The Journal of Physiology

TOPICAL REVIEW

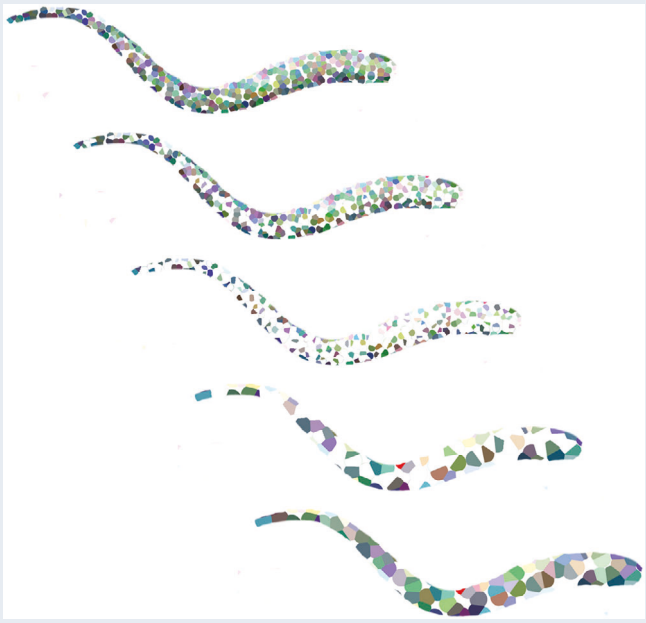
Resilience of neural networks for locomotion

Gal Haspel[1], Kristen E. Severi[1], Lisa J. Fauci[2], Netta Cohen[3], Eric D. Tytell[4] and Jennifer R. Morgan[5]

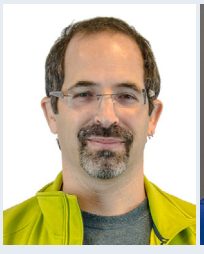
[1] *Federated Department of Biological Sciences, New Jersey Institute of Technology, Newark, NJ, 07102, USA*
[2] *Department of Mathematics, Tulane University, New Orleans, LA, 70118, USA*
[3] *School of Computing, University of Leeds, Leeds, LS2 9JT, UK*
[4] *Department of Biology, Tufts University, Medford, MA, 02155, USA*
[5] *The Eugene Bell Center for Regenerative Biology and Tissue Engineering, Marine Biological Laboratory, Woods Hole, MA, 02543, USA*

Edited by: Ian Forsythe & Vatsala Thirumalai

The peer review history is available in the Supporting Information section of this article (https://doi.org/10.1113/JP279214#support-information-section).



Gal Haspel is an Assistant Professor in the Federated Department of Biological Sciences at the New Jersey Institute of Technology and Rutgers University in Newark, NJ. Previous appointments include postdoctoral training with Anne C. Hart at Harvard Medical School, and with Michael O'Donovan at the National Institute of Neural Disorders and Stroke, after graduate training with Frederic Libersat at the Ben Gurion University. Gal is a neuroethologist studying the neural basis of locomotion and recovery from injury in the nematode *C. elegans*. **Kristen E. Severi** is an Assistant Professor in the Federated Department of Biological Sciences at the New Jersey Institute of Technology and Rutgers University in Newark, NJ. Previous appointments include postdoctoral training with Claire Wyart at the ICM, Paris, France, and graduate training with Florian Engert at Harvard University and Donald O'Malley at Northeastern University. Kristen focuses on the neural circuits underlying locomotor control in larval zebrafish.



Gal Haspel and Kristen E. Severi contributed equally to this review.

DOI: 10.1113/JP279214

Abstract Locomotion is an essential behaviour for the survival of all animals. The neural circuitry underlying locomotion is therefore highly robust to a wide variety of perturbations, including injury and abrupt changes in the environment. In the short term, fault tolerance in neural networks allows locomotion to persist immediately after mild to moderate injury. In the longer term, in many invertebrates and vertebrates, neural reorganization including anatomical regeneration can restore locomotion after severe perturbations that initially caused paralysis. Despite decades of research, very little is known about the mechanisms underlying locomotor resilience at the level of the underlying neural circuits and coordination of central pattern generators (CPGs). Undulatory locomotion is an ideal behaviour for exploring principles of circuit organization, neural control and resilience of locomotion, offering a number of unique advantages including experimental accessibility and modelling tractability. In comparing three well-characterized undulatory swimmers, lampreys, larval zebrafish and *Caenorhabditis elegans*, we find similarities in the manifestation of locomotor resilience. To advance our understanding, we propose a comparative approach, integrating experimental and modelling studies, that will allow the field to begin identifying shared and distinct solutions for overcoming perturbations to persist in orchestrating this essential behaviour.

(Received 26 March 2021; accepted after revision 22 June 2021; first published online 29 June 2021)
Corresponding authors G. Haspel and K. E. Severi: New Jersey Institute of Technology, Department of Biological Sciences, 100 Summit Street CKB420, Newark, NJ 07102, USA. Email: haspel@njit.edu; severi@njit.edu

Abstract figure legend Undulatory locomotion is an ideal behaviour for exploring principles of circuit organization, neural control and resilience of locomotion. The neural circuitry underlying locomotion is highly robust: in the short term, fault tolerance allows locomotion to persist immediately; while in the longer term neural reorganization can restore locomotion after severe perturbations.

Introduction

Neural systems possess remarkable resilience, leading to persistence of effective behaviours despite alterations in connectivity, activity, or environment. Nowhere is this more apparent than in locomotion, a behaviour that is critical for gathering food, evading predation, finding mates, and overall survival. Across phyla, following mild or moderate injury, motor circuits are fault tolerant – often continuing to generate adequate locomotor behaviours immediately after the perturbation. Following severe injuries to the invertebrate nerve cord or vertebrate spinal cord, many species recover some degree of locomotion through longer-term reorganization of motor circuits via neural regeneration and other physiological mechanisms (Yanik *et al*. 2004; Morgan & Shifman, 2014; Rasmussen & Sagasti, 2016; Morgan, 2017). Even in humans, where spinal cord damage notoriously results in permanent loss of movements, recent work shows that epidural stimulation coupled with exercise training can overcome paralysis in some chronic spinal cord injury patients, resulting in adaptive control of locomotion (Harkema *et al*. 2011; Angeli *et al*. 2018; Wagner *et al*. 2018). Thus, resilience in locomotor neural networks appears to be a highly conserved phenomenon that enables animals to overcome a wide range of injuries and conditions, thereby enabling persistence of the essential behaviour. However, the neural mechanisms underlying locomotor resilience are still poorly understood. Here, we review some fundamental observations on locomotor resilience and discuss open questions that are ripe for mechanistic exploration.

In all animals studied to date, descending input activates neuronal oscillators, termed central pattern generators (CPGs), to generate rhythmic locomotion (Brown, 1911; Wilson, 1961; Marder & Bucher, 2001; Ijspeert, 2008; Bucher *et al*. 2015). While CPGs can generate a motor pattern without sensory input, they also receive proprioceptive sensory inputs that can strongly modulate or stabilize their output (Wilson, 1961; Rossignol *et al*. 2006). The motor programme activates muscles in a spatiotemporal sequence for propulsion, as well as a more subtle tuning of the body's effective mechanical responses to its environment (Blight, 1977; Long, 1998; Berri *et al*. 2009; Tytell *et al*. 2018), a coordination that produces fluent and robust motion (Dickinson *et al*. 2000). Propagation of alternating activity of antagonistic muscles is a common feature across species of undulators and legged locomotors alike (Cohen, 1988; Grillner & El Manira, 2020). Rostro-caudal coupling of CPGs along the body axis enables the propagation of such contralaterally alternating neural and muscle activity (Fig. 1*A*), highlighting the common organizing principles of the neural circuits and their function.

For undulatory locomotion, the coordinated metachronal patterns are relatively simple and probably ancestral. Undulators, from microscopic nematodes to 13 m-long extinct snakes, generate thrust by propagating mechanical waves along their body, most commonly against the direction of locomotion (Gray, 1953; Cohen & Boyle, 2010). Across this range of sizes, animals experience vastly different physics, yet produce similar movements, suggesting similar requirements for pattern generation and resilience, and, potentially, comparable underlying mechanisms. All locomotion, and undulatory movement in particular, arises from the interaction between the dynamics of the body and the physics of the environment, an interaction that places strong constraints on the movement. When analysing undulatory locomotion, the body axis provides a convenient reference for interpreting and comparing muscle activity and locomotor phase across individuals as well as across disparate species. Furthermore, the neural and muscular activity that propagates the traveling wave along the neuraxis is cyclic, making it highly amenable to imaging, physiology, and behavioural recording, as well as analysis and comparison across individuals and species.

We focus on undulatory locomotion in three well-established model systems: lampreys (family *Petromyzontidae*), larval zebrafish (*Danio rerio*), and nematodes (*Caenorhabditis elegans*) (Fig. 1*B*). These model species offer a range of sizes and speeds, and are complementary in terms of our current knowledge and accessibility to techniques. Their nervous systems differ in size, number of neurons and connections, and in many details, but analogies can be drawn among the core components such as descending input, local circuit elements (e.g. cross-inhibition, proprioception), motor-units, and axial musculature (Fig. 1*A*). The lamprey CNS has experimental advantages that include large, identified neurons in the brain and spinal cord with known roles in locomotion, which facilitates imaging and physiology, and it is perhaps the best established model for neural regeneration of the three species (Rovainen, 1976; Selzer, 1978; Cohen *et al.* 1986; Davis& McClellan, 1994; Buchanan, 2001; Oliphint *et al.* 2010). The larval zebrafish is transparent and amenable to genetics and electrophysiology, as well as modern methods of optogenetics (for circuit activation or inactivation) and functional imaging while simultaneously measuring behaviours in semi-restrained and freely moving animals (McLean & Fetcho, 2011; Portugues *et al.* 2013; Albadri *et al.* 2017; Severi *et al.* 2018; Marques *et al.* 2020). *C. elegans* offers a relatively small, comprehensively identifiable and fully mapped nervous system (White *et al.* 1986; Haspel & O'Donovan, 2011; Reilly *et al.* 2020; Brittin *et al.* 2021), as well as established genetic and transgenic methods (Biron & Haspel, 2015; Corsi *et al.* 2015; Haspel *et al.* 2020), and optical transparency permitting analysis of circuit function and behaviour in individuals

