

Measuring and Reconstructing the Brain at the Synaptic Scale: Towards a Biofidelic Human Brain *in Silico*

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In the 100 years since Waldeyer-Hartz posited the Neuron Doctrine [1] and Golgi [2], Nissl [3], and Ramon y Cajal [4] published the first illustrations of individual neurons and their connections, experts in fields ranging from neuroscience to computer science have formulated detailed models of the brain to explain complex cognitive processes, create machines with artificial intelligence, prescribe psychoactive drugs to correct mental illness, and serve myriad other purposes. Amazingly, despite the fact that a fundamental assumption in all of these models is that the *connections* between neurons in the brain imbue it with its computational power, to-date no one has measured the complete connectivity of even a single vertebrate neuron! Therefore, previous large-scale brain simulations and emulations lack detailed knowledge of neural connectivity [5]. Today, however, a combination of new technologies provides the opportunity to radically change this state of affairs by creating large-scale three-dimensional images of real brains at nanometer resolutions, sufficient to observe neurons, synapses, and even individual vesicles. In this poster, we present our work on measuring and reconstructing the brain at the synaptic scale and provide a roadmap from today's state of the art to tomorrow's biofidelic human brain *in silico*.

The key enabling technologies underlying the current and upcoming revolution in human brain emulation include: (i) high-resolution, high-throughput nanoscopy, (ii) automated machine annotation of three-dimensional images, (iii) exabyte-scale data management, and (iv) massively parallel chip design. Collectively, these techniques will generate biologically accurate neural networks emulations, a reversely engineered brain. To make sense of these networks, though, we will also need advanced mathematics in graph theory and statistical inference to elucidate the recurring network motifs and identify the fundamental computing elements in the brain. We discuss the developments of each of these fields briefly below, along with our contributions.

In 2004, Denk and Horstmann published a landmark paper in which they showed that automating block-face imaging combined with serial sectioning can relatively efficiently reconstruct large three-dimensional tissue nanostructure, with resolution sub 10 nm in two dimensions, and sub 100 nm in the third [6]. Since then, we and several other groups have improved on this original design by making it faster, more robust, and capable of higher resolution. Our current state-of-the-art system combines a Thin Section Scanning Electron Microscopy (TSSEM) with an Automatic Tape-collecting Lathe UltraMicrotome (ATLUM) [7]. Together, this allows us to collect image data at a resolution of 3x3x30 nm. Although imaging a whole human brain today is impractical, parallel beam electron microscopes and other upgrades to our current system will allow for imaging a cortical column (approximately 1 mm³), presumed to be fundamental building block for cortical computations, in about 2 days. At that rate, we could image the whole brain in about 2 years.

Once the image data is collected, it must be stored in a manner to facilitate image processing. This is a non-trivial problem, as the three-dimensional image of an entire human brain will require 3.3 exabytes of data. Converting the raw images into information about neurons and synapses will require non-local information outside of the field of view of a single image plane, because neural processes are often complex, tree structured, three-dimensional objects, sometimes spanning across both hemispheres. Furthermore, their relationships may only be evident after the entire structure is known. To address this issue, we are designing database structures specifically tuned for efficient non-local queuing of image data and simultaneous access by hundreds or thousands of processes to ensure that the machine annotation effort can be effectively parallelized.

Because manual annotation of images comprising a cortical column or entire brain would likely take many decades, a machine annotation strategy is necessary to extract the desired information. We have recently made a number of promising advances in machine annotation—including three-dimensional segmentation and tracking of neural processes [8]— but manual interaction is still necessary. Improvements in the less often reported but critically important stages of image pre-processing to align, stitch and stack the volumetric images are also necessary.

Once the data is collected, stored efficiently, and annotated, dedicated software and potentially hardware will be used to simulate the human brain. While the jury is still out on whether large-scale brain simulations are best implemented on dedicated chips, several of the current state-of-the-art in large-scale brain simulations utilize massively parallel chips. In our work towards this goal, we have designed dynamically reconfigurable silicon chips, such that connectivity can be programmed into the chip, as more information comes online [10].

Although there is much work yet to be done, we are on the verge of a revolution in brain science, poised for the first time to see real biological neural networks and understand brain function at most fundamental level. This information will affect many fields of scientific inquiry and lead to countless new technologies including the first machines with true artificial intelligence, powerful neuromimetic computing systems, and the first biofidelic human brain emulation. Much like the sequencing the human genome allowed for rapid and unforeseen progress, becoming a central tool in genomics research, determining the complete wiring diagram of a human brain could have a similar impact. At a minimum, it will provide constraints on the kinds of networks typical of human brain circuits, upon which neuroanatomists, systems neuroscientists, and cognitive scientists can build new theories of brain operation and function. We are currently at the forefront of these developments and will soon start to reap the benefits of this new knowledge.

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