

possible to tailor the authors' protocol to generate skin that has the characteristics of different body sites, by altering the culture conditions in which the cells are grown.

The group's organoids will be a perfect tool for analysing the roles of various biological pathways in skin development – small-molecule inhibitors or inhibitory RNA molecules can be used to block proteins or pathways and to investigate the effects on skin growth. The organoids can be used in combination with genome-wide association studies or other genetic data to analyse how particular genetic mutations alter skin development. They can also help to model diseases of the skin and hair and to screen experimental drugs for any toxicities and for their efficacy.

Beyond these *in vitro* benefits, the authors demonstrated that the organoids have therapeutic potential *in vivo*. They transplanted the organoids onto immunodeficient mice (to ensure the graft was not rejected by the animals' immune system), and showed that just over half of organoids go on to form hair, which is distributed over the surface of the graft. This illustrates the exciting potential of introducing skin organoids into wounds to encourage healing and prevent scarring, or transplanting them into areas lacking hair.

However, several questions remain before this therapeutic approach becomes a reality. For instance, how efficiently and reproducibly do hairs develop? How many cells are needed to eventually form a hair follicle once grafted? Lee *et al.* began to answer the first of these questions by showing that a separate laboratory could grow hair in organoids using the same culture conditions. However, dealing with variability between individual stem cells and between the stem cells from different people are daunting challenges.

The prolonged length of time required for organoids to develop hair follicles mimics fetal skin development<sup>12</sup>. Similarly, in both settings, the skin undergoes a latent 'resting' phase before follicles begin to grow. This is a fascinating area for future study. However, it took 140 days before organoids were ready for engraftment, which could impede the therapeutic potential of the work – someone with burns, for instance, cannot wait that long for a skin graft. Further studies to understand the molecular events taking place during this latent phase should provide strategies for accelerating this process using molecules that alter relevant signalling pathways.

Several other aspects of the authors' approach will also need to be optimized before it can move to the clinic. The hairs that grew in the current study were small; in future, further optimization of culture conditions will be needed to form large scalp hairs. Better characterization of some components used in the culture cocktail – such as a protein mixture called Matrigel – will be necessary to ensure

that they comply with good manufacturing practices. And future work might need to move away from using pluripotent stem cells, which can have undesirable side effects, such as promoting tumour formation. An appealing alternative might be to use adult stem cells.

Despite these caveats, Lee and colleagues' study is a major step towards a 'cure' for baldness in humans, and paves a way towards other, greater therapeutic possibilities. At a minimum, it is worth a shout-out on a late-night show. The work holds great promise of clinical translation – we are confident that research will eventually see this promise realized.

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### Astrophysics

# A fast radio burst with an unexpected repeat period

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Observations of millisecond-long radio bursts from beyond the Milky Way have revealed a repeat pattern with a roughly 16-day period – a finding that adds to the enigma of the origin of these bursts. **See p.351**

Mysterious flashes of radio-frequency electromagnetic radiation, which last for just a few milliseconds, have baffled astrophysicists since their discovery<sup>1</sup> in 2007. Originating from outside the Milky Way<sup>2</sup>, most of these fast radio bursts (FRBs) seem to be one-off events, but some sporadically emit repeated signals<sup>3</sup>. On page 351, the Canadian Hydrogen Intensity Mapping Experiment Fast Radio Burst (CHIME/FRB) Collaboration<sup>4</sup> reports the first FRB source that produces an intriguingly regular pattern of bursts, with a period of about 16 days.

The CHIME telescope has a large, instantaneous field of view (about 200 square degrees) that observes light in the 400–800-megahertz frequency range, which is ideal for searching for FRBs. One of the earliest repeating FRB sources discovered<sup>5</sup> by CHIME was FRB 180916.J0158+65. Because the source regularly falls into the telescope's field of view, it has been automatically monitored daily for an extended period of time. From 16 September 2018 to 4 February 2020, the telescope detected 38 bursts from the source. These bursts show a period of  $16.35 \pm 0.15$  days. The window of activity during each period is about 5 days, with most bursts during this window

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concentrated into a time of roughly 0.6 days.

Establishing such a long periodicity for an astrophysical object is not easy, especially when only a few dozen events have been observed. One needs to carefully analyse the observational data to search for an active time window, a task that is complicated by the fact that the period of the putative regular bursts is unknown. False periods have been claimed before for other astronomical objects, such as quasars, because of overlooked red noise – random variations that can produce intervals of seemingly periodic behaviour<sup>6</sup>.

