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SYMPOSIUM

Mechanosensory Feedback in Lamprey Swimming Models and Applications in the Field of Spinal Cord Regeneration

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Synopsis The central pattern generator (CPG) in anguilliform swimming has served as a model for examining the neural basis of locomotion. This system has been particularly valuable for the development of mathematical models. As our biological understanding of the neural basis of locomotion has expanded, so too have these models. Recently, there have been significant advancements in our understanding of the critical role that mechanosensory feedback plays in robust locomotion. This work has led to a push in the field of mathematical modeling to incorporate mechanosensory feedback into CPG models. In this perspective piece, we review advances in the development of these models and discuss how newer complex models can support biological investigation. We highlight lamprey spinal cord regeneration as an area that can both inform these models and benefit from them.

Introduction

For over 100 years, the lamprey has served as an invaluable vertebrate model in the field of neuroscience (Freud 1878). Their relatively “simple” spinal circuit and large identifiable neurons make them amenable to *in vivo* electrophysiological investigation for studies on the neural basis of locomotion, and central pattern generators (CPGs) in particular (Rovainen1967a, 1967b). Experimental and computational studies have sought to shed light on the mechanisms underlying these systems, which drive behaviors such as swimming. Early experimental work described the processes behind rhythmic signal generation and found CPGs to be ubiquitous across the animal phylogeny (e.g., Wilson 1961; Grillner 1975; Vidal et al. 1979; Grillner 2011). Meanwhile, oscillator theory has been used to describe rhythmic patterns in biology, including some neurophysiological phenomena (Winfree 1967; Glass and Young 1979; Yamanishi et al. 1980). Researchers began to combine these efforts to develop a model of CPGs in lampreys based on weakly coupled oscillators. Since these early descriptions, many different types of models have developed to describe the entrainment ranges of CPGs (Previte et al. 2011; Haspel et al. 2021), patterns in fictive swimming (Cohen et al. 1992), and drive robotic and computational models (Thandiackal et al. 2021; Hamlet et al. 2023). As our understanding of lamprey neurophysiology has expanded, more refined models have emerged. However, as these models develop, a key feature is that studying each system in isolation limits our understanding of how the systems work together to produce locomotion.

Recent studies have highlighted the critical role for mechanosensory feedback in robust locomotion, emphasizing the need to better understand the mechanisms behind sensorimotor integration (Katz et al. 2021). Researchers have sought to understand the role of mechanosensation in stabilizing swimming behavior and compensating for external (obstacles) and internal (injury) types of perturbations in swimming (McClellan and Jang 1993). Though the CPG can produce rhythmic signals in isolation of the body, it is becoming more apparent that the feedback from the body itself plays a crucial role in stabilizing swimming through

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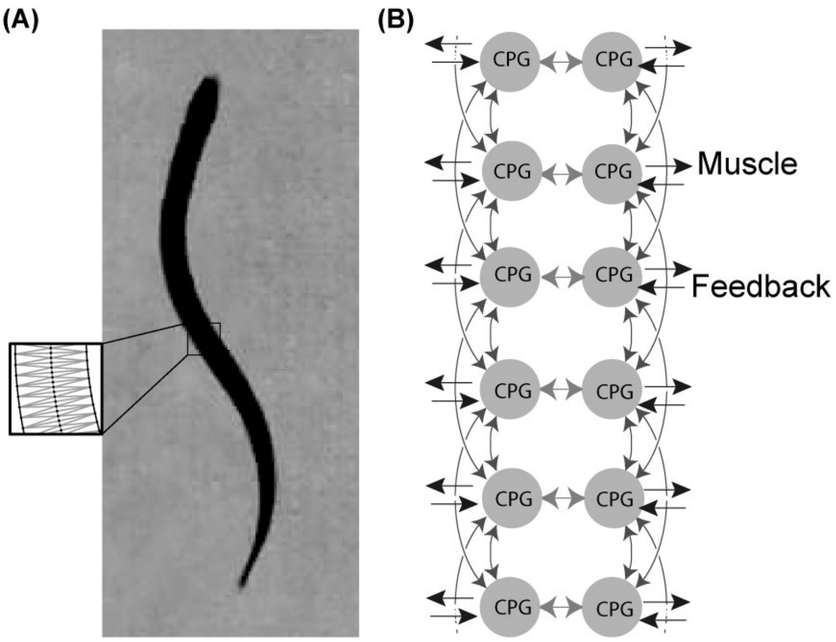

