



LETTERS

edited by Etta Kavanagh

Testing Climate Reconstructions

A 2005 U.S. CONGRESSIONAL ENQUIRY (1) FOCUSED ON THE VALIDITY of the climate reconstruction of the past millennium by Mann *et al.* (2) and referred to a *Science* Report that challenged the reconstruction method ("Reconstructing past climate from noisy data," H. von Storch *et al.*, 22 Oct. 2004, p. 679; published online 30 Sept. 2004). This Report was also discussed in the U.S. Senate in 2005 (3). In this discussion, it has been overlooked that von Storch *et al.*'s Supporting Online Material (SOM) in fact supports the Mann *et al.* reconstruction.

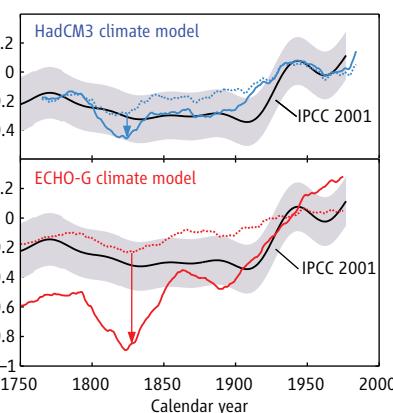
von Storch *et al.* presented tests of the climate proxy method with two climate models: the HadCM3 model (shown only in the SOM) and the ECHO-G model. Both are compared in the figure. The HadCM3 simulation (solid blue) is consistent with the climate proxy data reconstruction (grey band). The ECHO-G model has since been found to be afflicted by a major artificial climate drift due to an undocumented, inappropriate initialization procedure (4).

The error of simulated proxies (dotted blue) found in the HadCM3 model is smaller than the error margin given by Mann *et al.* for their method and shown in the IPCC report (5). For the time period common to both models, the RMS error of the simulated proxies is 0.24°C in ECHO-G, but only 0.07°C in HadCM3—less than one-third.

The two models thus give rather different, conflicting results about the potential errors of proxy reconstructions. This is not mentioned in the Report, which merely states, "Similar results are obtained with a simulation with the third Hadley Centre coupled model (HadCM3), demonstrating that the results obtained here are not dependent on the particular climate characteristics of the ECHO-G simulation" (p. 680).

In addition, it has since been found (6) that the proxy method was implemented incorrectly by von Storch *et al.*; with correct implementation, the error is even smaller in HadCM3 than the 0.07°C shown here. A similar, more recent test with the NCAR climate system model (7) also suggests only small errors for the proxy method, supporting the climate reconstruction of the past millennium by Mann *et al.*

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Test of proxy climate reconstruction method with two climate models, HadCM3 and ECHO-G. Solid lines show Northern Hemisphere temperature in the models (31-year running means); the dotted lines show simulated proxy reconstructions where the proxies are degraded with 75% noise. The error of the proxy method is the difference between the solid and dotted lines (arrows). For comparison, we show the Mann *et al.* 40-year-smoothed reconstruction for the Northern Hemisphere temperature (black) with its 95% confidence interval (grey), as shown in the IPCC Third Assessment Report (5).

STEFAN RAHMSTORF

Response

RAHMSTORF CRITICIZES OUR PREVIOUS CONCLUSIONS about the climate reconstruction method of Mann *et al.* (1) (MBH98). In our previous analyses (2, 3), we found that MBH98 underestimates past temperature variations when tested in climate simulations of the past few centuries. Rahmstorf argues that the simulated Northern Hemisphere temperature lies outside the uncertainty bounds of the pseudoreconstructions in the simulation with the model ECHO-G, but inside the uncertainty bounds in the HadCM3 simulation. He concludes that our analysis supports the Mann *et al.* (1) reconstructions. This conclusion is wrong. The problem is the determination of the error bounds.

To successfully compute uncertainty bounds requires an error model. Updated uncertainty bounds for the MBH98 series, on 40-year time scales, can be found in fig. 1B of Gerber *et al.* (4). Mann was a co-author on this study, and these uncertainties are consistent with the ones derived in our

analysis (3). Further, they are about a factor of 3 smaller than those published two years earlier in the IPCC Third Assessment Report (5) and used in Rahmstorf's Letter (2σ of roughly 0.07 K rather than 0.25 K for circa 1800). The result of the pseudoreconstruction and the target temperature in the HadCM3 model are therefore statistically well separated when using the proper uncertainties (3).