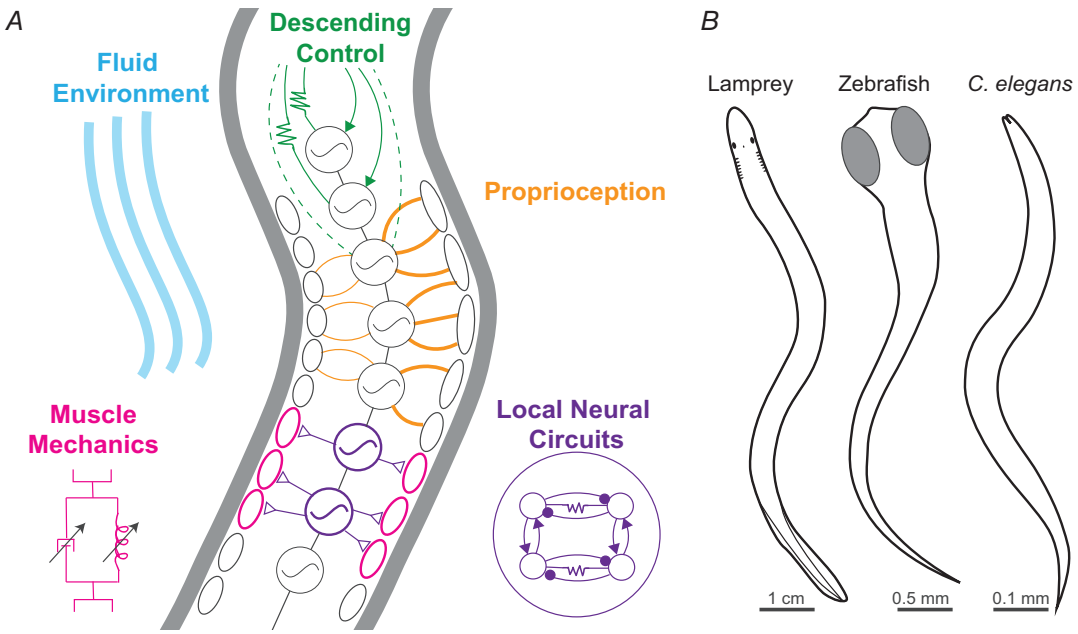


Figure 1. Undulatory locomotion
A, neural circuits that control locomotor behaviours. Descending neurons activate rostro-caudally coupled central pattern generators, resulting in propagation of contralaterally alternating muscle contractions that are tuned by proprioceptive feedback. *B*, lampreys, larval zebrafish and *C. elegans* use similar axial undulations to move in their environment, despite significant differences in size, overall nervous system organization, and fluid dynamics.

and populations of animals. This level of detail also presents an opportunity for whole-animal modelling (Bargmann & Marder, 2013; Sarma *et al*. 2018; Cohen & Denham, 2019). The nematode locomotion interneurons are analogous to reticulospinal neurons that provide descending input; its motoneurons are analogous to spinal interneurons, integrating sensory and descending inputs, while generating and coordinating motor programmes; and its muscle arms are analogous to spinal motoneurons (Haspel *et al*. 2020). While we focus on these three models, where possible we also extend these comparisons to other vertebrate and invertebrate undulatory swimmers, as well as legged animals.

Understanding the resilience of locomotion in these three undulators, therefore, provides an opportunity to study the interplay between neural control, biomechanics and sensory feedback. While undulatory locomotion has long provided an important foundation for understanding the basic neural mechanisms underlying locomotor behaviours, comparatively little is known about the neural mechanisms that restore locomotor behaviours after perturbations such as injury or environmental changes. We thus propose new avenues of investigation that build upon that foundation to identify both shared and distinct mechanisms underlying resilience of undulatory locomotion.

Locomotor networks are fault tolerant to acute perturbations

Locomotor circuits often continue to function immediately after perturbation or failure of individual components. Such fault tolerance appears to be conserved, because partial lesioning of either descending axons or local circuit neurons in lampreys, zebrafish (vertebrates), and *C. elegans* (an invertebrate) does not suddenly halt movement, but instead results in altered but functional locomotor behaviours. The disruption of locomotion can range in severity depending on which neurons are perturbed, allowing the behaviours to continue despite alterations in speed, body form, or gait.

Fault tolerance is well described in lampreys and larval zebrafish, two leading models for the study of vertebrate locomotion from cells through circuits to behaviour (Buchanan, 2001; Fetcho & McLean, 2010; Berg *et al*. 2018; Grillner & El Manira, 2020). Lampreys can retain functional swimming immediately following substantial damage to their spinal cords, before any regeneration can occur. For example, partial transection of medial spinal tracts, comprising descending reticulospinal axons, acutely alters but does not halt swimming (Fig. 2*A*) (McClellan, 1988). This result can be mimicked in a simulated model of a swimming lamprey, where active force generation stops at the lesion site, but the mechanical wave propagates passively to the tail (Fig. 2*B*). If the mechanical wave propagates across the lesion, local sensory input may be sufficient to activate and synchronize spinal circuits below the lesion even without descending control (Wallen, 1982). Similarly, hemi-lesions sparing half of the rostral spinal cord often result in seemingly normal swimming without any directional bias (McClellan, 1988), as well as normal alternating muscle activity (Shaw *et al*. 2010). In comparison, partial lesions of the lateral spinal tracts in lampreys cause a loss of muscle activity and swimming (McClellan, 1988; Shaw *et al*. 2010), suggesting that lateral spinal tracts are more important for maintaining locomotion. While the reason for this difference is unknown, one possibility is that the lateral tracts in lamprey spinal cord may comprise the axons of 'start' or 'maintain' RS neurons that fire at the beginning and throughout the duration of swimming activity (Juvin *et al*. 2016), which could be tested by tracing axonal projection patterns from the midbrain somata to their respective positions within the spinal cord.

Similarly, larval zebrafish are quite tolerant to spinal cord damage, as are many species during early development. Single-cell somatic ablations of subsets of descending reticulospinal neurons, or caudal spinal transection (Fig. 2*C*), do not stop locomotion but instead change locomotor frequency, timing, or swim speed (Orger *et al*. 2008; Huang *et al*. 2013; Severi *et al*. 2014; Liu *et al*. 2019). Likewise, removal of specific classes of spinal interneurons has demonstrated the resilience of swimming, which can persist in the absence of local circuit elements. For example, ablation of V2a glutamatergic interneurons alters swim speed without a total loss of swimming ability (McLean *et al*. 2007, 2008; Sternberg *et al*. 2016; Menelaou & McLean, 2019). Silencing or activation of GABAergic and glycinergic interneurons can affect swimming speed, cycle period, or rostral-caudal propagation while locomotion is maintained (Fidelin *et al*. 2015; Callahan *et al*. 2019; Kimura & Higashijima, 2019; Satou *et al*. 2020). In fish and amphibians, a pair of large bilateral hindbrain neurons called Mauthner cells (M-cells) mediate the fastest of startle responses (Korn & Faber, 2005; Sillar, 2009; Hale *et al*. 2016), and are probably necessary for any escape response (Hecker *et al*. 2020*b*). Yet even after M-cell ablation and loss of the fast startle response, fish retain the ability to perform other types of locomotor behaviours including swimming, demonstrating the complexity of the circuitry underlying distinct types of locomotor movements (Hecker *et al*. 2020*b*); when one type is lost, others may persist.

In *C. elegans*, interneuron axons along the ventral nerve cord provide the main source of descending input to locomotion motoneurons (Chalfie *et al*. 1985; White *et al*. 1986; Altun *et al*. 2009; Cohen & Denham, 2019; Haspel *et al*. 2020). Ablation or inactivation of specific

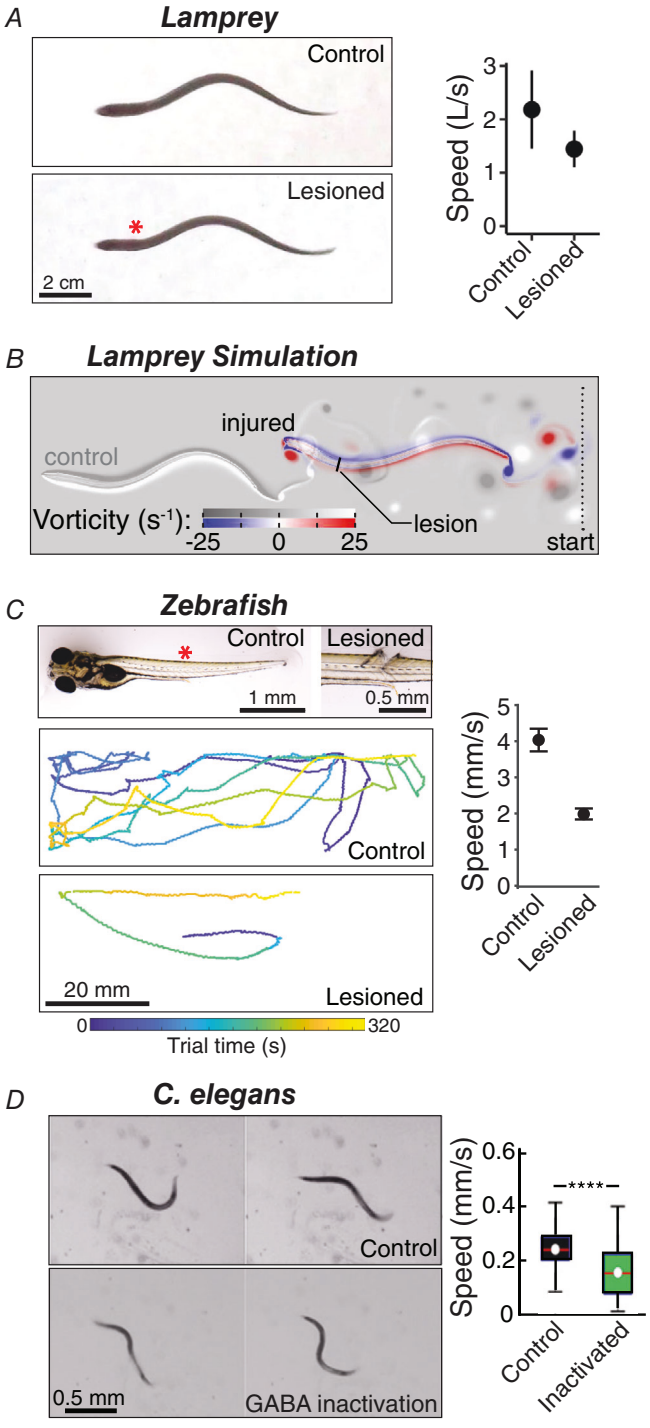


Figure 2. Fault tolerance in lampreys, larval zebrafish and *C. elegans*
A, left panel, uninjured lamprey before (control) and 2 h after partial lesioning of the medial spinal cord. Asterisk = lesion site. Right panel, lampreys continue to swim robustly, but with reduced swim speed (ANOVA $P < 0.005$). L = body length. (Data from Morgan and Tytell labs). *B*, simulation of a swimming lamprey. The injured lamprey, which has purely passive mechanical wave propagation below the lesion, swims slower. Vorticity, a measure of fluid motion, is shown in red and blue or shades of grey. (Data from C. Hamlet, Fauci and Tytell labs). Rostral is to the left in panels *A* and *B*. *C*, similarly, larval zebrafish lesioned at age 5 days post-fertilization are able to swim 24 h after a caudal spinal cord lesion, albeit with longer stops (paths over 320 s) and reduced mean swim speed over the trial period. (Data from M. Mohan Gowda and A. Mahajan, Severi lab; FishTracker2 software provided by Michael Orger lab). *D*, *C. elegans* also swim robustly but more slowly immediately after optogenetic inactivation of all GABAergic inhibitory neurons (adapted from Deng *et al*. 2021).

