# *Decision making in the assembly of sensory-motor circuits*

**Victor Luria**

**Department of Genetics & Motor Neuron Center**
**Columbia University, New York**

---

**Morphodynamics**
**KITP, Santa Barbara**
**September 16, 2009**

# *Columbia, New York*

**Ed Laufer**

**Tom Jessell**

**Angela Christiano**

---

***McGill & U de Montréal***

**Artur Kania**

**Dayana Krawchuk**

**Bryan Crenshaw** *Penn*
**Carol Mason** *Columbia*
**Mark Henkemeyer** *UT Southwestern*

***Laufer, Jessell, Mason, Christiano Labs***

**Alex Paul**
**Susan Brenner-Morton**
**Julia Kaltschmidt**
**Scott Williams**
**Ming Zhang**

*Funding*
Muscular Dystrophy Association
NY Spinal Cord Research Foundation
Motor Neuron Center, Columbia
Christopher & Dana Reeve Foundation

*Imperial College &*
*Cambridge*

**Aldo Faisal**

*Yale*

**John Murray**

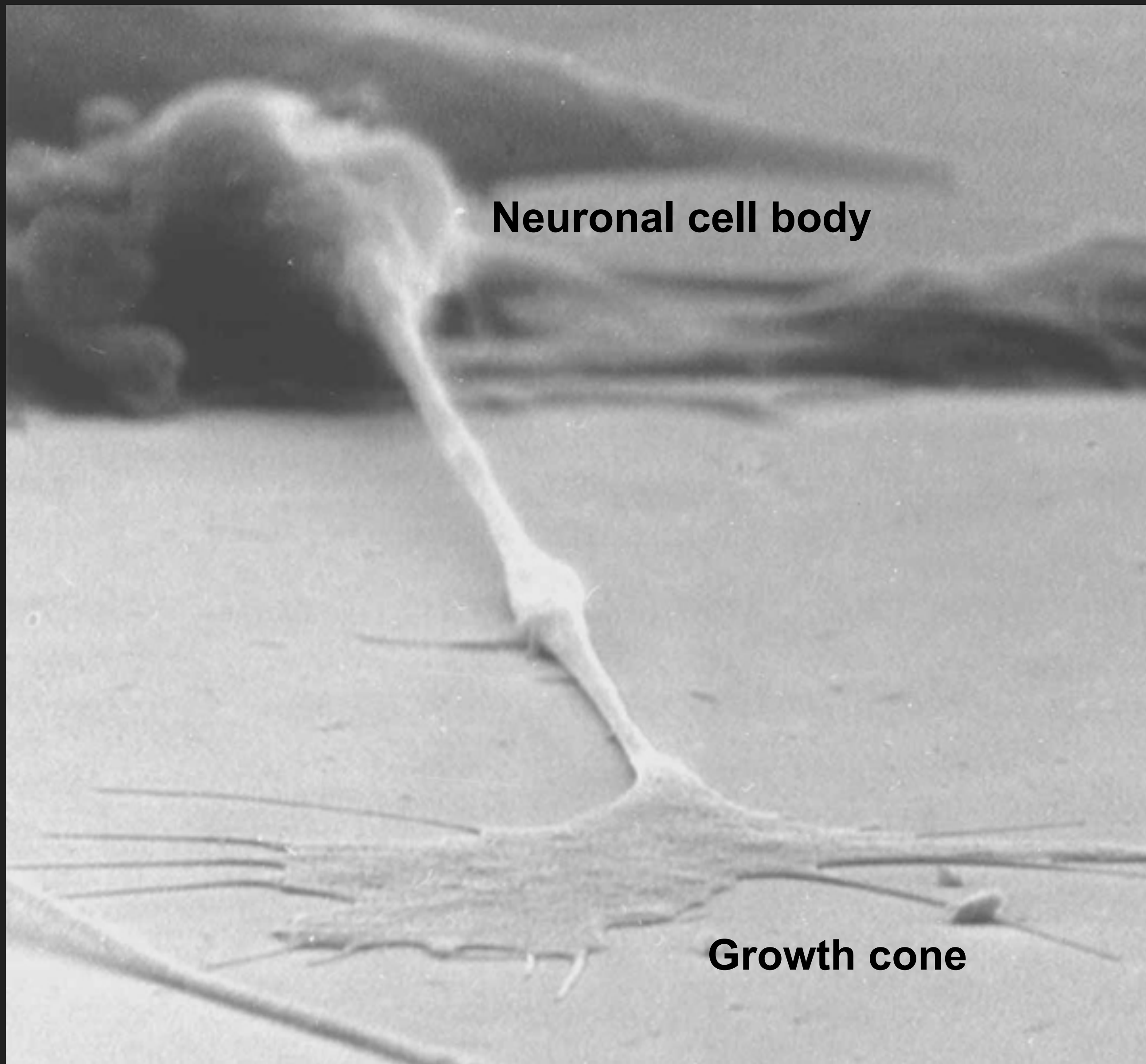
*Kavli Institute for Theoretical Physics,*
*UC Santa Barbara*

**Fred Wolf**
**Sara Solla**

**Gonzalo de Polavieja**
**Boris Shraiman**

*Princeton*
**Michael Berry**

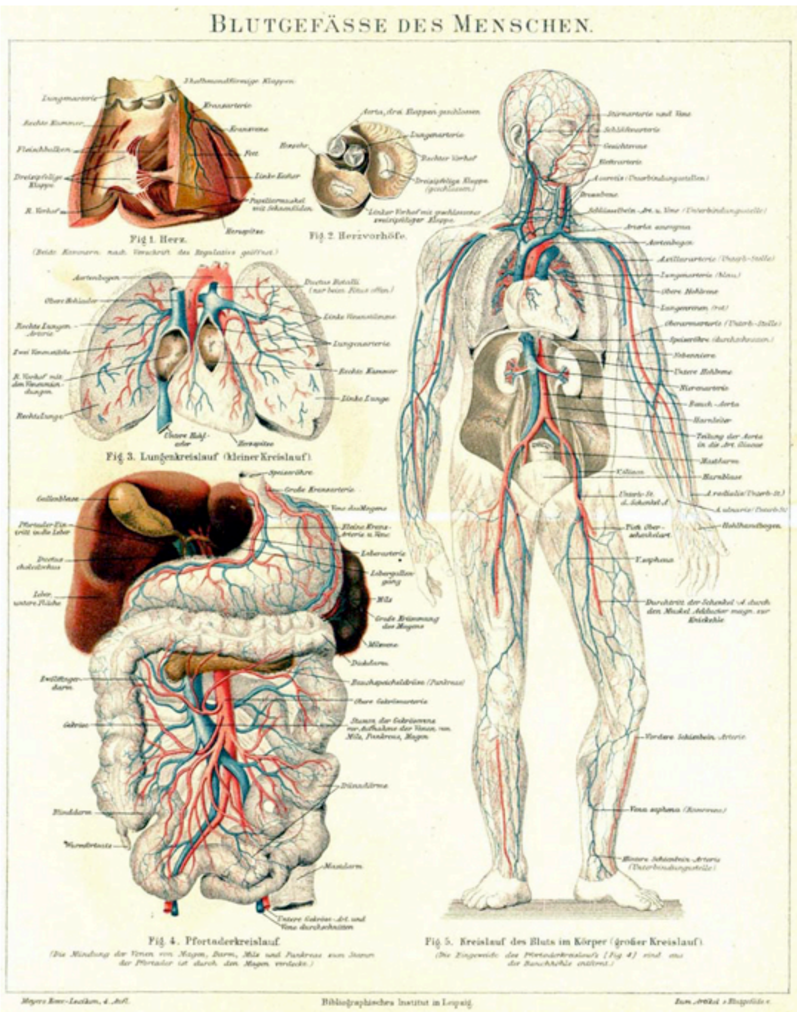
# Neurons send growth cones to faraway targets

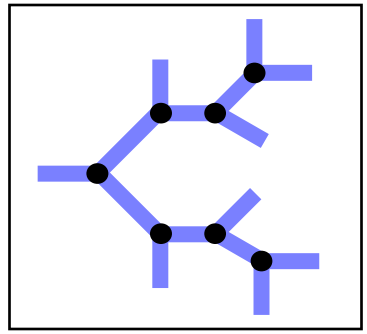



Kathryn Tosney

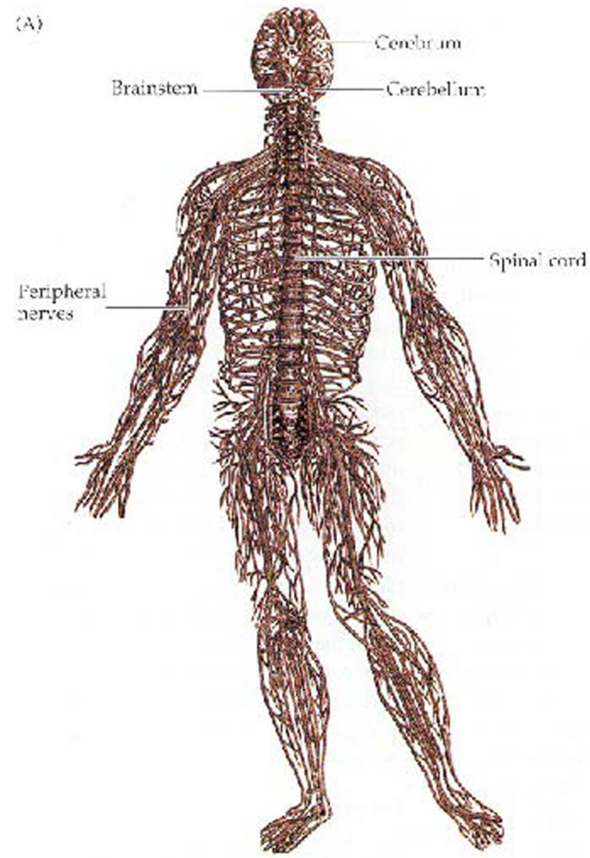
# Neural circuit construction is a *serial decision* process

