Dimensional scaling of thin-film stimulation electrode systems in translational research

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Abstract

Objective. Electrical stimulation of biological tissue is an established technique in research and clinical practice that uses implanted electrodes to deliver electrical pulses for a variety of therapies. Significant research currently explores new electrode system technologies and stimulation protocols in preclinical models, aiming at both improving the electrode performance and confirming therapeutic efficacy. Assessing the scalability of newly proposed electrode technology and their use for tissue stimulation remains, however, an open question. Approach. We propose a simplified electrical model that formalizes the dimensional scaling of stimulation electrode systems. We use established equations describing the electrode impedance, and apply them to the case of stimulation electrodes driven by a voltage-capped pulse generator. Main results. We find a hard, intrinsic upward scalability limit to the electrode radius that largely depends on the conductor technology. We finally provide a simple analytical formula predicting the maximum size of a stimulation electrode as a function of the stimulation parameters and conductor resistance. Significance. Our results highlight the importance of careful geometrical and electrical designs of electrode systems based on novel thin-film technologies and that become particularly relevant for their translational implementation with electrode geometries approaching clinical human size electrodes and interfacing with voltage-capped neurostimulation systems.

1. Introduction

Electrical stimulation of biological tissue is a well-established medical practice both as part of diagnostic monitoring protocols and delivery of therapy. Electrical stimulation can be deployed to different organs in the body to elicit effects such as restoring audition in the cochlea [1], alleviating the symptoms of Parkinson’s disease [2], regulating bladder function [3], inhibition of neuropathic pain pathways in the spinal cord [4], etc. Recently, progress in micro- and nanofabrication and the associated materials has enabled bioelectronic implants offering enhanced miniaturization, design versatility and structural biocompatibility [5–7], leveraging well-established thin-film technologies borrowed from the microelectronics field to demonstrate new promising implantable devices.

At the preclinical research stage, electrical stimulation technologies and paradigms are typically conceived and tested in animal models to confirm their safety and efficacy [8]. This entails developing and using electrodes and stimulation systems that are generally designed for small animal models (rodents being the prime choice) with anatomical structures significantly smaller than their human counterpart [8, 9]. Although preclinical research methodologies aim at confirming the viability of promising medical technologies, their translation towards larger animal models and eventually testing in patients requires careful development work that spans design, manufacturing, and validation paradigms [10]. Here, we focus on the aspect of upward dimensional scaling of stimulation electrodes. We introduce simple considerations on the laws that govern the impedance of stimulation electrodes, and apply them to
Figure 1. Equivalent Randles model of an electrode system based on thin-film track conductors and electrode coating. (a) Elements of an electrode that are modelled by the Randles cell [14]. (b) Equivalent circuit model with electrical parameters: the thin-film track conductor resistance $R_{\text{track}}$, the electrode spreading resistance $R_{\text{spread}}$, the interface capacitance $C_i$, and the interface charge transfer resistance $R_{\text{CT}}$. Reprinted from [14], Copyright (2020), with permission from Elsevier.

Table 1. List of the electrical components of the Randles equivalent circuit model.

| Impedance element | Equation | Technology | Design |
|-------------------|----------|------------|--------|
| Track resistance  | $R_{\text{track}} = R_s \frac{L}{w}$ | $R_s$: sheet resistance of the track conductor (material and process dependent) | $L$: length of track $w$: width of track |
| Spreading resistance | $R_{\text{spread}} = \frac{\rho}{4r}$ | — | $\rho$: resistivity of the medium $r$: radius of electrode |
| Interface capacitance ($C_i$) | $|Z_{C_i}| \propto \frac{1}{2\pi f \cdot \text{ESA}}$ | ESA: electrochemical surface area of the electrode (process, coating roughness, and electrode radius dependent) | $f$: frequency |
| Charge transfer resistance ($R_{\text{CT}}$) | $|Z_{\text{CT}}| = R_{\text{CT}}$ | $R_{\text{CT}}$: charge transfer resistance (electrode area and coating material dependent; the material affects the voltage onset of electrochemical reactions) |

the case of use with a voltage-capped pulse stimulator. Finally, we discuss the scalability of stimulation electrodes prepared with thin-film technologies and assess the impact of geometry when the electrode size is changed from the typical rodent model size (10–500 $\mu$m in diameter) to human size (mm–cm diameter).

