



50 YEARS AGO

"Influence of space flight on engineering and science"

— Within the past few years many scientists have predicted seriously and confidently that human beings from the Earth would, in the foreseeable future, travel to the Moon and the nearer planets. The ranks of those who would dispute this project are diminishing rapidly. Although much of the progress is still guarded by military necessity, space flight is emerging as an activity in its own right — one that can command the efforts of many scientists and engineers... A recent survey shows that the study of physics in American public high schools has been declining for more than half a century... why [does our youth] turn away from a career in science? We can only grope for the answer. Perhaps they sense, better than their elders, that too much of our scientific talent is engaged in the unproductive task of developing weapons for war. Is there much inspiration to devote one's life to this end, when we are rapidly approaching the borderline of total destruction? I believe that space flight might serve in no small measure to turn men's minds toward a more appealing scientific goal. As the exploits of Cabot, Drake and Davis inspired many generations of Englishmen to turn to the sea, so may the first astronauts reawaken our youth to the romance of scientific exploration.

Milton W. Rosen, Naval Research Laboratory, Washington, D.C.
From *Nature* 24 December 1955.

100 YEARS AGO

Heredity. By C. W. Saleeby, M. D. The appearance of a little shilling book on heredity is almost startling, when we consider the difficulty of the subject and the relative youth of its exact study. That a book like this should be possible indicates that considerable progress has been made in recent years. Was it not Leibnitz who said, "The more a science advances, the more it becomes concentrated in little books"?

From *Nature* 21 December 1905.

properties — were 'stepped' through their ranges of uncertainties. This process produced probability distribution functions that represent the probable range of the forcing. The relatively small uncertainty reported by Bellouin *et al.* arises from use of the relatively accurate MODIS optical depths, as compared with the wide range of optical depths generated by the aerosol chemical-transport models that contributed to the IPCC assessment.

So far, so good. But this won't be the end of the story. For example, one wonders how well global estimates of biases in the MODIS aerosol optical depths³, which Bellouin *et al.* attempted to remove, coupled with the aerosol optical properties derived from just six continental sites, characterize aerosols of anthropogenic rather than natural origin. Also, Bellouin *et al.* assumed that the aerosol direct radiative forcing for overcast regions was negligible. As they note, such forcing will be difficult to deduce, but it is bound to be as large as, if not greater than, their claimed uncertainty.

Likewise, the MODIS aerosol optical depth increases with increasing cloud cover⁵, whereas the comparisons with surface-based observations used to establish the accuracy of the MODIS aerosol properties favour largely cloud-free conditions³ — changes in aerosol properties in the vicinity of clouds suggest that the MODIS observations could have biases that have not yet been characterized. Finally, aerosols also affect the size and numbers of droplets in clouds, thereby altering the amount

of sunlight reflected by clouds. The extent of this effect, known as 'aerosol indirect radiative forcing', remains largely unknown. But it may offset greenhouse-gas warming even more than the aerosol direct radiative forcing⁶.

Assessments of climate change caused by human activity have been stymied in part by the sizeable uncertainty in estimates of the aerosol direct and indirect radiative forcings. The strategy of using combinations of global space-based and surface-based observations to constrain model estimates, as followed by Bellouin *et al.*, is a promising way of reducing these uncertainties. Space missions such as CALIPSO and CloudSat are to become part of the A-Train — the Aqua satellite constellation — early next year. They will help to improve the characterization of aerosols, particularly over continents where the direct radiative forcing is greatest, as well as the treatment of cloud-aerosol interactions. ■

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GENOMICS

Multiple moulds

André Goffeau

Three species of *Aspergillus* fungi are the latest organisms to have their genome sequenced. Comparison of the genomes sheds light on, among other things, what endows them with pathogenic or beneficial features.

The genome sequences of three *Aspergillus* fungi are reported in this issue: *Aspergillus oryzae*¹, used in making the Japanese drink sake; the human pathogen *Aspergillus fumigatus*²; and the genetic model species *Aspergillus nidulans*³. The 185 known species of *Aspergillus* include 20 human pathogens, numerous plant pathogens and a variety of species that we use to produce foods, chemicals and industrial enzymes. The genomes provide a wealth of information about the evolution of this fascinating group of organisms, and about the beneficial or detrimental characteristics of each species.

