imperfect — immunity following recovery from infection. Consequently, as Grassly *et al.* show, the dynamics of syphilis infection have many features of the well-known 'susceptible–infected–recovered' (SIR) model for microparasitic infections[4,5]. In SIR dynamics, oscillations in disease incidence can be driven by prolonged immunity following infection (combined with a relatively short infection period[4]). Cycles occur because major epidemics extinguish themselves by exhausting their supply of susceptible individuals (Fig. 1a); the numbers of individuals in at-risk groups then build up slowly, eventually providing enough scope for the next major outbreak.

Unlike syphilis, gonorrhoea can evade post-infection immunity by camouflaging itself with different arrays of surface proteins[7]. At the population level, this corresponds to the 'susceptible–infected–susceptible' (SIS) model of infection, in which the same individual can be infected repeatedly[4,8] (Fig. 1b). Thus in SIS dynamics, infection does not decrease the total number of susceptible individuals, preventing the boom-and-bust dynamics seen in acute SIR infections.

By contrast, the prolonged immunity seen in SIR systems causes overcompensatory dynamics and recurrent epidemics, which bear strong analogies to the cycles of many predator–prey systems in ecology. In fact, SIR dynamics are, like the SIS interaction, regulated by an upper population limit on cases and susceptible individuals[4]; the system therefore needs some form of regular or stochastic 'forcing' to drive strong epidemics. A dramatic illustration is given by acute, immunizing childhood infections such as measles, where seasonal variation in contact rates can produce violent biennial epidemics[5]. With its more sedate decadal dynamics, syphilis is unperturbed by seasonal influences. However, Grassly *et al.* show that random 'shocks' provided by demographic stochasticity (arising from the probabilistic nature of individual infection events, for example) are sufficient to excite oscillations in the model that closely resemble the cycles seen in the incidence data. On a longer timescale, external shocks, such as a reduction in sexually transmitted disease associated with control measures against the spread of HIV, further influence the dynamics of both syphilis and gonorrhoea.

Nonlinear overcompensatory interactions, as seen in syphilis, can lead to the emergence of space–time dynamics, such as sychronization of disease incidence across different locations, or waves of infection across geographical areas. Indeed, Grassly *et al.* document increasing synchronization of syphilis epidemics across US cities during the 1960s and 1970s. The authors argue convincingly that this is because the underlying network of sexual contacts is becoming increasingly interconnected. However, previous comparative analyses of the spatio-temporal dynamics of measles and whooping cough show that dynamic inference from such systems is not straightforward[6]. In these cases, spatial dynamics emerge through the interaction between local dynamics and spatial coupling between different local systems — sometimes coupling leads to enhanced synchrony, but sometimes synchrony can decay with time if increases in coupling accompany changes in local dynamics.

A challenge in the spatio-temporal dynamics of syphilis is to combine models for local transmission with models of spread across spatial networks[9]. As Grassly *et al.* point out, we must be very cautious in applying simple models to explain the spatial dynamics of human pathogens: basic distance-based networks fail to capture the complex nature of human population mixing. Such contact patterns are often hard to measure directly, and an intriguing task for future models will be to infer spatial patterns and temporal trends of mixing from the analysis of epidemic synchronicity.

Grassly and colleagues' dissection of cyclic versus non-cyclic behaviour is a valuable addition to the taxonomy of comparative disease dynamics. Using comparative studies to tease out the relative role of intrinsic dynamics and extrinsic shocks is an important process for understanding and predicting the dynamics and evolution of established and emerging infections. In the nonlinear, behaviourally and environmentally driven world of epidemics, though, we should always expect the unexpected. ■

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Cell biology

Border crossing

James U. Bowie

The 'translocon' complex, which determines whether a protein segment will be inserted into or pushed through the cell membrane, seems to make the decision by performing a thermodynamic measurement.

Cells have a border security system that would put any nation to shame. They need to decide millions of times every nanosecond whether to allow something in or out, and a mistake could mean death. The sentries entrusted with these life-or-death decisions are specialized proteins that reside in the cell membrane. Not just any 'wannabe' gets to be a membrane protein, however; it requires a special constitution and careful nurturing. A paper by von Heijne and colleagues in this issue (Hessa *et al.*[1], page 377) tells us a lot more about what it takes to get into the membrane.

Membrane proteins are usually not soluble in the aqueous cytoplasm inside the cell. So cells have developed specialized machinery for injecting them into the membrane as they emerge from the complex in which they are synthesized. Hessa *et al.*[1] focused on the ubiquitous and best-studied insertion machine, known as the Sec translocon[2,3].

