

# N7: Computational approaches

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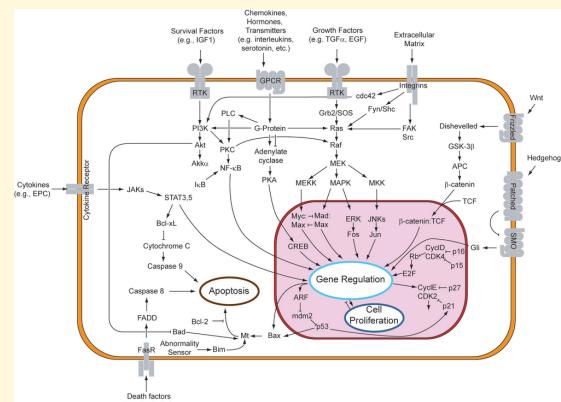
HTML Slides: <https://sje30.github.io/n7> (CC BY 4.0 license)

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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](https://en.wikipedia.org/wiki/Cell_signaling)

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### 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).

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## 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  $\alpha$ .

(n) Gates switch from open state to closed state with rate  $\beta$ .

i.e.

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

The terms  $\alpha$  and  $\beta$  themselves depend on membrane voltage.

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

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### Ionic flow determines membrane voltage.

We can derive an expression:

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

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:

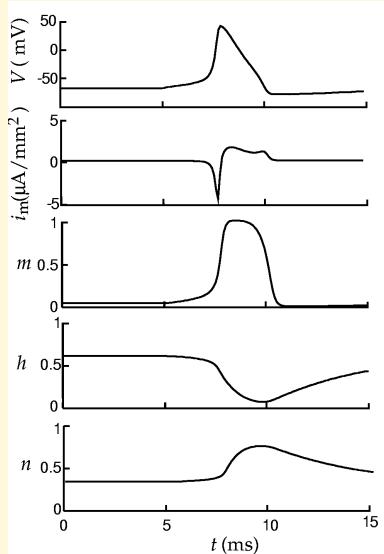
<https://demonstrations.wolfram.com/HodgkinHuxleyActionPotentialModel/>

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

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## Dynamics of channels and membrane voltage



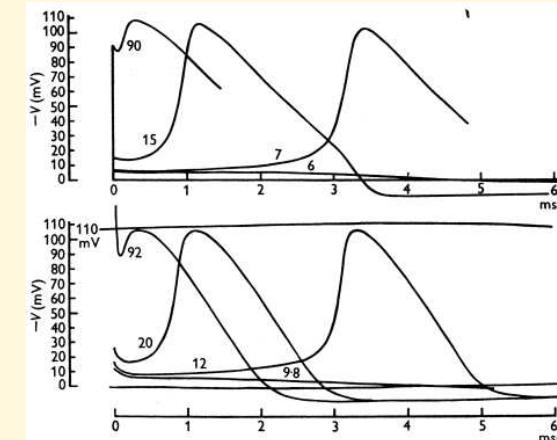
Dayan and Abbott (2002) fig 5.11.

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## Goodness of fit

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

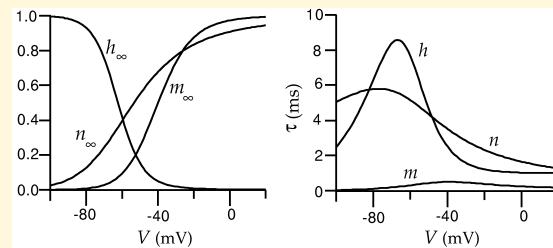
Data taken from squid giant axon; much wider axonal diameter (800  $\mu\text{m}$ ) than normal (2  $\mu\text{m}$ ) for rapid signal propagation [escape behaviour].



