TIME REPRESENTATIONS IN PURKINJE CELL DENDRITES

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ABSTRACT

Various lines of evidence, most importantly from studies of pavlovian eye blink conditioning, suggest that the cerebellar cortex provides a precise representation of the temporal relationship between successive events in the 0.1 - 1.5 s range. Current explanations for these timing capabilities rely on spectral decomposition of the inputs carried by parallel fibers (PFs) or delays in activation of PFs synapses on Purkinje cells (PCs). However, based on their length and transmission velocity, PFs cannot produce sufficiently long delays. On the other hand, spectral models cannot explain the trace version of the eye blink paradigm into which the conditioned and unconditioned stimuli are separated by a time gap. Here, we show that intrinsic electrical properties of PCs are sufficient to generate appropriate adaptive timing of the cerebellar cortex output. Using a biophysical model of electric signal integration in PC dendrites, it is shown that brief inputs from climbing fiber (CF) and PFs can trigger long-lasting PCs responses with adaptive duration. In both cases, the signals do not propagate actively. The CF-triggered responses invade the dendritic tree only if the CF input is distributed over smooth dendrites, in agreement with the actual anatomical CF synapse distribution. PFs-triggered responses reach the cell soma once a threshold current inversely related to the stimulated area is exceeded. These responses cannot be classified as spikes due to their non-propagating nature nor as electrotonus given their voltage threshold. They therefore represent a novel mechanism of excitability, which allows contextual information from mossy fibers to reliably control duration of PC responses to phasic inputs from PFs and the CF.
The cerebellum has been hypothesized to act as an interval timing system (Ivry and Spencer, 2004). This functional hypothesis is best documented in the eye blink conditioning, where paired conditioned (CS) and unconditioned (US) stimuli are repetitively presented to animals. Parallel fibers (PFs, the granule cells axons) convey the CS (Hesslow et al., 1999) while climbing fibers (CFs, axons of inferior olivary neurons) carry the US (Svensson and Ivarsson, 1999) to the cerebellar cortex. With training, animals learn to blink in response to the CS alone at the expected time of the US, with inter-stimulus intervals from 100ms to 1200ms (references Llimas). Time encoding of these responses putatively resides in Purkinje cells (PCs) as the CS and US converge on their dendrites. But the physiological mechanisms underlying these dendritic time computations remain obscure. Spectral models use an analogy between PCs and perceptrons to posit that PCs translate patterns of PFs activation into temporal codes. However, perceptrons can only associate concomitant inputs and outputs and these models cannot explain trace conditioning, where a time gap separates the two stimuli (Medina et al., 2000). An alternative hypothesis relies on sustained responses of PCs to brief stimuli. Fiala et al. (1996) have thus shown that dynamics of PCs metabotropic glutamate receptors (Batchelor et al., 1994) can reproduce time characteristics of eye blink conditioning. Induction of correctly timed conditioned responses in mice lacking metabotropic receptors (Aïba et al., 1994) however implicates that other master timing mechanisms are at work in the cerebellum. Dendritic plateau potentials (Llinás and Sugimori, 1992) represent another candidate for trace activities in PCs, as their duration ranges from 100ms to several seconds. Houk and colleagues (Berthier et al., 1993; Barto et al., 1999) have illustrated how plateaus endowed with adaptive duration could sculpt crude commands from the motor cortex to improve motor coordination. Genet and Delord (2002) have embodied this idea by showing in a biophysical model of the plateau mechanism, that tonic synaptic inputs may precisely control plateaus duration. This model also predicts mirror signals, termed ‘valley potentials’, that explain PC pauses in Houk’s model.

PCs have complex dendrites. How are plateaus and valleys excited and how do they integrate in the tree to set the timing properties of the neuron? We addressed these questions by investigating the mechanism of Genet and Delord (2002) in the PC dendrites architecture. Simulations in infinite dendrites show that Ca spikes and plateaus / valleys of infinite duration can intrinsically propagate whereas finite plateaus/valleys are non-propagating signals. In equivalent cable representations of a reconstructed PC, activation of the CF triggers traveling waveforms reproducing the diversity of complex spikes shapes. Paradoxically, finite plateaus and valleys triggered in dendrites reach the soma. Their threshold current relates inversely to the stimulated membrane area, like stimuli for propagating spikes in the somatopetal direction. These properties of plateaus / valleys are irreconcilable with features of classical spikes and spreading electrotonus. They lead us to propose that these signals represent a distinct mechanism of electric signaling and our simulations illustrate how PCs may use it to encode timed representations of their MFs and CF inputs.
MATHEMATICAL MODEL

Modeling strategy
The model aims at understanding excitation and propagation of complex spikes and plateau / valley potentials in Purkinje cell dendrites. It starts from the cable equation, which describes membrane potential, \( V \) (mV) dynamics along a uniform radius cable (Jack et al., 1983). Excitation and propagation of active electric signals predicted by this equation depend on the membrane ion currents that are introduced into it and on the geometry of dendrites to which the equation is applied (Vetter et al., 2000). In a first part, we describe ion currents in the model and derive a modified cable equation applying to the variable radius of PC dendrites. An equation modeling the internal \( \text{Ca}^{2+} \) ions concentration, \([Ca]_i\), dynamics is also derived as \([Ca]_i\) undergoes marked changes during Ca spikes and plateau potential (Miakawa et al., 1992; Callaway et al., 1995) and Ca currents couple \( V \) dynamics to these changes. Synaptic current appearing in the \( V \) equation are finally described in this first part. The second part describes our approach to implement the model in PC dendrites. We firstly justify that electric signals that the model can intrinsically propagate can be identified by studying its equations in infinite dendrites. We next detail how equivalent cable representations of a reconstructed PC were built to understand how the PC architecture determine excitation and propagation of signals identified in infinite dendrites.

Membrane ion currents
The unique inward current introduced in the model is the P-type Ca current since it represents the main Ca current expressed in mature PCs (Kaneda et al. 1990; Usowicz et al. 1992), whose dendrites are devoid of Na ion channels (Llinás and Sugimori 1992; Stuart and Haüsser 1994). Outward currents are provided by a delayed rectifier K current, \( I_{Kdr} \), which activation was correlated to the repolarization of Ca spikes by Gruol et al. (1991) and a sub-threshold K current, \( I_{Ksub} \), lumping several voltage-dependent channels activating below the Ca spike threshold whose molecular identity remains unclear (Gruol et al., 1991). \( I_{Ksub} \) was modeled to reproduce the sharp outward rectification of the PC membrane near the plateau voltage when Ca currents are blocked (Genet and Kado, 1997; Etzion and Grossman, 2001). A leakage current, \( I_{Leak} \), was introduced to adjust the resting membrane potential and input resistance of the model.

Some studies suggest that ion channels distribute differentially over PC dendrites, particularly with ‘hot spots’ of Ca channels at branch points (Llinás and Sugimori, 1980, Tank et al., 1988). This clustering of Ca channels has been hypothesized to safe propagation of Ca spikes by circumventing impedance mismatch stemming from radius changes. Without conclusive results on this issue, we assumed that all currents distribute homogeneously as it insures deriving the minimal conditions for electric signals propagation. All currents obey Ohm’s law

\[
I_{Ca} = g_{Ca} s(V - E_{Ca}) , \quad (1a)
\]

\[
I_{Ksub} = g_{Ksub} u^3(V - E_{Ksub}) , \quad (1b)
\]

\[
I_{Kdr} = g_{Kdr} n^4(V - E_{Kdr}) , \quad (1c)
\]

\[
I_{Leak} = g_{Leak}(V - E_{Leak}) , \quad (1d)
\]
into which \( g_{Ca}, g_{Ksub}, g_{Kdr} \) and \( g_{Leak} \) denote conductance densities; \( E_{Ca}, E_{Ksub}, E_{Kdr} \) and \( E_{Leak} \) are Nernst potentials of the currents. Variables \( s, n \) and \( u \) appearing in Eqs. 1a-d are Hodgkin-Huxley-type functions of \( V \) defined on the \([0,1]\) range and obeying first-order kinetics.

\[
\frac{dp}{dt} = \left( p_s(V) - p \right) / \tau_p(V), \quad p = \{s, n, u\},
\]

into which the steady-state value, \( p_\infty \), depends on \( V \) according to a Boltzmann’s function

\[
p_\infty(V) = \left(1 + \exp\left(-\frac{(V + V_p)}{k_p}\right)\right)^{-1},
\]

\( V_p \) being the half-activation potential and \( k_p \) the slope of change of variables \( p \) with \( V \).

Activation of the P-type Ca and sub-threshold K conductances is very fast (Regan, 1991, Martina et al., 2003) and the model therefore assumes that variables \( s \) and \( u \) reach instantaneously their steady-state values, i.e. \( u = u_\infty \) and \( s = s_\infty \). Slower activation of the \( I_{Kdr} \), is set by a \( V \)-dependent time constant, \( \tau_n \), modeled after function

\[
\tau_n(V) = \frac{\tau_n^0 + \tau_n^1}{\exp\left((-V + V_n)/k_n\right) + c_n/\exp\left((-V + V_n)/k_n\right)},
\]

reproducing the classical bell shape of delayed-rectifiers time constant (Hille, 1992; see Table 1 for parameters \( \tau_n^0, \tau_n^1, k_n, V_m \) and \( C_m \) in Eq.4). Nernst potentials of the leak and K currents are constants while that of the Ca current

\[
E_{Ca} = \frac{RT}{2F} \ln \left[\frac{[Ca]_i}{[Ca]_o}\right],
\]

depends on the varying \([Ca]_i\); \( R, T \) and \( F \) in Eq.5 have their usual signification and \([Ca]_o \) denotes the (constant) external \( Ca^{2+} \) ions concentration.

**Partial differential equations of the model**

From the above section, the model has three state variables, \( V \), \([Ca]_i \), and \( n \). We now derive equations governing their spatio-temporal evolution, beginning with the \( V \) equation.

Let \( i_a \) (nA) denote the axial electric current along a cylindrical dendrite segment parallel to an \( Ox \) axis and \( r_a \) (\( \Omega \)cm\(^{-1}\)) the electric resistance of the cytoplasm by unit length of the dendrite. From Ohm’s law, one gets

\[
\frac{\partial V}{\partial x} = -r_a i_a,
\]

with \( r_a = \frac{R_i}{\pi R_d^2}, \) \( R_i \) being the cytoplasmic resistivity and \( R_d \) the local dendritic radius.

