

A Multiscale-Multiphysics Model for Axon Pathfinding Simulation, the Example of the Olfactory System

G. Aletti, P. Causin, G.Naldi



UNIVERSITÀ
DEGLI STUDI
DI MILANO



*Dipartimento di Matematica "F.Enriques"
Universita degli Studi di Milano - Italy*

work in collaboration with: M. Gozzo, G. Merlo, A. Zaghetto



Laboratory of Molecular Morphogenesis, Dulbecco Telethon Institute at
CNR-ITB

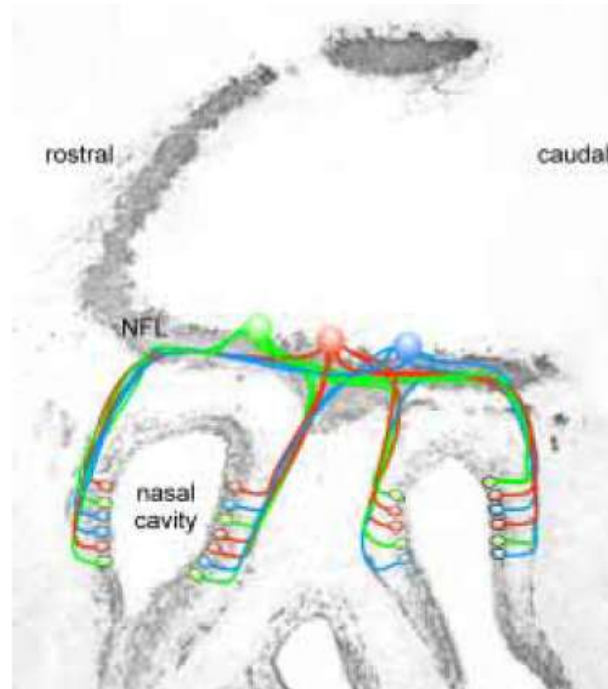
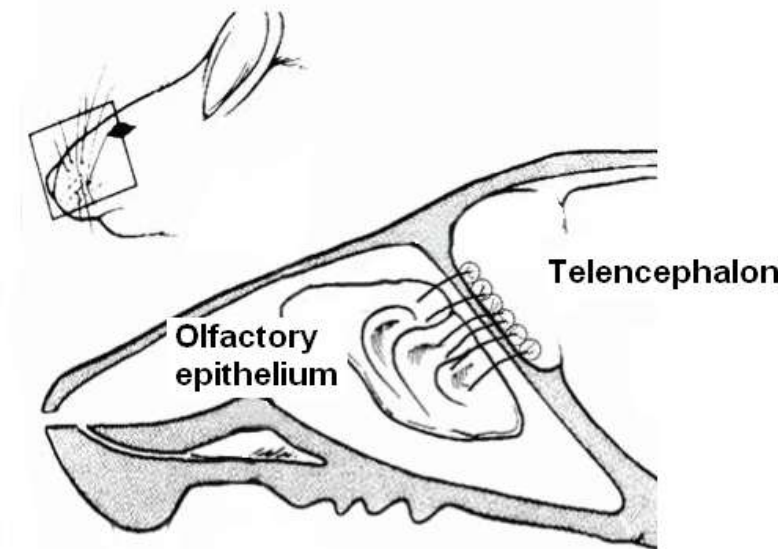
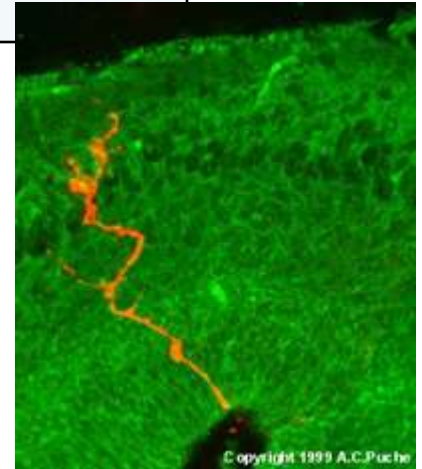
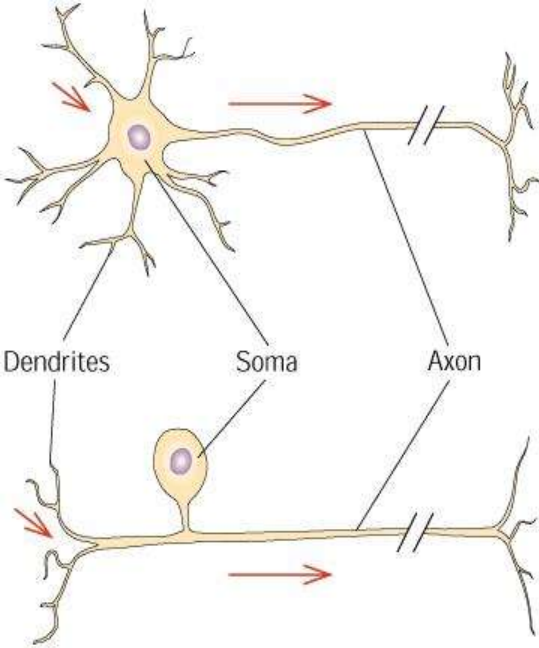
UNIVERSITÀ
DEGLI STUDI
DI TORINO
ALMA UNIVERSITAS
TAURINENSIS



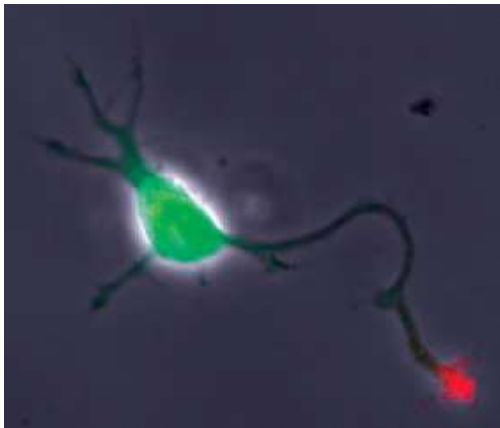
A. Puche (Univ. Maryland)



Neurogenesis in the development of the olfactory system



from J.A. St John et al., *Int. J. Dev. Biol.* **46**: 639-647 (2002)