## Vascular system

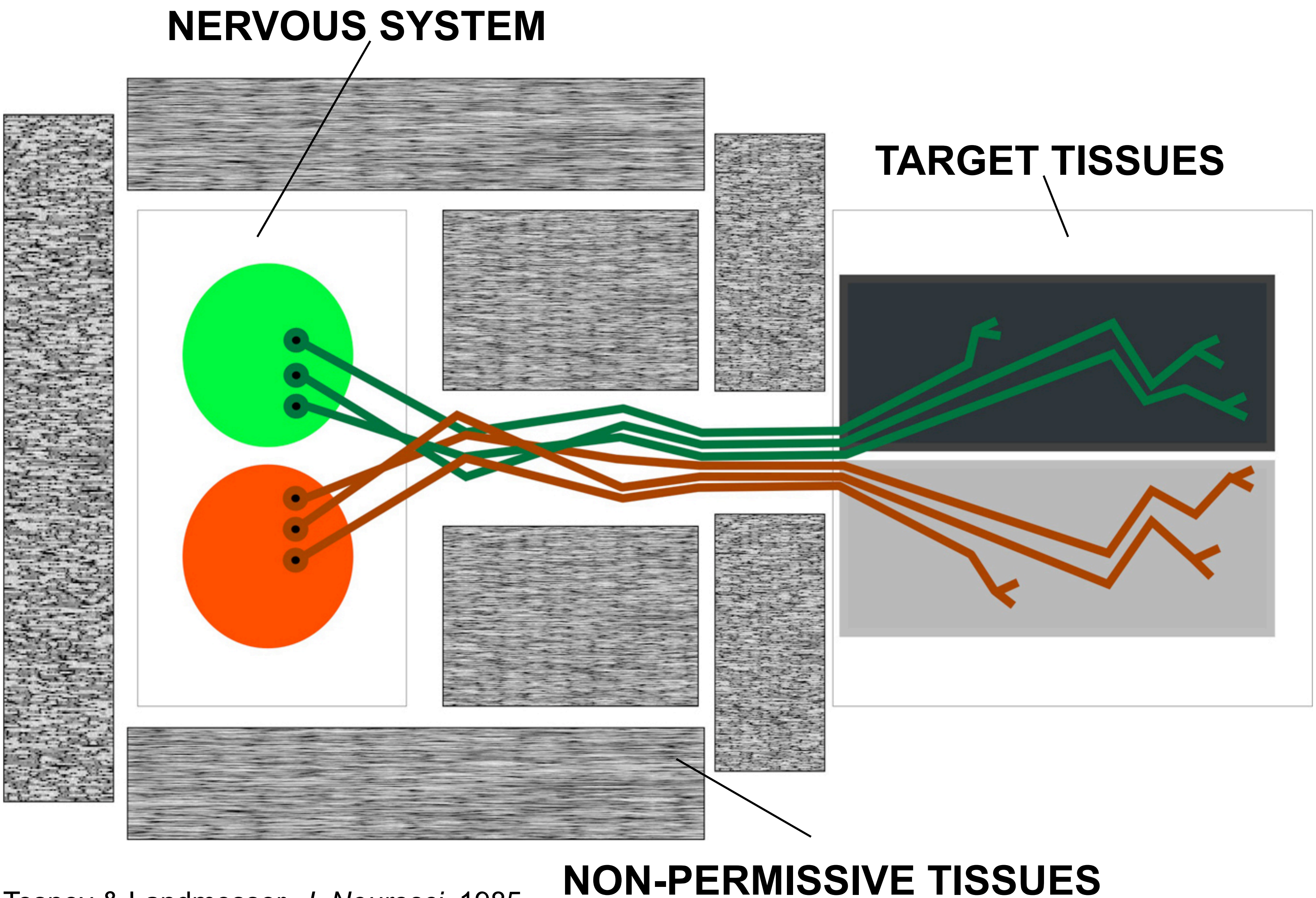


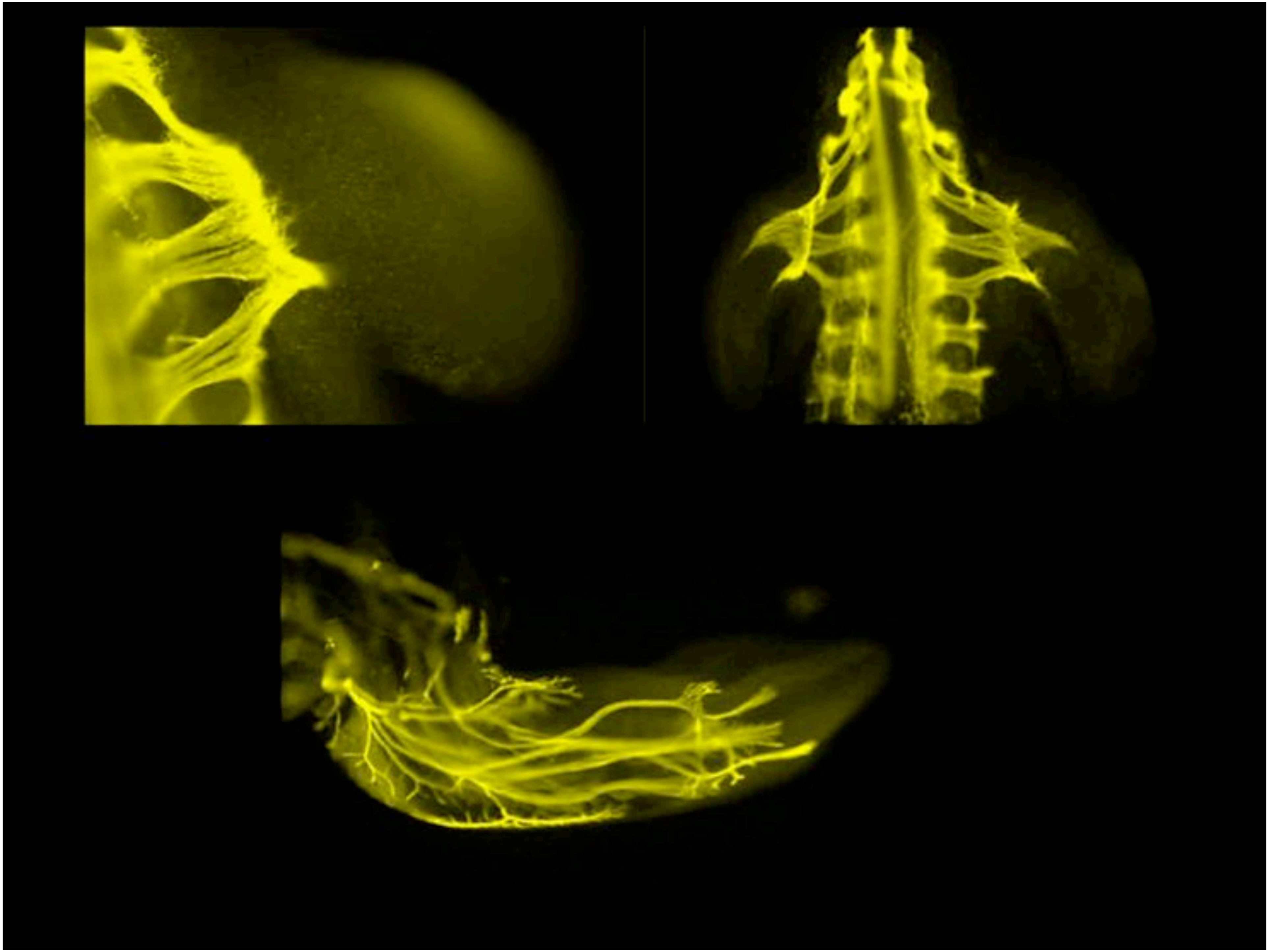
## Nervous system

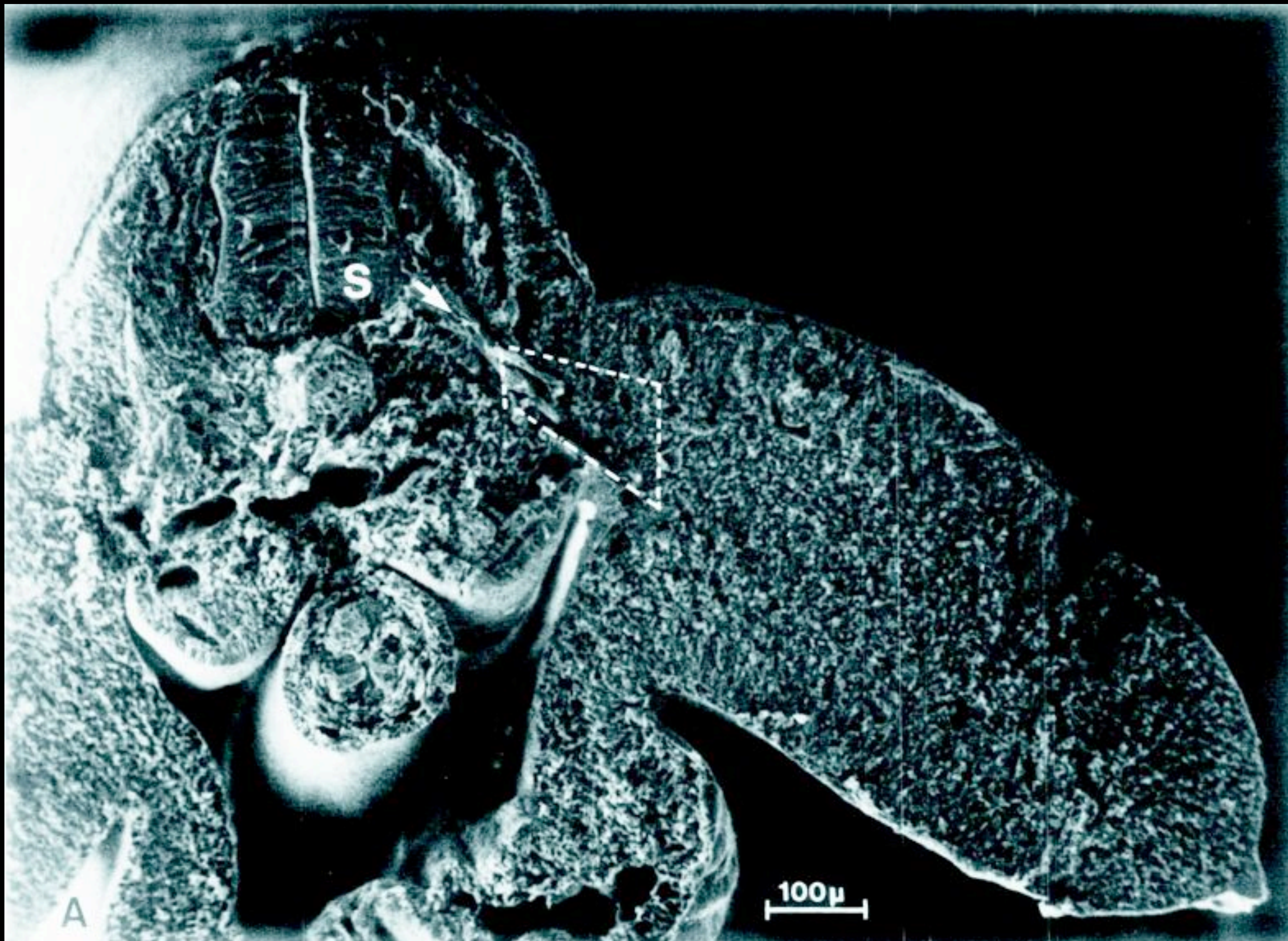


# Topographic mapping

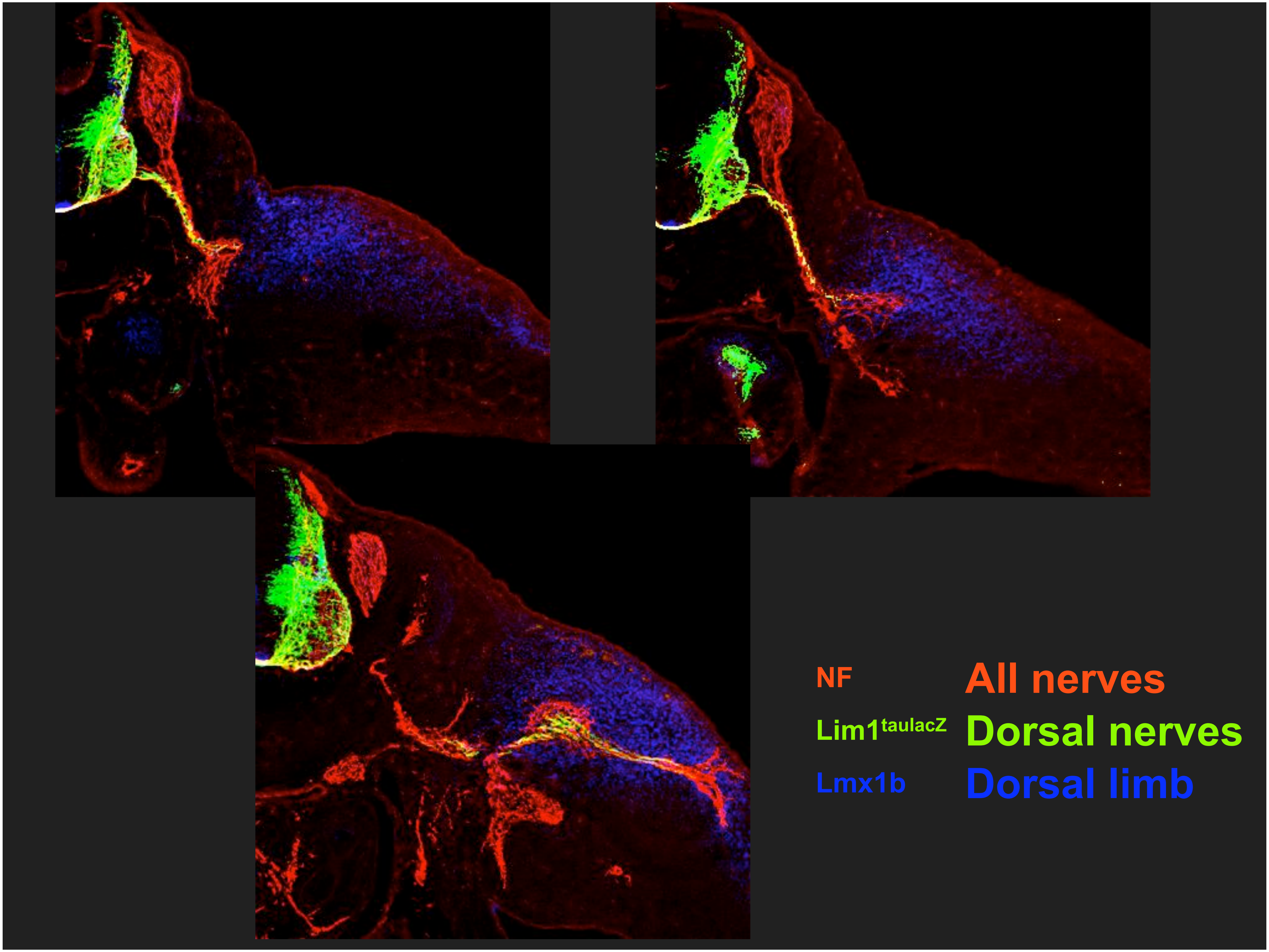



Tosney & Landmesser, *J. Neurosci.* 1985
Jessell, *Nat. Rev. Genet.* 2000





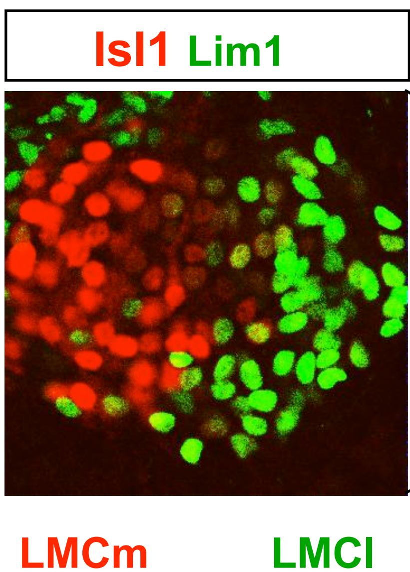

Tosney & Landmesser, *J. Neurosci.* 1985


NF
All nerves
Lim1taulacZ
Dorsal nerves
Lmx1b
Dorsal limb

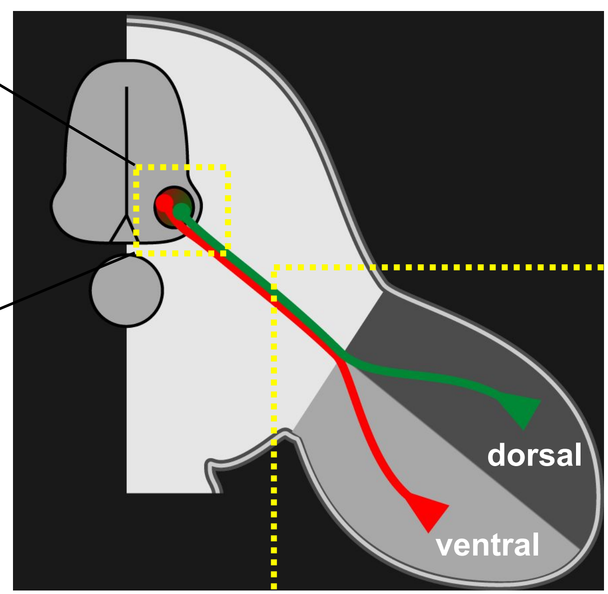
# Motor axon decision: towards *flexors* or *extensors*?

| Motor column | LIM HD code |
|---|---|
| LMCl | : Lim1 |
| LMCm | : Isl1 |

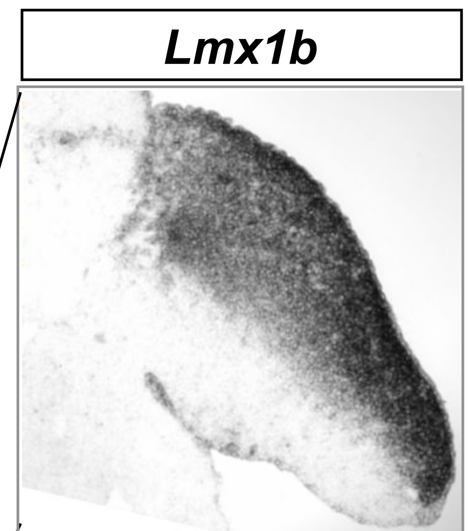
| Limb mesenchyme | Lmx1b |
|---|---|
| dorsal | + |
| ventral | – |