classes of interneurons induce direction-related effects, leaving one direction intact (Chalfie *et al.* 1985; Wicks & Rankin, 1995; Kawano *et al.* 2011), while ablating a single GABAergic head interneuron (namely RIS) acutely reduces stopping events (Turek *et al.* 2013). Only ablation of all premotor interneurons stops locomotion entirely (Zheng *et al.* 1999; Gao *et al.* 2018). Within the local circuits of the ventral nerve cord, ablation of about half of the 56 neurons that comprise two of six cholinergic and excitatory motoneuronal classes, eliminates one direction of locomotion, but spares the other (Chalfie *et al.* 1985). Similarly, eliminating or inactivating all 19 neurons that comprise the two GABAergic inhibitory motoneuronal classes (or interrupting the synthesis of GABA) eliminates rapid crawling and swimming, but leaves slow locomotion intact (Fig. 2*D*) (McIntire *et al.* 1993; Deng *et al.* 2021). Virtual ablations in computational models suggest a number of subtle and redundant inhibitory mechanisms (McIntire *et al.* 1993; Deng *et al.* 2021), which have yet to be tested experimentally.

Across the animal kingdom, such fault tolerance within locomotor networks is not limited to undulatory swimmers. For example, the ophiuroid brittle star, an echinoderm, produces highly modified yet effective gaits of locomotion following a series of amputations that sequentially reduce the number of arms from six to one (Kano *et al.* 2019). Similarly, many crabs and spiders change locomotor patterns to move effectively with multiple legs amputated (Pfeiffenberger, 2017; Wilshin *et al.* 2018). The new, compensating, motor programmes are generated immediately and innately. Another example of locomotor fault tolerance occurs during extreme perturbations in external forces. For example, zebrafish, lungfishes and *C. elegans* all maintain effective locomotion when researchers change the viscosity of their typical substrates (e.g. water or other Newtonian and non-Newtonian fluids), even by several orders of magnitude (Horner & Jayne, 2008; Berri *et al.* 2009; Fang-Yen *et al.* 2010; Danos & Lauder, 2012). Fish can also swim efficiently even in extremely turbulent water (Liao, 2007). Impressively, when a running cockroach experiences a lateral force more than 10 times larger than its normal thrust, caused by a miniature backpack cannon, their gait is only affected for a single step cycle (Jindrich & Full, 2002). This gait correction is too quick for neuronal feedback and is probably mediated by the biomechanics of the legs

and body. Even in mammals such as mice, rats and cats, partial spinal lesions often result in only transient changes in locomotion with some functional recovery and coordination returning over several weeks to months (Rossignol *et al*. 2009; Gorska *et al*. 2013). Acute spinalized cats treated with the noradrenergic receptor agonist clonidine can resume treadmill walking within hours post-lesion (Forssberg & Grillner, 1973). Thus, upon acute perturbations, the neural networks and body mechanics supporting locomotion rapidly compensate in order to persist the orchestration of this essential behaviour, and this phenomenon appears to be broadly conserved across many species.

Despite the numerous examples of fault tolerance in both invertebrates and vertebrates, there is surprisingly little known about the underlying neural and biomechanical mechanisms that support this type of acute resilience. Given all the different locomotor modalities and body plans, it is entirely possible that multiple, disparate mechanisms are deployed. It is generally assumed that fault tolerance within neural systems can emerge from a redundancy of elements with similar or overlapping functions, so that paralysis will occur only when all redundant elements are lost. For example, in larval zebrafish two morphologically and genetically distinct classes of excitatory interneurons are both recruited during slow speeds of locomotion (McLean *et al*. 2008; Menelaou & McLean, 2019); this circuit redundancy may be what allows any persistence of the slow locomotor network if one class is damaged. In theory, paralysis could occur with or without gradual degradation of the behaviour, though the nature of degradation has not been rigorously tested. Another hypothesis, is that there may be rapid cellular and synaptic compensatory changes in the locomotor network, producing alternative activity patterns that allow the behaviours to persist despite the loss of select inputs. For example, such compensation could be driven by uninjured CPGs or local and global sensory feedback. Broadly speaking, control theory provides insights into how appropriate feedback can compensate for the effects of damage to a mechanical or electrical control system (Ashby, 1956; Cowan *et al*. 2014), e.g. by maintaining robust (homeostatic) functionality within a dynamic range. In computational models, the bistability of *C. elegans* motoneurons (Boyle *et al*. 2012) is consistent with such enhancement of dynamic range. Moreover, proprioceptive sensing may be able to produce or maintain appropriate movements, even in the absence of neural coupling along the body, or across the two sides of the body. For example, immediately after spinal cord transection, which completely disconnects descending input, eels produce appropriately synchronized muscle activity below the lesion, suggesting that proprioceptors can activate the local CPG and synchronize it to passively propagated mechanical inputs (Wallen, 1982). Leeches also use the mechanical wave to synchronize body segments when the nerve cord is transected (Yu *et al*. 1999). While the roles for proprioception in normal locomotion are still being investigated, even for the well-characterized lamprey, zebrafish and *C. elegans* nervous systems (Daghfous *et al*. 2016; Fouad *et al*. 2018; Knafo & Wyart, 2018), it is likely that sensory activation plays a significant role in overcoming acute inactivation of descending input. Computational models have helped elucidate the conditions under which proprioceptive control suffices to generate undulations across a wide range of environmental and internal parameters, even with all inhibitory neurons ablated *in silico* (Boyle *et al*. 2012; Denham *et al*. 2018; Deng *et al*. 2021).

Locomotor networks undergo long-term reorganization to restore function

Other forms of locomotor resilience are observed with longer-term neural circuit reorganization that occurs after injury, which includes regenerative mechanisms. In response to severe lesions that cause paralysis, neural networks in many non-mammalian species spontaneously reorganize both anatomically and functionally (Morgan & Shifman, 2014; Rasmussen & Sagasti, 2016; Morgan, 2017), ultimately restoring locomotor behaviours ranging from mildly dysfunctional to functional and indistinguishable from control.

Undulatory swimmers have provided foundational studies on long-term functional reorganization of locomotor networks. In lampreys, complete transection of the rostral spinal cord leads to immediate paralysis, after which locomotor behaviours like swimming and burrowing gradually return over the course of a few months (Fig. 3*A*, top) (Rovainen, 1976; Selzer, 1978; Cohen *et al*. 1986; Oliphint *et al*. 2010; Katz *et al*. 2020). Remarkably, lampreys can recover nearly normal swimming after one or two complete spinal transections (Fig. 3*A* and *B*) (Hanslik *et al*. 2019), though with slower swim speed and mildly altered body kinematics (Oliphint *et al*. 2010; Fies *et al*. 2021). Functional recovery occurs even when only 30–50% of the descending reticulospinal axons regenerate across the lesion site, regrow in atypical paths, and terminate prematurely (Fig. 4*A*), making only a few, small synapses (Yin & Selzer, 1983; Davis &McClellan, 1994; Oliphint *et al*. 2010). In addition to regeneration of descending inputs, altered intrinsic and synaptic properties within local spinal circuits contribute to locomotor recovery in lampreys (Cooke & Parker, 2009; Becker & Parker, 2019). Such physiological changes occur both above and below the lesion site and are dynamic over time (Parker, 2017). One crucial shift, in our view, is the increase in sensitivity of local proprioceptive sensors (Hoffman & Parker, 2011), which increases the

importance of mechanical interactions that maintain function. Despite detailed knowledge of how some of the neural connections in the lamprey CPG reorganize after injury through axon regeneration and physiological compensation, the understanding of functional recovery at the network level is lacking.

Zebrafish and *Xenopus laevis* tadpoles also show remarkable resilience in response to removal of descending inputs, particularly when disrupted at early developmental stages. Both larval and adult zebrafish demonstrate robust regeneration and functional recovery after complete spinal transection, aided by glia and a dynamic immune response (Goldshmit *et al*. 2012; Becker & Becker, 2014; Briona & Dorsky, 2014; Tsarouchas *et al*. 2018). *Xenopus* can recover from complete transection with restored locomotion as a tadpole, but not as an adult frog, due to metamorphosis-induced changes in the transcriptional programme that subsequently limits axon regeneration (Gibbs & Szaro, 2006; Gibbs *et al*. 2011; Belrose *et al*. 2020). In adult zebrafish, transection of the caudal spinal cord does not halt swimming, due to intact rostral CPGs, but results in full paralysis past

