**Glacial Cycles and Indian Monsoon—A Southern Push**
Zhengyu Liu
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haps even directly inactivate the drug itself.

Chloroquine is the most widely used antimalarial drug, but the emergence of drug-resistant parasites is rapidly reducing its effectiveness as a single agent, and it is now most effective as part of an artemisinin-based drug combination (*3*). In this case, the parasite evolved a way to pump out chloroquine before the drug could accumulate to levels that would interfere with a process known as heme polymerization (which is needed to prevent the buildup of the toxic by-products of hemoglobin metabolism). A mutation in the gene MAL7P1.27 is responsible for the efflux activity (the gene is also known as *pfcrt*, the *P. falciparum* chloroquine resistance transporter) (*4*). Mutations in two other genes, *P. falciparum* dihydrofolate reductase (*pfdhfr*) and *P. falciparum* dihydroopterate synthase (*pfdhps*) are responsible for conferring resistance by altering two enzymes involved in folate biosynthesis; these changes produce resistance to the antimalarial drugs sulfadoxine and pyrimethamine (*5*). In addition, researchers believe a single mutation in the gene for cytochrome b (*6*) is responsible for the rapid selection of resistance to the drug atovaquone; as a result, the drug is now used only in combination with other drugs.

Although recent large-scale screening efforts have provided the antimalarial drug discovery community with an unprecedented number of "hits" to investigate (*7*–*9*), Yuan *et al*. took a different approach. By employing genome-wide association and linkage analyses, they identified candidate compounds with either complementary or distinct drug response signatures, meaning that the compounds act on either the same or different genes or biochemical pathways. This is important because using two drugs that target different mechanisms makes it less likely that the parasite will be able to evolve resistance to both drugs.

Yuan *et al*. tested 2816 compounds registered or approved for human or animal use against 61 malaria parasite lines from around the world. They identified 32 highly active compounds that inhibited the growth of at least 45 lines; 10 of these compounds had no previously reported antimalarial activity. Using pairwise comparisons, the authors then identified pairs of compounds that produced positively correlated response patterns, indicating that they acted on the same or similar targets, and negatively correlated responses, suggesting that the two compounds acted on different targets and would be good candidates to use in complementary combination treatments (see the figure).

Yuan *et al*. also used genome-wide association studies and linkage analyses to examine the whole genomes of each of the 61 parasite lines to determine how and where genes varied between isolates. The comprehensive nature of this study allowed them to evaluate how antimalarial drugs have influenced parasite evolution and population structure, and the results clearly suggest that chloroquine and other quinoline drugs have played a substantial and different role in the evolution of parasites in Africa and Asia. Perhaps surprisingly, the linkage analyses demonstrated that many differences in drug response were associated with just three genes: *pfcrt*, *pfmdr1*, and *pfdhfr*. This may reflect the limited chemical diversity within their tested compounds. If the same result appears in testing of bigger collections, however, it would suggest that researchers could face challenges in finding new drug combinations that will be effective against malaria parasites that are already resistant to current drugs of choice. That said, Yuan *et al*.'s results offer some hope that combinations can be found that, by acting on mutant forms of *pfcrt* or *pfmdr1*, would effectively treat chloroquine-resistant parasites.

Yuan *et al*. have taken a bold step into the complex world of malaria drug resistance and provided us with an approach and tools that will serve us well as we embark on efforts to better treat and eradicate this deadly disease. In the same way that large-scale phenotypic drug screening provided an unbiased way of identifying compounds that inhibit the malaria parasite, the genetic approach they describe allows a broad and unbiased way of studying the genetic determinants of resistance that face current and new malaria drugs. Our experience in developing other kinds of anti-infectives leaves no doubt that we can exploit this understanding to our advantage. It facilitates our profiling of new drugs against resistant strains, giving a first look at the combination potential of the compounds. It could also enable drug discoverers to use resistance selection experiments to rapidly identify the targets of the most promising compounds to emerge from large-scale screening efforts and, even if those compounds fail, help identify other molecules that could act on those targets.

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ATMOSPHERIC SCIENCE

# Glacial Cycles and Indian Monsoon—A Southern Push

**Zhengyu Liu**[1,2]

An analysis of ancient lake bed sediments challenges traditional views of Indian monsoon dynamics.

