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The neuroscience–systems biology disconnect: towards the NeuroPhysiome

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Introduction

This set of reports were first presented as talks in two ‘Featured Topic’ symposia at the Experimental Biology (EB) meeting in April 2011 in Washington DC, USA. These two symposia grew out of an earlier US–Japan Brain Research Cooperative Program Workshop held at the Okinawa Institute of Science and Technology (OIST) in October 2010. The US National Institutes of Health (NIH) and the Japanese Science and Technology Agency (JST) jointly sponsored this OIST workshop to initiate and explore opportunities at the interface of neuroscience and systems biology, with the intention of follow-up meetings such as the present symposia. The OIST US–Japan workshop was organized by Dr Bruce Lindsey (University of South Florida, FL, USA) and the authors together with Erik DeSchutter (OIST, Onna, Japan). The OIST US–Japan workshop had two main themes, which then became the titles of the two aforementioned EB Featured Topics symposia: *Multi-scale Modeling and Systems Biology of Synapses*, chaired by James Schwaber, and *Multi-scale Neuronal Control of Respiratory Function: Bridging Gene Networks to Neural Networks*, chaired by Kendall Morris. At our previous OIST workshop, we concluded that we had ‘made a start’ on these issues, and during the EB Featured Topic sessions we continued discussing and presenting bridging opportunities in methods and approaches that are applicable in systems biology practice and neuroscience. Specifically, the symposia examined how modelling of molecular processes can provide a foundation for understanding adaptive electrical behaviour of neurons, and how unbiased global data can be useful in deciding which receptors, channels and transmitters need to be considered in a simplified schematic of a functional neuronal group.

The apparent disconnect between computational neuroscience and systems biology has been observed previously and discussed at length in an article by Dr De Schutter, a featured presenter in the systems biology symposium (De Schutter, 2008). Commonly, computational neuroscience focuses on membrane models of different transmitter–receptor interactions and the effects of modulators (serotonin, etc.) on synaptic transmission and their impact on network behaviour, while systems biology focuses more deeply on signalling and genetic processes. Despite the conspicuous connections between neuronal membrane composition, signalling and gene expression, there is little bridging of this gap. The workshop was concerned with the commonalities between multiscale modelling of molecular processes and

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neuronal systems physiology. Our aim was to explore how robust function emerges from complex, plastic processes by combining computational neuroscience and the systems biology of functional, adaptive molecular processes.

In order to consider these and related issues, the OIST US–Japan workshop, and now the two EB Featured Topic symposia, were organized around the following two ‘focal points’.

Focus point – Featured Topic 1: multiscale neural control of cardio-respiratory function from genes to neural networks

From the multiple levels of analysis, including intracellular signalling, gene regulatory networks, neuronal circuits and organism behaviour, several common themes emerged and could be observed at all levels of exploration. These included the existence of transient and sustained transduction mechanisms, parallel signalling paths, system memory, system redundancy or degeneracy and its importance in network reconfiguration during development and environmental stressors. Featured presenter Akiko Arata presented an update on her novel work studying the development of breathing in knockout mice (Fujii *et al*. 2007). Co-featured presenter Thomas E. Dick discussed cardiorespiratory coupling from multiple perspectives (see Dick & Pilowsky, 2010; a Forward to a special issue of *Respiratory Physiology & Neurobiology*, dedicated to that subject).

Focus point – Featured Topic 2: multiscale modelling and systems biology of synapses and synaptic plasticity

A central goal of modern neuroscience is to understand the molecular mechanisms for the development of synaptic connections and pre- and postsynaptic functions, including plasticity and learning over multiple time scales, in health and disease. Presumably, these lasting changes in neural connections and electrophysiology are related to changes in neural signalling, transcription factor activity and gene expression, although the exact mechanisms by which this occurs are incompletely understood. Building on the long tradition of computational modelling of synaptic electrophysiology to incorporate a quantitative model addressing all scales relevant to synaptic plasticity with the emerging perspective of systems biology is an exciting challenge that raises several questions considered at the workshop.

Some of the types of general scientific/technical issues in consideration were as follows.

- How can high-throughput data-acquisition methods be used in neuroscience problems? How can they be used to tell us about the types of channels and receptors that are expressed in a neuronal group of functional interest? Which of these are modified in disease, or by environmental inputs? Which transmitters/modulators are expressed in particular neuron types or functional groups? Can technical hurdles be overcome to provide this information in individual neurons, or over time in physiological conditions?
- How can information of these types be relevant to the questions of computational neuroscience of neuronal systems? For example, similar to the Hodgkin–Huxley models, how can systems approaches help determine which parameters should be

incorporated in simulations and which should be focused on in disease or across distinct functional states? Or, more specifically, are there opportunities to populate or parameterize Hodgkin–Huxley neuron models with quantitative information about channel types or transmitters obtained from unbiased global data taken from relevant neuron classes?

