that shape. When one of these cores forms in solution, it is called a nucleation seed, and the assembly of the rest of the shape is accelerated at the expense of the other two shapes – a 'winner take all' outcome. This means that the shape that self-assembles from the full set of tiles can be controlled by choosing a particular combination of tile concentrations, called a concentration pattern, that promotes the formation of the nucleation seed for that shape.

Evans *et al*. used an algorithm to estimate the self-assembly rates of shapes from different concentration patterns, and thereby identified 37 nucleation seeds. The corresponding concentration patterns were then tested experimentally, using a 150-hour annealing process in which the tiles were slowly cooled in solution to allow them to self-assemble. The authors used fluorescent labels to monitor the assembly of each shape, and atomic force microscopy to image the shapes. Of the 37 proposed nucleation seeds, roughly half resulted in selective self-assembly of the desired shapes; the others did not, for unknown reasons.

To demonstrate the information-processing capabilities of their system, the authors used it to classify 18 greyscale images of 30 × 30 pixels on the basis of the shades (greyscale values) of the pixels in the image (Fig. 1b). The idea was to represent the greyscale value of each pixel in each image by the concentration of one of the tiles, so that the resulting concentration pattern of tiles promotes the assembly of a designated shape (H, A or M). The assignment of pixels to tiles was done computationally to maximize the self-assembly of the designated shape, while minimizing self-assembly of competing shapes. Crucially, this assignment was simultaneously optimized for all images, rather than independently for each one.

When the authors tested the concentration patterns for the 18 images experimentally, they observed that the desired shape did indeed assemble more often than any other, with greater than 80% selectivity for 13 of the images. In other words, the tile system recognized the different concentration patterns, and therefore the corresponding images, by assembling into the designated shapes. Crucially, the system also coped with 12 degraded versions of the images. For example, when the greyscale values of some of the pixels of a horse image were altered at random, thereby corrupting the corresponding concentration pattern, the system still reliably formed an H shape in preference to an A or an M, correctly classifying the image.

One of the main limitations of this work is the trade-off between the speed, accuracy and complexity of pattern recognition. In particular, the timescales of the experiments were chosen conservatively to minimize the formation of incorrect structures. The winner-take-all outcomes indicate that these timescales could be shortened substantially; the use of smaller assemblies consisting of fewer tiles could also speed things up. Because such DNA systems will probably find biological applications, rather than becoming replacements for silicon-based computations, speed considerations might be less important than having the ability to embed computations directly in biophysical processes at the nanoscale.

Overall, the latest findings demonstrate how computations needed for complex pattern recognition can be encoded at the molecular level in the biophysical process of self-assembly. The study also illustrates how previous theoretical[7] and experimental work[6] on DNA-tile assembly can support the design of sophisticated new experiments. Furthermore, it demonstrates how the programmability of DNA and the well-understood kinetics and thermodynamics of DNA base pairing can enable the design of a self-assembling system with more than 900 distinct components to carry out complicated computations.

From a computational perspective, a promising direction for future work is to further explore the connections between pattern recognition in self-assembling systems and other forms of neural computation. Evans *et al.* identify parallels between their tile system and neural network models known as Hopfield associative memories[8], and with the networks of place cells in the brain that store spatial memories, building on previous work[8,9]. Further exploration of the opportunities and limitations of embedding neural computation in biophysical processes would be valuable.

From an experimental perspective, as scientists' ability to design protein-based systems and predict their biophysical interactions continues to improve, the approaches outlined by Evans *et al.* could be used to design self-assembling protein structures that process information. For example, different protein complexes with distinct functions could self-assemble depending on the concentrations of their building blocks. More generally, this work also provides a conceptual and experimental framework for the future design of compact, robust and scalable computations embedded in biophysical processes.

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Biomedical materials

Composite gels designed to stick to biological tissue

Sophia J. Bailey & Eric A. Appel

Materials that adhere tightly to human tissues can promote healing and boost the sensitivity of biomedical diagnostic devices. An 'evolving' gel has been made that synergizes two strategies for forming interfaces with tissue.

