N7: Computational approaches

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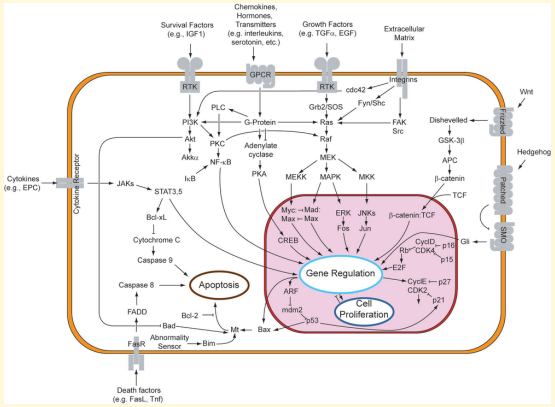
HTML Slides: https://sje30.github.io/n7 (CC BY 4.0 license)

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*.

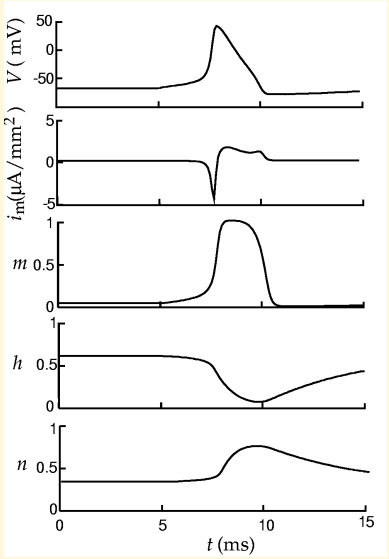
Demonstration

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

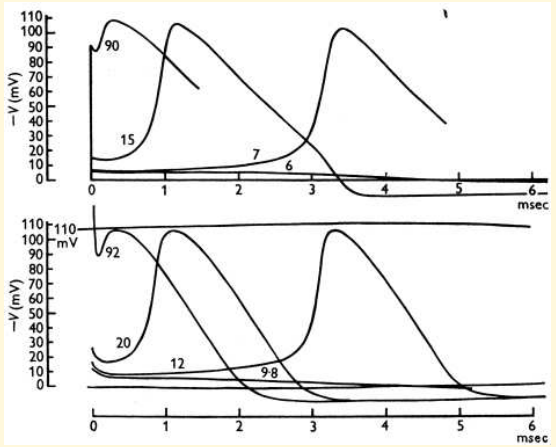


Dayan and Abbott (2002) fig 5.11.

Goodness of fit

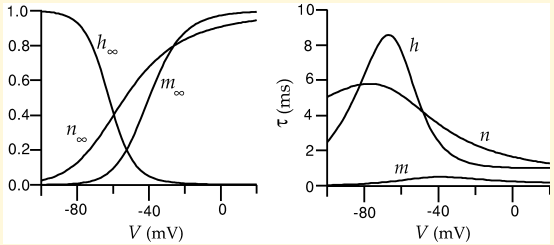
Hodgkin and Huxley(1952). Reproduced from David Sterratt. Upper trace: model; numbers give initial depolarisations (in mV); recordings at 6~C.

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):

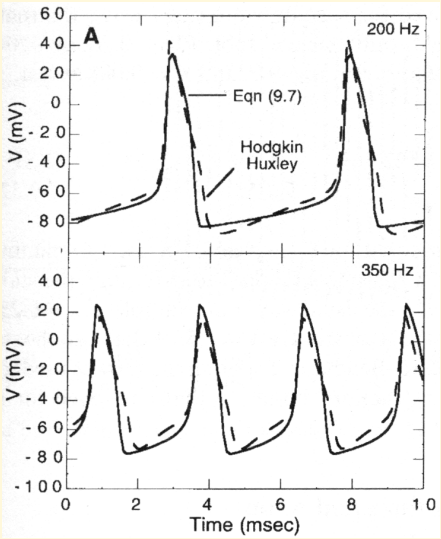


1. m reaches steady-state almost instantaneously.
2. h and $1 - n$ have similar voltage dependence, so model just one of them.

Dayan and Abbott (2002) fig 5.10.

