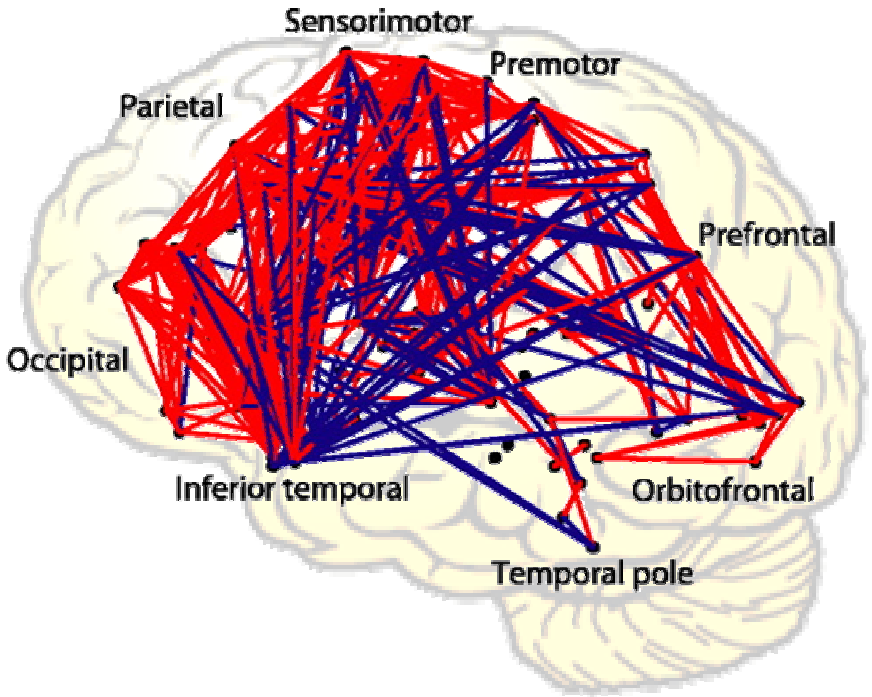
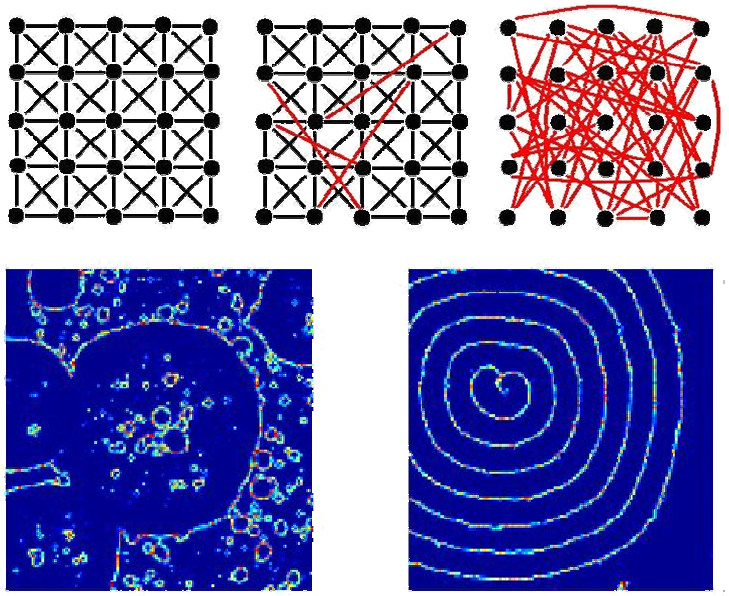
Complex Networks in the Brain:

From "small-world" of neurons & glia to the mind of a worm



Achard et al, PNAS



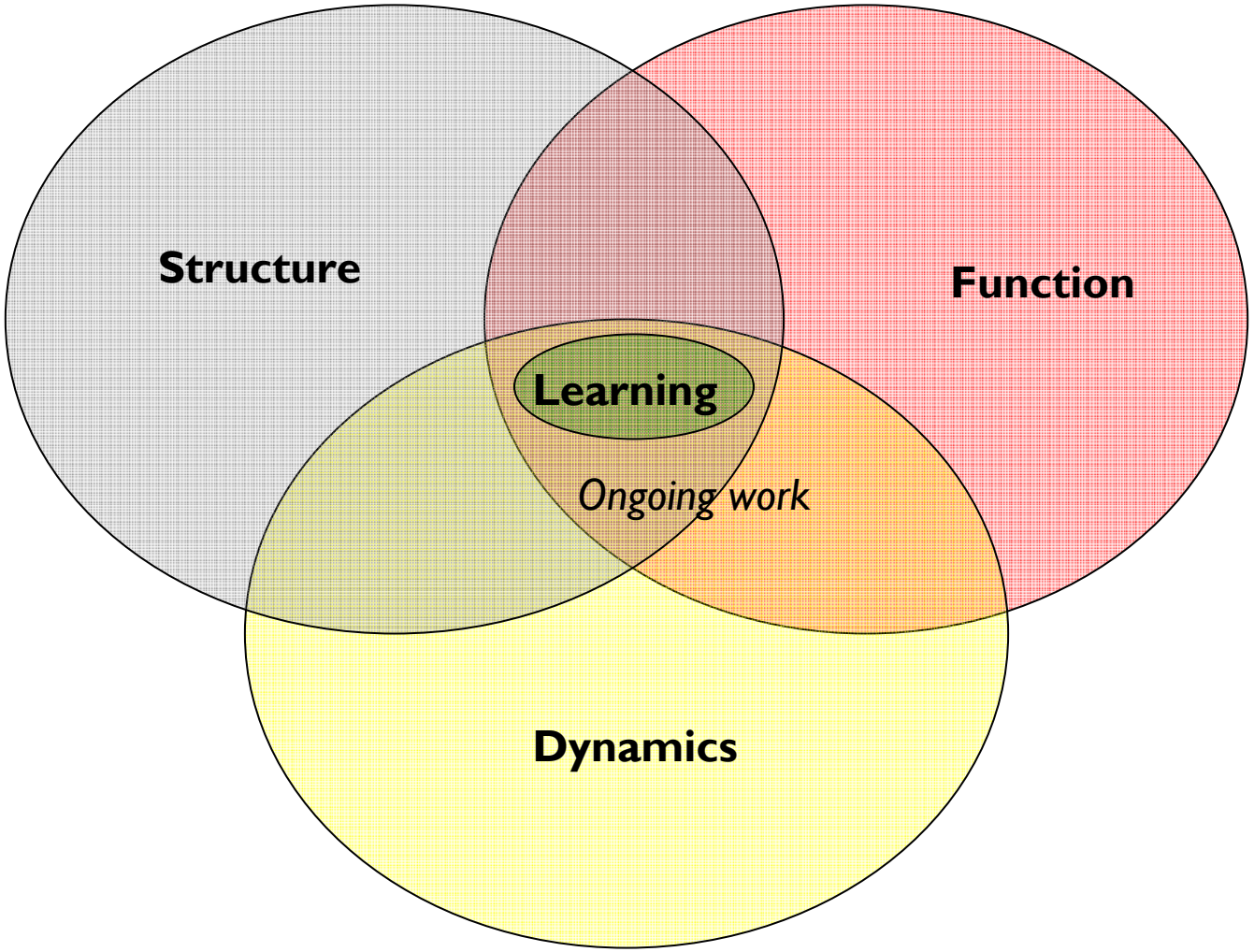
Sinha et al, PRE

Sitabhra Sinha

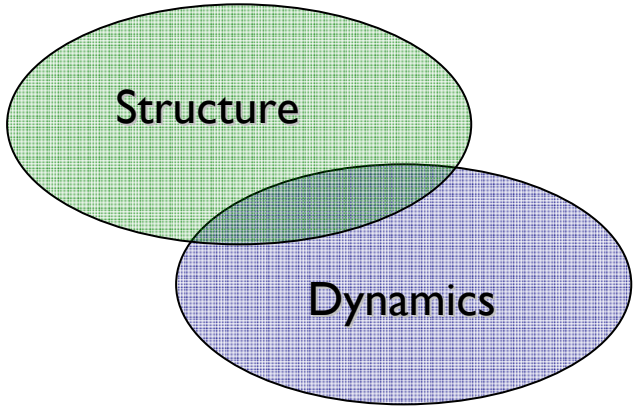
The Institute of Mathematical Sciences, Chennai

Network Neuroscience

The Research Program



Step I.

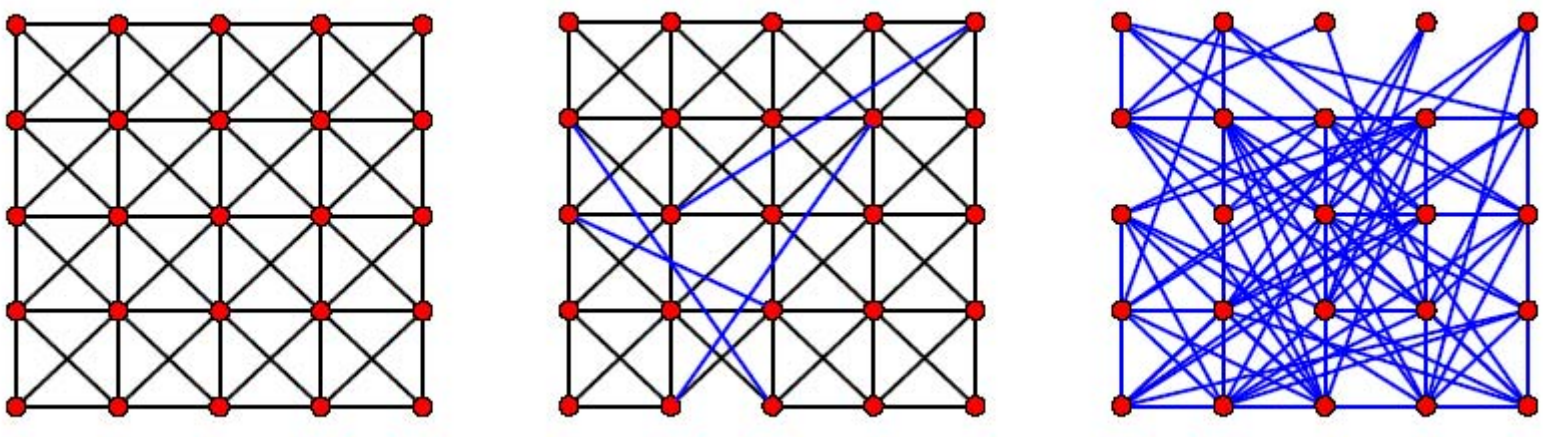


In brain, networks are not random – many have certain structural patterns

So…

How does network structure affect dynamics ?

