MAPK activation cascade. Furthermore, the Cdc2 and MAPK pathways activate each other. Except for the synthesis of a few key proteins such as Mos and cyclin, most of the signalling and feedback events in this system consist of phosphorylation[6].

Despite this wealth of molecular information about egg maturation, and the appreciation of positive feedback in the molecular circuitry, until now no one could explain how eggs persist in the mature state — with high Cdc2 and MAPK activity — long after progesterone has been removed. Ferrell and Xiong previously carried out theoretical studies of the problem[8], and found that positive feedback such as that seen in the Cdc2 and MAPK cascades could create a biochemical 'memory'. This prediction was certainly not intuitive, as these feedback events operate largely by phosphorylation — known to be rapid and readily reversible. Was it not more likely that a long-term response to a transient signal would be maintained by an irreversible event, such as the destruction of a key regulatory protein, maybe an inhibitor of Cdc2 or MAPK?

It appears not. Proof of Ferrell and Xiong's theoretical prediction required careful experimentation. In particular, the prediction demands that inhibiting the positive feedback will cause a mature egg to 'de-mature', at least with respect to key biochemical events. The authors now have compelling evidence to support this idea[1]. They find that three different treatments that block the positive feedback between MAPK and Mos result in transient, rather than sustained, activation of both MAPK and Cdc2. So, positive feedback is necessary to maintain the biochemical memory of a mature egg (Fig. 1). Xiong and Ferrell also provide an additional, theoretical explanation for their data, with computational simulations that show how an essentially reversible switch can be rendered irreversible depending on the strength of the positive feedback in the system.

Beyond its particular contributions regarding the maturation of eggs, the work of Xiong and Ferrell[1] should have much broader impact owing to the approach they present for addressing questions of cellular function. As in work regarding the cellular switch that controls entry into, and exit from, nuclear division[9,10], Xiong and Ferrell's experiments were driven by theoretical predictions about the fundamental mechanisms that control such switches. These predictions derive from a systems-level view, but require quantitative, reductionist-style experimentation to test their validity. The ability to think and work on such a broad scale, from system through to molecule, is the most impressive aspect of Xiong and Ferrell's work. The notion of pairing theoretical and computational biology with experimental cell biology should catch on, and the positive feedback inherent in this interdisciplinary brand of science is likely to drive many breakthroughs in our understanding of cellular controls. ■

Jill C. Sible is in the Biology Department, Virginia Polytechnic Institute and State University, Derring Hall, Blacksburg, Virginia 24061-0406, USA.
e-mail: siblej@v.edu

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Planetary science

Conveyed to the Kuiper belt

Rodney Gomes

The small icy bodies that make up the Kuiper belt are the most distant objects known in the Solar System. A consistent picture is now emerging which suggests that these objects formed much closer to the Sun.

Since the first member of the Kuiper belt was discovered[1] in 1992, many unexpected features of their orbits and physical properties have been uncovered. One surprise was the very low total mass observed in the belt — about one-tenth of the mass of the Earth, when it was predicted to be a hundred times larger than that. To explain the missing mass, it has been proposed that collisions between Kuiper-belt objects over the lifetime of the Solar System have gradually transformed most of their mass into dust; bombarded by solar radiation, these dust grains are eventually expelled from the Solar System. But such theories have never been able to satisfactorily explain the extent of the depletion of the original Kuiper-belt mass. On page 419 of this issue, Levison and Morbidelli[2] propose an alternative. They show that some objects that now exist in the Kuiper belt might have been pushed there from original positions near Neptune's present orbit: the original Kuiper-belt region could, in fact, have been virtually empty, and only a small amount of mass was subsequently deposited there.

