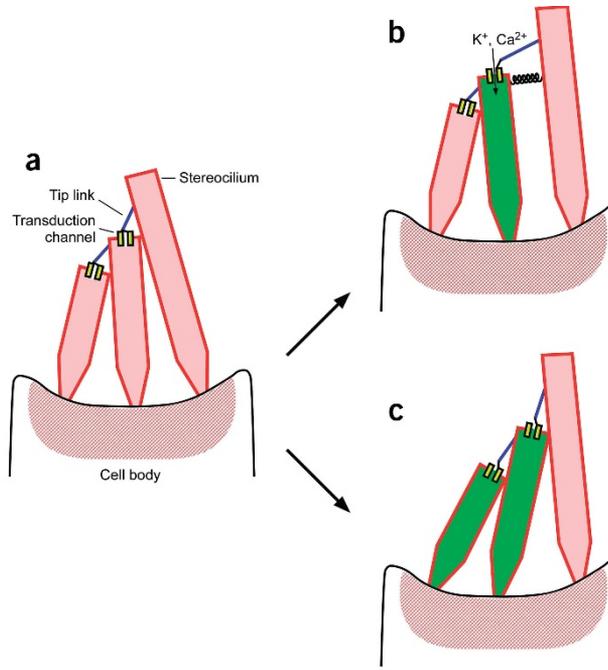


Figure 1 Parallel versus series gating of transduction channels.

(a) Hair bundles consist of stereocilia (red) coupled together by a variety of linkages, including tip links (blue). Right, deflection of hair bundles opens transduction channels; the green signifies an open channel. (b) A series arrangement leads to a lag in movement of the shorter stereocilia, arising from viscous drag, following a displacement of the largest ones. Channel opening is not coordinated; note that channel on middle stereocilium is open (green), but not one on the shorter stereocilium. (c) Parallel arrangement leads to simultaneous opening of both channels (two green cilia). This arrangement could arise if stereocilia are forced together at their tips by geometry, yet can slide on each other essentially without friction.



mechanically in parallel. The geometry of the hair bundle may be the key to concerted bundle movements, constraining the mechanical degrees of freedom of the stereocilia to coerce them to move as a unit. If the arrangement of the stereocilia forces them against one another, deflection of the bundle would allow each stereocilium to relax toward mechanical equilibrium, initiating an ensemble movement. Such behavior ensures coordinated channel gating, thus maximizing sensitivity, as well as enhancing the bundle's ability to amplify stimuli.

Future studies will need to address how these results correlate with behavior of auditory hair cells, which respond to much higher frequencies than the bullfrog sacculus and display wildly different bundle morphology. Intriguingly, Kozlov *et al.* refer to similar behaviors in preliminary experiments with gecko auditory cells. These results represent a significant step toward greater understanding of force transmission across the hair bundle; it will be interesting to learn whether and how hair bundle geometry is tuned to the physiological role of the hair cell.

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by modeling the expected results under conditions of varying stiffness in the gating spring, a mechanical element in series with the tip link that directly transmits force to the channel. When they used a value consistent with the experimentally determined gating spring stiffness, they predicted virtually no cross-correlation in the motions of individual stereocilia; even when they increased the

gating spring stiffness by more than 50-fold to simulate tighter coupling, they could not recapitulate the observed behaviors.

These data argue strongly for an equal distribution of stimulus forces across the bundle, with each channel seeing the identical force simultaneously. The observed behaviors are most consistent with an arrangement in which the stereocilia are

How dopamine neurons survive

Parkinson disease is caused by the degeneration of dopaminergic (DA) neurons in the midbrain. To treat this illness, many laboratories are looking for ways to prevent neuron loss or support the survival of remaining DA neurons at early stages. DA neurons in chick embryos require transforming growth factor- β (TGF β), but it has not been clear when TGF β acts in DA neuron development or how exactly it signals in this system. In general, TGF β signaling activates transcription factor complexes consisting of Smads and other cofactors.

Zhang *et al.* in this issue (pp 77–86) report that the Smad-associated cofactor HIPK2 is expressed in the developing midbrain. HIPK2-null mice showed peri- and postnatal loss of about 40% of DA neurons in the substantia nigra, even though the DA neurons were initially generated in normal numbers. The figure shows embryonic day 12.5 midbrain from HIPK2^{-/-} embryos in coronal section, stained for Ngn2 in red (to label progenitors) and tyrosine hydroxylase in green (labeling mature DA neurons). The tissue looks completely normal at this stage. These results support the idea that DA neurons, like several other neuron populations, are generated in excess, and their numbers are later adjusted by competition for limited amounts of survival factors such as TGF β .

The HIPK2-null mice showed Parkinson-like motor symptoms and may be useful as a new disease model. It remains to be seen, however, whether TGF β -Smad-HIPK2 signaling can rescue DA neurons late in life, when Parkinson disease typically manifests.

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