this lattice resulted in the emergence of two valleys in the energy–momentum band structure – the relationship between the energy and momentum of photons in the material. The authors made the holes quasi-hexagonal so that they broke the spatial-inversion symmetry of the lattice and rendered the two valleys topologically inequivalent. This led to the formation of topological edge states at the interface between two such crystal lattices in which the orientation of holes (and valleys) was flipped in one lattice with respect to the other.

Zeng and co-workers used these topological edge states to design and make a robust ring resonator (a type of optical cavity that traps light at certain 'resonance' frequencies) in the form of a triangle (Fig. 1). It is this triangular cavity that, along with the light amplification from the substrate material, forms a topological laser. The laser produces light of many frequencies that are separated by similar frequency gaps. These frequencies correspond to the resonance frequencies of the triangular cavity and fall within the frequency range of the QCL gain material.

The authors measured light emission from different points along the perimeter of the cavity and discovered that the emission at each point had the same resonance frequencies. This indicates that these waves travelled through the length of the cavity, traversing the sharp (60°) bends at the corners of the triangle. Furthermore, Zeng *et al.* found that the lasing frequencies did not change when they introduced defects, in the form of extra holes, around the cavity, demonstrating the robustness of the QCL.

Another key feature of this laser is that energy is 'pumped' into the device electrically. Previous topological lasers[6–8] have been optically pumped, which means that they require a second laser source to drive the topological laser to generate light. This pumping scheme severely limits practical applications. However, similar to many commonly used lasers (such as laser pointers), Zeng and colleagues' QCL can be directly driven by an electrical current, allowing it to be powered, in principle, by a battery or a wall outlet, rather than by another laser.

Robustness against defects and disorder is one defining characteristic of topological physics, but another important feature is a type of asymmetry called chirality. In particular, in the valley Hall effect, the two valleys are associated with photons of opposite circular polarization in the plane of the material. If right-circularly polarized photons travel to the left, then left-circularly polarized ones would travel to the right. Realizing this chirality represents a crucial future step towards terahertz topological lasers in which light waves flow around a ring resonator in only one direction. The chirality could be incorporated either by explicitly breaking time-reversal symmetry (a symmetry in which reversing the direction of light waves is equivalent to running time backwards) or by introducing directional light amplification in the cavity.

Zeng and co-workers' results pave the way for studying topology in a previously inaccessible part of the electromagnetic spectrum. One area of great interest for future research is the application of other topological models, such as exotic (higher-order) topological insulators, to make robust terahertz lasers that have other geometries. For example, these lasers could emit light at the corners, rather than at the edges, of a triangular cavity.

Another fascinating prospect is the exploration of non-Hermitian (open) physical systems at terahertz frequencies, in which the presence of light amplification and loss can lead to the emergence of features such as parity–time symmetry (symmetry under the combination of a mirror reflection and time reversal) and exceptional points (spectral features that correspond to coalescing resonances)[10]. The realization of topological photonics in the terahertz range could therefore serve as a catalyst for the development of practical devices, and also enable a better fundamental understanding of topological physics and complex (nonlinear) optoelectronics.

Sunil Mittal and **Edo Waks** are at the Joint Quantum Institute, University of Maryland, College Park, Maryland 20742, USA.
e-mails: mittals@umd.edu; edowaks@umd.edu

1. Faist, J. *et al. Science* **264**, 553–556 (1994).
2. Zeng, Y. *et al. Nature* **578**, 246–250 (2020).
3. Baba, T. *Nature Photon.* **2**, 465–473 (2008).
4. Hasan, M. Z. & Kane, C. L. *Rev. Mod. Phys.* **82**, 3045–3067 (2010).
5. Ozawa, T. *et al. Rev. Mod. Phys.* **91**, 015006 (2019).
6. Bandres, M. A. *et al. Science* **359**, eaar4005 (2018).
7. Bahari, B. *et al. Science* **358**, 636–640 (2017).
8. St-Jean, P. *et al. Nature Photon.* **11**, 651–656 (2017).
9. Ma, T. & Shvets, G. *New J. Phys.* **18**, 025012 (2016).
10. El-Ganainy, R. *et al. Nature Phys.* **14**, 11–19 (2018).

Structural biology

Long-distance coupling in a promiscuous protein

Thorsten Althoff & Jeff Abramson

Unlike many sugar-transporting proteins, a transporter in one species of malaria parasite can import several types of sugar equally effectively, aiding the parasite's survival. The structure of this protein reveals the reason for its versatility. **See p.321**

Most cases of malaria are caused by the protozoan parasite *Plasmodium falciparum*[1]. Given that there are more than 400,000 malaria-associated deaths annually, and that *P. falciparum* is constantly evolving to resist pharmacological therapies, opportunities for developing drugs that target this organism must be continuously explored. A protein called the *P. falciparum* hexose transporter 1 (PfHT1) has a proclivity for scavenging sugars from an infected host's red blood cells to improve the parasite's chances of survival in these cells, and is therefore a drug target. On page 321, Qureshi *et al.*[2] describe the 3D structure of PfHT1, and identify a mechanism that couples the docking of a sugar in the PfHT1 binding site to the process by which sugars are gated through the protein. This coupling facilitates the protein's substrate promiscuity – that is, its ability to transport a wide range of sugar molecules effectively, a feature that gives the parasite a distinct survival advantage.