2. Electrode impedance and dimensional scaling

The operation of an electrode has been extensively described in the literature with numerous models and equivalent electrical circuits [11, 12] describing the functioning of electrodes in different use cases. For the sake of simplicity, the elaborations herein are based on the simple Randles model [13] for the case of thin-film based electrode systems [6, 14], as illustrated in figure 1.

The simple Randles model includes four elements, as listed hereafter and table 1.

- The resistance of the track conductor ($R_{\text{track}}$), that depends on the conductor sheet resistance $R_s$, its length $L$ and width $W$.
- The spreading resistance ($R_{\text{spread}}$), which models the resistance through the medium (typically the nervous tissue in vivo, or the electrolyte, such as saline solution in vitro). It is proportional to the medium resistivity $\rho$ and inversely proportional to the electrode radius $r$.
- The interfacial capacitance of the electrode ($Z_{C_i}$), that models capacitive electronic to ionic transduction and whose impedance is inversely proportional to the electrochemical surface area (ESA) $A$ of the electrode and to the frequency $f$ at which the impedance is measured.
- The charge transfer resistance ($R_{\text{CT}}$), which models faradaic charge injection, typically through reduction–oxidation (red–ox) reactions, at the interface, and which is effectively a voltage dependent resistor governed by the Butler–Volmer equation or the Tafel equation for the case of low overpotential [15]. The charge transfer resistance is proportional to the electrode ESA.

The counter-electrode impedance is considered as negligible as the surface is significantly larger than that of the working electrode.

This simplified model excludes important aspects, such as constant-phase elements at the electrode-tissue interface which are typically used to model electrochemical impedance spectroscopy data [16], or non-ideal insulation effects such as capacitive coupling between the embedded conductor tracks and the surrounding tissue. However, these considerations are not relevant for the discussion below, as they would all represent a worst-case scenario to the following points.
Different laws govern the variation of electrode impedance with dimensional scaling. Larger electrodes display an increased interface capacitance, with a corresponding decrease of the capacitive impedance $Z_{Ci}$ proportional to the ESA. Similarly, the charge transfer resistance $R_{CT}$ scales with the inverse of the electrode ESA [\refcite{12}], due to the increased surface area available for the electrode material to participate in electrochemical reactions that mediate charge transduction [\refcite{17}].

Conversely, the track resistance, driven by technology and design parameters, constitutes a constant offset to the impedance regardless of the electrode size. The spreading resistance, instead, decreases proportionally to the radius for circular electrodes or the lateral dimension for square electrodes. For circular electrodes of radius $r$, the spreading resistance is given by [\refcite{18}]:

$$R_{\text{spread}} = \frac{\rho}{4r},$$

where $\rho$ is the resistivity of the medium (electrolyte or tissue) surrounding the electrode. A compendium of typical values for various tissues and species is reported by [\refcite{19}], with values of up to few 100 $\Omega$ cm reported for nerve tissue. We have further confirmed this scaling law experimentally in vitro by evaluating the spreading resistance on ad hoc electrodes of different radii manufactured with standard thin-film microfabrication processes. The spreading resistance was extracted from electrochemical impedance spectra using the peak resistance frequency (PRF) method [\refcite{20}] and subtracting the track resistance $R_{\text{track}}$ from the resistive impedance. The results, plotted in figure 2, show that indeed the spreading resistance follows the $r^{-1}$ dependency of equation (1). Details of the experimental procedure are described in the methods section.

3. Electrical stimulation protocols

When injecting square current pulses through electrodes, the biological effect elicited by the electrical stimulation depends on the volume of activated tissue. Although in general there is not a deterministic correlation between the volume of activation and the observed biological effect [\refcite{21}, \refcite{22}], stimulation protocols are typically defined by the charge density and charge per phase (i.e. how much charge per electrode unit area is to be delivered and how much in total) [\refcite{23}], as well as the pulse width. In fact, the safety of a stimulation protocol in the MedTech industry is currently ensured by limiting the charge density delivered per stimulation pulse to a maximum threshold for tissue safety (30 $\mu$C cm$^{-2}$ for most clinical applications) [\refcite{24}]. Once a charge density $Q$ is set, the corresponding stimulation current amplitude delivered through a circular electrode is:

$$I_{\text{stim}} = \frac{Q}{\text{PW} \pi r^2},$$

where PW is the pulse width, and $r$ is the electrode radius. A sample pulse with the corresponding parameters is illustrated in figure 3.

