likely to be responsible for the bump than is graphite, because increased graphite grain size should shift the bump to longer wavelengths. However, the bump would then be broader than that observed by Witstok and colleagues. That said, mixtures of PAHs of different sizes and structures could produce a bump with a range of peak wavelengths and widths[5].

The metallicity of JADES-GS-z6-0 (the abundance of elements heavier than helium) is only 0.2–0.3 times that of the Sun[3], which would seem to contradict the general idea that PAHs are deficient in low-metallicity galaxies[7]. Indeed, the local galaxy known as the Small Magellanic Cloud has a low metallicity, similar to that of JADES-GS-z6-0, and essentially no extinction bump, as well as weak PAH emission[15]. The detection of an extinction bump in other low-metallicity galaxies would therefore provide crucial insight into how the bump is related to PAHs and to metallicity. Indeed, close positive correlations have been found between the bump, PAH emission light and stellar mass (which is indicative of metallicity) for 86 galaxies that were observed at the cosmic noon — a time about 3 billion years after the Big Bang, when star and galaxy formation were at their peak[16].

One way to examine whether PAHs are indeed present in JADES-GS-z6-0 is to search for their thermal-emission signatures at wavelengths of 3.3, 6.2, 7.7, 8.6, 11.3 and 12.7 μm (ref. 7). The expansion of the Universe stretches the wavelength of the light emitted by JADES-GS-z6-0, so the 3.3 μm band (which is stretched out to 25.5 μm) is the only one accessible to JWST. Detecting this band in JADES-GS-z6-0 would help scientists to determine the rate of star formation for young galaxies at a time when the Universe was in its infancy. Searching for signatures of PAHs in other galaxies will help astronomers to chart a timeline of cosmic star-formation history[17] — to which Witstok and colleagues have just made an important contribution.

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1. Draine, B. T. in *Cosmic Dust — Near and Far* (eds Henning, T., Grün, E. & Steinacker, J.) **414**, 453–472 (Astron. Soc. Pacific Conf. Ser., 2009).
2. Salim, S. & Narayanan, D. *Annu. Rev. Astron. Astrophys.* **58**, 529–575 (2020).
3. Witstok, J. *et al. Nature* **621**, 267–270 (2023).
4. Stecher, T. P. *Astrophys. J.* **142**, 1683–1684 (1965).
5. Lin, Q., Yang, X. J. & Li, A. *Mon. Not. R. Astron. Soc.* **525**, 2380–2387 (2023).
6. Nittler, L. R. & Ciesla, F. *Annu. Rev. Astron. Astrophys.* **54**, 53–93 (2016).
7. Li, A. *Nature Astron.* **4**, 339–351 (2020).
8. Ma, X.-Y., Zhu, Y.-Y., Yan, Q.-B., You, J.-Y. & Su, G. *Mon. Not. R. Astron. Soc.* **497**, 2190–2200 (2020).
9. Draine, B. T. & Malhotra, S. *Astrophys. J.* **414**, 632–645 (1993).
10. Jones, A. P., Tielens, A. G. G. M. & Hollenbach, D. J. *Astrophys. J.* **469**, 740–764 (1996).
11. Todini, P. & Ferrara, A. *Mon. Not. R. Astron. Soc.* **325**, 726–736 (2001).
12. Scott, A., Duley, W. W. & Pinho, G. P. *Astrophys. J.* **489**, L193–L195 (1997).
13. Spilker, J. S. *et al. Nature* **618**, 708–711 (2023).
14. Wang, Q., Yang, X. J. & Li, A. *Mon. Not. R. Astron. Soc.* **525**, 983–993 (2023).
15. Sandstrom, K. M. *et al. Astrophys. J.* **715**, 701–723 (2010).
16. Shivaei, I. *et al. Mon. Not. R. Astron. Soc.* **514**, 1886–1894 (2022).
17. Xie, Y. & Ho, L. C. *Astrophys. J.* **884**, 136 (2019).