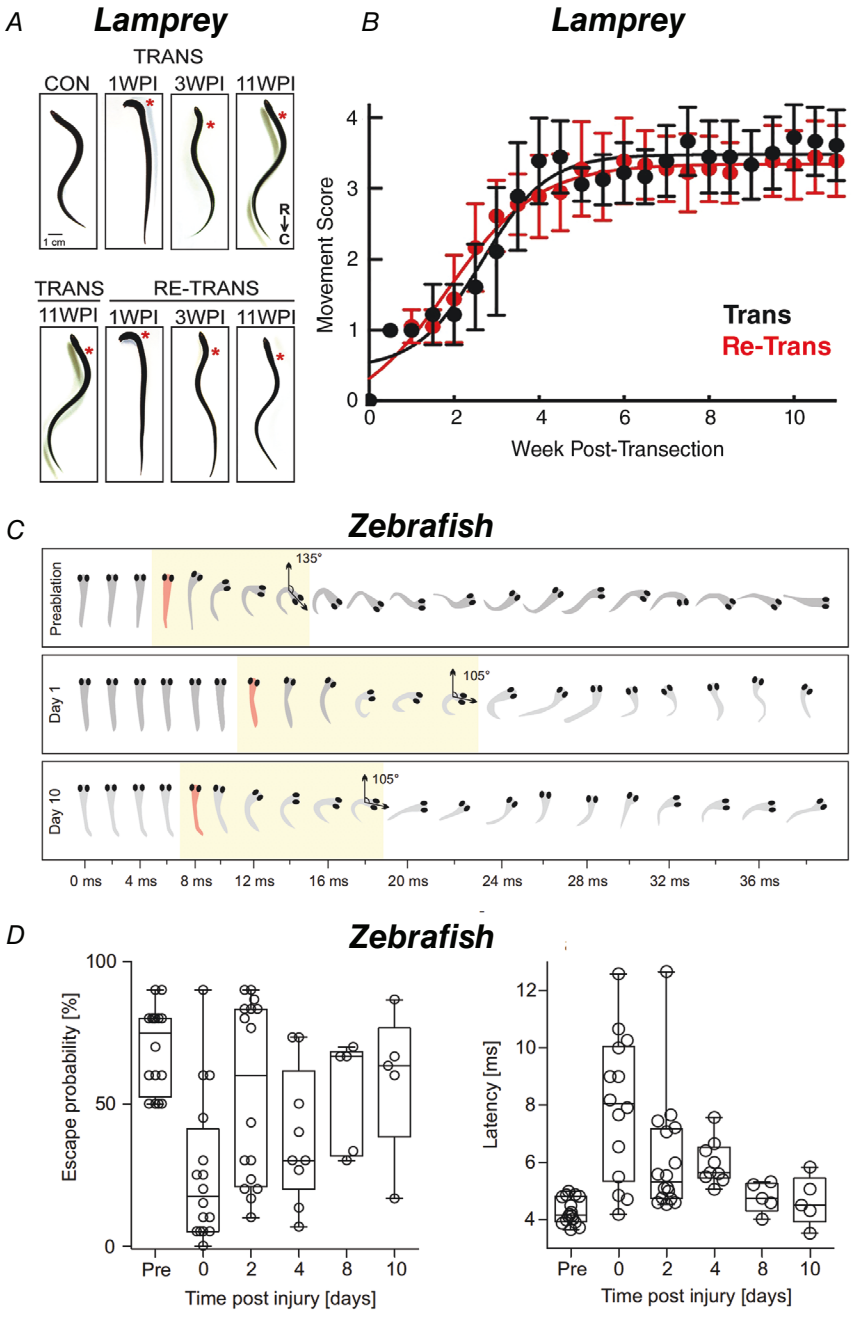


Figure 3. Recovery of locomotion in lampreys and larval zebrafish
A, top, after spinal transection, which initially results in paralysis, lampreys recover swimming behaviours within 11 weeks post-injury (WPI). Asterisks = lesion site. Bottom, upon spinal re-transection, lampreys undergo functional recovery a second time. *B*, movement scores showing that lampreys recover swimming behaviours equally well after spinal transection and a second re-transection. A score of 0 indicates paralysis, while a score of 4 indicates normal swimming. Panels *A* and *B* adapted from Hanslik *et al*. 2019. *C*, sequences showing C-starts in larval zebrafish before and after proximal injury to an M-cell axon. While latency (orange fish) and time to maximal bend (yellow section) are longer at 1 day post-injury, the C-start partially recovers by Day 10. *D*, recovery of escape probability and latency in larval zebrafish after M-cell axotomy. Panels *C* and *D* adapted from Hecker *et al*. 2020*a*, as stated under Creative Commons license https://creativecommons.org/licenses/by/4.0/.

the lesion site that gradually recovers over 4–6 weeks until the animals swim indistinguishably from controls (van Raamsdonk *et al.* 1998; Dias *et al.* 2012). Supporting locomotor recovery, regeneration of descending axons past the lesion is robust in both fish and amphibia, but with sparse connections relative to the uninjured spinal cord (Gibbs & Szaro, 2006; Goldshmit *et al.* 2012; Becker & Becker, 2014). In larval zebrafish, the M-cells do not easily regenerate upon spinal lesion, unless treated with a cAMP analogue (Bhatt *et al.* 2004), highlighting one of the few known pathways that promote axon regeneration from invertebrates to mammals (Hannila & Filbin, 2008; Ghosh-Roy *et al.* 2010). Interestingly, M-cells regenerate more robustly when lesioned closer to the soma, and short latency startle responses are restored (Fig. 3*C* and *D*), even when the M-cell axon regrowth is aberrant (Fig. 4*B*) (Hecker *et al.* 2020a).

Similarly in *C. elegans*, behavioural recovery occurs after only partial cellular regeneration of ventral cord neurons (Yanik *et al.* 2004) or aberrant regeneration (Fig. 4*C*). Following laser microsurgery on ventral cord neurons, the vast majority of proximal commissures (>80%) regrow towards the dorsal cord within 24 h (Yanik *et al.* 2004; Hammarlund *et al.* 2009), while the distal portion survives microsurgery and sometimes reconnects (Ohnmacht *et al.* 2016), thus restoring

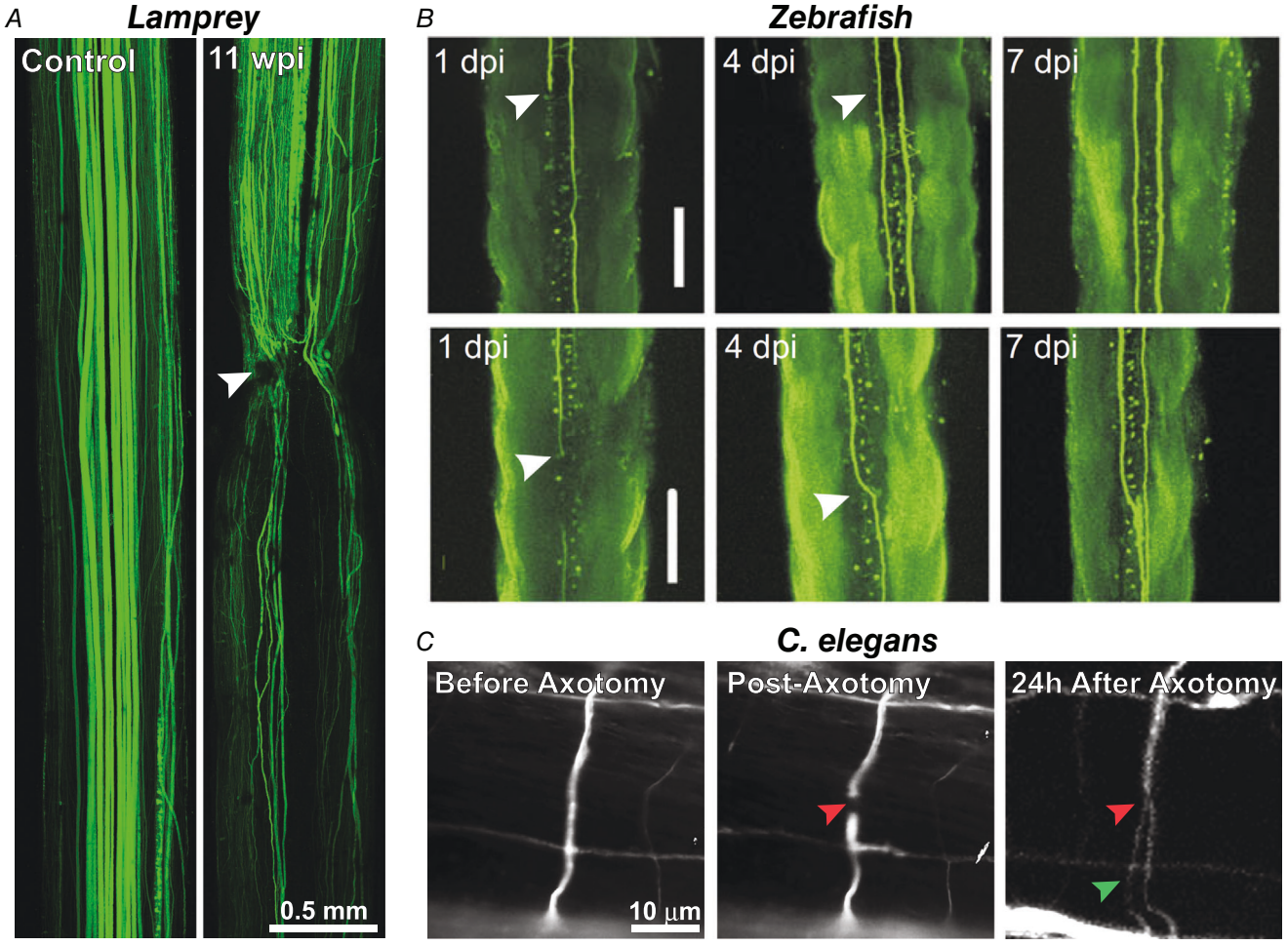


Figure 4. Long-term anatomical reorganization of descending locomotor circuits
A, AlexaFluor 488-labelled reticulospinal (RS) axons within the lamprey spinal cord. In the control spinal cord, RS axons project straight along the rostro-caudal axis. At 11 weeks post-injury (wpi) following complete spinal transection, only a subset of RS axons regenerate, often along atypical projection patterns. Despite this, the animal exhibited nearly normal swimming as in Fig. 3*A* and *B*. Arrow indicates lesion site. (Data from H. Katz, Morgan lab). *B*, proximal injury of an M-cell axon within the spinal cord of larval zebrafish leads to accurate (top) and in some cases aberrant (bottom) regeneration within 4 days post-injury (dpi). Arrows indicate ablation sites. Scale bars,100 μm. (Adapted from Hecker *et al.* 2020a, as stated under Creative Commons license https://creativecommons.org/licenses/by/4.0/). *C*, in *C elegans*, 24 h after axotomy of a DD motoneuron (red arrow), two axon branches regenerated (green arrow). Scale bar, 10 μm. (Data from M. B. Harreguy, Haspel lab). Rostral is up in panels *A* and *B* and left in panel *C*.

avoidance behaviour (Yanik *et al*. 2004). *A priori*, the recovery of normal locomotion suggests that some ventral cord neurons regain function. The likelihood of partial or complete regeneration seems to depend on neuronal classes (Gabel *et al*. 2008; Harreguy *et al*. 2020). Moreover, functional but uncoordinated locomotion is one of the most prevalent phenotypes following unbiased backward genetics screens, ever since *C. elegans* was established as a prominent neurogenetic model (Brenner, 1974). With a large variety of underlying causes, from impairments in neural development and synaptic transmission to cuticular defects and body shape, the 132 so-called '*unc*' (uncoordinated) mutant strains of animals exhibit abnormal locomotion phenotypes ranging from very subtle changes in the locomotion pattern to full paralysis, which occurs in only a few mutant strains. This variety demonstrates a remarkable ability to overcome severe perturbations by mechanisms that are probably a combination of developmental reorganization and compensatory proprioception.