Differentiating Eq. 6 with respect to space coordinate \( x \), we get

\[
\frac{\partial^2 V}{\partial x^2} = -\left( i_a \frac{dr_a}{dx} + r_a \frac{\partial i_a}{\partial x}\right),
\]

\( \partial^2 V/\partial x^2 \) being the second spatial derivative of \( V \) along the dendrite length.
into which we introduce the loss of axial current across the membrane by unit length of the dendrite, \( i_m = -\frac{\partial i_a}{\partial x} \) (nA cm\(^{-1}\)) to derive

\[
\frac{\partial^2 V}{\partial x^2} = -\left( i_a \frac{\partial r_a}{\partial x} - r_a i_m \right). \tag{8}
\]

A modified cable equation applying to tapering dendrites is obtained by introducing the membrane current expression

\[
i_m = 2\pi R_d \sqrt{1 + \left( \frac{dR_d}{dx} \right)^2} \left( C \frac{\partial V}{\partial t} + I_{\text{ion}} - I_p + I_{dc} \right) \text{ (nA cm}^{-1}\text{)}
\]

into Eq. 8

\[
C \frac{\partial V}{\partial t} = \left( \frac{R_d}{2R_s} \frac{\partial^2 V}{\partial x^2} + \frac{1}{R_s} \frac{dR_d}{dx} \frac{\partial V}{\partial x} \right) \sqrt{1 + \left( \frac{dR_d}{dx} \right)^2} - I_{\text{ion}} + I_p + I_{dc} \text{.} \tag{9A}
\]

\( I_{\text{ion}} \) in Eq. 9A represents the sum of membrane ionic currents \( I_{Ca} + I_{K_{sub}} + I_{K_{dr}} \), whereas \( I_p \) and \( I_{dc} \) stand respectively for the phasic and tonic components of synaptic currents (see Synaptic currents section below); \( C \) is the specific membrane capacitance.

To derive the \([Ca]\) equation we take into account that the endoplasmic reticulum limits the dendritic space into which \( Ca^{2+} \) ions entering dendrites can distribute (Terasaki et al., 1994). This restricted volume is modeled as a cylindrical shell adjacent to the membrane with thickness \( \delta \). The shell contains an immobile buffer with concentration to accommodate large concentrations of \( Ca \) buffering proteins found in Purkinje cells (Fierro and Llano, 1996), which participate to set the firing patterns of PCs (Servais et al., 2005). The free buffer concentration is assumed in equilibrium at each point in time due to fast buffering. The longitudinal density of \( Ca^{2+} \) ions flux over the cable section available for \( Ca \) diffusion reads

\[
J_{Ca} = -D_Ca \pi \delta (2R_d - \delta) \frac{\partial [Ca]}{\partial x} \text{ (mols}^{-1}\text{)} \text{ with } D_Ca \text{ denoting the diffusion coefficient of } \text{Ca}^{2+} \text{ ions. Introducing this flux definition into the balance equation of } \text{Ca}^{2+} \text{ ions, we obtain the following PDE for } [Ca],
\]

\[
\frac{\partial [Ca]}{\partial t} = \left( \frac{D_Ca}{\delta} \frac{\partial^2 [Ca]}{\partial x^2} + \frac{2D_Ca}{2R_d - \delta} \frac{dR_d}{dx} \frac{\partial [Ca]}{\partial x} \right) \left( 1 + \left( \frac{dR_d}{dx} \right)^2 \right) - \frac{10^7 I_{Ca} R_d}{R_s} - \frac{2k(Ca - Ca_s)(R_d - \delta)}{\delta (2R_d - \delta)} - \frac{B_f}{K_s (1 - 10^{-11} Ca / K_s)^2}.
\tag{9B}
\]

into which \([Ca]\) was rescaled according to \( Ca = 10^{11}[Ca] \) for numerical convenience.

The equation of variable \( n \) is obtained by writing Eq. 2 for this variable using the voltage-dependent time constant defined by Eq. 4. Together with Eqs. 9, it constitutes the general system of parabolic partial differential equations describing time and space dynamics of the model. As explained below, this model was simulated in cable structures where \( dR_d / dx \) vanishes, giving a simpler form to Eq 9A. Eq. 9B was also simplified by assuming \( D_Ca = 0 \), since this parameter has very small values inside neurons (Allbritton, 1992; Hodgkin
and Keynes, 1957). With these two simplifications, we obtain the simpler model studied in this paper

\[
\frac{C \partial V}{\partial t} = \frac{R_d}{2R_i} \frac{\partial^2 V}{\partial x^2} - I_{ion} + I_\phi + I_{dc},
\]  

(10A)

\[
\left(1 + \frac{[B]}{K_d(1+10^{-11}Ca/K_d)}^2\right) \frac{\partial Ca}{\partial t} = - \frac{10^2 I_{ca}R_d}{F\delta(2R_d - \delta)} - \frac{2k(Ca - Ca_b)(R_d - \delta)}{\delta(2R_d - \delta)},
\]  

(10B)

\[
\frac{\partial n}{\partial t} = \frac{(n_o - n)}{\tau_n}.
\]  

(10C)

**Synaptic currents**

The CF current and the phasic component of PFs currents (contributing to \(I_{\phi}\) in Eq. 10A) are modeled with bi-exponential functions \(I_i(t) = g_i(1 - e^{-t/\tau_o})e^{-t/\tau_c}(V - V_i)\), where \(\tau_o\) and \(\tau_c\) (ms) stand respectively for opening and closing time constants of constant \(I_i\), the maximum current conductance being denoted \(g_i\), with \(i = \{PF, CF\}\). Both excitatory currents have the same 0 mV inversion potential (Llano et al., 1991). We took \(\tau_o = 2.4\) ms and \(\tau_c = 6.3\) ms for PF (Barbour, 1993) and inhibitory synapses (the second contribution to \(I_{\phi}\)), latter synapses having an equilibrium potential of –80 mV. Opening and closure time constants of the CF current are set to 0.7 ms and 6.4 ms respectively (Llano et al., 1991). Owing to the large number of PFs contacting PC dendrites (>10⁵ in rats; Napper and Harvey, 1988), the background activity of these fibers (and inhibitory interneuron contacted by PFs and targeting on PC dendrites) is not modeled in detail but as an adjustable direct current (\(I_{dc}\) appearing in Eq. 10A, see Rapp et al., 1992).

**Model geometries**

The detailed morphology of several PCs has been made available, allowing simulations of \(V\) dynamics in neuron models endowed with realistic geometries (Bush and Sejnowski, 1991; De Schutter and Bower, 1994; Rapp et al., 1994; Roth and Haüsser, 2001). However, these models generate cumbersome to interpret data in the optics of deriving general conclusions on electric signal propagation as they require examining each branch in the dendritic tree. Moreover, if PCs are easily eye-identifiable from their morphology, they nevertheless exhibit highly variable shapes so that conclusions derived from a single cell may be irrelevant to the entire PC population. A thorough understanding of electric signals propagation in PC dendrites requires first to identify what electric signals their membrane properties intrinsically grant them to propagate (Infinite cables Section below) and next to examine how the dendritic tree architecture impact on their integration by the cell (Equivalent cable Section below).

**Infinite cables**

In the usual mathematical acceptance, a propagating wave of electric signal is defined as a voltage profile traveling along an infinite spatial domain with no shape change and uniform speed. Existence for such waves solutions in the model can be proved by rewriting the model in a co-moving frame of reference accompanying the waves. Indeed, after this coordinate change, the model reads as a simpler system of ordinary differential equations (ODEs, Eq. system 14 in Results). The problem of proving the existence of traveling solutions of the original model reduces to identify homoclinic and heteroclinic orbits to stationary points in
ODEs, i.e. orbits connecting a resting point to itself or connecting two different resting points. These orbits were searched with the HOMCONT numerical routines (Champneys et al., 1996) introduced by Bard Ermentrout into his XPP software. Numerical methods can only approximate these orbits as they work on finite time intervals whereas a dynamical system takes an infinite time to travel along these orbits. Algorithms in HOMCONT refine approximations of these orbits by extending them along a parameter $T$ multiplying the right-hand side of equations. Illustrated homo- and heteroclinics were computed with $T = 50$. We checked in a subset of computations that hundred-times larger $T$ values did not change the results significantly. These results were cross-validated by simulating the model in long cables approximating the infinite dendrite case. These simulations used the semi-implicit Crank-Nicholson method (Crank, 1956) in cables with sealed-end boundaries, the set of nonlinear algebraic equations resulting from spatial discretization of equations being solved at each time-step with Gauss-Seidel elimination. Illustrated orbits therefore represent reliable approximations of true homo- and heteroclinic solutions of the model.

Equivalent cable models of a reconstructed PC

Shelton (1985) has reconstructed the anatomy of a Golgi stained PC from an adult rat. We built simplified models of this cell capturing its essential electric properties, into which we simulated the model to understand how propagating signals identified in infinite cables can be actually excited and propagate in PC dendrites. Dendrites of Shelton’s PC have a branching power of 2, clearly deviating from the 3/2 value that would allow them to be collapsed into an equivalent cylinder (Rall, 1959). We tested alternative methods to reduce the dendritic tree into a non uniform radius, ‘equivalent cable’ by constraining either the membrane surface (Clements and Redman, 1989) or the axial resistance of the tree (Bush and Sejnowski, 1993). But these methods failed to provide a model reproducing all of Shelton’s PC electrotonic properties. We therefore developed a new method of reduction. Firstly, we followed Shelton by multiplying the geometrical dimensions of his rat cell by a scaling factor [1.36, Shelton, (1985)] to obtain the larger physical dimensions of a guinea pig PC, for which the propagation of electric signals represents an even more challenging issue. Secondly, we rescaled length $l$ and radius $R_d$ of each dendritic segment to introduce the dendritic spines according to

$$l' = l \alpha^{2/3}, \quad R_d' = R_d \alpha^{1/3},$$

(11)

primed symbols denoting scaled lengths and radii (Segev et al., 1992). Parameter $\alpha$ in Eq. 11 is the ratio of the total membrane surface to the membrane surface of dendritic spines per unit length of dendrite. It reads

$$\alpha = 1 + \frac{N_s S_s}{\pi R_d^2},$$

(12)

with $N_s$ ($\mu m^{-1}$) denoting the local linear density of spines and $S_s$ ($\mu m^2$) the membrane surface of an individual spine.