Example: *small-world* networks



Regular Network
p = 0

"Small-world" Network
0 < p < 1

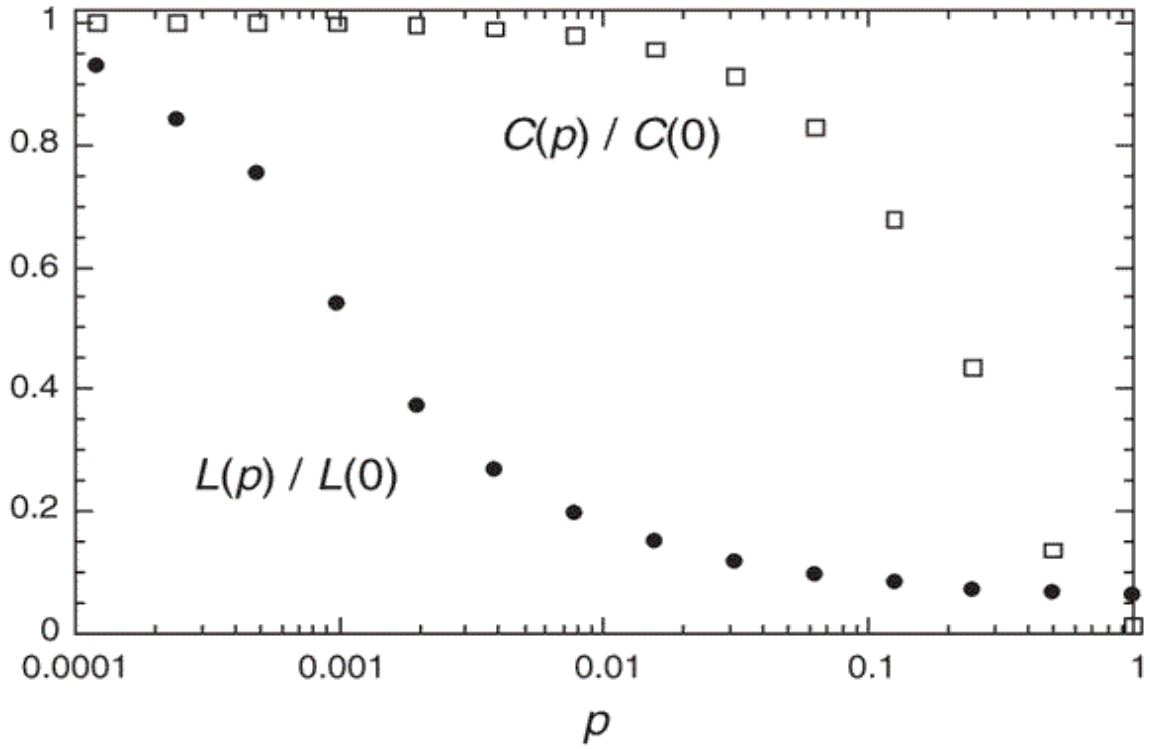
Random Network
p = 1

Increasing Randomness

p: fraction of random, long-range connections

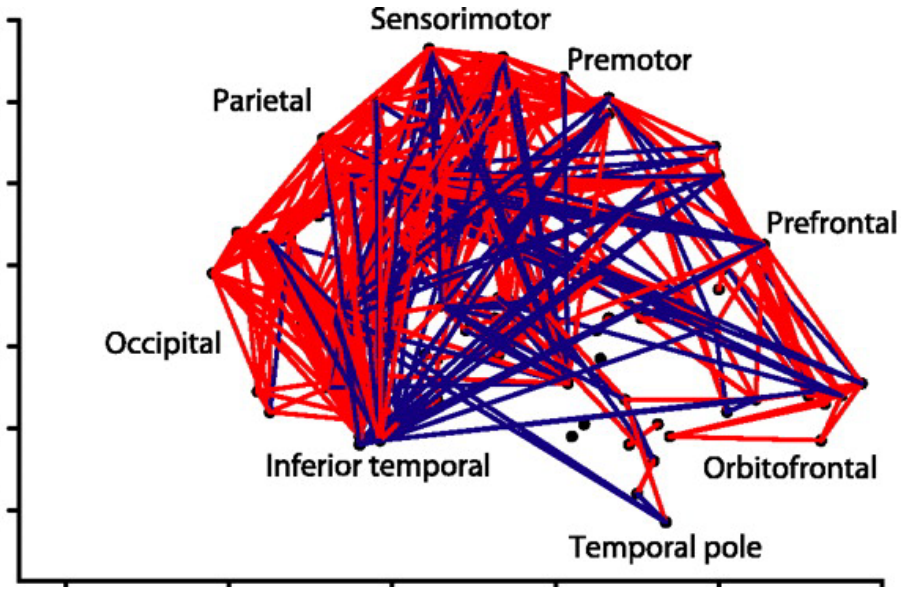
Watts and Strogatz (1998): Many biological, technological and social networks have connection topologies that lie between the two extremes of completely regular and completely random.

Small-world networks can be highly clustered (like regular networks), yet have small characteristic path lengths (as in random networks) and, thus, high communication efficiency



Characteristic path length ($\ell(p)$) and clustering coefficient ($C(p)$) as network randomness increases.

Human brain functional network [fMRI time series, linking 90 cortical & sub-cortical areas] (Achard et al)



Several brain functional networks, including the cortex of Humans, as well as Macaques and Cats, have been reported to show properties similar to small-world networks

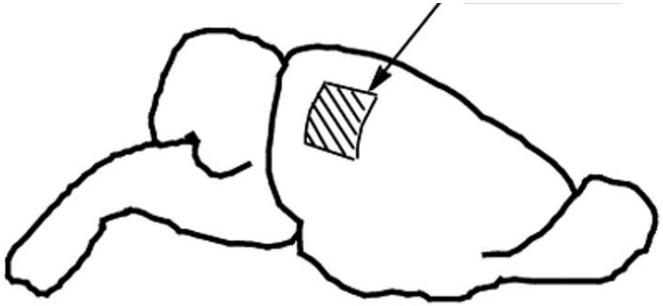
Question:

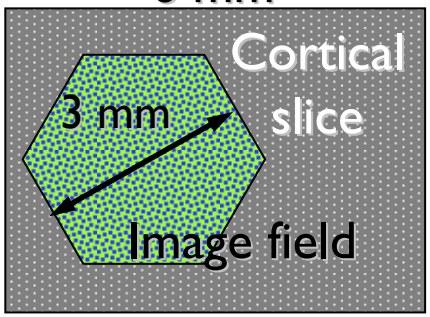
How relevant is small-world network architecture to brain dynamics?

Propagating Waves in Rat Neocortical Slices: Spiral Waves & Bursts

J Wu Lab, Georgetown Univ

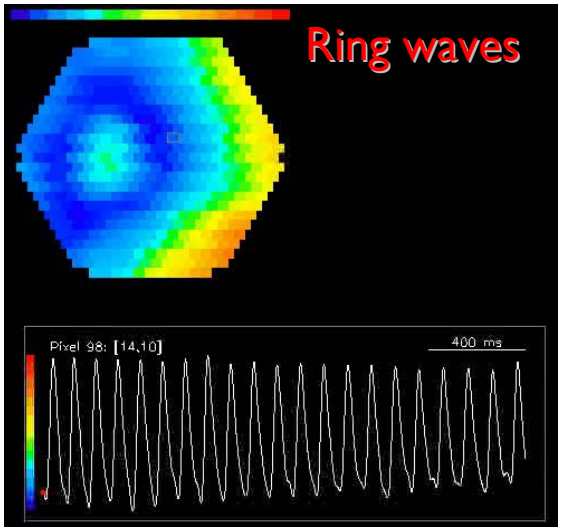
Tangential slices of rat occipatal cortex



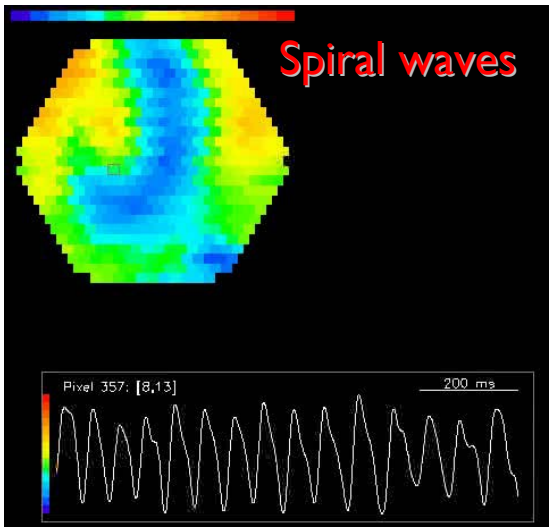


stained with voltage sensitive dye

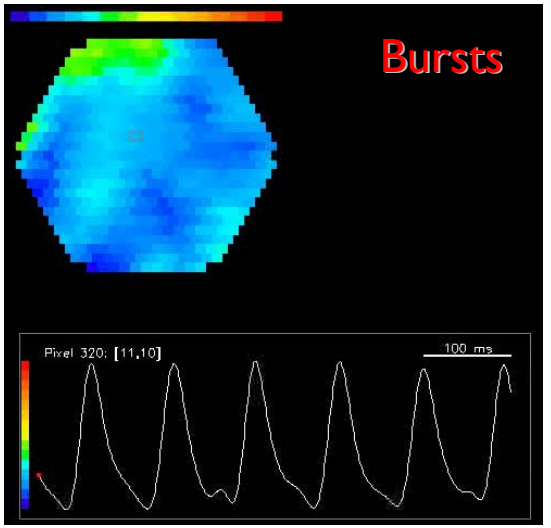
Optical signal on each photo detector = summation of activity of ~1000 neurons



Period ~ 100ms



Aperiodic,
dominant period ~ 70ms



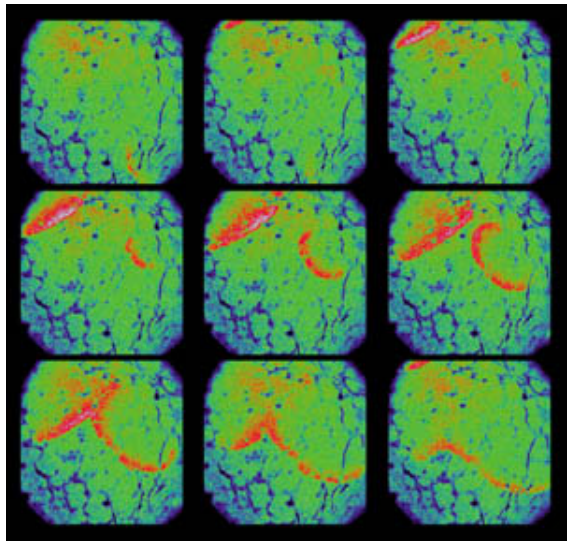
Period ~ 100ms

Spirals Everywhere

Pattern Formation in Excitable Media

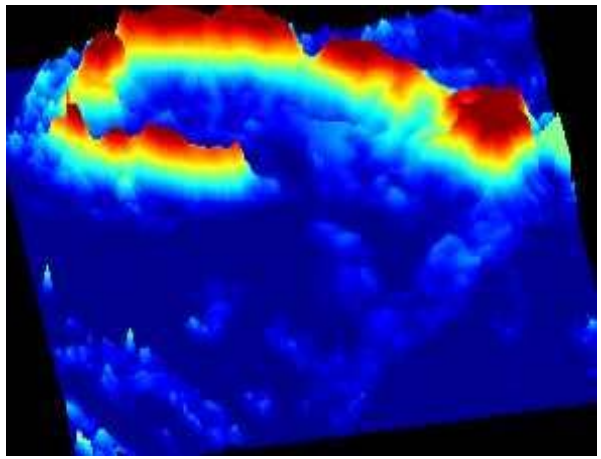
Aggregation of
Dictyostelium amoebae
by cAMP signalling