- Can high-dimensional data sets be collected and analysed to understand molecular networks and their dynamics? Can models at this level be used in computational neuroscience to understand adaptive neuronal and neuronal network physiology?
- Can our modelling approaches in computational neuroscience include molecular processes or biochemical reaction kinetics relevant to the functions under study? How can adaptive neuronal function resting on these processes be understood at the level of neural network physiology, including their effects on action potential firing and behaviour?
- How can large time and spatial scales be bridged, at least empirically, to bring synaptic events into a closed-loop system where millisecond-based electrophysiological events can be translated to enduring changes in neuronal behaviour and molecular network remodelling that ultimately changes membrane electrophysiology over a longer time scale?

About the articles

The papers presented here as symposium reports cover a few aspects of these topics and issues.

A collection of high-dimensional gene expression data sets from individual identified neurons and groups of neurons following pharmacological perturbation of blood pressure were described by Vadigepalli *et al*. (2012). These data were analysed to identify the adaptive responses to transient elevations in blood pressure inputs. By using these data and analyses, models were built of gene regulatory processes, signalling networks and adaptive effects on membrane electrophysiology. One particularly significant result was the observation of considerable variability in gene expression between single neurons, similar to that observed across whole nuclei taken across animals. The report examines the significance of biological variability and proposes new approaches for its study. The presentation summarized results across nuclei in different brain regions, in pooled groups of neurons from the A2 catecholaminergic population and in single A2 neurons. Additionally, the relevance of systems biology data on gene expression to computational neuroscience models of the Hodgkin–Huxley type was reviewed.

The airway protective behaviours of cough and swallow were described *in vivo*, and detailed simulations of neural network models were presented by Teresa E. Pitts (Pitts *et al*. 2012). Coordination of these behaviours is vital to protect the airway from further aspiration-promoting events, yet the co-ordination of cough and swallow are unknown. This knowledge will be necessary to understand and treatment of deficits in airway protection. Dystussia (impaired cough) and dysphagia are common in Parkinson’s and Alzheimer’s

diseases, as well as stroke, and are major causes of further morbidity and mortality in those diseases.

The potential of songbirds as a model system for the study of the relationship of vocalizations to control of the respiratory system was addressed by Mark Schmidt (Schmidt *et al*. 2012). A key discovery they discuss is how the respiratory system, through bilateral projections to thalamus, may synchronize premotor activity in both hemispheres of the birds, which lack a corpus calosum.

Conclusion

By beginning a dialogue, the present set of symposium reports, and cited literature, aim to address issues and opportunities to develop new work to fill the present void between computational neuroscience and systems biology. This summary follows up on the OIST US–Japan workshop and aims to find a more general audience for this opportunity. We hope it may promote continued development and evolution of efforts to bridge areas of neuroscience with systems biology, towards an integrated understanding of the NeuroPhysiome.

References

De Schutter E. Why are computational neuroscience and systems biology so separate? PloS Comput Biol. 2008; 4:1–6.

Dick TE, Pilowsky PM. Respiratory Physiology & Neurobiology. Foreword. Respir Physiol Neurobiol. 2010; 174:1–3. [PubMed: 20933107]

Fujii M, Arata A, Kanbara-Kume N, Saito K, Yanagawa Y, Obata K. Respiratory activity in brainstem of fetal mice lacking glutamate decarboxylase 65/67 and vesicular GABA transporter. Neuroscience. 2007; 146:1044–1052. [PubMed: 17418495]

Pitts T, Morris K, Lindsey B, Davenport P, Poliacek I, Bolser D. Co-ordination of cough and swallow *in vivo* and *in silico*. Exp Physiol. 2012; 97:469–473. [PubMed: 22198014]

Schmidt MF, McLean J, Goller F. Breathing and vocal control: the respiratory system as both a driver and a target of telencephalic vocal motor circuits in songbirds. Exp Physiol. 2012; 97:455–461. [PubMed: 21984733]

Vadigepalli R, Gonye GE, Paton JFR, Schwaber JS. Adaptive transcriptional dynamics of A2 neurons and central cardiovascular control pathways. Exp Physiol. 2012; 97:462–468. [PubMed: 22002872]