To build a reduced model of Shelton’s PC adequate to investigate the propagation of responses to CF activation toward the distal part of the tree, we first compute the electrotonic attenuation of a somatic input to each termination of the dendritic tree endowed with a passive leakage conductance using Rall’s iterative method (Rall, 1959) that we briefly recall. Solution of the usual cable equation for a passive dendrite with electrotonic length $L$ reads in electrotonic units of length $X = x/\lambda$
\[ V(X) = V(L) \frac{\cosh(L - X) + B \sinh(L - X)}{\cosh L + B \sinh L} \]  

(13)

where \( B \) is a parameter whose value is set by the amount of current leaving the cylinder through its section located at \( X = L \) (Rall, 1959) with space constant \( \lambda = \sqrt{R_d / (2R_g \sigma)} \) (\( g_m \) being the membrane conductance density). Starting from the pia, the \( B \) of each terminal segment is set to zero [see Jack et al. (1983) for the justification of treating terminal segments with an open-circuit termination]. The voltage along each of these terminating elements is computed with Eq. 13. Voltage along all parent branches is next computed iteratively toward the soma by calculating first the \( B_i \) of each segment according to

\[ B_i = \sum_{j=1}^{2} \beta_j \left( \frac{R_{d_h}}{R_{d_l}} \right)^{3/2} \]  

(14)

with

\[ \beta_j = \frac{B_j + \tanh L_j}{1 + B_j \tanh L_j}, j = 1, \ldots, 2 \]  

(15)

where \( j \) refers to the index of daughter segments of segment \( i \), and then using Eq. 13. The path with longest electrotonic length from the soma, \( L_{\text{max}} \) (connecting the soma to segment 13 of branch 68 following Shelton’s indexation) is then selected in the resulting dendrogram (see Fig.7B in Results). A non-uniform radius, unbranched cable comprising \( n \) cylindrical segments with identical electrotonic length, \( L_{\text{max}} / n \), but varying radii, \( R_{ci} \) with \( i = 1 \ldots n \), is then built as follows. With the radius of the more distal segment, \( R_{cn} \), set to an initial guess value, the voltage profile along this somatofugal equivalent cable is analytically expressed with Rall’s method. Voltage values at the termination of the \( n-1 \) remaining segments given by Eqs. 13-15, depending on the \( n-1 \) unknown radii, are then equated to the corresponding values computed along the longest electrotonic path in the tree, resulting in a set of \( n-1 \) non-linear algebraic equations. This system is solved iteratively for the \( n-1 \) unknown radii by varying \( R_{cn} \) until the total membrane surface of the equivalent cable and that of the uncollapsed dendritic tree match.

We build a second type of reduced model targeted to investigate the somatopetal propagation of plateau and valley potentials. Selecting a spiny branch in the tree, say number \( u \), we search the farthest dendritic segment from this branch in electrotonic units, say \( n^v (v,w) \), \( v \) denoting the branch number and \( w \) the particular segment in this branch. We then use the same recursive procedure as for the somatofugal cable to compute the voltage attenuation of an input delivered to branch \( u \) up to segment \( (v,w) \). The \( n-1 \) left diameters of a non-uniform cable are then computed iteratively, like with the somatofugal model above. However, the input resistance of branch \( u \) is chosen in this case to constrain the cable dimensions as input resistance met by a distally triggered, active electric signal crucially determines its conduction toward the soma (Segev and Rall, 1998).

Density of P-type Ca channels increases with distance from the soma (Llinás and Sugimori, 1992). It is impossible to introduce this non-uniform current distribution in the reduced somatopetal cable since the soma is lumped with a set of dendritic segments in this representation of the tree. We overcome this difficulty by endowing the soma in both reduced cables with the same density of active ion currents as the rest of the dendrites. This simplification cannot challenge our conclusions as the soma accounts for <1% of the cell area.
Thickness $\delta$ of the cytoplasmic shell in the two reduced models is rescaled at each electrotonic distance from the locus of synaptic currents to preserve the surface / volume ratios in the full cell in order to secure realistic Ca dynamics. All simulations used cylinders with length $<5\%$ of the local space constant $\lambda$, to ensure accurate simulations of $V$ dynamics (Cooley and Dodge, 1966). Simulations of system 9 with $D_{Ca} = 10^{-6} \text{cm}^2\text{s}^{-1}$ (Hille, 1992) show insignificant differences with those obtained from equation system 10 for a subset of parameter values, hence justifying the simplification of setting $D_{Ca} = 0$ in the full model.
RESULTS
Integration of electric signals in PC dendrites superimpose a geometrical aspect (relevant to how electric currents distribute in the dendrites architecture) to the intrinsic capability of membrane ion currents to travel electric waves (membrane currents represent the source of axial currents propagating excitation in dendrites). We addressed first the intrinsic aspect of this problem.

Local electroresponsiveness
The intrinsic electroresponsiveness of PC dendrites entailed by their membrane currents is captured by the spatially homogeneous model

\[
\left[ 1 + \frac{[\beta]}{K_d(1 + 10^{-11} Ca / K_d)^2} \right] \frac{dCa}{dt} = -\frac{10^2 I_{Ca} R_d}{F\delta(2R_d - \delta)} - \frac{2k(Ca - Ca_h)(R_d - \delta)}{\delta(2R_d - \delta)}, \quad (16a)
\]

\[
C \frac{dV}{dt} = -I_{ion} + I_v + I_{dc}, \quad (16b)
\]

\[
\frac{dn}{dt} = (n_n - n) / \tau_n, \quad (16c)
\]

obtained by zeroing the spatial derivative \( \partial^2 V / \partial x^2 \) in the model. Properties of this homogeneous model have been described before (Genet and Delord 2002). We recall them briefly as they constitute the backbone of more complex properties of the spatially distributed model. Figure 1A illustrates the bifurcation diagram of the homogeneous model with \( I_{dc} \) as the bifurcation parameter and \( R_d \) set to 0.5µm. Mossy fibers carry sensory-motor information to PC dendrites directly through parallel fibers (PFs, axons of granule cells excited by mossy fibers) and through relay stellate cells. \( I_{dc} \) represents contextual on-going inputs fed to PC dendrites by excitatory PF synapses and inhibitory synapses of stellate cells. Thus, this parameter was varied between an inhibition (\( I_{dc} < 0 \)) and an excitation (\( I_{dc} > 0 \)). The left-hand part of the diagram exhibits an “S”-shaped region, \( \Omega \), made up of two branches, R and P, corresponding respectively to resting states (R) and excited plateau states (P) which are both stable. These branches are connected by a middle branch of saddle points, denoted M. M states are unstable and act as thresholds between R and P states inside the \( \Omega \) region, which is edged by two saddle-node bifurcations. Within \( \Omega \), any membrane depolarization of R points above the M branch indefinitely switched the model to its P state while perturbations of the P states below the M branch switched the model back to its resting state. The homogeneous model is therefore bistable within \( \Omega \) (Fig.1A-B). Distortions in the vector field of Eq. system 16 in the neighborhood of \( \Omega \) (Fig.7B from Genet and Delord, 2002) give rise to finite duration depolarizations from the R state (plateaus) and hyperpolatizations from the P state (valleys). Thus, square pulses of depolarizing currents (130 nAcm\(^{-2}\), 100ms duration) delivered from R [\( I_{dc} < \inf(\Omega) \)], first triggered triangular plateau potentials, then rectangular plateaus with larger \( I_{dc} \) (compare voltage traces for –7 and 0 nAcm\(^{-2}\) on Fig.1B). Plateau duration was made infinite when \( I_{dc} \) was increased above inf(\( \Omega \)), resulting in R→P transitions (voltage trace with \( I_{dc} = 15nAcm^{-2} \) on Fig.1B). Symmetrically, square pulses of hyperpolarizing currents (-130 nAcm\(^{-2}\)), delivered to the model in its P state with \( I_{dc} > \sup(\Omega) \), triggered finite duration valley potentials, whose duration was increased by decreasing \( I_{dc} \) (voltage trace with \( I_{dc} = 70 \) and 50 nAcm\(^{-2}\) on Fig.1C). With \( I_{dc} \) below sup(\( \Omega \), phasic
hyperpolarizing currents triggered P→R transitions (voltage trace with $I_{dc} = 30\text{nAcm}^{-2}$ on Fig.1C). This homogeneous model is thus capable of reproducing indefinite dendritic state transitions as well as finite duration plateau potentials of PCs, contrarily to other models that reproduce at best the PC bistability (Guttman, 1991; Yuen et al., 1995; Loewenstein et al., 2005). It also predicts the existence of valley potentials. It finally suggests that repetitive firing of Ca spikes observed in response to large depolarizing current (Llinás and Sugimori, 1980) emerges from the P branch from either a Hopf or a homoclinic bifurcation to a limit cycle, depending on model parameters. Fig.1A illustrates the Hopf case, with Fig.1D representing a repetitive train of Ca spikes triggered by a 1000 nAcm$^{-2}$ amplitude, 1s duration pulse of depolarizing current. These dynamical features of the model held over the entire range of dendritic segment radii found in Shelton’s cell, for which a $\Omega$ region of bistability exists as illustrated on Fig.1E.

