Cerebellar internal model, Purkinje cell LTD as supervised learning rule supported by bioinformatics, and control of learning degree-of-freedom by electrical coupling in inferior Olive nucleus

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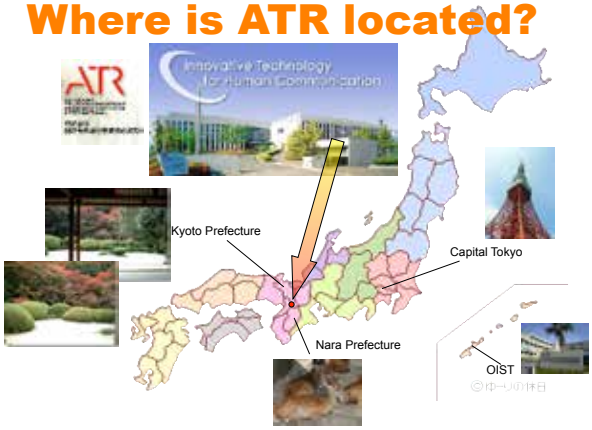
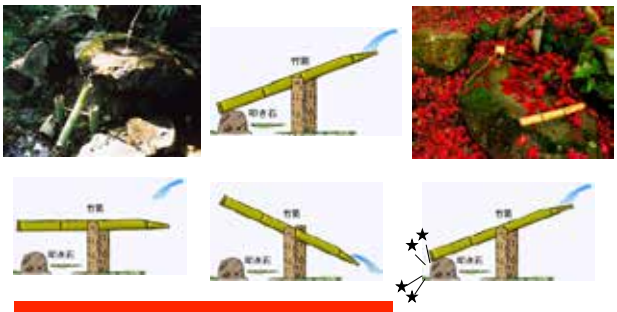
Discovery Channel

Where is ATR located?

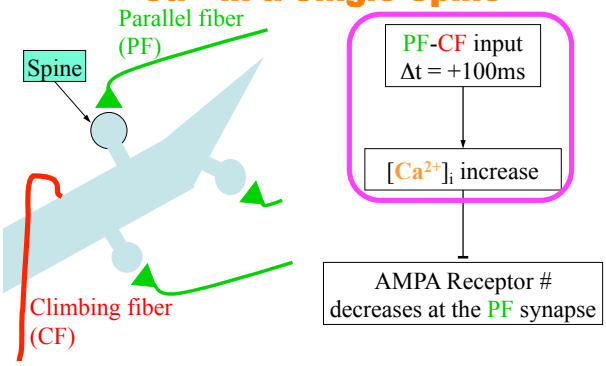


Shishi Odoshi (Deer Scaring)

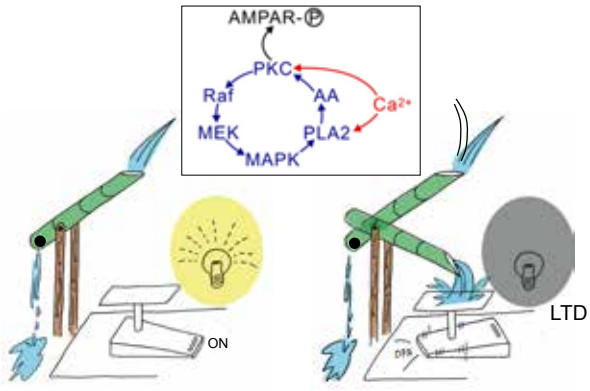


Kill Bill directed by Quentin Tarantino

Cerebellar Purkinje-cell Long-Term Depression is controlled by Ca^{2+} in a Single Spine



0-or-1 LTD is like Shishi Odoshi



Understanding the Brain by Creating the Brain

- Robots and computers are much inferior to humans.
- This demonstrates that we do not fully understand brain functions.
- Only if we try to create a brain, we can understand information processing in the brain.
- Creating only a brain does not make sense, and a body and its environment are essential.

Computational Neuroscience

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 brain, essentially in the same principle.

First!