The CHIME/FRB Collaboration carried out careful statistical analyses of its data, and claims that the chance of the periodicity arising from random flashes is only 1 in 10 million. There is a small possibility of 'aliasing' – the period might have been misidentified because the daily observation of the FRB source by the CHIME telescope was short. However, the authors argue that such aliasing is unlikely. Future independent confirmation of the periodicity using other telescopes would strengthen confidence in the authors' conclusion.

Let us accept that the reported period is real. Does this help us to identify the

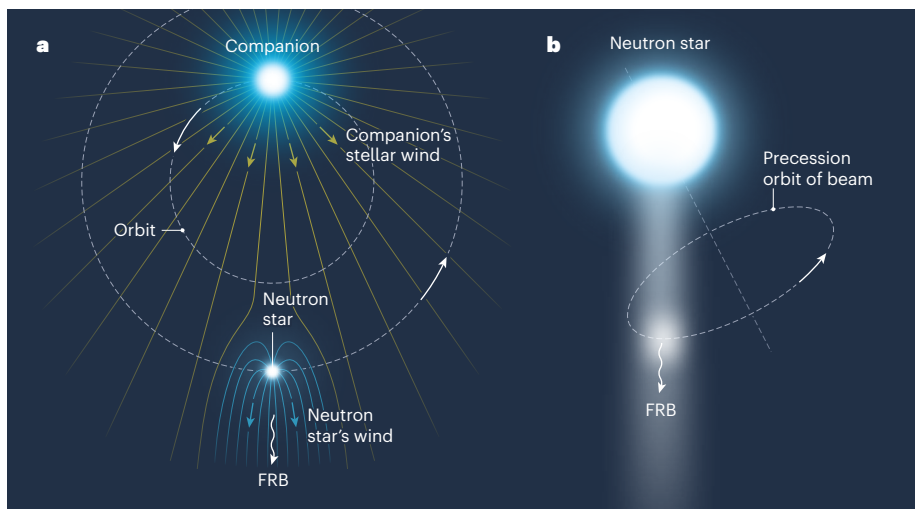
unknown mechanism that produces FRBs? Unfortunately, not really. Astronomers have so far not managed to identify the astrophysical source or sources of FRBs. At the time of writing, 51 models of FRBs have been collected in the FRB Theory Wiki page (see [go.nature.com/37acmx1](https://go.nature.com/37acmx1))<sup>7</sup>, but no ‘smoking gun’ observation has been made that narrows down the options. If a period was observed that is predicted by some of the models, it would provide a compelling clue, enabling us to limit the possibilities.

For example, various models suggest that stellar remnants known as neutron stars are emitters of FRBs – either magnetically powered neutron stars<sup>8</sup> or those powered by loss of rotational energy of the star<sup>9</sup>. The analogues of these objects in the Galaxy are called magnetars and radio pulsars, respectively, and spin with a period of the order of seconds or subseconds<sup>10</sup>. The identification of a seconds-long period from an FRB source would therefore immediately reveal it to be a neutron star. This happened for a less spectacular type of sporadic radio burst in our Galaxy, the rotating radio transients<sup>11</sup>.

However, searches for short periodicities from repeating FRBs have so far been fruitless<sup>12</sup>. The approximately 16-day period of FRB 180916.J0158+65 is too long to be the period of a spinning neutron star. Indeed, such a long period was not predicted by any FRB theory before this discovery.

The discovery therefore stirred up intense brainstorming within the CHIME/FRB Collaboration, and by other scientists studying FRBs, when the results were first released. One possibility considered by different groups is that the FRB source is in a binary system involving a neutron star, and that the approximately 16-day period is the orbital period of that system<sup>4,13,14</sup>. More specifically, it has been speculated<sup>15</sup> that FRBs could be produced by direct interactions between an astronomical stream of particles, such as an intense stellar wind produced by a massive star, and the magnetically charged region (the magnetosphere) around a neutron star.