According to current theory, the planets of the Solar System formed from a primordial disk of gas and dust, as the dust accumulated into gradually larger objects. Of course, in going from dust to planets there must have been intermediate stages, such as a disk of fledgling planets, or planetesimals, of roughly asteroid size. In regions where the total mass
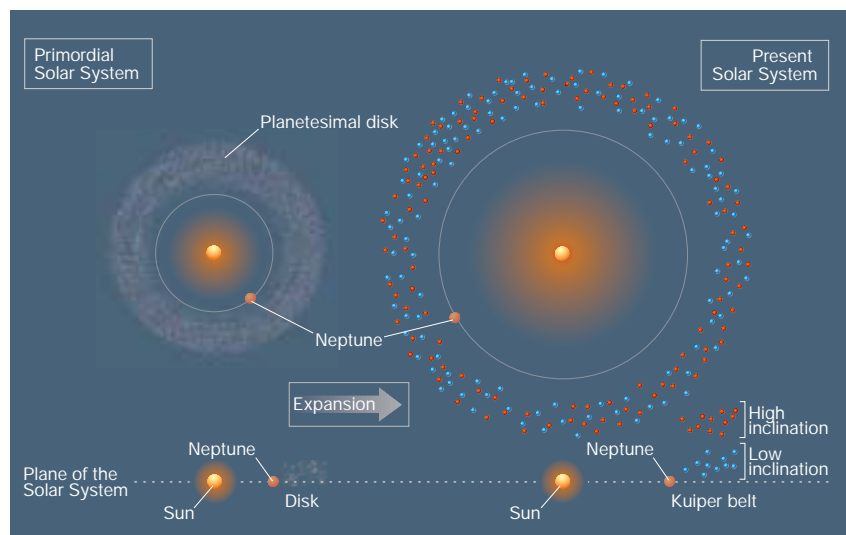

Figure 1 **Expansion plan. The primordial, compact Solar System (left) was surrounded by a disk of asteroid-size planetesimals, which extended roughly as far as Neptune's present orbit. The gravitational pull of this disk eventually induced a planetary migration, during which the orbits of all the major planets (except Jupiter) expanded. As a consequence, most planetesimals experienced close encounters with the planets and were ejected from the Solar System. A few remnants were pushed out into stable orbits, forming the present-day Kuiper belt (right). Two distinct, yet complementary, mechanisms of gravitational interaction explain how these remnants became divided between high-inclination orbits[3] and low-inclination orbits[2], with respect to the plane of the Solar System.**

in the disk was not large enough for the accumulation process to produce planets, this planetesimal disk would have been preserved to the present day. This would certainly be the case for the Kuiper belt: because of its less dense mass distribution and large distance from the Sun, the accretion process in the belt would have ended when object sizes were no bigger than Pluto. However, in contrast to the present estimate for the Kuiper-belt mass, this accretion theory would require there to be around 10 Earth masses in the Kuiper-belt region, to allow the formation of objects as big as those presently seen in the belt.

The paucity of mass in the Kuiper belt is not the only enigma. Lying at such great distances from the rest of the Solar System, and experiencing no great perturbations from other large bodies, Kuiper-belt objects were expected to have orbits that were nearly circular and located close to the average plane of the Solar System. In fact, the orbits are quite eccentric, and are inclined out of the Solar System plane (Fig. 1). Planetary scientists have wondered how these orbits could have been so dynamically excited. My own idea[3] is that these objects formed much closer to the Sun and were then propelled outwards by a mechanism involving close gravitational encounters with the outward-migrating, primordial Neptune. Other work[4] shows that, if there had originally been a large mass beyond Neptune's present position, this planet would have moved much further out than it is today (effectively, into the Kuiper-belt region).

Thus, the puzzle seemed to be nearly solved. On the one hand, the original planetesimal disk would be truncated near Neptune's present position (Fig. 1), and was massive enough to form the large bodies now observed in the Kuiper belt; on the other hand, some objects would have been transported to the belt from this dense inner planetesimal disk by a mechanism that induced high-inclination orbits through close encounters with Neptune[3]. However, there was one piece that didn't fit. In addition to the Kuiper-belt objects in high-inclination orbits, there is a roughly equal number of objects at low inclination. These could not have been pushed out by the same mechanism.

Levison and Morbidelli[2] propose a solution. Their premise is based on another enigma — the fact that the Kuiper belt is considered to have an outer edge at about 7×10^9 km from the Sun (equivalent to 48 AU, or astronomical units). This distance is significant: at this point, the orbital periods of Kuiper-belt objects are twice that of Neptune, a feature known as the '1:2 mean motion resonance'. As Neptune migrated outwards through the primordial Solar System, it pushed out some of the objects in this resonance trap[5,6]. This mechanism would naturally create orbit eccentricities, causing the resonant objects to approach close to Neptune and the other

major planets, such that they would eventually be ejected from the Solar System after a final gravitational encounter with Jupiter.

