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Peter Fromherz

Sheet conductor model of brain slices for stimulation and recording with planar electronic contacts

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Abstract Current and voltage in a brain slice are considered, taking into account the boundary conditions at the surface to an electrolyte bath and at the substrate of an electron conductor. A sheet conductor model is introduced with ohmic leak conductance to the bath and capacitive coupling to the substrate. It assigns a current-source density of neuronal activity to extracellular field potentials recorded by planar contacts, and it relates the current of planar capacitive contacts to the field potential that elicits neuronal activity. Two examples are analytically solved: the recording across a layered brain slice and the stimulation by a circular electrode. The study forms the basis for neurophysical experiments with brain slices or retinae on microelectronic chips.

Keywords Brain slice · Field potentials · Current-source density · Capacitive stimulation · Multielectrode array

Introduction

Thin layers of brain tissue are used in experiments with acute brain slices, organotypic brain slices and dissociated retinae. Neuronal excitation is elicited with pointed metal electrodes, and extracellular field potentials are recorded with micropipette electrodes. More sophisticated experiments may be enabled with arrays of planar metal contacts (Novak and Wheeler 1988; Meister et al. 1994; Egert et al. 1998; Jahnsen et al. 1999; Oka et al. 1999; Stett et al. 2000). To evaluate maps of recorded neuronal activity and to optimize capacitive stimulation by planar contacts, a theory is required that relates current and voltage. A brain slice between a solid substrate and an electrolyte bath differs from bulk brain because current and voltage depend on the boundary conditions at the substrate and bath. That issue is addressed in the present paper. To elucidate the basic physics, a model is introduced where the slice is described as a sheet conductor that is coupled to the bath by ohmic conductances and to the substrate by capacitive interactions. Stimulation by a circular electrode and recording across a layered brain slice are analytically evaluated.

P. Fromherz
Department of Membrane and Neurophysics,
Max Planck Institute for Biochemistry,
82152 Martinsried/Munich, Germany
E-mail: fromherz@biochem.mpg.de
Tel.: +49-89-85782820
Fax: +49-89-85782822

Results and discussion

Volume conductor

The mean electrical property of brain tissue is usually described by the volume conductor theory (Haberly and Shepherd 1973; Nicholson and Freeman 1975; Mitzdorf 1985; Richardson et al. 1987). A field potential V_{field} arises from currents per unit volume j_{source} of cellular sources or j_{stim} of stimulation electrodes. Assuming an isotropic and homogeneous specific resistance ρ, the curvature of the potential is proportional to the current-source density according to Eq. 1 with the Cartesian coordinates x, y and z:

$$-\frac{1}{\rho}\left(\frac{\partial^2 V_{\text{field}}}{\partial x^2}+\frac{\partial^2 V_{\text{field}}}{\partial y^2}+\frac{\partial^2 V_{\text{field}}}{\partial z^2}\right)=j_{\text{stim}}+j_{\text{source}} \tag{1}$$

For a layered brain such as the hippocampus, neuronal activity is rather homogeneous along the layers (Andersen et al. 1971). Without stimulation, the potential perpendicular to the layers in the x direction is defined by $-\mathrm{d}^2V_{\text{field}}/\mathrm{d}x^2=\rho j_{\text{source}}$, neglecting the curvature of the potential in the y and z directions. That relation is commonly used to evaluate the current-source density from experimental field potentials (Mitzdorf 1985). Stimulation is usually achieved with pointed electrodes. For a spherical tip with radius a_{el} we obtain from Eq. 1 the hyperbolic potential $V_{\text{field}}=J_{\text{stim}}\rho/4\pi a$ at a distance

$a > a_{el}$ for a current $J_{stim} = 4\pi a_{el}^2 c_{el} \mathrm{d}V_{el}/\mathrm{d}t$ with the specific capacitance c_{el} and the voltage V_{el}.

Brain slice

Let us consider a brain slice of height h between a solid and an electrolyte on ground potential (Fig. 1a). The solid may be an electronic conductor (metal, semiconductor) where the faradaic current is suppressed by the electrolytic/electronic junction itself or by a thin insulator. The volume conductor theory must account for the boundary conditions, an aspect not considered in previous studies (Wheeler and Novak 1986; Plenz and Aertsen 1993; Shimono et al. 2000).

