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Convergence of Action, Reaction, and Perception via Neural Oscillations in Dynamic Interaction with External Surroundings

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<http://dx.doi.org/10.5772/intechopen.76397>

Abstract

There has been a considerable interest in the role of time-dimension in functions of the brain, which has been limited to time perception and timing of behavior. However, during past few years it has become increasingly clear that the role of the time-dimension includes other complex cognitive functions, such as motor control of a vehicle, sensory perception and processing imageries to name a few. Role of the accurate representation of time-dimension is important for several neural mechanisms, which include temporal coupling, coincidence detection, and processing of Shannon information. These mechanisms play key roles in processing information during the interaction of the brain with the physical surroundings.

Keywords: temporal processing of information, temporal coupling, time-dimension in the brain, neural clocks, timing behavior, muscle synergy, action-reaction

1. Introduction

Physical time-dimension is an integral part of information processing in the brain by virtue of its role in representing the information as a spike pattern on the time axis [1]. Accordingly, the final product of information processing taking place in the brain, such as perception, action, or interaction with external environment, is dependent on the accurate representation of time-dimension in neural circuits. The physical surroundings with which humans interact is four dimensional, three geometric dimensions, and the time-dimension. Psychological time has been a subject of intellectual curiosity for most of the known history, but time-dimension

has been studied as the fourth physical dimension only during the last century [2, 3]. Time-dimension, unlike other physical qualities, is never perceived as a novelty but only reported as the flow of time [1], and therefore, it is not easy to study by observation alone.

Time-dimension plays a key role in many aspects of information processing in the brain. Temporal coupling of two or more events, neural or physical, occurs when they share the same coordinate on time-axis given that time-axis is represented accurately for all events. This allows the binding of events at the level of neural circuits or external physical surroundings. External events that are temporally coupled after processing in neural circuits lead to the subjective experience of entire repertoire of sensory inputs.

In coincidence detection, coincident activation of a third neuron by two oscillator circuits is proposed to play a role in analysis of frequency of auditory tones in the brain stem [4, 5]. The mental time travel is a fundamental ability of the human brain to “mentally” relocate oneself to a time point in the past or future [6]. The mental time travel allows the projection of self in past or future by referring a temporal order of events, which is processed by the hippocampus [7].

2. Interaction with external physical surroundings

Interval timing functions of the brain have arguably played a key role in the survival of the human species during most of their existence. Humans have been sustained by hunting and foraging [8], which requires interaction with external objects with a variety of physical characteristics, such speed, hardness, elasticity, and matter state—fluid or solid. These interactions are both (a) feedforward motor and (b) sensory—scene searching and sensory input. The feedforward motor control of external objects will be processed by sensory inputs resulting from reactional forces and impedance control (**Figure 3**). Mental time travel, by virtue of the

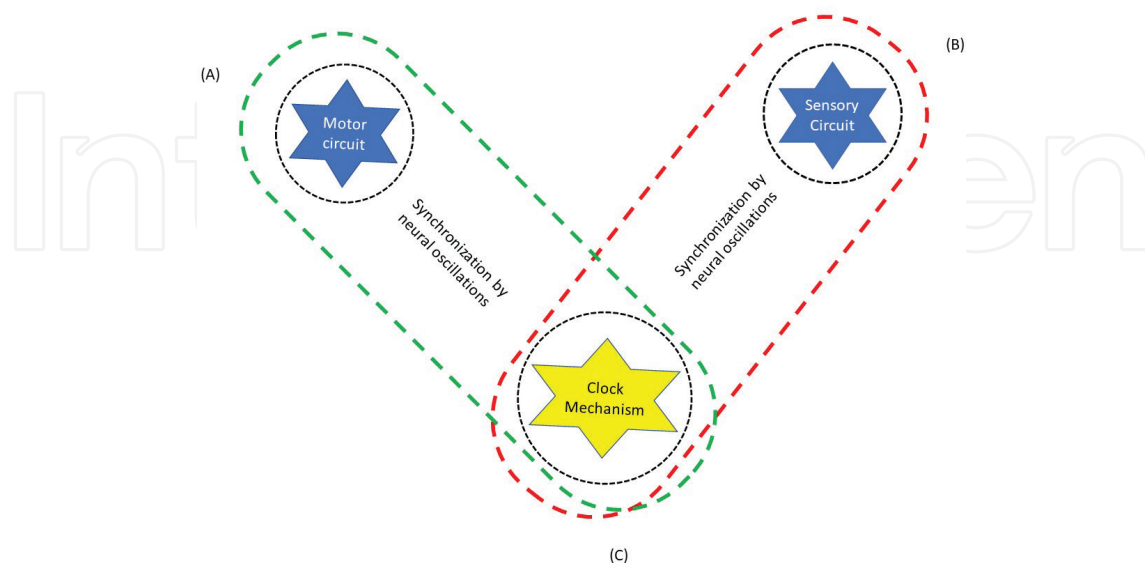


Figure 1. Depicts modular neural clock mechanism. Modular clock mechanism shown here is a prototype for the modular connections that form networks, processing information during interactions with external physical environment. The neural clock mechanism (C) can be synchronized with motor circuits (A) or sensory circuits (B) by low-frequency oscillations (broken rectangular lines).

ability to store the temporal order of events, helps to provide priors for the control of interaction with the environment as events unfold.

