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2012: The Connectome, WBE and AGI

Abstract. In order to grasp the entire complexity of the human nervous system, one needs to understand its physical substrate. Down to which level should a whole brain emulation keep all the structural details of the brain in order to achieve all of the functions of the biological brain? While a computer program could easily be emulated in order to achieve the same specified function, the human brain is a special case because of its enormously complex functions. For this reason, causal relations between brain structure and function are currently being made in neuroscience. Neuroscientific research is in this sense supporting WBE and therefore AGI, by providing important data, models and simulations of brain functions. The goals of this paper are to review the challenges for gathering and assembling connectome data and to provide directions for overcoming these challenges. Finally, the implications for AGI will be discussed.

Keywords: Whole Brain Emulation, Artificial General Intelligence, challenges, connectome data

For an overview on the different types of information neuroscience has to offer and the methods used to obtain this information, as well as the most recent models and simulations, please see Deca, IJMC 20121.

The data acquisition tools in neuroscience can be split roughly into imaging and electrical recording tools. Imaging tools provide images or movies showing what the brain does in different circumstances and make use of different chemicals in order to get a general idea of the electrical activity, while recording tools are used for quantifying the connection between electrical activity at different scales in the brain (ranging from single cells to entire brain areas to the whole brain) sometimes in connection to a stimulus in order to understand what the brain does when it perceives or does something. These two types of methods have very often been used in conjunction with each other in order to understand the connection between electrical and chemical changes in the brain.

A special feature of neuroscientific research is its extremely fast pace in that the problems it may point out to in 2011 might be solved by 2012, leading to further questions that would need to be answered in 2013 and so forth. Its rapid growth and indirect support of WBE and indirectly of AGI make it their main engine.

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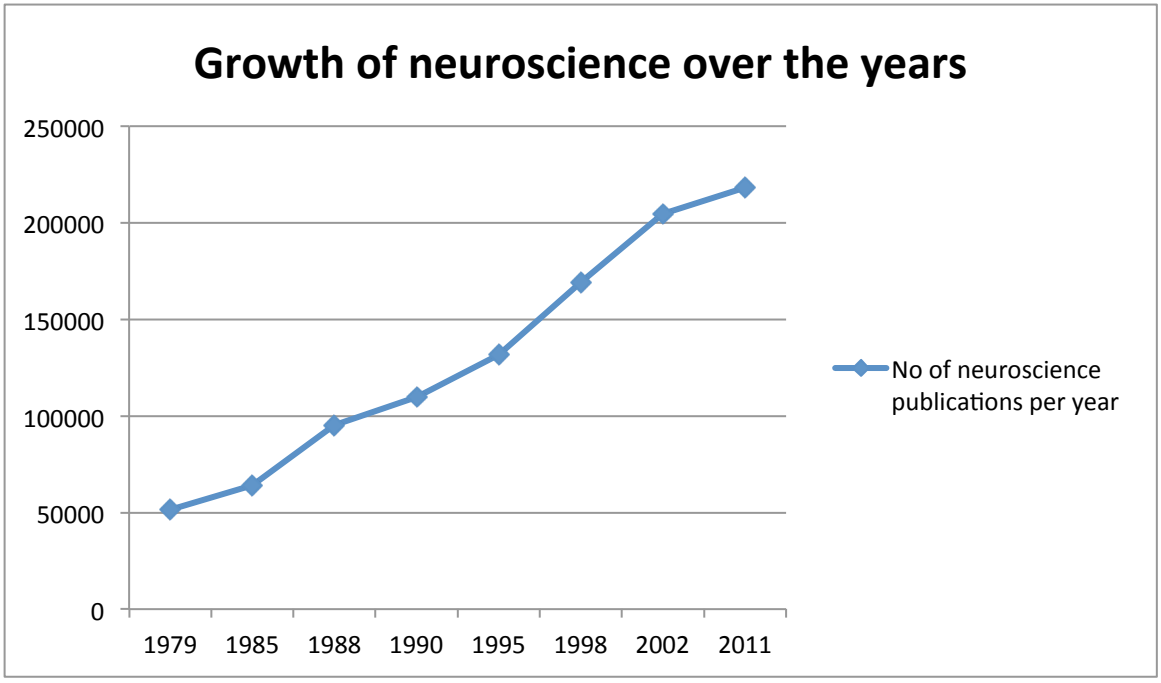

Fig. 1. The growth of the number of neuroscientific publications per year. The data were obtained by indexing the medical database[2,3].

