Impact of Electrode Position on the Dynamic Range of a Human Auditory Nerve Fiber

Frank Rattay (✉ frank.rattay@tuwien.ac.at)

Vienna University of Technology

Thomas Tanzer

Vienna University of Technology

Research Article

Keywords: electrode, dynamic range, human, fiber, cochlear implant, insertion depth, efficiency, dynamic range

Posted Date: June 17th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-618367/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at Journal of Neural Engineering on February 1st, 2022. See the published version at <https://doi.org/10.1088/1741-2552/ac50bf>.

Impact of electrode position on the dynamic range of a human auditory nerve fiber

Frank Rattay¹ and Thomas Tanzer¹

¹Institute of Analysis and Scientific Computing, Vienna University of Technology, Vienna, Austria.

Correspondence and requests for materials should be addressed to F.R. (email: frank.rattay@tuwien.ac.at)

Electrodes of a cochlear implant generate spikes in auditory nerve fibers. While the insertion depth of each of the electrodes is linked to a frequency section of the acoustic signal, the amplitude of the stimulating pulses controls the loudness of the related frequency band. The firing efficiency of an auditory nerve fiber, stimulated by a train of pulses varies between 0 and 100%. 100% firing efficiency means every pulse elicits a spike, 50% defines threshold. The dynamic range of an auditory nerve fiber is the range of stimulus intensities that causes a firing probability between 10 and 90%. This ‘electrical’ dynamic range is quite small in comparison to the variation of spiking rates measured during acoustic stimulation. Consequently, an increased dynamic range may improve the quality of auditory perception for cochlear implant users. Electrodes are often placed as close as possible to the center axis of the cochlea. Analysis of simulated auditory nerve firing showed that this placement is disadvantageous for the dynamic range. Five times larger dynamic ranges are expected for electrodes close to the terminal of the dendrite or at mid-dendritic placement.

The cochlea operates as a frequency analyzer where every inner hair cell mimics a band pass filtered microphone by transforming a small frequency band of the acoustical signal into an analog intracellular voltage. A single synaptic connection between an inner hair cell and the distal end of an auditory nerve fiber (ANF) converts this analog signal into a digital signal as a train of action potentials (spikes). According to this principle the spiking rate (spikes/s) of any afferent auditory nerve fiber increases with the loudness of the corresponding frequency.

The physiological task of the main part of the auditory nerve is a data bus that transfers all the action potentials (AP) generated by inner hair cells to the next neural processing center, the cochlear nucleus. In more anatomical detail, each element of the data bus is a so called type-1 spiral ganglion cell consisting of a dendrite, a soma, and an axon, where the diameters and the degree of myelination changes along the cell axis. These details have less impact for synaptic stimulation in the healthy ear in comparison with electrical stimulation where (i) spike initiation site depends on electrode position, (ii) thin degenerated dendrites may not be excited, and (iii) polarity sensitivity depends on cochlear status¹⁻⁴.

When generated from a cochlear implant (CI), the spiking patterns of the auditory nerve show severe deficits versus natural hearing⁵⁻⁸. Especially for difficult neural decoding tasks such as speech understanding in noisy environment, every single ANF crucially contributes with the own spiking rate and its temporal changes following the loudness variations in the corresponding frequency region of the acoustic source signal.

Spiking probability as a function of stimulus intensity is the key-control element in the input-output relation in functional electrical nerve stimulation. The range of intensities where the spiking probability of an ANF increases from 10% to 90% is defined as its dynamic range and indicates a fiber’s individual loudness contribution during CI stimulation¹. The firing probability, also called firing efficiency, can be found experimentally as the ratio (number of spikes)/(number of stimulating pulses). In the schematic diagram of Fig. 1 the spiking probability was extracted from five series á 100 pulses marked by x. The threshold (700 μ A) is defined by the 50% firing efficiency and the dynamic range was 128 μ A which is 18% (128/700). Note that the dynamic range during acoustic stimulation^{5,8} is about two orders

larger in comparison with this example that is typical for electrical stimulation of feline ANFs⁹.

Verveen¹⁰ introduced relative spread (RS) as another measure for the stochastic nature of an electrically stimulated nerve fiber. He plotted the firing probability in a similar way as shown by markers (x) in Fig. 1 and noted that the counted spike numbers approximated that of an integrated Gaussian curve. RS is the standard deviation of that Gaussian function divided by threshold. Comparison of both measures shows that the dynamic range (normalized by threshold) is 2.56 times RS.