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## Simplifications to H-H framework

Two observations (Rinzel, 1985):



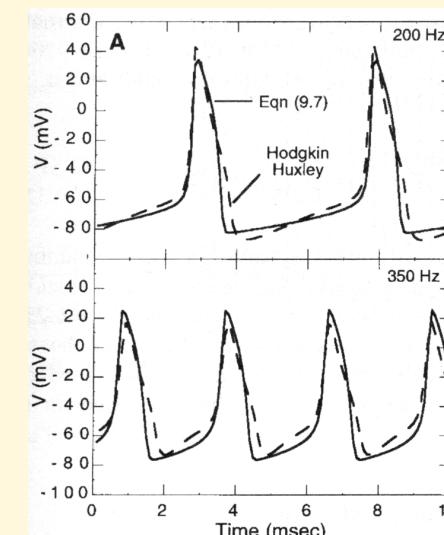
1.  $m$  reaches steady-state almost instantaneously.
2.  $h$  and  $1 - n$  have similar voltage dependence, so model just one of them.

Dayan and Abbott (2002) fig 5.10.

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## 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.

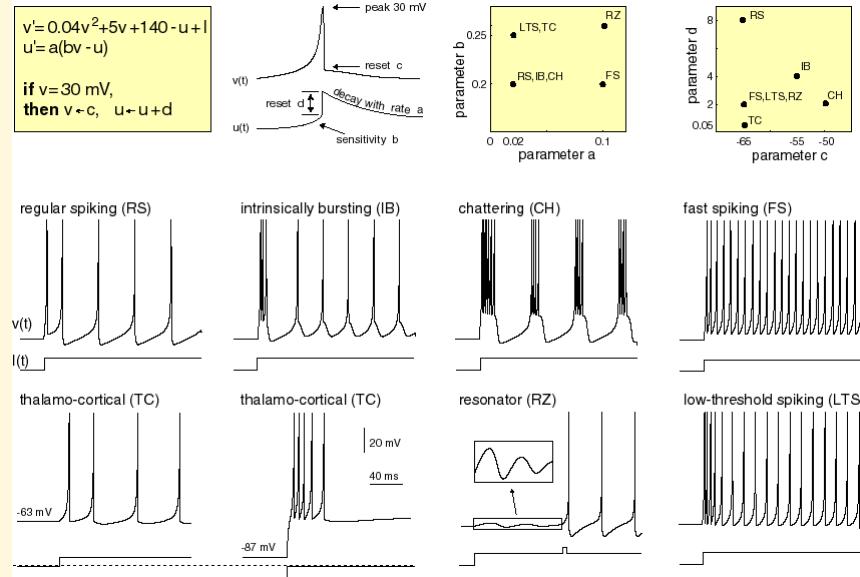


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## What is the 'right model' to use?

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

## What is the Izhikevich (2003) model?



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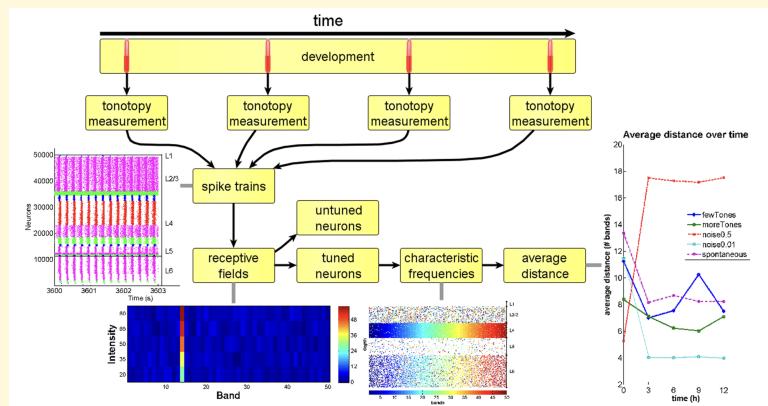
## Application of Izhikevich model neurons

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>

Connect 100 thousand neurons of 17 types in 6 cortical layers with 21 million synapses. Allow synapses to adapt using STDP.

Test the effect of different auditory stimulation paradigms on emergence of tonotopy.