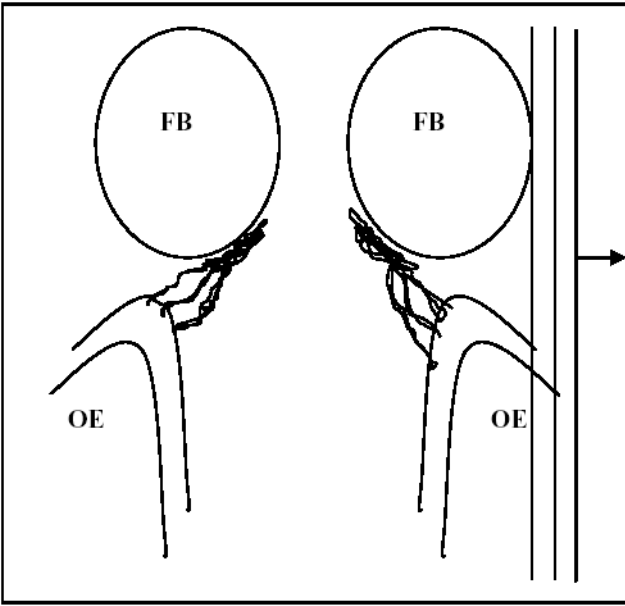
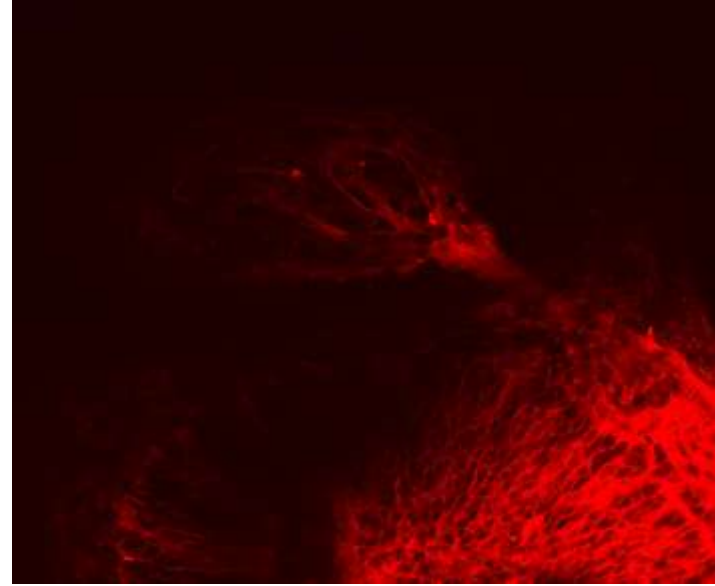


Toriyama, M. *et al.* Shootin1: a protein involved in the organization of an asymmetric signal for neuronal polarization. *J. Cell Biol.* 175, 147–157 (2006)

Outline

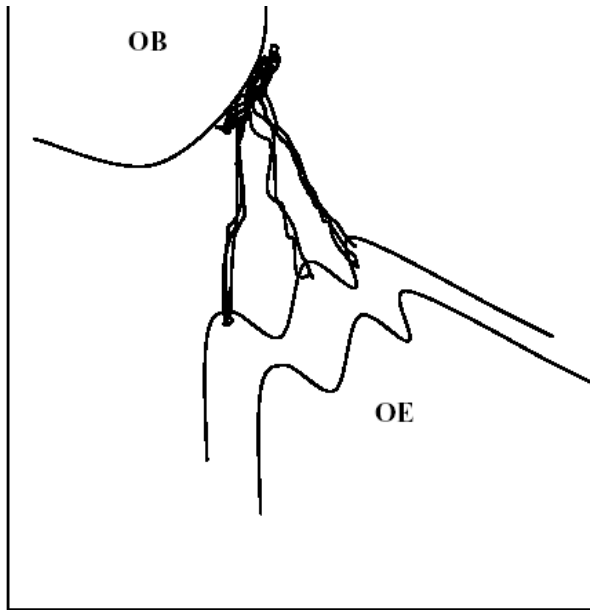
1. The “earliest” problem
2. Axon guidance: biological facts
3. Mathematical modelling
4. Full model simulations
5. Conclusions

