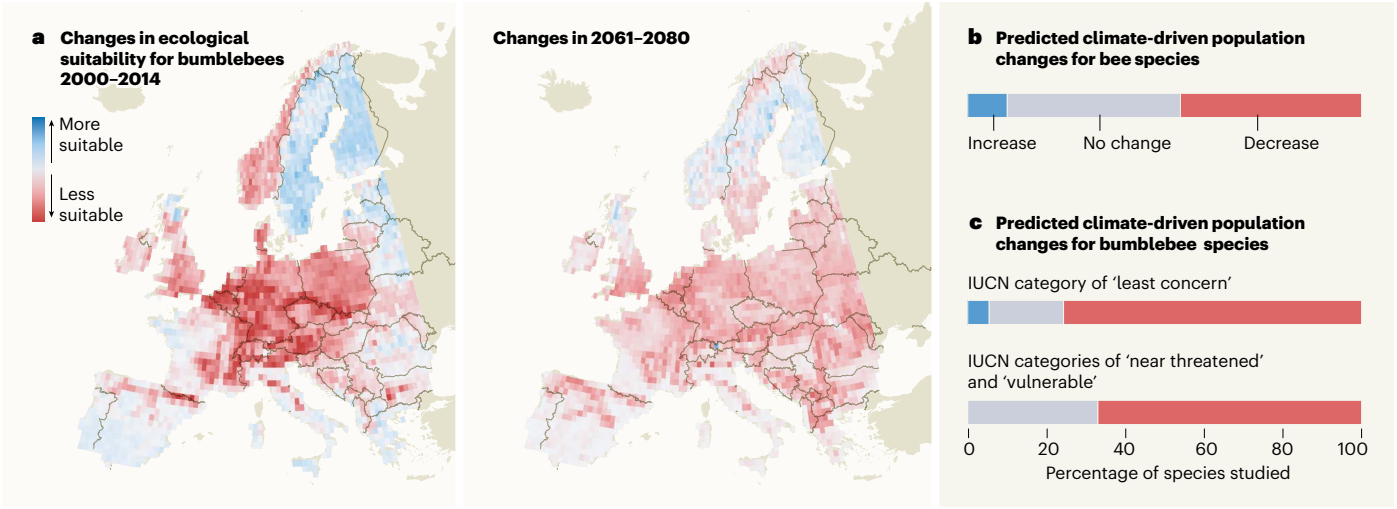

Figure 1 | The effect of climate on insect populations. a, Ghisbain *et al.*[4] assessed the effect of climate on habitat suitability for bumblebee populations in Europe. The data for 2000–2014 indicate that many regions in central Europe are becoming less suitable for bumblebees, with some exhibiting striking reductions in suitability. The geographical range of the inhospitable area is predicted to expand by 2061–2080 under a climate scenario for medium levels of carbon dioxide emissions called socio-economic pathway (SSP) 3, although further changes in suitability in a given population might not be as striking as those of 2000–2014. (Adapted from Fig. 1 of ref. 4.) **b**, Kazenel *et al.*[3] predict the effect on populations of 243 drought-sensitive bee species in the United States of a future climate scenario based on medium levels of greenhouse-gas emissions (representative concentration pathway 4.5). **c**, Ghisbain *et al.* predicted changes for bumblebees in the SSP3 scenario using categories in the classification system of the International Union for the Conservation of Nature (IUCN). The authors examined 37 species in the 'least concern' group and 9 in the 'near threatened' or 'vulnerable' groups.

travel extremely long distances (up to 200 kilometres)[12,13]. However, we currently do not know enough to reliably predict their potential dispersal distances, particularly across varied landscapes. We know even less about the dispersal capabilities of the 98% of bees not analysed in either study, hindering our ability to protect these crucial organisms.

Bees and bumblebees contribute to the production of the world's nutritious, flavourful foods and healthy ecosystems[14–16]. A decline in nearly half of bee species over the next 50 years, as predicted using evidence from these two studies, could be catastrophic to the ecosystem services that these insects provide. Nevertheless, the authors of both papers offer achievable strategies to mitigate losses — landscape redesigns that provide 'stepping stones' to climate refugia, establishing microclimate refugia in areas of stress and adjusting the IUCN status of species at risk of projected climate-induced declines. The response window is, however, closing quickly: widespread local extinctions are projected to occur by 2080.