In addition, these activities require multiple temporal couplings of sensory inputs with motor responses at the level of a single individual. The use of limited energy stores by muscles must be optimized, which will constrain the central nervous system to recruit only certain muscle activation patterns.

Ability of individuals to communicate in groups, which is important for foraging, depends upon the temporal coupling of same brain circuits of different individuals to same stimuli, which may be hand gestures. Such brain circuits, found in the posterior parietal and motor areas, form mirror mechanisms in monkeys [9–11]. This is supported by imaging studies done in humans, which showed that the posterior parietal areas and premotor areas became active during action-observation and imitation [12, 13]. Moreover, rich reciprocal connections are present between different areas of the posterior parietal cortex and the premotor cortex in monkeys, which provide the anatomical basis of the mirror neuron mechanism [14, 15].

3. Representation of time-dimension in the brain

Representation of time unit by regular events is inherent in the definition of a regular event—that repeats itself after the same interval every time. Time units, such as seconds, measured by swings of pendulum in a mechanical clock, can help in the measurement of a duration by counting the number of seconds or swings of a pendulum. Using this analogy, a neural temporal unit is defined as the interval between two adjacent regular spikes, spike bursts, and is proposed to represent time units in neural circuits [16].

According to the pacemaker-accumulator model, when neural temporal units are added (or counted) by the accumulator, it processes neural time intervals for various subjective or motor tasks. According to this model, if the neural temporal units represented by neural oscillators in the brain's timing circuits are smaller on the physical time scale, then subjective time reported in the task will be greater than the elapsed physical time. This will be the result of a greater number of neural temporal units present within a given external time duration. As predicted by the pacemaker-accumulator model, a greater number of neural temporal units within a timed interval will lead to subjective overestimation of intervals. This is supported by a study in which entrainment using visual flickers with faster frequency increased time measurement in a time reproduction task [17]. Entrainment by faster flickers increases the frequency of neural oscillators in the brain, which leads to a smaller temporal unit—a result of entrainment by faster rate of oscillations. Another study used auditory click trains to increase the speed of neural clocks, and its effect on pair-wise duration comparison and verbal time estimation task, and had arrived at similar conclusions [18]. However, not all entrainment studies agree with this conclusion [19]. Thus, a different role of neural oscillator is suggested within the modular clock model [16]. According to this formulation, the role of rhythmic activity is to only represent a physical property of the time-dimension in various neural clock mechanisms. Rhythmic activities are shown to be important for cognitive functions and various forms of behavior as reviewed by Herbst and Landau [20], but its precise role is yet to be understood.

4. Modular connections of neural clocks: basis for timing functions

Modular model of distributed neural clocks is proposed by Gupta [16] for interval timing functions of the brain, such as timed motor movements, time reproduction, and time estimation. As depicted in the schematic in **Figure 1**, the proposed neural clock mechanism has three main modular components [16]: (1) calibration module, which is sensory and motor circuits of the brain that are involved in feedback interaction with the external four-dimensional surrounding; (2) endogenous neural oscillator to represent physical time in neural circuits; and (3) a clock mechanism for timing the behavioral response.

The functional role of the calibration module in the neural clock mechanism is to transfer information about the physical time from external surroundings into neural circuits. Physical time information is transferred into neural circuits when motor and sensory information is processed during an interaction of the brain with external surroundings. During the feedback process resulting from the interaction with physical surroundings, circuits associated with motor and sensory functions produce neuronal activities that parallel the interactions between effector organs, muscles, sensory organs, and external physical objects. A comparison of the intervals between changes external to the body and the intervals between corresponding feedback changes in neural activities in the brain is proposed to serve as a basis for the calibration of neural clocks.

Endogenous neural oscillator is the second component of the proposed modular neural clock mechanism. Neural oscillators are the rhythmic neural activities within the brain, such as neural oscillations, periodic bursts, or rhythmic circuits. The idea of neural oscillator to represent time-dimension is very old, which is based on the intuitive role of the pendulum in mechanical clocks. Treisman [21] had originally proposed pacemaker-accumulator model. According to this model, a neural oscillator generates pulses, which are accumulated by a counter to encode time intervals in neural circuits [22].