From peripheral nerve fiber stimulation experiments Verveen estimated $\log RS = -1.5 - 0.8 \cdot \log d$ (diameter d in μm), which specifies how RS decreases with diameter¹¹. Our RS example of Fig. 1 for $1 \mu m$ diameter ANF fibers is more than twice the 3% (0.03) of Verveen's formula but it is still not comparable to acoustic stimulation where an increase from 25 to 150 spikes per second results from a stimulus (= loudness) increase of about 1000%⁸.

Figure 1. Relationship between stimulus intensity, firing efficiency, dynamic range, and relative spread. An integrated Gaussian curve is used to fit the counted spike numbers marked by x. The slope of this firing efficiency curve at threshold can be used for a guess of the dynamic range. The spread (magenta) is related with the dynamic range (cyan) by the formula (normalized) dynamic range = 2.56 x RS.

Based on an electrical circuit model with ion current fluctuations across the cell membrane, the actual study estimates the impact of electrode position on the dynamic range for human standard ANFs and ANFs with degenerated diameters. Following an approach of Rattay¹², a noise current is added in every segment with an active membrane (nodes of Ranvier, non-myelinated terminal, somatic region). Each segment's simulated noise current is proportional to the square root of the number of its sodium channels^{12,13}.

In this modeling study we show that the dynamic range increases with the electrode distance to the central axis of the cochlea.

Results

Dynamic range of a feline ANF. In our simple model approach a single parameter noise for Gaussian $N(0,1)$ controls all stochastic effects. In a proof of concept noise was set to 0.00125 (with unit $\mu\text{A mS}^{-1/2}$, see method section for details). The ANF consisted of a dendrite (diameter $d_1=1\text{ }\mu\text{m}$), 3 node – internode combinations with an internode length of $150\text{ }\mu\text{m}^{14}$, a myelinated spherical soma ($d=15\text{ }\mu\text{m}$, covered with 13 sheets of membrane)¹⁵ and a 4 mm long axon ($d_2=2\text{ }\mu\text{m}$, internode length = $300\text{ }\mu\text{m}$). The electrode center was $300\text{ }\mu\text{m}$ above the center of the dendrite and the axis of the cell was a straight line (Fig. 2). For a period of 0.5 ms before stimulus onset the enlarged plot of membrane voltage accurately demonstrated the decrease of membrane voltage fluctuations with increase of diameter as predicted by theory (Fig. 2, bottom). In this example where $d_2 = 2 * d_1$, the surface of the axonal node is twice the dendrite node but its noise current increases only by a factor $\sqrt{2}$. Indeed, the V_m range decreased from 2.4 to 1.7 which is exact the theoretical ratio $\sqrt{2}/1$.

Figure 2. Simulated response of a feline ANF to cathodic and anodic 100 μs pulses. The trans-membrane voltage V_m of every compartment is shown as a single line, shifted vertically according to the compartment number: nodes of Ranvier (green, peripheral nodes P and central nodes C), internodes (blue), soma (black). For cathodic stimulation, the strongest responses are expected in the nodes of Ranvier closest to the electrode. These are peripheral nodes P1 and P2. At pulse onset the slope of V_m in the active compartments changes along the ANF three times the sign of direction, indicating whether the stimulus has a positive (polarizing) or negative (hyperpolarizing) impact. The sequence of signs -(terminal), +(P1), +(P2), +(P3), +(C1), -(C2), -(C3), -(C4) favors P2 to be the site of spike initiation. During the anodic pulse the whole dendrite is hyperpolarized and the spike is elicited in the second axonal node C2. Enlarged V_m signals (bottom) demonstrate smaller oscillations in the thicker axon.

Application of cathodic 100 μ s pulses resulted in a threshold current of 99.7 μ A, RS = 5.05% and a dynamic range of 12.86 μ A (12.9% normalized to threshold). This RS is between Verveens 3% and data of Miller and coworkers⁹ where RS values between 2 and 20% (mean 6.6%) based on single ANF recordings were reported. Consequently, we used the same knoise=0.00125 for the human case where no single fiber recordings are possible because of ethical reasons.

Changing just the polarity and applying a positive pulse needs about doubled electrode current to elicit an AP which is initiated in the axon as both the complete dendrite and the soma is hyperpolarized during pulse application (Fig. 2). In comparison to cathodic stimulation RS is reduced from about 5% to 3%, which is a consequence of spike initiation in the thicker axon.

Dynamic range for electrode positions close to an ANF in a human cochlea. CIs are commonly inserted at the round window into scala tympani, the lower cavity of the cochlea. The electrodes are positioned either close to the outer wall or central close to the modiolus but also they may be placed in between (Fig. 3). In comparison with the feline ANF, in human the dendrite is longer and a bit thicker, there is a non-myelinated pre-somatic region, the soma is larger and non-myelinated, the axon is thicker and longer (Table 1).

