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# Chronaxie calculated from current–duration and voltage–duration data

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**Abstract**

To determine the rheobase and the chronaxie of excitable cells from strength–duration curves both constant-current pulses and constant-voltage pulses are applied. Since the complex impedance of the electrode-tissue interface varies with both the pulsewidth and the stimulation voltage, chronaxie values estimated from voltage–duration measurements will differ from the proper values as determined from current–duration measurements. To allow a comparison of chronaxie values obtained by the two stimulation methods, voltage–duration curves were measured in human subjects with a deep brain stimulation electrode implanted, while the current and the load impedance of the stimulation circuit were determined in vitro as a function of both stimulation voltage and pulsewidth. Chronaxie values calculated from voltage–duration data were shown to be 30–40% below those estimated from current–duration data. It was also shown that in the normal range of stimulation amplitudes (up to 7 V) the load impedance increases almost linearly with the pulsewidth. This result led us to present a simple method to convert voltage–duration data into current–duration data, thereby reducing the error in the calculated chronaxie values to $\approx 6\%$. For this purpose voltage–duration data have to be measured for pulses up to 10–20 times the expected chronaxie. 

*Keywords:* Current–duration measurements; Voltage–duration measurements; Chronaxie; Rheobase; Deep brain stimulation

## 1. Introduction

The strength–duration curve of an excitable cell represents the relation between the pulsewidth and the threshold stimulus current ($I_{th}$), or voltage ($V_{th}$). The curve is characterized by a reduction of the stimulus amplitude when the pulsewidth is increased. An example is shown in Fig. 1a. The curve is generally described by two parameters, the rheobase and the chronaxie. The rheobase ($I_{rh}$ or $V_{rh}$) is defined as the lowest stimulus amplitude, or threshold, needed for activation and relates to a large pulswidth. The chronaxie ($C$) is defined as the pulsewidth corresponding to twice the rheobase. Weiss (1901) proposed the following empirical equation, known as Weiss's law, to describe the (linear) relation between the pulsewidth (PW) and the threshold charge ($I_{th} \cdot PW$)

$$I_{th} \cdot PW = I_{rh} \cdot PW + I_{rh} \cdot C \quad (1a)$$

When constant-voltage pulses instead of constant-current pulses are applied, this equation is replaced by

$$V_{th} \cdot PW = V_{rh} \cdot PW + V_{rh} \cdot C \quad (1b)$$

$I_{th} \cdot PW$ (charge per pulse) and $V_{th} \cdot PW$ are linearly related to PW and the rheobase is the slope of this line. Fig. 1b shows the strength–duration curve of Fig. 1a converted according to Eq. (1b).

The non linear relations between PW and $I_{th}$ and between PW and $V_{th}$ follow from Eqs. (1a) and (1b), respectively.

$$I_{th} = I_{rh}(1 + C/PW) \quad (2a)$$

$$V_{th} = V_{rh}(1 + C/PW) \quad (2b)$$

According to the definition of chronaxie given above $C = PW$ when $I_{th} = 2I_{rh}$ (or $V_{th} = 2V_{rh}$).

Whereas the rheobase and the chronaxie are primarily related to passive membrane properties of the ex-

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citable cells (the leakage conductivity and the membrane time constant, respectively), these parameters are also affected by the voltage-dependent membrane conductance and by geometrical factors, such as the fiber diameter and the distance between the target cells and the stimulating electrode (Bostock, 1983; Bostock et al., 1997; West et al., 1983; Mogyoros et al., 1999).

Both constant-current pulses and constant-voltage pulses are used to determine strength–duration curves and to calculate the rheobase and the chronaxie (Ranck, 1975). However, the stimulus current and voltage will generally not be proportional, because the impedance of the electrode-tissue interface varies with both the stimulation voltage and frequency (Bard et al., 1980). When pulses are applied, their frequency content varies with the pulsewidth. Therefore, one would expect chronaxie values to be different when calculated from either current–duration ($I$–$t$) or voltage–duration ($V$–$t$) measurements. For a correct estimation of the rheobase and the chronaxie constant-current pulses should be applied, because voltage gradients in the resistive tissue surrounding an excitable cell and the resulting membrane currents are proportional to the injected current. Unfortunately, constant-current stimulators are not always available, particularly in stimulators for clinical use.

