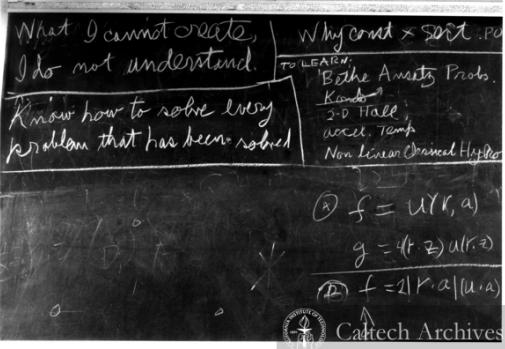
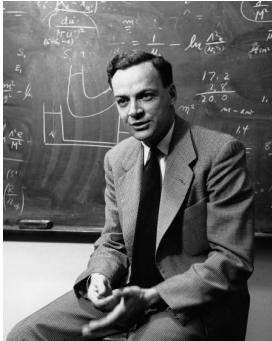


Realising a DREAM

"What I cannot **create**, I do not **understand**"

Richard Feynman



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The study of the BRAIN

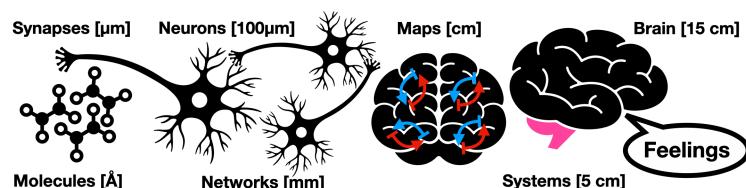


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The study of the BRAIN

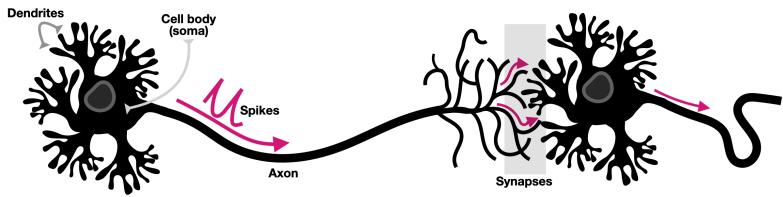
Level of abstraction in conceptualizing
and modelling the brain



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The computational building blocks of the brain



Main thesis - the neuron doctrine:

- The **soma** (site of signals integration), **dendrites** (synapses from source neurons) and **axon** (output pathway on target neurons)
- Neurons and synapses can be described by relatively compact, functional, phenomenological **mathematical models**.
- Neuronal communication can be summarized in binary, asynchronous messages (**spikes**).

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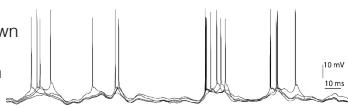
Neuro-physiology

- Spikes encode information. It is not clear how.
- Prominent view: information is encoded in terms of firing rate. Some information is encoded with timing



Cognitive Computing Hypothesis

- Spikes are the universal currency of neuronal communication
- A simulated network that reproduces the brain's temporal pattern of spiking constitute a sufficient simulation of neural computation.
- Are spikes the correct level of abstraction?
- Should we go up to higher level? or maybe down to the detailed dynamics of dendritic compartments, ion concentrations, and protein conformations?



