changes the discourse around eRNA functions, by demonstrating that these RNAs can have major, locus-specific roles in enhancer activity that do not require a particular RNA-sequence context or abundance. Furthermore, by providing strong evidence that CBP interacts with eRNAs as they are being transcribed, this study highlights the value of investigating nascent RNAs for understanding enhancer activity. ■

Karen Adelman *and* **Emily Egan** *are in the Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston, Massachusetts 02115, USA.*
e-mail: karen_adelman@hms.harvard.edu

1. Kim, T.-K. *et al. Nature* **465,** 182–187 (2010).
2. Bose, D. A. *et al. Cell* **168,** 135–149 (2017).
3. Hendrickson, D. G., Kelley, D. R., Tenen, D., Bernstein, B. & Rinn, J. L. *Genome Biol.* **17,** 28 (2016).
4. Yang, Y. W. *et al. eLife* **3,** e02046 (2014).
5. Beltran, M. *et al. Genome Res.* **26,** 896–907 (2016).
6. Kaneko, S., Son, J., Bonasio, R., Shen, S. S. & Reinberg, D. *Genes Dev.* **28,** 1983–1988 (2014).
7. Rada-Iglesias, A. *et al. Nature* **470,** 279–283 (2011).
8. Thompson, P. R. *et al. Nature Struct. Mol. Biol.* **11,** 308–315 (2004).
9. Kaikkonen, M. U. *et al. Mol. Cell* **51,** 310–325 (2013).
10. Scruggs, B. S. & Adelman, K. *Cold Spring Harb. Symp. Quant. Biol.* **80,** 33–44 (2015).

CONDENSED-MATTER PHYSICS

Marching to a different quantum beat

Periodic oscillations are common in nature but they generally decay or fall out of phase. Two experiments have found evidence for a Floquet time crystal, which is characterized by persistent in-phase oscillations. SEE LETTERS P.217 & P. 221

CHETAN NAYAK

Crystalline solids are a classic example of a state of matter in which a symmetry is 'spontaneously broken'. The equations of physics are invariant under spatial translations because the interactions within a collection of atoms are the same regardless of where the atoms are located — any position is just as good as any other. However, below a certain temperature, the atoms spontaneously settle into a state in which there are preferred locations (the sites of a crystal lattice), thereby breaking translational symmetry. Analogous broken-symmetry states such as magnets, liquid crystals and superfluids abound in nature.

It is natural to ask whether one can also spontaneously break the time-translational symmetry of the laws of physics — as far as these laws are concerned, any time is as good as any other. In 2012, the physicist Frank Wilczek proposed[1] the first concrete ideas about such a time crystal. Although subsequent work showed that time crystals, as initially envisaged, were unstable[2–4], the idea has recently been rebooted as a Floquet time crystal[5–8]. On pages 217 and 221, Zhang *et al.*[9] and Choi *et al.*[10] report experimental evidence for this exotic state of matter.

To understand Floquet time crystals, it is useful to consider the surface of a crystal. Because of the underlying spatial ordering of the atoms in a crystal, the surface possesses a discrete translational symmetry. When atoms of a different element are adsorbed on the surface, they could inherit the surface's crystal symmetry or they might, instead, form an atomic layer that has lower translational symmetry — for example, by occupying only alternating adsorption sites. If the latter occurs, the surface's discrete translational symmetry is spontaneously broken. Similarly, a system that is pumped periodically will have a discrete time-translational symmetry. If this symmetry is spontaneously broken, a Floquet time crystal results.

A potential problem with this idea is that the periodic drive is expected to heat up the system continually[11], thereby precluding any kind of ordered state. However, researchers have discovered two loopholes. First, if the frequency of the drive is large compared to the local energy scales of the system, heating occurs slowly and there is a long-lived quasi-steady state, called a pre-thermal state[12], in which non-trivial states of matter can manifest[13]. Second, if the system has a high density of immobile impurities, then a phenomenon called many-body localization[14] can occur, in which the necessary spreading of energy cannot take place because the impurities trap excitations. In this case, heating doesn't happen at all[15] and exotic states of matter such as a Floquet time crystal can survive indefinitely[6].

In the canonical theoretical model of a Floquet time crystal[6–8], a set of magnetic moments (spins) interact through a ferromagnetic interaction in the presence of a random-strength magnetic field nearly aligned with their preferred axis (Fig. 1). The spins are then subjected to a temporary magnetic field perpendicular to their preferred axis, called an approximate π-pulse, whose strength and duration are sufficient to rotate the spins by approximately 180° — but not necessarily exactly 180°. These two steps are repeated cyclically to form a periodic drive.

