Preface

Computational neurostimulation in basic and translational research

For a field that started with the application of a torpedo fish to the head for the treatment of migraine (Kellaway, 1946; Priori, 2003), neurostimulation has come a long way. Where once the humble torpedo fish delivered uncontrolled electricity to the head, neurostimulation devices are now engineered with sophistication and can deliver current to any region of the brain with precision voltage control. There is now no denying the contribution that both noninvasive brain stimulation (NIBS) techniques including transcranial direct current (tDCS), alternating current, and transcranial magnetic stimulation (TMS) as well as invasive deep brain stimulation (DBS) have made to improving our understanding of brain function and to helping treat carefully selected patients.

For example, DBS is now applied routinely for a growing number of neurological and psychiatric disorders, and electrical stimulation therapies are established for use in treating hearing loss (cochlear implants), with visual neurostimulation prosthetics currently under development. Several applications of transcranial NIBS techniques have now made the transition into clinical use, while phase 2 and 3 clinical trials for the application of NIBS are proliferating, and increasingly NIBS is also being used to augment healthy brain function, including home use (Bikson et al., 2013).

Neurostimulation in basic and translational research therefore remains a dynamic and innovative field. However, one can also observe that the success and application of different forms of neurostimulation has galloped ahead of our understanding of the mechanisms through which electrical stimulation of the brain expresses its effects. On the one hand, many applications of invasive or noninvasive brain stimulation, such as DBS or TMS, are now used widely for treatment of neurological and psychiatric disorders. In these cases, not having a deeper understanding about the underlying mechanism is acceptable if clinical benefits outweigh the possible concerns that arise from any mechanistic ignorance. On the other hand, ignorance delays progress and may even lead to intellectual and research investment in dead ends. For applications in basic and translational research, the dearth of understanding about key aspects of neurostimulation seems much less acceptable. Here, it leads to spurious inference, promotion of simplistic ideas, or plain wrong assumptions/procedures, and poses a hindrance to progressing forward beyond a peak of inflated expectations into a mature field of research, technology, and clinical use (Bestmann et al., 2015). Finally, side effects, even if subtle, may be less acceptable in healthy individuals. Using neurostimulation to improve brain function has several challenges (Bestmann et al., 2015; de Berker et al., 2013). A deeper understanding of how behavioral changes unfold with brain stimulation would surely help address these issues, spurn further innovation, and quell misuse.

The question then is: where should such a mechanistic insight come from? This is not trivially answered, not least because there is not one form of neurostimulation. Invasive DBS, for example, is focused on a relatively small spatial scale of several millimeters, targets subcortical structures, commonly uses high-frequency (~130 Hz) trains of short biphasic electrical pulses, and is exclusively applied in severe pathology. By contrast, most forms of NIBS stimulate several square centimeters of cortical tissue or even entire networks of the brain at once (Bestmann and Feredoes, 2013; Bestmann et al., 2015; de Berker et al., 2013). Pulsed stimulation techniques such as TMS are applied at frequencies rarely exceeding 50 Hz for more than a few pulses (Huang et al., 2005), whereas direct or alternating transcranial current stimulation techniques apply low currents continuously for tens of minutes at a time (Nitsche and Paulus, 2011). This panoply of ways to deliver stimulation complicates comparison of the resulting effects on physiology and behavior. The frequent creation of superficial analogies based on concepts used for all types of stimulation, such as changes in excitability, inhibition and excitation, plasticity, or virtual lesions, should thus probably be avoided (Bestmann et al., 2015; de Berker et al., 2013). Another crucial point that is often ignored is that different types of neurostimulation are predominantly investigated at very different levels of observation. Drawing parallels between them is often unwarranted or simplistic. For example, a lot of knowledge about the impact of DBS rests on direct recordings in animals and novel developments that allow for recording directly from the vicinity of the stimulation electrode in humans. These single neuron or local field potential (LFP) recordings starkly contrast with the level of observation for most of the NIBS techniques in humans, where behavioral and neuroimaging measures provide the mainstay of inference on how stimulation expresses its effects. As recently argued (Bestmann et al., 2015), even when data from invasive recordings in animals (e.g., Márquez-Ruiz et al., 2012; Rahman et al., 2013) complement current knowledge about the impact of stimulation in humans, the question remains how the effects of neurostimulation at these different levels of observation ought to relate to one another.