We think that the Letter [as does (5)] illustrates a common confusion in our field. There are two sources of uncertainty in reconstructing past climate from proxy records: (i) calibration uncertainty—which part of the signal is not captured by the statistical method; and (ii) residual uncertainty—how much additional, unrelated variability is engraved in the proxy records. Our most recent comment (3) did not make this point explicitly, but its uncer-

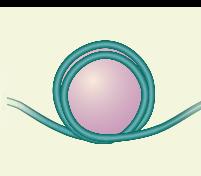
References and Notes

- See www.realclimate.org/index.php?p=172 for links to the request and the scientists' responses.
- M. E. Mann, R. S. Bradley, M. K. Hughes, *Geophys. Res. Lett.* **26**, 759 (1999).
- [See <http://inhouse.senate.gov/pressreleases/climateupdate.htm>.](http://inhouse.senate.gov/pressreleases/climateupdate.htm)
- T. J. Osborn, S. T. C. Raper, K. R. Briffa, *Clim. Dyn.* **27**, 185 (2006), DOI: 10.1007/s00382-006-0129-5.
- IPCC (Intergovernmental Panel on Climate Change), *Climate Change 2001: The Scientific Basis* (Cambridge Univ. Press, Cambridge, 2001), fig. 2.21, p. 134. The error bars for time scales >40 years shown there were computed by Mann *et al.* from calibration residuals, accounting for their spectral "redness." The data were obtained from the National Climate Data Center at http://www.ncdc.noaa.gov/paleo/pubs/mann_99.html.
- E. R. Wahl, D. M. Ritson, C. M. Amman, *Science* **312**, 529 (2006).
- M. E. Mann, S. Rutherford, E. Wahl, C. Amman, *J. Clim.* **18**, 4097 (2005).
- We thank von Storch *et al.* for providing the data of their simulations.



Mimicking enzymes

1885



Precision splicing

1886

tainty estimates are based on calibration error. We showed that the MBH98 method implemented in the simulations leads to pseudoreconstructed temperatures being too warm and with differences from the target temperature larger than our calibration uncertainty ranges.

Rahmstorf also alludes to a climate drift in the ECHO-G simulation (2). However, this drift mostly affects the earlier centuries of the millennium, when the pseudoreconstruction performs better, and is probably minor after 1400 A.D., when the pseudoreconstruction performs worse. For instance, ECHO-G simulates a difference in the Northern Hemisphere temperature between 1900 and 1980 (the calibration period) and the Late Maunder Minimum (around 1700) of 0.97 K, whereas a simulation with the CSM climate model from NCAR yields 0.87 K (6). Therefore, this issue cannot explain the bias of the reconstruction method.

In conclusion, we feel that the paleoreconstruction community would be well served if it used error models describing uncertainties from both calibration and “noise,” which leads to uncertainties that have complex, possibly intermittent nonstationary behavior on different time scales. We also urge the community to test methods using realistic “pseudo-proxies” as they offer a good laboratory.

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4. S. Gerber *et al.*, *Clim. Dyn.* **20**, 281 (2003).
5. IPCC (Intergovernmental Panel on Climate Change), *Climate Change 2001: The Scientific Basis* (Cambridge Univ. Press, Cambridge, 2001), fig. 2.21, p. 134.
6. M. E. Mann, S. Rutherford, E. Wahl, C. Ammann, *J. Clim.* **18**, 4097 (2005).

Team Science and the NIBIB

I WOULD LIKE TO EXPLORE ISSUES RELATING TO the funding of biomedical engineering and imaging at the National Institute of Biomedical Imaging and Bioengineering (NIBIB) that are raised in an article on the Whitaker Foundation

(“Spending itself out of existence, Whitaker brings a field to life,” D. Grimm, News Focus, 3 Feb., p. 600).

Fiscal year 2005 was the NIBIB’s third full year with an operating budget and its third year with a double-digit percentage annual growth in grant applications received. Even in the face of this large growth, the NIBIB’s budget projections and management plan resulted in paying to the 20th percentile, well within the range of paylines for the more established institutes. In addition, nearly all of the funded applications contained bioengineering, even those internally labeled as “imaging.” Because this type of science is fundamentally interdisciplinary, it is difficult to accurately describe the relative support of biomedical imaging and bioengineering, reflecting progress toward achieving the goal of team science.

