



Figure 1 | Enzymatic and synthetic cyclization reactions. **a**, Squalene undergoes a cyclization reaction to form hopene in bacteria, using an enzymatic equivalent of a chiral hydrogen ion (H⁺). **b**, Ishihara and colleagues⁴ prepared a chiral source of iodine ions (I⁺) that induces a similar halocyclization reaction, so achieving a long-standing goal in organic chemistry. Only one of two possible mirror-image products is made in the reaction.

enantioselectivity of enzymes — it seemed that such fine control could only be achieved with a complex biological catalyst. What is so striking about Ishihara and colleagues' method is that it uses relatively simple reagents. With a chiral jacket for iodine in the closet, the foundation is in place for catalytic versions of this reaction, and for the synthesis of halogenated, naturally occurring compounds. ■

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1. Wendt, K. U., Schulz, G. E., Corey, E. J. & Liu, D. R. *Angew. Chem. Int. Edn* **39**, 2812–2833 (2000).
2. Yoder, R. A. & Johnston, J. N. *Chem. Rev.* **105**, 4730–4756 (2005).
3. van Tamelen, E. E. & Hessler, E. J. *Chem. Commun.* 411–413 (1966).
4. Sakakura, A., Ukai, A. & Ishihara, K. *Nature* **445**, 900–903 (2007).
5. Ishibashi, H., Ishihara, K. & Yamamoto, H. *J. Am. Chem. Soc.* **126**, 11122–11123 (2004).
6. Butler, A. & Carter-Franklin, J. N. *Nat. Prod. Rep.* **21**, 180–188 (2004).

BIOMECHANICS

Fish feeding hardly a drag

Mason N. Dean and Adam P. Summers

Mathematical simulations of prey capture in an aqueous environment, tuned by observational data, have produced a fresh view of the forces generated by suction feeding in fishes.

For humans, suction feeding is a very occasional activity — used to acquire small balls of tapioca from the bottom of a trendy bubble tea, maybe. By contrast, most fishes use suction to obtain all of their food. Typically, a fish targets an individual prey item and swims close, then snaps open its mouth, drawing in a quantity of water along with its lunch. Peter Wainwright and Steven Day¹, writing in the

Journal of the Royal Society Interface, used fluid dynamic modelling and flow data from bluegill sunfish (*Lepomis macrochirus*) to show that the dominant force carrying the prey to its end is not drag from the flowing water, but rather the pressure gradient generated by the rapidly opened mouth.

Several forces, each governed by different equations and generated by the moving fluid,



50 YEARS AGO

Kapitza By A. M. Biew. — This book, written in Germany by a refugee, purports to tell how the U.S.S.R. developed the hydrogen bomb with Kapitza as the principal scientist and with Joffe and Kurtchatov as his principal colleagues... Practically every detail which can be checked is wrong. It is stated that by 1928 Kapitza "had already become in practice the head of the establishment", that is, the Cavendish Laboratory. This at a time when Rutherford was in his prime! The Royal Society Mond Laboratory, which was built for Kapitza's work, is referred to as the "Moon Laboratory". Sensational accounts are given of attempts to lure Kapitza back to the U.S.S.R. in the 1930's. In fact, he returned most years to see his mother and visit friends... The book states that the Russian atom bomb project started in 1937. While we may be permitted to be sceptical about this, we can at least check the few brief paragraphs about the physics of the project. These appear to be as bogus as the account of Kapitza's Cambridge period. **J. D. Cockcroft**
From *Nature* 23 February 1957.

100 YEARS AGO

The following illustration of Prof. Karl Pearson's "Random Path" problem may be of interest. Mr. Kipling in his story "The Strange Ride of Morrowbie Jukes" gives the following directions for finding the safe path across a quicksand, which directions are supposed to have been found by the hero of the story in the coat of an earlier victim: — "Four out from crow-clump; three left; nine out; two right; three back; two left; fourteen out; two left; seven out; one left; nine back; two right; six back; four right; seven back." These numbers were probably taken at random, and it will be noted that seventy five paces are taken, and the final position is only seven paces from the original position. This is a rather curious confirmation of Lord Rayleigh's solution to the problem.
From *Nature* 21 February 1907.

50 & 100 YEARS AGO

deliver the prey during suction feeding^{2,3}. The relative importance of pressure gradient over drag forces reveals to what degree the predator or prey has control. Drag force is determined by flow speed, which is limited by the predator's mouth shape, but also by the shape and size of the prey item. These two prey qualities are memorialized in the equation for drag force as the coefficient of drag and the area. Prey can reduce the coercion from drag by being more streamlined or smaller. By contrast, the pressure gradient is solely the domain of the predator. Either a smaller mouth or a more rapid expansion of the oral cavity will lead to steeper pressure gradients and therefore greater forces. The prey item has no say in the matter and, if feeding is pressure-dominated, suction capture should not affect the shape of the prey through natural selection.

