Through Thick and Thin
Eric Brown, *et al.*
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caC, whereas caC accumulates when TDG is depleted. These observations overturn the assumption associating TDG solely with deamination-mediated demethylation; TDG activity on the higher oxidation products of mC links two proposed players in DNA demethylation—oxidation and base excision repair—in a new and plausible manner.

As an important point of discrepancy, Ito *et al*. find that fC accumulates relative to caC, whereas He *et al*. report that hmC is efficiently converted to caC without any accumulation of fC. This raises the question of the identity of the penultimate cytosine oxidation product prior to the action of base excision repair. Mechanistically, it is feasible that fC could be the better substrate for TDG (*13*), given impacts on *N*-glycosidic bond stability. Higher relative amounts of fC in ES cells would support this possibility, and caC accumulation may reflect altered steady-state amounts given perturbed TDG or TET expression. A kinetic appraisal of the relative rates of formation of hmC, fC, and caC by TETs should resolve these possibilities.

The factors regulating the extent of TET-mediated oxidation must also be explored. Why does TET sometimes oxidize to hmC and at other times iteratively to fC or caC? Do fC and caC have roles in shaping the genome other than as intermediates in demethylation? Further, Ito *et al*. and He *et al*. demonstrate a viable demethylation pathway by examining oligonucleotides or by assessing global amounts of nucleotides. Neither shows that caC is specifically present in promoters undergoing demethylation. Additional experiments will need to confirm the coupling of iterative oxidation and base excision repair at activated promoters for this model to gain acceptance as a bona fide mechanism of DNA demethylation.

Although iterative oxidation coupled to base excision repair provides a plausible demethylation pathway, what becomes of observations that favor other pathways? Rather than viewing these mechanisms as mutually exclusive, it is possible that they may assume accessory roles. Pathways such as those involving deamination by activation-induced cytidine deaminase (*6*, *14*, *15*) may serve as bypass routes to cytosine in specific physiological settings such as primordial germ cells. Given the multitude of ways to manipulate cytosine, it is fortunate that a framework for demystifying demethylation is now at hand.

References

1. S. C. Wu, Y. Zhang, *Nat. Rev. Mol. Cell Biol.* **11**, 607 (2010).
2. S. Ito *et al*., *Science* **333**, 1300 (2011).
3. Y. F. He *et al, Science* **333**, 1303 (2011).
4. M. Tahiliani *et al*., *Science* **324**, 930 (2009).
5. D. Globisch *et al*., *PLoS ONE* **5**, e15367 (2010).
6. J. U. Guo, Y. Su, C. Zhong, G. L. Ming, H. Song, *Cell* **145**, 423 (2011).
7. S. Ito *et al*., *Nature* **466**, 1129 (2010).
8. K. Iqbal, S. G. Jin, G. P. Pfeifer, P. E. Szabó, *Proc. Natl. Acad. Sci. U.S.A.* **108**, 3642 (2011).
9. T. Pfaffeneder *et al*., *Angew. Chem. Int. Ed.* **50**, 7008 (2011).
10. R. M. Kohli, *Nat. Chem. Biol.* **6**, 866 (2010).
11. S. Cortellino *et al*., *Cell* **146**, 67 (2011).
12. D. Cortázar *et al*., *Nature* **470**, 419 (2011).
13. M. T. Bennett *et al*., *J. Am. Chem. Soc.* **128**, 12510 (2006).
14. K. Rai *et al*., *Cell* **135**, 1201 (2008).
15. N. Bhutani *et al*., *Nature* **463**, 1042 (2010).

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MATERIALS SCIENCE

Through Thick and Thin

New experimental results probe the relationship between rheology and particle-scale structure of suspensions.

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The ratio of shear stress to shear rate in a flowing fluid defines its viscosity, or resistance to shear. For a Newtonian fluid like water, the viscosity is constant. Such simple behavior can change drastically, however, when small particles are suspended in the liquid. In some instances, the viscosity decreases with increasing shear rate and the fluid is said to exhibit shear thinning. For applications such as paints, this is desirable because it keeps suspended pigments on the painted surface at rest but lets them flow easily when brushed. There is the opposite possibility of shear thickening whereby the viscosity increases with shear rate. For some suspensions, such as cornstarch in water, this effect can be so dramatic that a person can run across the surface of a pool filled with the suspension, but sinks when standing still. Such non-Newtonian flow behaviors are thought to be caused by changes in the particle arrangements under shear. To investigate this, Cheng *et al*. (*1*), on page 1276 of this issue, report direct measurements of particle arrangements while moving between regimes of shear thinning and thickening.