Fig. 1 Representative schematic of a computational model. (A) Still frame of a larval lamprey swimming with an inset schematic representing segments. Image provided by Hilary Katz. (B) Shows the structure of an integrative computational model that could be used to drive a swimming "lamprey." Neural activation drives muscle contraction and ultimately body movement. The body moves the surrounding fluid and receives feedback from the environment. Movement of the body also provides proprioceptive feedback, which influences neural activation and muscle contraction inputting back into the CPG. Arrows drawn between CPGs represent the coupling between CPGs. For simplicity, the directionality of signals from the CPG to the muscles and feedback from the body to the CPG are shown on one segment but operate similarly on each segment. Each body segment has a pair of oscillators that are in antiphase with each other. Along the lateral sides of the body, the segments on the same lateral side are weakly coupled. The strengths may differ in the ascending and descending directions.

the mechanism of mechanosensation (Hamlet et al. 2018).

In addition to locomotion, the lamprey has served as a model for successful spinal cord regeneration in vertebrates (Cohen et al. 1986). Following a complete spinal transection, lampreys can regenerate their spinal cord and achieve substantial functional recovery (Parker 2017). Research on spinal cord regeneration has primarily focused on the recovery of motor circuits and large reticulospinal (RS) axons (e.g., McClellan 1990; Romaus-Sanjurjo et al. 2018). There is a need to expand our understanding of mechanosensory integration in the regenerated circuit. Furthermore, proprioception is suspected to play a role in recovery from loss of function following a partial or complete transection of the spinal cord in lampreys. As computational models continue to increase in complexity and reduce in cost of labor, they provide an opportunity to shed light on the role of sensory feedback in stabilizing the motion of an integrative system. These models have the potential not only to describe behaviors but to propose and predict mechanisms that can then be tested experimentally.

Here we discuss the progress that has been made in developing computational models alongside biological investigation, beginning from the early CPG models through the construction of integrative models. We then summarize what is known about the mechanosensory system in the lamprey and see how this sensory feedback system has been applied to recent models to stabilize, drive, or even control locomotor behaviors. Finally, we review the lamprey as a model for spinal cord regeneration and discuss how these integrative mechanosensory models can provide insight into the regenerated neural circuit.

CPGs and phase oscillators

Anguilliform, eel-like, locomotion is driven by a series of CPGs along the body axis (Fig. 1; Cohen 1987). CPGs are simple neuronal networks that drive rhythmic behaviors, even in the absence of external input, and occur in every animal known and studied to date (Marder and Bucher 2001). In the lamprey, like other anguilliform swimmers, muscle activation travels along the body axis, driven by CPGs at each muscle segment along the body. Early experiments identified the nature of this traveling wave of activation: periodic with a characteristic phase lag along each lateral side as well as an antiphase pattern across a given segment (Paggett et al. 1998). This pattern of activation ultimately gives rise to the sinusoidal swimming that is characteristic among anguilliform swimmers (Fig. 1A; Cohen 1987; Paggett et al. 1998). Researchers in biological and mathematical fields found that the output driven by CPG circuits resembled that of phase oscillators. A mathematical "phase oscillator" exhibits a periodic sinusoidal oscillation, and depending on the phase of the oscillation, we can consider the output to be "active" or "inactive" (Cohen et al. 1982). These observations and early mathematical work relating oscillator theory to neurobiology led to mathematical models based on fictive swimming that could be used to better understand the CPG circuit (Cohen et al. 1982).