The "earliest" problem



FB: forebrain OE: olfactory epithelium

E11.0

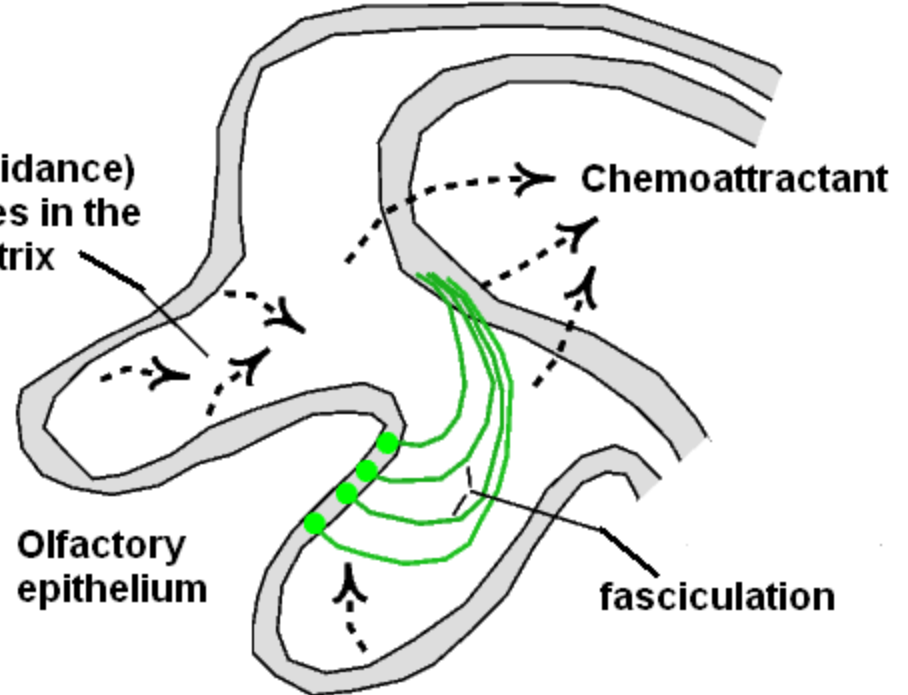


(guidance) cues in the matrix

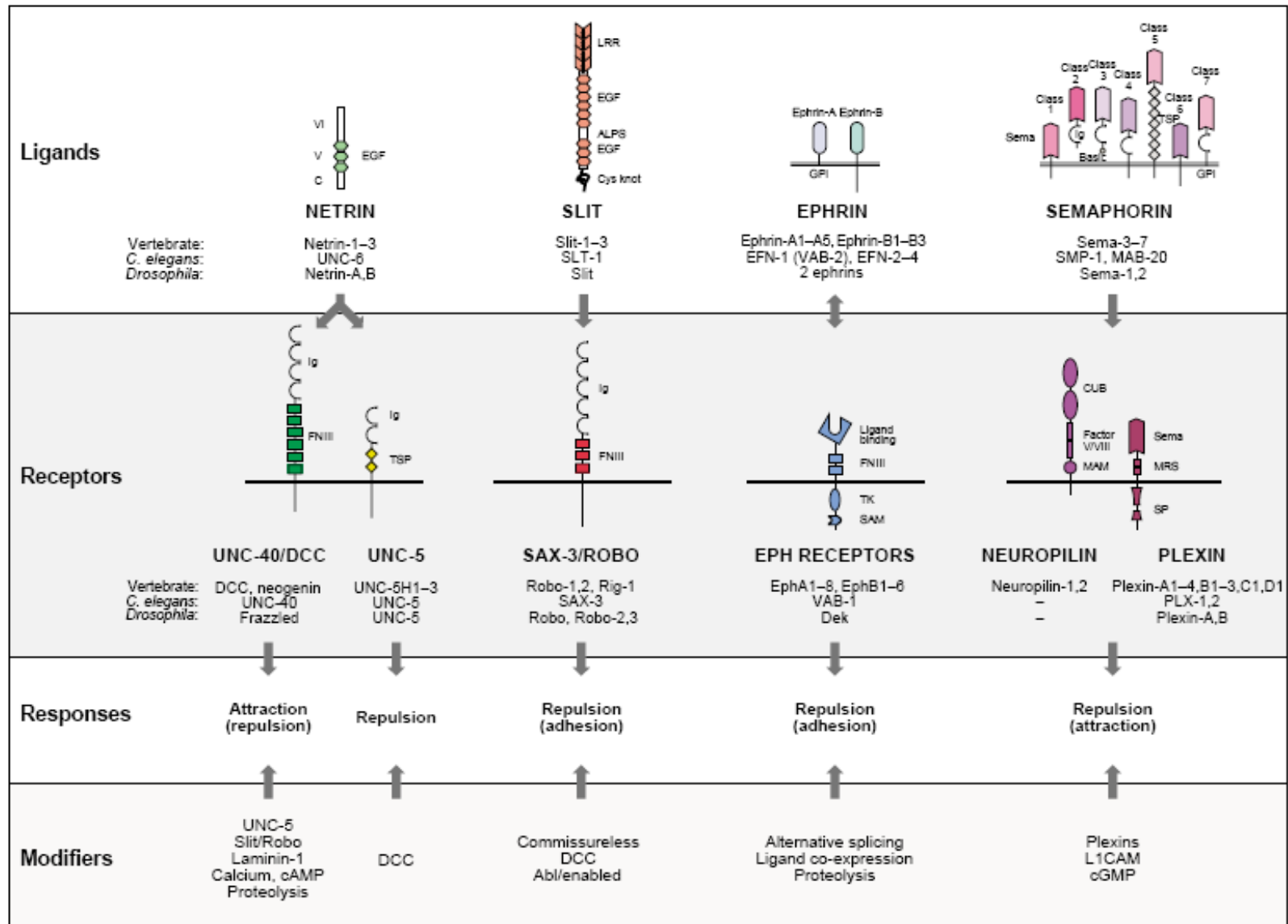
Chemoattractant

Olfactory epithelium

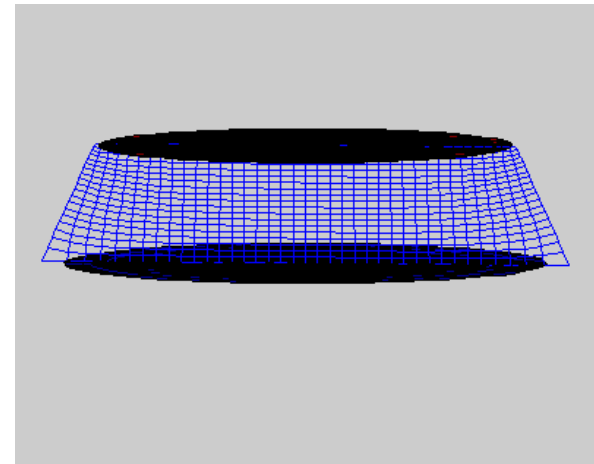
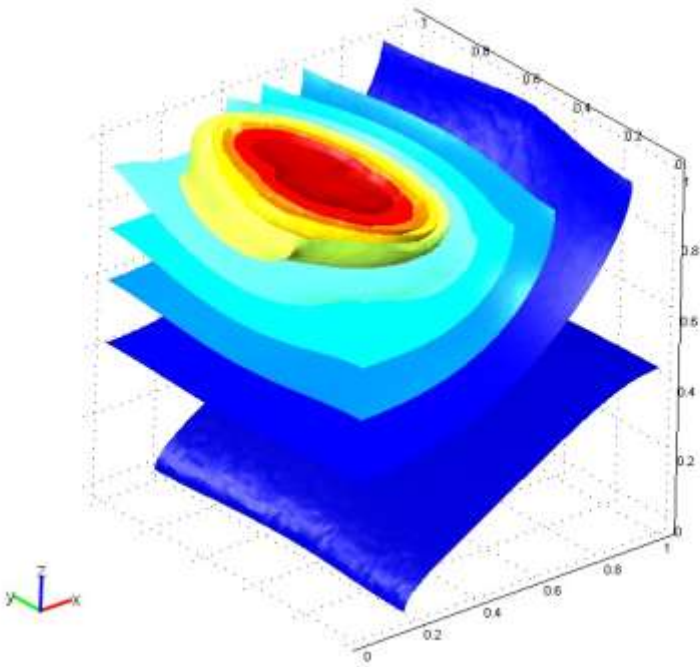
fasciculation



Many families of guidance cues



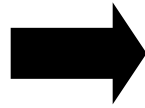
Chemoattractant, Phenomena in a variable domain



diffusion source degradation

$$\frac{\partial c}{\partial t} = D\Delta c + \alpha(c, x) - \frac{c}{\tau}$$

A multiscale problem (space)



