N7: Computational approaches

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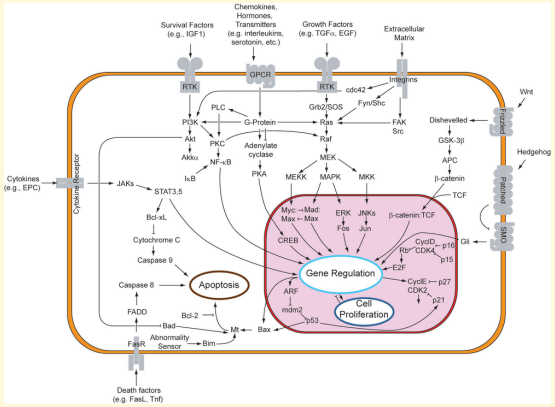
Part one: introduction

Why model?

- Everyone models.
- Model system (zebrafish / mouse / organoids).
- I just happen to use the language of maths/computers rather than verbal arguments.



https://en.wikipedia.org/wiki/Cell_signaling

What can we do with modelling

- Quantitative modelling: test that theories hold true, or test their limits.
- Qualitative modelling: make abstract models to capture essence of a system. (cf. epidemiological modelling since 2020).
- Experiments test for *necessity*; models test for *sufficiency*.
- Make predictions about novel situations.
- Made postdictions to explain past data sets (Abbott 2008).

Part two: Physiological models

We start with classic Hodgkin and Huxley (1952) model.

Mathematical description of ion channels

Voltage-gated channels: gating variables [0,1] to represent flow of ions.

For given voltage, e.g. K channel activation, gated by n:

(1-n) Gates switch from closed state to open state with rate α.

(n) Gates switch from open state to closed state with rate β.

i.e.

$$\frac{dn}{dt} = \alpha(1-n) - \beta n$$

The terms α and β themselves depend on membrane voltage

Similar expressions can be created for sodium activiation (m) and inactivation (h).

Ionic flow determines membrane voltage.

We can derive an expression:

$$c_m \frac{dV}{dt} = -g_L(E_L - V) - g_{Na} m^3 h (E_{Na} - V) - g_K n^4 (E_K - V) + I_e$$

where the g terms are the maximal conductances for each channel, and the E terms are the resting potentials for each channel.

This leads to four coupled differential equations.

Solving these requires methods of *numerical integration*.

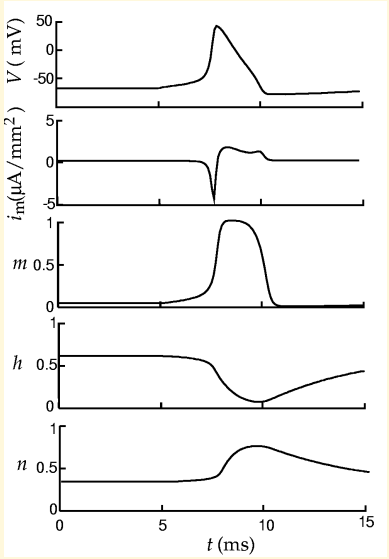
Demonstration

Live demo of all-or-nothing behaviour:

https://demonstrations.wolfram.com/HodgkinHuxleyActionPotentialModel/

As you vary external stimulus you can see emergence of an action potential.

Dynamics of channels and membrane voltage

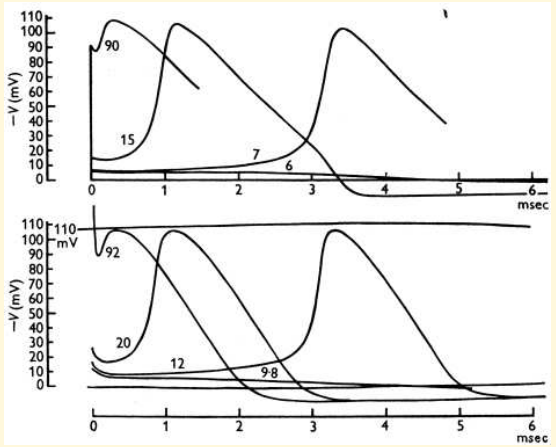


Dayan and Abbott (2002) fig 5.11.

Goodness of fit

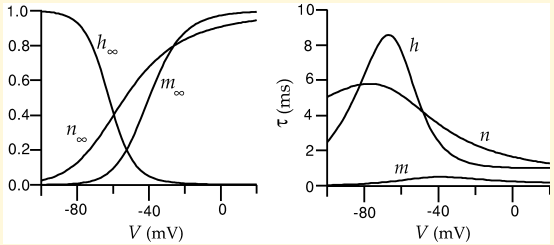
Hodgkin and Huxley(1952). Reproduced from David Sterratt. Upper trace: model; numbers give initial depolarisations (in mV); recordings at 6~C.

Data taken from squid giant axon; much wider axonal diameter (800 um) than normal (2 um) for rapid signal propagation [escape behaviour].



Simplifications to H-H framework

Two observations (Rinzel, 1985):

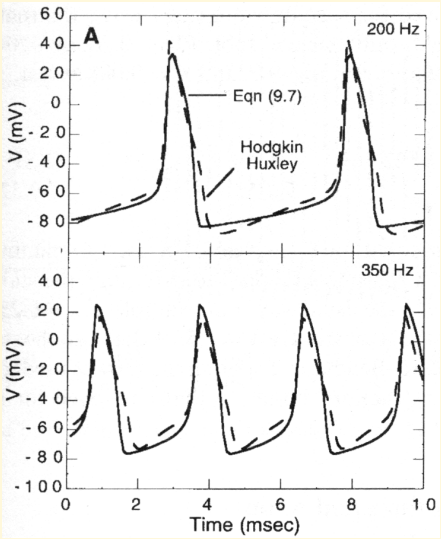


1. m reaches steady-state almost instantaneously.
2. h and $1 - n$ have similar voltage dependence, so model just one of them.

