EMBO reports

meeting point

Yeast evolution and ecology meet genomics

Maitreya J. Dunham & Edward J. Louis

The first EMBO Conference on Experimental Approaches to Evolution and Ecology in Yeast was held in Heidelberg, Germany, at the end of September 2010. What might sound like a rather narrow topic actually covered a broad range of interests, approaches, and systems and generated a great deal of excitement among participants. The applications of genomic methods to ecological and evolutionary questions emphasize that the yeasts are poised to make significant contributions to these fields.

More than 100 fungal biologists convened in Heidelberg between September 29 and October 3 for the first in a series of three conferences about yeast evolution and ecology. The conference was organized by Graham Bell (U. McGill, Canada), Michael Knop (EMBL, Heidelberg, Germany), Andrew Murray (Harvard U., USA) and Lars Steinmetz (EMBL, Heidelberg), following an EMBO workshop on this topic that took place two years ago, and brought together researchers from fields that rarely interact. An enthusiastic response to participation in that workshop highlighted the need for a forum for the interaction of ecologists, evolutionary biologists and molecular geneticists. The particular focus of this year's event was experimental approaches to these topics, and presentations ranged from molecular genetic studies of experimental evolution to ecological surveys of fungi growing in wild environments.

> **...presentations ranged from molecular genetic studies of experimental evolution to ecological surveys of fungi growing in wild environments**

Despite the broad range of interests, systems and approaches that were discussed, several themes were apparent at the meeting. First, next-generation sequencing is ushering in a new phase of fungal genetics. With the US$1,000 human genome in sight, tiny yeast genomes are easy and inexpensive to sequence. Interesting mutants, strain backgrounds and species are probably going to drive the field in future, as technical limitations are removed. Second, genotype–phenotype relationships remain difficult to pin down. Quantitative genetics approaches were common topics at the meeting, but in only a few cases is the link clear between the genetic variant and the trait. New methods that were discussed at the meeting for addressing these problems will probably lead to many discoveries, which will be reported at the next meeting in two years. Third, as many newly sequenced fungi are tractable in the laboratory, experimental approaches to comparative functional genomics are complementing the successes of sequence-based comparative analysis. Fourth, evolutionary theory is still a ripe source of ideas for experimenters to plumb. Finally, an appreciation of the ecology of the organism can enhance the understanding of its lifestyle and genomic structure. More work on yeast ecology is required to describe the selective pressures that yeasts encounter on a daily basis in the real world, outside the cozy confines of the laboratory.

Experimental evolution

These big topics in yeast evolution and ecology are complex. Experimental approaches to evolution seek to distil it into simpler constraints that are more easy to control and model. This field has been particularly enhanced by the rise of whole-genome sequencing; as the phenotypes associated with small shifts in competitive fitness are difficult to discover using traditional functional approaches—such as cloning by complementation—sequencing technology is allowing a new, comprehensive view of the mutations acquired during laboratory selection. Gavin Sherlock (Stanford U., USA) and Delphine Sicard (U. Paris, France) used next-generation sequencing to discover the catalogue of mutations in a series of yeast populations that had evolved under various nutrient conditions. They showed that in addition to unique mutations, shared genetic solutions exist when converging towards a phenotype, regardless of genetic

background. Sherlock and Frank Rosenzweig (U. Montana, USA)—who discussed partitioning strain improvements according to their effects on metabolism—used strains evolved almost 30 years ago in Paquin and Adams' foundational study. This showed the value of looking into our freezers for valuable strains from the past. However, the molecular details of how, why and which mutations tune fitness remain to be discovered, emphasizing that genotype–phenotype technologies are perhaps more important than ever in our post-genomic field.

> **...the molecular details of [...] which mutations tune fitness remain to be discovered [...] genotype–phenotype technologies are perhaps more important than ever in our post-genomic field**

Graham Bell offered a rebuke to this select-and-sequence style of experimental approach; he argued for the value of hypothesis-driven tests of evolutionary theory. His work investigates the effects of environmental degradation, a topic of considerable global interest writ small in 96-well plates. His laboratory has found that migration patterns and the rate of environmental change contribute to the ability of populations to adapt successfully to increasing salt concentrations. Paul Sniegowski (U. Pennsylvania, USA) tackled another fundamental evolutionary question by recreating a classic bacterial evolution experiment in yeast, to compare the evolutionary success of strains with different mutation rates. Similarly to that in bacteria, the success of mutator strains of yeast is frequency-dependent. Unlike bacteria, yeast strains with a high mutation rate show gross fitness defects, although the reason for this remains unclear. John Koschwanez from the Andrew Murray lab (Harvard U.) demonstrated ecology within yeast colonies. He addressed the issues of multicellularity and the interactions that confer an advantage over 'cheaters' in specific carbon-source uptake situations that require the expression of an extracellular enzyme.