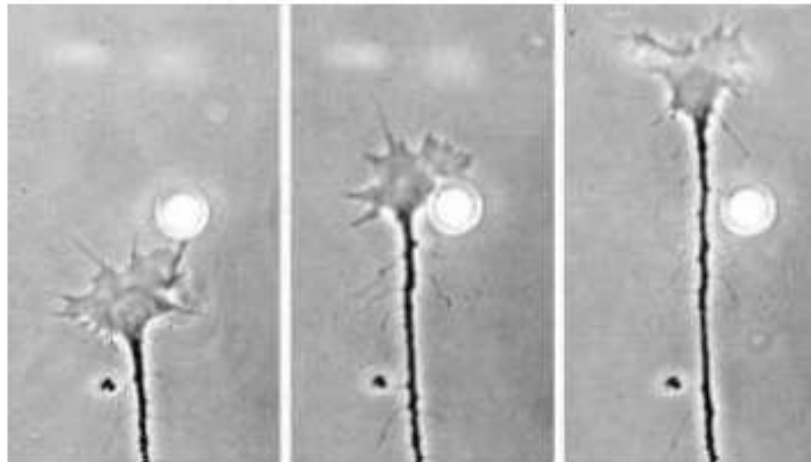
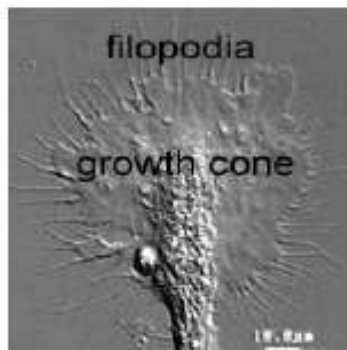
first ... axon guidance



In the developing nervous system, axons find the targets they will innervate navigating through the extracellular environment.

Pathfinding crucially relies on chemical cues and, among the others, guidance by gradients of diffusible ligands plays a key role [Tessier-Lavigne 1996, Song-Poo 2001]

Detection and transduction of navigational cues is mediated by the growth cone (GC), a highly dynamic structure located at the axon tip, provided of filopodia, thin filaments that protrude from the distal part of the GC and work like antennas to explore the surrounding environment



Axon guidance in a graded chemotropic field

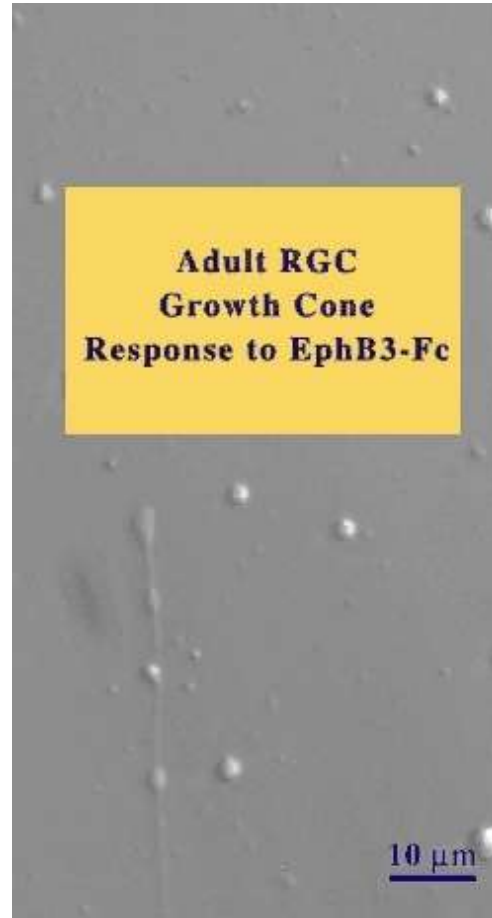
In absence of external perturbations, axons tend to grow in straight lines.

Under an external gradient of chemoattractant concentration:

- **receptors** distributed along filopodia and growth cone surface bind to ligand molecules and transmit information regarding their **occupational state**;
- a **spatial comparison of receptor signals** is performed at the level of the growth cone and unbalancings are detected;
- internal mechanisms are triggered that produce toward increasing concentration an **asymmetrical distribution of filopodia** that precedes growth cone displacements;
- the effect of “filopodia population” produces a **net traction towards the source**.

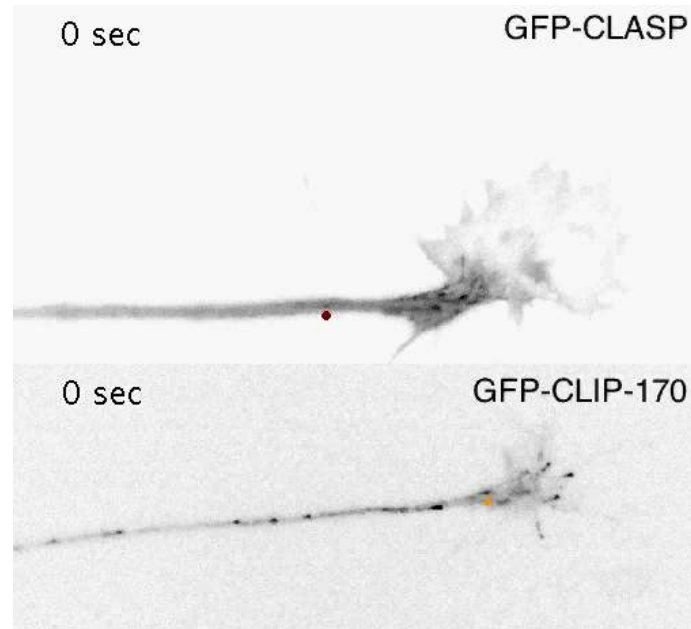
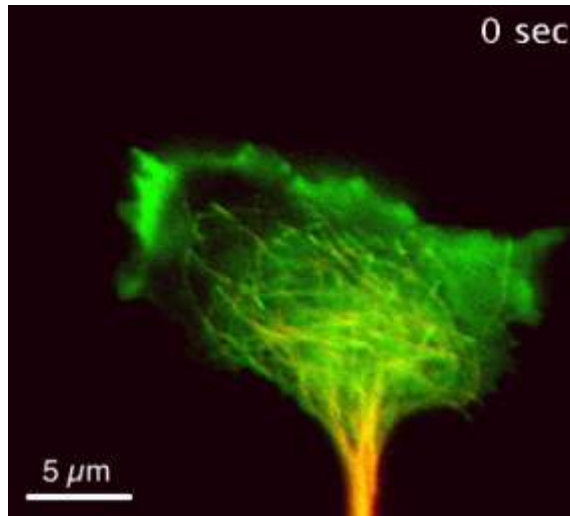
In contrast with the “pirouette”-like paths of bacteria or leukocytes, **axons display rather smooth trajectories**. Literature models developed in the former case cannot be straightforwardly applied.