1. At the substrate, a capacitive current per unit area $j_{stim}^{(2)}$ determines the gradient of the potential. Choosing the z direction normal to the substrate, we obtain $-(\mathrm{d}V_{field}/\mathrm{d}z)_0 = \rho j_{stim}^{(2)}$ at $z=0$.
2. At its surface the slice is on ground potential with $V_{field}(h)=0$ at $z=h$. That approximation neglects a voltage drop in the bath where the specific resistance is around 50 Ω cm, low compared to the 300 Ω cm of brain tissue (Lang et al. 1969; Holsheimer 1987). To illustrate the boundary conditions, we consider an ideal homogeneous slice. Using $-\mathrm{d}^2V_{field}/\mathrm{d}z^2 = \rho j_{source}$ with $j_{source}=$const. for recording and $j_{source}=0$ for stimulation, we obtain Eqs. 2 and 3. The leak current from slice to bath gives rise to potential profiles with maxima at the substrate:

$$V_{field}(z) = j_{stim}^{(2)} h\rho\left(1 - \frac{z}{h}\right) \tag{2}$$

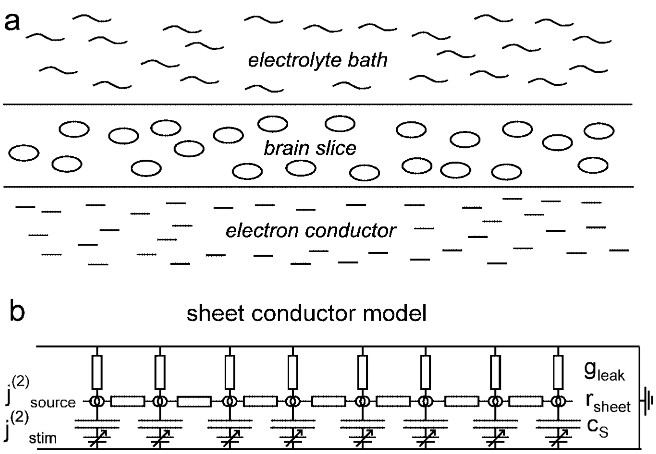

Fig. 1a, b Brain slice. **a** Sketch of brain slice between an electrolyte and the substrate of an electron conductor without lateral patterning. **b** Sheet conductor model. The symbols of the circuit represent infinitesimal elements: leak conductance from sheet to bath g_{leak} (S/m^2), sheet resistance r_{sheet} ($\Omega_\square$), capacitance of substrate interface c_s (F/m^2). The sheet is fed by neuronal current sources $j_{source}^{(2)}$ (A/m^2) and by capacitive currents $j_{stim}^{(2)} = c_s \mathrm{d}V_s/\mathrm{d}t$ (A/m^2) with a changing voltage V_s applied to the substrate

$$V_{field}(z) = \frac{j_{source} h^2 \rho}{2}\left(1 - \frac{z^2}{h^2}\right) \tag{3}$$

In a real system, stimulation current and current-source density are not constant along the slice in the x and y directions. In that case the leak current competes with current along the slice. For a pattern $j_{stim}^{(2)}(x,y)$ or $j_{source}(x,y,z)$ we could compute the potential $V_{field}(x,y,z)$ from Eq. 1 with the proper boundary conditions. However, that approach is difficult to apply: (1) we do not know the structure and current-source density across a slice; (2) along a slice, we know at best the potential sampled in two dimensions; (3) the bath potential is usually ill defined. For these reasons we do not follow that approach here. Instead, we propose a model that can be evaluated without knowing the structural details.

Sheet conductor model

We neglect the details of the current flow from slice to bath. We describe the shunting effect of the bath by an ohmic conductance per unit area g_{leak}, the slice itself by a sheet resistance r_{sheet} and the substrate by a capacitance per unit area c_s. Thus the slice is represented as a sheet conductor in the x-y plane with a capacitive bottom and a leaky cover (Fig. 1b). The neuronal current sources per unit area $j_{source}^{(2)}(x,y)$ and the stimulation current due to a changing voltage V_s are balanced by the current along the sheet and by the ohmic and capacitive shunting to bath and substrate. As a result we obtain Eq. 4 for the potential $V_{field}(x,y)$ with an isotropic and homogeneous sheet resistance r_{sheet}. A modulated capacitance $c_s(x,y)$ accounts for localized electrodes:

$$\begin{aligned} &-\frac{1}{r_{sheet}}\left(\frac{\partial^2 V_{field}}{\partial x^2} + \frac{\partial^2 V_{field}}{\partial y^2}\right) + g_{leak} V_{field} + c_s \frac{\partial V_{field}}{\partial t} \\ &\quad = j_{source}^{(2)} + c_s \frac{\partial V_s}{\partial t} \end{aligned} \tag{4}$$