BZ chemical reaction



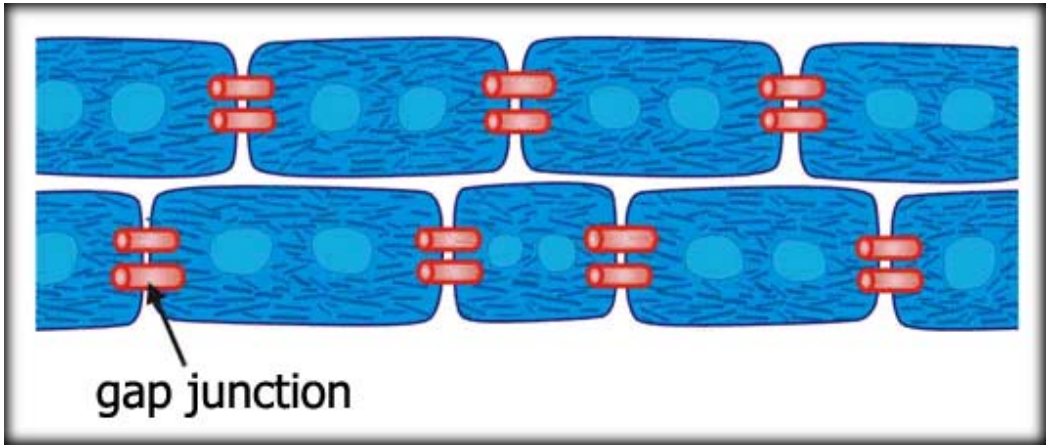
Ca^{++} waves in
cytoplasm of
Xenopus oocytes

Tachycardia in canine
ventricle



Waves of excitation in excitable media

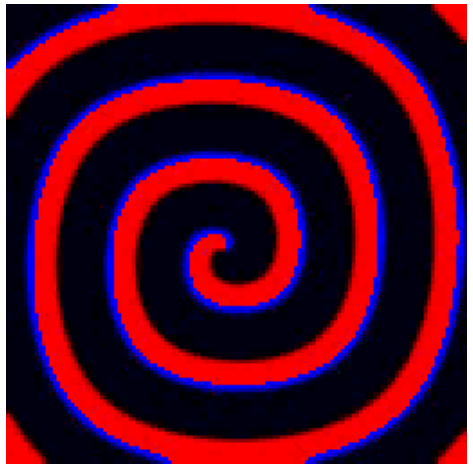
Excited cells can excite their neighboring cells through diffusion



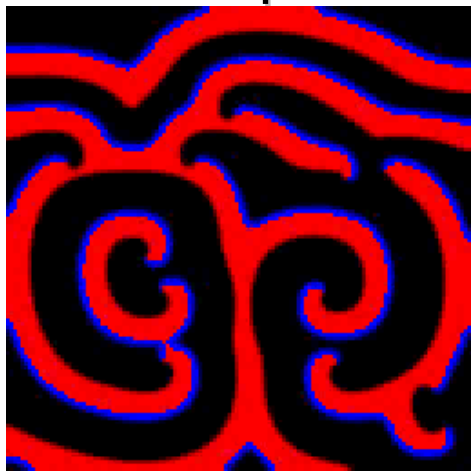
Waves annihilate on collision

A characteristic feature of wave propagation in excitable media is spontaneous pattern formation, in particular ….
Spiral Waves!

single spiral



broken spirals



But…

- Neurons are not connected in a regular, nearest neighbor topology
- Can have large number of long-range connections
- In fact, possibly resembles a random network

Whereas…

- Waves in excitable media get disrupted without regular arrangement, e.g., if cells connected with random topology

Puzzle:

How is sustained wave activity occurring in the brain ?

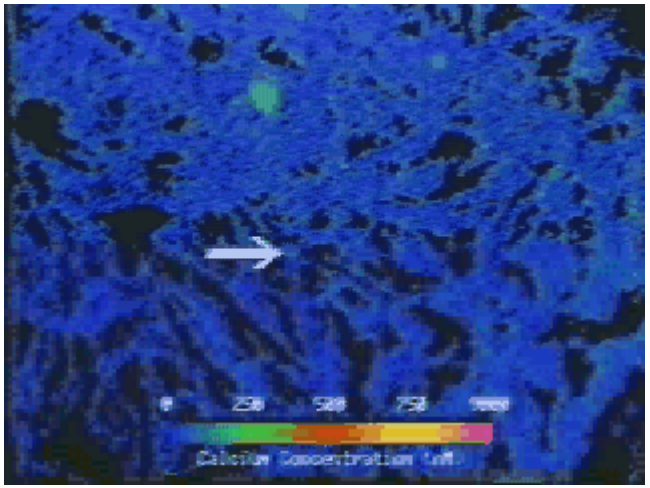
Clue

Neurons + Glial cells =

Small World Network ?

Glia (Gr., from glue) : *The Hidden Bulk of the Brain*

Outnumber neurons by 10 to 1 in some brain areas

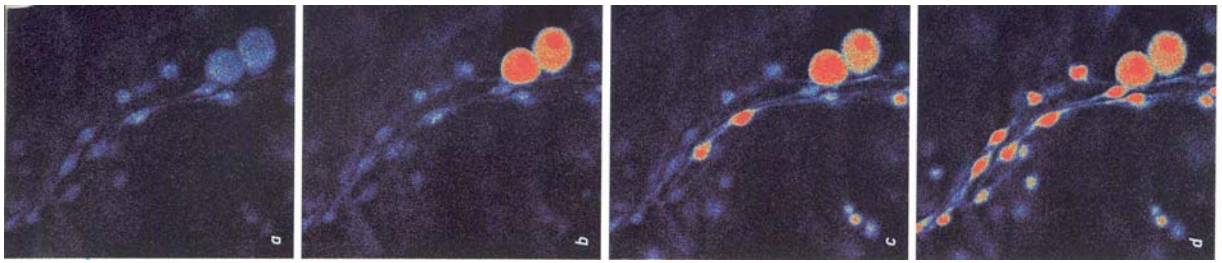


A C Charles Lab

•Glial cells form a matrix of regular topology : the syncytium

•Cells communicate with nearest neighbors through Calcium waves

•Neurons embedded on this regular structure: act as long-range links between spatially distant regions

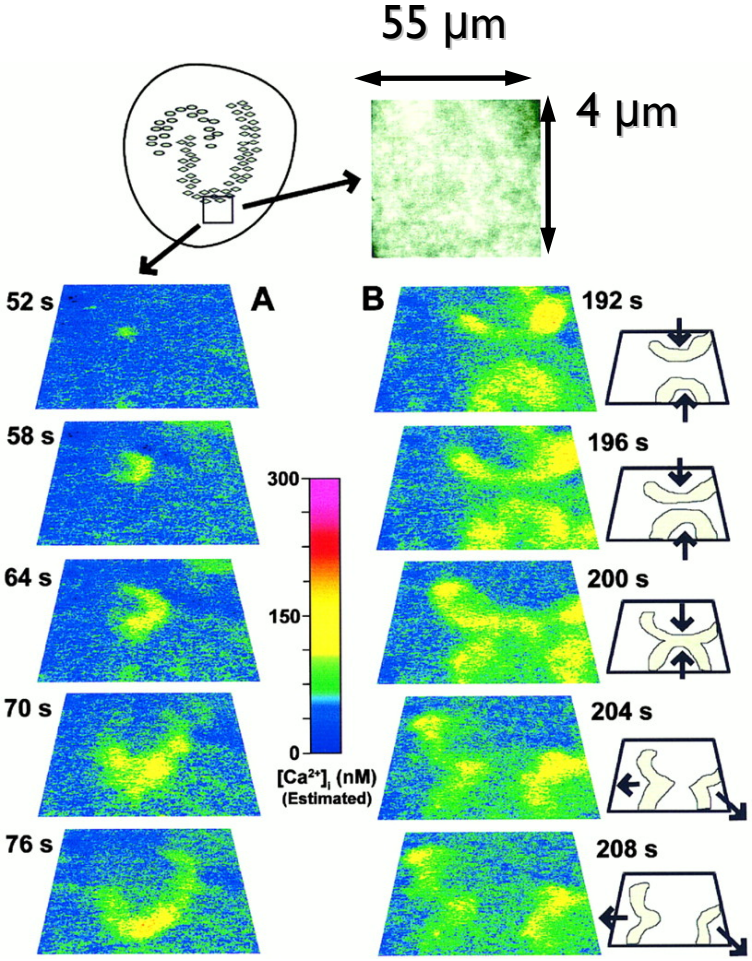


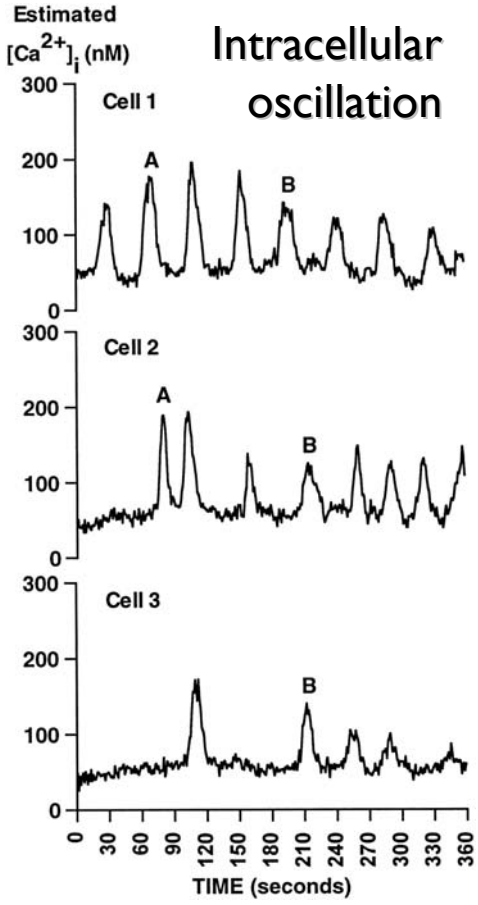
•Neurons & glia can communicate through Calcium waves