Liu, X., Hawkes, E., Ishimaru, T., Tran, T., Sretavan, D. EphB3 : An Endogenous Mediator of Adult Axon Plasticity After CNS Injury. J. Neurosci. 26: 3087-3101, 2006



These movies illustrate the responses of adult retinal ganglion cell (RGC) axon growth cones in culture to the application of EphB3-Fc and Fc proteins.

Lee et al. The Microtubule Plus End Tracking Protein Orbit/MAST/CLASP Acts Downstream of the Tyrosine Kinase Abl in Mediating Axon Guidance, *Neuron*, Vol 42, 6 913-926 24 June 2004

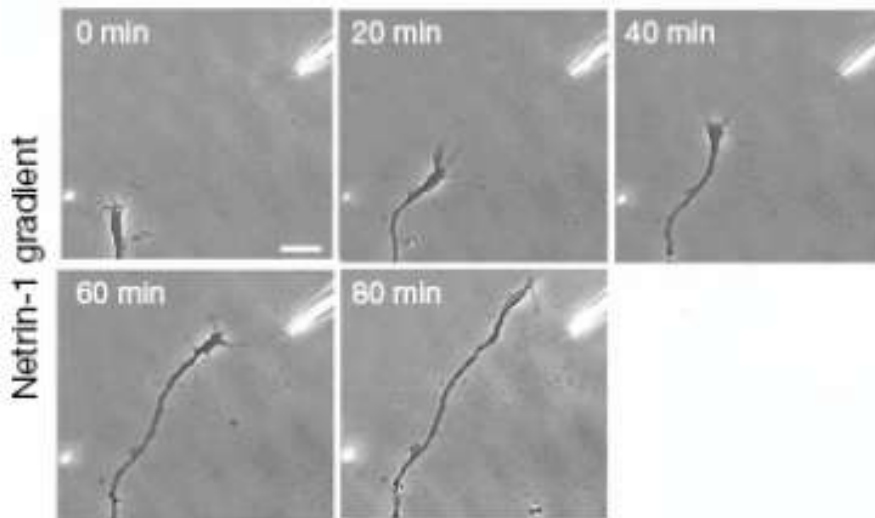


Autocatalytic loop, amplification and diffusion: a mathematical and computational model of cell polarization in neural chemotaxis, P. Causin, G. Facchetti, *PLOS Computational Biology* (2010)

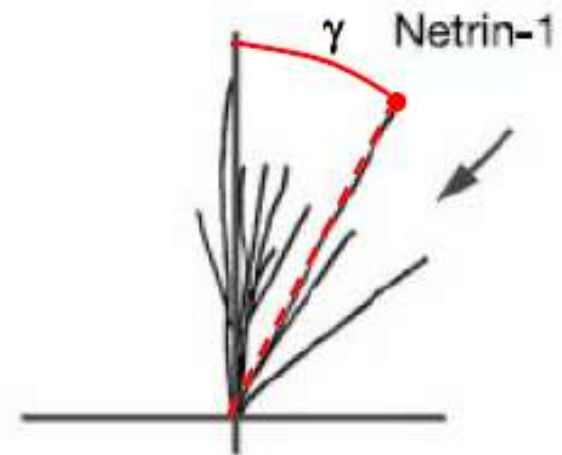
Axon guidance: a benchmark experiment

Typical in vitro assay:

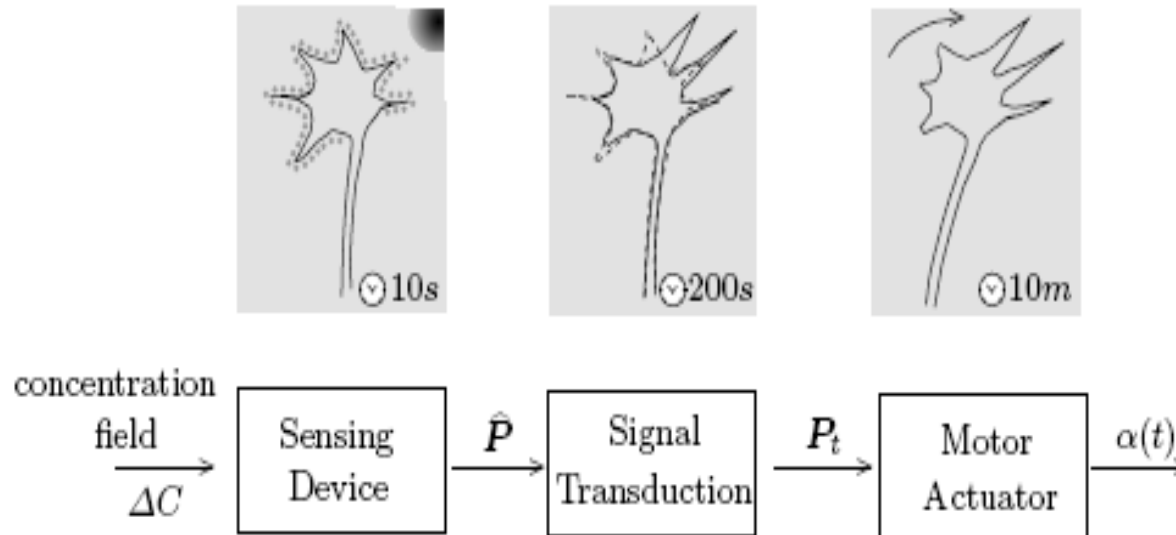
- a gradient of a given percentage change over a fixed distance of a diffusible chemoattractant (here, Netrin-1) is set on a substratum
- axon explants are let grown under the field
- axonal response is recorded after 1-2 h measuring the final angle γ of growth cone turning



Song, Ming, Poo [2002]



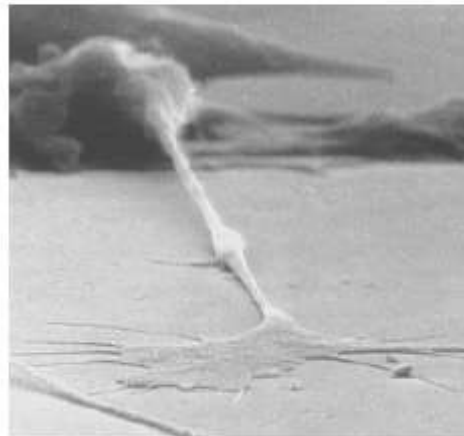
A multiscale problem (time)



Top row: cascade of macroscopical phenomena leading from gradient sensing to motion. Receptor binding state produces data on the concentration field; the polarized signaling pathway enhances reorganization of internal GC cytoskeleton; the trajectory is deviated. Characteristic times are indicated for each process. Bottom row: signal processing chain in the mathematical model. Sensing Device, Signal Transduction and Motor Actuator functions. Inputs and outputs refer to quantities of system (7).