The interfaces that form between living tissues and biomedical materials, often referred to as biointerfaces, greatly influence the ability to detect and treat disease. Unfortunately, the development of biomedical devices has historically involved a trade-off between using materials that can be fabricated easily into the devices and using those that adhere to tissues at the cellular level. Reporting in *Nature Chemical Engineering*, Shi *et al.*[1] present a clever, yet simple, strategy to make materials that combine easy handling with robust interface formation. The authors show that hydrogels – water-rich networks of polymers – embedded with tiny starch granules form dynamic biointerfaces that 'evolve' over time, and have many potential uses across biomedicine, from tissue regeneration to sensing.

Materials that are intended to help repair damaged tissues must provide a tight biointerface to promote cell–material interactions, and have a porous or degradable matrix to allow for cellular growth[2]. Typically, macroscopic patches are used to promote such

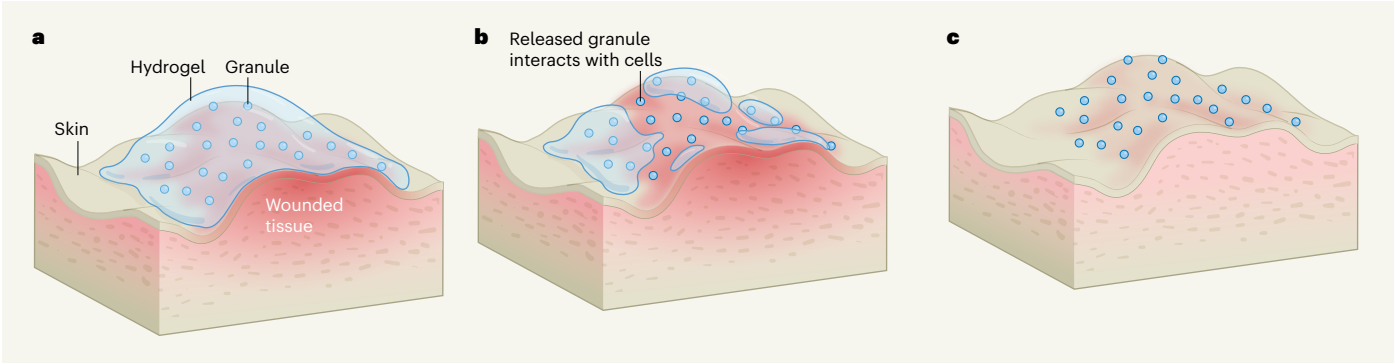

Figure 1 | Evolving hydrogels for biomedical applications. **a**, Shi *et al.*[1] present materials consisting of a biodegradable hydrogel (a water-rich network of gelatin proteins) embedded with micrometre-scale starch granules. The granules' surfaces were modified by the attachment of drugs such as aspirin, to encourage interactions with cells. The authors report that these composite hydrogels adhere tightly to tissue surfaces. **b**, **c**. Over time, the hydrogel matrix degrades, releasing the granules, which then interact with tissue cells. Applying these composites to damaged tissue speeds healing. When incorporated into diagnostic bioelectronic devices that are placed directly on tissue, the materials can boost the electrical signals produced by the devices (not shown).

healing, but patch materials are limited in their ability to conform tightly to damaged tissue that is irregularly shaped, and often do not adhere well to cells. Alternatively, therapeutic materials consisting of cell-sized microparticles can promote adhesion and provide ample space for cellular infiltration. However, the structural forms that can be fabricated from microparticles are severely limited (macroscopic patches, for example, are difficult to make). Special methods are needed to deliver such materials to the body — and the microparticles are then often not well retained.

Biointerfaces are also crucial for the sensitivity of diagnostic bioelectronic devices, because inadequate contact with tissues leads to poor sensing and transmission of electrical signals. Typically, attachment to tissues is promoted by using extremely thin and flexible devices combined with adhesives[3,4]. Hydrogels can improve contact at these interfaces because they are soft and flexible, allowing for conformal contact with irregular tissues, and because their high water content promotes ion transport and improves electrical conductivity[5]. Improving the adhesive properties of bioelectronics that incorporate hydrogels could further enhance device signals, and could extend a device's lifetime in challenging environments, such as on a beating heart.

Shi *et al.* now report a biointerface made from a hydrogel composite that addresses the need for materials that can be shaped easily into various forms, but that also provides tight, durable tissue adhesion. The hydrogel matrix is made up of gelatin — a protein derived from collagen, an important component of human tissues — to ensure biocompatibility and biodegradability.

