How well do we understand the cochlea?

Renato Nobili, Fabio Mammano and Jonathan Ashmore

As sensory cells, hair cells within the mammalian inner ear convert sounds into receptor potentials when their projecting stereocilia are deflected. The organ of Corti of the cochlea contains two types of hair cell, inner and outer hair cells, which differ in function. It has been appreciated for over two decades that although inner hair cells act as the primary receptor cell for the auditory system, the outer hair cells can also act as motor cells. Outer hair cells respond to variation in potential, and change length at rates unequaled by other motile cells. The forces generated by outer hair cells are capable of altering the delicate mechanics of the cochlear partition, increasing hearing sensitivity and frequency selectivity. The discovery of such hair-cell motility has modified our view of the cochlea as a simple frequency analyser into one where it is an active non-linear system that deals with complex aspects of hearing, particularly in the low-frequency range. The outer hair cells are capable of altering the delicate mechanics of the cochlear partition, increasing hearing sensitivity and frequency selectivity. The discovery of such hair-cell motility has modified our view of the cochlea as a simple frequency analyser into one where it is an active non-linear system that deals with complex aspects of hearing, particularly in the low-frequency range.

In this article we aim to show that, by integrating physical principles with novel information on sensory receptor function, a multidisciplinary research effort has substantially improved our view of cochlear mechanics, although many questions remain unresolved.

R.M. Ransohoff and M. Tani – Cerebrosides and leukocyte recruitment

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REVIEW

The basilar membrane of the mammalian cochlea is an elastic strip tensioned across the fluid-filled cochlear duct\(^a\). The membrane, whose different portions interact through the fluid\(^b\), is the supporting medium for ‘travelling waves’ that form when sound is transmitted through the middle ear. For the sake of physical clarity, the cochlea model proposed by Helmholtz and M. J. Longmans\(1364–1374\) is therefore more satisfactory to treat the micro-piston system as a continuum.

In the absence of fluid coupling, a local force impulse would produce an instantaneous membrane acceleration proportional to the force, with the proportionality factor being the inverse local mass (Fig. B). Correspondingly, under the action of a sinusoidal force synchronously acting over the whole membrane, the response would be a typical resonance profile (Fig. C), with 180° phase difference on opposite sides of the resonance point. This ‘dry cochlea’ model was originally proposed by Helmholtz and influenced cochlear physiology for over a century.

Hydrodynamic coupling alters substantially this acceleration pattern. The instantaneous membrane acceleration elicited by a local force impulse applied to the membrane at rest (as above) displays the profile in Fig. D. Fluid pressure spreads instantaneously from the force application site and pushes adjacent membrane segments in the direction opposite to the force impulse (curved blue arrows). Thus, in general, any local basilar membrane oscillation generates forces that tend to drive flanking modules to swing with opposite phases. However, due to the exponentially graded membrane stiffness, the effect is different at opposite sides, the response being smaller at the stiffer (more basal) side, so that the semi wavelength of the oscillation decreases from base to apex (Fig. E). Under the action of a sinusoidal input at the stapes, this dynamic effect results in a monotonically increasing phase delay of the local oscillations versus distance from stapes. This asymmetry bears important consequences on wave dynamics as the ‘apparent mass’ of the fluid locally involved in the oscillation decreases from base to apex far more rapidly than all other graded quantities, resulting in the characteristic shrinking of the travelling wavelength at a frequency-dependent critical point. The wave amplitude profile tends to elevate markedly in the proximity of this point, beyond which the membrane motion, as well as that of the fluid, undergoes a steep fall. The peak height of the travelling wave would increase without limit if the intrinsic viscosity fell to zero\(^c\).

**Box 1. Travelling wave generation**

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**Cochlear models**

The mammalian auditory system can rapidly detect and track the time-varying features of sound sources, notably those of biological significance, over a wide range of frequencies and amplitudes\(^d\). Interacting the world of mechanical vibrations with nerve signal transmission, the cochlea differs appreciably from a typical Fourier analyser, the cochlea model proposed by Helmholtz over one century ago\(^e\). Helmholtz proposed that the cochlea consisted of a set of uncoupled filters, ordered in frequency like the strings of a piano, each receiving the same input and corresponding to a nerve fibre. The filter was structured from the basilar membrane, which he represented as a dense set of elastic fibres tensioned across the fluid-filled cochlear duct with fibre stiffness decreasing exponentially along the coiled axis of the cochlea. With this arrangement, it was thought that the basilar membrane could...
organize incoming sounds into a pattern of activity in the auditory nerve.

