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Design of mechanosensory feedback during undulatory locomotion to enhance speed and stability

Claire Wyart and Martin Carbo-Tano

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Abstract

Undulatory locomotion relies on the propagation of a wave of excitation in the spinal cord leading to consequential activation of segmental skeletal muscles along the body. Although this process relies on self-generated oscillations of motor circuits in the spinal cord, mechanosensory feedback is crucial to entrain the underlying oscillatory activity and thereby, to enhance movement power and speed. This effect is achieved through directional projections of mechanosensory neurons either sensing stretching or compression of the trunk along the rostrocaudal axis. Different mechanosensory feedback pathways act in concert to shorten and fasten the excitatory wave propagating along the body. While inhibitory mechanosensory cells *feedback* inhibition on excitatory premotor interneurons and motor neurons, excitatory mechanosensory cells *feedforward* excitation to premotor excitatory interneurons. Together, diverse mechanosensory cells coordinate the activity of skeletal muscles controlling the head and tail to optimize speed and stabilize balance during fast locomotion.

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Keywords

Mechanosensory feedback, Proprioception, Interoception, Exteroception, Undulatory locomotion, Central pattern generator, Feedback, Feedforward, Entertainment, Power, Speed, Robustness.

Introduction

Undulatory locomotion relies on internally generated flexural waves propagating along the body to generate propulsion. Wave-like movement patterns typically progress from anterior to posterior to propel the animal

forward with alternated activity on the left and right sides. Early observations of fish swimming revealed an empirical relation linking the speed of the swimmer (V) to his length (L) and its tail beat frequency (f): $V/L \sim f$ [1]. Locomotor speed increases when the speed of the wave propagating along the body rises, which corresponds to higher cycle frequency in each segment, as well as when the amplitude of the tail bends increases. For locomotion by lateral undulation, the friction forces created at the border between an animal and its environment generate instead thrust and drag, that result in the production of alternating sideways forces propelling the body in the opposite direction to the traveling wave [2,3].

The size of the undulating body is essential for determining the forces at play and tuning the contribution of mechanosensory feedback. When an animal swims in a fluid, the resistance of the external fluid to shearing creates friction on the skin and is combined with a “form” force due to the difference in pressure on the surface of the body. The Reynolds number (Re) reflects the ratio between inertial and viscous forces. For small animals with low Re [4,5] such as larval zebrafish ($Re \sim 500$) [6], skin friction will dominate the thrust and drag, while the form force will only produce the thrust in large animals such as cetaceans or large migrating fish ($Re > 10^5$) [7].

For large as well as for small aquatic animals, proprioception is essential to the motion of the body as it enables the precise coupling of the endogenous dynamics of force production by the axial musculature, the exogenous dynamics of the friction forces due to the interaction of the organism with its environment, and the linear momentum balance of the body–environment system. One would expect that the fine-tuning of proprioceptive inputs may be critical when the animal needs to escape at high speed from danger by performing a C-start, during which the curvature of the body during the first bend of the bout maximizes the distance traveled to swim away [6]. As mechanosensory feedback requires at least one synapse to convey the feedback to motor neurons or premotor neurons, it is by definition intrinsically “late” compared to the muscle contraction itself. How is mechanosensory feedback therefore implemented to optimize the efficiency and speed of undulatory locomotion?

Although undulatory locomotion is deployed as well as by animals during crawling (in snakes (“swimming on land” [8]), caterpillars, and numerous insect larvae for which mechanosensory feedback also increases speed (e.g. larval *Drosophila* [9]), our review will focus here on aquatic swimming species such as fish and lampreys, which rely on contraction of muscles in the horizontal plane (alternating left and right) in order to propel their body forward.