Instead of serving as the source for temporal units for pulse accumulation in the Treisman model, the endogenous neural oscillator in the modular clock mechanism only represents a property of physical time. Further, note that the periodicity of the endogenous oscillator does not simply represent a number that is added numerically to process time intervals for neural or psychological processes. However, as mentioned later, the numerical quantification of time intervals in neural processes is likely encoded by spike patterns and their temporal relationship. Neural oscillators, representing physical time, along with the calibration module and various task-specific circuits, synchronously generate information in networks, forming modular clock mechanism (**Figure 1**) to encode timed behavior.

Task-relevant neural clock is the third module, which is generally a part of local circuits, distributed across the central nervous system. For example, the neural timers for visual time reproduction tasks in seconds range are present in the right dorsolateral prefrontal cortex [23–25].

At present, it is not clear how neural patterns, representing information, are coded and decoded to result in behavior, such as timing movements or time estimation. It is likely that a combination of different patterns, such as spike patterns, logic states of neural circuits,

ramping activity of neurons, are important for coding and decoding information, leading to timed behavioral responses [16].

Quantitative measurements, such as time intervals, are likely represented in neural circuits in numerical representations [26], such as spike patterns, which can be read as the binary numbers [1, 27]. Studies suggest that the information about behaviorally relevant quantities such as timing behavior is not represented by the rates of spikes but rather by the intervals between their arrivals at synapses [26]. Coincidental activation of neurons by two different sources in a periodicity analysis model is proposed by Langner and Bahmer [28] for analysis of auditory signals in the brain stem.

Although the neurobiological basis of information processing, underlying the timing of behavior, remains far from clear [26], some consensus is present, such as, neurons encode sensory information using a small number of active neurons, called sparse coding [29]. Independent activation of a small number of neurons is consistent with the cytoarchitectonic data that show a low level of connectivity among the neurons of the cortex.

5. Cytoarchitectural basis of modular connections

Modular connections of local circuits forming dynamic networks are supported by cytoarchitectural and electrophysiological data from the study of the cortex. The cerebral cortex is divided into tiny computational units of mm range size, called the canonical microcircuits [30]. The neurons forming the canonical microcircuits have limited but conserved patterns of inputs and outputs [31]. Although the neurons within a canonical microcircuit are interconnected in specific patterns, the connectivity rates between most neuron pairs in the cortex are very low, which are less than 10–20% in most cases [31]. Due to a low level of connectivity among neurons, different combinations of multiple canonical microcircuits can be configured into a large variety of neuronal circuits and, therefore, provide the ability to perform a wide variety of computations. This feature is particularly useful for the role of small areas of the cortex to act as relatively independent modules in neural networks.

Moreover, inputs relayed to the cortex are organized in spatial patterns. This, combined with a little direct interaction between the canonical circuits in horizontal direction, results in independence of small cortical areas, which allows small cortical areas to act as relatively independent local circuits or modules. Local circuits are interconnected by synchronization, processing information to allow the brain to interact with the external physical world. The synchronization of local circuits is due to the oscillating states of excitability and inhibition, which allows neurons to fire during a specific phase of a long-range oscillation when neurons are excitable—coupling the modules of a neural network [27, 32, 33]. Periodic excitability of neurons during synchronization, due to pacing by inhibitory neurons, produces oscillating extracellular currents that are recorded as neural oscillations [34], which show different patterns during different behaviors. The behavioral significance of synchronization is due to the temporal coupling of neural events that underlie action and perception.

6. Role of oscillations in the representation of time-dimension

Since the discovery of neural oscillations in electroencephalography (EEG) by Hans Berger at the University of Jena, our understanding about its importance in cognitive functions has grown exponentially. Theoretical consideration as well as experimental evidence suggests that time-dimension is represented in the central nervous system by rhythmic activity of neural oscillations [1, 16, 27]. The importance of neural oscillations in cognitive functions became known when synchronized neuronal firing pattern, which was tightly correlated with the phase and amplitude of an oscillatory local field potential in the cat visual cortex, was reported in 1989 by Gray and Singer [35]. Furthermore, the stimuli were correlated to the amplitude of the oscillatory field in specific neuron clusters [35]. Neural oscillations represent a common unit of physical time-dimension in information processing when they synchronize different parts of the brain into networks [27].

Accumulating body of evidence now suggests that beta-range neural oscillations represent physical time information in the brain [16, 19, 27, 36–40]. A recent study has concluded that beta oscillations play an important role in the retention and manipulation of time information held in working memory [37]. A causal relationship between beta oscillations and the control of movements [41] has been shown, which further suggests that beta oscillations are responsible for coupling the neural-timer mechanism with the motor circuits for the control of movements.