Stimulation current pulses are delivered by a current-controlled pulse generator that applies the voltage required to inject the selected current. In turn, delivering a set current will require more or less voltage depending on the electrode impedance, similarly to the current flowing through a resistor following Ohm's law. The battery used to power implantable bioelectronic devices can typically supply 3.2 to 10 V [\refcite{25}], and typical clinical stimulation protocols for neuromodulation use pulse widths of 10–500 $\mu$s and repetition rates between 10 and 300 Hz [\refcite{8}, \refcite{26}].

Let us consider a stimulation protocol with a certain charge density $Q$ and pulse width PW. If the electrode impedance were to be completely inversely
proportional to the electrode area, the increase in current required for bigger electrodes to maintain the same charge density would be balanced by a corresponding decrease in impedance. In other words, if we were to deliver the same charge density through an electrode of twice the surface area, we would need to inject twice the current amplitude ($I_{\text{stim}}$). If the impedance modulus of the bigger electrode were to be half that of the smaller electrode, the voltage required to inject the desired current remains unchanged regardless of the electrode area.

However, not all the governing equations of table 1 are inversely proportional to the electrode area, as the spreading ($R_{\text{spread}} = \frac{Q}{2}$) and track resistances ($R_{\text{track}} = R_{\text{IPG}} \frac{A}{2}$) rather scale with the electrode radius and remain constant, respectively. This means that when the electrode area is increased, the increase in current amplitude required to maintain the stimulation charge density constant is not completely balanced by the decrease in electrode impedance due to area effects. The spreading resistance decreases less than the impedances of the area-dependent components, therefore as the electrode area increases, the voltage required to maintain the same charge density in fact increases. This reveals a fundamental scaling limitation that we further elaborate hereinafter.

### 4. A simplified scaling model

Let us consider a circular electrode with an ideal electrode-tissue interface (i.e. with a perfect interface impedance $Z = 0$ achieved by a hypothetical electrode coating which ensures a seamless charge injection interface). This assumption eliminates the areal interface impedance and simplifies the equivalent Randles circuit model of the electrode into a series of two resistors describing the track conductors and the spreading resistance (figure 4). The electrode impedance in this case reduces to the sum of the resistances

$$Z = R_{\text{track}} + R_{\text{spread}},$$

with definitions in table 1.

It is important to keep in mind however, that such system cannot exist in reality, and moreover multiple studies have shown that the electrode-tissue interfacial impedance increases post-implantation typically due to scar tissue formation around the electrodes [16, 20, 27, 28].

With a view on ultimately translating stimulation protocols towards clinical practice, it is important that the electrodes for stimulation can be electrically interfaced with an implantable pulse generator (IPG) such as those used for cardiac pacemakers or neurostimulators. These are typically packaged in a metallic casing (used as stimulation counter electrode) that must incorporate a compact battery of limited voltage excursion $V_{\text{max}}$ (typically around $V_{\text{max}} = 10\, \text{V}$). When delivering therapy, the stimulator applies to the entire stimulation circuit (cables + stimulation electrode + counter electrode) the voltage required to inject the programmed current pulse (with parameters $I_{\text{stim}}$ and counter electrode) the voltage required to maintain the programmed current pulse (with parameters $I_{\text{stim}}$ and PW). The maximum voltage dictated by the battery directly translates into a limit in the current that can be delivered through a given electrode, depending on its size and track conductor technology. Assuming the simplified equivalent model of figure 4 (neglecting the interface impedance), this limit can be easily calculated as:

$$I_{\text{max}} = \frac{V_{\text{max}}}{Z} = \frac{V_{\text{max}}}{R_{\text{track}} + R_{\text{spread}}} = \frac{V_{\text{max}}}{R_{\text{track}} + \frac{Q}{2}}.$$  

