Brain structure and brain dynamics

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Introduction

To study a Neural Network (NN) model the following three elements have to be specified:

- Description of unit's dynamics
- Interaction between units (architecture of connections)
- Learning rule (adjustment of connection strength)

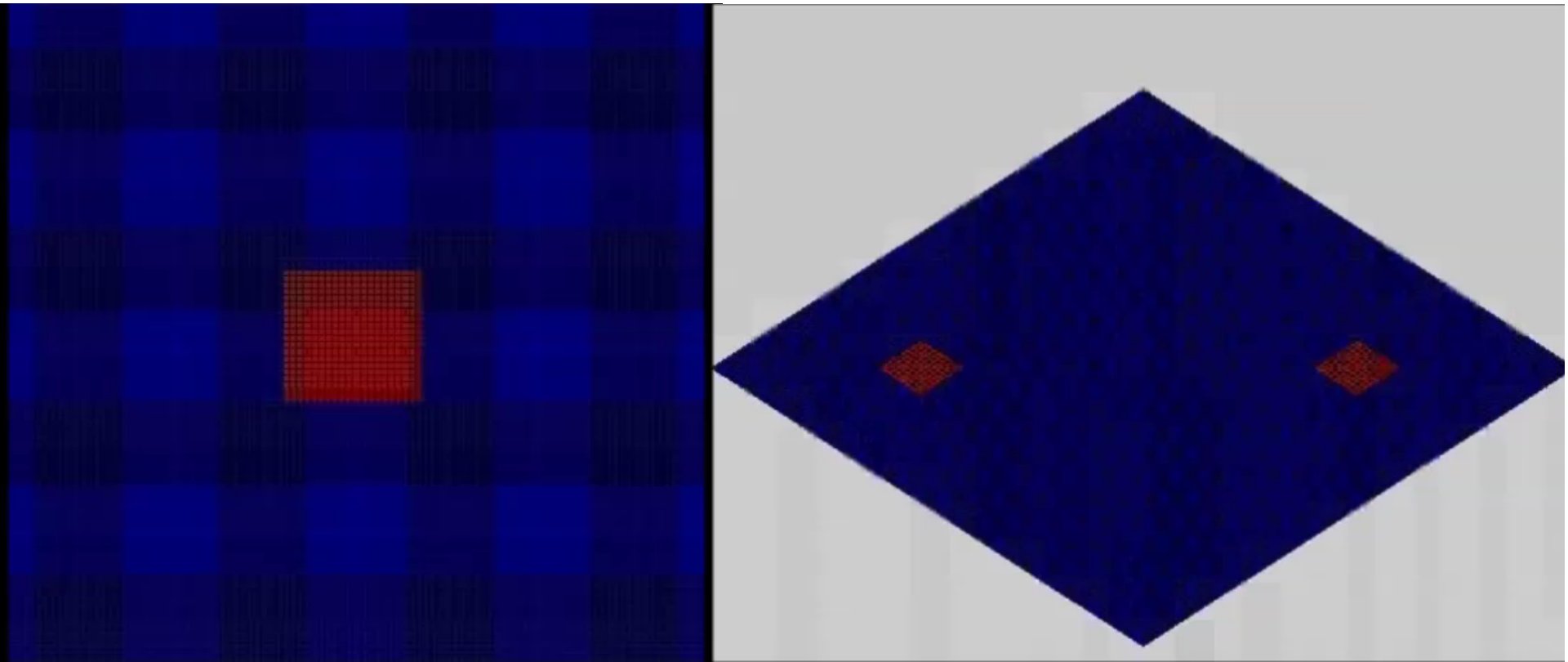
After that, the dynamics of neural activity can be studied. Usually, these PATTERNS of neural activity are solutions of a large system of ODEs (or DDEs).

Brain modelling

Citation from Steven Pinker (Psychology, Harvard):

- **Describe in 5 words how the brain works:**

"Brain cells fire in patterns“



Unit (Brain Cell) Activity: Action Potential (Spike)

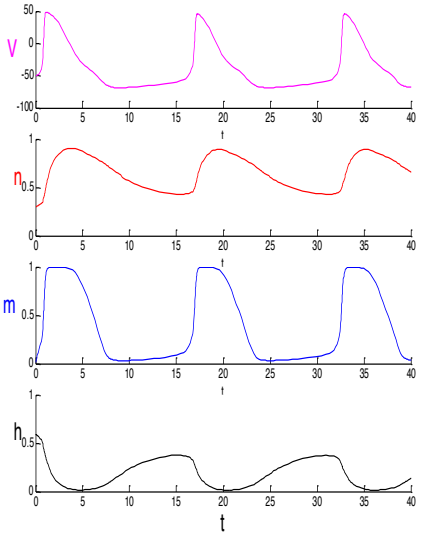
Hodgkin-Huxley model (1952, Nobel Prize)

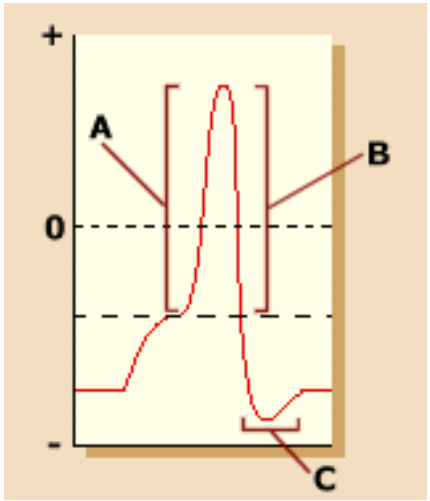
$$C\frac{dV}{dt} = -g_{Na}m^3h(V-E_{Na}) - g_K n^4(V-E_K) - g_L(V-E_L) + I_{app}$$

$$\tau_n(V)\frac{dn}{dt} = n - n_\infty(V)$$

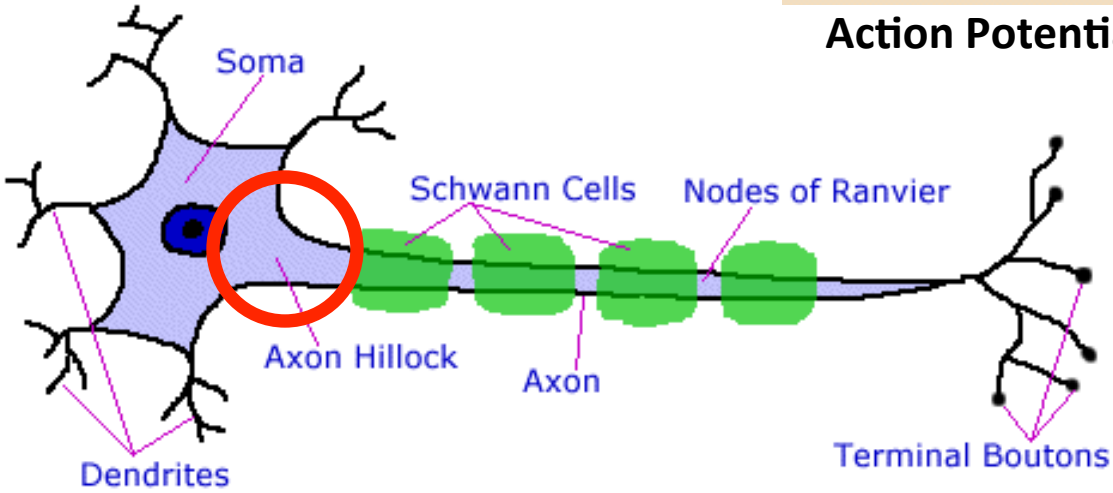
$$\tau_m(V)\frac{dm}{dt} = m - m_\infty(V)$$

$$\tau_h(V)\frac{dh}{dt} = h - h_\infty(V)$$

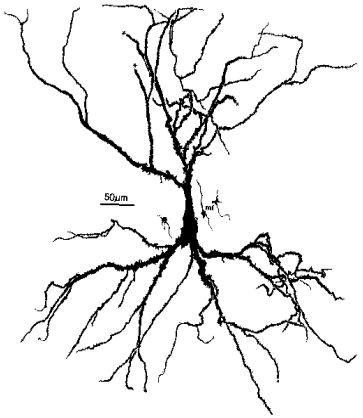




Action Potential



Neuron's PHOTO

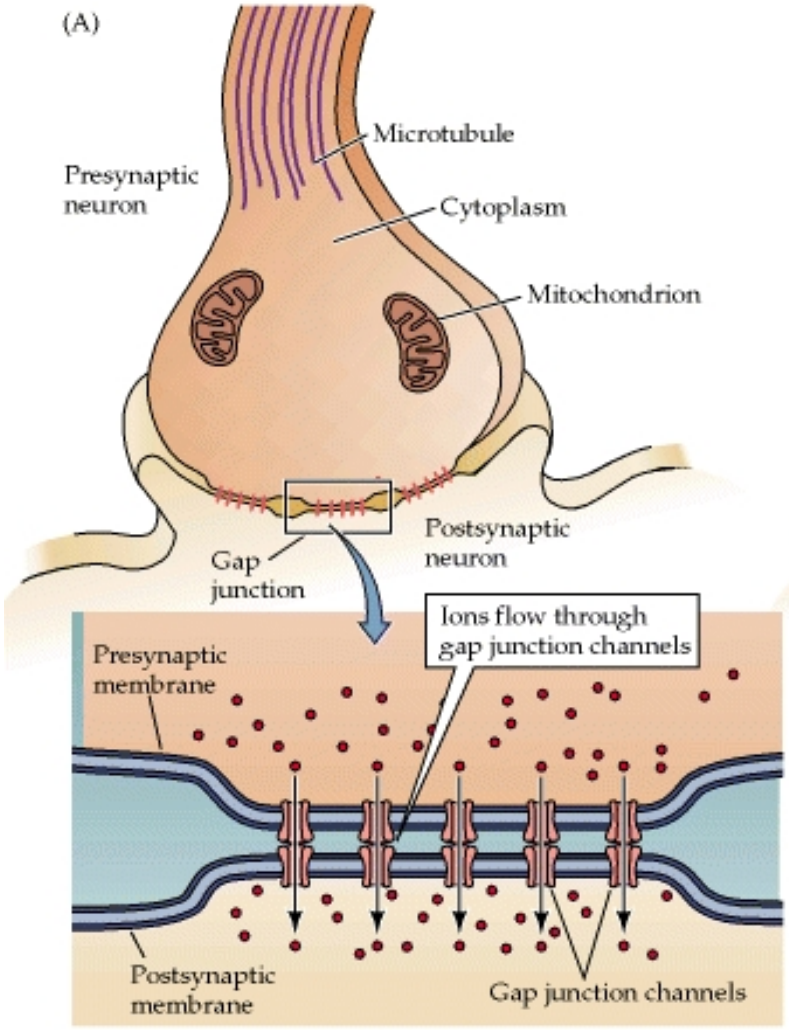


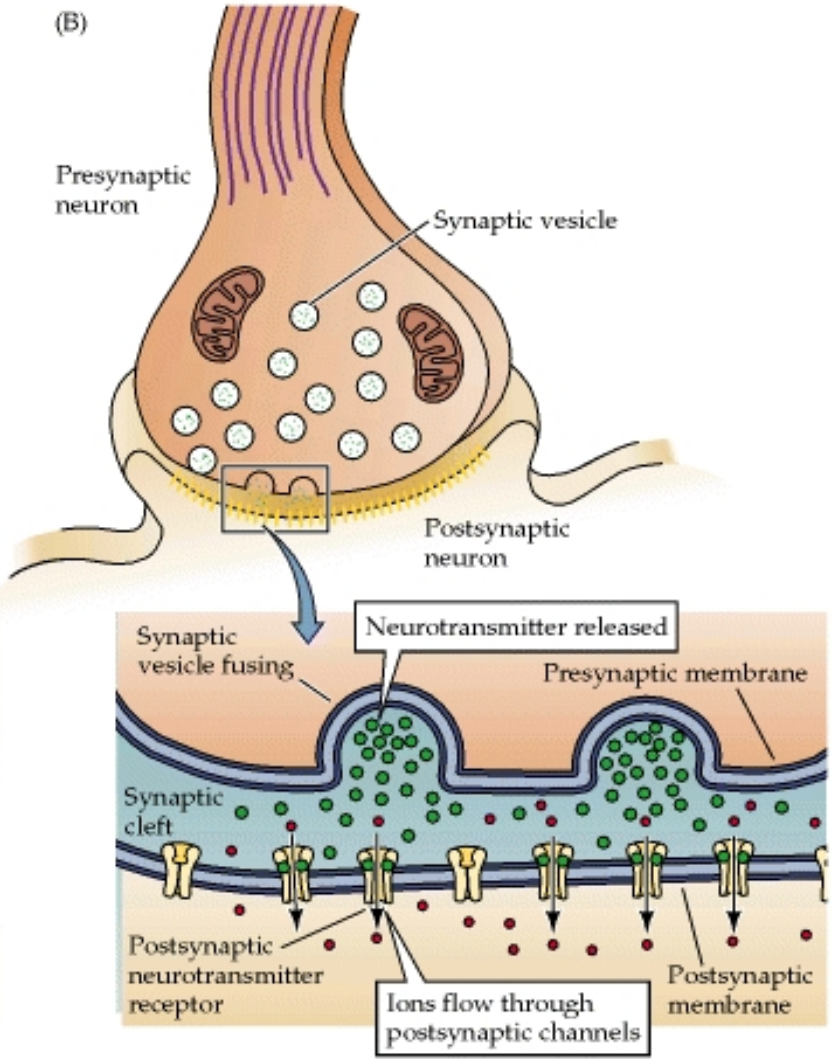
Introduction

Interaction between units is the most difficult part of NN specification.

- Usually, the number of units (N) is large and the number of connections grows as N^2.
- Standard approaches from statistical physics for dimensionality reduction are not applicable because the interactions are of different types and they also depend on the type of units

There are two major connection types:





Electrical coupling (gap junction)

Chemical synaptic connection

http://www.ncbi.nlm.nih.gov/books/NBK11164/

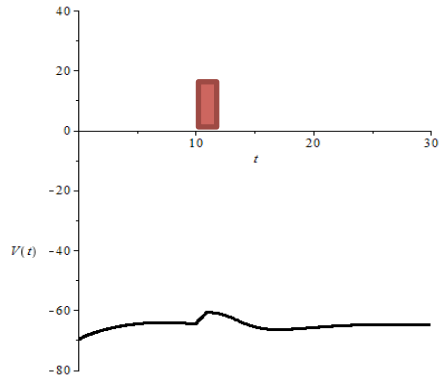
Introduction

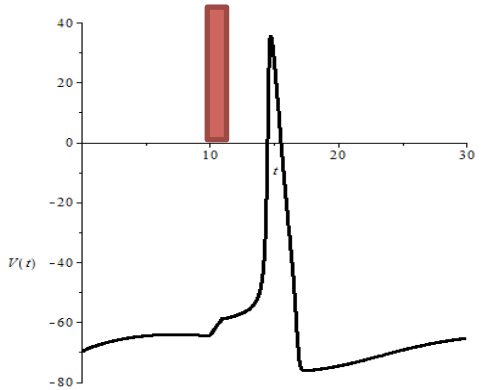
There are two major types of synaptic connections: **excitatory** and **inhibitory** connections. It means that a probability of action potential increases or decreases respectively.