Rinzel simplification vs HH model

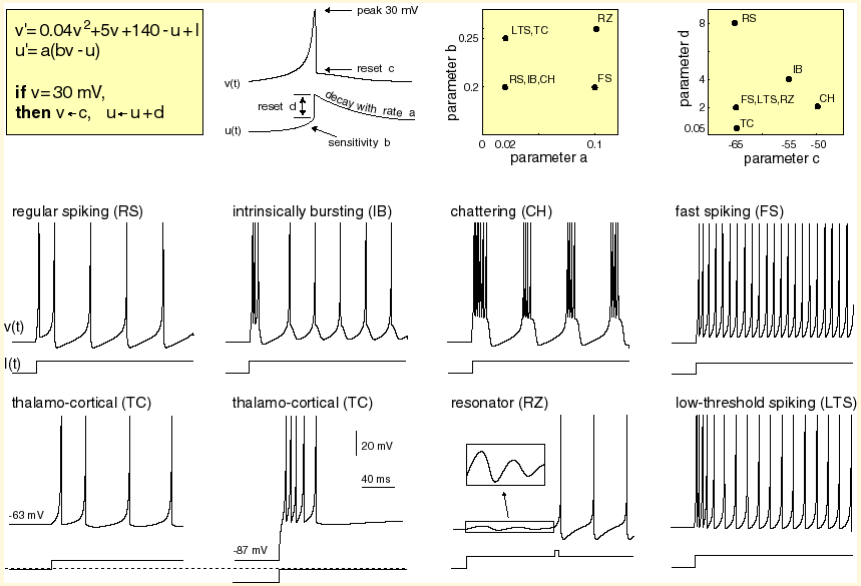
Wilson (1999) Fig 9.3. Comparison of HH model with Rinzel approximation (eqn 9.7). Both systems produce a reduced spike amplitude at higher frequencies.



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

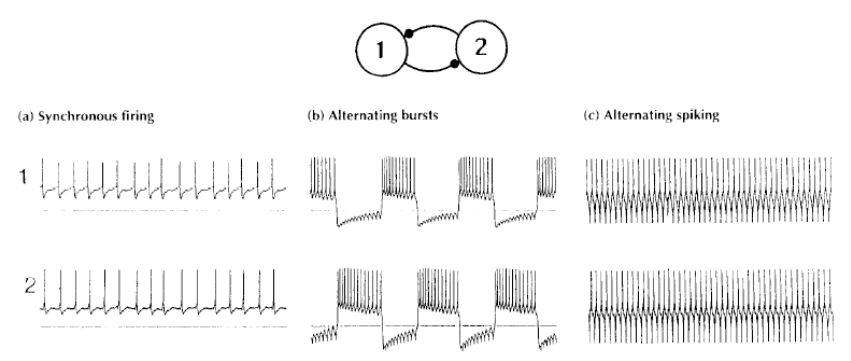
Dynamic clamp takes membrane voltage, and simulates current that will pass through a particular channel; that channel is injected real-time, as if that channel existed on the neuron.

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?

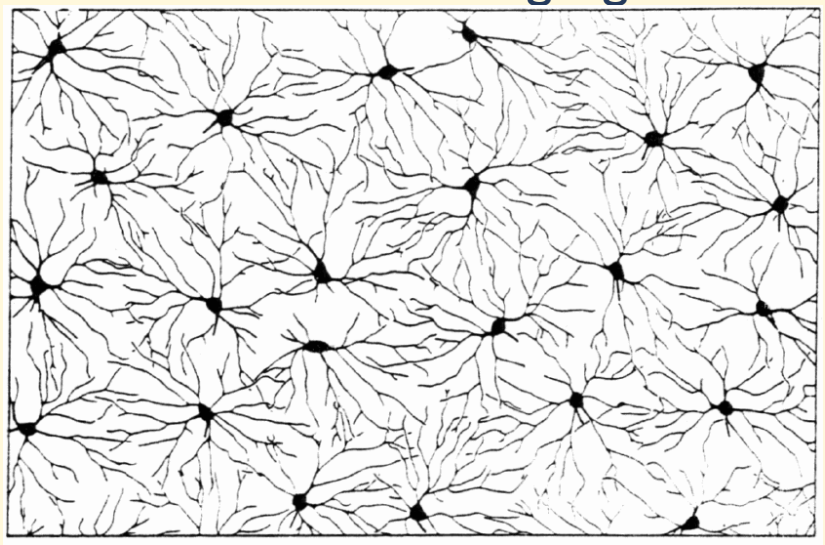
Use dynamic clamp to *virtually* connect two neurons.



