wild-type protein, both the LID and the AMPbd mutants decrease the occupancy of the fully folded structure, but they increase the stability of two different states in which either the LID or the AMPbd domain is locally unfolded (Fig. 1). The increased stability of these locally unfolded states stems from the fact that the footprint of a glycine amino-acid residue is smaller than that of other amino-acid residues, which means that the protein chains in the glycine mutants are more flexible than those in the wild-type protein. Remarkably, these two types of local unfolding alter different aspects of the enzyme’s function: LID unfolding decreases its binding affinity, whereas AMPbd unfolding increases its activity.

A particularly interesting aspect of the authors’ work is that it helps us to understand how surface glycine mutations act at a distance to support cold adaptation. This phenomenon might seem mysterious at first glance, but it is encapsulated in the idea of allosteric regulation — a common form of enzyme regulation in which the binding of a molecular partner at a site distant from the active site affects enzyme activity. The conventional view of allosteric regulation has been that binding of the partner causes small structural changes that propagate through the protein to alter the structure of the active site. However, there is now evidence for mechanisms involving changes in the dynamics (entropy), rather than in the structure, of the unbound state for many cases of allosteric regulation. The current work provides striking tests and examples of such entropic allosteric regulation for different enzyme properties.

Saavedra and colleagues’ results have substantial implications for the evolution of enzyme function. However, their mechanistic proposal for cold adaptation was tested for just one model enzyme, so its relevance for other cold-adapted enzymes requires further testing. Deeper insight into the biophysical mechanisms of cold adaptation will also benefit from more-detailed views of the structural fluctuations of enzymes afforded by single-molecule experiments. Nevertheless, the findings open up new avenues for exploring allosteric control of multiple modes of protein function, both in natural evolution and in rational protein engineering.

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not consider the effects of coastal-protection measures, such as the construction of dykes or dunes. If such measures were considered in the analysis, then the area and number of people exposed would change. Moreover, the construction of coastal defences will be largely driven by economic considerations, which will be different for different countries.

The authors define land at risk from sea-level rise as the 1-in-100-year coastal floodplain. But will people be driven away from such land by the infrequent floods, or will they accept the occasional inundation, moving away only temporarily as needed? It might be better to consider the area of land that will become permanently flooded to make a more direct estimate of the population that will be exposed to sea-level rise.

A limitation of the study is that Greenland, Antarctica and all glaciers elsewhere are lumped together as the land ice that contributes to sea-level rise. However, ice will probably melt at different rates in each of these regions. This will cause the relative contributions of the different sources to change over time. One way to improve the regional estimates of sea-level rise would therefore be to scale the contributions of the ice sheets according to their individual effects.

Nevertheless, studies such as those of Brown and colleagues are essential, because they show the complexity of the climate system’s response to change and how this affects society. By directly connecting the effects of climate change to the consequences for humans, the authors clearly show that climate mitigation needs to happen now for a better future.

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**GENE REGULATION**

**A new phase in transcription**

A subunit of the enzymatic complex P-TEFb can induce compartmentalization of proteins into liquid–like droplets in cells. This phase separation might help P-TEFb to promote gene transcription. **See Letter p.318**

**JAMES A. GOODRICH & DYLAN J. TAATJES**

Genomic DNA is not indiscriminately transcribed into RNA. Instead, select sequences are transcribed at any given time or in any given cell type. How this process is regulated has been an active area of research for decades, because of its complexity and importance in embryonic development and disease. On page 318, Lu et al. describe an aspect of transcription regulation that involves liquid–liquid phase separation — a process by which proteins, nucleic acids and other molecules self-organize into liquid-like droplets to enable subcellular compartmentalization.

Transcription is catalysed by the enzyme RNA polymerase II (Pol II). The activity of Pol II is, in turn, regulated by a complex called P-TEFb, which consists of the protein cyclin T1 (CCNT1) and the kinase enzyme CDK9. P-TEFb binds to the carboxy-terminal domain (CTD) of Pol II (ref. 2) — this domain consists of 52 repeats of 7 amino acids, 5 of which can be phosphorylated. The CCNT1 subunit regulates the activity of CDK9, which can phosphorylate the Pol II CTD many times to help control Pol II function.

Lu et al. first investigated which region of CCNT1 is responsible for regulating CDK9 activity. They found that mutations in a domain of CCNT1 rich in the amino acid histidine led to defects in the activation of