This early work relating neurophysiology to oscillator theory (Pavlidis and Pinsker 1977; Glass and Young 1979) led to the construction of an early model of the CPG signal in lampreys using a set of weakly coupled oscillators (Cohen et al. 1982). These mathematical models used fictive swimming signals, motor output measured by ventral root recordings in an isolated cord, as a guide to constructing a set of oscillators whose outputs reproduced the key components observed in experimental results. The earliest models included single-phase oscillators coupled in a series, as opposed to pairs of oscillators, so these models had no sidedness (Cohen et al. 1982). These phase oscillator models have found success in producing rhythmic patterns seen in fictive swimming experiments. They have also provided an opportunity to explore how pattern generation is affected by changing the coupling types, or how many oscillators in the series each oscillator is connected to, and changing the strength between each of those connections.

Since their initial construction, several types of oscillator models have been developed, incorporating different levels and types of biological information in their construction (e.g., Fig. 1B; Williams et al. 1990; Kopell et al. 1991; Cohen et al. 1992; Ekeberg and Grillner 1999). These later efforts (Cohen et al. 1992) investigated the nature of the coupling between segments and their role in producing rhythmic patterns similar to those seen in fictive motion. Equations for weakly coupled oscillators demonstrated fictive swimming frequencies similar to biological observations. Other investigations have focused on modeling the underlying cellular interactions among motor neurons, as opposed to modeling motor output, (Alford and Grillner 1991; Grillner 2003) to refine models beyond the early reduced-phase models. Many of these models describe neuronal signaling well for a limited number of segments. Still, they begin to see a loss of entrainment, or oscillator synchronization, as the number of segments increases to a biologically relevant number, indicating that critical neural signaling components remain unresolved in a detailed mechanistic model.

Sensory feedback in anguilliform locomotion

These early models considered CPGs in the absence of external feedback. However, in a living organism, the CPGs constantly receive feedback from several sources. These sources include the brain and/or ganglion clusters and sensory cells. This results in a closed-loop system in which the CPG continually responds to sensory feedback and adjusts the activation signals the rest of the body receives.

This sensorimotor integration allows animals to adjust to perturbations from internal systems, such as the deformation of the body, in addition to external perturbations from the environment (Grillner et al. 1981; Grillner et al. 1984). Mechanosensory input has been shown to be an essential component in robust locomotion (Knafo and Wyart 2018). Within the lamprey spinal cord, which many of the discussed mathematical models are based on, there are two primary sources of mechanosensory feedback: edge cells and dorsal cells. Edge cells are stretch receptor cells located on the margin of the spinal cord. These cells are known to excite ipsilateral muscle contractions and to inhibit contralateral contractions in response to stretch, though the exact functional form of this response is not well-resolved (Williams et al. 1990; McClellan and Jang 1993; Tytell and Cohen 2008). While other stretch-receptive mechanosensory cells have been identified in ray-finned fish (Knafo and Wyart 2018), it is unclear whether these populations are homologous. Lampreys have an additional population of mechanosensory neurons called dorsal cells. These cells are located along the medial track of the spinal cord (Rovainen 1967b). They have a rostral and a caudal projection, as well as a peripheral process that exits the spinal cord and projects to the skin. Their large size and location in the spinal cord make these cells easily identifiable under a dissecting scope without any labeling. While dorsal cells have not been extensively examined in the lamprey, they are thought to be homologous with Rohon–Beard neurons in fish and amphibians, which sense touch and nociception in the skin (Buchanan and Cohen 1982; Katz et al. 2021). Dorsal cell physiology has been characterized based on their response to intracellular current injections, and single-cell stimulation has been shown to disrupt ventral root bursting rhythm (Buchanan and Cohen 1982). These observations are consistent with work in larval zebrafish that indicate Rohon–Beard neurons likely play a role in several behaviors including startle behavior and modulation of swimming speed (Knafo et al. 2017; Liu and Hale 2017).