The Indian summer monsoon (ISM) is an important annual climate cycle that has major implications for human well-being, in part because it influences seasonal rainfall in South Asia. As a result, climate researchers have sought to understand the factors that cause the ISM's intensity to vary and how climate change may affect it. Traditionally, researchers have thought that, during the Pleistocene (~2.6 million years before the present), the ISM weakened during cooler periods as glaciers in the Northern Hemisphere (NH) expanded, and the monsoon strengthened during warmer periods as the ice sheets melted. This paradigm now faces a serious challenge. On page 719 of this issue, An *et al*. (*1*) present evidence that—contrary to the conventional view—the ISM often reached its weakest point, and even began to strengthen, before global volumes of glacial ice reached a maximum. They also propose that, during glacial periods, the development of the ISM was driven by cool-

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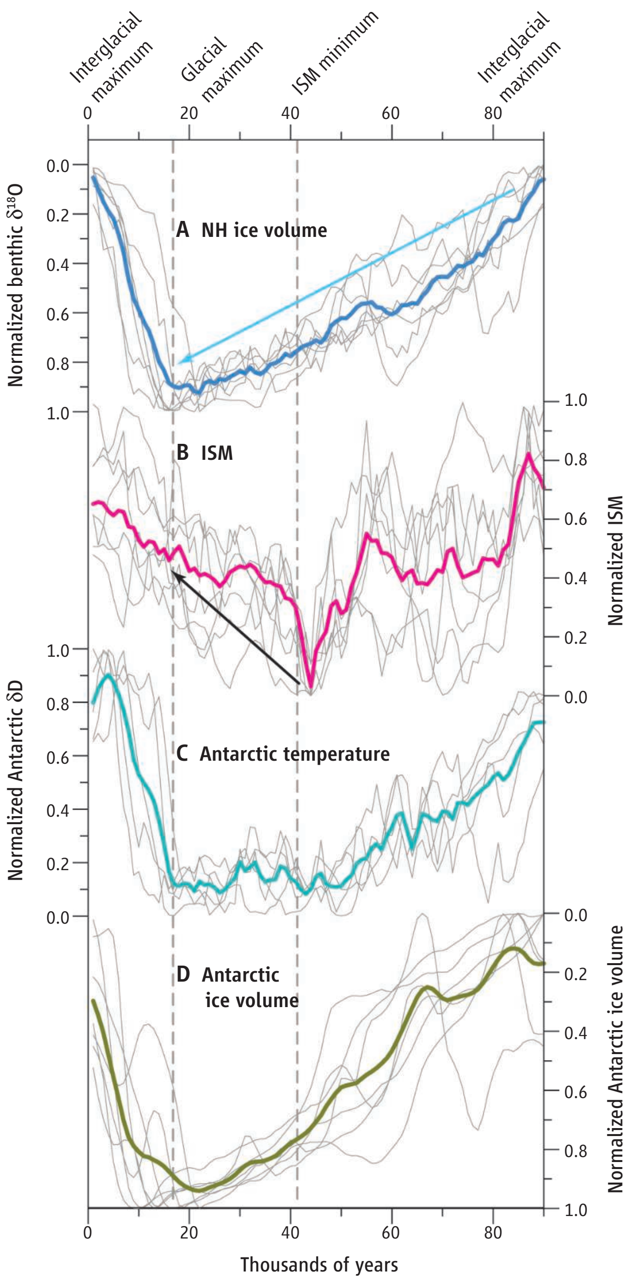


**ISM, temperatures, and ice.** To understand the factors that have influenced the strength of the ISM over the past 0.9 million years, researchers have reconstructed trends in (**A**) NH ice volume (*8*), (**B**) ISM intensity (*1*), (**C**) Antarctic temperatures (*7*), and (**D**) Antarctic ice volumes (*9*). Comparing the curves shows that, contrary to current theory, the ISM started to strengthen before ice volumes reached their maxima. (A), (B) and (D) cover seven glacial-interglacial cycles; (C) covers five cycles. Thin gray lines illustrate each event; thick colored lines represent the mean. The magnitude of each event is normalized. Time is also normalized: It is reset with the seven ISM minima lined up at 41 thousand years ago; each cycle is then rescaled so that the time between the ISM minimum and maximum becomes the average time of all seven events. The cycle between 700 and 780 thousand years ago was not included because it has a prominent interstadial during the glacial period. Adapted from (*1*).

ing in the Southern Hemisphere (SH), highlighting the role of interhemispheric interaction in governing the relationship between the ISM and glacial cycles.