Marder and Abbott 1995, Fig 2

Part three: Anatomical models

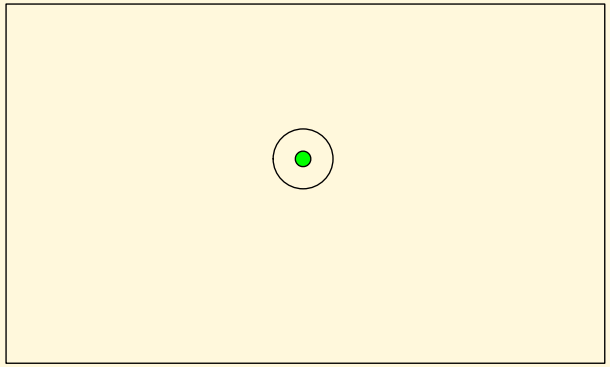
Retinal mosaics: α retinal ganglion cells



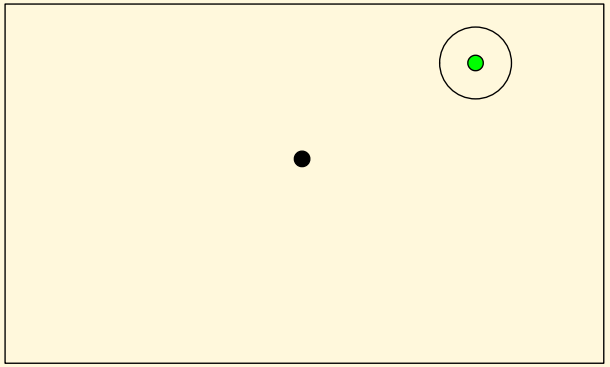
1.7×1.2 mm staining of cat retina (Wässle et al., 1981).