Microscopic model of filopodia (I)

“..when viewed on a coarse time scale, growth cone movements give an impression of steady progression. When viewed on a finer scale of our time-lapse studies, however, growth cones are actually seen to advance in a series of lurches, hesitations, and backtracking”².



We propose a macroscopic model that reproduces the “continuous” movement of the axon growth cone observed at a coarse time scale, based on a microscopic description of the intermittent filopodia movement at a finer time scale δt .

²Myers, Bastiani, J. Neurosci. (1993)

SDE for axon trajectory

On a coarser time scale, the trajectory evolution, that on a fine scale is an intermittent phenomenon, can be described as a continuous process, which is mathematically represented as the following stochastic differential system:

find for $0 \leq t \leq T$ the growth cone position $\mathbf{x}_d = \mathbf{x}_d(t)$, such that

$$\dot{\mathbf{x}}_d = \mathbf{v}_g,$$

$$\dot{\mathbf{v}}_g = \left(\mathbf{e}_g \wedge \frac{\mathbf{a}}{2} \right) \wedge \mathbf{e}_g,$$

$$d\mathbf{a} = -k(\mathbf{a} - \mathbf{a}_0)dt + \sigma d\mathbf{W}_t,$$

$$\mathbf{x}_d(0) = \mathbf{x}_d^0,$$

$$\mathbf{v}_g(0) = v_g \mathbf{e}_g^0,$$

$$\mathbf{a}(0) = \mathbf{0}.$$

Parameter fitting study (I)

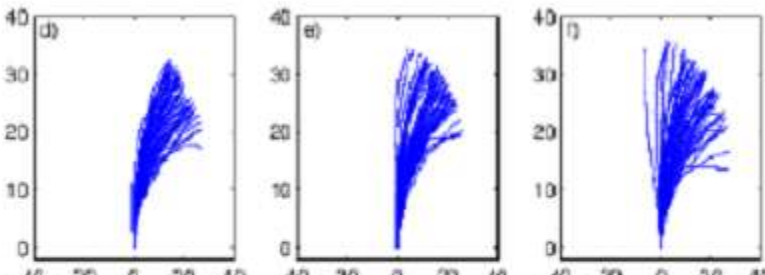
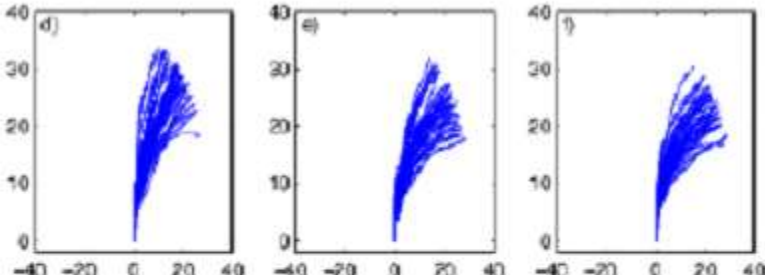
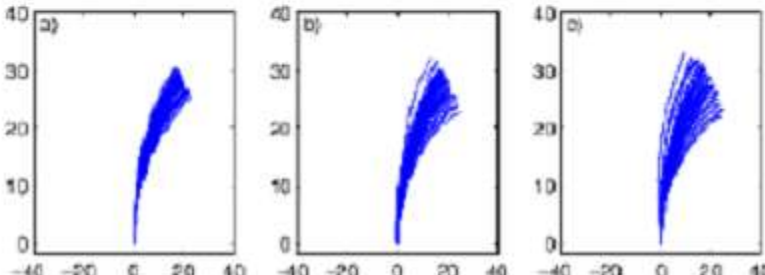
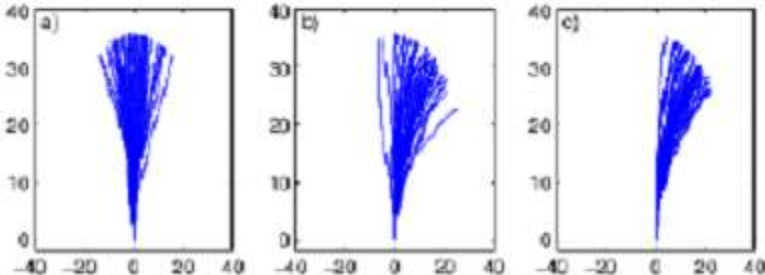
In order to fit the parameters entering the SDE system, we consider the single chemoattractant benchmark–experiment and we numerically simulate axon trajectories:

- an exponential concentration is set along the positive x -axis with a constant steepness $s = 5\%$;
- for each test, 2500 axons trajectories are simulated, each starting from the origin and initially moving along the positive y -axis for a total time of $2h$ using a time step $dt = 10s$;
- the final angle of growth cone turning and its distribution are measured at the final time.

Fitting the parameters corresponds to produce a transfer function from external solicitations to axonal response.