Traditional thinking about ISM dynamics is as follows: When the climate warms and ice sheets shrink, warming over the Indian Ocean enhances the ISM by increasing evaporation and moisture supply. The ISM can also be intensified by warming over the South Asian subcontinent, which intensifies land heating and low atmospheric pressure known as the monsoon low. The opposite situation occurs when the climate cools and ice sheets expand. This creates a mechanism called northern pulling.

This monsoon paradigm focused attention on the influence of the nearby NH on the ISM, but ignored the role of the SH. However, the region in which the ISM occurs is characterized by the atmosphere's strongest interhemispheric interaction. It involves the Somali jet, a strong cross-equatorial air current that transports moisture from the South Indian Ocean into the ISM region (*2*). Past research has suggested that the route and intensity of the Somali jet is "forced" by a variety of geographical and atmospheric factors (*3–5*), including cooling in the SH. As a result, researchers have suggested that SH climate forcing can be transmitted deep into South Asia, influencing the ISM. It has been difficult, however, to evaluate how these SH climate-forcing mechanisms influence the ISM in the real world, where climate influences such as orbital variations and changes in greenhouse gas concentrations generally force the ISM through multiple mechanisms simultaneously.

An *et al*. tackle this problem by analyzing evidence of Pleistocene climate changes and ISM variability left behind in ancient lake sediments in the Heqing Basin in southwestern China. They identified strong and weak monsoons by measuring the total organic carbon (TOC) in sediments and the ratio of rubindium (Rb) to strontium (Sr); high TOC indicates strong monsoon rainfalls (ISM maxima), whereas high Rb/Sr ratios correspond to weak weathering and in turn weaker monsoon rainfalls (ISM minima). They combined these proxy measurements to create an "ISM index." They validated the index's chronology by measuring sediment levels of pollen from conifer trees in the genus *Tsuga*; high pollen counts corresponded with warmer interglacial periods (glacial minima). This new index is unique in both its direct relevance to the rainfall intensity of the ISM and its robust chronology.

In agreement with the traditional paradigm, the index shows that, during the major glacial cycles of the past 0.9 million years, the timings of ISM maxima coincided with ice volume minima (the monsoon strengthened as the glaciers melted). In contrast, however, the index indicates that ISM minima occurred about 20,000 years before glacial maxima and that the ISM then intensified, despite increasing ice volume (see the figure). These earlier ISM minima also appear to be consistent with available ISM indices derived from marine proxies.

These findings required a new interpretation of the factors influencing ISM variability. An *et al*. noticed that glacial ISM minima occurred when Antarctic temperatures were near their lowest and when Antarctic ice volume continued to decrease (see the figure). This led them to propose that the strengthening of the glacial ISM is forced by increased SH cooling, an increased pole-to-equator temperature gradient and, in turn, an enhanced southern "pushing." At full glacial conditions, this southern pushing overwhelmed the NH forcing and reduced evaporation, both of which served to weaken the Indian low.

Independent observations and climate modeling are needed to confirm and understand this new paradigm. In the meantime, the new paradigm may help reduce the uncertainty surrounding the response of the ISM to global warming (*6*). During glacial cycles, atmospheric $CO_2$ levels correlate well with NH ice volumes and global temperatures (*7*), suggesting that rising $CO_2$ could influence the ISM. This research suggests, however, that ISM rainfall has responded differently to changing $CO_2$ concentrations during glacial and interglacial periods. During warm interglacials, ISM rainfall appears to vary with $CO_2$ concentrations because of the dominance of thermodynamic mechanisms and northern pulling. During colder glacials, however, ISM rainfall does not appear to vary with $CO_2$, due to the dominance of southern pushing. Because rising $CO_2$ tends to enhance northern pulling but weaken southern pushing, the future net dynamic forcing on the ISM remains uncertain. In the current climate, models suggest that rising $CO_2$ will enhance ISM rainfall but not winds (*6*), likely because of the dominance of enhanced evaporation and moisture supply. Were we in a colder climate, however, the ISM's response to global warming could be very different.


