Appendix 1

Evaluation of the Blue Brain Project and Human Brain Project

EPFL, Lausanne, March 28-31, 2011

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Evaluation Committee

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Introduction

The committee was requested to evaluate the Blue Brain Project (BBP) for its progress since its last evaluation in early 2008, and for its role as the core for the Human Brain Project (HBP) in its application for support by the ICT FET flagship initiative of the EC.

We organize this document accordingly, with sections for our review of the BBP followed by the potential role of the BBP in the HBP. Given the complexity of the two projects, we indicate the comprehensive organization and presentation by Professor Markram, and the evaluation by our committee of each subproject of both the BBP and the HBP as well as the overall direction and aims of both projects.

We begin with an executive summary, followed by the detailed evaluations.

Executive Summary

Blue Brain Project (BBP)

The BBP aims at a quantitative simulation of the intrinsic connectivity of the cerebral cortex with functional characterization of the neurons and microcircuits at an unprecedented scale. Different classes of cortical neurons are identified by their morphological properties, by their electrical properties in synaptically activating other neurons, as well as by their pharmacological and gene expressing profile. This research program leads to a comprehensive description of the wiring of a column of the cortex, which is being extended to neighboring columns, and ultimately to the whole brain. Dr. Markram and his colleagues make a persuasive case that this approach is critically important for understanding the neural basis of cortical function, as well as for understanding the neural basis of neurological and psychiatric disorders.

The findings are based on research and data from cortical slices. These findings are entered into databases which are linked to supercomputers which enable the information to be retrieved for quantitative analysis and visualization. The research requires cutting-edge supercomputing facilities to capture quantitatively the connectivity and physiological properties. This large-scale and detailed approach to computational models of the cortex is in turn influencing concepts underlying the development of the next generation of high performance computing.

In summary, the research in the BBP, unique in its scope, is redefining the science and technology of how to simulate the neural basis of brain function. The work in Switzerland is closely linked to complementary research in other laboratories throughout Europe, and is the central node of the Human Brain project. The opportunities for development of this work in the next five years are great. Based on this evidence, we therefore recommend with the highest enthusiasm the Blue Brain Project for an increased level of funding that will enable it to develop considerably over the next five years.

It is important that this funding includes long-term posts for two senior scientific project leaders as the program develops and enlarges; provision for the next generation of supercomputing facilities; and provision of support infrastructure including staff for software engineering. It would also be desirable to recruit staff for facilitating international collaboration and developments with industry that are likely to be important to the pharmaceutical industry in developing treatments for brain including psychiatric disorders.

Human Brain Project (HBP)

The Human Brain Project is a visionary multidisciplinary, multilevel, multi-laboratory program that builds on the high-performance computer simulations of nerve cells and neuronal microcircuits of the Blue Brain Project to enhance collaborative research in other critical areas of technology applied to brain science.

In this innovative endeavor, the BBP provides a fundamental foundation for the HBP, in that the ICT developed within the Blue Brain Project will be necessary for many of the developments envisaged within the HBP to understand the brain, including the importance of large scale computing to access the types of information that need to be stored, accessed and used in models of brain function for many aspects of the HBP. A specific foundation provided by the Blue Brain Project lies in the details of the connectivity of the cerebral cortex, and the ICT facility that is being built for utilising that information, in for example the large scale simulations of the cortex.

Because of the expertise in ICT of the Blue Brain Project, the evaluation committee believes that Prof. Markram is the ideal person to lead the Human Brain Project, and that having the Swiss facility developed in the Blue Brain Project as a key part of the Human Brain Project application is a great advantage. The committee notes that to enable the Blue Brain Project to continue to play a key part in Human Brain Project developments, extra investment in infrastructure (both in terms of both personnel and computing facilities) will be necessary, as detailed in the section on the Blue Brain Project above.

On the basis of this presentation, the committee recommends the HBP with the highest enthusiasm as providing a science-led way within the ICT for investigation of one of the most important areas that humans can now study: how their own brains work, and how such understanding will provide a foundation for better treatment of brain including mental disorders. This is a key challenge for the 21st century, and one that is now ripe for rapid developments. These rapid developments require a multidisciplinary approach. The Human Brain Project, and its ICT base, will greatly facilitate this by providing data and computational tools to access and utilise the data that will enable many scientists in Europe and internationally across many disciplines to contribute to the effort. This generous sharing of tools and expertise will be one of the most valuable aspects of the HBP, and the BBP should make an excellent contribution in this area.

Summary of the Visit

Blue Brain Project

The Blue Brain Project was presented to the committee over the course of two days.

Summary of Presentations

March 29 (Tuesday) Theme: Building Neurons

Morning

Prof. Patrick Aebischer, President of EPFL, opened the meeting by summarizing the background of how EPFL recruited Dr. Markram on the basis of his visionary goal in brain science, and as a symbol of the new commitment of the President to introducing the life sciences to EPFL. Both were high-risk initiatives, and he felt both had been highly successful. He is therefore deeply committed to continuing support by EPFL of the Blue Brain Project and the Human Brain Project. Prof. Aebischer also met with us at the end of the visit (Thursday PM), where we communicated the main points of our executive summary to him.

Prof. Markram gave an introductory overview of the BBP, its history beginning with the data on single cell recordings from cortical slices with Professor Bert Sakmann, that inspired him to use them as a foundation for building realistic models of the cerebral cortex, leading to his establishment of the BBP at EPFL. The BBP now comprises over 40 investigators at EPFL and in collaborating laboratories. Dr. Felix Schürmann gave an introduction to the computer methods that have been developed for simulating single nerve cells. Dr. Sean Hill described the methods developed for validating these models with experimental data.

Afternoon

In the afternoon, Prof. Markram summarized the methods used for generalizing the methods and the models. Prof. Idan Segev (Israel), a dedicated collaborator of the BBP, described a practical example from a current study of experimental data on clustered inhibitory synapses that gave uninterpretable results until subjected to analysis using the Blue Brain models.