Emergent Behaviour

a property of the whole not found in any of the parts



© Robert Wolstenholme/ Solent

Motivation

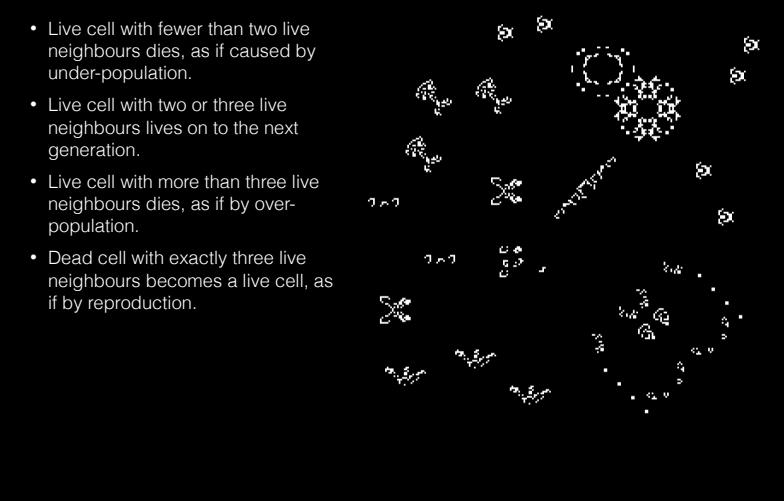
The **behavior** of the brain apparently **emerges** via **non-random**, correlated **interactions** between individual functional units - **the neurons**: a key characteristic of **organized complexity**.

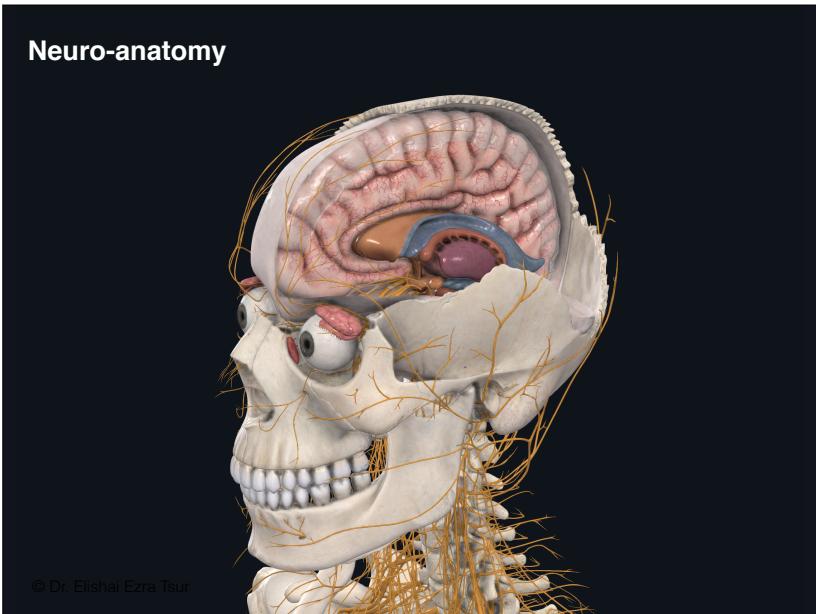


Emergent Behaviour

Simple rules - complex behaviour

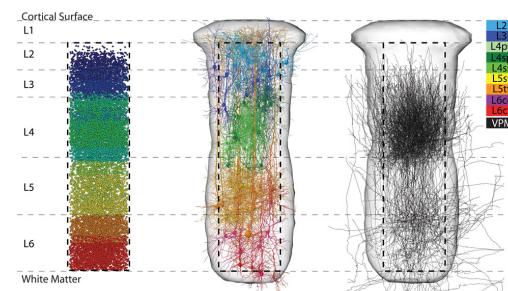
- Live cell with fewer than two live neighbours dies, as if caused by under-population.
- Live cell with two or three live neighbours lives on to the next generation.
- Live cell with more than three live neighbours dies, as if by over-population.
- Dead cell with exactly three live neighbours becomes a live cell, as if by reproduction.





Neuro-anatomy

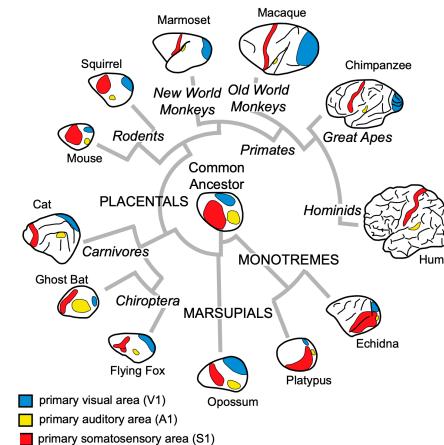
- 10's billions of neurons, 10's trillions of synapse, sparse connectivity
- The **cerebral cortex**: sheet (millimetres) of tissue at the brain's surface
- Cortex is organized horizontally in **layers** (6) and vertically in **columns** (millions, 100's microns in diameter). Limited lateral spread. Intra-laminar activity propagation.
- **Cerebral columns** have neurons with related characteristics, suggesting that columns are functional-structural entities.
- Columns are connected to create network of **cortical areas** (millimetres), which have high functions.