But if the companion of the neutron star is a massive star, the two stars would need to be separated by about one-quarter of the distance between Earth and the Sun to produce the period reported by the CHIME/FRB Collaboration. This is too far apart for such a direct-interaction scenario to work. It therefore seems that a binary system might not explain how the radio bursts of FRB 180916.J0158+65 are produced (although one model<sup>13</sup> suggests that an aurora-like inflow of particles from a companion to a neutron star is essential for driving the emissions). However, the periodicity of the emissions could be interpreted as a consequence of there being an FRB source in the binary: the stellar wind from the neutron star might open up a ‘window’ in the otherwise



**Figure 1 | Two possible scenarios to explain the observed periodicity of a fast radio burst (FRB).** The CHIME/FRB Collaboration<sup>4</sup> reports that FRBs from a source called FRB 180916.J0158+65 repeat with a period of about 16 days. **a**, The source might be a neutron star in a binary system with a massive companion star. The companion produces a strong ‘wind’ of particles that could obscure radio waves from the neutron star. But if the neutron star has its own stellar wind, this could deflect the companion star’s particle flow, opening up a window behind the neutron star from which FRBs can escape. These FRBs could be observed when the window orbits through Earth’s field of view. **b**, Another scenario is that the FRBs are emitted in focused ‘beams’ from the magnetosphere of a highly magnetized neutron star, or from regions far beyond the magnetosphere (the exact region of FRB emission is not shown here, for simplicity). These beams precess like a gyroscope, periodically entering Earth’s field of view.

radio-obscuring stellar wind of the companion star, allowing the FRBs to escape<sup>13,14</sup> (Fig. 1a). This window would be observed periodically from Earth as the binary system rotates.

A second possibility discussed by several groups<sup>4,16–18</sup> is that the FRB-generating neutron star is deformed, and that its emission region precesses like a gyroscope (Fig. 1b). In this scenario, the neutron star’s spin period is much shorter than 16 days, but its FRB emission is focused into a narrow beam – and this beam sweeps Earth about every 16 days, generating the observed period. The precession could be spontaneous<sup>16,17</sup>, or it could be induced by a companion in a close binary system<sup>18</sup>. However, such precession is probably not necessary to produce the FRBs in the first place.

Finally, one can argue that the roughly 16-day period is that of an extremely slow magnetar<sup>19</sup>. This is, however, quite a stretch – it is unclear whether such slow magnetars exist, and, if they do, whether they can generate repeating radio bursts. Overall, scientists will need to expend some effort to accommodate the reported period of FRB 180916.J0158+65 in their models.

Further monitoring of this and other repeating FRB sources is essential for solving the mystery of the unexpected period. One can imagine three possible outcomes. First, after long-term monitoring, bursts show up outside the active window reported by the CHIME/FRB Collaboration for this source. If so, the supposed periodicity would disappear – and at least some theorists would breathe a sigh of

relief. The second possibility is that long-term monitoring validates the claimed period of the bursts for this source, but that no other FRB source displays a clear long-term periodicity. The period of FRB 180916.J0158+65 can then be understood as a peculiarity of that system, and not as something that is intrinsic to FRB production in general.

But the final possibility is the most intriguing: that long-term periodicity is the norm for repeating FRBs. If so, then such periodicity might be at the heart of the FRB mechanism – and it would mean that these natural phenomena are defeating the ability of the human imagination to explain it. More-creative ideas would be needed to identify the missing link between theory and observation.

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Molecular biology

# How sex chromosomes break up to get together

Ericka Humphrey & Francesca Cole

Sex chromosomes must exchange genetic information at a short region during meiotic cell division. Molecular factors have now been found that alter sex-chromosome structure and enhance this exchange process. **See p.426**

Sperm and eggs are produced through a specialized type of cell division called meiosis, which ensures that the cells have only half the usual number of chromosomes – one copy of each chromosome instead of two in mammals. During meiosis, each set of parental chromosomes exchanges DNA sequences at equivalent (homologous) regions along their length. This exchange of information – a process called recombination – is induced by DNA double-strand breaks that occur about every 10 megabases<sup>1</sup>. However, X and Y chromosomes share only a short (about 700 kilobase) homologous region called the pseudoautosomal region (PAR); double-strand breaks must therefore occur<sup>2</sup> much more frequently in this region to ensure proper recombination between X and Y chromosomes. On page 426, Acquaviva *et al.*<sup>3</sup> show how a DNA element provides a platform for enhancing the frequency of double-strand breaks in the PAR.

The early part of meiosis consists of several steps. Each chromosome is duplicated, forming two identical copies, known as sister chromatids, that are connected to each other by cohesin protein complexes. Double-strand breaks are then formed along the chromatids by the protein SPO11, with the help of its accessory factors. The 3' ends of the breaks search for homologous sequences – this leads to pairing and alignment of homologous chromosomes (such as the X and Y, or both copies of any non-sex chromosome) along their lengths, in a process called synapsis. Finally, during recombination, chromatid arms are exchanged between the two homologous chromosomes. This last step is essential for the accurate segregation of each pair of homologous chromosomes into separate daughter cells. Insufficient recombination at the PAR is a major cause of developmental disability and infertility<sup>4</sup>. Indeed,

the sex chromosomes are the most frequently mis-segregated chromosomes in sperm<sup>4</sup>.

