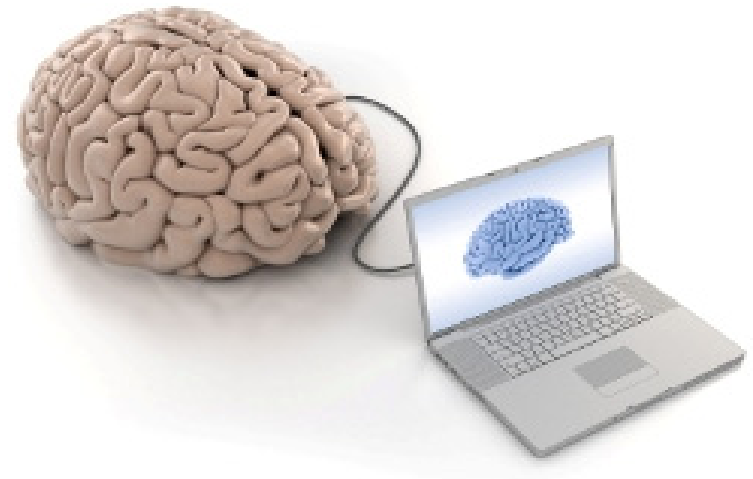

Computational Neuroscience

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COSC422 – lecture 1

Outline

- Brief history of Computational Neuroscience, i.e. computational modelling of biological neurons
- Blue Brain project
- My projects
- Basic concepts of computational modelling
 - Steps in constructing a model
 - Assumptions, variables, parameters, equations
 - Example: unlimited growth