However, the neurobiology is more complicated than this simple modelling scheme. For example, Post-Inhibitory Rebound (PIR) mechanism provides a possibility to generate an action potential after inhibition:

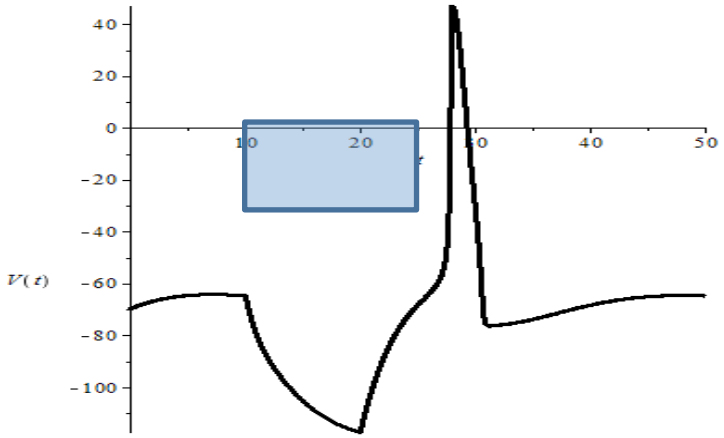
Action potential

Response to a short current injection and threshold property





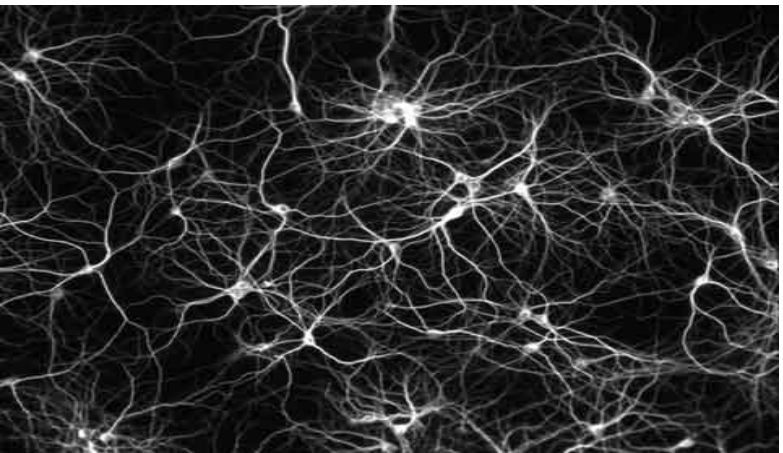
Post-Inhibitory Rebound: Spike is generated after inhibitory current injection

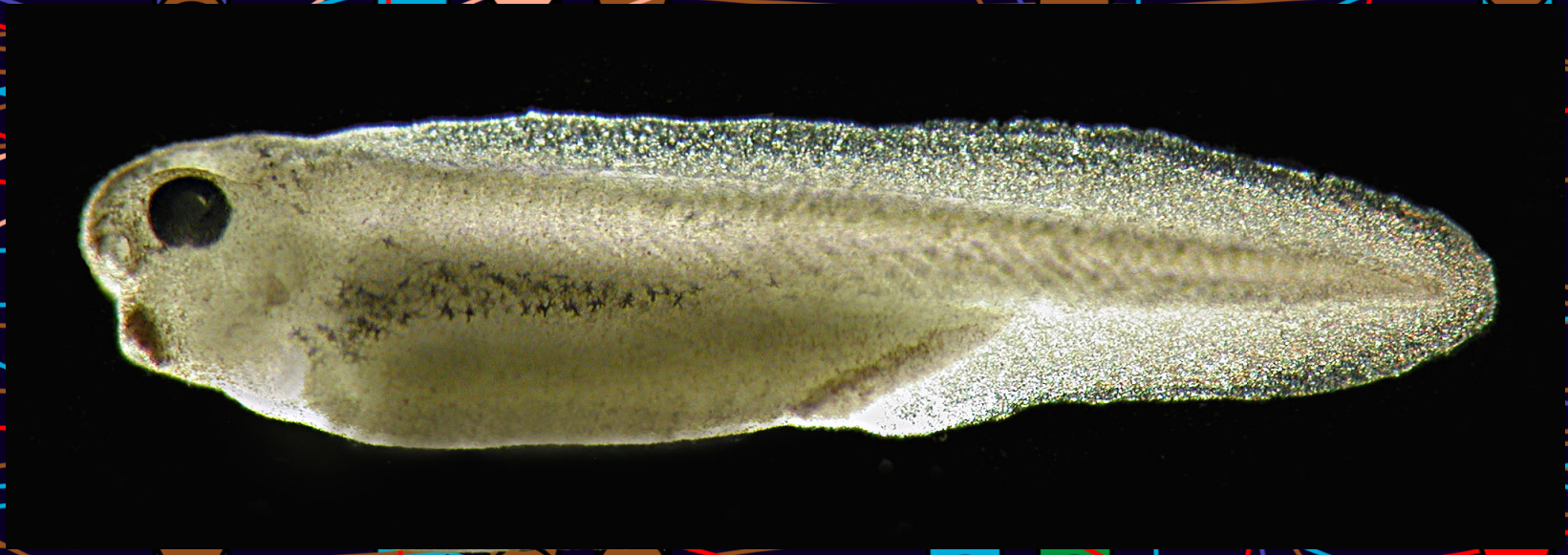


Developmental Approach

In TADPOLE project we address a long-standing ambition of neuroscience to understand **the structure–function problem (connectivity - activity pattern problem).**

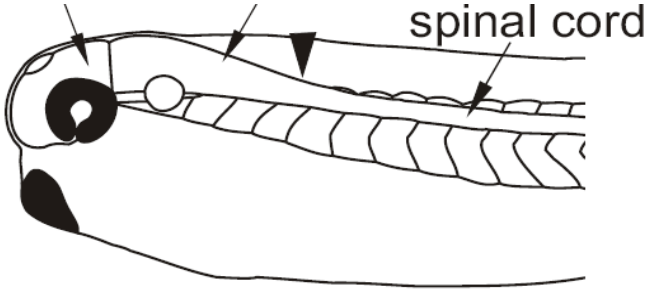
We study connections and spiking activity of neuronal circuit in the 2-day old hatchling Xenopus tadpole.

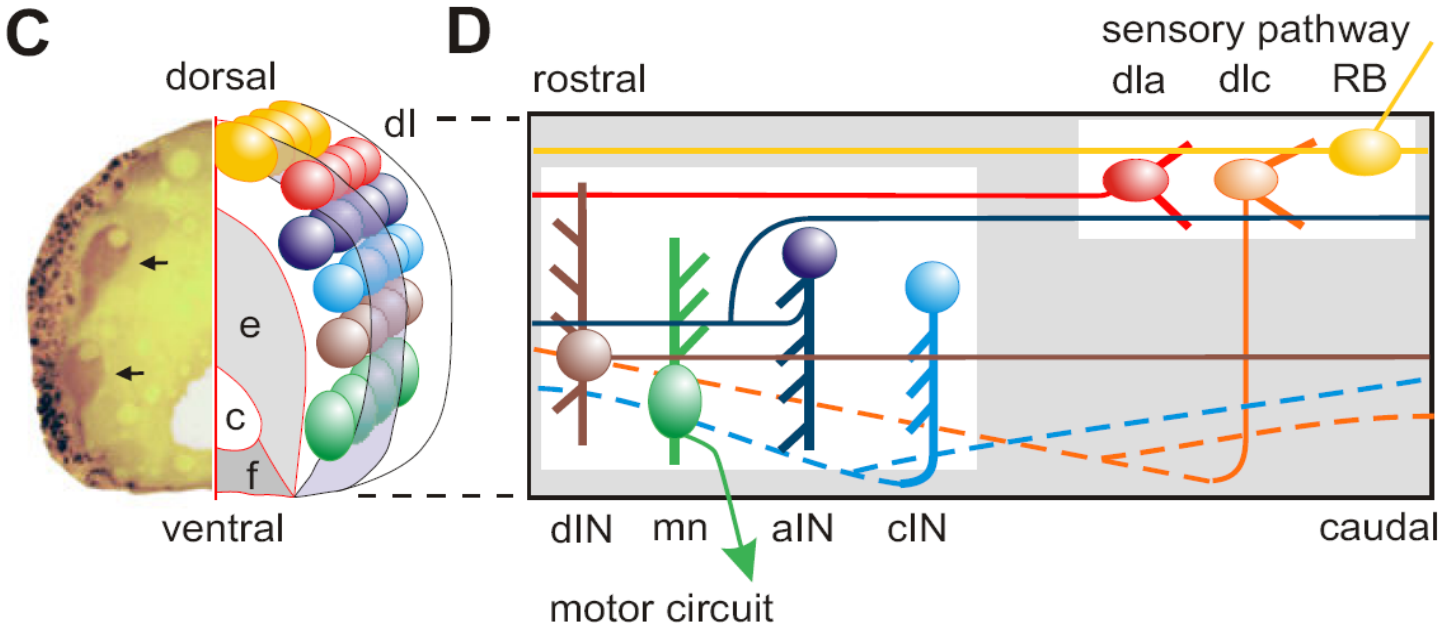




5 mm long, 2 days post fertilization

Tadpole Spinal Cord





- Specimens are two days old
- 5mm long
- Behaviour is limited to swimming and struggling

Developmental Approach

- Although the experimental neuroscience provides detailed knowledge on mechanism of spike generation and transmission, in many cases an important information about **connectivity is missing**.
- One reason is that experimental investigation of connections between neurons is extremely difficult. Thus, the detailed **mapping of contacts** between individual neurons is missing.

Li, et al., 2007, Neural Developm; Borisyuk et al., 2011, Front Neuroinform; Borisyuk et al., 2014, PLOS ONE

Developmental Approach

- What methods can identify the neuronal connections which lead to appropriate activity of a circuit?

Our research on connectivity of neurons in the tadpole spinal cord shows that computational modelling can help in finding a **detailed realistic connectivity diagram (connectome)**.

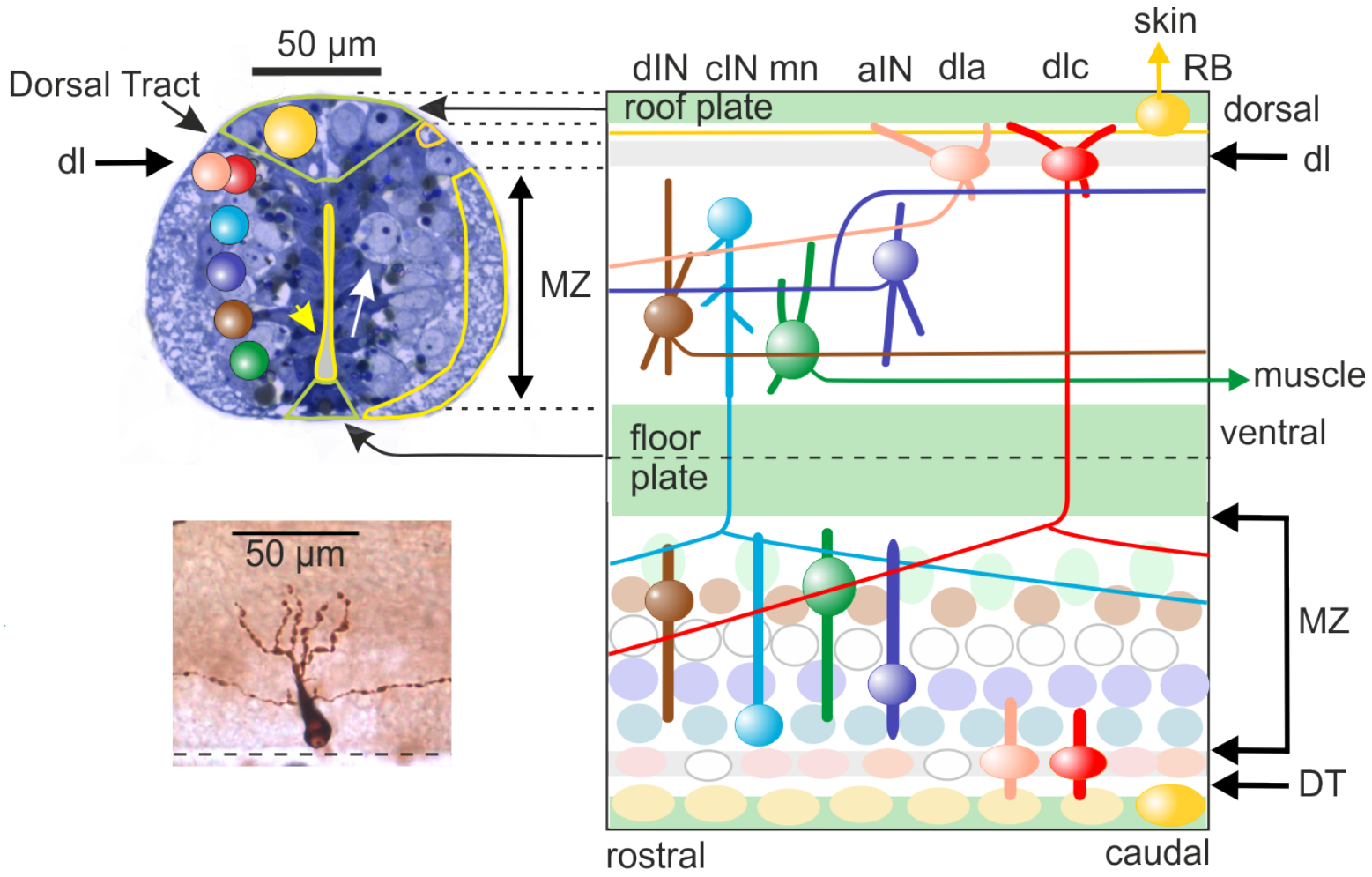
In our model connections are not prescribed, they appear during the “developmental process”.

Questions: CNS development

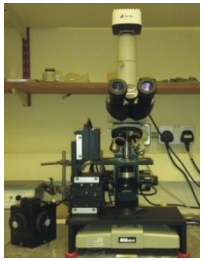
- Can axon growth be controlled by simple gradients?
- Does synapse formation require neuron recognition?
- Can simple rules allow the development of a functional swimming network?

