Millisecond Spike Timing Codes for Motor Control

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Abstract

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, muscle, and body. New mechanisms, model systems, and theories are revealing how these interactions shape behavior.

Keywords

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. Analyses of spike rates in individual neurons or population ensembles have shown that spike rates computed over relatively long time-bins predict the kinematics of movements in a number of vertebrate species, suggesting a rate-based control scheme [1]. Biomechanical considerations provide further rationale for rate coding because muscle force production is often modulated over timescales much longer than a typical spike and because force grossly scales with spike rate. Lastly, rate-based approaches are computationally tractable, and can account for many aspects of motor behavior. 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, many studies have emphasized

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the importance of precise spike timing in information processing [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, muscles 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 from a wide range of species and behaviors has shown that millisecond spike timing differences affect behavior. Mammalian motor units regularly exhibit doublets and triplets with inter-spike intervals of 5–10 ms; occurrences are more frequent as muscles fatigue, presumably to increase force via central mechanisms [3]. Several recent examples further show that spike timing correlates with variations in behavior in both fast and slow periodic behaviors, or to the selection of different behavioral programs (Fig. 1a). In hawk moths, the timing of spikes in the left and right downstroke power muscles are synchronized with submillisecond precision, and spike timing differences of only 8 ms between the left and right muscles 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 the acoustic structure of song syllables than do variations in spike rates over tens of milliseconds [6]. Moreover, during songbird breathing behaviors that unfold over hundreds of milliseconds, millisecond-scale changes in the timing of a single spike in a burst in respiratory muscle fibers predicts significant differences in breathing dynamics. In flies, millisecond-scale timing differences between a giant fiber interneuron and parallel circuits predict the choice between two escape behaviors, one slower and more stable, the other faster but less controlled [7].

Causal studies provide even stronger evidence for the importance of precise timing patterns in motor control. In mammalian muscle, using electrical stimulation to add one or two pulses with millisecond-scale intervals within a lower-frequency stimulation train increases peak muscle force by up to 50% without significantly altering spike rate; this effect is seen in both slow and fast muscles [3]. In *Aplysia*, "playbacks" of real and manipulated spike trains *in vitro* demonstrate that subtle changes in spike timing on the scale of ~10 ms have large effects on ingestion behaviors that manifest over several seconds [8] owing to transitions between different stable configurations of the body's biomechanics [4]. In insects, causal manipulations of spike timing show that millisecond-scale spiking precision indeed controls directional steering in the hawk moth, as well as the selection of escape behaviors in the fly [5, 7]. Finally, in songbirds, precisely-timed electrical stimulation of respiratory muscles demonstrate that millisecond-scale variations 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 single spike elicits a force twitch lasting 40–100ms 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) mechanical feedback, and (iii) biomechanical sensitivities (Fig. 1b).

A number of intrinsic muscle force-generating properties (Fig. 1b, "i") allow small differences in spike timing to result in large differences in force output [3, 4]. In a 'pure' rate-code framework, adding spikes in a motor neuron should linearly increase muscle force, regardless of the precise timing of the spikes. This however is not the case in reality, partly due to inescapable timing-dependent nonlinearities in force production. For one thing, the forces produced by muscle contractile proteins depend not only on a muscle's current state (activation, length, and velocity), but also the history of muscle states over a period of seconds [3, 4]. For example, the catchlike property of muscles describes supralinear force output produced by inter-spike intervals on the order of 5–10 ms in mammalian muscle, with the magnitude of the nonlinearity dependent on the prior state of the muscle [3]. A related issue is the *rate* of increase of muscle force. Constant firing rates in motor neurons are relatively ineffective in rapidly increase force, yet shortening even a single inter-spike interval, without altering the total number of spikes, can quickly increase muscle force [3, 9]. As such, short inter-spike intervals observed in both volleys of somatosensory feedback driving mammalian reflexes [10] as well as motor neuron outputs in voluntary behaviors [3] are likely essential for rapidly increasing muscle force.

