Supplementary notes for the computational model.

Methods: Equations for Cerebellum model

Inferior Olive

Here, we modeled the inferior olive (IO) neuron as a single-compartment unit. Our model was a slight modification of that in (1). We arranged the IO neurons in a linear chain connected by gap junctions. The i^{th} neuron is described by the ODE:

$$C_m \frac{dV_i}{dt} = I_{app} + I_{noise}(t) - I_L - I_{Na} - I_K - I_{Ca} - I_h + \frac{R(V_{i+1} + V_{i-1} - 2V_i)}{(1 + k * s_{DCN,i})},$$

where C_m($=1\ \mu$F) is the membrane capacitance, R ($= 0.4\ M\Omega$) is the gap junction resistance, k (=20) is the synaptic weight, and s_{DCN} is the GABAergeic gating variable for the DCN. The dynamics of s_{DCN} are described in the DCN section below. I_{app}, I_{noise}, I_L, I_{Na}, I_K, I_{Ca}, I_h are the membrane currents for baseline background current, white noise current, leak current, sodium current, potassium current, T-type calcium current, and HCN current respectively. I_{app} was informed by previous literature(*1*) and was uniformly distributed from -2 to $-1\ nA$. Here, I_{noise} was modeled as Gaussian white noise with standard deviation of $1.75\ nA$ and was randomly generated every time step of the simulation.

The active currents are described by the following equations:

$$I_L = g_l(V - E_L)$$
$$I_{Na} = g_{Na} m_\infty(V)^3 h(V - E_{Na})$$
$$I_K = g_K n^4(V - E_K)$$
$$I_{Ca} = g_{Ca} k^3 l(V - E_{Ca})$$
$$I_h = g_h q(V - E_h)$$

where g_l, g_{Na}, g_k, g_{Ca}, g_h, are the maximum conductance of the corresponding currents. The gating variables h, n, k, l, q are defined by the following ordinary differential equations:

$$\frac{dh}{dt} = \frac{h_\infty(V) - h}{\tau_h(V)}$$
$$\frac{dn}{dt} = \frac{n_\infty(V) - n}{\tau_n(V)}$$
$$\frac{dk}{dt} = \frac{k_\infty(V) - k}{\tau_k}$$
$$\frac{dl}{dt} = \frac{l_\infty(V) - l}{\tau_l(V)}$$
$$\frac{dq}{dt} = \frac{q_\infty(V) - h}{\tau_q(V)}$$

The sodium channel's gating functions obey the following equations:

$$m_\infty(V) = \frac{a_m(V)}{a_m(V) + b_m(V)}$$
$$a_m(V) = \frac{0.1(V+41)}{1 - e^{\frac{-(V+41)}{10}}}$$
$$b_m(V) = 9e^{\frac{-(V+66)}{20}}$$
$$h_\infty(V) = \frac{a_h(V)}{a_h(V) + b_h(V)}$$
$$\tau_h(V) = \frac{170}{a_h(V) + b_h(V)}$$
$$a_h(V) = 5 * e^{\frac{-(V+66)}{20}}$$
$$b_h(V) = \frac{V+50}{1 - e^{\frac{-(V+50)}{10}}}$$

The potassium channel's gating functions are defined by the following equations:

$$a_n(V) = \frac{V+41}{1 - e^{\frac{-(V+41)}{10}}}$$
$$b_n(V) = 12.5e^{\frac{-(V+51)}{80}}$$
$$n_\infty(V) = \frac{a_n(V)}{a_n(V) + b_n(V)}$$
$$\tau_n(V) = \frac{5}{a_n(V) + b_n(V)}$$

The calcium channel's gating functions are given by the following equations:

$$k_\infty(V) = \frac{1}{1 + e^{\frac{-(v+61)}{4.2}}}$$
$$\tau_k = 5$$
$$l_\infty(V) = \frac{1}{1 + e^{\frac{-(V+85.5)}{8.5}}}$$
$$\tau_l(V) = 35 + \frac{20e^{\frac{V+160}{30}}}{1 + e^{\frac{V+84}{7.3}}}$$

The H-Current channel's gating functions are described as the following equations:

$$q_\infty(V) = \frac{1}{1 + e^{\frac{V+75}{5.5}}}$$
$$\tau_q(V) = \frac{1}{e^{-(.086V+14)} + e^{(.07V-1.87)}}$$

The driving potentials for each ion were set as follows:

$$E_L = -70 \text{ mV}$$
$$E_{Na} = +55 \text{ mV}$$
$$E_K = -75 \text{ mV}$$
$$E_{Ca} = +120 \text{ mV}$$
$$E_H = -43 \text{ mV}$$

