Neuroscience

Neurons that control walking go round in circles

Martha W. Bagnall

Evidence from turtles and computer models indicates that a pattern of neuronal activity known as rotational dynamics governs locomotion. The finding challenges long-standing models of locomotor control. **See p.526**

Locomotion is a familiar series of rhythmic, patterned movements: the left and right sides of the body alternate, back and forth, as do pairs of flexor and extensor muscles in the limbs. The neuronal circuits that generate these patterns are found in the spinal cord, but how the circuits are organized remains largely unknown. In long-standing models of spinal locomotor circuits, activity bounces back and forth between two states, with mutual inhibition between neuronal populations enforcing the alternation[1]. On page 526, Lindén *et al.*[2] put forward a different idea, in which activity instead travels in a continuous circle of near-randomly connected neurons. The results offer a new way of thinking about spinal-cord activity.

Conventional models of locomotor circuits focus on the alternation between pairs of muscles. To capture this alternation, most models rely on pools of excitatory neurons that cause a burst of activity in one muscle, while driving inhibitory neurons to suppress activity in the neurons controlling the opposing muscle (Fig. 1a). As the first pool of excitatory neurons tires out, the opposing pool is activated, in turn inhibiting the first pool. This cycle oscillates back and forth to produce flexor–extensor alternation.

To characterize movement-related neuronal activity, Lindén et al. used turtles. The animals' spinal cords remain stable as their legs move — a major technical advantage for long-duration physiological recordings during movement. The authors implanted electrodes into the animals' spinal cords, and recorded the activity of hundreds of neurons simultaneously while tickling the shell to elicit scratching movements. Whereas muscle contractions occurred in discrete bouts, individual neurons were active at different times, such that the overall activity of the neuronal population did not mirror these bouts, but instead covered the entire cycle of a rhythmic scratch, producing a 'circular' activity pattern (Fig. 1b). This pattern of activity, known as rotational dynamics, has previously been identified in the cortical region of the primate brain, where it controls arm movement[3].

Building on these ideas, Lindén *et al.* developed a computational model to explain how spinal neurons might be organized to drive rotational dynamics. In their model, the neurons were near-randomly connected, and yet could still produce appropriate activity patterns to drive alternating muscles. The muscles themselves displayed simpler patterns of activity than did spinal neurons (real or modelled), implying that rotational dynamics is a property of the neuronal circuit, not simply a reflection of muscle dynamics.

A key advance of this model is how easily it can be adjusted to produce movements of different strengths or speeds. For example, increasing the overall gain (input–output relationship) throughout the network elicited stronger movements. To identify network changes that could alter the speed of movements, Lindén *et al.* adjusted the gain of individual neurons in the network, noting which ones affected the frequency of the dynamics, and so overall speed. By changing the gain of these neurons, the researchers identified 'accelerator' or 'brake' cells that respectively increased or decreased the speed of movement without altering its strength. Thus, movement strength and speed can be modified independently of each other, much as a violinist can independently adjust tempo and loudness.

This work is bound to generate controversy. In the past 25 years, research on spinal circuits in model organisms (mostly, mice and zebrafish, both of which are easy to manipulate genetically) has focused on identifying distinct spinal neuron classes, as defined by anatomical and genetic properties[4]. The ventral (stomach-side) portion of the spinal cord, which contains most of the circuits for movement, is now understood to comprise a mixture of motor neurons and five cardinal classes of spinal neurons, each of which can be further divided into subclasses. Most computational models of the spinal circuit are built out of these cell classes, linking them together to produce the expected locomotor output[5]. What is

