




Special Issue: Time in the Brain

## Forum

Millisecond Spike  
Timing Codes for  
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**Millisecond variations in spiking patterns can radically alter motor behavior, suggesting that traditional rate-based theories of motor control require revision. The importance of spike timing in sensorimotor control arises from dynamic interactions between the nervous system, muscles, and the body. New mechanisms, model systems, and theories are revealing how these interactions shape behavior.**

The brain uses sequences of spikes to encode sensory input and control motor output. In principle, neurons might encode information via their firing rates, the precise timing of their spikes, or some combination of the two. Rate-based approaches have generally dominated theories of motor coding, as they are computationally tractable and can account for many aspects of motor behavior. For example, spike rates in individual neurons or population ensembles computed over relatively long time-bins have predicted features of movement kinematics in a number of vertebrate species, suggesting a rate-based control scheme [1]. Another reason rate codes have dominated motor control is that muscle force production has been assumed to have slow dynamics and because muscle force grossly scales with spike rate. The role of spike timing, by contrast, is relatively underexplored in motor systems, although nonlinearities

in muscle force production and movement biomechanics hint at its potential importance [3,4]. Notably, in the context of sensory systems, the importance of precise spike timing in information processing has been shown [2]. Critically, however, whether precise spike timing causally affects either perception or behavior remains largely unknown. Here we explore growing evidence that millisecond-scale precision in spike timing patterns can control motor behavior.

Far from being just low-pass filters, muscle and body biomechanics can afford many opportunities for spike timing to profoundly impact motor output. We emphasize that the diversity of codes in motor systems is neither a dichotomy ('rate vs. timing') nor a continuum between two extremes. Phase codes, context-dependent codes mediated by biomechanics, and higher-order codes that extend across multiple neurons or inter-spike intervals (higher-order rate/timing codes) comprise a broader family of codes that motivate further exploration.

### When a Millisecond Matters: Correlative and Causal Evidence

Correlative evidence that millisecond spike timing differences affect behavior has been shown across a wide range of species and behaviors. Mammalian motor units regularly exhibit doublets and triplets with inter-spike intervals of 5–10 ms; occurrences increase as muscles fatigue, presumably to increase force via central mechanisms [3]. Recent examples show that spike timing correlates with variations in both fast and slow periodic behaviors, or with selection of different behavioral programs (Figure 1A). In hawk moths, spikes in the left and right wing power muscles are synchronized with sub-millisecond precision; left-right spike timing differences of only 8 ms can drive 200% changes in muscle power and predict torques during turning [5]. In songbird vocalization, 1-millisecond variations in spike timing in motor cortex

neurons provide far more information about song syllable acoustic structure than do variations in spike rates over tens of milliseconds [6]. Moreover, in songbird breathing behaviors, millisecond-scale changes in the timing of a single spike in a burst of respiratory muscle fibers predicts differences in breathing dynamics that unfold over hundreds of milliseconds. In flies, millisecond-scale timing differences between a giant fiber interneuron and parallel circuits predict a choice between escape behaviors: one slower and more stable, the other faster but less controlled [7].

Causal studies provide even stronger evidence for precise timing patterns in motor control. In both fast and slow mammalian muscles, adding one or two pulses of electrical stimulation at millisecond-scale intervals within a lower-frequency stimulation train increases peak muscle force by up to 50% without significantly altering spike rate [3]. In *Aplysia*, 'playbacks' of real and manipulated spike trains *in vitro* demonstrate that changes in spike timing on the scale of ~10 ms have large effects on ingestion behaviors that manifest over several seconds [4,8]. In insects, manipulating millisecond-scale spiking precision affects steering in hawk moths, and the selection of escape behaviors in flies [5,7]. Finally, in songbirds, precisely-timed millisecond-scale variations in electrical stimulation of respiratory muscles strongly modulate breathing output [9].