Exclusively for better parametrization, we introduce an equivalent slice of effective thickness h. The sheet resistance is written as $r_{sheet} = \rho/h$ with a specific resistance ρ, the leaks are expressed as $g_{leak} = 2/\rho h$, the conductance from the slice center to the bath, and an effective current-source density j_{source} is defined by $j_{source}^{(2)} = h j_{source}$. We obtain Eq. 5 for the current balance in a volume element of the equivalent slice:

$$\begin{aligned} &-\frac{1}{\rho}\left(\frac{\partial^2 V_{field}}{\partial x^2} + \frac{\partial^2 V_{field}}{\partial y^2}\right) + \frac{2}{h^2\rho} V_{field} + \frac{c_s}{h}\frac{\partial V_{field}}{\partial t} \\ &\quad = j_{source} + \frac{c_s}{h}\frac{\partial V_s}{\partial t} \end{aligned} \tag{5}$$

Equations 4 and 5 for the sheet conductor model fundamentally differ from Eq. 1. The Poisson equation is replaced by a telegraph equation, known from core-coat conductors and systems with heat conductance and distributed chemical reactions. Equation 4 is the basis to compute field potentials for given patterns of stimulation currents or of neuronal activity. On the other hand, Eq. 4 provides the current-source density from experimental maps of the field potential. For illustration, we consider two special cases that can be solved analytically, one for stimulation and one for recording.

Capacitive stimulation by circular contact

Capacitive current through a planar contact gives rise to a field potential in a slice that may elicit neuronal excitation. We neglect in Eq. 4 the neuronal activity and assume $\mathrm{d}V_{\mathrm{field}}/\mathrm{d}t << \mathrm{d}V_{\mathrm{s}}/\mathrm{d}t$. For circular symmetry we obtain Eq. 6 with the radius a and the length constant $\lambda_{\mathrm{sheet}} = 1/\sqrt{g_{\mathrm{leak}} r_{\mathrm{sheet}}}$:

$$-\lambda_{\mathrm{sheet}}^2 \left(\frac{\partial^2 V_{\mathrm{field}}}{\partial a^2} + \frac{1}{a} \frac{\partial V_{\mathrm{field}}}{\partial a} \right) + V_{\mathrm{field}} = \frac{c_{\mathrm{s}}}{g_{\mathrm{leak}}} \frac{\partial V_{\mathrm{s}}}{\partial t} \tag{6}$$

For an electrode with $c_{\mathrm{s}} \neq 0$ within a radius a_0, a stationary stimulation $\mathrm{d}V_{\mathrm{s}}/\mathrm{d}t = \text{const.}$ leads to Eq. 7 with the modified Bessel functions I_0, I_1, K_0 and K_1. The amplitude $(c_{\mathrm{s}}/g_{\mathrm{leak}})\mathrm{d}V_{\mathrm{s}}/\mathrm{d}t$ is the field potential for an infinite electrode:

$$V_{\mathrm{field}}(a) = \frac{c_{\mathrm{s}}}{g_{\mathrm{leak}}} \frac{\mathrm{d}V_{\mathrm{s}}}{\mathrm{d}t} \left\{ \begin{array}{ll} 1 - \frac{a_0}{\lambda_{\mathrm{sheet}}} K_1\left(\frac{a_0}{\lambda_{\mathrm{sheet}}}\right) I_0\left(\frac{a}{\lambda_{\mathrm{sheet}}}\right) & a < a_0 \\ \frac{a_0}{\lambda_{\mathrm{sheet}}} I_1\left(\frac{a_0}{\lambda_{\mathrm{sheet}}}\right) K_0\left(\frac{a}{\lambda_{\mathrm{sheet}}}\right) & a > a_0 \end{array} \right\} \tag{7}$$