Lab Presentations: Blue Brain experimental data generation (4-6pm)

The formal presentations cited results from use of many methodologies developed by the BBP which go considerably beyond methods available elsewhere. The committee was therefore keenly interested in seeing the methods in the laboratory and talking to the graduate students and postdoctoral fellows who do the work. This was possible during a two hour lab tour, during which the following methods and their investigators were presented.

Multi-neuron patch clamp - Dr. Rodrigo Perin
Innate assemblies - Dr. Rodrigo Perin
Patch-clamp, eCode stimulation for electrical profiling of neurons - Dr. Rodrigo Perin
Single cell multiplex RTPCR for genetically expressed ion channels - Dr. Emmanuelle Logette
Robotic screening of ion channels; Channelpedia - Rajnish Ranjan
Ion channel cell lines to probe biophysics of ion channels - Dr. Emmanuelle Logette
Dynamic patch-clamp to validate ion channel and neuron models - Rajnish Ranjan
MEA stimulation to validate emergent properties of circuits - Vincent Delattre
3D reconstructions to obtain neuronal morphologies - Julie Meystre & Ying Shi
Mesocircuitry; glass (transparent) brain; whole brain imaging; tract tracing - Jean-Pierre Ghobril
Single cell transcriptome - Dr. Jesper Ryge
Layer 1 Microcircuitry - Shruti Muralidhar

The impressive range of these studies speaks for itself. The quality across the studies appeared very high, in terms of the data produced, the innovation of the studies, and the close coordination between the studies. As an example, the first three demos covered the 12 patch setup demonstrated by Perin, producing data such as that published in Perin et al (2011).

March 30 (Wednesday) Theme: The Cortical Column

Morning

Dr. Sean Hill described the strategy involved in going from the single neuron simulations to the groups of neurons and their interconnections that form a single cortical column. Dr. Felix Schürmann described the methods for simulating and visualizing the cortical column, emphasizing the demands on supercomputing capacity for carrying this out and the need for exquisite planning to use maximally each moment on the supercomputing. The main simulations are carried out all day Thursday, and essentially all the rest of the week is used in preparing the simulations and analyzing the data.

Afternoon

Prof. Markram discussed the methods for validation of the models, and the insights gained. He and Dr. Schurman then discussed the plans for future development of the columnar architecture, including a demonstration of the visualization of the column in action.

Demonstrations: Blue Brain software technologies (3:30-5pm)

The afternoon ended with a tour of the software technology of the lab described by a number of investigators as follows.

Physical constraint for membrane proteins - Georges Khazen
Automated neuron modeling - Rajnish Ranjan/Werner van Geit
Blue hub/simulation - Jim King
BBP-SDK analysis in Matlab - Michael Reimann
Blue Search - Dr. Martin Telefont
Management of BBP - Dr. Felix Schürmann
Automating workflows - Nenad Buncic
Synthesizing neurons - Dr. Joe Graham
Ultrastructure builder - Dr. Daniel Keller
Meso-Scale circuits - Dr. Eilif Muller
Real-time 3D interactive visualization with RTNeuron - Juan Hernando/Dr. Eilif Muller

These analyses and simulation projects continued the high quality of the experimental studies. This included impressive methods for automated data generation, and the workflow management by the teams and the team leaders.

Computational Resources

Supercomputer resources have been critical to this project from the start. The BlueGene supercomputer appears to have fulfilled this role, and will continue to do so, with appropriate upgrades. The support of the EPFL for this resource has been crucial, and will continue to be so. With the rapid growth of supercomputing, it is important for the BBP to keep pace, both with regard to resources available at the EPFL, through access to the resources at Lugano, and through the HBP to the resources at Jülich in Germany.

Data Flow and Management

Given the large number of projects, we were interested how data went from experiment to analysis to correlation with the other projects. This process is highly optimized, so that data flow has been highly efficient for each work group, and for interactions between the groups. The process of experiment-design-simulation-evaluation of results is remarkably timed so that no time is wasted when accessing the super computer resources.

Project Governance

Prof. Markram, Dr. Schürmann and Dr. Hill explained their roles in providing the overall governance of the project. This involves close interactions with each other, and with the young investigators carrying out the projects. The interactions involve regular weekly meetings, as well as immediate interactions on specific experimental and simulation issues.

These interactions place considerable demands on the time of both Dr. Schürmann and Dr. Hill. As the senior project leaders, the committee felt they were spending too much time with administrative details that took away from the more active participation in the growing number of

scientific experimental and computational projects. Dr. Hill has recently accepted a major leadership position in neuroinformatics in Stockholm. It will be crucial for the future of the BBP to stabilize Dr. Schürmann's and Hill's positions with appropriately attractive academic positions, and provide them with administrative assistance for their management jobs.

Budget and Financial Issues

These issues were not within our mandate.

Evaluation of the BBP

This is a visionary project grounded in experimental analysis and computational synthesis of neural properties and connectivity at the scale of a cortical column, in which a neuronal network is generated from stored data and simulations run to investigate systematically the performance of the network. As such the project is at the cutting edge in data intensive computing, an emerging field within computational sciences that deals with the scientific data explosion.

The project promises to have a profound impact on scientific computing in neuroscience. But its potential goes far beyond the boundaries of neurobiology as it clearly has the potential to transform biology as a whole by showing in a unique manner how the experimental-computational integration should be done on the multiple scales necessary for understanding biological processes including the brain. Furthermore, the specific requirements of the simulations of the cerebral cortex will drive developments in high performance computing that will benefit other areas of science.

Advancing Brain Science

As indicated above, the visit was highly organized and we were given a systematic presentation of the entire project. We first briefly describe a sample of the scientific advances presented in talks, lab visits and discussions that were evaluated during the visit.

Most of the work has focused on mini-columns in the somatosensory cortex (SA1) of the rat, but the work has the potential to expand into other cortical areas. The rat is a good model in which to develop the processes and build an initial inventory of all the neurons, their features, physiological behaviors, and connections. These processes can then be repeated in any (including higher) animals, including humans. Rodents are typical model organisms for biology and most tools of gene expression etc are readily available. This enables a link between the neuronal-level networks and systems biology.

An important scientific question that arises from the work of the BBP is the robustness of the neuronal firing in the resting state of the local microcircuit. The computational work of the group has demonstrated that these resting states are quite stable and invariant with respect to perturbations of the neuronal connectivity. This is an empirical experimental result that raises new questions of theoretical significance.