### Why a Millisecond Matters: Motor Codes Interact with System Biomechanics

Intuitively, it would seem that a millisecond could hardly affect muscle force output, as a spike elicits a 40–100 ms force twitch in mammalian striated muscles [3]. Nonetheless, at least three classes of mechanisms enable small timing changes to profoundly alter motor output *in vivo*: (i) muscle properties, (ii)

## (A) Millisecond-scale differences in spike timing: a common mechanism for motor control across taxa

**Hawk moth**

Millisecond control of flight steering

**Fruit fly**

Millisecond control of escape behavior

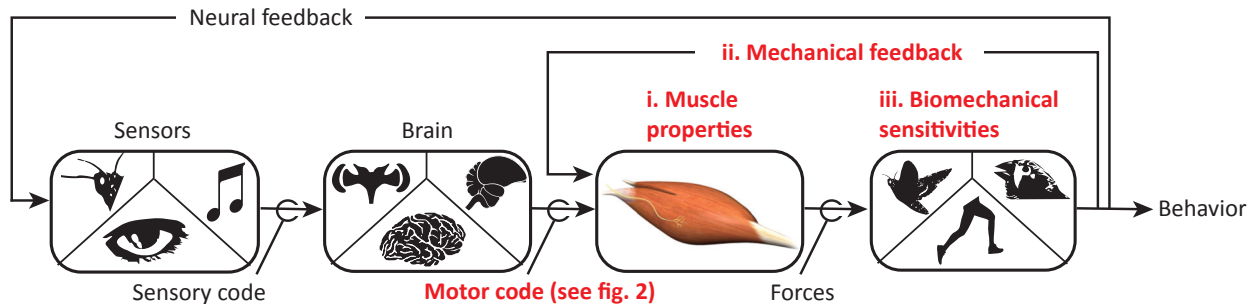
**Songbird**

Millisecond control of vocal acoustics, breathing

**Human**

Millisecond control of muscle force and body dynamics

## (B)



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**Figure 1. Across Taxa, Spike Timing Effects on Motor Behavior Arise from Biomechanical Mechanisms.** (A) Diverse animals use spike timing to control behavior. In the hawk moth (*Manduca sexta*), fruit fly (*Drosophila melanogaster*), and Bengalese finch (*Lonchura striata domestica*), explicit timing codes have been discovered that control fast-timescale behavior (flight maneuvers and song), slower tasks like respiration, and sensory-evoked decisions. In human (*Homo sapiens*) and other mammal systems, few peripheral motor codes have been examined with spike-level resolution, but a number of well-documented mechanisms [see (B)] may allow spike timing to strongly influence behavior in humans and other species. (B) Spike timing can affect motor behavior via three classes of mechanisms: muscle properties, mechanical feedback, and biomechanical sensitivities of the body (i–iii).