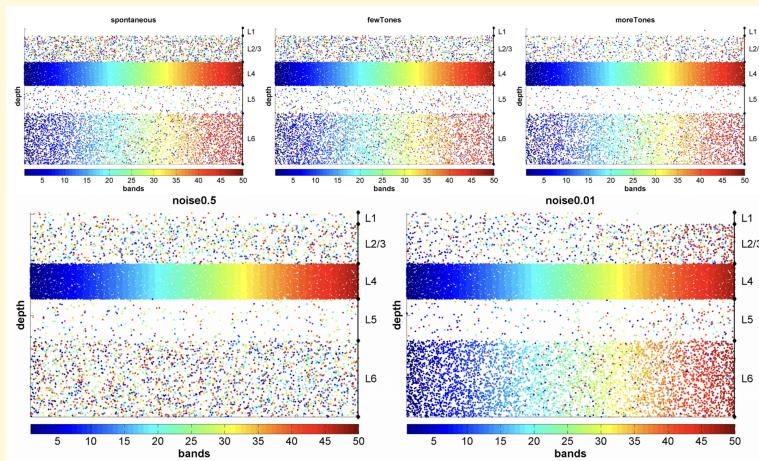
## Tomkova et al (2015) Fig 5



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## Tomkova et al (2015) Fig 7



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## 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.

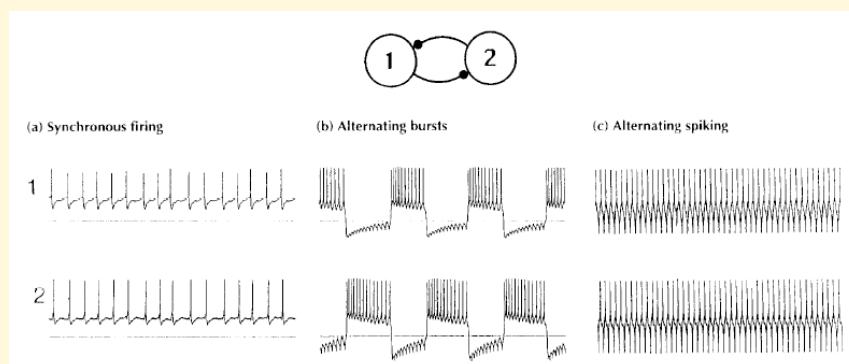
This allows us to use biology to worry about all the other conductances, rather than a modeller using poor estimates of the conductances.

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## Dynamic clamp application

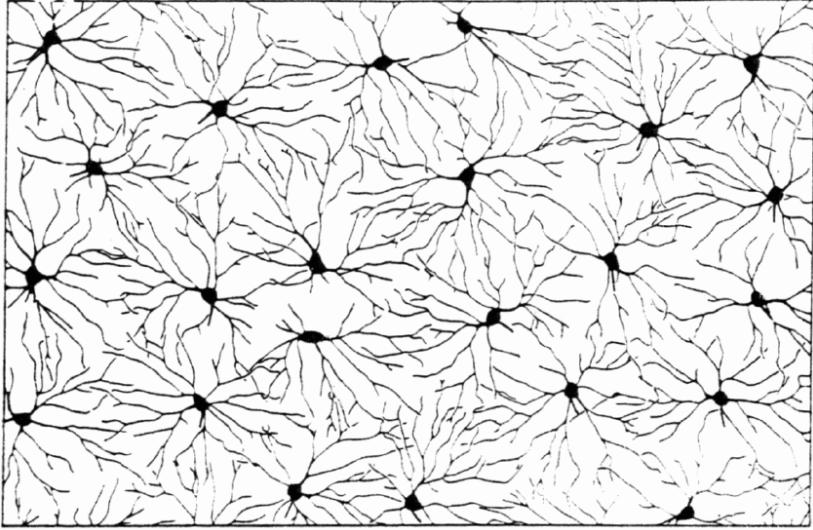
Can two mutually inhibitory neurons fire in synchrony?