The maximal conductance for each channel was slightly modified from (1) to account for the single-compartment model. These values correspond to healthy (non-harmaline) IO neurons. Where noted, we modulated the values of g_{Ca} as a function of harmaline.

$$g_L = 0.1\ \mu\text{S}$$
$$g_{Na} = 70\ \mu\text{S}$$
$$g_K = 18\ \mu\text{S}$$
$$g_{Ca} = 0.33\ \mu\text{S}$$
$$g_H = 0.66\ \mu\text{S}$$

Here, s_{IO} denotes the gating variable for the IO synapse (also referred to as the climbing fiber).

$$\frac{ds_{IO}}{dt} = \frac{1 + \tanh(V + 20) - s_{IO}}{\tau_{cf}}$$

The time constant was chosen to be $\tau_{cf} = 5\ msec$. Here, $1 + \tanh$ represents a continuous version of a delta spike. If the voltage passes above $-20\ mV$, the IO is considered to have fired a spike.

Purkinje Cell

In order to reduce computational complexity and minimize simulation time, we modeled the Purkinje cell as a two-compartment model with a somatic compartment and a proximal dendritic compartment. Because we were interested in complex spikes induced by climbing fiber activation, we simplified the parallel fiber input as a constant input I_{app}. Given the necessity of calcium dynamics for generating complex spikes, we also incorporated calcium dynamics and calcium ion diffusion.

Voltage Dynamics

The voltage dynamics of the dendritic and somatic compartments were governed by the following equations:

$$\begin{aligned} C_s \frac{dV_s}{dt} = \quad & I_{app} + I_{CF,s} - I_{L,s} - I_{Na} - I_K^{\text{slow}} - I_K^{\text{mid}} - I_K^{\text{fast}} \\ - \quad & I_{Ca}^{\text{PQ}} - I_{KCa}^{\text{BK}} - \frac{V_s - V_d}{R} \\ C_d \frac{dV_d}{dt} = \quad & I_{app} + I_{CF,d} - I_{L,d} - I_{Ca}^{\text{PQ}} - \text{I}_{KCa}^{\text{BK}} - \frac{V_d - V_s}{R} \end{aligned}$$

where $C_s(= 1\ nF)$ is the somatic membrane capacitance, $C_d(= 12\ nF)$ is the dendritic membrane capacitance, and R $(= 4\ M\Omega)$ is axial resistance. We set the applied currents I_{app} to $.75\ nA$, representing the average background synaptic current from the parallel fibers. All Is are membrane currents explained as follows.

We modeled the climbing fiber synapses as a simple current-based synapses. The synaptic currents are given by

$$\begin{aligned} I_{CF,s,i} &= \left(g_{IO,PC} + 3dis\right)s_{IO,i} + 3dis\left(s_{IO,i-1} + s_{IO,i-1}\right) \\ I_{CF,d,i} &= dend * \left(\left(g_{IO,PC} + 3dis\right)s_{IO,i} + 3dis\left(s_{IO,i-1} + s_{IO,i-1}\right)\right) \end{aligned}$$

We set $g_{IO,PC} = 1\ nA$. We used dis to represent the overgrowth of adjacent climbing fibers, as well as the increased innervation of climbing fibers onto the Purkinje cell distal dendritic tree (2). Here, we let dis represent the increasing the synaptic weights for the pathological connections. For healthy cerebella, $dis = 0$, while $dis = 1$ represented unhealthy cerebella afflicted with climbing fiber overgrowth. Where noted, dis can vary between 1 and 0. The relative strength of dendritic input to somatic input was greater; accordingly, we set $dend = 8$

The leak current was derived from unpublished data from Dr. David Friel's lab, and was described as:

$$I_L(V) = \quad g_L f(V + 12.5)$$
$$f(V) = \quad 0.4916 \frac{(V + 36.587)}{1 + e^{-.13(V+33.179)}}$$
$$+.046346 \frac{V + 57.528}{2.1}$$

We used a sodium current based on the model by Dr. De Schutter and Bower (3), with slight adjustments to enhance the dominance of the fast channel. Additionally, since Dr. De Schutter's resting potential differed from ours, we adjusted the voltage accordingly. The final model included a fast-activating sodium channel (labeled **F**) and a persistent sodium channel (labeled **P**). The sodium current is given by the equation:

$$I_{Na} = I_{Na,F} + I_{Na,P}$$
$$= g_{Na} \frac{15000 m_F^3 h_F + 10 m_P^3}{7510} (V - E_{Na})$$

