# Appendix

## E-GLIF model solution and parameter space

Considering the matrix form of the ODE system describing the model dynamics (Equ. 1):

$\frac{d}{dt}\left[\begin{array}{c}V\_{m}(t)\\I\_{adap}(t)\\I\_{dep}(t)\end{array}\right]= \left[\begin{matrix}\frac{1}{τ\_{m}}&-\frac{1}{C\_{m}}&\frac{1}{C\_{m}}\\k\_{adap}&-k\_{2}&0\\0&0&-k\_{1}\end{matrix}\right]∙\left[\begin{array}{c}V\_{m}(t)\\I\_{adap}(t)\\I\_{dep}(t)\end{array}\right]+\left[\begin{array}{c}-\frac{1}{τ\_{m}}E\_{L}+\frac{1}{C\_{m}}(I\_{e} + I\_{stim})\\-k\_{adap}∙E\_{L}\\0\end{array}\right]$ (A )

the general solution is:

$\left[\begin{array}{c}V\_{m}(t)\\I\_{adap}(t)\\I\_{dep}(t)\end{array}\right]=c\_{1}∙x\_{1}∙e^{λ\_{1}t}+c\_{2}∙x\_{2}∙e^{λ\_{2}t}+c\_{3}∙x\_{3}∙e^{λ\_{3}t}+\left[\begin{array}{c}V\_{m\\_inf}\\I\_{adap\\_inf}\\I\_{dep\\_inf}\end{array}\right]$ (A )

where:

$c\_{1}$, $c\_{2}$, $c\_{3}$ are arbitrary constants depending on the initial conditions

$λ\_{1},λ\_{2},λ\_{3}$ are the eigenvalues of the coefficient matrix, with values:

 $λ\_{1}$ = $-k\_{1}$, (∈ R-) (A 3)

 $λ\_{2} $ = $\frac{1}{2}∙\left[\left(\frac{1}{τ\_{m}}-k\_{2}\right)+\sqrt{\left(\frac{1}{τ\_{m}}-k\_{2}\right)^{2}-4∙(-\frac{k\_{2}}{τ\_{m}}+\frac{k\_{adap}}{C\_{m}})}\right]$ (A )

 $λ\_{3}$ = $\frac{1}{2}∙\left[\left(\frac{1}{τ\_{m}}-k\_{2}\right)-\sqrt{\left(\frac{1}{τ\_{m}}-k\_{2}\right)^{2}-4∙(-\frac{k\_{2}}{τ\_{m}}+\frac{k\_{adap}}{C\_{m}})}\right]$ (A )

$x\_{1}$, $x\_{2}$, $x\_{3}$ are the eigenvectors associated to each eigenvalue

$V\_{m\\_inf}$, $I\_{adap\\_inf}$, $I\_{dep\\_inf}$ are the stationary solutions for each state variable.

For the membrane potential, the solution is (Hertäg et al., 2012):

$V\_{m}\left(t\right)=c\_{1}∙x\_{1}^{(1)}∙e^{λ\_{1}t}+c\_{2}∙x\_{2}^{(1)}∙e^{λ\_{2}t}+c\_{3}∙x\_{3}^{(1)}∙e^{λ\_{3}t}+V\_{m\\_inf}$ (A )

Specifically:

$V\_{m\\_inf}= E\_{L}+\frac{-k\_{2}∙τ\_{m}}{C\_{m}∙k\_{2}-k\_{adap}∙τ\_{m}}∙(I\_{e}+I\_{stim})$ (A )

$x\_{1}^{(1)}=\frac{(k\_{1}-k\_{2})τ\_{m}}{(k\_{1}τ\_{m}-1)(k\_{2}-k\_{1})C\_{m}-k\_{2}τ\_{m}}$, (A )

the first component of the eigenvector associated to the eigenvalue $λ\_{1}$.

$x\_{2}^{(1)}=x\_{3}^{(1)}=1$, (A )

the first component of the eigenvectors associated to the eigenvalues $λ\_{2}$ and $λ\_{3}$, respectively

Considering that *k1* is real and positive, the dynamics of the solution depends on the discriminant:

$∆ = \left(\frac{1}{τ\_{m}}-k\_{2}\right)^{2}-4∙(-\frac{k\_{2}}{τ\_{m}}+\frac{k\_{adap}}{C\_{m}})$ (A )

1. exponential and stable solution; the following conditions need to be verified:
	* $∆ >0$⇒$λ\_{1},λ\_{2},λ\_{3}$ ∈ R (the solution is exponential)
	* $λ\_{1},λ\_{2},λ\_{3}$ *<* 0 (the solution is stable)

In addition, we need to verify that *Vm\_inf* ∝ *Ie+Istim,* i.e. *Vm\_inf* is proportional to the total input current through a positive coefficient, to have a coherent value of steady state membrane potential.