Names of parts of a neuron

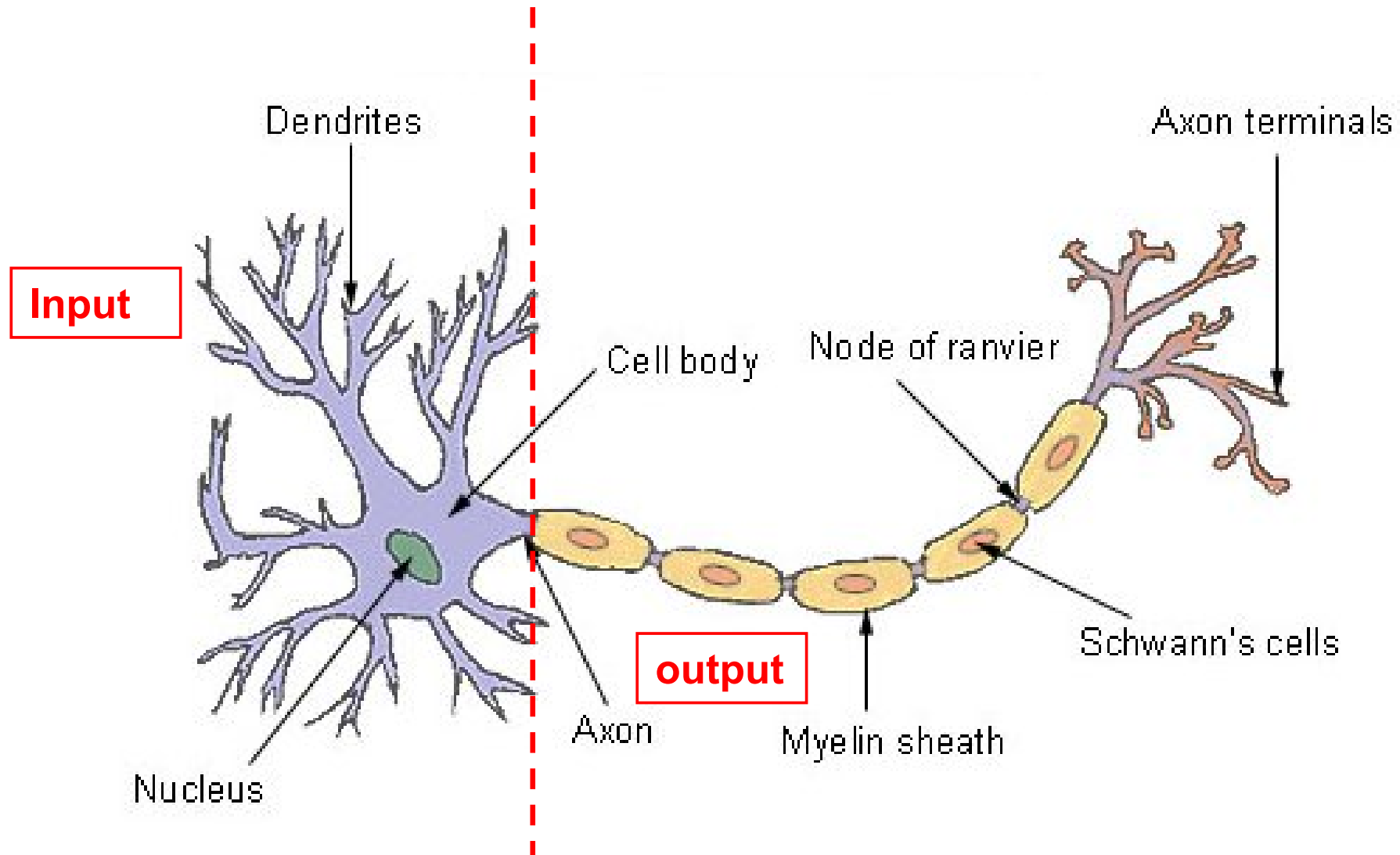
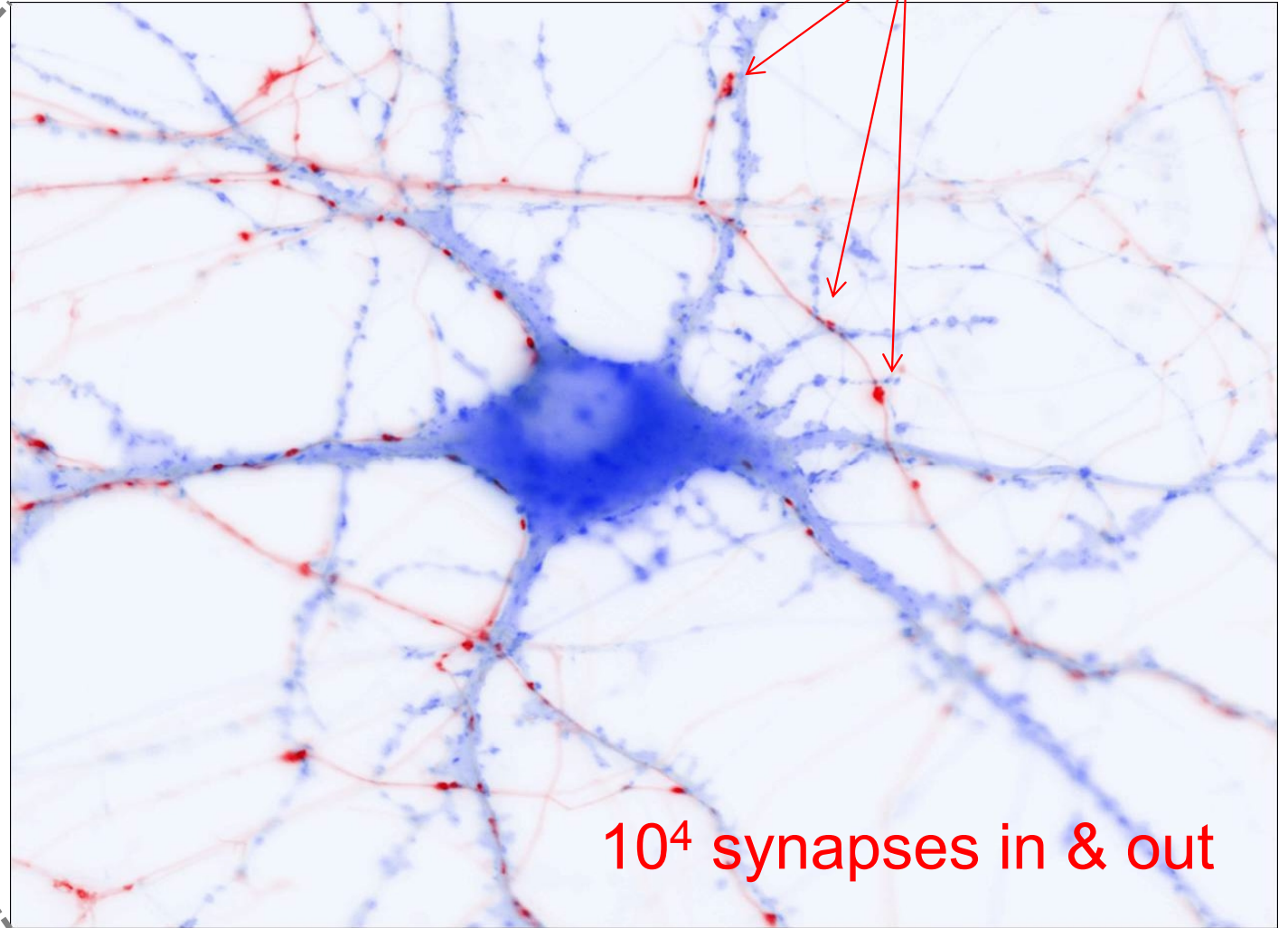


Image source: <http://www.daviddarling.info/encyclopedia/N/neuron.html>

Brain is comprised of networks of neurons
connected and communicating via synapses