Here, the gating kinetics are given by:

$$\frac{dm_F}{dt} = a m_F (V + 10)(1 - m_F) - b m_F (m_F)$$
$$\frac{dh_F}{dt} = a h_F (V + 10)(1 - h_F) - b h_F (h_F)$$
$$\frac{dm_P}{dt} = a m_P (V + 10)(1 - m_P) - b m_F (m_P)$$

The gating functions are given by:

$$a m_F(V) = \frac{35}{e^{\frac{-(V+5)}{10}}}$$
$$b m_F(V) = \frac{7}{e^{\frac{(V+65)}{20}}}$$
$$a h_F(V) = \frac{.225}{1 + e^{\frac{(V+80)}{10}}}$$
$$b h_F(V) = \frac{7.5}{e^{\frac{-(V-3)}{18}}}$$
$$a m_P(V) = \frac{200}{1 + e^{\frac{-(V-18)}{-16}}}$$
$$b m_P(V) = \frac{35}{1 + e^{\frac{(V+58)}{8}}}$$

The voltage-activated potassium channels included three components: a fast-activating current, a medium-activating current, and a slow-activating current. These channels were based on the model by Khaliq, Gouwens, and Raman (4). The potassium current was described by:

$$I_K^{\text{slow}} + I_K^{\text{mid}} + I_K^{\text{fast}} = g_K\left(2n_f^3 h_f + n_m^4 + 2n_s^4\right)(V - E_K)$$

Here the slow current is described by

$$I_K^{\text{slow}} = g_K n_s^4 (V - E_K)$$
$$\frac{dn_s}{dt} = \frac{n_{s_\infty}(V) - n_s}{\tau_{n_s}(V)}$$
$$n_{s_\infty}(V) = \frac{1}{e^{0.0543(-V-16.5)} + 1}$$
$$\tau_{n_s}(V) = \frac{1}{0.796 + \frac{1000}{e^{-0.0134(V-306.7)} + e^{0.0854(V+73.2)}}}$$

The medium current is

$$I_K^{\text{mid}} = g_K n_m^4 (V - E_K)$$
$$\frac{dn_m}{dt} = \frac{n_{m_\infty}(V) - n_m}{\tau_{n_m}(V)}$$
$$n_{m_\infty}(V) = \frac{1}{e^{0.0490(-V-24)} + 1}$$
$$\tau_{n_m}(V) = \begin{cases} 0.688 + \frac{1000}{e^{-0.0287(V-141.5)} + e^{0.154(V+64.2)}} & V < -20 \\ 0.16 + 0.8e^{-0.0267V} & V \geq -20 \end{cases}$$

Finally, the fast current is given by

$$I_K^{\text{fast}} = g_K n_f^3 h_f (V - E_K)$$
$$\frac{dn_f}{dt} = \frac{n_{f_\infty}(V) - n_f}{\tau_{n_f}(V)}$$
$$n_{f_\infty}(V) = \frac{1}{e^{0.06494(-V-24)} + 1}$$
$$\tau_{n_f}(V) = \begin{cases} 0.103 + 14.9e^{0.035V} & V < -35 \\ 0.129 + \frac{1000}{e^{0.043(56.3-V)} + e^{0.0775(V+100.7)}} & V \geq -35 \end{cases}$$
$$\frac{dh_f}{dt} = \frac{h_{f_\infty}(V - h_f)}{\tau_{h_f}(V)}$$
$$dh_{f_\infty}(V) = \frac{0.69}{e^{0.0893(V+5.8)} + 1}$$
$$\tau_{h_f}(V) = \begin{cases} 0.012 + 12e^{-0.000406(V+56.3)^2} & V \leq 0 \\ 1.2 + 2.3e^{-0.141V} & V > 0 \end{cases}$$

We included a P/Q-type calcium channel, notable for being the primary calcium current detected in both the dendrites and soma. As a calcium current, its driving potential was

originally governed by the Goldman–Hodgkin–Katz current equation. However, to improve computational efficiency, we simplified it to an Ohmic current to avoid unnecessary complexity and ODE stiffness. This channel was initially characterized by Miyasho (5).

$$I_{Ca}^{\text{PQ}} = g_{Ca} m_{Ca} (V - E_{Ca})$$

$$\frac{m_{Ca}}{dt} = \frac{m_{Ca_\infty}(V) - m_{Ca}}{\tau_{m_{Ca}}}$$

$$m_{Ca_\infty}(V) = \frac{\alpha_{Ca}(V)}{\alpha_{Ca}(V) + \beta_{Ca}(V)}$$

$$\tau_{Ca}(V) = \frac{1}{\alpha_{Ca}(V) + \beta_{Ca}(V)}$$

$$\alpha_{Ca}(V) = \frac{8.5}{1 + e^{\frac{V-8}{-12.5}}}$$

$$\beta_{Ca}(V) = \frac{35}{1 + e^{\frac{V+74}{14.5}}}$$

We included a BK current, a calcium-activated potassium current that depends on both voltage and intracellular calcium concentration. BK channels are found in both the dendrites and soma (6).