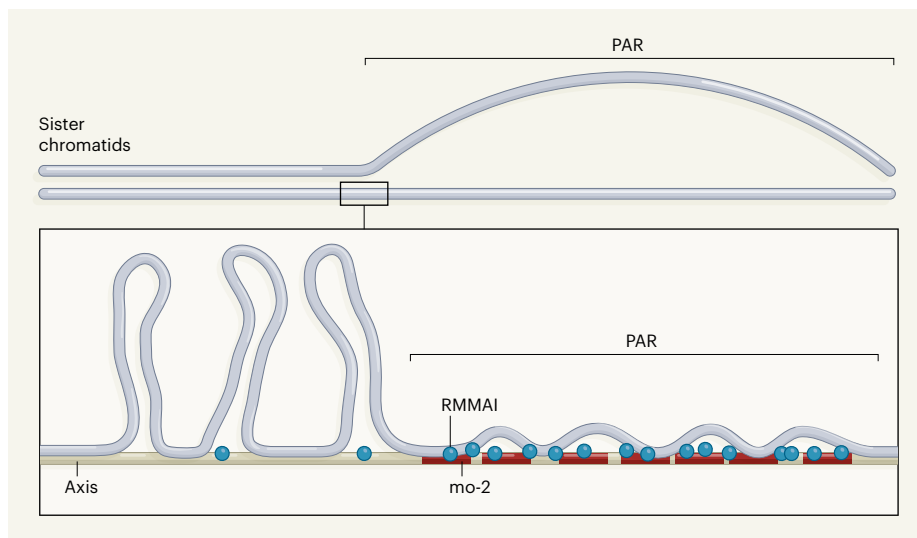
The frequency of meiotic double-strand breaks correlates with the number of chromatid structures called 'loop-axis units'. DNA loops emanate from a protein-rich DNA axis that makes up the backbone of the chromatid<sup>5</sup> (Fig. 1). Chromatid regions that have longer axes and shorter loops generally have more double-strand breaks than do those with shorter axes and longer loops. The PAR has a relatively long axis for the length of its genomic sequence, suggesting that

chromosome structure might promote the high frequency of breaks needed to ensure PAR recombination<sup>1</sup>.

How might this PAR-specific chromosome structure be formed and regulated? To answer this question, Acquaviva *et al.* analysed mouse spermatocytes (meiotic precursors of sperm). They found that the PAR is restructured before synapsis, both to elongate the axes of aligned sister chromatids and to separate them from one another at the PAR (Fig. 1).

The authors showed that the separated axes are strongly bound by five proteins that promote double-strand-break formation (REC114, MEI4, MEI1, ANKRD31 and IHO1; collectively dubbed RMMAI). These factors were already known to accumulate elsewhere in the nucleus<sup>6,7</sup>; Acquaviva and colleagues found that this accumulation occurs at regions of repetitive DNA sequences called mo-2 minisatellites. The researchers propose that mo-2 minisatellites could act to bind proteins and other molecules involved in chromosome restructuring and double-strand-break formation, including RMMAI proteins.

To test this model, the authors compared a mouse strain that naturally has few mo-2 minisatellites with a standard laboratory strain, which has many more. REC114 accumulation was lower in the 'low' mo-2 strain than in the 'high' mo-2 animals. The group then analysed PAR structure in spermatocytes from offspring of crosses between the low- and high-mo-2 strains. The sex chromosome derived from the high-mo-2 parent always showed high levels of RMMAI enrichment and axis remodelling



**Figure 1 | Formation of double-strand DNA breaks in sex chromosomes.** During meiotic cell division, chromosomes duplicate to form two identical sister chromatids that align lengthways. Double-strand breaks (DSBs, not shown) then form in DNA – a phenomenon essential for normal meiosis. DSBs form frequently in a short region of the X and Y chromosomes called the pseudoautosomal region (PAR). Acquaviva *et al.*<sup>3</sup> report that, in the meiotic precursors of sperm in mice, the PAR contains sections of repeated DNA sequences called mo-2 minisatellites, which promote the formation of many DSBs. The minisatellites exert this effect because they are highly bound by five DSB-promoting proteins, collectively dubbed RMMAI. In addition, they might act by altering a 'loop-axis' structure that governs how DNA loops away from a main axis along each chromatid, and by inducing the separation of aligned sister chromatids at the PAR.