One of the key questions in understanding the role of mechanosensation in locomotor behavior is how the organism translates the sensory feedback into a functional adjustment in behavior. Mathematical modeling offers a path to understanding the effect of these signals and proposing mechanisms by which a response to a stimulus at a cellular level can be converted into the appropriate change in the organism's behavior. While much has been studied regarding mechanosensation, many exact mechanisms describing the underlying phenomena remain unresolved. Mathematical modeling may allow us to explore potential connections that can then be tested *in vivo*.

In an effort to understand the effects of mechanosensory input on locomotion, some early phase oscillator models have explored entrainment ranges in chains of phase oscillators forced at different positions along the body (Masserelli et al. 2016). Entrainment ranges, in this context, refer to the range of frequencies at which the CPG can match the stimulus frequency (Masserelli et al. 2016). Results, including those of Williams et al. (1990), Kopell et al. (1991), Previte et al. (2011), and Masserelli et al. (2016), have explored the coupling required to produce entrainment or activation frequency, ranges comparable to experimental results with fictive swimming. Kopell and Ermentrout (1988) theoretically determined the general conditions under which entrainment can occur and conditions under which entrainment can be lost due to forcing at different locations along the chain. In the context of mechanosensation, these results provide insight into how a feedback signal from structures such as edge cells could induce a different frequency of oscillation along parts of the CPG with a given forcing signal at a few points along the body.

Moving from computational models of CPG to integrative swimming models

Advances in understanding of sensory feedback as well as neural signaling and cellular models (Grillner et al. 1991; Nishikawa et al. 2012; Williams 1992; Haspel et al. 2021) have supported the evolution from reductionist models, which focus on fictive motor output, to more integrative models of swimming behavior (Ijspeert et al. 1999; Tytell et al. 2010, Hamlet et al. 2016). More sophisticated models of neural signaling (Grillner 2003; Kiemel et al. 2003; Zhaoping et al. 2004) more capable of incorporating proprioceptive effects have shown promise in constructing integrative models to study the role of mechanosensation in lamprey swimming. These integrative models allow researchers to explore biological mechanisms and the physical limitations imposed by coordinating multiple systems to produce emergent behavior such as swimming (Fig. 2). For example, computational work has shown that asymmetric coupling between segments in the ascending and descending directions is required to observe CPG entrainment similar to that observed in lampreys (Previte et al. 2011). While reductionist models using phase oscillators have yielded many insights into pattern generation, interest in phenomena such as mechanosensation continue to drive the development of even more detailed neural models. In contrast to phase oscillators, which are modeled after the ventral root motor output, neural models incorporate the neural networks that produce the ventral root output, offering more ability to incorporate complex feedback mechanisms. While these results were for a limited number of segments, they have inspired broad research in pattern generation and control mechanisms for robotic design (Thandiackal et al. 2021).

One of the main goals of studying the effects of sensory feedback on the CPG is to understand the role that mechanosensation plays in overall locomotor behavior. Mathematical models that incorporate mechanosensory feedback allow us to explore the influence of variable input on motor output. As previously discussed, early modeling of the CPG revealed many characteristics found in fictive swimming (Cohen et al. 1982). However, as highlighted in the review by Tytell et al. (2011), outputs from neural circuits are essential but still only one part of a complicated system combining neural signaling to a mechanical system interacting with a fluid environment to produce swimming behaviors (Fig. 1). The interdependence of these sensory and motor systems has driven the development of integrative models in mathematics, computation, and bioinspired engineering design (Fig. 2).