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Biotechnology

A tool for optimizing messenger RNA sequence

Anna K. Blakney

With messenger RNA therapeutics being developed for uses beyond vaccines, problems of RNA instability must be addressed. A new algorithm optimizes mRNA sequence for both stability and the encoding of amino acids. **See p.396**

The SARS-CoV-2 pandemic greatly accelerated the development of messenger RNA technology by demonstrating the safety, effectiveness and scalability of mRNA-based vaccines[1]. On page 396, Zhang *et al.*[2] describe a tool that provides researchers with new ways to design mRNA sequences.

Messenger RNA is now used for various applications beyond vaccines for infectious diseases; these include treatments such as antibody therapy, cell therapies and personalized vaccines to boost immune responses to cancer. However, many challenges remain, including overcoming the low efficiency of mRNA-delivery systems and the need to modulate the immune response that the host generates as a result of this foreign RNA (immunogenicity).

RNA instability is the main hurdle to the development of mRNA medicines. For mRNA to be effective therapeutically, it must reach the cytoplasm of a target cell and persist there for long enough to express sufficient protein before being degraded. The sequence of the RNA affects its stability and the amount of protein expressed[3], but the specific features of RNA that govern these characteristics are poorly understood.

RNA stability must also be addressed in the context of the global distribution of vaccines. RNA is less stable at higher temperatures, necessitating its storage in freezers. Improving the stability of RNA might reduce its degradation during transport and storage.

One aspect that makes optimizing RNA sequences particularly difficult is the sheer number of potential sequence variations, which makes it impossible to test them all experimentally. For example, there are approximately 10^{632} possibilities in terms of RNA sequences that can encode the spike protein of SARS-CoV-2, which is the target of mRNA COVID-19 vaccines.

Zhang and colleagues introduce a powerful algorithm called LinearDesign that can

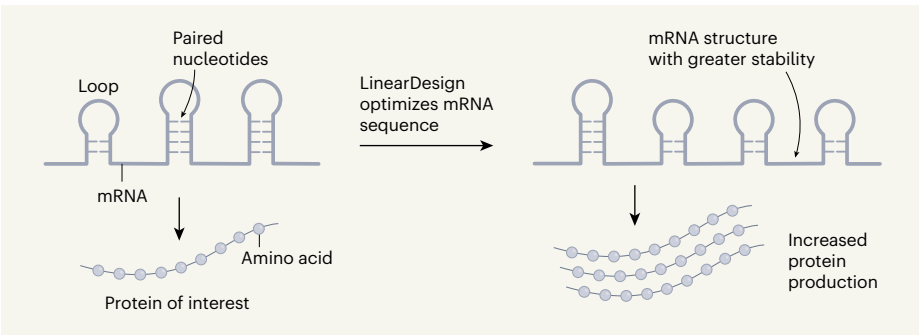

Figure 1 | An algorithm that aids the design of messenger RNA sequences. In most cases, various nucleotide sequences can encode a given amino acid. A protein can therefore be encoded by many possible mRNA sequences. These sequences can differ in their stability (which is affected by RNA structural elements such as loops that arise from nucleotide pairing) and the amount of protein that is made from the mRNA. Zhang *et al.*[2] present a tool for mRNA design called LinearDesign that can optimize mRNA selection. Having a stable sequence can help to limit mRNA loss through degradation.

simultaneously optimize mRNA in terms of the sequences chosen to encode amino acids (codon usage) and RNA stability (Fig. 1). Each of a protein's amino-acid residues is encoded by three consecutive nucleotides in RNA, termed a codon. For most amino acids, there are multiple possible options for the codons used. Some of these codons are preferred by cells over the alternatives, resulting in higher protein expression from sequences with some codons than from sequences with others. Stability is related directly to the specific 3D loops and 'hairpins' in each RNA molecule (termed its secondary structure), and these characteristics are governed by well-studied aspects of thermodynamic folding.