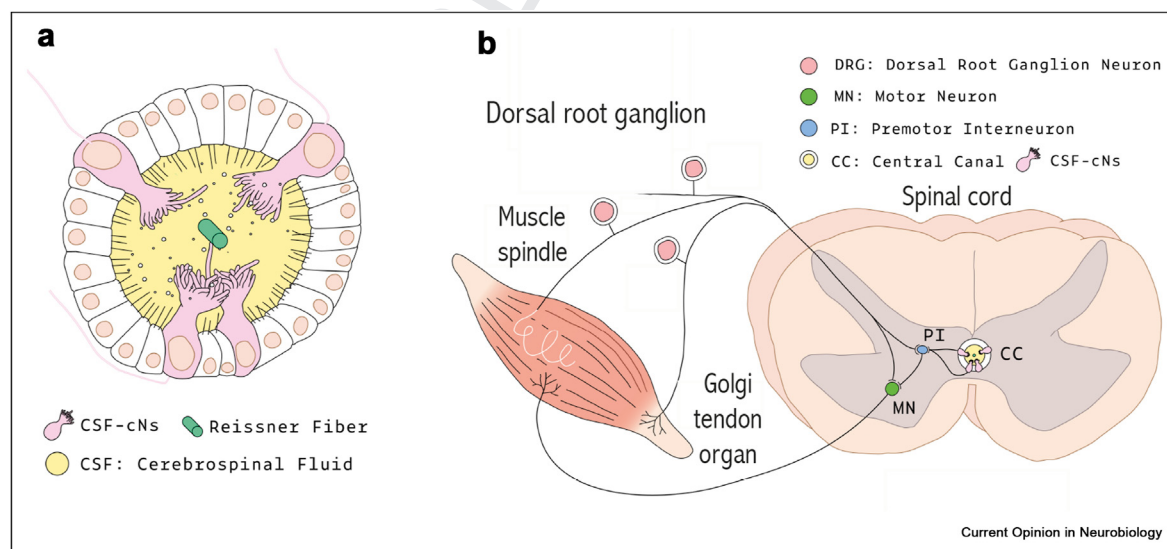
Peripheral and central excitatory mechanosensors with terminals under the skin provide direct excitation to premotor interneurons to speed up the traveling wave

In mammals, proprioception is classically thought to rely on mechanosensory dorsal root ganglion (DRG) neurons (Figure 1). The peripheral axon of DRG neurons innervates muscle spindles or Golgi tendon organs and transmits sensory information via their central axon to the spinal cord. These peripheral neurons can synapse directly on motor neurons or premotor interneurons in the spinal cord. In contrast, fish and lamprey lack muscle spindles to detect muscle distention [10,11]. Mechanosensory integration in limbless animals relies instead on sensing curvature along the body axis as flexural waves propagate. In particular, Rohon-Beard neurons and DRG neurons are excitatory mechanosensory cells that deploy vast axonal arborizations of naked nerve endings under the skin and project their axon in the dorsal column [12]. Their soma is located in the peripheral dorsal root ganglia, in the spinal cord for

innervation of the trunk [13], or in the hindbrain for some of the innervation of the pectoral fins [14]. In the trunk, the receptor field originates from dense axonal terminals constricted to a small section of the body along the rostrocaudal axis and only on one side [13]. The mechanisms by which this sensory system encodes external forces, such as friction and pressure applied to the body, compared to internal forces generated by muscular activity, have, to our knowledge, not yet been investigated.

In larval zebrafish, these mechanosensory pathways provide positive feedforward excitation onto glutamatergic premotor V2a interneurons belonging to the fast swimming module that increases locomotor speed [15]. As V2a interneurons are organized in a topographic manner in the spinal cord [16], the central axon of Rohon-Beard neurons in the dorsal column selectively reaches the dendrites of dorsalmost V2a interneurons involved in the highest locomotor frequency and shown to project onto primary motor neurons and other V2a interneurons [17]. Optogenetic-mediated activation of a single Rohon-Beard neuron is sufficient to elicit spiking of dorsal most V2a premotor excitatory interneurons via efficient monosynaptic connections [15] and can explain the mechanosensory-dependent enhancement of locomotion speed and power. The structure implemented for the feedback is remarkable and benefits from the topographical organization of premotor interneurons setting locomotor speed and power, that build on top of the column of motor neurons organized

