Title
Brouhaha over the other yeast

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theory and multiscale modelling in this and other areas.

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Genome sequencing

Brouhaha over the other yeast

Jonathan A. Eisen

The sequencing of the fission-yeast genome allows researchers to compare it with that of its cousin, budding yeast, and to identify genes that may distinguish eukaryotes (such as yeast) from prokaryotes (such as bacteria).

Having a famous relative can be a mixed blessing. This is certainly the case for the yeast *Schizosaccharomyces pombe*, commonly referred to as 'fission yeast' both because it divides by binary fission and to distinguish it from its distantly related cousin, *Saccharomyces cerevisiae* or 'budding yeast'. *Saccharomyces cerevisiae* is considered by many to be *the* single-celled model for research into eukaryotes[1] (those organisms, including humans, whose cells have a defined nucleus) and is also of major industrial importance. So, although those studying *S. pombe* have benefited from discoveries about *S. cerevisiae*, the fission yeast is often viewed as 'the other yeast', taking a back seat in research and funding.

Well, get ready everyone, because a fight for glory is brewing in the yeast family. First, a few months ago, Paul Nurse was announced as co-winner of the 2001 Nobel Prize in Physiology or Medicine, being recognized largely for his work on the cell cycle in *S. pombe*[2,3]. Now, on page 871 of this issue, Nurse and colleagues[4] report on the sequencing and analysis of the complete *S. pombe* genome, officially bringing the other yeast into the post-genomics era.

Schizosaccharomyces pombe is the sixth free-living eukaryotic species whose genome has been reported as completely sequenced[5–10]. (Some, such as the human genome, have been announced as 'completed' even though they are not; the *S. pombe* sequence is actually nearer to completion than many of the others.) The analyses presented in the new paper, the sequence itself and the many bits of extra information available on websites devoted to *S. pombe* (see, for example, ref. 11) together represent a landmark achievement. The analyses should also satisfy those who have asked: "Why another yeast genome?".

Wood *et al.*[4] use the *S. pombe* genome sequence to reveal new features of *S. pombe* biology, and to uncover further evidence of how different the fission and budding yeasts are. For example, *S. pombe* has hundreds of genes that are apparently absent in *S. cerevisiae*, and vice versa. The genetic differences are not as great in some areas as *S. pombe* researchers may have hoped; for example, there are only three disease-linked human genes that have counterparts in *S. pombe* but not in *S. cerevisiae*. But overall the differences are quite significant, and show why *S. cerevisiae* may not always be the preferred model eukaryote.

For instance, Wood *et al.* find that, compared with *S. cerevisiae*, *S. pombe* has significantly more 'intron' sequences (roughly 4,700 compared with 275), which interrupt the coding regions of genes, and very few transposable — mobile — genetic elements. *S. pombe* also has more proteins that appear to be involved in transporting sugars or other molecules; larger centromeres (chromosome regions needed for the accurate partitioning of chromosomes after cell division); and an apparent lack of recent whole-genome duplication. These differences could make *S. pombe* a better model than *S. cerevisiae* for understanding some eukaryotic processes.

It does not particularly surprise me that budding and fission yeast differ so much at the genomic level, as they are not very closely related[12], and many genetic and physical differences had been known before the genomes were sequenced (see, for example, ref. 13). But the fact that many further differences have been uncovered by genomic comparisons[4] suggests that it could prove valuable to sequence the genomes of other biologically diverse yeast species, and, more broadly, other fungi.

Wood *et al.* also attempt to identify genes that might be specific to eukaryotes (and so probably evolved on the branch of the evolutionary tree that separates these species from prokaryotes; Fig. 1). The authors use a very conservative approach, identifying only those genes that are highly conserved in eukaryotes and have no apparent matches in any prokaryote, so they may have missed many eukaryotic-specific genes. Nevertheless, many of those identified are predicted to function in processes specific to, or highly developed in, eukaryotes, such as the cell cycle, RNA 'splicing', construction of the cytoskeleton, protein degradation and signal transduction. So these genes may be fundamental to understanding the origin and evolution of eukaryotes. In a separate analysis, Wood *et al.* identified protein 'domains' — structurally defined portions of proteins — that are more abundant in eukaryotes than in prokaryotes; these may also be important in understanding eukaryotic biology.