**Traveling waves in infinite cables**

**Uniformly polarized dendrites**

The next task to assess electric signal integration in PC dendrites was explore the intrinsic capabilities of Ca spikes, plateaus and valleys found in the homogeneous model to propagate. This problem was investigated by simulating the model in infinite dendrites with a uniform radius. Indeed, if these signals can propagate, they must produce traveling waves with a uniform speed, $\theta$, and constant waveform along unbounded dendrites. Such waves must therefore be found as closed solutions of the model rewritten in a co-moving frame of reference, with coordinate $\xi = x - \theta t$ accompanying their propagation in the positive $x$-direction. Making this coordinate change in the model equations, we were left with the ‘traveling system’

\[
\frac{dV}{d\xi} = V_\xi, \quad (17A)
\]

\[
\frac{dV_\xi}{d\xi} = \frac{2R}{R_d} \left[ -C_0V_\xi + I_{ion} - I_{dc} \right], \quad (17B)
\]

\[
\theta \left[ 1 + \frac{[B]_d / K_d}{(1 + 10^{-11} Ca / K_d)^2} \right] \frac{dCa}{d\xi} = \frac{10^2 I_{Ca} R_d}{F\delta(2R_\delta - \delta)} + \frac{2k(Ca - Ca_b)(R_\delta - \delta)}{\delta(2R_\delta - \delta)}, \quad (17C)
\]

\[
\frac{dn}{d\xi} = -(n_\infty - n)/(\tau_n \theta), \quad (17D)
\]

i.e., a dynamical system with the additional parameter $\theta$. Fig.2 relates orbits searched in the co-moving frame to their counterparts in the time domain to ease translation between orbits computed from the traveling system and their appearance as a voltage profile along the dendrite frozen at a given instant. Fixed points in the traveling system corresponded to a uniformly polarized dendrite (spatially uniform steady state). Heteroclinic orbits connecting two steady states corresponded to traveling fronts whereas homoclinics to a single steady state translated into traveling pulses, representing finite duration plateaus/valley potentials, Ca spikes or a combination of both. Limit cycles in the $\xi$-frame corresponded to propagating trains of waves in the time-domain. The key problem of our computations was to find $\theta$ values allowing homo- and heteroclinic orbits to occur in order to prove existence of the
corresponding traveling waves in the model. We only considered positive values of $\theta$ for reasons of symmetry (i.e. setting $\theta \rightarrow -\theta$, $\xi \rightarrow -\xi$ and $V_\xi \rightarrow -V_\xi$ in Eqs. 10 gives a reflection-symmetric system).

The traveling system had resting points with the same $V$, $Ca$ and $n$ coordinates than the original model (Eqs. 10) and its spatially homogeneous version (Eqs. 16), with the additional coordinate $V_\xi = 0$ (i.e. no $V$ change). This result implicates that each stationary state in branches R, M and P of the homogeneous system translated into a spatially uniform state of PDEs. For example, a point in the R branch of the homogeneous system gave rise to a uniformly polarized dendrite in its resting state. Using classical algebraic criteria (see e.g. Tu, 1994), we showed that all resting states in the traveling system are unstable. However, the stability of resting points in the co-moving frame is unrelated to the stability of corresponding uniformly polarized dendrites in the physical frame (see Grinford, 1991). Solutions stability was assessed using small perturbations in finite dendrites with lengths sufficient to make boundary effects negligible. Hence, we proved that R and P uniform states are stable while the M state is unstable (not illustrated). This finding offered the possibility for the existence of traveling waves connecting either one of the two stable uniform steady states to itself, or fronts switching the whole dendrite between them, as described below.

**Propagated Ca spikes**

We investigated the model for solutions corresponding to traveling Ca spikes. Traveling Ca spikes were searched as large amplitude homoclinic and heteroclinic solutions of the traveling system. Figure 3A displays the speed of the different traveling solutions that were identified as a function of $I_{dc}$, with $R_d$ set to 0.5µm. Starting from the left, one first encounters $S_1$, a branch of points corresponding to homoclinic solutions. With higher $I_{dc}$, $S_1$ gave birth to five additional branches, $S_2$ to $S_6$, forming an ‘S’-shaped region (* – labeled box). The ** – labeled box locates sub-threshold propagating solutions which are analyzed in the next section. Fig.3B gives an enlarged illustration of the ‘S’-shaped region on Fig.3A (left), together with representative wave solutions illustrated in the time domain (right). Branch $S_1$ corresponded to a unique traveling Ca spike starting from R and ending on R after a finite duration plateau (mean potential -45mV). The duration of this plateau increased with $I_{dc}$ (Fig. 3C) and became infinite for $I_{dc} = 26.52$ nAcm$^{-2}$. At this $I_{dc}$ value, $S_1$ was replaced with $S_2$, a branch of heteroclinics where a Ca spike started from R and switched the system to P (Fig. 3B). Branch $S_2$ extended up to sup($\Omega$). $S_5$, a branch of heteroclinics symmetric to $S_2$, emerged at inf($\Omega$), with the Ca spike starting from P and terminating on R. At $I_{dc} = 47$ nAcm$^{-2}$, $S_5$ was replaced by $S_6$, a branch of homoclinics, the spike of which still started from P but also ended on P after a valley potential of long duration. With higher $I_{dc}$, the duration of the valley decreased smoothly (Fig. 3C). Simulations of the model in long dendrites proved that traveling solutions on branches $S_1$, $S_2$, $S_5$ and $S_6$ were stable. Two additional branches of heteroclinics where found in $\Omega$ : $S_4$ was identified for $I_{dc} \in ]$inf($\Omega$), 37.5[$ and consisted of orbits connecting M to R whereas $S_3$, corresponding to orbits connecting M to P was found for $I_{dc} \in ] 37.5, sup(\Omega)[$. Branches $S_3$ and $S_4$ have obviously no physiological signification since they start from an unstable state, which cannot be actually achieved due to natural fluctuations in dendrites (for example, spontaneous synaptic potentials or flickering in ion channels activation). Similar results were obtained using any radius $R_d$ in the range of Shelton’s PC dendrites. Notice that the 10 – 20 cms$^{-1}$ range of propagation speeds predicted for Ca spikes matches values measured in the alligator by Llinás et al. (1969), the only quantitative study of this parameter that we are aware of.

Further computations allowed us to identify additional branches of hetero- and homoclinics, similar to branches $S_{1-6}$, with the major difference however that they exhibited
two Ca spikes. That is, for each branch of one-spike orbits illustrated in Fig. 3A, we were able to compute a similar branch of two-spike orbits, as illustrated on Fig. 4A with the example of $I_{dc} = 0$ nAcm$^{-2}$. Branches of two-spike orbits are not illustrated on Fig. 3A because they had propagation speeds nearly identical to that of one-spike orbits ($<1\%$ difference). Durations of their late plateau / valley phase was also nearly identical. Interestingly, the second Ca spike in two-spike orbits had a systematically smaller amplitude than the first one (Fig. 4A). We could also compute three-spike orbits for a subset of tonic current values, an example of which is illustrated on Fig. 4A for $I_{dc} = 0$, confirming the amplitude decrease of successive spikes already noted with two spikes orbits. This results can be explained by reduced Ca currents due to increased $[Ca]$ after each spike. Notice that the duration of the terminating plateau was barely affected by the number of spikes. Two-spike orbits proved more difficult to compute than one-spike orbits due to a greater sensitivity of numerical methods to their initial approximation. These difficulties worsened with three spike orbits, preventing us to systematically extend branches of these orbits. We suspect however that the model can propagate $n$-spike orbits in correspondence to every one-spike orbit. These waveforms represented an attractive explanation for the variable shape of complex spikes, which exhibit 1-3 Ca spike components [with rare but interesting exceptions up to 5 (Schmolesky et al., 2002)], diminishing amplitude of successive spikes (Eccles et al., 1966) and sometimes end with a plateau depolarization lasting for up to several hundreds of milliseconds (Ekerot and Oscarsson, 1981). Capabilities of the model to reproduce the diversity of complex spikes waveforms and explain their propagation is studied below in equivalent cable representations of Shelton’s PC.

Recall that the homogeneous model had stable periodic solutions for $I_{dc} \gg \sup(\Omega)$ in the form of trains of Ca spikes (Fig. 1D). In an infinitely long dendrite stimulated uniformly with a sufficiently large $I_{dc}$, these solutions must translate into stationary, periodic waves (Volpert et al., 2000). The possible existence of large speed waves, periodic in space and close to these stationary solutions was investigated with the ‘small parameter method’ (Volpert et al., 2000). Substituting coordinate $\nu = -\xi / \theta$ into equation system 17, we derived the dynamical system

$$\frac{dV}{d\nu} = \frac{2 \alpha R}{R_d} \frac{d^2V}{d\nu^2} - I_{ion} + I_{dc}, \quad (18A)$$

$$\left[1 + \frac{[B]/K_i}{(1 + 10^{-11} Ca / K_i)^2}\right] \frac{dCa}{d\nu} = \frac{10^3 I_{Gd} R_d}{F \delta(2R_d - \delta)} + \frac{2k(Ca - Ca_\delta)(R_d - \delta)}{\delta(2R_d - \delta)}, \quad (18B)$$

$$\frac{dn}{d\nu} = (n_n - n) / \tau_n. \quad (18C)$$

into which $\alpha = 1/\theta^2$ becomes a small parameter as $\theta$ becomes large. Taking the limit of Eqs. 18 for $\theta \to \infty$, one recovers the homogeneous model (Eqs. 16), thereby guarantying the existence of stationary periodic waves from the above results. Limit cycles in Eq. system 18 emerged through Hopf bifurcations along parameter $\alpha$. The wave speed at the Hopf bifurcation points is illustrated as a function of $I_{dc}$ on Figure 3A. Contrarily to homoclincs and heteroclinics described above, that corresponded to a finite number of Ca spikes propagating with a unique speed, traveling trains of an infinite number of spikes had a continuous spectrum of speeds for each $I_{dc}$ value. This spectrum was related to the spikes frequency, $\nu$, by dispersion relations (Grinford, 1991; Miller and Rinzel, 1981), a
representative subset of which is illustrated on Fig. 4B. From the Hopf bifurcation point (filled circles), all curves eventually reached a turning point on the right of the figure. From this turning point, the speed on the upper branch of the curves increased as $\nu$ decreased, up to a limit frequency where $\theta$, and hence after the wavelength, became infinite. These waves with infinite propagation speed corresponded to waves stationary in space. Fig. 4C illustrates how the amplitude of spikes in the propagating trains of Ca spikes increased from the Hopf bifurcation point with $\theta$ and converged to these stationary waves. Their smallest wavelength was 678 $\mu$m, only 14% smaller than the longest dendritic path in the tree (789 $\mu$m). Therefore, we did not investigate the stability of these waves as they would be indistinguishable from stationary trains of spikes and would not participate in any time encoding in PC dendrites.

