

New and Notable
for BJ paper 2017BIOPHYSJ308207 entitled “Optocapacitive generation of neuronal
action potentials by microsecond laser pulses of nanojoule energy”

January 18, 2018

Brilliant Stimulation, one cell at a time

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The enormous growth in neurobiology since Steve Kuffler moved to Pharmacology at Harvard in 1969—and the Department of Neurobiology and the Society of Neuroscience were founded about a decade later—sometimes obscures a crucial fact. We know very little about the main function of the nervous system.

Little is known about how the nervous system processes information. It is as if we had fabulous measurements of the structure of a computer, even of its atoms and how they move, and knew where the computer heats up as it loses energy to friction, but we did not know whether we had a digital or analog computer in our hands, or a combination of both. It would be as if we had a digital computer and we did not know what its word length was, or whether the word was in one wire or a set of wires, or even whether it had a (stable robust) word at all!

Understanding how information is processed in the dense web of the central nervous system almost certainly requires the selective stimulation of neurons. That way there is some hope of defining a neurological ‘word’ if one exists in one cell, or if it only emerges and exists in an array of neurological elements, just as a word exists only in an array of wires in a computer. A nervous system will probably have to be grown in a ‘test tube’ to understand how it processes information. Stimulation of individual cells in their normal location and environment will be an essential tool, in my view.

The recent paper of Carvalho-de-Souza, Pinto, Pepperberg and Bezanilla presents the promising new method of ‘optocapacitance’ for stimulating individual neurons by attaching light absorbing nanoparticles and stimulating them by tiny amounts (nanojoules) of light without the difficult methods of optogenetics or optopharmacology. The light creates a sudden localized temperature change, which in turn injects displacement current i_C into the neuron

$$i_C = \frac{dQ}{dt} = C_m \frac{dV}{dt} + (V - V_s) \frac{d}{dt} C_m(t),$$

changing the potential across the cell membrane, fortunately in the depolarizing direction that can stimulate the cell. (Symbols are defined in Carvalho-de-Souza, Pinto, Pepperberg and Bezanilla). The displacement current is produced by the change in membrane capacitance with temperature (1) induced by sudden localized heating, as discovered previously (2), building on related work (3); and then extended by Carvalho-de-Souza et al (4). A sign error in the theory was discovered (5, 6), gracefully acknowledged (7, 8) and the present paper of Carvalho-de-Souza et al extends their original work in important ways. Strong evidence is provided for their view that displacement current (across the cell membrane) produced by heating of the nanoparticle produces the action potential. Photo-sensitivity is significantly improved as well in an important technical advance.

Displacement current is the general name for the current through the capacitance of cell membranes and it plays a special role in the properties of electricity, or electrodynamics as those properties are called by physical scientists and mathematicians (9). Displacement current is a **universal** property of electricity and its dependence on the electric field guarantees that the conservation of current is exact and universal (10) no matter how complex is the flux of charged masses—even nonlinear flux, driven by non-electrical forces that do not appear in the equations of electrodynamics at all, like diffusion or convection—or its polarization. Current is exactly the same (to many significant figures) in every component of a series circuit at all times and conditions, no matter what is the physics by which charged matter flows in each of the components of the circuit. Conservation of current is exact because the universal displacement current

$\epsilon_0 \partial E / \partial t$ is different in each device in series (see Fig. 2 of (11), where symbols are defined and explained). The universal displacement current $\epsilon_0 \partial E / \partial t$ changes (as a solution of the Maxwell equations) so the current is exactly the same in every device in series: the electric field is changed by Maxwell's equations so $\partial E / \partial t$ is different in each device, automatically adjusting to the physics of each device. The field is different everywhere in a series system so that the current can be the same, exactly, everywhere, at each instant of time.

Carvalho-de-Souza et al show that the briefer the pulse of light, the greater the displacement current, and the larger the voltage response of the neuron. At short times the rate of change in temperature is maximal, as is dC_m/dt and the voltage response. In measurements of the classical strength duration curve, the input is quite different from optical heating; see (12, 13) and Hill (14) for references, as well as (15) for Hill's misunderstanding of Hodgkin (16, 17), of historical proportions. Classical strength-duration curves were usually studied with pulses of extracellular ionic current. A small fraction of that current flowed across the cell membrane to create the membrane potential that creates the signal called the action potential, as analyzed in (18). Most extracellular current avoids the high resistance/impedance of cell membranes and is shunted around cells. The classical results do not apply when the input is displacement current created by heating, as in the opto-capacitive method.

Classical analysis had a cavalier treatment of the spatial spread of potential. The actual spatial spread of potential is enforced by a combination of the cable (i.e., telegrapher's or transmission line) equation in one dimension (19-22) that describes the properties of the axon 'cable', and Poisson's equation of electrodynamics in three dimensions (23-25). Rattay et al (18) have computed strength duration curves produced by extracellular stimulation, including the spatial dependence of potential, and found dramatic deviations from classical theory. The Least Action Principle of Mechanics can be used to analyze classical strength duration curves (26, 27) and would probably be a useful tool in analyzing opto-capacitance curves as well.

The history of optocapacitance serves as an admirable example of the scientific process. The original observation (1) that reactive impedance and capacitance varied with temperature seemed irrelevant to the main stream of biological work. A brilliant imaginative approach (2, 4) turned the irrelevant into the relevant and practical, but it was not quite right. It contained a significant sign error in the theory. The error was soon discovered (5, 6), and it was immediately acknowledged and corrected (7, 8). The original work is extended to great advantage here, by Carvalho-de-Souza, Pinto, Pepperberg and Bezanilla. The scientists involved (of both groups) avoided the natural but destructive trap of defending ego, that all of us can so easily fall into, much to their joint credit. The resulting paper I write about here is a major advance in our understanding and promises to become an important new tool for future investigations of how the nervous system processes information.

Acknowledgement

I thank the editors for giving me a chance to write this note. David Pepperberg kindly showed me a most useful analysis of strength duration curves. It is a particular pleasure to thank Francisco Bezanilla for correcting several of my references, and for so very much else.

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