

From “Understanding the Brain by Creating the Brain” toward Manipulative Neuroscience

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Abstract

Ten years have passed since the Japanese “Century of the Brain” was promoted, and its most notable objective, the unique “Creating the Brain” approach, has led us to apply a humanoid robot as a neuroscience tool. Here, we aim to understand the brain to the extent that we can make humanoid robots solve tasks typically solved by the human brain by using essentially the same principles. I postulate that this “Understanding the Brain by Creating the Brain” approach is the only way to fully understand neural mechanisms in a rigorous sense. Several humanoid robots and their demonstrations are introduced. A theory of cerebellar internal models and a systems-biology model of cerebellar synaptic plasticity are discussed. Both models are experimentally supported, but the latter is more easily verifiable while the former is still controversial. I argue that the major reason for this difference is that essential information can be experimentally manipulated in molecular and cellular neuroscience while it cannot be manipulated at the system level. I propose a new experimental paradigm, manipulative neuroscience, to overcome this difficulty and allow us to prove cause-and-effect relationships even at the system level.

(main text 8123 words)

1. “Creating the Brain” in the Japanese Century of the Brain

In April 1996, an ad hoc committee on brain science of the Science Council of

Japan, the nation's most prestigious association of scientists, issued an advisory called "Promotion of Brain Science" to the Japanese government. In August of the same year, a committee for brain science promotion in the Science and Technology Agency of the Japanese government proposed a huge national brain research project funded at two trillion yen (~\$20 billion) for twenty years within a blueprint for the "Century of the Brain". In May 1997, a brain science committee of the prime minister's Council of Science and Technology, the nation's highest science advisory body, established three major research areas for its long-term plan: Understanding the Brain, Protecting the Brain, and Creating the Brain. The Brain Science Institute of RIKEN (the Institute of Physical and Chemical Research) was started in 1997, closely following this long-term plan (Normile 1997). Ten years have passed since the Japanese Century of Brain was launched, but, surprisingly, according to Shun-ichi Amari, president of RIKEN's Brain Science Institute, the 2005 budget for Japanese brain science was only 18 billion yen, and it has been decreasing over the past 7 years after peaking in 2000 (Amari 2006), in sharp contrast to the magnitude of the original proposal.

Among the three ways of exploring the brain, Creating the Brain is unique to Japan. Computers and robots have improved dramatically, but they are still greatly inferior to humans in most brain functions such as natural language processing, visual scene understanding, smooth and dexterous manipulation of objects, and common-sense reasoning, all of which can be executed almost effortlessly by humans, at least at the conscious level. This situation indicates that computer science and robotics did not make as much progress as expected 50 years ago and that neuroscience has not provided sufficient information on these areas. The "Creating the Brain" was motivated by this reflection, with the aim to develop brain-style information processing and communication technologies. In Particular, the development of "brain-style" computer systems, with human-like intellectual and emotional capabilities, was set as this work's long-term goal.

Over the past 10 years, millions of artificial retinal chips were sold for

several billion yen per year, and many kinds of “neuro-” electric home appliances with learning capabilities based on artificial neural networks have been popular in the Japanese market. However, the current status of research is still far from the development of “brain-style” computer systems. The main difficulty is that conventional medical and biological approaches in neuroscience do not provide the type of knowledge that is essential for computer development. The accumulation of a vast amount of data on brain locations (which function is lost when a specific brain region is destroyed), on substances (a specific molecule is critical for some brain functions), and on correlations (firing rates of neurons in a specific brain area correlated to a hypothetical element in cognition) is unfortunately nearly useless in unraveling neural mechanisms, at least to the extent that principles of information processing can be learnt from the brain. On the other hand, these kinds of knowledge are useful for Protecting the Brain (e.g. avoiding the speech area in neurosurgical ablation) or at some levels of Understanding the Brain.

We cannot state that we fully understand brain functions by simply accumulating the above types of data on locations, substances and correlations. In the deepest sense of “Understanding the Brain”, we should reveal the secrets of neural mechanisms of brain functions to the extent that we can “Create the Brain”. Furthermore, definitions of computational neuroscience vary depending on the researchers involved in this area. For some, approaches that depend on computers, mathematics, physics, engineering or David Marr’s computational theory could be called “Computational Neuroscience”. From the mid-80s, we initiated our own approach to computational neuroscience with the following definition: “We elucidate information processing of the brain to the extent that artificial machines, either computer programs or robots, can be built to solve the same computational problems that are solved by the human brain, using essentially the same principles”. Many researchers, including our group, started to believe that the only possible methodology to fully understand how the brain works is to build or reconstruct artificial systems that can realize

brain functions. We call this approach “Understanding the Brain by Creating the Brain”, and it is currently the major approach taken in the Japanese “Creating the Brain” area; furthermore, this might be regarded as the Japanese definition of computational neuroscience. Generally speaking, this is the new direction of “analysis by synthesis” in biological disciplines, and it has common ground with synthetic biology in systems biology or bioinformatics of molecular and cellular biology, where the goal is to create artificial organisms *in silico* or in wet biology.

2. Humanoid Robots as a Neuroscience Tool

Even if we could create an artificial brain, we could not investigate its functions, such as vision or motor control, if we just let it float in incubation fluid in a jar. The brain must be connected to sensors and a motor apparatus so that it can interact with its environment. A humanoid robot controlled by an artificial brain, which is implemented as software based on computational models of brain functions, seems to be the most plausible candidate for this purpose, given currently available technology. With the slogan of “Understanding the Brain by Creating the Brain”, in the mid-80s we started to use robots for brain research ([Miyamoto & Kawato 1988](#)), and about 10 different kinds of robots have been used by our group at Osaka University’s Department of Biophysical Engineering, ATR Laboratories, ERATO Kawato Dynamic Brain Project ([ERATO 1996-2001](#)), and ICORP Kawato Computational Brain Project ([ICOPR 2004-2009](#)).

An optimal computational theory for one type of body may not be optimal for other types of bodies. Thus, if a humanoid robot is used for exploring and examining neuroscience theories rather than for engineering, it should be as close as possible to a human body. Within the ERATO project, in collaboration with the SARCOS research company led by Professor Stephen C. Jacobsen of the University of Utah, Dr. Stefan Schaal as a robot group leader and his colleagues developed a humanoid robot called DB (Dynamic

Brain) (Figure 1) with the aim of most closely replicating a human body, given the robotics technology of 1996. DB possessed 30 degrees-of-freedom and human-like size and weight. DB is mechanically compliant like a human body, and unlike most electric-motor-driven and highly-g geared humanoid robots, because the SARCOS' hydraulic actuators are powerful enough to avoid the necessity of using reduction mechanisms at the joints. Within its head, DB is equipped with an artificial vestibular organ (gyro sensor), which measures head velocity, and four cameras with vertical and horizontal degrees-of-freedom. Two of the cameras have telescopic lenses corresponding to foveal vision, while the other two have wide-angle lenses corresponding to peripheral vision. SARCOS developed the hardware and low-level analog feedback-loops, while the ERATO project developed high-level digital feedback-loops and all of the sensory-motor coordination software.

