Nanotechnology

&

Medicine

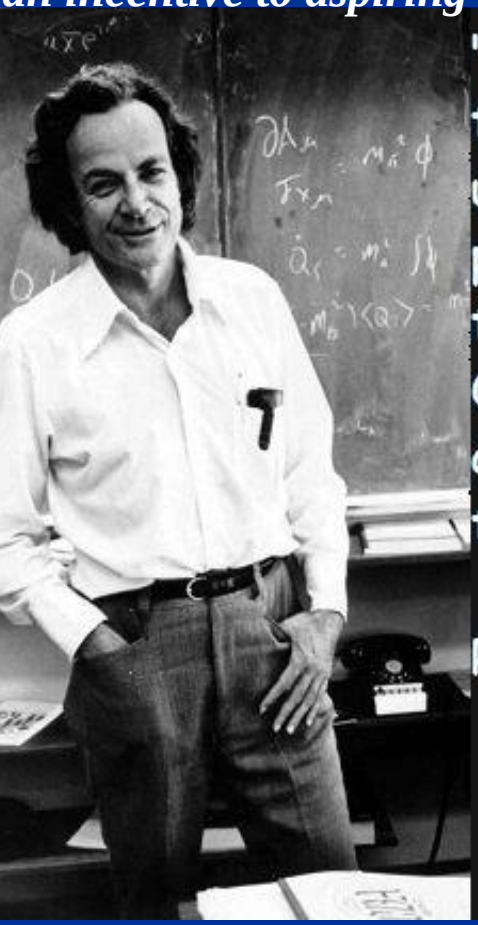
Nanoscience

- The prefix “nano”is a Greek word for “dwarf”
- One nanometer (nm) is equal to one-billionth of a meter
- About a width of 6 carbon atoms or 10 water molecules
- A human hair is approximately 80,000 nm wide
- Red blood cells is 7000 nm wide
- Atoms are smaller than 1 nanometer
- Molecules and some proteins are between 1 nm and above

Nanoscience

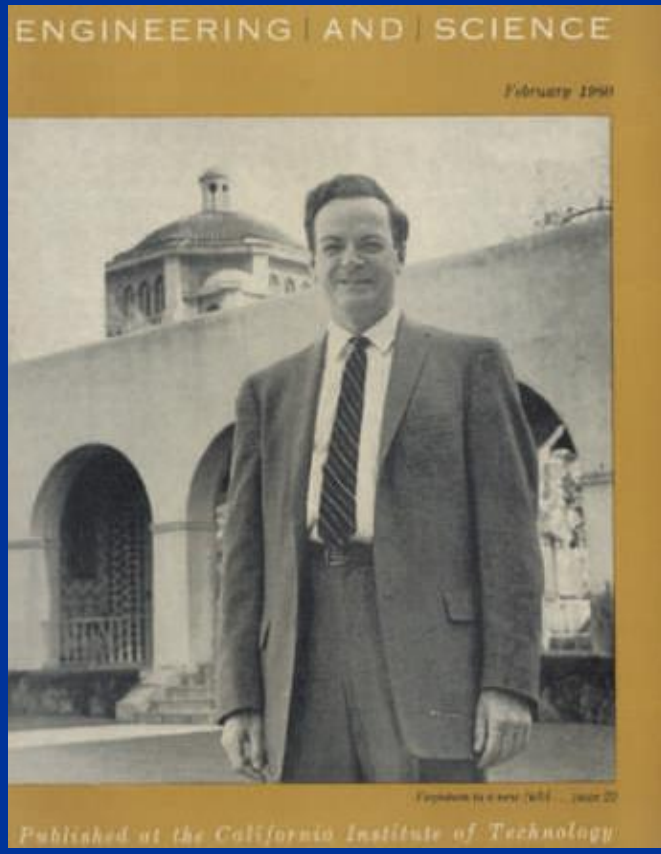
- The concept of nanotechnology was first coined by Richard Feynman in 1959 in his lecture "There's plenty of room at the bottom"
- Manipulating material at a scale of individual atoms and molecules
- Imagining the whole *Encyclopedia Britannica* written on head of a pin

In 1959 Richard Feynman, gave a talk at Caltech entitled "There's Plenty of Room at the Bottom" in which he imagined technologies that would enable us to peer at individual atoms and — perhaps more compelling to tool-using Homo Sapiens — actually manipulate atoms. He anticipated the atomic force microscope and the enormous potential inherent in the ability to explore the world at the atomic scale1. He also anticipated the development of nanotechnology capable of interacting directly with atoms and molecules and building nanoscale machines. He was particularly enamored of these "tiny machines" as he called them in a subsequent lecture and he issued several challenges for the creation of particular machines offering prize money as an incentive to aspiring inventors.



"We are at the very beginning of time for the human race. It is not unreasonable that we grapple with problems. But there are tens of thousands of years in the future. Our responsibility is to do what we can, learn what we can, improve the solutions, and pass them on."