When the electrode size is increased, for instance in an effort to translate findings from a rodent study to a large animal model or the human case, $I_{\text{max}}$ increases as the spreading resistance term in equation (1) decreases with $r^{-1}$ ($R_{\text{spread}} = \frac{Q}{2}$). Conversely, to maintain a constant charge density $Q$ as per our stimulation protocols, the required current must increase with $r^2$ ($I_{\text{stim}} = \frac{Q}{R_{\text{track}} \pi r^2}$). When we compare the scaling laws of the maximum current deliverable by the stimulator and the current maintaining constant charge density, it is clear that above a certain electrode radius, the current required by the stimulation protocol $I_{\text{stim}}$ is larger than the maximum current $I_{\text{max}}$ that the stimulator can deliver (figure 5). This is a fundamental limit that must be taken into account when evaluating the scalability of an electrode system and the associated stimulation protocols.

The intersection point between the $I_{\text{stim}}$ curve and the $I_{\text{max}}$ curve corresponding to the relevant $R_{\text{track}}$ technology parameter defines a maximum electrode radius $r_{\text{max}}$ above which stimulation at the intended charge density is physically impossible. It is important to stress that this extremely simplified model excludes
Figure 4. Simplified equivalent circuit model excluding the interface impedance.

Figure 5. Comparison of the stimulation current \( I_{\text{stim}} \) with the maximum admitted current \( I_{\text{max}} \) for different track resistances and two values of medium conductivity: \( \rho = 0.6 \, \Omega \, \text{m} \) (saline) and \( \rho = 3 \, \Omega \, \text{m} \) (nerve tissue) [19].

the interface impedance of the electrode. If this were accounted for, the total electrode impedance would be higher and frequency-dependent, and the maximum current \( I_{\text{max}} \) even lower than this ideal case. However, our goal is to keep our analysis simple and therefore suggest our depiction to be a best-case scenario (i.e. even with an ideal electrode coating, the electrode radius cannot be scaled above the found limit for a given stimulation protocol).

To aid the engineering, one can find the locus of the intersection points of the \( I_{\text{max}} \) and \( I_{\text{stim}} \) curves (red circles in figure 5) by solving for \( r_{\text{max}} \) the equation

\[
I_{\text{max}} = I_{\text{stim}},
\]

finding

\[
r_{\text{max}} = \sqrt{\frac{\rho^2}{16} + \frac{4R_{\text{track}}V_{\text{max}}PW}{\pi Q} - \frac{\rho}{4}}.
\]  

5. Track resistance, medium resistivity and pulse width dependency

In our simplified model, the limit radius \( r_{\text{max}} \) depends on several parameters. If we consider a fixed voltage limit \( V_{\text{max}} = 10 \, \text{V} \) and a fixed stimulation protocol of charge density \( Q = 30 \, \mu \text{C cm}^{-2} \), \( r_{\text{max}} \) depends on the track resistance, electrolyte or tissue resistance, and the selected pulse width, as illustrated in figure 6.

\( r_{\text{max}} \) decreases monotonically with \( R_{\text{track}} \), as larger track resistance entails a higher voltage drop across the conductor tracks, leaving less voltage available to drive the current through the spreading resistance. Analogously, when the resistivity of the medium or tissue increases, stricter limits apply to the electrode radius as the spreading resistance increases. It is worth noting that for large track resistance, the other parameters play a limited role and the maximum radius allowing electrical stimulation can be significantly reduced.

One way to mitigate the scaling limitation is to increase the pulse width of the stimulation pulse. As the charge density is fixed, a longer pulse width requires a lower current amplitude, and therefore a lower voltage supply. However, our simplified model does not take into account capacitive charging phenomena that occur at the interface and that play a role in the electrode polarization during a stimulation pulse. Holding a current for a longer time increases the interface charging, therefore making charge injection less favourable and more voltage-demanding. Longer pulse widths at constant charge have nevertheless proven to mitigate the total voltage excursion during stimulation [17]. The adequacy of different pulse width values must moreover be verified against the efficacy and effects of the resulting stimulation protocol in vivo. Finally, an increase in pulse width decreases the effective maximum stimulation repetition rate (RR), as \( RR < \frac{1}{PW} \) (for symmetrical biphasic pulses), which could be a limitation
for certain applications that require high frequency stimulation.

