pattern, piRNAs are not detectable in W^V mutant mice, which are missing differentiating germ cells (*2*, *5*), and piRNAs are reduced in *Miwi* mutants (*4*). piRNAs are detected throughout sperm development but appear to peak in abundance at the round-spermatid stage (*1–5*). The abundance of piRNAs in spermatids is staggering; about 1 million molecules are estimated per round-spermatid cell (*3*).

Although mammalian piRNAs are not associated with repetitive DNA, the situation might be different in *Drosophila*. On page 320 of this issue, Vagin *et al.* (*6*) describe repeat-associated siRNAs (rasiRNAs) in the fly germline as 24- to 29-nucleotide species that arise primarily from the antisense strand of repetitive sequences such as retrotransposons. These RNAs are associated with Piwi and another member of the Piwi subclade, and mutations in the Piwi class of genes cause derepressed retrotransposon silencing coupled with altered levels of rasiRNA abundance. Interestingly, these effects are not restricted to the male germline but also apply to the female germline. Perhaps rasiRNAs in *Drosophila* use a molecular mechanism similar to that of mammalian piRNAs to silence portions of the genome.

Many questions ensue from these studies. Are testis-specific piRNAs found in species other than mammals? Does piRC regulate male meiosis by regulating genome organization, or is it a surveillance mechanism to ensure genome integrity during germ cell maturation, including suppression of selfish elements? Is piRC male-specific, or are other classes of RNAs associated with Piwi in the female germline? How are piRNAs produced? Their structures might suggest a ribonuclease III–independent origin. Indeed, neither of the two Dicers from *Drosophila* is essential for rasiRNA biogenesis and repeat DNA silencing (*6*), although it is possible that each is redundant for the other or that a third enzyme, Drosha, carries out processing. Further investigation should reveal how piRCs regulate the genome.

References

1. N. C. Lau *et al.*, *Science* **313**, 363 (2006); published online 15 June 2006 (10.1126/science. 1130164).
2. A. Girard, R. Sachidanandam, G. J. Hannon, M. A. Carmell, *Nature* 10.1038/nature04917 (4 June 2006).
3. A. Aravin *et al.*, *Nature* 10.1038/nature 04916 (4 June 2006).
4. S. T. Grivna, E. Beyret, Z. Wang, H. Lin, *Genes Dev.* 10.1101/gad.1434406 (9 June 2006).
5. T. Watanabe *et al.*, *Genes Dev.* 10.1101/gad.1425706 (9 June 2006).
6. V. V. Vagin *et al.*, *Science* **313**, 320 (2006); published online 29 June 2006 (10.1126/science.1129333).
7. M. A. Carmell, Z. Xuan, M. Q. Zhang, G. J. Hannon, *Genes Dev.* **16**, 2733 (2002).
8. W. Deng, H. Lin, *Dev. Cell* **2**, 819 (2002).
9. S. Kuramochi-Miyagawa *et al.*, *Development* **131**, 839 (2004).
10. C. Cogoni, G. Macino, *Science* **286**, 2342 (1999).
11. M. A. Matzke, J. A. Birchler, *Nat. Rev. Genet.* **6**, 24 (2005).

10.1126/science.1131186

EVOLUTION

Darwin for All Seasons

A recent conference featured discussions of Darwin's approach to science in the 19th century and how his methods may apply to 21st-century research.

Eörs Szathmáry

Many regard the Darwinian theory of evolution by natural selection as one of the most important and powerful theories of our times, in the good company of the general theory of relativity and quantum theory. What will be Darwin's legacy in the 21st century? Will new work be mainly confirmatory, or can we expect new breakthroughs? What constitutes a Darwinian way of thinking in biology, or more broadly in science? Is it still timely to think in a genuine Darwinian way, or should we resort only to some basic Darwinian principles? These questions were discussed by researchers at a recent conference at Trinity College, Cambridge, UK (*1*), which was hosted by the president of the Royal Society, Martin Rees.

There was fair agreement among the participants that Darwin's way of approaching problems remains valid and should be encouraged if possible. A feel for the organism, theoretical ideas guiding and aided by keen observations of meticulous details, excellent knowledge of natural history: These traits were characteristic of Darwin (as discussed by Randal Keynes), and there is little hope for biology in this century if at least some people will not walk in Darwin's footsteps. It seems mandatory that "professional generalists," when they rarely surface, should be cultivated and encouraged. Presumably such individuals arise by nature rather than nurture, but a mechanism to identify and support such rare people is badly needed. As Darwin said: "My mind seems to have become a kind of machine for grinding general laws out of large collections of facts" (*2*). We should facilitate the emergence of this mindset in able people.