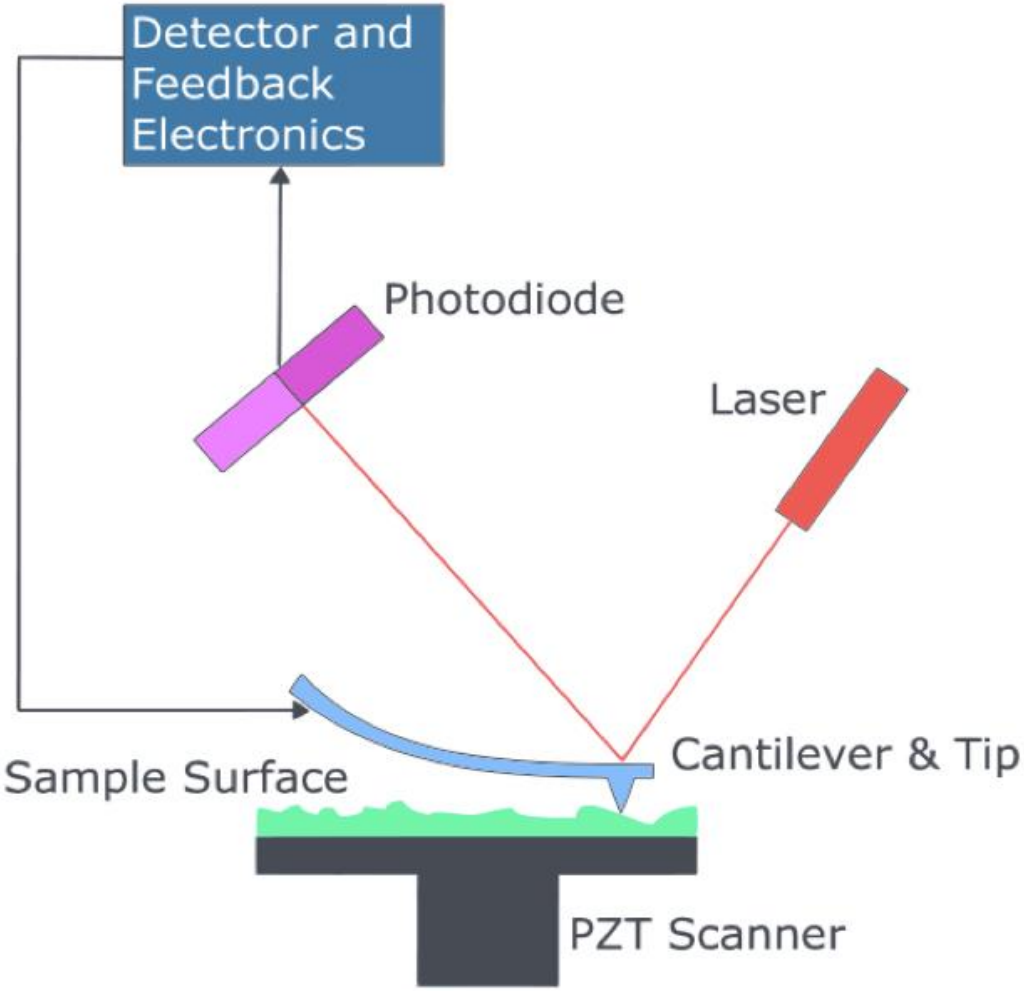
Richard P. Feynman



There's Plenty of Room at the Bottom

There's Plenty of Room at the Bottom is the title of a lecture given by physicist Richard Feynman at an American Physical Society meeting at Caltech on December 29, 1959. In this lecture, Feynman considered the possibility of direct manipulation of individual atoms as a powerful form of synthetic chemistry. His vision of the future inspired Eric Drexler among others and is now referred to as *nanotechnology*.

Tiny Targets: Atomic Force Microscope



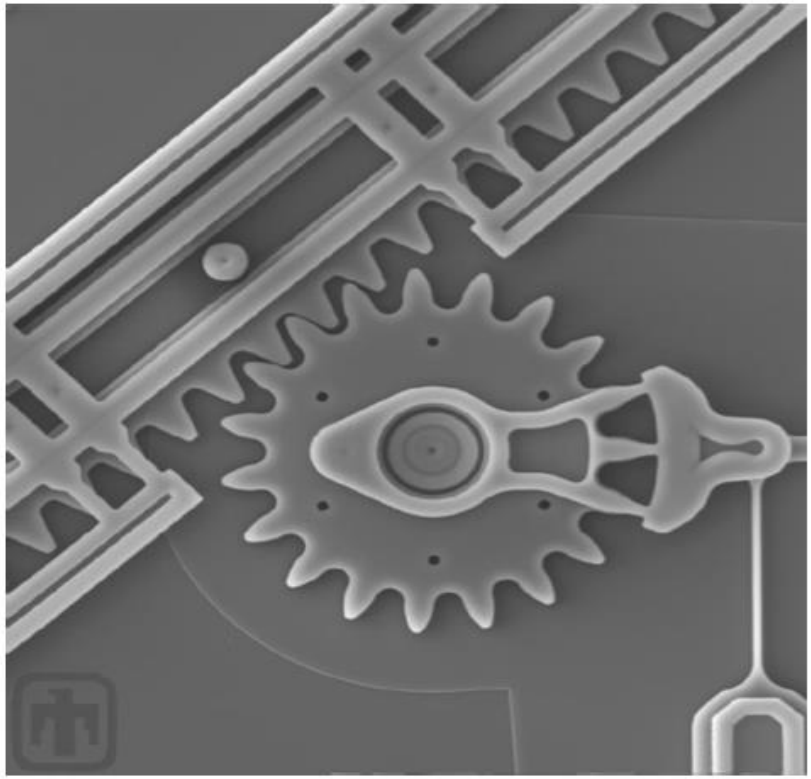
Along with John von Neumann, his former colleague at Los Alamos, Feynman fully appreciated that nature had already solved the problem of atomic-scale machines, and he considered biological machines a proof that such technology was possible and only a matter of time before engineers would match or surpass natural selection. He provided insights into the challenges faced by natural and man-made tiny machines, describing how, as you descend to smaller and smaller scales, different physical laws dominate. E. Coli use corkscrew-shaped flagella and molecule-sized motors to propel themselves through a watery fluid which is for them a viscous medium as thick as molasses. For organisms operating at millimeter scales, surface tension is an important consideration; at nanometer scales, Van der Waals force starts to play a key role