Computational models of anguilliform swimmers have been constructed using prescribed body shapes and elastic rod models by Carling et al. (1998) and McMillen et al. (2008), comparing their results to experimental results from Tytell and Lauder (2004). Using a fixed activation wave, these models represent an essential step in developing computational models of anguilliform swimmers. A major difficulty in simulating swimming is the fluid environment itself. Many models have modeled swimming behavior by approximating fluid forces (Lighthill 1969; McMillen et al. 2008). To study the fully coupled fluid-structure interaction problem, Tytell et al. (2010) constructed a multiscale, integrative computational lamprey in an immersed boundary framework. The immersed boundary method is a well-established computational method that allows highly deformable bodies to be coupled to a full Navier-Stokes model for a viscous, incompressible fluid, which facilitates the study of the interaction between a structure (in this case, a lamprey) and its fluid environment. Early immersed boundary models employed a prescribed activation wave, focusing on the

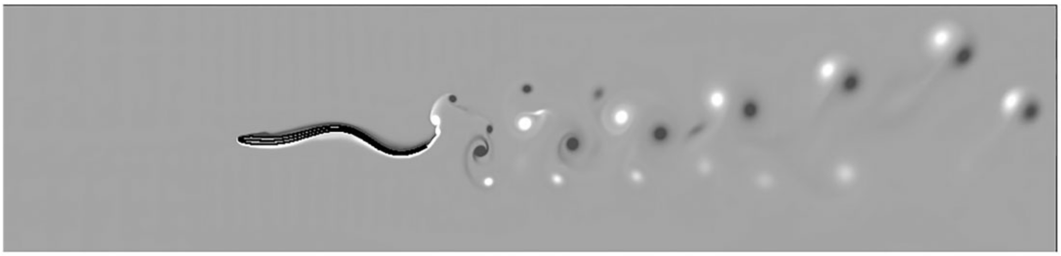

Fig. 2 Simulation of emergent swimming using an integrative computational model. Data provided by the Hamlet Lab. The computational model comprises coordinated models for calcium dynamics, muscle mechanics, passive body structures, and fluid structure interactions driven by a CPG based on phase oscillator models. Proprioception from edge cells is modeled as curvature changes. Such models can be employed to test and analyze changes to the CPG and swimming behavior in the presence of different feedback signals, external perturbations, or spinal cord injuries.

energetics and mechanical feedback forms such as muscle stiffness (Tytell et al. 2011; Hamlet et al. 2015). Later models have developed an integrative model driven by coupled phase oscillators capable of incorporating sensory feedback from edge cells and other forms of proprioception (Hamlet et al. 2018). In one of the most recent models (Hamlet et al. 2018, 2023), edge cell response is modeled using functions of local curvature, which is a reasonable approximation to the degree of stretch in a region. This model has been used to explore functional forms of mechanosensory feedback from edge cells and their effects on swimming performance. Results from this model have shown that different functional forms of proprioceptive feedback proportional to stretch can increase swimming speed while reducing metabolic cost, indicating that mechanosensation can stabilize locomotion during perturbations and enhance swimming performance even for steady swimming.

Other groups, such as Gazzola et al. (2015), have modeled the effects of mechanosensation computationally using elastic sheet models and incorporating proprioception directly into the torque experienced by the elastic sheet and the equations driving motion. Their results demonstrated some of the effects of proprioception on body stiffness, allowing organisms to switch to higher resonant frequencies and reproduce some observed complex gaits.

Some models have combined computational modeling and bioinspired design, such as Ijspeert et al. (2007) and Thandiackal et al. (2021). In Thandiackal et al. (2021), a segmental robotic swimmer is constructed and programmed to respond with parameters based on muscle mechanics, neural activation, and exteroceptive feedback. This exteroceptive feedback was modeled after the feedback that is hypothesized to be relayed by the lamprey dorsal cells. The coupling strengths were hand-tuned in this model, and both phase oscillator and neural network models were implemented. Using the robotic model, they were able to isolate and explore the roles of the CPG, intersegmental connections, and sensory feedback on locomotion, finding that both the CPG and sensory feedback were able to produce locomotor movements redundantly. These results indicate that some forms of mechanosensation may act redundantly with CPGs to ensure regular swimming even when part of the system is perturbed.

As these integrative models have grown in complexity, they provide an opportunity for new and exciting applications. One such application that has recently begun to be explored is in the field of spinal cord regeneration (Hamlet et al. 2023).