There are many open-access tools for optimizing codon usage and the thermodynamic stability of RNA, and many companies have developed their own proprietary approaches. However, until now, no single tool could take both aspects of RNA design into account. Optimizing mRNA for codon usage and stability using the conventional enumeration method is computationally unfeasible — the authors estimate that it would take some 10^{616} billion years to optimize RNA for the 1,273 amino-acid residues found in the SARS-CoV-2 spike protein. By contrast, Zhang *et al.* describe an algorithm that takes just 11 minutes to design the predicted most-stable mRNA that encodes the spike protein.

Zhang and colleagues base their algorithm on a previously developed method for finding the most grammatically correct sentence among many similar-sounding options, called lattice parsing. The authors prepared their 'design space' by compactly representing mRNA candidates in a way that scales exponentially and represents all the potential codons. They then took a lattice-parsing approach to find the most stable RNA in this design space. Each design is optimized for what are called the minimum free-energy change (MFE) and the codon adaptation index (CAI); the lower the MFE and CAI, the more stable the RNA will be, theoretically, and the greater the amount of protein it will produce.

Crucially, the relationship between the mRNA and the results scales (quadratically) with the length of the mRNA, making it feasible to optimize sequences for most real-world applications that might require long mRNA. For example, it is relevant for the nucleotide-editing tool CRISPR–Cas or for work on a type of mRNA called a self-amplifying RNA. Notably, the optimal design for the spike protein generated by this algorithm contains mostly a double-stranded secondary structure. This is in contrast to the mainly single-stranded structure for natural (wild-type) spike-protein RNA, and means that the double-stranded structure would confer greater stability on the designed RNA.

How does Zhang and colleagues' optimized sequence compare with the state-of-the-art sequences used in the mRNA COVID-19 vaccines? The authors compared the chemical stability of their mRNA designs with that of the Pfizer–BioNTech COVID-19 mRNA vaccine. The degradation rate of the authors' mRNA correlated well with the MFE, and designs with lower MFEs were more resistant to degradation when in solution than were designs with higher MFEs.

Given that the quantity of antigen (mRNA-encoded protein fragments recognized by immune cells) expressed as a result of vaccination will affect the immune response, the authors tested the relative levels of protein expression with their optimized designs. The optimized low-MFE designs resulted in approximately two- to threefold higher protein expression than the non-optimized benchmark sequence. When comparing vaccine effects in a mouse vaccination model, Zhang and colleagues found that two of their optimized sequences resulted in higher levels of anti-spike antibodies than did either the benchmark sequence or the Pfizer–BioNTech vaccine. The authors speculate that this is because their designed mRNA molecules are more stable *in vivo* than are the other mRNAs, resulting in enhanced protein expression and immunogenicity.

Is LinearDesign suitable for use in developing mRNA vaccines beyond those for COVID-19? The authors also designed sequences for a varicella zoster virus mRNA vaccine, and compared them with a sequence generated by GeneOptimizer, a codon-optimization tool developed by the biotechnology firm ThermoFisher. Again, the authors found that their optimized sequences had slower degradation rates and higher protein expression and immunogenicity than did the sequence generated by GeneOptimizer. The best designs had a combination of favourable MFE and CAI values, highlighting the importance of optimizing both codon usage and stability.

Zhang and colleagues' work introduces a powerful new tool. However, the authors focused on optimizing the protein-coding sequences, and did not include design of the section of mRNA called the untranslated region (UTR) in the algorithm — the UTR is essential for regulation of protein production from mRNA (translation)[4]. The algorithm is effective for mRNA vaccines tested in animal models, but its effectiveness is yet to be confirmed in the clinic, a crucial step.

Moreover, the activity of the innate branch of the immune system of mice in response to foreign RNA is muted relative to that of humans[5], and so results from mice might not be recapitulated in humans. The higher proportion of double-stranded RNA in the optimized designs is known to be more effective in generating an immune response against foreign RNA[6]. Also, the model does not take

From the archive

Concerns about the balance between the number of PhD and MSc students, and making art that will stand the test of time.

