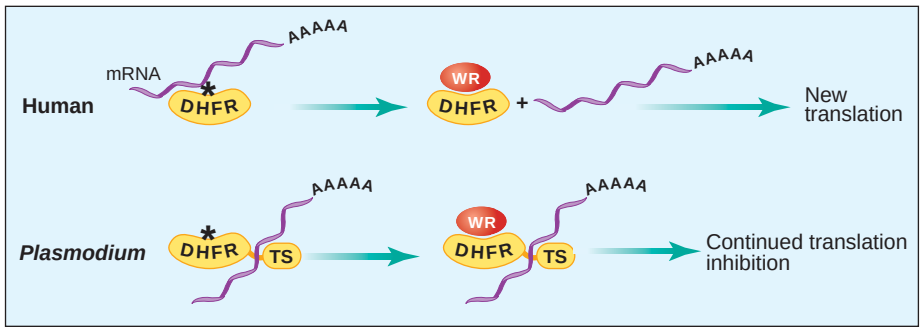


Empowering the host. Response of host and malaria parasite to the antifolate drug WR92210 (WR). Both the human and *Plasmodium* DHFR enzymes are efficiently inhibited by WR. Binding of WR to the human enzyme causes release of DHFR mRNA, leading to new protein synthesis and circumvention of the drug block. *Plasmodium* DHFR is a bifunctional enzyme (composed of DHFR and TS) whose mRNA transcript does not bind to the DHFR catalytic domain, but rather to the linker region that joins DHFR and TS. Therefore, WR binding does not release the mRNA and the parasite cannot respond to drug by making new enzyme. The asterisk denotes active site enzyme.

from its protein and new enzyme is synthesized (*8*, *9*) (see the figure). This allows mammalian cells to respond to substrate levels by translational control of enzyme concentration. DHFR inhibitors work in the same way as folate substrate, stimulating new protein synthesis and thus preventing DHFR blockade by the drug. *Plasmodium*, however, has a bifunctional enzyme composed of DHFR joined to thymidylate synthase (TS). The DHFR-TS mRNA is also bound to its protein, but the interaction appears to be in the linker region joining the DHFR and TS domains. Inhibitor treatment does not cause mRNA liberation, and new enzyme cannot be synthesized. The same mechanism seems to apply to TS: Treatment with a TS inhibitor results in increased enzyme synthesis in mammalian cells (*10*), but such inhibitors do not relieve the mRNA block of TS production in the parasite.

Why is there this difference between man and microbe? By making free DHFR mRNA responsive to substrate concentration, we humans are able to increase metabolic flux with relative ease by boosting translation of the mRNA. The parasite, however, has little need for such regulation. It lives inside an erythrocyte that gives the parasite a relatively constant ionic and nutrient environment. In fact, to date there is no substantive evidence for regulation of any *Plasmodium* gene expression in response to its environment. The parasite, much like a virus, regulates mRNA synthesis through a developmental program of on-off switches (*11*, *12*), but its ability to respond to unexpected changes may be quite limited. By cutting corners with respect to gene regulation, *Plasmodium* is able to streamline its genome. But in this regard, we are more sophisticated than the parasite, and thus we are provided with an opportunity.

No longer should we rely on mere kinetic comparison of host and pathogen enzymes for analysis of inhibitor selectivity. High-throughput enzyme inhibition screens done as simple head-to-head comparisons may miss important lead compounds. The effects on the target must be assessed on a cellular or even organismal level. Screens would even be feasible on a whole-proteome scale. One could look for proteins that were down-regulated in the parasite or up-regulated in the host upon treatment with an inhibitor. In addition to translational regulation, one could also look for differential uptake—for example, toxic L-nucleosides are taken up by *P. falciparum* but not by host erythrocytes (*13*). One could also investigate metabolic differences—for example, phosphorylation of acyclovir by a viral kinase contributes to selectivity of its antiherpesvirus action (*14*). One could exploit different rates of turnover—efluornathine works because, in contrast to the host, African trypanosomes cannot replace inhibited enzyme through new synthesis (*15*). Finally, one could look for differential penetration—ivermectin kills nematodes but not mammals because it cannot get through the blood-brain barrier to affect host neurons (*16*).