The *S. pombe* genome is the second of a

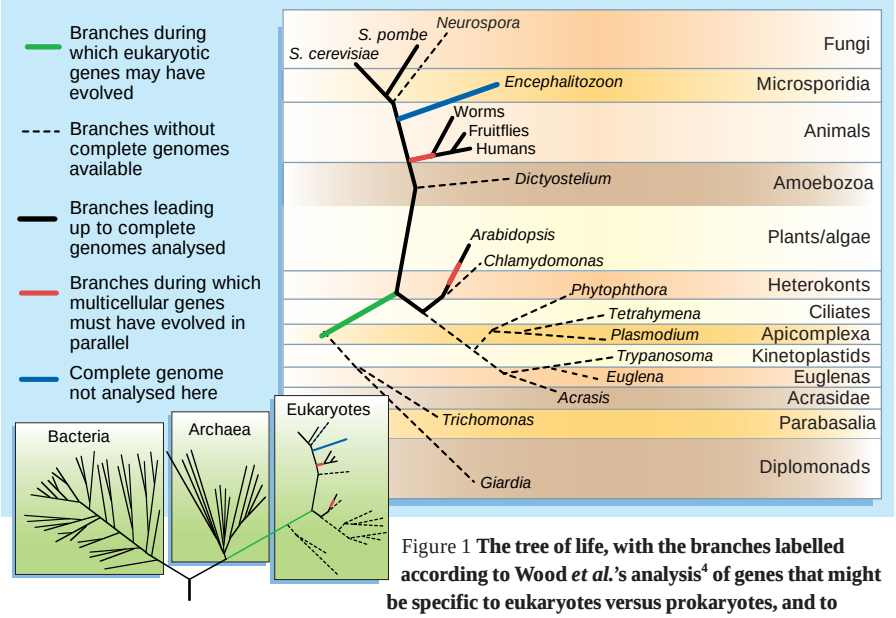


Figure 1 **The tree of life, with the branches labelled according to Wood *et al.*'s analysis[4] of genes that might be specific to eukaryotes versus prokaryotes, and to multicellular versus single-celled organisms. Bacteria and archaea are prokaryotes (they do not have nuclei). The eukaryotic part of the tree is based on ref. 18. Only representative lineages are shown.**

free-living, single-celled eukaryote to be completely sequenced (the first being that of *S. cerevisiae*). Wood *et al.* take advantage of this to try to identify genomic properties that are related to multicellularity. They used another conservative approach to compare the genomes of the two yeast species with the available genome sequences of multicellular eukaryotes (a plant and three animals), and found only three genes that were specific to all the multicellular species.

This may seem surprising, but it probably should not. First, the comparison did not take into account that multicellularity probably evolved separately in plants and animals[14] (Fig. 1), so different multicellularity-related genes may have evolved in these two evolutionary lineages. Second, the time interval during which these genes could have evolved is much shorter than for the eukaryotic versus prokaryotic comparison — in other words, there has been less time to 'invent' new genes. Perhaps more usefully here, the authors found that, even after correcting for differences in genome size, some protein domains are more common in the multicellular than in the unicellular organisms, probably reflecting the expansion of certain protein families. This implies that such expansions may have occurred in parallel during the evolution of multicellular animals and plants, but the same genes were rarely if ever invented by both groups.

So what next? Clearly, a better comparison of eukaryotes and prokaryotes requires complete genome sequences from a more diverse sampling, not just those eukaryotes from the 'top' of the tree (Fig. 1). Lumped together as 'protists', these other eukaryotes show remarkable diversity and include many parasitic species, such as the malaria-causing *Plasmodium*; species such as *Giardia* that lack the cellular powerhouses, mitochondria; and organisms with several nuclei and unusual genome-rearrangement processes, such as *Tetrahymena*. It will also be interesting to use the *S. pombe* and other fungal genomes to do a more thorough comparison with genomes from the Microsporidia, such as the parasitic *Encephalitozoon*[15]. These organisms were once classified with the protists but are now thought to be related to fungi[16].

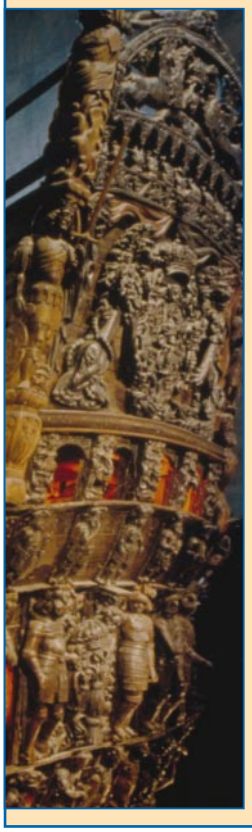
In all these comparisons, it will be important to go beyond simply identifying the similarities and differences between species, and to analyse the origin of the differences, for example the gain, loss and possible transfer of genes over time[17]. But today we should