Figure 1



Mechanosensory feedback during locomotion can originate from proprioceptive neurons in the periphery as well as interoceptive neurons in the spinal cord itself. (a) Across vertebrate species, cerebrospinal fluid-contacting neurons surround the central canal. In fish, these neurons detect spinal compression via a coupling with the Reissner fiber. (b) In mammals, dorsal root ganglion neurons in the periphery detect as well mechanosensory information associated with contraction of skeletal muscles via the muscle spindle and tension on the Golgi tendon organ.

around the size principle [18] that also follows a dorsoventral gradient in larval zebrafish.

Central compression sensors detect spinal curvature to enhance speed and balance

Kolmer and Agduhr revealed that across vertebrate species, the spinal cord hosts ciliated neurons contacting the cerebrospinal fluid (CSF) within the central canal in the vicinity of an internal acellular thread, the Reissner fiber [19,20] (Figure 1). These neurons referred to as Kolmer-Agduhr cells [21] or CSF-contacting neurons (CSF-cNs) constitute an axial sensory system aligned with the backbone in vertebrate species [22,23]. Optogenetics and calcium imaging *in vivo* in larval zebrafish uncovered the locomotor and postural roles of CSF-cNs [24–30]. Via coupling with the Reissner fiber under tension, CSF-cNs rely on the channel PKD2L1 to detect the concave curvature of the trunk [26,27,30]. Electrophysiology in an open book preparation of lamprey spinal cord uncovered the contribution of ASIC channels in the mechanosensory properties of CSF-cNs exposed to pressure application of artificial CSF [31]. Upon activation, CSF-cNs release GABA onto their targets, and thereby relay the body curvature information to local excitatory premotor neurons and motor neurons via local ipsilateral ascending axonal projections in the spinal cord and hindbrain [24,25,28,29].

Optogenetic activation revealed that CSF-cNs can control the initiation and stop of forward locomotion as a function of the motor state of the animal [24,25]. Behavioral analysis of animals deprived of this sensory pathway reveals that CSF-cNs increase the amplitude and speed of movement during escape responses [26,29], and enhances posture during fast locomotion [26,28,29]. Based on their connectivity with motor neurons and premotor excitatory neurons, our working model for how these inhibitory neurons operate is the following: while the wave of excitation is traveling down the spinal cord during forward locomotion, CSF-cNs inhibit the activity of proximal rostrally located excitatory premotor and motor neurons that were just recruited speeding up the traveling wave.

Rostralmost CSF-contacting neurons also stabilize active posture during fast swimming by the coordination of head and tail movement [28,29]. They can do so by projecting onto motor neurons involved in the C-bend [28] as well as widely modulating the descending command neurons transmitting information from brainstem to spinal cord as well as onto occipital motor neurons controlling head position [29]. Because primary motor neurons in the occipital column and spinal cord project on one side and ventrally only, their activation leads to a ventral torque: when CSF-cN sensory feedback is silenced or their secretory functions abolished,

larval zebrafish more often roll after the large initial tail bend of the escape response [28,29].

How is the sensory feedback integrated in the motor command? In terms of anatomy, in zebrafish like in lampreys, excitatory Rohon-Beard neurons and inhibitory CSF-cNs project an axon in the dorsal spinal cord that synapse on giant excitatory sensory interneurons (referred to as “CoPA” in zebrafish [32]). These giant sensory interneurons project a contralateral and ascending axon to innervate neurons in the rostralmost spinal segments and hindbrain. These sensory interneurons are in an ideal position to send a corollary discharge back to the motor command centers for information of the execution of past motor actions that could be used to coordinate head and tail movements [15,33,34].

