Role of gene mutations predicted from a computational model of the cochlea of the inner ear

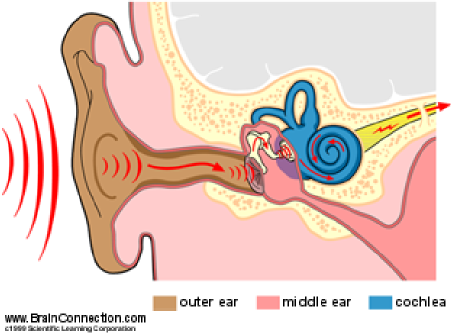
Pavel Mistrík

Learning in Computational Systems Biology

Outline

Mechanical Vibrations are Converted to Neural Activity

Complex Sounds are Decomposes into Tones



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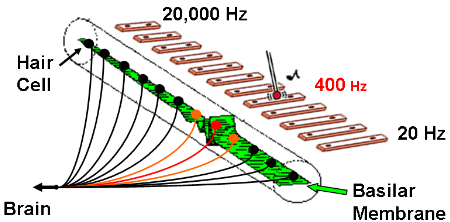


Genes Underlying Deafness

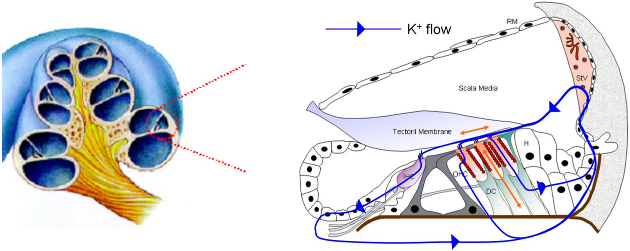
Gene	Gene product	Forms of human deafness
MYO7A, 15, 6, 3A, 1A	Myosin VIIA, XV, VI, IIIA, IA (motors)	DFNB2±retinopathya (Usher 1B), DFNA11
ACTG1	γ-Actin (cytoskeletal protein)	DFNA20 (DFNA26)
USH1C	Harmonin (PDZ domain-containing protein)	DFNB18±retinopathya (Usher 1C)
WHRN	Whirlin (PDZ domain-containing protein)	DFNB31
CDH23	Cadherin-23 (cell-adhesion protein)	DFNB12±retinopathya (Usher 1D)
PCDH15	Protocadherin-15 (cell-adhesion protein)	DFNB23±retinopathya (Usher 1F)
STRC	Stereocilin	DFNB16
SLC26A5	Prestin (anion transporter)	DFNB61
ESPN	Espin (actin-bundling protein)	DFNB36, DFNAib
KCNQ4	KCNQ4 (K^+ channel subunit)	DFNA2
TMC1	TMC1 (transmembr. channel-like protein)	DFNB7 (DFNB11), DFNA36
OTOF	Otoferlin (putative vesicle traffic protein)	DFNB9
POU4F3	POU4F3 (transcription factor)	DFNA15
GJB2, 6, 3	Connexin-26, 30, 31 (gap junction protein)	DFNB1, DFNA3±keratodermiaa, DFNAib
SLC26A4	Pendrin (I^--Cl^- transporter)	DFNB4±thyroid goitera (Pendred)
CRYM	μ-Cristallin (thyroid hormone-binding p)	DFNAib
OTOA	Otoancorin (cell-surface protein)	DFNB22
SLC12A7	KCC4 (K-Cl cotransporter)	DFNA6
BSND	Barttin (β-subunit of ClC-K channels)	DFNA3
CLDN14	Claudin-14 (tight-junction protein)	DFNB29
COCH	Cochlin (extracellular matrix component)	DFNA9
TMPRSS3	TMPRSS3 (transmembr. serine protease)	DFNB8 (DFNB10)
MYH9, MYH14	Myosin IIA, IIC (motor protein)	DFNA17±giant plateletsa; DFNA4
EYA4	EYA4 (transcriptional coactivator)	DFNA10
POU3F4	POU3F4 (transcription factor)	DFN3
COL11A2	Collagen XI (α2-chain)	DFNA13±osteochondro-dysplasia
TECTA	α-Tectorin (extracellular matrix)	DFNA8 (DFNA12), DFNB21

Potassium is Recycled in the Cochlea

K^+ Flow Drives the Electromotility of *Outer Hair Cells* (OHC)

Recycling pathways:

1. *Intercellular* through Gap Junctions in organ of Corti
2. *Extracellular* through Nuel's space