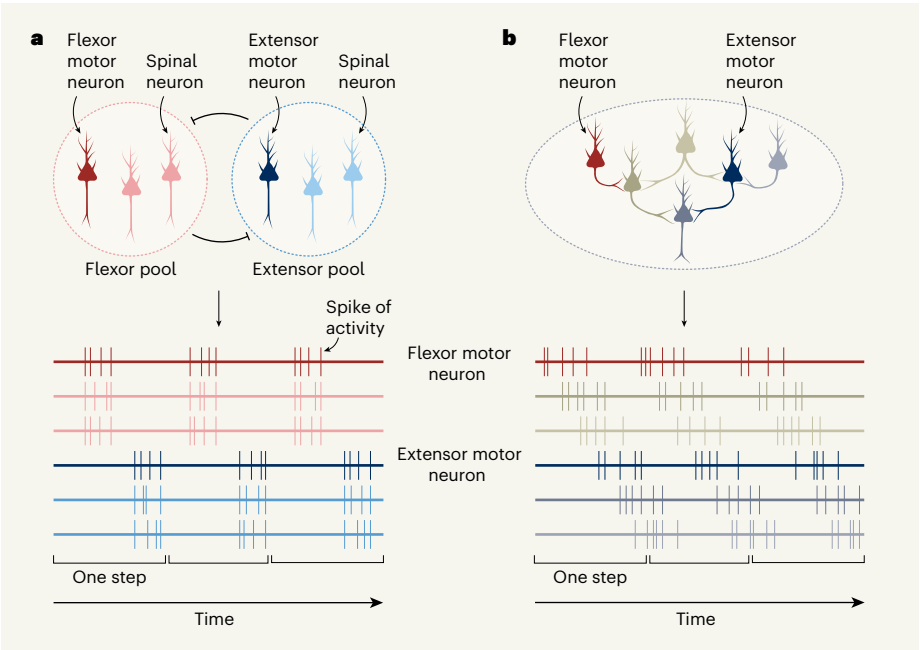

Figure 1 | Models of the spinal neuronal circuit that controls locomotion. a, Conventional spinal locomotor models are built from pools of motor and other spinal neurons. Each pool excites one of a pair of muscles — the flexor or extensor muscle — while inhibiting the activity of the other pool. This mutual inhibition means that neuronal activity (indicated for each neuron by vertical lines along a colour-coded timeline) alternates back and forth between the pools, including in the flexor and extensor motor neurons, which drive alternating muscle movements to create steps (or other types of movement). **b**, Lindén *et al.*[2] propose a different model in which the collective activity of a near-randomly connected pool of neurons covers all of the phases of one bout of movement. Each neuron contributes to this cyclical pattern of activity, with the flexor and extensor motor neurons still alternating as part of the cycle, driving muscle movement.

more, selective deletion of each class of neuron yields different behavioural outcomes, such as changes in gait or speed[6,7]. In this context, the idea that the spinal cord might be modelled just as well — if not better — by a near-random mishmash of neurons seems faintly heretical.

What is the rationale for developing a model of locomotor circuits in this way, rather than by making use of the extensive research on spinal-cell classes? One challenge in building a spinal network out of identified neuron classes is that these classes are far more numerous than was first appreciated. Each cardinal class of spinal neuron has been subdivided into as many as 50 subclasses[8,9], and researchers are largely in the dark as to their patterns of activity and interconnectivity. Lindén and colleagues do not dismiss the importance of these neuron classes, but they suggest that it might be beneficial to start from a fairly generic model that reproduces the physiological recordings, rather than from untested assumptions about connectivity. They point out that some of the neurons in their model can be 'identified' as belonging to putative spinal classes on the basis of their contribution to behaviour. This observation sets up the idea that future analyses might allow researchers to link particular genetically identified classes of neurons to their position in the spinal network and their role in dynamical activity.

A related advantage of the approach taken here is that it is rooted in physiological recordings of neuronal activity. Manipulations in mouse models involve long-term silencing of defined classes of neurons, followed by analysis of the resulting behavioural output. This approach provides insights into the possible roles of each class of neuron, but gives no indication about the consequences for the locomotor circuit — how does loss of one class of spinal neuron affect activity in the other classes? Furthermore, these long-term silencing approaches might drive compensatory changes that distort the apparent function of each neuron class. As a result, the field is still missing a defined mechanistic link between genetic manipulations and their consequences for behaviour.

The model put forward here makes a strong, testable prediction — that both excitatory and inhibitory neurons should exhibit activity at all phases of the locomotor cycle. It is currently difficult to address this prediction in turtles or, even, in mice, because neurons that release excitatory or inhibitory neurotransmitters are spatially intermingled, and cannot be distinguished with standard recording techniques. In zebrafish, some results do support the idea that inhibitory neurons are active throughout the locomotor cycle[10]; it will be interesting to extend this analysis to limbed vertebrates. In addition, integrating this rotational model with known spinal-neuron classes should spur a series of new experimental and modelling questions.