Finite duration plateaus / valleys fail to propagate
We searched the traveling system for traveling fronts between R and P with $I_{dc} \in \Omega$. Such solutions were found and are localized with the ** – labeled box on the global bifurcation diagram on Fig.3A, Fig.5A illustrating this box on a larger scale. We found traveling fronts connecting R to P (RP fronts), P to R (PR), M to R (MR) and M to P (MP). Fig.5B illustrates representative samples of these fronts in the time domain, as they would be recorded as time signal with a microelectrode in the dendrites. Starting from inf$(\Omega)$, one first encounters the MP branch. MP fronts cannot be observed experimentally due the impossibility to achieve the M unstable uniform state of dendritic polarization. The MP branch terminated at sup$(\Omega)$ and was replaced by branch RP$_1$. The RP$_1$ branch ended at $I_{dc} = 26.88$ nAcm$^{-2}$ and was replaced by branch RP$_2$. RP$_2$ fronts had smaller speeds of propagation and smaller slopes of voltage changes compared to RP$_1$ fronts (Fig.5B). Branch RP$_2$ ended at $I_{dc} = 27.64$ nAcm$^{-2}$, a current value where the front propagation speed vanished. Only waves with speeds consistent with those on the RP$_1$ branch were observed in simulations of PDEs in a long dendrite, suggesting that RP$_1$ fronts are stable whereas RP$_2$ fronts are unstable. On the right of the bifurcation diagram in Fig.5A, the MR branch emerged with a zero propagation speed. We do not discuss this branch further due to the instability of M points. The MR branch terminated at inf$(\Omega)$ and was replaced by branch PR$_1$. Branch PR$_1$ ended at $I_{dc} = 27.8$ nAcm$^{-2}$, to give birth to branch PR$_2$, which fronts has smaller propagation speeds than PR$_1$ fronts. Simulations in finite, long dendrites were only able to reproduce PR$_1$ solutions suggesting that the PR$_2$ fronts are unstable.

We then investigated whether spontaneously resetting plateau and valley potentials could also intrinsically propagate. Propagating finite plateaus / valleys were expected to appear as small radius homoclinic solutions of the traveling system in the neighborhood of $\Omega$ (see Fig.2). However, computations failed to identify such homoclinics, suggesting that spontaneously resetting plateaus and valley may intrinsically fail to propagate. We derived a definitive conclusion on this issue by investigating a geometrically tractable simplification of the model, derived as follows. Plateau potentials are slow electric events compared to the maximum value of the delayed rectifier time-constant ($\tau_n = 2.9$ms). We therefore simplified the model by setting $n = n_\infty$, i.e. by assuming instantaneous activation of $I_{Kdr}$. Moreover, the homogeneous model was shown to retains the capability to produce finite duration plateau and valley potentials when $[Ca]$ is set to its equilibrium value at each point in time (Genet and Delord, 2002). Introducing this second simplification, the traveling system reduced to the following set of differential-algebraic equations

\[
\frac{dV}{d\xi} = V_\xi \tag{19A}
\]
\[
\frac{dV_\xi}{d\xi} = \frac{2R_dR_i}{\delta(2R_d - \delta)}\left[-C\delta V_\xi + I_{ion} - I_{dc}\right]
\]  
\text{(19B)}

\[10^2 I_{eza}R_d / F + 2k(Ca - Ca_i)(R_d - \delta) = 0\]  
\text{(19C)}

With the example of \(R_d = 0.5 \mu m\), an approximate solution of Eq. 19C was given by

\[Ca(V) = 5 + 1/ e^{-(V+66)/5}\]  
\text{(20)}

Substituting this solution for Ca in Eq. 19B, Eq. system 19 reduced to a two-dimension dynamical system, with variables \(V\) and \(V_\xi\). We investigated these simpler model with phase-plane techniques (see e.g. Tu, 1994). Panels A-D on Fig. 6 illustrate how the 2D model explained geometrically the traveling fronts between P and R in the full model. Panel A illustrates the branch of the unstable manifold of the P point entering the \(N = \{V_\xi < 0\}\) half plane of the \(\{V, V_\xi\}\) phase space for three different values of the speed \(\theta\), with \(I_{dc} = 15\) nAcm\(^{-2}\). Recall that the full model can produce a \(P\rightarrow R\) traveling front for this tonic current value (branch \(PR_1\) on Fig.5B). With the smallest \(\theta\) value (0.45 cm\(^{-1}\)), the unstable manifold branch turned back inside \(N\) to intersect back \(V\)-axis at a point located at the right of the R point and continued in the \(P = \{V_\xi > 0\}\) half-plane (light gray curve). This intersection point was continuously shifted toward the left on the \(V\)-axis and approached R by increasing \(\theta\) (not illustrated). However, too large values of \(\theta\) enforced the unstable manifold to remain in \(N\) (\(\theta = 0.55\) cm\(^{-1}\), dark gray curve). In the latter case, the \(V_\xi\) variable took exploding negative value preventing the unstable manifold to connect back to the R point. It follows that there was a unique \(\theta\) value (0.497 cm\(^{-1}\), dark curve) for which a trajectory tended toward P as \(\xi \rightarrow -\infty\) and toward R as \(\xi \rightarrow +\infty\). At this \(\theta\) value, the P unstable manifold merged with the stable manifold of the R point to form a saddle-saddle, heteroclinic connection between these points, as illustrated in Fig.6B. Fig.6B depicts all branches of the R, M and P stable and unstable manifolds together with the 2D model nullclines. This heteroclinic corresponded to a traveling front from P to R, which propagation speed was of the same order as that of the \(PR_1\) front found in the full model (0.865 versus 0.497 cm\(^{-1}\)). The smaller front speed in the simplified model can be explained by the assumption of instantaneous activation of \(I_{Kdr}\), which evidently reduced the amount of inward membrane current with regard to the full model, thereby reducing the axial flux of currents exciting neighboring regions along the dendrite. Fig. 6A and 6B illustrates the phase plane of the 2D model with the example of \(R_d = 0.5 \mu m\) but the above geometrical argument for the existence of a traveling \(P\rightarrow R\) front holds for any dendritic radius value for which \(\Omega\) existed. A symmetrical topology of the vector field of system 19 accounted for \(R\rightarrow P\) transitions found in the full model with large tonic currents in \(\Omega\), as illustrated in Figure 5C and 5D with \(I_{dc} = 33\) nAcm\(^{-2}\). The branch of the R unstable manifold that entered the \(P\) half plane remained in it with large \(\theta\) (0.26 cm\(^{-1}\), light gray curve on Fig.6C). With smaller \(\theta\) values, the unstable manifold intersected the \(V\)-axis at an abscissa continuously shifted to the right by increasing \(\theta\) (see dark gray curve for \(\theta = 0.2\) cm\(^{-1}\)). Invoking again a continuity argument, it follows that there was a unique speed value at which the R and P states had a heteroclinic connection in the reduced model, corresponding to \(R\rightarrow P\) fronts found in the full model (RP\(_1\) branch in Fig.5B). Panel D in Fig.6 illustrates the 2D model phase plane with its nullclines and the stable and unstable manifolds of the three resting points at this particular speed value of 0.23 cm\(^{-1}\). This propagation speed was smaller than that of the corresponding front in the full model (0.6 cm\(^{-1}\)) which resulted from
assuming instantaneous equilibrium of \([\text{Ca}^2_]\): in the full model, \([\text{Ca}^2_]\) relaxes slowly from its high value in the P state, favoring K currents that increase the axial flux of currents repolarizing neighboring regions of the dendrite. These conclusions held for all dendritic radii allowing the existence of the \(\Omega\) region of bistability.

Having shown that the 2D model could explain the existence of traveling R\(\leftrightarrow\)P transitions in the full model, we used this simpler model to understand the apparent failure of finite duration plateau and valley potentials to propagate in the full model. This failure is understood from the phase-plane sketch of the 2D model for \(I_{dc} = 0\ \text{nAcm}^{-2}\), a tonic current value at which the spatially homogeneous model can produce finite-duration plateaus in response to a phasic depolarizing current (see Fig.1B). Thus, the \(V_\xi\) nullcline of the 2D model was located below the \(V\) nullcline (abscissas) for \(V > V_R\) for all \(\theta\) values (1 cm s\(^{-1}\) on Fig.6E), so that the trajectory leaving the R point along the right-branch of its unstable manifold remained inside \(P\) (Fig. 6E). Therefore, this trajectory could not intersect the \(V_\xi\) nullcline, preventing a homoclinic loop to connect the R point to itself. Upon a time reversal, the trajectory leaving R along its stable manifold crossed the middle branch of the \(V_\xi\) nullcline at some point where the slope of the curve changed its sign. But the trajectory subsequently intersected the right branch of the \(V_\xi\) nullcline and the slope of the curve changed its sign again so that the trajectory remained confined to the \(N\) half-plane, confirming the impossibility for a homoclinic to R to occur in the model whatever \(I_{dc}\) below \(\text{inf}(\Omega)\). This proved that finite-duration plateau potentials found in the homogeneous system cannot produce traveling waves along an infinite dendrite whatever its radius. Similar geometrical arguments held for P points, which could not form homoclinic loops with \(I_{dc} > \text{sup}(\Omega)\), as illustrated on Fig. 6F with the example of \(I_{dc} = 37.5\ \text{nAcm}^{-2}\) and \(\theta = 1\ \text{cms}^{-1}\). Thus the model suggested that finite-duration valley potentials can neither propagate.

**Signals integration in PC dendrites**

Investigation of the traveling system suggested that Ca spikes and switches between resting and plateau states intrinsically propagate but that finite duration plateau and valley potentials are non-propagating events in the usual spike acceptance. However, these conclusions were derived from idealized infinite dendrites which elude large impedances loads imposed on each dendritic segments by the rest of the tree. These loads crucially impede on electric signals integration in the tree (Segev and Rall, 1998). Thus, results from infinite dendrites did neither indicate how Ca spikes propagate nor how finite duration plateaus and valleys spread in the complex PC dendritic arbor. We investigated these questions by simulating the model in simplified representations of a reconstructed PC.