The photographs in Fig. 1 introduce 14 of the more than 30 different tasks that can be performed by DB (Atkeson et al. 2000). Most of the algorithms used for these task demonstrations are based roughly on principles of information processing in the brain, and many of them contain some or all of the three learning elements: imitation learning (Miyamoto et al. 1996; Schaal 1999; Ude & Atkeson 2003; Ude et al. 2004; Nakanishi et al. 2004), reinforcement learning, and supervised learning. Imitation learning (“Learning by Watching”, “Learning by Mimicking” or “Teaching by Demonstration”) was involved in Okinawan folk dance “Katya-shi” (Riley et al. 2000) (A), three-ball juggling (Atkeson et al. 2000) (B), devil-sticking (C), air-hockey (Bentivegna et al. 2004a; Bentivegna et al. 2004b) (D), pole balancing (E), sticky-hands interaction with a human (Hale & Pollick 2005) (L), tumbling a box (Pollard et al. 2002) (M), and a tennis swing (Ijspeert et al. 2002) (N). The air-hockey demonstration (Bentivegna et al. 2004a; Bentivegna et al. 2004b) (D) utilizes not only imitation learning but also a reinforcement-learning algorithm with reward (a puck enters the opponent’s goal) and penalty (a puck enters the robot’s goal) and skill learning (a kind of supervised learning). Demonstrations of pole-balancing (E) and visually guided arm reaching toward a target (F) utilized a supervised learning

scheme (Schaal & Atkeson 1998), which was motivated by our approach to cerebellar internal model learning, introduced in the next section. Demonstrations of adaptation of the vestibulo-ocular reflex (Shibata & Schaal 2001) (G), adaptation of smooth pursuit eye movement (H), and simultaneous realization of these two kinds of eye movements together with saccadic eye movements (I) were based on computational models of eye movements and their learning (Shibata et al. 2005). Demonstrations of drumming (J), paddling a ball (K), and a tennis swing (N) were based on central pattern generators.

The ICORP Computational Brain Project (2004-2009), which is an international collaboration project with Prof. Chris Atkeson of the Carnegie Mellon University, follows the ERATO Dynamic Brain Project in its slogan “Understanding the Brain by Creating the Brain” and “Humanoid Robots as a Tool for Neuroscience”. Again in collaboration with SARCOS, at the beginning of 2007 Dr. Gordon Cheng as a group leader with his colleagues developed a new humanoid robot called CB (Computational Brain), shown in Fig. 2. CB is even closer to a human body than DB. To improve the mechanical compliance of the body, CB also used hydraulic actuators rather than electric motors. The biggest improvement of CB over DB is its autonomy. DB was mounted at the pelvis because it needs to be powered by an external hydraulic pump, through oil hoses arranged around the mount. A computer system for DB was also connected to DB by wires. Thus, DB could not function autonomously. In contrast, CB carries both onboard power supplies (electric and hydraulic) and a computing system on its back, and thus it can function fully autonomously. CB was designed for full-body autonomous interaction, for walking and simple manipulations. It is equipped with a total of 51 degrees-of-freedom (DOF): 2x7 DOF legs, 2x7 DOF arms, 2x2 DOF eyes, 3 DOF neck/head, 1 DOF mouth, 3 DOF torso, and 2x6 DOF hands. CB is designed to have similar configurations, range of motion, power, and strength to a human body, allowing it to better reproduce natural human-like movements, in particular for locomotion and object manipulation.

Locomotion and posture control are the most challenging research topics for a human-like and autonomous humanoid robot such as CB, because of its mechanically compliant and 51-DOF body. Within the ICORP CB Project, biologically inspired control algorithms for locomotion have been studied using the three different humanoid robots shown in Fig. 3 (a: DB-chan (Nakanishi et al. 2004), b: Fujitsu Automation HOAP-2 (Matsubara et al. 2006), c: CB (Morimoto et al. 2006)) as well as the SONY small-size humanoid robot QRIO (Endo et al. 2005) as test beds. Successful locomotion algorithms utilize various aspects of biological control systems, such as neural networks for central pattern generators, phase resetting by various sensory feedbacks including adaptive gains, and hierarchical reinforcement learning algorithms. In the demonstration of robust locomotion shown in Fig. 3a, three biologically important aspects of control algorithms are utilized: imitation learning, a nonlinear dynamical system as a central pattern generator, and phase resetting by a foot-ground contact signal (Nakanishi et al. 2004). First, a neural network model developed by Schaal et al. (2003) quickly learns correctly demonstrated locomotion trajectories by humans or other robots. In order to synchronize this limit-cycle oscillator (central pattern generator) with a mechanical oscillator functioning through the robot body and the environment, the neural oscillator is phase-reset by foot-ground contact. This guarantees stable synchronization of neural and mechanical oscillators with respect to phase and frequency. The achieved locomotion is quite robust against different surfaces with various frictions and slopes, and it is human-like in the sense that the robot body's center of gravity is high while the knee is nearly fully extended at foot contact. This is in sharp contrast to locomotion engineered by zero-moment point control, which usually induces a low center of gravity and bent knees.

3. Cerebellar Internal Models

Many of the DB demonstrations mentioned in the previous section are based

on the cerebellar internal model theory, which we have been developing over the past 25 years (Kawato et al. 1987; Kawato & Gomi 1992; Kawato 1999): each micro-zone of the cerebellar cortex learns to acquire an internal model of some specific object in the external world, such as an arm or eye of one's own body, manipulative tools, or another person's brain. In this section, we briefly describe the background of this theory, the theory itself and some experimental support of this theory.

Among the many different models of the cerebellum, learning models have always been the most attractive, versatile and influential. The learning models are based on unique structures of the cerebellar cortex. The Purkinje cell, the only output neuron in the cerebellar cortex, receives two major excitatory inputs from climbing fibers and parallel fibers. A single climbing fiber axon makes multiple synapses on a single Purkinje cell and induces very strong excitatory postsynaptic potentials, which lead to complex spikes that consist of a few Ca^{2+} spikes. By contrast, 200,000 synapses from parallel fibers, which are the axons of $10^{10\sim 11}$ granule cells, generate simple spikes, each of which is a single Na^+ spike. Although early cerebellar learning models (Marr 1969; Ito 1970; Albus 1971) proposed that the cerebellum performs pattern recognition, probably influenced by a "perceptron", they are not consistent with physiological data showing that simple spike firing rates of Purkinje cells temporally change and encode dynamic and kinematic features of movements. Recent studies suggest that the human cerebellum is important for sensory and cognitive functions as well as for motor control. Might there be a general computation realized by the cerebellar cortex that covers the sensory, cognitive and motor domains and also conforms to existing hypotheses on such matters as timing, coordination, and error correction? Internal models seem to provide the most versatile and hypothesis-compatible computational entity satisfying these requirements. Internal models are neural networks inside the brain ("internal") that can mimic ("model") the input-output characteristics of some dynamical process outside the brain. In a motor control context, a forward model of a body can predict sensory consequences of movement from the efference copy of a motor

command. This is because the controlled objects in movements generate a trajectory from the motor commands. By contrast, an inverse model of a body and the external world can compute the necessary motor commands from a desired movement pattern. Internal models are useful for predictive computations in sensory, cognitive and motor functions. If an inverse dynamics model for a controlled object possessing dynamics and kinematics with multiple degrees of freedom is destroyed, the movement becomes clumsy, slow and not well corrected. This is because neither feedforward control (which is dependent on the inverse model) nor sophisticated feedback control (which is dependent on the forward model) is available. Thus, control must rely on poor and crude feedback control alone.