Spinal cord regeneration in lampreys

In addition to serving as a model for locomotion, lampreys are a model system for investigating mechanisms of successful spinal cord regeneration (Parker 2017). After a complete spinal transection, lampreys exhibit substantial neuronal regeneration and functional recovery. There has been a concerted effort to discern the mechanisms of successful regeneration as well as characterize the regenerated neural circuit and its relationship to observed behavior, but this is a challenging task. Recent work on lamprey modeling has been able to incorporate regeneration into computational models (Hamlet et al. 2023). This represents a new avenue for exploring sensorimotor connectivity patterns in the regenerated spinal cord. Additionally, investigating regenerated circuits allows us to explore the limits of neural redundancy *in vivo*, which can inform future computational models.

In the lamprey model, the term "regeneration" generally refers to the regrowth of axons across the injury site as opposed to the differentiation of new cells. The localized CPG circuits remain intact, as evidenced by fictive swimming observed via ventral root recordings (McClellan 1990). However, the regenerated axons form completely new synaptic connections above and below the injury site (Fig. 3A; Parker 2017; Hanslik et al. 2019). Axonal pathfinding varies across individuals. Axons may regenerate ipsilaterally or cross the midline at the injury site, and some axons have been observed to loop back on themselves before or past the injury site (Oliphint et al., 2010; Hanslik et al. 2019). Regeneration is always incomplete and can vary depending on the type of neuron and the location of the lesion (Jacobs et al. 1997; Yin and Selzer 1983). RS axons, which project from the brain down the length of the entire cord, exhibit a higher probability of regeneration at more rostral injuries, while more caudal injuries may result in less regeneration (Yin and Selzer, 1983; Fies et al. 2021). Overall, dorsal and edge cells located below the injury site regenerate rostrally (toward the lesion), but generally exhibit less regeneration than RS axons. Armstrong et al. (2003) found that a very small subset of these sensory cells regenerated at least as far as the injury site, indicating they could relay information across the injury site. However, unlike RS neurons, dorsal cells show the same level of rostral regeneration regardless of whether the lesion is located rostral or caudal (Yin and Selzer 1983). Changes in the number and structure of synapses have also been observed along RS axons with regenerated axons having fewer and smaller synapses at and below the injury site (Oliphint et al. 2010).

In addition to differences in the neural circuit, there are broad changes in the functional properties of individual neurons after spinal cord injury (Hoffman and Parker 2010; Hoffman and Parker 2011). In sensory cells, axon regeneration has been studied in both edge (Hoffman and Parker 2011) and dorsal cells (Yin and Selzer 1983; Armstrong et al. 2003), but recovery of sensory feedback has predominantly been examined with respect to edge cells. Hoffman and Parker (2011), assessed proprioceptive feedback in the regenerated spinal cord. At 8–10 weeks post-injury (WPI), they observed a significant increase in firing frequency and reduced adaptation in response to bending below the injury site as compared to uninjured cords. In addition to these changes in the spinal cord, they observed changes in physiological properties of edge cells. No relationship was found between this change in excitability and the degree of swimming recovery characterized by swimming score. This may indicate that more in-depth measurements of functional recovery are necessary to distinguish relationships between physiology and function.

Becker and Parker (2019), expanded upon this study by examining proprioceptive responses at 4, 20, and 24 WPI. The spinal cord showed no response to bending stimuli at 4 WPI, indicating that some proprioceptive feedback may be suppressed at earlier post-injury stages. However, the authors note that this may be the case for the specific stimulus presented and may not be universal. At 4 WPI, lampreys generally are capable of forward movement, but it tends to be uncoordinated with abnormal body waves and frequent stops and starts. Even before animals exhibit forward movement, they will respond to a tactile stimulus at the tail (Katz observation), so the animals likely maintain some form of mechanosensory feedback. This suggests that motor neurons are receiving input from local stimuli below the injury site and driving uncoordinated motor output. This indicates that mechanosensory cells, such as dorsal cells or edge cells, relay feedback below the injury site at early post-injury stages.