At the beginning of the 21st century, we are well equipped with the knowledge of two disciplines that were practically closed books to Darwin: classical and molecular genetics, and mathematical modeling. Units of evolution must multiply, have heredity, and possess variability; and among the heritable traits, some must affect survival and/or reproduction. If these criteria are met, evolution by natural selection is possible in a population of such entities. There are at least three remarkable features of this short description. First, it is extremely short, but very powerful [this is why philosopher Daniel Dennett speaks about "Darwin's dangerous idea" (*3*)]. Second, it is not restricted to living organisms, and if the criteria are met, Darwinian evolution may unfold in the realm of chemistry and culture as well. Third, although we have learned a lot since Darwin's times, Darwin would have presumably agreed with this telegraphic description.

There are still enormous challenges ahead of us in areas where a Darwinian way of thinking could turn out to be fruitful. The origin of evolvability lies in chemistry, and the origin of replicators and life may be (one of) the greatest challenges for that field. We do not know how RNA originated. We do not know how the first cells got organized, and there is no full scenario for the origin of the genetic code either. Chemistry has helped biology enormously: The development of biochemistry and molecular biology, and their contributions to our understanding of some fundamental features of life, have been profound. This may be the era when biology pays back its debt: Many fields within chemistry are more and more adopting evolutionary approaches. The triumph of in vitro genetics in producing catalytic RNA molecules (ribozymes) is a success story beyond doubt. An evolutionary approach toward nanotechnology may bear further fruits.

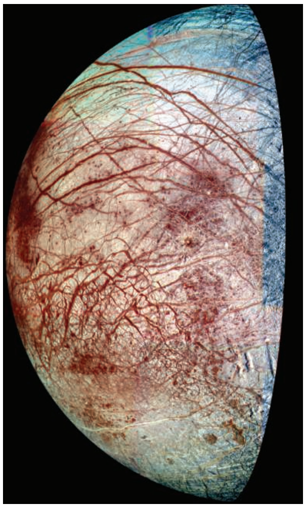
Mathematical modeling has contributed considerably to the foundations of modern evolutionary theory. Sometimes even the questions cannot be properly formulated without at least some elementary algebra or population dynamics. The problem of the evolutionary maintenance of sex in eukaryotes (consisting of cells much more complex than bacteria) is a good case in point. If an asexual female produces, on average, twice as many female progeny as a sexual one, then other things being equal, it is a miracle why the latter (with the necessary males) are still around. Many models have been put forward to solve this conundrum; some people would say far too many. What we need is more data. But relevant data are hard to arrive at. There is the

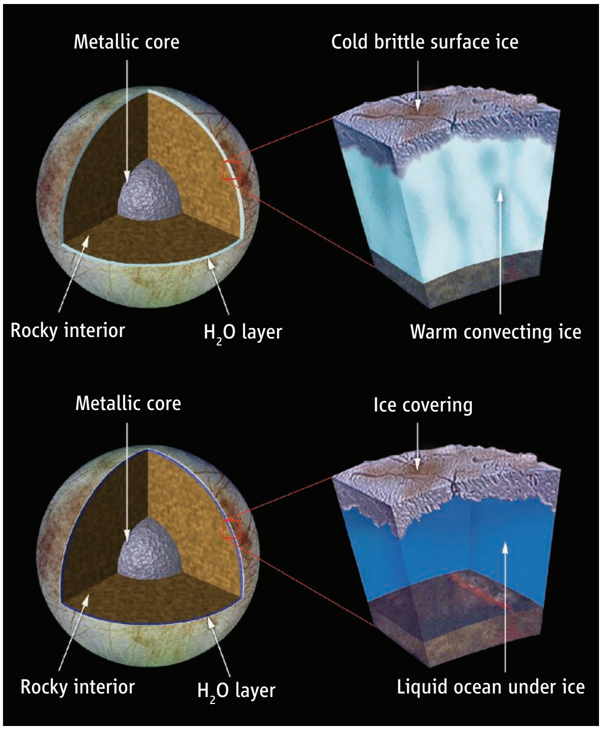
The author is at the Institute of Biology, Eötvös University Budapest, and Collegium Budapest (Institute for Advanced Study), 2 Szentháromság utca, H-1014 Budapest, Hungary. E-mail: szathmary@colbud.hu

Darwinian way: Field work related to the problem of sex is not the easiest. In this century we have a powerful tool about which Darwin could not have dreamed: bioinformatics. Its application to the problems mentioned here rests on genetics, statistics, and molecular biology, among others—disciplines Darwin knew little or nothing about. It seems that the emerging field of comparative/Darwinian genomics is a gold mine for testing old evolutionary ideas (as discussed by Laurence Hurst). Some regard this opportunity as the most rewarding by-product of the genome projects. Yet, this approach is very Darwinian in the sense that it is based on the comparative anatomy of genes, biochemical networks, and so on. This is going to be, without doubt, a very productive field.