A fundamental issue for neuroscience and for reverse engineering the brain is the connection between structure and function. The current methods only allow us to make some potential correlations at different levels in time and space. However, a complete mapping of function to structure of the human brain is lacking at the moment. One of the main issues in this sense is the complexity of the brain structure, but most importantly the complexity of its functions, since a function would need both an agent and an environment to work in. Therefore understanding this function in connection with the structure requires not only observations about the brain, but also about the physical world in which it acts in. This task gets also a bit reflexive, since

[2] http://www.ncbi.nlm.nih.gov/pubmed/

[3] Corlan,A.D., Medline trend: automated yearly statistics of PubMed results for any query, 2004. Web resource at URL:http://dan.corlan.net/medline-trend.html. The full trend can be viewed here (http://dan.corlan.net/cgi-bin/medline-trend?Q=neuro)

we are using our object of study in order to study it (the brain), and we are hoping to understand the object of study in full by looking at it with itself.

At the moment, this connection between structure and function is more poorly understood than in any other organ in the human body as Lichtman et al.[4] point out. One of the main reasons for this might be the fact that the brain controls the rest of the organs and triggers all other processes in the body. The human brain uses around 20 percent of the energy used by the entire body. Most of the energy used by the brain, in the form of ATP (adenosine triphosphate) is required for maintaining the chemical concentrations inside the neurons which would allow for electrical activity. The electrical activity sustains all of the brain functions we have. What is interesting and indeed a challenge for WBE is the fact that these electrochemical gradients are changing in response to the environment, leading to the neurons firing in response to different environmental cues, and to plasticity and thereby learning.

As an outline of the challenges for gathering connectome data in the neurosciences, I will make use of a paper written by J.Lichtman and W.Denk written in November 2011. While addressing the issues mentioned by them, I will also refer to another paper[5] providing another solution to the similar challenges they mention called the Brain Activity Map.

1) **Immense diversity of cell types in the brain**. The nervous system of the C elegans worm is composed of around 300 hundred neurons (compared to 86 billion in the human brain), yet each cell in its nervous system has a unique structure and function. This would translate into around 86 billion computational units, with structures which are almost unknown and unique at the fine level. One way around this is to find some common categories, and gradually add the different subtypes. A lot of these neuron types have been described, and genetic tools for selective manipulation have been created. 6 The Brainbow technique has also allowed selective labeling of different neuron types[7]. The current tools for genetic manipulation, selective labeling and in vivo manipula-

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[4] Lichtman, J. W., Denk, W. The Big and the Small: Challenges of Imaging the Brain's Cir-cuits. Science 4 November 2011: Vol. 334 no. 6056 pp. 618-623 DOI: 10.1126/science.1209168

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tion[8,9,10] are giving rise to a large number of projects aimed at correlating the structure of different neurons to their structure. The hope in this sense is to be able to understand their function both in terms of connectivity at the population level as well as at higher resolution in both time and space, in terms of functions of their particular dendritic and axonal segments. This is work in progress, however it is expected that the end result will lead to a number of categories (an already well established category is inhibitory vs. excitatory neurons, based on whether they activate or inactivate nearby neurons, place cells, orientation cells, etc.)

2) **Imaging electrical and chemical activity**. One of the challenges for neuroscientists has been to couple the chemical activity with electrical activity at different levels. In principle they should be the same (in the sense that there is a direct causal connection between the two); however explaining this causal connection in detail required the development of some new tools. One of them was a type of microscopy which allows for long term imaging inside the brain of a living animal, providing the chance of measuring enough photons that can be associated with the electrical activity of neurons. This method is now routinely used in many labs, and is called two photon microscopy.[11] Two photon microscopy is based on the principle of bringing a lot of photons (in the form of laser light) into a very small brain area for a short period of time. This leads to two photon excitation and allows for very fine measurements of changes in fluorescence. This, in combination with calcium indicators, has allowed for the direct quantification of calcium concentrations within neurons as a direct function of changes in membrane potential, both of which account for activity.[12] One of the main limitations with two photon imaging however is the limited penetration depth (up to max 1 mm in the mouse brain). The human cortex is known to be thicker therefore it is not known whether scientists would be able to record ac-

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[8] Kodandaramaiah, S.B., Franzesi, G.T., Chow, B.Y., Boyden, E.S., Forest, C.R. Automated whole-cell patch-clamp electrophysiology of neurons in vivo. Nature Methods 9, 585–587 (2012) doi:10.1038/nmeth.1993

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[10] Hirase H, Nikolenko V, Yuste R. Multiphoton stimulation of neurons and spines. Cold Spring Harb Protoc. 2012 Apr 1;2012(4):472-5. doi: 10.1101/pdb.prot068569.

