high $\Delta^{13}CH_3D$ values at CROMO suggest that methane here could be sourced from a mixture of thermogenic and microbial methane. Alternatively, lower $H_2$ availability at CROMO, compared with The Cedars (table S4), may support microbial methanogenesis under near-equilibrium conditions (Fig. 4). Regardless, the different isotopologue signatures in methane from CROMO versus The Cedars demonstrate that distinct processes contribute to methane formation in these two serpentinization systems.

Deep, ancient fracture fluids in the Kidd Creek mine in the Cretaceous Shield (33) contain copious quantities of both dissolved methane and hydrogen (5). The Kidd Creek methane occupies a distinct region in the diagram of $\Delta^{13}CH_3D$ versus $\epsilon_{CH4/water}$ (Fig. 2), due to strong $D/H$ disequilibria between methane and water (4) and low-$\Delta^{13}CH_3D$ temperature signals of $56^\circ$C to $90^\circ$C that are consistent with other temperature estimates for these groundwaters (4). Although the specific mechanisms by which the proposed abiotic hydrocarbons at Kidd Creek are generated remain under investigation (5, 32), the distinct isotopologue signals provide further support for the hypothesis that methane here is neither microbial nor thermogenic. Our results demonstrate that measurements of $\Delta^{13}CH_3D$ provide information beyond the simple formation temperature of methane. The combination of methane and water hydrogen-isotope fractionation and $\Delta^{13}CH_3D$ abundance enables the differentiation of methane that has been formed at extremely low rates in the subsurface (3, 21, 27) from methane formed in cattle and surface environments in which methanogenesis proceeds at comparatively high rates (33, 34).

REFERENCES AND NOTES

19. Materials and methods are available as supplementary materials on Science Online.
23. The abundance of $^{13}CH_3D$ is captured by a metric, $\Delta^{13}CH_3D$, that quantifies its deviation from a random distribution of isotopic substitutions among all isotologues in a sample of methane: $\Delta^{13}CH_3D = ln Q$, where Q is the reaction quotient of the isotope exchange reaction $^{12}CH_3 + ^{12}H_2O$ $\rightarrow$ $^{13}CH_3 + ^{12}H_2$. The reported $\Delta^{13}CH_3D$ values are conventional isotopic notation, e.g., $^{13}D$/$^{12}D$$_{sample}$/$^{13}D$/$^{12}D$$_{standard}$. $^{13}CH_3$D mass spectrometric measurements yield $\Delta^{13}CH_3D$, a parameter that quantifies the combined abundance of $^{13}CH_3D$ and $^{12}CH_3D$. For most natural samples of methane, $\Delta^{13}CH_3D$ temperature is fractionated to $\Delta^{13}CH_4D$ temperature, as measured by laser spectroscopy. The $D/H$ fractionation between methane and environmental water is defined as $\epsilon_{CH4/water}$ = ($D/H$_{sample}$)/($D/H$_{standard}$) – 1.

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SUPPLEMENTARY MATERIALS

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ISOTOPE GEOCHEMISTRY

Biological signatures in clumped isotopes of $O_2$

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The abundances of molecules containing more than one rare isotope have been applied broadly to determine formation temperatures of natural materials. These applications of “clumped” isotopes rely on the assumption that isotope-exchange equilibrium is reached, or at least approached, during the formation of those materials. In a closed-system terrarium experiment, we demonstrate that biological oxygen ($O_2$) cycling drives the clumped-isotope composition of $O_2$ away from isotopic equilibrium. Our model of the system suggests that unique biological signatures are present in clumped isotopes of $O_2$—and not formation temperatures. Photosynthetic $O_2$ is depleted in $^{18}O$ and $^{17}O$ relative to a stochastic distribution of isotopes, unlike at equilibrium, where heavy-isotope pairs are enriched. Similar signatures may be widespread in nature, offering new tracers of biological and geochemical cycling.