$$I_K^{\text{BK}} = g_{BK} m_{BK} z_{BK}^2 (V - E_K)$$

$$\frac{dm_{BK}}{dt} = \frac{m_{BK_\infty}(V) - m_{BK}}{\tau_{m_{BK}}(V)}$$

$$m_{BK_\infty}(V) = \frac{\alpha_{BK}(V)}{\alpha_{BK}(V) + \beta_{BK}(V)}$$

$$\tau_{BK}(V) = \frac{1}{\alpha_{BK}(V) + \beta_{BK}(V)}$$

$$\alpha_{BK}(V) = 7.5$$

$$\beta_{Ca}(V) = \frac{.11}{e^{\frac{V-35}{14.9}}}$$

$$\frac{dz_{BK}}{dt} = \frac{z_{BK_\infty}(Ca) - z_{BK}}{\tau_z(Ca)}$$

$$z_{BK_\infty}(Ca) = \frac{0.4Ca}{1 + 0.4Ca}$$

$$\tau_z(Ca) = 10$$

We set the ion driving potentials as:

$$\begin{aligned} E_{Na} &= 122 \text{ mV} \\ E_K &= -90 \text{ mV} \\ E_{Ca} &= 135 \text{ mV} \end{aligned}$$

The conductances for the healthy Purkinje cell are given below. Note that some channel conductances varied depending on the experimental condition and are noted where applicable. We denoted somatic compartment conductances as $g_{x,s}$ and dendritic compartment conductances as $g_{x,d}$. We set the conductances as follows:

$$\begin{aligned} g_{L,s} &= 1.369\ \mu\text{S} \\ g_{Na} &= 14.3\ \mu\text{S} \\ g_{K} &= 3.15\ \mu\text{S} \\ g_{PQ,s} &= 1.42\ \mu\text{S} \\ g_{BK,s} &= 10\ \mu\text{S} \\ g_{L,d} &= .75\ \mu\text{S} \\ g_{PQ,s} &= 10\ \mu\text{S} \\ g_{BK,s} &= 23\ \mu\text{S} \end{aligned}$$

Calcium Dynamics

We computed the internal calcium concentration (Ca) in three distinct compartments of the Purkinje cell: a thin shell beneath the somatic membrane Ca_{sh}, bulk cytosolic concentration Ca_{cy}, and the proximal dendritic concentration Ca_d. All calcium concentrations were measured in µM.

The change in calcium concentration was modeled as a function of all fluxes into and out of each compartment as follows:

$$\begin{aligned} \frac{dCa_{sh}}{dt} &= \frac{J_{Pq} - J_P + J_L}{\kappa vol_{sh}} - \frac{Ca_{sh} - Ca_{cy}}{D_{cy,sh}} \\ \frac{dCa_{cy}}{dt} &= -\frac{Ca_{cy} - Ca_{sh}}{D_{sh,cy}} - \frac{Ca_{cy} - Ca_d}{D_{d,cy}} \\ \frac{dCa_d}{dt} &= \frac{J_{Pq} - J_P + J_L}{\kappa vol_d} - \frac{Ca_d - Ca_{cy}}{D_{cy,d}} \end{aligned}$$

In this context, concentration dynamics are influenced by compartment volume and calcium buffering. We adopted the assumption of instantaneous buffering, characterized by a volume expansion factor $\kappa = 1000$. The compartment volumes were specified as $vol_{sh} = 6.6 \times 10^{-5}\ mm^3$ and $vol_d = 7.4 \times 10^{-5}\ mm^3$.

The terms $D_{x,y}$ represent flux between two compartments, and were set as:

$$\begin{aligned} D_{cy,sh} &= 759\ \text{msec} \\ D_{sh,cy} &= .149\ \text{msec} \\ D_{cy,d} &= .03725\ \text{msec} \\ D_{d,cy} &= .149\ \text{msec} \end{aligned}$$

We included the calcium-pump flux as J_P. Calcium pumps are responsible for transporting calcium ions from the cytosol to the extracellular space and were modeled as a linear process.

Here we model the somatic ($J_{P,sh}$) and dendritic ($J_{P,d}$) calcium pumps as separate processes. Similarly, $J_{L,sh}\ and\ J_{L,d}$ represented the linear calcium leak from the somatic and dendritic extracellular spaces into the cytosol. We balanced these two fluxes to maintain an internal calcium concentration of $0.08\mu\ mol$ at rest, when the P/Q channels were closed.