Scaling Laws: Different Forces Dominate

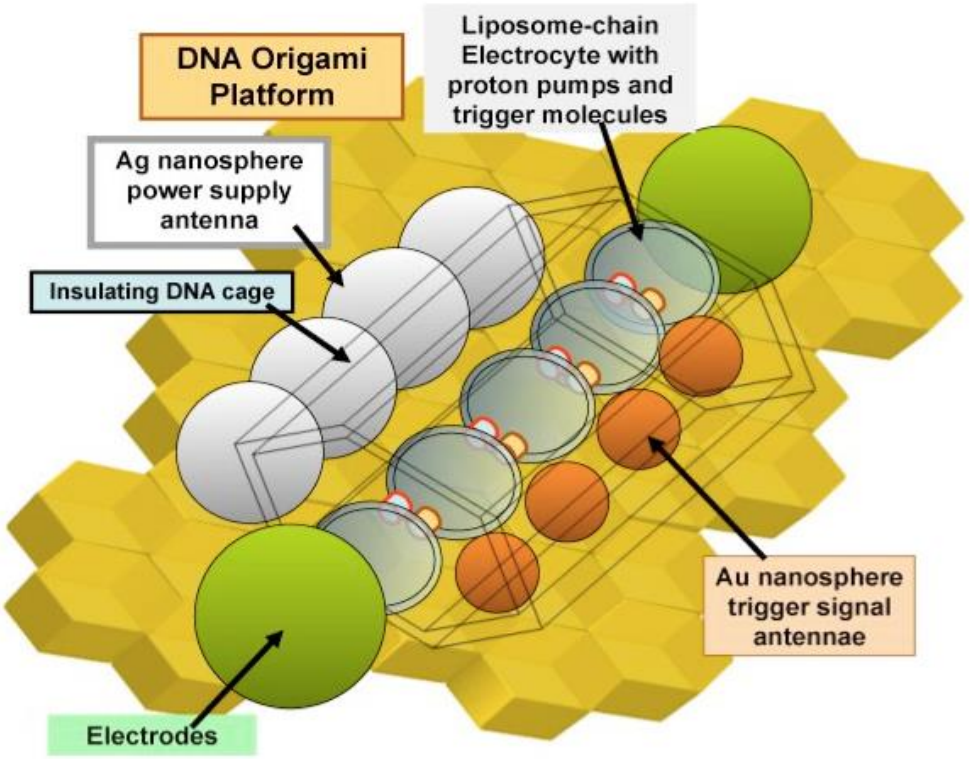
Submultiples			Multiples		
Value	Symbol	Name	Value	Symbol	Name
10^{-1} m	dm	decimetre	10^{1} m	dam	decametre
10^{-2} m	cm	centimetre	10^{2} m	hm	hectometre
10^{-3} m	mm	millimetre	10^{3} m	km	kilometre
10^{-6} m	µm	micrometre	10^{6} m	Mm	megametre
10^{-9} m	nm	nanometre	10^{9} m	Gm	gigametre
10^{-12} m	pm	picometre	10^{12} m	Tm	terametre
10^{-15} m	fm	femtometre	10^{15} m	Pm	petametre
10^{-18} m	am	attometre	10^{18} m	Em	exametre
10^{-21} m	zm	zeptometre	10^{21} m	Zm	zettametre
10^{-24} m	ym	yoctometre	10^{24} m	Ym	yottametre

Today, we frequently see articles in the main-stream press describing advances in microelectromechanical systems or MEMS which are devices typically manufactured using semiconductor fabrication technologies and consisting of components from 1 to 100 micrometres is size. At this scale electrostatic surface effects dominate over volume effects such as inertia or thermal mass. We are also seeing new materials that are hybrids combining, for example, biologically-based substrates constructed by folding strands of DNA into three-dimensional shapes, and then adding atoms of gold or other exotic materials as conductors to implement specialized sensors and communication devices.

