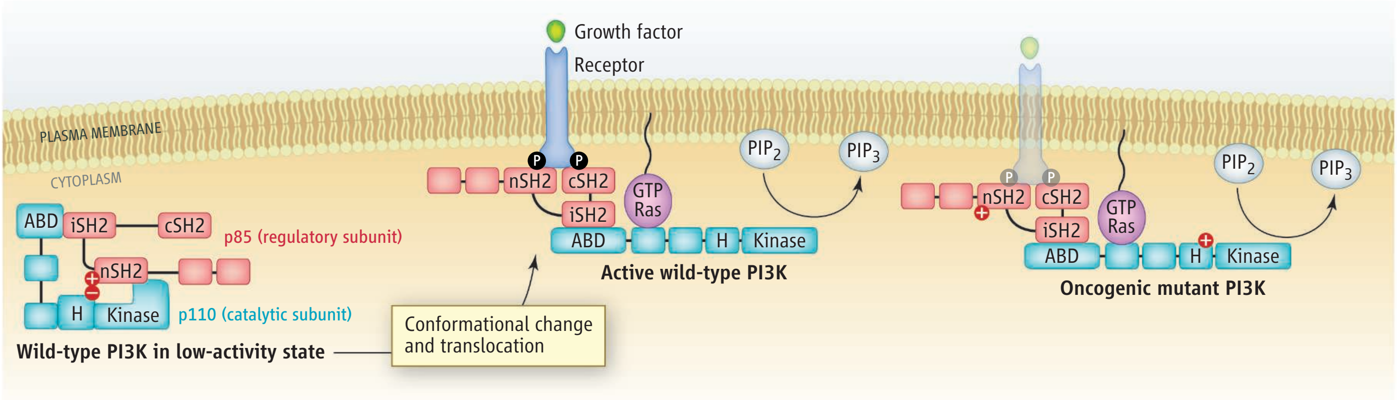

A cancer-linked mutation in PI3K. The major stabilizing interaction in PI3K involves the p85 iSH2 and p110α ABD domains. Inhibition of PI3K is mediated by a charge-charge interaction (shown as plus and minus signs) between the p85 nSH2 domain and the helical (H) domain of p110α. PI3K localizes to the membrane where interaction with an activated receptor relieves the inhibition. In PI3K with an oncogenic p110α charge-reversal mutation in the helical domain (E545K), the inhibitory interactions are abrogated, resulting in constitutive PI3K activation.

because it is not inhibited by the p85 nSH2 domain (see the figure).

It is less clear how the ABD mutations activate PI3K. Although the ABD binds to p85, ABD mutations are located on the exposed surface oriented away from the iSH2 domain, suggesting that ABD mutations do not directly interfere with p85-p110α interaction. Instead, they may distort orientation of the ABD with respect to the catalytic core, affecting the intrinsic enzymatic activity of p110α or its interactions with other proteins.

How does the E545K mutant promote cell growth and survival in the absence of growth factors? Although the mutation abrogates intermolecular inhibition, it does not explain its membrane localization. The p85 nSH2 domain, unencumbered by interaction with the p110α helical domain, might remain more tightly associated with receptors and adaptors, protecting critical tyrosine residues from dephosphorylation and thereby prolonging PIP_3 production. It is also possible that the mutant PI3K localizes to the membrane through membrane-bound Ras protein (p110α has a Ras-binding domain) or random encounters with membrane lipid substrate. The research by Miled *et al.* will hopefully spur efforts to crystallize the holoenzyme with both the wild-type and mutant p110α proteins.