Neuroscience

Schaal S, Sternad D, Osu R, Kawato M: Rhythmic arm movement is not discrete. *Nature Neuroscience*, **7** 1137-1144 (2004).
Nakanishi J, Morimoto J, Endo G, Cheng G, Schaal S, Kawato M: Learning from demonstration and adaptation of biped locomotion, *J. Robotics and Autonomous Systems*, **47** 79-91 (2004).

Object Recognition on a Humanoid Robot - Alesh Ude

Based on the capabilities of a humanoid visual system with foveated vision, we developed an object recognition system that integrates visuomotor processes and foveation to achieve reliable recognition. Training is done in interaction with the teacher. Self acquisition of multiple views by reaching, grasping and manipulation, explored also.

Active object recognition

Training the classifier

Humanoid Posture Control on Unstable Terrain - Sang-Ho Hyon

Brain-like control without vision or force feedback from foot

Unpredictable Incline

One-foot balance on unknown and unstable object

Cerebellum and Cerebral Cortex

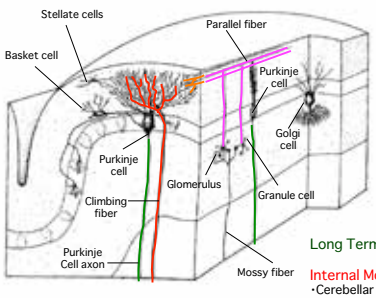
Lateral View

Medial View

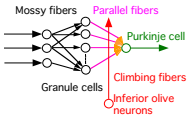
Bottom View

	Cerebellum		Cerebral Cortex
Weight	130	1 to 10	1,300g
Surface Area	50,000mm^2	1 to 2	80,000mm^2
Number of Neurons	10^{11}	>	10^{11}
Expansion from Average Primates	2.8	~	3.2

Neural Circuit, Synaptic Plasticity and Models of Cerebellum



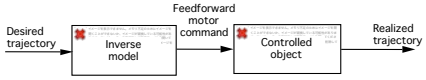
Marr-Albus-Ito (~1970)
Climbing fiber inputs as teacher (error signal)
Parallel-fiber-Purkinje-cell synapse changes its efficacy



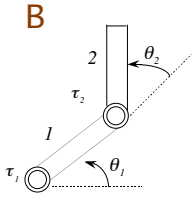
Long Term Depression, LTP, RP (~1982)

Internal Model Theory (~1984)
- Cerebellar cortex acquires internal models by learning
- Climbing fiber represents motor command error

A



B

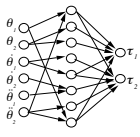


C

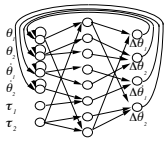
$$\tau_1 = (M_2L_1^2 + 2M_2L_1S_2\cos\theta_2 + I_1 + I_2)\ddot{\theta}_1 + (M_2L_1S_2\cos\theta_2 + I_2)\ddot{\theta}_2 - M_2L_1S_2(2\dot{\theta}_1 + \dot{\theta}_2)\dot{\theta}_2\sin\theta_2 + B_1\dot{\theta}_1$$

$$\tau_2 = (M_2L_1S_2\cos\theta_2 + I_2)\ddot{\theta}_1 + I_2\ddot{\theta}_2 + M_2L_1S_2\dot{\theta}_1^2\sin\theta_2 + B_2\dot{\theta}_2$$

Inverse Dynamics Model



Forward Dynamics Model



Cerebellar Internal Model Theory

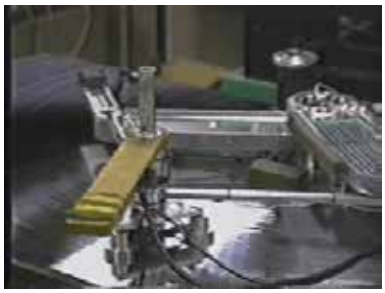
- The cerebellum consists of many modules (micro-zones) which perform different input-output transformations.
- Synaptic weights change and different transformations can be learned.
- Supervised learning guided by an error signal
- Different modules acquire internal models of controlled objects, tools, other brains, etc.

