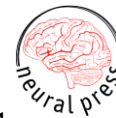


Brief Report

Some aspects of bidomain modeling with volume conductors



Roman R. Poznanski

*Integrative Neuroscience Initiative, Melbourne, Australia 3145*E-mail: romanpoznanski@gmail.comDOI: <https://doi.org/10.56280/1628864189>

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Abstract

The concept of dynamic multiscale modeling has changed our approach to multi-neuronal cable theory. Previously, computational neuroscientists considered individual neurons as neural masses or compartmental models, but now, a distributed representation of single neurons as ionic cable structures is most likely to lead to a greater understanding of how the distribution of ionic channels and synaptic input along the dendrites of a few neurons can offset the collective behavior of a large ensemble of neurons and, therefore, provide a measure of the dynamical brain. This change in perspective forms the basis of volume conductor-bidomain modeling, a new method that captures multiscale electrophysiology.

Keywords: Multiscale electrophysiology, volume conductor, bidomain model, neuropil, field potentials, ionic cable theory

1. Introduction

The functionality of the macroscale field theory of neuronal dynamics of the human brain is shaped by its geometry, as evidenced in neuroimaging studies (Pang et al., 2023). However, it ignores the dynamic continuity among dendritic neurons. In earlier models, synaptic plasticity remodels subcellular networks by regulating patterns for the synthesis of dynamic continuity that forms cognitive networks of associable representations (Cacha & Poznanski, 2011). This dynamic continuity through neuromodulation yields a unique functional organization, reflecting the brain's self-referential character. The process by which this occurs is nonsynaptic diffusion neurotransmission (Bach-y-Rita, 1995). Thus, the post-ontogenic functional organization is malleable under adaptive pressures (Freeman, 1975). A schema resulting from recurrent interconnections within a neural network and/or through volume transmission where the signal diffuses into a local volume or neuropil can be conceptualized in prototype models by embedding the neural networks in a *syncytium* that interacts with the

external microenvironment. Dye coupling between neuroglia in the brain forms large syncytial structures through gap junctions (Gutnick et al., 1981). Therefore, utilizing bidomain modeling (Poznanski, 1993) and volume conduction is crucial in developing dendritic and astrocytic networks (Poznanski & Riera, 2006) and their interaction within the neuropil, leading toward an integrative theory of cognition (Poznanski, 2002).

The frequency of firing at synapses can invoke a dispositional state formed through electrochemical changes involving subtle modulation of the activity of a neural network. Dispositional states require a subtle change to occur at the synaptic junctions, possibly involving the extracellular matrix surrounding the synaptic boutons through nonsynaptic diffusion via volume transmission (Zoli et al., 1998; Fuxe & Agnati, 1991). Indeed, neuroglia completes a tripartite configuration in which they can modulate signals by synthesizing and releasing neural transmitters (Araque et al., 1999). An example of a mechanism for

strengthening synaptic connections without affecting the long-term changes in the neuronal synaptic elements is glutamate activating IP₃ metabotropic receptors in neuroglia, causing a rapid influx of intracellular Ca²⁺ resulting in a retrograde Ca²⁺-dependent release of glutamate from neuroglia, activating NMDA-type receptors on the presynaptic neuron, thereby increasing the release of glutamate, and enhancing synaptic transmission (Pereira & Furlan, 2010).

2. Field potentials and volume conductor bidomain modeling

Field potentials are modeled using a continuum approach (Beurle, 1956; Griffith, 1963, 1965; Fischer, 1973; Wilson & Cowan, 1973) rather than populations of discrete networks where neural assemblies are represented as lumped nodes (Wilson & Cowan, 1972; Wilson 1999; Omurtag et al., 2000; Nykamp & Tranchina, 2000; Coop & Reeke, 2001). The approach entails modeling large assemblies of neurons as lumped nodes in a one-dimensional neural sheet or layer. A field description for the neuronal density and extracellular field potential is determined, which does not take into consideration the spatial distribution of neural masses but instead is based on the spread of firing activity between neural assemblies via pseudo connections and delays (Ventriglia, 1974; Ingber, 1982; Amari, 1983; Peretto, 1984; Mallot & Giannakopolous, 1996; Jirsa & Haken, 1997; Barna et al., 1998; Tuckwell, 1998; Liley et al., 1999).

Cortical activity and evoked (or event-related) potentials measured by EEG correlate with synaptic activity in the dendrites of neural masses in the form of extrasynaptic signals (Wright & Liley, 1996). Consequently, continuum models of undistributed neural aggregates of cortical activity localized to the gray matter and oriented perpendicularly to the cortical sheet have been developed for a volume element of neural tissue (Nunez, 1974, 1981, 1995; Rotterdam et al., 1982; Tuckwell, 2000). The extension of the continuum models to spatially distributed neural aggregates began with the current source density analysis (Nicholson & Llinas, 1971; Nicholson, 1973; Freeman, 1975; Nicholson & Freeman, 1975; Mitzdorf & Singer, 1977; Mitzdorf, 1985). The key assumption of this approach is that a microscopically inhomogeneous neural tissue is replaced by a macroscopically homogeneous medium with electrical properties represented as averaged quantities in a volume of tissue representing the dendritic activity of

a group of neurons. This results in a simple relation between the extracellular field potential and the current source density of an averaged neural mass of neurons but does not consider each neuron's individuality in the neuropil.