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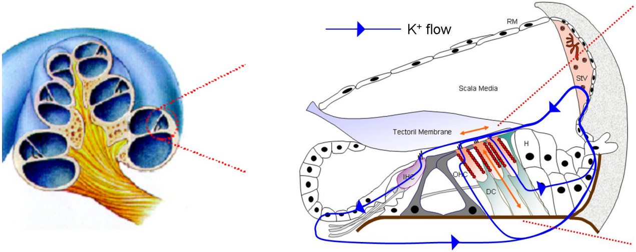
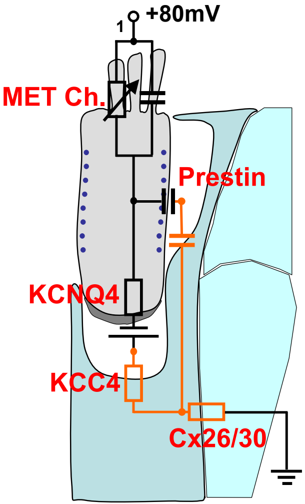


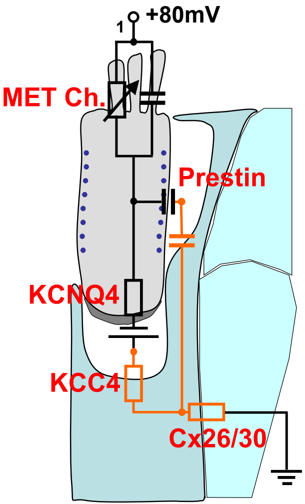
Outline

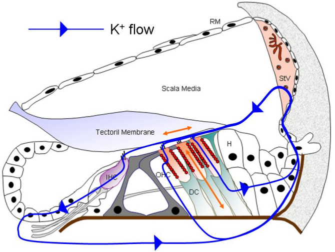
Molecular Recycling Pathways as Electrical Circuits

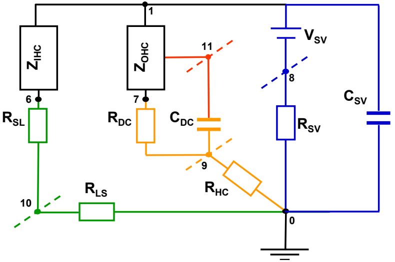


MET Ch.	Mechano-transducer channel
Prestin	OHC electromotor
KCNQ4	K^+ channel
KCC4	K^+ - Cl^- co-transporter
Cx26/30	Connexin 26, 30

Molecular Recycling Pathways as Electrical Circuits

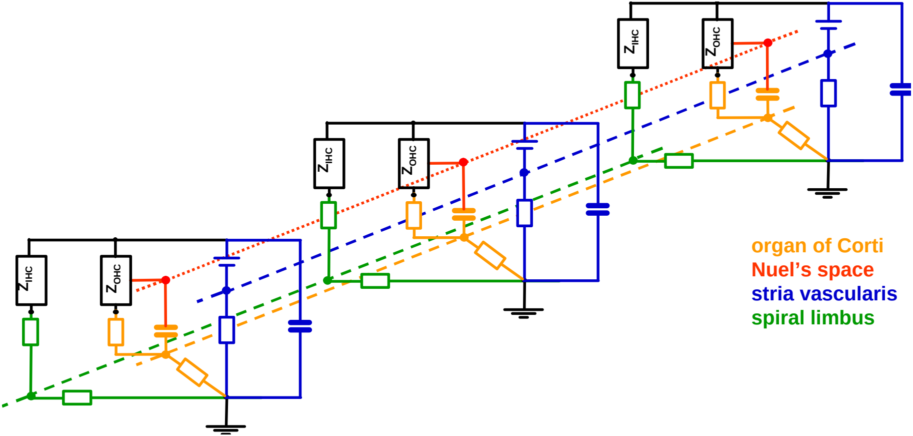






3D Model of *Current Flow* in the Cochlea

300 Cross-Sections Coupled Longitudinally by Resistive Links



organ of Corti
Nuel's space
stria vascularis
spiral limbus

Mathematical Description of *Current Flow*

Time Course Described by *Ordinary Differential Equations* (Matrices: 3300 × 3300)

$$\begin{bmatrix} C_{11} & & & 0 \\ & \ddots & & 0 \\ & & C_{nn} & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix} \begin{bmatrix} \frac{dV_1}{dt} \\ \vdots \\ \frac{dV_n}{dt} \\ 0 \end{bmatrix} + \begin{bmatrix} \frac{1}{R_{11}} & & & 0 \\ & \ddots & & 0 \\ & & \frac{1}{R_{nn}} & 1 \\ 0 & 0 & 1 & 0 \end{bmatrix} \begin{bmatrix} V_1 \\ \vdots \\ V_n \\ 0 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ U^1 \end{bmatrix}$$