Central stretch mechanosensors in each segment modulate the activity of spinal motor circuits

The preparation of lamprey fictive locomotion offers an exquisite advantage that the spinal cord can be mechanically manipulated on one end while neurons are stably recorded on the other [35–38]. By doing so, Grillner and colleagues identified in 1984 [39] that mechanically bending the spinal cord was sufficient to entrain the rhythm of the locomotor central pattern generators (CPGs). Consequently, the swimming rhythm is ten times slower during fictive locomotion than during active locomotion [40]. To explain this phenomenon, Grillner, Williams, and Lagerback identified stretch receptors (SRs) on the lateral edge of the lamprey spinal cord, referred therefore to as edge-cells, which are ideally located to sense stretch on the opposite side of muscle contraction [39,41]. Being the living representatives of the jawless vertebrates (agnathans), lampreys lack true vertebrae and have instead a series of cartilaginous structures called “arcualia” arranged above the notochord. SRs were found throughout the spinal cord in all segments organized in two types: excitatory ones that project ipsilaterally, and inhibitory ones that project contralaterally to the locomotor CPGs [37,38]. In the computational model of the spinal CPGs [42], the stretch receptors along the rostrocaudal axis can entrain the rhythm by sequentially recruiting sensory reflexive loops along the rostrocaudal direction in the spinal cord [38].

The advent of optical and genetic approaches in zebrafish has made it possible in the last decade to dynamically probe *in vivo* the functions of mechanosensory feedback and the underlying pathways modulating the kinematics of swimming [15,23–25,43,44]. In juvenile and adult zebrafish, inhibitory mechanosensors located on the lateral margin of each intervertebral disc act as stretch receptors. These receptors, called intraspinal lateral proprioceptors (ILPs), have a commissural axon

and share properties with lamprey edge-cells [44]. ILPs are glycinergic stretch receptors with a commissural axon and express PIEZO2 [44]. As seen before for other mechanoreceptors, their ablation reduces the locomotor frequency, thereby decreasing swimming velocity. ILPs form inhibitory projections onto other ILPs on the contralateral side as well as onto the excitatory premotor V2a interneurons in the spinal cord. The mechanisms by which these neurons enhance locomotor speed are not yet fully understood.

How much of these principles are conserved in mammalian locomotion?

An extensive body of literature has described in mammals the paths for integration of peripheral sensory feedback from DRG neurons in the spinal cord and brainstem [45]. DRG neurons express multiple mechanosensory receptors including the channels PIEZO1 and PIEZO2 [46,47]. CSF-cNs expressing PKD2L1 in the spinal cord are present in the mouse and macaque spinal cord [48]. Recent studies revealed that the connectivity and modulatory role of CSF-cNs to stabilize posture and enhance locomotor speed is conserved in mice [49–51]. Remarkably, in mice CSF-cNs project onto each other and need their cilia to modulate motor circuits. How CSF-cNs in mice detect spinal curvature remains to be further investigated.

In addition, there is multiple evidence for putative sensory neurons expressing PIEZO2 in subsets of neurons in the dorsal horn of juvenile macaques [52] and in adult human spinal cord [53,54]. These observations suggest that interoceptive mechanosensory signaling within the spinal cord could also occur and contribute to sensorimotor integration in macaques and humans.

Learning from elasto-hydrodynamic models

Gazzola et al. built an elasto-hydrodynamic model of fish swimming which takes the form of a nonlinear eigenvalue problem for the swimming speed and locomotion gait [55]. They came up with a solution to this problem that reveals how fish might use resonant interactions with the fluid environment to improve their speed and efficiency. Their model compares fish to an optimized diode that converts an alternating transverse motion to forward motion and provides a mechanistic theoretical basis for the linear relation of velocity divided by body length scaling with the animal's tail beat frequency. The authors propose that a simple form of proprioceptive sensory feedback, wherein local muscle activation scales with body curvature, is sufficient to drive elastic instabilities due to thrust production and leads to spontaneous swimming gait.