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Genomics

Mammals repress random DNA that yeast transcribes

Sean R. Eddy

In experiments dubbed the Random Genome Project, researchers have integrated DNA strands with random sequences into yeast and mouse cells to find the default transcriptional state of their genomes. **See p.373**

More of the DNA in the human genome is transcribed into RNAs than scientists can adequately account for. Transcription of around 20,000 known protein-coding genes covers about 40% of the genome, but at least 75% of the genome is transcribed reproducibly at a detectable level[1,2]. A decades-old debate in genomics has failed to resolve how much of the extra RNA transcribed — including thousands of long non-coding RNA sequences — is functional, and how much is 'noise'[3,4]. Central to the disagreement is a lack of clarity about the nature of this transcriptional noise[5]. In 2013, I suggested a 'Random Genome Project' to establish a baseline expectation for the biochemical activity of genomic DNA in the absence of any evolutionary selection for biological functions[6]. Fuelled by rapid advances in synthetic genomics, two studies, one on page 373 (ref. 7) and one in *Nature Structural and Molecular Biology*[8], describe versions of this experiment in yeast (*Saccharomyces*

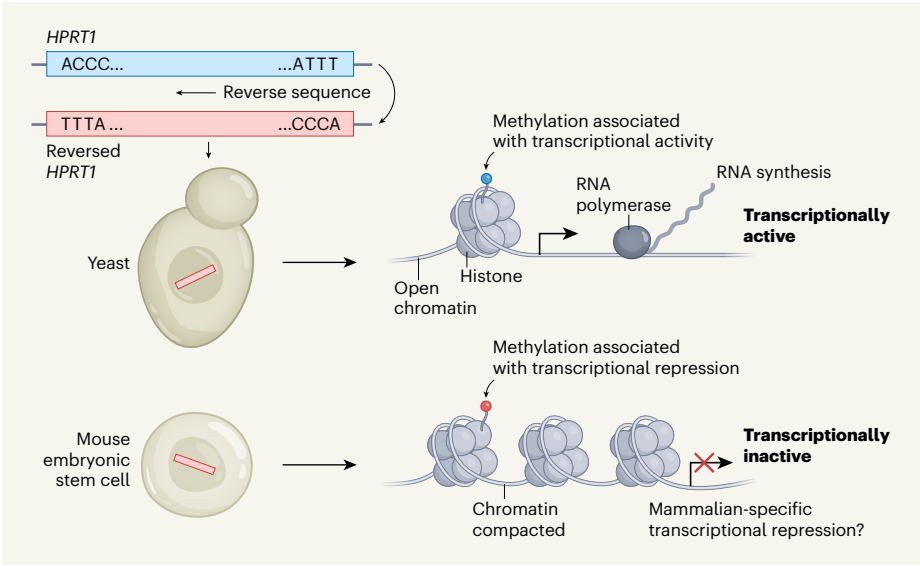

Figure 1 | Transcriptional activity of random DNA sequences integrated into yeast and mouse genomes. In many organisms, more of the genome is transcriptionally active than would be expected if only known genes were transcribed. To find out whether the extra RNA transcribed is just 'noise' or not, Camellato *et al.*[7] and Luthra *et al.*[8] conducted versions of a Random Genome Project to examine the baseline transcriptional activity of large pieces of DNA with effectively random sequences. Camellato *et al.* reversed the sequence of the human *HPRT1* gene and integrated it into the genomes of yeast cells or mouse embryonic stem cells. They then measured signs of transcriptional activity: RNA synthesis and recruitment of the protein (RNA polymerase) that mediates it; the accessibility (open or compacted) of DNA in complex with histone proteins, which together form chromatin; and the methylation state of histones. Both studies found that random DNA was transcriptionally active in yeast, but Camellato *et al.* found that it was almost completely transcriptionally inactive in mouse cells. This suggests that the default state of the mammalian genome is more 'off' than is the case in yeast, possibly because mammals have evolved more mechanisms to repress spurious transcription.

cerevisiae) and in mammalian cells.

A Random Genome Project would involve synthesizing a large swathe of DNA with a statistically random sequence and running the usual high-throughput genomics assays on it. Such experiments were not technically feasible at the time they were first proposed, but are possible today. Using large-scale genome synthesis methods that researchers in their laboratory helped to pioneer, Camellato *et al.*[7] constructed a piece of synthetic DNA that was 101 kilobase pairs in length, made of the reversed, not complementary, sequence of the human *HPRT1* gene. They integrated this reversed-sequence construct into the genomes of yeast and into two sites in the genomes of mouse embryonic stem cells.