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EVOLUTION

# Is Bigger Always Better?

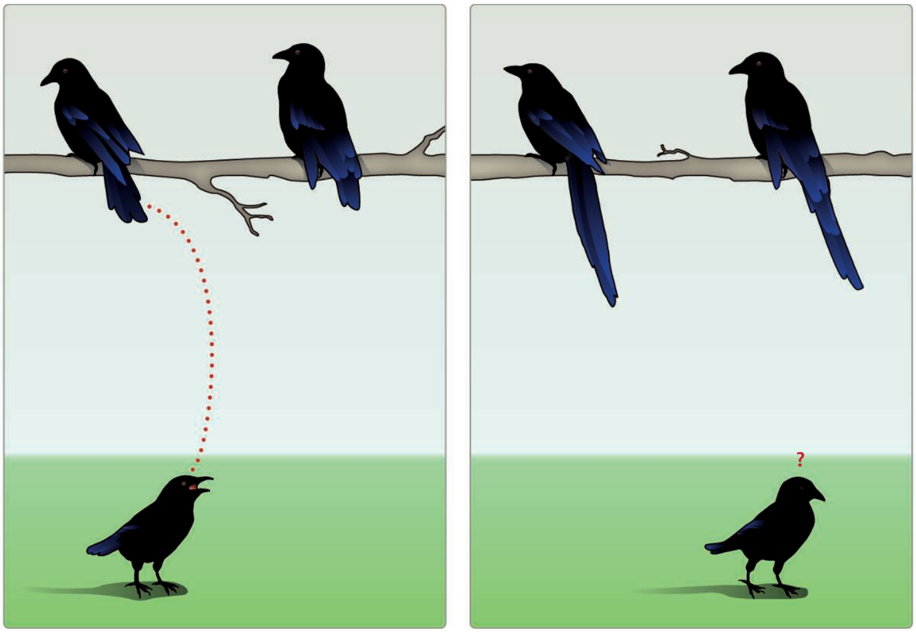
Female perceptual limitations may explain why sexual selection doesn't always lead to exaggerated male traits.

**Candy Rowe[1] and Susan D. Healy[2]**



Darwin was famously puzzled by the length of a peacock's train—what made it so big and so elaborate? The theory of sexual selection provided us with the answer: Females choose males with more exaggerated traits, such as a bigger tail, because they signal benefits for their offspring (*1*). Recent studies, however, have suggested that this is an oversimplification because the perceptual and cognitive mechanisms underlying female choice may not always lead to larger and more extravagant male traits (*2*, *3*). On page 751 of this issue, Akre *et al*. offer further evidence that female perception can make a big difference. They show that although female frogs prefer male frogs with longer calls, the females are less able to discriminate between males as their calls become longer, perhaps constraining the evolution of call length. The finding is consistent with Weber's law (*4*), which holds that as the magnitude of two stimuli increases, a greater difference is required to distinguish between them.

When an animal compares two stimuli, it must be able to perceive a difference between them in order to make a choice. Psychophysical experiments show that animals do this based on relative, not absolute, differences (*5*). For example, if a female bird is presented with two males with tails that are relatively short but of different lengths, Weber's law suggests she will more easily perceive even a slight difference (see the figure). As the tails get longer, however, the difference must be bigger for the female to detect the longer tail. This observation suggests that females may become less choosy as traits get bigger, because they become less able to discriminate between males with large traits. Therefore, sexual selection would get weaker as male ornament size increases, leading to a cessation in trait exaggeration.




**Perceiving a difference.** Weber's law suggests that females should choose males based on the relative, rather than the absolute, difference in their traits. A female bird considering two males with tails of different but relatively short lengths **(left)** should perceive the difference more readily than if she is comparing two males with longer tails **(right)**. This perceptual limitation may help to explain why sexual selection does not lead to ever bigger and showier male traits.

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Akre *et al*.'s data are the first to provide experimental support for this idea. They studied túngara frogs (*Physalaemus pustulosus*). Males gather in choruses and produce calls that consist of a whine followed by a number of "chucks" (0 to 7, although typically no more than 2) (*6*). Females are attracted to the chorusing males and tend to choose to mate with males that produce the calls with the most chucks (*7*). In Akre *et al*.'s experiment, the researchers played male calls of different lengths from two speakers, and then measured a female frog's discrimination ability by recording which speaker she chose to approach. Contrary to their

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