Figure 3. Main part of a midmodiolar cross-section of a human cochlea with 2 target ANFs in the basal and middle turn and possible electrode placements for an electrode center distance of 300 μ m to the ANF. The ANF has a two-dimensional curved pathway consisting of a 1.1 mm long dendrite with 4 nodes of Ranvier, a non-myelinated soma region and a myelinated axon.

In contrast to the straight cell axis of the feline example a curved two-dimensional ANF as introduced by earlier work² (Fig. 3) was evaluated to study more realistic electrode distances. Threshold and RS were calculated for four electrode positions, again with a constant distance of 300 μ m between electrode center and ANF axis: at the terminal, the dendrite center, close to the soma and 200 μ m further in central direction. The last position is not possible in most human cochlea turns but it is of interest for demonstrating the threshold sensitivity of the axon versus the dendrite.

	length [μm]	diameter [μm]	source
terminal	10	1.35	¹²
dendrite	1100	1.35	¹⁵
dendritic internode	200 *)	1.35	²
presomatic compartment	100 *)	1.35	
spherical soma	20	20	¹⁵
axon	4000	2.67	¹⁵
axonal internode	400 *)	2.67	
node of Ranvier	1.5	1.35 or 2.67	²

Table 1. Morphometric parameters for a healthy human ANF. For myelinated compartments the inner (axon) diameter is listed. In reality the non-myelinated terminal is longer and thinner but in the model it is substituted by a compartment with dendrite diameter d_1 and a surface close to the real one. The total human ANF length is about 32mm¹⁵ but for this study the axon was cut at 4mm to reduce computational costs.

*) no data available from literature

Dendrite diameters are often reduced in persons with hearing deficits. A recent study reported a peak in the dendritic (inner) diameter histogram at $d_1 = 0.5 \mu\text{m}$ and diameters down to $0.3 \mu\text{m}$ recorded from a profound deaf ear⁴. Table 2 shows the threshold and RS values for monophasic 100 μs pulses for a normal ANF with parameters of Table 1 and the corresponding data when just the dendrite diameter is reduced to half of the standard value. As expected, RS increases for all positions and both polarities if the diameter is reduced (Table 2, degenerated ANF).

electrode position at	healthy ANF $d_1=1.35 \mu\text{m}$				degenerated ANF, $d_1=0.7 \mu\text{m}$			
	cathodic pulse		anodic pulse		cathodic pulse		anodic pulse	
	threshold [μA]	RS [%]	Threshold [μA]	RS [%]	threshold [μA]	RS [%]	threshold [μA]	RS [%]
terminal	-114.7	9.58	+225.0	2.50	-176.7	15.83	+244.9	4.49
mid dendrite	-115.9	4.15	+105.9	8.76	-138.6	6.12	+124.6	15.22
soma	-470.1	2.31	+119.8	1.74	-529.0	3,20	+119.8	1.85
axon 200 μm after soma	-77.1	1.05	+ 82.4	1.05	-77.2	1.07	+ 82.4	1.07

Table 2. Thresholds and RS values for a healthy ANF and for a reduced dendrite diameter. Stimulation with monophasic cathodic and anodic 100 μs pulses.

For cathodic pulses RS is largest for the terminal electrode and the values decrease with the electrode distance from the terminal. For anodic stimulation the excitation process is more complicated and spike initiation site is commonly further away from the electrode^{16,17}. The mid-dendritic electrode has the largest RS for an anodic pulse, followed by a quite smaller RS for the terminal position. The large anodic RS for the mid-dendritic position is related with the more complicated excitation process which enable anodic pulses to initiate spikes both in the dendrite and in the axon, see Fig. 4.

The characteristic dependence of dynamic range (about 2.56 times RS) on diameter d_1 , electrode position and polarity is also shown in Fig. 5. According to the reversed recruitment order thicker fibers have lower thresholds^{18,19} which favors spikes to be elicited in the axon. On the other hand, an electrode can be placed closer to the dendrite resulting in a competition between dendrite and axon for the site of spike initiation. Accordingly, the low threshold value for the last electrode position in Table 2 is essentially lower than at the dendrite. As mentioned before, the shape of the scala tympani may hinder in many cases to set an electrode very close to an ANF axon (compare Fig.2).