The computational process of data synthesis not only gives results on its own but also sheds new light on the rules of cortical connectivity. For example, structural appositions in the 3D space of the cortical column appear to be a guiding principle that influences whether cortical neurons will be connected.

At the single cell level the BBP investigates the systematic description of the fundamental parameters of observed neurons and their morphoelectric features. Single cell transcriptomics is based on an innovative approach designed to mitigate the low precision of single cell transcriptome sequencing due to the low abundance of the transcript molecules. Single cells from homogenized brain samples taken from different regions are plated in 96 well plates as single cells. They are then lysed and the mRNAs modified by terminal addition of a hexamer (unique to each well). Following reverse transcription, the cDNAs are pooled and sequenced and sorted into groups using the unique hexamer sequences. These serve as standards or references for the following steps. The soma of cells that are identified under the microscope and for which the electromorphology has been determined are "blown out" and their transcripts sequenced. The transcriptomic profile is then compared to the reference library and the "gCode" of these cells is determined and associated with its electromorphology. This methodology allows the BBP to link

gene expression and thus channel and receptor expression to the other features of each identified neuron class.

In addition, the electrophysiological behavior of each channel is being explored by expressing each one in CHO cells and performing electrophysiology analysis. This will lead to a complete inventory of such behaviors which are then used to refine the models which are implemented in the BBP simulation environment.

The electron microscopy-based intracellular morphology of the neurons is being used to further refine the model of each neuron. Mapping the number of transcripts for each channel and receptor onto the fine three-dimensional morphology of the neuron will allow the BBP to define the density of these molecules, and thus to provide a high level of precision to the model and enable the link between systems biology (molecular networks) with neuronal networks. This will lead to advances in understanding the operations of cortical circuitry.

Other significant scientific studies and outcomes of the BBP are predicting gamma oscillations in a single cortical column without gap junctions between the neurons. These studies also show the importance of NMDA receptors and of threshold-dependent activation of the cortical column for gamma oscillations to arise.

Key scientific questions for the BBP in the future

Some of the key scientific questions for the BBP in the future include the following. Can the approach be scaled up to deal with several cortical columns, whole brain areas, and even groups of connected brain areas? Can the approach based on findings in a slice of the cortex be enriched and made more relevant to understanding how the brain computes by investigating the functional connectivity in vivo, and using this as a basis for developing the model of the cortex to apply to the normal operation of the cortex when natural inputs are applied? Can the approach, based largely on findings in P10 (very young) rats be extended to older rats, in which the cortical circuitry may be somewhat modified due to synaptic pruning? As the full details of the cortical connectivity are being discovered, can reduced computational models be produced that allow the main functional properties of the operation of the cortical circuitry to be incorporated? This would provide an important bridge to theoretical models of brain function, in which the crucial aspects of the circuitry for a particular computation are investigated quantitatively.

Advancing Computational Science

The group has invaluable expertise for driving the future Exascale computing agenda and data intensive computing in Switzerland and in Europe at large. The expertise covers a reasonable ecosystem of architectures to address several types of computational systems. These include blueGene/P, computer clusters, and shared memory servers such as an SGI. This is a very well managed time-share facility designed to exploit the blueGene/P machine on one day of the week and allow a very short, interactive, cycle of simulation and experiment. That is, a simulation can be run, and based on the results another simulation to analyse the system further can then be run. The rest of the week is used to prepare for the full day using only 1/16th of the system. This way of using supercomputers is completely different from the way that national centers typically operate.

Some of the key innovations in the computational sciences are the following. Beginning from the basic NEURON simulation in 2005 the group has developed the basic parallelization in 2006, and NEURON as a library soon after that (published in Hines et al, 2008a,b; King et al, 2009). One of the key problems that was solved was the reproducibility and random number generation in parallel. Equally important was the parallelization of the linear algebra in 2008 and the algorithms to save the state, and restart with different branch points. Also important was the new messaging below the MPI level through DCMF-multicast. All the work performed was fed back into the public source tree of NEURON. A key innovation in the NEURON engine is that there is no master in this simulation as each instance of the software is in one CPU. Spike exchange in the architecture is the limiting step of the computation.

Complementary to the advances in numerical analysis is the development of efficient and well-thought-out software flows to carry on the research. This is done through BBP-SDK, and integration of the needs of the supercomputing and neurocomputing parts. The API will be published to allow the community to use the facility. This will enable the establishment of a new model for scientific operations with distributed simulation capabilities. Here we must point out that

the quality of the software engineering is key in this program and therefore requires highly trained personnel. Indeed, the special architectural features of the hardware used requires that software engineers receive special BlueGene training. Furthermore, because this is a specialized scientific field, the software engineers also need to understand at least some neuroinformatics and neurobiology to be able to develop such a computational environment.

The synthesis of the column is done with the microcircuit builder. This tool is state-of-the-art in that it allows the construction of realistic neuronal circuits that are based on both the connectivity as well as the morphology of the neurons under the physical constraints of volume preserving structures. Although the work so far does not incorporate glial cells or vascularization, the actual software environment is general, and already some work has begun to incorporate the non-neural structures. Physical constraints are also incorporated in constructing the connectivity between neurons to obtain realistic connectivity patterns and synapse formation. The physical constraints on bouton density are the relevant neuroanatomical constraint here.

The project also focuses on the development of "virtual instruments" that allow experimentation and generation of data on the fly from local measurements such as patch clamp to whole brain fMRI type of experiments.

Concerns and Challenges

The budget has two major components, new hardware acquisition and personnel.

The facility has a state of the art machine the CADMOS IBM BlueGene/P. Additional machines include an aging SGI machine with 300Gb of shared memory. Given the future plans for the project it is safe to assume that this facility needs to stay state-of-the-art. The group has invaluable expertise to drive the future exascale computing agenda and data intensive computing in Switzerland and in Europe at large, and the plans for the acquisition of new computing hardware are well justified.

