word 'half-lives' are intrinsic constants of language, Swadesh anticipated by more than a decade the notion of the 'molecular clock' that is central to sequence-based evolutionary biology[2].

In fact there are striking correspondences between the objections to Swadesh's methods and issues faced in phylogenetic reconstruction[2]. Why should we believe that languages (or genomes) evolve at a constant rate over time, or that individual words and word classes (or proteins and protein families) have the same inherent rates as one another[4]? Do Swadesh lists (or core gene sets common to many genomes[5]) fairly represent overall evolutionary processes? How can we be sure that similarities reflect common ancestry, rather than chance convergences[6]? Conversely, how do we reliably recognize distant relatives whose spellings have drifted far apart (into what biologists call the 'twilight zone' of sequence similarity)? Why should we even presume that the 'tree of language' (or that of life) is a tree, as opposed to a sort of network, given that lexical borrowings and language mixture (and horizontal transfer between genomes[7]) are well-known occurrences? Box 1 provides some examples.

Over the years, historical linguists and evolutionary biologists have separately tackled such challenges with steadily increasing sophistication[8], for instance supplanting Swadesh's overall similarity measure (which phylogeneticists would call a 'distance' method) with cladistic techniques that account for each word (or gene, or sequence residue, or any other observable character) to model the actual process of evolution[6]. Gray and Atkinson[3] apply the latest computational tools — maximum-likelihood models and bayesian inference techniques, which offer a good framework for dealing with issues such as variable rates — to a data set of Indo-European languages developed and refined by lexicostatisticians[4].

The topology of the resulting tree of languages holds no surprises for linguists, but the work goes further to estimate absolute ages with statistical support. Calibrating and cross-validating various branchings against known historical events, Gray and Atkinson develop robust confidence intervals for the date of the root of the tree, whence the Indo-European languages arose. This range appears to be several millennia too early to support a prominent theory that the proto-language was disseminated by nomadic Kurgan horsemen from the steppes of Asia, beginning about 6,000 years ago. But the dates fit well with the notion that Indo-European originated among nascent farming communities in Anatolia, in modern-day Turkey, some 2,000–4,000 years before that.

By breathing new life into glottochronology, this work will doubtless revive old debates. But at the same time it should stimulate even more cross-fertilization of ideas among those studying the intertwined trees of life and language. ■

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1. Ventris, M. & Chadwick, J. *J. Hellenic Stud.* 73, 84–103 (1953).
2. Searls, D. B. *Nature* 420, 211–217 (2002).
3. Gray, R. D. & Atkinson, Q. D. *Nature* 426, 435–439 (2003).
4. Kruskal, J. B., Dyen, I. & Black, P. in *Lexicostatistics in Genetic Linguistics* (ed. Dyen, A.) 30–55 (Mouton, The Hague, 1973).
5. Makarova, K. S. & Koonin, E. V. *Genome Biol.* 4, 115 (2003).
6. Ringe, D., Warnow, T. & Taylor, A. *Trans. Philol. Soc.* 100, 59–129 (2002).
7. Brown, J. R. *Nature Rev. Genet.* 4, 121–132 (2003).
8. Renfrew, C., McMahon, A. & Trask, L. (eds) *Time Depth in Historical Linguistics* (McDonald Inst. Archaeol. Res., Cambridge, UK, 2000).

Cell biology

Thanks for the memory

Jill C. Sible

In response to a transient hormonal cue, a developing egg commits irreversibly to a mature state. Surprisingly, this irreversible switch is composed of intrinsically reversible components.

Few decisions in life are truly irrevocable, even at the cellular level. Yet there are times when it's crucial not to turn back — during the development of multicellular organisms, for instance, when cells must make an irreversible commitment to a new fate in response to a transient stimulus. This process, called differentiation, is well known, but it's not really clear how a cell 'remembers' its commitment long after the signal, frequently a hormone, has disappeared. On page 460 of this issue, Xiong and Ferrell[1] show how brief exposure to the hormone progesterone triggers an irreversible switch in cell fate in developing frog eggs. The memory is sustained by positive feedback loops in the underlying control system. When the positive feedback is perturbed, the cell does the unthinkable and 'dedifferentiates', reverting to characteristics of the immature egg.

