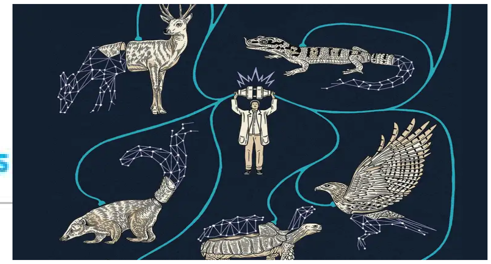

Grow with the flow: How electricity kicks life into shape

Bioelectrical signals direct blobs of cells to transform into any part of the body. Harnessing it can create freakish animals with two heads - and may spark a medical revolution

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By Jason Bittel

Bioelectricity shapes anatomy
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FROM the tail of the leafy sea-dragon to the toucan's beak and the human hand, each and every one of the myriad forms assumed by living things starts out as an amorphous blob of cells. It's one of the biggest mysteries of life: what choreographs billions of cells to create so many intricate anatomical patterns, what Charles Darwin preferred to call "endless forms most beautiful"?

It's all in the genes, of course. Except that it's not. These days, biologists are investigating a long-overlooked aspect of shape control: the electrical signals that constantly crackle between cells. Whether in embryonic development or repairing parts of the body, bioelectricity seems have a big say in telling cells how to grow and where to go. It also appears to play an important role in the astonishing knack some creatures have to regrow lost or damaged limbs.

If we can figure out precisely how it encodes patterns of tissue formation – if we can crack the "bioelectric code" – the possibilities would be startling. Not only will we get a deeper understanding of evolutionary change, we could revolutionise tissue engineering and regenerative medicine. "Once we know how anatomy is encoded, we will be able to make shapes on demand," says Michael Levin, a developmental biologist at Tufts University in Medford, Massachusetts.

We've known for a while that when it comes to development, the process that takes you from a single cell to a fully fledged organism, DNA only goes so far. "If you were to show someone the completed genome of a creature, and you didn't allow them to compare it with the genome of something they were familiar with, they would have absolutely no idea what that creature would look like," says Levin.

In that sense, DNA is less like a blueprint and more like a list of materials, only without a set of instructions for how to use them. Some direction comes in the form of chemical cues such as morphogens, which influence gene expression, and physical forces that guide migrating cells. But Levin and others think there is something else going on.

They are not the first to suspect as much. In the 1700s, Italian physician Luigi Galvani observed that dead and disarticulated frogs' legs could be made to kick as though they were still alive when he connected them to a source of electrical charge. Later, in the 1930s, Yale University's Harold Saxton Burr proposed that bioelectricity is the "organising principle" that kept living tissue from descending into chaos. Despite what we know about the power of electricity in the brain, however, his ideas were largely ignored – until recently.

If the idea of bioelectricity calls to mind sparks flying between neurons, you're not far off. In fact, the brain's electrical circuitry probably evolved from the simpler, slower bioelectrical connections found between cells elsewhere in the body. Every biological cell has a voltage, which changes depending on the balance of charged atoms called ions on either side of the cell membrane. These differences in electrical potential, governed by ion channels and pumps on cell membranes, carry information.

Salamanders can regrow limbs time and again, so why can't we?
Michael Durham/Minden Pictures

For a long time, we thought this intercellular chit-chat was mostly concerned with banal housekeeping duties: "Send this waste over there!", "More fuel needed here!". What we're learning now, however, is that it is much more important than that, says Nestor Oviedo at the University of California, Merced. "In a way, bioelectricity tells the cells whether to divide, whether to differentiate, whether to migrate," he says.