For the science to advance it is necessary to have industrial strength science-software co-development. Currently the project is under-staffed. Going forward it is imperative that the project personnel grows to support both the administrative and the engineering needs. To maintain top quality research and to assure the stability of the project certain steps must be taken. The first step is the creation of tenure track positions for key research personnel, starting with Felix Schürmann and Sean Hill. At the same time, new administrative and engineering personnel must assume responsibilities currently carried by Schürmann and Hill so that their time can be dedicated to pursue activities commensurate with their academic appointment. Of particular importance is engineering and administrative personnel to support the dissemination of curated data and tools to the scientific community at large in the planned time frame of 1 to 2 years, an aim rated as extremely important by the evaluation committee.

The final budget has to reflect both the acquisition of the new hardware as well as the recruiting to support the software development and the science in the project.

Broader Impact and Human relevance

The BBP has focused on the rat as the model for both data and model building. However, the tools and methods developed in this project are general and not species-specific. Hence as data becomes available the project will be able its approach to the understanding of the human brain. The generalization of the methods is very important. For example, even though the rat brain does not exhibit clear columnar organization, the tools are directly applicable to the analysis of columns. This is very relevant to understanding human brain function, and indeed in autism there is an observed shrinkage of columnar organization.

Community Impact

The BBP has advanced the state of the art in brain sciences, computational sciences, and high performance computing, and has developed a toolkit that encapsulates the complexity and the intricacies of the brain. The BBP system development toolkit (BBP-SDK) consists of a set of software classes (APIs) providing the functionality to utilize and inspect BBP models and simulations. Workshops are organized by the group aimed at giving the scientific community access to the BBP facility, and this is very important if the project receives national and international funding. CERN is one model for such cooperation, and the Human Brain Project may provide a corresponding model for collaboration in neuroscience. Understanding the brain is

such a large and medically relevant problem, and has strategic importance, that it is important that it is taken to the national level and beyond.

Overall Remarks

The strength of the research lies in the integrative aspects of the research program in establishing structural and functional connectivity of the cortex by incorporating evidence about ion channels, receptors, and neuron types. As such the experimental work such as the patch clamp and electrical stimulation methods to analyse the connectivity are important. Complementary use of high performance computing to describe the connectivity, to enable simulation models to be run, and to enable the rules of cortical connectivity to be investigated is highly innovative and state of the art.

Going forward the aims of the project should begin to address the following three concerns:

First, it is important to make use of the database of connectivity available to other scientists using their developed BBP-SDK (BlueBrainProject-SoftwareDevelopmentToolkit). This will facilitate the establishment of links with other groups investigating cortical computation at higher levels of investigation, including in vivo neuronal recordings, and theoretical neuroscience. Such links could be useful in both directions, for example to help guide the quantitative anatomical investigations towards particular questions that will be of value in understanding how the brain functions in health and disease. The Human Brain Project is seen to be an excellent example of the type of collaboration that would help the full potential of the Blue Brain Project to be realised.

Second, from an engineering and information/communication technology applications perspective an important aim is to facilitate the process of generating simplified simulation models that capture the details of the functional connectivity as analysed in fuller detail with high performance computing methods. These simplified models will help to attract scientists who have complementary expertise to be attracted into this area.

Third, it is important to provide infrastructure to enable these developments in understanding where pharmaceutical agents can influence cortical circuitry to be realised with applications to industry.

Publications

The first three years of the BBP (2005-2008) were focused on starting the various projects. The previous review in early 2008 encouraged moving toward publication. In the past three years this has been accomplished. Some 17 peer-reviewed publications have been generated from early 2008 to early 2011. These are nearly all in high profile highly regarded journals. The committee regards this as a highly successful period of beginning to demonstrate the effectiveness of the BBP approach to the wider neuroscience community. A list was provided, which follows.

BBP and BBP-related Publications (Peer-Reviewed)

2011

S.Romand, Y.Wang, M.Toledo-Rodriguez, and H.Markram: *Morphological development of thick-tufted layer v pyramidal cells in the rat somatosensory cortex*, Front Neuroanat. 2011 5:5, doi: 10.3389/fnana.2011.00005

R.Perin, TK.Berger, and H.Markram: *A synaptic organizing principle for cortical neuronal groups*, Proc Natl Acad Sci U S A. 2011 Mar 7, epub ahead of print

CA.Anastassiou, R.Perin, H.Markram, and C.Koch: *Ephaptic coupling of cortical neurons*, Nat Neurosci. 2011 Feb;14(2):217-23

S.Lasserre, J.Hernando, S.Hill, F.Schürmann, P. de Miguel Anasagasti, G.Abou Jaoudé, H.Markram: *A Neuron Mesh Representation for Visualization of Electrophysiological Simulations*, IEEE Transactions on Visualization and Computer Graphics, vol. 99, PrePrints, 2011

2010

TK.Berger, G.Silberberg, R.Perin, and H.Markram: *Brief bursts self-inhibit and correlate the pyramidal network*, PLoS Biol. 2010 Sep 7;8(9)

L.Bar-Ilan, A.Gidon, and I.Segev: *Inter-regional synaptic competition in neurons with multiple STDP-inducing signals*, J Neurophysiol (December 1, 2010), doi:10.1152/jn.00612.2010

2009

A.Loebel, G.Silberberg, D.Helbig, H.Markram, M.Tsodyks, MJ.Richardson: *Multiquantal release underlies the distribution of synaptic efficacies in the neocortex*, Front Comput Neurosci. 2009; 3:27

TK.Berger, R.Perin, G.Silberberg, and H.Markram: *Frequency-dependent disynaptic inhibition in the pyramidal network: a ubiquitous pathway in the developing rat neocortex*, J Physiol. 2009 Nov 15;587(Pt 22):5411-25

J.G.King, M.Hines, S.Hill, P.H.Goodman, H.Markram, F.Schürmann: *A component-based extension framework for large-scale parallel simulations in NEURON*, Front Neuroinformatics, 3:10, doi:10.3389/neuro.11.010.2009

2008

J.Kozloski, K.Sfyrakis, S.Hill, F.Schürmann, C.Peck, H.Markram: *Identifying, tabulating, and analyzing contacts between branched neuron morphologies*, IBM Journal of Research and Development, Vol 52, Number 1/2, 2008