Tsuchida et al., *Cell* 1994

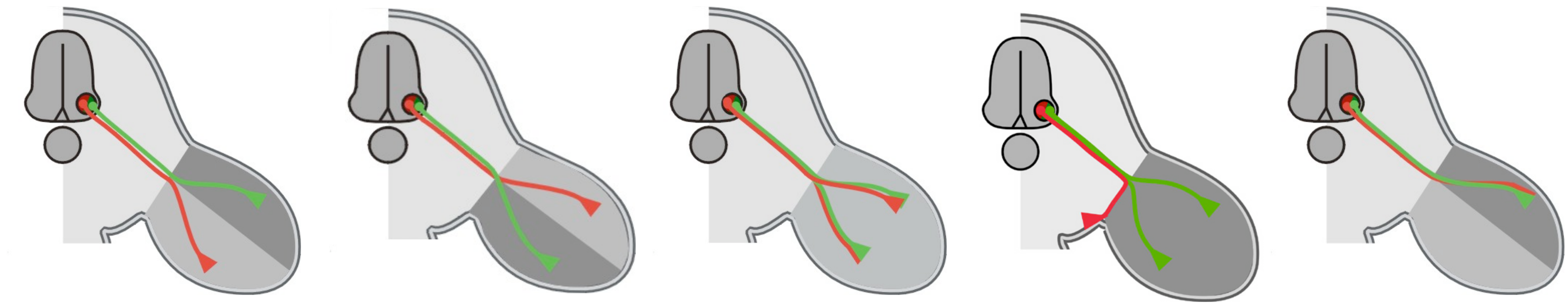



Landmesser, *J. Physiol.*1978




Riddle et al., *Cell* 1995

# Pathway selection is local and active



**Wild type**

Landmesser, *J. Physiol.* 1978
Tsuchida et al., *Cell* 1994

| | |
|---|---|
| LMC(l) | Dorsal Limb |
| LMC(m) | Ventral Limb |

**Reversal**

Whitelaw & Hollyday, *J. Neurosci.* 1983

| | |
|---|---|
| + | Ventral |
| + | Dorsal |

Reversed trajectories

**Bi-ventral *Lmx1b-/-***

Kania et al., *Cell* 2000

| | |
|---|---|
| + | – |
| + | + |

LMCm & LMCl randomized trajectories

**Bi-dorsal *Bmpr1a-/-***

Luria et al., *Neural Dev.* 2007

| | |
|---|---|
| + | + |
| + | – |

LMCl randomized trajectories, LMCm misrouted

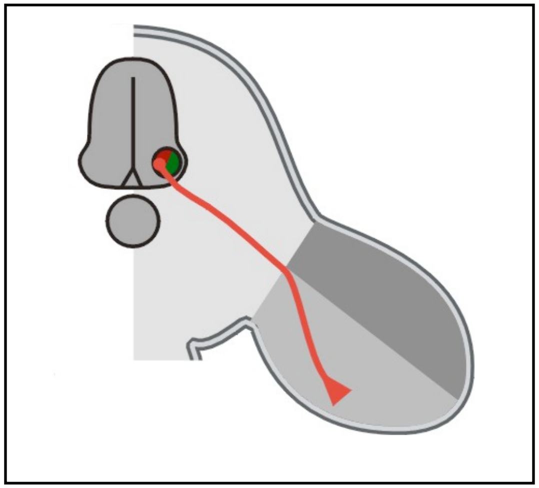
***EphA4* +++**

Eberhart et al., *Dev. Biol.* 2002
Kania & Jessell, *Neuron* 2003

| | |
|---|---|
| + | + |
| ++ | + |

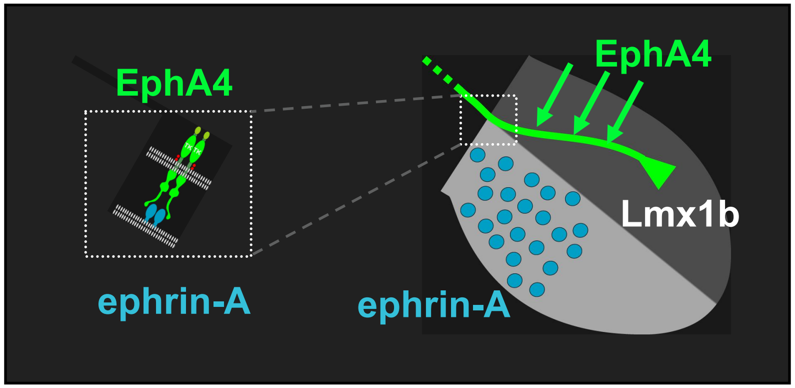
LMCm axons misrouted dorsally

***I. MOLECULAR LOGIC - What are the effector molecules that control LMCm trajectories?***



***II. Quantitative models, experimental predictions and tests***

# *I. What are the effector molecules that control LMCm trajectories?*

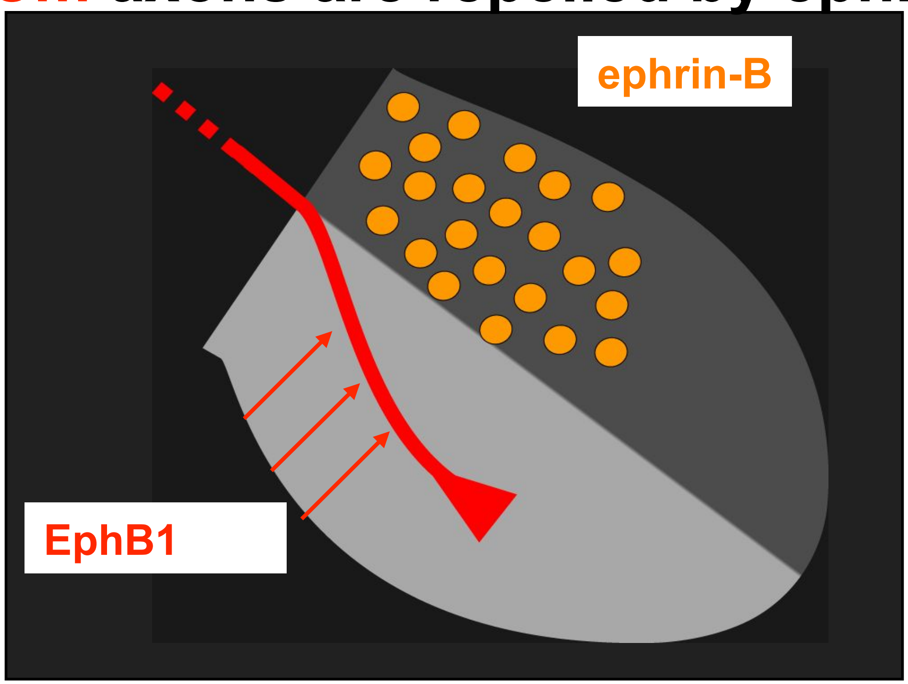



**ephrin-A/EphA, GDNF/c-ret, Sema/Npn signaling influence LMCl trajectories**

Kania et al., 2000
Helmbacher et al, 2000
Eberhart et al, 2002
Kania and Jessell, 2003
Huber et al., 2005
Kramer et al., 2006

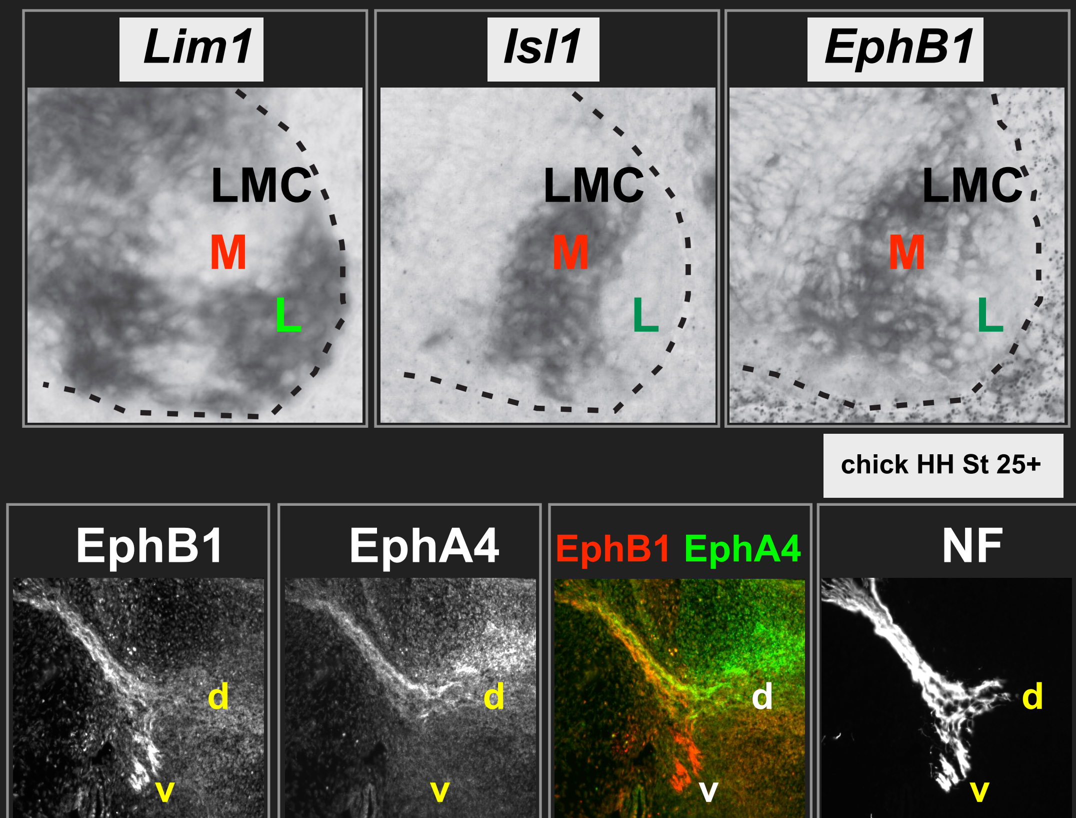
## *Hypothesis*

## EphB+ LMCm axons are repelled by ephrin-B+ dorsal limb

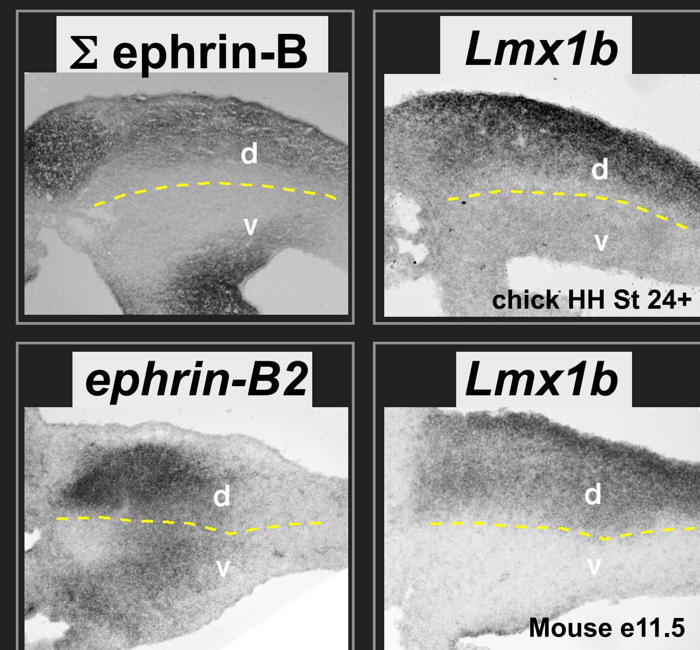


# Distribution of EphBs receptors and ephrin-Bs ligands

## RECEPTOR in NEURONS

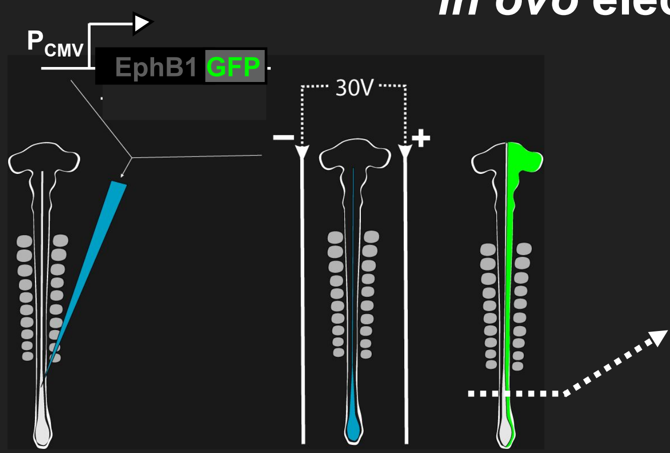


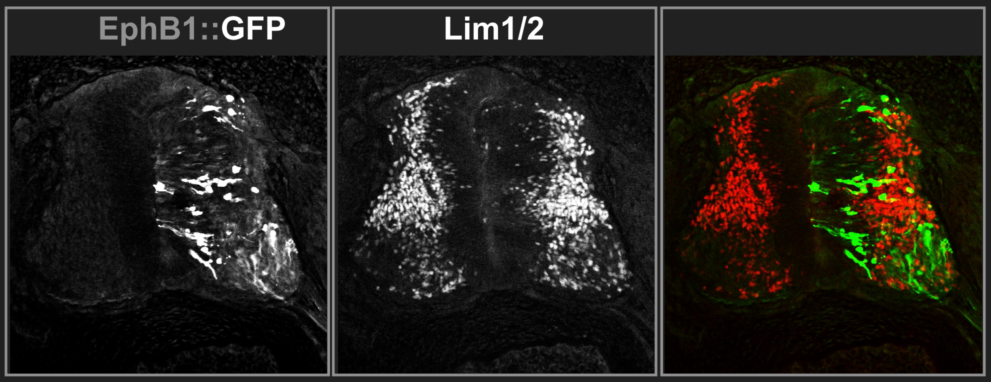

## LIGAND in *NON-TARGET* TISSUE



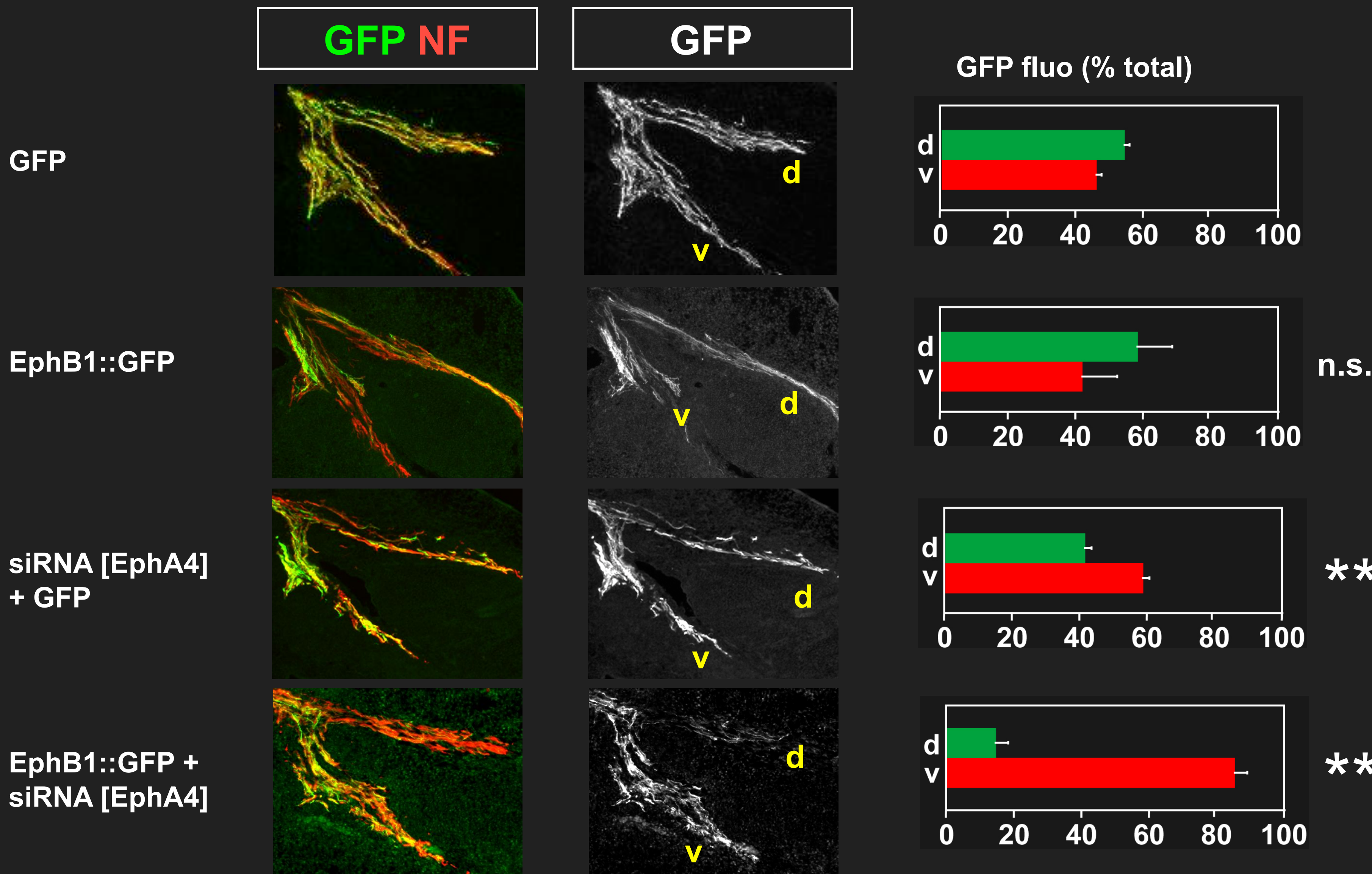
# Is EphB1 sufficient to guide LMC axons to the ventral limb?