Those of us who have studied the biology of clever parasites have developed a profound respect for the ability of these creatures to evade their hosts. Maybe it is time to give a little credit to us hosts, with our extra genomic and cellular complexity. With a little planning we should be able to exploit our mammalian sophistication to develop potent antiparasitic drugs.

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PERSPECTIVES: CLIMATE MODELING

How Accurate Are Climate Simulations?

Thomas M. Smith, Thomas R. Karl, Richard W. Reynolds

It is a fundamental tenet of the scientific method that theories must be consistent with observations. To test our understanding of the climate system, we must evaluate how accurately climate models reproduce not only today's climate (*1*), but also the climate of the past.

Over the past decade, the observed climate record has become more complete, allowing the climatic effects of natural agents and human-related changes in atmospheric composition (collectively referred to as climate forcing) to be estimated. We can now test how well climate models simulate century-scale variations in the observed climate record. There have been numerous intercomparisons of various climate model simulations of 20th-century climate, based on the best available estimates of the climate forcing (*2*).

A standard assumption in these intercomparisons is that the model simulations should reproduce as closely as possible observed climate variability. This assumption must, however, be viewed with caution.

Observational errors, sampling errors, and time-dependent biases degrade the climate record. Considerable effort has been spent at minimizing these biases (*3*, *4*), yet problems remain. Consider for example

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the worldwide record of sea surface temperatures (SSTs), which dates back to the 19th century. At present, several different estimates of time-dependent bias adjustments and the effects of incomplete and changing spatial sampling can be used to correct the observational record before 1942 (*2*–*5*). Different assumptions and adjustment techniques lead to additional uncertainty in the climate record.

Climate models are not perfect either. Errors evolve in climate simulations as a result of incomplete physical understanding and limited knowledge of past (or future) climate forcing. These errors must be considered along with the uncertainty related to climate chaos, which occurs because of nonlinear interactions in the global climate system. Climate chaos errors can be addressed through repeated runs of a climate model with the same forcing, but different starting conditions. These ensemble simulations can then be used to estimate the magnitude of the uncertainty introduced by a chaotic climate system (*2*).

The similarity of 20th-century climate-model simulations of SSTs, for example, to the observed climate record should not be expected to be closer than the combined uncertainty of the observed SSTs and the climate model chaos. Differences outside these bounds represent inadequacies in the model, the forcing, or the observed climate record, or a combination of all of these.