A textbook example of the role of particle arrangement in driving the behavior of suspensions is shear thinning resulting from the organization of particles into layers oriented along the direction of flow in which they can slide over each other more easily than if they were randomly distributed (*2*). Similarly, it was predicted that shear thickening could result from the formation of particle clusters (*3*, *4*). These "hydroclusters" form when the particles are pushed together by shear and can bunch together transiently as a result of large viscous drag forces in the thin lubrication layers between the particles, which slow their separation.

To test these ideas of suspension rheology, Cheng *et al*. developed a particularly fast and sensitive confocal rheometer that allows them to track the three-dimensional locations of individual, 1-μm-diameter particles suspended in a liquid while simultaneously shearing the sample and measuring the stresses. They can quantify subtle changes in the local particle arrangements as the sample transitions between shear-thinning, Newtonian, and shear-thickening regimes. Their data lead to two important results. First, the viscosity decrease during shear thinning can be quantitatively characterized as the sum of two contributions: a constant, Newtonian portion resulting from viscous stresses, and an entropic contribution that comes from the pressure produced by random collisions of particles under thermal motion, which decreases with shear rate. Second is the first direct experimental verification of clusters of nearly touching particles that grow as the suspension thickens, consistent with earlier predictions (*3*, *4*).

Not all suspensions show all the flow regimes seen in the model system investigated. For example, some suspensions do not shear thicken, some do not have any appreciable intervening Newtonian regime, and others do not exhibit entropic effects. However, the particle-scale detail revealed by the elegant Cornell experiments informs the broader problem in rheology of how to attribute suspension properties to particle interactions on the one hand and structural

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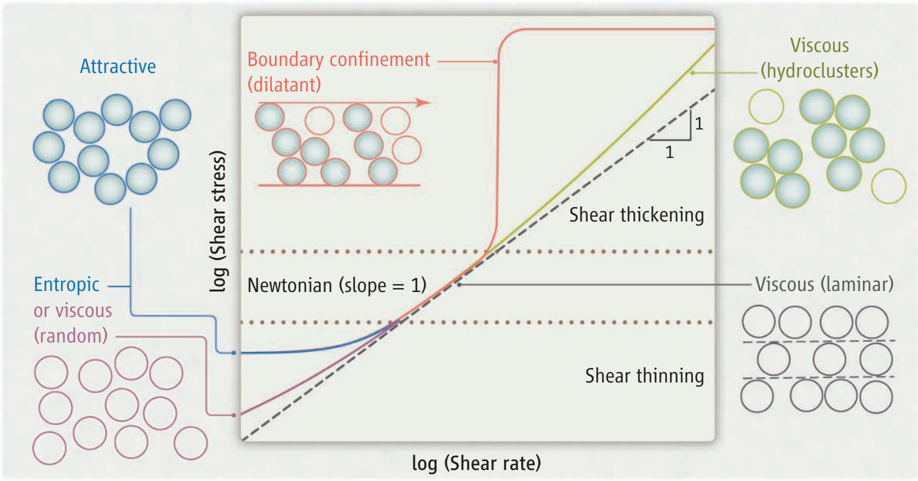

Shear suspension. Sketch of different shear stress versus shear rate relations for suspensions on a log-log scale. Various contributions to stresses and their associated particle arrangements are indicated for shear-thinning, Newtonian, and shear-thickening regimes.

changes on the other. An emerging picture is that changes in the suspension viscosity resulting from viscous-drag-mediated particle rearrangements are typically small compared with viscosity changes found when interparticle interactions introduce additional stress scales into the problem. It is therefore instructive to represent the rheological response by a sum of stress contributions, such that each regime is dominated by a different source of stress (see the figure).