Step 0: exclusion zone model

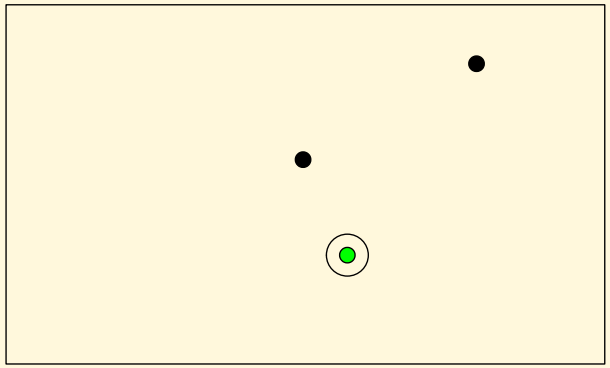
Step 1



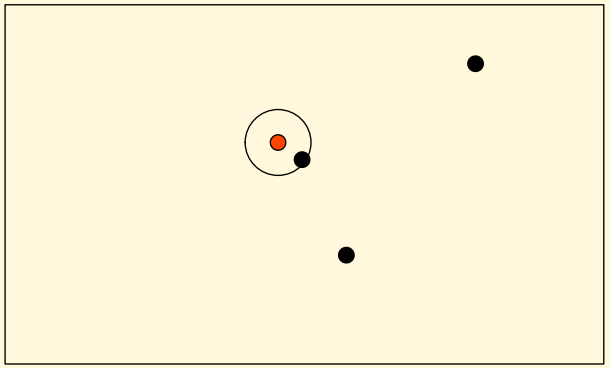
Step 2



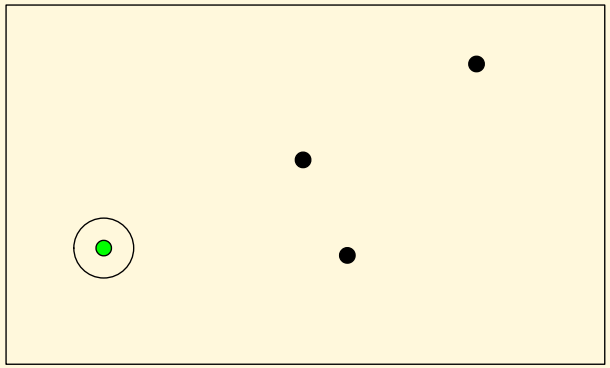
Step 3



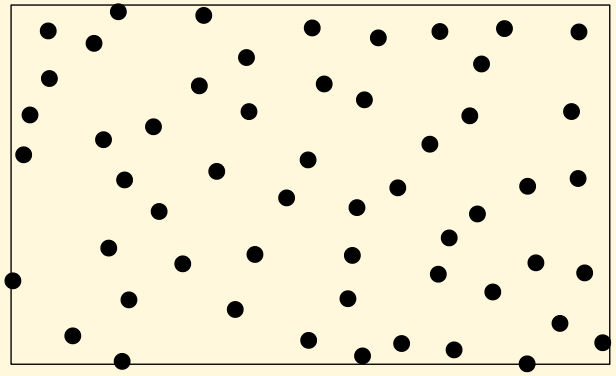
Step 4



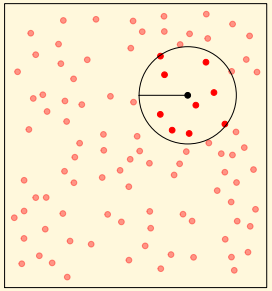
Step 5

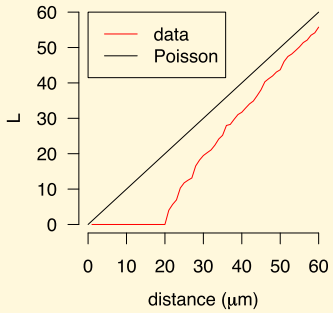


Step 6



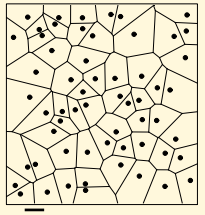
Evaluating regularity



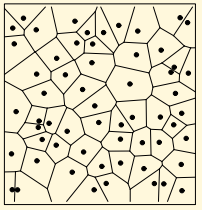


Regularity index (RI) = mean (nearest-neighbour dist) / sd (nearest-neighbour dist)

