the structures can be solved using X-ray crystallography. The compounds identified by Schmid *et al.* should also inform our understanding of signalling through G-protein-coupled receptors in general. Given that such receptors are implicated in many diseases, this could pave the way for the development of numerous drugs that have minimal side effects. ■

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GLOBAL WARMING

Homing in on a key factor of climate change

The sensitivity of Earth's climate to atmospheric carbon dioxide levels is a big unknown in predicting future global warming. A compelling analysis suggests that we can rule out high estimates of this sensitivity. SEE LETTER P.319

PIERS FORSTER

The quantity known as equilibrium climate sensitivity is crucial for understanding Earth's future temperature[1], and ongoing uncertainty about its value makes it harder to adequately prepare for the long-term effects of climate change[2]. This key parameter enumerates the increase in Earth's average surface temperature that would occur if atmospheric carbon dioxide concentrations were doubled and the climate system was given enough time to reach an equilibrium state. More than 150 estimates of equilibrium climate sensitivity (ECS) have been published[3], many of which suggest that worryingly high sensitivities are possible — including one that was published in *Nature* just a few weeks ago[4]. On page 319, Cox *et al.*[5] use an ingenious approach to rule out high estimates. If correct, this would improve the chances of achieving internationally agreed targets for minimizing global warming.

The measurements of many different properties, such as the height of Everest or the speed of light, have often been refined. This has helped to bring certainty to science and thereby driven progress. But ECS has not capitulated to these scientific norms and remains stubbornly uncertain. It has also become a focus for those who doubt the robustness of climate science, who use it to suggest that the field as a whole is intrinsically unreliable. Despite the huge progress in our understanding of climate science over the past 40 years, the Intergovernmental Panel on Climate Change (IPCC) concluded[1] in 2013 that there is a 66% likelihood of ECS being between 1.5 °C and 4.5 °C (Fig. 1). This is little different from the range first postulated[6] by the meteorologist Jule Charney and colleagues in 1979.

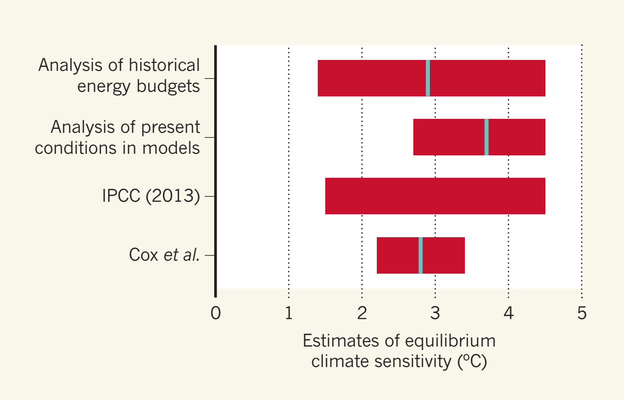

Figure 1 | Estimates of equilibrium climate sensitivity (ECS). ECS quantifies the increase in Earth's average surface temperature that would occur if atmospheric carbon dioxide levels were doubled and the climate system was allowed to reach an equilibrium state. Estimates of ECS vary depending on the evidence used (such as records of Earth's energy budget[9] and analyses[4] of present climate conditions produced by models). The estimate[1] from the Intergovernmental Panel on Climate Change (IPCC) published in 2013 is based on several lines of evidence. Cox *et al.*[5] now report estimates based on an analysis of surface-temperature variation predicted by climate models. Their analysis rules out high estimates of ECS. Bars depict ranges for which there is a 66% likelihood of the value being correct; for the top two bars, these ranges have been inferred from the data in references 4 and 9. Best estimates of ECS for each range, if available, are indicated by a blue line.

Cox and co-workers' estimate is exciting because it develops an underexplored line of evidence: the natural variability of global temperature. The authors also provide the first convincing evidence that we are not living in a world in which ECS is greater than the range of values thought likely by the IPCC. This is important, because estimates of ECS based on the historical temperature record have largely been unable to exclude high values that would invariably result in world-devastating warming of 4 °C or more by 2100.

Past research that seemingly constrained the top end of ECS estimates to lower values often excluded major uncertainties, or worked from a previous estimate of ECS that was skewed towards low values. The published ranges therefore depended on the researchers' assumptions about ECS, rather than the evidence. By contrast, Cox *et al.* started from climate-model values that are at the upper end of the IPCC range, and used evidence to effectively rule out catastrophically high values: they estimate that there is a 66% likelihood of ECS being between 2.2 °C and 3.4 °C, with less than a 1% chance of it being greater than 4.5 °C (Fig. 1).

The idea underpinning this work is so enviably simple that it will make climate scientists ask, "Why didn't I think of that?" The authors examined the variability of surface temperature in terms of its variance and autocorrelation — the 'memory' of a previous year's surface temperature that is retained in measurements taken the following year. They then developed a theory-derived metric of surface-temperature variability and evaluated this metric in historical simulations from 22 computational models of the Earth system, ultimately finding that it is a good predictor of the inherent ECS of each of the models.