Remote from questions about the origin of life there is the formidable set of problems that include the origin of human cooperation and the emergence of natural language. Some regard the latter as "the hardest problem of science" (*4*). This may be an exaggeration, but certainly a problem where processes of biological evolution, individual learning, and cultural transmission become intertwined cannot be considered trivial. It is perhaps no accident that cooperation in large non-kin groups, a developed theory of mind, tool use, teaching (different from learning), and natural language go together in our species. The uniqueness of language raises special problems. Some see this as a fundamental impediment to a successful Darwinian approach. I disagree. Uniqueness presents special methodological challenges, but we should bear in mind that the origin of the eukaryotic cell, as one example, was also unique in the sense that all eukaryotes today share the same common ancestor. This did not prohibit us from insights into the origin of, say, mitochondria, which seem to be closely related to some free-living bacteria. In fact, the endosymbiotic theory for the origin of mitochondria (our energy-producing cell organelles) and plastids (the photosynthetic factories in plant cells), envisaging the gradual evolutionary transformation of particular bacteria (living inside the host cell) into these organelles, is one of the great successes of 20th-century science. It could well be that explaining in at least broad but rigorous terms how the human condition has come about will be a success of the present century (as discussed by Stephen Mithen). Certainly, developments in comparative genomics, proteomics, and linguistics, as well as in neuroscience, hold promise that this endeavor may not be hopeless. It is again a safe bet that apt mathematical models of (cultural) group selection will be an indispensable ingredient of the explanation.

It was emphasized repeatedly at the meeting that Darwin's thinking was extremely integrative. This tradition must be kept up. The present century may cast a shadow on many previous ones if one of our old hopes comes true: finding extraterrestrial life. Astrobiology, a modern successor to exobiology, is regarded by some as the designated field to deal with this issue. Setting terminology aside, the potential implications are formidable. But one should be not overly optimistic, either. Even if there is some small biomass remaining on Mars, it is not unlikely that the Martians will turn out to be our relatives, due to the substantial exchange of geological material from there to here more than 3 billion years ago. In contrast, life on Jupiter's moon Europa (see the figure) could be an "independent experiment." If so, we may well know the answer before the end of the 21st century (not many of us will be around then, though). Must life have a "digital" way of storing genetic information? Probably yes. Will the genetic material of Europans resemble DNA? It could be. If they have a genetic alphabet like DNA, will it have four letters (cytosine, thymine, adenine, and guanine in our case), or fewer, or more? There are theories around that discuss the evolutionary optimality of genetic alphabets, but a natural answer would be best. What is more or less contingent about life? We will know more about this in this century.





Independent experiment. Jupiter's moon Europa may harbor life and provide a test bench for Darwinian thinking in the 21st century. **(Left)** Image of Europa's surface taken by NASA's Galileo spacecraft. **(Right)** Two proposed models of Europa's structure.

CREDIT: (LEFT) NASA/JET PROPULSION LAB, UNIVERSITY OF ARIZONA; (RIGHT) JET PROPULSION LAB/CALTECH

All this hinges, of course, on the assumption that we do not ruin the planet and its biota. It would be difficult to get rid of cyanobacteria, but it would be relatively easy to get rid of ourselves. This in turn depends on the ability of the "Earth system" to regulate itself. Part of this regulation is due to our lucky planetary constitution (including recycling of key materials through plate tectonic movements); other aspects may be selected products or unselected by-products of biological evolution. There are justified objections to simplistic approaches to what has become known as the Gaian view of the Earth system, but presumably a lot needs to be discovered about coevolution on the planetary scale (as discussed by Tim Lenton). Once again, at least one comparative case would be welcome.

Darwin was a peculiar combination of keen observer, experimenter, and calm revolutionary. Whereas details matter enormously (we believe in the testability of scientific ideas), it is healthy to keep a balance: Among some of the half-baked ideas today may lurk a few outstanding theories of the future. As Einstein explained to Paul Valéry (*5*), one does not need a notebook for brilliant ideas since they are exceptionally rare. I do not believe in the end of science: Brilliant theories of the highest rank are yet to come. But I hold it unlikely that the Darwinian approach will be overthrown in the way Aristotelian physics had been: We firmly remain on Darwin's side in the 21st century.

References

1. *Darwin and the 21st Century Science Seminar*, 23 to 24 March 2006, Cambridge, UK; organized by the Charles Darwin Trust.
2. C. Darwin, *The Autobiography of Charles Darwin 1809-1882*, N. Barlow, Ed. (Norton, New York, 1969), p. 139.
3. D. Dennett, *Darwin's Dangerous Idea* (Simon and Schuster, New York, 1996).
4. M. Christiansen, S. Kirby, *in Language Evolution*, M. Christiansen, S. Kirby, eds. (Oxford University Press, Oxford, UK, 2003), pp. 1–15.
5. B. Bryson, *A Short History of Nearly Everything* (Random House, New York, 2003).

10.1126/science.1128901

Published by AAAS