© Dr. Elishai Ezra Tsur

Neuro-anatomy

- The **cerebral cortex**: sheet (millimetres) of tissue at the brain's surface



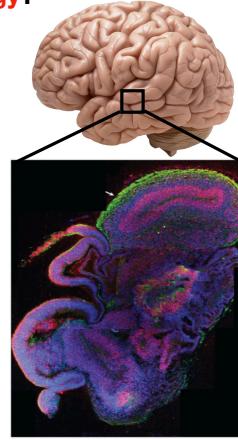
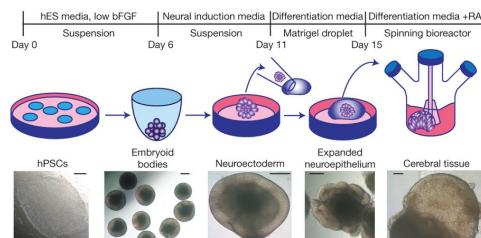
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Should we use biology?

Miniature human brains

A study shows that stem cells can be used to generate self-organizing three-dimensional tissues that mimic the developing human brain. These tissues provide a tool for modelling neurodevelopmental disorders. SEE ARTICLE p373



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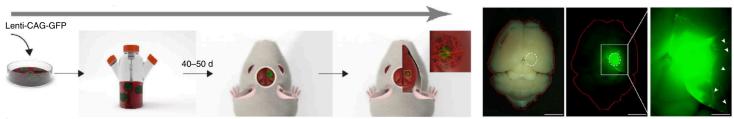


Should we use biology?

An *in vivo* model of functional and vascularized human brain organoids 

"To provide a vascularized and functional *in vivo* model of brain organoids, we established a method for **transplanting human brain organoids into the adult mouse brain...**

Organoid grafts showed growth of axons to multiple regions of the host brain.. revealed intragraft neuronal activity and suggested **graft-to-host functional synaptic connectivity**"



Mansur et al. Nature Biotechnology 2018

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OXFORD ACADEMIC
NSR National Science Review

Transgenic rhesus monkeys carrying the human MCPH1 gene copies show human-like neoteny of brain development 

Lei Shi, Xin Luo, Jin Jiang, Yongchang Chen, Cirong Liu, Ting Hu, Min Li, Qiang Lin, Yanjiao Li, Jun Huang ... [Show more](#)

National Science Review, nwz043, <https://doi.org/10.1093/nsr/nwz043>

Published: 27 March 2019

Brain size and cognitive skills are the most dramatically changed traits in **humans during evolution...** we successfully generated 11 transgenic rhesus monkeys carrying human copies of MCPH1, an **important gene for brain development**... indicated an **altered pattern of neural cell differentiation**, similar to the known evolutionary change of **developmental delay (neoteny) in humans...**

More importantly, the transgenic monkeys exhibited **better short-term memory** and **shorter reaction time** compared to the wild type controls.