•Therefore, the aggregate system:
neurons + glia ≡ "small-world" network of cells,
with neurons as *sparse* (neuron-glia ratio ≥ 1:10), *long-range* connections

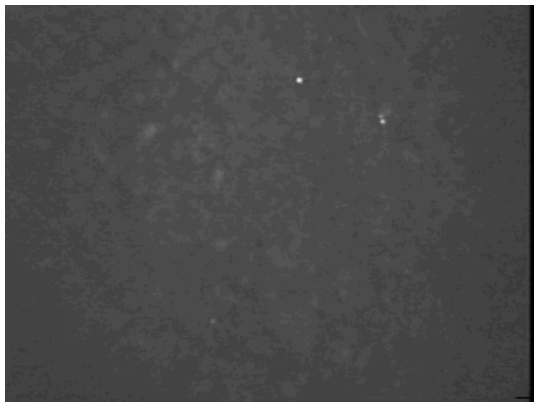
Spiral Waves in Mouse Hippocampus

Observation of intercellular Ca^{++} spiral waves in hippocampal slice cultures



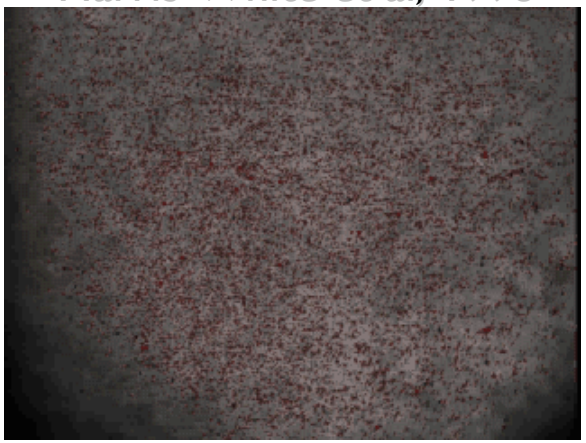


Intracellular oscillation



A C Charles Lab

Harris-White et al, 1998



Long-range excitation through neuron-glia communication ⇨ spiral waves ?

Small-world excitable media

- Each cell described by a 2-variable map

  $x_{n+1} = f(x,y) = x_n^2 \exp(y_n - x_n) + k$ *(fast variable)*

  $y_{n+1} = g(x,y) = a y_n - b x_n + c$ *(slow variable)*

  Parameters chosen, $a = 0.89$ ($0.88 \leq a \leq 0.93$), $b = 0.6$, $c = 0.28$, $c = 0.02$

- Each cell connected to nearest neighbors diffusively through fast variable *(approximating gap junctions)*

  $x^{i,j}_{n+1} = (1 - D) f(x_n^{i,j}, y_n^{i,j}) + (D/4) \sum_{q=\pm 1} f(x_n^{i+q,\, j+q}, y_n^{i+q,j+q})$

  D: Diffusion coefficient, determines propagation speed of excitation waves for most simulations chosen as = 0.2

- In addition to diffusive connections with nearest neighbors, each cell may have random long-range connections with another cell (with probability *p*)

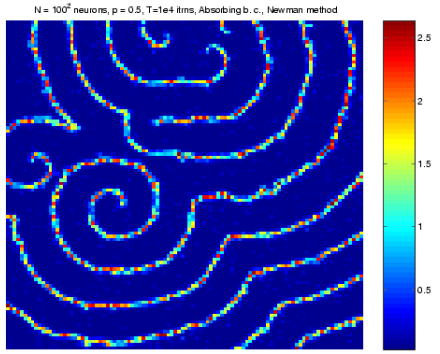
- Initial stimulation ($x = 1$) in central zone or a small number of randomly selected cells, other cells quiescent ($x=0$)

SS, Saramaki & Kaski, *PRE* 76 015101(R) 2007

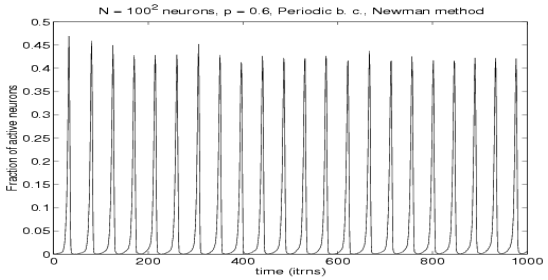
Activation dynamics in SW media

Increasing fraction of long-range connections

- $p = 0$: No self-sustained activity
- $p < p_c^l$: Spatial patterns (Single/Multiple Spiral Waves)
  Temporally irregular



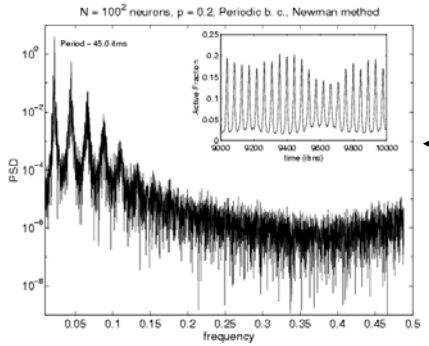
- $p_c^l < p < p_c^u$: Temporal patterns (Periodic Bursts)
  Spatially homogeneous



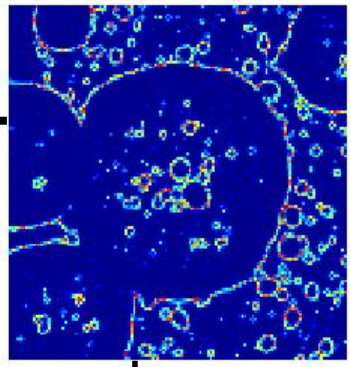
- $p > p_c^u$: Failure of self-sustained activity

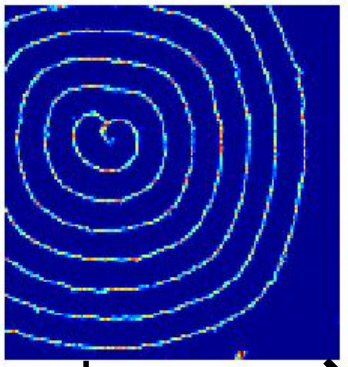
$p < p_c^1$: Spiral Waves

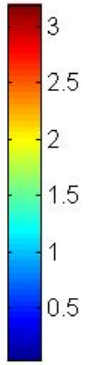
Spatial patterns, Temporally irregular



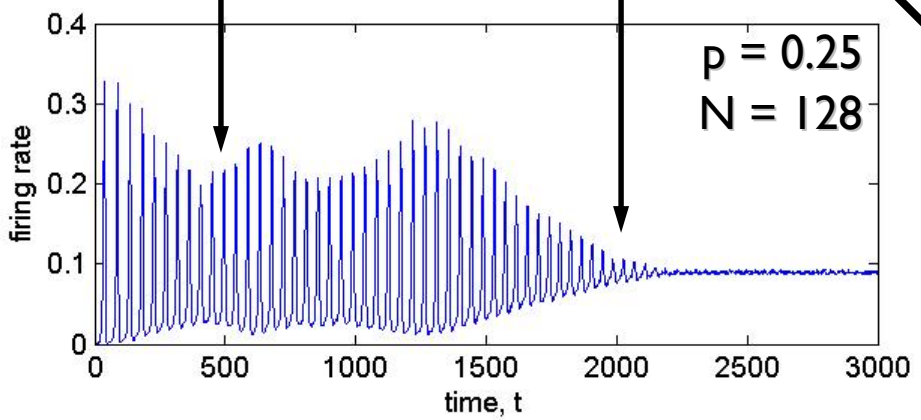
Power spectral density of transient phase: power-law decay (1/f noise)