Circuit elements

C_{ii} membrane capacitances

$1/R_{ii}$ membrane conductances

U^i electrochemical batteries

Dependence of Receptor Potential on Stimulus

Modified Nodal Analysis Used to Solve for Voltage

$$\mathbf{C}\frac{dV}{dt} = -\mathbf{G}V + \mathbf{U}$$

Presuming:

1. Tone ($\omega/2\pi$) generates perturbation $\mathbf{g}_0$ from steady-state $\mathbf{G}_0$

$$\mathbf{G} = \mathbf{G_0} + \mathbf{g_0}e^{j(\omega t+\theta)}$$

2. Solution of form: steady-state V_0 + **receptor potential** ΔV

$$V = V_0 + \Delta V e^{j\omega t}$$

Then, **receptor potential** generated by frequency f = $\omega/2\pi$:

$$\Delta V = (j\omega\mathbf{C} - \mathbf{G_0})^{-1}\mathbf{g_0}V_0 e^{j\theta}$$

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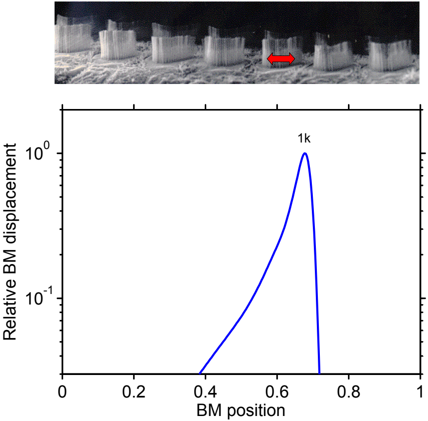
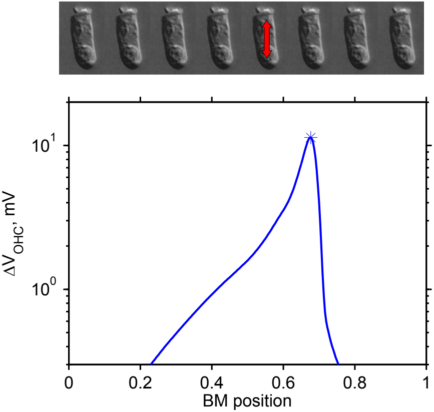
Signals in the Model

Mechanical stimulation of OHCs



Receptor potential of OHCs



Mammano F. & Nobili R. 1993 *J Acoust Soc Am* **93**:3320-32

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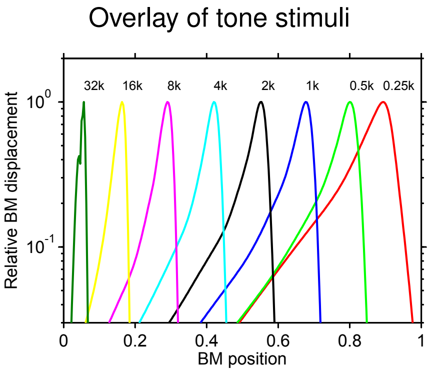
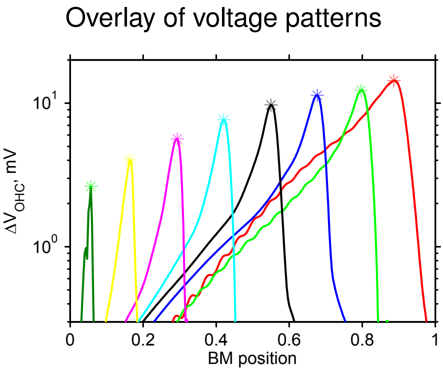
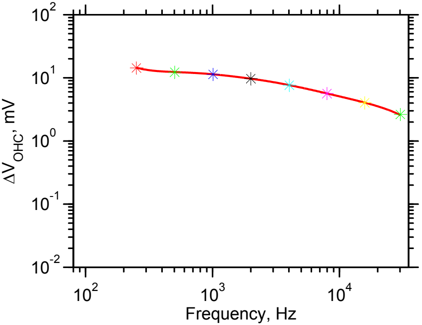