7. Representation of time-dimension in lower motor circuits

Central pattern generators (CPG) are networks of neurons in the spinal cord-forming oscillators that play a role in hierarchical control, generating rhythmic motor activities in animals, such as walking and chewing [42]. The rhythmic activity of CPG networks, according to the formulations of distributed modular clock mechanism, represents time-dimension in spinal cord motor circuits that help to control the temporal characteristics of locomotion. Although, CPG activity is observed after deafferentation or spinal cord injury, the sensory inputs, especially proprioceptive signals, are crucial for its role in locomotion [43]. The function of proprioceptive signals is likely the calibration of neural temporal units represented by rhythmic activity of the CPG [16].

The evidence for the direct role of spinal cord CPG networks in human locomotion is scant and is mostly indirect [44, 45]. Some beneficial effects are seen in spinal cord injury patients following locomotor training [46], which can be attributed in part to the plastic changes in spinal cord CPG networks following the training, which updates physical time-dimension information from sensory, especially proprioceptive inputs during training sessions [16].

8. Role of temporal coupling in information processing

Representation of time-dimension in the brain is important for human and nonhuman primates' ability to survive. As argued earlier, the representation of time-dimension in neural circuits plays a key role in the information processing underlying complex cognitive functions

of the primate brain. Survival in many circumstances depends on the temporal coupling of action with the perception during the interaction with the external physical surroundings.

Depending upon the demands of a task, such as speed, the cost of failure, and the degree of coupling between action and perception, may vary. To couple feedforward motor output with sensory inputs on a small temporal scale, a more accurate representation of time information in neural circuits is required.

9. Role of coincidence detection in information processing

Coincidence detection refers to occurrence of an event only when two or more events take place synchronously. Oscillations are hypothesized to play a role in decoding the temporal information in ramping neuronal activities [16] that are commonly observed in the cortex [47–50]. Coincidence detection would play a role in generating the information that produces timed behavior. This information is processed when coincidence detector neuron is stimulated by both excitatory presynaptic terminals controlled by gamma oscillations [51] and an increasing excitatory input coming from a ramping neuronal activity (**Figure 2**). This

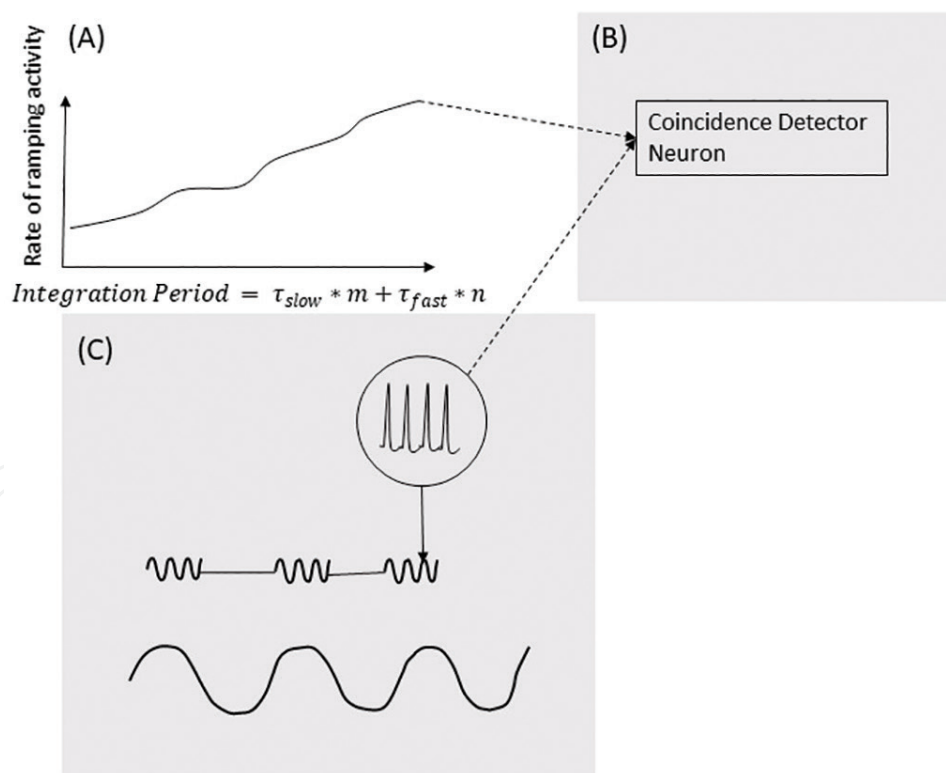


Figure 2. This figure shows how coincidence activation can result in the analysis of temporal information represented by neuronal ramping activities, commonly observed in the cortex. The ramping neuronal activity provides an increasing input to neuron that is synchronized by a high frequency nested within a low frequency (C). The neuron synchronized by (C) is excited by high frequency (periodicity is τ_{high}) gamma oscillations, within a specific phase of low frequency oscillation (periodicity is τ_{low}). The excitation of neuron (B) will result in an activity (coincidence detection), if there are three simultaneous events (1) input from neuron with climbing output (A) after reaching a particular level of activity (2) phase of long-range oscillations that allows gamma cycles (3) excitatory phase of gamma cycles. Thus, the integration period resulting from coincidence analysis will be represented by the formula shown within the figure, where m and n are integers.

coincidence detection model is based on the periodicity analyzing model for auditory signals in the brain stem proposed by Langner and Bahmer [28].