In addition to the pervasive bioengineering content in our research portfolio, the institute has multiple training programs that target bioengineering, interdisciplinary science, and young investigators. Indeed, the majority of the NIBIB’s current training budget supports such programs. Of note, the NIBIB seeks to significantly enhance the success of new investigators through its policy that increases the payline by 5 percentile points for first-time investigators. During the last fiscal year, this policy resulted in 33% more funded first-time NIBIB investigators.

It is the team science approach, inclusive of young investigators, that is critical for realizing our vision of profoundly improving health care through technological innovation.

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Funding for Young Investigators at Whitaker

WE WISH TO ADD SOME ADDITIONAL INFORMATION to the points made in the News Focus article “Spending itself out of existence, Whitaker brings a field to life” (D. Grimm, 3 Feb., p. 600). First, it should be noted that nonimaging-related biomedical engineering research was relatively underfunded, not that most of the funding was supporting clinical imaging research. For example, the 2004 numbers indicated that nonimaging research projects constituted less than 40% of the funded individual investigator-initiated grants. Second, the total

research support for biomedical imaging and bioengineering provided by the NIBIB is insufficient to meet the large demands spawned by the Whitaker Foundation in this exploding field. Not only is the NIBIB the second smallest institute, but because of its establishment in 2002, it did not benefit from the doubling of the NIH budget that all other institutes previously enjoyed. Finally, the comment about "not stepping up to the plate" by Nerem referred only to the issue of funding new investigators, which was the specific focus of the young investigator award program of the Whitaker Foundation. For the United States to remain the leader in this highly competitive field, it is important that the NIBIB step in with its own young investigator program to support the bright young people entering the world of biomedical imaging and bioengineering. It is equally important that Congress contribute by providing increased funding for the NIBIB so that the citizens of the United States can reap the benefits of this new area of science and technology.

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Caspase-10 in Mouse or Not?

THE FAMILY OF ASPARTATE-SPECIFIC AND CYSTEINE-dependent proteases, called caspases, is crucial not only for apoptosis but also for differentiation and cell cycle progression. Several research groups have recently published data ruling in or out the participation of caspase-10, an initiator caspase functioning at the apex of death receptor signaling, in diverse apoptotic processes and in neuroblastoma metastasis (1–5). Curiously, these conclusions were reached from experiments performed in mouse cells, a species that, according to all public databases and a recent study by Reed and colleagues (6), does not contain the *CASP-10* gene in its genome.

How is it possible that these reports still assume the presence of caspase-10 in the mouse? An explanation might be the use of inadequate tools to study processing and activation of caspase-10, such as antibodies and so-called caspase-specific inhibitory peptides. Indeed, all of the above studies used either unspecified caspase-10 antibodies or antibodies that are certified in their respective companies' data sheets to react with cellular extracts of human, mouse, and rat origin. The *CASP-10* gene is also absent from the rat genome. Indeed, a search for commercially available caspase-10 antibodies found that 19 out of 44 caspase-10 antibodies that are distributed by 24 companies are specified on their data sheets

to react with mouse or rat tissues. Another seven antibodies were only tested with human cells, and the specificity of at least six other caspase-10 antibodies that supposedly react only with extracts from human cells could be questioned, as they were generated with the same immunogenic peptide as were antibodies that cross-react with mouse and rat tissues.

In addition, many groups based their conclusions about the presence of caspase-10 in the mouse on the utilization of the alleged caspase-10-specific AEVD peptide. However, most caspases including caspase-3 and -8 display an even higher affinity for this substrate (K_i of 42 and 1.6 nM, respectively) than caspase-10 itself (K_i , 320 nM) (7).

Although the responsibility for this misconception lies clearly in the hands of the individual researchers (and maybe also with the reviewers of the manuscripts), the various companies claiming specificity and applicability of their antibodies in mouse systems are also responsible.