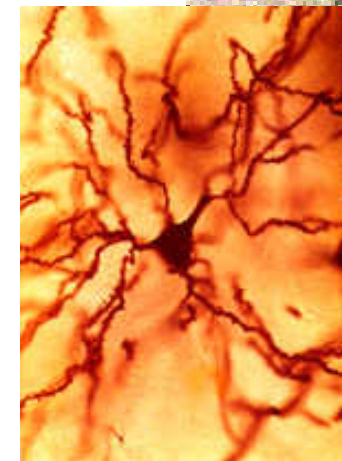
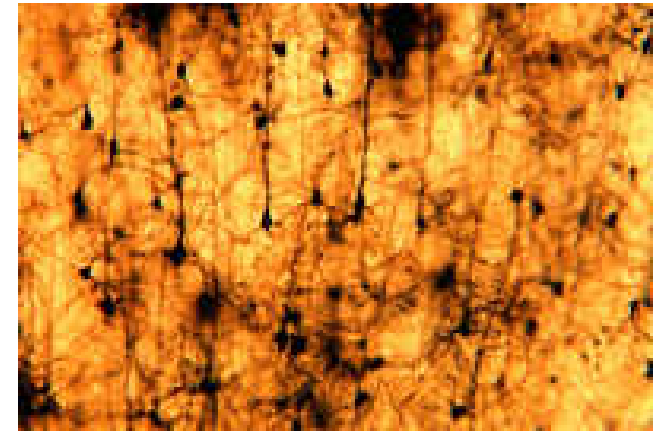
10^{12} neurons



10^4 synapses in & out

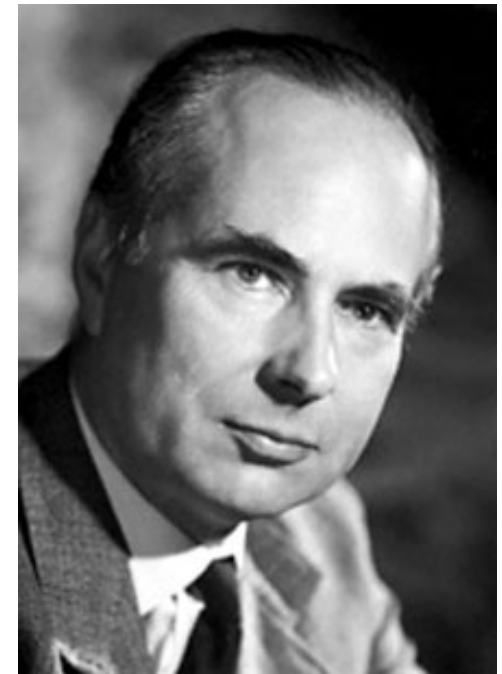
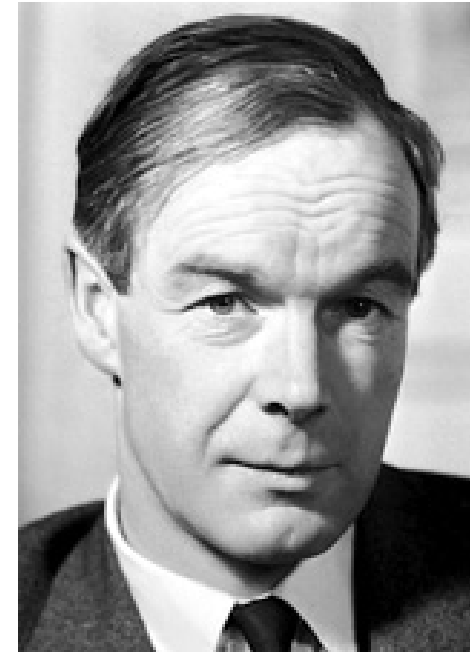
Neurons

- The information processing and communicating elements of the brain are called **neurons** (nerve cells)
- They relay information from the outside world to the brain, and from the brain to the outside world (via muscles)
- They do the computations inside the brain that we call “thought”
- These computations are based on electrical pulses called action potentials.



Hodgkin and Huxley

- In 1963, Brits Allan Hodgkin & Andrew Huxley received the Nobel prize in Physiology and Medicine for their work on axon potentials. (The 3rd laureate was Sir John Eccles for work on synapses.)
- H&H developed an action potential theory representing one of the earliest applications of a technique of electrophysiology, known as the "voltage clamp".
- Another critical element was the use of the giant axon of Atlantic squid, which enabled them to record ionic currents using the techniques of the time.



