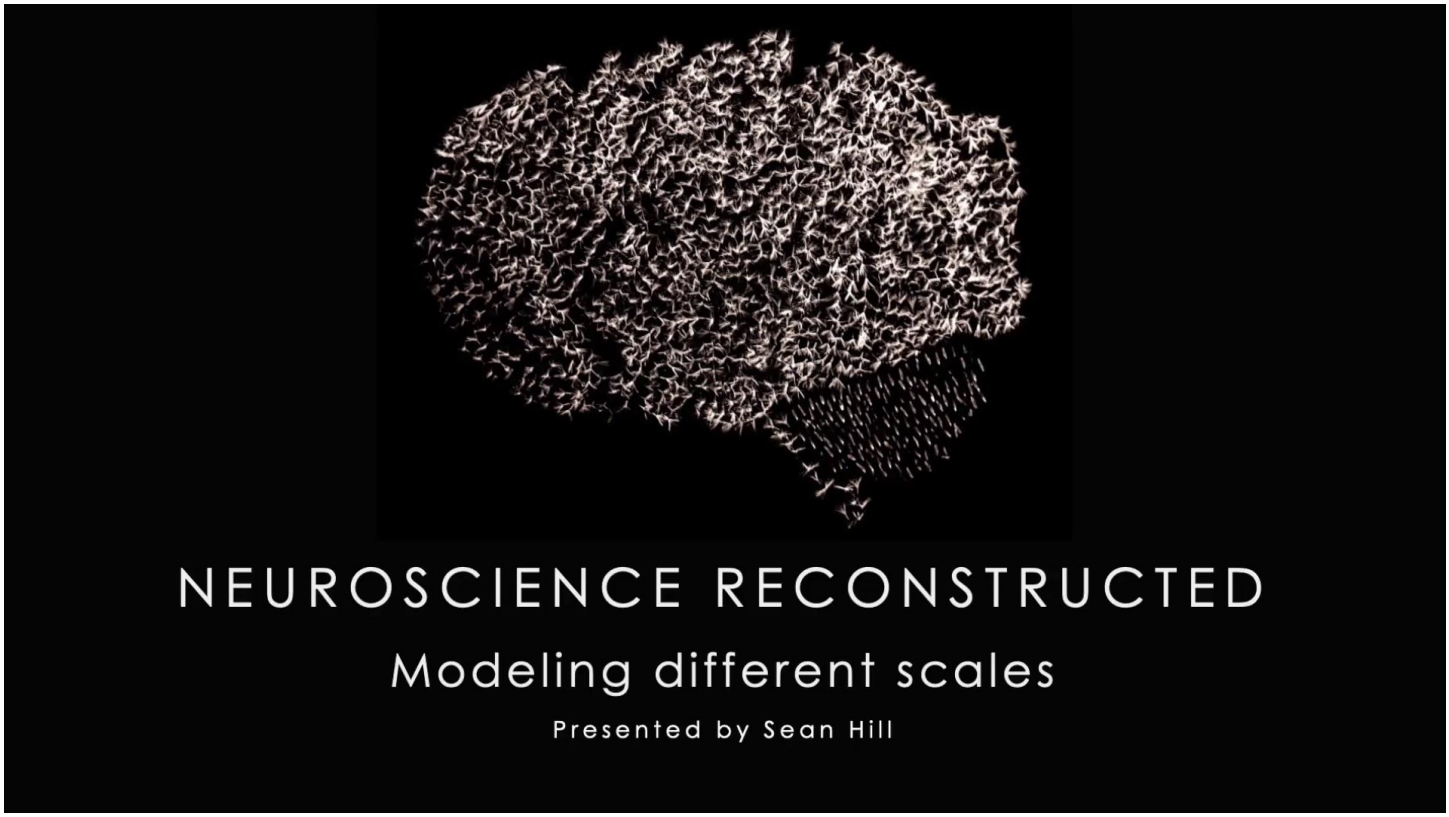

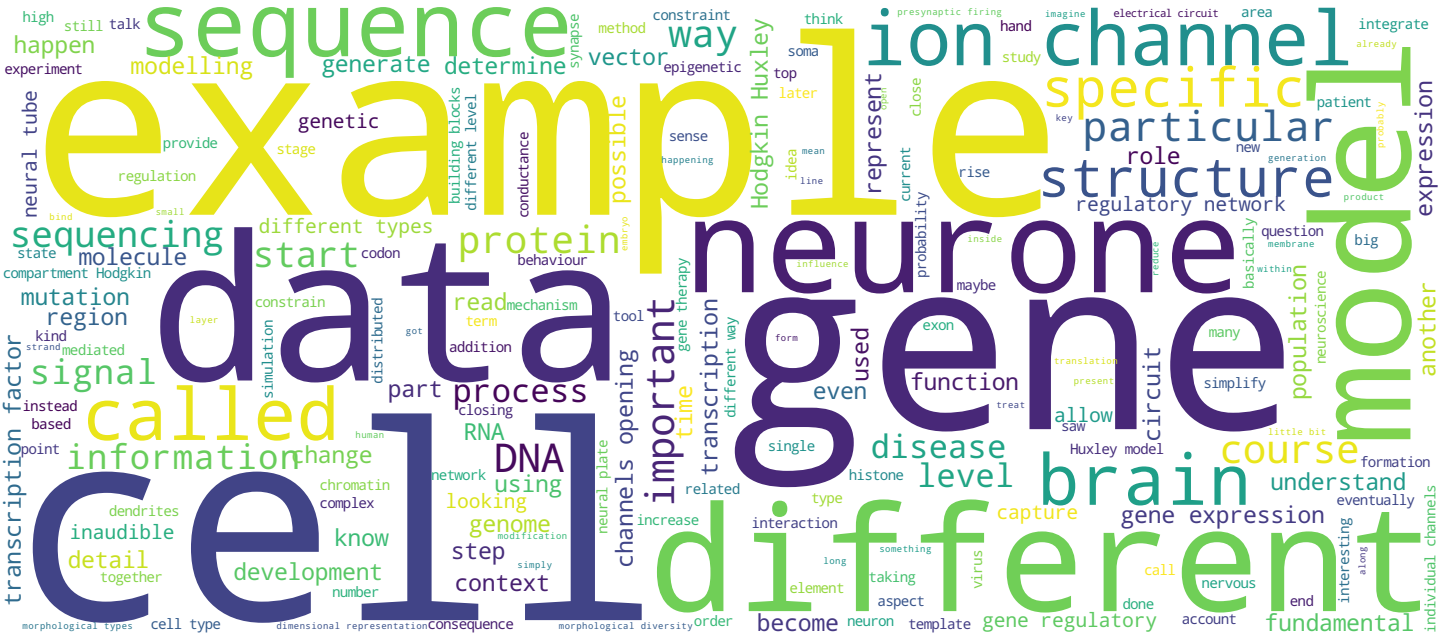

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EPFL

Modeling electrophysiology

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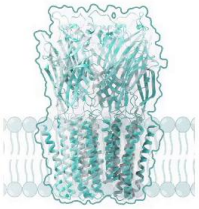
Models of **ion channels**:

- **Molecular models:** atom-scale modeling of ion channel structure
- **Hidden Markov models**: probabilistic models of the opening and closing of channels
- **Hodgkin-Huxley models**: differential equation models of the currents produced by populations of ion channels



At the subcellular level, thinking of models of single ion channels, there are also different ways of modelling those ion channels. For example, you could do molecular dynamic simulations, which take into account atom scale details of the ion channel structure. Of course, that takes a tremendous amount of computation and huge amount of simulation time to simulate microseconds. On the other hand, you can learn principles from the electrophysiological level about the behaviour, the probability of ion channels opening or closing, and build hidden Markov models. We're taking that even further where you look, instead of that individual channels and the probability of individual channels opening and closing, start looking at populations of ion channels opening and closing altogether. That becomes a Hodgkin-Huxley-level model where you're actually modelling the currents as the consequence of populations of ion channels opening and closing, and their dynamics.