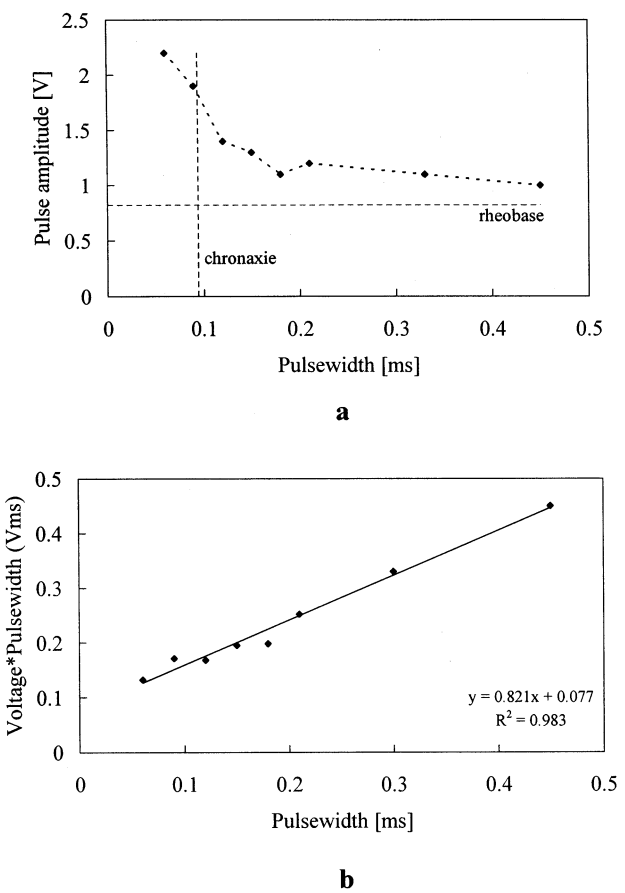


Fig. 1. (a) Experimental voltage–duration data, rheobase and chronaxie; (b) same data multiplied with pulsewidth and corresponding linear curve fit and $R^2$ value.

In this study we compared chronaxie values obtained with constant-voltage and constant-current stimulation, by measuring $V$–$t$ curves from human subjects stimulated with a deep brain stimulation (DBS) electrode for the elimination of tremor and determining the current and the load impedance of the stimulation circuit in-vitro as a function of the stimulation voltage and the pulsewidth. The current data were used to convert the $V$–$t$ data into charge–duration data and the chronaxie values were calculated according to Eq. (1a). Based on the results of this study, a simpler method to obtain a reliable estimate of the chronaxie from $V$–$t$ data is proposed. The patient data included in this study are part of a more extensive study on chronaxie to identify the target neuronal elements in DBS (Holsheimer et al., submitted).

## 2. Methods

### 2.1. Voltage–duration measurements

$V$–$t$ data were measured from seven patients suffering from Parkinson's disease or essential tremor. These patients had a quadrupolar DBS electrode (model 3387, Medtronic, MN) placed stereotactically in the ventral intermediate nucleus of the thalamus on one side or bilaterally (Benabid et al., 1993). All four cylindrical electrode contacts (90% Pt, 10% Ir), situated on the surface of a polyurethane tube with a diameter of 1.27 mm, had a length of 1.5 mm and were separated by 1.5 mm. The electrode was connected via a subcutaneous extension cable to a battery powered, constant voltage pulse generator (Itrel2 or Itrel3, Medtronic), placed subcutaneously in the chest or abdomen. Each electrode contact could selectably be connected as a cathode or an anode, or could be disconnected. All parameters, including pulse width, pulse rate, voltage and electrode connections, were set by an external programmer (model 7432, Medtronic).

At the time the $V$–$t$ measurements were done, the patients were on a stable dose of medication for at least 1 month. Pulses were applied bipolarly at a rate of 130 pps. During a test session, threshold voltages ($V_{th}$) for the elimination of tremor were determined in a patient at pulsewidths of 60, 90, 120, 150, 180, 210, 300 and 450 μs by increasing the stimulation voltage in steps of 0.1 V at 5 s intervals until the tremor vanished completely (which occurred within 2–3 s). The way the presence of tremor was determined remained constant throughout a test session for each patient. Among patients, however, the testing procedure could differ depending on the type of tremor (e.g. the patient held