*in ovo* electroporation of *EphB1::GFP*

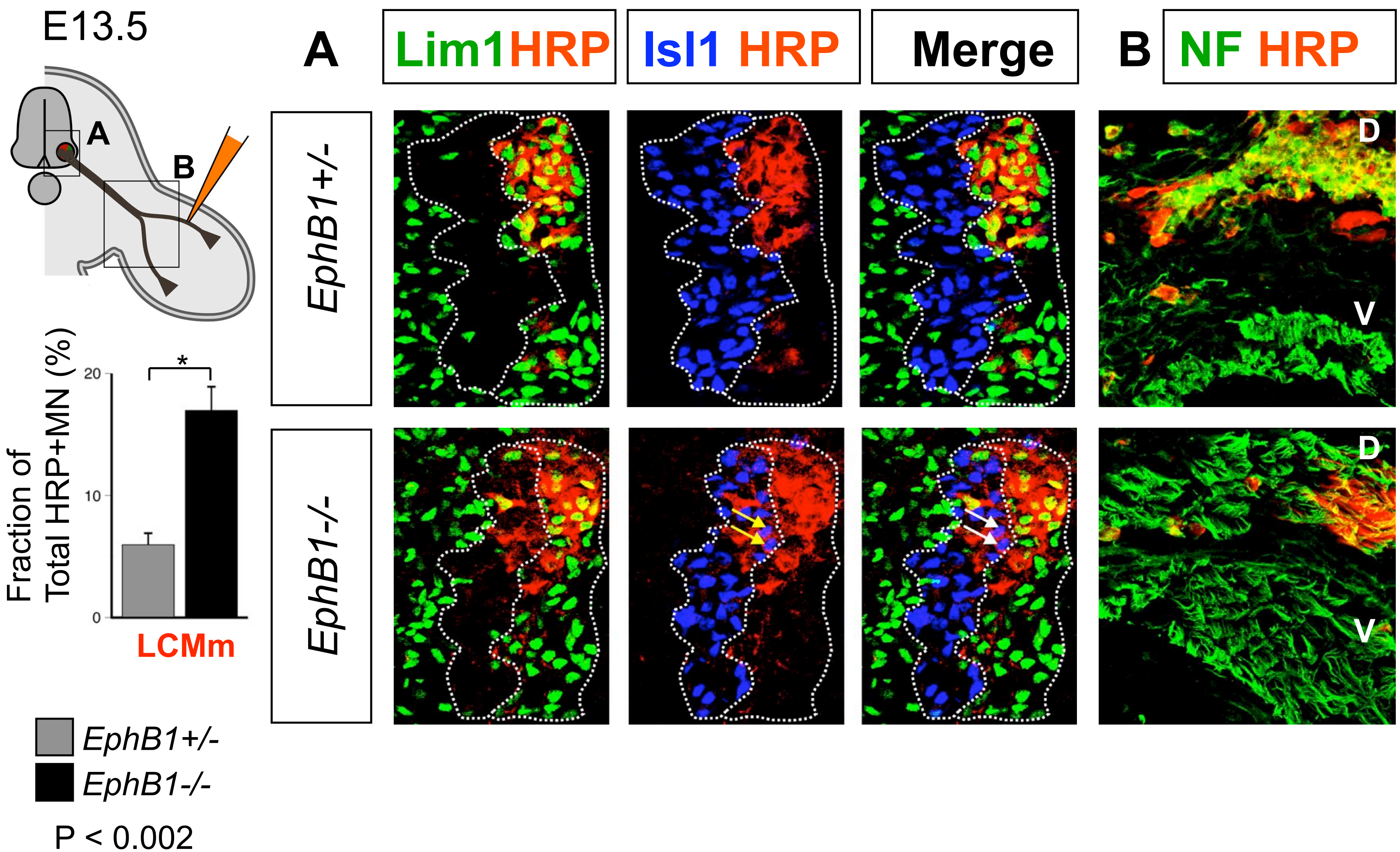


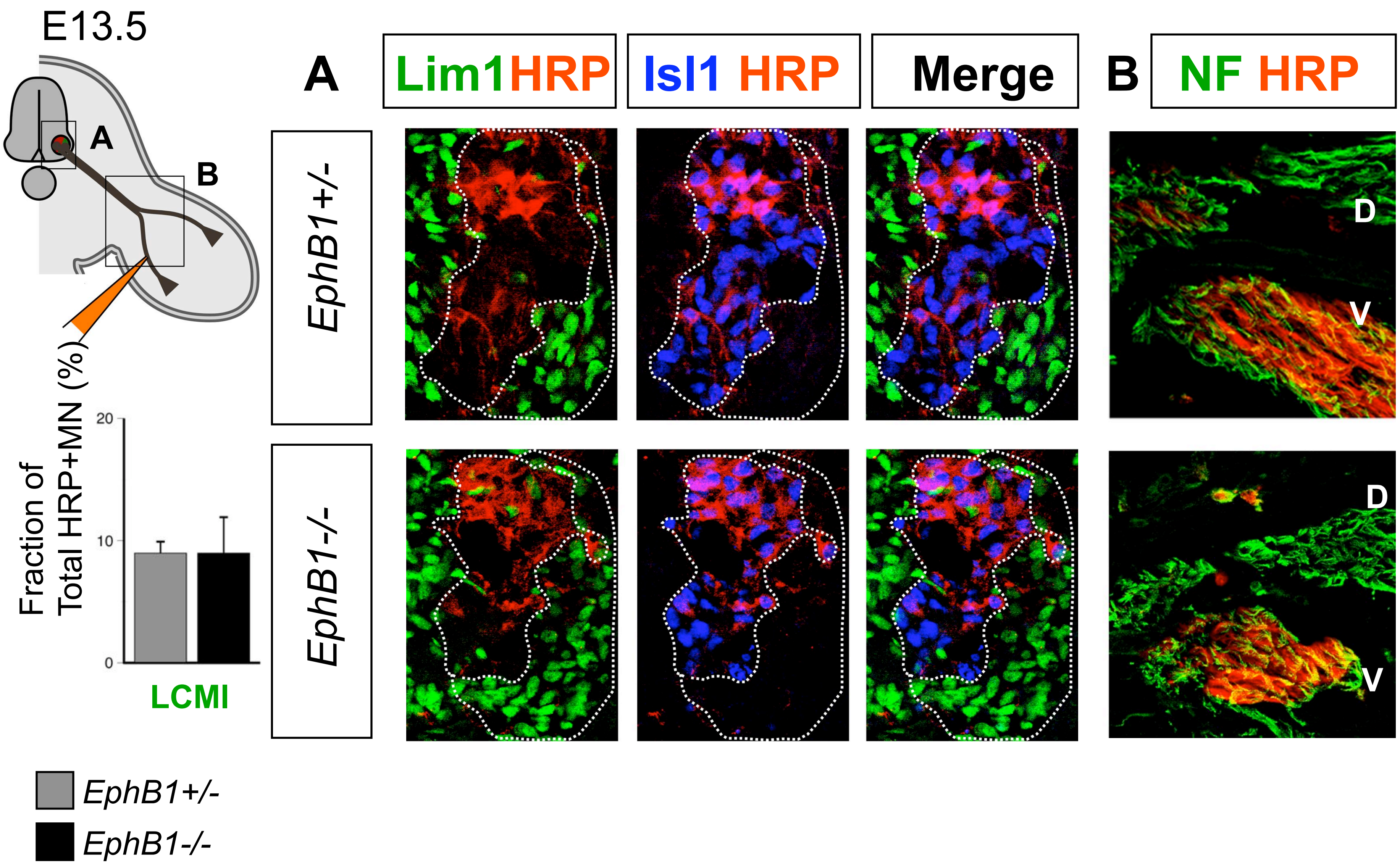
# EphB1 can *redirect* LMC axons to the ventral limb



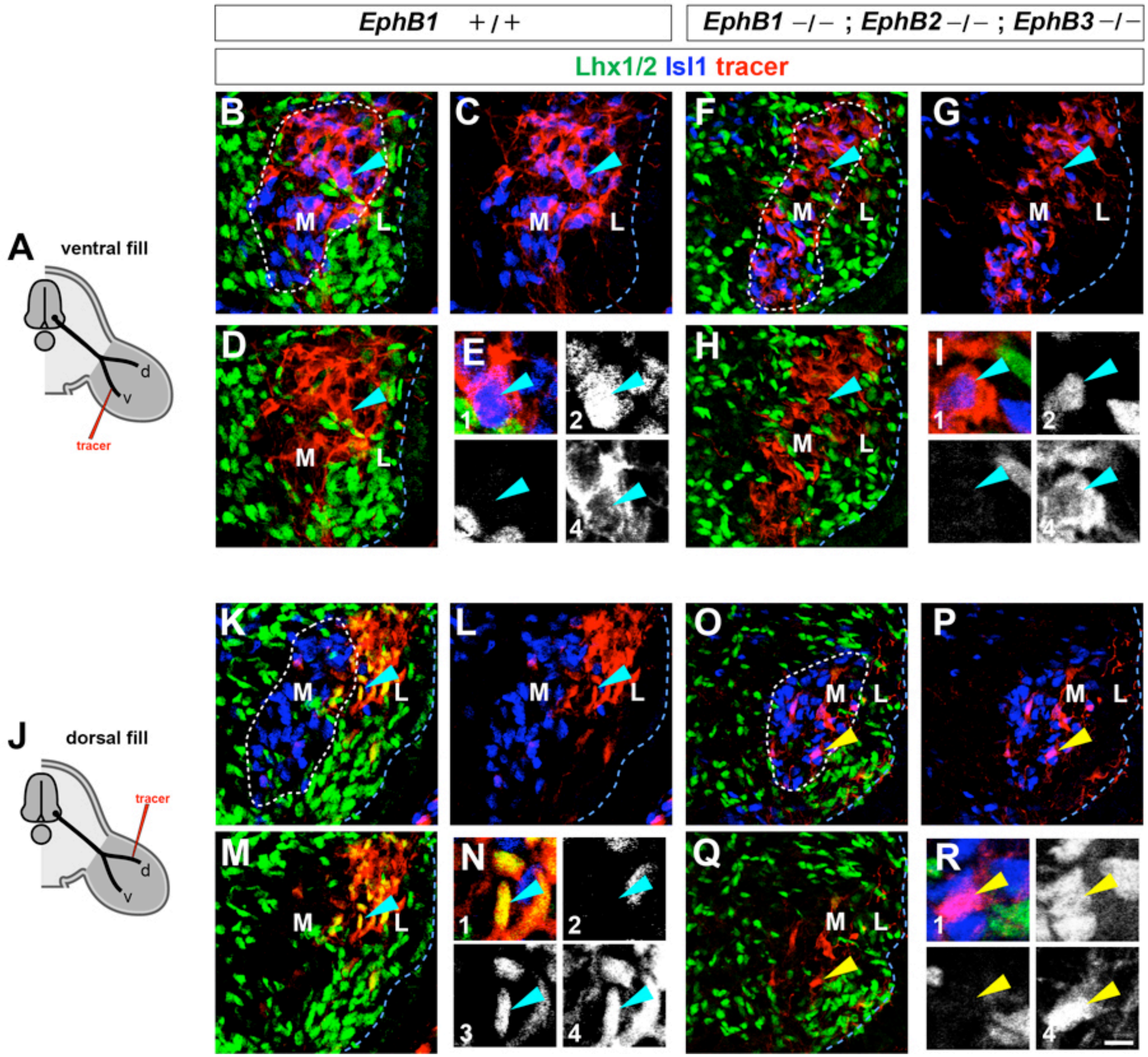
# *EphB1* is necessary for LMCm ventral targeting



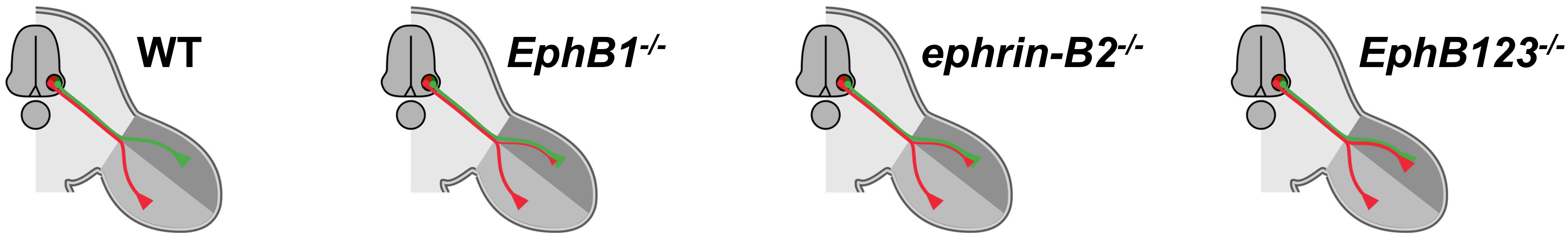
# *EphB1* does not influence LMCl projections



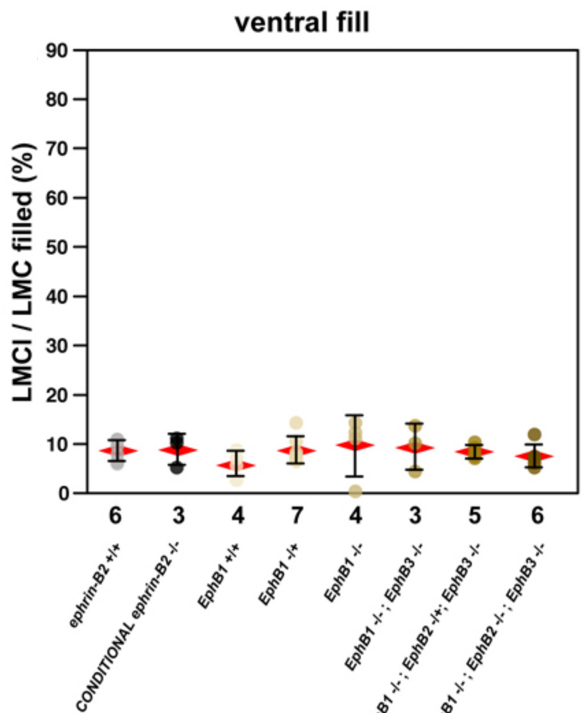
# *EphBs* are necessary for LMCm ventral targeting



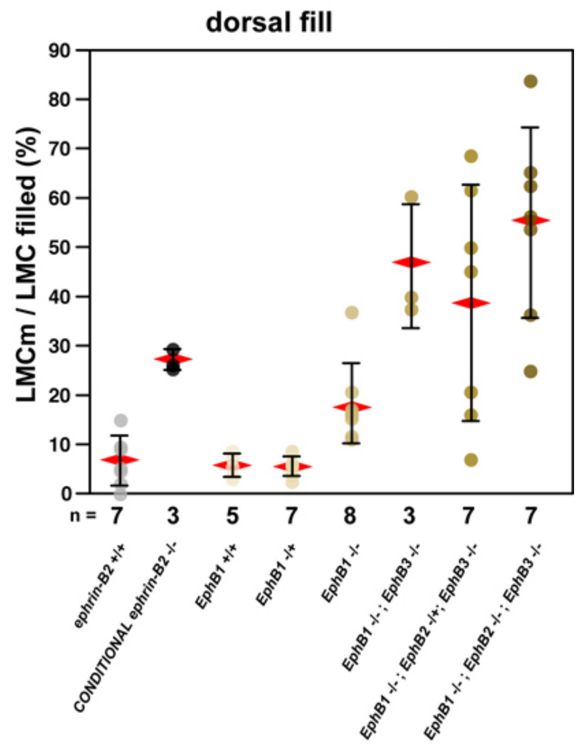
# LMCm projections are *randomized* AND *more variable* in compound mutants




## *mistargeted* LMCl




## *mistargeted* LMCm



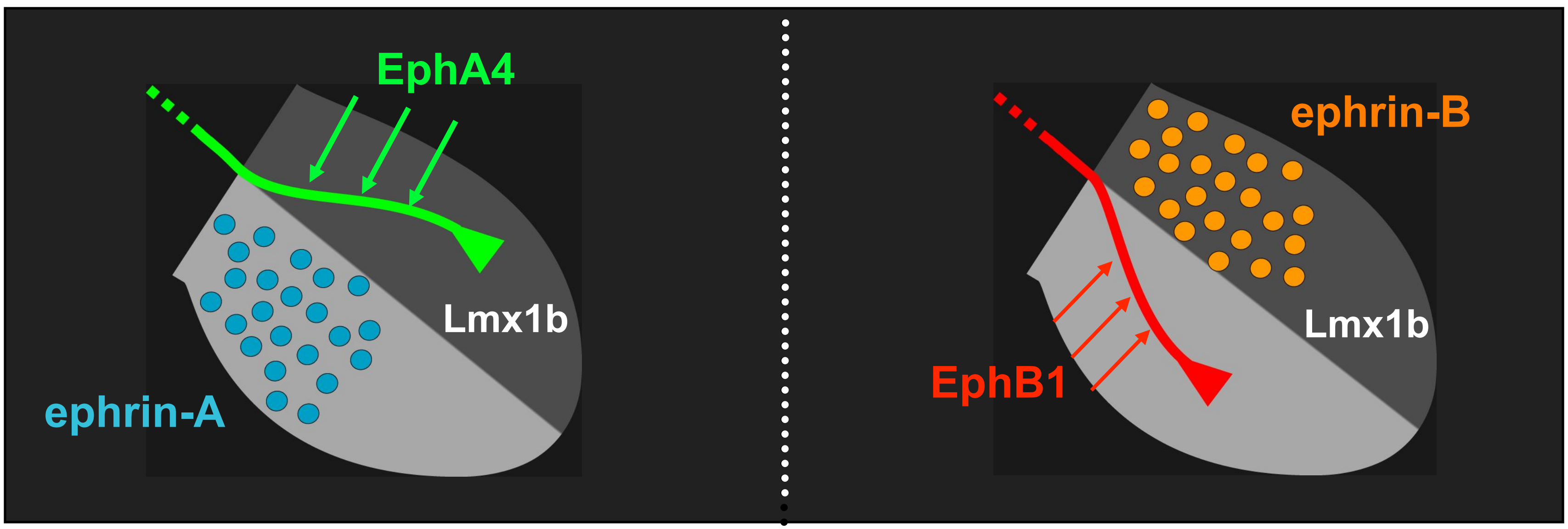
# SUMMARY I

## *Mirror symmetry* ephrin-Eph signaling controls motor axon trajectories to the limb

**EXPRESSION**

| | Ligands | Receptors |
|---|---|---|
| Dorsal limb | b | A |
| Ventral limb | a | B |

