that sequence, including at least one such sequence for every protein. For some proteins, the most effective mismatch occurred in the natural target sequence, making the protein bind to that sequence even more tightly. For others, the most effective mismatch occurred in a non-target sequence, and made the protein bind to that sequence at levels comparable to those of the natural target. In both cases, the same mechanism is predominant: the mismatch pays the energetic cost of distorting the DNA so that the protein doesn't have to.

Note that to actually improve binding, the mismatch must distort the DNA in the same way as the protein would through the shape-readout mechanism. Distorting the DNA in a different way would weaken binding. The mismatch also should not interfere with any chemical contacts between the protein and the DNA — although the authors did find that mismatches can sometimes introduce favourable contacts.

Afek and colleagues' work broadens our understanding of how proteins bind to DNA, and highlights the importance of the DNA conformational ensemble in this process. In future, perhaps nucleotides that do not occur in nature[4] could be used in SaMBA to thoroughly probe the array of conformations that DNA can adopt, similarly to the way in which unnatural amino acids have been used to investigate subtle changes in protein biophysics[5]. SaMBA could also potentially be adapted to find DNA-binding proteins that are intended to bind to mismatched or chemically modified targets; such proteins would be hard to find by other means. Given that roughly one-third of transcription factors (a key class of DNA-binding protein that regulates gene expression) have no known target sequences in humans[6], this could be a productive line of enquiry.

More broadly, the finding that mismatches often improve binding might have implications for diseases such as cancer. Even a transient mismatch in the genome could prompt a transcription factor to bind in the wrong place, where it could potentially misregulate a gene and put the cell in a cancerous transcriptional state that persists even after the mismatch is repaired. Given its temporary root cause, this idea would be difficult to study or confirm. But the clear propensity for mismatches to improve binding makes such a mechanism worth contemplating.

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Atmospheric science

Hurricanes last longer on land in a warming world

Dan Chavas & Jie Chen

Tropical cyclones weaken after they reach land. But it emerges that for the North Atlantic basin, storms are weakening more slowly as regional sea surface temperatures increase. **See p.230**

Tropical cyclones can cause substantial damage and death when they reach land, as a result of wind, storm surges and rainfall. It is known that tropical-cyclone intensity (measured by maximum wind speed) typically decreases rapidly after the storm reaches land[1]. However, existing models do not take into account whether and how this rate of storm decay after landfall depends on climate[1,2]. On page 230, Li and Chakraborty[3] report that the rate at which tropical cyclones from the North Atlantic decay after landfall has changed since the 1960s — their intensity has been decreasing more slowly over time. This shift is mainly due to warming sea surface temperatures. The authors' work adds weight to growing concerns[4] that tropical cyclones might become more damaging in the future.

Li and Chakraborty analysed historical intensity data for storms that made landfall over North America between 1967 and 2018. They used the decrease in storm intensity over the 24 hours after landfall to define a timescale of decay for each storm. They then examined trends in this timescale.

The authors found a significant long-term shift towards slower decay (so storms maintain a higher intensity on land for longer). Furthermore, this trend aligned with long-term increases in regional mean sea surface temperature over the Gulf of Mexico and the western Caribbean, which are adjacent to land and supply the moisture for the storms before landfall. The changing timescales of decay also correlate well with year-to-year variations in mean sea surface temperature (Fig. 1).

Li and Chakraborty next asked whether other factors could also contribute to the change in the timescale of decay. They found that a portion of the long-term trend could be attributed to an eastward shift in landfall location. By contrast, other factors — including the speed of storm movement at landfall and intensity at the time of landfall — were not important.

The authors bolstered their empirical findings by performing hurricane-landfall experiments using a simple, state-of-the-art atmospheric model. For a range of temperatures, they allowed a mature tropical cyclone to form over a water surface that had a fixed temperature. When each storm reached a fixed maximum wind speed, they mimicked

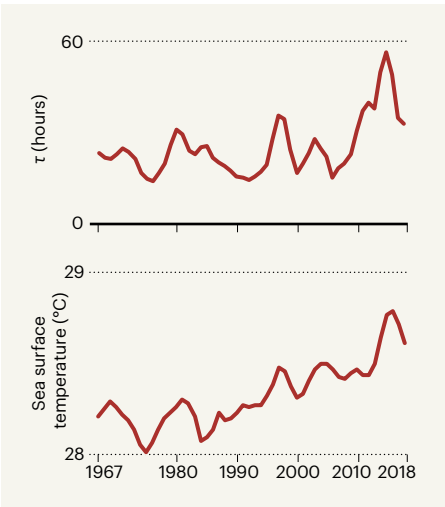

Figure 1 | Changes in the behaviour of tropical cyclones on land. Tropical cyclones become rapidly less intense once they reach land. Li and Chakraborty[3] examined how climate change might have affected the rate at which this decay occurred for storms that reached North America from the North Atlantic Ocean between 1967 and 2018. In the top graph, τ characterizes the rate of decay in hours — a bigger τ indicates a slower decay (a storm that is stronger for longer). The authors find that, since 1967, increases in τ have correlated with increases in the mean sea surface temperature of the adjacent ocean. Thus, storms are likely to persist for longer — and potentially do more damage — in a warmer future world. (Adapted from ref. 3.)

landfall by instantaneously changing the surface beneath the storm from wet to dry. Under this model, the timescale of decay again increases with temperature.