A previous study by some of the authors of the current work reported that granule-embedded hydrogels possess tissue-like properties such as viscoelasticity[6]: a combination of solid and liquid-like behaviours that enable tissues to maintain their shape and undergo dynamic reorganization. Shi *et al.* now exploit these properties to promote the initial adherence of their hydrogels to uneven tissue surfaces and to enable the subsequent release of starch granules, the surfaces of which had been modified with drugs such as aspirin to encourage cell-level interactions. The biointerfaces formed by the gels evolve over time. Initially, the interfaces consist of a macroscopic material that sticks to the tissue. But the gel matrix then releases granules and degrades, producing an interface consisting of granules interacting with cells (Fig. 1). The adhesion and release behaviours were observed in tissue both *ex vivo* and *in vivo*. These observations were corroborated through molecular-dynamics simulations, which showed that these behaviours underpinned the formation of tight biointerfaces.

"The authors address the need for materials that can be shaped easily, but that also provide tight, durable tissue adhesion."

Shi and colleagues demonstrated the versatility of their granule-embedded hydrogels for regenerative medicine using animal models of skin-wound healing, inflammatory colon disease and tissue recovery after heart attack. Tissue regeneration was observed to be better than after treatments that used the hydrogel or granule components alone. The therapeutic synergism of the hydrogel–granule combination arises because the gelatin matrix prolongs exposure to the granules over the course of treatment, and this is one of the hallmark benefits of hydrogels for drug delivery[7]. This slow release maintains the biointerface and is followed by slow degradation of the entire material.

The authors' hydrogel is also easy to manipulate and can be moulded into numerous forms — ranging from oral medications to bandages. In a particularly convincing demonstration of this ease of handling, the authors integrated the hydrogel into an intricate bioelectronic mesh device that records electrical signals directly from heart tissue. Impressively, the device recorded the beating of a rat's heart for 270 minutes, with granule release enabling stable adherence and promoting bioelectrical signal transmission. This long-term, surgically relevant recording shows that these evolving hydrogels provide beneficial interfaces for bioelectronics, and not just for tissue repair.

Although the findings are certainly compelling, the superiority of these granule-releasing hydrogels has been demonstrated only over historically lacklustre materials: granule-free gelatin hydrogels, which are minimally dynamic and unsophisticated. Numerous biomimetic hydrogels have been reported[8] to have viscoelastic properties that could also promote initial adherence to irregular tissue surfaces. And engineering of the surface chemistry of such materials (rather than of embedded granules) can also promote cellular interactions[9]. Future studies should investigate whether Shi and colleagues' composite materials provide benefits over state-of-the-art biomimetic hydrogels.

Moreover, the adhesion of the granules to tissues arises from nonspecific interactions that lack the complexity of natural biological interactions, such as those between receptors and proteins. It might be possible to engineer granules that recapitulate such complex interactions more directly. If so, exploring biologically relevant granule–cell interactions might open up other exciting therapeutic benefits.

Further studies are therefore needed to fully assess the advantages of Shi and colleagues' biointerface design strategy. But if this approach can indeed provide superior biointerfaces with a broad range of tissues, it could greatly improve treatment and diagnosis

throughout the field of medicine. Time will tell whether this design strategy truly sticks.

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Cell biology

DNA sensing and repair team up against cancer

Silvia Monticelli & Petr Cejka

DNA in the cytoplasm can be a sign of abnormalities such as viral infections or cancer. A protein with a role in DNA-damage response was unexpectedly found to activate defences against the threats indicated by cytoplasmic DNA. **See p.585**

Cellular DNA is usually found in the nucleus. It is rare to find DNA outside the nucleus, in the cytoplasm, and it can be a harbinger of viral infections or cancer. Among the cellular sensors of cytoplasmic DNA, a protein termed cGAS orchestrates defence pathways against threats posed by foreign or damaged DNA. On page 585, Cho *et al.*[1] reveal a previously unknown partnership that helps to activate cGAS and protect from cancer.

The cGAS pathway is part of a powerful defence signalling cascade that is triggered by cytoplasmic DNA and that probably evolved in response to viral infection. After infection, the presence of viral nucleic acids in the cytoplasm provides an opportunity for early detection of the unwanted intruder. In a sequence-independent, and hence highly versatile, manner, cGAS can bind to viral DNA, which triggers the enzymatic activity of cGAS, resulting in the synthesis of the molecule cGAMP from nucleotides.

cGAMP binds to and activates the protein STING, triggering an antiviral response program through the production of defence molecules such as interferon proteins and other inflammatory molecules called cytokines. However, excessive activation of this cGAS–STING pathway can be harmful and is associated with inflammatory, autoimmune and degenerative disorders[2]. Understanding how the pathway is regulated and how it distinguishes between cellular and foreign DNA is therefore relevant to its protective and disease-causing outcomes.

