The main goal of the IceCube Neutrino Observatory is to observe comparatively scarce neutrinos that are produced during some of the Universe's most violent astrophysical events. However, in its test of Lorentz invariance, the collaboration studied more-abundant neutrinos that are generated when fast-moving charged particles from space collide with atoms in Earth's atmosphere. There are three known types of neutrino: electron, muon and tau. Most of the neutrinos produced in the atmosphere are muon neutrinos.

Atmospheric neutrinos generated around the globe travel freely to the South Pole, but can change type along the way. Such changes stem from the fact that electron, muon and tau neutrinos are not particles in the usual sense. They are actually quantum combinations of three 'real' particles — ν_1, ν_2 and ν_3 — that have tiny but different masses.

In a simple approximation relevant to the IceCube experiment, the birth of a muon neutrino in the atmosphere can be thought of as the simultaneous production of two quantum-mechanical waves: one for ν_2 and one for ν_3 (Fig. 1). These waves are observed as a muon neutrino only because they are in phase, which means the peaks of the two waves are seen at the same time. By contrast, a tau neutrino results from out-of-phase waves, whereby the peak of one wave arrives with the valley of the other.

If neutrinos were massless and Lorentz invariance held exactly, the two waves would simply travel in unison, always maintaining the in-phase muon-neutrino state. However, small differences in the masses of ν_2 and ν_3 or broken Lorentz invariance could cause the waves to travel at slightly different speeds, leading to a gradual shift from the muon-neutrino state to the out-of-phase tau-neutrino state. Such transitions are known as neutrino oscillations and enable the IceCube detector to pick out potential violations of Lorentz invariance. Oscillations resulting from mass differences are expected to be negligible at the neutrino energies considered in the authors' analysis, so the observation of an oscillation would signal a possible breakdown of special relativity.

The IceCube Collaboration is not the first group to seek Lorentz-invariance violation in neutrino oscillations[5–10]. However, two key factors allowed the authors to carry out the most precise search so far. First, atmospheric neutrinos that are produced on the opposite side of Earth to the detector travel a large distance (almost 13,000 km) before being observed, maximizing the probability that a potential oscillation will occur. Second, the large size of the detector allows neutrinos to be observed that have much higher energies than those that can be seen in other experiments.

Such high energies imply that the quantum-mechanical waves have tiny wavelengths, down to less than one-billionth of the width of an atom. The IceCube Collaboration saw no sign of oscillations, and therefore inferred that the peaks of the waves associated with ν_2 and ν_3 are shifted by no more than this distance after travelling the diameter of Earth. Consequently, the speeds of the waves differ by no more than a few parts per 10^{28} — a result that is one of the most precise speed comparisons in history.

The authors' analysis provides support for special relativity and places tight constraints on a number of different classes of Lorentz-invariance violation, many for the first time. Although already impressive, the IceCube experiment has yet to reach its full potential. Because of limited data, the authors restricted their attention to violations that are independent of the direction of neutrino propagation, neglecting possible direction-dependent violations that could arise more generally.

With a greater number of neutrino detections, the experiment, or a larger future version[11], could search for direction-dependent violations. Eventually, similar studies involving more-energetic astrophysical neutrinos propagating over astronomical distances could test the foundations of physics at unprecedented levels. ■

Matthew Mewes *is in the Department of Physics, College of Science and Mathematics, California Polytechnic State University, San Luis Obispo, California 93407, USA.*
e-mail: mmewes@calpoly.edu

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GENOME EDITING

Chromosomes get together

Genome-editing approaches have been used to fuse 16 yeast chromosomes to produce yeast strains with only 1 or 2 chromosomes. Surprisingly, this fusion has little effect on cell fitness. SEE ARTICLE P.331 & LETTER P.392

GIANNI LITI

The genomes of nucleus-bearing organisms are divided into linear chromosomes. The number of chromosomes ranges from one to hundreds across species. But why is there such variation? Do specific chromosome numbers hold an advantage for particular species? Shao *et al.*[1] (page 331) and Luo *et al.*[2] (page 392) independently manipulate the genome of the budding yeast *Saccharomyces cerevisiae* by systematically fusing chromosomes, enabling the researchers to explore the consequences of chromosome-number reduction.