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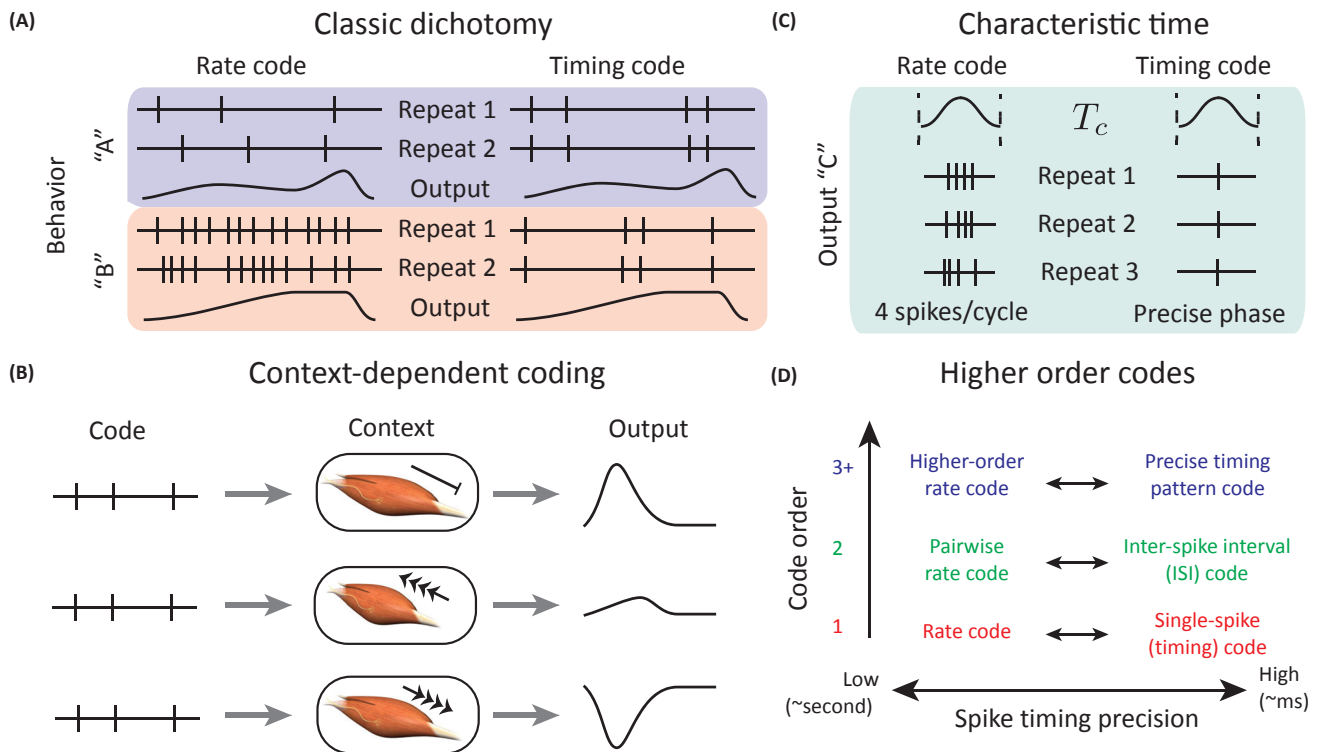
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mechanical feedback, and (iii) biomechanical sensitivities (Figure 1B).

A number of intrinsic muscle force-generating properties (Figure 1B, i) allow small differences in spike timing and inter-spike intervals to cause large differences in force output [3,4]. In a ‘pure’ rate-code framework, the number of spikes generated by a motor neuron in a characteristic time would increase muscle force regardless of the specific time interval between

spikes (Figure 2A, left). But, in reality, there are a number of timing-dependent nonlinearities in force production. The forces produced by muscle contractile proteins depend not only on a muscle’s current state (activation, length, and velocity), but also on the history of muscle states over a period of seconds [3,4]. A notable example is the catch-like property of muscles, which is important for increasing muscle force rapidly. Increasing the motor neuron spike rate generally

causes slow changes in muscle force. But, shortening even a single inter-spike interval to ~5–10 ms (milliseconds) without altering either the total number of spikes or the spike rate (e.g., Figure 2A, upper right panel), can dramatically increase peak muscle force and speed the rate of force development in a manner that is dependent on the prior activation and velocity of the muscle [3,9]. As such, short inter-spike intervals observed in volleys of somatosensory feedback driving



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**Figure 2. A Diversity, Rather Than Dichotomy, of Spike Codes Are Used to Produce Movement.** (A) Example of the classical dichotomy between timing and rate codes. Different motor outputs ('A' and 'B') can be encoded either by a rate code (left) or a precise timing code (right), exemplified by differences in the number (left) or timing (right) of spikes fired across repeated production of behaviors 'A' and 'B'. (B) The biomechanical context (i.e., length and velocity and history of the muscle and body), can interact with an identical timing code to produce a full range of force outputs, where the muscle can act as a motor, spring, or brake. (C) The characteristic time or periodicity of a behavior can also distinguish rate codes and timing codes by providing a reference time, allowing information to be coded in the number of spikes per cycle (periodic count) or timing during the cycle (phase). (D) The motor systems may use a diversity of spike codes to control motor output, going beyond the conventional timing versus rate dichotomy. Controlling behavior via correlations among spike rates across many neurons (higher-order rate codes), or correlations among spike timing patterns either within or across neurons (higher-order timing codes) illustrates a family of ways in which patterns of spikes could represent and control motor behavior.

mammalian reflexes [10] as well as motor neuron outputs in voluntary behaviors [3] are likely essential for rapidly increasing muscle force.