Copy number variants: gene duplication

The mutational mechanisms by which cells can adapt to environments were also a common topic at the meeting. Copy number variants seem to have a role in this, in both laboratory and natural strains. The expansion and contraction of runs of nucleotide repeats within coding and regulatory regions of various genes are linked to changes in function or expression, according to Kevin Verstrepen (K. U. Leuven, Belgium). At the other end of the spectrum, Norman Pavelka in Rong Li's lab (Stowers Institute, USA) discussed work to generate strains carrying deviant numbers of entire chromosomes. Although aneuploidy was confirmed as being generally deleterious under standard laboratory conditions, a subset of the aneuploid strains grew better in conditions that were severely detrimental to euploid cells. Jan Korbel (EMBL, Heidelberg) began his talk with a discussion of the importance of copy number variants in human genetic variation and the use of yeast systems to explore how these events are generated. In this context, Roy Kishony (Harvard U.) looked into the gene paralogues in *Saccharomyces cerevisiae* created by an ancient whole-genome duplication event: his lab has found several duplicates that remain functionally redundant and show interesting gene-expression dependencies. Verstrepen also talked about recreating an ancient gene copy by inferring the ancestral sequence from the modern variants of the *mal* gene family and then constructing the consensus by gene synthesis. The ancestral *mal* gene product is active against a variety of substrates, whereas the derived alleles seem to have specialized. In natural strains isolated from 'evolution canyon'—a region in Israel where extremely different but geographically close environments have driven adaptation in species from yeasts to flies—Jun-Yi Leu (Academia Sinica, Taiwan) found that chromosomal and gene copy number differences were linked to copper tolerance. However, copy number variation is not the only mechanism for adaptation to adverse environments; tolerance to cadmium was caused by point mutations in the promoter of the *PCA1* gene.

Quantitative genetics

What might be called 'next-generation linkage mapping' was another theme of the meeting. The impact of the genome sequences and strains delivered two years ago by the *Saccharomyces* Genome Resequencing Project is starting to be felt, and they are being used for a range of applications. Gianni Liti (U. Nottingham, UK) discussed a clever multi-round crossing strategy for creating large outbred populations.

> **An informal session to discuss the development of *S. paradoxus* as a model system for ecology and evolution was attended by about 40 people**

Placing these pools in selective conditions enriches for favourable genotypes, which can then be detected by sequencing the entire pool. Aimée Dudley (Institute for Systems Biology, Seattle, USA) described how her lab is automating some aspects of quantitative genetics—for example, by using FACS analysis to speed up tetrad analysis—and for high-dimensional phenotype analysis. Looking at the complex 'fluffy' colony morphologies displayed by many of the wild and industrial yeast isolates, she has developed an image analysis pipeline to describe this phenotype more systematically, in a way that is amenable to genetic analysis. Daniel Jarosz from Sue Lindquist's lab (Whitehead Institute, USA) described how these mapped quantitative trait loci (QTL) could change depending on the chaperone status of the mapping population, by using a heat-shock protein 90 inhibitor to uncover cryptic genetic variation. Gael Yvert's lab (ENS Lyon, France) has taken these quantitative-genetic concepts one step further, to investigate how epigenetic marks also segregate in outcrosses.

Sequencing and genetics in other yeast

These experiments are a hint of what is to come as the the pace of sequencing accelerates in the field. Justin Fay's lab (Washington U., USA) announced the sequencing of an additional 27 isolates of *S. cerevisiae*. Darren Platt (Amyris, USA) described how the company is leveraging the sequences of 11 industrial strains to improve bioproduct yield. They found 2.5-fold improvements in yields from testing different genetic backgrounds derived from these heterozygous strains. Jurg Bahler's (U. College London, UK) talk described how fission yeasts are getting in on the action as well: they have collected 130 diverse strains of *Schizosaccharomyces pombe* for sequencing and QTL mapping. Ken Wolfe (Trinity College Dublin, Ireland) talked about a new analysis of genome sequences across a yeast phylogeny that points towards the evolutionary forces around the MAT locus. These new bouquets of species provide fodder for comparative sequence analysis along several clades of similar depth across a large tree.