50 years ago

The provision of 7,000 new postgraduate places in universities ... could be overgenerous unless the emphasis in research degrees is changed from PhDs to MScs, according to Professor B. A. Cross ... At a symposium on the future of the postgraduate in the next decade ... Professor Cross ... attacked the rapid growth of PhD student numbers, and accused the universities of "acquiescing to academic inflation". As a result the value of the PhD is being undermined ... he said. Departments tend to acquire large numbers of PhD students as a status symbol ... Supervisors are also reluctant to give adverse reports on their students, even to the extent that they will help out with experiments and write the student's thesis. PhD students, Professor Cross said, "use a lot of time, resources, energies and spiritual reserves of the academic staff who can usually be more creative working with collaborators and postdoctoral fellows." The answer ... according to Professor Cross, is to develop a binary system of postgraduate education in which more students take MSc courses which allow the student to acquire new techniques and to make a disciplined attack on a problem.

From *Nature* 14 September 1973

100 years ago

How to Paint Permanent Pictures. By Prof. M. Toch — The reviewer has often wondered, when looking at paintings of great merit which are gradually fading away or cracking in pieces, why artists do not spend a little time in learning something about their materials ... It would seem desirable, therefore, to direct attention to this small book by Dr. Toch, which deals with the properties of pigments simply yet scientifically, and should be valuable to all who paint pictures. In it are described those colours which are permanent and those which may be expected to fade away more or less completely with lapse of time.

From *Nature* 15 September 1923

into account modified versions of nucleotides, which can be crucial for the effectiveness of mRNA vaccines[7,8]. Nevertheless, Zhang and colleagues' approach for the optimization of mRNA sequences should boost the chances of developing improved RNA molecules.

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1. Rubin, E. J. & Longo, D. L. *N. Engl. J. Med.* **386**, 183–185 (2022).
2. Zhang, H. *et al. Nature* **621**, 396–403 (2023).
3. Leppek, K. *et al. Nature Commun.* **13**, 1536 (2022).
4. Leppek, K., Das, R. & Barna, M. *Nature Rev. Mol. Cell Biol.* **19**, 158–174 (2018).
5. Tahtinen, S. *et al. Nature Immunol.* **23**, 532–542 (2022).
6. Baiersdörfer, M. *et al. Mol. Ther. Nucleic Acids* **15**, 26–35 (2019).
7. Karikó, K. *et al. Mol. Ther.* **16**, 1833–1840 (2008).
8. Kremsner, P. G. *et al. Wien. Klin. Wochenschr.* **133**, 931–941 (2021).

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Ecology

Rethinking the effect of marine heatwaves on fish

Mark R. Payne

Marine heatwaves are on the rise. A surprising result from the analysis of data for fish populations in Europe and North America could change ways of thinking about the ecological consequences of such events. **See p.324**

The British biologist Thomas Huxley observed that the great tragedy of science is the slaying of a beautiful hypothesis by an ugly fact[1]. Such inconvenient truths are, however, crucial for the advancement of knowledge, and they force a reassessment of what has been taken for granted. On page 324, Fredston *et al.*[2] report a result that will cause a rethink about how marine heatwaves, periods of unusually warm temperatures in the ocean[3], affect fish communities. Contrary to the authors' expectations and to existing research, Fredston and colleagues were unable to detect an effect of these events at the ecosystem level. This unexpected negative result changes our understanding of how these heatwaves affect marine ecosystems and raises many questions.

Although most people have an understanding of heatwaves on land, fewer people are used to thinking about them in the ocean. Analogous to terrestrial heatwaves, marine heatwaves are discrete periods of sustained extreme temperatures[3]. Fredston and colleagues defined a marine heatwave as five or more consecutive days during which the temperature is in the uppermost 5% of historical temperatures — that is, those in the 95th percentile.