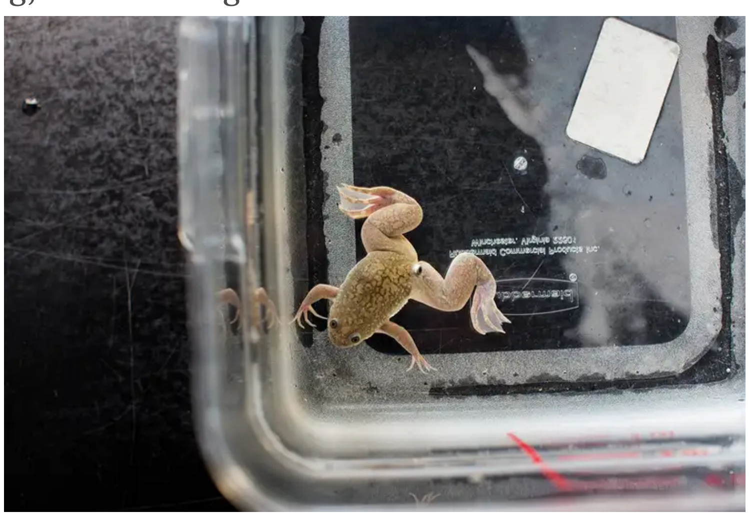
That much is clear from a series of experiments that give a whole new meaning to the question "heads or tails?". The most striking have involved planarians, otherwise known as flatworms – simple, squiggly organisms that resemble a 5-millimetre-long smear of snot with crossed eyes.

Caught in two minds

Like salamanders, planarians are remarkable regenerators – slice off a tail and it will quickly grow back. But unlike salamanders, planarians can also survive decapitation. In fact, you can cut a planarian into 200 pieces and each will grow into a new, perfectly healthy whole animal over the course of a few weeks.

In 2010, Levin and Oviedo lopped off planarians' heads and tails, and treated the remaining fragments with a chemical bath known to inhibit the flow of ions between cells. Rather than regrow replicas of the parts that had gone missing, in the normal way, these planarians grew heads on both ends. "That showed, for the first time, that these electrical synapses are important for deciding head versus tail," says Levin.

And here's where things get really kooky. In follow-up experiments, the team put the two-headed worms in plain water for a few weeks, with no electricity-tampering chemicals. They then hacked off each end again. When the flatworms regenerated, they didn't revert to their original programming, but instead grew two new heads.



This doesn't make sense, says Levin – at least not without the bioelectricity's influence. The experiments did nothing to alter the planarians' genomes and so, after all the chemically altered tissue is cut off, one might assume that the worm would go back to building the same body plan it has always built. But it doesn't. Instead, the cells somehow remember the new instructions.

Even when the researchers allowed their creations to reproduce asexually, as they would in the wild, they produced offspring with two heads. So it seems that simply by altering its bioelectric signalling patterns, you can permanently rewrite an organism's body plan.

You can also get it to regrow body parts resembling those from other species. Last year, Levin and his colleagues disrupted electrical signalling between cells in decapitated specimens of the planarian *Girardia dorotocephala*. Instead of making a new version of their own heads, they regenerated heads with a distinctive shape and brain anatomy that belonged to a different, albeit closely related, species.

Levin is not the only one revealing the power of bioelectricity. Min Zhao at the University of California, Davis, is investigating the role bioelectricity plays in wound healing. We previously thought that cell movements in response to injury were dictated by chemical cues. But Zhao has demonstrated that electric fields can mobilise and guide sheets of cells towards a wound.

To begin with, Zhao's results met with some scepticism. Josef Penninger at the Institute of Molecular Biotechnology in Vienna, Austria, was one of the doubters. "I was sceptical because to me, it was an entirely new concept," he says. However, that changed when Zhao travelled to Penninger's lab and showed him a video of sheets of skin cells migrating in the same direction when exposed to an electrical field. "I and everyone in my lab was mesmerised," Penninger says.

Zhao understands the scepticism because there is still so much to learn. We don't know how patterns of flickering electrical potential translate into patterns of tissue formation, for a start, although Levin suspects there are parallels with the brain or some forms of computer memory.

What is obvious, though, is that all this could have far-reaching implications for our understanding of evolutionary change. Imagine a scenario in which the lab-built two-headed flatworms were released into the wild: a biologist could stumble on them and think they were a new species, and yet they would find that these worms and their one-headed kin are genetically identical.

Two-headed flatworms are proof of the body-shaping power of electricity
Junji Morokuma

According to Levin, this suggests evolution may not be limited to genomic mutation. If environmental stimuli can produce worms with two heads or the heads of other species in the lab, then perhaps such things can happen in nature, too. "This is a potentially whole new way of entering body plans into the evolutionary record."

"Bioelectrical signalling could have far-reaching implications for our picture of evolution"

Others are more cautious. We already know that the same genome can produce strikingly different body shapes, says Mary Jane West-Eberhard at the Smithsonian Tropical Research Institute in Costa Rica: it's called phenotypic plasticity. "Consider the larval and adult forms of a butterfly," she says. "The differences are due to gene expression."