Experimental work with these species is also on the rise. Oliver Zill from Jasper Rine's lab (U. Berkeley, USA) discussed one aspect of biology in which *S. cerevisiae* might not be representative of the other yeasts: silencing. *Saccharomyces bayanus*, a sister species of *S. cerevisiae*, has more *SIR1* paralogues in its genome, these are necessary for silencing through the 'weaker' silencer elements found in *S. bayanus*. Furthermore, *S. cerevisiae SIR4* functions in a limited range of species, suggesting that Sir1, Sir4 and silencers have co-evolved in the *S. cerevisiae* lineage. Rachel Brem (U. Berkeley, USA) explored differences in gene expression between these two species on a genomic scale, using short-read sequencing methods applied to hybrid strains.

We can probably expect *Saccharomyces paradoxus* to be an important topic at the next meeting. Since the previous meeting two years ago, it has become clear that the *S. cerevisiae* genome has been shaped largely by human dispersal and artificial selection pressures associated with domestication. *S. paradoxus* shows fewer signs of these influences and is being embraced as a more ecologically relevant model yeast. Vassiliki Koufopanou (Imperial College, London, UK) uses *S. paradoxus* population genetics to estimate important parameters of lifestyle such as the frequency of sexual reproduction and the proportion of this that is outbreeding. Their predominantly asexual mode of reproduction has implications for how we interpret and model evolutionary history in these yeasts. An informal session to discuss the development of *S. paradoxus* as a model system for ecology and evolution was attended by about 40 people. Several people gave brief accounts of their research with *S. paradoxus*, after which there was a general discussion of how resources and results might be organized and shared most effectively. Duncan Greig offered to further this discussion by hosting a website for the *S. paradoxus* project at the Max Planck Institute, Plön, Germany. The session concluded with general agreement that there should be a mini-symposium dedicated to *S. paradoxus* as part of the next EMBO workshop in 2012.

...yeasts and their relatives are poised to become the driving force in ecological and evolutionary studies, as we learn more about the ecology and natural history of this 'model' model organism

These discussions also emphasized the importance of understanding the ecology of fungi. Primrose Boynton and Anne Pringle (Harvard U.) displayed a welcome taste for serious ecology, using yeasts found in wild pitcher plants and a collection of "charismatic macrofungi". Duccio Cavalieri (U. Florence, Italy) and Fred Dietrich (Duke U., USA) both discussed insect vectors for *Saccharomyces* and *Ashbya* species.

Cavalieri also discussed a novel role for *Saccharomyces* yeast in human disease. This is an unusual niche for this species, as the *Candida* species are more frequently identified as human pathogens and commensals. In fact, studies of *Candida* evolution and ecology were all but absent from the conference, with only one talk on this topic. This talk, however, was a fascinating one; exploring the unique codon usage in the *Candida* clade. The CUG codon encodes serine instead of leucine in these species. Manuel Santos (U. Aveiro, Portugal) returned the transfer RNA to its ancestral state, and the strain remained viable, although with an increase in unusual colony morphology.

In addition to the geneticists tackling ecological and evolutionary questions, and the ecologists and evolutionary biologists bringing genomics into their approaches, there were several discussions centred on genomics, in which advances are being made in functional characterization of genes, proteins and their interactions, which will be beneficial from an ecological and evolutionary perspective.

Baker's yeast has been at the forefront of genomics for decades because it was the first eukaryotic genome to be sequenced and there are powerful molecular and genetic tools available. There is also, perhaps most importantly, a large and vibrant community of researchers working on it. In general, yeasts and their relatives are poised to become the driving force in ecological and evolutionary studies, as we learn more about the ecology and natural history of this 'model' model organism. This, in conjuction with efficient and sensitive genetic and genomic tools, will allow us to apply ourselves to the big, important questions. We look forward to the next conference in the series, at which some significant advances and surprises should be reported.

Maitreya J. Dunham is at the Department of Genome Sciences, University of Washington, Seattle, WA, USA. E-mail: maitreya@uw.edu.
Edward J. Louis is at the Centre for Genetics and Genomics, University of Nottingham, Queen's Medical Centre, Nottingham, UK. E-mail: ed.louis@nottingham.ac.uk

Published online 10 December 2010

EMBO *reports* (2011) **12,** 8–10.
doi:10.1038/embor.2010.204