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0m 05s

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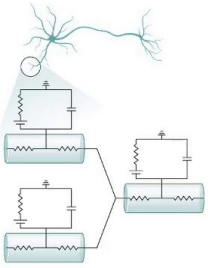
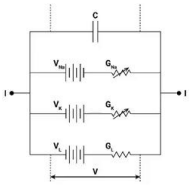
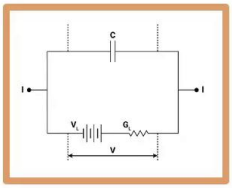
Models of **single neurons**:

- **Multiple compartment HH models:** take neuron morphology and distribution of ion channels into account across axons and dendrites
- **Single compartment HH models**: simplifies the neuron to a single sphere - all ion channels are at the soma.
- **Integrate-and-fire models**: simplified phenomenological model of a neuron – sum all input and fire (and reset membrane potential) if the threshold is reached.







When you get to the cellular level, similarly, you can choose different levels of detail. For example, the multiple compartment Hodgkin-Huxley models would start by looking at the full extent of the morphology of a neurone, including the dendrites, the axons, the soma, the axon initial segment, for example, modelling the distribution of ion channels across those neurites, and working to see, well, what data can you use to constrain those models? On the other hand, you may want computationally simplified neurone models or just to simply represent the firing of neurones, in which case you may simplify those models to more reduced representations. For example, the single compartment Hodgkin-Huxley model simplifies the neurones to a single sphere with all ion channels uniformly distributed over that sphere. Or you can simply say, "Look, we don't want to know the details of all of the ion channels. Let's simply create a phenomenological model of a neurone, an integrate and fire model, which really represents the behaviour of a neurone." Much more simply saying, you sum up all of the synaptic input. If you hit a threshold, you fire, you reset the membrane potential and go on.

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1m 20s

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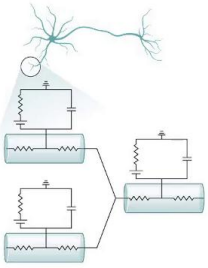

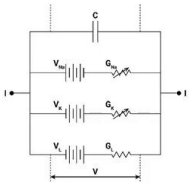

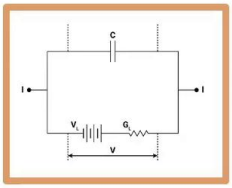

That's another option for a much more reduced model. All of it, again, depends on what question do you want to answer. If you want to understand the role of ion channels in the dendrites, you're probably going to want to model a multi-compartment Hodgkin-Huxley neurone. Otherwise, more reduced formulations may suffice.

