in the VEGFR-1–mediated growth and survival pathway, because Kupffer cells (macrophages located within the liver sinusoids) express VEGFR-1 and secrete multiple cytokines in response to injury. The importance of these other cell types in this pathway could be addressed by making a conditional knockout mouse in which all of the endothelial cells in the adult lack VEGFR-1. Such a mouse model could be used to investigate whether the VEGFR-1 pathway is activated during injury to other organs.

The relatively specific effects of the VEGFR-1 pathway on the liver pave the way for the development of therapeutic drugs to treat or protect hepatocytes from diseases such as liver cirrhosis or chronic hepatitis. Ligands such as Flt^{sel}, or small-molecule VEGFR-1 agonists, may offer a biological advantage over other hepato-protective molecules. For example, HGF is a potent hepato-protective agent, but it can also affect other organ systems and possesses an intrinsic ability to promote the invasiveness of neoplastic cells (*9*). As we learn more about the signals that are exchanged between the endothelium and organs, we may discover other tissue-specific pathways that can be therapeutically targeted. Like all good relationships, it is just a matter of finding the right "chemistry."

References and Notes

1. J. LeCouter *et al.*, *Science* **299**, 890 (2003).
2. R. S. Cotran, V. Kumar, T. Collins, *Robbins Pathologic Basis of Disease* (Saunders, Philadelphia, PA, 1999).
3. K. Matsumoto *et al.*, *Science* **294**, 559 (2001).
4. N. Bahary, L. I. Zon, *Science* **294**, 530 (2001).
5. Reviewed in N. Fausto, J. S. Campbell, *Mech. Dev.* **120**, 117 (2003).
6. K. Ishikawa *et al.*, *Biochem. Biophys. Res. Commun.* **254**, 587 (1999).
7. T. Kaido *et al.*, *FEBS Lett.* **411**, 378 (1997).
8. S. Hiratsuka *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **95**, 9349 (1998).
9. M. Jeffers *et al.*, *Mol. Cell. Biol.* **16**, 1115 (1996).

COMPUTATIONAL MATHEMATICS

Full Steam Ahead—Probably

Ralph Lorenz

Complex systems like Earth's climate may organize themselves to produce entropy at the maximum rate permitted by their circumstance. A paper in the *Journal of Physics A* (*1*) shows why, but concedes that it is only usually true.

Carnot (*2*) compared the flow of heat from hot to cold to the downhill flow of water, although he said nothing about how fast the heat would flow. Much modern thermodynamics considers just such non-equilibrium situations in which an external input flow of energy keeps things moving. Planetary climate is just such a situation, with the tropics being kept warm by extra sunlight. As heat flows from warm to cold, it can perform work, generating our weather. But how much work?

Edward Lorenz (*3*), the "father of chaos," pointed out in 1960 that the work output of Earth's atmosphere might be close to the maximum possible. Based on the observed state of the Earth, he argued that if the heat flow were lower than it is, the resulting large temperature gradients would drive motions more vigorously. The system should therefore tend to a maximum in work output.

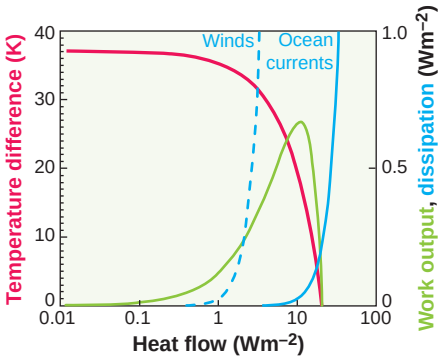
More recent investigations tend to be inspired by the work of Paltridge (*4*). Likening the ever-increasing resolution of general circulation models (GCMs) to attempts to understand a gas by monitoring every molecule, Paltridge sought an overall principle that might capture the net behavior of the atmosphere. He found that satisfactory agreement with Earth's climate state could be obtained by assuming that the atmospheric heat transports organized themselves to a maximum entropy production (MEP) state—a state in which the work output, the product of the heat flux and the temperature gradient driving it, is largest.

Like the Gaia hypothesis, this idea smacks of endowing the system with teleological intent and presents philosophical challenges to the deterministic dynamical approach of conventional meteorology. It suffered from two main criticisms. First, Paltridge's result, while not disputed, could simply be coincidence. But that argument became harder to sustain with the realization (*5*) that Saturn's moon Titan seems also to be in an MEP state: The temperatures observed there require heat transport to be very weak, as predicted from MEP, whereas the conventional expectation would be that transport should be very strong on this small, slowly rotating world with its thick atmosphere.