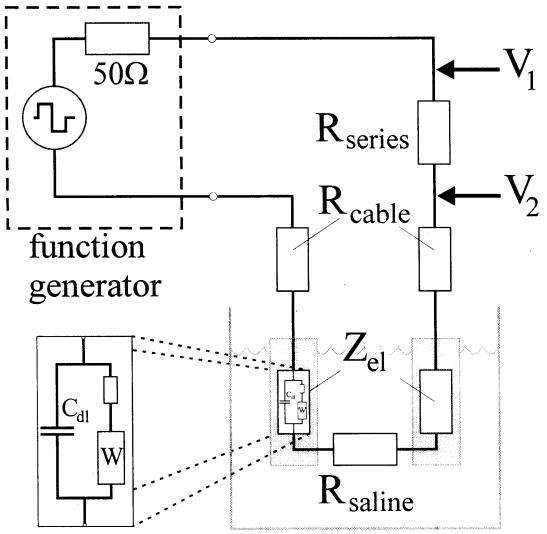


Fig. 2. Experimental setup to determine the electrode impedance $Z_{el}$ for different pulsewidths and voltages; for details see text.

the arm stretched horizontally, or the arm was in a relaxed position). When during a test session a change in symptomatology was observed between stimulation off periods, the $V$–$t$ data of the corresponding patient were excluded from this study.

From the $V$–$t$ data $V_{th}$·PW was calculated and graphs were made of $V_{th}$·PW as a function of PW (Fig. 1b). A linear regression line fitting the data points best (minimum root mean square error) was calculated, as well as the corresponding squared correlation coefficient ($R^2$). The rheobase and chronaxie were determined from the regression line according to Eq. (1b).

The stimulation system allowed the measurement of the load impedance as well. This measurement was calibrated for a pulse amplitude of 1.0 V and a pulsewidth of 0.21 ms.

### 2.2. In-vitro impedance measurements

The measurement arrangement is shown in Fig. 2. A model 3387 DBS electrode was immersed in physiological saline (0.9% NaCl) and two contacts were connected to a voltage source via a series resistance ($R_{series}$) and the electrode cable ($R_{cable}$). The contacts have an electrode-tissue impedance $Z_{el}$ and are connected by the resistance of the saline ($R_{saline}$). $Z_{el}$ consists of a double layer capacitance ($C_{dl}$) in parallel to a voltage-dependent impedance which includes the Warburg impedance ($W$) (see inset Fig. 2). When the voltage across $Z_{el}$ is below the threshold of anodal/cathodal electrolysis all current flows via $C_{dl}$. $R_{series}$ was chosen such that the total load impedance ($Z_{load}$) for a 1.0 V/0.21 ms pulse is similar to the mean value as measured in the brain. In this way a realistic voltage across the electrode-tissue interface was obtained at any stimulation voltage. The voltages on both sides of $R_{series}$ ($V_1$ and $V_2$) were measured.

A HP 33120A waveform generator was used as a constant voltage source (50 Ω internal resistance), providing rectangular 0.5 ms pulses with amplitude $V_1$ (0.5–7.0 V, at 0.5 V intervals). Each monophasic pulse was immediately followed by an identical pulse of opposite polarity to quickly unload the electrode double layer capacitance ($C_{dl}$). The interval between the pulse pairs was 70 ms. $V_1$ and $V_2$ were measured by a digital oscilloscope (HP 54520A) at sample intervals $dt = 4$ μs and averaged over 256 pulses.

From the voltages $V_1$ and $V_2$ the following parameters were calculated:

- the instantaneous current $I$ passing the circuit

$$I(t) = (V_1(t) - V_2(t))/R_{series} \quad (3)$$

- the instantaneous load impedance $Z_{load}$

$$Z_{load}(t) = V_1(t)/I(t) \quad (4)$$

- the average load impedance $\overline{Z}_{load}$ for pulsewidth PW (0–0.5 ms)

$$\tilde{Z}_{load}(PW) = \frac{1}{n}\sum_{i=1}^{n} Z_{load,i} \quad (5)$$

- the instantaneous impedance of each electrode $Z_{el}$

$$Z_{el}(t) = (Z_{load}(t) - (R_{series} + 2R_{cable} + R_{saline}))/2 \quad (6)$$

- the charge $Q$ injected by a monophasic pulse with duration PW (0–0.5 ms)

$$Q(PW) = \frac{PW}{n}\sum_{i=1}^{n} I_i \quad (7)$$

The voltages of the measured $V$–$t$ data were substituted by the charge calculated for the corresponding pulsewidths. These data were used to calculate the chronaxie according to Eq. (1a) and to compare the results with those obtained by using the original $V$–$t$ data and Eq. (1b).