Tiny Machines: MEMS and Nanotech



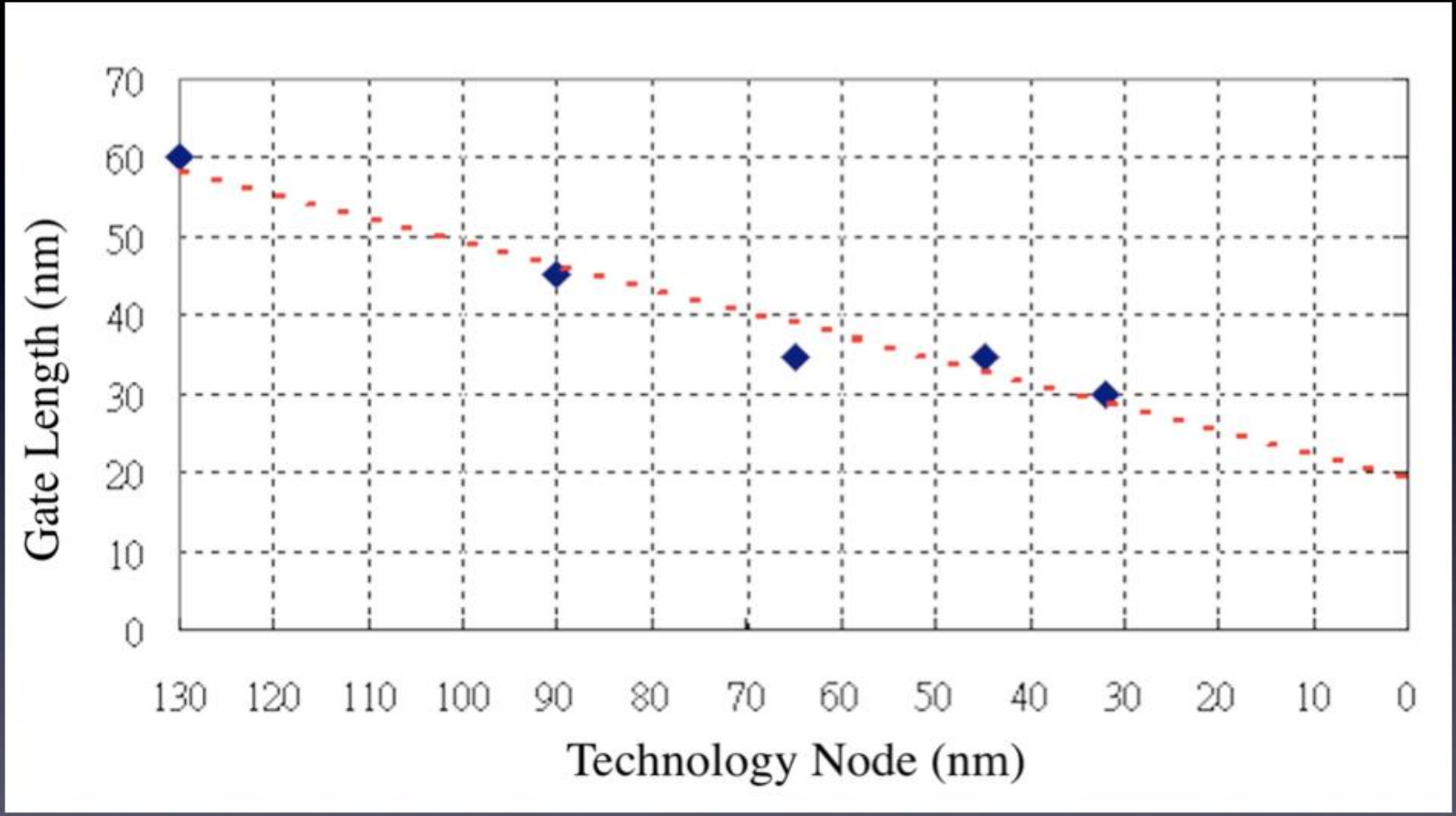
Source: Los Alamos



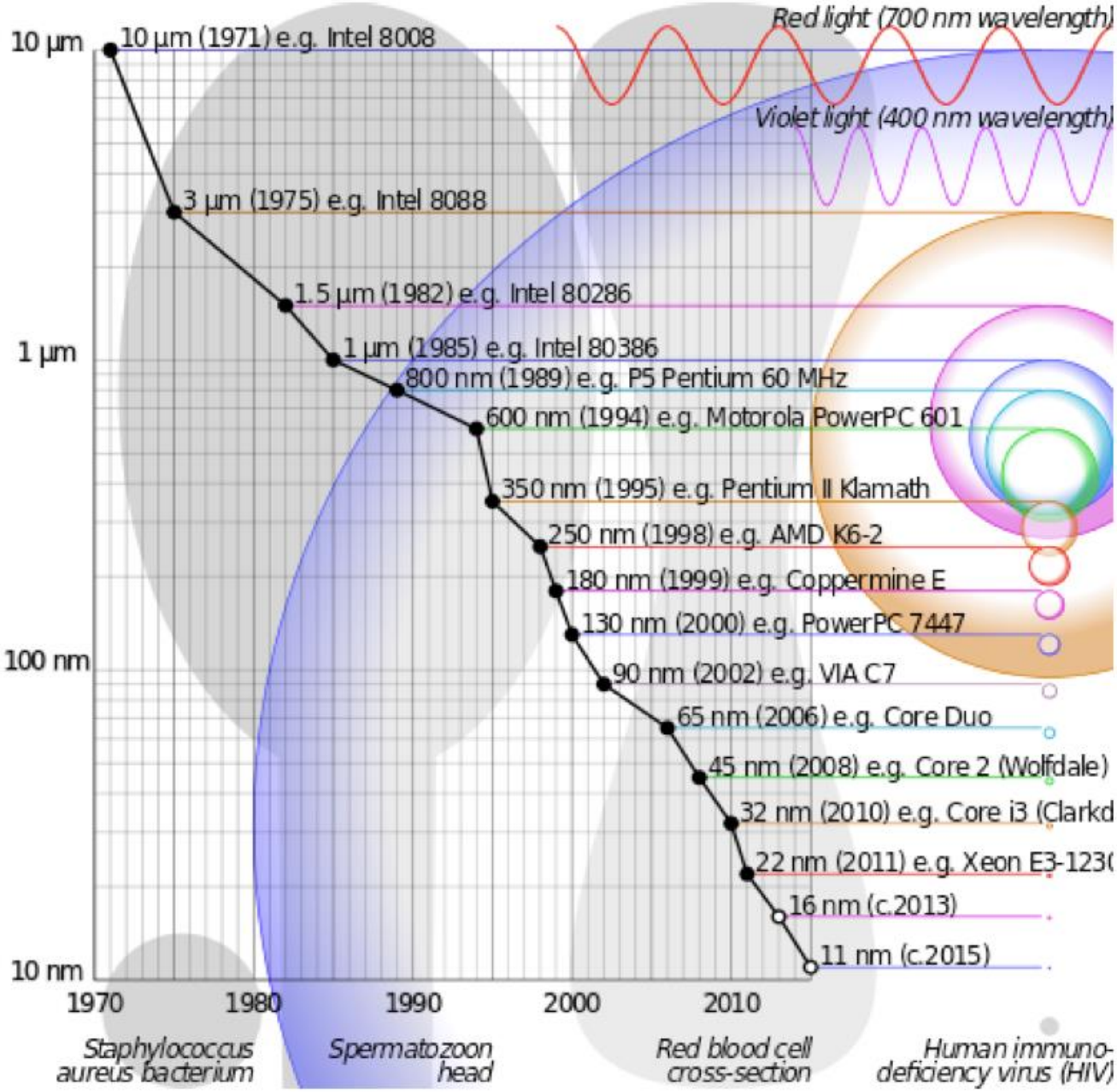
Source: Rudy Diaz (ASU)

In 1965, Gordon Moore made the observation that over the history of modern computing hardware, beginning with the invention of the integrated circuit in 1958, the number of transistors on an integrated circuit doubled approximately every two years. This exponential trend has continued more or less unabated to this day and promises to continue for some indeterminate time into the future. In this graph, the fabrication process — a modern version of lithography — referred to here as "technology nodes" — is now around 22 nanometers which allows printed lines etched on a silicon die — referred to here as "gate lengths" — of around 30 nanometers. The molecular machines in your cells — called "ribosomes" — responsible for manufacturing proteins are about 20 nanometers end to end and ribosomes are considerably more complicated machines than a single logic gate.