[11] Denk, W., Strickler, J.W., Webb, W.W. Two-photon laser scanning fluorescence micros-copy. Science 6 April 1990: Vol. 248 no. 4951 pp. 73-76 DOI: 10.1126/science.2321027

[12] Grienberger C, Konnerth A. Imaging calcium in neurons. Neuron. 2012 Mar 8;73(5):862-85. Review.

tivity from neurons in the human brain with the available techniques without having to remove parts of the brain. The takeout message here is that the correlation between electrical and chemical activity in the brain is now clear both theoretically and experimentally and that there is no reason to believe that the most fundamental principles of physics and chemistry would not hold in the human brain as well.

3) **Neurons extend over vast volumes**. Since Cajal showed how neurons are connected, many people in the field have related the issue of connectivity to that of function. The dendritic tree of a neuron (which receives many inputs from other neurons) can span from one brain hemisphere to another (therefore more than one meter), which is an enormous distance when compared to the diameter of its nucleus or soma (max. 18 micrometers.) This is a large volume, which needs to be described at very high resolution in vivo. In microscopy, the general tradeoff is made between resolution and volume: higher resolution usually entails smaller volume and the other way around. However, this tradeoff in the neurosciences generates competition in the microscopy market, which is then aiming at combining both in the best way possible. A possible way around this is the automation of these recordings, enabling the extraction of very large amounts of high resolution data which can then be put together into one large whole[13] .

4) **Need for Dense or Saturated Reconstruction**. Indeed, most of today's image of neuronal circuitry is based on Cajals drawings, which are still at the border between science and art. The evolution of imaging techniques has allowed for some mapping of this circuitry, but no large scale movies correlating the function and structure are yet available. For now, only a small muscle that moves in the mouse ear is one of the few parts of the nervous system were the circuitry has been mapped completely14. Some other projects include the in silico cortical column and numerous other projects within the connectome consortium. It is expected that the appropriate areas for complete circuitry mapping are some of the most fundamental and old ones, such as the visual or auditory cortex, where there is less variability between species and individuals even at the finer level. One promising method for tracking connectivity is the rabies virus, which spreads from one neuron only to the neuron it communicates with and making them fluorescent 15 (add reference

[13] http://www.neuro.mpg.de/english/emeritus/columninsilico

[14] Lu, J.,Tapia,J.C., White,O.L., Lichtman,J.W. The Interscutularis Muscle Connectome PLoS Biol. 7, e1000032 (2009).

[15] Lois, J.H., Rice,C.D., Yates, B.J. . Neural circuits controlling diaphragm function in the cat revealed by transneuronal tracing Journal of Applied PhysiologyJanuary 2009 vol. 106 no. 1 138-152doi: 10.1152/japplphysiol.91125.2008

> http://jap.physiology.org/content/106/1/138.full) . Another way of tracking connectivity is to label the different circuits with different colors, for example with the Brainbow method. However, one of the main problems with tracking connectivity is the slow human analysis partially due to the small number of computer scientists with enough knowledge of neurobiology who can optimize the analysis methods. Resolving one cubic millimeter of brain tissue in terms of neural connection would take, given the current method, months or even years of imaging and even more time for analysis. With this in mind, the research community is getting reorganized in order to overcome this problem (eg. the numbers of undergraduate students doing such tedious work for free is growing exponentially) and in parallel different methods are being tested, such as the tape to sem. Furthermore, different computational models for artificial neural networks are emerging and their connectivity rules are constantly being update in the light of new data on the neurophysiological processes behind functional neural rewiring. However, as Alivisatos et al16 estimate, 7 x 10(6) mouse brain cells would need around 5 x 10(16) bytes, which is less than the global genome data. They envision that, just like the analysis of the genome gave rise to the field of Genomics, another field called Connectomics should emerge as a result to such analysis, which has proven to be a correct intuition.17,18