About 25 years ago, my colleagues and I proposed that different parts of the cerebellum contain either forward or inverse models ([Tsukahara & Kawato 1982](#); [Kawato et al. 1987](#)) and also that a computational scheme called feedback-error-learning is used to acquire an inverse model in the supervised learning scheme as shown in Fig. 4 ([Kawato et al. 1987](#), [Kawato 1990](#), [Kawato & Gomi 1992](#)). If supervised learning takes place in the brain for motor control, the following difficult computational problem called “distal teacher”, formulated by [Jordan & Rumelhart \(1992\)](#), should be resolved. The error between desired and actual movement patterns can be measured by sensory organs, but these movement errors could be very different in spatial coordinates as well as in temporal dynamics from the necessary error signal for the motor command. Furthermore, it should be emphasized that there exists no teaching signal for motor commands in supervised motor learning, since if it did exist, it would be directly utilized for motor control and there would be no need for learning.

In the feedback-error-learning model depicted in Figure 4, the inverse model first transforms a desired trajectory into a feedforward motor command. Second, a crude feedback controller generates a feedback motor command from the sensory error. Third, the summation of the feedforward and feedback motor commands is sent to the controlled object. Finally, and most

importantly, the feedback motor command is used as the error signal for motor commands in the supervised learning to acquire the inverse model. Stability and convergence of the feedback-error-learning algorithm have been mathematically proven (Nakanishi & Schaal 2004) as well as successfully applied to several robotic demonstrations (e.g. Miyamoto et al. 1988). Here, simple spikes represent feedforward motor commands and the parallel fiber inputs represent the desired trajectory as well as the sensory feedback of the current status of the controlled object. A microzone of the cerebellar cortex constitutes part of an inverse model of a specific controlled object, such as the eye or arm. Most importantly, climbing fiber inputs are assumed to carry a copy of the feedback motor commands generated by the feedback control circuit. Thus, the complex spikes are assumed to be trajectory error signals already expressed in motor command coordinates. Climbing fiber inputs are delayed by 100 msec with respect to the responsible parallel fiber inputs that caused the movement and the resulting error, but the spike-timing dependency of parallel-fiber Purkinje-cell long term depression (LTD) selectively decreases the efficacy of only the responsible parallel fiber synapses, explained in the next section.

Kenji Kawano and his colleagues supported the cerebellar feedback-error-learning model with neurophysiological studies in the ventral paraflocculus of the monkey cerebellum during ocular-following responses (Kawano 1999; Kawato 1999; Shidara et al. 1993; Gomi et al. 1998; Kobayashi et al. 1998; Takemura et al. 2001; Yamamoto et al. 2002). Ocular-following responses are tracking movements of the eyes evoked by movements in a large visual scene that are thought to be important for visual stabilization of gaze. In the neural circuit controlling this response, the phylogenetically older and cruder feedback circuit is comprised of the retina, the accessory optic system and the brain stem. The phylogenetically newer and more sophisticated feedforward pathway and the inverse dynamics model correspond to the cerebral and cerebellar cortical pathway and the cerebellum, respectively. The sensory error signal is computed as the image motion on the retina (retinal slip). This is different from the scheme of

Fig. 4, where some neural mechanisms explicitly compute the difference (error) between the desired and actual states. However, in the case of eye movement control such as ocular-following responses or vestibulo-ocular reflexes, the desired state is eye movement in which the retinal image does not move, and thus the optical computation (retinal slip detection) can replace subtraction of the desired and actual states. On the other hand, the desired trajectory information transmitted to the flocculus for the vestibulo-ocular reflex is the head motion signal detected by semi-circular canals, whereas for the ocular following responses this is the image motion signal conveyed by the visual areas in the cerebral cortex.

During ocular following responses, the time-courses of simple spike-firing frequency show complicated patterns. However, they were quite accurately reconstructed by using an inverse-dynamics representation of eye movement (Shidara et al. 1993; Gomi et al. 1998). The model fit was good for the majority of the neurons studied under a wide range of visual stimulus conditions, different eye movements, and different firing patterns. The same inverse dynamics analysis for the medial superior temporal area (MST) of the cerebral cortex and dorsolateral pontine nucleus, which provide visual mossy fiber inputs, revealed that their firing time-courses were not well reconstructed from motor commands but were well reconstructed from visual retinal slip (Takemura et al. 2001). Taken together, these data suggest that the ventral paraflocculus is the major site of the inverse dynamics model of the eye for ocular-following responses.

Motor commands, conveyed by simple spikes, should be directly modified and acquired by LTD while guided by motor-command errors, which are conveyed by climbing fiber inputs. For this to work, the climbing fiber inputs need to convey comparable details of temporal and spatial information to the motor commands, but the ultra-low discharge rates of the latter would appear to rule this out. This apparently discrete and sporadic nature of climbing fiber inputs was characterized as an unexpected event detector, and it suggested a reinforcement-learning-type theory. However, if thousands of

trials are averaged, the firing rates actually conveyed very accurate and reliable time-courses of motor command error within a few hundreds of milliseconds (Kobayashi et al. 1998). More specifically, complex spike time-courses are better reconstructed by retinal slip than eye movements, but in the motor command coordinates rather than in visual coordinates as detailed below. Because LTD has recently been shown to temporally leaky-integrate a postsynaptic Ca^{2+} signal (Tanaka et al. 2007) as introduced in the next section, it can perform temporal averaging. Consequently, the firing probability of climbing fiber inputs can convey high-frequency temporal information that matches information of the dynamic command signal.

The preferred directions of MST and pontine neurons were evenly distributed over 360 degrees. Thus, the visual coordinates are uniformly distributed over all possible directions. On the other hand, projections of the 3-D spatial coordinates of the extraocular muscles were in either a horizontal or vertical direction, and they were entirely different from the visual coordinates. Preferred directions of simple spikes were either downward or ipsiversive (i.e. toward the same side), and at the site of each recording, electrical stimulation of a Purkinje cell elicited eye movement toward the preferred direction of the simple spike (Kawano 1999). These data indicate that the simple spike coordinate framework is already that of the motor commands. Thus, at the parallel fiber-Purkinje cell synapse, a drastic visuomotor coordinate transformation occurs. The neural representation dramatically changes from population coding in the MST and pontine nucleus to firing-rate coding of Purkinje cells at the parallel fiber-Purkinje cell synapse. What, then, is the origin of this drastic transformation? The theory proposes that the complex spikes, and ultimately the accessory optic system, are the source of this motor command spatial framework. The preferred directions of pretectum neurons are upward, and those of the contralateral nucleus of optic tract neurons are ipsiversive (thus contraversive for the cerebellum). Their signals are conveyed to the inferior olive and further to the cerebellum to produce the complex spikes. In

summary, the coordinate frame of the climbing fibers was vertical and horizontal, forming the motor coordinates, not the visual coordinates of MST or pontine nucleus. A realistic neural network model successfully simulated all of these experimental findings (Yamamoto et al. 2002). The coordinates of semicircular canals and the extraocular muscles are very similar, and it is rather difficult to evaluate coordinate transformation in the vestibulo-ocular reflex and flocculus compared with ocular following responses. However, recent physiological studies indicate that climbing fiber inputs encode motor error rather than sensory error (Winkelman & Frens 2006). This argues against a class of model that assumes sensorimotor transformation downstream of the Purkinje cells, including de-correlation models (Dean et al. 2002).