Hodgkin-Huxley model

- Besides measuring membrane currents and voltages in the axon they also developed the first mathematical model of axon potential generation.
- This is historically the first model of biological neurons explaining the ionic mechanisms underlying the initiation and propagation of action potentials in the squid giant axon (1952).
- The Hodgkin–Huxley model applies to all axons and is still used today:

$$i_m = g_{Na} m^3 h (V - E_{Na}) + g_K n^4 (V - E_K) + g_L (V - E_L)$$

Sir John Eccles (3rd Nobel Prize winner with HH)

- Australian neurophysiologist Sir John Eccles, became a Professor at **University of Otago** during 1944-1951, then he went back to Australia.
- He is known for his pioneering work in neuroscience, especially the synaptic transmission and nature of reflexes.
- He was never able to find a satisfactory explanation for the interaction of mind and body and was an open proponent of dualistic theistic philosophy.



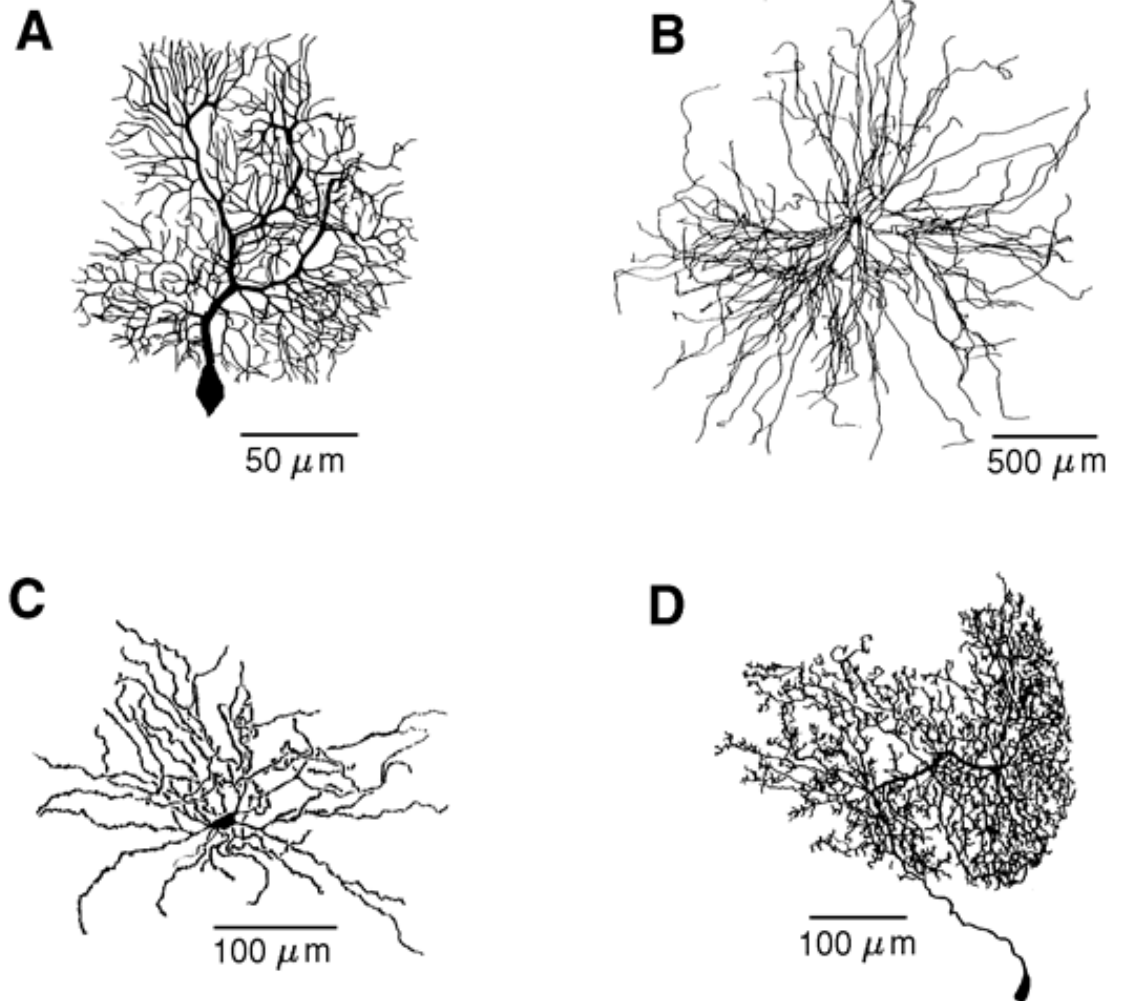
Wilfrid Rall

- He is considered one of the founders of computational neuroscience.
- After WWII, he moved to the **University of Otago** to work with Sir John Eccles for his PhD, and remained here until 1954, then went back to U.S.
- Rall originated the use of cable theory in neuroscience, and developed passive and active compartmental models of the neuron dendritic tree.