M.Hines, H.Eichner, F.Schürmann: *Neuron splitting in compute-bound parallel network simulations enables runtime scaling with twice as many processors*, J. Comput. Neurosci., 25(1):203-10, 2008

M.Hines, H.Markram, F.Schürmann: *Fully Implicit Parallel Simulation of Single Neurons*, J. Comput. Neurosci., 25(3):439-48, 2008

S.Druckmann, T.Berger, S.Hill, F.Schürmann, H.Markram, I.Segev: Evaluating automated parameter constraining procedures of neuron models by experimental and surrogate data, Biol Cybern, 99(4-5):371-9, 2008

C.Calì, TK.Berger, M.Pignatelli, A.Carleton, H.Markram, M.Giugliano: *Inferring connection proximity in networks of electrically coupled cells by subthreshold frequency response analysis*, J Comput Neurosci. 2008 Jun;24(3):330-45. Epub 2007 Nov 28.

O.Melamed, O.Barak, G.Silberberg, H.Markram, M.Tsodyks: *Slow oscillations in neural networks with facilitating synapses*, J Comput Neurosci. 2008 Oct;25(2):308-16.

GA.Ascoli, Alonso-Nanclares L, Anderson SA, Barrionuevo G, Benavides-Piccione R, Burkhalter A, Buzsáki G, Cauli B, Defelipe J, Fairén A, Feldmeyer D, Fishell G, Fregnac Y, Freund TF, Gardner D, Gardner EP, Goldberg JH, Helmstaedter M, Hestrin S, Karube F, Kisvárday ZF, Lambolez B, Lewis DA, Marin O, Markram H, Muñoz A, Packer A, Petersen CC, Rockland KS, Rossier J, Rudy B, Somogyi P, Staiger JF, Tamas G, Thomson AM, Toledo-Rodriguez M, Wang Y, West DC, Yuste R.: *Petilla terminology: nomenclature of features of GABAergic interneurons of the cerebral cortex*, Nat Rev Neurosci. 2008 Jul;9(7):557-68

H.Markram: *Fixing the location and dimensions of functional neocortical columns*, HFSP J. 2008 Jun;2(3):132-5

Publications in Preparation

TK.Berger et al.: *Layer 6 microcircuitry of the juvenile rat somatosensory cortex*

Druckmann et al.: *Objective classification of the electrical types of cortical interneurons*

A.Gidon and I.Segev: *Principles governing the operation of synaptic inhibition in dendrites*, for Science

M.Hines, S.Kumar, and F.Schürmann: *Comparison of neuronal spike exchange methods on a Blue Gene/P supercomputer*, for Journal of Computational Neuroscience

G.Khazen, D.Keller, S.Hill, F.Schürmann, and H.Markram: *Physical Constraints of Membrane Proteins in Neocortical Neurons*, for Neuroinformatics

Human Brain Project

Overview and Introduction

We were asked to review the potential contribution of the Blue Brain Project to the Human Brain Project.

The Human Brain Project - Preparatory Study (HBP-PS) was presented on Thursday, March 31, 2009, by Prof. Markram and 8 leaders of the 12 scientific and technical work groups (pillars) that will form the HBP consortium. These were distinguished leaders of their fields; the committee was impressed by their commitment to the project, and willingness to travel from as far away as London and Spain for a half day of presentations.

We first summarize the presentations of each pillar, designated in the application as work package (WP), together with comments by the committee, followed by an overall evaluation.

WP1 Strategy and Operational Framework (Prof. Markram)

For orientation, Prof. Markram began with an overview of the ICT FET flagship initiative, the HBP-PS, and the overall organization of the HBP, introducing each leader of the pillars and their role in the project. The organization appears to be logical and efficient.

WP2 High Performance Computing (Prof. Markram, Alan Gara)

Prof. Markram recapitulated the BBP as providing a High Performance Computing Pillar of the HBP, emphasizing how the ICT developed within the BBP would provide an essential driving force for the whole project.

Alan Gara from IBM made a presentation representing the role of IBM in providing the high performance computational resources for the Blue Brain Project from its inception in 2005. He summarized the buildup through the BlueGene L to the current Blue Gene P supercomputer. He then discussed projections in the industry toward exascale supercomputers within only a few years, and the challenges in terms of flops, memory, and energy consumption. He pointed out that optical interconnects and 3D integration are the key technological advances that are pushing the state oft he art in super computing technology. The point was made that solving these problems would likely benefit from understanding how high performance computing takes place within the brain, as revealed by the simulations in the Blue Brain Project. Dr. Gara made clear the deep and continuring commitment to supporting the Blue Brain Project and its interactions with the pillars of the HBP. The committee regarded this commitment as crucial to the BBP and HBP.

Prof. Anastassia Ailamaki of EPFL gave a presentation on data intensive computing, an emerging field of computer science.

WP3: Neuroscience Connectomics (Prof. DeFelipe, UPM Spain)

Professor DeFelipe presented his current work in three main areas relevant to the HBP. His current studies of spines are providing new data on spine distributions on dendrites utilizing several visualization methods. Spines are the sites of most of the excitatory synapses of cortical pyramidal and stellate cells, and this work therefore complements very closely the reconstructions of dendrites for the simulations in WP 1. He showed movies of labeled synapses in 3D stacks using state of the art high resolution focused ion beam methods combined with scanning electron microscopy (FIB/SEM). This was a dramatic demonstration of how cutting-edge technology is permitting high quality reconstruction of significant volumes of cortical neuropil. This is particularly relevant to the aims of the BBP and HBP to develop a multilevel simulation of the brain. De Felipe leads the Cajal Blue Brain project in Madrid, and is already interacting with Prof. Markram in WP 1 (Simulation), so this is already an effective group to serve as a pillar in the HBP. In addition, he will interact with WP5 (Theoretical Neuroscience, Sompolinsky) on theoretical development of the organizing principles of the connectivity revealed, and with Theoretical Neuroscience (Grillner WP7) on the development of databases and informatics tools for sharing and analyzing the data. Prof. DeFelipe's contributions to the anatomical basis of the HBP, together with the lines of collaboration between the BBP and the Cajal BBP in Madrid, are invaluable for the HBP.

