Computational modeling predicts the ionic mechanism of late-onset responses in Unipolar Brush Cells
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Background
Unipolar Brush Cells (UBCs) have been suggested to play a critical role in cerebellar functioning, yet the corresponding cellular mechanisms remain poorly understood. UBCs have recently been reported to generate, in addition to early-onset glutamate receptor-dependent synaptic responses, a late-onset response (LOR) composed of a slow depolarizing ramp followed by a spike burst (Locatelli et al., 2013). The LOR activates as a consequence of synaptic activity and involves an intracellular cascade modulating H- and TRP-current gating. In order to assess the LOR mechanisms, we have developed a UBC multi-compartmental model (including soma, dendrite, initial segment and axon) incorporating biologically realistic representations of ionic currents and a cytoplasmic coupling mechanism regulating TRP and H channel gating (Russo et al., 2007).

Methods
This work presents a combined modeling (I) and experimental analysis (II) of UBC electroresponsiveness, in which the models was accurately matched to biological responses (III). The model was written in NEURON.

Results
The model finely reproduced UBC responses to current injection, including a burst triggered by a low-threshold spike sustained by CaLVA currents, a persistent discharge sustained by CaHVA currents, and a rebound burst following hyperpolarization sustained by H- and CaLVA-currents (Diana et al., 2007; Fig. 1A). This study shows that regulation of H- and TRP-currents by an intracellular factor can generate the LOR, a slow depolarization driven by synaptic activity recently observed in cerebellar UBCs. Moreover, the model predicted that H- and TRP-current regulation was necessary and sufficient to generate the LOR and its dependence on the intensity and duration of mossy fiber activity (Fig. 1B). Therefore, the model showed that, using a basic set of ionic channels, UBCs generate a rich repertoire of bursts, which could effectively implement tunable delaylines in the local microcircuit (Kennedy et al., 2014). Although, the model was manually tuned, the robustness study of the model for the ionic conductances could be a good estimate to be used as the delimiters, to generate a population of UBC using MOEA – NSGA II Algorithm. This work was supported by grants of European Union to ED (CEREBNET FP7-ITN238686, REALNET FP7-ICT270434) and by grants of the Italian Ministry of Health to ED (RF-2009-1475845) and to SS (GR-2009-1493804).

Fig. 1. Simulations of UBC response.

Reference