Nonlinear physics

Déjà vu in optics

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Using optical fibres, experimentalists have confirmed that a physical version of *déjà vu* — whereby a system returns to its original state — does occur with light waves.

Have you ever experienced a phenomenon called *déjà vu*? An event from the past appears to be happening again as clearly as the first time you experienced it. It is a neurological phenomenon whose roots are mysterious and unclear. No matter how complicated the processes in our brains may be, *déjà vu* can have analogues in the inanimate world. In physics it is called the Fermi–Pasta–Ulam recurrence. As reported in *Physical Review Letters*, Van Simaeys *et al.*[1] have now observed this recurrence phenomenon in a fibre-optics experiment.

Since the advent of computers, physicists have been using them to model the physical world. In 1953, the well-known physicist Enrico Fermi, together with two experts in mathematics, John Pasta and Stanislaw Ulam, used one of the earliest digital computers — a machine at Los Alamos called MANIAC — to model the properties of complex nonlinear systems[2]. In particular, they wanted to simulate oscillations of a string consisting of 64 particles with nonlinear forces between them — such forces are nonlinear if equal amounts of the force do not always produce equal effects. Their intention was to study the 'thermalization' of the system — or how energy is distributed among the many possible oscillations generated by the string.

The results of the calculations were not what Fermi and his collaborators expected[2]. After starting the system with all the energy associated with one type of string oscillation (the initial mode), they expected that the total energy would gradually become shared between all the modes of the system. To their great surprise, the opposite happened. After a relatively short time, the energy returned to the same mode that was excited initially. To understand why this is so unexpected, consider this rough analogy: if we heat a piece of iron from one end, the heat will spread across the whole metal homogeneously. Clearly, no-one would expect that it would ever return to its original state — with only one end being hot.

Some ten years later, in an attempt to solve this mystery, Zabusky and Kruskal[3] used more advanced computers and modified the equations used by Fermi, Pasta and Ulam. Specifically, they solved the Korteweg–de Vries equation, which describes shallow water waves or long-period waves in nonlinear crystal lattices. Using this approach to the Fermi–Pasta–Ulam problem, Zabusky and Kruskal numerically discovered in the system a wave which they called the 'soliton'. This is a solitary wave that propagates without ever changing shape, and was first observed over 150 years ago by John Scott Russell as a hump of fast-moving water on the Edinburgh to Glasgow canal. Zabusky and Kruskal's theoretical discovery of the soliton had a lasting impact on twentieth-century mathematical physics. Their work led to a number of important developments related to 'integrable nonlinear models', in which solitons are one of the possible solutions. But the Fermi–Pasta–Ulam mystery was not completely solved. Although Zabusky and Kruskal observed a return to the approximate initial conditions, this was not a recurrence in the way that we understand this phenomenon today.

Later, with the development of mathematical physics, the nonlinear Schrödinger wave equation came to the fore as another completely integrable nonlinear equation that also has soliton solutions[4]. But it is not only solitons that are of interest here. It was previously shown[5,6] that continuous waves described by the nonlinear Schrödinger equation will break up into small wave packets when there are slight perturbations (secondary waves) on top of the initial continuous wave. This process is known as a modulation instability and it was later found to be closely related to the problem of Fermi, Pasta and Ulam. The crucial point is that, when the secondary perturbation is regular — say it consists of a single mode — then after growing to some maximal amplitude, the perturbation reduces in size and eventually disappears. Like the letters in a palindrome, the initial unperturbed continuous wave is completely restored in reverse order[7]. So essentially the Fermi–Pasta–Ulam recurrence is a periodic solution of the nonlinear Schrödinger wave equation; it has a variable period (though the period may be infinitely long), and the theory has been developed exactly for this situation[7,8].

The Fermi–Pasta–Ulam recurrence has been much harder to demonstrate experimentally, even though the theory is known to be fairly accurate for a physical system such as an optical fibre. Figure 1 shows the theoretical evolution of the frequency components of the wave during the modulation instability of a continuous wave. Initially all the energy is concentrated in the central mode but, over time, energy flows from the central mode into the two weak seed modes. As a result, the energy in the central mode decreases. An infinite number of modes can become excited (although only three are shown in Fig. 1) until a certain point is reached at which the energy starts to flow back from the side modes into the central component. This reciprocal energy exchange between the central mode and an infinite number of side modes is the Fermi–Pasta–Ulam recurrence[9].