10. Input of time-dimension during the Cochlear processing contributes to sound perception

Psychoacoustical studies have indicated that perception of speech is not adequately accounted by place frequency mechanisms [52]. But the temporal information represented in sounds is also important in the perception of speech [52]. Therefore, it noteworthy that recent theoretical work and a growing number of experimental studies indicate that time-dimension is an integral part of information processing underlying perceptual functions of the cortex [16, 27].

Most natural sounds are modulated in amplitude, which can be explained by a mixture of sound waves of slightly different frequencies producing destructive interference near the tails and summation near the peak in the center [53, 54]. Thus, time-dimension is represented by the modulation frequency in addition to fine oscillations of air pressures causing sound waves. The oscillations of both frequencies, forming the structure of natural sounds, represent physical time-dimension [16]. The processing of sound waves by the cochlea produces amplitude modulation (AM) signals in the brain stem. The spike structure of AM signals is phase locked to changes in pressure produced by amplitude-modulated sound waves during the transduction by the cochlea. Studies also suggest the presence of tonotopic organization of subpopulations of neurons tuned to modulation frequencies [53], consistent with the transduction of time information in modulated sound waves, which is later processed in the auditory cortical areas contributing to perceptual qualities of sound.

11. Role of time-dimension in movements

11.1. What are muscle synergies?

Muscle synergies represent the central nervous system's response to the redundancy problem in motor movements. There are many more degrees of movements possible than are the number of muscle activation patterns that can produce movements [55, 56]. Several studies in vertebrates and non-vertebrates demonstrate the presence of elements or muscle synergies, from which complex patterns of motor movements can be constructed [56–58].

11.2. Computational models of muscle synergies

According to the computational models of muscle synergy, a synergy can be described as a D-dimensional vector field, where D is the number of muscles involved in movements [59, 60]. The level of contraction of each muscle, represented by weighting coefficient (W_i) multiplied by a coefficient (C_i) to yield $(C_i(t)W_i)$, represents one of the dimensions. The level of contraction (Coefficient*W, W is the weight of contraction) is referred to as synergy in the following computational models of synergy. The synergies are extracted using non-negative

matrix factorization of EMG patterns. Prior to the analysis, EMG data is adjusted by subtracting the tonic component of EMG activity responsible for postural activity and balance [60] or by normalizing EMG data as discussed earlier [61].

The maximum number of dimensions (D) in muscle synergies after extraction is the number (D) of all muscles that could play a role in the movement. After the extraction of muscle synergies from EMG patterns, the minimum number (N) of synergies is computed, such that they account for 80–90% of variability of the movements by choosing either coefficient of determination (CD) or variability accounted for (VAF) criteria. It has been observed that a small number of extracted muscle synergies can account for most of the variability of movements, while others account for 10–20% of the variability [59]. This provides a solution to the redundancy problem: few patterns of movements are preferred over far larger number of possible movements.

11.2.1. Spatial or time-invariant synergy model

$$m(t) = \sum_{i=1}^N C_i(t)W_i \quad (1)$$

In time-invariant synergy, there is a fixed level of contractions (weights) of muscles (M_1, M_2, \dots, M_n)— W_i for i th synergy. Each time-invariant i th synergy is activated by the nervous system temporally, represented by a time-varying coefficient ($C_i(t)$ for i th synergy at time t). In this muscle (i th) synergy, fixed weights of contraction of muscles are multiplied by a time-varying non-negative coefficient C_i to obtain muscle activation contributed by each synergy (W_i) [58]. Time invariant or spatial synergies can be described at a more abstract level as the uniform modulation of a D-dimensional vector field wherein the amplitude of the vector is the fixed levels of contraction of individual muscles.

11.2.2. Time-varying synergy model

$$m(t) = \sum_{i=1}^N C_i W_i(t - t_i) \quad (2)$$

In time-varying synergy, there are multiple waveforms corresponding to muscle contractions or vector amplitudes of individual synergies. Synchronous contraction waveforms of different muscles are multiplied by the same coefficient (C_i) for the i th synergy and shifted in time by a delay t_i and added to generate muscle activity pattern [59].

