

## another kind of harmony

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Would Nature not tend instinctively towards symmetry? In our eyes, symmetry often spells equilibrium, a source of beauty. Consider the work of architects, or engineers. Houses, skyscrapers, bridges and dams are usually symmetric which is not only, and in a mysterious way, emotionally reassuring but also in keeping with the laws of physics. In the same vein, a face that strikes us as being attractive is a face whose sides echo one another. Anything that drifts from these unsaid boundaries strikes us as being odd, if not ugly: think of the Elephant Man. Despite this, life is defined by an underlying lack of symmetry. In fact, Nature frequently seeks a way to break symmetry. Take humans: our heart is not symmetric, neither is the arrangement of our organs inside us, and our brain hemispheres are involved in very different aspects of intelligence. Why has Nature chosen asymmetry? And how does it occur in the first place? The field of research is relatively recent and the answers to these questions are still far from satisfactory. However, we do know that a certain form of myosin, known as myosin 1D, is directly involved in paving the paths of asymmetry in zebrafish.



The Great Wave

by Katsushika Hokusai (1760 -1849)

Many forms of asymmetry are immediately apparent: take the claws of lobsters and crabs, or the coiling of snail shells or pigs' tails. Now slice a human in two, from the head down. At a first glance, it all seems quite symmetric: two eyes, two ears, two arms, two legs. But peel away the skin and asymmetry becomes obvious: our heart is placed a little to the left, our spleen seems to have been squeezed into a dark corner and our liver shifted to one side. This is exactly what may have happened: our guts are rather long and awkward, and to fit them inside us in the most efficient way would have required the relocation of a few organs from our middle. This, however, only explains organisational asymmetry but it does not explain functional asymmetry – such as the brain – or

morphological asymmetry, such as the heart, and even behavioural asymmetry that defines left- or right-handedness. There must be a deeper-lying reason.

There are various theories. One is molecular chirality. Chirality is a particular form of asymmetry. Your left hand and right hand are chiral – that is to say, though they are mirror images of one another, you cannot superimpose them. It so happens that molecules at the very basis of life are also chiral, like all but one amino acid and the double helix. Could it be that chirality, already so deeply rooted in an organism's biology, forms a sort of building block to greater asymmetry? Perhaps so. A cell's cytoskeleton can also be chiral and thus act as a scaffolding for asymmetry as it places some parts of a cell on one side rather than on the other, creating what is known as lateral left-right (LR) asymmetry. In fact, scientists are beginning to realise, to their surprise, that LR asymmetry seems to occur differently in different organisms. In the very early stages of zebrafish development, for instance, a unique fluid flow is generated, literally twisting original symmetry into LR asymmetry. This singular flow arises within an organ known as Kupffer's vesicle (KV) in the zebrafish embryo.

The German anatomist Karl Wilhelm von Kupffer was the first to describe the vesicle in the 1800s. This proto-organ is spherical in shape and formed by about 24 dorsal forerunner cells. The inside

lumen is filled with fluid into which protrude cilia. The cilia are oriented in such a way in the lumen that their beat forms a sort of liquid cue that brings about downstream lateral LR asymmetry. So, in this case, cilia orientation seems to be at the heart of LR asymmetry. Cilia are ubiquitous in organisms and have many diverse roles: they line the Fallopian tube to carry ovules, some plant gametes use them for mobility and they even amplify sound in the inner ear. What is the particular property of KV cilia which interferes with an embryo's symmetry?

Myosin. Myosins are actin-binding proteins that hydrolyse ATP to produce power – such as in muscle tissue contraction or the beat of cilia for example. Tom Pollard and Ed Korn were the first to describe a myosin protein extracted from an amoeba in the 1970s – although it had already been discovered in muscle in the 1900s, hence its name. Since then, over 30 different myosin isoforms have been identified whose structure and function have been well-conserved over time and across species. Their structure? They look like golf clubs, with a large globular head on one end from which protrudes a long chain. Typically, one myosin molecule is composed of two “golf clubs”, so that two globular heads appear side by side at one extremity and their chains intertwine to form a tail. It is the globular heads of myosin which bind to actin and hydrolyse ATP to produce the power stroke.

A myosin named myo1D is directly involved in shaping KVs as well as organising left-right morphogenesis and laterality in zebrafish. How? Firstly, it ensures the correct trafficking and delivery of vacuoles into the KV. Once there, the

vacuoles evacuate fluid into the lumen as they pump up the KV so it expands like a balloon. Secondly, the singular spherical shape of Kupffer's vesicle lends a unique beat to the cilia creating a counter-clockwise fluid flow. This particular flow then mediates asymmetric gene expression, which finally brings about LR asymmetry in the growing embryo. It is an astonishing biological process and the reason KVs have also been coined LR organizers.

Why, you wonder, would Nature consider asymmetry in the first place? Is it all just a question of survival and adaptation? Breaking symmetry seems to have increased the evolutionary fitness of species over time. Certainly, left-right orientations are important for many organs – you cannot replace one side of our brain, or one side of our heart, with the other. There are, however, rare cases of *situs inversus* where people have their heart on their right side and the location of their abdominal organs is reversed. However, because the relationship between each organ is untouched, people suffering from this condition are otherwise perfectly healthy individuals. The fact that chirality already exists at the molecular level is also a sign that asymmetry is not to be taken lightly. This said, to date, still very little is known about this fascinating field of research. Though, in mammals, myo1D seems to have little to do with LR asymmetry, getting to know the protein more intimately, as well as the proteins it interacts with, should give biologists and medical researchers valuable insight. Certainly, Nature continues to surprise us by choosing – and very early on – to shed a certain kind of balance, for another.

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