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1. Grillner, S. *et al. Prog. Brain Res.* **165**, 221–234 (2007).
2. Lindén, H., Petersen, P. C., Vestergaard, M. & Berg, R. W. *Nature* **610**, 526–531 (2022).
3. Churchland, M. M. *et al. Nature* **487**, 51–56 (2012).
4. Goulding, M. *Nature Rev. Neurosci.* **10**, 507–518 (2009).
5. Danner, S. M., Shevtsova, N. A., Frigon, A. & Rybak, I. A. *eLife* **6**, e31050 (2017).
6. Gosgnach, S. *et al. Nature* **440**, 215–219 (2006).
7. Crone, S. A. *et al. Neuron* **60**, 70–83 (2008).
8. Bikoff, J. B. *et al. Cell* **165**, 207–219 (2016).
9. Hayashi, M. *et al. Neuron* **97**, 869–884 (2018).
10. Kishore, S., Bagnall, M. W. & McLean, D. L. *J. Neurosci.* **34**, 14046–14054 (2014).

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Ancient genetics

The first genomic portrait of a Neanderthal family

Lara M. Cassidy

Ancient genomic data have been retrieved for 13 Neanderthals from 2 caves in Siberia. The genomes provide unprecedented insights into the social organization of Neanderthal communities. **See p.519**

Like all humans, Neanderthals lived their lives embedded in communities. They ate, slept, loved and died in the company of their kin. These communities were connected to others in larger webs of interaction, together forming a region's Neanderthal population. But how were the communities organized? What relationships formed the fabric of a group? Who left home to join another clan and who stayed put? On page 519, Skov *et al.*[1] address these questions, by sequencing DNA from the bones of 13 Neanderthal men, women and children.

Since 2010, genome-wide data have been recovered for only 18 Neanderthals (see Fig. 1 of the paper[1]), so this is a major data milestone and attests to the continued improvements in extraction and isolation of ancient DNA spearheaded by this research group. But what makes this work particularly remarkable is that the sequenced individuals are not scattered widely across the vast expanse of Neanderthal existence, but are concentrated at a specific point in time and space, thus providing the first snapshot of a family group.

The authors take us to the northwestern foothills of the Altai Mountains in Asia. There, sometime between 51,000 and 59,000 years ago, Neanderthals at the easternmost edge of their range hunted migrating bison, and retreated to Chagyrskaya Cave (Fig. 1) to enjoy their spoils[2]. Their living space was cramped, but occupation was probably only seasonal. Approximately 90,000 stone artefacts have been found in this cave, along with the largest collection of Neanderthal remains known for north Asia[3].

It was from these remains that Skov *et al.* sequenced 11 Neanderthal genomes, along with those of 2 individuals from the nearby Okladnikov Cave. All seemed to be part of the same broad population — the descendants of a late expansion of eastern European Neanderthals into Siberia, distinct from the earlier occupants of Denisova Cave, only 100 kilometres to the east[3]. Archaeological data suggest that Chagyrskaya was used by Neanderthals for a few millennia[2], an unwieldy time span for a study of social organization. But the authors' discovery of biological kinship at the site changes this arithmetic; at least some individuals were contemporaries.

Among those present were members of a nuclear family — a father and his adolescent daughter — as well as a male–female pair of second-degree relatives (those who share about 25% of their DNA). A male individual who was a maternal relative of the aforementioned father was also identified, owing to a genetic phenomenon called heteroplasmy. In heteroplasmy, an individual has two different versions of mtDNA (a maternally inherited loop of DNA housed in cellular organelles called mitochondria).These different versions coexist for only a few generations, and thus individuals who share a heteroplasmy are expected to be recently related along the female line. Skov *et al.* speculate that these men might have shared a grandmother, but note that their approach is not designed to detect relationships beyond the second degree.

This lack of resolution is frustrating, but understandable — the study relies on estimates of overall genome similarity to measure relatedness, and sparsity of data keeps the error bars large. In the future, deeper sequencing of the Chagyrskaya remains might provide a clearer picture, by enabling analyses of the number and length of genomic