For arm movements under multiple force fields, firings of many Purkinje cells correlate with dynamics (Yamamoto et al. 2007). fMRI studies mapped forward and inverse models of tools and manipulated objects in the cerebellar cortex (Imamizu et al. 2000; Kawato et al. 2003). Thus, we have been accumulating experimental support for the cerebellar internal model theory for arm movements, the human cerebellum for tool use, and forward models in addition to inverse models. Having said this, I must admit that experimental support outside the inverse dynamics model for the ocular following responses in the ventral paraflocculus is rather indirect and circumstantial, and these issues are still controversial (for example, compare Yamamoto et al. 2007 and Pasalar et al. 2006). However, because the neural circuit of the cerebellar cortex is so uniform for different regions and different functions, unlike the cerebral cortex, I predict that a theory fully supported even for only a single function in a small region of the cerebellum should possess some computational principles that can be generalized to all functions and regions of the cerebellum.

4. Systems-Biology Models of Cerebellar LTD

If the long-term depression (LTD) of parallel fiber-Purkinje cell synapses is the elementary cellular process of supervised learning, as postulated in cerebellar learning theory, it must satisfy the following three requirements. First, LTD should be associative. That is, LTD should be induced only when both parallel fiber inputs and climbing fiber inputs are conjunctively activated. Second, LTD should be maximally induced when climbing fiber activation is delayed by 50 to 200 msec with respect to parallel fiber activation. This is because the time window of LTD should compensate for the delay of the refferent climbing fiber inputs to feed back the consequences of the parallel-fiber-simple-spike-induced movements. Third, LTD should be synapse-specific; only a parallel fiber synapse that is conjointly activated with a climbing fiber input should be depressed and not other synapses. However, a considerable number of studies have reported violations of these three requirements under some experimental conditions; consequently, LTD has been questioned several times as the elementary process of cerebellar supervised learning (Llinas et al. 1997) and has been postulated for other functions, such as the normalization of total synaptic efficacies on a single Purkinje cell (de Schutter 1995). The kinetic simulation model of LTD signal-transduction pathways in a Purkinje-cell dendritic spine (Fig. 5), which has been developed in a series of publications from our group (Kuroda et al. 2001; Doi et al. 2005; Ogasawara et al. 2007) and was recently supported experimentally (Tanaka et al. 2007), provided a coherent perspective on these confusing experimental data and competing theoretical hypotheses, and it is introduced in this section.

Climbing fiber inputs activate AMPA receptors (AMPA-Rs) on dendritic shafts and induce depolarization, which opens the voltage-gated calcium channels (VGCCs) on a spine as indicated by the broken line in Fig. 5, leading to Ca^{2+} influx from the extracellular space into the spine head, reaching a concentration of about $1 \mu\text{M}$. Parallel fiber inputs also induce AMPA-R activation on dendritic spines, just as a climbing fiber input does but with a smaller depolarization and Ca^{2+} influx. In addition, they simultaneously activate metabotropic glutamate receptors (mGluRs).

Furthermore, they presynaptically synthesize nitric oxide (NO), which diffuses into the spine. In the metabotropic pathway, activated mGluRs induce production of inositol 1,4,5-triphosphate (IP₃) and diacylglycerol (DAG) via G-proteins (Gq) and phospholipase C β (PLC β) at the postsynaptic density. IP₃ then diffuses into the cytosol and binds to IP₃ receptors (IP₃Rs), which are IP₃-gated Ca²⁺ channels on the intracellular Ca²⁺ stores, such as the endoplasmic reticulum (ER). Cytosolic Ca²⁺ above some threshold triggers a regenerative cycle of IP₃-dependent and Ca²⁺-induced Ca²⁺ release (depicted as a red positive feedback loop between Ca²⁺ and IP₃Rs in Fig. 5) from the ER via IP₃Rs opened by binding of both IP₃ and Ca²⁺. This means that the open probability of IP₃Rs increases with Ca²⁺ concentration and the Ca²⁺ threshold of this regenerative cycle decreases with IP₃ concentration. An increase in cytosolic IP₃ concentration was simulated to be maximal at 3 μ M about 100 msec after the parallel fiber input. This slow rate of increase in IP₃ concentration is due to the slow dynamics of the metabotropic pathway. Because Ca²⁺ influx via VGCCs due to climbing fiber activation is an immediate event, when the climbing fiber input is delayed about 100 msec with respect to the parallel fiber input, Ca²⁺ increase coincides with IP₃ increase, and together they trigger the Ca²⁺-induced Ca²⁺ release of 10 μ M. If either climbing fiber input or parallel fiber input alone is activated, this large Ca²⁺ release does not occur because either IP₃ or Ca²⁺, respectively, does not reach the threshold for the regenerative cycle. Consequently, the Ca²⁺ nonlinear excitable dynamics model of [Doi et al. \(2005\)](#) (right 1/3 of Fig. 5) reproduced the associative nature and the spike-timing-dependent plasticity (STDP) of cerebellar LTD.

In the model proposed by [Kuroda et al. \(2001\)](#), the large Ca²⁺ increase, which is caused by the conjunctive parallel fiber input and the delayed climbing fiber input, induces the activation of linear cascades of phosphorylation of protein kinase C (PKC) followed by phosphorylation and then internalization of AMPA-R, which explains the early phase of LTD up to about 10 minutes. On the other hand, the intermediate phase of LTD up to several tens of minutes is mediated by a mitogen-activated protein (MAP) kinase-dependent

positive feedback loop, which consists of PKC, Raf, MAP/extracellular signal-regulated kinase (MEK), MAP kinase, cytosolic phospholipase A₂ (PLA₂), arachidonic acid (AA), and back to PKC (the magenta loop in the middle of Fig. 5). This positive feedback loop has two stable equilibrium points separated by a saddle point that determines the threshold of LTD. At the low equilibrium point, the MAP-kinase positive feedback loop is not activated, but if strong or long-lasting Ca²⁺ elevation occurs, the state jumps to the higher equilibrium over the saddle point and AMPA-Rs continue to be phosphorylated and internalized during this prolonged activation of the positive feedback loop. Consequently, this MAP-kinase positive feedback model (middle 1/3 of Fig. 5) explains the long-term nature of LTD.

In the NO model (left 1/3 of Fig. 5), which was first proposed by [Kuroda et al. \(2001\)](#) and then extensively studied in combination with electrical properties of dendrites by [Ogasawara et al. \(2007\)](#), NO activates soluble guanylyl cyclase (sGC), and the activated sGC catalyzes the conversion of GTP into cGMP, which activates cGMP-dependent protein kinase (PKG). PKG phosphorylates its substrate, G-substrate, and the phosphorylated G-substrate preferentially inhibits protein phosphatase 2A (PP2A). Activated PP2A dephosphorylates MEK and AMPA-R. Inhibition of the dephosphorylation of MEK was required for the activation of the MAP-kinase positive feedback loop. Therefore, by ultimately inhibiting PP2A and activating the positive feedback loop, NO plays a permissive role in the induction of LTD.

The Ca²⁺ dynamics model coherently reproduced both the associative and non-associative natures of LTD, and the spike-timing dependency of associative LTD, as follows. Within the physiological ranges of input strength, the conjunctive stimulation of the parallel fiber input and the delayed climbing fiber input is essential to induce a large, regenerative Ca²⁺ increase, which is necessary for crossing the MAP-kinase positive-feedback-loop threshold and inducing LTD. However, if stimulation of parallel fiber bundles is strong enough, or if uncaged Ca²⁺ or IP₃ is large

enough, these stimuli alone can increase the Ca^{2+} concentration so that it crosses the Ca^{2+} dynamics threshold, resulting in a large enough Ca^{2+} -induced Ca^{2+} release from the ER to reproduce non-associative LTD. In the hippocampal and cerebral pyramidal neurons, backpropagation of somatic action potentials removes the magnesium block of NMDA receptors, and when coincided with glutamate-release by pre-spiking, NMDA receptors are fully activated and lead to supralinear Ca^{2+} influx, resulting in the induction of LTP. The coincidence of glutamate-release with backpropagation in this order within a ten-millisecond order is essential for NMDA receptor-dependent STDP there. Backpropagation of somatic action potentials require firing of postsynaptic cells, which is the essential condition of Hebbian learning. Neither backpropagation nor the functional NMDA receptors exist in Purkinje cells, suggesting completely different cellular mechanisms of Purkinje-cell supervised learning with 100-msec STDP from cerebral Hebbian learning with STDP of tens of msec. These systems-biology models explain diverse LTD experiments and clearly demonstrate that LTD is a supervised learning rule, and not anti-Hebbian as characterized elsewhere ([Dayan & Abbott 1999](#)).