Fluid interactions were completely overlooked by Helmholz. As demonstrated later by von Békésy, the basilar membrane supports ‘travelling waves’ that form under the action of the fluid-pressure field transmitted by the stapes in the middle ear to the high-frequency end of the cochlea. Von Békésy’s discovery that the basilar membrane responds to pure tones by peaking at frequency-dependent locations established a mechanical model that maps a ‘characteristic frequency’ with each site along the cochlea. In more refined models that instantaneous hydrodynamic coupling among different basilar membrane portions has a long-range character that is only approximately represented by nearest-neighbour transmission-line interactions (Box 1). Models must also account for the observation that frequency selectivity depends on the extent to which the active processes of the cochlea influence basilar-membrane dynamics (Box 2) and is much broader for sounds of normal loudness than for low-level sounds.

It is now clear that the dynamics of the cochlea are yet more subtle. Cochlear models must include the finding that instantaneous hydrodynamic coupling among different basilar membrane portions has a long-range character that is only approximately represented by nearest-neighbour transmission-line interactions (Box 1). Models must also account for the observation that frequency selectivity depends on the extent to which the active processes of the cochlea influence basilar-membrane dynamics (Box 2) and is much broader for sounds of normal loudness than for low-level sounds.

The traditional view of the cochlea as a spectral analyser thus needs to be modified to include those non-linear properties that allow only the perceptually relevant features of sound to be transmitted. Once the frequency selection by the cochlea has been carried out, the information is encoded directly in the firing rates in the auditory nerve fibres and the intervals between peaks of neural activity (Box 3).
REVIEW

The elementary differential equation governing the elongation \( x \) of a harmonic oscillator under the action of an external force \( f(t) \) is:

\[
m \frac{d^2x}{dt^2} + h \frac{dx}{dt} + kx = f(t),
\]

where \( m \) is the oscillator mass, \( h \) its viscosity and \( k \) its stiffness. The filter bank equation is a simple generalization of the above equation to a set of \( N \) oscillators:

\[
m_i \frac{d^2x_i}{dt^2} + h \frac{dx_i}{dt} + k_i x_i = f_i(t),
\]

where \( i = 1, \ldots, N \). All quantities depend on oscillator index \( i \) in such a way that the corresponding set of proper frequencies and frequency resolutions take suitable values. In Helmholtz’s model, \( f_i(t) \) is the force generated by the negative acceleration \( a_i(t) \) of the stapes and transmitted by the cochlear fluid to oscillator \( i \). These forces can be written as:

\[
f_i(t) = -G_i a_i(t),
\]

where \( G_i \) are suitable positive constants. This equation set represents the filter bank model of the cochlea. It can only be an approximation because three important force terms have been neglected on the right hand side of this equation:

1. The hydrodynamic term:

\[
\sum_j G_{ij} \frac{d^2x_j}{dt^2},
\]

representing the force caused by the negative acceleration of oscillator \( j \) and transmitted to oscillator \( i \) by the fluid pressure field. The fluid coupling is represented by positive coefficients \( G_{ij} \).

2. The shear viscosity term:

\[
\sum_i G_i \frac{dx_i}{dt} \frac{dx_j}{dt},
\]

representing the viscous forces acting on oscillator \( i \) caused by possible different velocities of its adjacent partners, \( x_i \) and \( x_j \), are the visco-constituents at the two sides. Shear viscosity depresses wave amplitudes at the short wavelength portions of the collective oscillation pattern.

3. The force term to oppose damping (i.e. to produce ‘undamping’):

\[
-x_i(0),
\]

representing the forces generated by the outer hair-cell motors when the steroconical undergo displacements \( y_i \). This force term vanishes at \( y_i = 0 \) and has a sigmoidal shape to account for the saturation properties of the cochlear amplifier.

Putting all the components together, and assuming \( x_i = x_j = x \) for simplicity, the motion equation of the cochlea can be written as:

\[
\sum_i (G_i + m_i) \frac{d^2x_i}{dt^2} + h \frac{dx_i}{dt} + k x_i = f_i(t) + G_i a_i(t),
\]

where the Kronecker delta \( \delta_{ij} = 1 \) for \( i = j \) and \( = 0 \) otherwise.