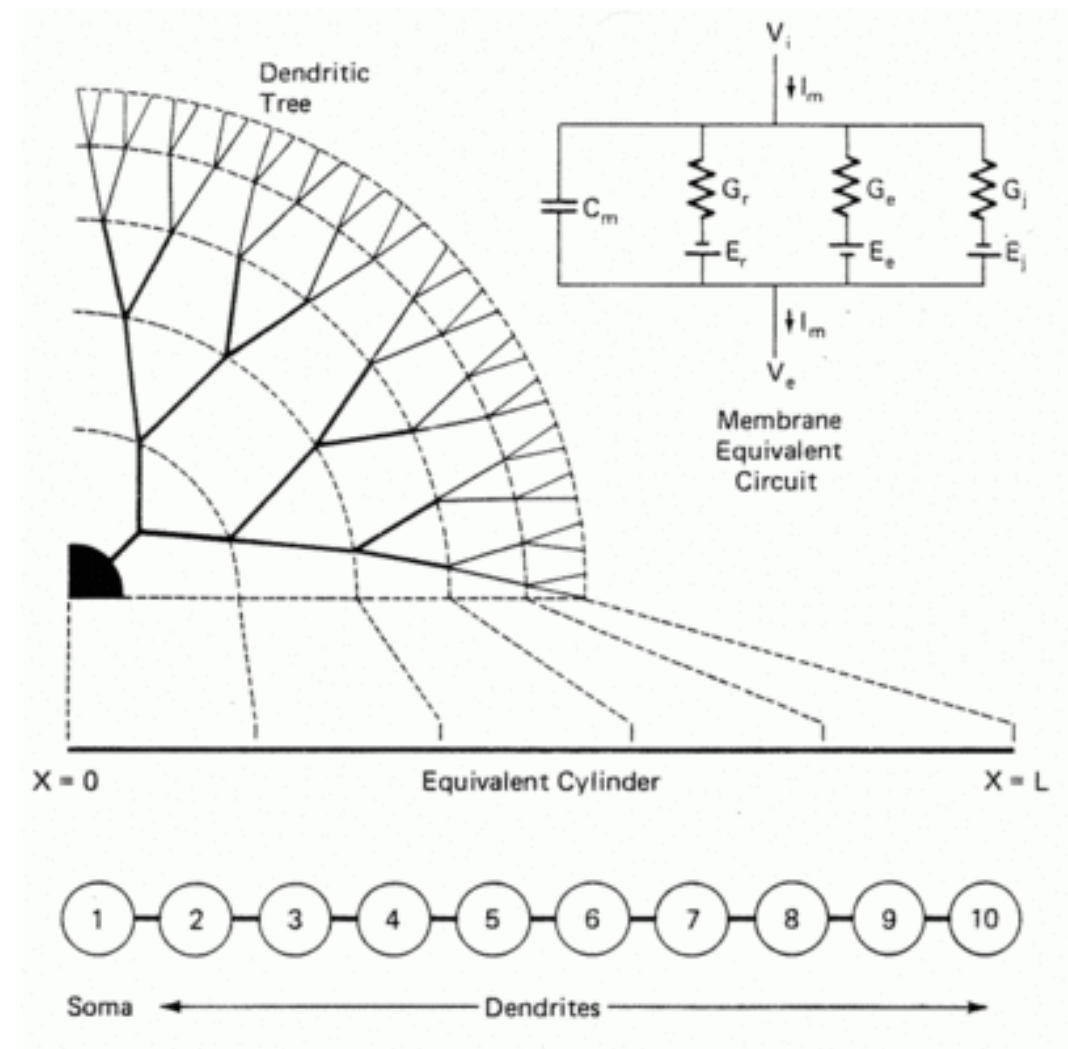
Dendritic trees and postsynaptic potentials (PSP)

- Extensively branched dendritic trees are neurons' major input area for incoming signals.
- The distribution of membrane potential along each and every branch and the final total PSP at the soma are complex functions of spatio-temporal summation of individual synaptic EPSPs and IPSPs and the geometry of the tree.



Rall's model

- Is a simplified biophysical model of a dendritic tree.
- Rall mathematically showed that the tree can be mapped to an equivalent single electric cable.
- It was possible to obtain analytical solutions to many of interesting problems.



Next developments (1980-present)

- Scientists like Christoph Koch, Tommaso Poggio, Idan Segev, and many others developed theories of dendritic trees taking into account their full complexity.
- Current status: scientists use specialized software to simulate neurons.



Simulation environment NEURON

- A free open source software developed at Duke and Yale by Michael Hines and Ted Carnevale available at <http://www.neuron.yale.edu/neuron/neuron>
- Used world-wide to build and simulate neurons with realistic dendritic trees and biological networks of hundreds of neurons. 900 scientific publications reported work that was done with NEURON.
- NEURON is actively developed and supported, with new standard releases each year, supplemented by bug fixes as needed. Available for a number of operating systems (i.e., Linux, Windows, MacOS, etc).
- ModelDB website provides a free location for storing and retrieving computational neuroscience models for sharing.