Further, because a muscle's force affects its own motion, a 'mechanical feedback' loop exists wherein the muscle's force-generating capability is instantaneously affected by the motion it generates [4]. It should be emphasized that mechanical feedback loops stem from how the muscles, connective tissue, and body interact, and do not involve sensing. In contrast to the unidirectional

dependencies described above (mechanism 'i'), mechanical feedback represents a reciprocal interplay between muscle force production and length, each depending on the other (Figure 1B, ii). For example, a spike generating muscle force to shorten the muscle would increase shortening velocity which reduces muscle force. The resulting muscle length and velocity depend on how the body interacts with the environment, meaning that how a muscle transforms its spikes into force critically depends on context (Figure 2B) [4,11]. Context is especially important when muscles

shorten and lengthen in periodic cycles, as in rhythmic behaviors such as locomotion and respiration, and can amplify or switch the effects of small spike timing differences. For example, a specific pattern of spikes in a cockroach leg muscle smoothly increases muscle force in posture control. But in a periodic running gait, the same pattern initiated just before the transition from stance to swing creates a positive feedback loop; the leg gets 'stuck' in stance phase because the muscle's force prolongs stance, increasing the time of muscle force development and further prolonging stance [11].

Beyond the determinants of muscle force production, biomechanical sensitivities (Figure 1B, iii) can be exploited by precise spike timing to transition the body from one stable mechanical state to the next [4]. Musculoskeletal systems can be highly sensitive to small changes in muscle force and spike timing, particularly when interacting with unstable objects or environments. A prominent example is in gait, where precisely-timed muscle activity is commonly seen around foot-ground contact events in terrestrial animals, including humans. The pendulum-like dynamics of multi-jointed limbs are chaotic, meaning that their movements can be highly sensitive to small changes in force. Mechanical sensitivities exist in soft bodied animals as well. In *Aplysia*, small changes in spike timing transitions one muscle's function from grabbing food to either swallowing or rejecting food, depending on how the feeding apparatus transitions from one stable biomechanical state to another [4]. Understanding such biomechanical sensitivities is critical to predicting when movements are robust versus highly sensitive to precise timing codes, and why some aspects of motor timing are highly conserved across individuals, whereas other vary considerably [4,9,12].

Given that the same spiking pattern can have very different consequences depending on the state of the motor periphery (Figure 2B), both rate and timing codes are inherently context-dependent. Most dramatically, muscle function can switch entirely in response to subtle changes in motor commands. In a cockroach limb, for instance, adding the same pattern (number and timing) of spikes in a leg muscle can cause the animal to accelerate vertically, turn left, or turn right depending on the phase of the gait cycles and whether the limb is in motion and activated [4,11]. Additionally, the characteristic time-scale of a behavior, such as the periodicity of gait, can define the

dynamics of both the movement and the effect of a single spike. In these cases, both rate (number of spikes per period) and timing (spike phase) can be interpreted relative to movement phase (Figure 2C); a single spike, such as in insect flight muscles [5], can code temporal information because of the underlying periodicity.

### A Diversity, Not a Dichotomy, of Spike Codes

Recent computational, experimental, and analytical innovations emphasize the diversity of motor codes beyond the classic dichotomy of rate versus timing (Figure 2A); both sensory and motor timing codes can differ across many dimensions (Figure 2D). One crucial issue is whether sensory or motor information is encoded by the timing of individual spikes ('single-spike code'), the relative timing of two spikes ('inter-spike-interval code'), or more spikes ('pattern code'). Furthermore, both rate and timing codes might be distributed across multiple neurons, with behavior driven by ensembles of covarying of spike rates [1], or precise timing patterns across neural populations. Analyzing higher-order codes is computationally complex and extremely data-intensive, requiring new experimental [9] and mathematical tools. Although one could view single-spike codes as somewhat equivalent to a precisely-timed rate code, such descriptions become rather unwieldy, especially when considering higher-order codes. Expressing timing codes as rate codes would characterize a single spike fired with 0.2 ms precision as a spike rate that increases from 0 to ~5 kHz (a physiologically implausible figure) for a fraction of a millisecond, and returns to zero. The need for higher-order codes is highlighted in recent songbird work [9] where pattern codes, the precise pattern of inter-spike intervals of three or more spikes, are shown to control behavior. Whereas a rate code would describe a pattern as a

series of multiple precisely-timed and rapidly co-varying rate changes, precise timing patterns provide a more elegant and plausible description.