The effect of the tectorial membrane can be modelled through the dynamical coupling of the set \( y_i \) of steroconical displacements to the acceleration of \( x_i \). Although viscously coupled, the tectorial membrane behaves approximately like a second array of damped oscillators resonating at frequencies close to the characteristic frequencies of the primary oscillators, whose degree of freedom is described by \( x_i \).

The equations of motion of the second oscillator set have the form:

\[
\frac{d^2y_i}{dt^2} + C_i \frac{dy_i}{dt} = -C_i \frac{dx_i}{dt},
\]

for \( i = 1, \ldots, N \) where \( m_i \), \( h_i \), \( k_i \), \( y_i \) represent mass, damping, stiffness and coupling constants, respectively. Shear viscosity between adjacent oscillators can be neglected. At resonance, the first and third terms at the left hand side of the above equations cancel leaving after time integration:

\[
y_i = \frac{C_i}{R_i} \frac{dx_i}{dt},
\]

Therefore, the outer hair-cell force term \( U_i(y_i) \), in the linear approximation, behave like negative viscosity terms and undamp cochlear motion.

Active mechanics

For each input frequency, the amplitude of the basilar membrane vibration at the characteristic frequency does not increase linearly with intensity (as would be expected for a simple passive system) but shows signs of saturating, even within the physiological input range of 30–90 dB sound pressure level (SPL)’s for comparison, the lowest threshold for hearing is 0 dB SPL and normal speech is typically at a level of 40–70 dB SPL. This phenomenon, referred to as ‘compressive non-linearity’, arises because there are energy-dependent processes operating within the cochlea that neutralize viscous damping over a limited range of input sound levels by positive mechanical feedback (Fig. 1).

The cellular basis of such active processes is now thought to depend on the correct operation of outer ear cells of the organ of Corti. This structure is highly organized and resides on the basilar membrane. The organ of Corti also contains an acellular structure, the tectorial membrane, that lies above the reticular lamina (the top surface)’s. The tectorial membrane is attached to the tallest stereocilia of the outer hair cells (Fig. 2A). The organ of Corti contains two types of sensory cells, inner hair cells and outer hair cells (OHCs) (about 15,000 cells in the human cochlea). Both types of hair cell convert the displacement of their stereocilia’’s, caused by the relative motion of the reticular lamina and the tectorial membrane, into transducer current’’s that produces a modulation of the cell receptor potential’’s. There is considerable evidence that inner hair cells are the sensory cells of the cochlea because they synapse directly on to the auditory nerve. OHCs are motile and can convert membrane potential potential’’s into neural activity. The rate of change of the motor and the absence of ionic-current flow indicate that the motor is not an ion channel, but its molecular identity is not known.
Fig. 1. Travelling waves on the basilar membrane of the cochlea. (A) A longitudinal section of the uncoiled cochlea is represented with vertical dimension expanded by about three times. A travelling wave elicited by a 3 kHz tone is shown as a red line displacing the basilar membrane (unbroken black line) from its resting position (the wave amplitude has been magnified about 10^6 times for clarity). Arrows around wave peaks indicate the direction of local fluid flow. The fluid mass affects the dynamics of the basilar membrane, leading to different paths by amounts that depend upon the local wave length. Notice the progressive shortening of the wave length up to a critical point beyond which both the basilar membrane and the fluid remain at rest. (B) Cross-section of the cochlear duct, showing that the basilar membrane is laterally clamped across the duct and supports the organ of Corti that hosts two types of sensory hair cells: inner hair cells, that transmit signals to the acoustic nerve, and outer hair cells (OHCs), that provide mechanical amplification to the basilar membrane motion. (C) Two travelling waves, produced by a low-level input, are shown for different amplification levels (broken lines). Solid lines are wave-amplitude envelopes. (D) Basilar membrane velocity (in dB relative to 1 m sec^{-1}) versus input sound pressure level (in dB SPL) at fixed input characteristic frequency for the same two amplification levels as in (C). When the OHCs function properly (red line), the basilar membrane motion at low-input levels (below 20 dB SPL) is linear but greatly enhanced (40–60 dB) compared with the passive case (blue line). At higher input levels transducer currents saturate, limiting the undamping action provided by OHCs, and producing a compressive non-linearity in the basilar membrane response between 30 and 90 dB SPL. Above 90 dB SPL OHC forces are negligible compared with the intrinsic viscous forces and the response approaches the linear, passive case.

