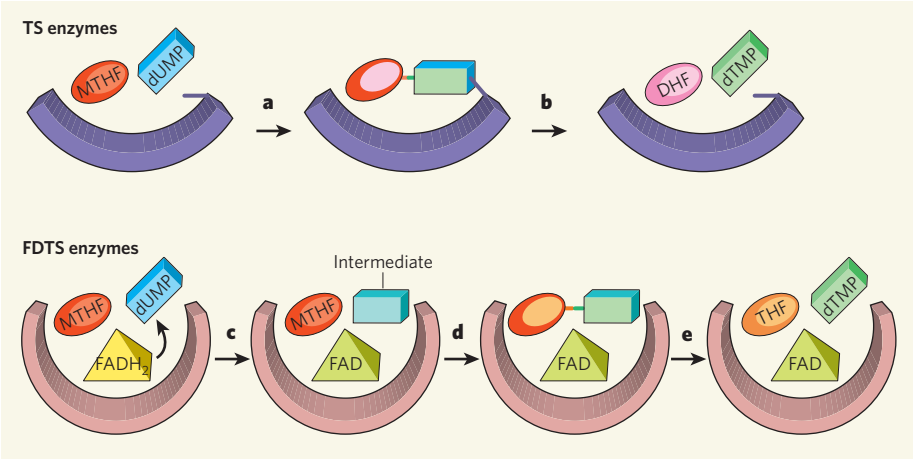

Figure 1 | Different mechanisms in the biosynthesis of dTMP. Thymidylate synthase enzymes make deoxythymidine nucleotide (dTMP), which is necessary for the synthesis of DNA. Two groups of these enzymes exist: TS enzymes in mammals and FDTS enzymes in certain microorganisms. **a**, In TS enzymes, the substrate (deoxyuridine nucleotide, dUMP) is first anchored to the active site, whereupon it reacts with a cofactor (MTHF). **b**, The products of the reaction (dTMP and the spent cofactor, DHF) are then released. **c**, Koehn *et al.*[1] propose that, in FDTS enzymes, dUMP first reacts with a different cofactor, $FADH_2$, to form an intermediate and a side product (FAD). **d**, **e**, The intermediate reacts with MTHF to form dTMP and another side product, THF. No anchoring of dUMP occurs in FDTS enzymes.

produced misleading evidence about the mechanism of action of the enzymes.

The reactivity of the dUMP molecule (specifically, of its uracil nucleotide base) in the FDTS active site is very different from its reactivity in the TS active site, providing another indication of differences between the two classes of enzymes. Koehn *et al.*[1] propose that a third component of FDTS reactions, the '$FADH_2$ cofactor', is responsible for this difference. They claim that an unusual reaction occurs in which a hydrogen atom is transferred from $FADH_2$ to a carbon in the uracil base — the same carbon that is anchored covalently in TS enzymes (see Fig. 1c on page 920).

The authors found evidence for this theory by introducing hydrogen isotopes into the various components of the FDTS reaction, and following the movements of the isotopes as the reaction progressed. They thus showed that $FADH_2$ is the source of the hydrogen atom that ends up in the uracil core of dUMP. Further evidence came from the authors' X-ray crystal structures of FDTS in complex with analogues of dUMP and with FAD (the side product formed from $FADH_2$). The distance between the active-site serine and the uracil carbon atom is too great to allow a covalent bond to form between them (as occurs in TS enzymes). Instead, the FAD molecule lies close to the reactive carbon atom, as would be expected if the $FADH_2$ cofactor transfers a hydrogen atom to dUMP's uracil. The complete picture emerging from Koehn and colleagues' multidisciplinary work convincingly shows that the reaction pathway occurring in certain microbial thymidylate synthases is different from that occurring in mammals.

The unravelling of the entire FDTS pathway through to the end products remains incomplete, and other loose ends must still be tied up — for example, the formation of the 'dead-end complex'. As it is unlikely that FDTS is simply a reaction vessel for dUMP and the two cofactors, the enzyme's contribution to the mechanism must also be clearly characterized in the future.