Use dynamic clamp to *virtually* connect two neurons.



## Part three: Anatomical models

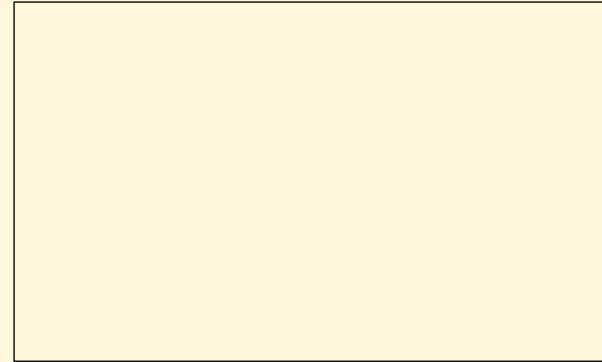
## Retinal mosaics: $\alpha$ retinal ganglion cells



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

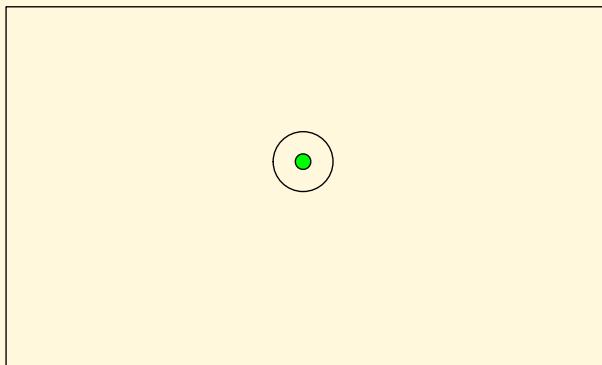
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## Step 0: exclusion zone model



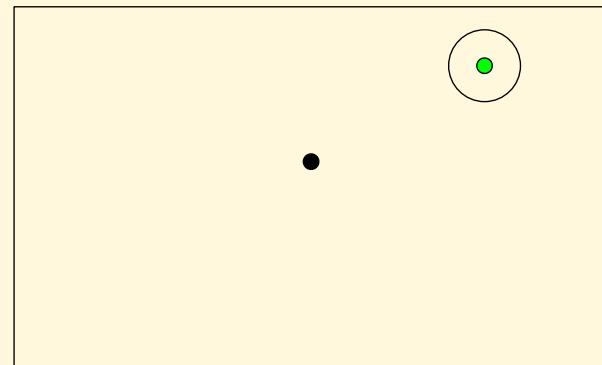
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## Step 1



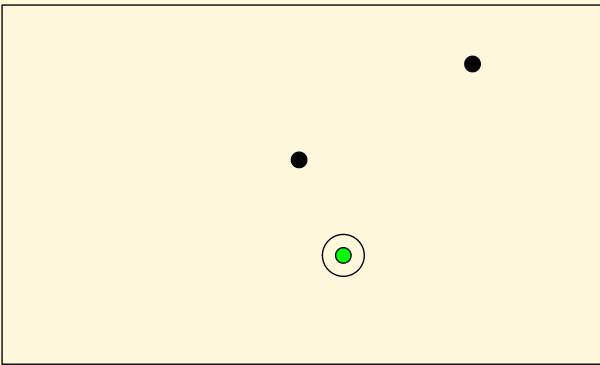
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## Step 2



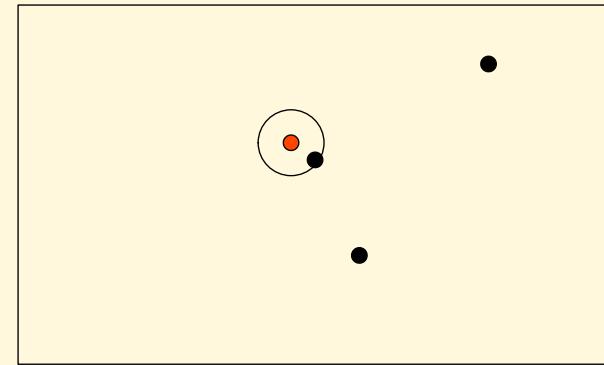
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### Step 3