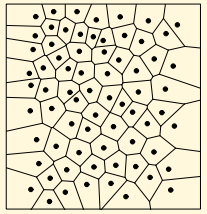
Minimal distance model: results



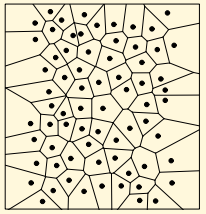
dopaminergic amacrines
RI 3.2



dmin 100 ± 50 μm
RI 3.2

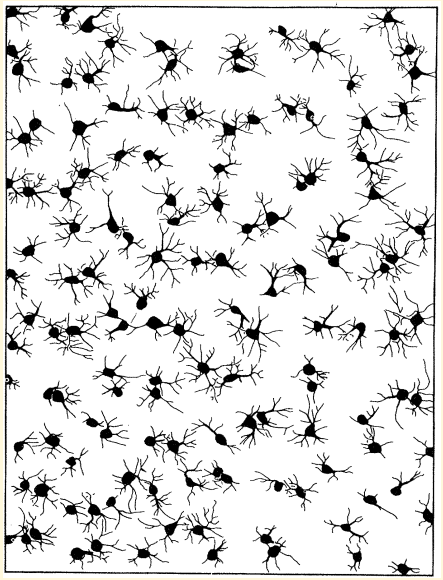


off beta RGCs
RI 4.7

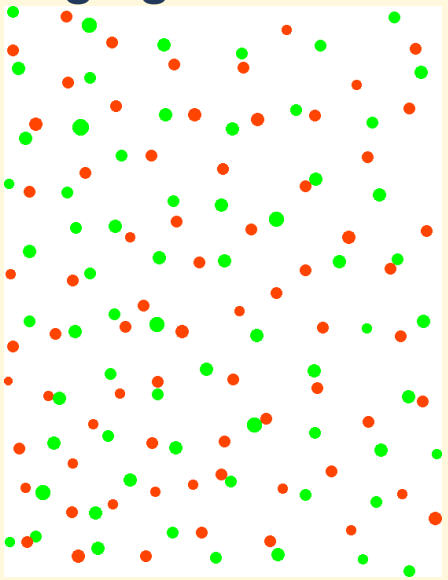


dmin 90 ± 15 μm
RI 5.4

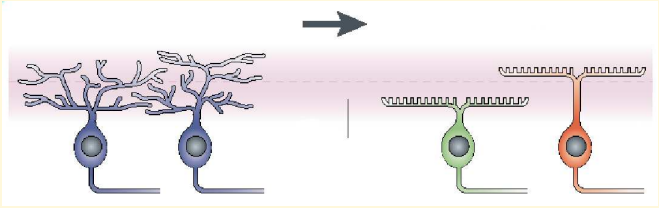
Cat β retinal ganglion cells



Cat β retinal ganglion cells



Development of RGCs (Wong and Ghosh 2002)



Possible mechanisms underlying development:

- Competition among neighbours (Perry)
- Cell death (Chalupa)
- Some other combination?

Model of Delta Notch signalling

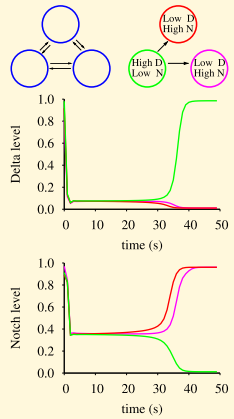
- High levels of Delta (ligand) in one cell induce higher Notch (receptor) activation in its neighbours, decreasing Delta expression in these cells (Collier et al. 1996).

$$\dot{n}_i = f(\langle d_i \rangle) - n_i$$

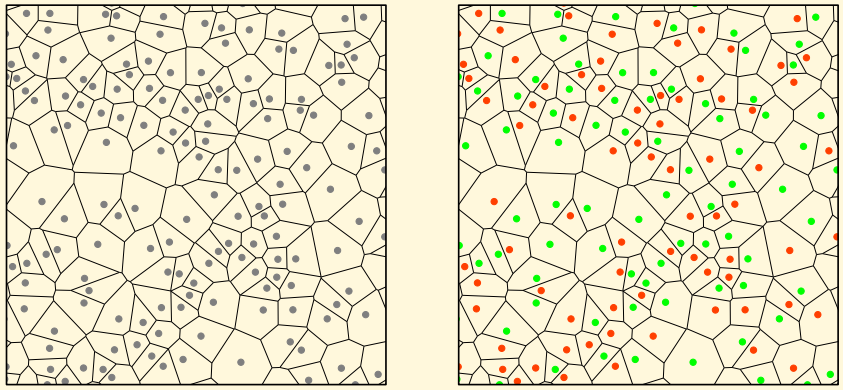
$$f(x) = x^2/(k_1 + x^2)$$

$$\dot{d}_i = g(n_i) - d_i$$

$$g(x) = 1/(1 + k_2 x^2)$$

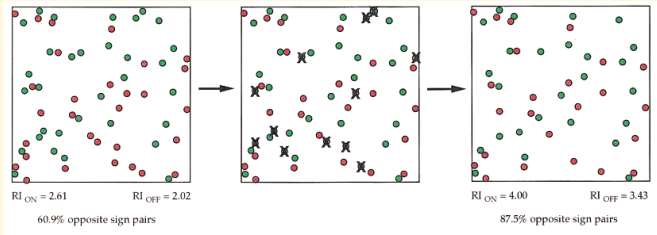


Typical outcome from competition



Cell death

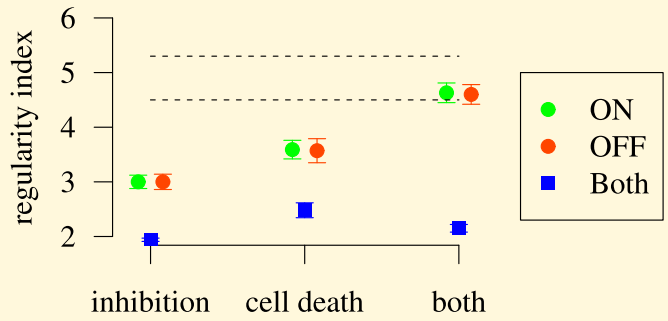
- 20% cell death in alpha RGCs postnatally; mosaic changes from random to regular during that period.
- Cell death removes cells that are too close to each other.



