Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Neurobiology

Comparative approaches to cortical microcircuits

Mike Hemberger[1], Lorenz Pammer[1] and Gilles Laurent

Recent trends in neuroscience have narrowed the scope of this field, notably through the progressive elimination of 'model systems' that were key to the development of modern molecular, developmental and functional neuroscience. Although the fantastic opportunities offered by modern molecular biology entirely justify the use of selected organisms (e.g., for their genetic advantages), we argue that a diversity of model systems is essential if we wish to identify the brain's computational principles. It is through comparisons that we can hope to separate mechanistic details (results of each organism's specific history) from functional principles, those that will hopefully one day lead to a theory of the brain.

Address
Max Planck Institute for Brain Research, Max-von-Laue-Str. 4, 60438 Frankfurt am Main, Germany

Corresponding author: Laurent, Gilles (gilles.laurent@brain.mpg.de)
[1] Equal contributions.

Current Opinion in Neurobiology 2016, **41**:24–30

This review comes from a themed issue on **Microcircuit computation and evolution**

Edited by **Thomas R Clandinin** and **Eve Marder**

For a complete overview see the Issue and the Editorial

Available online 6th August 2016

http://dx.doi.org/10.1016/j.conb.2016.07.009

Brains, like all biological organs, are the result of long evolutionary processes. An evolutionary or comparative perspective on brain function can be informative on at least two levels: the mechanistic, by identifying inherited features (e.g., molecular components); and the algorithmic, by pointing to similar forms of solutions to common problems (e.g., circuit graphs, cellular operations, among others). Of particular interest are cases where common algorithms are not inherited, but rather result from evolutionary convergence. Those instances, clear evidence for which is still admittedly rare, may point to the essence of an operation, identifying both computation and algorithmic solutions, independently of implementation. A comparative approach to understanding brains as information processing systems thus meets David Marr's classical distinction between levels of understanding [1,2].

An evolutionary approach to brain function requires comparisons. One great practical difficulty in this exercise lies in defining the objects of these comparisons (Figure 1). Should they be gene or protein sequences, spatio-temporal gene expression patterns, cell morphologies, architectonics, connectivity graphs, gross structural features, biophysical and synaptic characteristics, emergent properties (e.g., travelling waves, consciousness), or functional consequences (e.g., gain control), to take but a few examples? In other words, what are the relevant dimensions? At a time when modern technology takes us from an artisanal to an industrial phase of neurobiological investigation, do we acquire all data that can be had, on the premise that any data are useful? If so, should we (and if so, how?) harmonize data acquisition, archiving and cataloguing? Or do we make some wise operational choices? If so, which ones? These questions are very important if we wish, for example, to cluster and compare datasets. The answers depend much on how we conceive of 'understanding the brain'. Understanding implies reducing the description, that is, throwing away. But what can we throw away? How do we know *a priori*? A comparative approach is thus useful also in that it forces us to identify, or at least be explicit about, the features and dimensions that should matter to reach a functional understanding.