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A Second DREAM

Ada Lovelace, 1815

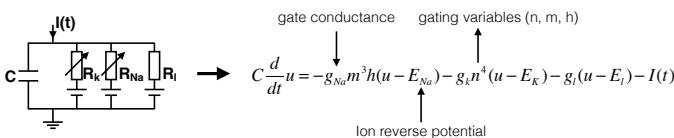
"I have my **hopes**, and very distinct ones too, of one day getting **cerebral phenomena** such that I can put them into **mathematical equations**--in short, a law or laws for the mutual actions of the molecules of brain. I hope to bequeath to the generations a **calculus of the nervous system.**"



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150 years later

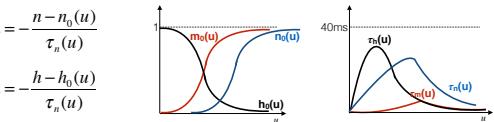
The Hodgkin-Huxley model



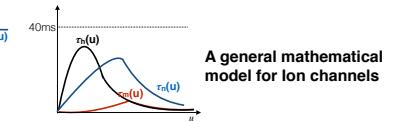
Gating variables:

$$\frac{d}{dt}m = -\frac{m - m_0(u)}{\tau_m(u)} \rightarrow m(t) = m_0(u_1) + [m_0(u_0) - m_0(u_1)] \exp\left[\frac{-(t - t_0)}{\tau_m(u_1)}\right]$$

$$\frac{d}{dt}n = -\frac{n - n_0(u)}{\tau_n(u)}$$

$$\frac{d}{dt}h = -\frac{h - h_0(u)}{\tau_h(u)}$$


A general mathematical model for ion channels



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The Nobel Prize in Physiology or Medicine 1963



Sir John Carew
Eccles
Prize share: 1/3



Alan Lloyd Hodgkin
Prize share: 1/3



Andrew Fielding
Huxley
Prize share: 1/3

The Nobel Prize in Physiology or Medicine 1963 was awarded jointly to Sir John Carew Eccles, Alan Lloyd Hodgkin and Andrew Fielding Huxley "for their discoveries concerning the ionic mechanisms involved in excitation and inhibition in the peripheral and central portions of the nerve cell membrane".

Neuro-simulations

Neuroanatomy and neurophysiology → structural and dynamical computational constraints

Aimed to **integrate** and **operationalize** a subset of these constraints into a single computational platform

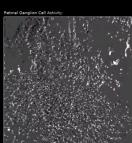
- Phenomenological model neurons exhibiting a vast behavioral repertoire
- Spiking communication
- Dynamic synaptic channels: plastic synapses, structural plasticity
- Multi-scale network architecture: layers, mini-columns, hyper-columns, cortical areas, and multi-area networks

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50 years later

digiCortex



16.7 Million Neurons, 4 Billion Synapses

Three primary resources of computing systems:



memory



computation



communication

The cat cerebral cortex: 10^9 neurons, 10^{13} synapses -1B/synapse: 6TB of main memory (near real-time simulation, current efficient synaptic data structures require 16B / synapse).

When a neuron fires, a spike message is sent to each of the synapses made by its axon. In most simulations, neurons are clock-driven and synapses are event-driven. For a cat scale, this amounts to a total of 10^{13} messages/second, assuming a 1 Hertz neuronal firing rate.

Neuron update every 1ms, resulting in 10^{12} updates/second

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Supercomputing simulations

Since the 1950s, research in cortical simulations has progressed along two paths: detail and scale.

Incorporating fine biophysical detail renders the task of near-real-time simulations at mammalian scale computationally impractical. Using compact phenomenological neurons, may not map to reality as well.

Current objective is to push the boundaries of the state of the art along the dimensions of model scale and neuroanatomical detail while achieving near-real-time simulation speed.



Level of abstraction in conceptualizing and modeling the brain

High levels of abstraction

The Cat is Out of the Bag: Cortical Simulations with 10^9 Neurons, 10^{13} Synapses

Rajagopal Ananthanarayanan¹, Steven K. Esser¹
Horst D. Simon², and Dharmendra S. Modha¹

¹IBM Almaden Research Center, 650 Harry Road, San Jose, CA 95120
²Lawrence Berkeley National Laboratory, One Cyclotron Road, Berkeley, CA 94720
[ananthr,esser]@us.ibm.com, hdsimon@lbl.gov, dmmodha@us.ibm.com