Moore's Law: Transistor Size and Chip Fabrication



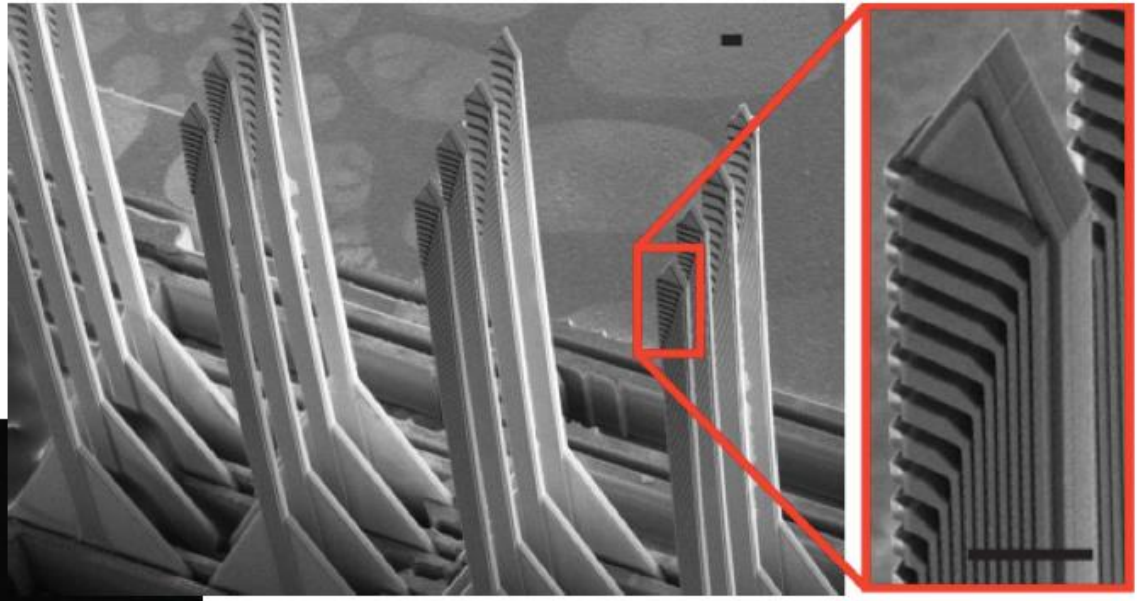
For instance, the size of a transistor in an Intel 8008, a microprocessor introduced in 1972, is depicted by the large bluish-purple circle and is about twice the size of a red-blood cell, and the size of a transistor in a present-day Xeon server is about half the size of an HIV virus.


10 µm
1 µm
100 nm
10 nm
1970
1980
1990
2000
2010
10 µm (1971) e.g. Intel 8008
3 µm (1975) e.g. Intel 8088
1.5 µm (1982) e.g. Intel 80286
1 µm (1985) e.g. Intel 80386
800 nm (1989) e.g. P5 Pentium 60 MHz
600 nm (1994) e.g. Motorola PowerPC 601
350 nm (1995) e.g. Pentium II Klamath
250 nm (1998) e.g. AMD K6-2
180 nm (1999) e.g. Coppermine E
130 nm (2000) e.g. PowerPC 7447
90 nm (2002) e.g. VIA C7
65 nm (2006) e.g. Core Duo
45 nm (2008) e.g. Core 2 (Wolfdale)
32 nm (2010) e.g. Core i3 (Clarkd
22 nm (2011) e.g. Xeon E3-123(
16 nm (c.2013)
11 nm (c.2015)
Red light (700 nm wavelength)
Violet light (400 nm wavelength)
Staphylococcus aureus bacterium
Spermatozoon head
Red blood cell cross-section
Human immuno-deficiency virus (HIV)

The challenge of scalable neuroscience is to build instruments that enable us to record the behavior of ensembles of billions of neurons at millisecond temporal resolutions where each neuron is a machine of incredible complexity, and infer from this virtual deluge of data — "tsunami" is perhaps a more apt metaphor, the function of individual neurons and predict the collective behavior of an entire brain in both its normal and pathological operating regimes.

Much of modern experimental neuroscience is based on single-cell recordings of individual neurons or multiple neurons within a small, roughly planar area of brain tissue using an array of probes arranged in a regular grid — 10 × 10 is common — that is inserted into the brain an awake animal. Ed Boyden and his team at MIT are pushing the state of the art to enable each probe in such an array to record at multiple sites along its length thereby allowing us to collect information from many neurons in a 3-D volume.

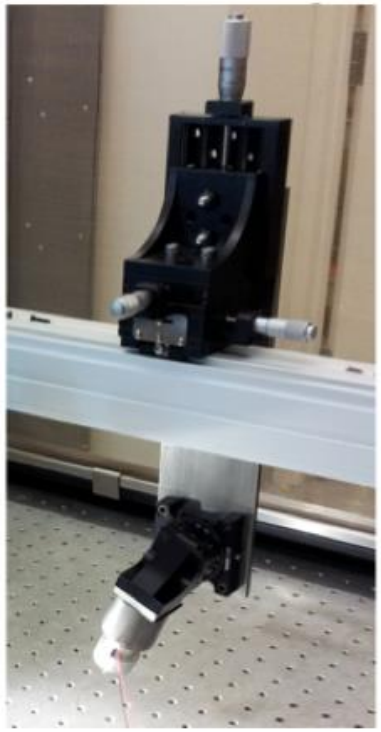
Scalable Neuroscience: Multiple Cell Recording