Normal *S. cerevisiae* genomes have 16 distinct chromosomes ($n = 16$), which range from 230 to 1,532 kilobases in length[3]. To function correctly, yeast chromosomes need protective structures called telomeres at both ends, and only one centromere — a region that ensures the accurate segregation of chromosomes into mother and daughter cells during cell division. Simply fusing the ends of two chromosomes is therefore not a viable strategy for reducing chromosome number because it would produce chromosomes containing two centromeres.

To solve this problem, the two groups used genome-editing tools to fuse sequences found adjacent to one of the telomeres in each chromosome, and to simultaneously remove one of the two centromeres (Fig. 1). Using this approach, they reduced the chromosome number step by step, producing strains that had progressively lower values of n. The fusion strains comprised genomic material that is almost identical to that of normal *S. cerevisiae*, differing only in chromosome number and by a few non-essential genes that were deleted during strain creation.

Luo *et al.* produced an $n = 2$ strain containing chromosomes that were each about 6,000 kb long. However, they were unable to fuse the two chromosomes into one as part of a viable cell. By contrast, Shao *et al.* successfully fused the entire *S. cerevisiae* genome into a single chromosome in a functional yeast.

Given that each group used similar strategies, it is interesting to consider why only one of the teams could fuse the final two chromosomes. A possible explanation is that

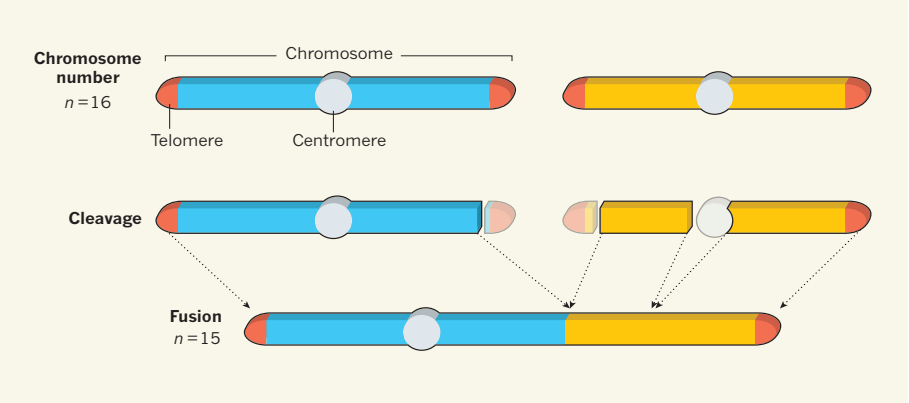

Figure 1 | Fusing chromosomes one by one. Two groups[1,2] have fused all 16 chromosomes ($n = 16$) of the budding yeast *Saccharomyces cerevisiae* to produce strains that have only one[1] or two[2] long chromosomes. In *S. cerevisiae*, each chromosome must have protective structures known as telomeres at both ends, as well as a single structure called a centromere that is essential for normal chromosome segregation during cell division. To generate fused chromosomes with this composition, the groups used genome-editing techniques to cleave sequences found next to one of the telomeres in each chromosome, and simultaneously removed one of the two centromeres (just one cleavage site is sufficient to trigger removal of the entire centromere). They then fused the cleaved portions. By repeating this process, they reduced the chromosome number in a stepwise manner, producing yeast cells that have progressively lower values of n.

the groups fused the yeast chromosomes in different orders and orientations. Perhaps such factors matter, which could mean that only certain final genome structures are attainable. In the future, reducing the chromosome number through a variety of fusion paths might reveal how chromosomal structures affect cell viability. Another possibility is that mutations introduced accidentally during the chromosome-fusion experiments affected cell tolerance to the new genome organization.

Both groups then investigated the biological implications of chromosome fusion. Overall, organismal traits such as cell growth, size and shape seem to be buffered throughout the series of fusions. Notably, the expression of only a few genes was altered considerably in either the $n = 2$ or $n = 1$ strains. Most of the observed increases in gene expression can be explained by there being fewer genes located near telomeres, which promote transcriptional silencing[4].