Levin argues that what we're seeing with the two-headed planarians is different. "It's a new type of phenotypic plasticity, one that resides not in the cascade of molecules that regulate gene expression but in bioelectric networks and their ability to compute and remember."

Wresting control of this voltage-based communication might also have a big impact on human health. If we can understand how the body creates its structures in the first place, and how some creatures can repeat the process, then perhaps we can commandeer the process in humans. “At this point, it’s dreaming about what the application could be,” says Emily Bates, a geneticist at the University of Colorado in Denver.

Several developmental diseases are caused by channelopathies, or malfunctions of our ion channels. They include Timothy syndrome and Andersen-Tawil syndrome, rare diseases that cause neurological, heart, and skull and facial defects. Even fetal alcohol syndrome, which can develop if a woman drinks during her pregnancy, can produce similar defects because alcohol blocks many of the same ion channels.

Bates says it may never be possible to treat these disorders given the way they manifest in embryonic development, but she is confident that bioelectricity will have practical applications elsewhere.

Reversing cancer

It could help us tackle cancer. Earlier this year, Levin and his colleagues took advantage of a technique called optogenetics, which involves genetically engineering cells to respond to a flash of laser light. When they hacked a particular set of ion channels in this way to alter bioelectrical signalling in tadpoles that were engineered to develop cancer, the team were able to reduce the incidence of tumour formation. But they didn’t just shrink the tumours; they made more tumour cells return to their original healthy state, like the monstrous Mr Hyde turning back into mild-mannered Dr Jekyll. So instead of trying to kill cancer cells as you do with chemotherapy and radiation, which both have unpleasant side effects, you might hack bioelectricity to “normalise” them.

Rehabilitating cancer cells would be impressive; regenerating limbs or organs would be astonishing. That has to be most exciting prospect raised by our new insights into the ways that bioelectricity controls pattern formation.

Humans’ regeneration abilities pale in comparison to those of the planarian, of course, but just the ability to mend a fractured finger is an amazing feat. It relies on bone morphogenetic proteins (BMPs), which help stimulate new growth. The trouble is that the body seems to prioritise BMP production in bones that support weight, like the tibia, so lighter bones like the jaw sometimes don’t heal well.

We can make these proteins in the lab, but it’s expensive. What’s more, BMPs can cause problems when injected, such as stimulating too much bone growth – “kind of like a tumour”, says Bates. But there might be a better way. Bates has shown in fruit flies that electrical activity plays a role in the release of BMP. If you could selectively target the relevant ion channels, says Bates, you could potentially deploy a person’s own molecules to fix their bones – even if their body is stingy with BMP.

What are the chances we could regenerate human limbs, or even grow organs on demand? In 2013, working with froglets, Levin and his colleagues used a chemical cocktail to induce the flow of sodium ions, and thereby increase the biolectrical chit-chat between cells. The animals were past the age at which they can regenerate full limbs, and yet that is exactly what they did after treatment.

"The frogs were past the age where they can regrow limbs, yet they did"

"Plasticity definitely varies," says Levin. Salamanders and planarians seem to retain their regenerative abilities for life, while tadpoles lose their superpower somewhere along the way to becoming frogs. Humans lose the power early on too. Split a fertilised egg cell down the middle when it is a few days old and it will form two genetically identical twins. Try a similar splitting feat a few weeks later, and you'll get a tragically different result.

It's one thing to take a trial-and-error approach to determining the bioelectrical pattern behind an ability animals already have: building a limb, for example. It's quite another to load that pattern into animals that lack that ability. But the fact that humans have regenerative capabilities, even if only briefly, is suggestive. If we can identify what suppresses them, Levin argues, we could potentially unlock that innate repair apparatus.

Identifying such patterns and translating them into something we can use is a tall order. It's not enough to work out bioelectricity's secrets at the cellular level – we must decipher its rhythms and logic if we want to build a structure. If Levin is right that bioelectrical information is analogous to computer memory or brains, then tools from computational neuroscience should help. Artificial intelligence might also come into play.

"Once we crack the code, we will know precisely how we have to rewrite the default electric patterns, so as to make the anatomy we want," says Levin. Even early sceptics like Penninger are excited by the potential: "I think it's a field waiting to explode," he says.

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