**FUNCTIONAL**

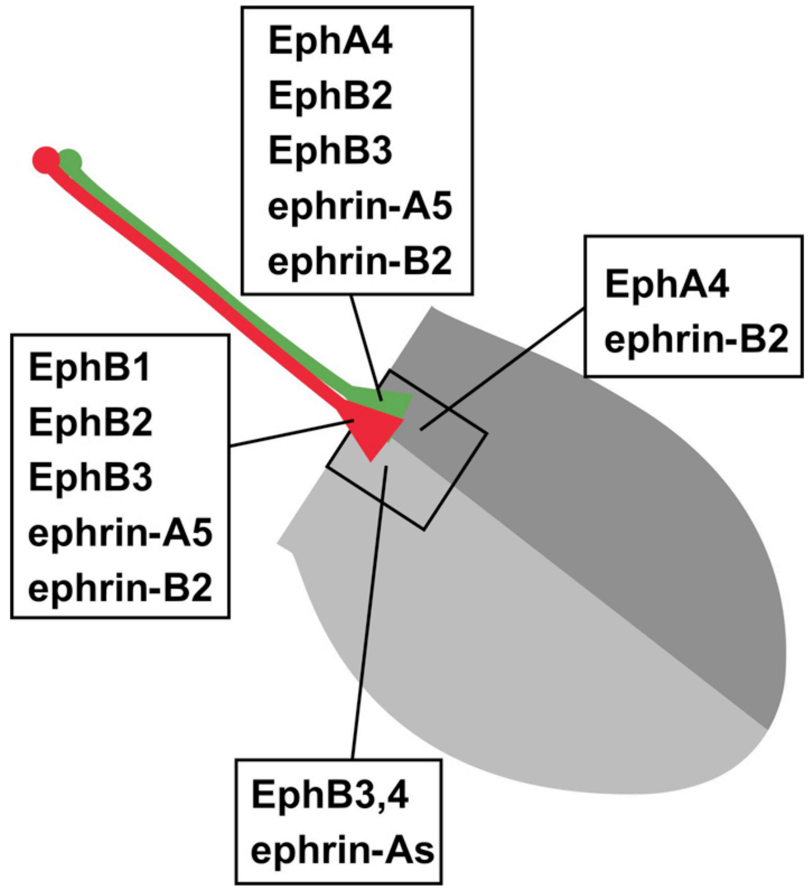



LMCl → EphA4 → Dorsal limb | LMCm → EphB1 → Ventral limb

Luria et al., *Neuron*, 2008

# *II. Quantitative models, experimental predictions and tests*

## Axons integrate multiple cues at limb entry



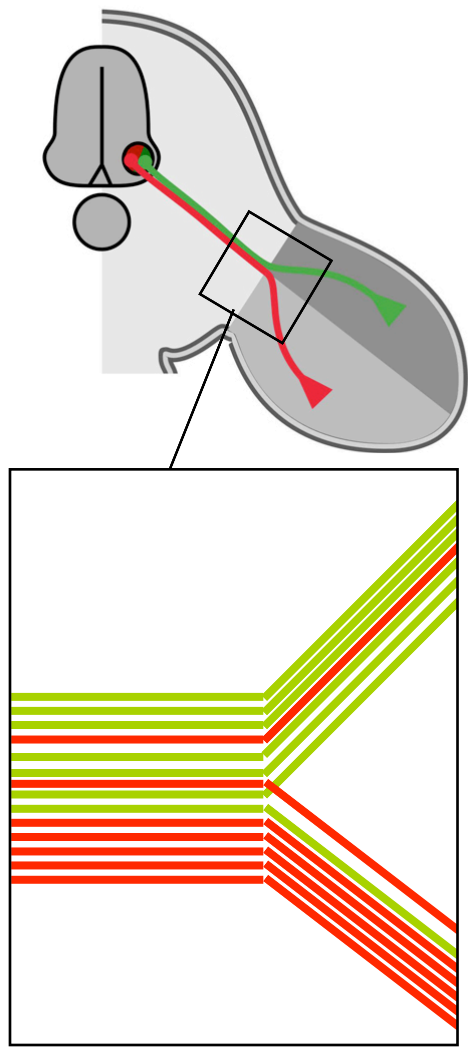

| Axon | Interaction | Limb | Symbol |
|---|---|---|---|
| EphB1 | >—< | ephrin-B2 | $B_1b_2$ |
| EphB2 | >—< | ephrin-B2 | $B_2b_2$ |
| EphB3 | >—< | ephrin-B2 | $B_3b_2$ |
| EphB2 | >—< | ephrin-As | $B_2a$ |
| EphA4 | >—< | ephrin-As | $A_4a$ |
| EphA4 | >—< | ephrin-B2 | $A_4b_2$ |
| ephrin-B2 | <—> | EphB3,4 | $b_2B_{34}$ |
| ephrin-A5 | <—> | EphA4 | $a_5A_4$ |
| ephrin-B2 | <—> | EphA4 | $b_2A_4$ |

$$\Sigma \text{lateral axons} = + A_4a + B_2a + a_5A_4 + b_2A_4 - A_4b_2 - B_2b_2 - B_3b_2 - b_2B_{34} > 0$$

$$\Sigma \text{medial axons} = - B_1b_2 - B_2b_2 - B_3b_2 - b_2B_{34} + B_2a + a_5A_4 + b_2A_4 < 0$$

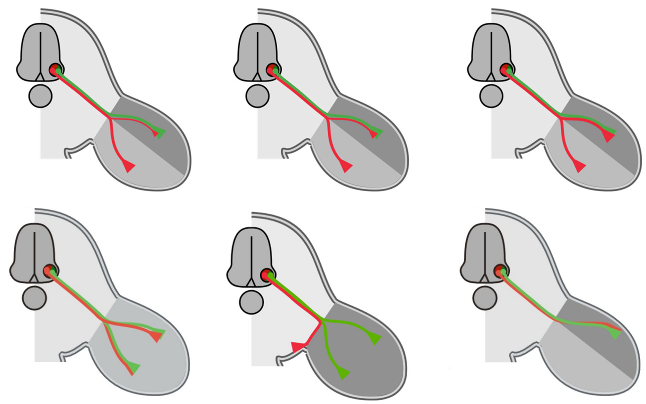
# Neural connectivity is *almost* exact, but defects are NOT corrected

## Wild type



**~95% - 5%**

## Various guidance gene mutants

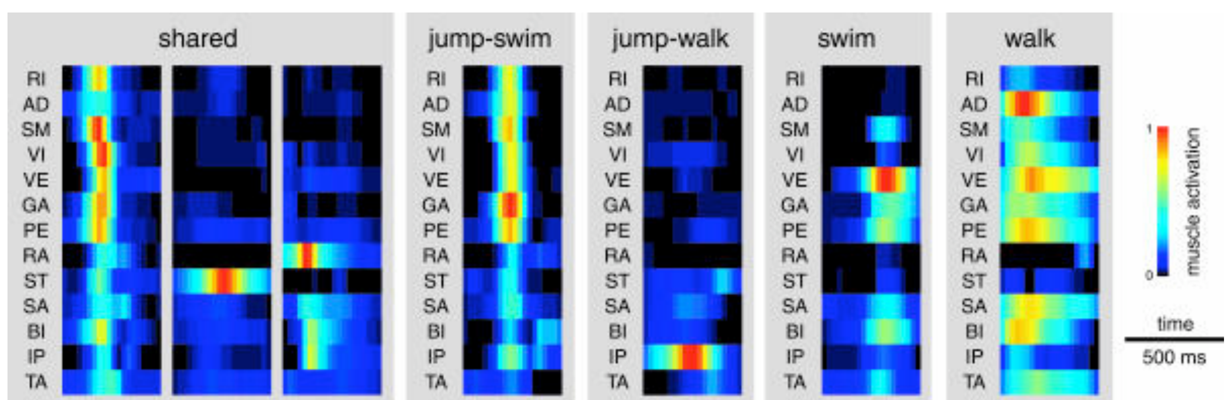


d'Avella & Bizzi, *PNAS* 2005

**Shared and specific muscle synergies in natural motor behaviors**

Andrea d'Avella*† and Emilio Bizzi‡§

*Department of Neuromotor Physiology, Istituto di Ricovero e Cura a Carattere Scientifico Fondazione Santa Lucia, 00179 Rome, Italy; †Department of Brain and Cognitive Sciences and McGovern Institute for Brain Research, Massachusetts Institute of Technology, Cambridge, MA 02139; and §European Brain Research Institute, 00143 Rome, Italy




***Lmx1b$^{-/-}$***

Kania et al., *Cell* 2000

***Bmprla$^{flox/-}$***

Luria et al., *Neural Dev.* 2007

***EphA4$^{-/-}$***

Helmbacher et al., *Development* 2000

***Sema3F$^{-/-}$ , Npn2$^{-/-}$***

Huber et al., *Neuron* 2005

***EphB1$^{-/-}$ in optic chiasma***

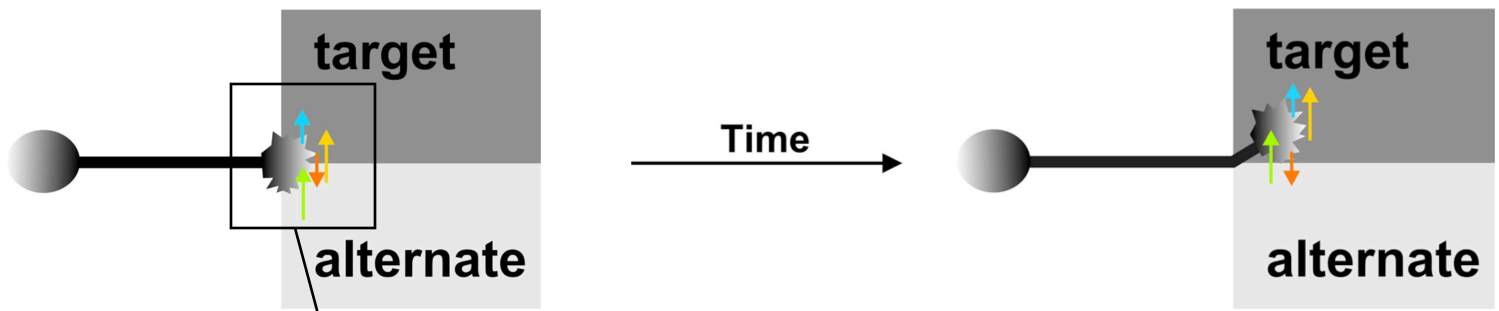
Williams et al., *Neuron* 2003

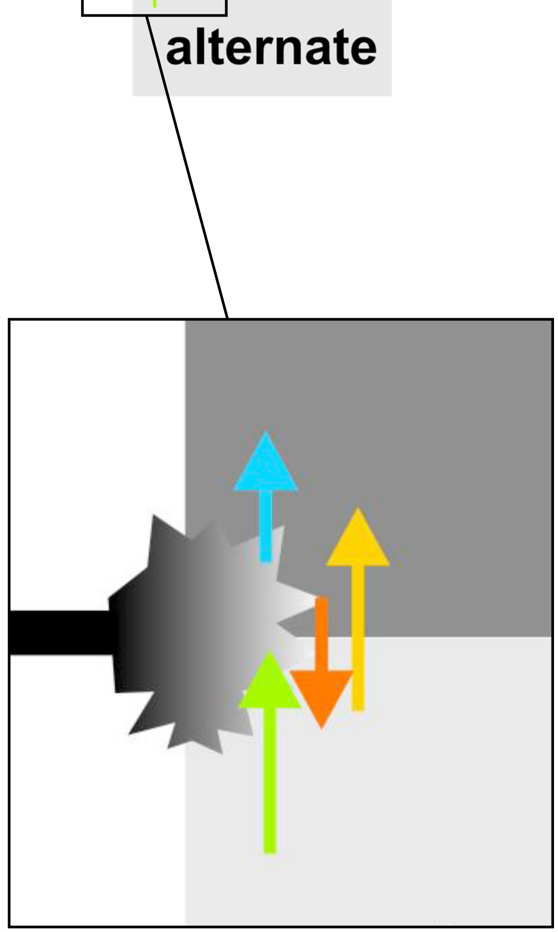
***EphB1,3,13,123$^{-/-}$***

***ephrin-B2$^{-/-}$***

Luria et al., *Neuron* 2008

# Axons integrate multiple cues at choice points



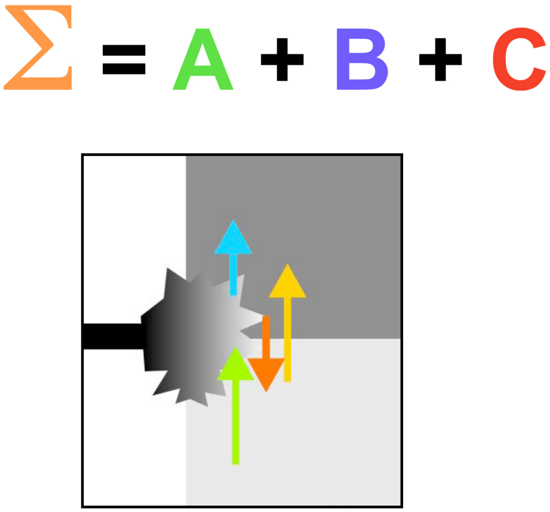
**A** repels axons from non-target tissue