Parameter fitting study

Axon paths



Varying a_0

Varying process volatility

The full model

We describe each axon as a 1D elastic fiber immersed in the extracellular matrix, modeled as a 2D continuum deformable body

The axon trajectory is represented by the successive positions of the axon head, given by

$$\frac{d\mathbf{x}_d}{dt} = \underbrace{\mathbf{v}_g(t)}_{\text{intrinsic growth velocity}} + \underbrace{\mathbf{v}_\varphi(t)}_{\text{time rate variation of the matrix shape}}$$

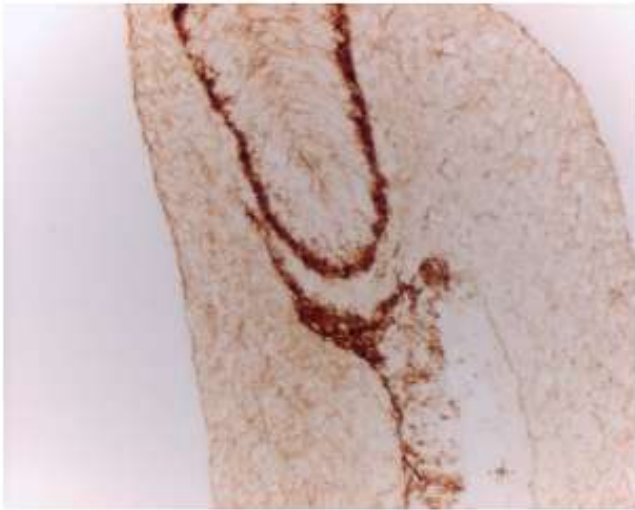
chemical cues (microscopic model of filopodia)
axon mechanical properties (bending vs. axial stiffness)
stochastic noise

Mathematical model of shape evolution

- We suppose the mesenchyme to be a deformable elastic body that undergoes large deformations due to an imposed motion of its (computational) boundaries
- when disposing of digitally segmented section from laboratory experiments, the field of imposed motion can be directly inferred from the data
- we consider the mesenchyme to be an hyperelastic material. We adopt the simplest isotropic St.Venant–Kirchhoff model (the extracellular matrix is known to exhibit a viscoelastic mechanical behavior: a more detailed characterization of the mechanical properties should be done)
- upon discretizing the elastic problem with the finite element method, we obtain the field of matrix displacements and velocity \mathbf{v}_φ .

Experimental data

Histological sections of axon projection in the murine olfactory system
(from Laboratory of Molecular Morphogenesis, Dulbecco Telethon
Institute at CNR-ITB) at different embryonal stages



morphology at E11



morphology at E14

Also some movies ... 

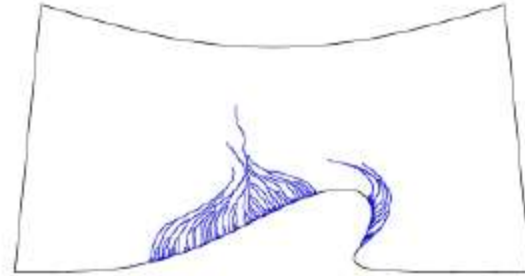
Numerical results: complete model (I)

- we integrate numerically the SDE complete model
- we consider 500 axons, randomly seeded along the bottom boundary and assigned different birth times
- a prescribed motion is imposed to the top and bottom borders.
- a weak attractive diffusible cue is placed in the top-central part of the domain. Repulsive cues are placed close to the corners.

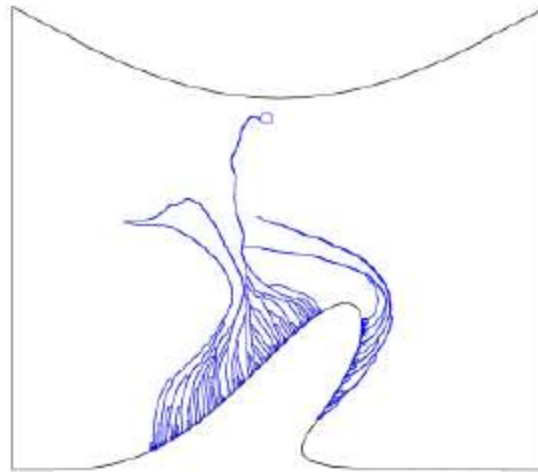
2D Simulation



initial time



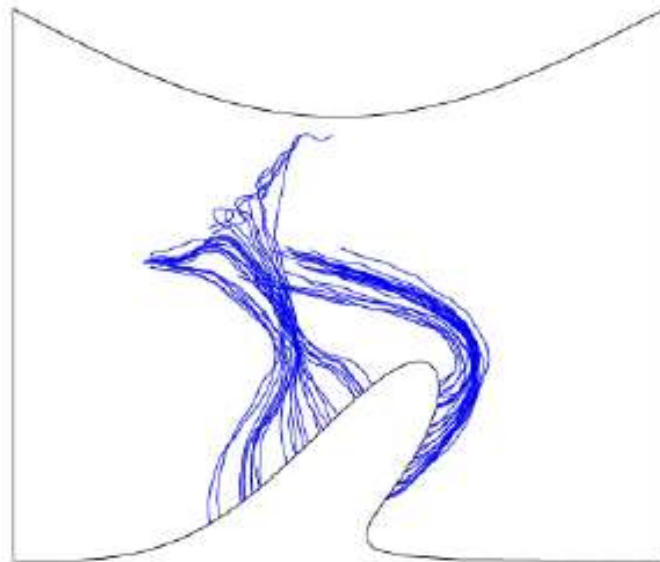
half time span



final time

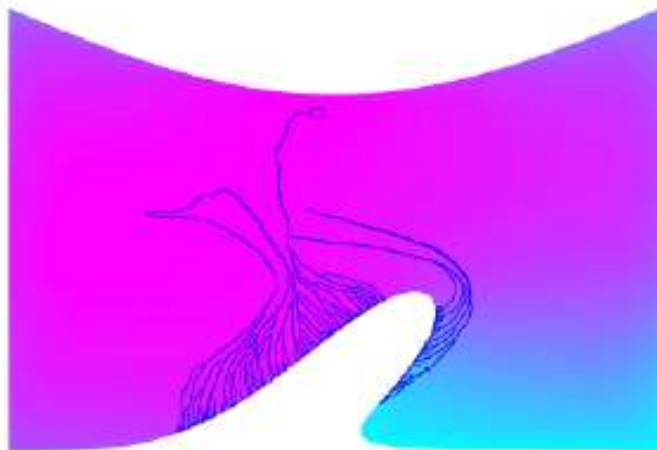
Numerical results: turn off fasciculation

- We study the morphology of the nerve when there is no fasciculation
- in this simulation only 50 axons are considered
- diffusible chemical cues drive axons near but, in absence of homophilic attraction, they do not form a coherent structure and they depart in a fan