These conditions result in the following constraints on parameters:

*⇒* $\left\{\begin{array}{c}k\_{adap}<\frac{C\_{m}}{4}(k\_{2}+\frac{1}{τ\_{m}})^{2} \\k\_{adap}> \frac{C\_{m}}{τ\_{m}}∙k\_{2} AND k\_{2}> \frac{1}{τ\_{m}} [stable] \\ \end{array}\right.$(A )

1. oscillatory solution; the following conditions need to be verified:
	* $∆ <0$⇒$λ\_{1},λ\_{2},λ\_{3}$ *∈ C* (the solution is oscillatory);
		+ If *Re[*$λ\_{1},λ\_{2},λ\_{3}$*] = 0* ⇒ the oscillations have null damping;
		+ If *Re[*$λ\_{1},λ\_{2},λ\_{3}$*] < 0* ⇒ the oscillations are damped and the solution is stable.

Analogously to the previous case, we need to verify that *Vm\_inf* ∝ *Ie+Istim* through a positive coefficient.

The resulting constraints among parameters are:

*⇒* $\left\{\begin{array}{c}k\_{adap}>\frac{C\_{m}}{4}(k\_{2}+\frac{1}{τ\_{m}})^{2} \\ k\_{2}= \frac{1}{τ\_{m}} \left[null damping\right] or k\_{2}> \frac{1}{τ\_{m}} [stable] \left(⇒k\_{2}>0 \right) \\k\_{adap}> \frac{C\_{m}}{τ\_{m}}∙k\_{2} (being k\_{2}>0 ) \end{array}\right.$(A )

In this case, oscillations depend on the imaginary part of the eigenvalues ($\frac{\sqrt{\left|∆\right|}}{2}$) and thus have angular frequency$ω= \frac{\sqrt{\left|∆\right|}}{2}$and related frequency$f\_{osc}= \frac{2∙π}{ω}$.

The analytical solution was exploited in the E-GLIF optimization process to define the cost function and the parameter constraints.

During PyNEST simulations, the neuron model response over a membrane potential threshold was approximated to a spike. For neurophysiological realism, a spike was generated at time *tspk* depending on the escape rate function $λ(t)$ (Equ. 2) accounting for stochasticity and the refractory interval$ ∆t\_{ref}$, if:

$\left\{\begin{array}{c}t\_{spk}\notin ∆t\_{ref} \\rnd<(1-e^{-λ(t\_{spk})t\_{spk}})\end{array}\right.$ (A 13)

where *rnd* = random number in the interval [0, 1]

# E-GLIF optimization for cerebellar Golgi cells: parameter constraints

In order to obtain the expected neurophysiological behavior when simulating cerebellar GoCs, E-GLIF optimization took into account multiple parameter constraints. Specifically:

Nonlinear constraints:

Negative discriminant ($∆ <0)$ to obtain an oscillatory membrane potential (as described in Appendix, I):

$k\_{adap}>\frac{C\_{m}}{4}∙(k\_{2}+\frac{1}{τ\_{m}})^{2}$ (A 14)

Controlled *Vm* oscillation frequency: 3 < *fOSC < 8 Hz*, where *fOSC* is defined in Section 2.1.

Controlled amplitude of oscillations ($\left|V\_{m\\_osc}\right|$), during the intervals $∆t\_{1}^{(zero\\_stim)}$, $∆t\_{2}^{(zero\\_stim)}$,$∆t\_{ss}^{(zero\\_stim)}$of the zero-current phase (*Istim* = 0 pA) and during the hyperpolarizing interval *hyp* (with *Istim = inh*):

$\left|V\_{m\\_osc}\right|\_{∆t\_{1}^{(zero\\_stim)},∆t\_{2}^{(zero\\_stim)},∆t\_{ss}^{(zero\\_stim)}}<100mV$ (A 15)

$\left|V\_{m\\_osc}\right|\_{hyp}<200mV$ (A 16)

$V\_{m}\left(1.1∙t\_{1\\_des}^{(zero\\_stim)}\right)> V\_{th}$ to constraint the occurrence of the first spike event during the zero-current phase, so to trigger all the spike-reset-update mechanisms.

Linear constraints:

GoC show faster dynamics of the sodium ion current with respect to potassium one (accounted for by the current updates *A1* and *A2*):

$A\_{1}>A\_{2}>0$ pA (A 17)

Parameter bounds:

 Not-damped *Vm* oscillations (see Appendix, I):

$k\_{2}= \frac{1}{τ\_{m}}$ (A 18)

After $∆t\_{ref}$, negligible contribution of the depolarizing current *Idep*, during the zero-current phase (*Istim* = 0), to avoid interference with the neuron spontaneous activity, being *Idep* the depolarizing spike-triggered current, with decay *k1*:

$ \frac{3}{mean(tonic\\_freq)}< k\_{1}< \frac{3}{∆t\_{ref}}$ (A 19)

Realistic values of *Idep* and *Iadap* based on the neurophysiological values of sodium and potassium ion currents (Solinas et al., 2007a):

$A\_{1}$, $A\_{2}$ **<** 500 pA (A 20)

Limited values of the endogenous current:

$0<I\_{e}$ < 50 pA (A 21)