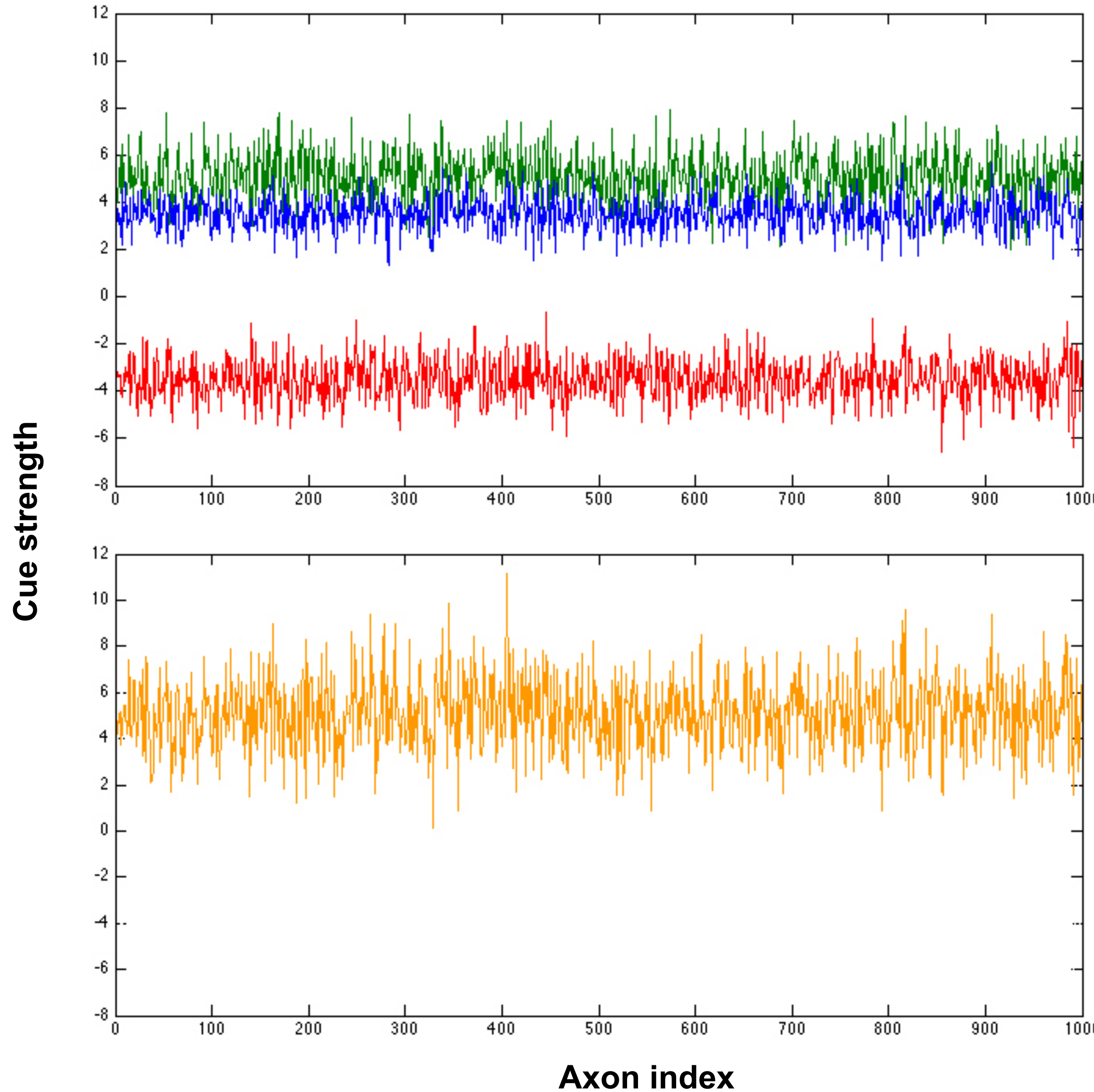
**B** attracts axons to target tissue

**C** repels axons from target tissue

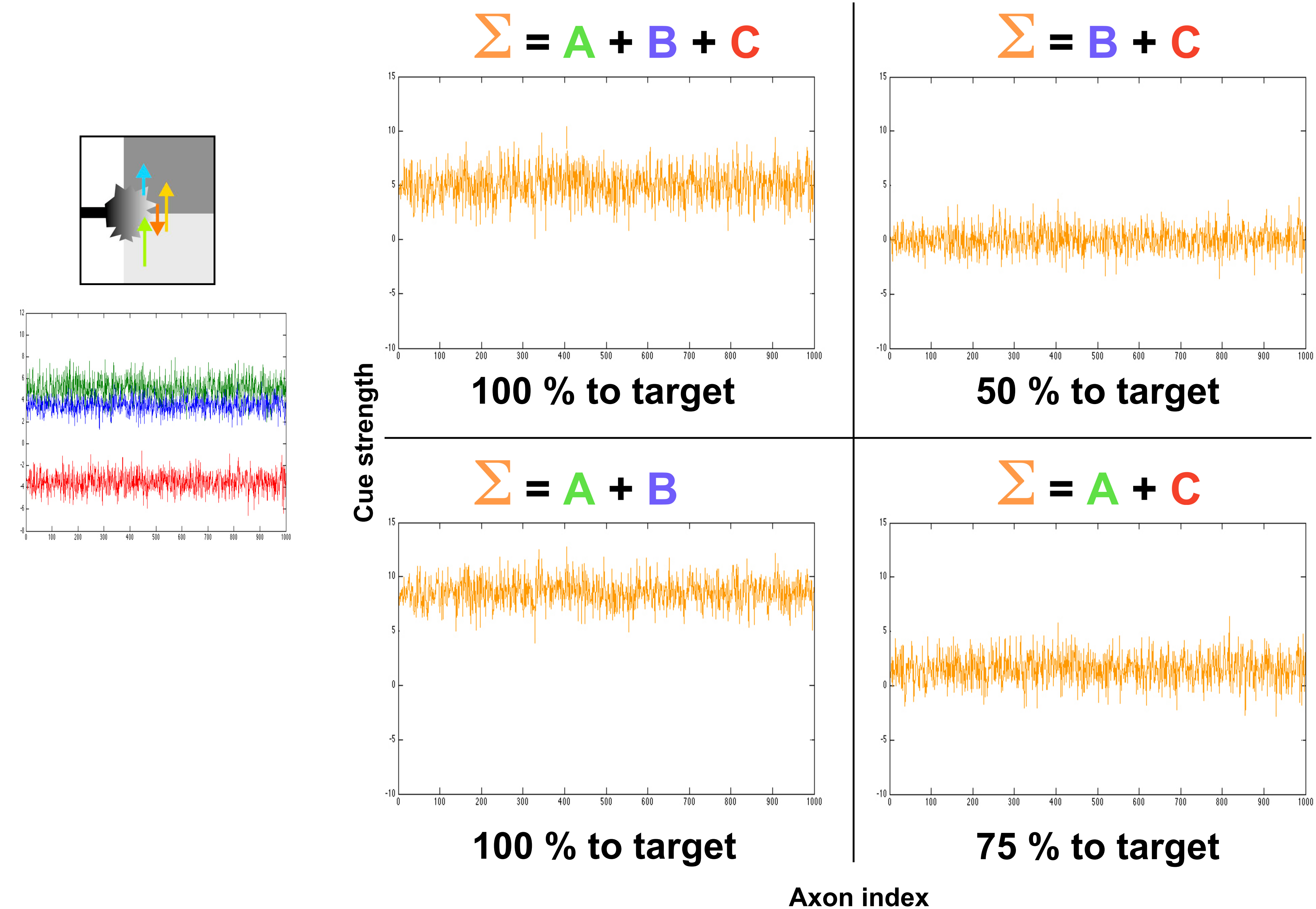
$$\sum = A + B + C$$

# Individual cues are noisy, the summed cue even more so

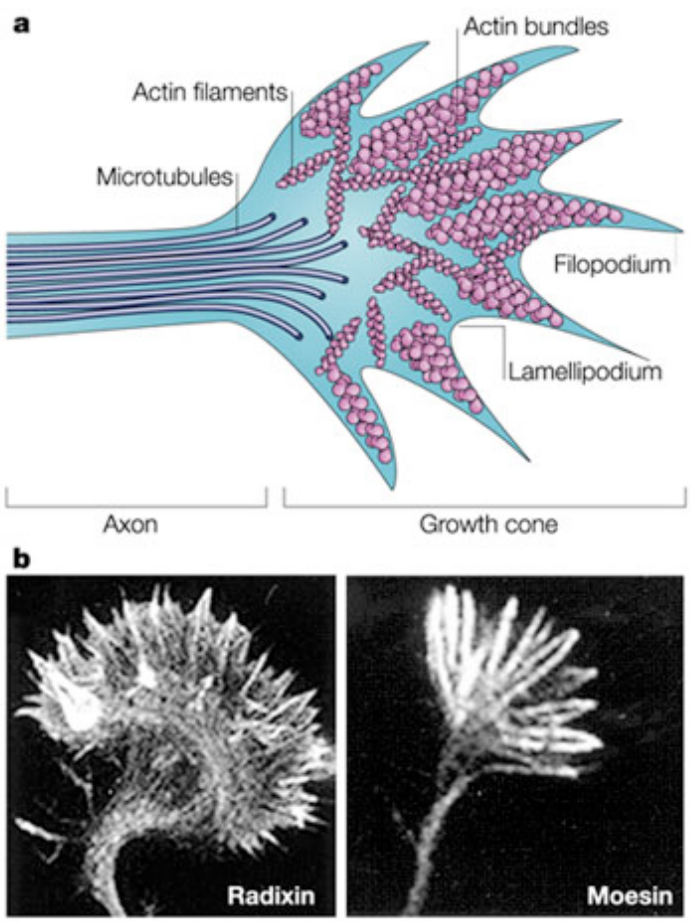


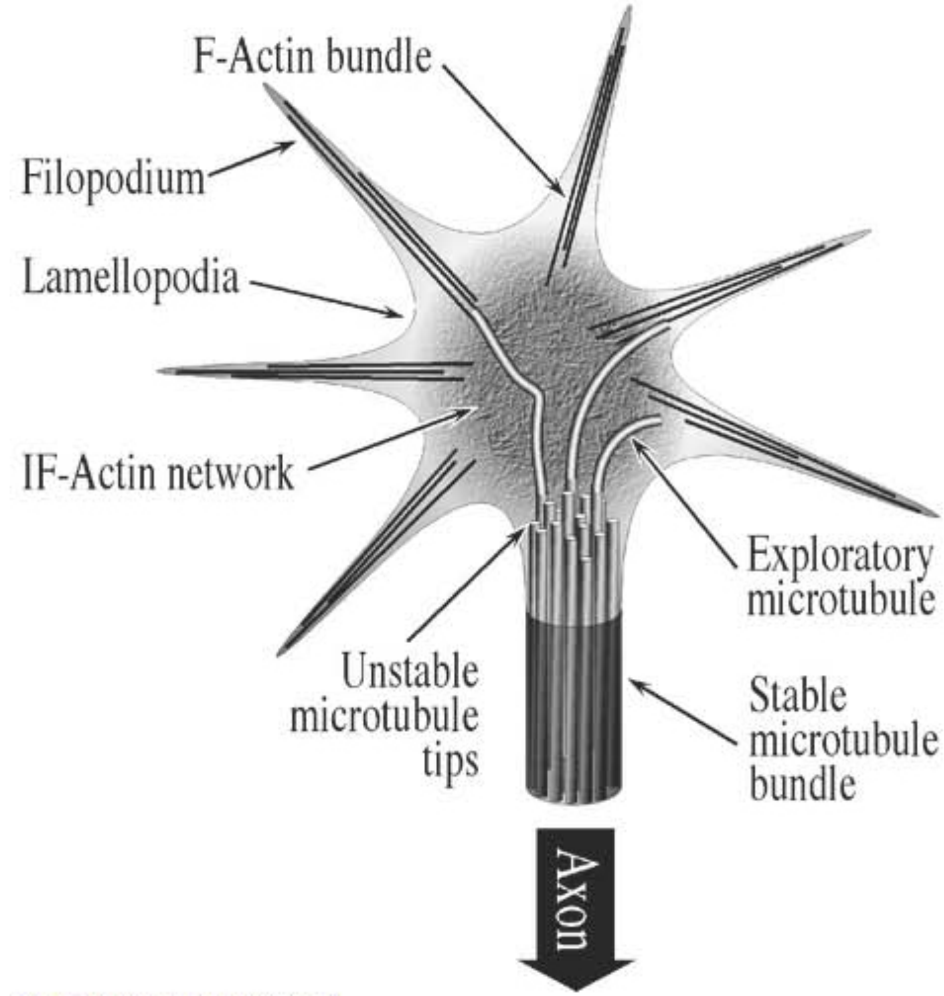
# Cue noise can explain guidance defects of mutants



# Growth cone machinery is a dynamic structure susceptible to stochastic events

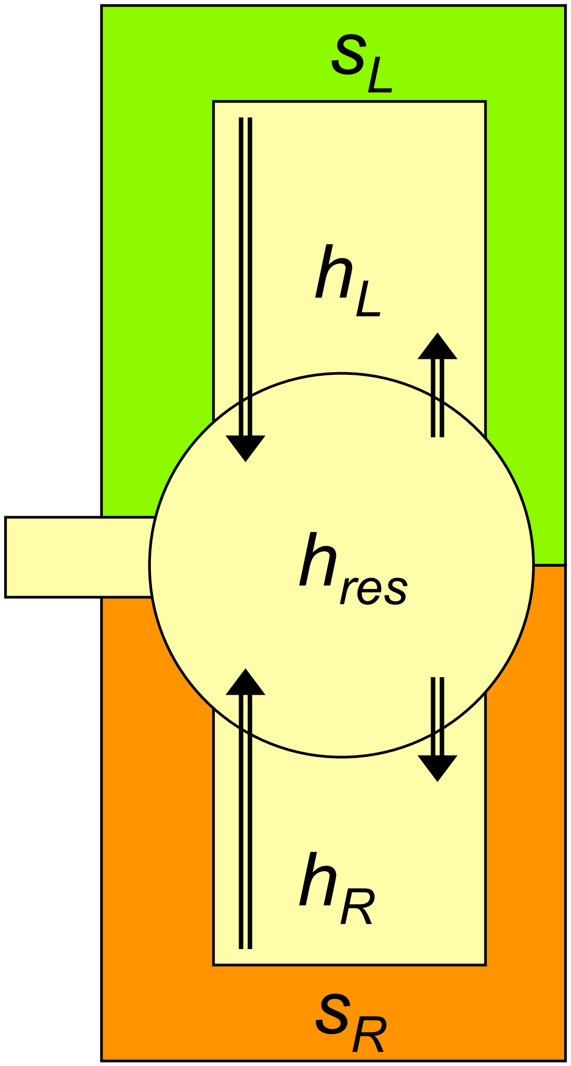



Vijaya Ramesh
*Nature Reviews Neuroscience* 2004




Maskery and Shinbrot
*Annual Review in Biomedical Engineering* 2005

# Dynamical model of cue integration




Summation: $$s_{L,R} = \sum_i c_i^{L,R} + \eta_i$$

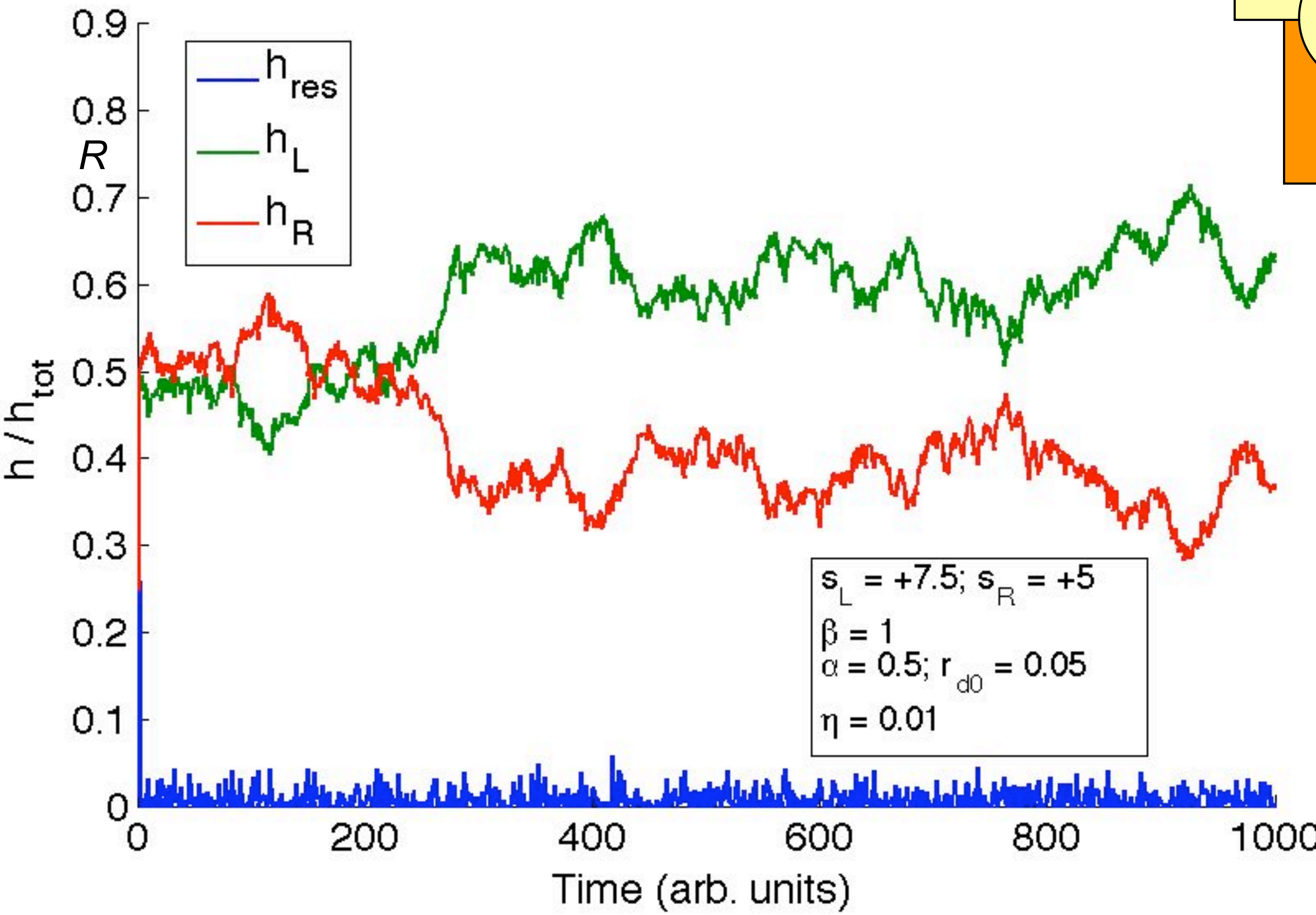
Dynamics: $$\frac{d\,h_{L,R}}{dt} = \alpha\, h_{res} - r_d\left(s_{L,R}\right) + \eta$$

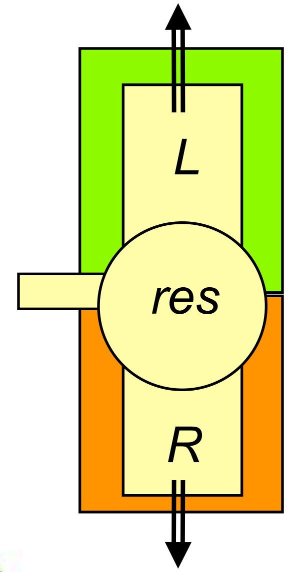
$$\frac{d\,h_{res}}{dt} = -\frac{d\,h_L}{dt} - \frac{d\,h_R}{dt}$$

Degradation rate: $$r_d\left(s\right) = 2r_0\left(\frac{1}{1+\exp(\beta\, s)}\right)$$