As previously discussed, this simplified model represents a best-case scenario. In reality, the electrode-tissue interface will participate with a further contribution to the total impedance, exacerbating (and likely to a significant extent) the voltage requirements for electrical stimulation. In this respect, the scaling limitations identified herein are to be considered as a hard limit and an ‘optimistic’ one, since in real cases the total electrode impedance inclusive of the electrode-tissue interface may significantly decrease the maximum electrode radius. It is significant and worth of attention, therefore, that even in this best-case scenario, by inputting typical parameters values in the equations above, we find max radius limits within the dimensional range of interest for human-size electrodes. If a more realistic analytical model were to be built including the interfacial impedance, harsher scaling limitations would be found, further limiting the electrode upward scalability.

6. Discussion

Our simple argumentations reveal a fundamental limit to the upward scalability of electrodes for electrical stimulation, with strong dependency on the track conductor technology. An important application of this limit is the case of preclinical studies using electrical stimulation with modern flexible/stretchable conductors (soft bioelectronics). As mechanical compliance is brought in by using soft materials, the conductors used as flexible/stretchable interconnects offer lower electrical conductivity compared to conventional metallization or wires [14].

As an illustration, we refer to our work on spinal cord stimulation in non-human primates (NHP) [10]. The maximum current density delivered in vivo for lumbar stimulation was $Q \sim 40 \mu C \text{ cm}^{-2}$, with a pulse width $\text{PW} = 0.3 \text{ ms}$ and electrodes of area of $1.4 \text{ mm}^2$. Assuming conservatively $\rho = 3 \Omega \text{ m}$ [19] for neural tissue, and an IPG of maximum voltage $V_{\text{max}} = 10 \text{ V}$, then the $r_{\text{max}}$-$R_{\text{track}}$ scaling curve corresponding to this stimulation experiment is plotted in figure 7.

With a thought experiment, we can translate this protocol to the human case. We assume using a clinical spinal cord stimulation electrode (e.g. Medtronic, 6 mm$^2$ area) to deliver the same charge density $Q = 40 \mu C \text{ cm}^{-2}$. Converting areas to equivalent electrode radii, the equivalent NHP and human radii are 0.67 and 1.38 mm, respectively. For a scaled electrode radius of 1.38 mm, the maximum track resistance value admitted by the stimulator is $R_{\text{track}} \sim 700 \Omega$. Else, for higher $R_{\text{track}}$ values, the electrode radius must be less than $r_{\text{max}} = 1.38 \text{ mm}$, otherwise the IPG cannot deliver the selected stimulation protocol. Importantly, the found limit for the track resistance falls within the typical values of new generation bioelectronics technology. In this specific example, an average track resistance of $\sim 500–1000 \Omega$ was used in the NHP experiment [10]. A human-scale design would entail longer conductor tracks, with the track resistance likely to surpass the limit value found of $R_{\text{track}} \sim 700 \Omega$. If we further consider that this model neglects the interface impedance, it is clear that this scaling limitation is highly relevant to current designs and technology.

Importantly, the limitation illustrated herein becomes relevant with the rise of thin-film microfabricated conductors, particularly the class of compliant conductive materials, as these typically trade-off electrical conductivity with mechanical compliance [6]. Current clinical electrode systems use discrete conductor wires soldered individually to each electrode (i.e. $R_{\text{track}}$ is negligible). The scaling problem illustrated in this paper is therefore an unexplored
Figure 7. Example of scaling limitation for spinal cord stimulation electrodes. Insets: Medtronic spinal cord stimulation paddle (top), and NHP electronic dura mater electrode array \([10]\). Reprinted from \([14]\), Copyright (2020), with permission from Elsevier.

challenge that must be taken into account when new advanced electrode systems and technologies are proposed for future translational implementations of bioelectronic implants \([29–31]\).

