughput production, they offer limited control over particle geometry. By contrast, top-down strategies[4–7] produce particles by breaking down bulk materials, using moulds, for example. Top-down approaches can overcome the shortcomings of bottom-up techniques, providing pathways towards improved shape control, but such methods produce only 2D or simple 3D particles. On page 306, Kronenfeld *et al.*[8] present an innovative high-throughput fabrication method that enables microparticles to be 3D printed rapidly, and with complex geometries.

The technique of 3D printing is widely regarded as being a versatile way to manufacture complicated 3D objects, so it would seem to be an ideal candidate for circumventing the limitations of existing microparticle-fabrication techniques. The same research group as Kronenberg *et al.* previously developed a light-based 3D-printing method called continuous liquid interface production (CLIP)[9,10], which offers fast, accurate printing of microscale particles in a variety of materials. In CLIP, 2D images are generated by slicing a digital 3D model of a structure along its vertical axis. These images are then projected into a transparent vat containing light-sensitive liquid resin. Light selectively polymerizes the resin to form a solid 3D object on a stage that is pulled out of the resin vat, as the structure materializes.

This approach can be used to fabricate intricate 3D architectures with high-quality surfaces — a capability that results from the presence of an oxygen-induced 'dead zone' at the bottom of the vat, which ensures that the printed object doesn't stick to the vat while being produced at high speeds. However, the process is static, and automating it to allow the continuous fabrication of many objects involves yet another engineering challenge, which Kronenfeld *et al.* have surmounted with a technique that they call roll-to-roll CLIP (r2rCLIP).

Roll-to-roll technologies are typically associated with the high-throughput production of devices such as electronic circuits, light-emitting diodes and batteries. The idea is to take a roll of flexible material, print devices onto it in an automated or semi-automated way and then rewind the material into an output roll containing the manufactured devices. The authors made use of this principle by integrating the stage into a high-resolution CLIP printer with a continuous roll of film on which the particles are printed (Fig. 1a). This allowed them to continuously print a large quantity of objects using CLIP, but it also automated some of the post-processing tasks, such as cleaning and collecting the 3D-printed particles.

Kronenfeld and colleagues' r2rCLIP device can print one million particles in a single day, whereas the fastest alternative approach manages around 85,000 per day[11]. The structural quality of the particles generated with r2rCLIP is highly reproducible — much more so than is the output of existing approaches. The inherent versatility of 3D printing enables r2rCLIP to manufacture particles with complex 3D geometries (Fig. 1b). Such shapes are either not possible to produce using moulding

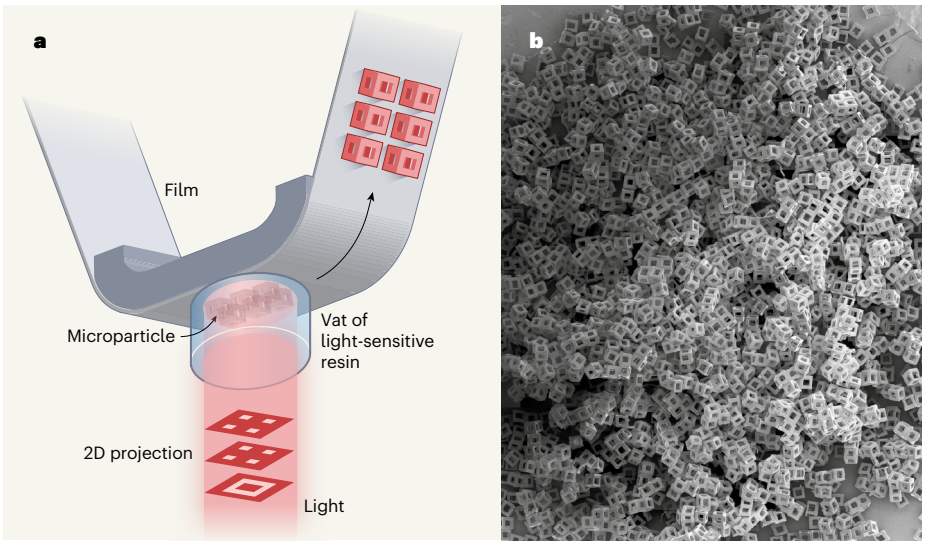

Figure 1 | A high-throughput method for creating intricate microparticles. Kronenfeld *et al.*[8] developed r2rCLIP, a high-throughput technique for 3D printing micrometre-sized particles with high-resolution structural features. **a**, The approach involves projecting 2D slices of a 3D design into a transparent vat containing liquid resin, which polymerizes in response to light, thereby printing the 3D objects onto a continuous roll of film. **b**, The authors' strategy outperforms existing techniques by producing 3D microparticles at a rate of one million particles per day, with surface features as small as 4 μm^2. (Adapted from Fig. 1 of ref. 8.)

techniques, or producible only by using processes that exhaust both time and resources. The authors' method can also make particles with surface features as small as 4 μm^2, offering the potential to create extremely intricate microfeatures of high quality.