WP5: Theoretical Neuroscience (Professor Haim Sompolinsky, Jerusalem)

The Blue Brain project provides an important foundation for the theoretical neuroscience envisioned within the HBP. The Blue Brain Project is concerned to a great extent with the detailed anatomy of the cerebral cortex. This detailed anatomy must be taken into account by theoretical neuroscience models of brain function, for example by attractor-based models of short-term memory, long-term memory, and decision-making. This is a major challenge for ICT and neuroscience that can be facilitated by the HBP. Part of the importance of this is that when the brain functions abnormally, for example in psychiatric states, knowledge of the pharmacology of each of the types of connection between neurons in the cerebral cortex is likely to be important in developing treatments. This may well be important in treating disorders such as schizophrenia, and also in ameliorating some of the changes in memory that occur during normal aging. The insights of the theoretical neuroscience approach into cortical function will also enhance the ability of the Blue Brain project to extend its interests beyond its prime focus at present, the properties and connectivity of the cortex, to consider how they provide the basis for computations involved in processing natural inputs, an important ultimate goal of the HBP. For this goal, the committee recommends that as the cortical column model is achieved in the next 1-2 years, the Blue Brain core move toward in vivo recordings using natural stimuli combined with incorporation of long range connectivity between columns. This will enable the responses of the neurons functioning under in vivo conditions to be incorporated into the simulations, increasing their value for applications by the other pillars in the HBP consortium and other laboratories analysing brain function. Investigations in preparations older than rat pups will also be valuable, so that the findings can be validatedf for juvenile/adult cortical connectivity and function.

WP7: Neuroinformatics Dr. Sean Hill (Grillner, Karolinska, Sweden)

Dr. Sean Hill presented the current status of development of the new field of neuroinformatics which involves developing the digital tools and databases for data management and integration. He emphasized the needs in interpreting neuroscientific data for integration through simulation, a leitmotif for both the BBP and the HBP. A current focus in neuroinformatics is developing ontologies for neurons and neuron regions to agree on names that have unambiguous meanings so that they can serve as the basis for improved classification. He pointed the way to methods for automatic neuron classification, which will greatly enhance the classification of the many diverse neuron types generated by the work by Markram's group in the BBP and WP2 and DeFelipe's group in WP3 among others. Hill's new role as director of the International Neuroinformatics Coordinating Facility (INCF), which is the main body responsible for coordinating this field worldwide, will provide a unique opportunity for the HBP to leverage this facility. In addition to WP2 and WP3, most of the WPs in the HBP will be able to benefit from links to the INCF. The committee regards this inclusion of neuroinformatics as a unique advantage of the HBP in harnessing the power of digital tools to the technical developments within the ICT.

WP8: High Performance Computing (Dr. Lippert, FZJ Germany)

The HPC pillar is based on the existing close interactions between IBM and the Blue Brain project. IBM is keen to understand the needs of the project and IBM is willing to work with the HBP as IBM press forward to the development of new machines for the scientific community. The roadmap to future Exascale HPC is directly influenced by limitations of existing memory technologies, and it is noted that energy is a fundamental concern in future development. Key technologies that will play a role in the future are optical interconnects, 3D technology, as well as software/hardware co-design to address the fundamental bottlenecks in computer architecture especially in the context of data intensive high performance computing, which is at the heart of the Human Brain Project. This WP ensures that the HBP will be linked to the cutting-edge in development of peta-flop supercomputers capable of simulating up to 100 million realistic neurons, an ultimate goal of the BBP, and up to 100 billion neurons in neural networks.

WP9: Medical ICT: (Professor Richard Frackowiak, Lausanne)

Within ICT the Human Brain Project includes aims to advance the science of medicine by using advanced ICT methods to enhance diagnosis of brain disorders, by linking very large databases of brain measures such as imaging of atrophic regions of the brain with the associated

diagnosis. This is likely to be important not only in medical diagnosis, but also in developing much better classification of neurological as well as neuropsychiatric disorders, by taking into account many types of data, including brain imaging data, and using powerful ICT-based classification methods to separate underlying subgroups. This better categorisation of disorders is likely to have a major impact on their treatment. The models of brain function that are being produced by the research in the Blue Brain Project will also be useful in modelling the cognitive and other changes that occur in neurological and psychiatric disorders, by analysing how the computations being performed by different cortical areas may be influenced by differences between individuals in the underlying connectivity, pharmacology, ion channels, etc. Understanding how the disorders arise should lead to innovative methods to treat disorders pharmacologically, for example to restore stability in a cortical circuit by a treatment that can compensate for the original cause of the instability. The simulation of these models at the required level of detail to capitalise on this potential is again a major aim for the ICT as embodied in the Human Brain Project and the Blue Brain Project.

WP11: Neuromorphic Computing Technologies (Prof. Meier, UHEI, Germany)

The neuromorphic pillar builds on the foundation and interactions of the Blue Brain project with prior FET projects such as FACETS as well as the soon to start FET-supported BrainScales project. The latter will provide the support to finish the work started in the FACETs project toward a custom neuromorphic simulation facility in Heidelberg. The ultimate goal of the neuromorphic pillar is to turn the scientific advances in brain sciences into tangible engineering applications and artifacts. It is envisioned that the design of such advanced integrated circuits is automated and directly derived from scientific knowledge about the connectivity obtained in the Blue Brain infrastructure. The team will explore emerging technologies such as nano-electronics and 3D integration in future micro-electronic designs. Several industrial European partners will be directly involved with this project. This WP therefore appears to be an attractive element in the HBP.

WP 12: Neurorobotics (Prof. Knoll, TUM Germany)

Alois Knoll presented a strong case for the importance of robotics within the HBP framework. There are many approaches to implementing robots, but his emphasis was on the power of integrative devices that were either brain inspired or brain derived. He divided the devices into three tiers. Tier 1 comprises individual sensors and other devices that interact directly with the environment. Tier 2 is in the form of neuromorphic devices, based on accurate simulations of brain systems; this is the tier where the HBP will be especially strong, drawing on the simulations of Markram's WP2 (Simulation) and Meier's WP 11 (Neuromorphic Computing). Tier 3 comprises devices with human-like abilities. Tier 2 and 3 will include devices controlled by supercomputer running the neuromorphic simulations, opening up new possibilities for complex behaviors of these devices. From a technical point of view this WP will be able to draw on all the cutting edge technologies of the other WPs to explore breakthroughs of importance for brain-based robotics in engineering, IC technology, and medical prostheses.