Finally, the main issue in making a universal model for how neurons rewire in order to achieve a specific function within a specific context is the fact that this will depend a lot on the specific context, therefore at the fine level every instantiation of this connectivity will differ from all the other ones. The main task here is to generate the main categories for such branching, and deciding at which level to stop but still achieve the connectome (the synaptic level is already generating very different instantiations , even in the worm brain). The good part is that there must be general rules that the neurons follow in order to achieve this, therefore the more physiological data the next aritificial neural network will be based on, the closer these networks will be to the real brain and the more functions it will be able to have. A good analogy in this sense is the game of chess. A good way of learning about chess is to watch a chess game, understanding the basic rules and then playing based on these rules. If a player has a good mind and some understanding of the basic rules, then it will invariably get better and better at chess by experiencing different instantiations of it.

Alivisatos et al[19] propose a new way of gathering and analyzing connectome data in the form of BAP (the Brain Activity Map Project). They employ the philosophical stance of emergentism[20] (that is, the neural circuit function is emergent from complex

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[16] Idem 5
[17] http://hebb.mit.edu/courses/connectomics/
[18] http://en.wikipedia.org/wiki/Connectomics
[19] Idem 5
[20] http://en.wikipedia.org/wiki/Emergentism

interactions among constitutent parts). In order to understand these emerging properties of neural circuitry, they propose to record every single action potential from every neuron within a given circuit. For now, calcium imaging could provide a useful tool but as they suggest, it can only approximate the electrical activity. Therefore a better alternative for this would be voltage imaging[21], however this technique does not allow for large-scale high resolution recordings. They believe that this is a feasible goal which can accomplished by means of large scale electrical recordings with nanoprobes, which would now allow researchers to record electrical activity at dozens of sites per silicon neural probe[22] . One limitation with this sense might be the fact that these probes would not be able to record subthreshold activity in the neuron, and how different inputs in the neuron contribute to the activity recorded as a whole. Ideally, one would have a method that can reveal electrical activity in each neuron up to the level of dendritic spines[23] .

1 How the current state of neuroscientific research affects the Connectome, the WBE and AGI

The goal of this paper was to review the main problems for WBE that neuroscience is currently dealing with. I will briefly outline the three main issues and mention their respective solutions.

The problems are:

Immense diversity of cell types. Solution: Categories are being made in the light of new data. Meanwhile, new methods are being made for faster data acquisition and analysis.

Imaging electrical and chemical activity. Solution: combining methods- imaging can be made with Ca indicators, which is directly correlated with electrical activity. Alternatively, voltage imaging can be used, as well as large-scale electrical recording with nanoprobes.

Neurons extend over vast volumes, so a large volume has to be analyzed at very high scale. So how to get very high resolution imaging data from such large

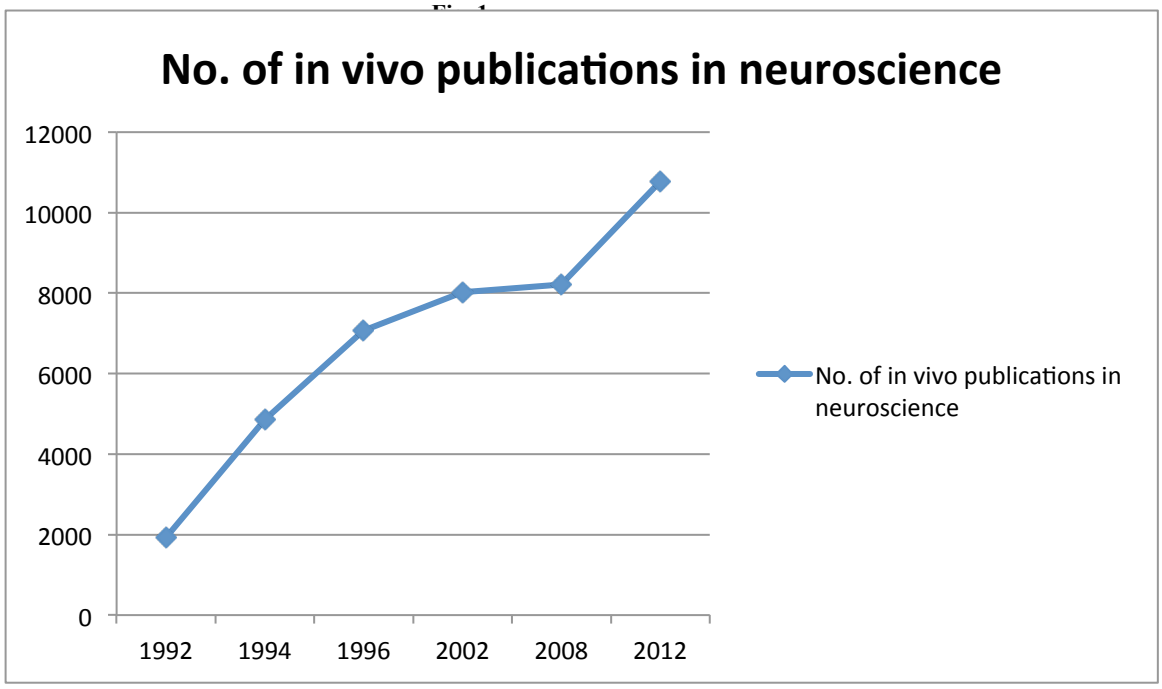
[21] Peterka DS, Takahashi H, Yuste R. Voltage Imaging in Neurons. Neuron 2011 Jan 13;69(1):9-21