Transporter proteins shuttle substrate molecules across the otherwise impermeable lipid bilayer of the cell membrane. The functional and dynamic properties of these membrane-embedded proteins are fundamentally related to their 3D structures, which are modulated at the atomic level over a broad range of timescales. Membrane transporters use the alternating-access mechanism for gating[3], in which access to the substrate-binding site switches from one side of the membrane to the other (Fig. 1).

The development of methods for determining the structures of membrane proteins in the past few years has produced near-complete pictures of the translocation mechanisms of several classes of transporter – that is, the global rearrangements that the proteins undergo during translocation cycles of substrate binding, transport and release have been visualized at atomic resolution. Intuitively, the substrate specificity of transporters has generally been found to depend on the amino-acid residues at the binding

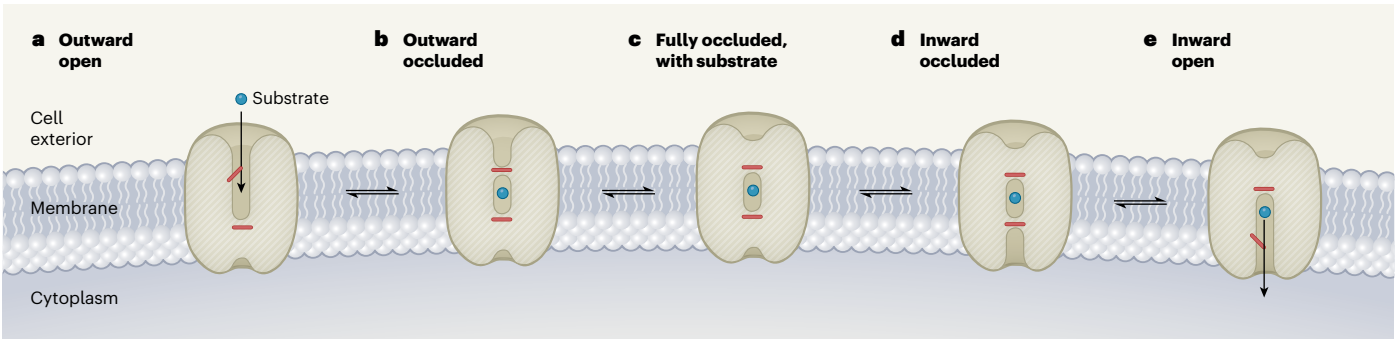

Figure 1 | The alternating-access mechanism. Transporter proteins facilitate the passage of substrate molecules across cell membranes. Access to the substrate-binding site in the middle of transporters is controlled by two gates (red). **a**, In the outward open state, a pathway from the cell exterior allows substrates into the protein. **b**, In the outward occluded state, a substrate is trapped between the gates, but the outward-facing pathway is still present. **c**, In the fully occluded state with a bound substrate, no pathways are available. **d**, In the inward occluded state, a pathway to the cytoplasm has formed, but the gate remains closed. **e**, In the inward open state, substrates can exit to the cytoplasm. Qureshi *et al.*[2] report the structure of PfHT1, a sugar transporter from the malaria parasite *Plasmodium falciparum*. They find that the binding of a sugar substrate to the structure shown in **a** is coupled to the gating mechanism, and that the transition from **a** to **c** occurs much faster than in other sugar transporters. This explains why PfHT1 transports a wide range of sugar molecules equally effectively, unlike other sugar transporters.

site. The structure of PfHT1 now implies that another mechanism affecting substrate specificity might be at play.

Red blood cells infected by *P. falciparum* consume about 100 times more glucose than do non-infected cells[4] because the parasite continuously metabolizes sugars from these cells to support its growth and replication. Because PfHT1 is responsible for transporting sugars from host cells, it has a crucial role in supporting this metabolism. It belongs to the well-studied major facilitator superfamily (MFS) of transporters, which promote the diffusion of substrates across the cellular membrane. It has the same overall 3D structure as the distantly related human GLUT transporters[5]. But whereas these specialize in the transport of either D-glucose or D-fructose, PfHT1 transports both of these sugars, and some others, with comparable efficiency.