Further, because the force of a muscle affects its own motion, a "mechanical feedback" loop exists wherein the muscle's force-generating capability is instantaneously affected by the motion resulting from muscle activation [4]. These mechanical feedback loops, it should be emphasized, stem from how the muscle, connective tissue and body interact, and do not involve sensing. This mechanical feedback, in contrast to the unidirectional, nonlinear dependencies described above (mechanism "i"), represents reciprocal interplay between muscle force production and length, each depending on the other (Fig. 1b, "ii"). For example, a muscle's force could shorten muscle length and increase shortening velocity, which in turn would change muscle force produced in response to a spike. The muscle length and velocity cannot be predicted based on muscle state alone, depending on interactions with the body and environment [4, 11]. During many behaviors, muscles dynamically shorten and lengthen in periodic cycles. Mechanical feedback through these dynamics can amplify or switch the motor effects of small spike timing differences. For example, increased muscle activation just before a muscle stops shortening can cause it to enter a positive feedback loop wherein more force prolongs shortening, and more shortening gives more time for more force to develop [11].

Beyond the determinants of muscle force production, biomechanical sensitivities (Fig. 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 comes from the area of limb biomechanics and gait. Precise timing of muscles is commonly seen around foot contact events in terrestrial animals, including humans; and the pendulum-like dynamics of multiple limbs are chaotic, meaning that their movements can be highly sensitive to small changes in force. Another example of biomechanical sensitivity can be seen in the feeding behaviors of *Aplysia*. Here, sensitive timing-dependence arises because it is necessary to transition the buccal apparatus from grabbing food to either swallowing or rejecting food [4]. This transition arises because the effects of one muscle's force changes as the feeding apparatus transitions between two stable states, food swallowing versus food rejection. Understanding 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].

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 vs. timing (Fig. 2a). An important aspect of all motor coding schemes is their context dependence. Given that the same spiking pattern can have very different consequences depending on the state of the motor periphery (Fig. 2b), both rate and timing codes are inherently context-dependent. The distinction between rate and timing codes is further blurred by the observation that muscle function can change entirely in response to subtle changes in the motor command. In a cockroach limb, for instance, adding action potentials or changing their timing switches the muscle from dissipating (like a brake) to generating mechanical energy (like a motor) during running [4]. Additionally, many behaviors have a characteristic timescale – such as the periodicity of a locomotor pattern – that define the dynamics of both the movement and the effect of even a single spike. In these cases, both rate (number of spikes per period) and timing (spike phase) can be interpreted relative to the underlying periodicity (Fig. 2c). In this way even a single spike, like those of some insects' downstroke muscles [5], can code temporal information because there is an underlying temporal basis.

Both sensory and motor timing codes can differ across many dimensions in addition to the accuracy of spike timing (Fig. 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 either by ensembles of covarying of spike rates [1], or precise timing patterns across neural populations. Analyzing higher-order codes is both computationally complex and extremely data-intensive, requiring new experimental [9] and mathematical tools. It is sometimes argued that timing codes are simply rate codes where rates fluctuate very rapidly and over wide ranges. It is important to note though that this interpretation is limited to a single-spike codes, and is not applicable for more complex coding schemes such as pattern codes, as seen for instance in songbirds [9].

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 sometimes 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 sitatuions [4, 12]? And do motor timing principles generalize across animal size, given the differences in the biomechanical properties (e.g. muscle mass, length, etc.)? 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.

Acknowledgements

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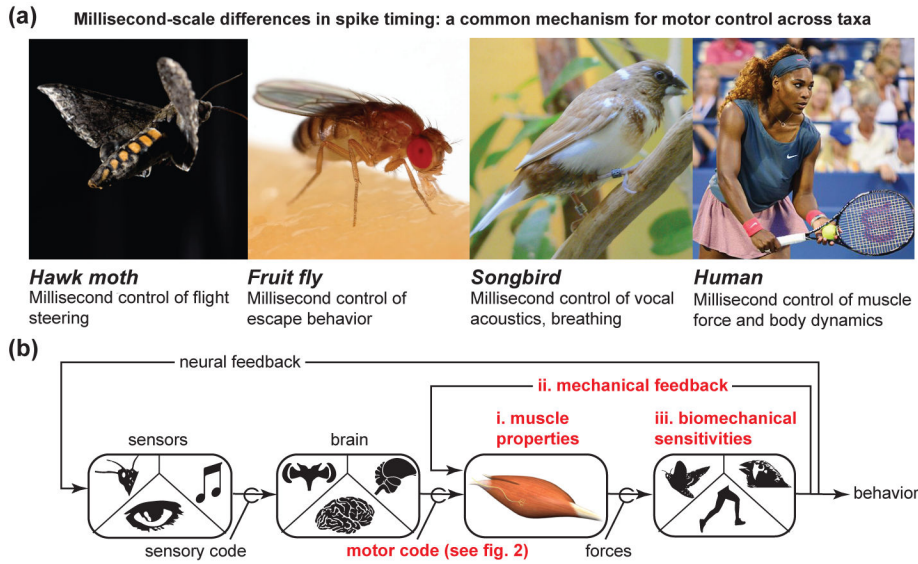
(a) Millisecond-scale differences in spike timing: a common mechanism for motor control across taxa