Figure 4. Latencies of spikes until they arrive at central node C4 depend on spike initiation site and stimulus intensity. Cathodic stimulation causes spike initiation always in the dendrite (a, b), whereas spikes generated by anodic pulses can be elicited in the dendrite (c, weak stimulation) or both in dendrite and axon (d, stronger stimulation). In case e two spikes are generated, one in dendrite one in the axon; however, when the dendritic spike arrives at the axon it is stopped by collision and generates a weak (subthreshold) second excitation. The large jitter at threshold (a, c) is tremendously reduced already at 1.2 times threshold (b, e). The green rectangle indicates a 240 μ s longer delay of for spikes generated in the dendrite. 10 runs per case, electrode in mid-dendritic position, $d_1=1.35 \mu$ m.

The ratio of axon diameter d_2 and dendrite diameter d_1 has a large impact on the decision whether the spike is generated in the dendrite or in the axon. While for $d_1 > 0.6 \mu$ m the terminal electrode position preferentially initiates dendritic spikes, a change to the axon is shown in Fig. 5.

Figure 5. Spiking efficiency with color coded spike initiation site for an electrode at the terminal (a-c), at mid-dendrite (d-e), and soma position (f). Cathodic stimulation: Even for a thin dendrite of diameter $d1=0.7 \mu\text{m}$ almost all spikes are initiated in the dendrite (a) but reduction to $d1 = 0.6 \mu\text{m}$ favors spike generation in the axon, especially for stronger pulses. Further reduction of $d1$ to $0.5 \mu\text{m}$ initiate most spikes in the axon (c). A shift of the electrode from terminal to mid-dendrite position increases axonal spike initiation (a vs. d). Note the decreased dynamic range (marked as green lines) for mid-dendritic (d) versus terminal (a) electrode position and the increase of dynamic range for reducing diameter (a-c). For anodic stimulation dynamic range of mid-dendritic electrode position is larger than the cathodic (e vs. d) and for anodic soma position (e vs. f). Stimulation with $100\mu\text{s}$ pulses, 500 pulses for each bin, intensities relative to threshold.

In the next example, spike initiation site for stimulation with biphasic pulses, $50 \mu\text{s}$ per phase, are studied for the mid-dendritic electrode position. Two cases are compared concerning the polarity of the first phase. Cathodic first stimulation needs less current versus anodic first and for both polarities spikes are elicited in the terminal P0 by the anodic phase (Fig. 6).

Surprisingly, the anodic phase is in this case more effective. However, it is a combination of the ANF pathway relative to the electrode position and the 2 phases which lets P0 win the threshold competition. Several other compartments, marked by dashed lines in Fig. 6, are

candidates for the spike initiation site as they are close to threshold voltage during the stimulation period. A small increase of the electrode current would make one of them the winner during the first phase. For cathodic first stimulation, P1 reached the highest membrane voltage V_m in the first phase, followed by P2 and P4. The inset on the top of Fig. 6 shows V_m of P0 and P1 at the same baseline (without the vertical shift for each compartment) and demonstrates that V_m at P1 (dashed green line) essentially exceeds V_m at P0 during the stimulation time. A small variation of the noise signal can initiate the spike in P1. Note that the second phase was able to stop spike excitation in P1, but for comparison a quite similar condition enables to generate the P0 spike in the anodic first phase (Fig. 6b) in spite of the repolarizing second phase. For the anodic first pulse the axon compartment C2 is the second candidate for the spike initiation site.

Thresholds and RS are listed in Table 3 for both polarities of biphasic pulses. All electrode positions with exception of soma have lower thresholds for cathodic first pulses. In comparison with Table 2, the thresholds (again with exception of soma) are essentially higher for the short 50 μ s phase. In contrast to monophasic pulses the RS differences are similar for terminal and mid-dendrite position. For the biphasic case, terminal and mid-dendritic position has more than five times higher RS values as at the axon.

electrode position at	+ - threshold [μ A]	RS [%]	- + threshold [μ A]	RS [%]
terminal	419.9	5.82	368.5	6.85
mid dendrite	231.9	5,57	193.4	5,61
soma	345.1	1,12	517.8	1,17
axon 200 μ m after soma	168.9	1,02	165.3	1,02

Table 3. Thresholds and RS for biphasic stimulation, 50 μ s per phase. +- means anodic pulse first and vice versa.

Discussion

The resolution of loudness perception of each of the frequency bands covered by the electrode array of a CI is a bottle neck for electrical stimulation. The dynamic range of an electrically stimulated ANF is at least one order lower than its dynamic range during acoustic input. Thus, in comparison to natural hearing, neural patterns generated from CIs miss a lot of acoustic information. According to the presented modelling study electrode placement has a large impact on the dynamic range of a target ANF. A good electrode place for a larger dynamic range is close to the dendrite but without being close to the soma or axon.