The researchers then sought a physical explanation for why warming causes slower decay. The primary energy source for a tropical cyclone is the evaporation of water from the surface beneath the eyewall[5] (the band of cloud that surrounds the eye of the storm), which is rapidly cut off at landfall. But residual moisture in the storm provides a smaller, temporary, secondary source of energy[6]. The levels of this residual moisture are expected to increase with temperature on the basis of the laws of thermodynamics for moist air.

The authors tested the hypothesis that increased levels of residual moisture could cause slower decay using a second set of modelling experiments in which, in addition to drying the surface to mimic landfall, they removed all residual moisture in the atmosphere. These storms all showed identical timescales of decay, despite their different temperatures. Thus, it is the increased residual store of atmospheric moisture at warmer temperatures that slows the weakening of the storm.

A key outstanding question is the exact degree to which the decay rate depends on temperature. Although the empirical and modelling results are in qualitative agreement, temperature had a smaller effect on decay rate in the simulations than was estimated empirically. This difference might be due to the small size of the historical data set or to confounding factors in it. For example, there have been changes in the spatial distribution of landfall locations over time, and hence differences in the surface properties felt by the storms on land, such as surface moisture and roughness.

In addition, it is unclear whether the long-term trends seen in the historical data set might be affected by ongoing changes in the technologies with which researchers observe storms or in methods for estimating maximum storm wind speed over land. Information about these uncertainties is not readily available publicly, but an in-depth investigation of estimation practices would be worthwhile.

Analysis of historical data along coastal regions in other parts of the world, along with simulations over a broader range of temperatures and climates, could help to further test the robustness of the authors' findings for predicting future changes in decay rates. The effects of residual storm moisture also warrant further investigation to clarify how this effect can slow decay after landfall.

Li and Chakraborty's work highlights a key component of risk models that has been largely overlooked so far. Slower storm decay after landfall in the future would directly result in increases in total damage, and this would be exacerbated by increases in peak wind speed and total rainfall, both of which are expected to occur in a warming climate[7]. The extent of damage occurring inland depends on both the rate of storm decay and the speed of storm motion at landfall. Hence, a slower decay could also lead to increases in damage farther inland, although changes in the speed of motion remain a point of contention[8,9]. Longer-lived storms might also increase the chances of interaction with the jet stream, which can sometimes produce hazardous weather that can extend much farther inland[10].

More generally, the current results indicate the need to broaden our thinking about how climate change affects tropical cyclones after landfall. We must take into account residual atmospheric effects from the adjacent ocean, landfall location and effects induced by the land surface itself[6]. Integrating this understanding into hurricane models should help to improve our predictions of the future risks posed by individual storms and over the long term.

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Immunology

Caspase-8 protein cuts a brake on immune defences

Igor E. Brodsky

The enzyme caspase-8 can induce cell death or promote survival and the expression of inflammatory proteins. The discovery of a previously unknown caspase-8 target solves one mystery about immune-defence regulation. **See p.275**

Activation of the protein caspase-8 can have consequences that include triggering a type of cell death called apoptosis, preventing another type of cell death termed necroptosis, and promoting gene expression that leads to inflammation. How the activity of this single protein regulates these distinct functions is unclear. On page 275, Gitlin *et al.*[1] shed light on how caspase-8 drives pro-inflammatory responses in mammalian cells (Fig. 1).

Caspase-8 is a protease, an enzyme that cleaves its target proteins. It is a central regulator of the various possible outcomes of cell-signalling pathways leading from receptors of the Toll-like receptor (TLR) or the tumour-necrosis factor receptor (TNFR) superfamilies[2]. Such signalling cascades ultimately activate the transcription-factor proteins NF-κB and AP-1, which modulate the expression of hundreds to thousands of genes that mediate inflammatory and antimicrobial responses during the innate immune response — the earliest response to infection.

Among the best studied of these genes are those encoding cytokine proteins that promote inflammation, which include tumour-necrosis factor (TNF), IL-6, IL-1 and IL-12, as well as members of a subfamily of cytokines called chemokines. These factors collectively marshal immune defences against infection, but can be associated with severe disease if their expression is not properly controlled[3]. Indeed, anti-TNF therapies are used extensively in the treatment of inflammatory diseases, but such treatments can also blunt defence against infections.

One potential outcome of caspase-8 activation after TLR or TNFR signalling is apoptosis. However, NF-κB, in addition to inducing the expression of mediators of inflammation, induces expression of genes that encode 'survival factors', which prevent cells from undergoing apoptosis[4,5]. In most healthy cells, therefore, these TLR or TNFR signalling pathways induce inflammation but do not cause cell death. However, if this receptor-mediated signalling is accompanied by a blockade of NF-κB, which occurs during infection by certain microorganisms, this triggers apoptosis that depends on caspase-8 and the enzyme RIPK1.