Beyond undulatory locomotors, long-term functional reorganization and behavioural recovery of locomotion occur widely across vertebrate taxa. For example, many fishes, amphibians and reptiles achieve functional recovery of locomotion after spinal lesion, supported by regeneration of descending axons (Tanaka & Ferretti, 2009; Morgan & Shifman, 2014; Rasmussen & Sagasti, 2016). After spinal cord crush injuries in adult goldfish, startle responses recover but often with lower probability and longer latency, even under conditions of aberrant M-cell regeneration, suggesting compensatory mechanisms (Zottoli *et al*. 1994; Zottoli & Freemer, 2003). Adult salamanders recover undulatory swimming after spinal transection, supported by descending axon regeneration, but with altered swimming kinematics (Davis *et al*. 1990; Chevallier *et al*. 2004; Zukor *et al*. 2011). Similarly, coordinated overground stepping is also restored after complete spinal transection in salamanders and turtles, but with long-term changes in stepping kinematics (Chevallier *et al*. 2004; Rehermann *et al*. 2009). Interestingly, in salamanders, the long-term deficits in locomotor kinematics are more pronounced for swimming recovery than for stepping, indicating differences in the adaptive plasticity mechanisms between the two locomotor modalities (Chevallier *et al*. 2004). Multiple studies in salamanders indicate lack of sensory axon regeneration (Stensaas, 1983; Chevallier *et al*. 2004; Zukor *et al*. 2011), suggesting a lack of mechano-sensory coupling across the lesion that may occur in lampreys and other anguilliform fishes and therefore distinct mechanisms (Wallen, 1982). Even in spinal transected neonatal rats (but not adults), stepping is restored, and this occurs in the absence of axon regeneration (Tillakaratne *et al*. 2010).

In all animals studied thus far, locomotor networks that restore behaviours are both anatomically and functionally reorganized, often dramatically, lending support for the notion that the regenerated spinal cord is a 'new' locomotor circuit (Bradbury & McMahon, 2006; Blesch & Tuszynski, 2009; Parker, 2017). Conserved molecular pathways that promote axon regeneration across both invertebrate and vertebrate species are emerging, including cAMP and regeneration-associated genes (which are transcription factors) (Bhatt *et al*. 2004; Ghosh-Roy *et al*. 2010; Lau *et al*. 2013; Chandran *et al*. 2016; Herman *et al*. 2018). However, with the exception of the lamprey model, the neurophysiological mechanisms underlying functional recovery of locomotor behaviours in most other species remain vastly underexplored, leaving a significant gap in our understanding of resilience mechanisms.

Future directions

Despite decades of research, we still have only a limited and rudimentary understanding of the neural circuit and network mechanisms that underlie both short-term fault tolerance and longer-term functional reorganization in locomotor systems. Even in undulatory locomotors where these phenomena are fairly well described, it is not understood how central pattern generation, circuit function, and active wave propagation are restored after injury at the neural network level. While excellent foundational work has been done on plasticity of individual cell types within lamprey and zebrafish spinal circuits (Yin & Selzer, 1983; Becker & Becker, 2014; Becker & Parker, 2019; Hecker *et al*. 2020*a*), much less is known about network-level plasticity across neuronal populations or contributions of other local circuit components in any of our models. In *C. elegans*, no studies have recorded network activity, functional reorganization, and behaviour in the same animals during regeneration, nor has regeneration of premotor interneurons been tested. To move the field forward will therefore require revisiting these phenomena with new methods that permit precise neuronal lesion and simultaneous assessment of neural network activity and behavioural output.

We therefore suggest a synergistic and comparative approach that begins with lamprey, larval zebrafish and *C. elegans*, leveraging the foundational work on locomotion in these undulatory swimmers. To achieve a better understanding of the underlying neural circuit mechanisms, both shared and distinct, will require experimenters to perform similar types of ablations to analogous neural circuit elements, and observe the physiological and behavioural consequences both acutely and over time as the neural circuits functionally reorganize. A

variety of optogenetic inactivators and cell-ablation tools will reduce experimental barriers across models when targeted to analogous neuronal classes via gene editing technologies such as CRISPR (Sternberg *et al.* 2016; Kimura & Higashijima, 2019; Liu *et al.* 2019; Antinucci *et al.* 2020). Techniques like GRASP (GFP Reconstitution Across Synaptic Partners) are becoming more widespread and will provide new ways to determine connectivity within networks (Feinberg *et al.* 2008; Kishore *et al.* 2020). To measure circuit dynamics and reorganization in real time, the rise of all-optical approaches and whole nervous system imaging in zebrafish and *C. elegans* combined with microscopy advances to visualize large volumes and with moving animals lend the ability to see near simultaneous pan-neuronal activity (Ahrens *et al.* 2013; Kim *et al.* 2017). Although lagging behind *C. elegans* and zebrafish, genetic advances in lamprey will facilitate comparable studies (Kusakabe *et al.* 2003; York & McCauley, 2020), ideally when combined with new optical approaches to visualize neural activity within larger tissue volumes (Abrahamsson *et al.* 2013). Voltage imaging will complement calcium imaging with higher temporal resolution and recording of membrane hyperpolarization following constant improvements in sensors and optics (Mollinedo-Gajate *et al.* 2019). Such advances in new imaging technologies will foster more synergy between model systems.

Computational modelling also presents a powerful approach where the interplay of neural network activity, functional reorganization and behavioural output of undulatory swimmers can be explored and then used for predictive testing. Early models of lamprey elegantly captured fictive travelling wave in terms of weakly coupled neural oscillators (Cohen *et al.* 1982), suggesting that the travelling wave is formed by coordinating the patterns along a chain of oscillators. Later experimental work showed that coupling is strong (Kiemel *et al.* 2003), but models based on the weak coupling assumption have proven accurate nevertheless (Varkonyi *et al.* 2008). Each oscillator is highly non-linear, producing stable oscillations with frequencies and patterns that can be tuned and dynamically modulated, and combined to produce a rich repertoire of behaviours. Two principles – local neurons or neural circuits acting as relaxation oscillators, and weak coupling between these oscillators – have generalized to other locomotor systems and have been pivotal in developing mathematical models of undulations, from fish (Kopell, 1987) to worms (Ji *et al.* 2020). They have also inspired a generation of biologically inspired robots of undulators, crawlers and legged locomotors (Ijspeert *et al.* 2007; Ding *et al.* 2013; Dutta *et al.* 2019), and have provided key insights into possible mechanisms of resilience (Sproewitz *et al.* 2008).

There have been recent advances in integrative models that couple different aspects of neural signalling, muscle mechanics, material properties of the animal's body with external fluid mechanics and sensory feedback in lampreys (Hamlet *et al.* 2018; Tytell *et al.* 2018), other fishes (Gazzola *et al.* 2015), and *C. elegans* (Boyle *et al.* 2012; Denham *et al.* 2018; Izquierdo, 2019; Deng *et al.* 2021). In these models, as in the animals, waveform of the swimmer is not pre-set, but emerges from the coupled neuromechanical system, providing a direct comparison with experimental measurements of undulatory kinematics. *In silico* injuries to the neural network may be simulated by adjusting the topology and strengths of the connections, resulting in altered body kinematics (see Fig. 2*B*). This computational testbed may then be used to probe numerous neural circuit reorganization strategies that could restore locomotor behaviour, in ways not possible in a laboratory, either due to limitations in our ability to target the biological system or due to the labour-intensive nature of physiology and imaging experiments. The results of the computational experiments, comparing hypotheses, and sweeping over synaptic strengths and connectivities, proprioceptive mechanisms, and material properties, in both intact and injured models, will continue to provide insight and guide further lab experiments. Comparing models of the different organisms, particularly by reduction to approximate models such as phase-oscillator models of CPGs, embedded within a physical body, can illuminate shared (perhaps conserved) and distinct principles of locomotor resilience across scales and evolutionary history.

Summary

Resilience of motor systems is not only ubiquitous; it is a defining characteristic of animal behaviour and their nervous systems. Identifying conserved and distinct mechanisms that underlie resilience holds the promise of insights for design of autonomous vehicles, robots and therapeutic approaches (Boyle *et al.* 2013; Ijspeert, 2014; Iosa *et al.* 2016; Courtine & Sofroniew, 2019).

References

Abrahamsson S, Chen J, Hajj B, Stallinga S, Katsov AY, Wisniewski J, Mizuguchi G, Soule P, Mueller F, Dugast Darzacq C, Darzacq X, Wu C, Bargmann CI, Agard DA, Dahan M & Gustafsson MG (2013). Fast multicolor 3D imaging using aberration-corrected multifocus microscopy. *Nat Methods* **10**, 60–63.

Ahrens MB, Orger MB, Robson DN, Li JM & Keller PJ (2013). Whole-brain functional imaging at cellular resolution using light-sheet microscopy. *Nat Methods* **10**, 413–420.

Albadri S, De Santis F, Di Donato V & Del Bene F (2017). CRISPR/Cas9-mediated knockin and knockout in zebrafish. In *Genome Editing in Neurosciences*, eds Jaenisch R, Zhang F & Gage F, pp. 41–49. Springer.

Altun ZF, Chen B, Wang ZW & Hall DH (2009). High resolution map of Caenorhabditis elegans gap junction proteins. *Dev Dyn* **238**, 1936–1950.

Angeli CA, Boakye M, Morton RA, Vogt J, Benton K, Chen Y, Ferreira CK & Harkema SJ (2018). Recovery of over-ground walking after chronic motor complete spinal cord injury. *N Engl J Med* **379**, 1244–1250.

Antinucci P, Dumitrescu A, Deleuze C, Morley HJ, Leung K, Hagley T, Kubo F, Baier H, Bianco IH & Wyart C (2020). A calibrated optogenetic toolbox of stable zebrafish opsin lines. *Elife* **9**, e54937.

Ashby WR (1956). *An Introduction to Cybernetics*. Chapman and Hall, London, UK.

Bargmann CI & Marder E (2013). From the connectome to brain function. *Nat Methods* **10**, 483–490.

Becker T & Becker CG (2014). Axonal regeneration in zebrafish. *Curr Opin Neurobiol* **27**, 186–191.

Becker M & Parker D (2019). Time course of functional changes in locomotor and sensory systems after spinal cord lesions in lamprey. *J Neurophysiol* **121**, 2323–2335.

Belrose JL, Prasad A, Sammons MA, Gibbs KM & Szaro BG (2020). Comparative gene expression profiling between optic nerve and spinal cord injury in Xenopus laevis reveals a core set of genes inherent in successful regeneration of vertebrate central nervous system axons. *BMC Genomics* **21**, 540.

Berg EM, Bjornfors ER, Pallucchi I, Picton LD & El Manira A (2018). Principles governing locomotion in vertebrates: Lessons from zebrafish. *Front Neural Circuits* **12**, 73.

Berri S, Boyle JH, Tassieri M, Hope IA & Cohen N (2009). Forward locomotion of the nematode C. elegans is achieved through modulation of a single gait. *HFSP J* **3**, 186–193.

Bhatt DH, Otto SJ, Depoister B & Fetcho JR (2004). Cyclic AMP-induced repair of zebrafish spinal circuits. *Science* **305**, 254–258.