Marine archaeology

Acid attack

HANS HAMMARSKIÖLD/VASA MUSEUM, STOCKHOLM

If you were planning to visit the impressive restoration of the *Vasa*, now is a good time. The *Vasa* was a 61-metre,1,210-tonne warship, which sank in Stockholm harbour on its maiden voyage in 1628, but was raised in 1961 and restored for display in a museum in Stockholm (see pictures). A multidisciplinary group of researchers, however, has discovered that the ship's timbers are in danger of disintegrating. As Magnus Sandström and colleagues report in this issue (*Nature* **415,** 893–897; 2002), and describe in an exhibition that opens this week in the Vasa Museum, sulphuric acid is being produced within the beams of the ship. The acid attacks the wood both chemically, by acid hydrolysis of cellulose, and physically, as the sulphate minerals expand during crystallization.



So where is the sulphuric acid coming from? Alerted by sulphate crystals forming on the surface of the *Vasa*'s timbers, Sandström *et al.* went on to find large quantities of elemental sulphur inside the wood. They believe that hydrogen sulphide — a common product of bacterial decomposition in anoxic waters — permeated the ship's timbers and was gradually transformed to elemental sulphur during the 333 years that the ship lay at the bottom of Stockholm harbour. This created a reservoir of sulphur, which, if fully oxidized, could produce as much as five tonnes of sulphuric acid.

A complicating factor comes from the legacy of the ship's 9,000 original iron bolts that have largely rusted away. Iron (III) ions are effectively a catalyst here, gradually oxidizing elemental sulphur to sulphuric acid. The reduced iron is then itself re-oxidized by oxygen from the air, ready to go through the cycle once more.

Museum curators are well aware of the threat of oxidation to waterlogged wooden artefacts after salvage. As well as stabilizing the fragile lattice of remaining wood by replacing the water with non-volatile preservatives, conservation methods routinely involve limiting further biological and chemical oxidation with sterilizing solutions, and carefully controlling humidity and temperature. But the newly observed sulphur threat calls for different measures. Neutralizing five tonnes of sulphuric acid is not really feasible, and the most promising solution lies in tackling the iron catalyst. One proposal of Sandström *et al.* is to identify an agent that will form a complex with the iron solutes, making them inert, and possibly even extractable by rinsing the ship with alkali.

What about other wrecks? Fortunately, the *Vasa* seems to be an extreme case. The decision in the sixteenth century to close off two inlets into Stockholm harbour, to hinder attack from the Russians, along with centuries of sewage disposal in the harbour, helped to create an especially stagnant and sulphurous resting place. Moreover, the threat of sulphur acidification in wrecks that were completely buried in sediments, such as the *Mary Rose*, now on display in Portsmouth, UK, should be smaller. Indeed, Sandström *et al.* found that sulphur accumulation was greatest in the exposed timbers of the *Vasa*. But in ships that were not buried — the *Batavia* of the Dutch East India Company, for instance, which was wrecked off Western Australia in 1629 — initial analyses confirm that the sulphur problem is more common, if not as severe as in the *Vasa*.

These new investigations support recent moves to let sunken ships lie, and preserve and study them where they sank (*Nature* **415,** 460; 2002) — virtual technology would still allow the public to view the wrecks and their sites. After all, why not capitalize on the preserving features of marine sediments, rather than let them express their acidic side later on?

Jim Gillon

do a little dance for the other yeast, and hope that in the future, when someone says 'yeast', scientists will give equal thought to the species that was first isolated from a traditional African beer known as Pombe. ■

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Evolutionary biology

How insects lose their limbs

Mike Levine

Evolution has produced marvellous variety in the arthropods, and in their various appendages. The evolutionary processes are themselves proving highly diverse.

From the standpoint of diversity in form and sheer number, the arthropods are the most successful animals on Earth. They embrace four remarkable groups: trilobites (sadly extinct), insects, crustaceans (shrimp, lobsters, crabs and so on), and chelicerates (horseshoe crabs, spiders and scorpions). The success of the arthropods stems, in part, from their modular architecture. They are composed of a series of repeating body segments that can be modified in seemingly limitless ways. Some segments carry wings, whereas others have antennae, legs, feeding organs or specialized mating devices.