Role and CBLM

Neuroscience: Tilting Against a Major Theory of Movement Control

Stiffness Measurement by PFM

Hiroaki Gomi



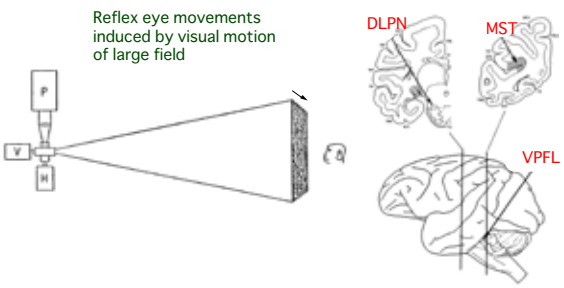
Mechanical perturbations in 8 directions were given during point-to-point movement and reaction forces were measured. Then stiffness and viscosity were estimated.

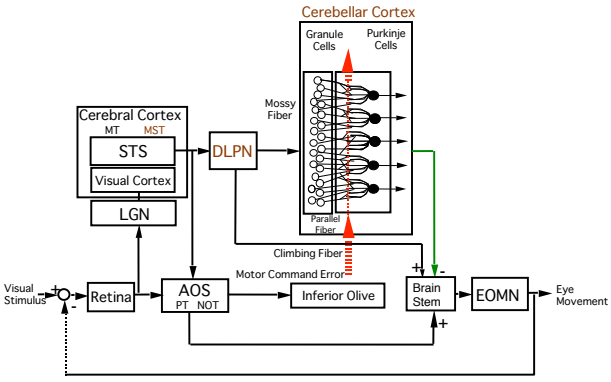
Jun Nakanishi and Stefan Schaal : Feedback error learning and nonlinear adaptive control. *Neural Networks*, **17,** 1453-1451 (2004)

Ocular Following Responses and Related Brain Regions

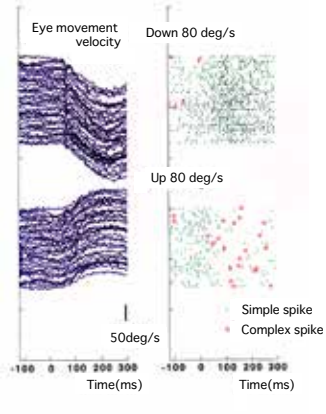
Experiments by Kawano, Shidara, Takemura, Kobayashi et al. (ETL at Tsukuba)

Reflex eye movements induced by visual motion of large field





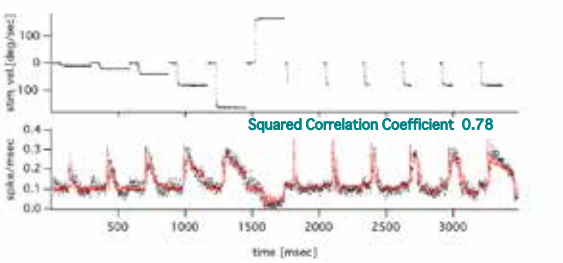
Direction Selectivity of Simple and Complex Spikes



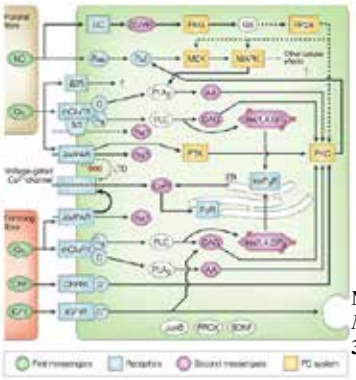
Reconstruction of Firing Frequency for Different Stimulus Speeds and Duration

$f(t)$: firing frequency $\theta(t)$: eye movement

$$f(t) = M\ddot{\theta}(t+\delta) + B\dot{\theta}(t+\delta) + K\theta(t+\delta) + f_{bias}$$