The model predicts a surprisingly large polarity dependence of the RS ratio for the electrode positions terminal and mid-dendrite. According to Table 2 cathodic pulses cause 2.3 times larger RS for terminal vs. mid-dendrite, whereas for anodic pulses mid-dendrite has the largest RS with a ratio of 3.5 for these positions. Halving of dendrite diameter, a consequence of degeneration related with hearing deficits⁴, showed a RS increase close to the theoretical value of $\sqrt{2}$ and caused quite similar RS ratios for terminal and mid-dendrite.

This extreme polarity dependence of monophasic pulses seen for terminal and mid-dendritic electrode positions is changed in direction of average values for biphasic stimulations (Tables 2 and 3) with rather small differences with respect to the leading pulse polarity.

Figure 6. Spike initiation with biphasic pulses about 10% above threshold, 50 μs per phase, from an electrode in mid-dendritic position. Spike initiation is here always in the terminal P0 during the anodic phase. Several other compartments, marked by dashed lines, are candidates for spike initiation sites if stimulus intensity is increased. Insert at top of a) contrasts size of membrane voltage V_m at P0 against P1 during pulse application, demonstrating a high V_m of P1 at the end of the first pulse which fails to generate a spike in the way as it was possible by the magenta V_m curve of P0 in b).

Biphasic pulses are commonly used in CIs. For such pulses, model evaluations predict for both terminal and mid-dendritic positions a five times larger dynamic range compared to electrodes close to the soma or to the axon (Table 3). This advantage of a large dynamic range depends, however, on the degeneration status of the dendrite. Degeneration of an ANF means either the loss of its dendrite or a reduction in diameter^{4,20,21}. In cochlear regions where the greater part of ANFs lost their whole dendrites it is not advantageous to place the electrode close to the outer wall.

Limitations of the model. The purpose of the study was a first approach of the dynamic range of human ANFs and its dependence on electrode positions in the scala tympani. A more accurate model should be based on the geometry and the tissue depending electrical conductances of the human cochlea as well as on morphometric details of ANFs including their 3-dimensional pathways^{4,22-27}. Considering more details enables better predictions, e.g. (i) for possible electrode positions close to the axon and the soma which vary with the cochlear turns, (ii) on the effect of reduced myelinization or (iii) on the impact of spatial fine structure of ANFs.

A fundamental problem is the modeling concept for the noisy currents to simulate post-stimulus and interval histograms as observed in electrically stimulated ANFs^{1,6,28,29}. Here, we used a computationally efficient approach (Rattay 2000) which assumes a noise current with constant rms (root mean square) amplitude that reflects the prominent impact of each single sodium channel in the cell membrane (Sigworth 1980). A single parameter, *knoise*, defines the stochasticity of every compartment via its maximum sodium ion conductance. A more realistic fit incorporates how current fluctuations depend on ion channel gating³⁰ or introduces correction terms for fiber diameters and membrane voltage³¹. In comparison with the last two methods, our approach overestimates the current fluctuations in the resting state.

However, the chosen *knoise* parameter fit the RS of feline ANFs which are a bit smaller in diameter than the human ones. Reported RS mean values for cat monophasic, monopolar stimulation were 6.6%⁹, 9%¹ and Dynes³² found RS in the range 5-10%. Our model test for a straight feline ANF ($d_1 = 1 \mu\text{m}$, $d_2 = 2 \mu\text{m}$, electrode at mid-dendrite, Fig. 2) resulted in RS of 5 and 3% for cathodic and anodic pulses, respectively. The cathodic 3% RS value is exact in accordance with Verveen's formula for peripheral axons. Verveen did not observe polarity dependent differences in his data. According to Table 2 ($RS = 1.05$), the human axon diameter of $2.67 \mu\text{m}$ underestimates the $RS = 1.81\%$ of Verveen's formula. Comparing all these RS data, a judgement of our results point to a bit larger *knoise* value as our values are comparable with the lower border of the reported RS range. Tests showed a rather linear relationship between *knoise* and RS for small changes³³ which makes it easy to calculate an adjustment factor to be in accordance with reported RS of a specific article. Moreover, RS was reported to be quite independent of pulse duration³⁰.