Model Output

Frequency Dependence of the OHC Receptor Potential ΔV_{OHC}



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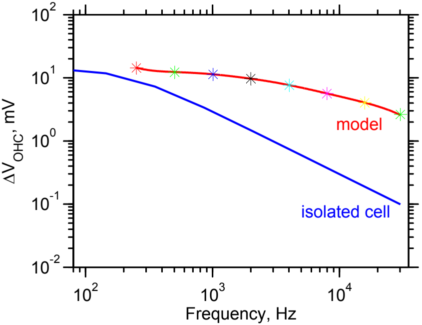

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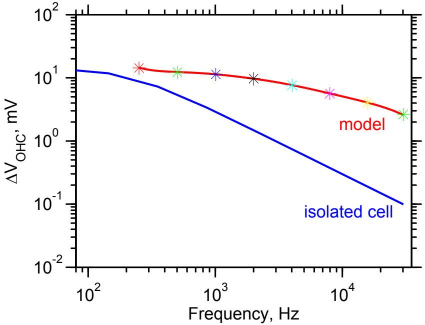
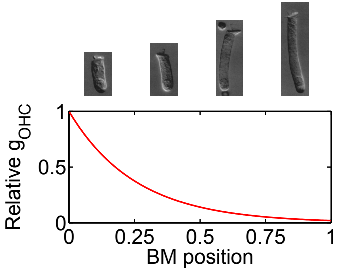


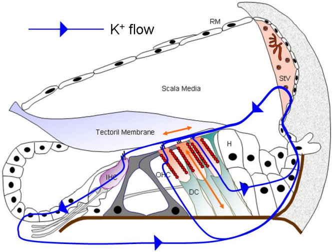


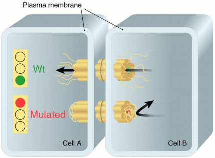
Housley & Ashmore 1992 *J Physiol* ***448****:73-98*
Dannhof, Roth & Bruns 1991 *Naturwiss.* **78**:570-3

Outline

Mutations in *Connexin 26* with Residual Conductance

Gap Junctions are Built From *Connexin* (*Cx*) Molecules





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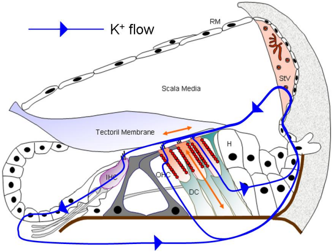
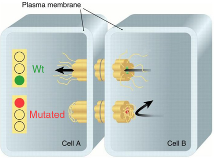
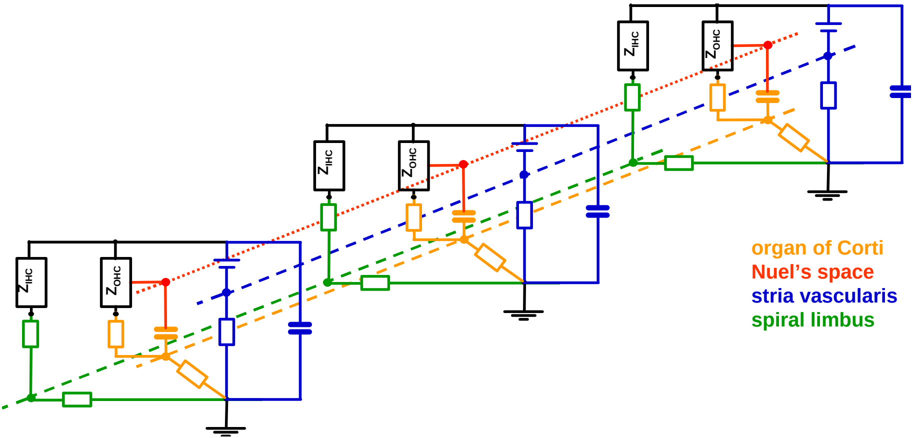




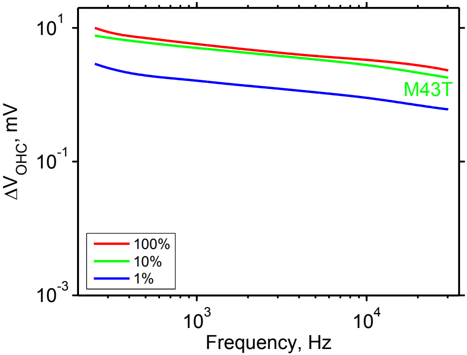
Mutant	g_{GJ}(%)
V37I	<1
M34T	11
W77R	1
F83L	71
V84L	110
L90P	<1
S113R	<1
M163V	1