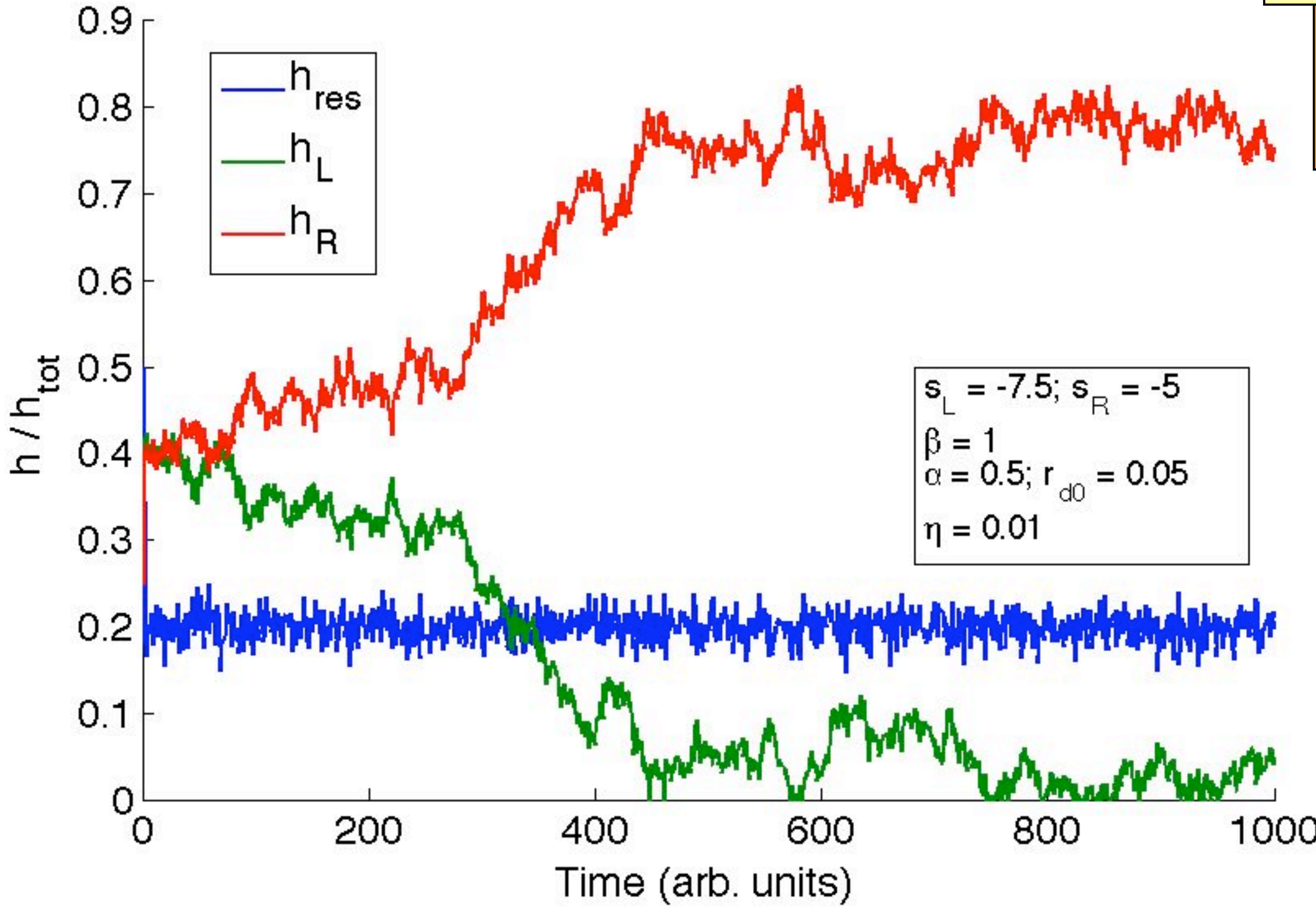
Conservation: $$h_{tot} = h_L + h_R + h_{res} + h_{noise}$$

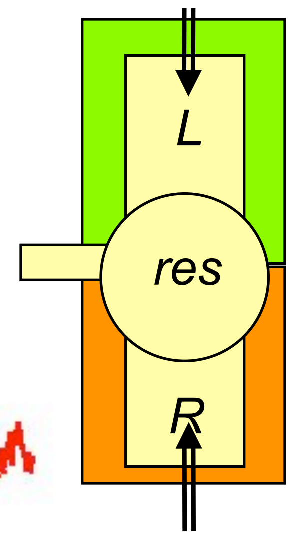
# Attractive inputs



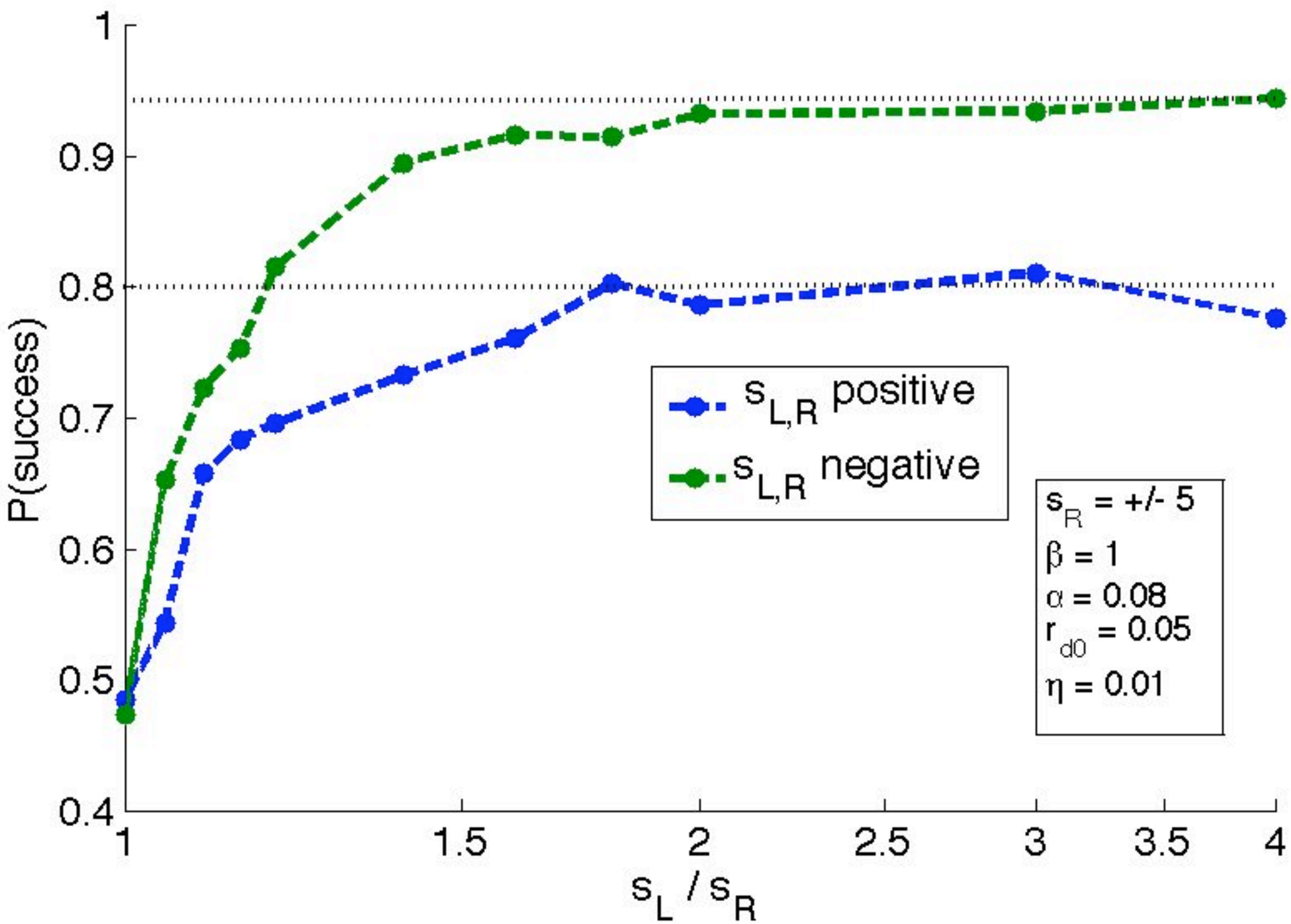



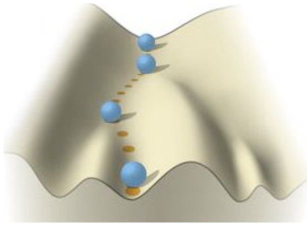
# Repulsive inputs



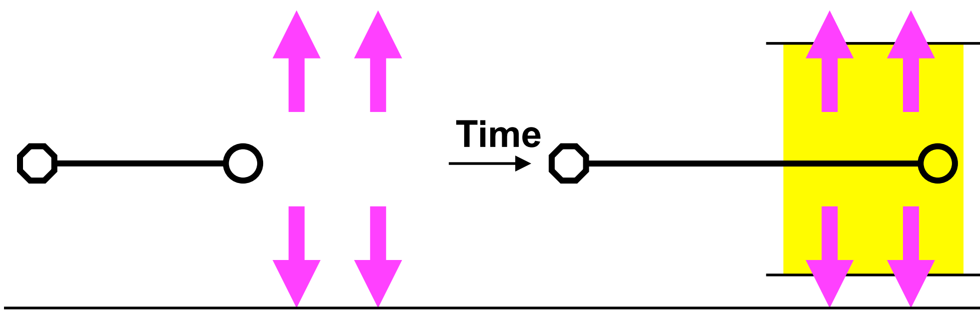
# Stochastic choice behavior & positive/negative asymmetry

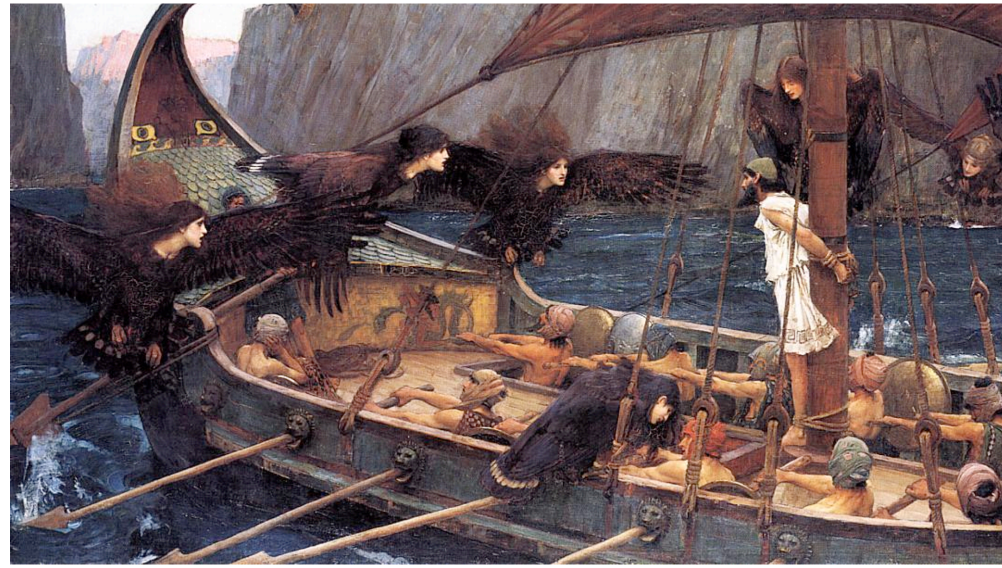




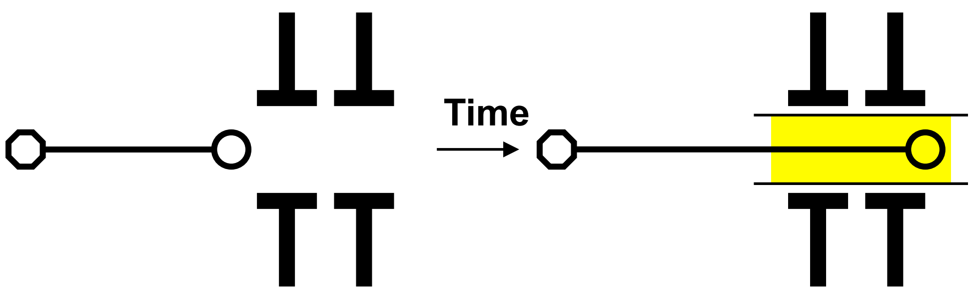
# Competing cues and system stability

**ATTRACTIVE cues**
**--> *unstable* trajectories**



**REPULSIVE cues**
**--> *stable* trajectories**




# Summed cue strength is limited by sensor noise and amplification

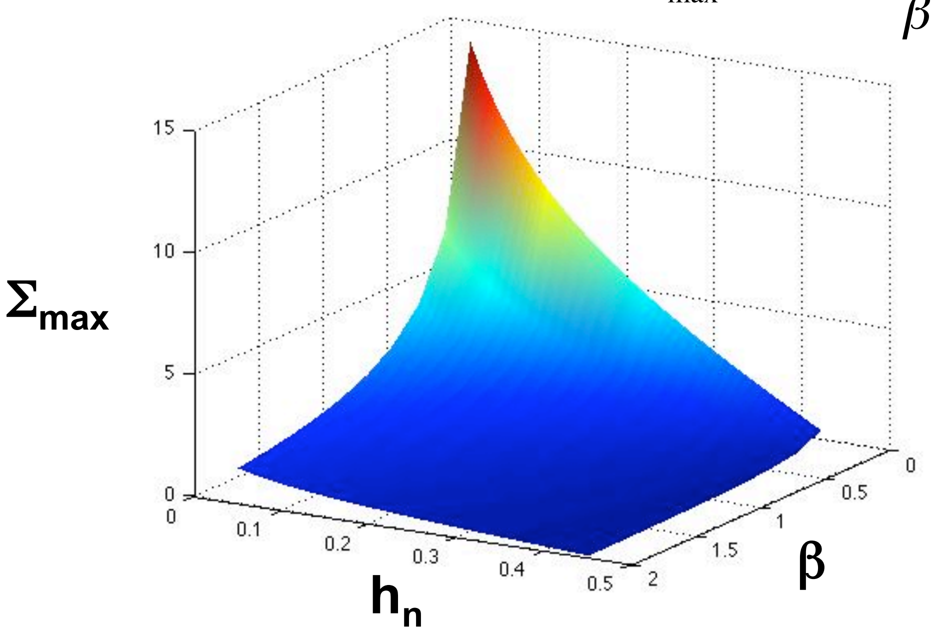
$$h = h_{engaged} + h_{available} + h_{noise}$$

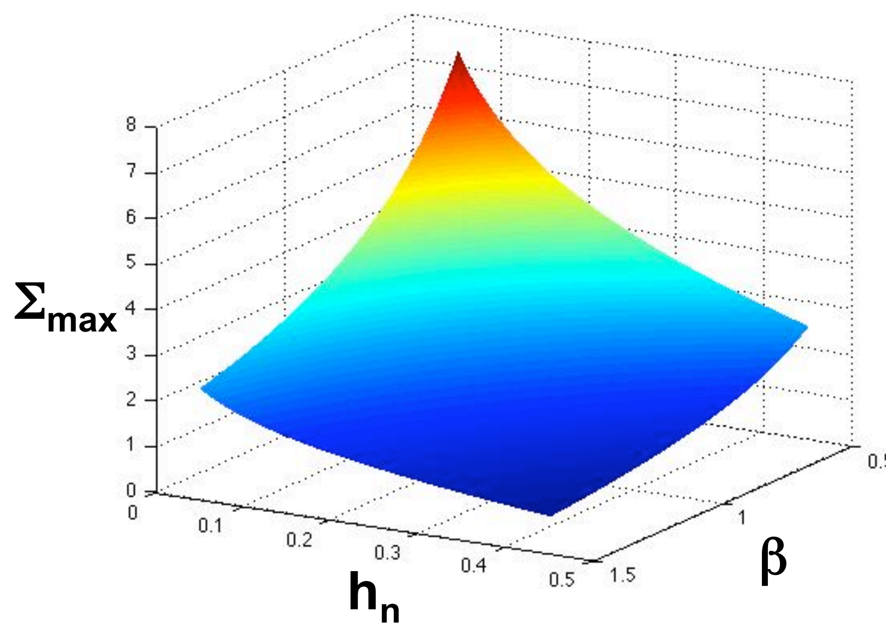
$$h_{engaged} = h\left(\frac{1}{1+\frac{1}{e^{\beta\Sigma}}}\right)$$

$$h_{engaged} \leq h - h_{noise}$$

$$\Sigma_{\max} = \frac{\log\left(\frac{h - h_{noise}}{h_{noise}}\right)}{\beta}$$

h = sensing cytoskeletal material
Σ = summed cue
β = signal transduction strength