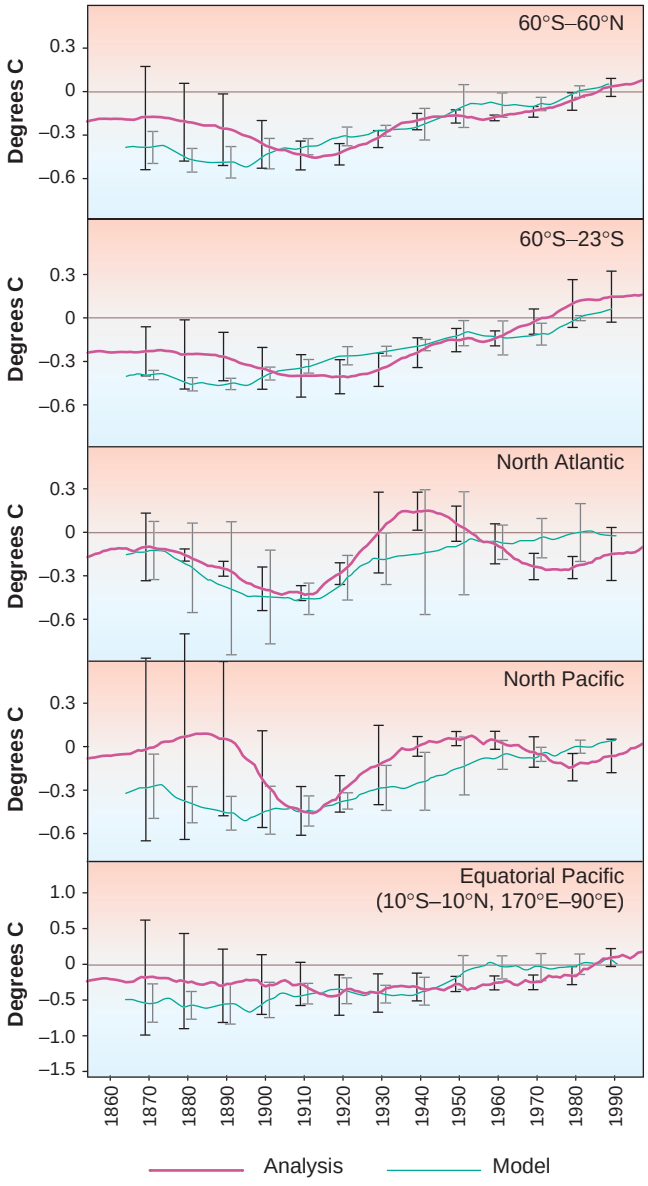
To illustrate the amount of chaos in low-frequency SST changes that is typical in modern climate models, we have used three separate simulations of the GFDL coupled ocean-atmosphere model (*9*). The simulations were forced with the same greenhouse gases and sulfate aerosols, but were started from different initial conditions. To remove model variations unrelated to climate forcing, we filtered the SST with a 21-year running mean. For the near-global average SST, the model does as well as can be expected, but chaos uncertainty is not constant across the analysis period (see the figure). This suggests that more simulation would be desirable to fully assess chaos uncertainty, although in all periods it is typically about 0.1°C. The uncertainty due to chaos across the full period can be estimated by pooling all the 21-year samples.

Next, we consider the errors that can arise from the observational record. We use observed SST fields computed with different analysis methods, some different data, and different historical bias adjustments (*6*–*8*). The range of SSTs from the different analyses is used to determine the time-dependent errors due to uncertain bias adjustments to the data and differing analysis methods (*9*). Sampling error is estimated by using the historical pattern of ocean observations to mask the model SST anomalies and then comparing the analyzed SST to the full model SST. The combined error from analysis methods and sampling error is used to compute the uncertainty of the observational data (see the figure).

The errors in analyzed SSTs are comparable to the uncertainty estimate associated with climate chaos over much of the 20th century. After 1950 sampling errors are greatly reduced (see the figure), but some analysis uncertainty persists even in well-sampled regions. For example, after 1950, errors in the analysis methods can produce typical SST uncertainty of 0.1°C averaged over the North Atlantic and North Pacific.

Today's models are thus within the observed uncertainty of the observations, at least with respect to the global SST record, which spans more than 100 years. This does not imply that the model simulations are perfect; rather, it indicates that more attention must be given to improving the records of past climate and ensuring that future climate records have little or no time-dependent biases.

It is unsettling that the uncertainty related to treatment of the data are increasing in recent decades in the most-sampled oceans. This points to the importance of developing a global observing system that not only has good spatial coverage, but more importantly, strictly adheres to guidelines and principles articulated by the U.S. National Academy of Sciences (*10*) for long-term climate monitoring.



Model versus observation. Average SST anomalies for 60°S–60°N, 60°S–23°S, the North Atlantic, the North Pacific, and the equatorial Pacific. Shown are the analysis of observed SST anomalies with 95% confidence intervals associated with sampling and analysis methods uncertainty (solid lines), and model SST anomalies with 95% confidence intervals associated with climate chaos (dashed lines). Note that the scale is different for the equatorial Pacific.

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