Biron D & Haspel G (2015). *C. Elegans: Methods and Applications*. Humana Press.

Blesch A & Tuszynski MH (2009). Spinal cord injury: plasticity, regeneration and the challenge of translational drug development. *Trends Neurosci* **32**, 41–47.

Blight AR (1977). The muscular control of vertebrate swimming movements. *Biological Reviews* **52**, 181–218.

Boyle JH, Berri S & Cohen N (2012). Gait modulation in C. elegans: An integrated neuromechanical model. *Front Comput Neurosci* **6**, 10.

Boyle JH, Johnson S & Dehghani-Sanij AA (2013). Adaptive undulatory locomotion of a C. elegans inspired robot. *IEEE/ASME Trans Mechatron* **18**, 439–448.

Bradbury EJ & McMahon SB (2006). Spinal cord repair strategies: why do they work?. *Nat Rev Neurosci* **7**, 644–653.

Brenner S (1974). The genetics of Caenorhabditis elegans. *Genetics* **77**, 71–94.

Briona LK & Dorsky RI (2014). Spinal cord transection in the larval zebrafish. *J Vis Exp* **87**, 51479

Brittin CA, Cook SJ, Hall DH, Emmons SW & Cohen N (2021). A multi-scale brain map derived from whole-brain volumetric reconstructions. *Nature* **591**, 105–110.

Brown TG (1911). The intrinsic factors in the act of progression in the mammal. *Proc R Soc London, Ser B* **84**, 308–319.

Buchanan JT (2001). Contributions of identifiable neurons and neuron classes to lamprey vertebrate neurobiology. *Prog Neurobiol* **63**, 441–466.

Bucher D, Haspel G, Golowasch J & Nadim F (2015). Central pattern generators. In *eLS.*. John Wiley & Sons, Ltd, Chichester. DOI: 10.1002/9780470015902.a0000032.pub2.

Callahan RA, Roberts R, Sengupta M, Kimura Y, Higashijima SI & Bagnall MW (2019). Spinal V2b neurons reveal a role for ipsilateral inhibition in speed control. *Elife* **8**, e47837.

Chalfie M, Sulston JE, White JG, Southgate E, Thomson JN & Brenner S (1985). The neural circuit for touch sensitivity in Caenorhabditis elegans. *J Neurosci* **5**, 956–964.

Chandran V, Coppola G, Nawabi H, Omura T, Versano R, Huebner EA, Zhang A, Costigan M, Yekkirala A, Barrett L, Blesch A, Michaelevski I, Davis-Turak J, Gao F, Langfelder P, Horvath S, He Z, Benowitz L, Fainzilber M, Tuszynski M, Woolf CJ & Geschwind DH (2016). A systems-level analysis of the peripheral nerve intrinsic axonal growth program. *Neuron* **89**, 956–970.

Chevallier S, Landry M, Nagy F & Cabelguen JM (2004). Recovery of bimodal locomotion in the spinal-transected salamander, Pleurodeles waltlii. *Eur J Neurosci* **20**, 1995–2007.

Cohen AH (1988). Evolution of the vertebrate central pattern generator for locomotion. In *Neural Control of Rhythmic Movements in Vertebrates* pp. 129–166. Wiley-Interscience, New York.

Cohen AH, Holmes PJ & Rand RH (1982). The nature of the coupling between segmental oscillators of the lamprey spinal generator for locomotion: a mathematical model. *J Math Biol* **13**, 345–369.

Cohen AH, Mackler SA & Selzer ME (1986). Functional regeneration following spinal transection demonstrated in the isolated spinal cord of the larval sea lamprey. *Proc Natl Acad Sci U S A* **83**, 2763–2766.

Cohen N & Boyle JH (2010). Swimming at low Reynolds number: a beginners guide to undulatory locomotion. *Contemp Phys* **51**, 103–123.

Cohen N & Denham JE (2019). Whole animal modeling: piecing together nematode locomotion. *Curr Opin Syst Biol* **13**, 150–160.

Cooke RM & Parker D (2009). Locomotor recovery after spinal cord lesions in the lamprey is associated with functional and ultrastructural changes below lesion sites. *J Neurotrauma* **26**, 597–612.

Corsi AK, Wightman B & Chalfie M (2015). A Transparent window into biology: A primer on Caenorhabditis elegans. *Genetics* **200**, 387–407.

Courtine G & Sofroniew MV (2019). Spinal cord repair: advances in biology and technology. *Nat Med* **25**, 898–908.

Cowan NJ, Ankarali MM, Dyhr JP, Madhav MS, Roth E, Sefati S, Sponberg S, Stamper SA, Fortune ES & Daniel TL (2014). Feedback control as a framework for understanding tradeoffs in biology. *Integr Comp Biol* **54**, 223–237.

Daghfous G, Green WW, Alford ST, Zielinski BS & Dubuc R (2016). Sensory activation of command cells for locomotion and modulatory mechanisms: lessons from lampreys. *Front Neural Circuits* **10**, 18.

Danos N & Lauder GV (2012). Challenging zebrafish escape responses by increasing water viscosity. *J Exp Biol* **215**, 1854–1862.

Davis BM, Ayers JL, Koran L, Carlson J, Anderson MC & Simpson SB Jr (1990). Time course of salamander spinal cord regeneration and recovery of swimming: HRP retrograde pathway tracing and kinematic analysis. *Exp Neurol* **108**, 198–213.

Davis GR Jr & McClellan AD (1994). Long distance axonal regeneration of identified lamprey reticulospinal neurons. *Exp Neurol* **127**, 94–105.

Deng L, Denham JE, Arya C, Yuval O, Cohen N & Haspel G (2021). Inhibition underlies fast undulatory locomotion in Caenorhabditis elegans. *eNeuro* **8**, ENEURO.0241-20.2020.

Denham JE, Ranner T & Cohen N (2018). Signatures of proprioceptive control in Caenorhabditis elegans locomotion. *Philos Trans R Soc Lond B Biol Sci* **373**, 20180208.

Dias TB, Yang YJ, Ogai K, Becker T & Becker CG (2012). Notch signaling controls generation of motor neurons in the lesioned spinal cord of adult zebrafish. *J Neurosci* **32**, 3245–3252.

Dickinson MH, Farley CT, Full RJ, Koehl MA, Kram R & Lehman S (2000). How animals move: an integrative view. *Science* **288**, 100–106.

Ding R, Yu J, Yang Q & Tan M (2013). Dynamic Modelling of a C00PG-controlled amphibious biomimetic swimming robot. *Int J Adv Rob Syst* **10**, 199. https://doi.org/10.5772/56059.

Dutta S, Parihar A, Khanna A, Gomez J, Chakraborty W, Jerry M, Grisafe B, Raychowdhury A & Datta S (2019). Programmable coupled oscillators for synchronized locomotion. *Nat Commun* **10**, 3299.

Fang-Yen C, Wyart M, Xie J, Kawai R, Kodger T, Chen S, Wen Q & Samuel AD (2010). Biomechanical analysis of gait adaptation in the nematode Caenorhabditis elegans. *Proc Natl Acad Sci U S A* **107**, 20323–20328.

Feinberg EH, Vanhoven MK, Bendesky A, Wang G, Fetter RD, Shen K & Bargmann CI (2008). GFP Reconstitution Across Synaptic Partners (GRASP) defines cell contacts and synapses in living nervous systems. *Neuron* **57**, 353–363.

Fetcho JR & McLean DL (2010). Some principles of organization of spinal neurons underlying locomotion in zebrafish and their implications. *Ann N Y Acad Sci* **1198**, 94–104.

Fidelin K, Djenoune L, Stokes C, Prendergast A, Gomez J, Baradel A, Del Bene F & Wyart C (2015). State-dependent modulation of locomotion by GABAergic spinal sensory neurons. *Curr Biol* **25**, 3035–3047.

Fies J, Gemmell BJ, Fogerson SM, Costello JH, Morgan JR, Tytell ED & Colin SP (2021). Swimming kinematics and performance of spinal transected lampreys with different levels of axon regeneration. *bioRxiv*. 2021.1103.1126.437228.

Forssberg H & Grillner S (1973). The locomotion of the acute spinal cat injected with clonidine i.v. *Brain Res* **50**, 184–186.

Fouad AD, Teng S, Mark JR, Liu A, Alvarez-Illera P, Ji H, Du A, Bhirgoo PD, Cornblath E, Guan SA & Fang-Yen C (2018). Distributed rhythm generators underlie Caenorhabditis elegans forward locomotion. *Elife* **7**, e29913.

Gabel CV, Antoine F, Chuang CF, Samuel AD & Chang C (2008). Distinct cellular and molecular mechanisms mediate initial axon development and adult-stage axon regeneration in C. elegans. *Development* **135**, 1129–1136.

Gao S, Guan SA, Fouad AD, Meng J, Kawano T, Huang YC, Li Y, Alcaire S, Hung W, Lu Y, Qi YB, Jin Y, Alkema M, Fang-Yen C & Zhen M (2018). Excitatory motor neurons are local oscillators for backward locomotion. *Elife* **7**, e29915.

Gazzola M, Argentina M & Mahadevan L (2015). Gait and speed selection in slender inertial swimmers. *Proc Natl Acad Sci U S A* **112**, 3874–3879.

Ghosh-Roy A, Wu Z, Goncharov A, Jin Y & Chisholm AD (2010). Calcium and cyclic AMP promote axonal regeneration in Caenorhabditis elegans and require DLK-1 kinase. *J Neurosci* **30**, 3175–3183.

Gibbs KM, Chittur SV & Szaro BG (2011). Metamorphosis and the regenerative capacity of spinal cord axons in Xenopus laevis. *Eur J Neurosci* **33**, 9–25.

Gibbs KM & Szaro BG (2006). Regeneration of descending projections in Xenopus laevis tadpole spinal cord demonstrated by retrograde double labeling. *Brain Res* **1088**, 68–72.

Goldshmit Y, Sztal TE, Jusuf PR, Hall TE, Nguyen-Chi M & Currie PD (2012). Fgf-dependent glial cell bridges facilitate spinal cord regeneration in zebrafish. *J Neurosci* **32**, 7477–7492.

Gorska T, Chojnicka-Gittins B, Majczynski H & Zmyslowski W (2013). Changes in forelimb-hindlimb coordination after partial spinal lesions of different extent in the rat. *Behav Brain Res* **239**, 121–138.

Gray J (1953). Undulatory propulsion. *J Cell Sci* **s3-94**, 551–578.

Grillner S & El Manira A (2020). Current principles of motor control, with special reference to vertebrate locomotion. *Physiol Rev* **100**, 271–320.