In addition to these work groups (pillars), the committee noted other pillars playing essential roles in the HBP but not presented due to prior committments by their leaders:

WP4 Brain Screening (Seth Grant)

WP10 Brain Interfaces (Kris Verstreken)

These both appear to be relevant and lead by outstanding investigators.

In addition, several pillars were included for which leaders have not yet been indicated. These appear to be important for the educational and ethical considerations, as well as for preparation of the eventual proposal.

WP13 Education
WP14 Ethics, Law and Society
WP15 Integration and Editing of the HBP proposal
WP16 Dissemination and Outreach

Evaluation of the potential contribution of the BBP to the HBP

All of the outstanding qualities of the BBP apply to its role as the core of the Human Brain Project. In particular, the HBP will benefit from the organizing expertise of Dr. Markram and his team, with their focus on both experimental data and computational cutting-edge methods, the creation of accessible databases of the data and sharing of tools, integration of the data into multiscale models from the single neuron level through microcircuits and mesocircuits to macrocircuits and ultimately the whole brain, and the constant drive for innovative state-of-the-art high-performance computational methods and supercomputer applications. We value highly this commitment of the BBP to a community approach to high-performance computer simulations, which makes the BBP a natural for a leadership role.

Each of the projects has a logical place in the consortium dedicated to a comprehensive approach to applying cutting edge technology to obtain breakthroughs in understanding the brain and its disorders. Each is led by a leader in their fields. In brief summary, **WP1 on Strategy and Operational Framework** (Dr. Markram) provides the overall leadership, for which he appears to be ideally suited. **WP2 on High Performance Computing** (Dr. Markram, Gara) provides the support needed for the supercomputing applications and the commitment (Dr. Gara) by IBM for the Blue Gene machines, which is essential to the project. **WP3 on Neuroscience Connectomics** (Dr. DeFelipe) provides critical data on cutting edge anatomical reconstructions at the electron-microscopical level relevant for the intrinsic connectomics within the microcircuits. **WP4 on Brain Screening** (Dr. Grant) provides data at the molecular level for the diversity of proteins that make up the functional architecture of the neuron and the microcircuits they form through their synaptic connections. For **WP5 on Theoretical Neuroscience,** Dr. Sompolinsky gave an impassioned justification for the crucial relevance of theory in providing the necessary analytical and synthetic mathematical tools to interpret the experimental data and computational simulations, particularly as they are applied to natural behavior. **WP6 on Cognition and Behavio**r fulfills a needed bridge from the detailed neural and microcircuits to the higher cognitive functions of the behaving animal and human, and is led by Dr. Dehaene, one of the leading experts in these studies. **WP 7 on Neuroinformatics** (Grillner, Hill) provides the valuable tools for creating databases and search capabilities, as well as promoting the cultural change needed to encourage the sharing of experimental data and modeling solftware and results. **WP8 on High Performance Computing** (Dr. Lippert) enormously enhances the ability of the HBP, together with the BBP, to assume a leading role in the development of high-performance computing as applied to a crucial area of science, the simulation of the human brain. As noted elsewhere, this can benefit not only the brain simulations, but the brain simulations can also inform the construction of the next generation of high performance computing as it extends beyond the capabilities of traditional computer hardware and architectures. **WP9 on Medical ICT** is represented by Dr. Frackowiak, one of the world's leaders in functional imaging of the human brain in health and disease, who is ideally suited to apply the results of both neural and vascular simulations to one of the key current problems, the energy demands that underlie the functional images. **WP10 Brain Interfaces** (Dr. Verstreken) will develop novel bioelectronic technologies to interface with the brain during in vitro and in vivo experiments; these will have extensive applications to other WPs. **WP11 on Neuromorphic Computing Technologies** (Dr. Meier) is ideally suited to meet the goal of turning advances in brain science, as produced by the HBP, into new devices for information, communication and medical technologies as well as micro-electronic designs. **WP12 in Neurobotics** will provide a critical area for application of the results of the BBP simulations through robotic devices in engineering, IC technology and medical prostheses, as described by Dr. Knoll.

In sum, these investigators are well established and leaders in their respective fields. Their presentations were of a uniformly high quality. An attraction of the WPs is that here will be numerous interactions between them, as detailed above and in the application. The sharing of cutting edge tools, already established by the BBP, extended to all of the participating laboratories, will be one of the most attractive and cost-effective features of the HBP. Although the time of the presentations was too brief (15-25 minutes each) for in depth evaluation, the

committee was able to conclude that there is a high probability that their current work would be greatly leveraged by the interactions to be expected within the HBP, and that in turn the BBP brain simulation facility would greatly enhance the HBP, and would in turn be greatly enhanced by the feedback involved in these collaborations.

In implementing these interactions within the consortium, the high effectiveness of the organization of the current BBP and the high quality of its experimental data and multilevel simulations gives assurance that the consortium is well organized and should lead to cutting edge advances across these many fields.

In summary, the committee recommends support for BBP to enable it to provide the key leadership for the HBP with the highest enthusiasm.

Terms of reference (TOR)

Most of the questions posed in the TOR have been covered in the body of our report on both the BBP and the HBP, but we here provide specific answers to each of them, as requested.

1. Scientific quality & expected outcome

1a) Evaluation of the Blue Brain Project (BBP)

The scientific evaluation should provide judgments to the following topics:

- The quality of the **neuroscience** on which the simulation models are based;

As indicated in the report, the quality of the quantitative functional properties and connectivity studies which are the heart of the BlueBrain project is excellent and internationally unique.

- The quality and novelty of the neuroinformatics, mathematical and **computer science** approaches developed for data driven modeling;

The computational science aspects of the project are excellent.