\textbf{Statistical thermodynamics predicts that heavy isotopes will be bound together in a molecule more often than predicted by chance alone, provided the system is at iso-}

topic equilibrium (1, 2). This preference for heavy-isotope pairing and its variation with temperature forms the basis of clumped-isotope thermometry (3–5), a class of approaches based on precise measurements of molecules containing more than one rare isotope. When isotope-exchange reactions facilitate the equilibration of heavy-isotope pairs, the resulting isotopic distribution

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has indeed been shown to achieve equilibrium across a wide range of temperatures (4, 6–8); however, isotopic equilibration is the exception rather than the rule in nature. Biogenic substances, for example, are often formed through irreversible enzymatic reactions for which isotope-exchange equilibrium cannot be expected a priori. Yet, many natural materials with kinetically constrained and/or biological origins (e.g., carbonate shells) show only minor departures from equilibrium isotope fractionation (9–11). Large biological and physical effects on heavy-isotope pairing could complicate the interpretation of emerging clumped-isotope thermometers in methane, O₂, and other candidate systems (4, 5, 12).

Here, we consider photosynthetic O₂ formation from water at the oxygen-evolving complex of Photosystem II (OEC). In the OEC, O–O bond formation occurs at the end of a five-step light-dependent sequence (Fig. 1). This reaction most likely does not equilibrate O–O isotope pairs given the lack of isotopic equilibration between water and the O₂ produced (13–16). We argue that the tendency for two heavy oxygen isotopes to be bound together during oxygenic photosynthesis reflects primarily the isotopic preferences of water molecules binding to the OEC. These patterns of heavy-isotope pairing should be apparent in clumped isotopes of O₂. Measurements of the 36ΟΟ(36) and 18ΟΟ(35) isotopologues of O₂, together with bulk isotopic ratios (18Ο/16Ο and 17Ο/16Ο), characterize the number of heavy-isotope pairs in a sample relative to the number expected by chance alone (i.e., the stochastic distribution). These deviations are quantified as Δ35 and Δ36 values: Excesses of 18Ο/16Ο and 17Ο/16Ο relative to the stochastic distribution of isotope abundances in the sample results in Δ35 > 0 and Δ36 > 0, respectively. A deficit in 18Ο/16Ο and 17Ο/16Ο results in Δ35 < 0 and Δ36 < 0.

The Δ35 and Δ36 signatures of oxygenic photosynthesis can thus be estimated by assigning each water-binding site its own isotopic fractionation factor α = ∆Oxygen/∆Water, where ∆H is the ratio of O₂ to ^{16}O atoms in each reservoir. At natural isotopic abundances, the bulk isotopic composition of photosynthetic O₂ is the weighted sum of those contributions—i.e., 18ο = 1/2(18ο Rwater × αα) + 1/2(18ο Rwater × αa), with binding sites A and B each contributing one of two oxygen atoms in each O₂ molecule. The probability of generating 18Ο/16Ο bonds is therefore 18ο = 1/2(18ο Rwater × αα) + 1/2(18ο Rwater × αa). The stochastic distribution of 18Ο atoms is calculated from the bulk 36Ο/16Ο ratio as 36ο = 1/2(36ο Rwater × αα) + 1/2(36ο Rwater × αa). The expression for Δ35,R values then reduces to (17)

\[ \Delta_{35,R} = \frac{\alpha_a - \alpha_R}{\alpha_a + \alpha_R} \]  

Equation 1 reveals that, in all cases, Δ35,R ≤ 0; contrary to the enhanced heavy-isotope pairing that would be expected at isotopic equilibrium, there is an apparent aversion to heavy-isotope pairing associated with photosynthetic O₂ production. If the isotopic preferences at each water-binding site are equal (αa = αR), then Δ35,R = 0. If the binding sites are not equivalent (αa ≠ αR), as isotope-labeling studies indicate (18, 19), then 0 ≥ Δ35,R > -1/2 per mil (‰) for plausible α-values between 0.97 and 1.03 (20, 21). A similar expression can be derived for Δ35,R values, which are predicted to be about half those of Δ35,R (see the supplementary text). These values cannot be interpreted as formation temperatures because all equilibrated samples have Δa ≥ 0 (2). Photosynthesis should therefore impart a distinct non-equilibrium clumped-isotope signature on O₂.

