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Locomotion: Why We Walk the Way We Walk

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The way we walk determines the energetic investment needed. Humans spontaneously alter their walking style to exploit energetic opportunities. New research demonstrates the sensitivity and timing of this optimization and opens the door to discovering the underlying mechanisms.

The substrate that we walk across defines the surface landscape we have to contend with. But when walking we are also tied to another landscape, the energy landscape of 'metabolic cost' [1]. Negotiating the everyday world effectively can require using a range of walking modes. As every movement we make involves an investment in metabolic energy, the myriad combinations of stride lengths, frequencies and speeds that constitute our potential repertoire of walking motions combine to generate a surface, the metabolic cost landscape (Figure 1). Certain points on this surface will provide the best solution under a given set of circumstances. For instance, our preferred walking speed is located near the global minimum [2] and the best combinations of stride frequency and stride length to walk faster or slower run along the valley perpendicular to the speed axis (Figure 1) [3]. Optimization of energy use is to be expected and could arise from a variety of forms of adaptation, such as adaptation of the species over evolutionary history, or of the individual over a lifetime's experience with walking. It is uncertain, however, whether this cost landscape is utilized on a moment-by-moment basis. How would an individual respond if the shape of this cost landscape suddenly changed? A new study by Jessica Selinger and colleagues [4] in this issue of *Current Biology* sheds new light on this aspect of locomotion coordination.

Locomotion is initiated by the motor control centers of the brain, and is subsequently influenced by various ascending and descending features of the neuromuscular and mechanical systems of the body [5]. However, our bodies move in a manner that cannot neglect the influence of the physical environment. This is a complex issue, doubtless with a variety of key inputs. How does the brain choose the best strategy to drive the motion and placement of the limbs? Even for constant speed locomotion, such as walking or running on a treadmill, this question currently remains open. Although an interesting and fundamental

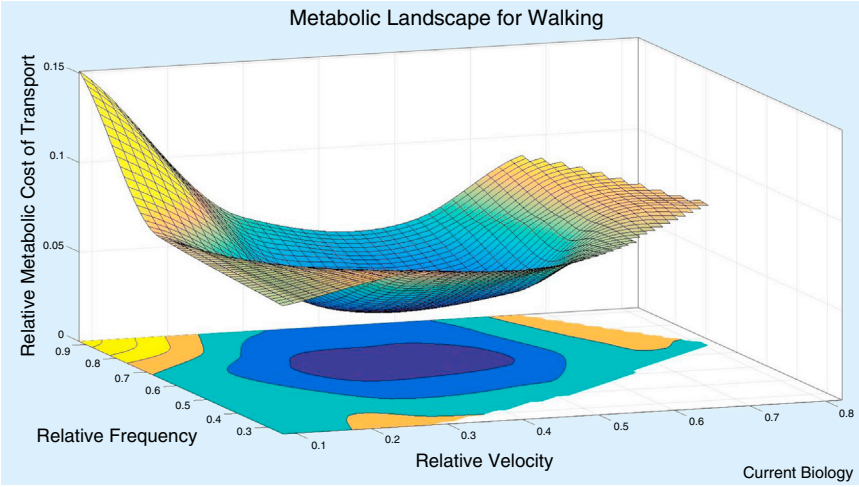

Figure 1. A plot of the metabolic cost surface (landscape) for normal human walking.
Each position on the surface represents the metabolic cost of the movement pattern selected. A study in this issue of *Current Biology* [4] subtly manipulates this surface to show that individuals quickly optimize their walking strategy. Velocity, step frequency and metabolic cost of transport are in dimensionless units; data adapted from [1].

basic question, finding the answer to this will have many practical implications. Understanding how the brain integrates its control program with changes in the function or circumstances in which the body operates will influence our ability to predict the outcomes of various interventions, whether surgical, rehabilitative or prosthetic. The ever-growing field of enhanced function and performance provided by artificial bio-integrated 'exoskeleton' devices will depend on understanding how the body will react to such influence [6]. The Selinger *et al.* study [4] adds some fundamental insight to this area. Through artificial manipulation of the metabolic landscape, the authors begin to determine how, and over what time frame, an individual responds. In doing so, they discovered some intriguing features of locomotion control that had not previously been appreciated.

The study is a clever repurposing of a previously published knee torque energy harvester that used natural braking motions around the knee to power an electric generator [7,8]. In the present study, the device is used as a controllable 'exoskeleton' to effect knee function to penalize either high or low stride frequency. This intervention shifts the metabolic cost of walking and the authors followed the spontaneous adjustment of stride frequency by the subject. The device adjusts the metabolic cost landscape and creates new distinct optima, at either higher or lower than normal stride frequency.

The study involved two parts — each reinforcing the other. In the first set of studies the knee 'exoskeleton' applied a frequency-dependent torque to the knee to subtly penalize normal stride frequency walking. The device could be set to penalize-low — where walking with a higher than normal frequency (and shorter stride length) allowed the most cost-effective walking — or penalize-high — where lower frequencies (and longer stride lengths) provided the best energetic option. It was found that the subjects did indeed change their motor control program to select the new, energetically advantageous stride parameters.