A second objection was that Paltridge offered no reason for why systems should choose this state. Dewar's paper (*1*) may have finally filled that void by showing, with the formal algebra of information theory and statistical mechanics developed by Jaynes (*6*), how the maximum entropy production state becomes the most probable state—if the system is forced weakly enough to be able to choose which state to reside in.

This result is not an imperative, but rather a statistical likelihood. This lack of rigor applies to the second law of thermodynamics itself. The second law says entropy must increase. Yet, the statistics of atomic collisions are such that every so often more molecules will hit an object (such as a pollen grain) on one side than on the other, and the object will appear to move spontaneously—an apparent gain of ordered kinetic energy from nowhere. Energy is conserved, in that the molecules transfer it to the object, but entropy fleetingly decreases, in that the random motions of molecules have conspired to move a macroscopic object. The statistics of these fluctuations, whose probability tends to zero as the duration or magnitude rises, were recently determined (*7*) in a delicate experiment to be exactly in accordance with predictions.

We can also use a statistical approach to determine whether Earth's climate is in an MEP state. There are many modes of transporting heat. Some, like fluctuating winds, involve lots of mechanical dissipation (*8*), whereas others, like the ocean currents, do not (see the figure). A steady-state solution will balance the dissipation required by the combination of modes with the work that the corresponding heat flow can produce. Despite the empirical agreement tuned into



Maximizing the work. In a two-box model of Earth's climate (low and high latitudes), the temperature contrast (red line) falls as the atmospheric and ocean heat flows increase. The corresponding work that can be produced (green line) has a maximum at the present climate, exactly where the maximum in entropy production occurs. The work that can be produced is balanced by frictional dissipation. The dashed blue line shows dissipation for a high-loss mode, like winds, while the solid blue line shows an efficient mode, like ocean currents. In a stable-climate solution, a linear combination of the two modes (and the many others) dissipate exactly the amount of work they produce. At the peak in work production, there is room for more combinations than elsewhere, so the climate is most likely to be in that state.

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GCMs, this is an underconstrained problem with many possible solutions. Similar problems are encountered in astronomy when trying to determine which of many possible original images was blurred by an imperfect telescope to yield the observed smudge.

A "best guess" approach to such underconstrained problems was advocated by Jaynes, whose work is extended by Dewar. The best guess is that which has the highest Shannon entropy (a measure of information content). As long as the system can choose from a rich ensemble of modes, it follows that it will most probably reside in or close to the states with maximum dissipation. These states offer the largest number of possible solutions (combinations of modes that exactly dissipate the work that is produced). Similar ideas have been explored in river network self-organization (*9*).

The MEP idea also holds for constrained nonequilibrium systems that fix the gradient or flux—such as the temperature gradient in a Rayleigh-Benard convection experiment (in which a fluid is heated from below), or the sand flux on a sandpile (*10*). In response to the constraint, the systems maximize the other parameter—the heat flow in convection, the angle in the sandpile experiment—thereby maximizing their product, the entropy production. As a result, the heat flux in convection is maximized, and the angle of a sandpile is generally limited to the angle of repose.

Dewar's work puts MEP on a much sounder footing. Laboratory investigations that demonstrate MEP would be an important further advance. The growth of NH_4Cl crystals has already been shown (*11*) to switch modes to select MEP. Entropy production is now being explored in numerical climate models. In one recent study (*12*), perturbations to an ocean circulation model always resulted in a jump to a state with higher entropy production, except when the perturbation destroyed the system's initial state altogether.

Some puzzles remain. All else being equal, MEP would predict a planet's meridional temperature contrast to be independent of its rotation rate. This disagrees with some rudimentary GCM experiments, and with meteorologists' intuition. The MEP idea continues to generate considerable friction among climate modelers—but perhaps that is exactly what we should expect.

References

1. R. L. Dewar, *J. Phys. A. Math. Gen.* **36**, 631 (2003); preprint available at http://arxiv.org/abs/cond-mat/0005382).
2. S. Carnot, *Reflections on the Motive Power of Heat* (Bachelier, Paris, 1824).
3. E. N. Lorenz, in *Dynamics of Climate*, R. L. Pfeffer, Ed. (Pergamon, Oxford, 1960), pp. 86–92.
4. G. W. Paltridge, *Q. J. R. Meteorol. Soc.* **101**, 475 (1975).
5. R. D. Lorenz, J. I. Lunine, C. P. McKay, P. G. Withers, *Geophys. Res. Lett.* **28**, 415 (2001).
6. E. T. Jaynes, *Phys. Rev.* **106**, 620 (1957).
7. G. M. Wang, E. M. Sevick, E. Mittag, D. J. Searles, D. J. Evans, *Phys. Rev. Lett.* **89**, 050601 (2002).
8. R. D. Lorenz, *J. Non-Equilib. Thermodyn.* **27**, 229 (2002).
9. A. Rinaldo *et al.*, *Phys. Rev. Lett.* **76**, 3364 (1996).
10. P. Bak, *How Nature Works* (Springer-Verlag, New York, 1998).
11. A. Hill, *Nature* **348**, 426 (1990).
12. S. Shimokawa, H. Ozawa, *Q. J. R. Meteorol. Soc.* **128**, 2115 (2002).

