

Many questions remain about the efficacy of the disclination hypothesis for resolving the Von Mises problem in peridotites. For example, how does their density and mobility evolve during deformation and with changes in thermodynamic conditions, and how are the dynamics of disclinations influenced by the anisotropic (direction-dependent) elastic properties of olivine? How are grain-boundary disclinations involved with grain-boundary sliding? Can the inclusion of disclinations in polycrystalline-deformation models help to resolve questions regarding the evolution of lattice-preferred orientations

in olivine aggregates deformed to high deformation? The latter problem is crucial for the interpretation of the seismic structure of Earth's mantle, which in turn is currently our best observational technique to explore convective motions inside Earth. Research on these topics promises to provide insights into the viscosity of the terrestrial planets and into the interpretation of a broad range of geophysical observations. ■

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BIOLOGICAL TECHNIQUES

Wrapped around the heart

An elastic membrane cast around a three-dimensional printed model of a specific heart allows diverse aspects of cardiac function to be monitored and modified, and paves the way to new diagnostic and therapeutic approaches.

COLLEEN E. CLANCY & YANG K. XIANG

A long-sought goal has been to observe, diagnose and treat dangerous disturbances to cardiac rhythm, an unfortunately common situation that occurs when electrical impulses in the heart become disordered. The major roadblock in the quest to understand and treat abnormal cardiac rhythms (arrhythmias) is that there is no straightforward approach for detailed inspection of the underlying electrical, metabolic and mechanical changes and the interactions between them. Writing in *Nature Communications*, Xu *et al.*¹ have begun to address this deficit by developing three-dimensional membranes that uniquely conform to the heart surface, providing a platform for flexible arrays of multifunctional sensors.

The devices, termed three-dimensional multifunctional integumentary membranes (3D-MIMs), offer several key features. They are inherently elastic and mechanically stable, and they provide a uniform, non-invasive interface to all points on the heart, allowing high-resolution measurement or high-density stimulation of cardiac function (Fig. 1). Furthermore, the components of the attached sensors can be distinctively configured to allow a variety of functions, including electrical, thermal and optical stimulation, or measurement of pH, temperature, voltage or strain.

The 3D-MIMs are made by casting a thin layer of silicone elastomer (a silicone-containing, rubber-like material) over a 3D-printed reconstruction of the heart of interest, which

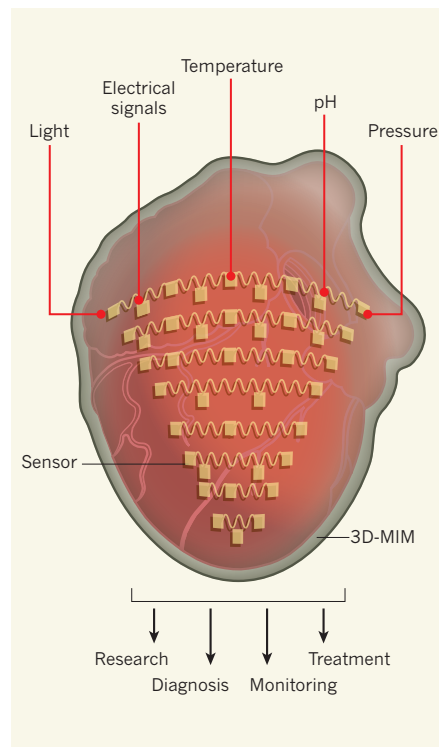


Figure 1 | Multifunctional monitoring. Xu *et al.*¹ have developed three-dimensional elastic membranes (3D-MIMs) that conform to the surface of a specific heart, creating a platform for arrays of multifunctional sensors and electronic and optoelectronic components that can stimulate and measure the pH, temperature, voltage or strain in the heart. These devices could be used in research applications and in the clinic for diagnosis, monitoring and treatment.

is generated using scanning techniques involving optical segmentation, magnetic resonance imaging or computed tomography. This process produces an artificial envelope that uniquely conforms to a specific heart. The manufacturing technique can be applied to different species and, importantly, to individual patients.