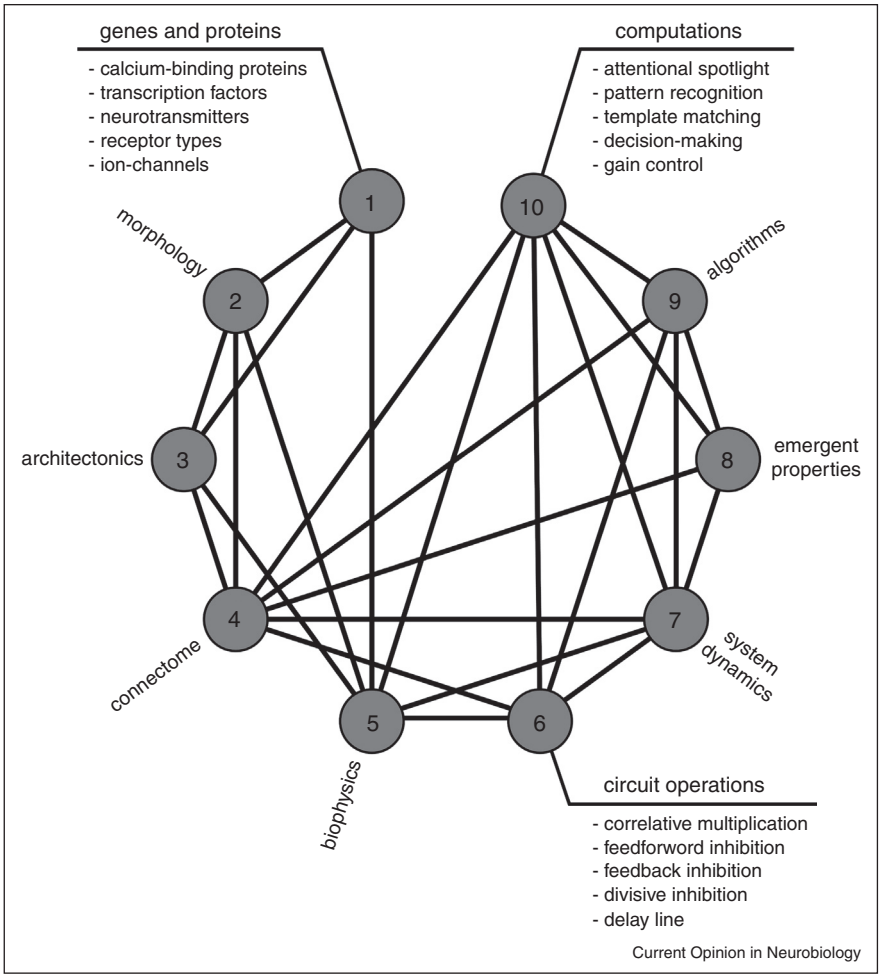
The complexity of multi-scale problems

The multi-level organization of the brain makes it difficult to define precisely meaningful entities for comparisons (Figure 1). The outcome of a comparison (e.g., across cell types or circuits) depends on the features selected and on their relative weightings. Results based on some features or dimensions may not map clearly onto classifications based on other dimensions. In addition, classification and feature profiles themselves may change with developmental time or brain state [3]. In some cases, these parametric variations may be linked to the homeostatic stabilization of some high-level set point, itself often unknown. If so, the parametric variations are only sets of solutions to a larger overarching goal [4,5], but not necessarily interesting in and of themselves. In other cases, they may underlie true state transitions, and thus be critical to a functional understanding. Finally, the variability of data collected across hundreds of laboratories using many finicky techniques makes comparability a central problem of neuroscience. How then do we deal with comparative outcomes that are based on these data? Industrial scale initiatives, such as those of the Allen Institute [6,7,8••], strive towards explicit standardization. But is the time ripe for worldwide standardization?

Harmonization of data and techniques, open-source

As the world neuroscience community engages in ambitious large-scale national or multi-national efforts,

Figure 1



Comparing brains or circuits is a challenging multi-scale problem. This circular diagram illustrates some important features of neural systems and some of the possible mappings between them. Nodes 1 to 10 are meant to represent different levels of analysis, from the molecular to the computational. Each node represents a large class of descriptors, that can be more or less independent of one another. A few examples are given for nodes 1, 6 and 10. (The nodes and links depicted are in no way exhausive.) Not depicted here is the fact that there usually exists many possible mappings between pairs of nodes. For example, a given computation may result from several biophysical or circuit implementations, which may themselves result from several molecular/developmental histories. The challenge is to encover, through these comparisons and linkages, some overarching principles of brain function.

discussions have been initiated on the topics of data formats (e.g., [9]), management and storage [10], on the need for standardization of techniques and of nomenclature (as with the bird brain consortium [11], the Petilla terminology for inhibitory interneurons [12,13] and newer efforts [14,15•]). The challenges posed are not linked only to the political/sociological difficulty of building a consensus in a large, widespread and heterogeneous community [16]. It is also linked to the complexity of the scientific questions (see Figure 1), their fuzziness sometimes, and thus to the absence of an agreed-upon ranking of the features that we should care most about. Other fields of biology in which large-scale efforts and standardization have been solved with success (such as sequencing or even functional brain imaging) are ones in which the scientific questions or goals were constrained and well posed. This led to targeted technological development, the spread of analysis routines and machines and consequently, the harmonization of these fields. Understanding the brain (from molecules to cells, circuits, behavior, perception and disease) is so multi-faceted that a push for harmonization may seem premature. Harmonization will likely happen *de facto* as soon as the questions are clearly posed, the methods well adapted, and the market of methodologies open and free. What seems increasingly important is therefore the open sharing of methods, the use of open-source platforms, the use of common test/