A multiscale approach that does not assume a macroscopically homogeneous neural tissue (although neurons are chosen as point source fields) is based on current flow density analysis in a volume conductor (Kwan & Murphy, 1974; Klee & Rall, 1977; Rotterdam, 1980; Halsheimer et al., 1982; Feenstra et al., 1984). An even more realistic approach is considering the relationship between each neuron's extracellular field potential and transmembrane current density in a volume conductor (Rotterdam, 1987). Therefore, each neuron is represented as a core-conductor (i.e., a cable with extracellular sheath surrounding the core)(Clark & Plonsey, 1968; Bennett et al., 1999) at the microscopic level, and at the macroscopic level as nodes in a 3D realistic, inhomogeneous volume conductor (cf. Bennett et al., 2001). Such multi-level models capture the essence of intra-cortical pathways exhibited throughout the neocortex (Nunez, 1995; Bullock, 1997).

How significant are extrasynaptic signals (or local field potentials) in the neuropil as a basis for cognition? What role do the local field potentials play before neural firing in cognition? As a starting point to better understand the role of local field potentials, a more realistic attempt at modeling neuronal geometry is required (Bedard et al., 2017; Harris Bozer, 2017). An important aspect of neuronal geometry is its embedding in 3D space. Still, extrasynaptic signals between neurons in 3D space due to synaptic activity in the dendritic neuropil have received little theoretical attention since most models assume that the extracellular space is isopotential. How important is volume transmission in the electrical activity of the brain? This question must be answered with biologically realistic neural networks based on simplified models of single neurons embedded in 3D space rather than lumped models without spatial structure. In their model of cortical spreading depression, Tuckwell & Miura (1978) state that no account of the contribution from glial syncytium was considered, but its inclusion is required for a complete model. A monodomain approach advocated by Tuckwell (1980; 1981) for the cortical spreading depression model needs to be extended to include both neuronal and glial depolarizations.

MacLennan (1993) developed a mathematically tractable and biologically plausible model of information processing in the neuropil. The model includes a closely packed matrix of dendrites, axons, somas, and glia as precursor conditions for complex interactions in a system of ion fluxes, extrasynaptic potentials and neuromodulators of neuronal activity. However, field effects in dendrites, because of synaptic potential activation in large populations of neurons, will require building more realistic models of neurons and neural networks, allowing for the 3D characterization of neurons and networks to be included in the neuropil. This requires a simplification in the geometry, which can be made by assuming that the interstitial and intracellular domains are linked everywhere by a membrane. Therefore, the outflow of current from one domain ought to be equal to the inflow of current to the other domain, as stipulated by Kirchoff's current law and the continuity of current, with the convention that the positive current direction is out through the membrane:

$$-\sigma \int_U \nabla \phi_e dU = \sum_{j=1}^M \int_{M_j} I_{M_j} ds$$

where U is the interstitial volume in the neuropil, M is the number of ionic cables in the neuropil, σ is the conductivity tensor describing the anisotropic interstitial 3D-space, ϕ_e is the interstitial (extracellular) potential, M_j is the membrane surface of the j th ionic cable, and the I_{M_j} is the transmembrane current of the j th ionic cable is given by

$$I_{M_j} = (\beta/R_m)(\phi_j - \phi_e) + \beta C_m \partial[\phi_j - \phi_e]/\partial t + \sum_{r=1}^R \bar{I}_{ion}^r + \sum_{p=1}^P \bar{I}_{syn}^p$$

where ϕ_j is the intracellular potential of the j th ionic cable, β is the ratio of the membrane surface area to the volume occupied by the neuropil, R is the total number of ionic channels, P is the total number of synaptic connections, R_m is the membrane surface resistivity, C_m is the membrane capacitance, \bar{I}_{ion} is the ionic current flowing into the j th ionic cable, and \bar{I}_{syn} is the synaptic current flowing into the j th ionic cable. The analytic expressions for \bar{I}_{ion} and for \bar{I}_{syn} are complicated nonlinear functional of intracellular and

interstitial potentials determined using discrete Green's functions (Gruner, 1968). The above approach is called a bisyncytia or bidomain model (Schmitt, 1969; Peskoff, 1979; Plonsey, 1989; Poznanski, 1993).

It assumes that all varieties of cations and anions are grouped together to form a "macroscopic" field potential. The effects of changes in ionic concentrations lead to changes in Nernst potentials, resting membrane potentials, and synaptic transmission. As a first approximation, the effects of such ionic composition changes can be neglected, but a full understanding of ionic diffusion in the extracellular space requires the dynamics described by time-dependent Nernst-Planck equations (Maex, 2017; Pods, 2017) as well as those described by ionic cable theory (Poznanski & Bell, 2000a,b; Iannella & Tanaka, 2006, 2007; Xiang et al., 2017) to be incorporated in a single unified theory. This consequently permits ionic channels to be treated as discrete current sources, allowing analytical solutions to the Frankenhauser-Huxley equations (Poznanski, 2004) and, more recently, the backpropagation of action potential (Iannella & Poznanski, 2023) and Ca^{2+} driven synaptic plasticity (Iannella & Poznanski, 2024).

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