## 3. Results

### 3.1. Voltage–duration measurements

$V$–$t$ and load impedance measurements were performed at the neurosurgery department of the University hospital Gasthuisberg (Leuven, Belgium). Data on seven subjects were included in this study. From each subject the $V_{th}$ data were converted into $V_{th} \cdot PW$ data

and the rheobase and chronaxie were determined from the linear regression line, according to Eq. (1b). The means, S.D.'s and minimum/maximum values are presented in Table 1.

### 3.2. In-vitro impedance measurements

To obtain a realistic $Z_{load}$, similar to the mean measured value, the selected value of $R_{series}$ was 1000 Ω, resulting in an average load impedance $\overline{Z}_{load}$ of 1243 Ω for a 1.0 V /0.21 ms pulse (see Fig. 3b).

Table 1
Means, S.D.'s, minima and maxima of electrical parameters obtained from seven subjects and correlation of linear approximation

| | Load (Ω) | Rheobase ($V$) | Chronaxie (μs) | $R^2$ |
|---|---|---|---|---|
| Mean | 1297 | 1.34 | 66.1 | 0.97 |
| S.D. | 185 | 0.68 | 15.4 | 0.02 |
| Minimum | 1068 | 0.75 | 47.7 | 0.94 |
| Maximum | 1540 | 2.55 | 93.8 | 0.99 |

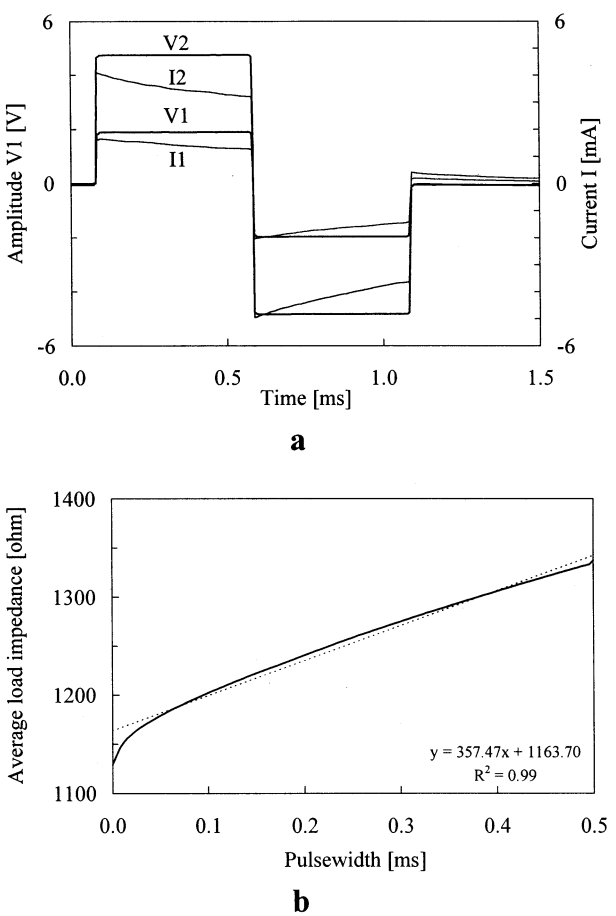


Fig. 3. (a) Voltage and current measured during biphasic constant-voltage pulses of 2 V (V1, I1) and 5 V (V2, I2); (b) solid line: average load impedance as a function of pulsewidth, obtained from almost identical curves at 1–7 V amplitude; dashed line: linear curve fit (with equation and correlation coefficient).