We assume $r_{\mathrm{sheet}} = 60\ \mathrm{k\Omega}$ and $g_{\mathrm{leak}} = 13.3\ \mathrm{nS/\mu m^2}$ for the sheet resistance and the leak conductance. These parameters correspond to an equivalent slice with a thickness $h = 50\ \mu\mathrm{m}$ and a specific resistance $\rho = 300\ \Omega\ \mathrm{cm}$. The length constant is $\lambda_{\mathrm{sheet}} = 1/\sqrt{h} \approx 35\ \mu\mathrm{m}$. We apply a voltage ramp for 100 μs with an amplitude of 1 V to a contact with a radius $a_0 = 25\ \mu\mathrm{m}$ and a specific capacitance $c_{\mathrm{s}} = 30\ \mu\mathrm{F/cm^2}$. The field potential is plotted in Fig. 2. The maximum is 60 mV, far below the amplitude $(c_{\mathrm{s}}/g_{\mathrm{leak}})\mathrm{d}V_{\mathrm{s}}/\mathrm{d}t = 225$ mV. The profile is rather smooth and spreads over more than 100 μm. In a first approximation, the efficiency of the neuronal excitation is given by the potential $V_{\mathrm{field}}(a)$ itself because the effective potential gradient across the slice dominates. An improved confinement of $V_{\mathrm{field}}(a)$ can be achieved with a smaller electrode and a negative current applied to a ring-shaped contact at $a_0 < a < a_0^{\mathrm{surr}}$. The potential for a center-surround stimulation is obtained as a superposition of two solutions of Eq. 7 with a positive current for $a < a_0$ and a negative current for $a < a_0^{\mathrm{surr}}$. The potential profile is plotted in Fig. 2 with $(c_{\mathrm{s}}/g_{\mathrm{leak}})\mathrm{d}V_{\mathrm{s}}/\mathrm{d}t = 225$ mV in the center at $a < 25$ μm and $(c_{\mathrm{s}}/g_{\mathrm{leak}})\mathrm{d}V_{\mathrm{s}}/\mathrm{d}t = -135$ mV in the surround at $25\ \mu\mathrm{m} < a < 40\ \mu\mathrm{m}$.

The sheet conductor model allows the computation of the potential in brain slices for planar stimulation electrodes. Obviously, the smooth potential profiles qualitatively differ from pointed electrodes in bulk tissue. The current to the bath plays a crucial role. A localized stimulation is achieved with small electrodes and center-surround stimulation. That confinement must be compensated by a distinctly enhanced current density.

Recording in layered brain slice

We consider the neuronal activity in a slice cut across a layered brain such as the hippocampus. The x axis of soma-dendrite direction and the y axis along the brain layers are in the plane of the slice. The current-source density along the y direction is assumed to be homogeneous, as in the intact brain. From Eq. 4 we obtain Eq. 8 without stimulation and with $c_{\mathrm{s}}\mathrm{d}V_{\mathrm{field}}/\mathrm{d}t \ll g_{\mathrm{leak}} V_{\mathrm{field}}$:

$$-\lambda_{\mathrm{sheet}}^2 \frac{\mathrm{d}^2 V_{\mathrm{field}}}{\mathrm{d}x^2} + V_{\mathrm{field}} = \frac{j_{\mathrm{source}}^{(2)}}{g_{\mathrm{leak}}} \tag{8}$$

For a constant $j_{\mathrm{source}}^{(2)}$ in a range $-x_0 < x < x_0$ the field potential is given by Eq. 9, where the amplitude $j_{\mathrm{source}}^{(2)}/g_{\mathrm{leak}}$ is the potential in an infinite homogeneous sheet:

$$V_{\mathrm{field}}(x) = \frac{j_{\mathrm{source}}^{(2)}}{g_{\mathrm{leak}}} \left\{ \begin{array}{ll} 1 - \exp\left(-\frac{x_0}{\lambda_{\mathrm{sheet}}}\right) \cosh\left(\frac{|x|}{\lambda_{\mathrm{sheet}}}\right) & |x| < x_0 \\ \sinh\left(\frac{x_0}{\lambda_{\mathrm{sheet}}}\right) \exp\left(-\frac{|x|}{\lambda_{\mathrm{sheet}}}\right) & |x| > x_0 \end{array} \right\} \tag{9}$$

In the hippocampus, a narrow layer of cell bodies is adjacent to a dendrite layer with synaptic input. For illustration we consider a constant outward current-source density in the stratum pyramidale that balances a

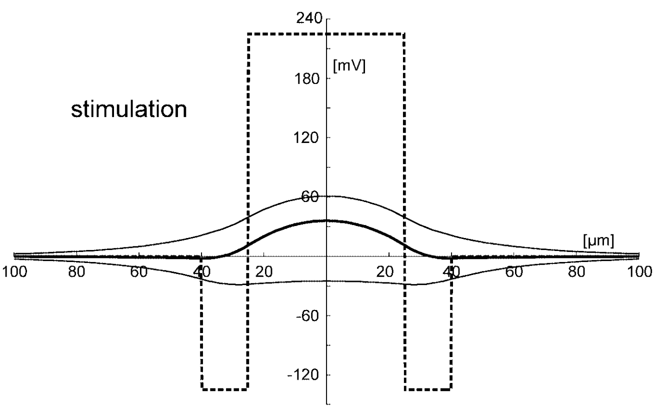

Fig. 2 Field potential versus radial coordinate computed by the sheet conductor model for capacitive stimulation with a length constant $\lambda_{\mathrm{sheet}} = 35$ μm. The central area of an electronic contact has a radius of 25 μm. The ring-shaped surround has a width of 15 μm. The stimulation current per unit area $(c_{\mathrm{s}}/g_{\mathrm{leak}})\mathrm{d}V_{\mathrm{s}}/\mathrm{d}t$ is indicated as a *dashed line* (leak conductance $g_{\mathrm{leak}} = 13.3\ \mathrm{nS/\mu m^2}$). The potential profile $V_{\mathrm{field}}(a)$ due to center-surround stimulation is plotted (*heavy line*), as well the profiles due to positive stimulation in the center (*upper thin line*) and negative stimulation in the surround (*lower thin line*)