Fig. 2. Organ of Corti mechanics. (A) The basilar membrane (BM) supports a rigid structure formed by the pillar cells (PC) and the reticular lamina (RL). One inner hair cell (IHC) sits at the left of the pillars with its stereocilia (St) close to, but not inserted in, the overlying tectorial membrane. A triplet of outer hair cells (OHCs), firmly anchored at their apex within the reticular lamina and cupped by Deiters’ cells (DC), have their tallest stereocilia inserted in the tectorial membrane (TM). Deiters’ cells provide visco-elastic coupling between the motile OHCs and the elastic basilar membrane. (B) The organ of Corti distorts under hair-cell contraction: the lever effect associated with cell-length change forces the arch structure formed by PCs to pivot around the inner attachment of the basilar membrane. The outermost basilar membrane segment keeps almost at rest. (C) Functional representation of the organ of Corti with the OHCs represented as a displacement generator and the visco-elastic components added as shown. The tectorial membrane is coupled visco-elastically to the reticular lamina through the cell stereocilia and the interposed fluid layer. Viscosity plays an important role in organ of Corti dynamics; the viscosity of the organ of Corti itself acts as a mechanical high-pass filter that enhances the for-the-motion of the high-pass filtering of the OHC receptor potential. An analogous compensation for the IHC capacitance might be provided by the high-pass filtering properties of the coupling between the stereocilia and the tectorial membrane.
Changes in membrane potential might act as the driving force for the re-arrangement of molecular motors in the plane of the membrane. The axial stiffness of the cell (3 \times 10^{-10} \text{N m}^{-1}) depends primarily on the structure of the plasma membrane, which contains a high density of membrane proteins and is much stiffer than, for instance, the membrane of red blood cells (1 \times 10^{-11} \text{N m}^{-1}). Cell deformation is funnelled along the longitudinal axis of the cell by the cortical cytoskeleton, a highly orthotropic structure that lines the inner surface of the plasma membrane. Cell membrane stiffness must account for a considerable fraction of the total axial stiffness, otherwise most of the energy associated with the motor protein conformational change would be stored as plasma membrane internal energy and the cell would not undergo appreciable resting-length changes. These mechanical properties make OHCs work like springs of variable resting length. The axial stiffness of the cell determines how much force they can deliver and how the forces are matched to the visco-elastic properties of the organ of Corti in which they are embedded.

Another class of cell within the organ of Corti appears to be important in estimating the contribution of OHC to cochlear mechanics. Deiters' cells surround the OHCs at their basal ends and make contact with the basilar membrane while the apical end of the hair cell, the cuticular plate, appears to be held firmly within the reticular lamina (Fig. 2A). Cell motility, which produces forces along the OHC length, contributes to a tight, mechanical feedback loop capable of damping the organ of Corti and altering basilar membrane dynamics; however, the compliance of the Deiters' cells determines how OHC forces are distributed to the basilar membrane.

A contentious issue surrounding this proposed mechanism arises because the OHC transducer current is shunted by the cell membrane capacitance, producing, at high frequencies, a severe attenuation of the receptor potential would be expected to produce a fall-off with frequency of the cell motile response, while at the same time it would be expected that the internal viscous forces would increase with frequency. How, then, can OHCs be responsible for undamping a range of frequencies extending up to tens of kHz? Several attempts to solve this problem have been proposed and it currently seems likely that, despite electrical capacitative shunts, the potential across the basolateral membrane of the OHCs might be sufficient to drive motility in the intact cochlea. The question can also be addressed on a purely mechanical basis by considering the functional aspects of the organ of Corti.