PI3K inhibitors are now being evaluated in clinical trials. Analogous to the success of drugs that block kinases—trastuzumab in *HER2*-amplified breast cancers, imatinib in Philadelphia-chromosome chronic myelogenous leukemia, and gefitinib in *EGFR*-mutant lung cancers—cancers with genetic activation of PI3K signaling could be susceptible to PI3K inhibitors. Thus, cancers with *PIK3CA* mutations (or *PTEN* loss) will be carefully investigated for sensitivity to PI3K inhibitors. The p110α E545K mutant may be susceptible to compounds that bind to its unique helical domain surface. Such a specific therapy would be expected not to inhibit wild-type PI3K, thus reducing unwanted side effects. Moreover, different *PIK3CA* mutations may be functionally distinct and their effects on cellular responses to inhibitors could also be variable. Thus, we are reminded not to necessarily group all cancers with *PIK3CA* mutations together when analyzing cancers and their response to targeted therapies.

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CLIMATE CHANGE

A Changing Climate for Prediction

Peter Cox and David Stephenson

Standard climate model projections, which have shown the significance of global warming, must be redesigned to inform climate change adaptation and mitigation policy.

The latest report by the Intergovernmental Panel on Climate Change (IPCC) makes it clear that recent global warming is significant in the context of natural climate variations, and that human activities are very likely to be the cause of this climate change. As a result, businesses, policy-makers, and members of the public are seeking the advice of climate scientists on what they should do to prepare for the inevitable further climate change over the next few decades (adaptation) and how they can help to avoid dangerous climate change in the longer term (mitigation).

Current climate change projections produce a wide range of estimates of global warming by 2100. These projections are useful for stressing the consequences of different greenhouse gas emission scenarios, but too long-term and uncertain to guide regional adaptation to climate change. Standard climate projections are also insufficiently focused on quantifying the risk of dangerous climate change to properly inform mitigation policy under the United Nations Framework Convention on Climate Change. (The UNFCCC is an international treaty joined by most countries; the Kyoto Protocol is an addendum to that treaty.) How can projections be designed so that they better inform policy?

Uncertainties in climate predictions vary with the averaging period over which the climate is defined and with the lead time of the prediction. Consider, for example, the prediction of the global mean decadal temperature over the next century, with forecast lead times

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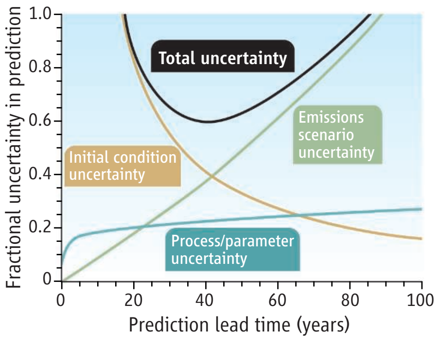


Minimizing uncertainties. Contributions to uncertainty in the predicted decadal mean temperature vary with the lead time of the prediction. Here the fractional uncertainty is defined as the prediction error divided by its central estimate. Climate predictions focusing on lead times of ~30 to 50 years have the lowest fractional uncertainty. This schematic is based on simple modeling.

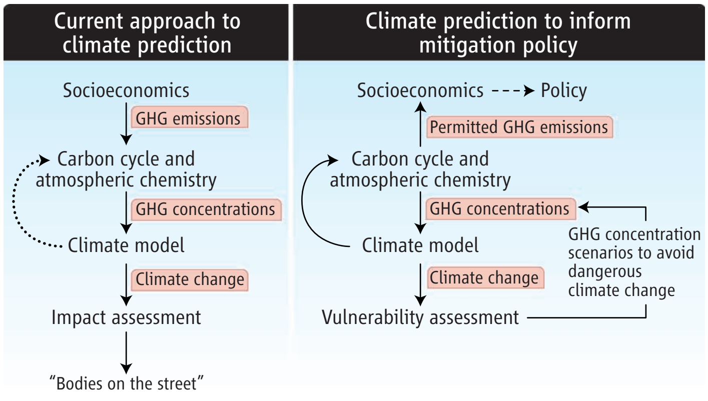
varying between 1 and 100 years. On lead times of less than 10 years, the signal of anthropogenic climate change is relatively small compared to natural decadal climate variability, and uncertainties in initial conditions dominate the overall uncertainty of the prediction (see the first figure) (*1*).