The excitable dynamics of the Ca^{2+} model and bistable dynamics of the MAP-kinase positive feedback loop model may provide a possible molecular mechanism to resolve the “plasticity-stability” dilemma, maintaining memory stably while still being sensitive to delicate environmental changes. Each spine is equipped with a surprisingly small number of molecules (e.g. only 40 AMPA-Rs). With a cascade of excitable and bistable dynamics starting from Ca^{2+} dynamics, followed by the MAP-kinase positive feedback loop, internalization of AMPA receptors, a possible change in cytoskeleton and membrane proteins, and finally a morphological change in the spine, LTD could be induced by very delicate and low-energy inputs but still maintain acquired memory over a prolonged period of days, even under stochasticity due to the small numbers of molecules.

The synapse-specificity of LTD is also well explained by the NO model

combined with an electrical cable model of Purkinje-cell dendrite and spines, the Ca^{2+} dynamics model, and the MAP-kinase positive feedback loop model (Ogasawara et al. 2007). When no nearby parallel fiber is activated and NO is low, not even a conjunction of the parallel fiber and climbing fiber inputs can induce LTD. If too many surrounding parallel fibers are stimulated and NO is very high, even the synapse, which is not stimulated, exhibits LTD only by climbing fiber stimulation. In this case, a spread of LTD occurs and the synapse-specificity of LTD is lost. Only when a modest number of parallel fibers are activated and NO is within an intermediate range can synapse-specific LTD occur; the contextual information for storing different motor skills might be conveyed by this gating mechanism. This strongly predicts the sparseness of parallel fiber coding *in vivo*, which has recently gained much experimental support (e.g. Chadderton et al. 2004).

Taken together, the LTD kinetic simulation models provide a comprehensive account of several seemingly diverse, conflicting and unrelated experimental data within the framework of complicated nonlinear dynamics regulated by Ca^{2+} , IP_3 , and NO concentrations. We must note that because of the nonlinear summation effects of these signaling molecules, non-physiological stimuli *in vitro*, such as parallel fiber bundle stimulation and uncaging (i.e. direct and instant application of interested molecules by photolysis of its caged-compounds) of Ca^{2+} or IP_3 , might induce qualitatively different characteristics from *in vivo* LTD in terms of its associative nature, spike-timing dependency, and synapse-specificity.

The systems-biology models of LTD recently gained strong experimental support. First, in the same Journal of Neuroscience that published our paper on the Ca^{2+} dynamics model (Doi et al. 2005), IP_3 was found to increase slowly with a 100-msec time scale in Purkinje cell dendrites after parallel fiber stimulation (Okubo et al. 2004). Slow IP_3 increase, the key prediction of our model, was thus confirmed. Yet, we must note that the measurement was not for a single spine because of technical difficulties, and future high-spatial resolution experiments are expected to examine this prediction

more precisely. Second, very recently, George Augustine and his colleagues examined with us Ca^{2+} dose-response curves of Purkinje-cell LTD in a slice by systematically varying magnitudes and durations of the Ca^{2+} elevation, which was controlled by uncaging and simultaneously measuring Ca^{2+} (Tanaka et al. 2007). They demonstrated that LTD is a highly cooperative phenomena with large Hill coefficients, and suggested that the MAPK positive feedback loop leaky-integrates the incoming Ca^{2+} time course and determines whether to trigger the entire process of LTD in an all-or-nothing manner by comparing the leaky-integrated Ca^{2+} with its threshold for the bistable dynamics. Because the measurements of the postsynaptic currents were summed over roughly 30 spines and not shown for a single spine, the above suggestion is not yet conclusive, but one enigma regarding the stability of our memory might be nearly resolved in the following scenario. Bistability of nonlinear dynamics within the MAPK positive feedback loop guarantees memory *maintenance* in the first place, and cerebellar memory is *discrete* in its nature at the single-spine level.

5. Toward Manipulative Neuroscience

Ten years have not yet elapsed since the cerebellar-LTD MAPK positive-feedback-loop model was first published (Kuroda et al. 2001), before experiments firmly supported its essential proposition that the bistability of nonlinear dynamics is the elementary process of memory (Tanaka et al. 2007) (see section 4). This is in sharp contrast to the cerebellar internal model theory, for which two completely opposing experimental papers were published (Pasalar et al. 2006; Yamamoto et al. 2007), although 25 years have passed since its first proposal in a preliminary form (Tsukahara & Kawato 1982) (see section 3). One possible reason for this marked difference could be that LTD within a single spine is a much more small-scale and simpler phenomenon than learning of internal models in sensory-motor coordination as well as in cognitive function, which utilizes not only the cerebellum but also all of its loops with the cerebral cortex and other brain

regions. Or, some might even argue that the former theory is correct but the latter theory is wrong. I of course do not agree with this view but believe that the biggest difference between the two concepts is in the availability of experimental methodology that permits manipulation of essential information within a given system. In the LTD example within the molecular cellular biology domain, the time-course of Ca^{2+} concentration, the most important intracellular signal, can be directly manipulated by uncaging and directly measured by bioimaging techniques. In contrast, systems neuroscience does not possess any experimental technique for direct manipulation or control of information at the system level; information such as an error signal in motor command coordinates is carried by climbing fibers, or feedforward motor commands represented by simple spikes, in the case of cerebellar internal model theory. Anatomical ablation or electrocoagulation can destroy neural substrates but cannot manipulate information. Electrical stimulation may excite or suppress neurons indefinitely but cannot manipulate information such as the error signal or motor commands. Furthermore, in most cases at the system level, we do not even know how neural firing and its coherence represent information. Consequently, computational theories are essential to make the initial assumptions about what is represented in the brain and how it is neuronally represented.

Several decades ago, systems neuroscientists could get excited by finding a mere temporal correlation between neural firing rates or an fMRI signal, with some experimental parameters (e.g. attributes of sensory stimuli, movement parameters), or with some hypothetical cognitive aspects of the task performed by subjects. However, as explained in section 1, mere accumulation of this kind of correlation data does not lead to understanding the neural mechanism of any brain function, in other words, it does not lead to a rigorous science that explains cause and effect relationships. I recently heard the criticism from scientists in other disciplines that systems neuroscientists do not know what should be revealed before they can state that they ultimately understand the brain. Answering this criticism, I define

the ultimate goal of system neuroscience as follows. We can simultaneously measure the activities of all neurons in the brain, and we can freely change these activities experimentally. Thereby we can control the arbitrary information in the brain based on computational theories that explain how information is represented by neural activities, and the theories can predict the resulting changes in the organisms regarding their sensation, movements, emotions and thoughts. The current status of systems neuroscience is far from reaching this ultimate goal in all aspects of measurement, control, manipulation of information, and theory. However, regarding measurement of neuron and brain activities, much progress has been made, such as optical imaging of Ca^{2+} or voltage and many non-invasive brain activity measurement techniques. Regarding control of neuron activities, promising work in development includes the juxta-cellular clamp, the voltage clamp for simulating synaptic currents (dynamic clamp), and genetic engineering methods of using channelrhodopsin-2 and its photostimulation (Boyden et al. 2005). For simpler organisms such as *C-elegans*, simultaneous measurement and control of all neural activities might be achieved within ten years. However, at least for several decades, it will be very difficult for mammals *in vivo*, and it seems almost impossible for humans unless new physical principles for observation and control are invented.