The sequences, published by teams from Japan, the United States and Europe, cover an average of nearly 95% of each genome. In total across the three species, more than 95 megabases have been sequenced, crammed with

over 33,500 protein-coding genes contained on 24 chromosomes (eight chromosomes per species). By comparison, the human genome has about 30,000 protein-coding genes in 3,000 megabases.

Aspergillus oryzae has been used for nearly a thousand years to produce traditional Japanese fermented foods and drinks. Its genome¹ has about seven to nine megabases more DNA than *A. fumigatus* and *A. nidulans*. To account for this, the authors propose that some genes were transferred to *A. oryzae* from other species during evolution. The extra DNA stretches are dispersed throughout the genome and are enriched in genes involved in the synthesis and the transport of numerous secondary metabolites — the chemical compounds in an organism that are not directly involved in normal growth, development or reproduction.

Secondary metabolites are often specific to one or a few species, so they provide a window on the particular biology of the species.

Species closely related to *A. oryzae*, such as *Aspergillus flavus* and *Aspergillus niger*, have similar gene acquisitions. For instance, the toxic *A. flavus* has 25 genes encoding proteins involved in the pathway that produces the poisonous 'aflatoxin'. These genes are present in *A. oryzae* but are not expressed. It is likely that an ancestor of *A. flavus* passed these genes to *A. oryzae*, and that they were then inactivated during the subsequent evolution of *A. oryzae*.

Aspergillus fumigatus is a potentially deadly human pathogen and a major allergen. The *A. fumigatus* sequence² pinpoints nine previously unknown allergens, numerous genes involved in the production of specific secondary metabolites, and a set of essential genes that may be potential targets for drugs. However, the factors that underlie the pathogenicity of this species are complex, and their identification required other approaches to complement the genome analysis. For instance, for *A. fumigatus* to thrive inside warm-blooded creatures such as ourselves, it must be able to tolerate our high body temperature (compared with that of the external environment). Using DNA microarray analysis, a set of 'thermotolerance genes' whose activity increases at 37 °C has been identified. But it seems that warming up to 37 °C is insufficient to turn on many genes that are associated with virulence in this species.

Aspergillus nidulans has long been a model organism used to study the genetics of fungi. Its genome³ was crucial for the comparative analysis of the three aspergilli, but it also had some features of its own to reveal. For instance, the regulation of several of its genes was clarified, with the identification of putative binding sites for gene regulatory factors and control elements, as well as many short open reading frames that lie upstream of genes; these short sequences may stall the expression of neighbouring genes. In addition, the sequence disclosed many previously unknown genes involved in peculiar metabolic (fatty-acid oxidation), developmental (polarized growth) and DNA-repair pathways.

The three species diverged several hundred million years ago, and their genomes differ considerably³. There are almost 3,000 proteins that are closely related, or 'homologous', among the genomes. On average, these proteins have only 68% of their constituent amino acids present in all three genomes — a value comparable to that of proteins homologous between mammals and fish, which diverged around 450 million years ago. Nevertheless, the order of the homologous proteins along chromosomes (synteny) is conserved in the three species, indicating that no whole-genome duplication occurred during evolution. However, large regions lack any synteny because of small tandem repeats, gene rearrangements in the chromosome extremities, and considerable random breakage and