The Sec translocon must make several tricky decisions as the protein is being made; based on the emerging protein's amino-acid sequence, the translocon must choose whether to pump the segment into the exoplasm outside the cell, push it sideways into the membrane, or flip it before releasing it into the membrane. Making the correct decision is essential if the protein is to fold properly, so the emerging peptide and the translocon must work in concert. Thus, to predict protein structure from amino-acid sequence, we need to understand how the translocon works with the nascent polypeptide to generate the final fold. The paper by Hessa *et al.*[1] helps to define how one of the decisions is made — how the translocon 'decides' whether to move a segment into the membrane or the exoplasm.

The cell membrane is a complex environment, and only specialized polypeptides, with equally complex and variable surface properties, reside there[4,5]. For simplicity, we can divide the membrane into three regions (Fig. 1, overleaf): the central core of lipid hydrocarbon chains (about 30 Å thick); the interfacial region near the lipid head groups (about 15 Å thick); and the aqueous region. These environments are dramatically different, and so the structure of a membrane

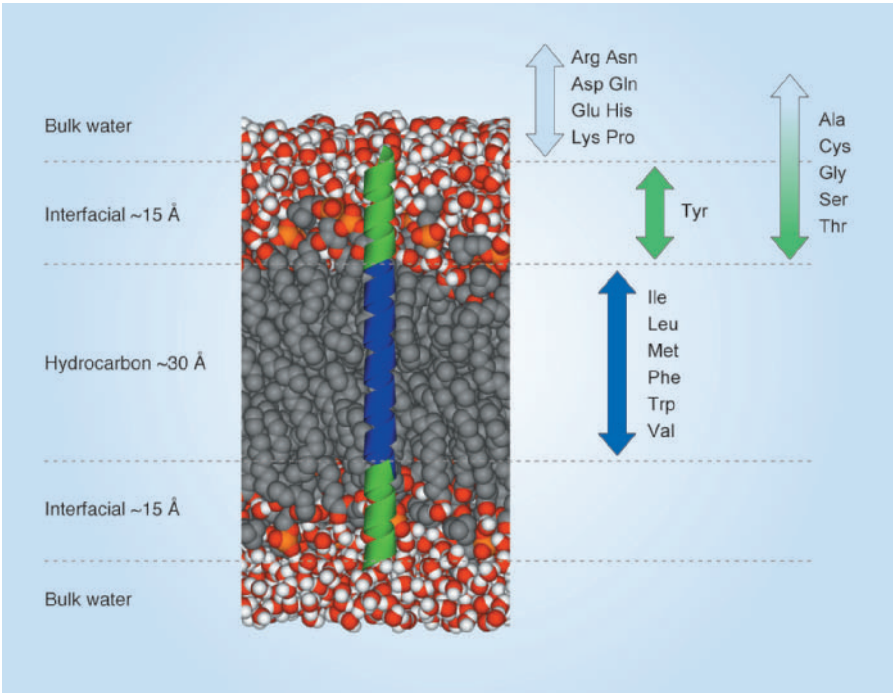

Figure 1 **Membrane regions and preferred amino-acid locations. A snapshot of a lipid bilayer membrane[11] and its three major regions. Grey, carbon atoms; red, oxygen; white, hydrogen bound to oxygen; orange, phosphorus. In an α-helix, 20 amino acids (blue) can span the hydrocarbon core, and 10 amino acids (green) can span the interfacial region. Arrows indicate where most of each amino acid (denoted by its three-letter symbol) would be found at equilibrium based on transfer free-energy measurements[7,8].**

protein needs to be such that each amino acid can interact favourably with its local environment. In previous studies[6–8] to assess where in the membrane individual amino acids tend to go, Wimley and White measured the free energies required for transferring each of the 20 amino acids from water to either the interfacial region or the core region (summarized in Fig. 1). They found that amino acids containing apolar (hydrophobic) side chains prefer the hydrocarbon core, those that are moderately polar prefer the interfacial region, and the strongly polar amino acids prefer to be in water.

To assess the rules for membrane insertion by the Sec translocon, Hessa *et al.*[1] used a rapid assay for distinguishing whether the translocon inserted a 19-amino-acid test segment into the membrane or pushed the segment across it. By varying the sequence of amino-acid residues in the test peptide, they could explore the determinants of the decision process. A 19-residue peptide in a helical conformation (the most common structure for traversing the membrane bilayer) is just large enough to span the membrane's hydrocarbon core (Fig. 1). According to the Wimley and White hydrophobicity scale[6–8], a 19-residue sequence consisting entirely of alanine amino acids (polyalanine) should prefer to remain outside the hydrocarbon region of the bilayer. To make it sufficiently hydrophobic to favour insertion in the membrane, four or five leucine amino acids would need to be added.