- Approach: build model, deleting cells that are too close to each other. Test effect of deleting up to 40% of cells.

(Jeyarasasingam et al., 1998)

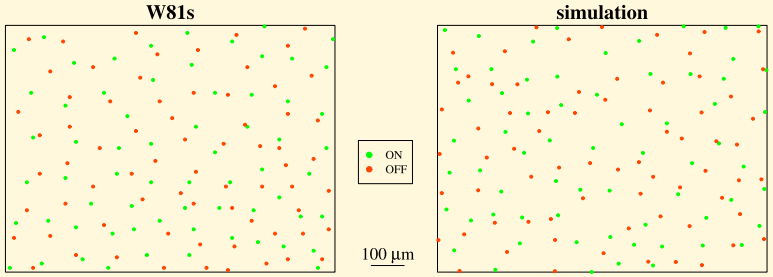
Evaluation of hypotheses



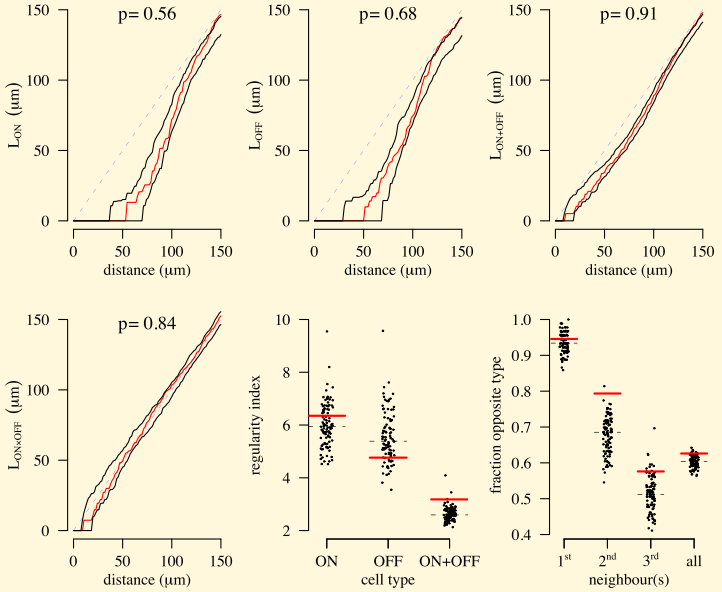
Functional independence

- Maybe there is no functional dependence between the on- and off-centre arrays.
- What happens if we simulate the two arrays independently, just preventing somal overlap?
- Approach: extend exclusion zone model to bivariate case.
- Justifiable on the grounds that mechanistic models support the phenomenological dmin model.

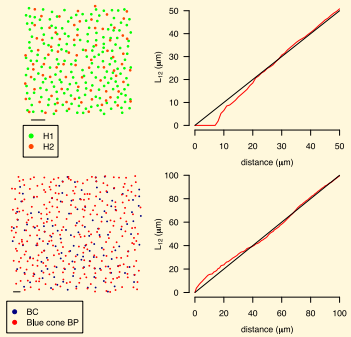
Compare model and data (1)



Compare model and data (2)



How general is principle of functional independence?



Scale bar in each case is 50 um

Conclusions

- "All models are wrong, but some are useful" (Box)
- Hodgkin-Huxley: allows us to be precise *mechanistically*, but demanding.
- Izhikevich: allows us to capture *phenomenology* and is efficient.
- Retinal mosaics: models have shown the sufficiency of local exclusion zones among cells of same type.
- Interactions between cells type are predicted to be rare.