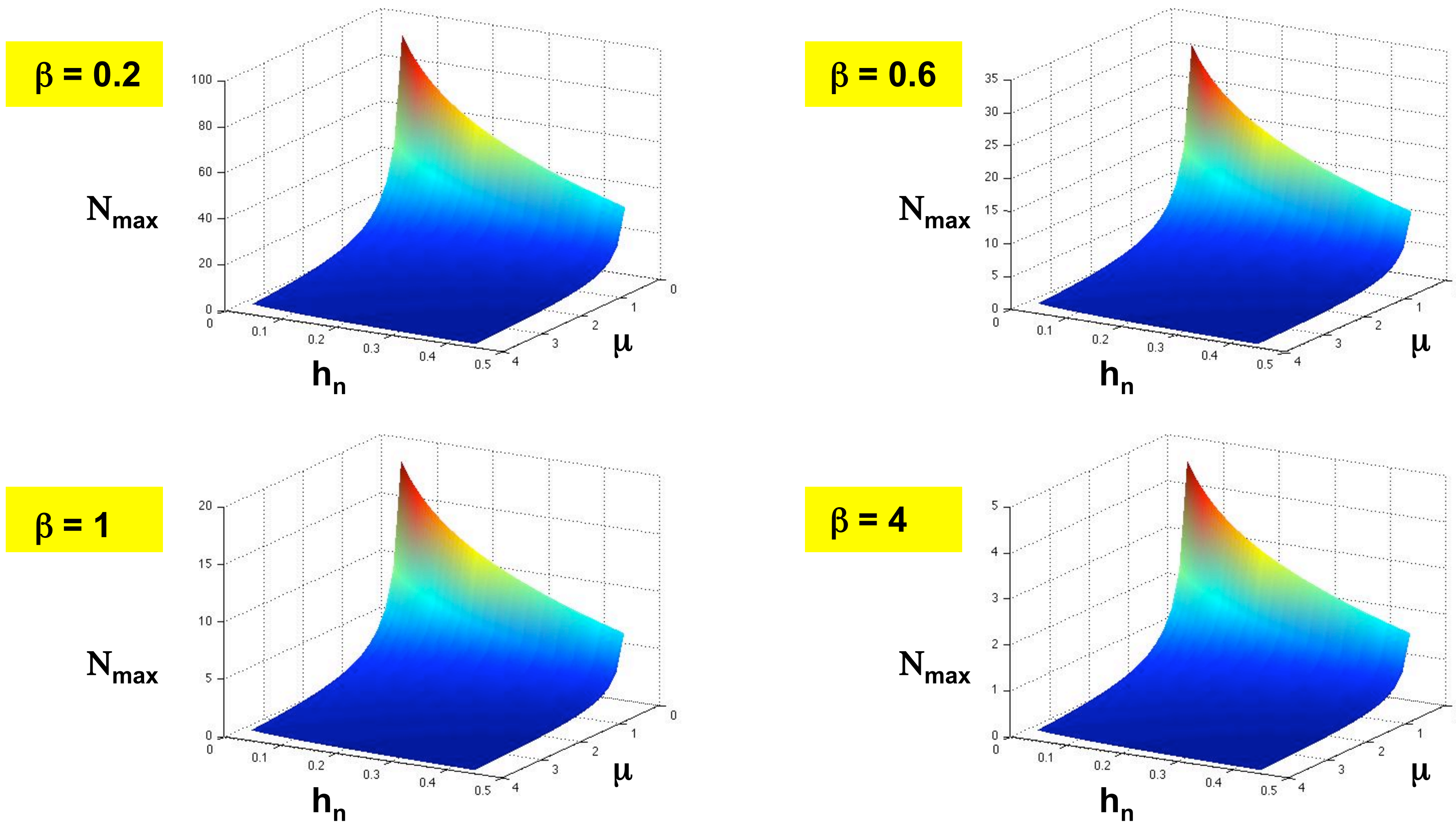



# Cue number depends on sensor noise and mean cue strength

$$\Sigma_{\max} = N_{\max} \times \mu$$

$$N_{\max} = \frac{\log\left(\frac{h - h_{noise}}{h_{noise}}\right)}{\beta \times \mu}$$

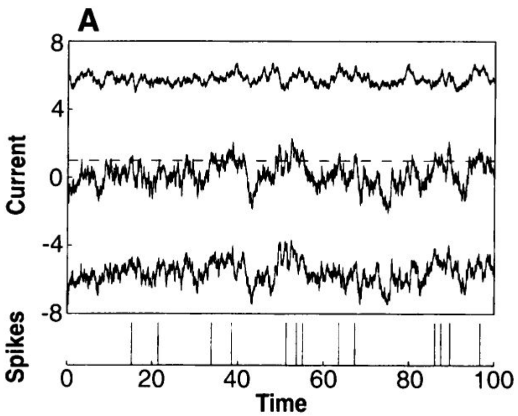
h = sensing cytoskeletal material
Σ = summed cue
β = signal transduction strength
μ = mean cue strength
N = number of cues



# *Too-much-information* hypothesis
## Noise and finite sensing capacity *limit* information

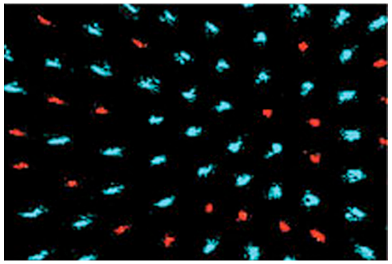
**Construction of neural circuits**

Luria et al., *Neuron* 2008




**Neuronal firing rates**

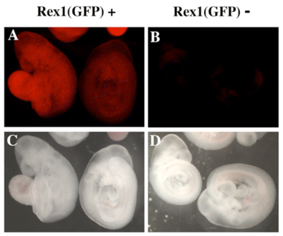
Van Vreeswisjk & Sompolinsky, *Science* 1996



**Drosophila photoreceptor fields**

**70% - 30% unequal partitioning**

Wernet et al., *Nature* 2006

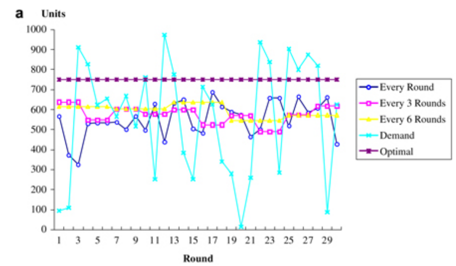



**Embryonic stem cells transient differentiation**

Toyooka et al., *Development* 2008

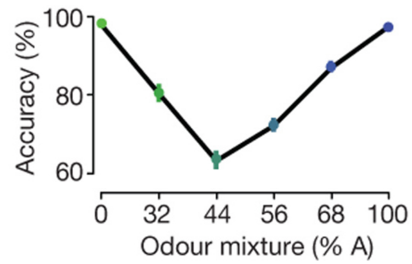
# Finance - the anti-portfolio effect

Vlad et al., *PNAS* 2007




# Consumer choices

Lurie and Swaminathan,
*Organizational Behavior and Human Decision Processes* 2009




# Olfactory behavior choices

Kepecs et al., Nature 2008

# Other behavioral decisions?…

## SUMMARY AND FUTURE WORK

**1. Control of axon trajectories**
**A/B ephrin-Eph *mirror symmetry***

**2. *EphBs* suppress phenotypic variability**

**General variability suppressors - *Hsp90*,** Rutherford and Lindquist, *Nature* 1998, 2003
**Specific variability suppressors - *Eph* genes**

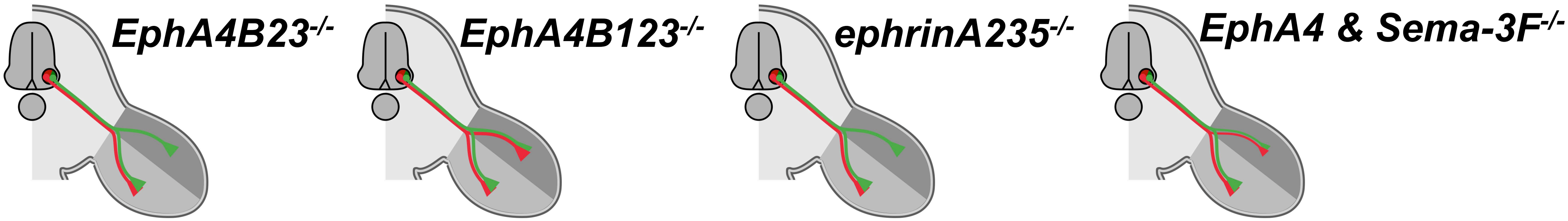
***EphA4***, Helmbacher et al., *Development* 2000
***EphBs***, Luria et al., *Neuron* 2008

**3. Theoretical modeling**

**suggests how *genetic variability* is translated into *phenotypic variability***
**suggests noise limits the amount of information controlling binary decisions**
**generates experimental predictions**

# **Genetic experiments**

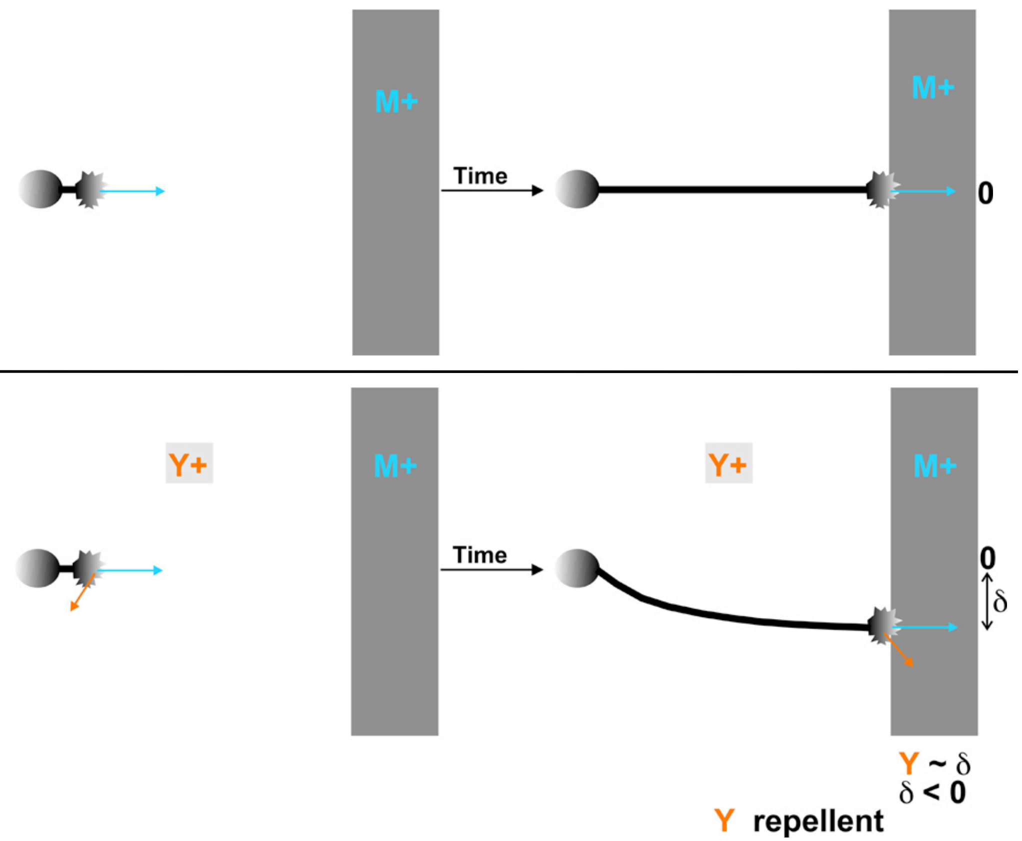
**mutants**




**soft perturbations: RNAi**

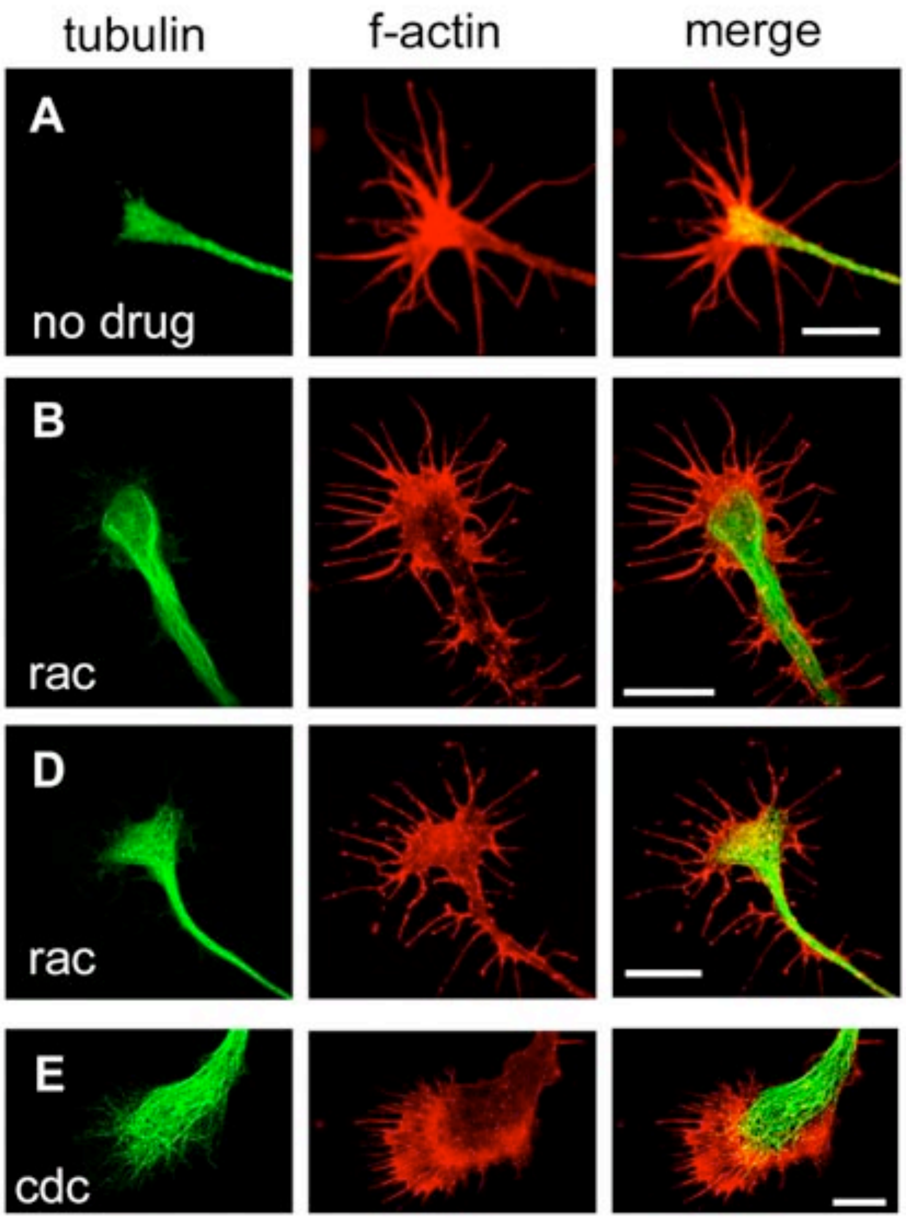
---

# **Biophysical experiments**




| Diffusible | Surface-bound |
|---|---|
| Mu-ming Poo<br>Christine Holt<br>Geoff Goodhill | Friedrich Bonhoeffer<br>Ludwig von Philipsborn |

# Growth cones reorient in response to electrical fields




**(A-E)** *Xenopus* spinal neuron growth cones in an electric field for 5h, with the cathode at left.

**(B,D)** A peptide that blocks rac effector binding stimulates filopodia relative to lamellipodia.

**(E)** A peptide that blocks cdc42 effector binding stimulates lamellipodia relative to filopodia.

Modified from Fig 5
Rajnicek et al. 2006.
*J Cell Science*
**119:** 1736-45.

**Physiology**

**Molecular mechanisms**

Keith Robinson
Claudio Stern
Mu-ming Poo
***Colin McCaig***

# Cue strength: quantification using benchmarks