- The quality and novelty of the **models** constructed by the project;

The quality of the connectivity models is excellent, as they provide ways to understand the rules of the organization of the cortex. The quality of the models is seen in the emergence of properties at higher levels of organization.

- The quality and novelty of the approaches developed and used to simulate the models on **supercomputers**;

The use of supercomputers is absolutely essential to the aims of the project. The project is using its supercomputer resources in a very effective manner, which paves the way for simulations of response to increasingly relevant physiological inputs to the models.

- The **efficiency** of use of EPFLs supercomputing resources;

The project team is remarkably efficient and disciplined in organizing the work flows to make maximum use of the supercomputing resources.

- The quality and novelty of the **software** developed in the project as a foundation for simulation based brain research;

A wide range of highly innovative software is being developed to aid in understanding brain structure and function. The team has paid particular attention to developing from the start an SDK with an API of high quality which will be available to the scientific community. The reviewers rate this highly, and recommend further development in the future which would greatly benefit from sustained professional software engineering.

- The importance and originality of the **simulation strategy** that is used by the project;

The simulation strategy is world leading in importance and originality.

- A benchmark of the **facility** that has been developed compared to any similar projects in the world;

We are not aware of another facility devoted to the cellular basis of cortical organization that compares with this one. The Allen Brain Institute would be an example of a center of excellence with aims that are complementary to the Blue Brain project.

- The importance of the **insights** obtained (*scientific output, e.g. publications*) and expected for neuroscience, neuroinformatics, and modeling;

The insights into cellular anatomy of the cortex and morphoelectrical characterization are new and fundamental to understanding cortical function, as are the hypotheses regarding the rules that determine it.

- The relevance of the **contribution** of the Blue Brain Project to high performance computing and advanced scientific visualization;

The Blue Brain project is at the forefront of pushing the limits of current supercomputer technology in the world wide effort to understand the human brain.

- The **management** of the project and the effective **use of the budget**.

The management of the project is excellent. For future growth there is an urgent need to stabilize two senior staff with permanent academic appointments. Furthermore, support is needed for engineering and administrative tasks, to allow the scientists to focus on the research goals. Present staff is stressed, and would be greatly aided by personnel acting as scientific liaison officers for public and industrial relations including knowledge transfer and business development.

The budget appears to be used in a highly efficient manner. However, with the rapid development of the activities of the project, there will be a need for further funds to recruit and retain senior staff as explained above and to invest in the next generation of supercomputers.

1b) Evaluation of the Human Brain Project (HBP)

Evaluate the **scaling up of the BBP** to serve as the Brain Simulation Facility for the HBP, aiming for the technical capability to simulate the brain at higher resolutions (molecular) and at larger scales (whole brain).

- Does the BBP facility serve as an appropriate foundation for the proposed *Brain Simulation Facility* of the HBP?

Yes, this is an excellent foundation because the BBP has built a facility that has the required types of information in its database and allows that to be retrieved and shared with the other WPs, including its brain simulations.

- Is the complexity of the brain, the models required, the supercomputing resources needed, taken into account in an appropriate and feasible way?

The BBP regards the complexity as a fundamental challenge at multiple levels, from molecular to anatomy to physiology to theory. Modeling at all levels is at the core of the BBP approach. The supercomputing resources have been central to the BBP approach. In sum, these factors have all been taken into account in an appropriate and feasible way.

- Judge the scientific value of the provided hypotheses related to the planned modeling of the brain.

The planned modeling will provide a foundation of high scientific value for understanding the operation of the cerebral cortex in health and disease.

Supercomputing:

- Based on the results of the BBP, and the current trends in neuroscience, neuroinformatics, modeling, supercomputing, is it the **right time** to start an ambitious project such as the Human Brain Project?

Given the advances in knowledge of connectivity (partly achieved through the BBP), and empirical and theoretical neuroscience, the time is ripe for a major project of this nature.

- Are the estimations for the needed **computing resources** of the HBP reasonable?

Given the cutting edge nature of the simulations, with multilevel representations of neuronal connectivity and properties, the need for state of the art supercomputing resources is apparent.

- How do you judge the chances that the HBP will make significant contributions to **HPC hardware and software** technologies?

It is likely that during this project our fundamental understanding of brain architecture will have a signficant impact on the design of exascale and beyond computing systems.

- If the HBP is granted as a Flagship project for Europe, what would the consequences be for the needed computing capacity within **Switzerland**?

We would hope that this would stimulate further development of supercomputing resources in Switzerland and be coordinated with the high performance computing development strategy.

- In what way could the BBP/HBP leverage the National HPCN strategy (hosting of future supercomputers dedicated to BBP/HBP at new CSCS facility, access to national HPCN-funded peta- and future exascale supercomputers, application development in the context of the HP2C platform, etc.)?

We have not been provided with information about these issues.

Applications, medical treatments:

- How do you judge the chances the project will lead to new **medical treatments** in brain diseases?

Developments in analyzing cortical function and dysfunction as outlined here is likely to provide an important foundation for understanding many neurological and psychiatric disorders and the processes involved in normal ageing.

2. Management (governance & structure) and financial aspects

- What do you recommend in terms of **governance** of the HBP, notably for Switzerland?

Dr. Markram has provided a structure to enable the project to function in a well integrated manner at the same time enhancing high risk and innovative scientific exploration.

- In the HBP, how do you judge the different **budgetary items**?

We were not given budgets or budgetary items to evaluate.

- How do judge the **timeframe** for the needed finances? From a scientific point of view are the requested tranches over time well in line with the scientific plan?

We do not have information on this issue.

- In case the **Swiss Parliament** would not be willing to contribute the requested matching amount and the Human Brain Project is awarded, what would the consequences be?

The first consequence would be to miss the opportunity to put Switzerland in the leadership of developing the center for a multinational European effort in state of the art technology for breakthroughs in brain science and related fields.

- What are the **benefits and risks for Switzerland** to lead the Human Brain Project?

The benefits are to support a unique multidisciplinary multilevel multinational project combining science and technology for the benefit of understanding the normal brain and neurological and psychiatric disorders. The risks are to miss out on this opportunity and lose this position of leadership.