Cox *et al.* then used the relationship between the metric and the ECS found in the models as a constraint on ECS in the real world. Their analysis revealed that only climate models that produce relatively small values of ECS match the variability seen in the historical temperature record. It turns out that, in general, climate models have considerable memory in their climate systems, so if one year is abnormally hot, for example, then the next year is likely also to be hot. The historical temperature record, however, does not seem to have as much system memory as most models. This means that some models have both autocorrelations and ECS values that are too high.

These new findings must be interpreted carefully. ECS is arguably the main factor that governs uncertainty in projected temperatures, but is not the only factor. For example, Earth-system feedbacks such as the effects of permafrost melting are expected to increase warming. Climate models often exclude these feedbacks, reducing the projected warming. In models that have an ECS that is too high, such exclusions could potentially compensate for the effects of the inflated ECS value.

It is also crucial to examine other lines of evidence when assessing ECS. The best estimates of ECS that have been made by analysing Earth's energy budget (the balance of the energy received by Earth from the Sun and the energy radiated back to space) are relatively low, at around 2 °C (ref. 7). But recent work[8] is helping us to understand that ECS values inferred from energy-budget changes over the past century are probably low, and shows that a higher value is more applicable when projecting future change. Applying such a correction to the original estimates[9] brings their values very much in line with Cox and co-workers' estimate (Fig. 1).

By contrast, analyses[3] of present climate conditions (particularly cloud properties) produced by models show that the models that best represent today's climate have ECS values greater than 3 °C. Indeed, one of the most recent of these analyses[4] showed that models with an ECS of around 4 °C best captured today's climate across nine emergent constraints (Fig. 1). In my view, Cox and colleagues' estimate and the estimates produced by analysing the historical energy budget carry the most weight, because they are based on simpler physical theories of climate forcing and response, and do not directly require the use of a climate model that correctly represents cloud. To resolve which estimates are most accurate, more research is needed to compare the different lines of evidence and to improve the representation of clouds in models.

> ***"The idea underpinning this work is so enviably simple that it will make climate scientists ask, "Why didn't I think of that?"***

I hope that a much more refined estimate of ECS can be made from the different lines of evidence by the time the next IPCC assessment is published in 2021. If the upper limit of ECS can truly be constrained to a lower value than is currently expected, then the risk of very high surface-temperature changes occurring in the future will decrease. This, in turn, would improve the chances of keeping the temperature increase well below 2 °C above pre-industrial levels, the target of the Paris Agreement under the United Nations Framework Convention on Climate Change. So, rather than be jealous, I should thank Cox and colleagues for helping me to sleep a little easier in my bed at night. ■

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MOLECULAR BIOLOGY

Limitless translation limits translation

Evidence has now been found that ribosomes — the cell's translational apparatus — can pass beyond the main protein-coding region of messenger RNAs to form 'traffic jams' that inhibit protein expression. SEE LETTER P.356

PETRA VAN DAMME

During the process of translation, molecular machines in the cell called ribosomes use sequences encoded by messenger RNAs as templates for protein synthesis. On page 356, Yordanova *et al.*[1] propose an intriguing mechanism that might limit the number of protein molecules that can be synthesized from a single mRNA. It involves the formation of a queue of ribosomes on the mRNA, downstream of the main protein-coding region.

The conventional view of translation in eukaryotes — organisms such as fungi, plants and animals — is that each mRNA consists of a stretch of nucleotides that contains an open reading frame (ORF), which encodes a single protein containing more than 100 amino-acid residues. But over the past decade, the advent of technologies such as ribosome profiling[2] has revealed that a more-diverse range of ORF sequences can, in fact, be translated. For example, numerous small upstream ORFs (uORFs) have been identified whose translation might regulate expression of the main ORF.

Ribosome profiling has also revealed a wealth of events in which translation is initiated at alternative start codons[3] (triplets of nucleotides other than the triplets at which translation is normally assumed to initiate), and read-through events[4] in which translation continues beyond the stop codon (the nucleotide triplet at the end of the ORF). Not only do these two types of event increase the overall diversity of proteoforms (molecular forms of proteins produced from genes)[5], but they have also emerged as regulatory mechanisms for hundreds of genes in eukaryotic genomes. Other regulatory mechanisms for translation are also known, including ribosome stalling, in which obstacles impede ribosome movement along mRNAs.

Yordanova *et al.* now propose another evolutionarily conserved mechanism for translational control. They suggest that sporadic stop-codon read-throughs can lead to the formation of ribosome queues at downstream stalling sites, such that the queue length is proportional to the number of protein molecules that have been synthesized. The authors define the region between the end of the main ORF and the next in-frame stop codon (that is, the next nucleotide triplet that would be recognized as a stop codon by a