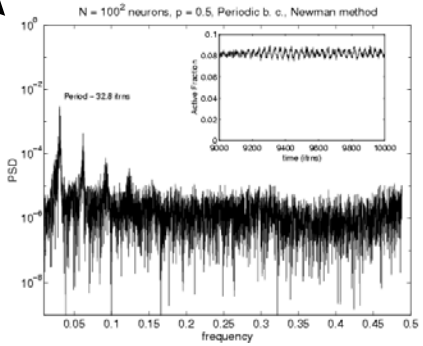






Power spectral density of sustained spiral state: flat spectrum



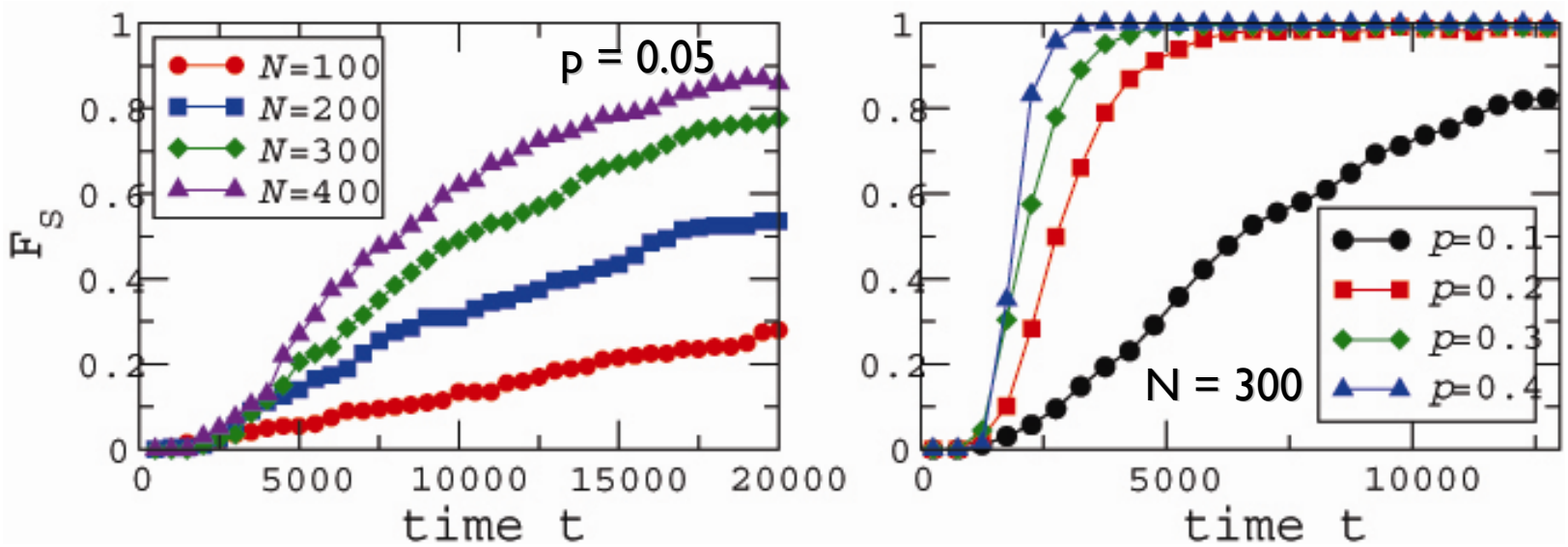


initial transient period with multiple coexisting circular waves

Spiral waves take over after the transient period

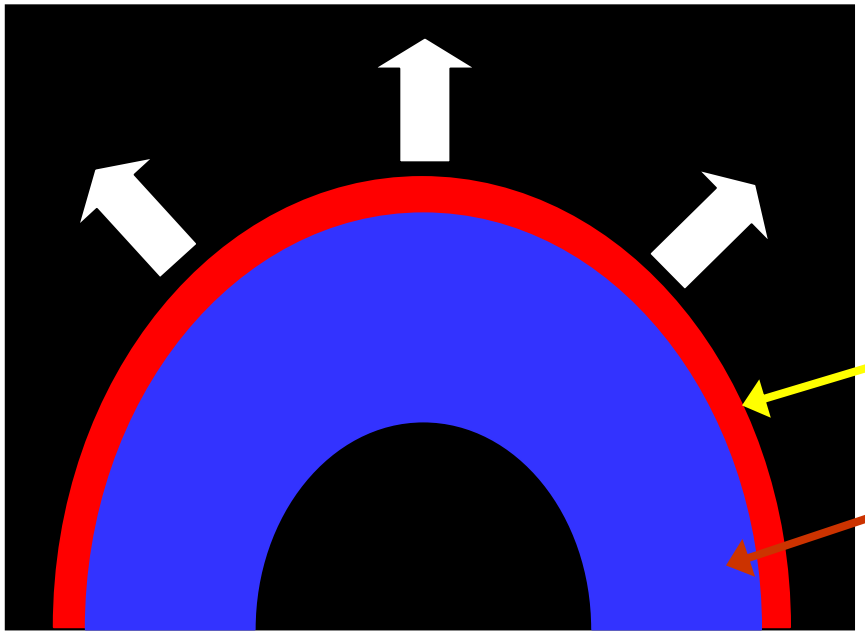
Occurrence of spiral waves

Probability of spiral creation (per unit time) increases with
- System size N^2
- Shortcut probability p



For $p < p_c^l$, at long times and large N, random shortcuts always result in spiral waves

Genesis of spiral waves



Created by shortcut-induced excitations in the refractory "shadow" of a circular wavefront

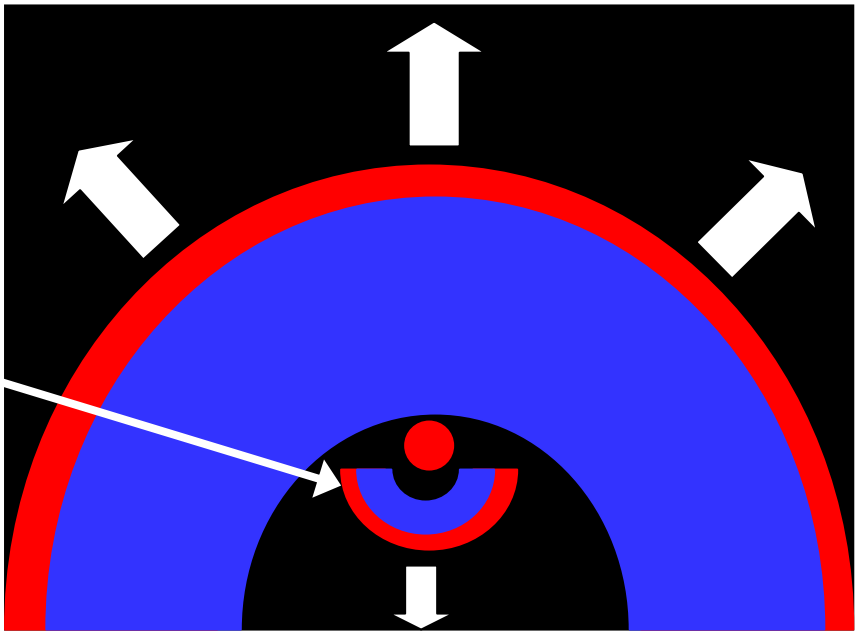
Wavefront

Refractory region

Sparks a semi-circular wave whose transmission is partially blocked by "shadow"

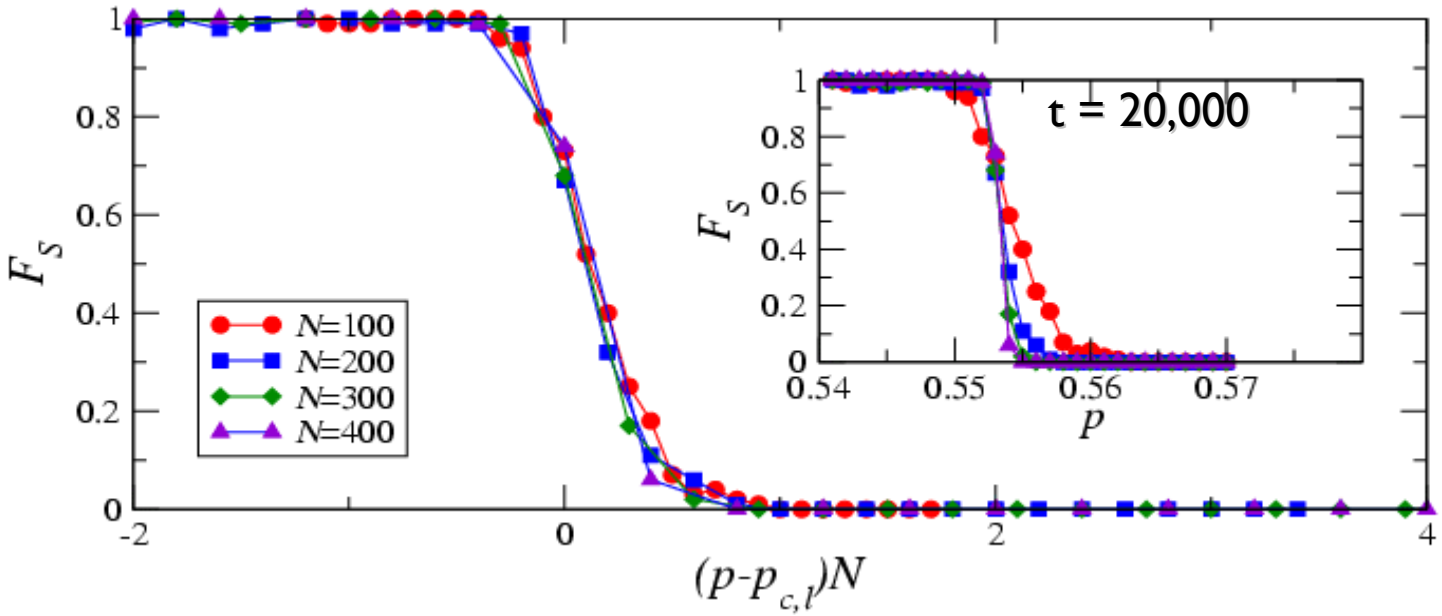
Wavefront ends turn into Spiral Waves

Once created, spiral wave takes over as it has the highest frequency compared to all other excitations



Transition to new pattern regime

For high enough p, shortcut induced excitations are too numerous for sustaining spiral waves



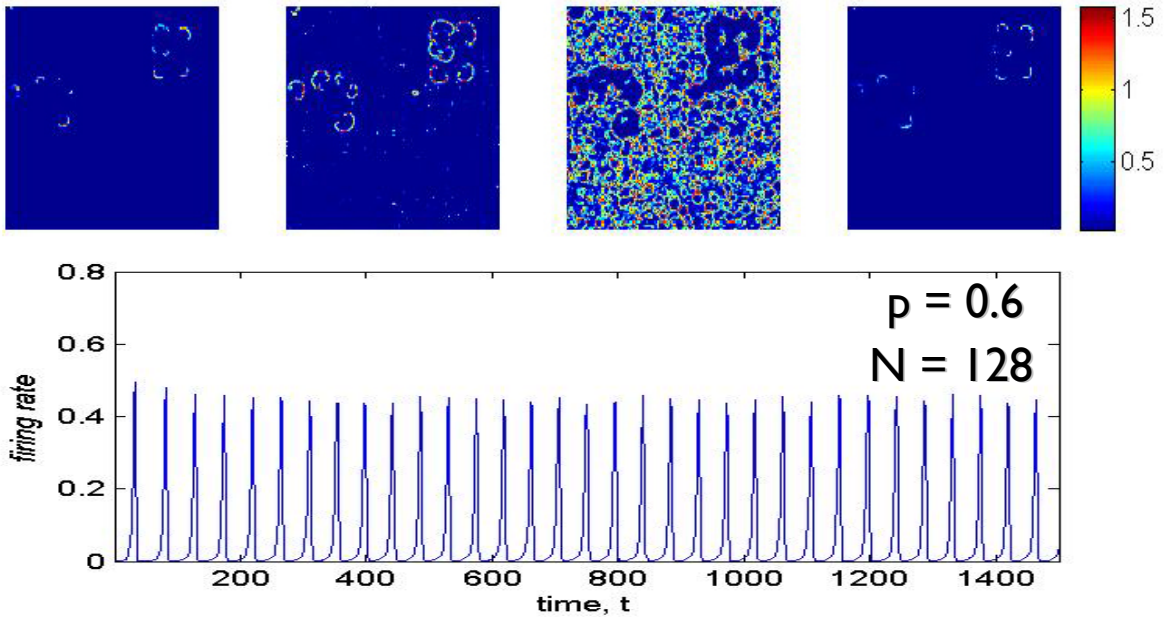
Almost every cell can be excited with frequency ~ (refractory period)$^{-1}$

Spirals become unstable → transition to new regime at $p \approx p_c^l \approx 0.553$
Transition point is independent of system size

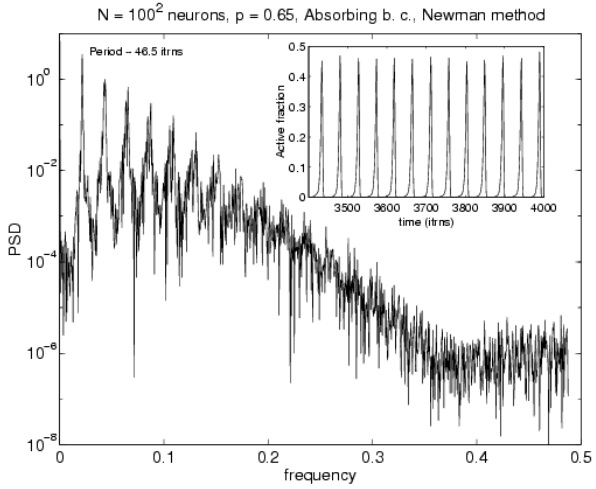
$p_c^l < p < p_c^u$: Periodic Recurrence