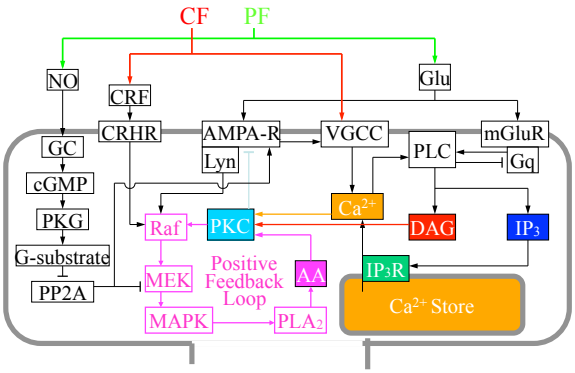


Signaling Networks in Cerebellar LTD



Masao Ito, *Nat Rev Neurosci* **3**, 896-902 (2002)

Model of Cerebellar LTD

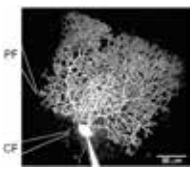


Kuroda S, Schweighofer N, Kawato M: Exploration of signal transduction pathways in cerebellar long-term depression by kinetic simulation. *Journal of Neuroscience*, **21** 5693-5702 (2001).

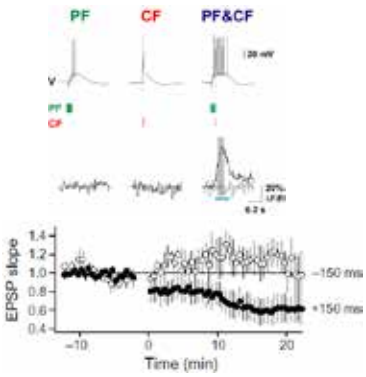
Ca^{2+} Dynamics Model for Coherent Understanding of Diverse and Confusing Experimental Data on LTD Time Window

- Cerebellar learning theories require LTD time window where CF is delayed with respect to PF for 100-200 msec.
- Several experimental supports to this prediction
- Strong bundle stimulation to PF alone, uncaging of Ca^{2+} or IP_3 can induce LTD without PF-CF conjunction or time delay.
- Some experiments even reported CF preceding PF is optimal.
- Serious doubts and criticisms on LTD as a cellular basis of cerebellar supervised learning

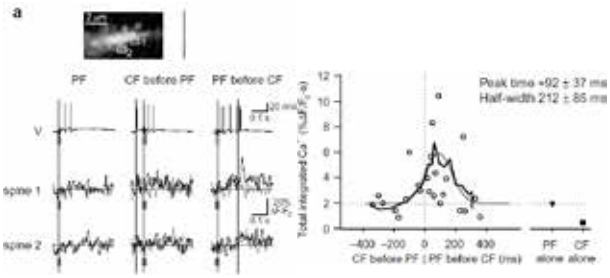
Ca^{2+} Imaging in Purkinje-cell Spines



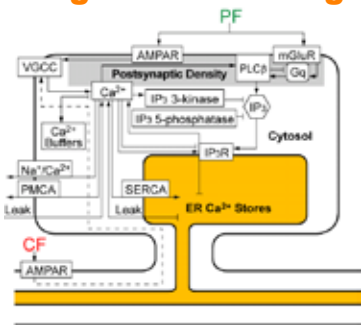
Wang *et al.*, *Nat Neurosci* **3**, 1266-1273 (2000)



Temporal Window of Spike Timing Dependent Plasticity of LTD



Block Diagram of Ca^{2+} Signaling



PF input → Ca^{2+} influx & IP_3 production
CF input → Ca^{2+} influx

Doi T, Kuroda S, Michikawa T, Kawato M: IP3-dependent Ca2+ threshold dynamics detect spike-timing in cerebellar Purkinje Cells. *Journal of Neuroscience*, **25**, 950-961 (2005).