To assess transcriptional activity, the authors measured expression of RNA and the accessibility of DNA to transcriptional machinery. They also looked at two marks that signify the addition of methyl groups (methylation) to proteins called histones, around which DNA is packaged as chromatin. These marks, referred to as H3K4me3 and H3K27me3, are associated with transcriptionally active and repressed chromatin states, respectively. The bottom line is that the reversed sequence is extensively transcriptionally active in yeast — but nearly silent in the mouse cells (Fig. 1).

In a related set of experiments, Luthra *et al.*[8] introduced two large pieces of human DNA (760 kb and 811 kb) as yeast artificial chromosomes, on the assumption that humans and yeast are so evolutionarily diverged from each other that human DNA would effectively seem like a random sequence to the yeast transcriptional machinery. As in the study by Camellato *et al.*, Luthra *et al.* find that this 'random' DNA shows extensive transcriptional activity in yeast. To address what happens to random DNA in mammalian cells, they used a state-of-the-art computational deep-learning method for inferring mammalian transcriptional features to predict that synthetic random sequences should also be transcriptionally active in mammalian cells. Luthra and colleagues' computational predictions highlight that the surprise is not that the random sequence is transcriptionally active in yeast, but that Camellato *et al.* find that random sequences are not very active in mammalian cells.

Other studies published in the past few years have seen broadly the same result in yeast using different DNAs that are random, non-biological or not native to yeast (exogenous). The DNAs in these studies included an 18-kb synthetic, uniformly random sequence[9], a 254-kb synthetic DNA that encodes a digital image file as an example of using DNA for data storage[10], and exogenous pieces of DNA such as the whole genomes of the bacteria *Mycoplasma pneumoniae* (around 800 kb) and *Mycoplasma mycoides* (around 1,200 kb)[11]. For all of these sequences, discrete RNA products and signatures of active chromatin are observed in yeast.

Why would mammalian and yeast cells be so different in what they do with the same random DNA? The core transcriptional machinery of yeast and mammals is generally similar. The explanation might instead lie in genome surveillance systems that suppress expression of DNA of foreign origin that has been integrated into the mammalian genome throughout evolution, such as transposons and endogenous viruses. It could also lie in the RNA quality-control systems that suppress spurious RNA transcripts. Compared with yeast, maybe mammalian systems have extra or stronger noise-suppression systems to defend their larger genomes against a larger load of genomic parasites.

For example, Camellato *et al.* observed that the reversed synthetic DNA is marked by H3K27me3 in both integration sites in mouse cells, indicative of transcriptional repression by the Polycomb protein complex — a prime example of a repression system found in mammals but not in yeast. Polycomb recruitment in mammals correlates with the number of sites in which cytosine and guanine bases are found next to each other (the CpG dinucleotide content), which is strongly and distinctively depleted in evolved mammalian genome sequences. But Polycomb-mediated repression turns out not to be the explanation here. Camellato *et al.* tested this possibility by synthesizing and inserting a different reversed sequence from which every CpG dinucleotide had been removed. Bafflingly, although the reversed DNA without CpG no longer showed H3K27me3 enrichment, it remained transcriptionally nearly silent.

Is there another system that could be suppressing expression of RNA from the random sequence in mammalian cells? One good candidate might be the HUSH (human silencing hub) protein complex, which is found in vertebrates but not in yeast[12]. The HUSH complex transcriptionally silences foreign DNA that expresses RNA transcripts without introns (intervening sequences that are removed from the transcript by a process called splicing) as a general innate defence system against RNA-based foreign genetic elements called retrotransposons. The mechanism of HUSH-mediated repression is still not fully understood, but it usually correlates with H3K9 methylation of the repressed foreign DNA. The repressive H3K9 histone mark was not assayed by Camellato *et al.*, but it would be interesting to do this in the future.