If the ferromagnetic interaction is weak, the spins relax at late times to a state that has the periodicity of the drive — except in the fine-tuned case of an exact π-pulse. However, if the interaction is strong, the spins flip precisely

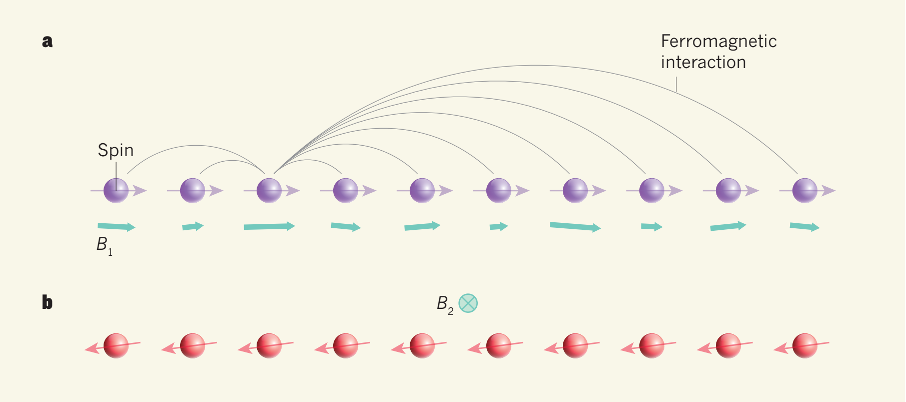

Figure 1 | A Floquet time crystal. Zhang *et al.*[9] and Choi *et al.*[10] have obtained experimental evidence for an exotic state of matter called a Floquet time crystal. A simplified theoretical model is shown here. **a**, A set of magnetic moments (spins, whose directions are indicated by purple arrows) experience a ferromagnetic interaction in the presence of a random-strength magnetic field (B_1) nearly aligned with their preferred axis. For illustrative purposes, only the interaction between the third spin and the other spins is shown, together with the evolution from an initial state in which all the spins are pointing in the same direction — a time crystal does not require such a special initial state. **b**, The spins are then subjected to a temporary magnetic field (B_2) perpendicular to their preferred axis, whose strength and duration are sufficient to rotate the spins by approximately 180° (red arrows). These two steps are repeated cyclically. If the ferromagnetic interaction is strong, the spins return to their original state after two cycles — even when B_2 does not rotate the spins by exactly 180°. This feature breaks 'time-translation symmetry', a characteristic signature of a time crystal. (Adapted from ref. 9.)

twice and return to their original state after two cycles, thereby breaking discrete time-translational symmetry. The ferromagnetic interaction endows the system with rigidity so that thermal or quantum fluctuations do not wipe out the symmetry breaking, even when the approximate π-pulse is noticeably different from an exact π-pulse and the drive deviates somewhat from the canonical model. The system exhibits long-range order, which means that ordering in one region and time is correlated with that in arbitrarily distant regions and late times. This property distinguishes such a system from other oscillations that occur in nature.

Zhang *et al.* and Choi *et al.* now report experimental data consistent with a Floquet time crystal. There are obvious similarities between the two experiments. First, both research groups use a property called spin-dependent fluorescence to show that well-isolated driven interacting quantum systems exhibit lower time-translational symmetry than the drive. Second, their systems are demonstrably stabilized by interactions that maintain phase coherence over time. However, it is also important to recognize the differences.

In Zhang and colleagues' work, a system of up to 14 trapped ions is subjected to a periodic sequence of pulses that favour many-body localization. Because the system is small, its quantum-mechanical equations of motion are known and can be reliably simulated; the authors find excellent agreement between theory[8] and experiment. However, because the system is small and the duration of the experiment is relatively short — owing to the painstaking way in which the authors apply the random-strength magnetic field one ion at a time — one could argue that long-range order has not been fully demonstrated.

Conversely, Choi and colleagues use approximately one million nitrogen-vacancy (NV) centres that are randomly distributed in diamond. The authors apply a prescribed sequence of pulses to the NV centres, but the dipolar interactions between these centres are random and, in any case, are too numerous to simulate. The authors' system is not expected to undergo many-body localization or to generate a pre-thermal state, but — for reasons that are unclear — the system heats up extremely slowly, although not negligibly.