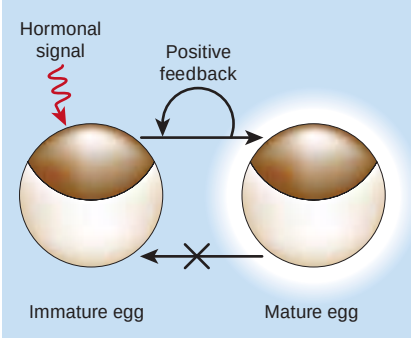

Figure 1 **No turning back. When a hormone stimulates an egg cell to mature, the switch in cell fate is irreversible even after the hormonal signal is gone. Xiong and Ferrell[1] show that this long-term cellular memory is sustained by strong positive feedback in the underlying molecular control system.**

For more than 30 years, investigation of the maturation of frog eggs has been fertile ground for discoveries about how cells divide and differentiate. In 1971, Masui and Markert[2] demonstrated that a bit of cytoplasm taken from a mature frog egg and injected into an immature egg would induce maturation, replacing the need for progesterone. The authors named this mysterious activity MPF, for maturation-promoting factor. MPF was purified in 1988, and was shown to consist of two proteins — an enzyme called Cdc2, which attaches phosphate groups to other proteins, and an unstable co-factor called a cyclin, which is required for Cdc2 activity[3,4]. A few years later, the activity of a second enzyme, MAPK, was shown to be required for egg maturation[5]. MAPK also phosphorylates proteins.

Subsequently, intensive biochemical and molecular investigations by many laboratories have produced a detailed picture of the signalling cascades that are elicited in an immature egg by progesterone. The picture has become quite complicated, with more than 30 different molecules involved. In fact, a recent comprehensive review of the literature[6] required a poster-sized insert to depict all of the known biochemical responses of eggs to progesterone. In an attempt to sort through this web of molecular information, most scientists organize their thoughts around the two key enzymes — Cdc2 and MAPK — and the signalling events that activate each of them[7].

Organizing the network in this way has helped investigators to appreciate the extensive positive feedback that is inherent in the molecular control system underlying egg maturation (see Fig. 1 on page 461). Positive feedback occurs when a molecule that is activated by a signalling pathway activates some earlier step in that pathway, thus strengthening and perpetuating the signal. Cdc2 activates itself in many ways: by inducing the synthesis of cyclin, by phosphorylating and turning off a Cdc2 inhibitor, and by phosphorylating and turning on a Cdc2 activator. Likewise, MAPK triggers the synthesis of Mos, a protein upstream in the

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. ■

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1. Xiong, W. & Ferrell, J. E. Jr *Nature* **426,** 460–465 (2003).
2. Masui, Y. & Markert, C. L. *J. Exp. Zool.* **177,** 129–145 (1971).
3. Gautier, J., Norbury, C. H., Lohka, M., Nurse, P. & Maller, J. L. *Cell* **54,** 433–439 (1988).
4. Gautier, J. *et al. Cell* **60,** 487–494 (1990).
5. Kosako, H., Gotoh, Y. & Nisheda, E. *EMBO J.* **13,** 2131–2138 (1994).
6. Schmitt, A. & Nebreda, A. R. *J. Cell Sci.* **115,** 2457–2459 (2002).
7. Abrieu, A., Doree, M. & Fisher, D. *J. Cell Sci.* **114,** 257–267 (2001).
8. Ferrell, J. E. Jr & Xiong, W. *Chaos* **11,** 227–236 (2001).
9. Pomerening, J. R., Sontag, E. D. & Ferrell, J. E. Jr *Nature Cell Biol.* **5,** 346–351 (2003).
10. Sha, W. *et al. Proc. Natl Acad. Sci. USA* **100,** 975–980 (2003).

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

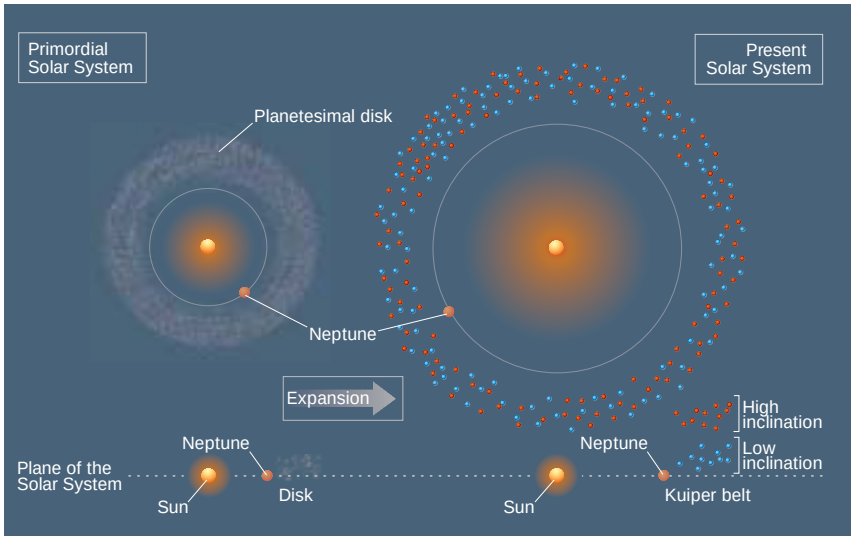

Figure 1 **Expansion plan. The primordial, compact Solar System (left) was surrounded by a disk of asteroid-size planetesimals, which extended roughly as far as Neptune's present orbit. The gravitational pull of this disk eventually induced a planetary migration, during which the orbits of all the major 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.**