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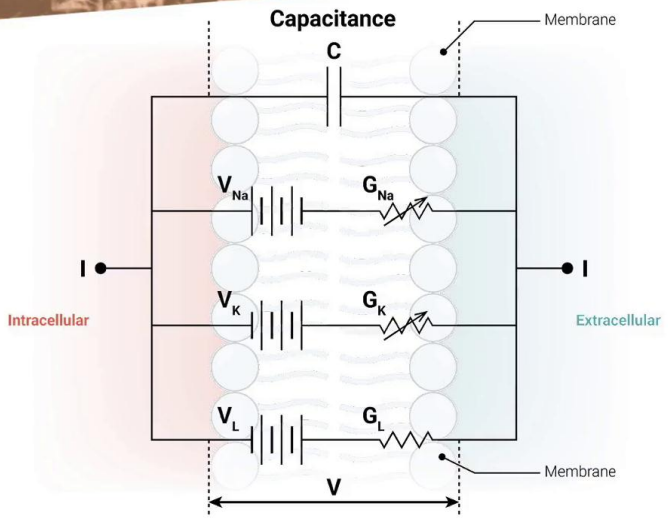
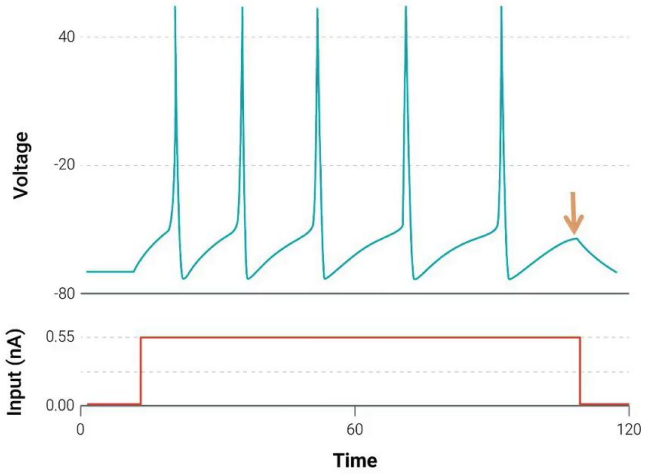
2m 49s

Example: HH model





$$I = C_M \frac{dV}{dt} + \bar{g}_K n^4 (V - V_K)$$

$$+ \bar{g}_{Na} m^3 h (V - V_{Na}) + \bar{g}_l (V - V_l)$$

In the context of the Hodgkin-Huxley model, really what's happening is you're representing each of these populations of ions and their conductance through the ion channels in a formulation very much along the lines of an electrical circuit. In this case, the cell's membrane capacitance and the current flowing through that membrane. The current, these variable resistors, the rate at which they open and close, or those resistances, those conductances actually increase or decrease, are determined by the parameters in the equation. This gives us a way of modelling the voltage changes between the inside of the cell and the outside of the cell, the intracellular space and the extracellular space across the membrane, which is mediated, for example, by sodium conductances, by potassium conductances, and by leak conductances, and by that potential, that transmembrane potential that's mediated in this electrical circuit. When you inject a current into this cell, what you see is that the voltage actually undergoes an excursion up to the firing threshold, which triggers the sodium current, creates depolarisation, the potassium kicks in and hyperpolarises the cell until the whole cell renormalises at the resting potential, or if the current continues, it persists and repeatedly fires until the stimulus is stopped.

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3m 14s

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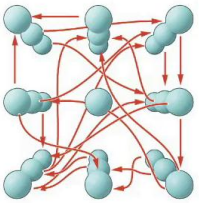
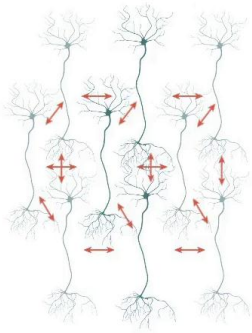
Models of **microcircuits** (networks of neurons):

- **Types of neurons**: different types of neurons
- **Details of neuron models**: HH to IF neurons
- **Morphology**: Number of compartments, spatial coordinates
- **Spatial dimensions**: 1-, 2- or 3-dimensional
- **Types of connections**: different types or strength of synapses





In modelling electrophysiology, again, and looking at microcircuit levels, make a lot of choices about what is it you want to represent in the model? What are the different types of neurones? What are the details of the neurones that are important to capture? Do you need to represent morphology, the shape of the neurones? Are you modelling this true to the three-dimensional space, or is it sufficient to simplify this to a one- or two-dimensional representation of space? And that's, of course, intertwined with the question of how are you modelling connectivity. Are you taking into account the different types of synapses? Are they placed in three dimensions? Where are they connecting? Is it just to the soma or is it to dendrites, for example? In the end, all of this is about, well, what kind of constraints from the biology do you actually want to take into account, or which are you going to simplify and reduce in order to capture them in a model?