Zhang and colleagues' experiment is a more direct realization of a version[8] of the canonical model of a Floquet time crystal, whereas Choi *et al.* show that this state of matter might occur more readily in nature than expected, therefore hinting at potential applications in fields such as metrology. Both groups present evidence of a time crystal, but their combined results point to the need for experiments that truly show that the oscillations remain in phase over extended times and are not washed out by the inevitable fluctuations. ■

Chetan Nayak *is at Microsoft Research, Station Q, and in the Department of Physics, University of California, Santa Barbara, California 93106, USA.*
e-mail: cnayak@microsoft.com

1. Wilczek, F. *Phys. Rev. Lett.* **109,** 160401 (2012).
2. Bruno, P. *Phys. Rev. Lett.* **111,** 070402 (2013).
3. Nozières, P. *Europhys. Lett.* **103,** 57008 (2013).
4. Watanabe, H. & Oshikawa, M. *Phys. Rev. Lett.* **114,** 251603 (2015).
5. Sacha, K. *Phys. Rev. A* **91,** 033617 (2015).
6. Khemani, V. *et al. Phys. Rev. Lett.* **116,** 250401 (2016).
7. Else, D. V., Bauer, B. & Nayak, C. *Phys. Rev. Lett.* **117,** 090402 (2016).
8. Yao, N. Y., Potter, A. C., Potirniche, I.-D. & Vishwanath, A. *Phys. Rev. Lett.* **118,** 030401 (2017).
9. Zhang, J. *et al. Nature* **543**, 217–220 (2017).
10. Choi, S. *et al. Nature* **543**, 221–225 (2017).
11. D'Alessio, L. & Rigol, M. *Phys. Rev. X* **4,** 041048 (2014).
12. Abanin, D. *et al.* Preprint at http://arXiv.org/abs/1509.05386 (2015).
13. Else, D. V., Bauer, B. & Nayak, C. *Phys. Rev. X* (in the press); preprint at http://arXiv.org/abs/1607.05277 (2016).
14. Basko, D. M., Aleiner, I. L. & Altshuler, B. L. *Ann. Phys.* **321,** 1126–1205 (2006).
15. Ponte, P., Chandran, A., Papić, Z. & Abanin, D. A. *Ann. Phys.* **353,** 196–204 (2015).

CANCER EPIGENETICS

Reading the future of leukaemia

The identification of the regulatory protein ENL as essential to an aggressive form of leukaemia provides insight into transcriptional regulation and highlights potential avenues for therapy. See Letters p.265 & p.270

ALEX W. WILKINSON & OR GOZANI

Blood cancers are frequently driven by chromosomal translocations that generate disease-causing fusion proteins — formed by the joining of fragments of two proteins. Fusion proteins that involve the regulatory protein mixed lineage leukaemia (MLL) are commonly found in aggressive paediatric leukaemias and are associated with poor prognosis[1]. There is, therefore, a great need to develop therapeutic strategies for leukaemias that involve MLL-rearranged (MLL-r) fusion proteins. In this issue, Erb *et al.*[2] (page 270) and Wan *et al.*[3] (page 265) converge on the identification of the protein ENL as a crucial factor for the viability of MLL-r cells in leukaemia.

Histone proteins are structural and signalling factors around which DNA is wrapped in cells. Their modification by the addition or removal of molecular groups regulates gene expression. A notable structural feature of ENL is a distinctive fold of about 75 amino acids called a YEATS domain, which is a reader of acetylation — it recognizes and associates with residues of the amino acid lysine in histones that have been modified by the addition of an acetyl moiety[4]. Erb *et al.* and Wan *et al.* provide compelling evidence that this 'reader' ability of ENL on acetylated histones is crucial to the induction of MLL-r leukaemia.

MLL fusion partners are predominantly related to two protein complexes implicated in epigenetic regulation[5,6] — the modulation of gene expression independently of DNA sequence. The first is the super elongation complex (SEC), which facilitates a phase of gene transcription called elongation. The second is the DOT1L-containing complex (DotCom), which adds methyl groups to the residue lysine 79 on histone H3 (abbreviated as H3K79). The translocations that generate these fusions typically occur on one of the two sets of chromosomes present in mammals.

The prevailing view is that MLL-containing fusion proteins promote the localization of SEC and DotCom, containing proteins encoded on both chromosomes (fusion and normal non-fused proteins), to regions of the genome where they drive the expression of genes that promote the development of leukaemia[6,7].

Erb *et al.* and Wan *et al.* uncover another, complementary mechanism of SEC and DotCom stabilization. The groups found that inactivation of ENL impaired the function of SEC and DotCom in MLL-r cells. The ability of ENL to physically associate with both SEC and DotCom[8] suggests a model in which the protein — through recognition of acetylated H3 by its YEATS domain — coordinates SEC and DotCom stabilization and activity at abnormal regions of the genome (Fig. 1).

This new model raises the possibility that drugs such as small-molecule inhibitors that target the ENL YEATS domain could selectively kill leukaemic MLL-r cells. Other cell types seem to be largely tolerant of ENL loss, but SEC, DotCom and ENL are ubiquitously expressed, so it will be important to understand the molecular basis of this difference in tolerance as such drugs are developed.

The requirement for ENL in MLL-r leukaemias is consistent with observations[9–13] that properly regulated DOT1L activity is necessary for the development and maintenance