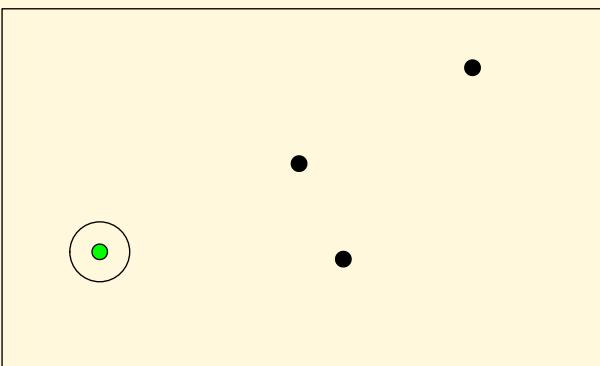
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### Step 4



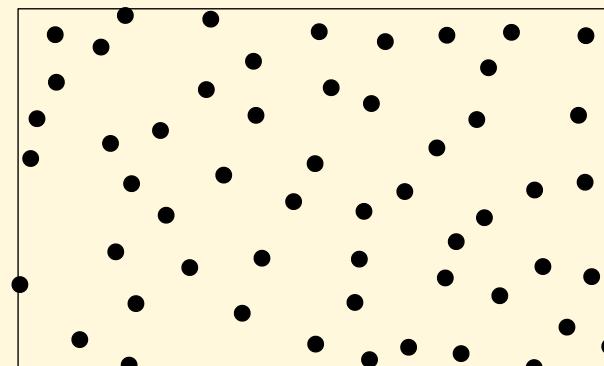
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### Step 5



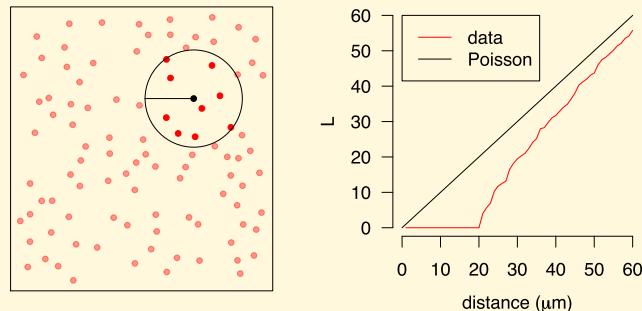
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### Step 6



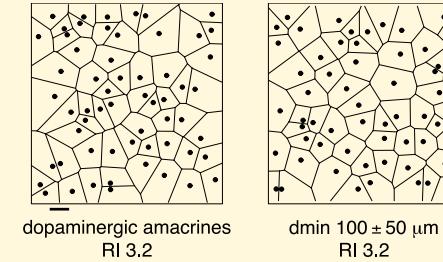
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## Evaluating regularity

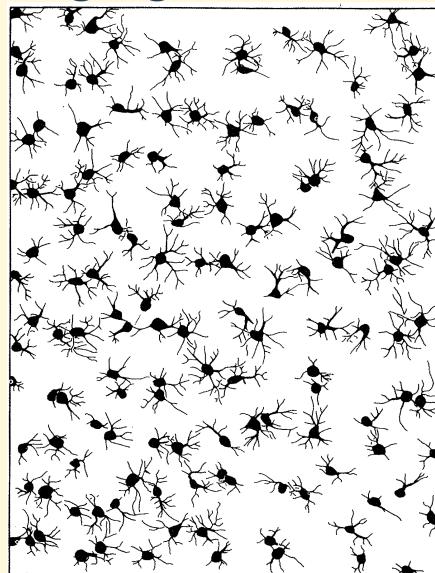


Regularity index (RI) = mean (nearest-neighbour dist) / sd (nearest-neighbour dist)