Li, Cooke, Sautois, Soffe, Borisyuk and Roberts, 2007, Neural Developm

CNS: spinal neurons

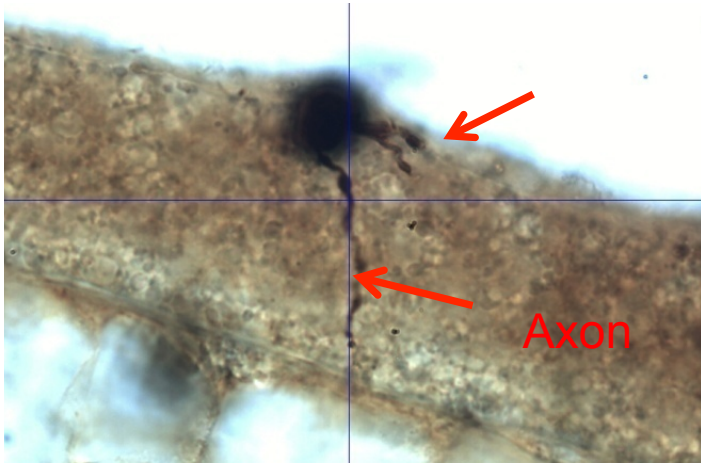


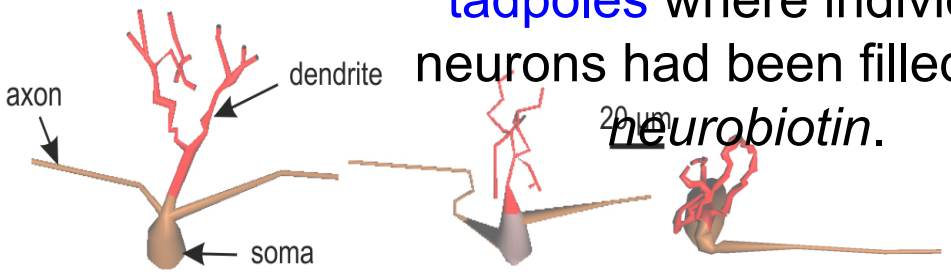
Anatomical measurements



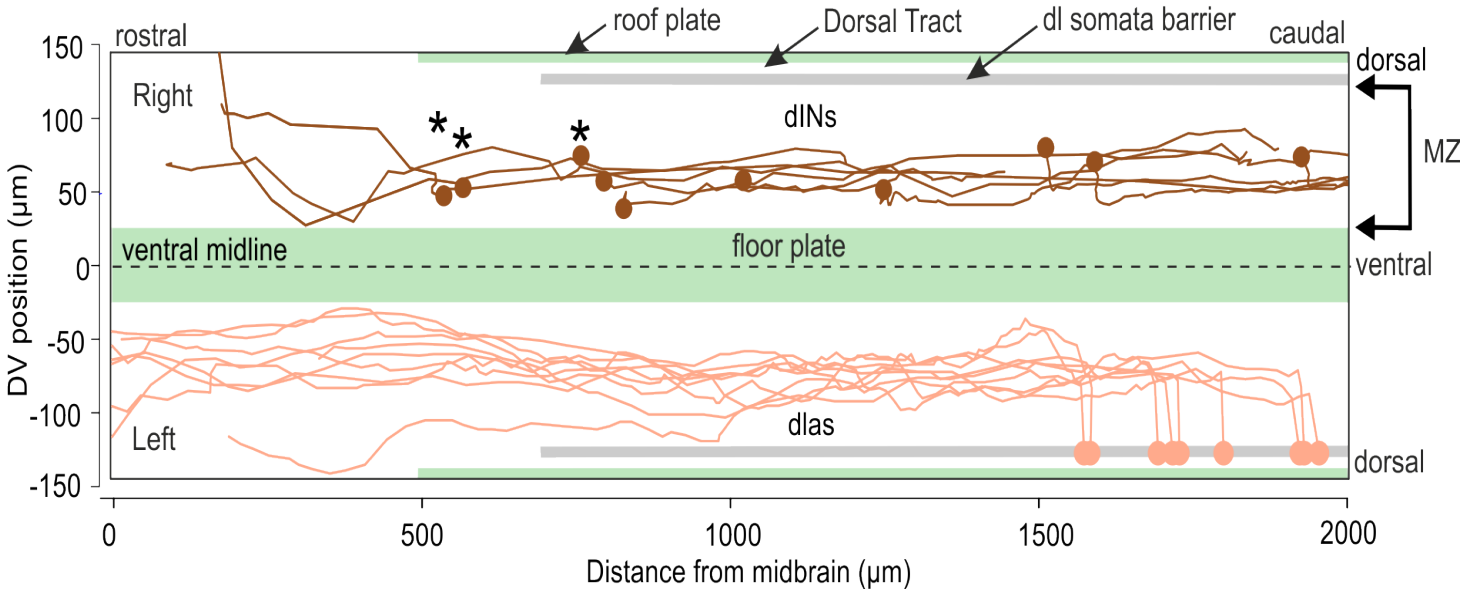
3D spinal neuron

Dendrite

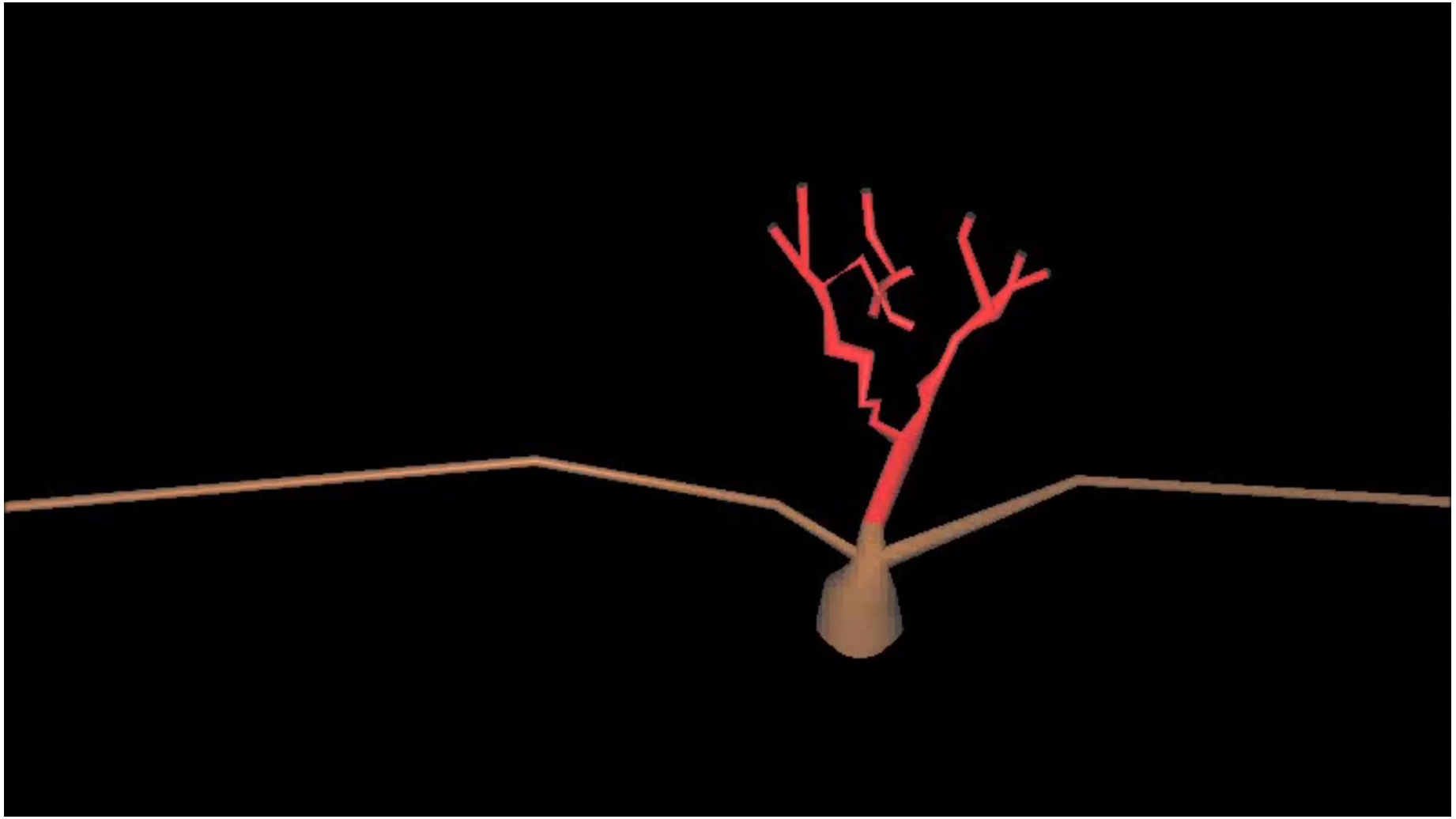




3D measurements of neuron morphology were made in isolated nervous systems of tadpoles where individual neurons had been filled with *neurobiotin*.

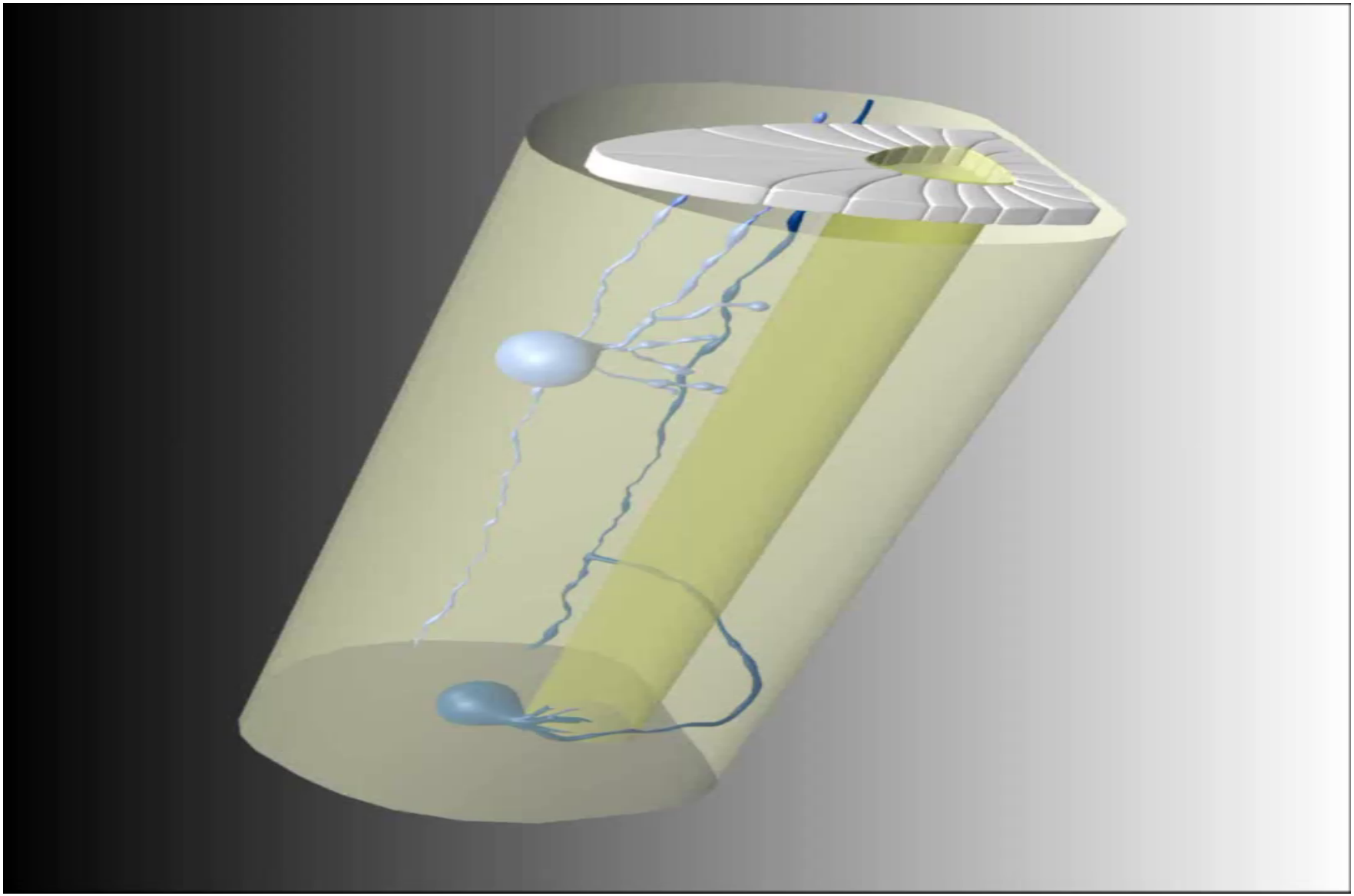


Measured excitatory neuron (dIN)

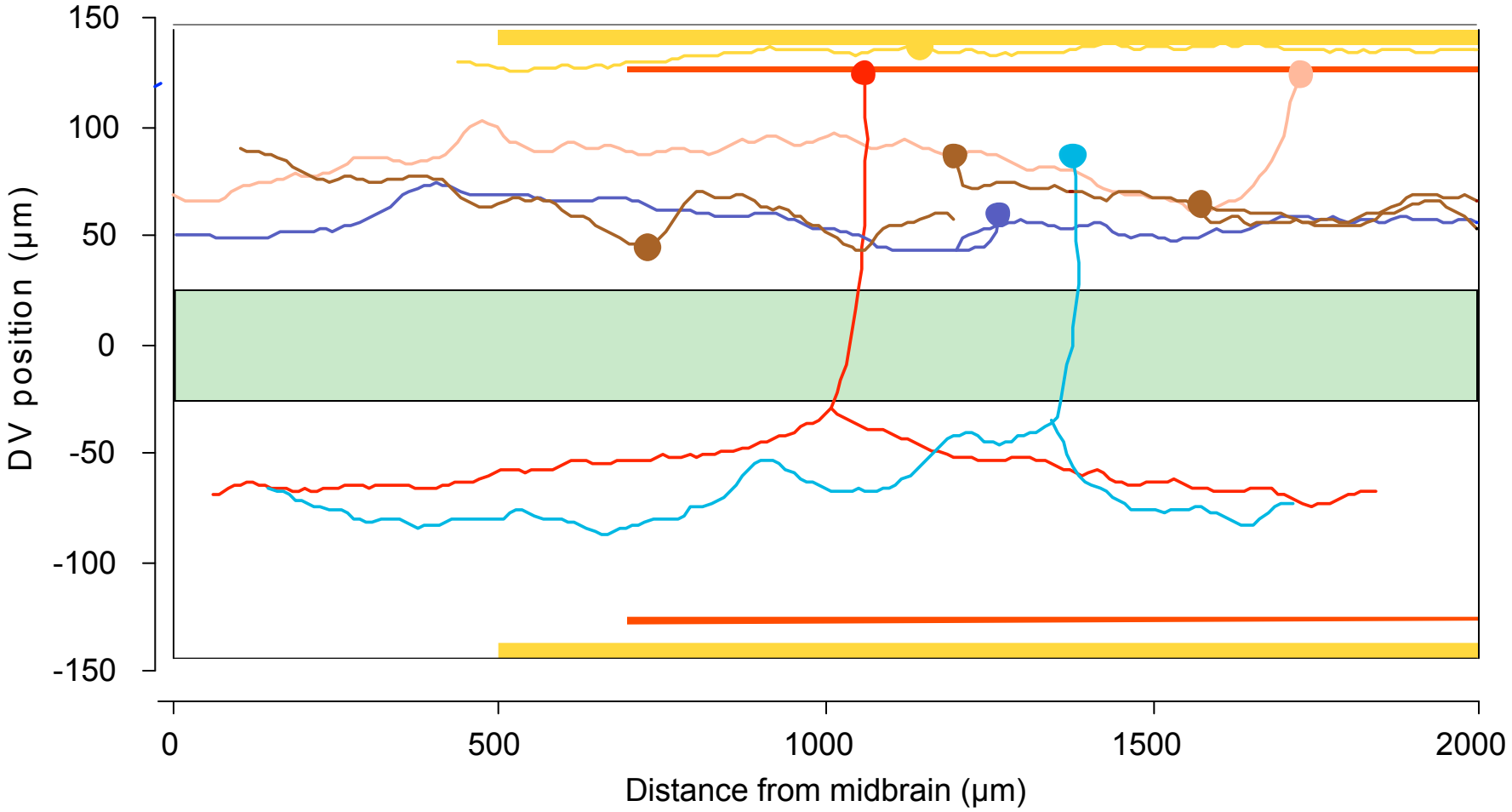


Soma diameter ~ 10 μm

2D plan of tadpole spinal cord

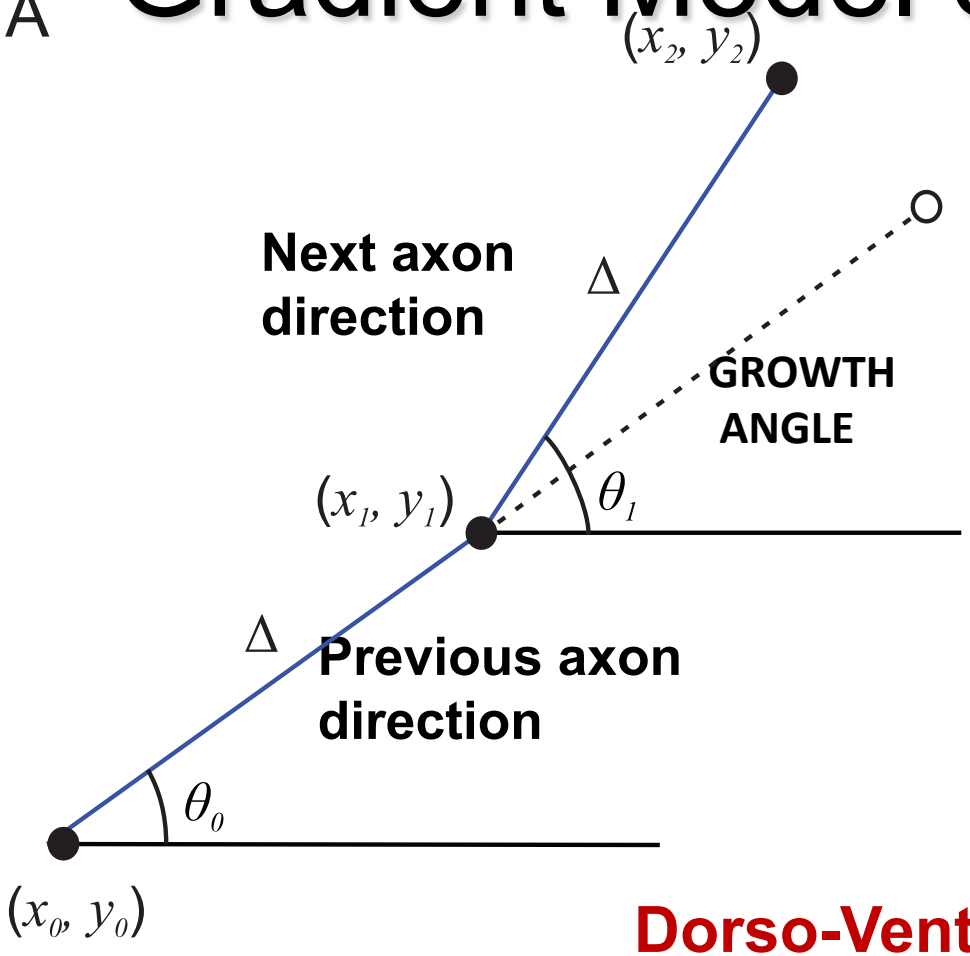


Neurons mapped onto 2D surface



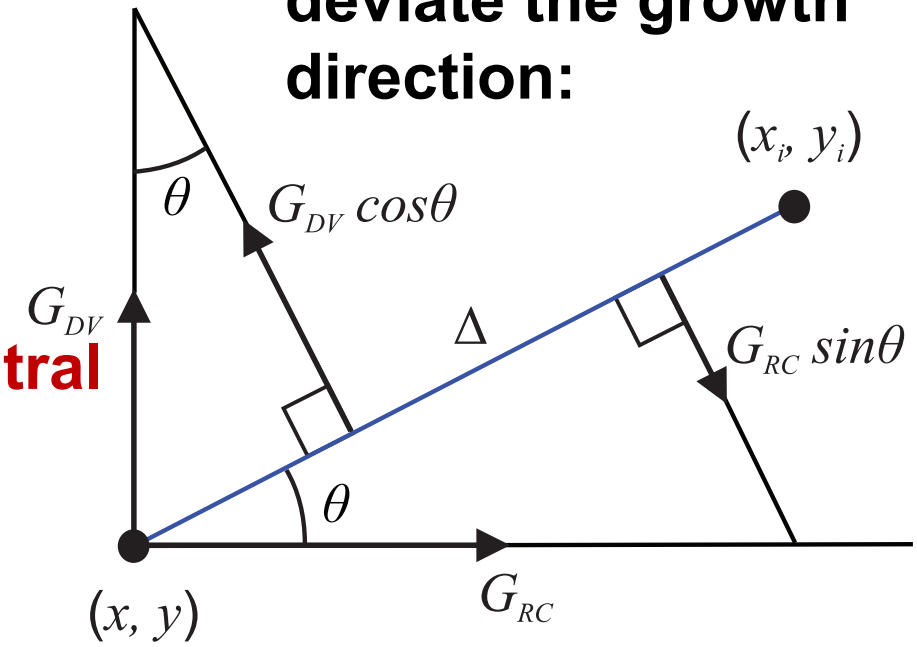
A

Gradient Model of Axon Growth



Dorso-Ventral gradients

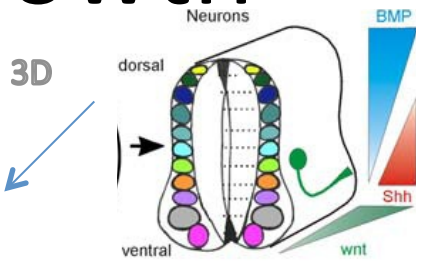
GRADIENTS deviate the growth direction:



Gradient along the body

Borisyuk et al., 2014, PLOS ONE

Gradient Model of Axon Growth



$$x_{n+1} = x_n + \Delta \cos\theta_n$$

$$y_{n+1} = y_n + \Delta \sin\theta_n$$

$$\theta_{n+1} = \theta_n - G_{RC}(x_n, y_n)\sin\theta_n + G_{DV}(x_n, y_n)\cos\theta_n + \xi_n$$

where (x_n, y_n, θ_n) describe the current coordinates of the growth cone and growth angle at step n $(n = 0,1,2,...N)$; Δ is an axon elongation at each step (1 micron).

