In this issue . . .

Mapping past Solar System dynamics

Lake sediments in a Pennsylvania quarry, showing lake level cycles of the type used in the Geological Orrery.

Solutions of models for planetary motions are valid only within the past 60 million years, due to the chaotic nature of the Solar System. Geological records of climate variations modulated by orbital variations, which are older than 60 million years, could help extend such solutions further back in time. Paul Olsen et al. (pp. 10664–10673) used highly resolved data from two scientific coring experiments in lake sediments from the Late Triassic and Early Jurassic Epochs, approximately 220–199 million years ago. Using the data sets as a Geological Orrery—named after 18th-century mechanical planetaria—the authors recovered precise and accurate values for the precession frequencies of the perihelions of Mercury, Venus, Earth, Mars, and Jupiter. Certain combinations of the frequencies give rise to oscillations in Earth's motion that produce corresponding variations in climate, the 405-thousand-year pacing by Jupiter and Venus being the most stable clock. The Geological Orrery could be extended by the addition of paired low-latitude and high-latitude records spanning the early Paleogene to Permian Periods, 50–299 million years ago, allowing empirical mapping of orbital frequencies over this period. According to the authors, such mapping could constrain models of Solar System evolution and provide further tests of gravitational models. — B.D.

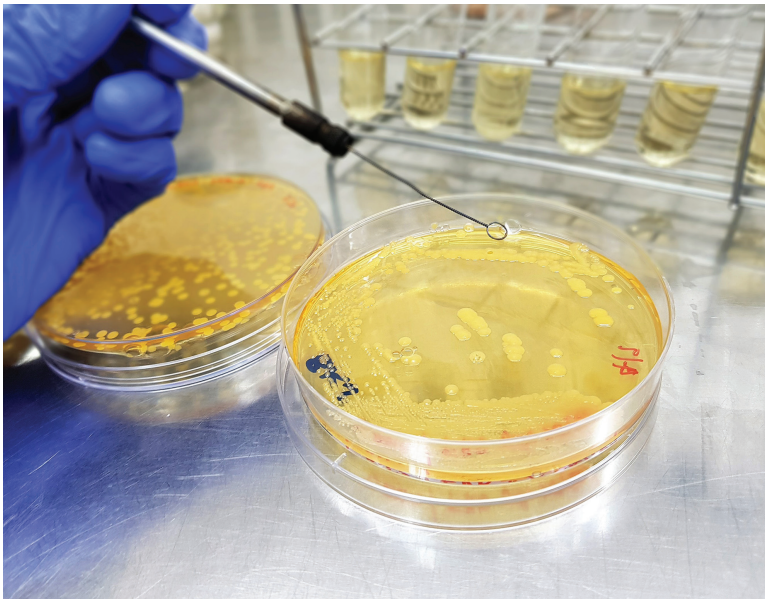
Institutional prestige and scientific productivity

Faculty at more prestigious institutions produce more of the scientific literature than faculty at less prestigious institutions. This imbalance is often attributed to a meritocratic system that rewards an individual's skill or effort. Exploring an alternative view, Samuel Way et al. (pp. 10729–10733) tested the extent to which external factors such as past and current work environments influence productivity. The authors analyzed a comprehensive dataset that documents the doctorate-to-faculty transitions of 2,453 tenure-track faculty at all 205 PhD-granting computer science departments in the United States and Canada, spanning 1970–2011, along with complete records of scholarly output through 2017. For matched pairs of faculty with appointments at similarly prestigious institutions, the individual who received doctoral training at the more prestigious institution was not more productive in the first 5 years after being hired. For matched pairs of faculty who received doctoral training at similarly prestigious institutions, the individual employed at the more prestigious institution produced, on average, 5.1 additional papers in the first 5 years after being hired. The results indicate that the scientific productivity of early-career faculty is influenced by the prestige of their current place of employment, not the prestige of their past training environment. According to the authors, the findings

suggest that past successes are locked in via placement into more prestigious departments, which directly facilitate future success. — J.W.

Engineered microbial production of grape flavoring

Methyl anthranilate (MANT) is a common grape flavoring and odorant compound currently produced through a petroleum-based process that uses large volumes of toxic acid catalysts. Zi Wei Luo, Jae Sung Cho, et al. (pp. 10749–10756) demonstrated production of MANT, a naturally occurring compound, via engineered bacteria. The authors



Engineered bacteria that produce grape flavor.