Much progress has been made with respect to close interactions between computational theories and neurophysiological and neuroimaging experiments. Many experiments are nowadays designed for proving or disproving predictions of computational models, or at least motivated by them. In the new experimental paradigms, which are named “computational-model-based neurophysiology and computational-model-based neuroimaging”, interactions between theories and experimental designs are even more intimate. Here, animal or human subjects are given sensory stimuli and a series of reward/penalty signals and asked to execute some tasks and conduct movements. Computational models such as the cerebellar internal model theory or basal-ganglia reinforcement

learning theory are employed to quantitatively simulate subjects' behaviors while the models are given exactly the same sensory stimuli and series of reward/penalty signals for the subjects. First of all, we expect that computational models fairly well reproduce subjects' behaviors. Then, within each computational model, there exist some hypothetical computational variables such as the error signal or the feedforward motor command in the case of the cerebellar internal model theory, or the reward prediction error or value functions in the basal-ganglia reinforcement learning theory example. Each of these hypothetical variables can be used as an explanatory variable in correlation analysis with an fMRI signal or firing frequency of neurons. By using this correlation analysis, researchers can make statements such as "climbing fiber inputs may represent error signals in motor command coordinates" (Kobayashi et al. 1998) or "putamen neurons may encode action and state dependent reward prediction..." (Samejima et al. 2005, Haruno & Kawato 2006a) "while the caudate nucleus may encode reward-prediction error" (Haruno & Kawato 2006b). Our group as well as other groups have recently published a fair amount along this experimental paradigm (Imamizu et al. 2000; Imamizu et al. 2003; Haruno et al. 2004; Tanaka et al. 2004; Samejima et al. 2005; Haruno & Kawato 2006a, 2006b). Computational-model-based neuroscience is a major advance over the classical approach of simply correlating neural or brain activities with stimulus attributes, movement parameters or some conceptual aspects of the task. If only the former two had been utilized as explanatory variables, cognitive functions remote from sensory and motor interfaces of the brain would never have been directly studied. An ad hoc conceptual aspect of the task could be informative in giving some clues to brain mechanisms, but this is far from quantitative understanding or revealing cause and effect relationships. A computational-model-based approach is attractive first because it is a quantitative theory, which can be disproved because it makes testable predictions. Second, it tries to reproduce behaviors as well as neural or brain activities. Third, computational models try to explain the whole sequence of information processing necessary for some task, while ad hoc cognitive hypotheses tend to explain just a fragmentary aspect within the

whole processing sequence. However, we tend to be frustrated by the difficulties of computational models and this approach's weakness in demonstrating cause and effect relationships, even after advocating this approach for 10 years.

The first difficulty is in computational models. We still have not yet developed a powerful enough computational model to simultaneously explain a large variety of behaviors and whole-brain activities. Thus, in many cases, only a small part of the behavioral data can be reproduced by a single model. In this case, many models could equally well reproduce experimental data, and thus it is difficult to select one best model. The second difficulty is the likely complicated relationship between information and its carrier, such as neural firing rates and coherence or fMRI signals, due to possible population coding, sparse coding, or temporal coding. The third and most critical difficulty is that what we can demonstrate in computational-model-based neuroscience is still just the temporal correlation between hypothetical computational variables and neural/brain activities. We can never prove cause and effect relationships, no matter how high the correlation coefficient is, how much of the behavioral data the model explains, or how deeply the theory goes into the core of cognition.

Consequently, among the four key factors necessary for ultimate systems neuroscience—(1) measurement and (2) control of neural/brain activity, (3) manipulation of information, and (4) computational theories—we have made significant progress or are about to make major improvements on all the factors except the manipulation of information. The manipulation of information is theoretically and technically the most difficult first because we do not know how information is represented, second because there exist complicated relationships between neural/brain activities and represented information, and third because simultaneous control of neural/brain activities from many neurons and in many areas is necessary but extremely difficult. However, without the manipulation of information, we can never prove cause and effect relationships at the system level.

Based on these reflections on the computational-model-based approach, we have started to advocate and promote a new approach named “manipulative neuroscience”, where we aim to manipulate the information even for human subjects. Technically, this is based on computational theories, a brain-network interface, and non-invasive decoding algorithms. Masa-aki Sato and his colleagues at ATR Computational Neuroscience Laboratories (ATR-CNS) have been developing a “brain-network interface” based on a hierarchical, variational Bayesian technique to combine information from fMRI and magnetoencephalography ([Sato et al. 2004](#)). They succeeded in estimating brain activities with spatial resolution of a few millimeters and millisecond-level temporal resolution for various domains such as visual perception, visual feature attention, and voluntary finger movements. In collaboration with the Shimazu company, we aim to develop within 10 years a portable and wireless combined EEG/NIRS (electroencephalography/near infrared spectroscopy)-based Bayesian estimator for millimeter and millisecond accuracy. “Brain-network interface” is a term we have created for this project, and it is like a brain-machine interface or a brain-computer interface. A brain-network interface non-invasively estimates brain activity by solving the inverse problem, and it also estimates neural activities and reconstructs represented information. Accordingly, it is not a brain-machine interface because it is non-invasive, and it is not a brain-computer interface because it does not require extensive user training since it decodes information. Researchers at ATR-CNS have already succeeded, for example, in estimating the velocity of wrist movements from single-trial data without subject training. Furthermore, Honda Research Institute of Japan in collaboration with ATR-CNS demonstrated real-time control of a robot hand by decoding three motor primitives (rock-paper-scissors, as in the children’s game) from the fMRI data of a subject’s primary motor cortex activity ([Press Release 2006](#)). This was based on the machine learning algorithms previously developed by [Kamitani and Tong \(2005, 2006\)](#) for decoding the attributes of visual stimuli from fMRI data.

Manipulative neuroscience can be achieved by combining computational theories, brain-network interfaces, and non-invasive decoding algorithms as follows. Human subjects execute a task. We assume that we have already developed a computational theory that postulates that specified neural networks solve necessary computational problems and that some information is represented in a specified way by brain activities within a certain area. During task execution, this information is reconstructed by a brain-network interface and decoding algorithm in real time, and it is then fed back to the subject in any sensory modality or even by transcranial magnetic or electrical stimulation. Then, based on a prediction by the computational model, some manipulation is applied to the extracted information. Predicted changes in brain activities and behaviors are examined experimentally. Although we discussed a human example with non-invasive measurements, the same idea can be applied to animals with neural recordings. In that case, information is decoded from multiple neural activities and then manipulated and fed back to the animal by any available method.