In fact, it has taken another 16 years to observe this optical recurrence experimentally. In their experiment, Van Simaeys *et al.*[1] saw recurrence for the first time when they were observing the effect of a modulation instability in an optical fibre. By pumping energy into the central frequency mode at the input to an optical fibre, they were able to watch the energy spread between the frequency components, followed by all the

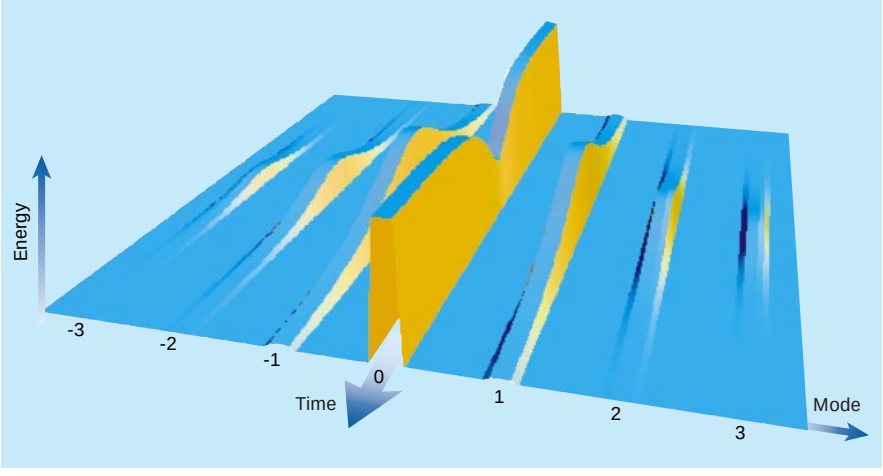

Figure 1 **The Fermi–Pasta–Ulam recurrence as seen in this solution of the nonlinear Schrödinger wave equation. As the frequency components of a continuous wave evolve, energy flows from the central mode into the side modes. The energy eventually returns, restoring the wave to its initial state. Such a Fermi–Pasta–Ulam recurrence has been demonstrated by Van Simaeys *et al.*[1] in a recent fibre-optics experiment.**

energy flowing back to the original mode, just as Fig. 1 shows. In other words, by sending a slightly modulated 'continuous' wave (actually a well-shaped rectangular pulse) along the optical fibre, the researchers were able to see an increase in the amplitude of the modulated components and subsequent restoration of the initial wave. Because they took great care when setting up the initial conditions, the recurrence they saw was almost perfect. ■

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1. Van Simaeys, G., Emplit, Ph. & Haelterman, M. *Phys. Rev. Lett.* **87,** 033902 (2001).
2. Fermi, E., Pasta, J. & Ulam, S. *Studies of Nonlinear Problems I* (Los Alamos report LA-1940, 1955); reprinted in *E. Fermi. Collected Papers* Vol II (ed. Segrè, E.) 978 (Univ. Chicago Press, 1965).
3. Zabusky, N. J. & Kruskal, M. D. *Phys. Rev. Lett.* **15,** 240–243 (1965).
4. Zakharov, V. E. & Shabat, A. B. *Sov. Phys. JETP* **34,** 62–69 (1971).
5. Benjamin, T. B. & Feir, J. E. *J. Fluid Mech.* **27,** 417–430 (1967).
6. Bespalov, V. I. & Talanov, V. I. *Sov. Phys. JETP Lett.* **3,** 471–473 (1966).
7. Akhmediev, N. N. & Korneev, V. I. *Theor. Math. Phys.* **69,** 1089–1092 (1986).
8. Akhmediev, N. N. & Ankiewicz, A. *Solitons, Nonlinear Pulses and Beams* (Chapman & Hall, London, 1997).
9. Akhmediev, N. N., Heatley, D. R., Stegeman, G. I. & Wright, E. M. *Phys. Rev. Lett.* **65,** 1423–1426 (1990).

Cell cycle

Archipelago of destruction

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The finely balanced activity of enzymes and their regulators keeps the cell-division cycle under control. A newly discovered molecule that ensures the timely destruction of one regulator is mutated in some cancer cells.

The cell cycle is the process by which cells grow, replicate their genome, segregate the two copies of the genome, and divide. The progression of these events is controlled by enzymes known as cyclin-dependent kinases (CDKs), whose activity in turn depends on their association with proteins called cyclins. For example, Cdk2 works with cyclin E to catalyse two key processes — the start of DNA replication and duplication of the centrosome, the precursor to the chromosome-separating apparatus[1]. The onset and demise of CDK activity is controlled mainly by the scheduled degradation of proteins that inhibit CDKs and of cyclins[2]. The timely appearance and disappearance of cyclin E is crucial: excessive activity of the cyclin E–Cdk2 complex drives cells to copy their DNA prematurely, resulting in genome instability[3]; moreover, cyclin E levels are often higher than normal in human tumours[4]. Three groups, writing on pages 311 and 316 of this issue[5,6] and in *Science*[7], have now identified the crucial factor that directs cyclin E to the degradation machinery.