We conducted a closed-system terrarium experiment with six water hyacinths (Eichhornia crassipes) to explore the effects of biological oxygen cycling on five isotopologues of O₂ (17). The terrarium was illuminated with fluorescent lights on a 12-hour/12-hour light-dark cycle. Headspace samples were purified and analyzed over a 1-year period for both the bulk and clumped isotopic composition of O₂. We found that biological oxygen cycling altered isotopic ordering in the headspace O₂, yielding apparent steady-state Δ35 and Δ36 values that are inconsistent with O₂ formation temperatures and more consistent with the predicted photosynthetic endmembers (Fig. 2 and table S3). The Δ35 and Δ36 values of O₂ were driven down from atmospheric values (2‰ and 1‰, respectively) and down past equilibrium values at 25°C (1.5‰ and 0.8‰, respectively), finally approaching an apparent isotopic steady state at the schematic distribution of isotopes (Δ35 = -0.01 ± 0.08‰, and Δ36 = 0.0 ± 0.18‰; 1 SEM, n = 4). The plant community shifted to an algae-dominated ecosystem during the first 6 months, altering the isotopic, chemical, and physical properties of the terrarium (fig. S1). However, the clumped-isotope composition of the headspace O₂ evolved steadily toward its apparent steady state, similar to the evolution of the oxygen triple-isotope composition. Steady-state D18O values were 165 parts per million (ppm), consistent with those reported in similar experiments (22, 23).

Dark incubations of the terrarium, which consumed up to 35% of the headspace O₂, caused Δ35,R values to increase linearly with time up to ~1‰ (Fig. 2). The Δ35,R values, in contrast, remained generally constant (means of 0.9 ± 0.1‰ and 0.3 ± 0.05‰, 1 SD). Returning to light-dark cycles restored the clumped-isotope composition to its apparent steady-state value after 6 months (Δ35 = -0.09 ± 0.06‰, and Δ36 = 0.0 ± 0.18‰, 1 SEM, n = 3). To test the veracity of these measurements, headspace O₂ samples drawn from both light and dark incubations were photolytically equilibrated at known temperatures (4). The equilibriums yielded Δ35,R and Δ36,R values of O₂ consistent with isotope-exchange equilibrium (table S3), suggesting that our observations are unlikely to be analytical artifacts. Atmospheric O₂ leaking into the terrarium would increase 18O significantly too rapidly relative to Δ35,R to explain these observations. The observed clumped-isotope variations therefore most likely arise from biological and physical processes inside the terrarium.

We constructed a two-reservoir model of O₂ (i.e., in headspace and water) in the terrarium that accounts for photosynthetic O₂ formation, fractionation of O₂ due to respiration, and air-water gas exchange (17). We included kinetic isotope fractionation for gas transfer into and out of solution (180, 180 kinetic = 0.9972) for O₂ (24). The model was run with a range of plausible isotope fractionation factors for respiration (180 kinetic = 0.97 – 0.99 (25, 26)) and gas-exchange rates (24, 27) to examine the sensitivity of the terrarium headspace to changes in those quantities. The oxygen triple-isotope composition of the terrarium water was measured and used as the bulk isotopic composition of photosynthetic O₂ (13, 15, 17). No single set of parameters explained all of the isotopic variations during the entire experiment, likely due to the evolving biological community, so we focus on isotopic variations at steady state and during dark incubations.