Conclusions & perspectives

A large body of work on the process of swimming in aquatic species has shed light on the cellular and network

mechanisms of mechanosensory feedback during active motion. These studies have provided insights on how sensory systems along the body, in the periphery and in the spinal cord itself, allow the instantaneous detection of the local curvature of the body axis and convey this information directionally in the spinal cord and hindbrain to enhance the activity of fast module motor circuits and stabilize posture. Mechanosensory cells are located all along the traveling wave in key positions to detect either stretch or compression of the myotomal muscles that bend the spinal cord, power the trunk bends and propel the animal forward. These mechanosensors act locally in the segment as well as across segments in the spinal cord and hindbrain to maximize speed and coordinate body parts during movement. Optogenetic mapping in larval zebrafish revealed that such increase in speed occurs for excitatory mechanosensors via the effective recruitment of local and caudal excitatory premotor neurons in the spinal cord sustaining fast swimming. Central inhibitory mechanosensors CSF-cNs in contact with the Reissner fiber also enhance speed, likely by terminating the activity of rostral motor neurons and premotor interneurons that were immediately recruited, to accelerate the propagation of the undulatory wave. CSF-cNs play a crucial role in stabilizing posture to prevent rolling during escape responses. They achieve this by projecting onto motor neurons in the spinal cord and hindbrain, as well as onto the axons of reticulospinal neurons.

The propagation speed of the traveling wave in fish is directly linked to the consecutive activation of spinal segments as well as to the left-right alternation on each side within one segment. Remarkably, mechanosensory feedback from edge-cells, ILPs, and CSF-cNs is directional. CSF-cNs only send ipsilaterally ascending projections in the spinal cord. Their action on locomotor frequency likely involves projections onto critical premotor interneurons as well as projections onto themselves. The mechanics to impact speed can rely on improving the coordination of segments to speed up the traveling wave by increasing excitation on the points of maximal curvature or increasing inhibition where the wave just traveled. By improving in phase excitation and phase-shift inhibition, directed mechanosensory feedback relying on ascending and descending neurons, despite being slow, can effectively shape and change the timing of the traveling wave and thereby improve speed.

In addition to vestibular integration to correct the body position [56], recent experiments targeting specific mechanosensory sensors in zebrafish during active locomotion uncovered their specific role in enhancing postural control during movement. This role relies on projection onto key motor neurons in the caudal hindbrain that controls head positioning. Open questions raised by the investigations of mechanosensory feedback during locomotion: If mechanosensory feedback increases active posture, the amplitude, and frequency of

movement, how is it tuned to proceed in a homeostatic manner? How should we manipulate dynamically the mechanosensory feedback to dissect how it increases speed and power of locomotion? An exciting avenue of research consists in understanding the similarities and differences in motor circuits controlling fins versus limbs [57] as many physiological investigations point toward a strong conservation of features.

To understand the role of the different sensory pathways, neurobiologists may find inspiration from efficient control of stable oscillators that requires feedback. In the design of electronic systems, negative feedback is classically used for stability (https://en.wikipedia.org/wiki/Operational_amplifier; https://en.wikipedia.org/wiki/Negative_feedback#:~:text=A%20basic%20and%20common%20example,life%20that%20can%20grow%20increases) while positive feedback is deployed to generate oscillators (https://en.wikipedia.org/wiki/Positive_feedback). The optimization of stable oscillators over a wide range of frequencies requires a finely tuned control of feedback (<https://www.controleng.com/articles/efficient-controls-require-feedback/>). A thorough comparison of the contribution of positive and negative feedback between electronic devices and animal integrative sensory reflexes, despite occurring on different timescales (microsecond versus millisecond, respectively), should enable to draw general principles enabling homeostasis and flexibility.

Credit author statement

Claire Wyart drafted the manuscript with feedback from Martin Carbo-Tano.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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