[22] Du,J. et al 2009 J. Micromech. Microeng. 19 075008 doi:10.1088/0960-1317/19/7/075008

[23] Chen X, Leischner U, Rochefort NL, Nelken I, Konnerth A. Functional mapping of single spines in cortical neurons in vivo. Nature. 2011 Jun 26;475(7357):501-5. doi: 10.1038/nature10193.

volumes? The pace of imaging developments is also growing very fast, such examples are the STED and the 2P, and a lot of very high tech variants of electron microscopy. In parallel, novel methods for recording electrical activity directly from many sites are being developed and tested.

The timeframe for overcoming the different drawbacks for WBE depend a lot on the funding, but not only. There are physical limitations in terms of imaging (eg. How deep the 2P laser can go into different tissues, what electron microscopy can show, photodamage due to light into cortical tissue). As Alivisatos et al point out, recording electrical activity from all neurons within a given circuit requires increasing the number of imaged neurons as well as the depth of the imaged tissue. Some of the techniques that they mention include: more powerful sources for two photon excitation without damaging living cortical tissue, faster scanning strategies, developing better microscope objectives with larger fields of view, better scattering corrections in microscopes as well as better 3D reconstruction techniques. It would appear from this that it is vital that the in vivo projects grow exponentially, in order for scientists to get a better idea of the connection between function and structure. There is already an important tendency towards that in neuroscience, given simply by the fact that the in vivo situation is now possible to achieve experimentally, and implies less assumptions about the physiological process itself. Therefore in vivo experiments in neuroscience are considered to be more reliable and have a higher chance of getting serious attention. As such, there is also a bigger chance for in vivo projects and labs to get funded. As these projects get funded, breakthroughs in the data acquisition tools are more and more strongly supported.



Given that problem no. 2 is already more or less solved, in the sense that the gathering of electrophysiological and imaging data is obtained simultaneously routinely in many labs, we are then left with problem no. 3, which would appear to be conceptual (how to bind structure and function within an entire neuron whose dendritic tree extends over such vast volumes?).

However, the structure/function issue within the neuron can also be solved with the aid of new methods already mentioned (STED, ATLUM, 2P, silicon probes, optogenetics, automated patch clamp). Their development will inevitably lead to the complete mapping of the neurome in different contexts. The neurome will then serve as the main computational unit for the connectome, which can then be built in silico.

2 Implications for AGI

Neuroscientific research is inevitably gathering connectome data. Connectome data is currently being modeled by neuroscientists with the end goal of achieving a complete connectome. A full connectome can then be easily rebuilt in silico once all the information is made available, and this will constitute a whole brain emulation. A

whole brain emulation that is able to perform computations in manner which is similar enough to the human brain is a form of artificial general intelligence. This paper has aimed at providing an important update on the current state of what will become a main branch of AGI, namely connectome data acquisition, modeling and simulation. Speculations about the potential directions that this field will take are beyond the scope of this paper. However, based on the development of neuroscience so far, it is suggested that there is competitive pressure for achieving the AGI in the form of the Connectome simulation. From the point of view of a neuroscientist, the reason for this pressure is not achieving AGI in particular, but rather advancing the understanding of the brain in the most rigorous way possible.

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