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.

Anna K. Blakney is in the Michael Smith Laboratories and at the School of Biomedical Engineering, University of British Columbia, Vancouver, British Columbia V6T 1Z4, Canada.
e-mail: anna.blakney@msl.ubc.ca

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).

The author declares no competing interests.
This article was published online on 30 May 2023.

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.

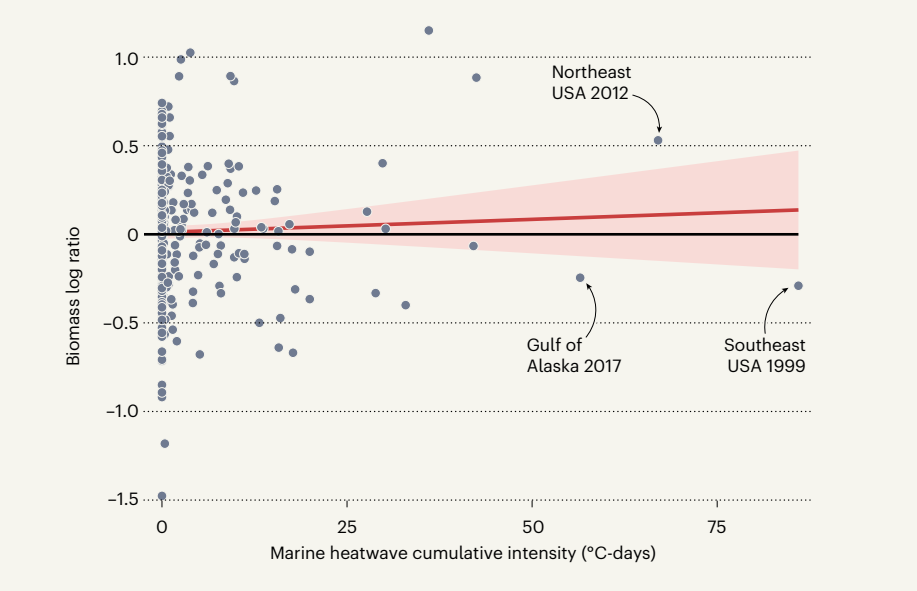

Figure 1 | Evidence that marine heatwaves have no effect on ecosystem biomass. Fredston *et al.*[2] examined data for fish populations to determine the effect of marine heatwaves. The change in ecosystem biomass between years (expressed as the logarithm of the biomass ratio from one year to the next) 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.)

Taken in isolation, it would be tempting to conclude that this paper dismisses the idea that marine heatwaves are an ecologically important phenomenon. That would be a mistake. Fredston and colleagues' results do not negate the hundreds of papers that have documented ecological consequences of such heatwaves. But how can this negative result be reconciled with almost everything published previously in this realm?

Previous work on the effect of marine heatwaves has focused mainly on the most visible responses. Organisms that suddenly appear thousands of kilometres away from their home range, and mass die-offs of fish and seabirds, are eye-catching and garner much attention from scientists and the public. There might, therefore, be a bias in scientific research towards examining these extreme events that are not representative of more general processes. Fredston and colleagues' analysis circumvents this problem by looking for effects in an ecosystem-level data set that comprises many heatwaves, and the authors therefore gain a different perspective.

The authors' analysis might be criticized for being too broad and generic. For example, the implicit assumption of a common response to marine heatwaves across all ecosystems might not be valid (and is certainly not supported by the evidence available). How individual ecosystems respond to these heatwaves will reflect the unique grouping of the species present and their ability to tolerate extreme temperatures. Ecosystems comprising different species might give different responses to the same heatwave conditions.

The authors also tested for the effect of heatwaves at the individual ecosystem level (thereby relaxing the assumption of a common response), but did not find any statistically significant effects. However, it is worth noting that the amount of data available to make such tests is substantially reduced compared with the analysis across many ecosystems, and the statistical power of the analysis is therefore lower – strong signals might still be there but hidden in the 'noise' of individual ecosystems.

Furthermore, this work focuses solely on fish species that are caught on or close to the bottom of continental shelves (sites located near land and less than 500 metres deep). The effects of heatwaves have been reported for many other groups of organisms, including coral reefs, kelp forests, surface-dwelling (pelagic) fish, marine mammals, seabirds and species that dwell in the sea bed (benthic species)[6]. The sensitivity of each of these groups to marine heatwaves might differ from that of bottom-dwelling fish, reflecting their differing abilities to tolerate (and potentially adapt to) extreme temperatures.