Simulation environment GENESIS

- GENESIS (the GEneral NEural SIMulation System) is freely available at <http://www.genesis-sim.org/GENESIS/>
- GENESIS was originally developed in the laboratory of Dr. James M. Bower at Caltech.
- GENESIS was the first broad scale modeling system in computational biology and is based on Unix.
- But wasn't open source so it lost the race with NEURON.
- Now it's open source too.

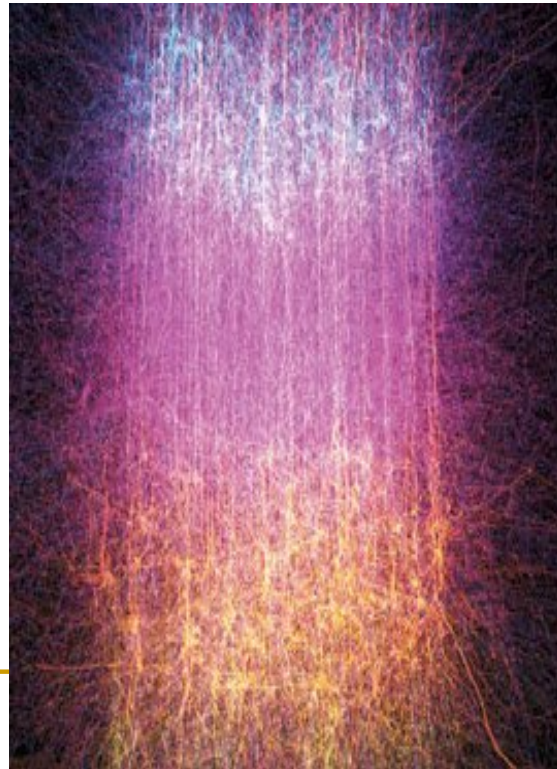
The Blue Brain project



- <http://bluebrain.epfl.ch/> or video:
 - 15 min: www.youtube.com/watch?v=LS3wMC2BpxU&feature=related
- The aim: to study the brain by means of computational models.
- Founded in 2005 by Prof. Henry Markram, Director of the Brain and Mind Institute of the EPFL, Switzerland.
- Using the IBM Blue Gene supercomputer and **NEURON software**, the simulation involves biologically realistic models of neurons and circuits.
- Funding: Swiss and European grants and private individuals.

The Blue Brain project

- From the data from 15,000 experiments in rat somatosensory cortex they have constructed a model of a neocortical column, which
 - ❑ consists of 10,000 3D digitizations of real neurons
 - ❑ populated with models of dozens of ion channels
 - ❑ of over 200 different types of neurons.



The Blue Brain project: future goals

- First, extension to the subcellular domain, which will integrate additional biological detail into the existing neocortical column model.
 - Incorporating the molecular structures, processes and effects is an important step towards pharmacological, genetic and medical research “in silico”. (Silicon is used in microchips.)
- Second, the facility will be extended to model larger portions of cortex and other brain structures.
- Ultimately, given additional resources, the facility will be extended to permit whole brain modeling, simulation and experimentation.

My research projects

- Investigation of rules governing synaptic plasticity with Prof. Cliff Abraham from Department of Psychology, Dr. Peter Jedlička (read Yedlichka) from J.W.Goethe University, Germany, Prof. Jörg Fraundiener from Math & Stats Dept. (PhD student Azam Shirrafi).
- Research on gene regulatory networks involved in synaptic plasticity with Dr. Joanna Williams from Dept. of Anatomy & Structural Biology (PhD student Gonzalo Nido).
- Functional networks of the brain with A/Prof. Liz Franz from the Department of Psychology (PhD student Paul McCarthy).

Computational modelling

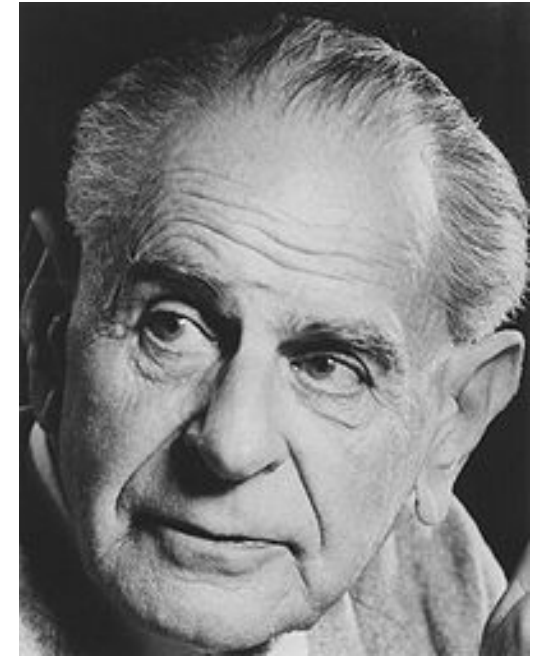
- Turning the rules that govern the change of some quantity over time into a MATHEMATICAL equation is called modelling.
- Our goal is to use this equation to predict the future value of the quantity being modelled.
- Modelling is about understanding the rules that govern the changes that occur to some quantity.
- Equations can be solved analytically (using a pencil) or numerically (using a computer). The latter refers to **computational modelling**.