11.3. Recruitment of muscle synergies: a computational strategy by the brain to optimize motor movements within the constraints of musculoskeletal system, energy cost, and external physical surroundings

The computational models of muscle synergies reveal the modular control of muscles during movements. The muscle synergy recruitment in computational model can be explained by two orthogonal components. The spatial synergy model (Eq. 1) suggests that signals originating from a cortical circuit (from convergent to divergent) (defined as type I) control multiple muscles by sending signals of different strengths to different muscle with a fixed amplitude relationship between them, while another circuit (defined as type II) modulates

the activity of type I circuits, producing a time-varying modulation of fixed levels of muscle contractions constrained by the amplitude relationship, reflecting the spatial demands of the task. During a movement, synergies are recruited by sending signals from type II circuits to type I circuits. When several synergies (W_i) (type I circuit) are recruited by several corresponding sources of time-varying signals (type II circuit), it leads to the movement to be constructed by a computational mechanism. The orthogonal components of spatial synergies are detected by decomposing EMG patterns.

The type II circuits, which produce time-varying signals, represent time-dimension in the information processing that underlies the control of movements. Due to the representation of time-dimension, type II circuits are likely to be controlled by dynamic inputs, such as speed and temporal coupling. Type I circuits are responsible for representing the spatial directions of movements. Muscle contractions represented by type I circuit will determine the set of conditions, representing limb and joint positions for specific directions required for external task conditions. Furthermore, types I and II circuits are orthogonal or statistically independent, which is suggested by the decomposition of EMG patterns by the matrix factorization.

It is noteworthy that movements in humans are smooth. This suggests that muscles are not controlled individually by independent feedback processes, which would increase variations between contraction states of individual muscles, thereby decreasing the smoothness of movements. Instead, the muscles in each spatial synergy is controlled by a single signal (represented by time-varying coefficient in Eq. 1), which helps to reduce the number of variables being controlled, leading to an overall reduction in variations within movements. Thus, muscle synergies represent simpler computational solutions implemented by the central nervous system for controlling movements. Moreover, only a limited number of synergies can be recruited within the constraints of musculoskeletal system.

11.4. Control of muscle synergy recruitment

According to the classical view of the control of reaching movements to catch a ball, there is a creation of a neural representation of endpoint of the task, such as the hand meeting the ball in the physical space to execute a catch [62, 63]. This neural representation is formed by an initial approximation, which then evolves temporally [63]. The motor movements are produced by recruiting a limited number of synergies by the central nervous system, which can be directed by the neural representation of the prospective endpoint of the task. State estimators, which are discussed later, play a key role in optimum feedback control as it would predict the neural representation of the endpoint. The time-varying coefficient represents the time-dimension in the information processing movements, as it is modulated with time. Thus, time-varying signal (C_i) helps to determine the speed of movement, while the other orthogonal component, muscle synergies, is a response to spatial and musculoskeletal constraints.

Temporo-parietal cortical areas are believed to play a significant role in the feedback processes that help to represent the musculoskeletal system in the external four-dimensional environment [64, 65]. Studies of the computational models of muscle synergies indicate that the nervous system recruits a limited number of synergies that optimizes according to a temporally evolving map of the neural representation of the hand meeting the ball. Recruitment

of muscle synergies is also due to the numerous specific, reciprocal connections between the regions of the parietal cortical areas and frontal motor areas [66]. These specific multiple, reciprocal connections may form the basis for the recruitment of muscle synergies as well as the temporally evolving map of the neural representation of the map of the endpoint of the task. Furthermore, it is likely that the direct effect of state estimator module of the optimum feedback control is on the neural representation of the endpoint of the task rather than on muscle activities. The muscles are controlled from frontal motor areas, which are functionally connected to temporo-parietal areas where the multimodal integration of sensory information—proprioceptive, vestibular, and visual—takes place [64, 65].

11.5. Optimum feedback control theory

Although motor movements in humans are smooth, but the motor performance shows a large variability from trial to trial. This large variability in the movements is a reflection of inherent noise in the motor circuits, also called signal generated noise, in addition to the noise present in sensory circuits, and the external source of sensory inputs. Optimum feedback control is used by the central nervous system to modify feedback signal to control some index of motor function, such as minimization of endpoint errors or achieving a maximum jump. The control of motor outcome is optimum when it meets the spatiotemporal constraints of a task, such as hand meeting a ball during a catch. As a result, there is a decrease in the variations along the trajectory of the task; however, this is accompanied by the increase in variations in task-irrelevant trajectories. State estimator functions provide outputs to the feedback controller which helps to produce the optimum outcome [67].