Qureshi *et al.* resolved the 3D structure of PfHT1 in which D-glucose is captured in the sugar-binding site, and found that the protein was in a fully occluded conformation — that is, the transporter protein completely shielded the sugar from the aqueous environments on either side of the cell membrane. The structure therefore provides a snapshot of the substrate during a part of the translocation cycle that had not previously been visualized for an MFS transporter.

Armed with their structure, the authors carried out extensive transport studies to try to work out why PfHT1 has less substrate selectivity than its human GLUT counterparts. They first demonstrated that the same set of amino-acid residues in PfHT1 is required to bind D-glucose and D-fructose. They then replaced residues in and around the sugar-binding site of PfHT1 by residues found in GLUT transporters, but none of these mutations conferred GLUT-like selectivity on the resulting proteins. They thus concluded that the unusual lack of selectivity of PfHT1 cannot be explained on the basis of the sugar-binding residues alone.

So how can the substrate promiscuity of PfHT1 be explained? It has been known since the first structures of MFS transporters were reported[6,7] in 2003 that bundles of α-helices in the proteins 'rock' around the central substrate-binding site, thereby establishing the alternating pathways for substrates through the protein: an outward-facing pathway, which allows substrates into the transporter from the cell exterior, and an inward-facing pathway that allows substrates to enter the cytoplasm (Fig. 1). By considering their structure of the fully occluded state of PfHT1 alongside structures of other sugar transporters captured at different stages in the translocation of D-glucose[8–13], Qureshi *et al.* were able to describe a complete translocation cycle.

The authors found that, surprisingly, all of the sugar-binding residues maintain their orientations throughout the cycle. This implies that the switches from the outward-facing conformation of PfHT1 to the fully occluded state, and then to the inward-facing conformation, are not driven by structural rearrangements at the sugar-binding site. Instead, they are driven by a previously unknown mechanism.

Qureshi and co-workers' analysis of the gating mechanism of PfHT1 revealed interactions involving hydrophilic amino-acid residues in two transmembrane α-helices in the occluded state. By contrast, in human GLUT proteins, the equivalent residues are larger and more hydrophobic. Experiments in which the authors substituted these gating residues in PfHT1 with other residues demonstrated that they are crucial for sugar transport. Notably, the gating residues are about 15 ångströms away from the sugar-binding site — a large distance. This indicates that the binding of a sugar is coupled to remote conformational changes associated with gating of the transporter, a type of mechanism known as allosteric coupling. Thus, the ability of PfHT1, unlike its human counterparts, to transport many similar substrates results from its substrate-driven gating dynamics, which allows it to adopt the occluded conformation more easily and rapidly.

The authors also carried out experiments to investigate how PfHT1 is inhibited by two small-molecule antimalarial drugs (C3361 and MMV009085). This allowed them to identify a hydrophobic pocket in the transporter that probably facilitates the binding of inhibitory drug molecules, and that might help to guide the design of new antimalarial compounds. However, the most exciting finding is the allosteric coupling between substrate binding and gating — it suggests that substrate recognition in transporters can be a consequence of the transporter's conformational dynamics, rather than being the result of protein–substrate interactions, which underpin the conventional 'lock and key' model of how molecules interact with their biological targets.

Thorsten Althoff and **Jeff Abramson** are in the Department of Physiology, University of California, Los Angeles, Los Angeles, California 90095, USA.
e-mail: jabramson@mednet.ucla.edu

1. World Health Organization. *World Malaria Report 2019* https://www.who.int/news-room/feature-stories/detail/world-malaria-report-2019 (2019).
2. Qureshi, A. A. *et al. Nature* **578**, 321–325 (2020).
3. Jardetzky, O. *Nature* **211**, 969–970 (1966).
4. Roth, E. Jr *Blood Cells* **16**, 453–466 (1990).
5. Woodrow, C. J., Burchmore, J. R. & Krishna, S. *Proc. Natl Acad. Sci. USA* **97**, 9931–9936 (2000).
6. Abramson, J. *et al. Science* **301**, 610–615 (2003).
7. Huang, Y., Lemieux, M. J., Song, J., Auer, M. & Wang, D.-N. *Science* **301**, 616–662 (2003).
8. Deng, D. *et al. Nature* **526**, 391–396 (2015).
9. Nomura, N. *et al. Nature* **526**, 397–401 (2015).
10. Deng, D. *et al. Nature* **510**, 121–125 (2014).
11. Sun, L. *et al. Nature* **490**, 361–366 (2012).
12. Quistgaard, E. M., Löw, C., Moberg, P., Trésaugues, L. & Nordlund, P. *Nature Struct. Mol. Biol.* **20**, 766–768 (2013).
13. Wisedchaisri, G., Park, M.-S., Iadanza, M. G., Zheng, H. & Gonen, T. *Nature Commun.* **5**, 4521 (2014).

This article was published online on 29 January 2020.