The increase of headspace Δ35,R and Δ36,R values in the dark implies that the apparent steady-state values near zero can only be reached if light-dependent processes drive Δ35,R and Δ36,R values below zero. Equation 1 suggests that photosynthesis could be the relevant mechanism, because the O₂ generated is likely to have Δ35,R and Δ35,R values less than zero. To estimate the composition of this source, we note that kinetic and equilibrium isotope effects for relevant photosynthetic fractionations are probably in the range 0.96 > ∆18O > 1.04 (20, 21), which we broaden to a more conservative plausible range of 0.9 > ∆18O > 1.1. This range of isotope effects gives lower limits on Δ35,R and Δ36,R of ~10‰ and ~5‰, respectively.

If the Δ36,R increase during dark incubations were solely caused by fractionation in respiration, then large isotope effects in water-enzyme binding would be required: Δ35,R < -10‰ is needed to achieve steady-state values of Δ35,R near zero (17). In addition, the associated Δ35,R < ~5‰
endmember composition causes poor agreement between measured and modeled $\Delta_{35}$ values (fig. S4C). Furthermore, an increase in respiration rates would drive $\Delta_{35}$ and $\Delta_{36}$ values higher, whereas a decrease in respiration rates would drive the $O_2$ toward its $\Delta_{36P}$ and $\Delta_{35P}$ photosynthetic values (17). Therefore, when the $O_2$ cycle was out of balance in the first 6 months, $\Delta_{35}$ would have fluctuated inversely with $O_2$ concentration (fig. S4, B and C). Instead, both $\Delta_{35}$ and $\Delta_{36}$ decreased nearly monotonically.

Isotopologue fractionation during nonequilibrium $O_2$ gas exchange could explain the increases of headspace $\Delta_{35}$ and $\Delta_{36}$ values during dark incubations. The fractionation in headspace $^{16}O^{18}O/^{16}O^{16}O$ is closer to that for gas exchange than that for respiration ($^{16}O^{18}O/^{16}O^{16}O = 0.995$ versus $^{16}O^{18}O/^{16}O^{16}O = 0.9972$ versus $^{16}O^{18}O/^{16}O^{16}O = 0.98$), suggesting that the $\Delta_{35}$ and $\Delta_{36}$ increases are similarly dominated by gas exchange. Modeling the mass dependence of $O_2$ consumption in the dark, $\Delta_{35}$ and $\Delta_{36}$ are also more robust to imbalances in the $O_2$ cycle (17). Other oxygen-consumption mechanisms, such as sulfide oxidation, could impart additional isotopologue signatures (28), so attributing isotopologue discrimination in the dark to a single process is necessarily a simplification. Indeed, the implied mass dependence of $O_2$ consumption in the dark terrain is unusual, and it merits further investigation (17). A detailed understanding of isotopologue fractionation factors will require more controlled experiments of isolated biological and physical processes. Yet, the specific isotopologue discrimination during dark incubations does not affect the conclusion that photosynthesis generates $O_2$ with an “anticlumped” isotopologue distribution (i.e., $\Delta_{35} < 0$ and $\Delta_{36} < 0$). This biological signature in $O_2$ may be readily observed in the surface ocean, where it could be used to constrain gross primary productivity by exploiting the contrast between biological and atmospheric $O_2$ clumped-isotope signatures (29). Isotopic ordering in atmospheric $O_2$ is relatively unaffected by biological $O_2$ cycling because photochemical equilibration of $O_2$ exceeds rates of biological cycling by at least a factor of 100 (4, 30). Using a biological endmember composition of $\Delta_{35} = 0$, we calculate that biological effects on the tropospheric $\Delta_{35}$ budget are therefore most likely on the order of 0.01‰.

Our observations indicate that variations in the isotopologue abundance of even simple molecules like $O_2$ capture the chemistry of complex natural systems. Broader application of these techniques could yield insights into the mechanisms of biomolecule synthesis, e.g., methanogenesis, nitrogen reduction during denitrification, and molecular hydrogen release during nitrogen fixation (31). Moreover, because clumped-isotope signatures can depend only on isotope fractionation factors and not on the isotopic composition of substrates, a new class of reservoir-insensitive approaches for tracing biogeochemical cycling could emerge from these molecular-scale insights.