In the quest for cognitive computing, we have built a **massively parallel cortical simulator**, C2, that incorporates a number of innovations in computation, memory, and communication. Using C2 on LLNL's Dawn Blue Gene/P supercomputer with **147,456 CPUs** and **144 TB** of main memory, we report two cortical simulations – at unprecedented scale – that effectively saturate the entire memory capacity and refresh it at least every simulated second. The simulation consists of **1.6 billion neurons** and **8.87 trillion synapses** with experimentally-measured gray matter thalamocortical connectivity. We demonstrate nearly perfect weak scaling and attractive strong scaling. The simulations, which incorporate phenomenological spiking neurons, individual learning synapses, axonal delays, and dynamic synaptic channels, exceed the scale of the cat cortex, marking the dawn of a new era in the scale of cortical simulations.



Supercomputing simulations

A Blue Gene/P supercomputer at Argonne National Laboratory



- BG can reach operating speeds in the petaFLOPS (10^{15}) range (Floating point operations per second)



Neuroscience Expert Dr. Henry Markram on the IBM “Cat Brain” Simulation: “IBM’s claim is a HOAX”

Shortly after IBM announced their cat-scale brain simulation, [Henry Markram](#) of the [Blue Brain Project](#) published a very strong criticism of the claim. He called it "**a mega public relations stunt - a clear case of scientific deception of the public**". According to Markram these simulations do not come close to the complexity of an ant brain, let alone that of a cat brain.

Markram's first argument was that although the number of simulated neurons roughly equals that of a cat brain, the **model** used for each individual neuron was **trivially simple**. The neurons were modeled as single compartment "dots" completely lacking in biological realism. **Genuine simulation** of real neurons requires solving **millions of times more equations** than were used by IBM. Thus, **not even a millionth of a cat brain was simulated**.



Creativity Emerges from Spontaneous Neural Activity

Life Sciences 22.10.2020

Resting-State Fluctuations Underlie Free and Creative Verbal Behaviors in the Human Brain

Rotem Broday-Dvir, Rafael Malach

Cerebral Cortex, bhaa221, <https://doi.org/10.1093/cercor/bhaa221>

Published: 16 September 2020 Article history ▾

Structured noise is the way our brain takes the familiar learned material and 'shakes it up' in a way that gives rise to new, original ideas



Reconstruction and Simulation of Neocortical Microcircuitry

Henry Markram,^{1,2,19,*} Eilif Muller,^{1,18} Srikanth Ramaswamy,^{1,19} Michael W. Reimann,^{1,19} Marwan Abdellah,¹ Carlos Aguado Sanchez,¹ Anastasia Alamaki,¹ Lidia Alonso-Nanclares,^{3,7} Nicolas Antille,¹ Selim Arsever,¹ Guy Audebert,¹ Gergely Bercsenyi,¹ Daniel Berninger,¹ Anna Bligert,¹ Nelly Boucsein,¹ Athanasios Chrysoulopoulos,¹ Giuseppe Chincarini,¹ Jean-Denis Courcoul,¹ Fabien Daloze,¹ Vincent Delattre,¹ Stéphane Drucker,^{1,20} Raphael Dumusc,¹ James Dynes,¹ Stefan Eilemann,¹ Eyal Gal,⁴ Michael Emiel Gevaert,¹ Jean-Pierre Ghobril,² Albert Gidon,³ Joe W. Graham,¹ Anirudh Gupta,¹ Valentijn Haenel,¹ Etay Hay,^{3,4} Thomas Heinis,^{1,16,17} Juan B. Hernando,⁸ Michael Hines,¹ Lida Kanari,¹ Daniel Keller,¹ John Kenyon,¹ Georges Khazen,¹ Yihwa Kim,¹ James G. King,¹ Zoltan Kisvarday,¹³ Pramod Kumbhar,¹ Sébastien Lasserre,^{1,15} Jean-Vincent Le Bé,¹ Bruno R.C. Magalhães,¹ Angel Merchán-Pérez,^{6,7} Julie Meystre,² Benjamin Roy Morrice,¹ Jeffrey Muller,¹ Alberto Muñoz-Céspedes,^{6,7} Shrujan Mundhadas,¹ Keerthan Mutturasa,¹ Daniela Naci,¹ Taylor H. Nelson,¹ Max Norden,¹ Aleksandr Ovcharenko,¹ Juan Pascual,¹ Luis Pedro Mordinio,¹ Peter Rajan,¹ Daniel Ricciardi,¹ Daniel Rodriguez-Ramos,¹ Juan Luis Riquelme,¹ Christian Rössert,¹ Konstantinos Strykakis,¹ Ying Shi,^{1,2} Julian C. Shillcock,¹ Gilad Silberberg,¹⁸ Ricardo Silva,¹ Farhan Taheed,^{1,16} Martin Telefont,¹ Maria Toledo-Rodríguez,^{1,4} Thomas Tränkle,¹ Werner Van Geit,¹ Jafet Villafanca Diaz,¹ Richard Walker,¹ Yun Wang,^{1,3,11} Stefano M. Zaninetta,¹ Javier DeFelipe,^{6,7,20} Sean L. Hill,^{1,20} Idan Segev,^{3,4,20} and Felix Schürmann^{1,20}