Wainwright and Day¹ explore the parameters of suction predation by hatching a mathematical model fish and 'feeding' it a variety of prey. The authors' initial abstraction was a fish feeding on a neutrally buoyant, spherical prey of 5 millimetres in diameter and with no escape behaviour. In this simple system they demonstrated that prey within a distance of one-and-a-half mouth widths is completely entrained in the flow into the fish's mouth. Because the prey moves along with the water, there is no relative flow to generate drag forces and capture is determined entirely by the pressure gradient. This approximation is probably accurate for fish feeding on phytoplankton and many of the less mobile aquatic invertebrates.

Not all prey are keen on being lunch, and some try to make a run for it. Surprisingly, when the 5-millimetre sphere is endowed with realistic evasive ability it is still captured, and drag forces make only a small contribution to its demise. Even for zooplankton with a good sensory system and an effective swimming response, death is the inevitable result when a

predator is allowed to approach within a couple of mouth widths. Flow speed drops quickly with distance from the predator, however, so just three or four mouth widths away is beyond the effective range of suction.

In both these examples the flow velocity experienced by the prey is small compared with the velocity of water entering the predator's mouth. This would not be the case for a stubborn little critter clinging to a rock while, for example, a butterfly fish (Fig. 1) tried to suck it off the surface⁴. In this case the water flow over the prey is equal to the flow into the mouth, and drag becomes a more important player — about 30% of the force due to the pressure gradient. For prey items with a good grip on the substrate, drag really does matter but may be irrelevant: some predators may change the game and snatch the prey with a quick nibble.

In the evolutionary arms race between predator and prey, the forces driving prey anatomies and behaviours clearly differ according to the

prey's habitat. In the case of free-swimming prey, the selective pressures should be on the early detection and avoidance of predators. After all, once a fish is close enough to pounce, the prey is gullet-bound regardless of its shape and swimming ability. But for substrate-hugging prey there is a selective pressure to be small enough to fit the roughness of that substrate and streamlined enough to prevent drag forces building up when a butterfly fish comes calling. ■

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1. Wainwright, P. C. & Day, S. W. *J. R. Soc. Interface* doi:10.1098/rsif.2006.0197 (2007).
2. Müller, M., Osse, J. W. M. & Verhagen, J. H. G. *J. Theor. Biol.* **95**, 49–79 (1982).
3. Day, S. W., Higham, T. E., Cheer, A. Y. & Wainwright, P. C. *J. Exp. Biol.* **208**, 2661–2671 (2005).
4. Nauwelaerts, S., Wilga, C. D., Sanford, C. & Lauder, G. V. *J. R. Soc. Interface* doi:10.1098/rsif.2006.0180 (2006).

HUMAN GENETICS

Variants in common diseases

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Most common diseases arise from interaction between multiple genetic variations and factors such as diet. Studies of such diseases that exploit the rich data on variation in the human genome are just beginning.

The results of the first genome-wide-association (GWA) surveys of common diseases are trickling out. This trickle will soon be a flood of data, much anticipated but challenging to interpret. These initial studies will calibrate our expectations for future investigations, and help to establish the principles for how they are best reported.

On page 881 of this issue, Sladek *et al.*¹ report the results of such a survey of type 2 diabetes*. It is the largest GWA study so far, and tackles a very common disease that is rising in prevalence throughout the world. More than one in three Americans born in 2000 will develop type 2 diabetes, and its rise is particularly rapid in populations that have recently adopted Western lifestyles — hence the efforts to understand the interplay between genetic and environmental risk factors in generating the high frequency of the disease. Sladek *et al.* contribute to these efforts. They demonstrate an unequivocal association between type 2 diabetes and a previously identified² genetic locus (*TCF7L2*), and substantial — but preliminary — evidence for several new loci.

To evaluate GWA studies, we must revise our notion that a discovery in human genetics consists of identifying 'the gene' for a disease. This notion derives from investigations

of rare diseases, which could, in a single study, be associated definitively with mutations in a single gene. Such mutations could be predicted to devastate the function of the proteins encoded by the gene, and thus to cause disease. Yet the 'genetic architecture' of common diseases, such as asthma and depression as well as diabetes, is not built on such obvious deleterious mutations. Rather, it arises from the combined increase in disease risk generated by an unknown number of genetic variants, some of which might not encode proteins, and are thus difficult to identify. In this situation, false positive results are to be expected, and statistically significant results in one study need to be replicated. Even after a gene locus is unequivocally implicated in disease susceptibility, it remains difficult to prove which associated variant is responsible.

For context, it is useful to consider the choices Sladek *et al.* made in terms of the strategy to be used for evaluating genome-wide genetic variation and of the number of individuals to be genotyped. All recent GWA studies assay genome variation using single nucleotide polymorphisms (SNPs); these base substitutions comprise most of the variation in the human genome, and current technology permits economical genotyping of hundreds of thousands of SNPs in a single experiment. Although some studies have successfully used

*This article and the paper concerned¹ were published online on 11 February 2007.



Figure 1 | Prey's-eye view. A raccoon butterfly fish on the prowl.