Hale ME, Katz HR, Peek MY & Fremont RT (2016). Neural circuits that drive startle behavior, with a focus on the Mauthner cells and spiral fiber neurons of fishes. *J Neurogenet* **30**, 89–100.

Hamlet CL, Hoffman KA, Tytell ED & Fauci LJ (2018). The role of curvature feedback in the energetics and dynamics of lamprey swimming: A closed-loop model. *PLoS Comput Biol* **14**, e1006324.

Hammarlund M, Nix P, Hauth L, Jorgensen EM & Bastiani M (2009). Axon regeneration requires a conserved MAP kinase pathway. *Science* **323**, 802–806.

Hannila SS & Filbin MT (2008). The role of cyclic AMP signaling in promoting axonal regeneration after spinal cord injury. *Exp Neurol* **209**, 321–332.

Hanslik KL, Allen SR, Harkenrider TL, Fogerson SM, Guadarrama E & Morgan JR (2019). Regenerative capacity in the lamprey spinal cord is not altered after a repeated transection. *PLoS One* **14**, e0204193.

Harkema S, Gerasimenko Y, Hodes J, Burdick J, Angeli C, Chen Y, Ferreira C, Willhite A, Rejc E, Grossman RG & Edgerton VR (2011). Effect of epidural stimulation of the lumbosacral spinal cord on voluntary movement, standing, and assisted stepping after motor complete paraplegia: a case study. *Lancet* **377**, 1938–1947.

Harreguy MB, Marfil V, Grooms NWF, Gabel CV, Chung SH & Haspel G (2020). Ytterbium-doped fibre femtosecond laser offers robust operation with deep and precise microsurgery of C. elegans neurons. *Sci Rep* **10**, 4545.

Haspel G, Deng L, Harreguy MB & Tanvir Z (2020). Elegantly. In *The Neural Control of Movement: Model Systems and Tools to Study Locomotor Function*, pp. 3–29. Academic Press.

Haspel G & O'Donovan MJ (2011). A perimotor framework reveals functional segmentation in the motoneuronal network controlling locomotion in Caenorhabditis elegans. *J Neurosci* **31**, 14611–14623.

Hecker A, Anger P, Braaker PN, Schulze W & Schuster S (2020*a*). High-resolution mapping of injury-site dependent functional recovery in a single axon in zebrafish. *Commun Biol* **3**, 307.

Hecker A, Schulze W, Oster J, Richter DO & Schuster S (2020*b*). Removing a single neuron in a vertebrate brain forever abolishes an essential behavior. *Proc Natl Acad Sci U S A* **117**, 3254–3260.

Herman PE, Papatheodorou A, Bryant SA, Waterbury CKM, Herdy JR, Arcese AA, Buxbaum JD, Smith JJ, Morgan JR & Bloom O (2018). Highly conserved molecular pathways, including Wnt signaling, promote functional recovery from spinal cord injury in lampreys. *Sci Rep* **8**, 742.

Hoffman N & Parker D (2011). Interactive and individual effects of sensory potentiation and region-specific changes in excitability after spinal cord injury. *Neuroscience* **199**, 563–576.

Horner AM & Jayne BC (2008). The effects of viscosity on the axial motor pattern and kinematics of the African lungfish (Protopterus annectens) during lateral undulatory swimming. *J Exp Biol* **211**, 1612–1622.

Huang KH, Ahrens MB, Dunn TW & Engert F (2013). Spinal projection neurons control turning behaviors in zebrafish. *Curr Biol* **23**, 1566–1573.

Ijspeert AJ (2008). Central pattern generators for locomotion control in animals and robots: a review. *Neural Netw* **21**, 642–653.

Ijspeert AJ (2014). Biorobotics: using robots to emulate and investigate agile locomotion. *Science* **346**, 196–203.

Ijspeert AJ, Crespi A, Ryczko D & Cabelguen JM (2007). From swimming to walking with a salamander robot driven by a spinal cord model. *Science* **315**, 1416–1420.

Iosa M, Morone G, Cherubini A & Paolucci S (2016). The three laws of neurorobotics: A review on what neurorehabilitation robots should do for patients and clinicians. *J Med Biol Eng* **36**, 1–11.

Izquierdo EJ (2019). Role of simulation models in understanding the generation of behavior in C. elegans. *Curr Opin Syst Biol* **13**, 93–101.

Ji H, Fouad AD, Teng S, Liu A, Alvarez-Illera P, Yao B, Li Z & Fang-Yen C (2020). Phase response analyses support a relaxation oscillator model of locomotor rhythm generation in Caenorhabditis elegans. *bioRxiv*, 2020.1106.1122.164939.

Jindrich DL & Full RJ (2002). Dynamic stabilization of rapid hexapedal locomotion. *J Exp Biol* **205**, 2803–2823.

Juvin L, Gratsch S, Trillaud-Doppia E, Gariepy JF, Buschges A & Dubuc R (2016). A specific population of reticulospinal neurons controls the termination of locomotion. *Cell Rep* **15**, 2377–2386.

Kano T, Kanauchi D, Ono T, Aonuma H & Ishiguro A (2019). Flexible coordination of flexible limbs: Decentralized control scheme for inter- and intra-limb coordination in brittle stars' locomotion. *Front Neurorobot* **13**, 104.

Katz HR, Fouke KE, Losurdo NA & Morgan JR (2020). Recovery of burrowing behavior after spinal cord injury in the larval sea lamprey. *Biol Bull* **239**, 174–182.

Kawano T, Po MD, Gao S, Leung G, Ryu WS & Zhen M (2011). An imbalancing act: gap junctions reduce the backward motor circuit activity to bias C. elegans for forward locomotion. *Neuron* **72**, 572–586.

Kiemel T, Gormley KM, Guan L, Williams TL & Cohen AH (2003). Estimating the strength and direction of functional coupling in the lamprey spinal cord. *J Comput Neurosci* **15**, 233–245.

Kim DH, Kim J, Marques JC, Grama A, Hildebrand DGC, Gu W, Li JM & Robson DN (2017). Pan-neuronal calcium imaging with cellular resolution in freely swimming zebrafish. *Nat Methods* **14**, 1107–1114.

Kimura Y & Higashijima SI (2019). Regulation of locomotor speed and selection of active sets of neurons by V1 neurons. *Nat Commun* **10**, 2268.

Kishore S, Cadoff EB, Agha MA & McLean DL (2020). Orderly compartmental mapping of premotor inhibition in the developing zebrafish spinal cord. *Science* **370**, 431–436.

Knafo S & Wyart C (2018). Active mechanosensory feedback during locomotion in the zebrafish spinal cord. *Curr Opin Neurobiol* **52**, 48–53.

Kopell N (1987). Coupled oscillators and locomotion by fish. In *Nonlinear Oscillations in Biology and Chemistry*, ed. Othmer HG, pp. 160–174. Springer.

Korn H & Faber DS (2005). The Mauthner cell half a century later: a neurobiological model for decision-making? *Neuron* **47**, 13–28.

Kusakabe R, Tochinai S & Kuratani S (2003). Expression of foreign genes in lamprey embryos: an approach to study evolutionary changes in gene regulation. *J Exp Zool B Mol Dev Evol* **296B**, 87–97.

Lau BY, Fogerson SM, Walsh RB & Morgan JR (2013). Cyclic AMP promotes axon regeneration, lesion repair and neuronal survival in lampreys after spinal cord injury. *Exp Neurol* **250**, 31–42.

Liao JC (2007). A review of fish swimming mechanics and behaviour in altered flows. *Philos Trans R Soc Lond B Biol Sci* **362**, 1973–1993.

Liu Q, Sinnen BL, Boxer EE, Schneider MW, Grybko MJ, Buchta WC, Gibson ES, Wysoczynski CL, Ford CP, Gottschalk A, Aoto J, Tucker CL & Kennedy MJ (2019). A photoactivatable botulinum neurotoxin for inducible control of neurotransmission. *Neuron* **101**, 863–875.e6.

Long JH (1998). Muscles, elastic energy, and the dynamics of body stiffness in swimming eels. *Am Zool* **38**, 771–792.

McClellan AD (1988). Brainstem command systems for locomotion in the lamprey: localization of descending pathways in the spinal cord. *Brain Res* **457**, 338–349.

McIntire SL, Jorgensen E, Kaplan J & Horvitz HR (1993). The GABAergic nervous system of Caenorhabditis elegans. *Nature* **364**, 337–341.

McLean DL, Fan J, Higashijima S, Hale ME & Fetcho JR (2007). A topographic map of recruitment in spinal cord. *Nature* **446**, 71–75.

McLean DL & Fetcho JR (2011). Movement, technology and discovery in the zebrafish. *Curr Opin Neurobiol* **21**, 110–115.

McLean DL, Masino MA, Koh IY, Lindquist WB & Fetcho JR (2008). Continuous shifts in the active set of spinal interneurons during changes in locomotor speed. *Nat Neurosci* **11**, 1419–1429.

Marder E & Bucher D (2001). Central pattern generators and the control of rhythmic movements. *Curr Biol* **11**, R986–R996.

Marques JC, Li M, Schaak D, Robson DN & Li JM (2020). Internal state dynamics shape brainwide activity and foraging behaviour. *Nature* **577**, 239–243.

Menelaou E & McLean DL (2019). Hierarchical control of locomotion by distinct types of spinal V2a interneurons in zebrafish. *Nat Commun* **10**, 4197.

Mollinedo-Gajate I, Song C & Knopfel T (2019). Genetically encoded fluorescent calcium and voltage indicators. *Handb Exp Pharmacol* **260**, 209–229.

Morgan JR (2017). Spinal cord repair and regeneration. In *Regenerative Engineering and Developmental Biology*, ed. Gardiner D, pp. 477–497. CRC Press, Taylor and Francis Group, LLC, Boca Raton, FL, USA.

Morgan JR & Shifman MI (2014). *Non-Mammalian Models of Nerve Regeneration*, vol. **1**. Cambridge University Press, Cambridge, UK.

Ohnmacht J, Yang Y, Maurer GW, Barreiro-Iglesias A, Tsarouchas TM, Wehner D, Sieger D, Becker CG & Becker T (2016). Spinal motor neurons are regenerated after mechanical lesion and genetic ablation in larval zebrafish. *Development* **143**, 1464–1474.

Oliphint PA, Alieva N, Foldes AE, Tytell ED, Lau BY, Pariseau JS, Cohen AH & Morgan JR (2010). Regenerated synapses in lamprey spinal cord are sparse and small even after functional recovery from injury. *J Comp Neurol* **518**, 2854–2872.

Orger MB, Kampff AR, Severi KE, Bollmann JH & Engert F (2008). Control of visually guided behavior by distinct populations of spinal projection neurons. *Nat Neurosci* **11**, 327–333.

Parker D (2017). The lesioned spinal cord is a "new" spinal cord: evidence from functional changes after spinal injury in lamprey. *Front Neural Circuits* **11**, 84.