$G_{RC}(x, y)$ and $G_{DV}(x, y)$ are Rostro-Caudal and Dorso-Ventral gradients

ξ_n is the value of a random variable (uniform in $[-\alpha, \alpha]$)

Gradient Model of Axon Growth

- The effects of the rostro-caudal and dorso-ventral gradients are actually an interaction between two components: the environmental cue itself and the sensitivity of the axon tip to that cue. The resulting influence depends on the position of the axon tip:

$$G_{RC}(x,y) = g_R\, H_R(x) - g_C\, H_C(x),$$

$$G_{DV}(x,y) = g_D\, H_D(y) - g_V H_V(y),$$

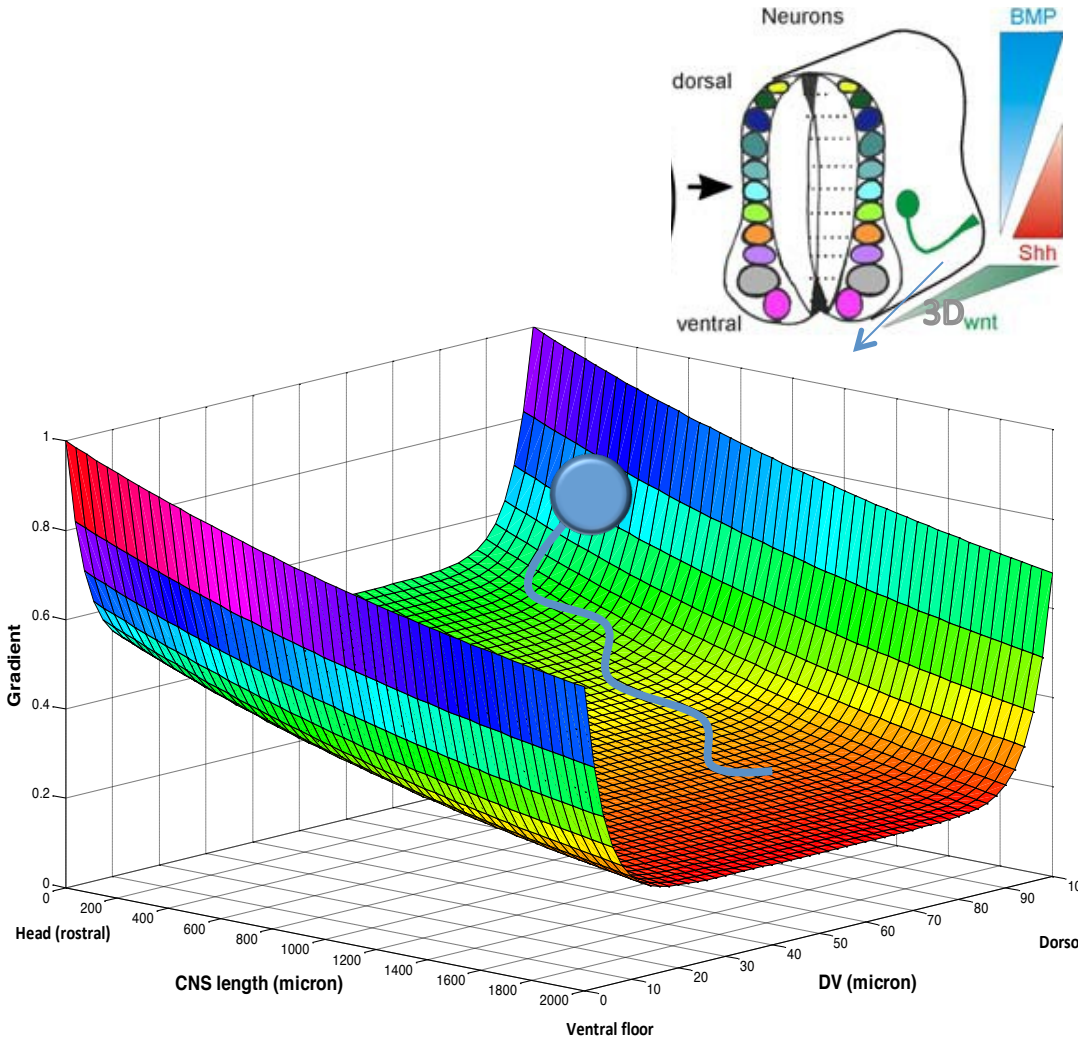
where H_R, H_C, H_V, H_D describe the **environmental gradient cues** which are universal for all axons while functions $g_R(x,y), g_C(x,y), g_D(x,y), g_V(x,y)$ describe the **sensitivities of axon tip** to each element of the gradient field.

Borisyuk et al., 2014, PLOS ONE

Gradient Model of Axon Growth

The gradient environment is assumed to be common for all growing axons (neurons of all types).

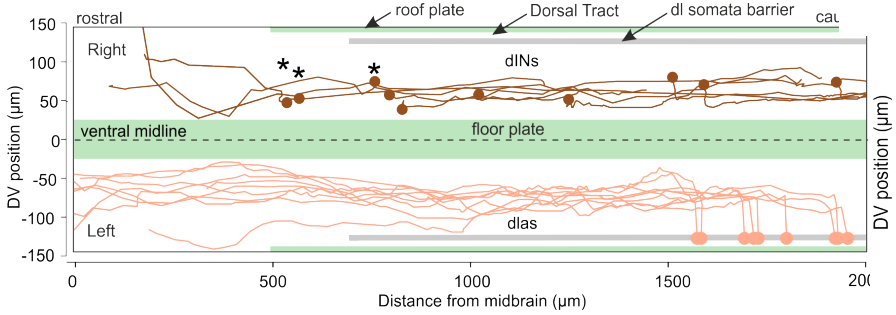
Axon sensitivities to these gradient field are specific for neurons of different types.



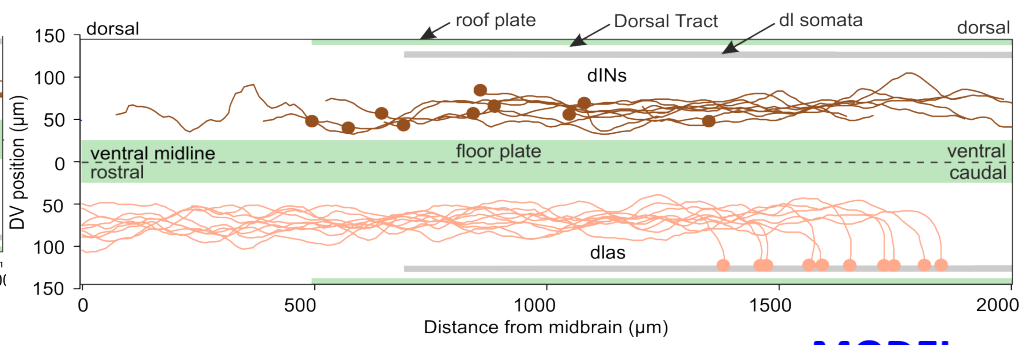
A profile of the gradient field on one side of the tadpole spinal cord guides the axon growth

Developmental Approach

- The idea of a new **Developmental Approach** is to analyse the experimental data on neuron anatomy and extract their "characteristic features" which are then used for modelling.
- Thus, the model is able to **generalize** from the data and generate an extended set of artificial objects with the **same statistical characteristics** as the experimental evidence.

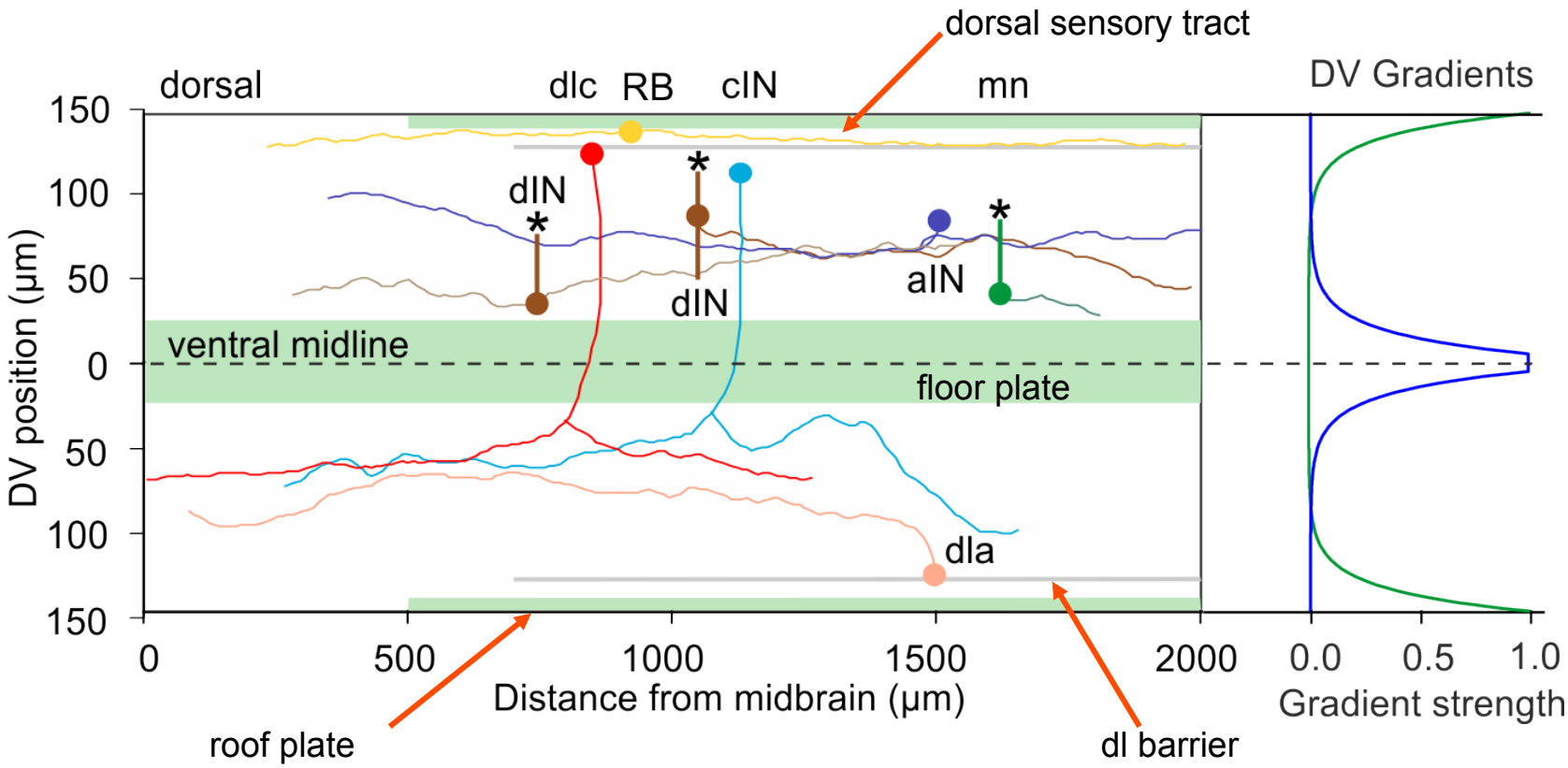


REAL



MODEL

CNS development:



Neurons lie in 2D axon growth environment with longitudinal polarity and 2 DV gradients shown on right

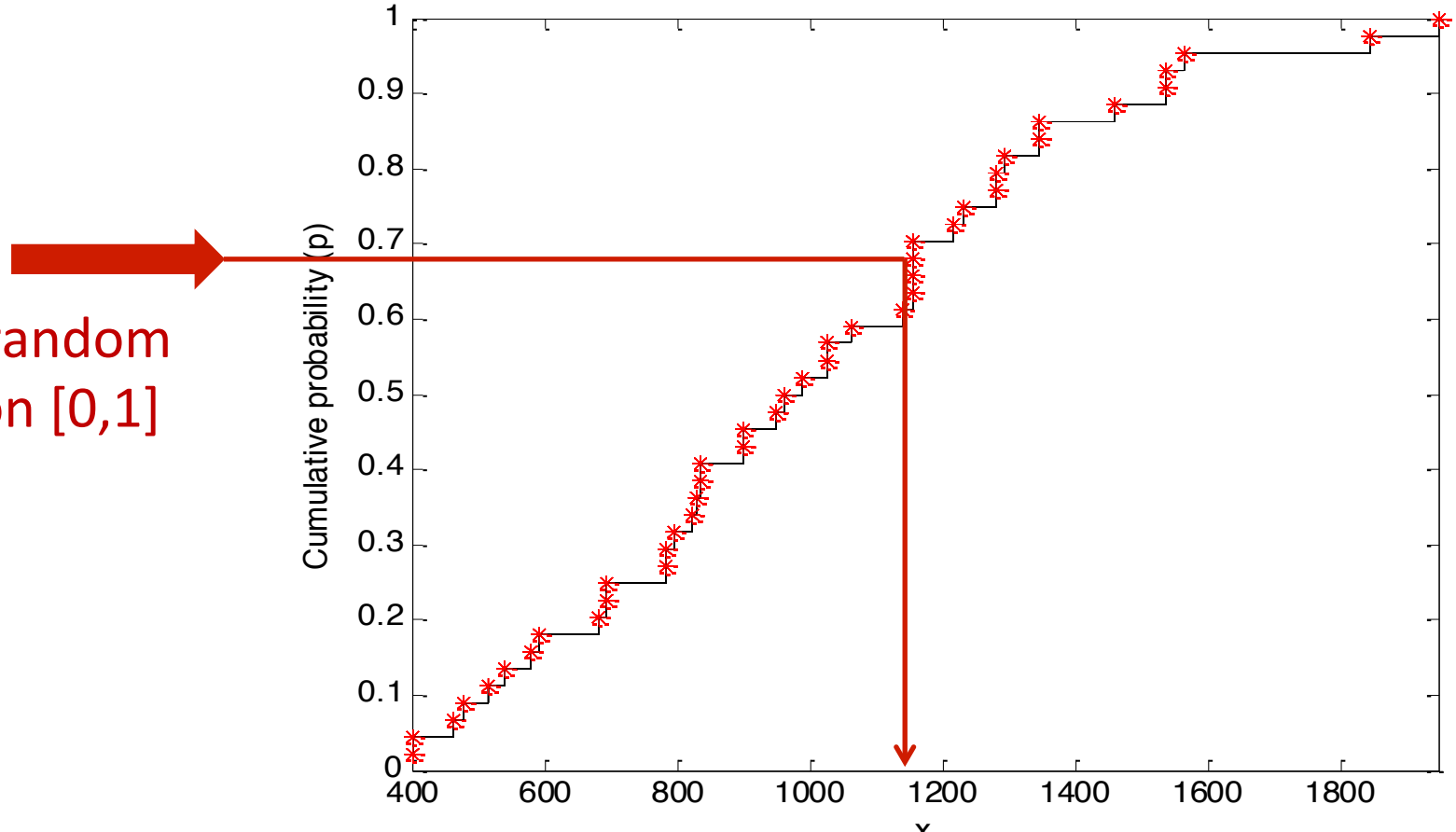
Generalization from data

- To simulate the axon growth we have to specify the initial coordinates, initial growth angle and the axon length.
- These values are extracted from experimental measurements using the generalisation procedure.
- Starting from a sample we calculate the cumulative distribution function to estimate a value of the random variable.