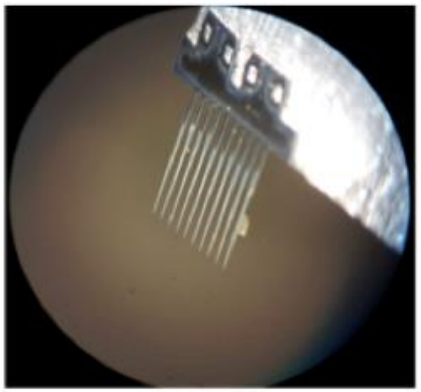


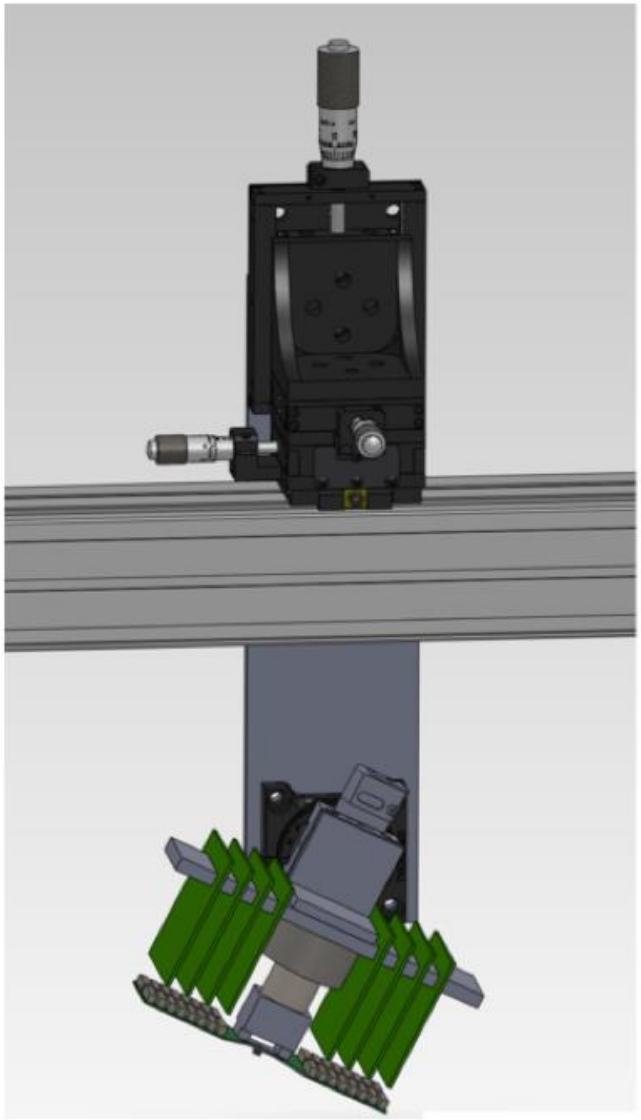
Source: Ed Boyden (MIT)

Ed has pioneered methods for using robots to insert probes in experimental animals thus eliminating one source of human error and allowing precise placement under program control. He is also applying optogenetic techniques — which we will discuss in a moment — that allow us to use light to both activate and silence individual neurons.

Scalable Neuroscience: Robotic Probe Placement





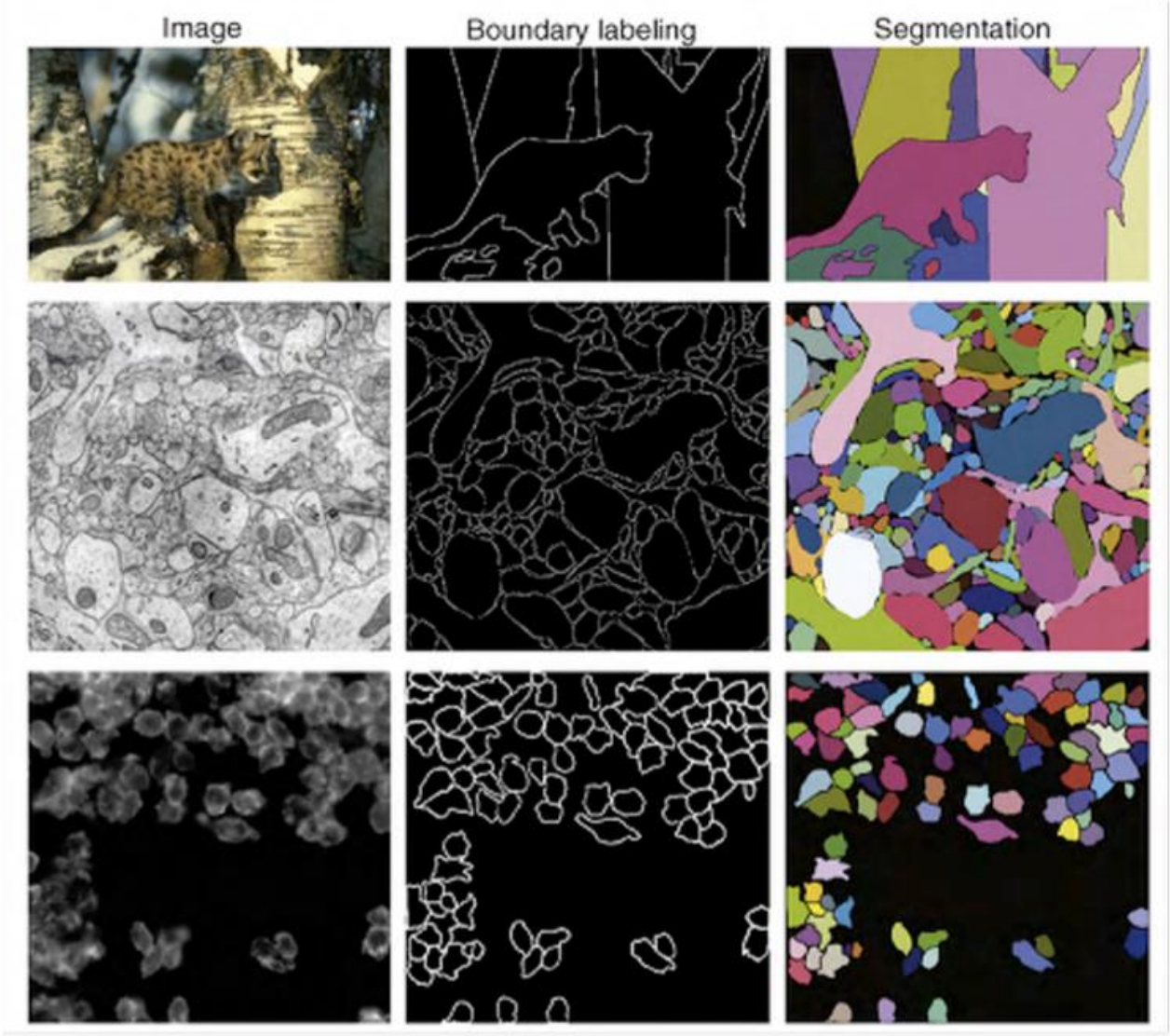


Source: Ed Boyden (MIT)

As long as we have had microscopes powerful enough to resolve individual neurons, scientists have been refining methods for imaging neural tissues using specialized preparations that make neuron cell bodies stand out and utilizing ever more powerful devices, with scanning electron microscopes currently now common in academic labs. Once the tissue is prepared and an image taken, it is generally the task of a trained neurophysiologist to interpret the image and determine where one cell leaves off and another one begins. Having skilled humans in the loop, whether working with the tissue samples or interpreting images doesn't scale, and so research labs led by Winfried Denk at Max Planck and Sebastian Seung at MIT are developing robotic devices for handling the tissue and interpreting the results of imaging [3, 15].