Dayan and Abbott (2002) fig 5.10.

Rinzel simplification vs HH model

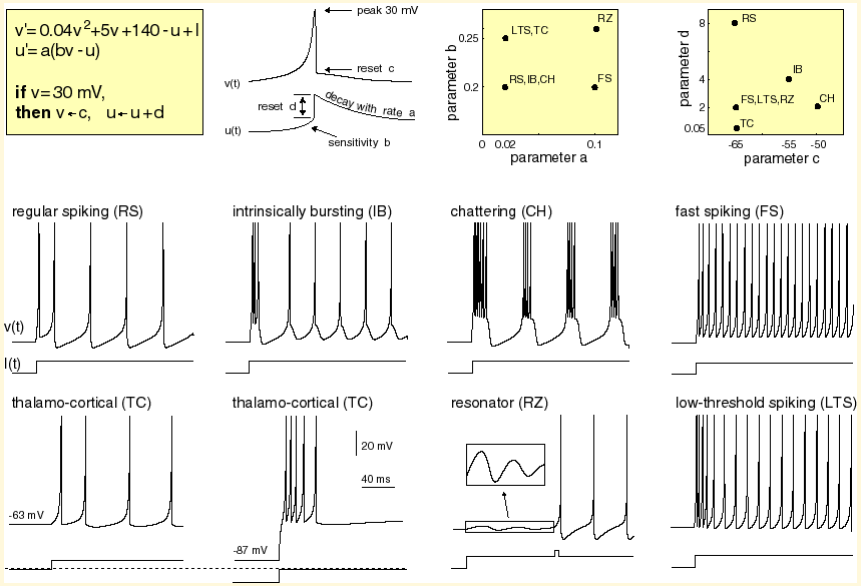
Wilson (1999) Fig 9.3. Comparison of HH model with Rinzel approximation (eqn 9.7). Both systems produce a reduced spike amplitude at higher frequencies.



What is the 'right model' to use?

Various simplifications to Hodgkin-Huxley (Izhikevich, 2004; Figure 2):

What is the Izhikevich (2003) model?



Application of Izhikevich model neurons

We can now build model circuits using these neurons. e.g. Tomkova et al 2015: https://paperpile.com/app/p/5529195b-9246-0d04-8449-09b3cc7289db

Dynamic clamp

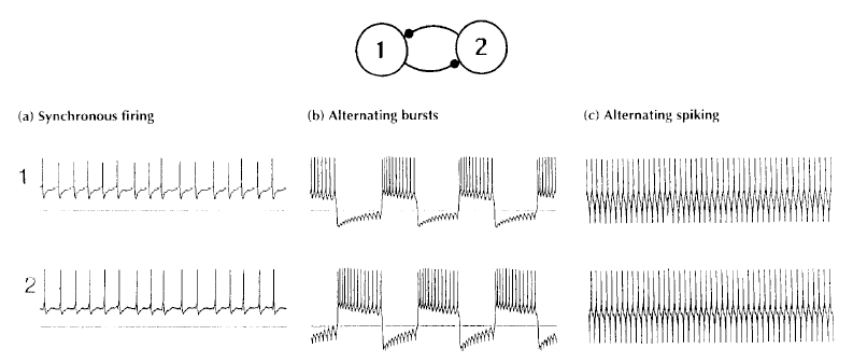
Dynamic clamp takes membrane voltage, and simulates current that will pass through a particular channel; that channel is injected real-time, as if that channel existed on the neuron.

This allows us to use biology to worry about all the other conductances, rather than a modeller using poor estimates of the conductances.

Dynamic clamp application

Can two mutually inhibitory neurons fire in synchrony?

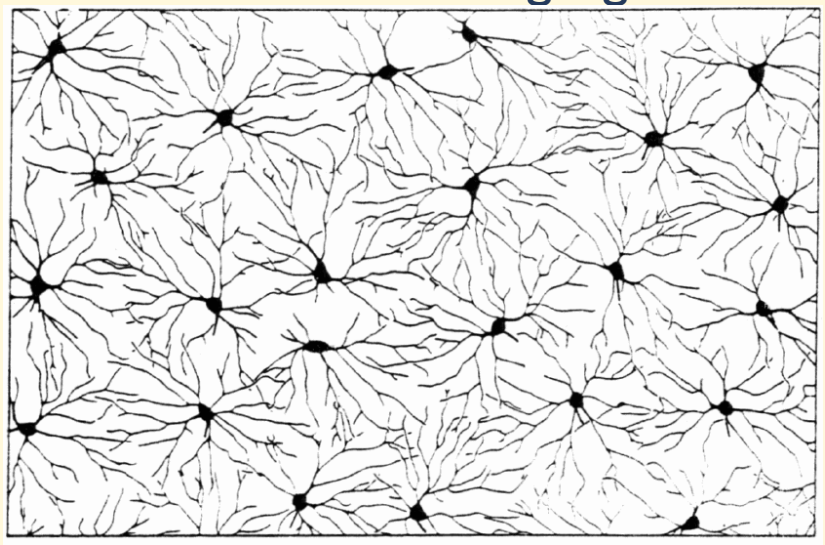
Use dynamic clamp to *virtually* connect two neurons.



Marder and Abbott 1995, Fig 2

Part three: Anatomical models

Retinal mosaics: α retinal ganglion cells



1.7×1.2 mm staining of cat retina (Wässle et al., 1981).

Minimal distance (dmin") serial model