### New Directions in Timing and the Motor System

Our growing appreciation of timing codes raises as many questions as it answers. One challenge is completeness. Most neural recordings sample a (very) limited subset of the signals involved in motor processing, and often from a single anatomical structure. Questions of timing and rate, consistency, and redundancy would benefit from comprehensive recordings of the motor code, especially with spike level resolution, to capture a more complete picture of the motor program. Spiking datasets recorded concurrently from large neural populations [1] can be re-analyzed in timing-based computational frameworks [4–6,9,10] to determine how much additional information about behavior (i.e., beyond the information obtained based on spike rates) can be extracted from spike timing. Even with small recordings, there remains a question of the precision with which the motor system can coordinate spike timing, how this precision trades off with noise and reliability, and when different coding strategies might have generalizable advantages. Biomechanical interactions are a crucial (and often overlooked) aspect of motor coding, and therefore explicit models of these interactions, and experimental paradigms that factor them in, will be necessary to fully understand the roles of spike timing in motor control. For instance, how is it that some motor systems are highly sensitive to precise spike timing in certain behavioral contexts but robust to spike timing in other situations [4,12]? And do motor timing principles generalize across differences due to animal size, morphology, and species? Lastly, we are just beginning to understand how the nervous system first acquires precisely-timed spiking patterns

during development, and how those patterns are revised during sensorimotor learning in adulthood.

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## Forum

# Evolution of Locomotor Rhythms

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**Nervous systems control locomotion using rhythmically active networks that orchestrate motor neuron firing patterns. Whether animals use common or distinct genetic programs to encode motor rhythmicity remains unclear. Cross-species comparisons have revealed remarkably conserved neural patterning systems but have also unveiled divergent circuit architectures that can generate similar locomotor behaviors.**

In both simple and complex nervous systems, the speed and pattern of locomotion is regulated by oscillatory neural circuits that direct rhythmic contraction of muscle. Our understanding of the evolution of locomotor networks has benefited from comparisons of genetic pathways that specify neuronal classes in diverse species (a ‘bottom-up’ approach) [1], as well as through dissection of locomotor circuit designs in mature organisms (a ‘top-down’ approach) [2]. Recent studies provide insights into how motor rhythmicity is encoded at a molecular and circuit level and reveal clues about the origin of locomotor behaviors.

## Conserved Developmental Patterning in Animal Nervous Systems

All motor behaviors rely on the generation of functionally diverse neuronal cell types; therefore, cross-species comparisons of developmental programs can shed light on the composition of the hypothesized ‘urbilaterian’ ancestor that gave rise to all bilaterally symmetric animals. While the cellular organization of the earliest nervous systems is still under debate [3], studies of neural patterning in invertebrates suggest that it was fairly complex and likely relied on the expression of homologs of genes essential for neural progenitor patterning in modern vertebrates (Figure 1A). An important unanswered question is how ancient gene networks were utilized to shape the architecture of circuits that control basic motor functions.

Because neuronal identity can be defined by which sets of genes are uniquely expressed within a given cell type, many studies have focused on conserved expression domains of transcriptional regulators. However, whether conserved transcription factor expression within a progenitor domain generates similar neuronal classes across species is less clear. The most thoroughly studied neuronal class essential for locomotion are motor neurons (MNs). Studies in flies, worms, and vertebrates have revealed sets of conserved transcription factors essential for specifying MN progenitors, as well as postmitotic fate determinants including Lim- and Mnx homeodomain proteins (Figure 1A). Furthermore, in many species the subsequent diversification of MNs into muscle-specific subtypes is mediated by the large family of Hox transcription factors [1].

## Rhythm and Pattern Generation in Locomotor Circuits

While there is evidence for deep conservation of MN specification programs,