## Minimal distance model: results

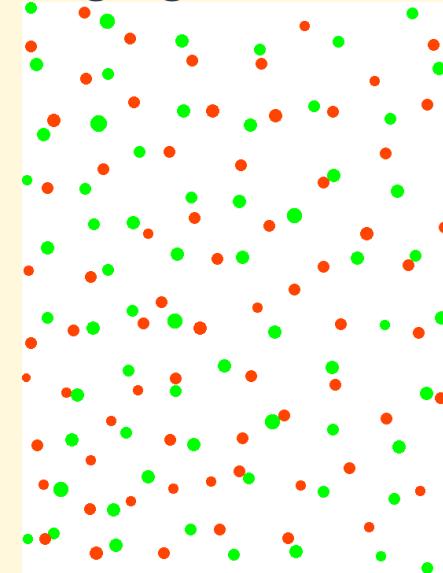


## Cat $\beta$ retinal ganglion cells



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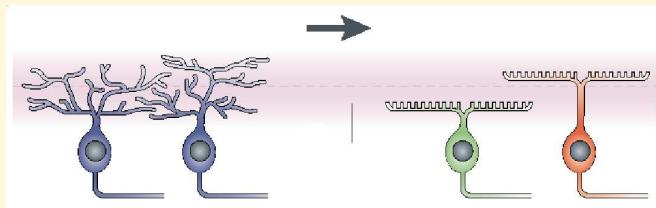


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## Development of RGCs (Wong and Ghosh 2002)



Possible mechanisms underlying development:

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

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## Model of Delta Notch signalling

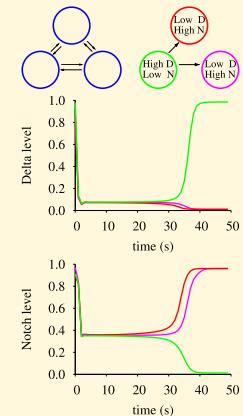
- High levels of Delta (ligand) in one cell induce higher Notch (receptor) activation in its neighbours, decreasing Delta expression in these cells (Collier et al. 1996).

$$n_i = f(\langle d_i \rangle) - n_i$$

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

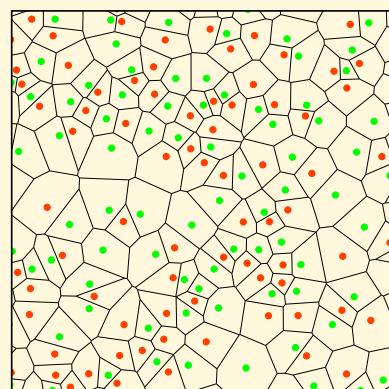
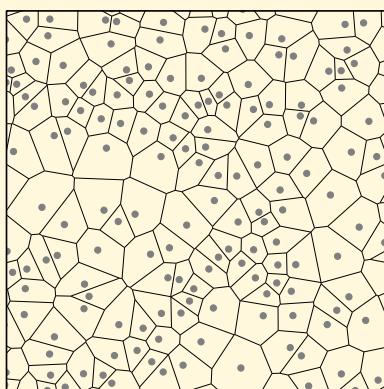
$$\dot{d}_i = g(n_i) - d_i$$

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



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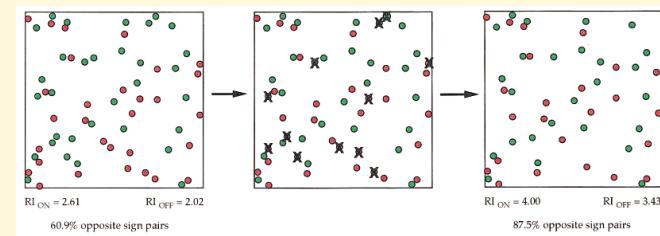
## Typical outcome from competition



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## 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.