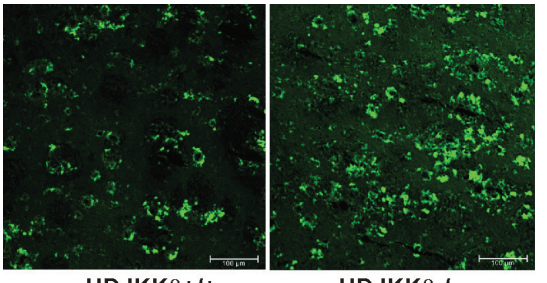
engineered strains of *Escherichia coli* and *Corynebacterium glutamicum* to produce MANT through a plant-based engineered metabolic pathway. The authors tuned the bacterial metabolic pathway by optimizing the levels of AAMT1, the key enzyme in the process. To maximize production of MANT, the authors tested six strategies, including increasing the supply of a precursor compound and enhancing the availability of a cosubstrate. The most productive strategy proved to be a two-phase extractive culture, in which the MANT was extracted into a solvent. This strategy produced MANT on the scale of 4.47 to 5.74 g/L, a significant amount considering that engineered microbes produce most natural products at a scale of milligrams or micrograms per liter. According to the authors, the results suggest that MANT and other related molecules produced through industrial processes can be produced at a feasible scale by engineered microbes in a manner that would allow them to be marketed as natural, instead of artificial, flavors. — P.G.

Angiotensin blockers and solid tumor immunotherapy

Immune checkpoint blockers (ICBs) unleash the brakes that prevent immune cells from recognizing and attacking cancer cells. Although ICBs have produced successful outcomes in some cancers, only a relatively small subset of patients have benefited from the approach, primarily due to the complex microenvironment that supports tumor growth. Vikash Chauhan, Ivy Chen, Rong Tong, et al. (pp. 10674–10680) report a therapeutic approach for solid tumors that combines ICBs with angiotensin receptor blockers (ARBs). The approach is aimed at switching off immunosuppressive cancer-associated fibroblasts (CAFs) found in the microenvironment of some nonresponsive tumors. Used primarily to treat high blood pressure, ARBs are also shown to inactivate the myofibroblast state of CAFs. To both mitigate systemic side effects, such as hypotension, and enhance the drug's specificity, the authors developed ARB nanoconjugates that preferentially accumulate in solid tumors by chemically linking ARBs to polymers chosen for their sensitivity to the tumor microenvironment. This approach allows tumor microenvironment-activated ARBs (TMA-ARBs) to remain inactive until they reach their targets. According to the authors' experiments using mice, TMA-ARBs can reprogram the tumor microenvironment into one that stimulates the immune system, tamps down CAFs, alleviates tumor hypoxia, and improves ICB treatment outcomes. — T.J.

Autophagy and neurodegeneration in Huntington's disease

In Huntington's disease (HD), a genetic mutation expands a polyglutamine repeat sequence within the huntingtin (HTT) protein, causing the protein to misfold and aggregate. In the healthy human brain,



IKK-ß reduction in an HD mouse model enhances neurodegeneration (Fluoro-Jade B staining) in striatal tissue.

HTT facilitates autophagy, a mechanism that delivers harmful proteins and damaged organelles to lysosomes for degradation. Joseph Ochaba et al. (pp. 10952–10961) report a potential relationship

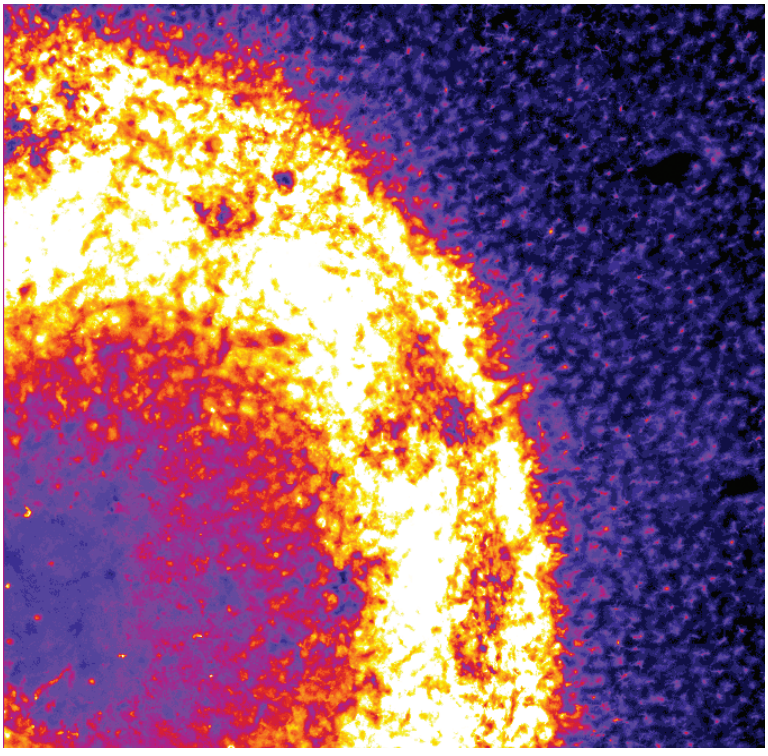
between HD pathogenesis and IKKβ—a subunit of the inflammatory IκB kinase complex—that stems from the role of the kinase in HTT phosphorylation and autophagy. Combining IKKβ knockout with an established HD mouse model, the authors demonstrated that loss of IKKβ function reduces HTT phosphorylation in both mutant HD mice and wild-type controls, and that IKKβ knockout exacerbates disease severity in HD mice in concert with decreased levels of endogenous phosphorylated HTT. The authors also found that the expression of a number of genes with known links to autophagy appear to be upregulated in HD mice relative to controls. However, IKKβ knockout diminished such upregulation in HD mice. The findings suggest that autophagy imbalance may tip the scale from cell survival to neurodegeneration in HD, and that early intervention via IKK activation may help slow the progression of HD. — T.J.