Levison and Morbidelli argue, however, that the influence of other, so-called secular resonances, inside the 1:2 resonance, would have kept the eccentricities and inclinations of some resonant objects low. A secular resonance is also based on commensurability of periods — not of the periods of the objects' motion around the Sun, but instead of the motion of the orbits themselves around the Sun. Such resonances are powerful, and can induce large variations in orbital eccentricities and inclinations, either raising or lowering them. According to Levison and Morbidelli's simulations, a small fraction of the resonance-trapped objects, once released through the rather jumpy migration of Neptune, would eventually be left in fairly low-inclination orbits in the Kuiper belt, owing to the influence of secular resonances. A few other objects remaining in the 1:2 resonance would set up the

outer edge of the Solar System as it is today.

Of course, this new set of ideas raises further questions. The main one is, how could the primordial Solar System be formed in a truncated disk? The few observations made of other planetary systems as they are forming indicate that they have radially expanded disks. Is the Solar System then a rare case? Regardless of the answer, what conditions could cause this truncation of a developing planetary system? This, I believe, will be a major topic in planetary science for years to come. ■

Rodney Gomes is at the Observatório do Valongo, Universidade Federal do Rio de Janeiro, and at the Observatório Nacional, Ladeira do Pedro Antonio 43, Rio de Janeiro 20080-090, Brazil.
e-mail: rodney@ov.ufrj.br

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Comparative genomics

Two worms are better than one

Mark Blaxter

The genome of the microscopic worm *Caenorhabditis briggsae* has been sequenced, and shows some remarkable differences from the genome of the better known — and physically similar — *C. elegans*.

In the early 1960s, when biologist Sydney Brenner was searching for a new model organism with which to study animal development and neurobiology, he screened a wide range of invertebrate species and chose the nematode *Caenorhabditis elegans* because it is easy to culture and transparent at all stages of its life cycle[1]. This small worm is now famous, not least for being the first animal to have its whole genome sequenced[2]. A close relative of *C. elegans* also passed by Brenner's microscope, and narrowly missed this accolade. This creature, *C. briggsae*, is physically very similar to *C. elegans* (it takes an expert to distinguish them), and the two have near-identical biology, even down to the minutiae of developmental processes. Surprisingly, however, their genomes are not so similar, as the sequencing of the *C. briggsae* genome to around 98% completion, reported in *Public Library of Science Biology*, now reveals[3]. Comparing the two species offers a new view of the patterns and processes that have shaped genomes, and raises many questions for the future.

From the first draft of the *C. elegans* genome[2], it was predicted that this microscopic worm has more than 19,000 protein-coding genes and 1,000 RNA-encoding genes. With the completion of the sequence to the last base pair (all 100,258,171 of

them[4]) in late 2002, these numbers have grown respectively to around 21,000 and 3,000. There is still vigorous debate as to how many of these genes are actually functional[5], but what is clear is that the complexity of the *C. elegans* gene set contrasts markedly with the organism's morphological simplicity. For comparison, the more physically complicated fruitfly *Drosophila melanogaster* has only around 15,000 protein-coding genes[6], and humans have some 40,000 (refs 7, 8).

The *C. briggsae* sequence reported by Stein *et al.*[3], with its 19,500 protein-coding genes, provides comparative confirmation of most of the *C. elegans* gene set and, surprisingly, suggests that there may be another 1,300 *C. elegans* genes to add to the list. Stein *et al.* also propose more than 4,800 changes to current *C. elegans* gene predictions, such as the existence of new exons (the coding parts of genes, as opposed to their intervening, non-coding regions). These refinements will be crucial in exploiting this nematode as a model system. There are also some fascinating differences between the two species (why, for instance, does *C. elegans* have more than 700 chemoreceptor genes when *C. briggsae* gets by on just 430?), and many genes unique to each (about 800 per species).

Two other pairs of related genomes have been sequenced: humans[7,8] and mice[9] last