The third methodology of science

- Computational modelling has become the third methodology of science along with theory and experiment:
 - <http://access.ncsa.illinois.edu/Briefs/98Briefs/981102.Nobel-Chem.html>
- Theory is the way to interpret the results of experiments, the way to analyze experiments and to design new experiments.
- Without experiments there is no point in theorizing--theory becomes speculation. Theory is corroborated or falsified by experiments.
- Computational approach provides a third way, allowing more elaborate tests of theory than would be possible by experiment, thus enabling new ways to refine the theory. It also allows a much more sophisticated analysis of experiment than theory alone could provide.

Karl Popper

- Popper, one of the greatest philosophers of science of the 20th century (empirical falsification).
 - Scientific theory is such theory that can be falsified by experiment or observation.
- Was with the Canterbury University College New Zealand (at Christchurch) in 1938-1946.
- Computational models have the faith of theories, i.e. single real experiment can falsify them, and even countless agreeing experimental data can only corroborate them.



Mathematical model: comparison with data

- Once we develop a mathematical model, we have to compare predictions of the model with data from the system.
- If the model prediction and the data agree, then we can gain confidence the assumptions we have made in creating the model are reasonable, and that we can use the model to make further predictions.
- If the model prediction and the data disagree, then we must study and improve our assumptions and re-formulate the model.
- In either case we learn more about the modelled system.

Basic steps in creating the model

- **Step 1:** Clearly state the assumptions on which the model will be based. These assumptions should describe the relationship among the quantities to be studied.
- **Step 2:** Completely describe the quantities, i.e. variables and parameters to be studied in the model.
- **Step 3:** Use the assumptions formulated in Step 1 to derive equations relating the quantities in Step 2.
- **Step 4:** use mathematical knowledge or computer program to solve the equations and make predictions about the evolution of studied quantities in the future.

Step 1: assumptions

- Assumptions should describe what we think about relationships between variables we want to model.
 - E.g., there are 2 types of inputs to each neuron: excitatory and inhibitory.
- The quality of assumptions determines the validity of the model and the situations to which the model is relevant.
- We must avoid “hidden assumptions” that make the model seem mysterious or magical.
 - i.e., we include something in the equation that makes it work but corresponds to nothing in reality.

Step 2: defining the quantities

- **Independent variables**
 - The independent variable is almost always time (t). Time t is independent of any other quantity in the model.
- **Dependent variables** are the quantities that are functions of the independent variable.
 - For example, membrane voltage changes over time, $V = V(t)$, i.e. we say voltage is a function of time.
- **Parameters** are quantities that do not change with time (independent variable), but their value has a profound influence on the behaviour of the dependent variable as a function of time.

Variables and parameters

- The goal of a model is to describe the behaviour of the dependent variable as the independent variable changes.
 - For example we may ask whether the dependent variable (e.g. voltage) increases or decreases with time, or whether it oscillates or tends to a limit.
- Observing how the behaviour of the dependent variable changes when we change the values of parameters can be the most important aspect of the study of a model.
 - For example, we may ask how the voltage evolves when the strength of excitatory inputs is the same as the strength of inhibitory inputs or how voltage will evolve when these strengths differ, while the strengths of excitatory and inhibitory inputs are the parameters of the model.

Step3: the most difficult part

- The hardest part in using the maths to study phenomena is the translation from real life into mathematical formalism.
- It is difficult because it involves
 - knowledge of maths;
 - the conversion of imprecise assumptions into precise formulas (i.e. mathematical equations).



August Rodin: The thinker

Equations, i.e. something = something

- We know that the dependent variable changes over time. Thus we are looking for a “rate of change of ...” or “rate of increase of ...” dependent variable over time.
- Mathematically, the rate of increase of something corresponds to the thing called “derivative”, being written as:

$$\frac{dV}{dt}$$

- Where that “something” is for example membrane voltage, V .
- In other words, the rate of change is synonymous with derivative.

Equation, i.e. derivative = something

- We want to express what is the rate of change, i.e. what the derivative amounts to. That is, we want to know what is the “something” in the following equation:

$$\frac{dV}{dt} = \text{something}$$

- The phrase “ A is proportional to B ” means $A = k B$, where k is the so-called proportionality constant. So, to be mathematically correct we have to write the above equation as

$$\frac{dV}{dt} = k \text{ something}$$

- i.e. the rate of change of voltage is proportional to something. Proportionality constant k is often a parameter of the model.