The programmed degradation of many proteins that regulate the cell cycle is carried out by the ubiquitin–proteasome system. A cascade of enzymes[8] — generically termed E1, E2 and E3 — catalyses the addition of polymers of the small protein ubiquitin to the protein substrates. This polyubiquitin tag acts as an address label, directing substrates to the 26S proteasome, where they are destroyed. Specificity in the ubiquitin system is controlled largely by E3 enzymes, also known as ubiquitin ligases.

Ubiquitin ligases termed SCF complexes are necessary for the onset of S phase (the cell-cycle stage during which DNA is replicated)[2]. SCF complexes consist of three core subunits, which couple to any one of several 'F-box' proteins (Fig. 1) — so called because they contain the F-box, a sequence of amino acids first identified in cyclin F[9]. The F-box proteins also contain certain domains, such as the WD40 motif, that recognize specific substrates, usually ones that have been phosphorylated. Genetic evidence[10,11] has implicated several proteins in the destruction of cyclin E, including an F-box protein called Skp2. However, the presumed F-box protein that controls the specificity of ubiquitination of phosphorylated cyclin E has, until now, escaped identification.

As is often the case, the breakthrough came from studies of model organisms — in this case, by investigating the genes needed for cyclin E degradation. Moberg *et al.*[5] started by screening fruitflies (*Drosophila melanogaster*) for mutant cells that have a proliferative advantage over normal cells. From this screen, they picked out the *archipelago* (*ago*) gene, and determined that levels of cyclin E protein — but not cyclin E messenger RNA — are higher than normal in *ago* mutant cells. These and other results imply that the degradation of cyclin E protein does not proceed normally in these cells, and that *ago* is involved in cyclin E degradation. The *ago* gene encodes a counterpart of the budding yeast Cdc4 and nematode and mouse SEL-10 proteins — related F-box proteins implicated in the degradation of various substrates.

Meanwhile, Strohmaier *et al.*[6] and Koepp *et al.*[7] used yeast cells with mutations in various components of the SCF complex as an entry point into the cyclin E degradation pathway. Both groups found that cyclin E is stabilized in cells with mutations in Cdc4, and that the human counterpart of Cdc4 — which they respectively term hCdc4 and Fbw7 — specifically interacts with cyclin E. This interaction depends on cyclin E being phosphorylated on the threonine at position 380 in the amino-acid chain, an event also required for cyclin E degradation *in vivo*[10]. Mutations in the WD40 domain of hCdc4/Fbw7 stop it from binding to phosphorylated cyclin E, implying that this domain forms a docking site for phosphorylated substrates. Gratifyingly, a fully assembled SCF complex containing hCdc4/Fbw7 robustly ubiquitinates phosphorylated cyclin E *in vitro*.

In some tumours, cyclin E protein often accumulates at high levels[4]. So an obvious question was whether mutant forms of hCdc4/Fbw7/Ago occur in cancer cells. Moberg *et al.*[5] and Strohmaier *et al.*[6] show that several tumour cell lines that have high levels of cyclin E protein also bear mutations in the WD40 domain of hCdc4/Fbw7/Ago. This and other evidence[5,6], including a phenomenon known as loss of heterozygosity, seen in two cell lines, suggests that hCdc4/Fbw7/Ago is a tumour suppressor — a negative regulator of cell proliferation that normally prevents cancer progression. In multicellular organisms, cells with mutations in this protein that lead to a reduction in its function, and so to high levels of cyclin E protein, might gain a proliferative advantage over normal cells. More important, such mutations might also result in genome instability, the driving force behind the changeable characteristics of early cancer cells[3].

In a second compelling disease connection, it turns out that SEL-10 (the nematode and mouse counterpart of hCdc4/Fbw7/Ago) is implicated in the control of signalling pathways involving the presenilin or Notch proteins[12–14]. Alterations in the presenilin signalling pathway are thought to underlie some forms of Alzheimer's disease, so it will be important to find out whether hCdc4/Fbw7/Ago is involved in this pathway. And some activated forms of Notch are potent oncogenes, promoting cell division[15], so disruption of hCdc4/Fbw7/Ago may well deregulate cell division at more than one level. It should be possible to test these ideas by deleting the corresponding gene in mice.

Some mechanistic details of the degradation of cyclin E have yet to be unravelled. For example, what is the role of the F-box protein Skp2 — a long-time contender for involvement in cyclin E degradation? Although cyclin E is stabilized in mouse cells that lack Skp2 (ref. 11), Strohmaier *et al.*[6] found that, in side-by-side *in vitro* comparisons with hCdc4/Fbw7/Ago, Skp2 neither binds nor ubiquitinates cyclin E. So the effects of Skp2 on cyclin E might be indirect. Skp2 targets the Cdk2 inhibitor p27 for ubiquitination