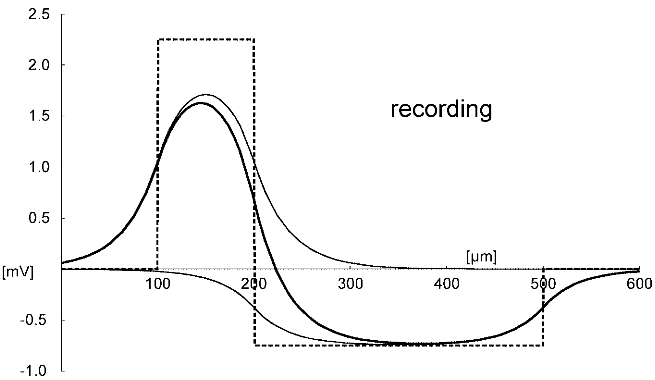

Fig. 3 Field potential of neuronal activity across a layered slice computed by the sheet conductor model with a length constant $\lambda_{\text{sheet}} = 35$ μm. The cell bodies are between 100 μm and 200 μm (stratum pyramidale), the dendrites between 200 μm and 500 μm (stratum radiatum). The scaled current-source density per unit area $j^{(2)}_{\text{source}}/g_{\text{leak}}$ is indicated as a *dashed line* (leak conductance $g_{\text{leak}} = 13.3$ nS/μm^2). The total field potential $V_{\text{field}}(x)$ is plotted (*heavy line*) as well as the potentials caused by the inward current in the stratum radiatum and by the outward current in the stratum pyramidale (*thin lines*)

constant inward synaptic current-source density in the stratum radiatum. With $j^{(2)}_{\text{source}} = 30\ \text{pA}/\mu\text{m}^2$ from 100 μm to 200 μm and $j^{(2)}_{\text{source}} = -13.3\ \text{pA}/\mu\text{m}^2$ from 200 μm to 500 μm, the field potential is given by a superposition of two solutions of Eq. 8. Again we assume $r_{\text{sheet}} = 60\ \text{k}\Omega$, $g_{\text{leak}} = 13.3\ \text{nS}/\mu\text{m}^2$ and $\lambda_{\text{sheet}} = 35\ \mu\text{m}$. With the amplitudes $j^{(2)}_{\text{source}}/g_{\text{leak}} = 2.25\ \text{mV}$ and $j^{(2)}_{\text{source}}/g_{\text{leak}} = -0.75\ \text{mV}$ we obtain the profile plotted in Fig. 3. There is a wide potential trough in perfect correspondence with the trough of the synaptic current. Within a length constant the potential jumps to the bell-shaped profile of the narrow stratum pyramidale.

The leak conductance from a slice to the bath plays a crucial role for the field potential created by neuronal activity. The field potential itself is a smoothed image of the current-source density, quite in contrast to the bulk brain where the curvature of the potential matches the current-source density. Significant changes of the potential occur within a length constant at the borders of strata. A narrow sampling of the field potential is required, in order to obtain a reliable map of the current-source density. Metal electrode arrays with spacings of hundreds of micrometers have to considered with care. Transistor arrays with spacings of a few micrometers may solve the problem (Besl and Fromherz 2002).

Conclusions

In brain slices or dissociated retinae, extracellular stimulation and recording are quite different from bulk brain, because current and potential depend on the boundary conditions at the substrate and bath. To elucidate the basic features of the problem, the model of a sheet conductor is introduced. It allows an estimate of the potentials along a slice for arbitrary patterns of planar stimulation electrodes and of neuronal activity. Examples demonstrate that the leak conductance to the bath gives rise to a characteristic length constant that governs stimulation and recording. The sheet conductor model is a tool for the design of semiconductor chips with optimized arrays of microelectronic devices for brain slices and retinae. It may initiate computations by the full-fledged volume conductor theory with proper boundary conditions to obtain potential maps V_{field} (x,y,z) along and across a slice.

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