Temporal pattern periodic, Spatially more homogeneous

•Large fraction of system becomes simultaneously active and then decays in order to recover



Power spectral density

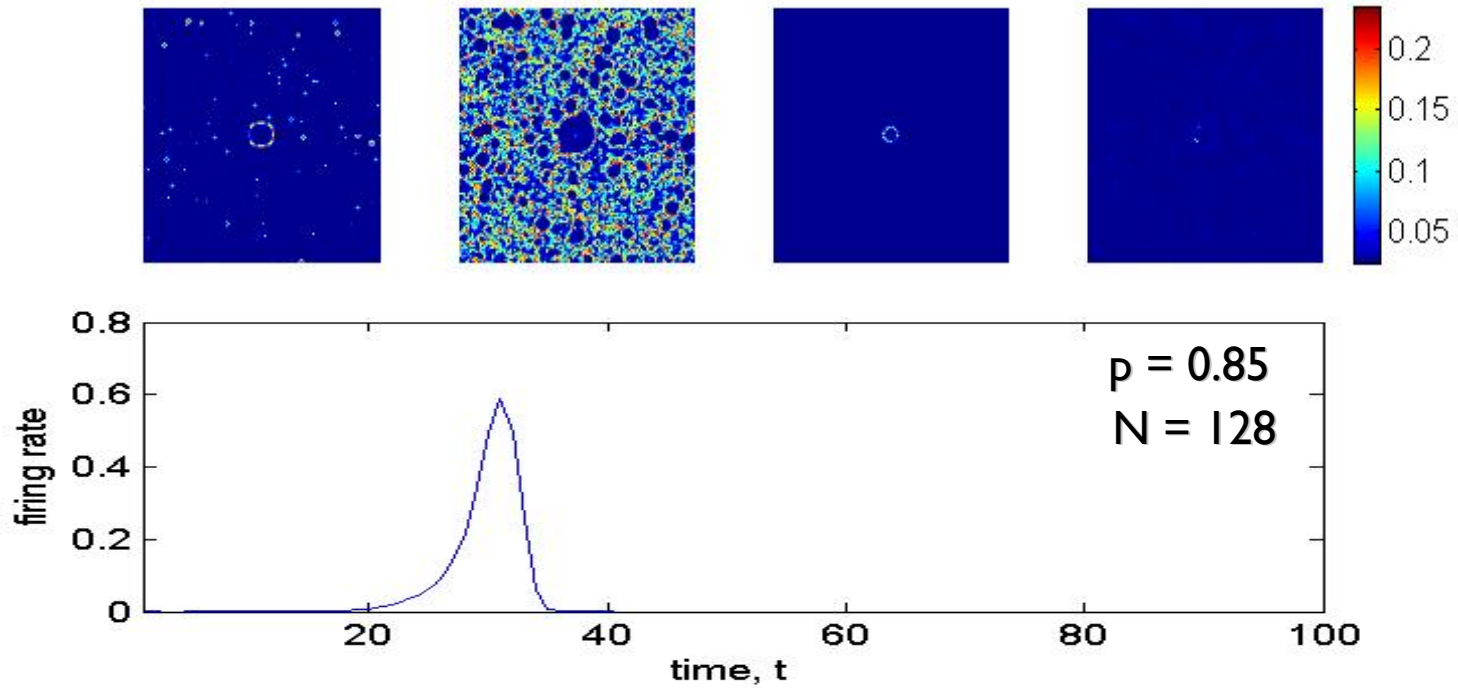


•Few cells not part of the excitation wave carry activity to next cycle

•Activity again spreads through almost entire system

$p > p_c^u$: Failure of activity

For even larger *p*, extremely high shortcut connections spread the excitation simultaneously to all cells

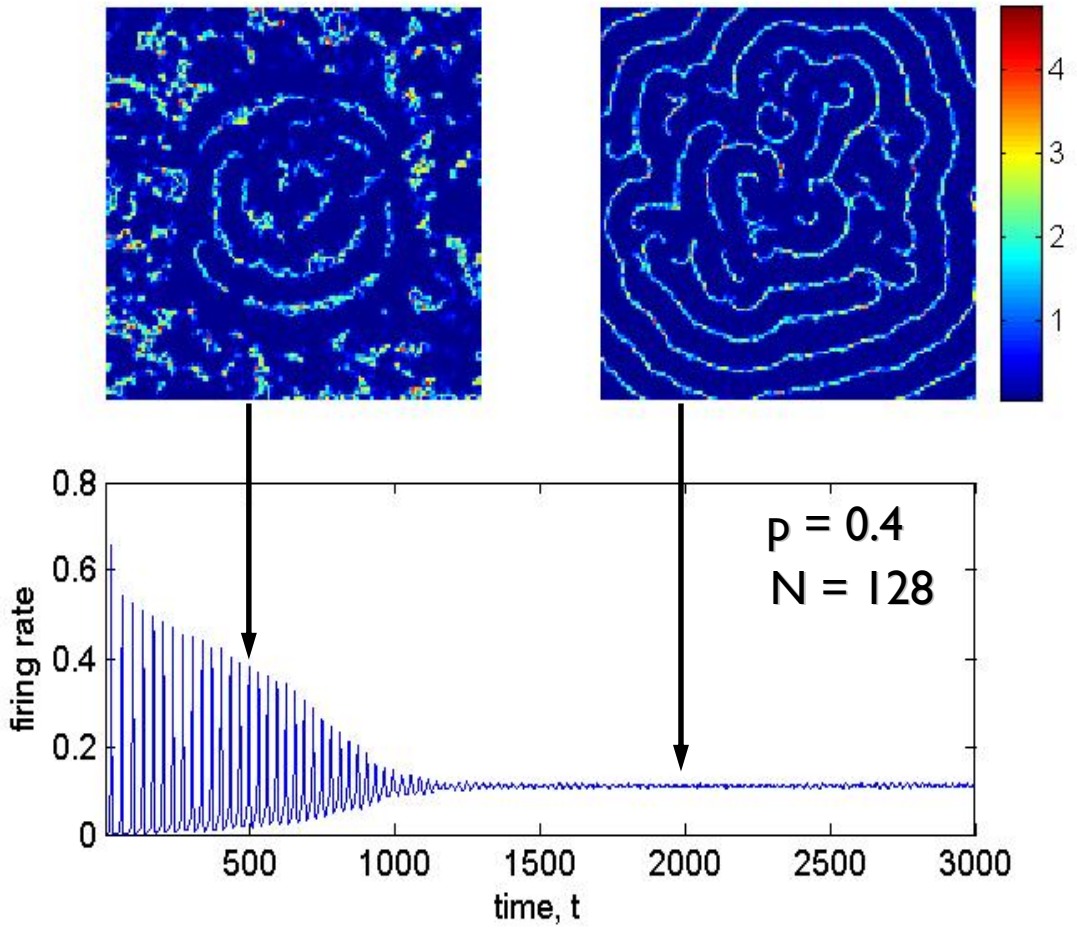


The dynamics of the system "burns out" : After the initial transient event, not enough suscpetible cells are left to sustain the activity

Introducing disorder

•In nature, cells are not exactly alike

•Can be simulated by introducing disorder in parameters controlling cell dynamics



•*Example*: Value of *a* (parameter determining recovery period) randomly chosen from uniform distribution [0.89,0.92]

•Tendency of greater fragmentation of waves

•Increasing number of coexisting spirals

But overall, the results are robust w.r.t. disorder

Structure → Dynamics

Spontaneous, self-sustaining pattern formation in excitable media with random, long-range ("small-world") connections

Exhibits non-trivial transition point as pattern goes from

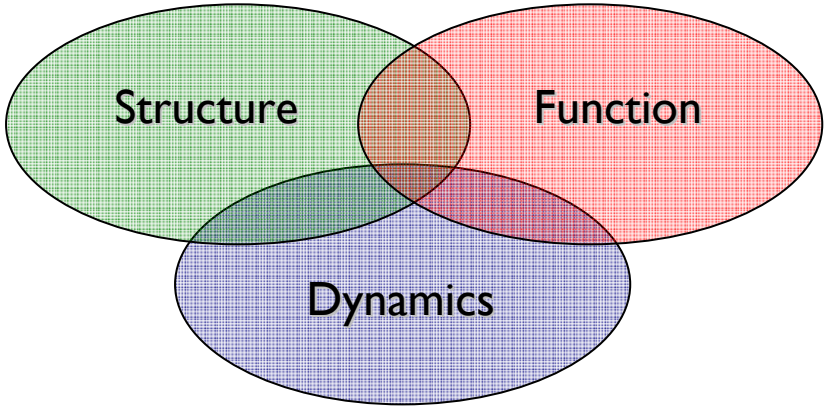
- Spatial (multiple coexisting spiral waves) to
- Temporal (global activity shows large oscillations)

Relevance for all natural systems having wave propagation & sparse, long-range connections,