How dry air increases susceptibility to influenza

Influenza viruses cause seasonal outbreaks in temperate regions, with an increase in disease and mortality in the winter months. Dry air combined with cold temperature is known to enable viral transmission, but the impact of ambient humidity on host response to influenza virus infection and disease outcome remains unclear. Eriko Kudo, Eric Song, Laura Yockey, et al. (pp. 10905–10910) found that exposure to low humidity increases the susceptibility of mice infected with the influenza virus to severe disease by impairing tissue repair, mucociliary clearance, and innate antiviral defenses. The authors housed mice at low (10–20%) or high (50%) relative humidity for 4–5 days prior to respiratory challenge with a highly virulent strain of the influenza A virus. Mice housed at low humidity suffered a worse disease course due to caspase-1/11 signaling, with more rapid weight loss, a drop in body temperature, and shortened survival, compared with mice housed at high humidity. Exposure to low humidity also impaired airway tissue repair, reduced tracheal mucociliary clearance—an innate defense mechanism that removes pathogens, allergens, and debris—and decreased the expression of interferon-stimulated genes, which restrict the spread of the influenza virus. According to the authors, the results suggest that controlling relative humidity may be important for preventing influenza infection and disease symptoms during winter. — J.W.

Adrenergic receptor antagonism may reduce stroke damage

In acute stroke, spontaneous waves of depolarization slowly propagate across the stroke-affected cortical surface of the brain. Known as cortical spreading depolarization, this creeping electrophysical disturbance is accompanied by massive increases in extracellular potassium ions (K^+) and a prolonged suppression of electrical activity that leads to permanent brain damage and compromises recovery. Hiromu Monai et al. (pp. 11010–11019) tested whether reestablishing K^+ homeostasis could offer a potential therapeutic strategy for ischemic stroke. Using a mouse model, the authors demonstrate that systemic adrenergic receptor (AdR) blockade helps normalize the extracellular ion environment, reduce ischemic brain damage, and speed motor recovery following photothrombotic stroke. Notably, the authors also show that noradrenergic antagonism, both before and after stroke, stabilizes expression and polarization of the membrane channel protein aquaporin 4 (AQP4); both processes are suppressed after photothrombotic stroke. The latter finding supports a model positing that AQP4 helps regulate ion homeostasis in the brain via extracellular fluid movement and excess K^+ clearance. The findings suggest that AdR antagonism represents a therapeutic strategy in stroke's immediate aftermath, helping to minimize brain damage from prolonged depolarization and accelerating functional recovery. — T.J.



Photothrombotic stroke (*Lower Left Corner*) and glial reactivity in a horizontal cerebral cortical section.

Kinship and violence in Neolithic Poland

The Bronze Age began in the third millennium BCE. The Globular Amphora culture existed during this time in Europe, but little is known about their

relations with the neighboring Corded Ware culture. Hannes Schroeder, Ashot Margaryan, et al. (pp. 10705–10710) sequenced the genomes of 15 individuals found in a mass grave excavated in Koszyce, Poland, that dates to approximately 2880–2776 BCE. Analyses revealed that the individuals were part of an extended family, with most of the remains belonging to mothers and children. The authors found that mothers were placed next to their children and siblings were placed next to each other within the grave. Older males and fathers appeared to be missing from the grave. All bodies exhibited injuries and cranial fractures that likely occurred around the time of death, suggesting death by mortal blows to the head. None of the individuals from the Globular Amphora culture shared DNA with their Corded Ware neighbors, and the authors suggest that the massacre may have been tied to the expansion of the Corded Ware groups. The findings suggest that the family's older men may have been absent during the massacre and may have buried the bodies. According to the authors, the study supports the notion that Neolithic violence was a common response to population pressure and competition for resources. — M.S.

The mass grave at Koszyce, southern Poland. Photograph of the 15 skeletons and grave goods buried at Koszyce site 3, licensed under CC BY-NC-ND 4.0.