A modification of optimum feedback control would consider the feedforward motor output via synergy recruitment. State estimator would recruit a limited number of muscle synergies that would account for 80–90% of variability of the movements according to VAF or CD criteria. The mechanism to explain the control of the recruitment of synergies must take into the constraints that limit movements. Muscle contraction velocity profiles, due to the constraints of viscoelastic properties as well as the biochemical events underlying sliding filament mechanism, are bell-shaped. The allowed muscle contractions must minimize the energy cost in the use of skeletal muscles, which is imposed as inheritable features on neural circuits due to evolutionary pressures. Furthermore, only certain movements are allowed by the joints, which depend on various factors, such as the shape and the structure of joints. The function of state estimator depends upon sensory inputs and efferent copy of cortical motor commands, which provides estimation of online changes occurring in the state of the musculoskeletal system [67].

Please note that sensory inputs and efferent copies of motor commands must be integrated with time-dimension in order to serve as state estimator for the optimum control of motor movements via synergy recruitment. The early online control of movements likely involves the integration of unimodal sensory state estimates instead of a single multimodal state estimate [68]. Studies have shown that during reaching movement task, joint angle variability peaked mid-way during the task [69], but there is a high accuracy at the endpoint [70], which suggests optimum feedback control of movements.

Optimum feedback control depends on a set of distributed circuits, among which the primary motor cortex appears to play a key role. It has been shown that the primary motor cortex receives inputs from several brain areas, which include the premotor cortex, primary somatosensory cortex, posterior parietal cortex, and pathways via the thalamus from the cerebellum, forming some of the structures involved in optimum feedback control. A recent study also shows that if feedback controller is represented in the primary motor cortex, the optimum feedback control describes multiple representation of preferred directions of torque or movements in which muscles are most active [71]. This is consistent with the role of the primary motor cortex as the site where individual synergies, involved in constructing voluntary movements, are recruited by the activation of individual spatial synergies by time-varying signals.

12. Controlling a motor vehicle: a special case of convergence of action, reaction, and perception

Newton's third law of motion states that for every action, there is an equal and opposite reaction. Newton's third law can be applied to analyze the interaction of the brain with the four-dimensional physical surroundings. The action, which results from movements, produces the reactional forces on the human body, resulting in changes in the activity of mechanoreceptors, which then modifies the activity of the musculoskeletal system responsible for movements in a feedback process. Thus, pairs of forces, action, and reaction forces during interaction between primates and their environment lead to changes in the activities of sensory and motor functions of the brain via feedback processes. In addition, successful interaction between the brain and the external environment depends on several other factors, which includes the representation of time and spatial dimensions in neural circuits of the brain. During this interaction, there is a complex interplay between feedforward motor process and sensory inputs. An important example of such a complex interaction is a driver controlling a motor vehicle (**Figure 3**). The control of the vehicle involved is due to two main motor actions, pressing the gas pedal to change the speed of the vehicle and the steering wheel to change the direction. The motor control of the vehicle, which is the feedforward motor prediction based on internally generated top-down feedforward output, is directed by a negative feedback process involving sensory inputs of different modalities.

Visual input, after processing in the posterior parietal cortex, is relayed to the primary motor cortex, which will be important for the control of movements with the help of visual cues. The premotor cortex is involved with the planning of movements and the internally generated signals, while the primary somatosensory cortex plays a role in processing inputs related to the perturbations of musculoskeletal system during movements.

Scene processing involves recognizing the environment, searching the information in the environment, and navigating through the environment [72]. Visual scene-selective regions are occipital place area, parahippocampal place area, and retrosplenial complex, which are on the lateral occipital, ventral temporal, and medial parietal cortical surfaces, respectively [72, 73]. Parahippocampal place area is believed to reflect a wide range of properties, such as spatial