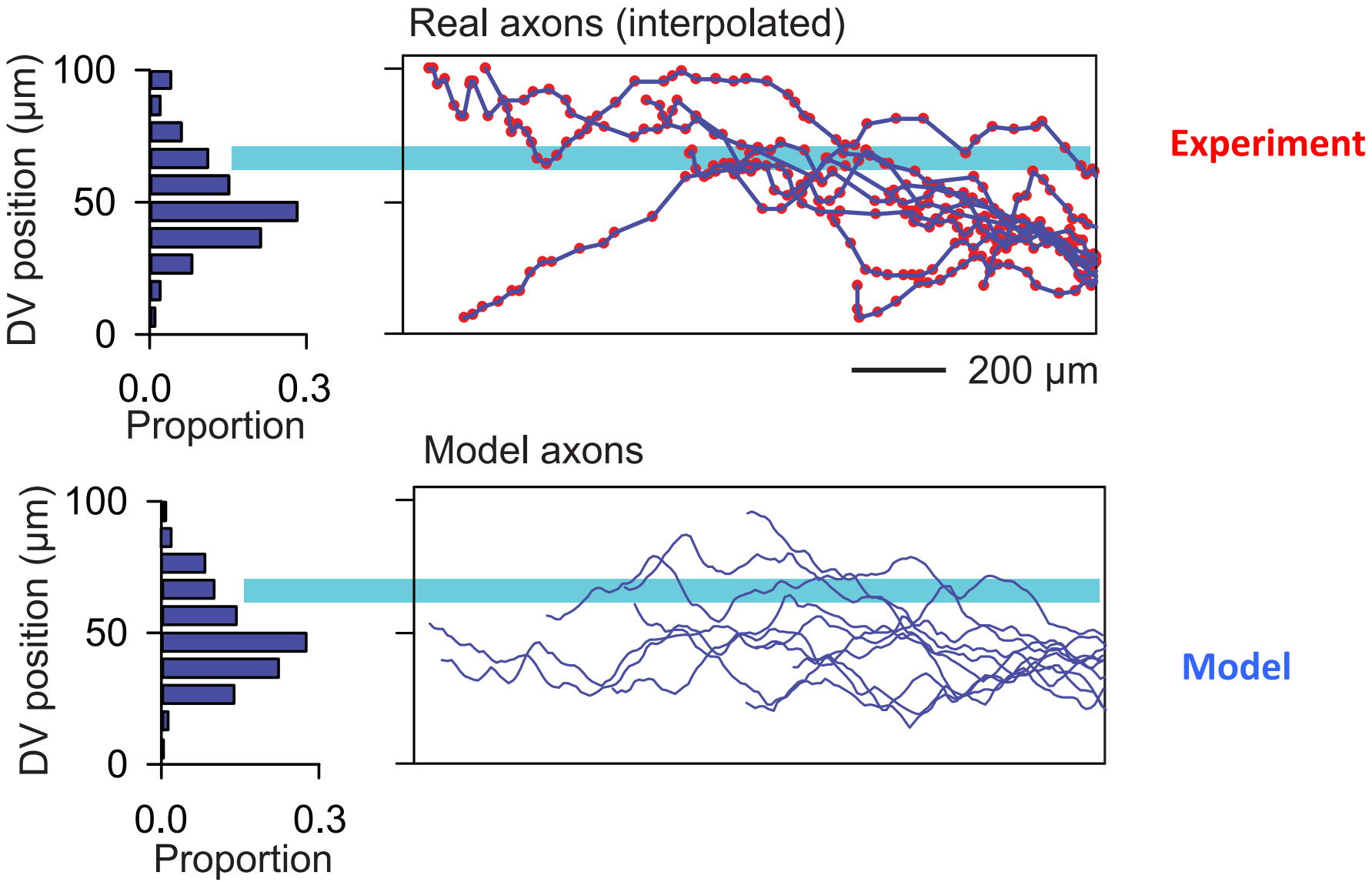
Generalization from data

Example: Random value of the axon length is generalised from experimental recordings of 33 axons. The cumulative distribution function is calculated.

Uniform random variable on [0,1]



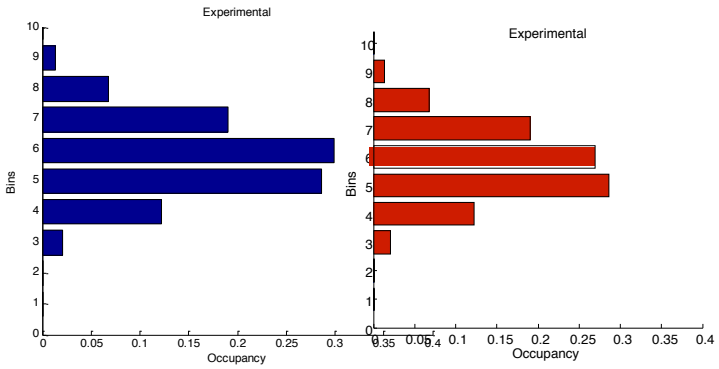
Cost function: Dorso-Ventral projection of axon coordinates



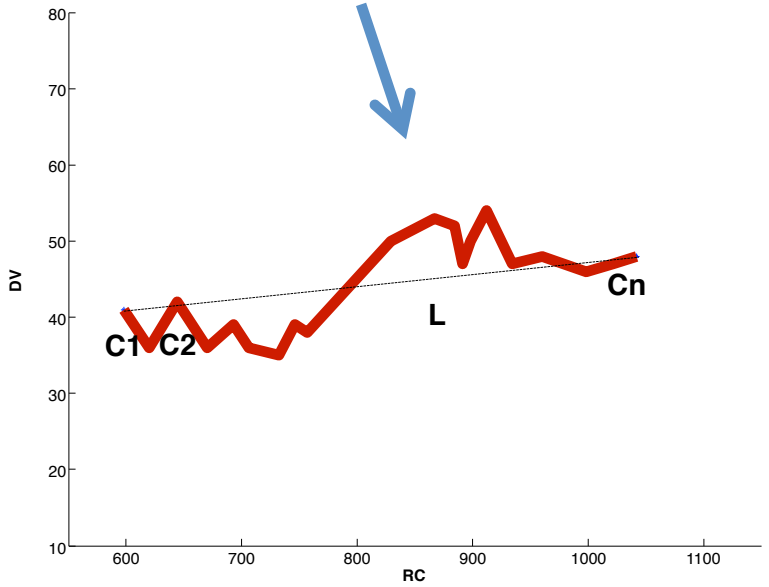
Optimizing model parameters

Cost-function:

$$f_c = \sum_{i=1}^{10} (y_i^e - y_i^m)^2 + \varepsilon(\overline{T^e} - \overline{T^m})^2$$



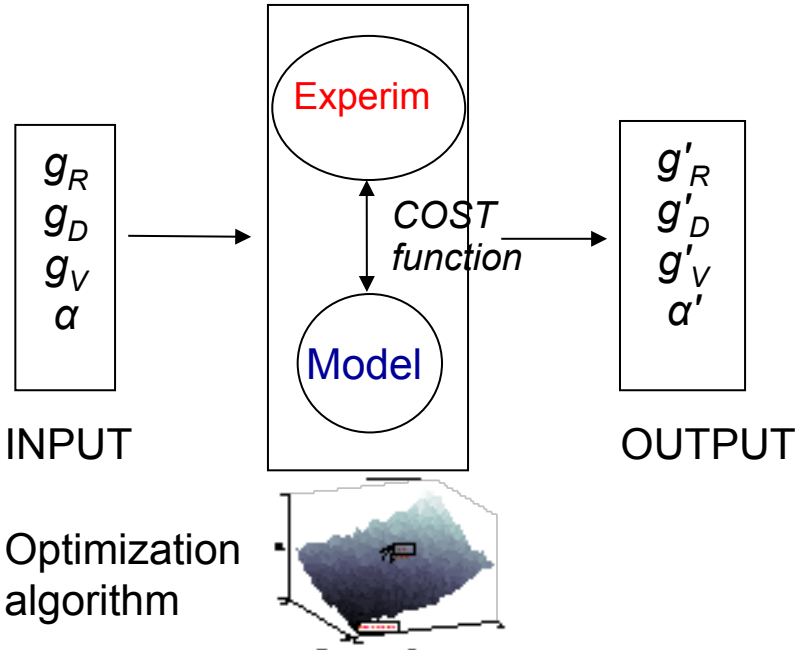
Squared difference of experimental and modelled projections



Tortuosity:
Squared difference of experimental and modelled average tortuosity

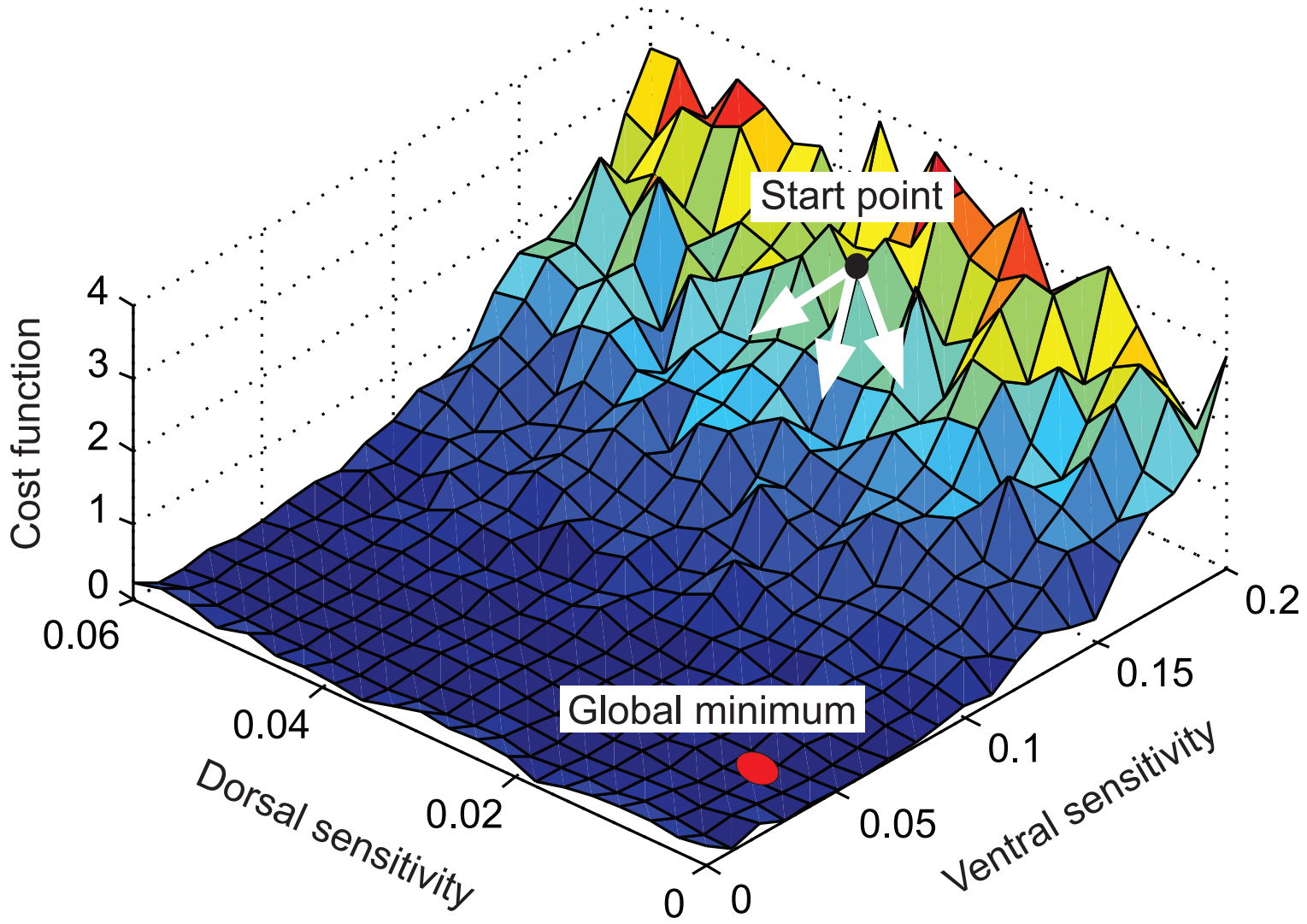
Optimizing model parameters

For each type of spinal cord neurons, the model of axon growth is fitted to experimental measurements of axon positions.
To find the best parameter values, the cost function is specified and minimised.
The cost function is not smooth, therefore a stochastic programming approach is used to optimise fitting

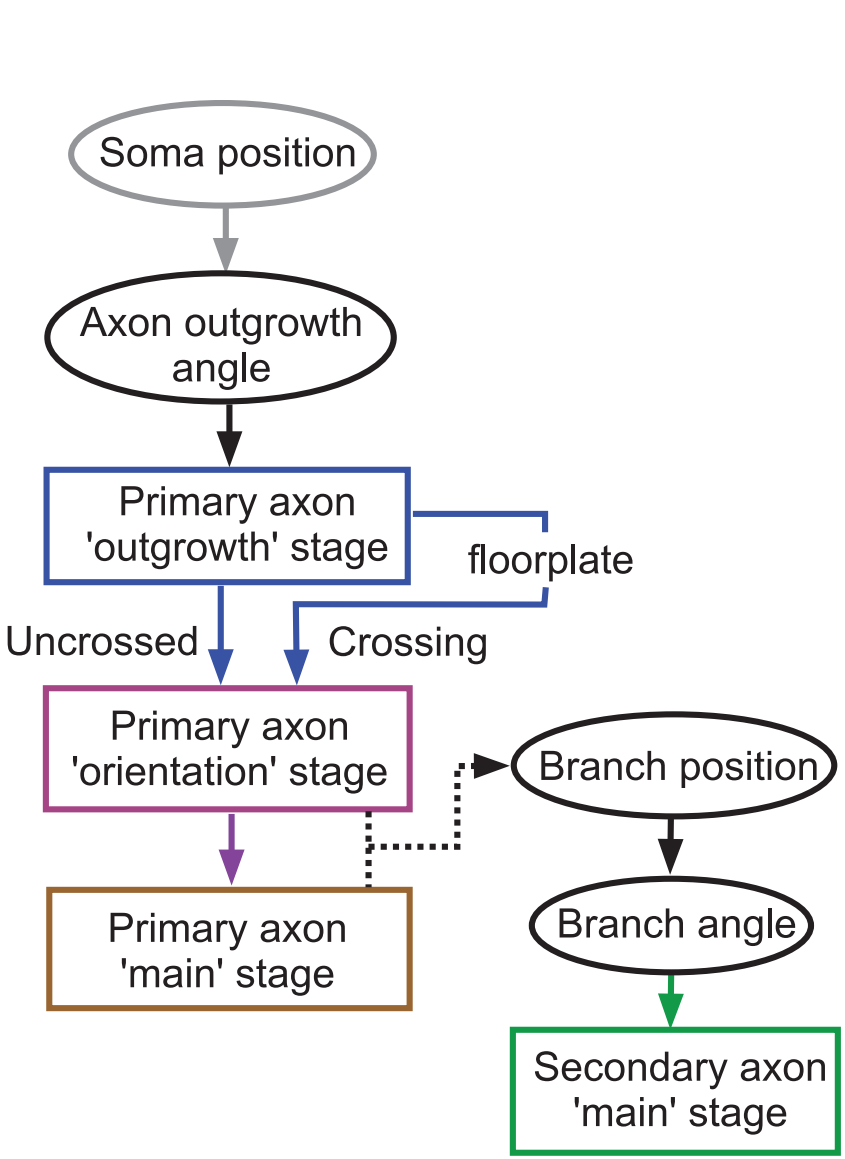


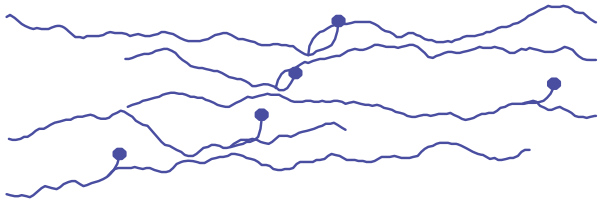
Pattern search optimization method requires only function value and not the derivatives.