Unfortunately, automating the segmentation of cell bodies is more difficult than you might imagine [26, 21]. You can plainly see the leopard cub in the top sequence of images of this slide, differentiating its torso from the tree to which it clings. Segmenting the dendrites and axons in the middle row of frames is much more difficult. You may imagine individual neurons gracefully spread out in the neural tissue like free-floating seaweed fronds, but it is more accurate to imagine the neurons as spaghetti nooodles densely packed into a can. The task is made somewhat more tractable by highlighting selected neurons using color-coded fluorescent markers [14] — see Brainbow — as shown in the bottom panel, but this technology is not likely to scale due to the combinatorics involved in differentiating so many closely packed cell bodies.

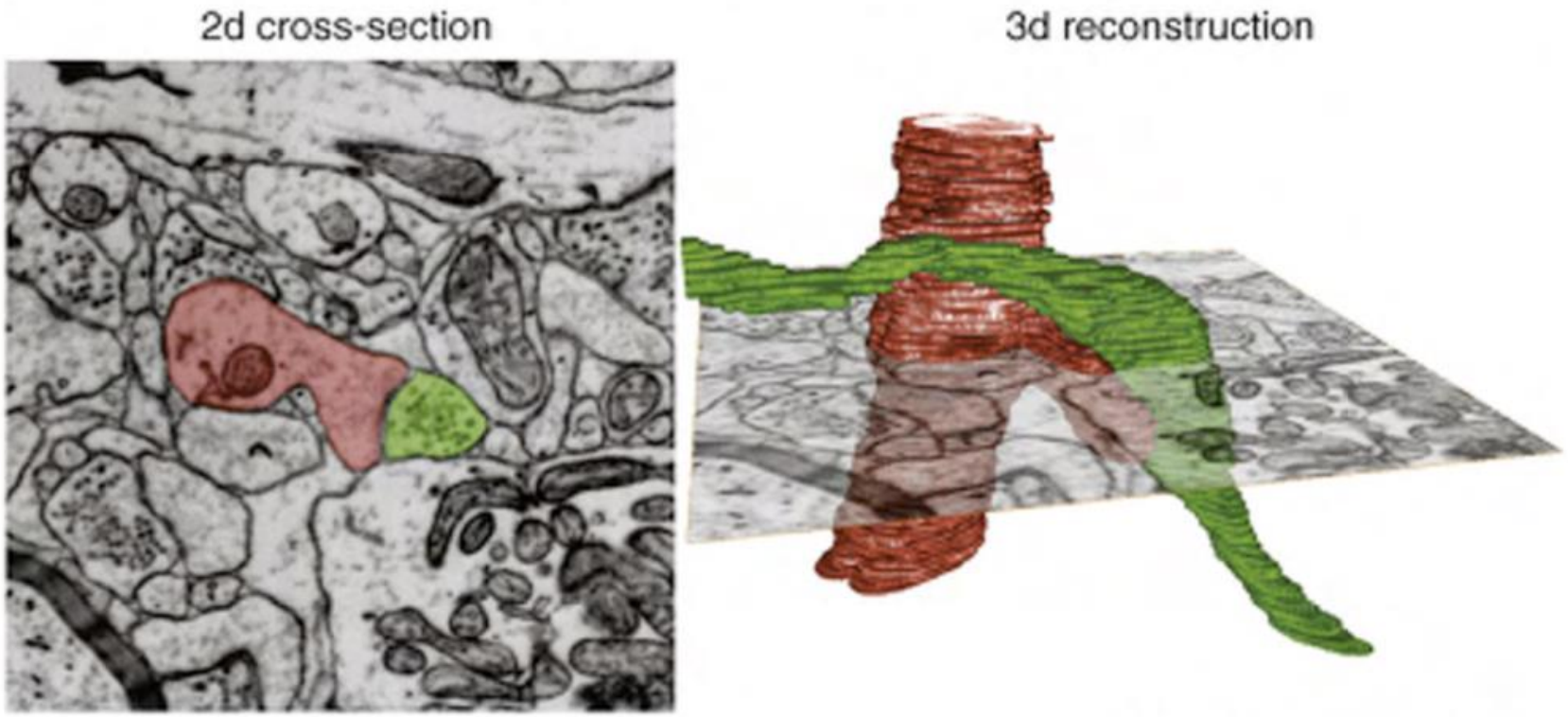
Scalable Neuroscience: Connectomics



Source: Sebastian Seung (MIT)

Sebastian's goal is to compute the connectome — the graph of neurons and their active connections — for interesting tissue samples, starting with the retina, then a mouse brain and ultimately a human brain [25]. Even if we can improve our image processing algorithms to accurately segment cell bodies, we would still need a warehouse full of robotic tissue handlers and electron microscopes to process even a single mouse brain in a reasonable amount of time. A single cubic millimeter of neural tissue produces a petabyte of image data when scanned. One would hope there's a better way.