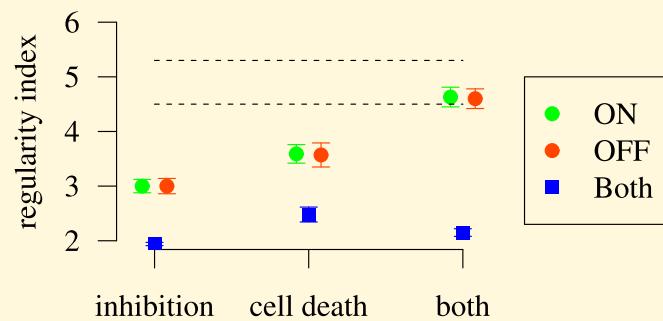


- Approach: build model, deleting cells that are too close to each other. Test effect of deleting up to 40% of cells.

(Jeyarasasingam et al., 1998)

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## Evaluation of hypotheses



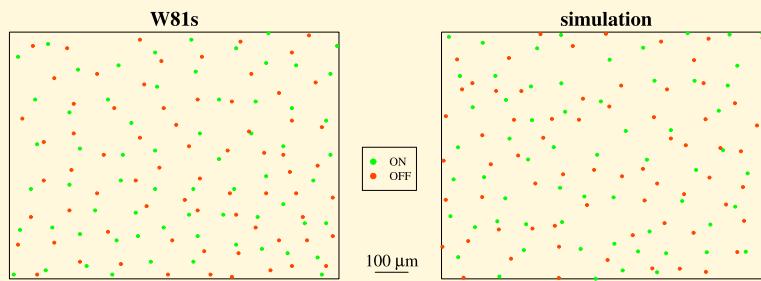
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## Functional independence

- 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.

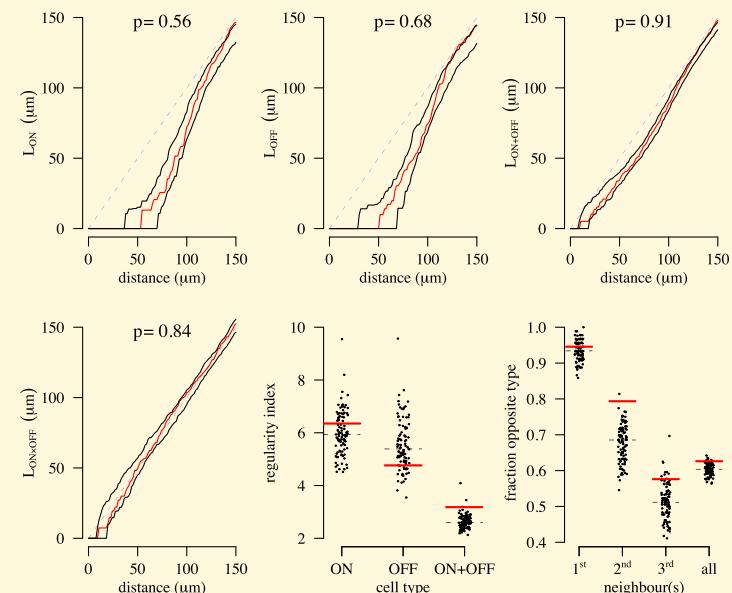
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## Compare model and data (1)



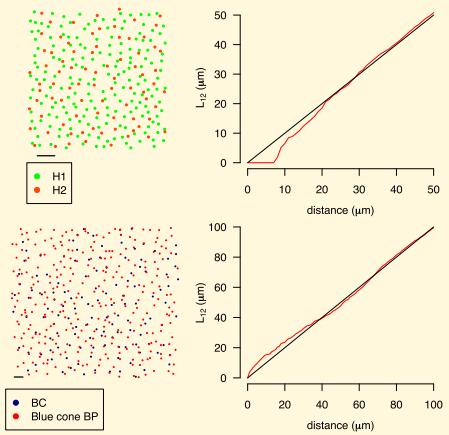
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## Compare model and data (2)



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# How general is principle of functional independence?



Scale bar in each case is 50  $\mu\text{m}$

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## 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.

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