Methods

A type 1 spiral ganglion cell, which connects an inner hair cells with a neuron in the cochlear nucleus, consists of several subunits as shown in Fig. 7a with parameters listed in Table 1. Every of these subunits, terminal, internode, node of Ranvier, etc. is simulated as a single compartment with exception of four compartments for the non-myelinated presomatic segment. According to Fig. 7a, the cell consists of segments with active membranes with high (marked red) and low ion channel density (pink). Additionally, there are myelinated internodes (gray) where the membrane is assumed to be passive, which means no voltage sensitive ion channel gating mechanisms are considered. The high ion channel density, here modeled as 10 fold Hodgkin Huxley membrane conductance, is needed for signal amplification along the neural pathway^{12,34}. This sodium channel density is comparable to nodes of Ranvier in axons of the mammalian peripheral nerve system^{35,36}. Beside the peripheral terminal and the nodes of Ranvier, the high sodium concentration is applied in the pre- and postsomatic compartment.

Figure 7. Compartment model of a type I spiral ganglion cell. a) Geometry. Myelinated segments are shown in gray. Excitable (active) membranes with high ion channel densities (red segments) in the peripheral terminal P0 and in the nodes of Ranvier are needed for spike amplification. b) Electrical network model. The currents are defined by extracellular potential V_e , intracellular potential V_i , membrane capacitance C_m , membrane conductance G_m and intracellular resistance R . A noise current is applied to each compartment with an active cell membrane.

Applying Kirchhoff's law (the sum of all currents is zero) to the n -th compartment of the electric network of Fig. 7b results in

$$\frac{d(V_{i,n} - V_{e,n})}{dt} C_{m,n} + I_{ion,n} + \frac{V_{i,n} - V_{i,n-1}}{R_n/2 + R_{n-1}/2} + \frac{V_{i,n} - V_{i,n+1}}{R_n/2 + R_{n+1}/2} = 0 \quad (1)$$

where the first two terms are capacitance current and ion current across the membrane whereas the next two terms describe the intracellular current flow to the left and right compartment. Introducing the reduced membrane voltage $V = V_i - V_e - V_{rest}$ (V_i , V_e and V_{rest} are the intracellular, extracellular and resting potential, respectively) leads to the following system of differential equations^{12,36,37}

$$\begin{aligned} \frac{dV_n}{dt} = & [-I_{ion,n} + \frac{V_{n-1} - V_n}{R_{n-1}/2 + R_n/2} + \frac{V_{n+1} - V_n}{R_{n+1}/2 + R_n/2}] / C_{m,n} \\ & + [\frac{V_{e,n-1} - V_{e,n}}{R_{n-1}/2 + R_n/2} + \frac{V_{e,n+1} - V_{e,n}}{R_{n+1}/2 + R_n/2}] / C_{m,n} \quad (2) \end{aligned}$$

For the first (last) compartment Eqs. 1 and 2 have a reduced form because of lack of neighbors. The membrane surface A_n of every compartment has to be calculated to find $C_{m,n} = A_n \cdot c_{m,n}$ ($c_{m,n}$ is the specific membrane capacitance; note that the capacitance of N layers of membranes is proportional to $1/N$). In order to calculate the extracellular potentials V_e , needed in Eq. 2, we assumed an infinite homogeneous extracellular medium. Ignoring capacitance effects of tissue, the extracellular potential was calculated as

$$V_e = \rho_e \cdot I_{electrode} / 4\pi r \quad (3)$$

where r is the center-center distance between a compartment of interest and a spherical electrode. $\rho_e = 300 \text{ Ohm.cm}$ was assumed to be the mean resistivity of the extracellular medium².

The ion membrane current is governed by the gating mechanisms of specific voltage sensitive ion channels. It consists of two components

$$I_{ion} = A_n \cdot i_{ion,n} + I_{noise,n} \quad (4)$$

where i_{ion} is the ionic membrane current density and $I_{noise,n}$ represents ion channel current fluctuations in active compartments. The effective noise current measured in μA is assumed to be proportional to the square root of the number of sodium channels within a compartment

$$I_{noise,n} = GAUSS \cdot knoise \cdot \sqrt{A_n \cdot g_{Na}} \quad (5)$$

where GAUSS is a Gaussian noise current term (mean = 0, $\sigma = 1$) that changes its value every 2.5 μs , $knoise = 0.00125 \mu A \text{ mS}^{-1/2}$ is a factor common to all compartments, A_n denotes membrane area in cm^2 , and g_{Na} is the maximum sodium conductance ($g_{Na} = 1200 \text{ mS/cm}^2$ for the regions simulated with 10-fold channel density, $g_{Na} = 120 \text{ mS/cm}^2$ for the human soma, $g_{Na} = 0$ for all myelinated internodes and cat's soma¹²).