For organisms that live in the ocean, marine heatwaves can be every bit as disruptive as the consequences of a cyclone, earthquake or flood on land. For example, between 2014 and 2016, a high-profile heatwave known as The Blob was associated with extreme temperatures across much of the northeast Pacific Ocean. This led to species being found hundreds and even thousands of kilometres outside their typical range, outbreaks of harmful algal blooms, mass die-offs of sea birds and breeding failures in marine mammals[4]. In other areas, heatwaves have driven loss of algae in coral reefs (coral-reef bleaching)[5] and die-offs of aquatic kelp forests[6]. Socio-economic consequences have also been documented for many marine heatwaves[7].

Given the lengthy and ever-growing list of effects, it would be natural to assume that heatwaves are a dominant driver of change in marine ecosystems. Fredston *et al.* set out to test this hypothesis systematically by analysing a compilation of scientific field-survey results used to monitor bottom-dwelling (demersal) marine fish communities from around Europe and North America. The authors' analyses compared changes in biomass, abundance and biodiversity in the presence and absence of heatwaves from year to year, looking for a common effect across ecosystems. Yet surprisingly, they found no systematic effect across heatwaves for any of the tests that they performed (Fig. 1).

To give their analyses context, the authors performed a 'power analysis', which gave them a way to assess how strong an effect, if any, could be detected using the data sets and methods available. Fredston and colleagues estimated that they had sufficient data to detect an effect of marine heatwaves on ecosystem biomass if the biomass change was on a scale of 8–9% or greater. Their results imply, therefore, that the effect of marine heatwaves at the ecosystem level is relatively small in magnitude, and certainly on a scale that is lower than the combination of natural and sampling variability in their data.

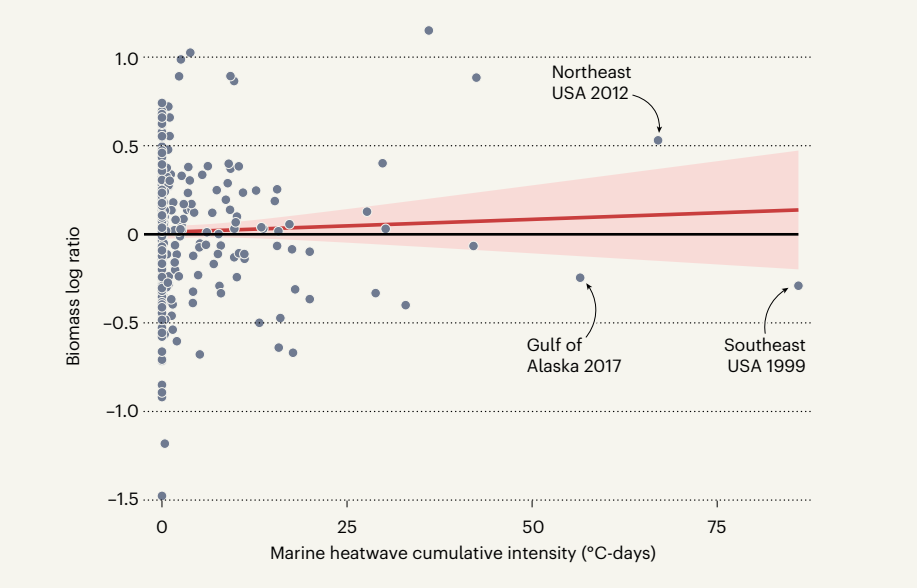

Figure 1 | Evidence that marine heatwaves have no effect on ecosystem biomass. Fredston *et al.*[2] examined data for fish populations to determine the effect of marine heatwaves. The change in ecosystem biomass between years (expressed as the logarithm of the biomass ratio from one year to the next) was assessed, as was the intensity of any marine heatwaves (tracked using a high-temperature metric called cumulative intensity that is measured in units called °C-days) experienced during the same time. No significant relationship was found between biomass and heatwaves (the red line indicates the average effect and the 95% confidence interval is shown in pink). Some notable marine heatwaves are indicated. (Adapted from Fig. 2a of ref. 2.)