Cochlear micromechanics

Understanding how the organ of Corti reacts to cellular forces is central to cochlear micromechanics. One simple scheme is that, during OHC contraction, the organ of Corti would distort as shown in Fig. 2B (Ref. 29). This hypothesis is consistent with experiments that also show that the coupling between the basilar membrane and the reticular lamina, provided by the OHCs, is dominated by the viscosity of the Deiters' cells (Fig. 2C). Such viscous coupling makes the force applied to the basilar membrane by the OHCs increase with frequency, whereas the attenuation of the receptor potential with frequency operates to cancel this effect. Cancellation can ensure that any residual frequency dependence of the OHC force is determined by the stimulus applied to the stereocilia and suggests that the tectorial membrane might control the receptor potential generation in a crucial manner.

There is little experimental information about tectorial-membrane dynamics. However, some of its properties can be inferred semi-quantitatively if we assume that it has the properties of a collagen gel: for oscillatory motion, at the characteristic frequency, the coherence length (that is, the distance over which a transversal structure remains, or to move as a single structure) is about 120 \mu m at the base and 1.2 mm at the apex of the cochlea. Both these figures are in exact agreement with the observations of the basilar membrane thickness, implying that it oscillates like a solid mass attached to the top of the OHC stereocilia bundles. These considerations support the suggestion made nearly 20 years ago that the tectorial membrane resonates and contributes to the magnitude of the displacement applied to the tips of the stereocilia of both OHCs and inner hair cells.

Accordingly, let us assume that various portions of the tectorial membrane behave as a secondary system of oscillators affected by appreciable damping, with resonance frequencies close to the characteristic frequency all along the basilar membrane length. With this hypothesis, a straightforward computation shows that, at resonance (that is, near the characteristic frequency), tectorial-membrane radial displacement, and therefore stereocilia deflection, is proportional to basilar membrane velocity. Also, because viscous force, which affects the motion of the cochlear partition is proportional to velocity, but with opposite sign, it produces undamping, neutralizing viscous losses in the range of relatively small oscillations (up to about 10 nm). At larger amplitudes the transducer current saturates, undamping is overcome by viscous losses and the basilar-membrane response approaches that of a passive cochlea. The transition between the two different damping levels makes the basilar membrane input/output function highly non-linear (Fig. 1D). It is noteworthy that, for speech sounds of normal intensity, the cochlea works across the transition region between two different regimes.

Non-linearity

If the cochlea operated linearly, it would perform like a bank of linear filters which separated the Fourier components in a sound, and travelling waves would be equivalent to linear combinations of harmonic oscillation modes as in Helmholtz's model. Mechanical non-linearity breaks down this equivalence, producing effects that are important for acoustic-signal processing at normal loudness levels. Ironically, discovery of the active processes shifted researchers' attention towards the sharp profiles of threshold-tuning curves, which reflect the behaviour of the cochlea in the linear undamped regime, to no longer emphasizing the idea of the cochlea as a bank of narrow-band filters. If the responses to synthesized speech-like sounds with long-lasting OHC stereocilia fibres are analysed in the time domain, the patterning suggests that groups of fibres respond similarly, even though their characteristic frequencies might differ by...
nearly an octave\textsuperscript{35}. This segregation suggests that the effective bandwidths of cochlear filters are much wider than the narrow tuning curves found in mechanical and neural measures based upon iso-


time scales: a rapid action (tens of milliseconds) is responsible for modulating nerve responses to re-


centient acoustic stimulation, whereas a slower action (tens of seconds) is thought to protect the ear from acoustic overstimulation\textsuperscript{71}. Whole cell patch recordings from isolated OHCs of the mammalian cochlea provide functional evidence for a cholinergic efferent pathway\textsuperscript{55,56}. The action of ACh is mediated by a novel ACh receptor\textsuperscript{57,58}, and in vivo ACh infusion through the cochlea can elevate thresholds for basilar membrane displacements\textsuperscript{59}. There are also docu-


ted effects of ACh on cell axial stiffness\textsuperscript{60} that indicate that the inhibitory influence of ACh on basi-


lar membrane motion in vivo could be explained as OHC axial stiffness determining the amount of force that can be applied on the basilar membrane\textsuperscript{61}.