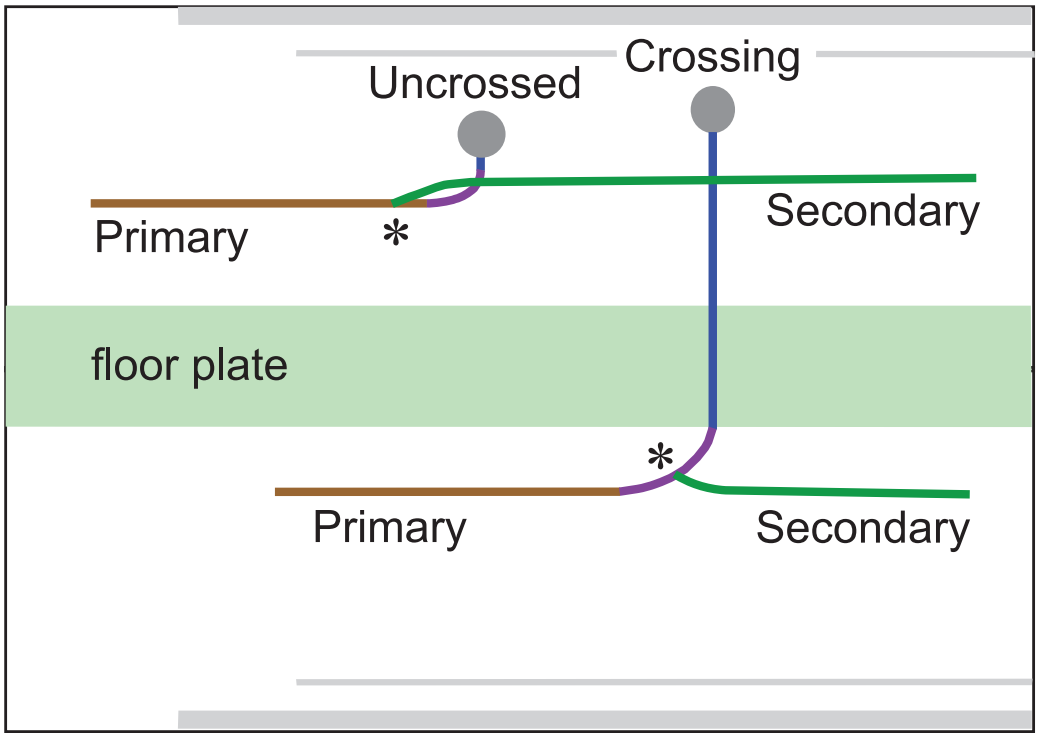
Stochastic optimization in 4D

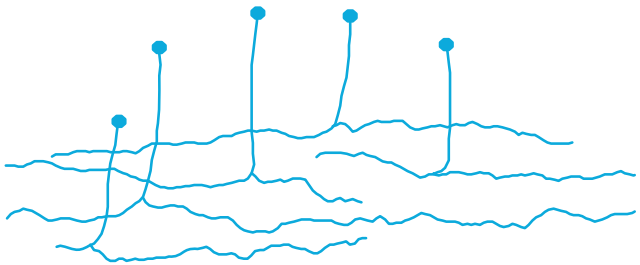


Stages of axon growth

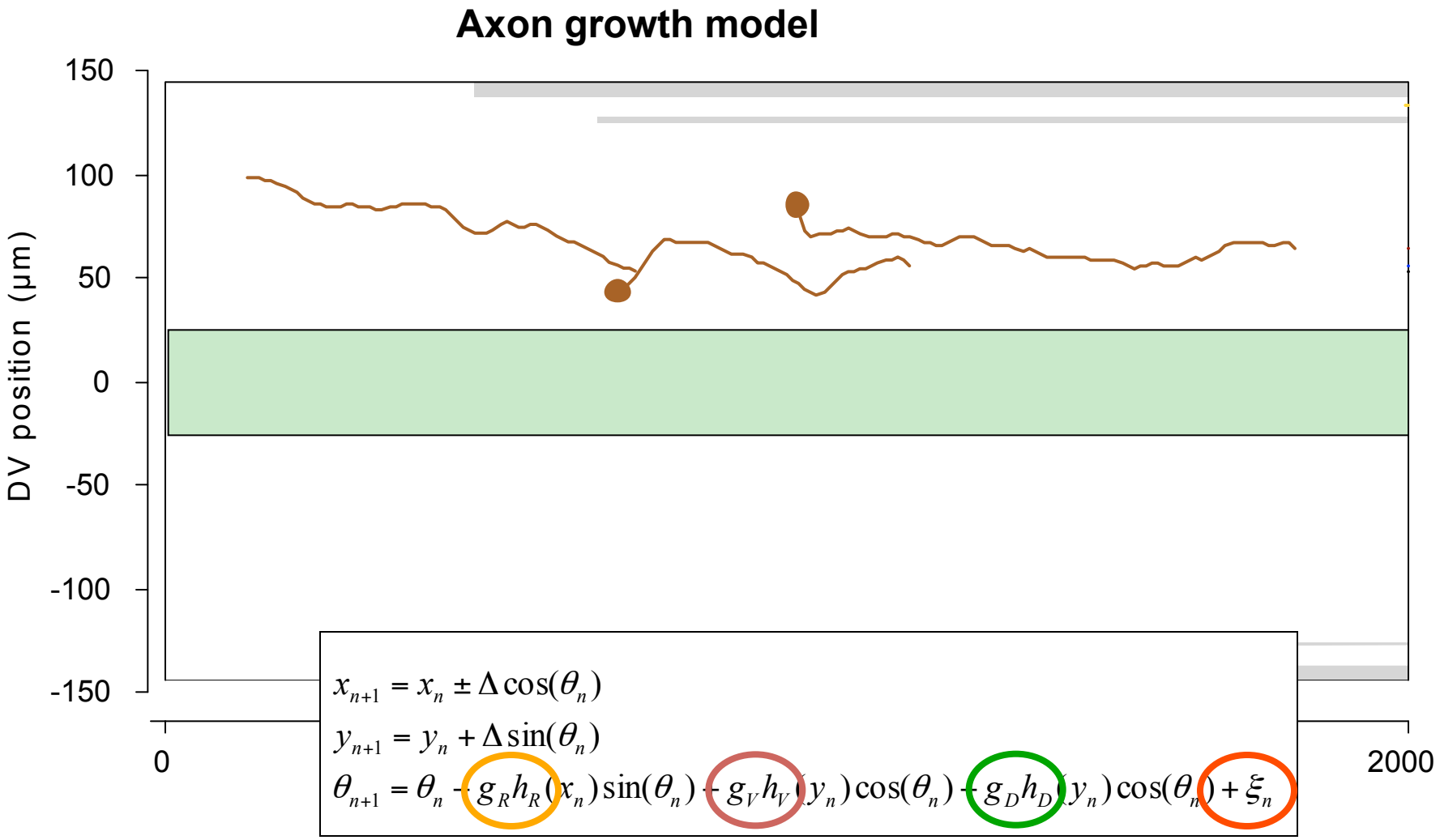






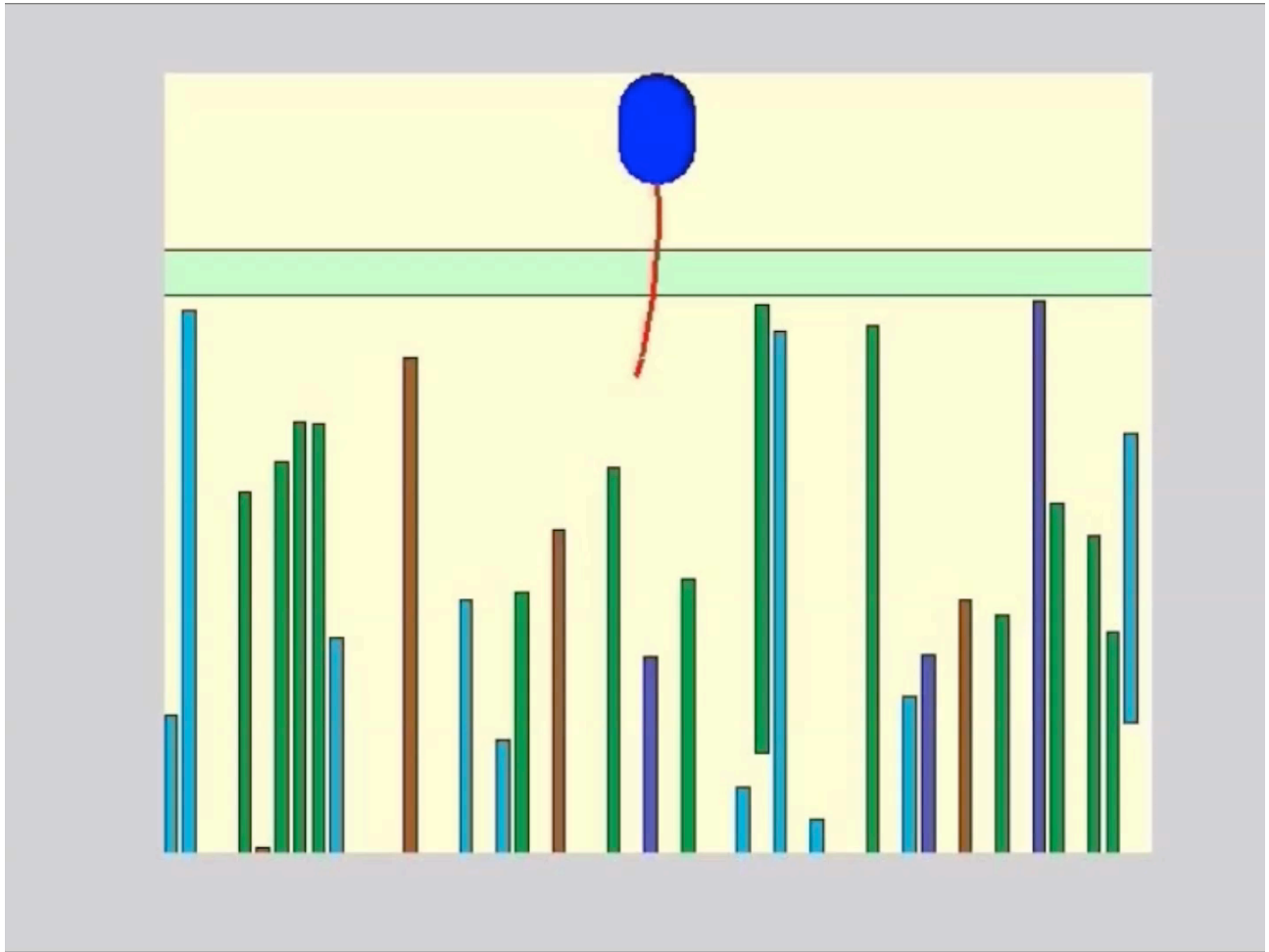


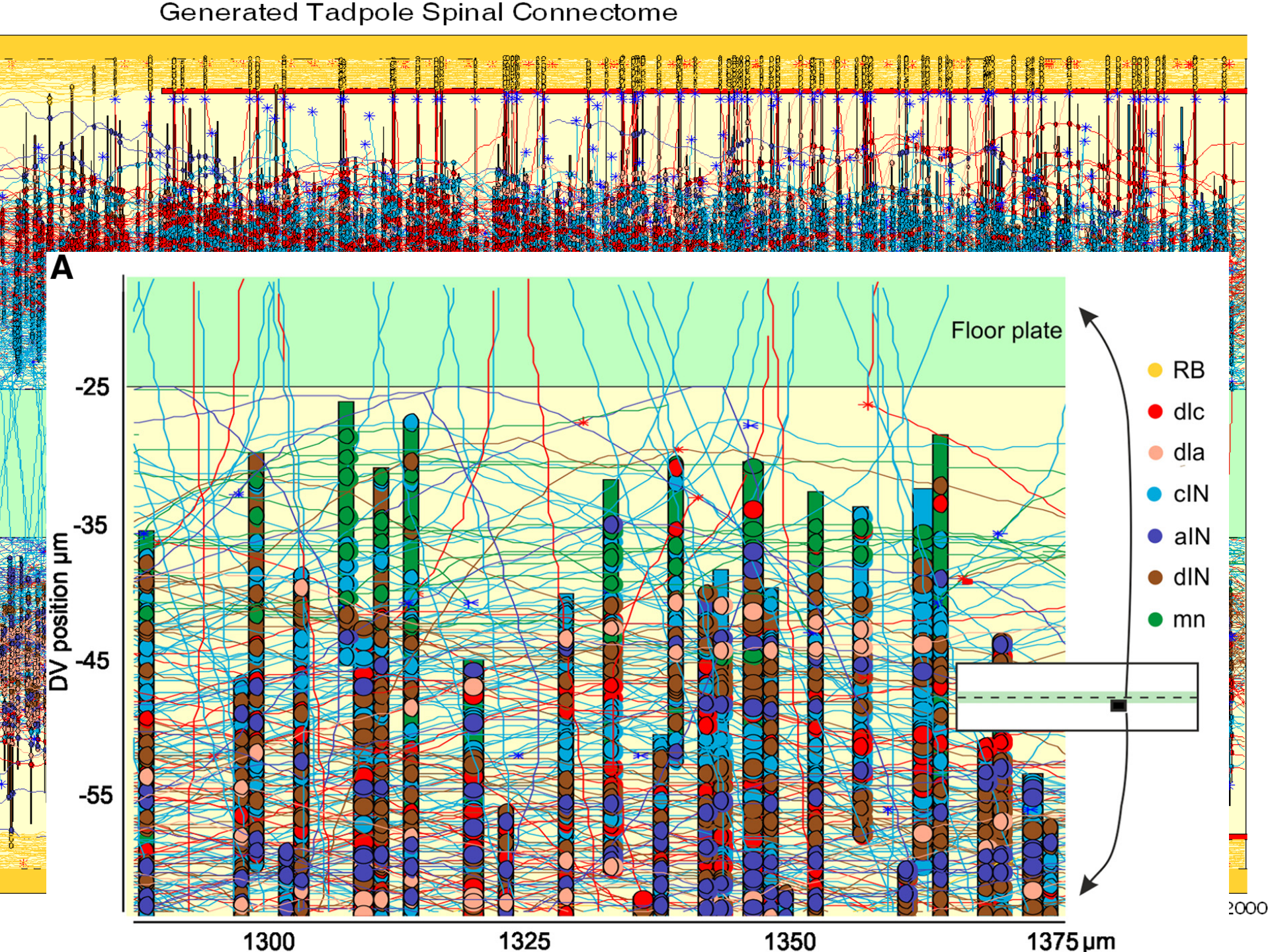
CNS development:



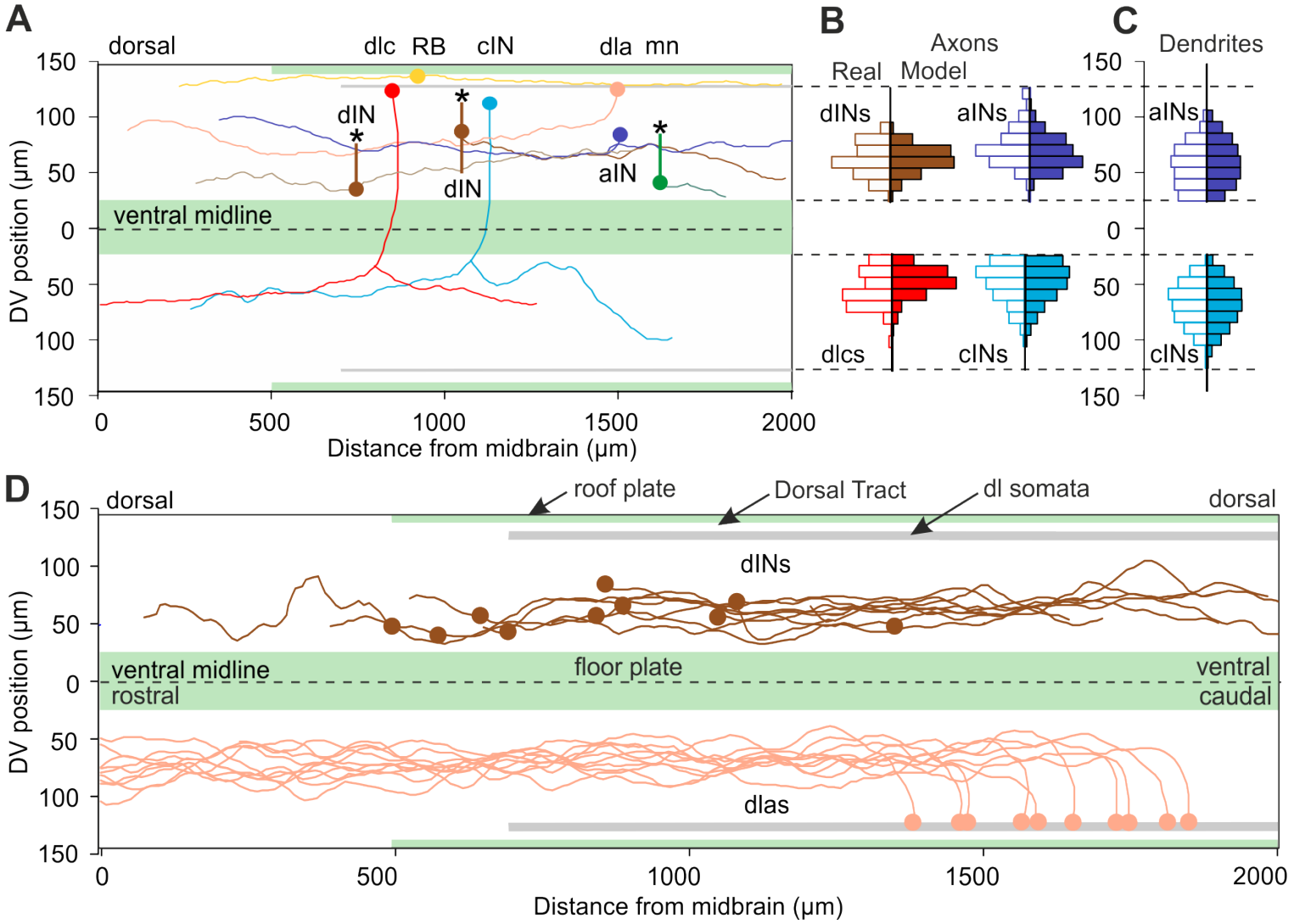
Developmental Approach

Computational model generates a growing axon and synapses appear (with some probability) when the axon intersects a dendrite.