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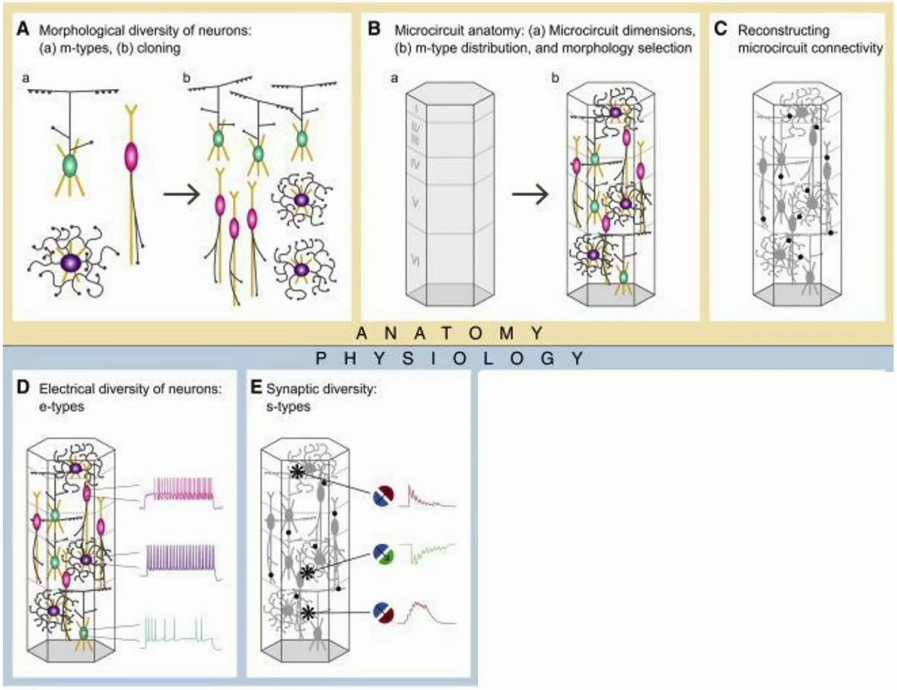
5m 04s

Example: microcircuit



Markram H. et al. Reconstruction and Simulation of Neocortical Microcircuitry. *Cell. 2015 Oct 8;163(2):456-92.* doi: 10.1016/j.cell.2015.09.029.

In the context of the Blue Brain's Reconstruction and Simulation of a Neocortical Microcircuit, there's a very specific workflow defined that starts from the anatomy and the structure of the circuit. First of all, identifying the building blocks of the circuit. What are the morphological diversity of neurones? What are these M-types or morphological types? Assembling that collection of the building blocks, you then determine the microcircuit dimensions, where those morphological types are distributed, and how much of them are distributed in which aspects of the microcircuit. Using that, putting together all of those constraints, you get a biophysical three-dimensional representation of the structure of a circuit. Then you've got to layer in the electrical properties. Again, in addition to the morphological diversity, there's an electrical diversity of the neurones, different firing types, different ways in which these neurones respond to inputs and present either an adapting response, a continuous firing response, or maybe an irregular response, and as well as a synaptic diversity of how these neurones communicate with each other. Some synapses actually depress very rapidly.