What about the big question — do the results of Camellato and colleagues mean that the default state of a mammalian genome is

'off', and therefore that those thousands of observed mammalian long non-coding RNAs should be considered likely to be functional? Unfortunately, the jury remains out on this. The synthetic DNA was 'only' 101 kb long, which is not enough to address the question definitively. Long non-coding RNA genes, by most accounts, occur at a density of around one per 50–100 kb in the human genome[7]. This means that even if the majority of human long non-coding RNAs arise from transcriptional noise, Camellato *et al*. might easily not have observed any random long non-coding RNA genes in their 101-kb random sample.

Furthermore, Camellato and colleagues' analyses focus on fairly abundant transcripts rather than delving down into low-level transcription, which is worth noting because most long non-coding RNA genes are detected at steady-state levels that are about 100-fold lower than those of typical messenger RNAs[4]. Finally, the answers to questions about the cell-type specificity of noise also await experiments in more cell types than mouse embryonic stem cells. We're going to need a bigger Random Genome Project.

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Forum: Metrology

Melting ice delays leap-second problem

Humans' effect on the polar ice sheets is slowing Earth's rotation, posing challenges for its alignment with the official time standard. Two researchers discuss the science behind the slowdown and the impact it has on timekeeping. **See p.333**

The topic in brief

- **Timekeeping is determined by ultraprecise devices called atomic clocks, but it is also aligned with Earth's rotation, mainly for historical reasons.**
- **Because the planet's rate of rotation fluctuates, this alignment is maintained with the occasional addition of 'leap seconds' to the official time standard.**
- **Now, Earth's rotation seems to have accelerated, outpacing the time standard, and raising the possibility that an unprecedented 'negative' leap second might soon be required — a daunting prospect in a world reliant on consistent timekeeping.**
- **Agnew[1] reports that human-induced melting of polar ice exerts a slowing effect on Earth's rotation, effectively delaying a decision on the need for a negative leap second.**

Patrizia Tavella
International timekeeping

In 1967, the internationally accepted definition of the second changed. The time measurement standard had been linked to Earth's rotation, but instead became determined by a quantum transition between two states of a caesium atom. The change was motivated by accuracy: caesium atomic clocks keep time on the basis of the ultrastable frequency of the photons exchanged in the quantum transition. This seemed like a safer bet than Earth's movements, which weren't as regular as was first assumed.

But sailors still relied on the Sun and stars to navigate, and they wanted a time standard that remained tied in some way to Earth's rotation. It was therefore decided that the new international reference, known as coordinated universal time (UTC), would be set by atomic clocks, but kept apace with the rotational angle of Earth, which is known as universal time (UT1). Since 1972, UTC has been adjusted to meet this goal by adding a leap second whenever the discrepancy between the two standards approaches one second.

Atomic clocks have enabled the development of great technologies, such as satellite navigation and, in an age of the global navigation satellite system (GNSS), celestial navigation is much less relevant than it was in 1972. GNSS satellites themselves have onboard atomic clocks that regulate their timekeeping, and the insertion of a leap second generates risk of failures. Perhaps more importantly, the addition of leap seconds can have drastic effects on computer infrastructure in the increasingly connected modern world (see go.nature.com/44y88yp).

For these reasons, after more than 20 years of discussion, metrologists proposed that UTC be kept in line with Earth's rotation, but that the tolerance for adding an adjustment be increased to a value larger than one second[2]. This proposal, which delays the need to make any adjustment for at least another century, was adopted by the General Conference on Weights and Measures (CGPM) in 2022.

The CGPM resolution stipulates that the maximum difference between the two times (denoted UT1 − UTC) will be increased in or before 2035, and that the details of the new maximum and how it is to be implemented will be decided at the next CGPM meeting in 2026 (see go.nature.com/3vqddy2). Most delegates urge a quick implementation of the new rules, although others ask for more time to adapt their systems. The radiocommunication sector of the International Telecommunication Union — the organization that regulates the transmission of time signals — endorsed the CGPM decisions at the World Radiocommunication Conference in 2023.

UTC is currently computed using data from about 450 atomic clocks, which are maintained in more than 80 institutions around the world. It is disseminated in real time by these time laboratories, by means such as radio or telephone signals, the Internet or optical fibre protocols, and also through GNSS signals. Since 1972, irregularities in Earth's movement have called for 27 leap seconds to be added — at irregular intervals and with a maximum of only 6 months' notice each time. The irony is that metrologists now face the challenge of removing a leap second from UTC for the first time, because Earth's rotation is gradually getting faster than the time standard set by atomic clocks (Fig. 1).