Generated Tadpole Spinal Connectome
A
Floor plate
-25
-35
-45
-55
DV position µm
1300
1325
1350
1375 µm
RB
dlc
dla
cIN
aIN
dIN
mn

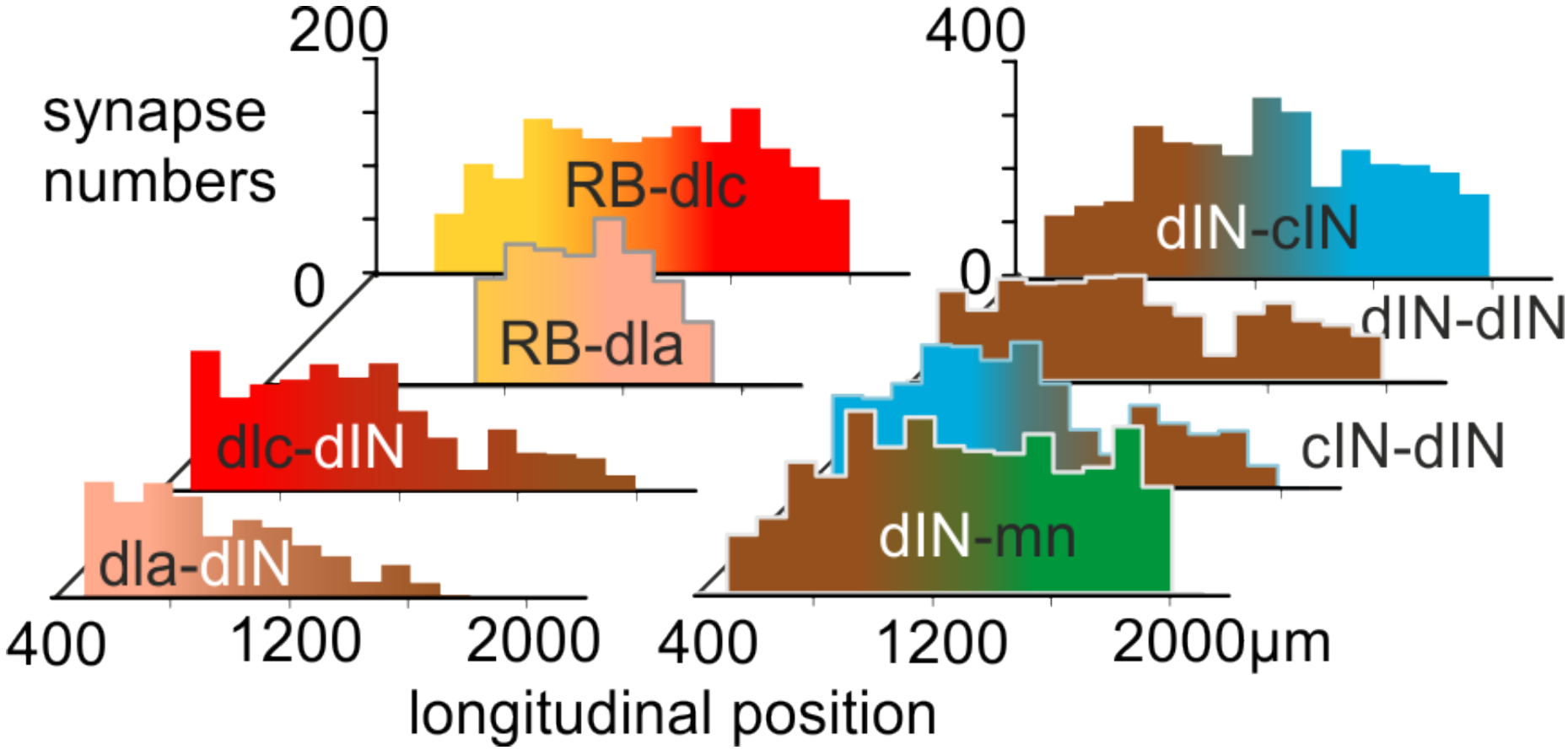
CNS development:



Roberts et al., 2014, J Neurosc

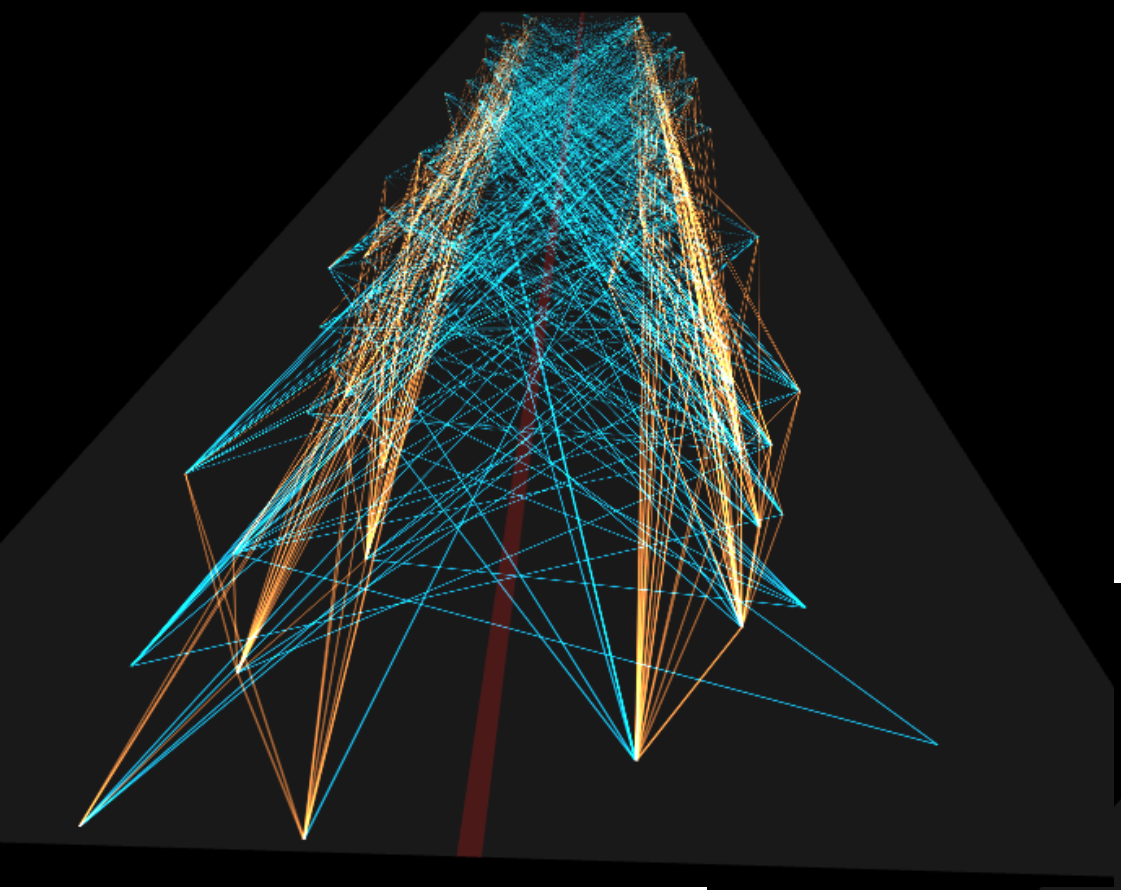
Li et al., 2014, J Neurosc

Distribution of synaptic connections along the body

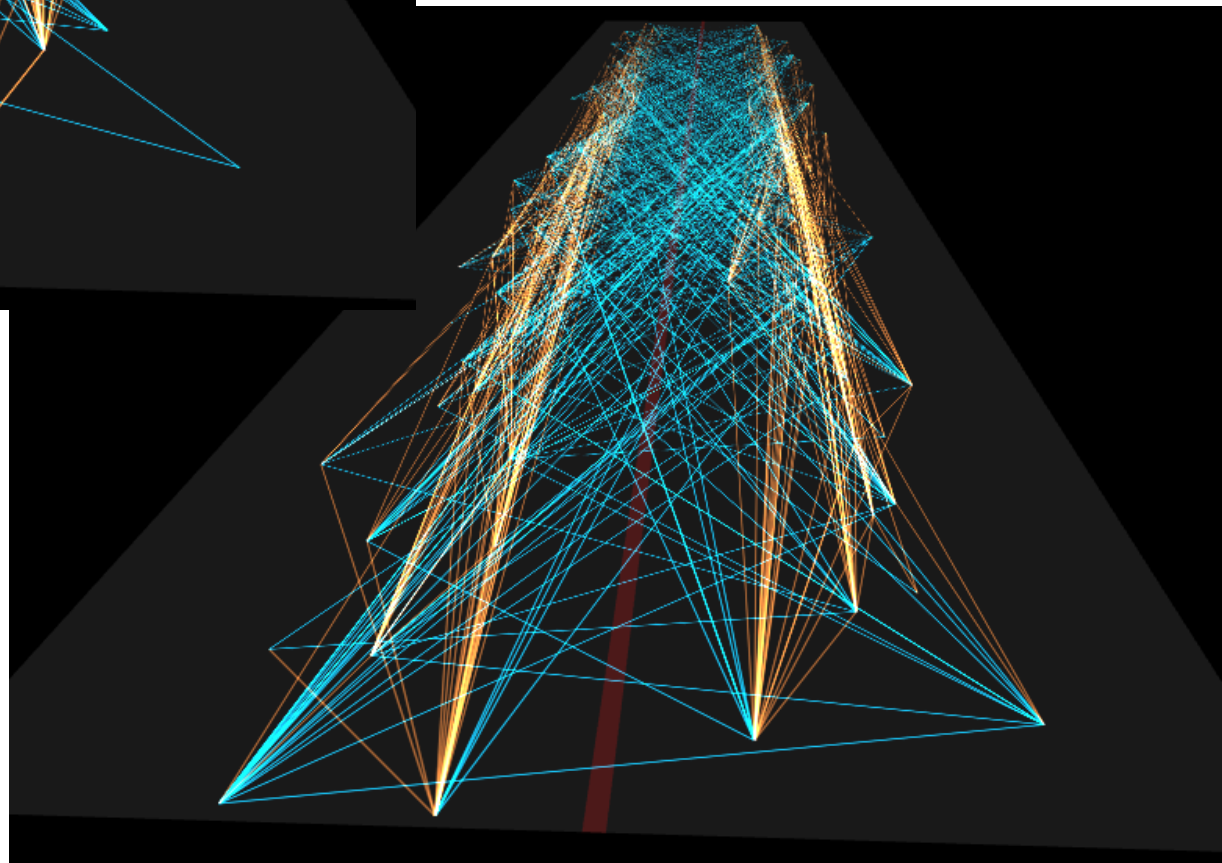


Sensory pathway

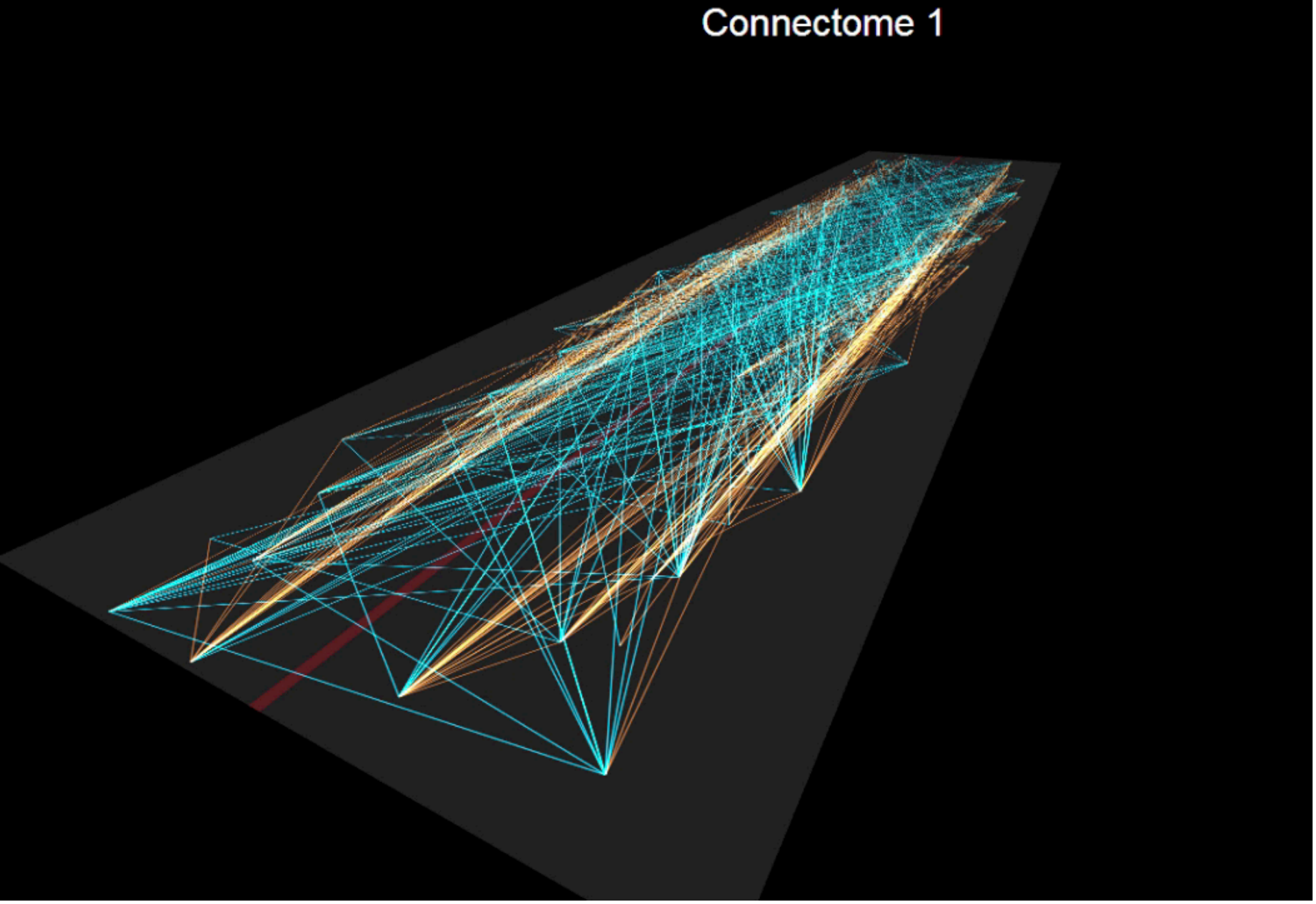
Pattern generator



Sub-graphs of excitatory connections from dINs and inhibitory connections from cINs (blue)



Graphs are different but activity patterns are the same


Connectome 1

Connectome

- Using developmental approach and generalization from the data, a complete biologically realistic neural connectome is generated.
- 2000 cell bodies and their dendrites are distributed on both sides of the body. For each cell type the axon growth model with optimal parameter values is used to generate an axon of each cell.
- If an axon passes the dendrite (a vertical bar) synaptic contact is generated with some probability.
- A total number of synapses is about 140,000.

Experiment: swimming on touch

Network swimming

- Hatchling *Xenopus* tadpoles swim for many seconds in response to a brief skin stimulus.