The second part of the study involved forcing the subjects beyond the former optimum (either higher or lower) by having them pace their strides to a metronome beat. When the metronome was turned off, while the frequency-dependent penalty continued, the subjects quickly by-passed their former normal optimum to locate the new, device-determined optimum. This transition occurred rapidly, with all subjects finding the artificially induced optimum stride frequency in 10 seconds or less. The double experiment, involving an initial demonstration of optimization with the follow-up indicating subjects would spontaneously bypass their former preferred stride frequency to quickly settle to the new optimum, makes the results very robust and provides a model in experimental rigor that we can hope others will emulate.

Manipulation of mechanics or physiology, especially in a complex behavior like walking, needs to be done with care. It is certainly possible for unintended effects to creep into the study and obscure results. Factors, such as instability, could influence how the subjects responded, but these studies do not appear to challenge stability. Of more relevant concern for a study such as this would be avoiding a localized response to mechanical effects. Overloading the knee extensors, for instance, could result in a similar shift away from a natural gait. Could it be that the knee torque device alters the optimum for knee function, so that the immediate response is more one of proprioceptor feedback rather than metabolic optimization? Although, as the authors acknowledge, it is not possible to design control functions that rule out all alternatives simultaneously, they substantially reduced the likelihood of generating ambiguous results by designing their controller so that the artificially induced energetic optimum did not coincide with minimizing resistance of the device for knee extension or flexion.

Interestingly, initially the group was not able to elicit a consistent response from their subjects using this device. The team discovered that it was first necessary to provide the subjects with an exploratory experience, demonstrating to them what the new 'cost landscape' was. Following this, the subjects would spontaneously select a walking frequency that minimized the metabolic cost of locomotion. Although the experiments strongly indicate that humans can utilize short-term information on the energetic cost of walking, under most circumstances we may not be rigorously searching the available options, at least for those conditions that are far from our immediate experience.

A similar effect is seen following the metronome overshoot trials. When released from the metronome constraint, the subjects rapidly adjust gait to locate the cost minimum. However, when the knee torque device

is turned off, and the 'cost landscape' returns to normal, the subjects displayed a surprisingly long latency, where they maintained a stride frequency that would have satisfied the previous artificially induced landscape optimization. One would assume that if individuals are indeed sensitive to the cost of walking, they would spontaneously return to their former (normal) minimum cost stride frequency. This could also be an important clue regarding how the system operates. The authors point out that removing the influence of the torque device results in a lowering of the walking cost, even if the subjects do not alter their stride frequency [4]. What motivation is there to locate a new minimum if the system is provided with a 'windfall' of reduced cost without having to adjust control? As a result, the movement strategy loiters at the previous optimum much longer than it does when given an increased cost with a newly available optimum.

We observe that healthy humans generally walk in a similar manner. Is this because of species-level evolutionary adaptation, because our coordination systems develop and learn in the same way or because we are all solving basically the same energetic problem? Certainly all these factors (and more) have their influence. The Selinger *et al.* study [4] conclusively demonstrates that humans do solve at least part of the problem by coordinating their movements to optimize immediate metabolic energy expenditure. At this point, the mechanisms through which this is accomplished are not clear, but it is impossible to identify mechanisms unless their effects are recognized. This study adds a new dimension (and a novel technique) to our understanding of how humans move the way they do in walking.

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Neurodegeneration: The Size Takes It All

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There is increasing computational evidence that the exceptionally high vulnerability of dopaminergic neurons in Parkinson's disease may be due to their unique axonal architecture and resulting metabolic needs. A new experimental study has actually demonstrated this.

Why specific subsets of neurons in Parkinson's disease (PD) are particularly vulnerable is one of the central unresolved mysteries, not only relevant to PD but to every neurodegenerative disorder. The motor manifestations of PD are largely due to degeneration of dopamine (DA) neurons in the substantia nigra pars compacta (SNpc). Various hypotheses regarding the pathogenesis of the disease suggest that the mechanisms underlying dopaminergic cell death might be the consequence of mitochondrial dysfunction, alteration of protein degradation pathways, misfolding and aggregation of proteins such as α-synuclein, and/or the presence of neuroinflammation. However, our current knowledge about the selective vulnerability of DA neurons is still limited. DA itself was first viewed as a culprit as it readily oxidizes to react with proteins, lipids and nucleic acids, forms neurotoxic derivatives, including 6-hydroxy-DA, and interacts with intracellular iron or products of monoamine oxidase to form toxic oxygen radicals [1]. Another feature of SNpc DA neurons is their distinct physiological phenotype; adult SNpc DA neurons are autonomously active, generating regular, broad action potentials in the absence of synaptic input that rely in part on L-type Ca(v)1.3 Ca^{2+} channels. The opening of L-type calcium channels during autonomous pacemaking results in sustained calcium entry into the cytoplasm of DA neurons, resulting in elevated mitochondrial oxidant stress and rendering them more vulnerable to stressors [2].

More recently, using computational methods to look specifically at