Formulation of Biochemical Reaction

(1) Binding Reaction

$$A + B \underset{k_b}{\overset{k_f}{\rightleftharpoons}} AB$$

$$d[AB]/dt = + k_f[A][B] - k_b[AB]$$

Dissociation Constant, $K_d = k_b / k_f$: equilibrium point
Time Constant, $\tau = 1/(k_f + k_b)$: speed for convergence

Formulation of Biochemical Reaction

(1) Binding Reaction

$$A + B \underset{k_b}{\overset{k_f}{\rightleftharpoons}} AB$$

(2) Enzymatic Reaction (Michaelis-Menten)

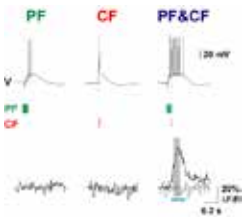
$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_{cat}} E + P$$

$$K_m = \frac{k_{-1} + k_{cat}}{k_1}$$

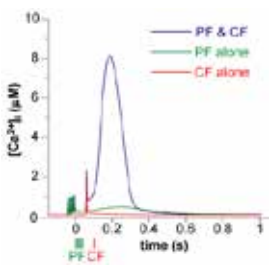
E: Enzyme, S: Substrate, P: Product

Supralinear Ca^{2+} signal appears when PF is followed by CF

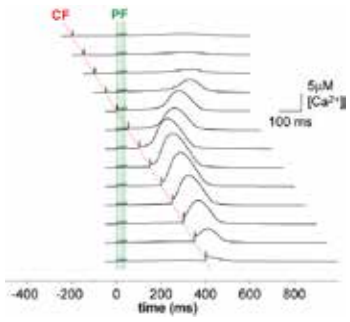
Ca^{2+} Imaging
Wang *et al*., (2000) *Nat Neurosci*



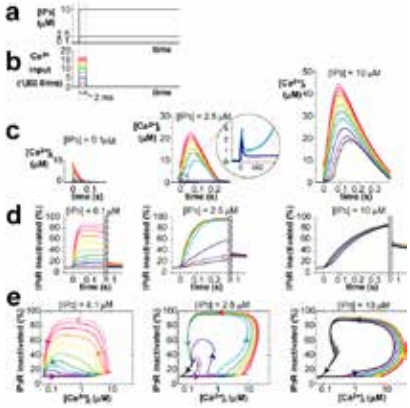
Simulation



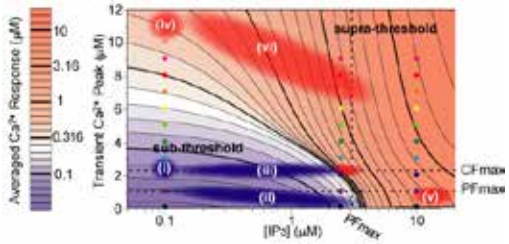
Ca^{2+} Signaling is determined by Timing of PF and CF Inputs



IP_3-dependent Ca^{2+} Dynamics

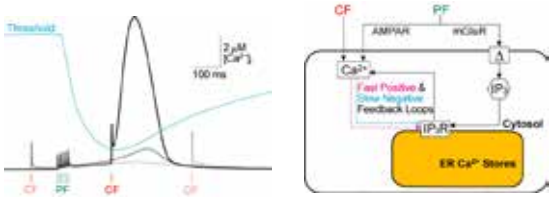


Ca^{2+} Dynamics and LTD Experiments



(i) CF alone does not induce LTD
(ii) PF alone does not induce LTD
(iii) Conjunctive PF-CF induces LTD
(iv) Ca^{2+} uncaging induces LTD
(v) IP_3 uncaging induces LTD
(vi) Massive PF stimulus induces LTD

Schematic Model of Timing-detection



- Delay in slow PF metabotropic pathway compared with fast CF electrical pathway as a mechanism for timing-detection
- Fast positive feedback loop generates large Ca^{2+} signals.
- Slow negative feedback loop shuts down the Ca^{2+} increase.

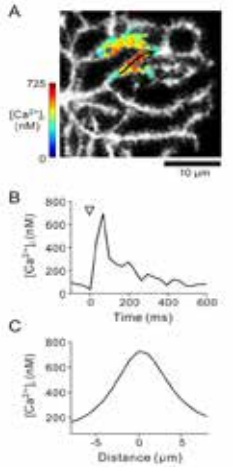
Experimental tests of Kuroda et al. positive feedback model

Collaborations with George Augustine and Keiko Tanaka and their colleagues at Duke University under De Schutter HFSP

A positive feedback signal transduction loop determines timing of cerebellar long-term depression.Tanaka K, Augustine GJ.Neuron. 2008 Aug 28;59(4): 608-20.