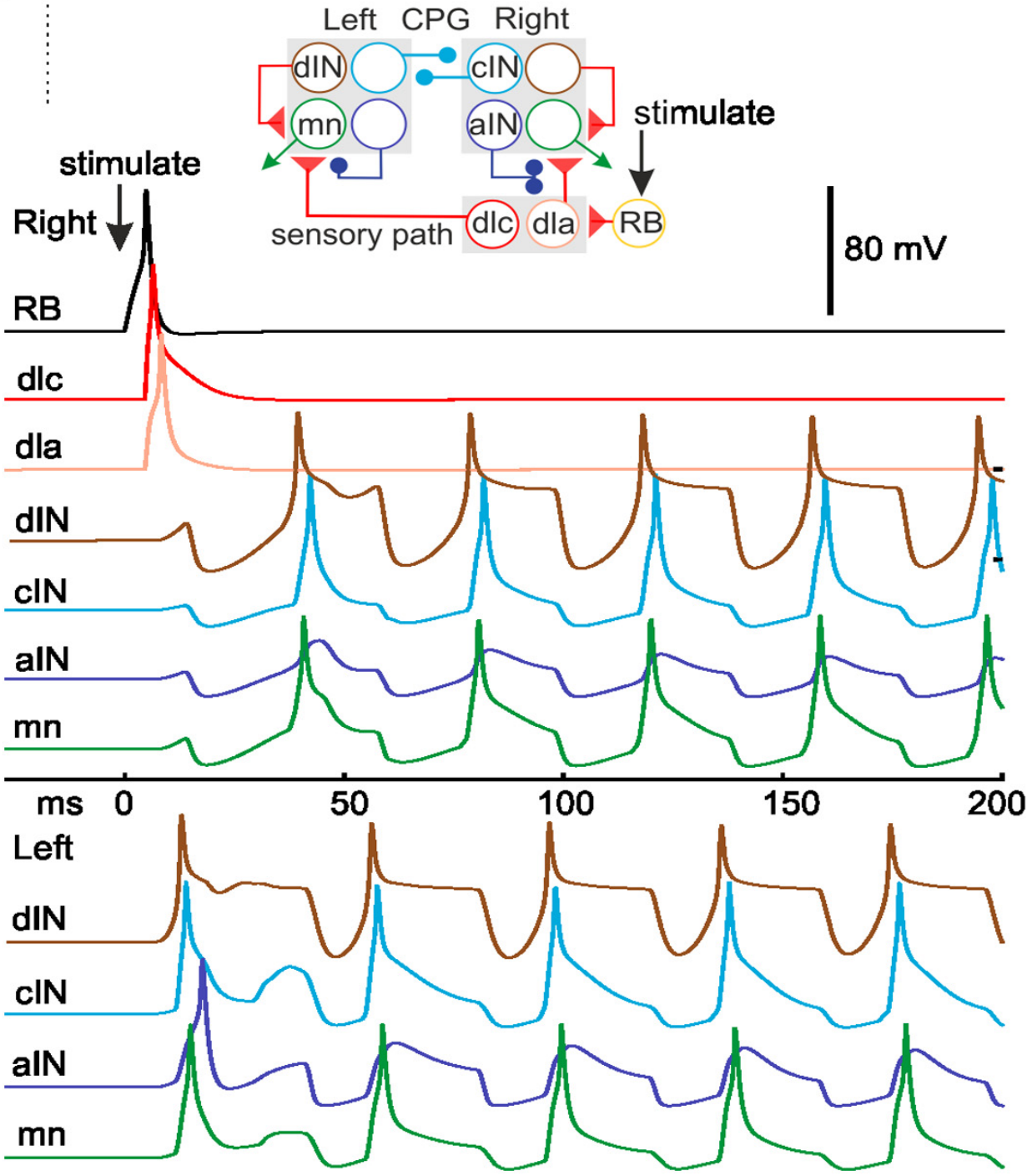
- The anatomy, properties and synaptic connections of 7 types of neuron underlying this behaviour were assessed directly by recording pairs of neurons.

- Swimming depends on network connections + special properties of excitatory dINs with postinhibitory rebound firing and mutual excitation (AMPA + NMDA)

Model of swimming pattern

- Spiking activity of each neuron is modelled by a conductance based model of the Hodgkin-Huxley type.
- Connections between neurons are defined by the generated connectome.
- There are several characteristic elelctro-physiological features typical for tadpole swimming pattern (e.g. pacemaker properties of dIN neurons).
- Model includes both electrical and synaptic connections, delays in spike propagation, randomised parameters in particular, connection strengths.

Swimming initiation

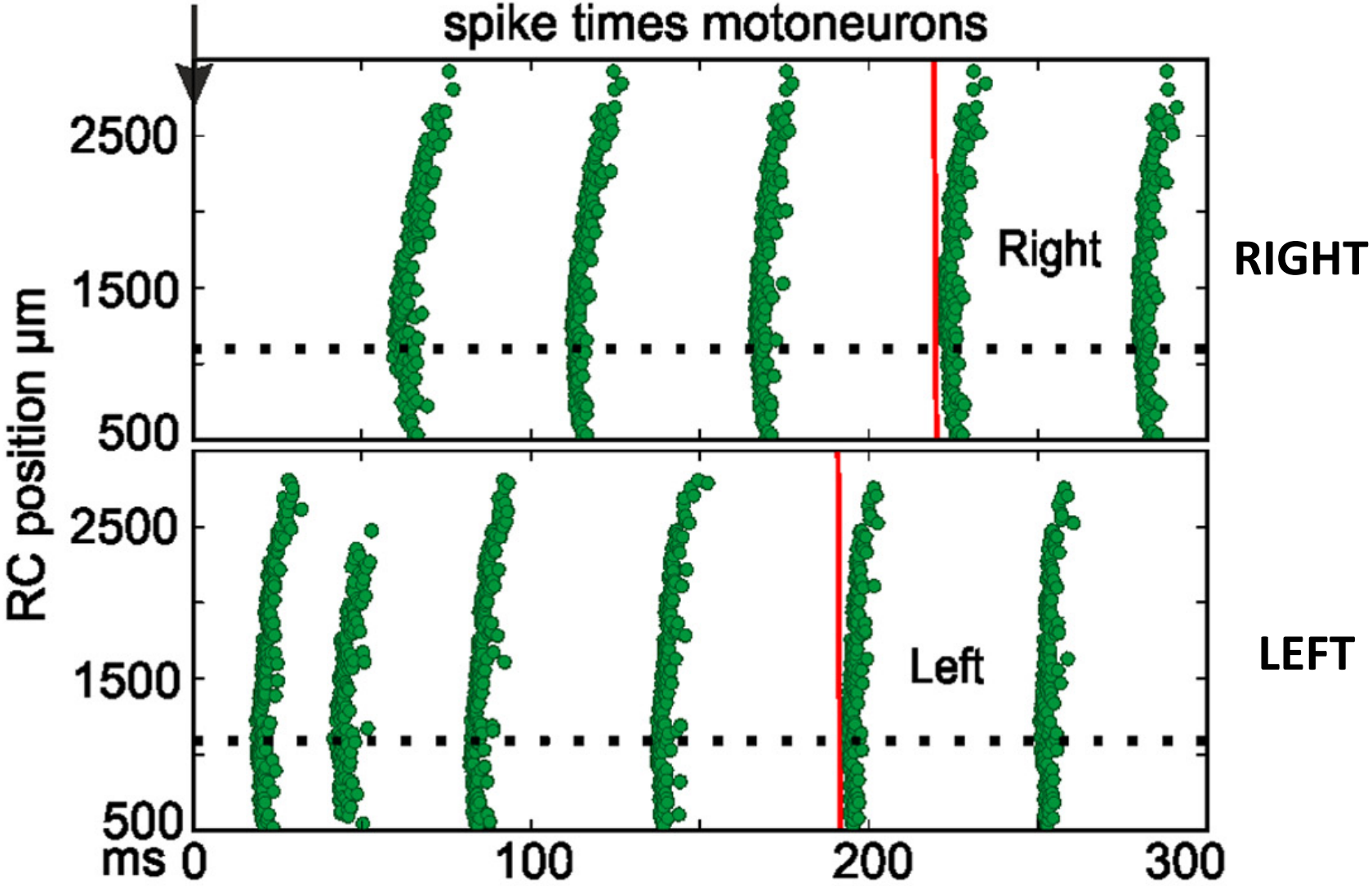


Roberts et al., 2014, J Neurosc
Li et al., 2014, J Neurosc

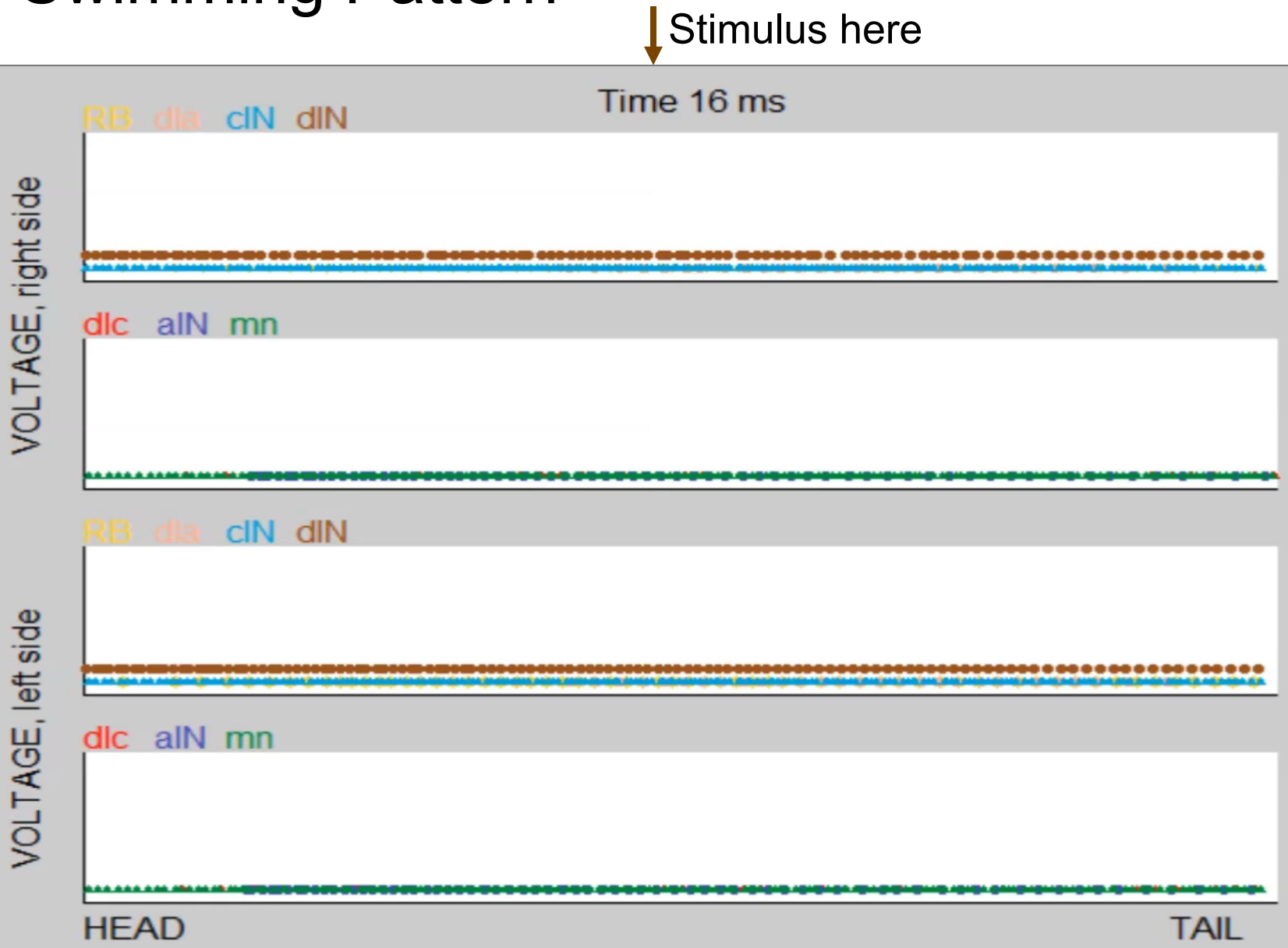
Initiation of swimming

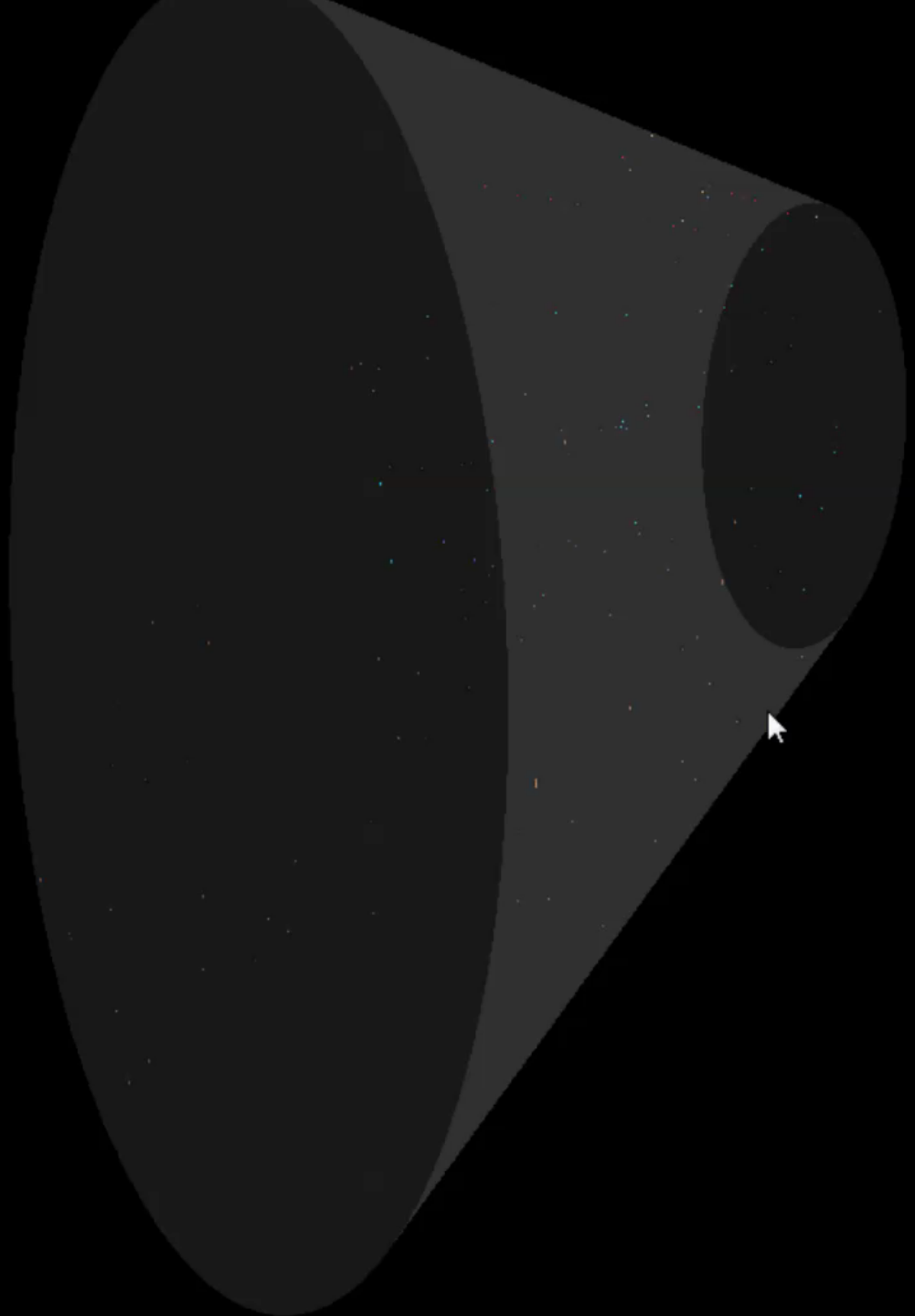
We model a sensory pathway of swimming initiation:
On a skin touch (left side) a small group of sensory interneurons (RB-cells) produces spikes.
These spikes excite dla-neurons near the middle of the body. These cells have long dendrites and they deliver excitation to the head.
Also, dlc-cells are excited and they deliver excitation to the right side.
After that pacemaker activity of dIN-neurons excites cIN-cells which inhibit dIN-neurons of the opposite side to produce the anti-phase oscillations.
Motor neurons on each side deliver excitation to muscles to produce the swimming pattern

Antiphase spike propagation



Swimming Pattern





Conclusions:

• A simple axon growth model with physical barriers separating off sensory axons can match real axon projections and generate a synaptic connection map or “connectome” for the swim network

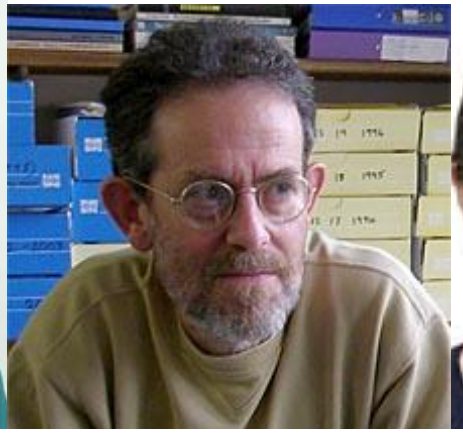
• When this connectome is mapped onto a functional model, it can swim in response to brief “sensory” stimuli even without detailed axon projection features

•Pattern of swimming activity appears without any training the neural network, this pattern is very robust and exits in a broad range of parameter variation

• The results suggest that simple rules without specific neuron recognition may allow basic neuronal networks to self-assemble and generate appropriate patterns of spiking activity

Acknowledgement

BRISTOL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