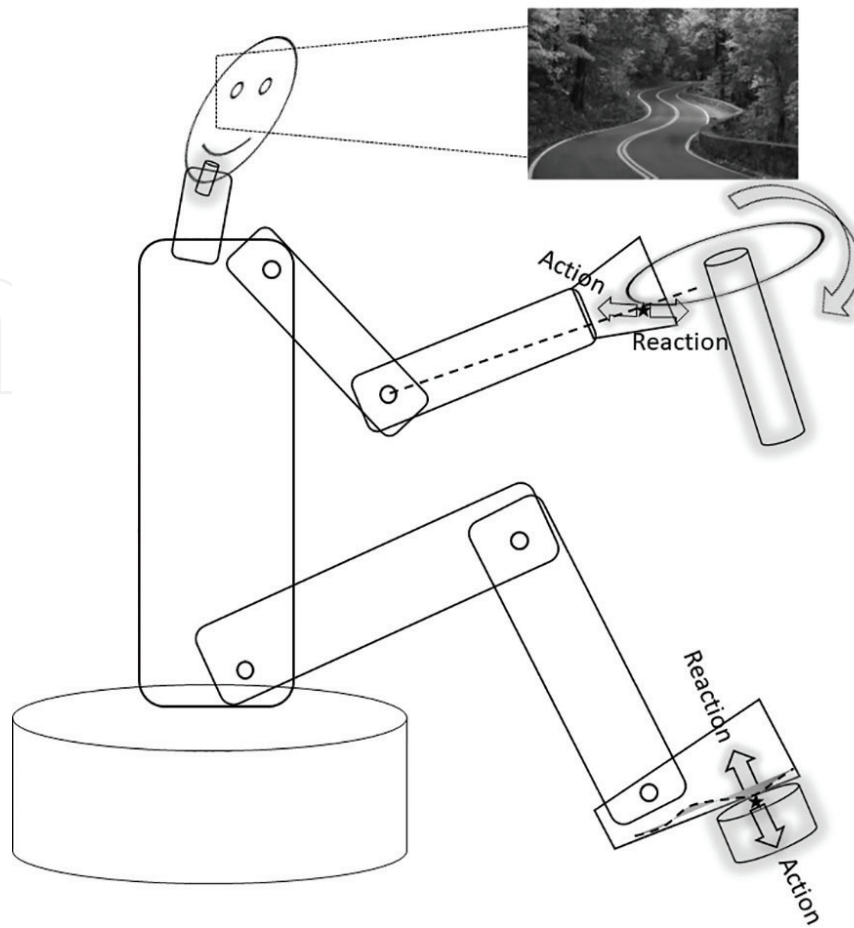


Figure 3. It depicts the interaction between feedforward motor output and feedback sensory input resulting from the stimulation of proprioceptors by reactional forces acting on the foot and hand. Visual information from the scene is actively gathered to provide additional but crucial sensory input.

frequency, orientation, texture, object identity, as well as size of a space [72]. A recent study has shown that the networking of the visual cortex with retrosplenial cortex is important for mental time travel, which would play a role in constructing prospective scenes [74], such as seeing an increasing number of brake lights will suggest a slowing traffic. The self-projection in time, called mental time travel, relies on various neural structures, encoding memory, mental imagery, and self, which is critical for the judgments during interactions with the physical environment [6]. Mental time travel recruits a network, which includes the anteromedial temporal, posterior parietal, inferior frontal, temporo-parietal, and insular cortices [6].

13. Biochemical and genetic basis of inter-individual variations in timing functions

A recent study of review-based evidence, which examined a large number of studies, suggests a key role of the dopaminergic system in various temporal functions of the brain [75]. These conclusions are based on various combinations of genetic, pharmacological, physiological, and

psychophysical evidence [75]. This review suggests an important role of certain key molecules, which influence the concentration of synaptic dopamine, in various timing functions of the brain. These molecules includes catechol-O-methyltransferase (COMT) that degrades synaptic dopamine and dopamine transporter (DAT), which removes dopamine from the synaptic cleft. Studies of common gene polymorphisms, COMT gene (COMT Val158Met) and DAT gene (SLC6A3 3'-VNTR variant), suggest the involvement of dopaminergic system in time perception.

Study of the effects of dopamine agonists, such as cocaine and metamphetamine and dopamine antagonists, haloperidol, on peak interval task suggests that both attentional and clock mechanisms are dependent on dopaminergic neurotransmission to some extent [76]. As argued earlier, cognitive functions are functionally dependent on timing as time-dimension is a part of the physical environment with which the brain interacts. In addition, neural oscillations, which represent time-dimension in neural circuits [16], help to form networks that form the basis of perception and action coupling [27]. Thus, we propose that dopaminergic system is one of the main chemical bases of timing circuits. This is consistent with the anatomical evidence, showing the extensive presence of dopamine terminals in layer I, with more specific presence in deeper cortical layers V and VI, which has neurons, projecting to the thalamus and striatum [77]. Dopamine can also play roles in the maintenance of homeostasis of neural circuits via cortico-striatal-thalamic-cortical loops [16]. This is consistent with the importance of dopaminergic system in cognitive and timing functions [78]. This view is further supported by the well-known role played by abnormal dopaminergic system in schizophrenia, which is a disorder of cognitive functions and time perception. Furthermore, the genetic variations in expression of molecules related to dopaminergic system in the brain are likely to contribute significantly to the variations in timing and cognitive functions between individuals.

14. Conclusion

Time-dimension plays a key role in all aspects of the brain functions. However, the focus study of time-dimension has been on a limited number of functions, which include timing behavior, subjective time perception, and temporal order. In this book chapter, we have extended the importance of time-dimension in the study of other aspects, such as movements, perception, and highlighted the importance of temporal coupling of neural and physical events during the interaction with external environment.

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