Although Koehn and colleagues work[1] raises the possibility of developing antibiotics that selectively block microbial FDTS, but not mammalian TS, this remains to be demonstrated, and obstacles certainly exist: only a few inhibitors[6] of FDTS have been discovered since the protein was first reported in 2002. Nevertheless, the prospect of such an antibiotic is exciting, as several pathogenic bacteria, including that responsible for tuberculosis, should be susceptible. More broadly, the authors have discovered a new concept in antibiotic drug discovery — compounds that resemble an enzyme's substrate, but that incorporate significant changes to the core structure (such as that occurring in dUMP when it accepts a hydrogen atom from $FADH_2$), might selectively attack bacteria, and so be less toxic to humans. ■

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SOLID-STATE PHYSICS

Bouncing spins

Lieven M. K. Vandersypen

The conventional approach to flipping electron spins in a semiconductor requires an external alternating field. It seems that the same job can be accomplished without external excitation of any kind.

A mother pushing her son on a swing knows that she must push the swing in synchrony with the swinging motion. Similarly, to flip the spin of an electron in a static magnetic field, we must apply an alternating magnetic field whose frequency matches the wobbling motion of the electron's spin orientation about the static field. Or so we thought. In their report on page 868 of this issue, Frolov *et al.*[1] show that electron spins can be flipped with electric fields, which is unusual in itself, and that the fields are purely static. This sounds as if the mother were pushing the swing in the same direction all the time, but the swing nevertheless rocks back and forth.

Spin flips have been achieved using external electric fields in previous studies, but these fields were always oscillating, such that electrons in the material under study were pulled back and forth periodically. This in turn, by means of a quantum effect known as spin–orbit interaction, creates the alternating magnetic field required to flip the spin: when an electron moves through the material, its spin experiences a magnetic field that is proportional to the electron's velocity (orbit). The orientation of this field is reversed when the electron's direction of motion is reversed. This approach has been used to flip spins in a variety of systems, from two-dimensional gases of electrons[2] to 'quantum dots'[3]. But what would be desirable for electronic applications is the ability to manipulate spins without any external excitation, using for example static electric fields, which are easier to generate on a chip than oscillating fields.

Using a clever and original approach, Frolov *et al.*[1] accomplish just that by making electrons

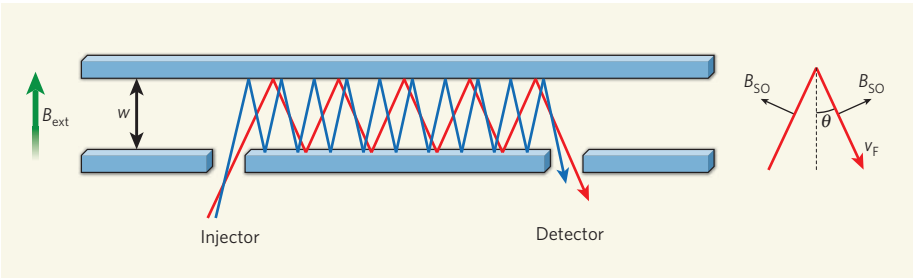

Figure 1 | Flipping electron spins. Electrons injected into a semiconductor channel through a narrow opening (injector), which filters electrons with spins oriented along a static magnetic field (B_{ext}), bounce back and forth between the channel walls and experience an alternating magnetic field (B_{SO}) through a process known as spin–orbit interaction. A second opening (detector), 20 micrometres down the channel, verifies whether electron spins have been flipped by the oscillating field. Frolov *et al.*[1] show that if the bouncing frequency (which depends on the channel width, w, the characteristic velocity, v_F, with which electrons move through the channel, and the deflection angle, θ) matches the frequency of the alternating magnetic field, electron spins will be flipped.

bounce back and forth between the two walls of a micrometre-wide semiconductor channel using solely static electric fields. The spin–orbit-induced magnetic field then alternates with a frequency that corresponds to the electron's bouncing frequency, which depends only on the separation between the channel walls and on the Fermi velocity — the characteristic velocity with which electrons move through the semiconductor.