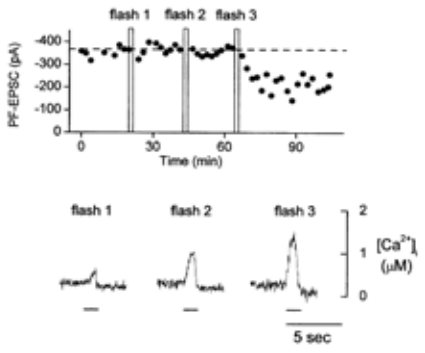
Ca2+ requirements for cerebellar long-term synaptic depression: role for a postsynaptic leaky integrator.Tanaka K, Khiroug L, Santamaria F, Doi T, Ogasawara H, Ellis-Davies GC, Kawato M, Augustine GJ.Neuron. 2007 Jun 7;54(5):787-800.

Un-caging and imaging of Ca^{2+}, PF stimulation and Purkinje cell voltage clamp
Keiko Tanaka, George Augustine, Tomokazu Doi et al.
Neuron, **54**, 787-800, 2007

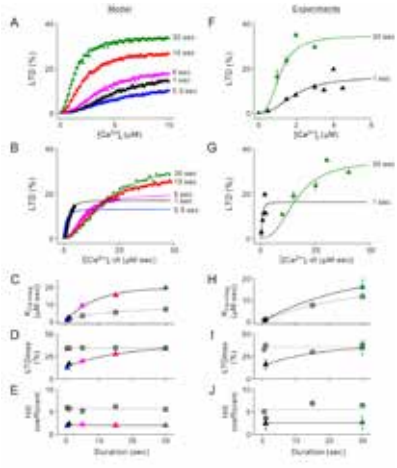


- LTD is suggested 0 or 1 at single synapse
- Leaky integration of Ca^{2+} by MAPK positive feedback loop and resulting bistability

Ca^{2+} threshold for LTD induction



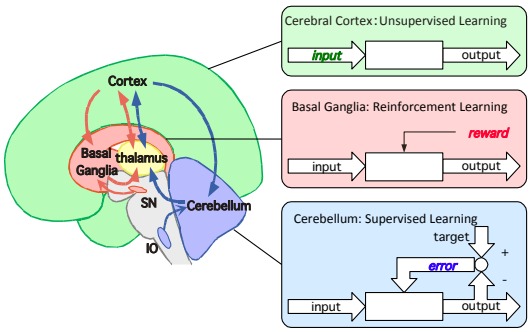
Experimental confirmation that dynamic Ca^{2+} threshold depends on MAPK positive feedback loop



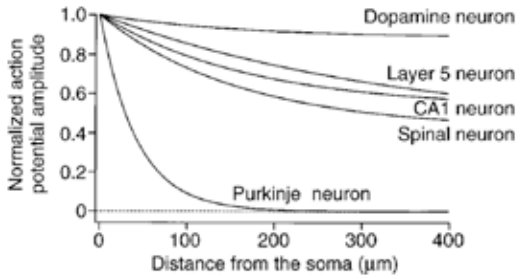
All or Nothing Nature of Single Synapse LTD

- Each PF-PC synapse on a spine undergoes LTD in all-or-none manner
  - Cooperativity (large Hill coefficients)
  - Constant maximum LTD
  - Reproduction of experimental data by bistable dynamics

Specialization by Learning Algorithms (Doya K, *Neural Networks* 1999)



Spruston Lecture and Hebbian Rule



Hebbian synaptic plasticity rule … *When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased.*

Purkinje-cell LTD is **not** anti-Hebbian but Supervised

- No backpropagation of somatic action potentials (too much dendritic branching); output does not matter; different from statistical or reinforcement learning rule; not Hebbian (Spruston OCNC Lecture, Stuart et al. 1994, Vetter et al. 2001)
- No functional NMDA receptors in adults
- STDP of 100 msec order
- Supervised learning with the Ca^{2+} error signal carried by decisive climbing fiber