Functional recovery after spinal cord injury

Despite the substantial individual variation in neural circuitry and physiology post-injury, lampreys exhibit substantial, and consistent functional recovery of swimming and burrowing behaviors following spinal cord injury (Rovainen 1976; Hanslik et al. 2019; Katz et al. 2020). Recovery of swimming behavior has been studied most extensively, predominantly by developing scoring rubrics to characterize stages of swimming recovery based on forward movement, frequency of aberrant movements, and presence of sinusoidal swimming (Fig. 3B; Becker and Parker 2019; Hanslik et al. 2019; Katz et al. 2020). While there are slight differences in these rubrics between research groups, there is a general consensus that lampreys display a very consistent and robust trajectory of swimming recovery within about 10–12 WPI. However, kinematic comparisons between uninjured and regenerated animals show that regenerated animals display differences in swimming (Oliphint et al. 2010; Fies et al. 2021). At 10–12 WPI, lampreys exhibit slower swimming speeds, higher tailbeat frequency, lower amplitude, and shorter wavelengths (Oliphint et al. 2010; Fies et al. 2021). These results indicate a reduction in swimming efficiency following regeneration.

While swimming has been studied most extensively in the larval sea lamprey, in their natural environment, these animals are most commonly found burrowed in substrate (Moore 1980). Burrowing behavior can be broken down into two components: initial and final (Paggett et al. 1998). The initial component resembles swimming, with sinusoidal waves along the body that drive the head into the substrate. During the final component, these waves cease, and the tail is pulled into the substrate (Paggett et al. 1998). Recent work has demonstrated that lampreys do not recover burrowing behavior to the same degree as swimming (Katz et al. 2020). At

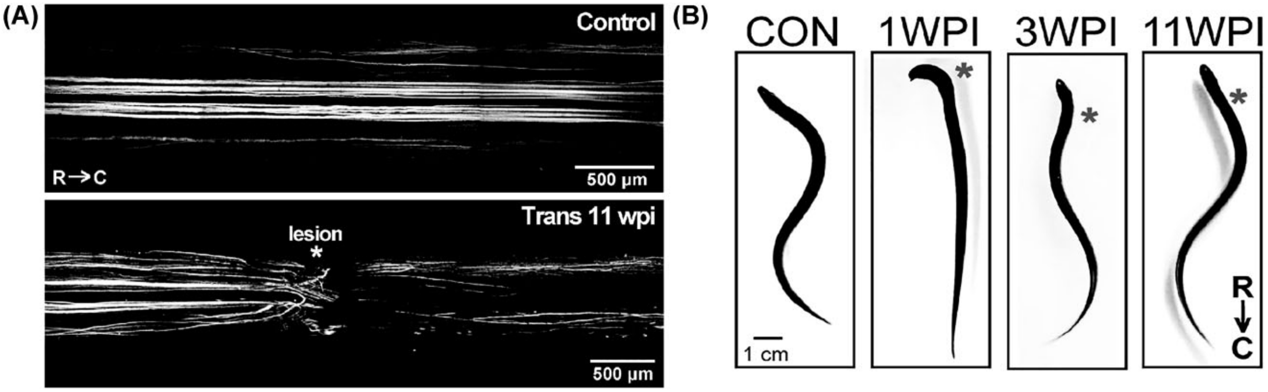

Fig. 3 Regeneration in the larval sea lamprey *Petromyzon marinus*. Images modified from Hanslik et al. (2019). (A) Bulk-labeled axons in an uninjured control spinal cord and a regenerated cord at 11 WPI. (B) Representative still-frame images of lamprey swimming recovery following a complete spinal transection at control (uninjured), 1, 3, and 11 WPI timepoints. Asterisks indicate location of lesion.

11 WPI, many animals are unable to burrow completely, and animals that can burrow take significantly longer to do so. These behavioral differences post-injury indicate that there are changes in the neural circuit that impact distinct components of motor control and potentially sensorimotor integration.