**Complex spikes**

Fig. 7A illustrates the architecture of Shelton’s cell without its dendritic spines. As spines account for >80% of the overall dendritic area, the geometrical dimensions of the cell were rescaled to introduce them (see Mathematical model section) and we also adopted the larger physical dimensions of a guinea pig cell that Shelton (1985) used to estimate the cell leakage membrane conductance used in our model. The dendogram illustrated on Fig.7B shows that spiny branches in the rescaled PC ended at variable electrotonic distances from the soma, with a maximum of 0.55 at the tip of segment 13 of spiny branch 68 (using Shelton’s indexation). This maximum was larger than that derived by Shelton (0.33) but was close to values delivered in more recent studies of PC dendrites passive properties (0.57 in De Schutter and Bower, 1994; 0.59 in Segev et al., 1991). The discrepancy with Shelton’s estimate resulted from the small density of spines Shelton used in his model before histological data provided larger estimates for this parameter (Harris and Stevens, 1988; Napper and Harvey, 1988),
used in the latest models including our own. The maximum value of 0.55 means that a steady voltage applied to the soma can be attenuated by up to 42% at the tip of dendrites. Most theories of the cerebellum regard complex spikes triggered by the CF as a mean to overcome this attenuation to deliver unitary teaching signals by safely propagating active electric signals in the dendrites. Consistent with this view, the conservation of the cross sectional area at each branch point in the tree (Shelton, 1985) entails an impedance increase from the soma, theoretically increasing the safety factor of Ca spikes propagating in the somatofugal direction. However, occasional failures of CF-triggered Ca spikes to invade the whole dendritic tree have been reported (Miyakawa et al., 1992). Moreover, complex spikes exhibit highly variable shapes and both causes for this variability and how these waveforms propagate in the tree are currently unknown. The question arises whether these failures result from an intrinsic failure of Ca spikes to propagate due to limitations of the dendritic membrane to feed enough inward current or whether they reflect the activation of inhibitory synapses, as suggested by Miyakawa et al. (1992). We analyzed these questions by simulating the model in an equivalent cable representation of Shelton’s PC designed to simulate the propagation of complex spikes (see Model geometries section). The best fit ‘somatofugal model’ had a 73.5 µm diameter for its segment most distal from the soma and a total membrane area of 410730 µm$^2$ (0.6% difference with the membrane area of the full cell). Its somatic input resistance was 26.9 MΩ, 33% larger than the value in the full cell. It follows that CF conductance values used below to trigger propagated complex spikes along the equivalent cable must be regarded as minimal.

We first addressed the significance of the distributed synapse of the CF regarding propagation of complex spikes by simulating responses of the equivalent cable to the activation of a CF conductance distributed over different fractions of the cable area. The total CF conductance was set to 1.2 µS. In the hypothetical situation where this conductance would be confined to the cell soma, the CF triggered a full Ca spike in the soma, followed by a 600 ms duration plateau potential (Fig.7C$_1$). Notice that the model does not encompass Na conductances and cannot therefore reproduce the initial fast Na spike of CFRs (Schmolesky et al., 2002). The late plateau propagated up to the tip of the equivalent cable, while the spike component rapidly faded away from the soma and had nearly completely vanished at L = 0.147. When the CF conductance was distributed over smooth dendrites (Fig.7C$_2$, actual distribution of CF synapses), both the Ca spike and its accompanying plateau propagated over the entire cable. A slight decrease in spike amplitude is noticeable at the end of smooth dendrites (L = 0.196). Further away from the soma, the Ca spike recovered a close to constant amplitude. These amplitude changes cannot be attributed to the well-known effect of sealed boundary on spike propagation (Jaslove, 1992) and therefore reflected the capability of the model to propagate Ca spikes evidenced in infinite cables (Fig.3B). We finally simulated the opposite hypothetical situation where CF synapses would distribute over the whole dendritic tree (Fig.7C$_3$). In this case, the CF current triggered two Ca spikes propagating over the entire cable length but the CF response lacked the subsequent plateau. Full propagation of Ca spikes and plateau components of the CF response were only observed with focal distributions of the CF conductance over membrane areas deviating from that of smooth dendrites by less than 15% in absolute magnitude. By contrast, these propagated signals proved robust to changes in the magnitude of $g_{CF}$ up to 20% of its reference value.

We then explored how $I_{dc}$ affects the shape of propagated CFRs. Let us denote CFRs starting from R and ending on R after a finite duration plateau as RspR (R→spikes→plateau→R) responses. As illustrated on Fig.7D, the plateau in these responses was smoothly lengthened by increasing $I_{dc}$, Fig.7E$_1$ giving examples of RspR responses for five $I_{dc}$ values. At $I_{dc} = -24.9$ nAcm$^{-2}$, the plateau duration of RspR responses became infinite. From this value, and up to sup($\Omega$), activation of $g_{CF}$ triggered a burst of Ca spikes followed by
a switch to P (RsP responses; Fig.7E1). More complex responses were observed when $g_{CF}$ was activated from the P state. Activation of the CF triggered a burst of Ca spikes with diminishing amplitude, followed by a plateau ending on R (PspR responses observed with $I_{dc} \in [\inf(\Omega),-12.75]$; Fig.7E2). The plateau duration in PspR responses became infinite at $I_{dc} = -12.75$ nAcm^2, resulting in a PsP response. PsP responses were observed up to $I_{dc} = 28.545$ nAcm^2, with little variations in their shape. At this value, however, a marked shape change occurred, as the Ca spike burst was terminated by a larger amplitude Ca spike that switched the entire cable to R (PsR responses observed up to 29.65 nAcm^2; Fig.7E2). With $I_{dc} > 29.65$ nAcm^2, CFRs consisted in a Ca spikes burst ended by valley potentials (PsVP responses; Fig.7E3). The duration of valleys in PsVP responses smoothly decreased with $I_{dc}$ (Fig.7D). Thus, the abrupt P→R transition triggered by $g_{CF}$ at $I_{dc} = 29.65$ nAcm^2 resulted from the valley potential duration becoming infinite at this $I_{dc}$ value. Notice that somatic waveforms illustrated on Fig.7E propagated to the tip of the equivalent cable with little attenuation of their Ca-spike components. As these different waveforms reproduce all of the reported shapes of CFRs, these results suggest that the natural distribution of CF synapses over smooth dendrites grants the safe propagation over PC dendrites of both Ca spikes and after plateau / valley potential components of the complex spike. Such robustness support the premise of Miyakawa et al. (1992) that activation of inhibitory synapses at branch points in the dendritic tree may be responsible for the occasional failure of Ca spikes to invade all branches of PC dendrites.

**Plateaus and valleys**

Synaptic signals suffer a steeper attenuation when conducted toward the soma than toward distal regions of the tree (Segev et Rall, 1998). Fig. 8A1 illustrates this feature in Shelton’s PC by pooling attenuations along all branches of the tree of a steady voltage signal applied to the tip of the arbitrarily chosen 13th segment of spiny branch 69the voltage. Voltage attenuation was >80% at the tip of the 23rd segment of spiny branch 23, the most distant locus from the stimulation point, in large excess to attenuation of somatofugal signals (Fig.7A). The somatofugal equivalent cable was therefore inadequate to investigate propagation of plateau and valley potentials triggered by peripheral synaptic inputs. We built a second type of equivalent cable to investigate this problem (see Model geometries section), allowing to compute the global attenuation of signals delivered to arbitrarily chosen spiny branches. With the example of spiny branch 69 as the locus of synaptic inputs, the best-fit somatopetal equivalent cable model (Fig.8A2) had a terminal radius of 511µm and an input resistance of 52 MΩ at the origin of branch 69 (0.7% default difference with the value in the uncollapsed tree). The equivalent cable had however a ~1.5 larger membrane surface than the full cell, so that conditions for exciting plateau and valleys that we derive using this model must be regarded as minimal.

Branch 69 of the somatopetal equivalent cable was stimulated with trains of PF EPSCs to check the model predictions against the in vivo recordings of plateau potentials in PC dendrites from Campbell et al. (1983). The voltage response in branchlet 13 of branch 69 to 5, 8 and 10 shocks with a 20ms ISI is illustrated on Figure 8B. After 5 large EPSPs (Fig.B1), $V$ relaxed exponentially toward its resting state as observed by Campbell et al. (1983, see their Fig.4). A prominent shouldering in the voltage response appeared after EPSPs when the shock number was increased to 8 (Fig.B2), in close agreement with experimental data. Finally, the model produced an 800 ms plateau potential after 10 shocks (Fig.B3), to compare with the 250ms duration plateau on Fig.4 from Campbell et al. (1983). With the exception of different durations for long plateaus, simulations of the somatopetal equivalent cable therefore closely mimicked dendritic recordings of Campbell et al. (1983). Campbell et al. could only speculate on the propagation of these signals in the dendritic tree from their
point recordings. But the superimposed voltage traces in the soma and branchlet 13 of the equivalent cable on Fig.8B suggest that, while EPSPs suffered a steep attenuation at the soma, the plateau potential triggered in the spiny branch readily invaded the rest of the tree, as the plateau part of the response was nearly identical at both locations in the model. Fig.8B illustrates comparable responses to 6 hyperpolarizing shocks delivered to spiny branch 69 with the equivalent cable turned to its plateau state by a 45 nAcm\(^{-2}\) tonic current. These voltage traces evidence similar capabilities of finite duration valley potentials triggered by a distributed input to invade the whole equivalent cable.