**REFERENCES AND NOTES**

RESEARCH | REPORTS

Big names or big ideas: Do peer-review panels select the best science proposals?

Danielle Li1* and Leila Agha2,*

This paper examines the success of peer-review panels in predicting the future quality of proposed research. We construct new data to track publication, citation, and patenting outcomes associated with more than 130,000 research project (R01) grants funded by the U.S. National Institutes of Health from 1980 to 2008. We find that better peer-review scores are consistently associated with better research outcomes and that this relationship persists even when we include detailed controls for an investigator’s publication history, grant history, institutional affiliations, career stage, and degree types. A one-standard deviation worse peer-review score among awarded grants is associated with 15% fewer citations, 7% fewer publications, 19% fewer high-impact publications, and 14% fewer follow-on patents.

In 2014, the combined budgets of the U.S. National Institutes of Health (NIH), the U.S. National Science Foundation, and the European Research Council totaled almost $40 billion. The majority of these funds were allocated to external researchers whose applications were vetted by committees of expert reviewers. But as funding has become more competitive and application award probabilities have fallen, some observers have posited that “the system now favors those who can guarantee results rather than those with potentially path-breaking ideas that, by definition, cannot promise success” (2, 3). Despite its importance for guiding research investments, there have been few attempts to assess the efficacy of peer review.

Peer-review committees are unique in their ability to assess research proposals based on broad expertise but may be undermined by biases, insufficient effort, dysfunctional committee dynamics, or limited subject knowledge (2,3). Disagreement about what constitutes important research may introduce randomness into the process (4). Existing research in this area has focused on understanding whether there is a correlation between good peer-review scores and successful research outcomes and yields mixed results (5–7). Yet raw correlations do not reveal whether reviewers are generating insight about the scientific merit of proposals. For example, if applicants from elite institutions generally produce more highly cited research, then a system that rewarded institutional rankings without even reading applications may appear effective at identifying promising research.

In this paper, we investigate whether peer-review generates new insights about the scientific quality of grant applications. We call this ability peer-review’s “value-added.” The value-added of NIH peer review is conceptually distinct from the value of NIH funding itself. For example, even if reviewers did a poor job of identifying the best applications, receiving a grant may still improve a researcher’s productivity by allowing her to maintain a laboratory and support students. Whereas previous work has studied the impact of receiving NIH funds on the productivity of awardees (8,9), our paper asks whether NIH selects the most promising projects to support. Because NIH cannot possibly fund every application it receives, the ability to distinguish potential among applications is important for its success.

We say that peer review has high value-added if differences in grants’ scores are predictive of differences in their subsequent research output, after controlling for previous accomplishments of the applicants. This may be the case if reviewers generate additional insights about an application’s potential, but peer review may also have zero or even negative value-added if reviewers are biased, mistaken, or focused on different goals (10).

Because research outcomes are often skewed, with many low-quality or incremental contributions and relatively few ground-breaking discoveries (2,11), we assess the value-added of peer review for identifying research that is highly influential or shows commercial promise. We also test the effectiveness of peer review in screening out applications that result in unsuccessful research (see the supplementary materials for full details on data and methods).

NIH is the world’s largest funder of biomedical research (12). With an annual budget of approximately $30 billion, it supports more than 300,000 research personnel at more than 2500 institutions (12,13). A funding application is assigned to topic one of approximately 200 peer-review committees (known as study sections).

Our main explanatory variable is the “percentile score,” ranging from 0 to 100, which reflects an application’s ranking among all other applications reviewed by a study section in a given fiscal year; lower scores correspond to higher-quality applications. In general, applications are funded in order of their percentile score until the budget of their assigned NIH institute is exhausted. The average score in our sample is 14.2, with a standard deviation (SD) of 10.2; only about 1% of funded grants in our sample had a score worse than 50. Funding has become more competitive in recent years; only 14% of applications were funded in 2013.

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SUPPLEMENTARY MATERIALS

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