In compartments with passive membranes (internodes) the term I_{ion} of Eqs. 1 and 2 is a current with constant conductance $I_{ion} = g_m A_n V_n / N$, where membrane conductance g_m is 1 mS/cm^2 and the number of insulating layers of cell membranes N is 40 and 80 for dendrite and axon, respectively².

The ion currents of active membranes were simulated with original Hodgkin Huxley kinetics³⁸ at a temperature of 28.9°C ³⁹. The system of ordinary differential equations was computed in C++ using the backward Euler method with time steps of 2.5 μs .

References

1. Shepherd, R. K., & Javel, E. (1997). Electrical stimulation of the auditory nerve. I. Correlation of physiological responses with cochlear status. *Hearing research*, **108**, 112-144.
2. Rattay, F., Lutter, P., & Felix, H. (2001). A model of the electrically excited human cochlear neuron: I. Contribution of neural substructures to the generation and propagation of spikes. *Hearing research*, **153**, 43-63.
3. Undurraga, J. A., Carlyon, R. P., Wouters, J., & Van Wieringen, A. (2013). The polarity sensitivity of the electrically stimulated human auditory nerve measured at the level of the brainstem. *Journal of the Association for Research in Otolaryngology*, **14**, 359-377.
4. Heshmat, A., Sajedi, S., Chacko, L. J., Fischer, N., Schrott-Fischer, A., & Rattay, F. (2020). Dendritic Degeneration of Human Auditory Nerve Fibers and Its Impact on the Spiking Pattern Under Regular Conditions and During Cochlear Implant Stimulation. *Frontiers in Neuroscience*, **14**.
5. Sachs, M. B., & Abbas, P. J. (1974). Rate versus level functions for auditory-nerve fibers in cats: tone-burst stimuli. *The Journal of the Acoustical Society of America*, **56**, 1835-1847.
6. Hochmair-Desoyer, I. J., Hochmair, E. S., Motz, H., & Rattay, F. (1984). A model for the electrostimulation of the nervus acusticus. *Neuroscience*, **13**, 553-562.
7. Ghitza, O. (1993). Adequacy of auditory models to predict human internal representation of speech sounds. *The Journal of the Acoustical Society of America*, **93**, 2160-2171.
8. Rattay, F., & Lutter, P. (1997). Speech sound representation in the auditory nerve: computer simulation studies on inner ear mechanisms. *ZAMM-Journal of Applied Mathematics and Mechanics/Zeitschrift für Angewandte Mathematik und Mechanik*, **77**, 935-943.

9. Miller, C. A., Abbas, P. J., Robinson, B. K., Rubinstein, J. T., & Matsuoka, A. J. (1999). Electrically evoked single-fiber action potentials from cat: responses to monopolar, monophasic stimulation. *Hearing research*, **130**, 197-218.
10. Verveen, A. A. (1960). On the fluctuation of threshold of the nerve fibre. *Structure and function of the cerebral cortex*, 282-288.
11. Verveen, A. A. (1962). Axon diameter and fluctuation in excitability. *Acta Morphol Neerl Scand*, **5**, 79-85.
12. Rattay, F. (2000). Basics of hearing theory and noise in cochlear implants. *Chaos, Solitons & Fractals*, **11**, 1875-1884.
13. Sigworth, F. J. (1980). The variance of sodium current fluctuations at the node of Ranvier. *The Journal of physiology*, **307**, 97-129.
14. Liberman, M. C., & Oliver, M. E. (1984). Morphometry of intracellularly labeled neurons of the auditory nerve: correlations with functional properties. *Journal of Comparative Neurology*, **223**, 163-176.
15. Rattay, F., Potrusil, T., Wenger, C., Wise, A. K., Glueckert, R., & Schrott-Fischer, A. (2013). Impact of morphometry, myelination and synaptic current strength on spike conduction in human and cat spiral ganglion neurons. *PloS one*, **8**(11), e79256.
16. Rattay, F. (1986). Analysis of models for external stimulation of axons. *IEEE transactions on biomedical engineering*, **10**, 974-977.
17. Rattay, F. (2013). Research in electrical stimulation fundamentals. *Artif Organs*, **37**, 1023-1026
18. Blair, E. A., & Erlanger, J. (1933). A comparison of the characteristics of axons through their individual electrical responses. *American Journal of Physiology-Legacy Content*, **106**, 524-564.
19. Rattay, F. (1990). *Electrical nerve stimulation*. Wien: Springer.
20. Nadol Jr, J. B. (1990). Degeneration of cochlear neurons as seen in the spiral ganglion of man. *Hearing research*, **49**, 141-154.
21. Wu, P. Z., Liberman, L. D., Bennett, K., De Gruttola, V., O'Malley, J. T., & Liberman, M. C. (2019). Primary neural degeneration in the human cochlea: evidence for hidden hearing loss in the aging ear. *Neuroscience*, **407**, 8-20.
22. Rattay, F., Leao, R. N., & Felix, H. (2001). A model of the electrically excited human cochlear neuron. II. Influence of the three-dimensional cochlear structure on neural excitability. *Hearing research*, **153**, 64-79.
23. Rask-Andersen, H., Liu, W., Erixon, E., Kinnefors, A., Pfaller, K., Schrott-Fischer, A., & Glueckert, R. (2012). Human cochlea: anatomical characteristics and their relevance for cochlear implantation. *The Anatomical Record: Advances in Integrative Anatomy and Evolutionary Biology*, **295**, 1791-1811.
24. Kalkman, R. K., Briare, J. J., Dekker, D. M., & Frijns, J. H. (2014). Place pitch versus electrode location in a realistic computational model of the implanted human cochlea. *Hearing research*, **315**, 10-24.
25. Bai, S., Encke, J., Obando-Leitón, M., Weiß, R., Schäfer, F., Eberharter, J., ... & Hemmert, W. (2019). Electrical stimulation in the human cochlea: A computational study based on high-resolution micro-CT scans. *Frontiers in neuroscience*, **13**, 1312.
26. Potrusil, T., Wenger, C., Glueckert, R., Schrott-Fischer, A., & Rattay, F. (2012). Morphometric classification and spatial organization of spiral ganglion neurons in the human cochlea: consequences for single fiber response to electrical stimulation. *Neuroscience*, **214**, 120-135.
27. Potrusil, T., Heshmat, A., Sajedi, S., Wenger, C., Chacko, L. J., et al. (2020). Finite element analysis and three-dimensional reconstruction of tonotopically aligned human auditory fiber pathways: a computational environment for modeling electrical stimulation by a cochlear implant based on micro-CT. *Hearing Research*, **393**, 108001.