Having defined manipulative neuroscience in this way, it becomes apparent that almost all systems-neuroscience experiments try to change or at least influence information representations in the brain by giving sensory stimuli, assigning reward/penalty, imposing tasks, requiring movements, and so on, and then they examine changes in behavior and cognition as well as neural/brain activities. Computational-model-based neuroscience further employs a computational model to reproduce behaviors and correlate its hypothetical variable with neural/brain activity, which should somehow represent the relevant information. The new approach also utilizes a computational model but in prediction rather than correlation, and it directly manipulates information rather than attempts to indirectly influence information. If subjects' behavior and neural/brain activity change as predicted by a computational model when the extracted information is manipulated while guided by the computational theory, we are in a much better position to state that the model is experimentally supported and that

the hypothetical information has a causal relationship with the altered behavior and neural/brain activity. This is because the information and the neural/brain activities that carry it are directly manipulated in the new paradigm, and this manipulation's effects are compared with model predictions. This level of understanding has been very rare in traditional systems neuroscience or computational-model-based neuroscience. We are very aware of the difficulty and risks of the new approach but at the same time believe that this is probably the only persuasive way to fully understand brain functions.

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Figure Legends

Figure 1

Demonstrations of 14 different tasks by the ERATO humanoid robot DB

Figure 2

New humanoid robot called CB (Computational Brain)

Figure 3

Biologically motivated biped locomotion of three humanoid robots

(a) DB-chan with learning from demonstration and a nonlinear dynamical system for motor primitives ([Nakanishi et al. 2004](#))

(b) HOAP2 with central pattern generators and reinforcement learning algorithms ([Matsubara et al. 2006](#))

(c) CB with coupled oscillators that are phase regulated by reaction forces from the floor ([Morimoto et al. 2006](#))

Figure 4

(a) General feedback-error-learning model.

(b) Cerebellar feedback-error-learning model ([Kawato 1999](#)). The ‘controlled object’ is a physical entity that needs to be controlled by the central nervous system, such as the eyes, hands, legs or torso.

Figure 5

Signal transduction model of cerebellar LTD

(AA: arachidonic acid; CF: climbing fibers; ER: endoplasmic reticulum; Glu: glutamate; Gq: G-proteins; IP₃: inositol 1,4,5-triphosphate; IP₃Rs: IP₃ receptors; MAP: mitogen-activated protein; MEK: MAP/extracellular signal-regulated kinase; mGluRs: metabotropic glutamate receptors; NO: nitric oxide; PF: parallel fibers; PKC: protein kinase C; PKG: cGMP-dependent protein kinase; PP2A: protein phosphatase 2A; PLA2: cytosolic phospholipase A2; PLC β : phospholipase C β ; sGC: soluble guanylyl cyclase; VGCCs: voltage-gated calcium channels)