Pfeiffenberger JA (2017). Biomechanical control mechanisms and morphology for locomotion in challenging scenarios. Dissertation, Department of Biology, Temple University.

Portugues R, Severi KE, Wyart C & Ahrens MB (2013). Optogenetics in a transparent animal: circuit function in the larval zebrafish. *Curr Opin Neurobiol* **23**, 119–126.

Rasmussen JP & Sagasti A (2016). Learning to swim, again: Axon regeneration in fish. *Exp Neurol* **287**, 318-330.

Rehermann MI, Marichal N, Russo RE & Trujillo-Cenoz O (2009). Neural reconnection in the transected spinal cord of the freshwater turtle Trachemys dorbignyi. *J Comp Neurol* **515**, 197–214.

Reilly MB, Cros C, Varol E, Yemini E & Hobert O (2020). Unique homeobox codes delineate all the neuron classes of C. elegans. *Nature* **584**, 595–601.

Rossignol S, Barriere G, Alluin O & Frigon A (2009). Re-expression of locomotor function after partial spinal cord injury. *Physiology (Bethesda)* **24**, 127–139.

Rossignol S, Dubuc R & Gossard JP (2006). Dynamic sensorimotor interactions in locomotion. *Physiol Rev* **86**, 89–154.

Rovainen CM (1976). Regeneration of Muller and Mauthner axons after spinal transection in larval lampreys. *J Comp Neurol* **168**, 545–554.

Sarma GP, Lee CW, Portegys T, Ghayoomie V, Jacobs T, Alicea B, Cantarelli M, Currie M, Gerkin RC, Gingell S, Gleeson P, Gordon R, Hasani RM, Idili G, Khayrulin S, Lung D, Palyanov A, Watts M & Larson SD (2018). OpenWorm: overview and recent advances in integrative biological simulation of Caenorhabditis elegans. *Philos Trans R Soc Lond B Biol Sci* **373**, 20170382.

Satou C, Sugioka T, Uemura Y, Shimazaki T, Zmarz P, Kimura Y & Higashijima SI (2020). Functional diversity of glycinergic commissural inhibitory neurons in larval zebrafish. *Cell Rep* **30**, 3036-3050.e4.

Selzer ME (1978). Mechanisms of functional recovery and regeneration after spinal cord transection in larval sea lamprey. *J Physiol* **277**, 395–408.

Severi KE, Bohm UL & Wyart C (2018). Investigation of hindbrain activity during active locomotion reveals inhibitory neurons involved in sensorimotor processing. *Sci Rep* **8**, 13615.

Severi KE, Portugues R, Marques JC, O'Malley DM, Orger MB & Engert F (2014). Neural control and modulation of swimming speed in the larval zebrafish. *Neuron* **83**, 692–707.

Shaw AC, Jackson AW, Holmes T, Thurman S, Davis GR & McClellan AD (2010). Descending brain neurons in larval lamprey: spinal projection patterns and initiation of locomotion. *Exp Neurol* **224**, 527–541.

Sillar KT (2009). Mauthner cells. *Curr Biol* **19**, R353-R355.

Sproewitz A, Moeckel R, Maye J & Ijspeert AJ (2008). Learning to move in modular robots using central pattern generators and online optimization. *Int J Rob Res* **27**, 423–443.

Stensaas LJ (1983). Regeneration in the spinal cord of the newt Notophtalmus (triturus) pyrrhogaster. In *Spinal Cord Reconstruction*, eds Kao CC, Bunge RP & Reier PJ, pp. 121–149. Raven Press, New York.

Sternberg JR, Severi KE, Fidelin K, Gomez J, Ihara H, Alcheikh Y, Hubbard JM, Kawakami K, Suster M & Wyart C (2016). Optimization of a neurotoxin to investigate the contribution of excitatory interneurons to speed modulation in vivo. *Curr Biol* **26**, 2319–2328.

Tanaka EM & Ferretti P (2009). Considering the evolution of regeneration in the central nervous system. *Nat Rev Neurosci* **10**, 713–723.

Tillakaratne NJ, Guu JJ, de Leon RD, Bigbee AJ, London NJ, Zhong H, Ziegler MD, Joynes RL, Roy RR & Edgerton VR (2010). Functional recovery of stepping in rats after a complete neonatal spinal cord transection is not due to regrowth across the lesion site. *Neuroscience* **166**, 23–33.

Tsarouchas TM, Wehner D, Cavone L, Munir T, Keatinge M, Lambertus M, Underhill A, Barrett T, Kassapis E, Ogryzko N, Feng Y, van Ham TJ, Becker T & Becker CG (2018). Dynamic control of proinflammatory cytokines Il-1beta and Tnf-alpha by macrophages in zebrafish spinal cord regeneration. *Nat Commun* **9**, 4670.

Turek M, Lewandrowski I & Bringmann H (2013). An AP2 transcription factor is required for a sleep-active neuron to induce sleep-like quiescence in C. elegans. *Curr Biol* **23**, 2215–2223.

Tytell ED, Carr JA, Danos N, Wagenbach C, Sullivan CM, Kiemel T, Cowan NJ & Ankarali MM (2018). Body stiffness and damping depend sensitively on the timing of muscle activation in lampreys. *Integr Comp Biol* **58**, 860–873.

van Raamsdonk W, Maslam S, de Jong DH, Smit-Onel MJ & Velzing E (1998). Long term effects of spinal cord transection in zebrafish: swimming performances, and metabolic properties of the neuromuscular system. *Acta Histochem* **100**, 117–131.

Varkonyi PL, Kiemel T, Hoffman K, Cohen AH & Holmes P (2008). On the derivation and tuning of phase oscillator models for lamprey central pattern generators. *J Comput Neurosci* **25**, 245–261.

Wagner FB, Mignardot JB, Le Goff-Mignardot CG, Demesmaeker R, Komi S, Capogrosso M, Rowald A, Seanez I, Caban M, Pirondini E, Vat M, McCracken LA, Heimgartner R, Fodor I, Watrin A, Seguin P, Paoles E, Van Den Keybus K, Eberle G, Schurch B, Pralong E, Becce F, Prior J, Buse N, Buschman R, Neufeld E, Kuster N, Carda S, von Zitzewitz J, Delattre V, Denison T, Lambert H, Minassian K, Bloch J & Courtine G (2018). Targeted neurotechnology restores walking in humans with spinal cord injury. *Nature* **563**, 65–71.

Wallen P (1982). Spinal mechanisms controlling locomotion in dogfish and lamprey. *Acta Physiol Scand Suppl* **503**, 1–45.

White JG, Southgate E, Thomson JN & Brenner S (1986). The structure of the nervous system of the nematode *Caenorhabditis elegans*. *Philos Trans R Soc Lond B Biol Sci* **314**, 1–340.

Wicks SR & Rankin CH (1995). Integration of mechanosensory stimuli in Caenorhabditis elegans. *J Neurosci* **15**, 2434–2444.

Wilshin S, Shamble PS, Hovey KJ, Harris R, Spence AJ & Hsieh ST (2018). Limping following limb loss increases locomotor stability. *J Exp Biol* **221**.

Wilson DM (1961). The central nervous control of flight in a locust. *J Exp Biol* **38**, 471–490.

Yanik MF, Cinar H, Cinar HN, Chisholm AD, Jin Y & Ben-Yakar A (2004). Neurosurgery: functional regeneration after laser axotomy. *Nature* **432**, 822.

Yin HS & Selzer ME (1983). Axonal regeneration in lamprey spinal cord. *J Neurosci* **3**, 1135–1144.

York JR & McCauley DW (2020). Functional genetic analysis in a jawless vertebrate, the sea lamprey: insights into the developmental evolution of early vertebrates. *J Exp Biol* **223**, jeb206433.

Yu X, Nguyen B & Friesen WO (1999). Sensory feedback can coordinate the swimming activity of the leech. *J Neurosci* **19**, 4634–4643.

Zheng Y, Brockie PJ, Mellem JE, Madsen DM & Maricq AV (1999). Neuronal control of locomotion in C. elegans is modified by a dominant mutation in the GLR-1 ionotropic glutamate receptor. *Neuron* **24**, 347–361.

Zottoli SJ, Bentley AP, Feiner DG, Hering JR, Prendergast BJ & Rieff HI (1994). Spinal cord regeneration in adult goldfish: implications for functional recovery in vertebrates. *Prog Brain Res* **103**, 219–228.

Zottoli SJ & Freemer MM (2003). Recovery of C-starts, equilibrium and targeted feeding after whole spinal cord crush in the adult goldfish Carassius auratus. *J Exp Biol* **206**, 3015–3029.

Zukor KA, Kent DT & Odelberg SJ (2011). Meningeal cells and glia establish a permissive environment for axon regeneration after spinal cord injury in newts. *Neural Dev* **6**, 1.

Additional information

Competing interests

All authors declare no conflict of interest in accordance with journal policy.

Author contributions

Conception or design of the work: G.H., K.E.S., L.J.F., N.C., E.D.T., J.R.M.; acquisition or analysis or interpretation of data: G.H., K.E.S., E.D.T., J.R.M.; drafting the work or revising it critically for important intellectual content: G.H., K.E.S., L.J.F., N.C., E.D.T., J.R.M.; agreement to be accountable for all aspects of the work: G.H., K.E.S., L.J.F., N.C., E.D.T., J.R.M. All authors approved the final version of the manuscript. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

Funding

G.H: New Jersey Commission on spinal Cord Research (NJCSCR), CSCR14ERG002; K.E.S.: New Jersey Institute of Technology (NJIT), Institutional start up; L.J.F: National Science Foundation (NSF), DMS1951707; N.C.: The Engineering and Physical Sciences Research Council (EPSRC, UK), EP/S01540X/1; E.D.T.: National Science Foundation (NSF), IOS 1652582; J.R.M.: Marine Biological Laboratory (MBL), Eugene Bell Center Endowment Fund.

Acknowledgements

We thank Hilary Katz (Morgan lab) for providing the lamprey spinal cord regeneration images (Fig. 2*A*), Christina Hamlet (Fauci and Tytell labs), for providing data used for Fig. 2*B*, Mahathi Mohan Gowda and Aryan Mahajan (Severi lab) for contributing to experimental design for Fig. 2*C*, and Maria Belen Harreguy (Haspel lab) for providing the *C. elegans* regeneration images (Fig. 4*C*). Netta Cohen acknowleges funding from the Engineering and Physical Sciences Research Council (EPSRC, UK) number EP/S01540X/1.

Keywords

caenorhabditis elegans, computational neuroscience, injury, lamprey, locomotion, mathematical modelling, reticulospinal, sensorimotor control, zebrafish

Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the HTML view of the article. Supporting information files available:

Peer Review History