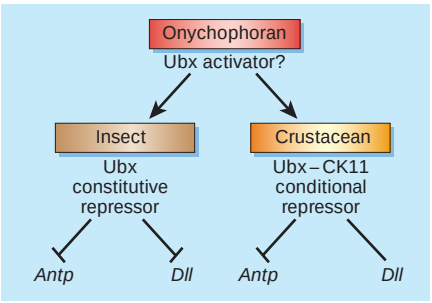

Figure 1 **Evolution through changes in Hox protein function. An interpretation of the new results[1,2] runs like this. Onychophorans, such as velvet worms, are close relatives of the arthropods, and have limbs on every segment. Here Ubx protein may function as an activator, but when onychophorans and arthropods diverged it acquired one or more repression domains, which suppressed limb development. In insects these domains mediate constitutive repression of target genes, such as *Antp* and *Dll*. During the subsequent crustacean–insect divergence, Ubx in crustaceans acquired a regulatory peptide containing potential CKII phosphorylation sites, making Ubx act as a conditional repressor. In the brineshrimp *Artemia*, for instance, Ubx represses *Antp* without influencing the expression of *Dll*. An alternative view is that the onychophoran protein contains both a repression domain and a regulatory peptide, the peptide being lost in insects but retained in crustaceans.**

Another item can be added to the list of things that are special about the arthropods: we know more about the evolutionary processes responsible for their diversification than for any other group of animals. These insights have been made possible by detailed study of the genetic mechanisms underlying the development of that most thoroughly characterized of animals — an insect, the fruitfly *Drosophila melanogaster*. After nearly a century of genetic analysis, many of the genes responsible for segmentation and limb development have been identified. Foremost among these is a class of regulatory genes, the Hox genes, which encode DNA-binding proteins and control early development. During the past ten years this information has been used in the burgeoning field of 'evo–devo', which lies at the cusp of evolutionary biology and embryology, to determine how limbs have diversified among different arthropods.

Children are taught that insects have six legs, two on each of the three thoracic (middle) segments, and this applies to every one of the more than a million species of insect. By contrast, other arthropods, such as crustaceans, have a variable number of swimming limbs. Some crustaceans have limbs on every segment in both the thorax and abdomen. Papers on pages 910 and 914 of this issue, by Galant and Carroll[1], and by Ronshaugen *et al.*[2], provide new insights into how insects have lost abdominal limbs, and so contain only six legs.

The two groups[1,2] provide evidence that suppression of abdominal limbs in insects depends on functional changes in a protein called Ultrabithorax (Ubx), which is encoded by a Hox gene. Ubx represses the expression of another gene, *Distalless* (*Dll*), which is required for limb formation, in the anterior abdomen of the *Drosophila* embryo. However, in crustaceans, such as the brine shrimp *Artemia*, all of the developing limbs have high levels of Ubx.

The other comparison to be made here is with velvet worms. These are members of the Onychophora — close relatives of the arthropods — which have limbs on all segments. In velvet worms, Ubx is expressed in at least a subset of these limbs. So Ubx expression is compatible with limb development in crustaceans and onychophorans, but is incompatible with limb development in *Drosophila* (and other insects).

The new work involved misexpression of the *Drosophila* Ubx protein in the presumptive thorax of transgenic fruitfly embryos. Limb development was suppressed because of repression of Dll. By contrast, the misexpression of onychophoran and crustacean Ubx proteins did not interfere with Dll expression and the formation of thoracic limbs. These results raised the possibility that the *Drosophila* Ubx protein is functionally distinct from Ubx in onychophorans and crustaceans. One study suggests that *Drosophila* Ubx has acquired an alanine-rich peptide that mediates the repression of gene transcription; this peptide is lacking in

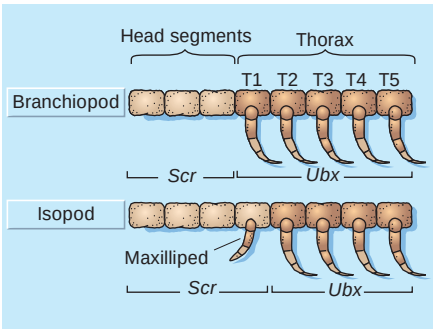

Figure 2 **Evolution through changes in Hox gene expression. In crustaceans known as branchiopods (top), the head contains feeding appendages, whereas thoracic segment T1, nearest the head, contains swimming appendages that are like those further back on the thorax (segments T2–T5). In these animals, expression of one Hox gene (*Scr*) is restricted to head segments, and *Ubx* is expressed in all thoracic segments. In other crustaceans, such as isopods (bottom), the first thoracic appendages have been modified into feeding structures called maxillipeds. This change correlates with altered patterns of Hox gene expression: *Ubx* is replaced by *Scr* expression in the first thoracic segment.**