28. Hartmann, R., Topp, G., & Klinke, R. (1984). Discharge patterns of cat primary auditory fibers with electrical stimulation of the cochlea. *Hearing research*, **13**, 47-62.
29. Van den Honert, C., & Stypulkowski, P. H. (1984). Physiological properties of the electrically stimulated auditory nerve. II. Single fiber recordings. *Hearing research*, **14**, 225-243.
30. Rubinstein, J. T. (1995). Threshold fluctuations in an N sodium channel model of the node of Ranvier. *Biophysical journal*, **68**, 779-785.
31. Badenhorst, W., Hanekom, T., & Hanekom, J. J. (2016). Development of a voltage-dependent current noise algorithm for conductance-based stochastic modelling of auditory nerve fibres. *Biological cybernetics*, **110**, 403-416.
32. Dynes, S. B. C. (1996). *Discharge characteristics of auditory nerve fibers for pulsatile electrical stimuli* (Doctoral dissertation, Massachusetts Institute of Technology).
33. Tanzer, T., Sogand, S., Heshmat, A., & Rattay, F. (2012). Conference on Implantable Auditory Prostheses (CIAP).
34. Rattay, F., & Danner, S. M. (2014). Peak I of the human auditory brainstem response results from the somatic regions of type I spiral ganglion cells: evidence from computer modeling. *Hearing research*, **315**, 67-79.
35. Rattay, F., & Aberham, M. (1993). Modeling axon membranes for functional electrical stimulation. *IEEE Transactions on Biomedical Engineering*, **40**, 1201-1209.
36. Rattay, F., Greenberg, R. J., & Resatz, S. (2002). Neuron modeling. *Handbook of Neuroprosthetic Methods*, 39-71.
37. Rattay, F. (1999). The basic mechanism for the electrical stimulation of the nervous system. *Neuroscience*, **89**, 335-346.
38. Hodgkin, A. L., & Huxley, A. F. (1952). A quantitative description of membrane current and its application to conduction and excitation in nerve. *The Journal of physiology*, **117**, 500-544.
39. Motz, H., & Rattay, F. (1986). A study of the application of the Hodgkin-Huxley and the Frankenhaeuser-Huxley model for electrostimulation of the acoustic nerve. *Neuroscience*, **18**, 699-712.

Acknowledgements

The research was supported by the Austrian Science Fund (FWF), grant No. P-29650.

Author Contributions

F.R. conceived and designed the study. T.T. performed the computational simulations. F.R. analyzed the data. All authors drafted the manuscript, read and approved the final version.

Additional Information

Competing Interests: The authors declare that they have no competing interests.