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Role of iNOS in Human Host Defense

IN 2001, S. THOMA-USZYNSKI *ET AL.* WROTE IN *Science*, "in humans the TLR-activated antimicrobial pathway is NO [nitric oxide]–independent" (1). In the Report "Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response" (P. T. Liu *et al.*, 24 Mar., p. 1770; published online on 23 Feb.), authors from the same laboratories expanded this view to assert that "antimicrobial activity against intracellular bacteria ... in murine, but not human, monocytes and macrophages is mediated principally by nitric oxide" and that this establishes "the evolution of divergent antimicrobial pathways in mice ... versus humans. ..." The conclusion that humans lack this nitric oxide defense pathway in mononuclear phagocytes is based on *in vitro* findings that differ in a critical respect from observations of human macrophages *in vivo* and *ex vivo*. Thoma-Uzynski *et al.* (1) and Liu *et al.* cultured human monocytes under conditions that result in little or no expression of inducible NO synthase (iNOS). In contrast, *in vivo* and

ex vivo, human macrophages do express iNOS in people with infectious and inflammatory diseases (2, 3), notably in tuberculosis.

The role of iNOS in human host defense remains unresolved. The experiments (4–6) that established the role of iNOS in host defense in mice cannot be performed in people. However, when macrophages expressing iNOS were recovered from patients and infected with mycobacteria *in vitro*, iNOS inhibitors abolished the macrophages' antimycobacterial activity (7).

When a cell type consistently expresses an enzyme *in vivo*, but differentiates *in vitro* so that the enzyme is lacking, the cell culture system must be considered deficient as a model. Results in a nonphysiologic cell culture system are not a sound basis for declaring that human evolution has branched off to abandon the use of NO in host defense.

The shortcomings of *in vitro* systems for human macrophage differentiation are frustrating, particularly because it is so difficult to access human macrophages that have undergone full differentiation and immunologic activation *in vivo*. Nonetheless, a cell culture model is useful only to the extent that it reflects the biology of the organism. At present, scientists lack the ability to induce iNOS consistently in human macrophages derived *in vitro* from the monocytes of healthy donors. *In vitro* studies that truly assess the role of iNOS in human host defense await the development of techniques for iNOS induction in cultured human macrophages that can match that in macrophages of people with disease.

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Response

A KEY POINT IN OUR RECENT PAPER WAS ONLY partially quoted by Nathan. The complete quote follows: "In innate immune responses, activation of Toll-like receptors (TLRs) triggers direct antimicrobial activity against intracellular bacteria, which in murine, but not human, monocytes and macrophages is mediated principally by nitric oxide." Our data do establish mechanisms by which activation of the innate immune system via TLRs leads to antimicrobial activity, and in this context, it is not unreasonable to suggest "the evolution of divergent antimicrobial pathways in mice (nocturnal animals that use nitric oxide) versus

humans (daytime creatures that synthesize vitamin D₃ in the skin on exposure to UV light)." We were careful to state in the paper that, "We do not imply that this is the only antimicrobial mechanism available to human macrophages." Nathan's research on nitric oxide in acquired immunity is clearly important and is cited in our paper. We look forward to learning the mechanism by which nitric oxide is activated in human macrophages and contributes to immunity to tuberculosis.

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TECHNICAL COMMENT ABSTRACTS

COMMENT ON "Ancient DNA from the First European Farmers in 7500-Year-Old Neolithic Sites"

Albert J. Ammerman, Ron Pinhasi,
Eszter Bánffy

On the basis of analysis of ancient DNA from early European farmers, Haak *et al.* (Reports, 11 November 2005, p. 1016) argued for the Paleolithic ancestry of modern Europeans. We stress that the study is more limited in scope than the authors claim, in part because not all of the skeletal samples date to the time of the Neolithic transition in a given area of Europe.

Full text at www.sciencemag.org/cgi/content/full/312/5782/1875a

RESPONSE TO COMMENT ON "Ancient DNA from the First European Farmers in 7500-Year-Old Neolithic Sites"

Joachim Burger, Detlef Gronenborn,
Peter Forster, Shuichi Matsumura,
Barbara Bramanti, Wolfgang Haak

The discovery of mitochondrial type N1a in Central European Neolithic skeletons at a high frequency enabled us to answer the question of whether the modern population is maternally descended from the early farmers, instead of addressing the traditional question of the origin of early European farmers.

Full text at www.sciencemag.org/cgi/content/full/312/5782/1875b

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Testing Climate Reconstructions

Stefan Rahmstorf

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