In the authors' experiment, electrons are injected into the semiconductor channel via a narrow opening that filters electrons, selecting those with a spin axis oriented along a static magnetic field. The electrons then move through the channel, bouncing back and forth between the channel walls along the way. A second opening, 20 micrometres down the channel, acts as a spin detector and thus tests whether the electron spins have been flipped or not (Fig. 1).

But how do Frolov and colleagues know whether their technique of flipping electron spins really works? After all, there can be other reasons — apart from the bouncing between channel walls — for electron spins to flip between injector and detector[4]. To confirm their technique, the authors performed two tests. The first test consisted of assessing whether a spin flip occurred only when the electron's bouncing frequency matched the spin resonance frequency (the magnetic-field frequency necessary to trigger the spin flip), which is proportional to the strength of the static magnetic field. And indeed, spin flips were detected only for a specific magnetic field strength. Furthermore, the required magnetic-field strength changed as predicted with the channel width, as well as with the Fermi velocity (which is controlled by the electron density), both of which affect the bouncing frequency.

The second crucial test involved aligning the static magnetic field along the channel axis rather than perpendicular to it, as was the case in the first test. The spin–orbit-induced magnetic field was then parallel to the induced field expected, which should not — and did not — lead to spin flips. The two tests thus confirm the authors' novel technique as a robust method of flipping spins.

But there's a catch. As far as electronic applications are concerned, the technique comes with a major limitation: it does not flip electron spins in a coherent manner, but rather does so randomly — that is, it cannot rotate the electron spins to a specific orientation. Although the authors used an ultraclean semiconductor material, electrons still scatter off charged impurities in the vicinity of the channel, randomizing the bouncing path, and hence the rotation of their spins. In addition, electrons enter the semiconductor channel and hit the walls with a range of incidence angles (Fig. 1), leading to a large array of bouncing frequencies and hence of spin orientations. But it may be possible to circumvent this limitation by using even cleaner materials and, as Frolov and colleagues suggest, by applying electron-focusing techniques to obtain a well-defined angle of incidence and a more sharply defined bouncing frequency.

In the future, one could imagine applying the authors' technique of flipping spins to entire solid-state electronic circuits in which information is encoded in the spin state of the electrons. This is the vision of the field of spintronics[5], which has already led to discoveries such as 'giant magnetoresistance' and the subsequent miniaturization of hard-disk drives. One step beyond lies the coherent control of quantum-mechanical superpositions of electron spin states[6], which may one day lead to applications in quantum-information processing. ■

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NEUROSCIENCE

A bar code for differentiation

Nicholas C. Spitzer

Regulating neuronal development can be complicated. But genetic control of neurotransmitter expression — as exemplified by differentiation of dopamine-secreting neurons — turns out to be relatively straightforward.

Specifying how nerve cells differentiate is a Herculean challenge: a huge number of neurons with extraordinary diversity of elaborate architectures and sophisticated functions materialize almost magically during a brief period of embryonic development. Differentiation of neurons into groups with distinct characteristics is known to require coordinated synthesis of many proteins, including enzymes that produce, and transporters that package, neurotransmitters. Success results from the orchestrated expression of batteries of genes, but the way in which this is achieved has remained unclear. In a remarkable paper in this issue (page 885), Flames and Hobert[1] demonstrate how the differentiation of neurons of different lineages that share the ability to secrete the neurotransmitter dopamine is regulated at the level of gene transcription.

Because cells with common features often originate from distinct cell lineages, different populations of cells could acquire common characteristics when different switches turn on the same genes. To investigate whether this is the case for dopamine-secreting (dopaminergic) neurons, Flames and Hobert analysed neuronal development in the nematode worm *Caenorhabditis elegans* — a relatively simple organism with a nervous system of 302 neurons, which include four classes of lineage-unrelated dopaminergic nerve cells. They found that the five genes that encode proteins for the synthesis and transport of dopamine (the dopamine-pathway genes) share an evolutionarily conserved DNA sequence in their regulatory regions. This sequence was sufficient to drive the expression of these genes in dopaminergic neurons, and its mutation abolished their expression.

On further inspection, the authors narrowed