Bruzzone, R. et al. *FEBS L.* 2003 **553**:79-88
Beltramello, M. et al. *Nature Cell Biol.* 2005 **7**:63-69
Bicego, M et al. *Hum. Mol Genet.* 2006 **15**:2569-2587

Reduced *Intercellular* Connectivity in Organ of Corti



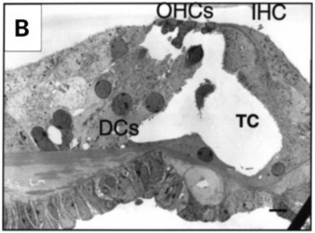
Effect of Mutation M34T in *Connexin 26* Gene



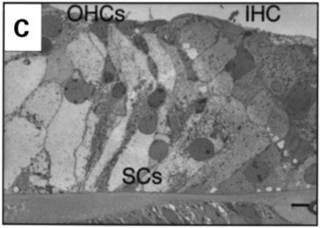
Mutation R75W Reduces Nuel's Space

Smaller *Extracellular* Conductivity

WT



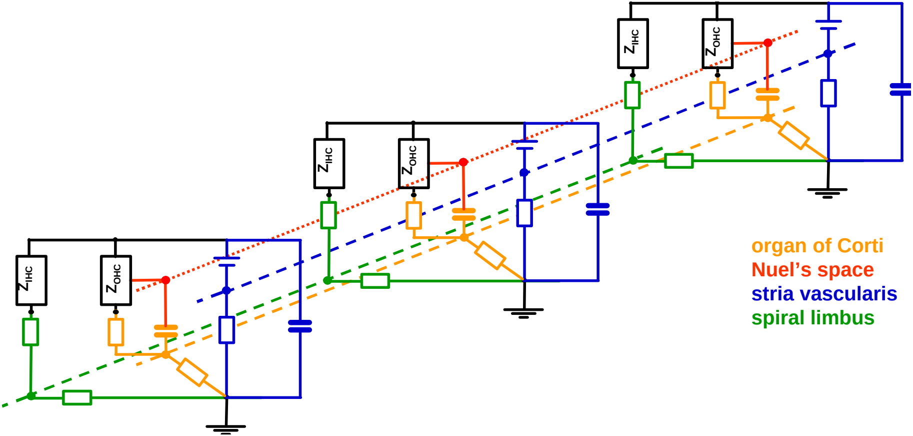
R75W



Kudo, T. et al. *Hum Mol. Genet.* 2003 **12**:995-1004

Reduced *Intercellular* and *Extracellular* Connectivity

Both Organ of Corti and Nuel's Space are Affected



organ of Corti
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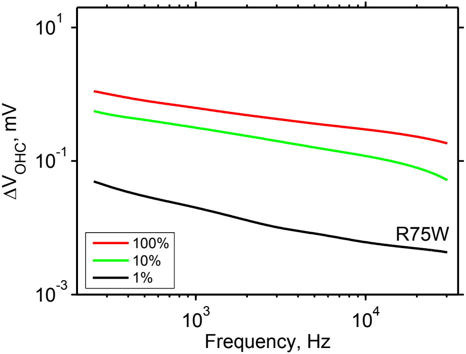
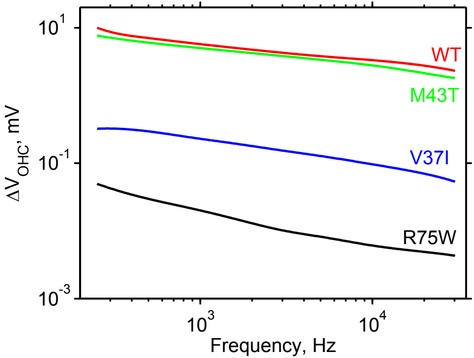
Effect of Mutation R75W in *Connexin 26* Gene

Smaller Amplitude Means Reduced OHC Electromotility



Effect of *Cx26 Mutations* on OHC Receptor Potential

Sound Amplification Can Be Seriously Reduced



Summary

- Cx26-related deafness can be due to reduced OHC amplification
- May explain deafness of individuals carrying the 35delG mutation (Engel-Yeger, B. *Hear Res.* 2002 **163**:93-100).

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Acknowledgement

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