One of the immediate research applications of 3D-MIMs will be to perform multiple simultaneous measurements of a working (beating) heart during normal or abnormal cardiac cycles. Such measurements include temperature, tension and pH, any or all of which can be recorded simultaneously from electrical signals. Currently, optical mapping with voltage-sensitive dyes is the best available technique for measuring electrical function with high spatial resolution in the intact heart. However, one of the acknowledged shortcomings of this approach is that it relies on excitation–contraction uncoupling drugs that allow recording only in the motionless heart. 3D-MIMs overcome this limitation, allowing the first possibility of high-resolution measurements of excitable and metabolic states in the beating heart.

Different actuators for electrical, thermal and optical stimulation can also be embedded in 3D-MIMs. This would allow the potential integration of optogenetic tools² (involving light-responsive proteins) or genetically coded biosensors³ for monitoring electrical and biochemical signals, or to locally activate or deactivate genes or proteins in normal or diseased hearts. Furthermore, such measurements or interventions could be applied to hearts in the resting state or when they are subject to various stressors.

In the clinical realm, 3D-MIMs have almost limitless potential for the construction of patient-specific devices for diagnostic and therapeutic purposes. During open-heart surgery, 3D-MIMs with various combinations of components will be useful for diagnosing the region of an abnormality, such as arrhythmias, ischaemia or heart failure, which will help to determine appropriate surgical or drug treatment strategies. The membranes might even be used to deliver therapeutic interventions during

surgery, including localized tissue ablation, pacing or acute low-energy defibrillation⁴.

Although the immediate potential for using 3D-MIMs in such open-chest surgical scenarios is clear, chronic implantation of 3D-MIMs in patients could prove especially effective. Such implantation might eventually allow for post-surgery monitoring involving continuous measurements of local metabolic, excitable, ionic, contractile and/or thermal states of the heart in response to various insults, diseases or therapies. These diagnostic data might then be used to activate the device remotely to deliver targeted electrical therapy without the need for further surgery. The membranes might also be developed as a platform for low-energy control or defibrillation methods to regulate electrical turbulence

in the heart⁴. In the same vein, 3D-MIMs could conceivably be used for localized and targeted delivery of stem cells, viral vectors or drugs.

There is also the future possibility of creating an *in vivo* optical-mapping system using externally applied dyes or internal fluorescent indicators. This application would require the development of diverse light sources that could be integrated into the membranes and provide enough power to illuminate both dyes and sensors locally or in the whole heart. It also remains to be seen whether 3D-MIMs can be effectively integrated with other developing technologies, such as stem-cell bio-patches, or encapsulated viral vectors or drugs. Other challenges to the application of these membranes for chronic implantation include power supply, control, durability and encapsulation.

However, although the technology is in its infancy, the development of a 3D-MIM prototype represents a breakthrough technology with the potential to significantly expand diagnosis and treatment options for common cardiac-excitability disorders. ■

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not phosphorylated and mediates low-affinity uptake of the abundant substrate⁵ (Fig. 1). But how Thr 101 phosphorylation regulates K_m is yet to be defined. The two new studies, by Sun *et al.*¹ (page 73) and Parker and Newstead² (page 68), provide different, although not necessarily conflicting, explanations.

A transporter has three main conformational states: outward-facing (substrate site open to the external environment), occluded (closed to both sides of the membrane) and inward-facing (open to the cell cytoplasm)⁶. Using crystallography, the two groups analysed the inward-facing conformation of unphosphorylated NRT1.1, and report essentially identical structures. NRT1.1 is known to be comprised of 12 transmembrane helices (TMHs), and the researchers observed that — as with other members of the major facilitator superfamily (MFS) of membrane transporter proteins — the TMHs form a cavity open to the cytoplasm, within which the substrate