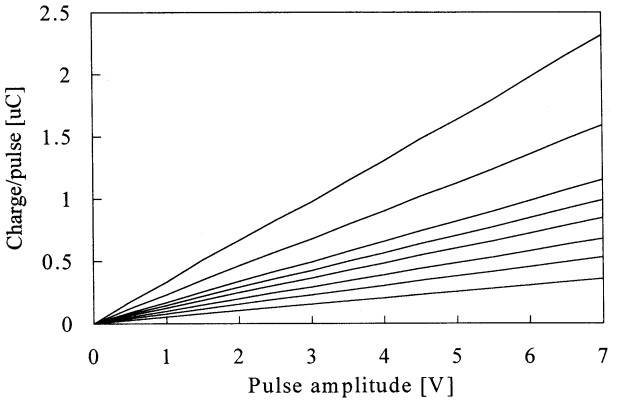


Fig. 4. Charge per pulse as a function of amplitude calculated for constant-voltage pulses of (from lower to upper curve) 60, 90, 120, 150, 180, 210, 300 and 450 μs pulsewidth.

In Fig. 3a, two values of the applied voltage $V_1$ and the corresponding currents (according to Eq. (3)) are presented. It is shown that the current declined with increasing pulsewidth. Since $V_1$ was virtually constant, $Z_{load}$ will increase with increasing pulsewidth. Because the curves of $\overline{Z}_{load}$ measured at 0.5–7 V pulses as a function of the pulsewidth (Eq. (5)), were almost identical, only the mean of all curves is presented in Fig. 3b. As shown by the linear regression line in this figure, $\overline{Z}_{load}$ increased almost proportional to the pulsewidth ($R^2 = 0.99$) from $\approx 1164$ Ω (PW $\approx 0$ ms) to $\approx 1343$ Ω (PW $= 0.5$ ms), being an increase of $\approx 15.4\%$.

When PW $\approx 0$ ms, the impedance of the double layer capacitance $C_{dl}$ of the electrodes will be 0 and $\overline{Z}_{load}$ will include only the resistive components of the stimulation circuit, i.e. $R_{series}$ (1000 Ω), $2R_{lead}$ (76 Ω) and $R_{saline}$ (Fig. 2). The latter was thus $\approx 88$ Ω, whereas the instantaneous $Z_{el}$ increased from 0 to $\approx 179$ Ω at PW $= 0.5$ ms.

The injected charge $Q$(PW) was calculated by integrating the current corresponding to each stimulation pulse $V_1$ (0.5–7 V) over time, according to Eq. (7). In Fig. 4 the charge is presented as a function of $V_1$ for any pulsewidth used in the $V$–$t$ measurements on patients (60–450 μs). It is shown that the injected charge increased linearly with increasing $V_1$ for any pulsewidth, although the gradients $Q/V$ were not proportional to the pulsewidths, as shown in Table 2. E.g. the ratio of the gradients for PW $= 450$ and 90 μs was 4.37 instead of 5.0. This discrepancy results from the increase of $\overline{Z}_{load}$ with increasing pulsewidth.

### 3.3. Conversion of voltage–duration data into charge-duration data

The in vitro measurement data relating pulse charge to pulse voltage and pulsewidth (Table 2) were used to convert $V$–$t$ measurement data into charge–duration ($Q$–$t$) data which correspond to (fictive) $I$–$t$ measure-

Table 2
Pulsewidths and corresponding gradients of the injected charge as a function of the stimulation voltage (Fig. 4)

| PW (μs) | 60 | 90 | 120 | 150 | 180 | 210 | 300 | 450 |
|---|---|---|---|---|---|---|---|---|
| $Q/V$ (μ$C/V$) | 0.051 | 0.075 | 0.096 | 0.120 | 0.140 | 0.163 | 0.225 | 0.328 |

ment data. In Table 3 the chronaxie values estimated from both the $V$–$t$ measurement data of three subjects and the corresponding calculated $Q$–$t$ data are presented. The three selected data sets corresponded with the highest, the lowest and an intermediate chronaxie value and the linear approximations had an $R^2$ value of at least 0.97. The data show that the chronaxie estimated from $V$–$t$ measurements is $\approx$30–40% less than the value estimated from $I$–$t$ measurements.