By contrast, climate predictions on time scales of a century are much less sensitive to initial conditions, because the signal of anthropogenic climate change is typically much larger at longer time scales and because most elements of the climate system have a "memory" of past climate-forcing factors that is shorter than a few decades. The major source of uncertainty here lies in the future anthropogenic emissions of greenhouse gases and aerosols (see the first figure) (*2*). This uncertainty can be seen as humankind's free will concerning future climate change.

The parameters used to specify climate processes in climate models are also a source of uncertainty. These parameters determine, for example, the behavior of clouds and the strength of atmospheric convection in the models. They have a large impact on the sensitivity of the modeled climate to a doubling of the carbon dioxide (CO_2) concentration (*3*, *4*). The net effect of all these uncertainties is that the fractional uncertainty is smallest when lead times are between 30 and 50 years (see the first figure). Fortunately, this is also the time scale over which most longer-term policy and business planning is carried out.

Mitigation, as defined by the UNFCCC, is concerned with even longer time scales. The UNFCCC aims to stabilize greenhouse gases at a concentration that avoids dangerous interference in the climate system. The convention, therefore, focuses on the risk of dangerous climate change as a function of the concentration of greenhouse gases and on the relation between CO_2 emissions and increases in atmospheric CO_2 concentrations through climate–carbon cycle feedbacks (*5*, *6*).

These issues are not easily addressed with the model simulations currently used by the IPCC (see the second figure, left panel). In the IPCC approach, scenarios of possible future emissions of greenhouse gases and aerosols are generated with socioeconomic models that take into account a range of "story lines" covering global population growth, economic development, energy use, and a variable mix of future energy sources. These emission scenarios are used to drive atmospheric chemistry and carbon cycle models that simulate changes in the concentration of greenhouse gases and aerosols. The resulting concentration scenarios are put into general circulation models (GCMs) of the climate system, which generate climate change scenarios that in turn drive models of the impacts on human and natural systems.



Models for informing policy. The design of climate model studies must change to inform climate change mitigation policy. **(Left)** Current IPCC process. **(Right)** Proposed new experimental design (*7*). GHG, greenhouse gas.

Mitigation policy requires a different, less linear structure, beginning with an assessment of the vulnerability of natural and human systems to climate change as a function of the magnitude of global warming and ending with scenarios of greenhouse gas emissions that avoid the most damaging impacts (see the second figure, right panel). Given the emphasis on avoiding dangerous change in the light of inevitable uncertainty, the UNFCCC also requires a reliable probabilistic risk assessment to inform emission-reduction targets. The mitigation policy agenda, as defined by the UNFCCC, therefore demands an overhaul of the design of climate change assessments (*7*).

Climate change adaptation and climate change mitigation may at first sight appear to require different modeling strategies. Observations of the contemporary Earth system are the key that must tie these modeling strands together. Informing adaptation on decadal time scales requires data on the slower climate system components (especially the ocean) to initialize high-resolution climate predictions (*8*). The interpretation of observations in a manner consistent with the model (through "model-data fusion" or "data assimilation") is common in numerical weather prediction and seasonal to decadal prediction (*9*), but is not yet used to constrain the climate projections of the IPCC.

For climate change mitigation, the dominant uncertainties are associated with climate system processes and feedbacks, rather than uncertainties in initial conditions. However, the major constraints on these processes and feedbacks also come from observations of the historical and contemporary climate. We can therefore envisage a climate diagnosis and prediction system that assimilates data into a climate model not only to define the initial conditions for decadal projections, but also to refine estimates of the key internal model parameters that influence climate sensitivity (*10*). Such a system would provide data-constrained estimates of the range of possible future climate changes on decadal to century time scales, which could be updated on the basis of new observations.

Climate projections have been instrumental in convincing many of the need for action to limit future climate change. It is now time for modelers to turn their expertise toward developing forecasting systems better suited for active management of the climate system.

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