Feedback control

The mechanical feedback loop provided by the OHC must be finely regulated to guarantee optimal functioning of the cochlear amplifier and its mainte-


Cochlear evolution

Mammalian hearing has evolved to use frequencies above one kHz to improve detection and commu-


ication in noisy environments and to improve the ability to localize discrete sound sources. To do so it has exploited cellular mechanisms rather than a purely electrical or neural mechanism to enhance the extrac-
Box 4. Web sites

This design, particularly where the hair cell uses electrical tuning, has been described extensively in reptiles and in amphibians. In aquatic specialists such as bats and toothed whales, the demands of echolocation have evolved cochleas that can detect incoming sound in some species at frequencies above 100 kHz (Ref. 73). Evolutionary adaptations that appear to have evolved the system of mechanical tuning, has been described extensively in reptiles and in amphibia. In acoustic specialists such as bats and toothed whales, the demands of echolocation have evolved cochleas that can detect incoming sound in some species at frequencies above 100 kHz (Ref. 73).

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R. Nobili et al. – Frequency tuning by the cochlea
Pro-epileptic changes in synaptic function can be accompanied by pro-epileptic changes in neuronal excitability

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Repetitive sensory input, stroboscopic lights or repeated sounds can induce epileptic seizures in susceptible individuals. In order to understand the process we have to consider multiple factors. The output of a set of neurons is determined by the amount of excitatory synaptic input, the degree of positive feedback and their inherent electrical excitability, which can be modified by synaptic inhibition. Recent research has shown that it is possible to separate these phenomena, and that they do not always behave in unison.


EPILEPTIC SEIZURES result from multiple, synchronous discharges from a population of neurons. Temporal lobe epilepsy accounts for ~40% of the total incidence of epilepsy, and is more a multi-factorial syndrome than a tightly defined disease process. The pattern of useful pharmacological interventions reveals some commonality within the syndrome: enhancement of GABAergic inhibition, reduction of glutamatergic excitation and reduction of neuronal excitability appear to be the common mechanisms of beneficial drug action. However, the underlying neuronal pathologies and compensations are not well understood and are the subject of a large body of research directed at improving treatments and the possibility of interventions. In temporal lobe epilepsy, the hippocampus has been shown to have the lowest threshold for induction of transient and sustained high-frequency discharge in the EEG.

For cellular and biophysical studies it is necessary to use experimental animal models of epilepsy, hippocampal activity, similar to that observed in humans, has been shown to be mediated by populations of principal neurones together with their synaptic connections. CA1 pyramidal cells intrinsically produce bursts of electrical activity ('bursting') and provide a synchronous synaptic drive for the downstream CA1 pyramidal cells. Although CA1 pyramidal cells themselves do not burst intrinsically, under certain conditions they have been shown to become hyper-excitatory and even spontaneously active, generating prolonged bursts of action-potential (AP) discharges. These neurones also form a major output of the hippocampus to the cortex. A stimulus-evoked synchronized burst of activity from a population of CA1 pyramidal neurones, referred to as an epileptiform burst, is illustrated in Fig. 1.

'Epileptiform' bursts of action potentials in the CA1 region of the hippocampus

Assuming that pathological changes to the function of the CA1 pyramidal neurones are a potential mechanism for epilepsy, it becomes important to understand the underlying mechanisms. In this article we will concentrate on the analysis of one of these animal models of epilepsy, the kainic acid (KA)-lesioned hippocampus of the rat, which has been studied in detail at the cellular and synaptic level. Unilateral intraventricular injection of kainate leads to a reproducible pattern of change that occurs over several weeks and involves loss of ipsilateral CA3 pyramidal neurones and synaptic reorganization. This results in 'epileptiform' bursts of CA1 pyramidal cell discharge in isolated hippocampal slices in response to stimuli.

In this model, three potential contributions to 'epileptiform' activity can be assessed: first, the intrinsic properties of the pyramidal cells could be modified such that the neurones themselves are hyper-responsive to excitatory inputs, or even spontaneously active; second, the synaptic inhibition could be dysfunctional, leading to a failure to terminate activity; and third, the excitatory input could be strengthened or modified to lead to sustained activity.

When recorded intracellularly from the KA-lesioned hippocampus of the rat, epileptiform bursts are observed as multiple APs superimposed on a depolarizing wave (Fig. 1). These action potentials involve both Na+ and Ca2+ currents through voltage-gated channels. Control CA1 pyramidal cells do not show intrinsic bursting at the soma level but bursts can be evoked in the dendrites.

Presumably there are inherent processes that prevent multiple AP discharge from the soma passing down the axon. One possible mechanism is that...