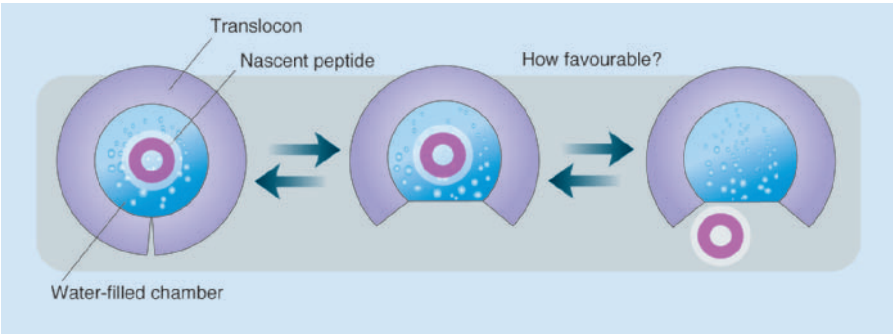

Figure 2 **A possible scheme for the membrane-insertion decision, as proposed by Hessa *et al.*[1]. A top view of the membrane and the translocon pore that crosses it. Inside the pore is a peptide helix surrounded by water. The pore opens sideways into the membrane, allowing the helix to interact with the membrane lipids. If the peptide is more compatible with lipid than with water, it will transfer into the membrane; otherwise, it will continue to be moved through the pore. The figure is only intended to convey the basic principle, and omits many mechanistic and structural issues.**

There is no reason why the insertion machinery must be tied directly to the thermodynamics of membrane–water transfer, as it is not hard to imagine that an amino-acid segment could be trapped kinetically in the membrane. But, remarkably, the system behaves almost as though it were consulting the Wimley and White scale. When the test segment was entirely polyalanine, almost none was inserted into the membrane. But as more and more leucines were added, an increasing percentage of the test segment was inserted — when five leucines were present, more than 90% of the segment went into the membrane. This gives the impression that the translocon machinery somehow directs peptides according to a thermodynamic scale.

Strikingly, Hessa *et al.*[1] found that their data could be accurately modelled by imagining that an equilibrium between the translocated and inserted forms actually exists, providing a quantitative framework for their results. By replacing an amino acid within the test segment with each of the 20 possible amino acids, one at a time, they could measure apparent exoplasm–membrane transfer free energies for the insertion of each amino acid. This 'biological' scale correlates surprisingly well with the physical chemistry scale discussed above. The authors also examined how insertion probabilities vary according to the location of the amino acid in the test segment. As would be expected from the physical chemistry, amino-acid residues that favour the interfacial or aqueous regions of the membrane are more likely to be inserted in the membrane if they occur towards the end of the peptide. In addition, the peptide is more likely to be pushed through the membrane as it becomes more amphipathic (with one side of the helix being more polar than the other).

These results strongly suggest that the translocon decides whether to insert a segment into the membrane by measuring whether the segment best suits a hydrocarbon, interfacial or aqueous environment. How can it determine these free-energy values? One model (depicted in simplified form in Fig. 2) posits that the nascent polypeptide enters an aqueous translocon pore that can open towards the membrane core on one side[2,9]. A potential lateral opening site is seen in the recent crystal structure of a related translocon[10]. Thus, the translocating polypeptide segment would find itself able to interact with both an aqueous and a bilayer environment. If the rate of translocation is slow enough relative to the rate of lateral opening and closing, it could be possible to establish an equilibrium between the aqueous and lipid environments. The more strongly the equilibrium favours the

membrane environment, the higher the probability that the segment will stay there. Moreover, an amphipathic segment would find a favourable location in the lipid–water interface near the opening site, decreasing the likelihood that it will partition into the membrane.

Hessa and colleagues' results establish rules for membrane-protein insertion and folding. The thermodynamic scale derived in this work provides a starting point for understanding the preferences for the insertion of isolated helices. It seems likely that other factors will also contribute to this process, however. For example, interactions between neighbouring helices are likely to be a major factor. If a previously inserted helix interacts strongly with a translocating segment, it could drive the putative equilibrium in favour of membrane insertion, even if that segment would not normally insert in isolation. Loop lengths and loop folding could have a similar role. In addition, other proteins (such as TRAM[2]) could be involved in chaperoning the transmembrane segments into the membrane. Nevertheless, the work of Hessa *et al.* builds a quantitative thermodynamic foundation that will allow these questions to be addressed. It also provides an important step towards the ultimate goal of predicting membrane-protein structure from sequence information. ■

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Materials science

Build your own superlattice

Guus Rijnders and Dave H. A. Blank

Artificial materials made from oxide building blocks turn out to be excellent ferroelectrics. This shows that materials with specific properties can be designed by atomic-scale tailoring of their composition.