While some axon regrowth is observed following spinal cord transection, the connection between this regrowth and recovery of locomotion is unclear (Fies et al. 2021). One possible hypothesis is that the amplification of mechanosensory feedback can improve or completely restore swimming in injured lampreys, an example of fault tolerance (Haspel et al. 2021). Such amplification has been observed in animals at late stages of regeneration (Hoffman and Parker 2011). Recent computational work using phase oscillators has demonstrated this phenomenon in numerical models based on injured lampreys (Hamlet et al. 2023). This amplified mechanosensory feedback may support the animal in transitioning from the uncoordinated forward movement that is initially observed to the nearly normal sinusoidal swimming observed at 10–12 WPI.

Questions that remain

Both *in vivo* and computational models will be critical to expanding our understanding of mechanosensory integration in the locomotor circuit, particularly in the context of regeneration. Mathematical and computational models offer an opportunity to explore not just observed behaviors but to explore proposed connections and offer predictive tests to guide experimental inquiry. This is especially valuable in light of the substantial variation in neural regeneration observed in the lamprey model. From the original models of phase oscillators, which captured many of the key aspects of fictive swimming, to the more recent integrative models, which produce emergent behavior based on multiscale coordination, modeling, and experiment have worked together to provide insight into the mechanisms underlying locomotion. In this way, computation, modeling, and experimentation form a closed system, each informing on the explorations and understanding of the other. Computational modeling offers the opportunity to study injuries that affect the system's underlying architecture, performing *in silico* experiments not possible in living biological systems to reveal connections and emergent properties. Given the variability in spinal regeneration, it would be virtually impossible to explore every potential circuit outcome following regeneration *in vivo*. In the future, models could be developed to allow us to explore an infinite number of possible connections in the regenerated cord and provide insight into the functional consequences.

Challenges that remain

There are distinct challenges associated with studying mechanosensory systems. In the lamprey, the edge cells have received significantly more attention than the dorsal cells. This is most likely because a stimulus can be presented to these cells in an isolated spinal cord. To study mechanosensory feedback in dorsal cells, it will be necessary to develop a novel prep for the lamprey that allows for mechanical stimulation of the skin while maintaining the integrity of both the central and peripheral circuits. Such preps have been developed for larval zebrafish (Katz et al. 2021) and leech (Pirschel and Kretzberg 2016), but they are very specific to the organismal system. Studying the regenerated spinal cord presents novel challenges as well. While broad changes in physiology and behavior have been identified, lampreys exhibit substantial individual variation in axonal regeneration. Mathematical models can allow researchers to explore the range of neural connections that may be possible in the regenerated cord. This could help researchers identify which systems are critical to specific behaviors and which may be redundant.

Coordinating complicated systems, especially ones coupled to a model of the fluid environment, requires significant computational power. There are still a lot of difficulties in extending mechanistic models to a sizable number of segments. Phenomenological models sometimes still rely on the prescription of some physical quantities. Several successful models provide insight into possible bio-inspired design and non-physiological systems but are not viable or testable in an experimental setting with natural lampreys (Ijspeert et al. 1999). Coupling models together and then into a fluid environment is still computationally expensive. Many models find great success in two dimensions when trying to capture critical phenomena. Three-dimensional models may provide some solutions to problems with existing models, but will add significant complexity and introduce new challenges.

Conclusion

In this paper, we have highlighted the significant progress made in the development of computational models of anguilliform locomotion, particularly with the integration of mechanosensory feedback. Moving forward, we propose that these models can serve as valuable tools for gaining insight into mechanisms of successful spinal cord regeneration. For example, the field of spinal cord regeneration has predominantly focused on molecular mechanisms of successful regeneration. However, work by Hamlet et al. (2023) has shown that mechanosensory feedback is likely an important factor as well, and warrants more in-depth investigation. Additionally, as these models have evolved in complexity, they can allow biologists to explore connections between proposed neural networks and functional output in the regenerated spinal cord.

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Conflict of interest

The authors declare no conflict of interest.

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