SUMMARY

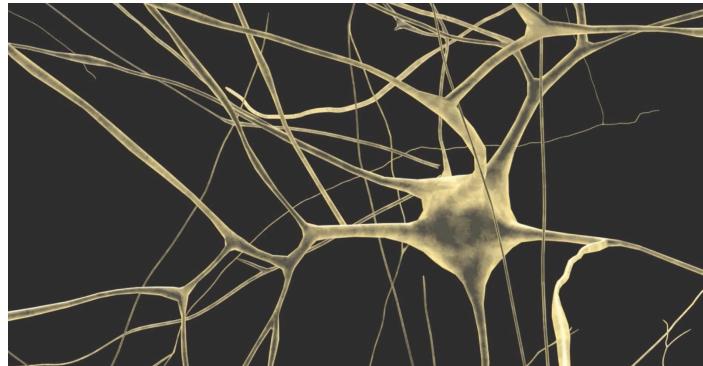
We present a first-draft digital reconstruction of the microcircuitry of somatosensory cortex of juvenile rat. The reconstruction uses cellular and synaptic organizing principles to algorithmically reconstruct detailed anatomy and physiology from sparse experimental data. An objective anatomical method defines a neocortical volume of $0.29 \pm 0.01 \text{ mm}^3$ containing $\sim 31,000$ neurons, and patch-clamp studies identify 55 layer-specific morphological and 207 morphoelectrical neuron subtypes. When digitally reconstructed neurons are positioned in the volume and synapse formation is restricted to biological bouton densities and numbers of synapses per connection,

their overlapping arbors form ~ 8 million connections with ~ 37 million synapses. Simulations reproduce an array of *in vitro* and *in vivo* experiments without parameter tuning. Additionally, we find a spectrum of network states with a sharp transition from synchronous to asynchronous activity, modulated by physiological mechanisms. The spectrum of network states, dynamically reconfigured around this transition, supports diverse information processing strategies.



The Blue Brain Project

- The blue-brain project: simulating a neocortical volume of 0.3 mm^3 containing 31,000 neurons on IBM's Blue Gene super computer
- Cellular level simulations



SCIENCE

The Human Brain Project Hasn't Lived Up to Its Promise

Ten years ago, a neuroscientist said that within a decade he could simulate a human brain. Spoiler: It didn't happen.

ED YONG JULY 22, 2019

Two years before, the European Union had awarded Markram \$1.3 billion to spend the next decade building a computerized human brain. But not long after, hundreds of EU scientists revolted against that initiative, the Human Brain Project. In the summer of 2015, they penned an open letter questioning the scientific value of the project and threatening to boycott unless it was reformed.

Moritz Helmstaedter, director of the Max Planck Institute for Brain Research, said at the time that the paper confirmed his worst suspicions about the project: "There are no real findings. Putting together lots and lots of data does not create new science." Blue Brain's utility to neuroscientists still remained far from clear.