Notes

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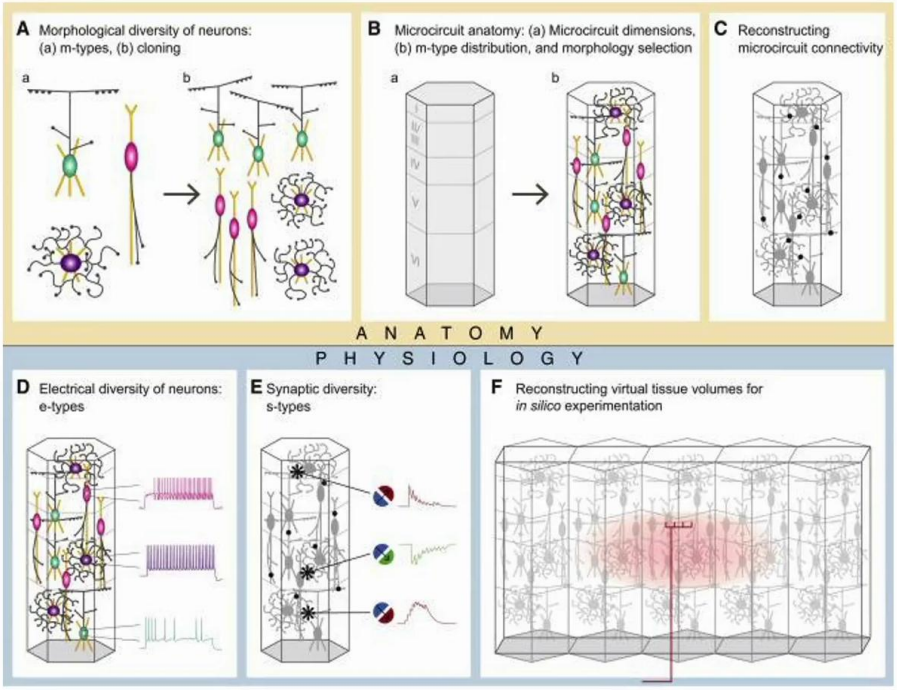
6m 08s

Example: microcircuit



Markram H. et al. Reconstruction and Simulation of Neocortical Microcircuitry. *Cell. 2015 Oct 8;163(2):456-92.* doi: 10.1016/j.cell.2015.09.029.

They weaken with presynaptic firing. Some facilitate or increase their strength with presynaptic firing, and some remain more or less linear, pseudo linear responses. Understanding and layering in those constraints creates another physiological level to the model. Putting all of that together, you can reconstruct virtual tissue volumes with which you can then experiment and complete something we call in silico experimentation, where you treat this as a virtual slice, a virtual brain slice to simulate virtual experiments.

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7m 31s

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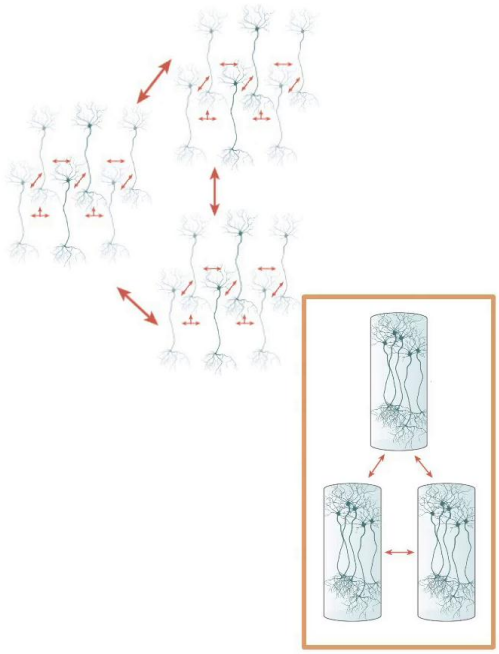
Models of **regions and areas**:

- **Networks of spiking neurons networks:** signals propagating through more or less simplified interconnected neurons; 1-, 2- or 3-dimensional
- **Mean field models**: average activity of neuron populations in a given volume



Modelling regions and brain areas, again, the same sorts of choices come into play. What are some of the simplifications that can be feasibly done? Do you have enough data to constrain? And of course, if you have the computational power, you can represent the full biological detail, or you may choose for some portions of the circuit to simplify that and create a coarse-grained model that represents populations of neurones in a much more simplified way, either as these integrate and fire type of neurones or something called mean field models, where the average activity of a neurone population is actually modelled as a single unit. Again, through differential equations that capture the dynamics of that population given the input presented.

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8m 13s