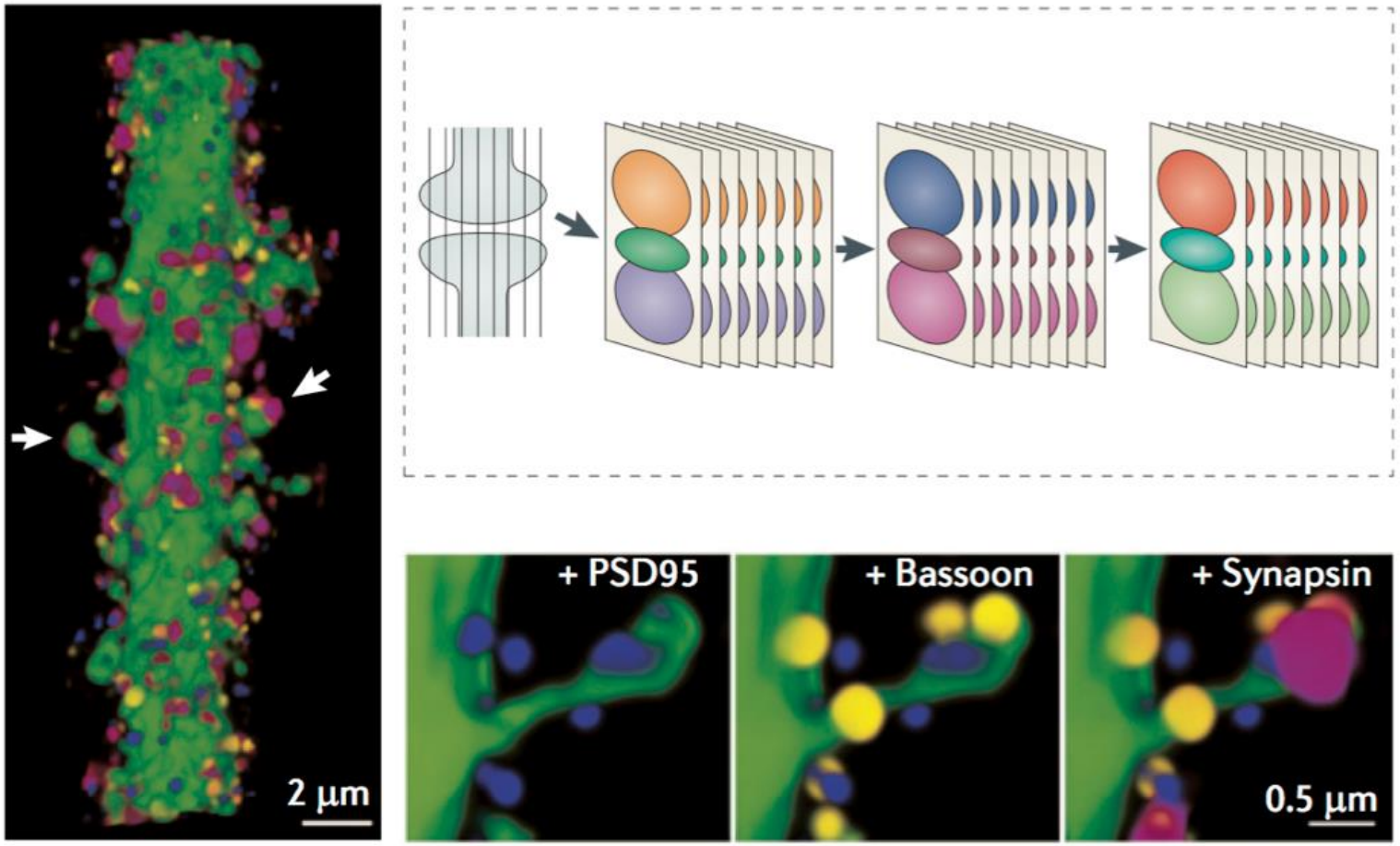
Scalable Neuroscience: Automated Cell Segmentation



Source: Sebastian Seung (MIT)

The method of preparing a tissue sample, slicing it into thin sections, and scanning each slice with an electron microscope that is being used to reconstruct the connectome can also be applied to determine where in the cell different proteins are utilized. Stephen Smith and his colleagues at Stanford have developed a new imaging technique they call array tomography that combines electron microscopy with immunofluorescence to visualize the distribution of specific proteins in the cell [20]. Immunofluorescence takes advantage of the specificity of antibodies to their corresponding antigens to tag proteins with fluorescent dyes so they can be imaged with a scanning electron microscope. Smith and his team have used this technique to investigate the diversity of different synapse types as identified by their characteristic protein signatures [22] and the Allen Institute for Brain Science has used similar techniques in generating data for their incredibly useful Brain Atlas resources.

Scalable Neuroscience: Array Tomography Proteomics



Source: Stephen Smith (Stanford)

To get a better idea of the scale of the problems we're considering, here are some numbers that quantitative neuroscientists keep in mind when doing back-of-the-envelope calculations. 100 billion of anything is a lot, but 100 billion sophisticated computing machines is staggering. White matter consists mostly of glial cells and myelinated3 axons that covered with an insulating sheath that speeds transmission and ameliorates the effects of noise and the potential for crosstalk.

Numbers Every Neuroscientist Ought to Know

- Average number of neurons in the brain = 100 billion (10^{11})
- Diameter of neuron = 4–100 μm (micron) [granule, motor]
- Ratio grey to white matter = [1.3, 1.1, 1.5] by age [20, 50, 100]
- Percentage of oxygen consumption by white matter = 6%
- Percentage of oxygen consumption by gray matter = 94%
- Number of neocortical neurons 20 billion (10^{10})
- Average loss of neocortical neurons = 100,000 per day (10^{5})
- Number of synapses in cortex = 0.1 quadrillion (10^{14})
- Number of cortical layers = 6
- Thickness of cerebral cortex = 1.5–4.5 mm
- Total surface area of the cerebral cortex = 2,500 cm^2

The number of neurons is perhaps less important than the number of active connections or synapses. Scott McNealy at SUN Microsystems was fond of saying “It’s the network stupid”, and his statement applies to computing in the brain as well as computing networks that characterize modern cloud computing architectures. There are something on the order of 1000 trillion synapses in a human brain and the molecular machinery operating at these connections is similarly complex.

Numbers Every Neuroscientist Ought to Know

- Number of synapses for a "typical" neuron = 1,000 to 10,000
- Single sodium pump transport rate = 200/100 Na/K ions/sec
- Number of sodium pumps = 1000 per μm^2 of membrane
- Total number of sodium pumps for a small neuron = 1 million
- Voltage-gated sodium channels at each node = 1,000 per μm^2
- Voltage-gated sodium channels between nodes = 25 per μm^2
- Sodium channels in unmyelinated axon = 100 per μm^2
- Membrane surface area of a "typical" neuron = 250,000 μm^2
- Area of 100 billion neurons = 25,000 m^2 (four soccer fields)
- Neurotransmitter molecules in one synaptic vesicle = 5,000
- Action potential [1, 10, 100] m/sec by diameter [0.1, 1, 10] μm