PLANT SCIENCE

How to switch affinity

The protein NRT1.1 transports nitrate ions into plants over a wide range of concentrations. Two studies provide structural insight into this unusual behaviour, but give different explanations for it. SEE ARTICLES P.68 & P.73

YI-FANG TSAY

To acquire nutrients from their surroundings, cells produce proteins that act as transporters, channels and pumps, creating passages in the plasma membrane through which molecules can pass. Unlike channels, pumps and transporters must undergo conformational changes to transfer substrates across the membrane. In plants, the transporter NRT1.1 (also known as CHL1 or NPF6.3) is essential for cellular uptake of nitrate. Unusually for a transporter, NRT1.1 regulates ion uptake by changing its affinity for nitrate ions depending on the availability of nitrate in the soil. However, the structural basis of this behaviour is not understood. Two articles^{1,2} in this issue provide possible answers, by finally determining structures of NRT1.1 two decades after its identification³.

Like enzymes, transporters exhibit an affinity for specific substrates, and their behaviour can be described by the Michaelis constant K_m , which determines the range of extracellular substrate concentrations at which a transporter can operate (a low K_m indicates that the transporter has a high affinity for a given substrate, and a high K_m indicates low affinity). The amount of nutrient available to a cell can fluctuate considerably, so, to ensure that nutrients can be acquired over a wide range of concentrations, cells have high- and low-affinity transport systems. Typically, the two are mediated by distinct transporters; however,

NRT1.1 is a dual-affinity transporter, which can switch affinity by phosphorylation and dephosphorylation at a threonine amino-acid residue (designated Thr 101)⁴.

Regulation of a transporter by phosphorylation can allow cells to rapidly respond to nutrient fluctuation. At low nitrate concentrations, NRT1.1 is phosphorylated at Thr 101, and functions as a high-affinity nitrate transporter, able to acquire scant nitrate from the soil. At high nitrate concentrations, NRT1.1 is

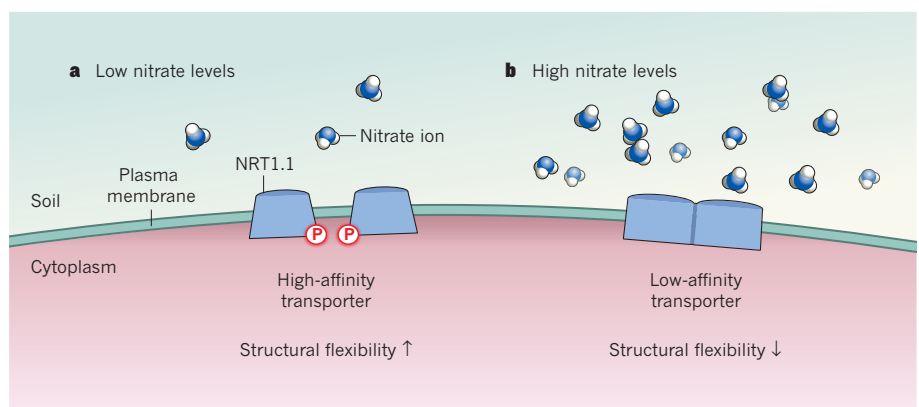


Figure 1 | Changing the affinity of the NRT1.1 protein for nitrate. The nitrate transporter NRT1.1, which spans the plasma membrane of plant cells, is responsible for the uptake of nitrate from the external environment into the cell cytoplasm. **a**, When nitrate concentration is low, NRT1.1 is phosphorylated (P) at the amino-acid residue Thr 101, giving it a high affinity for nitrate. **b**, When nitrate is abundant, Thr 101 is not phosphorylated, and NRT1.1 acts as a low-affinity transporter⁴. Sun *et al.*¹ and Parker and Newstead² have resolved the structure of unphosphorylated NRT1.1, and find that it forms a dimer. Although Sun *et al.* propose that this dimerization itself alters affinity, Parker and Newstead suggest that dephosphorylation decreases structural flexibility, modulating nitrate uptake.