These findings were confounding given the demonstration that finite duration plateaus and valleys are non-propagating signals (Fig.6). We therefore investigated the stimulation patterns allowing plateau and valley potentials to invade the whole somatopetal equivalent cable. Fig. 8C\(_1\) displays the color-coded duration of plateau potentials at the soma location in the equivalent cable, triggered by a variable \(g_{PF}\) (ordinates) distributed over a variable number of branchlets in spiny branch 69 (abscissas); magnitude of the stimulating conductance reads as the product of \(g_{PF}\) time the stimulated area. Fig. 8C\(_1\) shows that focal excitation of narrow portions of branch 69 area failed to trigger plateau potentials whatever physiologically acceptable magnitudes for \(g_{PF}\). Plateau potentials could only be triggered when at least half of the branch area was excited with a conductance of 1.1µScm\(^{-2}\). Increasing \(g_{PF}\) shortened the plateau duration as the larger conductance allowed more Ca\(^{2+}\) ions to enter dendrites, thereby decreasing \(E_{Ca}\) and shifting the balance of membrane ion currents in favor of hyperpolarizing K currents. Distributing the excitatory conductance over a larger membrane area allowed smaller \(g_{PF}\) to trigger plateau potentials over the whole dendritic tree. Thus, \(g_{PF} = 0.3\) µScm\(^{-2}\) sufficed to trigger a ~1s duration plateau potential when the conductance was distributed over the whole 69 branch. Fig.8C\(_1\) thus shows that the voltage threshold of plateau potentials in the homogeneous model translated into a condition of minimal excited membrane area for triggering a plateau potential over the entire tree. This feature was reminiscent of stimulation conditions increasing the safety factor for classical spikes to propagate from the dendrites toward the soma (Segv and Rall, 1998). However, computations revealed that plateaus could invade the whole cable without the total membrane current becoming inward (not illustrated), this condition, known as ‘Cole’s theorem’, being necessary to propagate a spike over distributed structures (Jack et al., 1983). The ensuing conclusion is that occurrence of plateau potentials in the soma following a peripheral stimulation in the dendritic tree does not repose on a spike propagation mechanism. These ‘spreading plateaus’ can neither be regarded as an electrotonus given that plateaus have a voltage threshold. Further simulations showed that the duration of somatic plateaus triggered in dendrites of the equivalent cable were lengthened by increasing \(I_{dc}\) and shortened by lowering the tonic current (not illustrated). These results agree well with responses of turtle PC dendrites to PF activation, which include a plateau component prolonged by depolarization and shortened by hyperpolarization of the membrane (Chan et al., 1989).

We also investigated conditions allowing phasic hyperpolarizing currents to trigger valley potentials to invade the equivalent cable switched in its P state. The graph of valley potential durations versus the magnitude and spatial extension of an inhibitory conductance distributed in spiny branch 69 is illustrated on Fig.8C\(_2\). It exhibits similar features with that of plateau potentials (Fig.8C\(_1\)), showing that valleys shared same triggering conditions to invade the dendritic tree. Conductances used to trigger plateaus and valleys in these simulations induced large E/IPSPs. These cannot however be confused with Ca spikes owing their smaller magnitude. Such EPSPs may considered unrealistically large but one must notice that their triggering conductance was distributed only over spiny branch 69 whose area accounts for only 1.8% of the total membrane cell surface. With this conductance, the number of E/IPSCs required to trigger plateau/valleys at the soma decreased with the number of EPSCs as
illustrated on Fig.8C with the example of plateau potentials. These results clearly show that both duration and magnitude of synaptic inputs to trigger plateau / valley potentials decreased when the stimulated area increases. These results therefore put on the idea that plateau and valley potentials in PC dendrites represent an original mechanism of electrical signaling intermediate between the auto-regenerative propagation of classical action potentials and decrementing electrotonus, by which PCs have evolved to produce timed responses to inputs focalized in space and time over their dendritic tree, the duration of which is controlled by ongoing background synaptic activity.
DISCUSSION
The first contribution of this modeling study is an understanding of dendritic mechanisms timing long steps and pauses in somatic Na spike firing exhibited by PCs in vivo (Miller et al., 2002). Dendritic plateaus exhibit a constant voltage (~ -45mV; Llinas and Sugimori, 1980; Genet and Kado, 1997; Llinas and Sugimori, 1992), at which the cell soma fires Na spikes [see Fig.8.6 in Llinas and Sugimori (1992) and Figs 1&6 in Loewenstein et al. (2005)]. Valleys should interrupt this firing since their mean voltage (~-55mV) lays below the Na spikes threshold. Together with the current load that the overwhelmingly large dendritic area of PCs imposes on their soma, these features strongly suggest that lasting activities and pauses in PCs output originate in dendritic plateau and valley potentials. Experiments have given confounding results regarding the site of initiation and propagation of plateaus. Thus, recordings from turtle PCs, which share a similar conductance distribution with mammalian PCs (Hounsggaard and Midtgaard, 1988) suggested first that plateaus are triggered in proximal dendrites (Chan et al., 1989). Later recordings from mammalian PCs rather concluded that they originate in spiny dendrites and invade the whole dendritic tree (Llinas and Sugimori, 1992). These advert conclusions may reflect different signal integration in reptilian and mammalian PCs due to their different dendritic branching patterns. Our model reconciles these results in a manner more plausible in light of the preserved intrinsic properties of PCs throughout the invertebrate phylogeny (Midtgaard, 1994). It suggests that plateaus and valleys can be triggered from any dendritic location due to an unusual mechanism of electrogenesis. Plateaus and valleys in the model exhibit features in striking contrast with the two known modes of electrical conduction in excitable cells. They cannot be classified as spikes as we have proved their intrinsic failure to propagate and as they fail the all-inward current condition for spike propagation in a distributed structure (Jack et al., 1983, results not illustrated). They can neither be regarded as a spreading electrotonus given their voltage threshold. These electric signals can invade the whole dendritic tree once a distributed current threshold condition is exceeded. This threshold inversely relates density of excitatory/inhibitory currents to the stimulated surface in total independence of the location at which inputs occur. This study therefore concludes that plateau and valley potentials constitute an original mode of dendritic excitability by which PCs can produce long lasting steps and pauses in their somatic outputs in response to brief, synchronous excitation/inhibition distributed over large dendritic patches. Plateau potentials triggered in mammalian PCs by stimulating large PF bundles (Campbell et al., 1983) support this interpretation. Such a synchronous PF activation was deemed physiologically unrealistic. But the long-lasting depolarizations of PCs that can be triggered by weak activation of synapses of the ascending portion of PFs [the major activating input to PCs (Cohen and Yarom, 1998)] (Jaeger and Bower, 1994) suggest that these signals represent physiological PC outputs.

The second contribution of the model is an explanation for the puzzling variable shape of complex spikes, completed by clues on how PC dendrites integrate these electrical responses. The model reproduces the various patterns of Ca spike and after effects of CFRs (chapter 8 in Ito, 1984). Thus, it predicts that increasing tonic currents must change the late part of CFRs from plateau potentials with increasing duration, to switching between the R and P states and finally to shortening valley potentials. Recordings from turtle PCs support the model results on plateaus in complex spikes: this plateau is prolonged by depolarization and abolished by hyperpolarization of the membrane, as predicted by the model (Fig.7D). The narrowness of the Ω zone into which the CF can induce R→P and P→R transitions in the model explains straightforwardly the low percentage of mammalian PCs into which the CF triggers these state transitions (Loewenstein et al. 2005), as scarce PCs are expected to receive a tonic input falling in Ω. Finally, valley potentials terminating complex spikes for
large tonic inputs in the model offer an attractive explanation for the occasional pauses in simple spike firing following activation of the CF initially reported by Granit and Phillips (1956). Together, these results suggest that the variability of complex spikes among PCs must be attributed to different states of activation of their dendritic conductances by varying MF inputs, in agreement with the fact that these various responses are also observed over time in single PC units. A chief prediction of our model is that the natural distribution of the CF multiple synapses over smooth dendrites entails the propagation over the entire dendritic tree of Ca-spikes and terminating plateaus and valleys components of complex spikes. This propagation being robust to large variations in the CF conductance, we propose that the segregation of CF synapses over smooth dendrites represents an evolutionary adaptation granting the propagation of unitary voltage transients with adaptive duration over PC dendrites.

The unique features of plateau and valley potentials unraveled by the model offer a challenging possibility to extend the postulated function of PCs as pattern selection devices to the time domain. The distribution of active synapses achieving optimal computations in a perceptron was recently shown to match that of active PF synapses on PCs (Brunel et al. 2004), suggesting that the classical analogy between the PC and the perceptron is sound. However, in the classical perceptron, both input and output patterns to be associated must be imposed to the cell, whereas outputs with a precise duration are what PCs must produce from their mossy and climbing fiber inputs. According to the model, PCs solve this computational problem by allowing ongoing tonic inputs in the MF system to control the duration of plateaus and valleys potentials triggered in their dendrites by brief focal inputs. This interpretation overcomes the incapacity of spectral models to explain adaptive timing in the trace version of the eye blink conditioning. Calculations from the model reveal that <1 pA changes in the total tonic current delivered to the dendritic arbor could change the duration of >1.5s lasting plateaus and valleys by as much as 500 ms. This finding sets an upper theoretical limit to time intervals that PCs can reliably encode since PF synapse have unitary EPSCs in the order of tens of pA (Barbour, 1993). The passive membrane time constant of PCs sets a lower limit of 100 ms to these intervals, resulting in a time range encompassing ISIs used to probe the cerebellum function (Hore et al., 1991 ; Ivry and Keele, 1989). We posit that the upper time limit explain recruitment of other brain areas (basal ganglia and cerebral cortex) to encode longer time representations.