Ferroelectric oxides are used in a wide range of applications — random-access memories in computers, accelerometers in airbags or inkjet printers, telecommunication signal-processing devices and high-frequency devices for ultrasonic medical imaging, to name just a few. Predictions[1] that the performance of a ferroelectric oxide can be significantly improved by combining it with other oxides in a carefully tailored lattice have now been borne out by experiment. On page 395 of this issue, Lee *et al.*[2] show that such a 'superlattice' has a 50% enhancement in ferroelectric polarization compared with barium titanate, its only ferroelectric component. One of the key aspects of their method is the degree of control achieved at the atomic level during the growth of this artificial material.

Ferroelectrics are materials in which positive and negative charge centres separate spontaneously so that one side of the material is positive and the other negative. This polarization of charge exists even in the absence of an external electric field and is stable until an electric field is applied to change its direction. Device applications often make use of the piezoelectric properties of ferroelectric materials; when a voltage is applied across a piezoelectric material, it undergoes a mechanical distortion in response and vice versa.

A potential application of ferroelectric materials lies in ultra-high-density memory devices, produced by controlling the ferroelectric domains at the nanometre scale[3]. Such storage devices would be non-volatile (and so able to retain the stored data for long periods of time without any power supply) and have short boot-up times.

Most materials used for ferroelectric devices are perovskites — oxides with a structure like that of the natural mineral $CaTiO_3$. Although the crystal structure of all perovskites is similar, their properties can differ significantly. For example, $CaTiO_3$ is a dielectric (resistant to electrical current), but replacing calcium with barium or lead produces piezoelectric materials. Partial substitution of titanium by zirconium in lead titanate gives lead zirconium titanate, at present the most widely used piezoelectric material.

Interest in perovskites received a boost with the discovery of high-temperature superconductivity in La–Ba–Cu-oxide in 1986 by Bednorz and Müller[4]. In the past decade, thin films of perovskites have been extensively studied to explore their electrical, magnetic and optical properties further. In the course of this work, progress has been made in controlling the growth of films at an atomic level, and Lee *et al.*[2] have built on several developments to make their superlattice structure — a stack of hundreds of thin perovskite layers.

To grow the films, Lee and co-workers used pulsed laser deposition, a technique that is particularly suitable for growing multi-component oxide structures. In this approach, a plasma is created by using laser pulses to evaporate oxide material from solid targets; this plasma has the same composition as that of the target. The approach can be used at relatively high oxygen pressures, which makes it possible to deposit stable units of perovskites under a wide range of conditions. To control the assembly of these units into a superlattice structure, Lee *et al.* make use of reflection high-energy electron diffraction.

When building up a superlattice, the layers must be grown carefully on top of each other so that their atomic lattices match. The termination (final atomic configuration) of each deposited layer will influence how well the layers grow, and consequently determine the device's performance. A prerequisite for controlling termination is an atomically flat substrate to start from. It was therefore a step forward when it became possible to prepare substrates that are terminated in a single configuration, and so are atomically flat[5,6]. Lee and colleagues need a conducting electrode, and use $SrRuO_3$, a metallic ferromagnetic perovskite, as a substrate. It can be grown atomically smooth, with a termination of SrO (refs 7, 8).

Previous work showed that superlattices can be designed with specific properties; for example, neither $BaCuO_2$ nor $SrCuO_2$ exhibits superconducting behaviour, whereas a superlattice consisting of thin layers of both oxides does so[9]. Another example is the superlattice of $SrZrO_3/SrTiO_3$. Neither of the two building blocks is ferroelectric, but the superlattice is[10].

Lee *et al.* assemble their superlattice with three different building blocks — $BaTiO_3$, $SrTiO_3$ and $CaTiO_3$ (Fig. 1, overleaf). The use of three different compounds breaks the inversion symmetry that often occurs in two-component superlattices[11]. Typically, ferroelectric materials display symmetric two-state polarization (that is, the applied electric field required to change it in either direction is equal). In the three-component superlattice, inversion symmetry is broken, resulting in asymmetric polarization and an extra degree of freedom for optimizing the ferroelectric properties.

Growing thin layers on top of each other can lead to considerable 'epitaxial' strain in