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)

Figure 1: Function and mechanisms of spike timing in motor systems across taxa.
(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)) might 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). (Images adapted from https://en.wikipedia.org/wiki/Drosophila_melanogaster and republished under license https://creativecommons.org/licenses/by-sa/4.0/; https://commons.wikimedia.org/wiki/File:Japanisches_Mövchen_060319_2.jpg under license https://creativecommons.org/licenses/by-sa/3.0/deed.en; and https://commons.wikimedia.org/wiki/File:Serena_Williams_US_Open_2013.jpg under license https://creativecommons.org/licenses/by/2.0/deed.en)
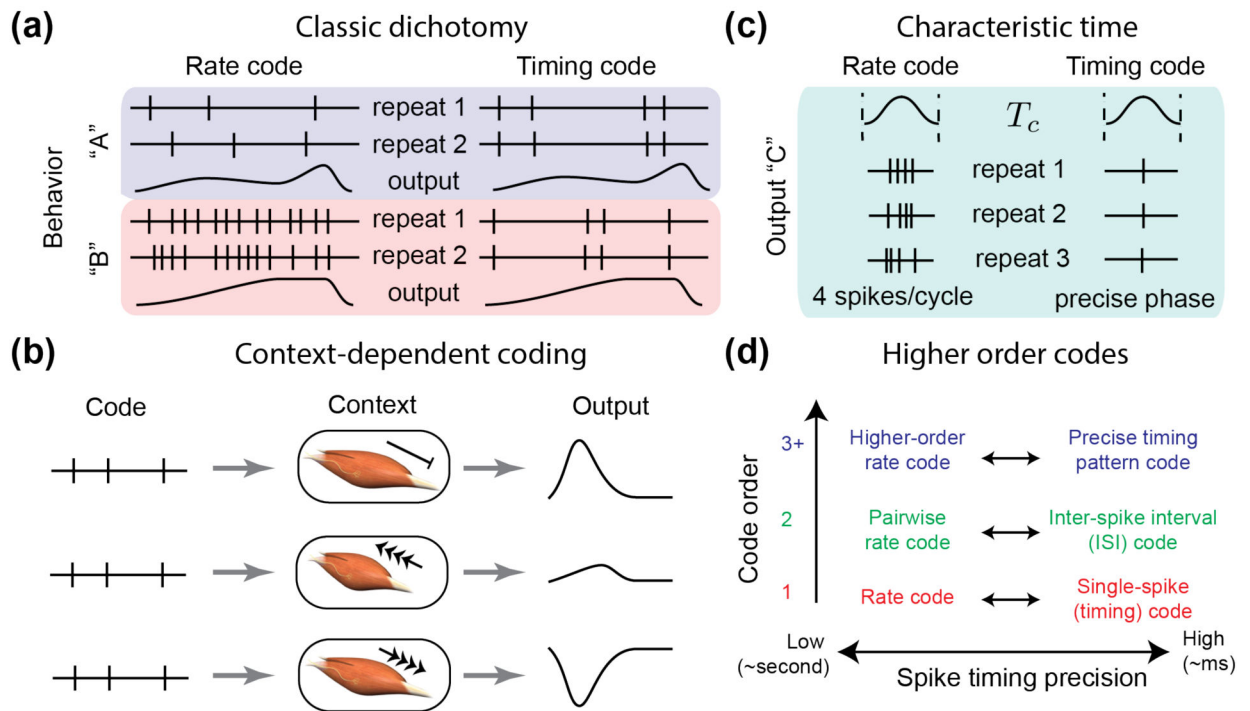
Figure 2: A diversity – not a dichotomy – of spike codes.
(a) Example of the classical dichotomy between timing and rate codes. Different motor outputs ("A" and "B") can be encoded either by a rate code (left) or a precise timing code (right), exemplified by differences in the number (left) or timing (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 vs. 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.