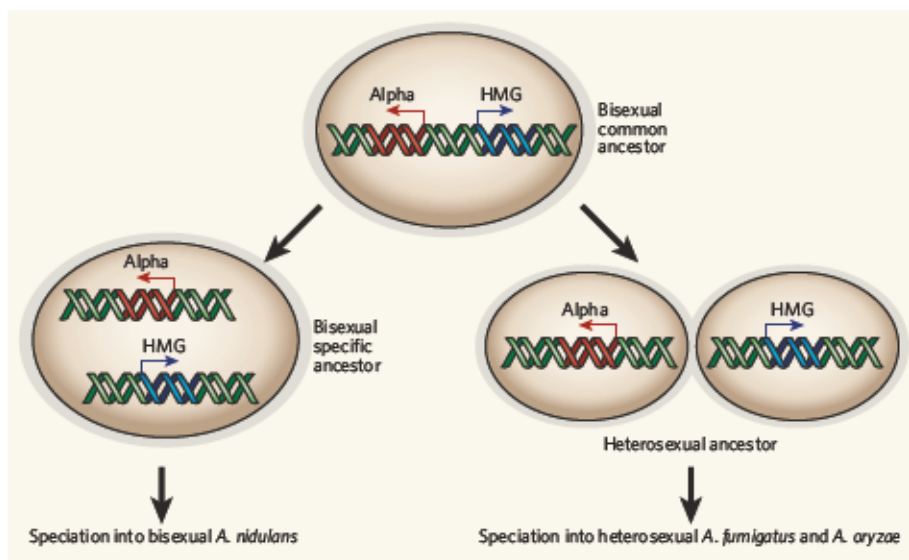


Figure 1 | Evolutionary model of the *Aspergillus* mating genes. In a bisexual common ancestor, the two mating-type genes, alpha (red) and HMG (blue), were fused head to tail on the same chromosome and share a similar flanking, regulatory region (green). In the bisexual *A. nidulans*, the chromosome is broken and the two mating-type genes end up on different chromosomes (with their flanking regions). In the ancestor of *A. oryzae* and *A. fumigatus*, the two mating-type genes dissociate in different strains, but remain flanked by similar genes. After speciation, both *A. fumigatus* and *A. oryzae* become fully heterosexual, with some isolates having only the alpha mating type and others only the HMG mating type, both being in similar chromosomal environments.

rearrangements of syntenic blocks. Such genome reorganization is seen to a greater extent in *A. oryzae* than in *A. fumigatus*. The rates of amino-acid evolution within homologous genes are similar for all three species, so the evolution of large structural rearrangements does not parallel the rate of individual amino-acid changes.

The chief revelation from the three-genome comparison is the mating systems in *A. fumigatus* and *A. oryzae*. Sexual reproduction in yeast can take place only between individuals of opposite mating type, or 'sex', as determined by mating-type genes. *Aspergillus nidulans* has two mating-type genes: one contains an alpha box and the other a high-mobility-group (HMG) domain. So each cell can have two sexes at once, and *A. nidulans* is self-fertile. *Aspergillus nidulans* can also reproduce asexually by 'mitotic reproduction', creating spores that are sprinkled by structures known as conidiophores.

Aspergillus fumigatus and *A. oryzae* were believed to reproduce only through the asexual mitotic process. Unexpectedly, however, the *A. oryzae* and *A. fumigatus* genomes each have a mating-type gene: the *A. oryzae* sequence contains an alpha mating-type gene, whereas the *A. fumigatus* sequence has an HMG mating-type gene. These genes occupy nearly identical positions in their respective genomes, with conserved synteny for 1.7 megabases on either side. In addition, 215 genes implicated in different phases of the *A. nidulans* mating process occur in *A. oryzae* and *A. fumigatus*. These and other recent data⁴ raise the possibility that *A. fumigatus* and *A. oryzae* are heterosexual, and that conversion of bisexuality to heterosexuality occurred during

the evolution of the *Aspergillus* genus (Fig. 1).

These reports describe only the initial examination of the genomes, of course, and the sequences provide much scope for further analyses. The sequencing of other *Aspergillus* genomes is under way and will provide an even broader perspective on the biology and evolution of these fungi. The most keenly anticipated *Aspergillus* sequence is that of *A. niger*, which has long been used in the industrial production of citric acid⁵. The commercial significance of several *Aspergillus* species has meant that their genome sequences, including that of *A. niger*, have been kept behind the closed doors of biotechnology companies for some time. However, this practice seems to be changing: a consortium of Japanese companies has agreed to release its *A. oryzae* sequence, and Monsanto provided access to its *A. nidulans* genome sequence, so that they could be added to the publicly funded sequences now published. And, fortunately, the US Department of Energy has undertaken to complete one of the industrial *A. niger* sequences (which is currently of low coverage) to make public a useful version of this genome. Perhaps the time when genome sequences belong exclusively to industry is over.

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