Shear thinning results when there is a stress dominating at low shear rates that does not increase with shear rate as fast as the Newtonian viscous stress. Besides entropic stresses studied by Cheng *et al.*, any source of a nearly constant stress results in an arbitrarily strong shear thinning, because in the zero shear rate limit the viscosity becomes infinite. These other sources of stress include interparticle attractions (*5*), repulsions from an electrostatic potential (*6*), steric (solid particle) repulsion (*7*, *8*), gravitational pressure (*9*, *10*), and attractions from induced electric or magnetic dipoles (*11*). In contrast, the viscosity decrease from viscous-mediated layer formation is relatively small (*12*). In line with this, Cheng *et al.* argue that layering alone cannot be primarily responsible for the observed shear thinning. Strong shear thinning can occur in suspensions with particle structures that are either loosely connected (attractive forces) or random (entropic forces). On the other hand, random particle arrangements can be found along with either strong (entropic) or weak (viscous) shear thinning. These examples demonstrate that large changes in the viscosity do not necessarily correspond to 1-to-1 changes in structure.

In the shear-thickening regime, the viscous-drag-mediated interactions involving hydroclusters similarly result in a relatively mild viscosity increase, typically less than 50% (*1*, *3*). On the other hand, strong shear thickening in concentrated suspensions such as cornstarch and water can result in a nearly discontinuous jump in viscosity of a few orders of magnitude. This has been attributed to frictional particle contacts that form when dense particle arrangements begin to dilate and push against boundaries (*10*). Therefore, as was the case for shear thinning, dramatic shear thickening can be attributed to the introduction of a new stress scale, in this case the stiffness of the boundary.

One intriguing outstanding issue concerns whether there is any connection between the weak viscous and strong frictional mechanisms for shear thickening. A possible scenario is that the hydroclusters eventually become large enough that they span the system and jam. If the boundaries exert sufficient stress to frustrate dilation, then this, in turn, could lead to stronger shear thickening. The ability to track individual particles as demonstrated by Cheng *et al.* opens up the possibility to investigate such a connection.

References

1. X. Cheng *et al.*, *Science* **333**, 1276 (2011).
2. R. G. Larson, *The Structure and Rheology of Complex Fluids* (Oxford Univ. Press, Oxford, 1999).
3. J. F. Brady, G. Bossis, *J. Fluid Mech.* **155**, 105 (1985).
4. N. J. Wagner, J. F. Brady, *Phys. Today* **62**, 27 (2009).
5. V. Trappe *et al.*, *Nature* **411**, 772 (2001).
6. B. J. Maranzano, N. J. Wagner, *J. Chem. Phys.* **114**, 10514 (2001).
7. R. L. Hoffman, *J. Rheol. (N.Y.N.Y.)* **42**, 111 (1998).
8. C. S. O'Hern, L. E. Silbert, A. J. Liu, S. R. Nagel, *Phys. Rev. E Stat. Nonlin. Soft Matter Phys.* **68**, 011306 (2003).
9. A. Fall *et al.*, *Phys. Rev. Lett.* **103**, 178301 (2009).
10. E. Brown, H. M. Jaeger, http://arxiv.org/abs/1010.4921.
11. E. Brown *et al.*, *Nat. Mater.* **9**, 220 (2010).
12. G. N. Choi, I. M. Krieger, *J. Colloid Interface Sci.* **113**, 101 (1986).

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ECOLOGY

Food and Biodiversity

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Density-yield curves help evaluate whether land sharing or land sparing most benefits biodiversity.

The number of people on Earth continues to increase, although it is likely to peak at between 9 and 10 billion later in this century (*1*). Not only will there be more people, but they will be wealthier and will demand a more varied diet. This increasing pressure to produce more food comes at a time when productive land is being lost to urbanization and to the net negative effects of climate change (*2*). In the face of these threats, conservationists have long debated how best to preserve biodiversity. Some argue that the priority should be "land sharing"—simultaneously using agricultural landscapes for less-intensive cultivation (sacrificing crop yields) and conservation. Others favor "land sparing," or maximizing agricultural outputs from some land in order to allow other land to be set aside for conservation (*3*, *4*). On page 1289 of this issue, Phalan *et al.* (*5*) draw on surveys of biodiversity in landscapes in Ghana and India to provide some valuable hard data to inform this discussion.

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Phalan *et al.* studied tropical landscapes that consisted of a mosaic of habitats, including natural forests, mixed woodlands and farmlands, and more intensively managed farmlands. In each study area, they identified a set of 1-km^2 squares that included the full range of habitats. Then they estimated the population densities of selected bird and tree species, as well as the agricultural yields, within each square. This enabled them to construct "density-yield" curves for each species (see the figure). They found that some species were "losers"; their population densities always declined when land was converted from forest to agriculture. Others were "win-