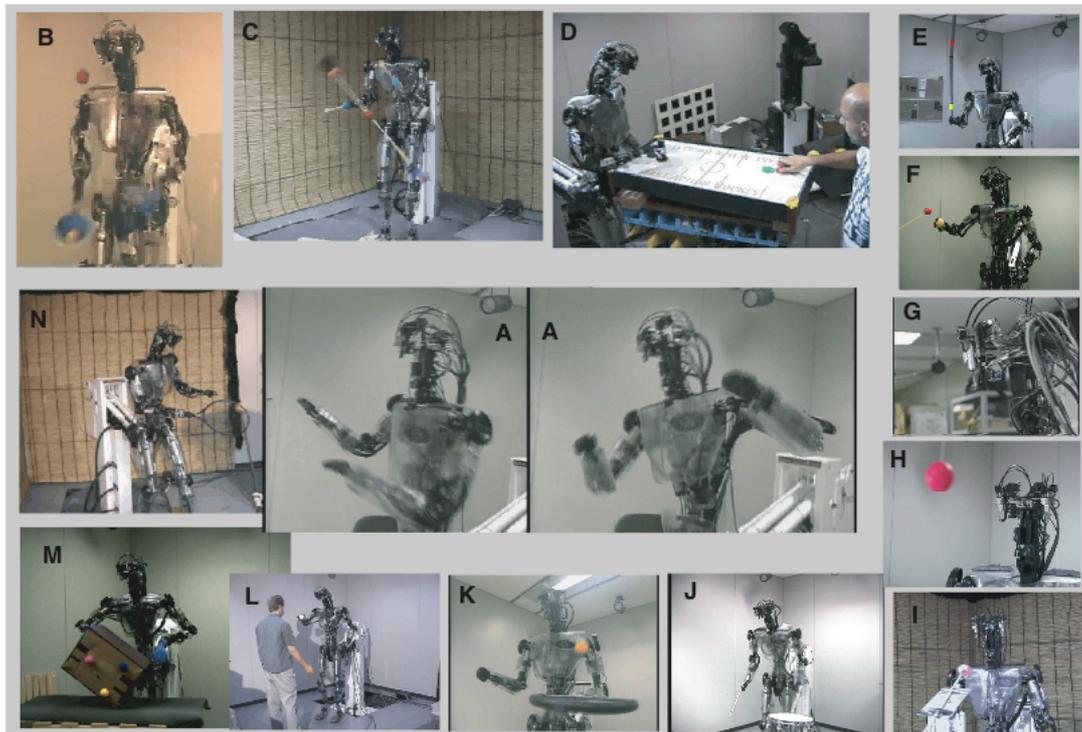


Figure 1



Figure 2

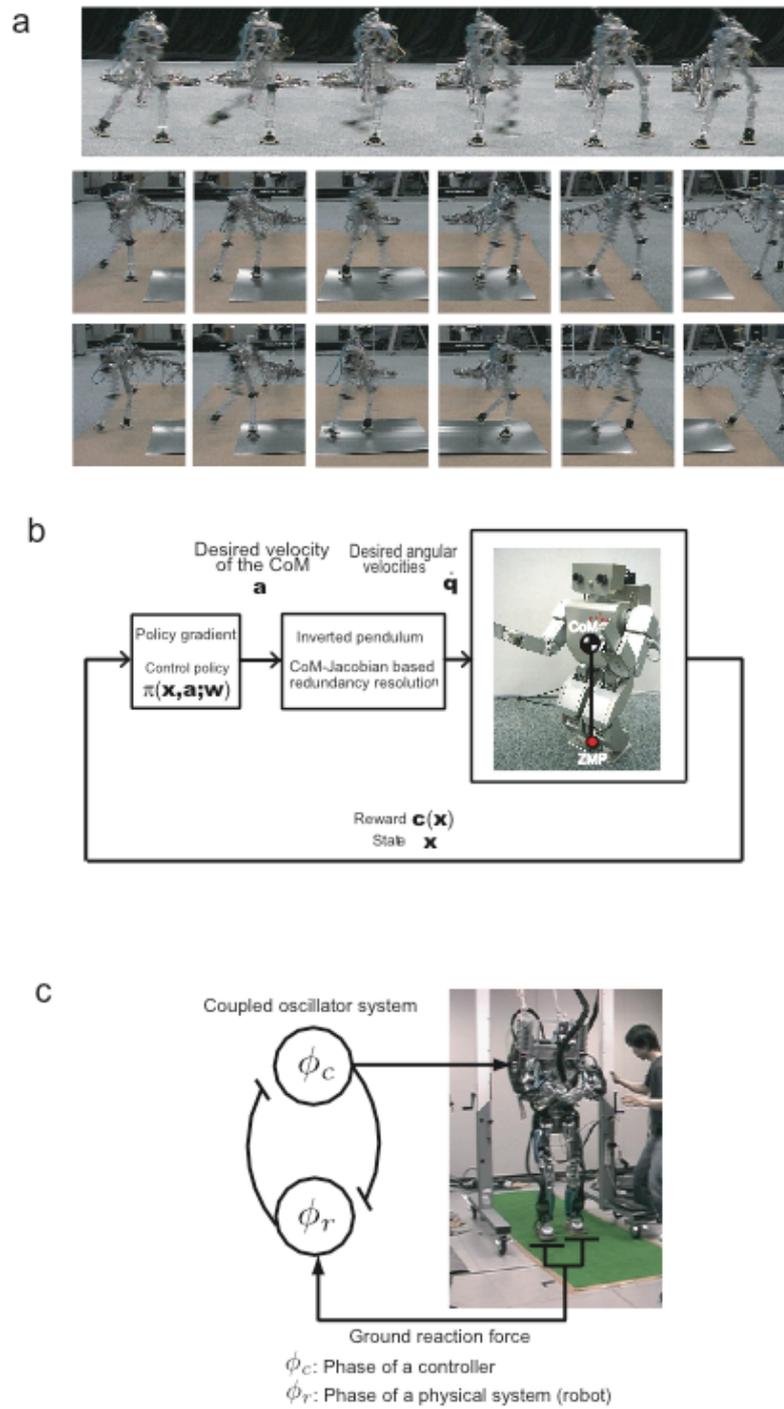


Figure 3

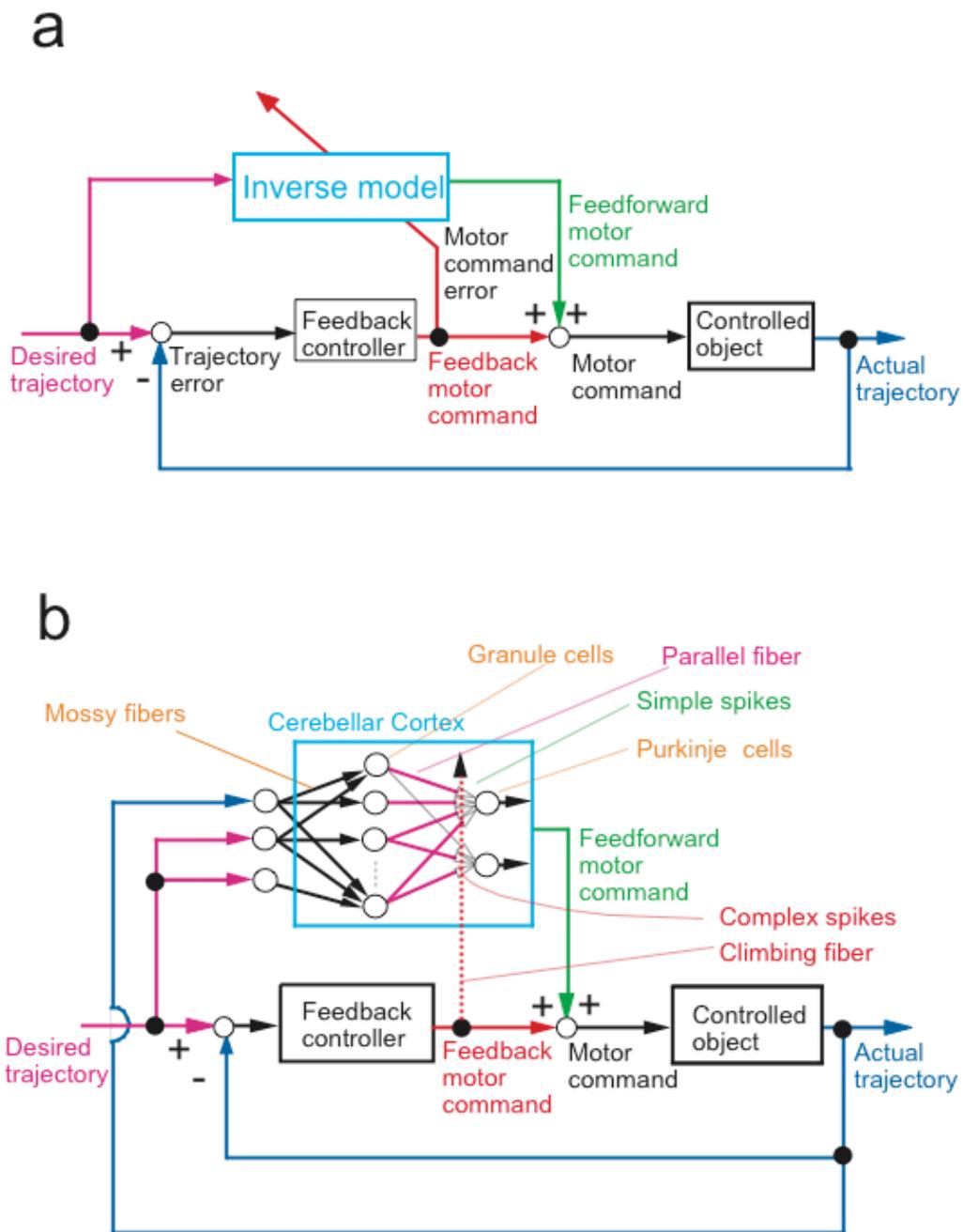


Figure 4

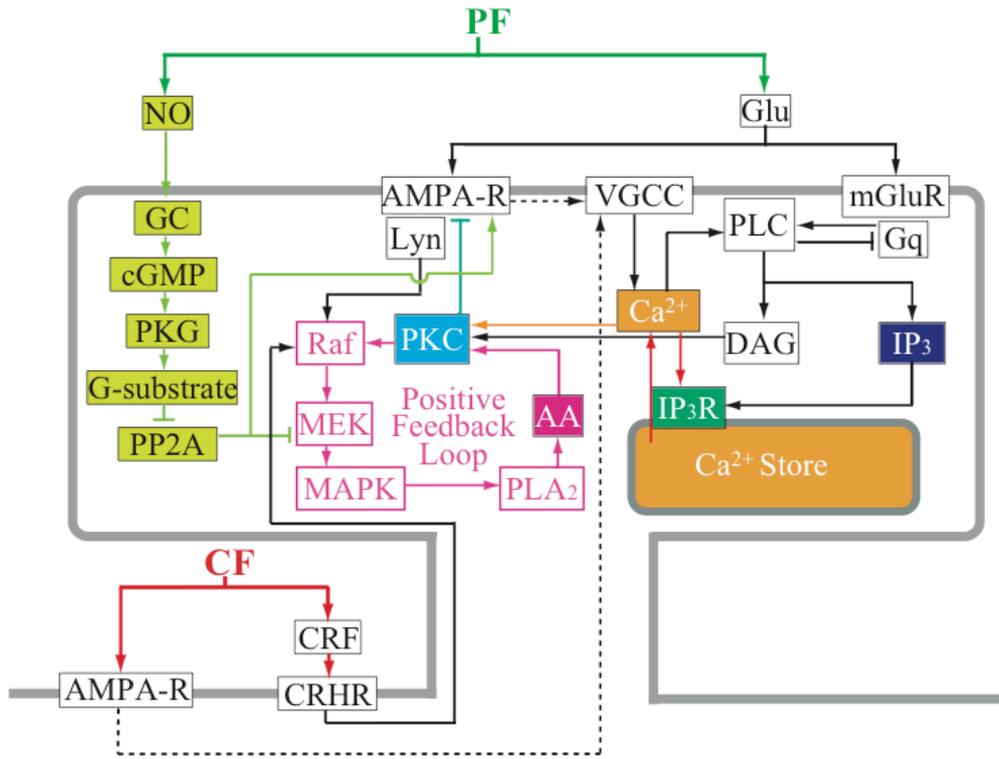


Figure 5