Equation, i.e. derivative = k something

- The equation: $\frac{d(\text{dependent variable})}{dt} = k \text{ something}$
- is at the core of all models in computational neuroscience.
- Dependent variable can be anything from voltage, current, field potential to number of synapses or concentration of neurotransmitter.
- The biggest challenge is to come up with “something”...

Concrete example: population growth

- We can develop and study mathematical models of systems that change (evolve) over time, for instance the number of rabbits.
- Except time itself, the changes depend on other variables as well.
- For example, the evolution of population of rabbits in Central Otago depends on the amount of food they can access, number of hunters, number of hawks, amount of poison, rabbit diseases, etc.
- In order to make a model of evolution of rabbit population simple enough to understand, we have to make simplifying assumptions and neglect the things we know nothing about or not enough.

Unlimited population growth

- Step 1: The assumption: the rate of growth of population depends only on the size of the population and nothing else. The more rabbits there are the more offspring they have.
- Step 2: definition of quantities:
 - t = time (independent variable)
 - P = population size (dependent variable), i.e. $P = P(t)$
 - k = proportionality constant (parameter)
- How about the units of these quantities? They obviously depend on species and environment. If we are talking about population of people then t would be years and P would be millions. If talking about rabbits, then t would be months and P thousands.

Mathematical equation for the growth

- Step 3: let's express our assumption as an equation. The rate of growth of the population is the derivative:

$$\frac{dP}{dt}$$

- Being proportional to the population size is expressed as a product of the proportionality constant k and the population size P , i.e. $k P$.
- Hence our assumption is expressed as the (differential) equation:

$$\frac{dP}{dt} = k P$$

- Read as: Derivative of P according to time t equals k times P .

Step 4: analytical solution

- If we know the size of population at time zero P_0 , the so-called initial condition, i.e.

$$P(t_0) = P_0 > 0$$

- and we want to predict the value of P at various times in the future, e.g. $P(10)$ or $P(100)$, then we need to figure out the shape of the function $P(t)$ that satisfies this equation:

$$\frac{dP}{dt} = k P$$

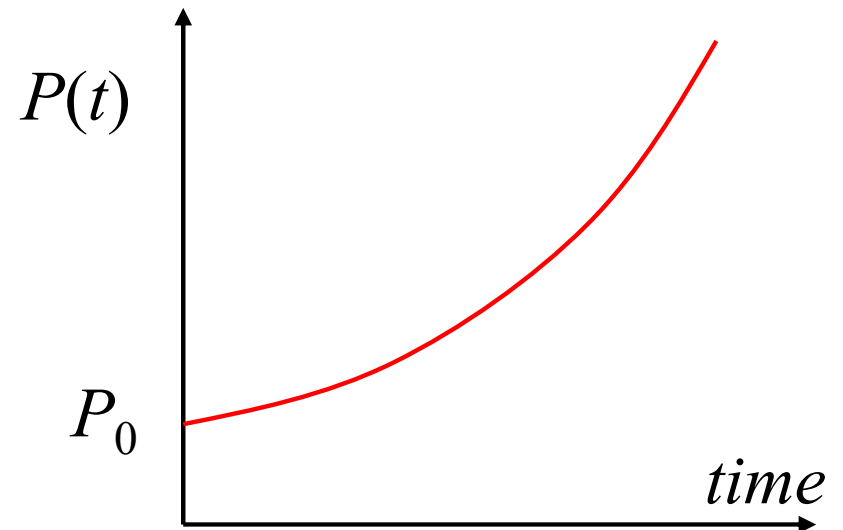
- To find a solution to this equation means to find a function $P(t)$ whose derivative is the product k with $P(t)$.

What does the model predict?

- The solution of the differential equation: $\frac{dP}{dt} = k P$
- is an exponential function

$$P(t) = P_0 e^{kt}$$

$$P(t_0) = P_0 > 0$$



- Now we can make predictions about the size of the population in the future provided we know the value P_0 and k . The value of k can be derived by fitting the model to real data. We simply try different values of k and see which one yields the best fit with the data.

4th year related papers at Otago

- Nowadays we can speak about neuroscientific experimentation “in vivo”, “in vitro” and “in silico”. The latter being the computational neuroscience.
- To reflect this development the Department of Computer Science is offering 3 related papers (now worth 18 pt and 20 pt from 2013):
 - ❑ COSC 422 (S2, even years): Introduction to Computational Neuroscience
<http://cs.otago.ac.nz/student/papers.php?name=COSC422>
 - ❑ COSC 421 (S2, odd years): Neural models of language (A. Knott)
<http://cs.otago.ac.nz/student/papers.php?name=COSC421>
 - ❑ COSC 420 (S1, all years): Neural Networks (A. Robins)
<http://cs.otago.ac.nz/student/papers.php?name=COSC420>