The r2rCLIP technique is compatible with a wide range of printable materials, including standard polymers, ceramics and hydrogels. Ceramic materials are attractive for many applications, such as functional microcomponents in the smallest precision instruments and in microelectromechanical systems that are used in the electronics and telecommunications industries. The applicability of the authors' method to the mass production of hydrogel particles could have an impact on drug delivery and on other bioengineering technologies. One key factor for these biomedical applications is the versatility and uniformity of the particles produced, as well as the structural precision with which they can be manufactured. These features make the authors' approach well suited to therapies that require specific particles to distribute drugs through different means; for example, by injection or inhalation.

Kronenfeld and colleagues' technique is remarkable in its performance and in the quality of the particles it produces. The development of custom-designed materials for r2rCLIP might be the next key step. In particular, the authors' method could have a pronounced effect on a wide range of fields, including biomedicine and robotics, if it were integrated with materials that exhibit smart features, such as the ability to interact with the surrounding environment.

In devising r2rCLIP, Kronenfeld *et al.* have provided academia and industry with an excellent strategy for manufacturing microparticles, which is impressive in terms of the versatility of the shapes it produces and the materials it can use. The technique is also superior to existing approaches in terms of the resolution of intricate features it can engineer, the creation of complex geometries and the speed and volume of the manufacturing process. It will be exciting to see the ways in which this technology can improve production processes in many areas of science and technology.

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Immunology

Interactions between immune cells recorded

Michael A. Wheeler

Direct interactions between cells in tissue are incompletely understood because the advanced technologies required to examine them are still in their infancy. A new method can decipher cell–cell interactions on a large scale. **See p.399**

In living tissues, millions of cells communicate with each other within fractions of a second. How are these dynamic intercellular interactions orchestrated? On page 399, Nakandakari-Higa *et al.*[1] present a method called universal LIPSTIC (uLIPSTIC) that offers a way to address the challenge of investigating transient interactions between cells of the immune system that come into close physical proximity. This technique can also be adapted to study interactions between other cell types.

During sickness, a remarkable molecular dialogue occurs across the body through the release of immune-signalling proteins called cytokines. A spatially distributed set of immune cells acts to translate these signals and drive host defence responses. Effective immune-system action requires the precise coordination of a vast array of interacting cell types. In some cases, these interactions include physical contacts between interacting immune cells. Such contacts generate molecular complexes called immunological synapses at the interface of these cells, which are required for responses to harmful agents (pathogens).

"The authors have demonstrated the broad utility of this technique across tissues, cell types and immune challenges."

Although experiments first identified where an immunological synapse is located on the surface of two interacting cells more than 26 years ago[2], several questions remain to be answered. In particular, how does the diversity of immune responses in the body arise through exquisitely specific, yet transient, interactions between cells?

Specialized contacts similar to those of the immunological synapse are made by other interacting cell types throughout tissues. A growing number of tools are being developed to study cell communication in various organs[3], and these methods involve a combination of techniques, such as high-throughput genomics[4–6], proximity-based labelling by enzymes[7], microfluidics[8] and bioinformatics[9]. But none of these methods is appropriate for addressing the paradoxical communication scenario of immune cells, which are predisposed both to contacts on the cell surface and to frequent cellular turnover.

To find a way forward, Nakandakari-Higa *et al.* capitalized on a technology called LIPSTIC ('labelling immune partnerships by sortagging intercellular contacts') that was previously developed[10] by members of the same team. The method exploits a low-affinity interaction between two molecules: a bacterial enzyme called SrtA on the surface of a donor cell; and its target, a stretch of five glycine amino-acid residues (G_5) on the surface of an acceptor cell. SrtA catalyses the transfer of a peptide substrate — attached to a molecular label called biotin — to G_5, which is part of a protein on the acceptor-cell surface (Fig. 1).

Cells labelled with biotin are inferred to have interacted with a donor cell because the peptide substrate can be transferred from SrtA-expressing to G_5-expressing cells only when the local concentration of peptide substrate is high enough to result in the occurrence of the otherwise low-affinity interaction between SrtA and G_5. Physical contacts at the immunological synapse fulfil this criterion because the estimated distance between cellular membranes is approximately 15 nanometres — a distance so small that any quantity