- in particular, role of non-trivial network topology on brain functioning

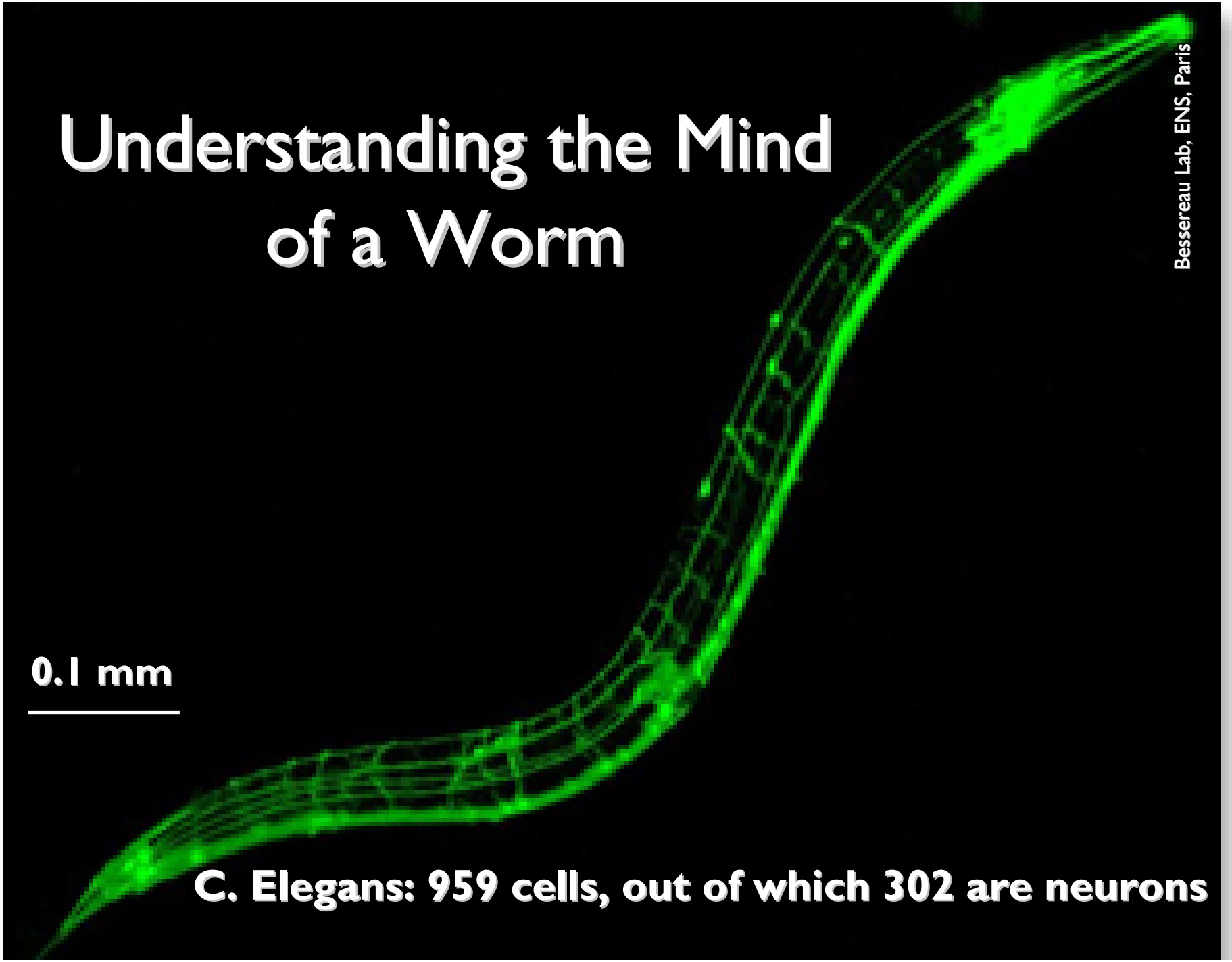
- Possible functional role of small-world topology in epileptic seizures and bursts

Step II.



But…
how does network structure & dynamics in the brain connect to behavior ?

Dynamics ↔ Function ↔ Structure

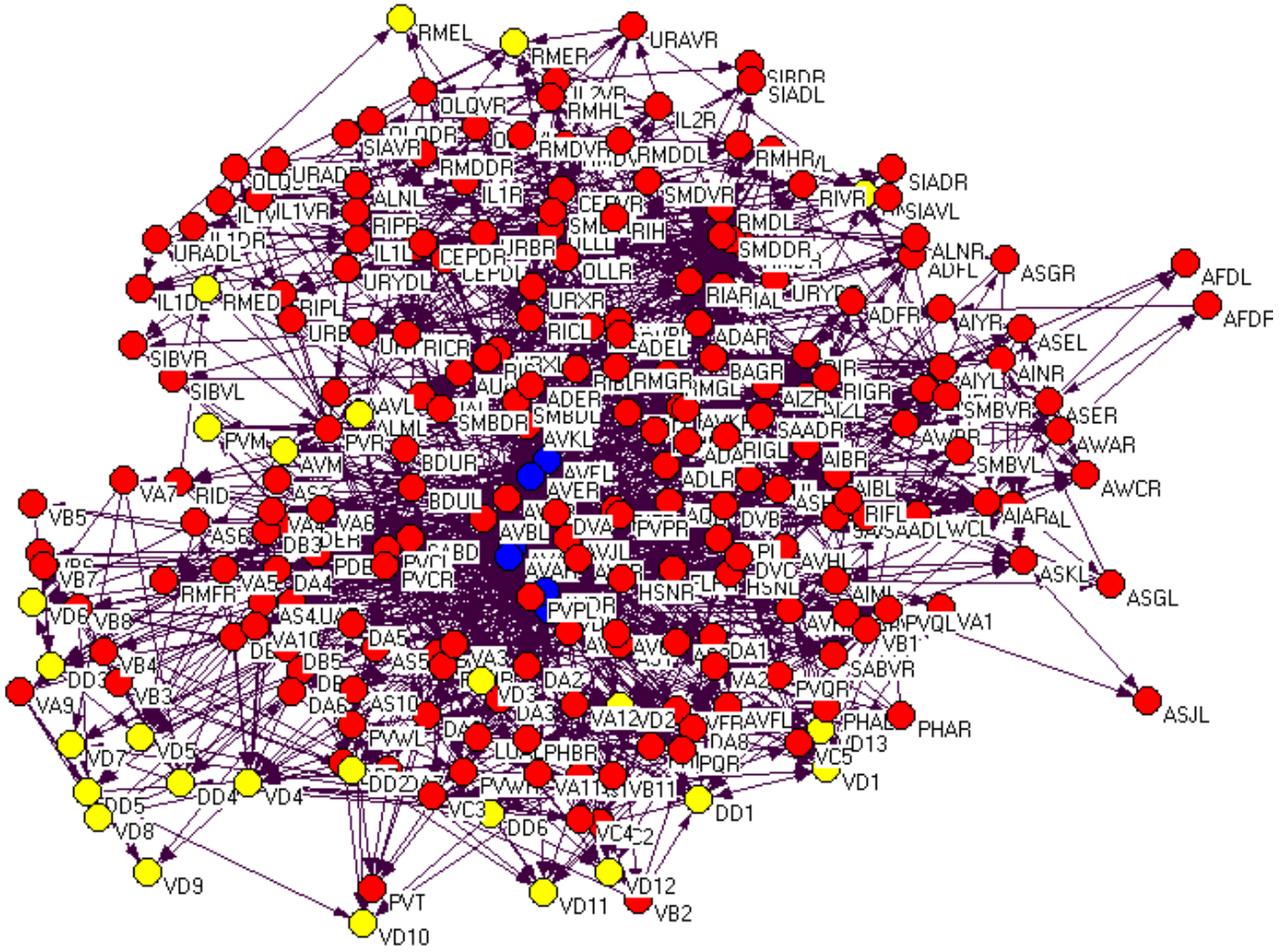

Understanding the Mind
of a Worm
Bessereau Lab, ENS, Paris
0.1 mm
C. Elegans: 959 cells, out of which 302 are neurons

Why ?

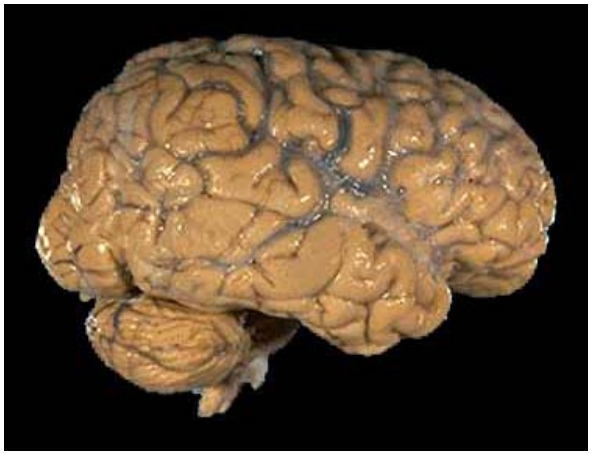
- neurons ~ 300
- connections ~ 3000

(synaptic ~ 2500, gap juncs ~ 500)

- graded potentials (analog signals)



much simpler than …

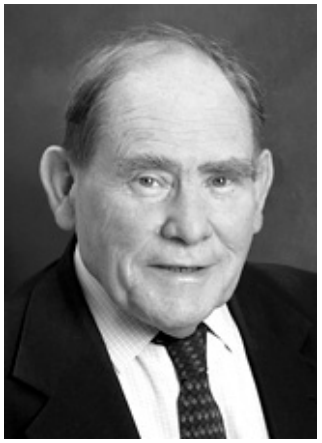


- neurons ~ 10^{9}
- connections ~ 10^{12}
- action potentials

(binary signal)

Motivation

- Mind ≡ Behavior



Nobel Prize in Physiology, 2002

Sydney Brenner (1974):

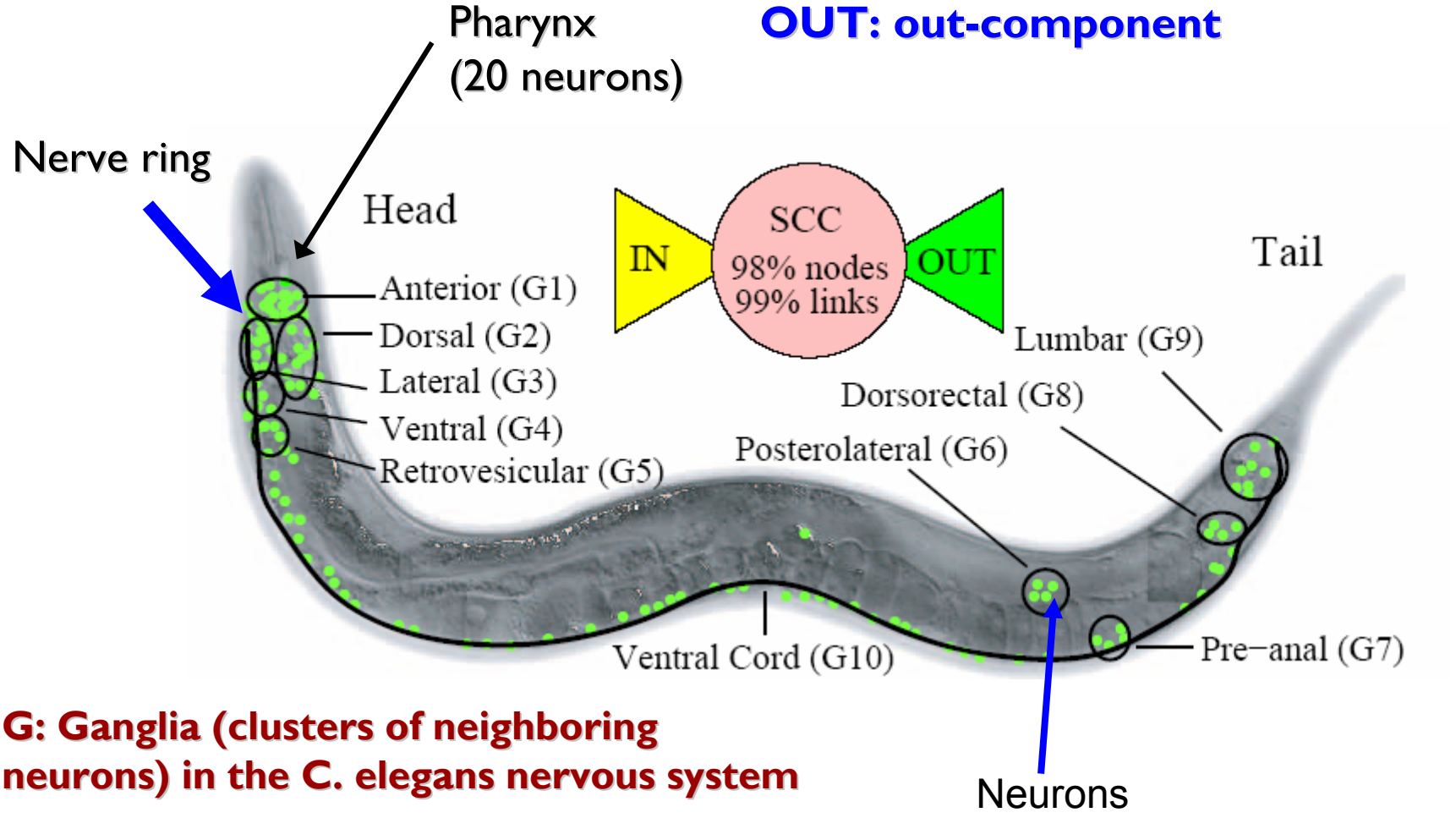
"Behavior is the result of a complex and ill-understood set of computations performed by nervous systems and it seems essential to decompose the problem into two:
•one concerned with the question of the genetic specification of the nervous system, and,
•the other with the way nervous systems work to produce behavior."