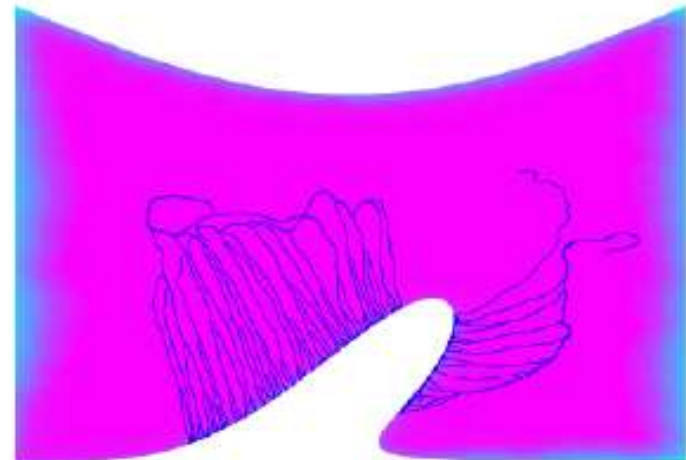


Numerical results: turn off diffusive cues

- When diffusive cues are turned off, axons tend to grow straight and to disperse in the extracellular matrix
- axon fasciculation is observable at a certain degree, being promoted by random movements and geometrical neighborhood.
- along the borders short-range repulsive cues are used to keep axons confined in the computational domain
- in the complete model, purple indicates an attractive zone, whilst light blue a repulsive one, with intermediate modulations. In the partial model, purple indicates absence of chemical substances.

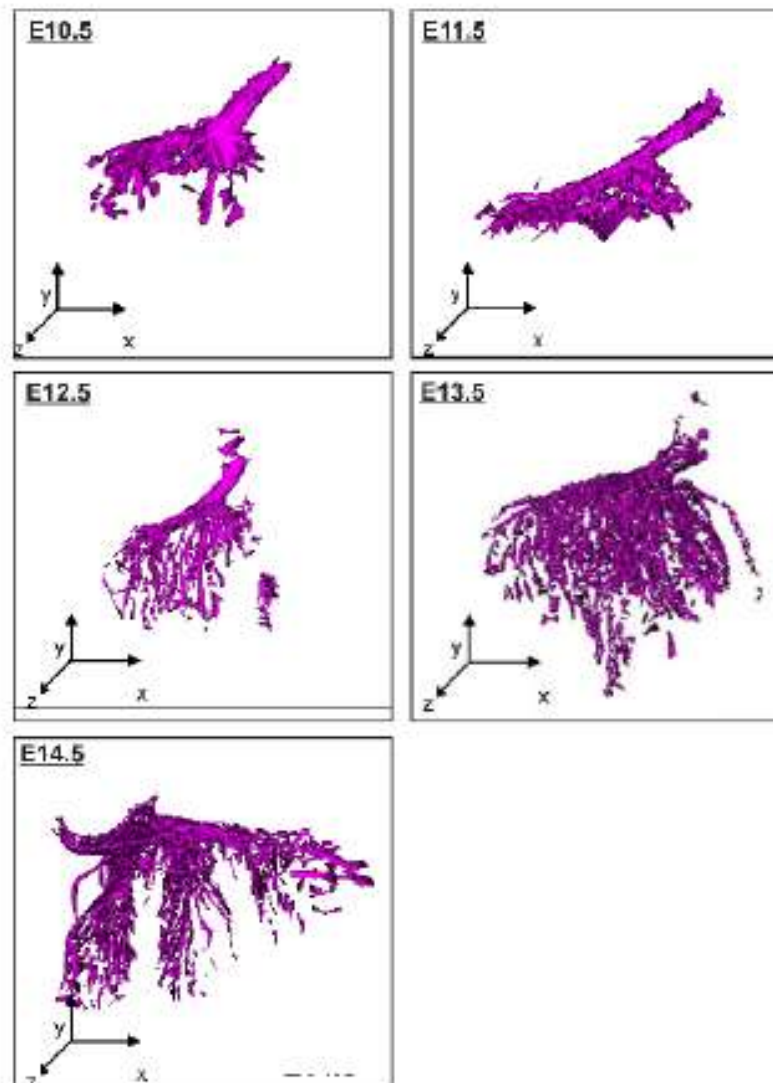


complete model



no diffusive cues

3D reconstruction of olfactory nerve



Results:

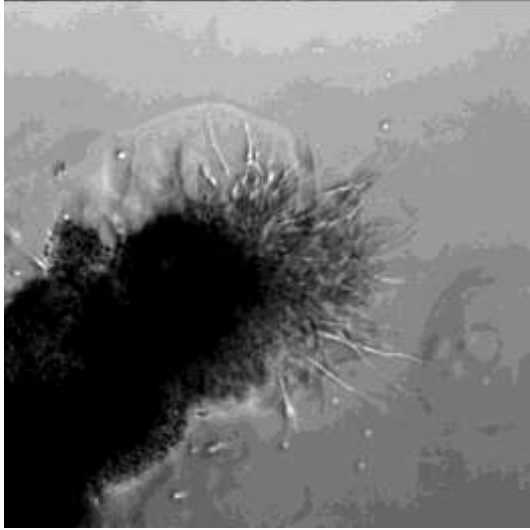
- We have proposed a mathematical and numerical framework aimed to obtain a quantitative description of axons trajectories;
- we have introduced a macroscopic model for the axon growth cone motion based on a lumped description of the filopodia movement;
- we have considered the effect of mechanical deformations, a significant aspect in embryo development;
- simulation results are being used to obtain predictions about axon targetting in the developing olfactory system.

Some good opportunity for:  4.3:

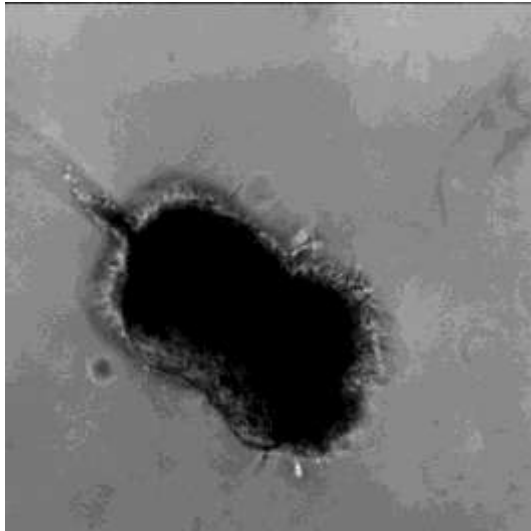
- Mechanical properties of the extracellular matrix;
- Diffusion of different chemotactic cues.

But ...

Next time some tools for stochastic differential equations will be available?



KO-type



W-type