Fredston and colleagues' work reshapes our understanding of how marine systems are affected by heatwaves. Although heatwaves clearly have striking effects in some individual cases, the authors find no evidence for large systematic effects at the community-level for bottom-dwelling fish. Future work needs to address the processes that drive striking effects for some species, but not for others – particularly given that marine heatwaves are becoming more common in a changing climate[8]. As ever in science, the downfall of one hypothesis will give rise to many more questions to answer.

Mark R. Payne is in the National Center for Climate Research at the Danish Meterological Institute, 2100 Copenhagen, Denmark.
e-mail: mapa@dmi.dk

1. *Nature* **2**, 399–406 (1870).
2. Fredston, A. L. *et al. Nature* **621**, 324–329 (2023).
3. Hobday, A. J. *et al. Prog. Oceanogr.* **141**, 227–238 (2016).
4. Cavole, L. M. *et al. Oceanography* **29**, 273–285 (2016).
5. Hughes, T. P. *et al. Nature* **543**, 373–377 (2017).
6. Smale, D. A. *et al. Nature Clim. Change* **9**, 306–312 (2019).
7. Mills, K. E. *et al. Oceanography* **26**, 191–195 (2013).
8. Frölicher, T. L., Fischer, E. M. & Gruber, N. *Nature* **560**, 360–364 (2018).

The author declares no competing interests.
This article was published online on 30 August 2023.

Medical research

Calligraphy clues to pancreatic cancer origins

Filip Bednar & Marina Pasca di Magliano

Understanding the processes that lead to tumour formation in the pancreas might help in efforts to develop therapies. A new bioinformatics tool called Calligraphy analyses cell–cell signalling to provide fresh insights into how tumours arise.

The process by which normal cells transform into cancer remains unclear. Writing in *Science*, Burdziak *et al.*[1] solve a piece of the puzzle for how such a transformation occurs during the onset of pancreatic cancer.

The pancreas is a complex organ that serves two main functions, each associated with a specific cellular compartment. One – the endocrine pancreas – is formed by structures called the islets of Langerhans, and helps the body to regulate glucose. The other compartment, the exocrine pancreas, includes acinar and ductal cells (which are both a type of epithelial cell), that, respectively, produce digestive enzymes and line the tissue that transports these enzymes to the digestive tract.

The most common form of pancreatic cancer – pancreatic ductal adenocarcinoma – originates from the exocrine pancreas. Pancreatic cancer is a deadly malignancy that bears distinct genetic alterations, most commonly those resulting in cancer-promoting versions of the gene *KRAS* (called oncogenic mutations)[2].

On the basis of this knowledge, genetically engineered mouse models have been designed to express oncogenic *KRAS* in the epithelial cells of the pancreas[3]. Although most of these animal models express oncogenic versions of *KRAS* throughout the pancreas, they only sporadically develop premalignant lesions – known as pancreatic intraepithelial neoplasia (PanIN) – that are composed of altered epithelial cells. The induction of pancreatic inflammation, called pancreatitis, joins forces with oncogenic *KRAS* to drive widespread PanIN[4,5].

Burdziak and colleagues used a combination of biological and computational approaches to understand how early lesions form in the normal pancreas. Furthermore, the authors set the stage to interrogate the progression from early lesions to signs of overt malignancy.

Mouse models of PanIN formation have been described for more than 20 years[6]. However, the advent of technologies for single-cell analysis has enabled researchers to re-examine the process through which normal epithelial cells of the pancreas become malignant. The conventional progression model, colloquially described as PanINgram[7], is based on evaluation of the lesions using histology and genetic-characterization approaches. It also relies on determining whether differentiated acinar or ductal cells of the pancreas revert from their differentiated state to form a duct-like progenitor cell in a process known as acinar-ductal metaplasia (ADM). (Acinar origin is prevalent in mice.) Over time, ADM gives rise to PanIN and, after genetic events such as the loss of tumour-suppressor genes, to cancer[8].

In the absence of oncogenic *KRAS*, ADM occurs after injury (Fig. 1) and is a transient and necessary part of the repair response. Detailed single-cell analysis of inflammatory injury has revealed multiple transient cell