Another method to estimate the chronaxie from $V$–$t$ measurements takes advantage of the result of the in vitro measurements that the load impedance increases almost linearly with the pulsewidth (Fig. 3b). This method is illustrated by the curves shown in Fig. 5. Curve A represents an $I$–$t$ curve, calculated according to Eq. (2a) with arbitrary values of the rheobase (1 mA) and the chronaxie (0.1 ms). The $V$–$t$ curve (B) is calculated from curve A, using an arbitrary load impedance (1000 Ω) at the smallest pulsewidth and an arbitrary linear increase of 40% for each ms increase. Curve B is now considered as the set of $V$–$t$ measurement data. If curve A would have reached the (constant) rheobase level at e.g. 1 ms pulsewidth, the slope of curve B beyond 1 ms would have been identical to the slope of the load impedance and the $I$–$t$ curve could be determined exactly by subtracting values from the $V$–$t$ curve (B) corresponding to its slope beyond 1 ms. However, since curve A is still slightly descending beyond 1 ms (5% from 1 to 2 ms), the corresponding part of curve B does not represent the slope of the load impedance accurately. Since curve A approximates a constant amplitude most at the largest pulsewidths available, the slope of the load impedance will fit the slope of curve B best at these large pulsewidths. Accordingly, the slope of curve B between 1.5 and 2 ms was taken as the slope of the load impedance for the whole range of pulsewidths, as shown by curve C. (This slope was 8% less than the value initially applied to curve A to obtain curve B.) Now the $I$–$t$ curve (with arbitrary current values) can simply be constructed by subtracting the values of curve C from the corresponding ones of curve B. These $I$–$t$ data are indicated in Fig. 5 by triangles. It is shown that for pulsewidths exceeding 0.4 ms these datapoints differ slightly from the initial $I$–$t$ curve A. Therefore, only datapoints up to 0.4 ms pulsewidth were used to estimate the chronaxie. Its value was 0.094 ms, being 6% below the correct value (0.1 ms). When all $I-t$ datapoints up to 2 ms pulsewidth were used, the corresponding chronaxie was 21% too low (0.079 ms). Calculation from datapoints up to 0.4 ms pulsewidth from the $V$–$t$ curve (B) resulted in a chronaxie 30% too low. The correlation coefficient of the data and the linear regression line exceeded 0.99 in all cases.

## 4. Discussion

It has been shown that the chronaxie calculated from strength–duration measurements using constant-voltage stimuli is 30–40% below the value estimated in a correct way, i.e. from constant-current measurements. This discrepancy is due to the non linear relation between stimulation voltage and current, caused by the complex electrode impedance ($Z_{el}$) which varies with both pulsewidth and voltage across $Z_{el}$. Under the conditions of clinical DBS, as investigated in this study, the current flows via the double layer capacitance ($\approx$ 1.5 μF) and results in an almost linear increase of $Z_{el}$ with increasing pulsewidth. (A capacitor has a similar,

Table 3
Chronaxie values based on $V$–$t$ data and data corrected for variable electrode impedance

| Subject | Chronaxie (μs) | |
|---|---|---|
| | $V$–$t$ data | $I$–$t$ data |
| 1 | 94 | 132 |
| 2 | 48 | 76 |
| 3 | 74 | 109 |

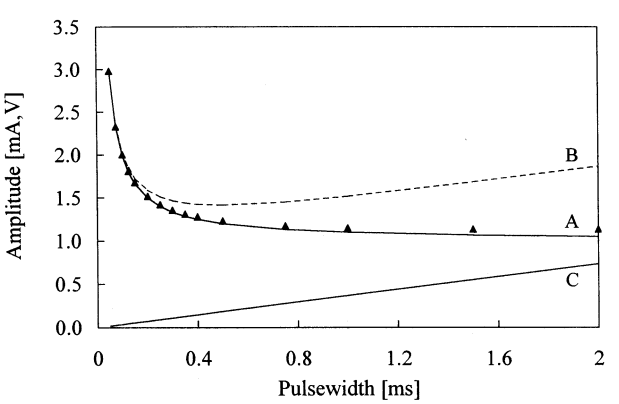


Fig. 5. Curve A: modeled $I$–$t$ curve, 1 V rheobase, 0.1 ms chronaxie; curve B: $V$–$t$ curve calculated from A using 1000 Ω impedance at 50 μs pulsewidth and 40% increase/ms; curve C: slope of curve B between 1.5 and 2.0 ms; ▲: $I$–$t$ data calculated by subtraction of curve C from curve B.