Such transcriptional stability is in contrast to the widespread transcriptional variation that is seen when yeast undergoes other types of chromosomal modification, such as inversions of particular regions[5]. Shao *et al.* show that this stability reflects the fact that there are only modest changes to the intrachromosomal interactions that usually take place, which can modulate gene expression. However, the interchromosomal-interaction landscape changes drastically, owing to the depletion of centromeres, which drive the 3D configuration of the yeast genome[6].

The yeast strains generated by the groups are haploid — they contain only one copy of each chromosome. Haploid yeast reproduce asexually, but they can also mate through sexual reproduction to form diploid yeast, which contain two copies of each chromosome. Diploid yeast can then divide through a process called meiosis to produce haploid spores that mature into haploid cells. The groups showed that the $n = 1$ and $n = 2$ strains can undergo sexual reproduction, albeit with reduced efficiency compared with wild-type yeast, and produce spores that are slightly less viable.

During meiosis, genetic material is exchanged between paired chromosomes in a process called recombination. Because the genomes of all cells from a given fusion strain are identical, they lack the genetic variability that researchers need to map recombination through the generations. As such, the two groups could not characterize how chromosome reduction affects recombination. The high spore viability of each fusion strain indicates that some recombination might occur, ensuring proper chromosome segregation. However, the greatly reduced chromosome number essentially eliminates any risk of mis-segregation.

Luo *et al.* mated strains that had different chromosome numbers, and then investigated spore viability and production in the resulting hybrid strains, to determine at what point the fusion strain could no longer produce viable spores (a phenomenon called reproductive isolation). As predicted[7], an increasing difference in chromosome number had an increasing effect on spore viability until, in hybrids generated by crossing haploid strains that have $n = 16$ and $n = 8$, none of the spores produced were viable. Moreover, spore production was arrested when the difference in chromosome number became any larger.

This is unexpected, especially given that diploid hybrids that are sterile because of high sequence divergence or differently arranged genomes between their two sets of chromosomes can progress efficiently through meiosis, despite producing inviable spores[7]. The mechanism that underlies the reproductive isolation seen by Luo and colleagues remains to be determined. Future work using synthetic genomes, which can be edited at the single-nucleotide level, will allow the introduction of genetic variants on both local and genome-wide scales, enabling the in-depth, systematic analysis of the factors that prevent species from breeding, as well as the genomic changes that prompt reproductive isolation.

Both studies concluded that reduced chromosome number causes no major growth defects when cells are grown under various conditions and stresses. Small fitness defects were most evident in the $n = 1$ strain, consistent with the fact that this chromosome configuration is challenging to obtain. Although these fitness differences seem mild in a laboratory setting, they could become more harmful in the natural environment. Indeed, Shao and colleagues' $n = 1$ strain was quickly outcompeted by a normal strain of *S. cerevisiae* when the two were cultured together. This is consistent with the idea that the structure of *S. cerevisiae* chromosomes has remained highly stable for several million years[8,9], although reductions in chromosome number through telomere fusion and centromere loss occurred repeatedly over longer evolutionary timescales[10].

The short generation time of *S. cerevisiae* means that, in the future, the evolution of strains that have a reduced chromosome number could be tracked in the lab, in long-term experiments that run for months or years. Such experiments will enable researchers to map adaptive changes that restore fitness in strains that have a reduced number of chromosomes, and to accurately measure genome stability in these yeast.

Beyond the current findings, these engineered yeast strains constitute powerful resources for studying fundamental concepts in chromosome biology, including replication, recombination and segregation. The chromosome-engineering approach might also be applicable to organisms that have more-complex genomes. However, the presence of highly complex DNA sequences in the regions that surround telomeres and centromeres in these organisms will make this a challenging task. ■

Gianni Liti *is at the University of Côte d'Azur, CNRS, INSERM, IRCAN, 06107 Nice, France.*
e-mail: gianni.liti@unice.fr

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