CELL BIOLOGY

NO Says Yes to Mitochondria

Guy C. Brown

Mitochondria are the microscopic powerhouses in our cells. They generate almost all of our energy and heat, and consume most of our oxygen and food calories. They are also the central controllers of cellular metabolism and the executioners of programmed cell death (apoptosis). The gas nitric oxide (NO)—identified in 1987 as a vasodilator of blood vessels—undertakes a bewildering array of regulatory tasks in the cell, many of which involve mitochondria. On page 896 of this issue, Nisoli *et al.* (*1*) tie these separate fields together with their finding that NO stimulates the synthesis (biogenesis) of new mitochondria.

Enhanced online at www.sciencemag.org/cgi/content/full/299/5608/838

Originally identified as a vasodilator, NO regulates the flow of blood to tissues. This in turn controls the supply of oxygen and respiratory substrates to mitochondria, and the redistribution of heat generated by those mitochondria. More recently, NO has been found to directly regulate the binding and release of oxygen from hemoglobin (*2*), and in this way controls the supply of oxygen to mitochondria. NO also carries out a very different task for the innate immune system: the killing of virally infected cells, tumor cells, and parasitic pathogens (*3*). The inducible isoform of NO synthase (iNOS) produces large quantities of cytotoxic NO, but normally only during inflammation. (If inflammation becomes chronic, then healthy host cells also may be killed by NO, contributing to inflammatory pathologies.) NO is cytotoxic partly because it inactivates the mitochondrial respiratory chain enzymes of virally infected cells, tumor cells, and parasites, and partly because it stimulates the mitochondrial pathway of apoptosis (*3*–*5*). At high concentrations, NO inhibits many components of the respiratory chain, including the oxygen binding site of cytochrome oxidase (*4*, *5*). This ability of NO to reversibly block mitochondrial respiration and oxidative phosphorylation has led to the idea that NO may regulate mitochondrial energy production (*3*, *4*). The finding that mitochondria contain their own isoform of NO synthase, mitochondrial NOS (mtNOS), is consistent with direct regulation of mitochondrial energy production by NO (*6*).

The ability to regulate the number of mitochondria in our cells is crucial for all sorts of physiological processes, including embryonic development, movement, fat metabolism, and aging. But how do cells control the number of mitochondria they contain? The recent discovery of a master regulator of mitochondrial biogenesis, PGC-1α (peroxisome proliferator-activated receptor γ coactivator 1α), is beginning to shed light on the underlying mechanisms. Overexpression of PGC-1α in transgenic mice results in increased numbers of mitochondria in cardiac and skeletal muscle (*7*, *8*). PGC-1α is a transcriptional coactivator that increases expression of nuclear respiratory factor–1 (NRF-1) and mitochondrial transcription factor A (mtTFA), which in turn promote the expression, respectively, of nuclear and mitochondrial genes that are required for mitochondrial biogenesis (*8*). PGC-1α is known to be up-regulated under conditions that promote the synthesis of new mitochondria (*7*, *8*), for example, during prolonged exposure of rats to cold temperatures. Cold exposure activates the rat's brown adipose tissue through stimulation of β_3-adrenergic receptors, leading to an increase in cellular calcium ions and in the signaling molecule, cAMP (see the figure). This results in enhanced PGC-1α production and an increase in the numbers of mitochondria in the adipocyte cells of brown fat, which generates body heat (*6*). Nisoli and colleagues now report the missing link in this causal chain: NO generated by endothelial nitric oxide synthase (eNOS), which may have been activated by calcium ions and/or phosphorylation, increases cGMP levels (*1*). This in turn up-regulates production of PGC-1α and biogenesis of mitochondria. These authors found that overexpression of NO, cGMP, or eNOS dramatically increased the numbers of mitochondria in a range of cell lines and in differentiating brown fat adipocytes. Furthermore, mice lacking functional eNOS exhibited decreased numbers of mitochondria in a wide range of tissues, decreased energy metabolism, and increased weight gain (*1*). The implication is that NO produced by

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