slight reduction of the slope of its average load impedance as the curve shown in Fig. 3b.) Because the other components of the stimulation circuit, including the tissue in-between the electrode contacts are resistive, the total load impedance increases almost linearly with the pulsewidth as well. An additional current via the Warburg impedance and thus a reduction of $Z_{el}$ would only occur at stimulation amplitudes resulting in a voltage across $Z_{el}$ exceeding the threshold for anodal/cathodal electrolysis (Bard et al., 1980). Due to the shape of the strength–duration curve, however, this effect is highly unlikely. At the smallest pulsewidth applied (0.06 ms) the maximum value of each $Z_{el}$ was only 1.55% of the load impedance. Since at this pulsewidth the applied voltage did never exceed 7.0 V, the voltage across $Z_{el}$ was 0.1 V at most. Similarly, the maximum voltage across $Z_{el}$ did not exceed 0.4 V at the end of the widest pulse (0.45 ms, maximum stimulus 3 V, 13.5% of the load impedance across $Z_{el}$)

Due to the increase of the load impedance with increasing pulsewidth the $V–t$ curve gets proportionally higher than the corresponding $I–t$ curve. Beyond some pulsewidth the negative voltage gradient changes into a positive one, whereas the corresponding currents are still diminishing, as illustrated in Fig. 5 by curves B and A, respectively. Accordingly, the minimum amplitude ('rheobase') in $V–t$ measurements is attained at a smaller pulsewidth than in $I–t$ measurements. Because the chronaxie is defined as the pulsewidth related to twice the minimum amplitude, the chronaxie estimated from $V–t$ measurements will be less than from $I–t$ measurements. We calculated that the chronaxie estimated from $V–t$ measurements with a DBS electrode is 30–40% too low.

In this study the stimulator has been considered to be either a perfect constant-current or constant-voltage pulse generator. Stimulators are, however, not always so perfect. Stimuli applied by the DBS pulse generators used in this study are generated by a capacitor. During its discharge, a reduction of the stimulation voltage, inversely related to the load impedance, will occur. For a load of 1300 Ω the Itrel2 gave a linear reduction of the output voltage of 3.6% during a 0.2 ms pulse. Accordingly, the mean voltage of the widest pulse applied (0.45 ms) is 4% less than indicated, which corresponds to an average reduction of 0.05 V of the related near-rheobase amplitudes ($1.3 \pm 0.7$ V). This reduction is, however, within the uncertainty range of the threshold voltages as introduced by the discrete 0.1 V steps by which the stimulator output is set.

When the stimulation electrode is implanted in the brain, the electrical circuit of Fig. 2 should be extended with the resistance of an extension cable (model 7495, Medtronic), being $\approx 30–40$ Ω, whereas $K_{series}$ is included in the tissue resistance between the electrode contacts, replacing $R_{saline}$ of the in vitro experiment. Accordingly, the resistance of this tissue, including an encapsulation sheath and surrounding nervous tissue, will equal the sum of $R_{saline}$ ($\approx 88$ Ω) and $R_{series}$ (1000 Ω) from the in vitro experiment minus the resistance of the extension cable, thus having a mean value of $\approx 1050$ Ω. This value is high as compared to the average $Z_{el}$ ($\approx 90$ Ω for each electrode contact at a 0.5 ms pulsewidth). The variation of the load impedance among subjects is rather high (Table 1) and is most likely due to differences in the morphology of the tissue adjacent to the electrode contacts, i.e. the thickness and density of the encapsulation layer. According to Grill et al. (1994) a tight layer of fibroblasts and collagen has a resistivity of $627 \pm 108$ Ω·cm, whereas loose encapsulation tissue has a resistivity of $195 \pm 88$ Ω·cm.

A new method has been introduced to estimate the chronaxie from $V–t$ measurements in a fairly reliable way, thus reducing the error substantially. In this method pulses up to 10–20 times the expected chronaxie have to be applied. The only assumption to be made is that the load impedance increases linearly with the pulsewidth. We have shown this linear relation experimentally for DBS electrodes (Fig. 3b). The new method includes the estimation of the slope of the measured $V–t$ curve at the largest pulsewidths and the subtraction of a line with this slope from the $V–t$ curve to obtain the corresponding $I–t$ curve (with arbitrary current values). Because some error will still be present in the estimated slope of the $V–t$ curve, only calculated '$I–t$' datapoints corresponding to smaller pulsewidths (having smaller errors) should be used to estimate the chronaxie. By modeling $I–t$ and $V–t$ curves we have shown that by this method the error in the chronaxie estimated from $V–t$ curves is reduced from 30 to 40% to $\approx 6\%$.

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