Initially, cGAS was thought to function mainly from its cytoplasmic location. However, it has become clear that the protein is also present in the nucleus[3]. The activation of nuclear cGAS by genomic self DNA is prevented by several mechanisms, including those that rely on the presence of the DNA-binding protein BAF (ref. 4), and interactions with the histones H2A and H2B (refs 5–9). Histones are the protein components of nucleosomes, which help to package long genomic DNA into the tight 3D space in the nucleus.

The mechanisms that lead to the release of cGAS from nucleosomes have not been clear. Now, Cho and colleagues have identified a human protein that helps to release inactivated cGAS from nucleosomes (Fig. 1). Once it has been released, cGAS can move into the cytoplasm, where it becomes activated on contact with DNA. The protein that aids cGAS release from nucleosomes is MRE11, a component of a three-protein complex termed MRE11–RAD50–NBN (MRN), which has a well-established role in the response to DNA double-strand breaks[10].

MRE11 is a nuclease, a type of enzyme that has DNA-cleaving abilities, and the MRN complex has DNA-tethering functions that it uses during the process of repairing DNA breaks. When bound to the ends of broken DNA, MRN is also essential for the activation of an enzyme called ATM (which is a kinase – an enzyme that can attach phosphate groups to proteins in a process called phosphorylation). ATM phosphorylates various protein targets to drive responses to DNA breaks, including the activation of proteins involved in DNA repair and in regulation of the cell cycle[10]. Cho and colleagues demonstrate that MRE11's role in the release of cGAS from nucleosomal DNA is independent of its nuclease and ATM-activation roles but is dependent on having an intact MRN complex.

The authors present *in vitro* experiments showing that MRN binds to nucleosomes and can help to liberate cGAS. Treating cells with a drug that causes DNA breaks notably

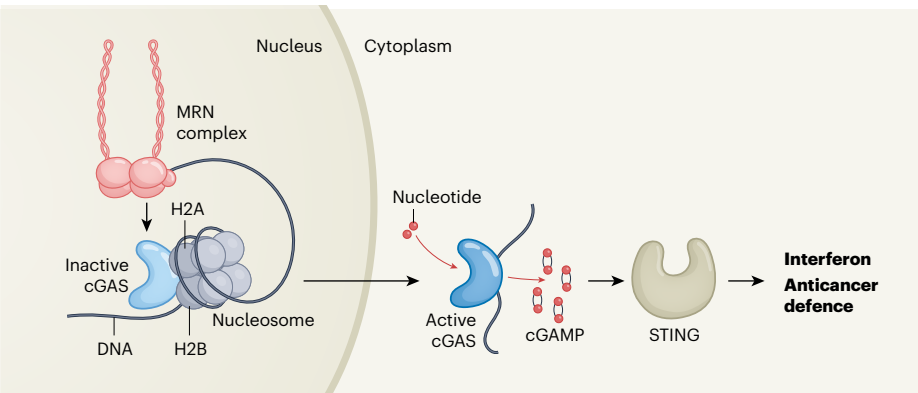

Figure 1 | The activation of a pathway that defends against foreign or abnormal cytoplasmic DNA. The presence of DNA in the cytoplasm can be a sign of problems, such as the high levels of DNA damage associated with cancer. When the protein cGAS, which is usually trapped in the nucleus[3], senses DNA in the cytoplasm, it becomes activated and uses nucleotides to generate the molecule cGAMP. cGAMP then activates the protein STING, which aids production of interferon proteins to promote anticancer defences. Cho *et al.*[1] shed light on how cGAS is activated. The activation depends on a complex called MRE11–RAD50–NBN (MRN) and, in particular, one of its constituent proteins, called MRE11, which is involved in recognizing DNA damage[10]. When MRE11 is present as part of this intact complex, it can free cGAS from interaction with the histone proteins (H2A and H2B) that bind to nuclear DNA in a structure called a nucleosome, thereby enabling cGAS to enter the cytoplasm.