PCs are probably the most complex neuron in the brain as they express a wealth of different ion currents distributing differentially over an extremely ramified dendritic tree. Selecting the level of details to include in our model to address mechanisms of timing at play in this neuron was challenging as detailed models have proven unable to reproduce its various discharge patterns with a single parameter set (De Schutter and Bower, 1994). We targeted our model to dissect underlying mechanisms of CFRs, plateaus and valleys without getting entangled in inextricable non-linear mechanisms interacting in a branched structure that cannot be reduced to an equivalent cylinder. Thus, our model does not include the \( I_h \) current of PCs (Crepel and Penit-Soria, 1986) which shapes their bistable properties (Williams et al., 2002). By discarding this current, our model cannot provide a faithful account of PC dendrites bistability. However, the set of currents in our model proves able to reproduce it qualitatively as well as finite duration plateaus of PCs. It also predict valley potentials which, together with finite duration plateaus offer larger time encoding capabilities to PCs than bistable models (Loewenstein et al., 2005). In the same way, we derived geometrical reductions of the dendritic tree to address the global integration properties of the cell. Finally, rather than trying to examine exhaustively traveling solutions in the model, we focused on identifying those solutions reproducing electric waveforms recorded from point locations in PCs and then used the distributed model structure to understand how these signals are processed in dendrites.
Membrane potential dynamics illustrated in this paper should not distract the reader from the fact that Ca dynamics are an integral part of the model, allowing simulations of the intradendritic Ca concentration during plateaus, valleys and CFRs. Recall that the dominant cellular event associated with a complex spike is a large Ca influx which induces plastic changes at the different synapses onto PC dendrites (Hansel et al., 2001), whose impairment severely alters cerebellum performances (Koekkoek et al., 2003). The model is readily usable to investigate how synaptic plasticity may teach PCs to produce the timed plateaus and valleys put forward in control theories (Houk, 1989; Berthier et al., 1993; Barto et al., 1999).
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FIGURE CAPTIONS

Fig. 1. Dynamics of the spatially homogeneous model. A Bifurcation diagram of the homogeneous system along $I_{dc}$, the density of tonic synaptic inputs; steady solutions are depicted as thin lines and periodic solutions as thick ones; solid (/dashed) lines correspond to stable (/unstable) solutions. R: resting states, P: plateaus, M: threshold points between R and P states in the hysteresis region $\Omega = [5.85, 42.76]$ (nAcm$^{-2}$). B The same square pulse of depolarizing current (100 ms, 130 nAcm$^{-2}$) triggers a triangular, a rectangular finite duration plateau potential and a R$\rightarrow$P transition with growing $I_{dc}$. C Irreversible P$\rightarrow$R transition, rectangular and triangular valley potentials triggered by pulses of hyperpolarizing current (100 ms, -150 nAcm$^{-2}$) illustrate a symmetrical behavior with growing $I_{dc}$s at the right of $\Omega$. D Repetitive train of Ca spikes triggered by a 1s, 575 nAcm$^{-2}$ amplitude depolarizing pulse. Dendritic radius $R_d = 0.5\mu$m in A-C. E Upper $[\sup(\Omega)]$ and lower $[\inf(\Omega)]$ boundaries of $\Omega$ versus $R_d$. Vertical bars delimit the range of dendritic radii in Shelton’s PC.

Fig. 2. Traveling wave solutions in an infinite dendrite. The different traveling waveforms that were searched in the model are schematically represented as they appear in a co-moving frame of reference, with coordinate $\xi = x - \theta t$ ($x$: spatial coordinate, $\theta$: propagation speed, $t$: time) accompanying the wave propagation (left) and as corresponding membrane potential ($V$) profiles along an infinitely long dendrites frozen at a given time (right; arrows indicate the propagation direction). Open circles represent unstable steady states; $V_\xi$ is the derivative of $V$ with respect to $\xi$.

Fig. 3. Propagation of Ca spikes along infinite dendrites (I). A Bifurcation diagram of the different traveling solutions identified in the model. For small $I_{dc}$ values, 6 distinct branches of unitary traveling Ca spikes were found ($S_{1-6}$), overlapping in $\Omega$ (* labeled – box.). Above $I_{dc} = 561.5$ nAcm$^{-2}$, the model produced periodic waves of Ca spikes, whose propagation speed is illustrated at their Hopf bifurcation point of emergence. Sub-threshold propagating solutions were found in $\Omega$ and their speed is depicted with a larger ordinate scale in the ** – box (see Fig. 5 for detailed illustrations). B Left: enlargement of the * labeled – box. Right: Sample illustrations of unitary traveling Ca spikes from the $S_{1-6}$ branches in the time domain. Notice the various spike-induced transitions between the R, M and P states depending on $I_{dc}$. Dashed lines locate the voltage of the M point on each curve. C Duration of plateau and valley potentials in orbit branches $S_1$ and $S_6$ versus $I_{dc}$. $R_d = 0.5\mu$m in all computations.

Fig. 4. Propagation of Ca spikes along infinite dendrites (II). A Superimposed waveforms of one, two and three spike traveling solutions of the model for $I_{dc} = 0$ nAcm$^{-2}$. Notice weak impact of the spike number on duration of the terminating plateau potential. B Dispersion relations of propagated trains of spikes for three different $I_{dc}$ values: 561.5 (light gray), 600 (dark gray) and 1000 nAcm$^{-2}$ (black). Filled circles indicate the Hopf bifurcation current origin of wave trains on each curve. Vertical asymptotes to the upper part of the curves correspond to standing waves, periodic in space. C Envelope of the propagated trains of spikes versus $\theta$ for the same $I_{dc}$ values used in B and with the same gray-tone coding.
Fig. 5. Propagated sub-threshold solutions along infinite dendrites. A Enlargement of the ** box on Fig.3, illustrating bifurcations of sub-threshold traveling solutions versus $I_{dc}$. Branches are labeled after two letter symbols: first letter denotes the initial homogeneous state of the dendrite and the second letter the final state (e.g. the MP branch corresponds to M → P traveling fronts). B Time course of membrane potential $V$ at a fixed location in the infinite dendrite for representative examples of the different branches of traveling solutions depicted on A. Only the PR$_1$ and RP$_1$ kinds of solutions are stable (see Results). Dashed lines locate the voltage of the M point on each curve. Orbits computed with $R_d = 0.5\mu m$.

Fig. 6. Phase plane analysis of sub-threshold traveling solutions in a simplified model. Overall propagation of slow, sub-threshold signals are captured geometrically by a 2D simplification of the model, derived by assuming instantaneous activation of the delayed-rectifier K current and instantaneous equilibrium of $[Ca]$. Panels illustrate the $(V_\xi, V)$ phase-plane of this reduced model written in the $\xi$ reference frame with $I_{dc} = 15$ (A, B), 33 (C, D), 0 (E) and 37.5 nAcm$^{-2}$ (F). Solid thick curves represent the $V$ and $V_\xi$ nullclines, i.e. sets of points at which the $\xi$ derivative of $V$ and $V_\xi$ respectively vanishes. Intersection points between nullclines correspond hence to steady states of the 2D model, i.e. homogenous solutions in the spatial domain. Dotted thin curves represent the stable and unstable manifolds of these resting points. A Propagation speed $\theta = 0.45$ (light gray curve), 0.497 (black curve) and 0.55 cm$^{-1}$ (dark gray curve). A heteroclinic connection between P and R occurs at the intermediate speed. B Fully illustrated phase space in the heteroclinic case found in A, corresponding to the propagation of a P→R front. C $\theta = 0.2$ (light gray), 0.230 (dark) and 0.26 (dark gray) cm$^{-1}$. At the intermediate speed, the R and P points are connected by a heteroclinic orbit corresponding to a traveling R→P front. D Phase-plane for $\theta = 0.230$ cm$^{-1}$ illustrating the R-P heteroclinic connection. E With $I_{dc} = 0$ nAcm$^{-2}$, the unstable manifold of the R point entering the upper phase-plane remains in it because the $V_\xi$ nullcline is located below the $V$ nullcline; trajectories arising from the unstable manifold branch located in the lower phase space intersect twice the $V_\xi$ nullcline and cannot therefore emerge from the upper unstable manifold branch: finite duration plateaus cannot thus propagate along an infinite dendrite. F With $I_{dc} = 45$ nAcm$^{-2}$, the unstable manifold of the P point also crossed twice the $V_\xi$ nullcline, preventing the propagation of finite duration valley potentials. $\theta = 1$ cm$^{-1}$ in E-F.

Fig. 7. Climbing fiber signals in the somatofugal reduction of PC. A Morphology of Shelton’s rat PC with its smooth (black segments) and spiny (gray segments) dendrites. This sketch represents dendritic shafts without spines and locates the more distant point from the soma in electrotonic units (tip of segment 13 from branch 68) and the more distant point from branch 69 (tip of segment 23 from branch 23). B Attenuation of a somatic input along all branches of the tree depicted in A after its dimensions were rescaled to introduce dendritic spines and larger physical dimensions of a guinea-pig cell (see results); the membrane was endowed with a passive conductance $g_{Leak} = 20 \mu S$cm$^{-2}$. Abscissas indicate distance from the soma in electrotonic $X$ units. C Simulation of membrane potential time-course along the somatofugal cable representation of the active dendritic tree in response to a CF input distributed over different membrane areas. The equivalent cable model is represented on the left with blackened zones indicating stimulated compartments; sketch C$_2$ corresponds to the actual distribution of CF synapses over smooth dendrites. Total CF conductance, $g_{CF}$, was 1.2 $\mu S$ with a uniform $I_{dc} = -40$ nAcm$^{-2}$. D After an initial spike burst starting from the R or P states, the CF triggered a burst of Ca spikes (s) after which the cable settled to the R or P
states following a plateau (p) or valley (v) potential giving rise to RspR, PspR, Rsp, PsP and PsvP forms of CFRs. Graph illustrates the duration of plateau and valleys in RspR, PspR and PsvP responses versus $I_{dc}$. E: samples of the various CFRs obtained by varying $I_{dc}$, (tonic current value is indicated on each curve. E1: RsR, RspR and RsP responses; E2: PspR and PsP responses; E3: PsvP and PsR responses.

**Fig. 8.** Responses of the somatopetal reduced cable to mossy fiber inputs. Attenuation profiles along branches of Shelton’s PC for an electric signal triggered in spiny branch 69 (A1) were used to build a reduced somatopetal cable mode (illustrated on A2; see Methods). B Responses of the somatopetal cable to trains of E/IPSCs delivered to the whole spiny branch 69; dark curves: $V$ time course in segment 13 from spiny branch 69, gray curves: somatic membrane potential. B1: 5, B2: 8 and B3: 10 depolarizing shocks with $g_\phi = 0.1 \mu S/cm^2$, a 20 ms ISI and no $I_{dc}$. B4: 6 hyperpolarizing shocks with same $g_\phi$ and ISI as on B1-3 but $I_{dc} = 45 \, \text{nA/cm}^2$ to switch the Somatopetal model in the P state. C Color-coded duration of plateau (C1, $I_{dc} = 25 \, \text{nA/cm}^2$) and valley potentials (C2, $I_{dc} = 45 \, \text{nA/cm}^2$) in response to E/IPSCs (20ms ISI) delivered to a variable number of branchlets in spiny branch 69 (expressed as the stimulated membrane surface on the abscissa). C1: 6 EPSCs with variable $g_\phi$; C2: 6 IPSCs with variable $g_\phi$; C3: variable number of EPSCs with $g_\phi = 0.5 \, \mu S/cm^2$. 
Figure 1
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