The simple scaling law calculated for \(r_{\text{max}}\) equation \((5)\) can be also adapted to the case of square electrodes by using the corresponding expression for the spreading resistance \([18]\):

\[
R_{\text{spread, sq.}} = \frac{\rho \ln 4}{\pi l},
\]

where \(l\) is the lateral dimension of the square electrode. In this case, following the same argumentations as for the case of circular electrodes, one can find the scaling equation for square electrodes,

\[
l_{\text{max}} = \sqrt{\left(\frac{\rho \ln 4}{\pi}\right)^2 + \frac{4R_{\text{track}}V_{\text{max}}PW}{Q} - \frac{\rho \ln 4}{2R_{\text{track}}} \pi}.
\]

### 7. Outlook

Significant research is currently focused on achieving bionintegrated interface materials (electrode coatings, biocompatible encapsulations, etc). In our elaboration, we omit the effect of the interfacial impedance by assuming an ideal electrode coating. Even with this simplification, the limitations to electrode dimensional scaling appear relevant to the typical electrical parameters used in current research. Including the interface effects would further increase the significance of our findings by decreasing the maximum radius admitted for a given stimulation protocol and conductor technology. Quantifying this aspect is however not trivial and will require further modelling. Moreover, current trends in low-power neuromodulation hardware have introduced implantable circuitry that offer significantly lower voltage excursions to drive the stimulation current compared to clinical IPGs \([32, 33]\). This introduces a dramatic exacerbation of the limitations described herein as the \(V_{\text{max}}\) parameter in our model would be reduced by more than a factor of two.

In light of these considerations, we use the simple argumentations in this paper to propose complementary aspects in the development of flexible/stretchable electrodes for neurostimulation that we believe deserve priority within the soft bioelectronic research roadmap \([6, 34]\). Specifically, we would like to bring to the attention of our community the importance of funnelling research efforts towards high performance (i.e. highly conductive), compliant conductors for soft bioelectronics, as this will play a key role in the successful translational implementation of fully implantable and low-power neurostimulation systems.

### 8. Methods

8.1. Electrode fabrication

Test electrodes were produced using standard microfabrication techniques in a class 100 cleanroom. Electrodes were designed with constant track length \(L = 25\text{ mm}\) and varying radius. The devices were fabricated with a platinum thin film conductor sandwiched between two layers of polyimide (PI) on
49 Silicon wafers. Detailed fabrication methods are available in the supplementary information (available online at stacks.iop.org/JNE/18/046054/mmedia).

8.2. Electrochemical impedance spectrum (EIS) measurements

EIS measurements were taken by immersing the device under test in a beaker containing phosphate buffered saline solution (Gibco PBS, pH 7.4, 1X), along with a platinum wire as counter electrode and a Ag/AgCl reference electrode (Metrohm, El. Ag/AgCl DJ RN SC: KCl). In this three-electrode configuration, electrochemical impedance spectra were acquired at room temperature using a Gamry Instruments Reference 600 potentiostat (100 mV amplitude, 1 Hz–1 MHz frequency). The conductivity of the medium was measured with a conductivity meter (Lutron Electronics CD-4307SD).

8.3. Extraction of the spreading resistance from the electrochemical impedance

The resistive impedance \( Z_R = R_{\text{track}} + R_{\text{spread}} \) was estimated from the high-frequency EIS spectra using the PRF method described in [20]. The track resistance \( R_{\text{track}} \) was quantified by measuring the 4-point resistance of ad hoc Kelvin bridge test structures (length = 25 mm, width = 0.1 mm) patterned on the device wafer and extracting the sheet resistance \( R_S \) of the metallization. This was used to calculate the conductor track resistance using the formula \( R_{\text{track}} = R_S L/W \). The spreading resistance was then estimated as \( R_{\text{spread}} = Z_R - R_{\text{track}} \). To compare the extracted value of \( R_{\text{spread}} \) with the theoretical value, the conductivity \( \rho \) of the medium was modulated by diluting the PBS solution and measuring the solution resistivity \( \rho \) with a conductivity meter (Lutron Electronics CD-4307SD).

Data availability

The datasets used herein are available upon reasonable request.

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Conflict of interest

S P L is a co-founder of Onward; S P L and N V are co-founders of Neurosoft Bioelectronics.

Author contributions

G S, N V: Conceptualization. G S, N V, Y V: Data curation, Methodology, Investigation, Writing—original draft. G S, Y V: Visualization. G S, N V, Y V, S P L: Writing—review and editing. S P L: Resources.

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