We argue that the field of neurostimulation is now at a stage where quantitative computational models must guide further progress. Put simply, there is a striking paucity of quantitative models that span across levels of description and link dose of stimulation through neurophysiology to behavior. Computational neurostimulation, as envisaged here, is the use of mechanistic, quantitative models for understanding the physiological and behavioral consequences of neurostimulation. Such models must meet several requirements: first, they must be biologically and biophysically grounded in current knowledge. This inevitably requires many assumptions with sufficient uncertainty about the specific parameters one should use to incorporate current knowledge into a model. Second, they must address the question at hand at an appropriate level of description that is suited to answer that specific question. While they may draw upon knowledge (and other models) cast at lower or higher levels of description, the choice of model should be governed by the type of data the model seeks to explain, and that one can obtain experimentally to inform the iterative process between modeling and experimentation. Third, models ought to provide "mathematical/computational microscopes" (Moran et al., 2011) in that they can probe unobservable or hidden processes and interactions in observed data. Fourth, and related, models should seek to explain what it is that the observed data actually represent in terms of a task or computation that is carried out by a specific system. Fifth, and most pertinent to this volume, is the need to explain how the physiological changes produced by stimulation ultimately influence or change cognition and behavior, in both health and disease. The last point is unlikely to be achieved without substantial progress on the other requirements, but because neurostimulation is used to alter behavior and cognition, it should remain the ultimate goal. Many important issues merit discussion: what levels of description (microscopic–mesoscopic–macroscopic) are most suited to address a specific question at hand; how realistic (i.e., complex) should models be and how should one trade-off biological realism with model complexity and the possibility of overfitting; how generalizable across individuals and behaviors should models be? It is an exciting development that recent work has initiated discussion on these issues and the possible role of different forms of computational models for the field of neurostimulation (Bestmann et al., 2015; Bikson et al., 2015; Bonaiuto and Bestmann, 2015; Frohlich, 2015; Grill, 2015; Hartwigsen et al., 2015; Little and Bestmann, 2015; Moran, 2015; Neggers et al., 2015; Rahman et al., 2015; Triesch et al., 2015; Wang et al., 2015).

Of course, substantial advances in the use of models for the field of neurostimulation have already been made. Perhaps the most advanced and accepted use of models is in the field of DBS, where neural network models and simulations have made substantial contributions to understanding how different waveforms and stimulation regimes affect local firing (Grill, 2015; Little and Bestmann, 2015). The contributions from this work have started to be applied in designing novel, energy-efficient DBS stimulators. In other fields of neurostimulation, particularly the group of NIBS techniques, the use of models is in a much earlier stage of infancy. Here, the use of detailed head models and finite element methods to estimate current flow through the brain based on individual MRI scans are most notable, and for tDCS applications (Datta et al., 2013; Kuo et al., 2013) and TMS (Thielscher et al., 2011; Windhoff et al., 2013) are now on the verge of becoming standard procedure.

Yet, few models presently seek to explain the computations carried out by neural circuits and how these are affected by stimulation, in the sense that they do address what it is these circuits do and what the information they process reflects. A simple example may serve to illustrate this crucial point: if we were to understand a book written in a foreign language, then simulations of current flow are analogous to predicting the distribution of ink on the pages; neural network models then attempt to predict the patterns of letters on each page, and whether these patterns are influenced by stimulation; but crucially, none of these tell us what those letters actually mean. If neurostimulation is seen as an attempt to edit the meaning of the letters of a book, then understanding the meaning of the letters first seems crucial.

The imminent issue that requires addressing is thus to develop quantitative models that span across these level of understanding, and make predictions about how different stimulation procedures culminate in behavioral changes including side effects. The reason there is a need for such models is that they force us to formalize our ideas about the physiological basis of brain stimulation, and constrain the possible conclusions we might draw from observed data. Such models can be used to simulate data, under specific assumptions about the parameters of the model (e.g., connectivity profiles), which are then compared to observed data. Alternatively, generative models incorporate an expected (prior) distribution of parameter values (e.g., baseline firing rates of different types of neurons of a model) based on current knowledge, and a so-called forward model that quantifies the probability that a specific pattern of data (e.g., firing rates in STN neurons, evoked potentials in EEG recordings) results from the parameters of the model. In principle, this allows for estimating the (posterior) probability for a specific parameter or set of parameters of the model, given the data one actually observes experimentally.

Regardless of the specific structure and modeling approach, models explicitly formalize the hypotheses one might have about a mechanism and process, in this case how brain stimulation influences neural circuits. Common to all models that will be useful to this debate is that their quantitative nature allows for comparing how the predictions from a model hold up against data observed *in vivo*. This illustrates the iterative loop through which modeling and experimentation inform one another.

As Arthur C. Clarke observed, "Any sufficiently advanced technology is indistinguishable from magic," and at this stage some of the results emerging from different applications of neurostimulation indeed seem magical. It perhaps also seems that some magic is now much needed to develop computational models that will be able to accurately explain how neurostimulation alters neural circuits with sufficient biological realism to accurately predict behavioral outcome and side effects in individuals resulting from these alterations. Despite perhaps appearing quixotic at this stage, the field must confront these challenges and should not be deterred from starting the quest for such models. The debate is not whether such models are needed, but rather that the field must seek consensus about what the appropriate models and levels of description ought to be in order to help put the field of neurostimulation on a proper mechanistic footing. The advances in other fields of neuroscience are testament to how modeling can help to understand complex processes in biology and stimulate novel questions and hypotheses (Moran et al., 2011; Stephan et al., 2015). Computational neurostimulation is in its infancy, but recent work is now initiating a much needed debate and encouraging efforts into the development of appropriate models (Bestmann et al., 2015; Bikson et al., 2015; Bonaiuto and Bestmann, 2015; de Berker et al., 2013; Frohlich, 2015; Grill, 2015; Hartwigsen et al., 2015; Little and Bestmann, 2015; Moran, 2015; Rahman et al., 2015; Triesch et al., 2015; Wang et al., 2015). It is hoped that in the not too distant future, the developments this will spawn will make the current state of the field appear much like how using a fish on the head to treat migraine does to us now.

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