The two pump terms are described by the following equations:

$$\begin{aligned} J_{P,sh} &= k_{p,sh}Ca_{sh} \\ J_{P,d} &= k_{p,d}Ca_d \end{aligned}$$

With pump strengths $k_{p,sh} = 19.2$ msec^{-1} and $k_{p,d} = .68$ msec^{-1} . Likewise, the two leak terms are given by

$$\begin{aligned} J_{L,sh} &= k_{l,sh}(Ca_o - Ca_{sh}) \\ J_{L,d} &= k_{l,d}(Ca_0 - Ca_d) \end{aligned}$$

Likewise, we set the leak strengths as $k_{l,sh} = 1.67$ msec^{-1} and $k_{l,d} = .05$ msec^{-1}. With Ca_o representing the external calcium concentration and set at $Ca_o = 1000\ \mu M$

The flux from the PQ calcium channel is denoted as J_{Pq}, and is given by the following equations:

$$\begin{aligned} J_{Pq,sh} &= \frac{g_{pq,s}m_{pq,s}(V_s - E_{Ca})}{2F} \\ J_{Pq,d} &= \frac{g_{pq,d}m_{pq,d}(V_d - E_{Ca})}{2F} \end{aligned}$$

where $F = 9.648846\ \frac{C}{\text{mmol}}$ is Faraday's constant. Recall because calcium is a divalent ion, we included a factor of 2. Here, g_{pq} is the maximal conductance listed above, and m_{pq} is the gating variable described above.

Synaptic gate

The gating variable for the PC synapse is given by s_{PC}, with its dynamics described by the following equation:

$$\frac{ds_{PC}}{dt} = \frac{1 + \tanh(V_s + 10) - s_{PC}}{\tau_{PC}}$$

The time constant τ_{PC} was set at $10msec$. As before, $1 + \tanh$ represents a continuous version of a delta spike. If the voltage passes above $-10\ mV$, the PC is considered to have fired a spike.

Our investigation revealed that applying these currents resulted in a Purkinje cell model that exhibited a high degree of physiological accuracy while remaining computationally tractable. This simplified computational representation enabled rapid, sufficiently precise simulations and facilitated the implementation of moderately sized neural circuits on standard laptop hardware.

Deep Cerebellar Nuclei

In our study, we classified Deep Cerebellar Nuclei (DCN) neurons as relatively straightforward units responsible for relaying information back to the IO. Notably, DCN neurons projecting to the IO are GABAergic, primarily influencing the effective gap-junction dynamics among IO neurons. We modeled Purkinje cells as the exclusive input source to the DCN. In the absence of PC input, DCN neurons tonically spiked; when exposed to weak PC input, their firing rate diminished, whereas strong input rendered them silent. To implement this model, we employed a Morris–Lecar neuron framework, qualitatively aligning its input–frequency response curve to replicate established DCN behavior. The resultant DCN neuron model was characterized by the following equations:

$$\begin{aligned}
\frac{dV}{dt} = \quad & -g_{PC,d}s_{PC,i}(V - E_{GABA}) - g_L(V - E_L) \\
& -g_K w(V - E_K) - g_{Ca}m_\infty(V)(V - E_{Ca}) + i_{app} \\
\frac{dw}{dt} = \quad & \frac{w_\infty(V) - w}{\tau_w(V)} \\
\frac{ds_{DCN}}{dt} = \quad & \frac{1 + \tanh(V) - s_D}{\tau_{DCN}}
\end{aligned}$$

We set the conductances and driving potentials to be:

$$\begin{aligned}
E_{Ca} &= 100 \text{ mV} \\
E_K &= -70 \text{ mV} \\
E_L &= -50 \text{ mV} \\
E_{GABA} &= -100 \text{ mV} \\
g_{Ca} &= 1\ \mu\text{S} \\
g_K &= 2\ \mu\text{S} \\
g_L &= .5\ \mu\text{S} \\
i_{app} &= .17\text{nA}
\end{aligned}$$

The instantaneous functions are described by the following equations:

$$\begin{aligned}
m_\infty(V) &= \frac{1 + \tanh\left(\frac{v - 1}{14.5}\right)}{2} \\
w_\infty(V) &= \frac{1 + \tanh\left(\frac{v - 10}{15}\right)}{2} \\
\tau_w(V) &= \frac{\cosh\left(\frac{V - 10}{30}\right)}{3}
\end{aligned}$$

Finally, the synaptic variable τ_{DCN} was set to $10\ msec$.

Reference

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