- How do the components of the worm nervous system work together ?
- How is the activity of neurons, interacting with each other, translated into behavior of the whole organism ?

Structure of the nervous system

We concentrate on the 282 non-pharyngeal neurons

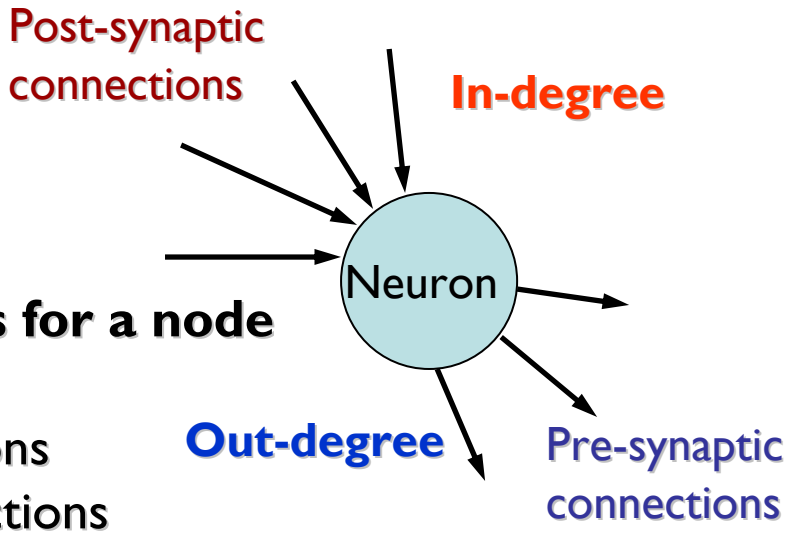
SCC: strongly connected component
IN: in-component
OUT: out-component



G: Ganglia (clusters of neighboring neurons) in the C. elegans nervous system

Degree

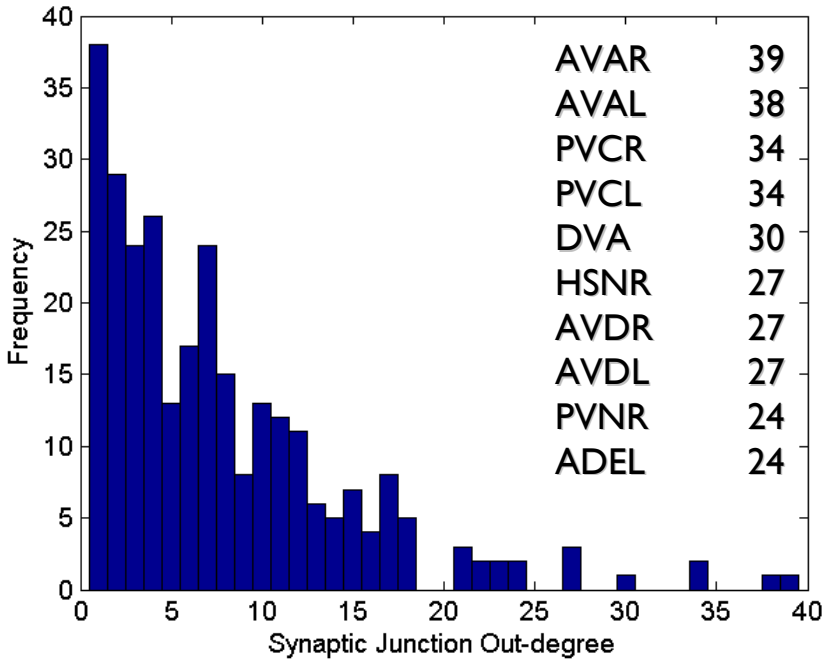
In-degree & out-degree

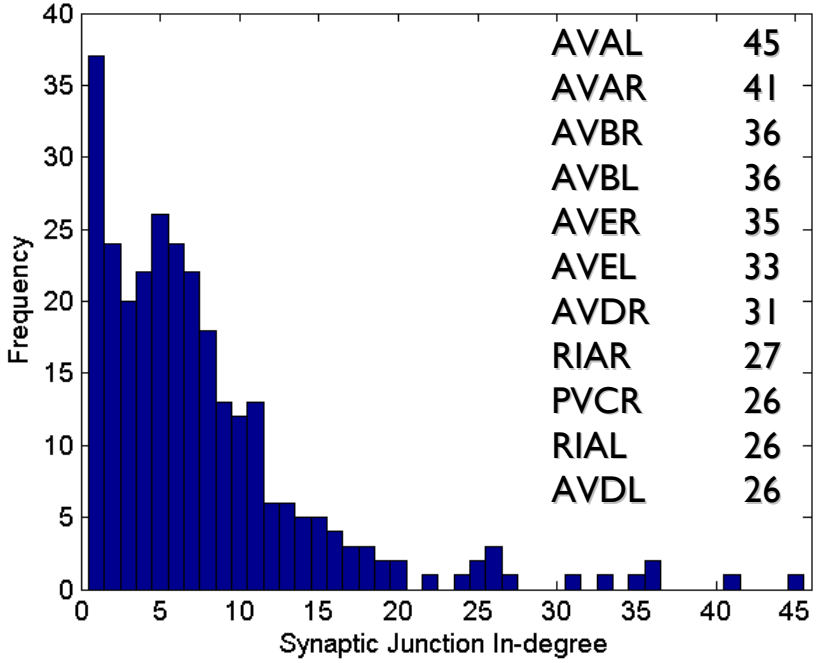


Degree: total number of connections for a node

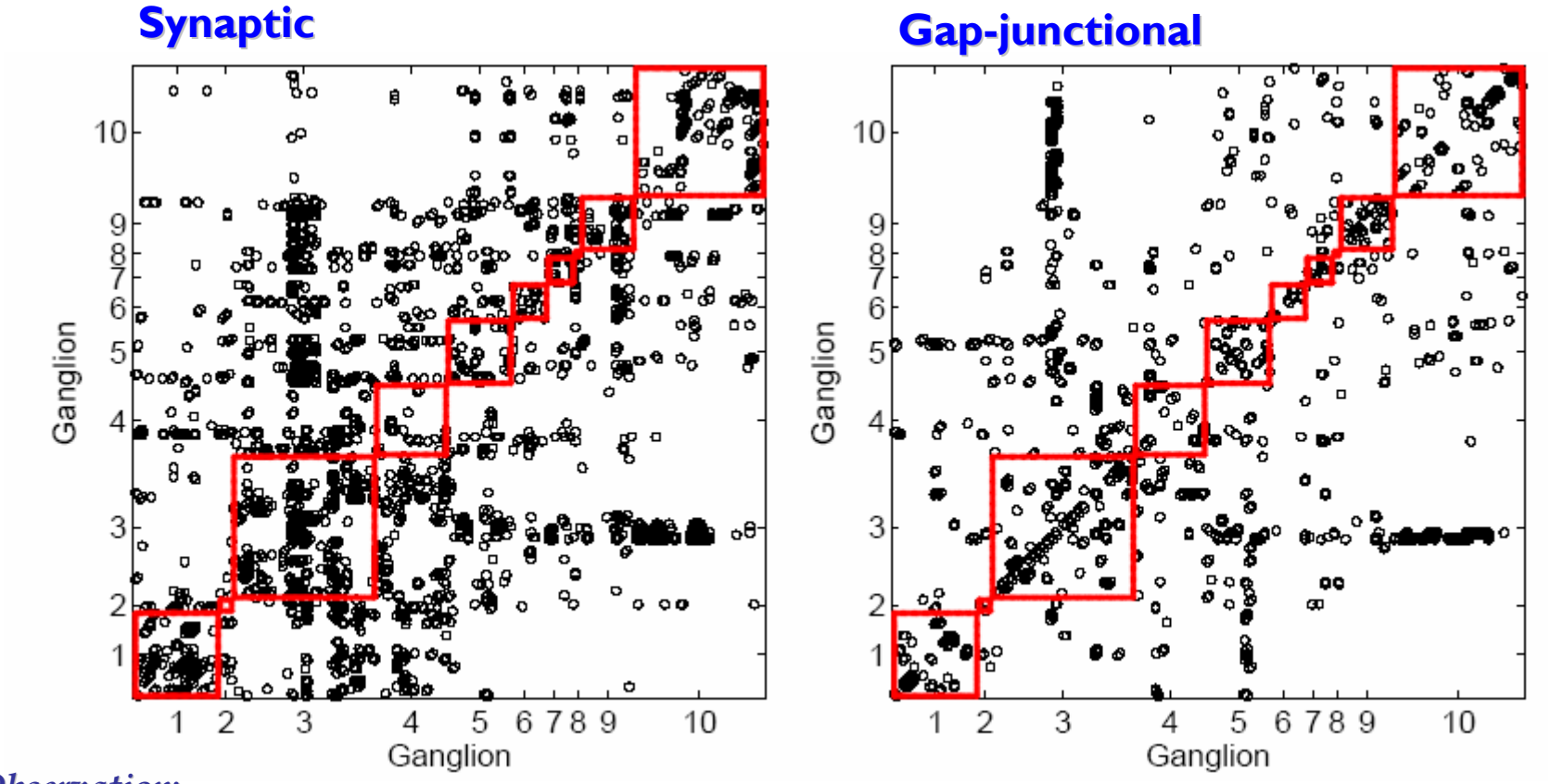
- In-degree: number of incoming connections
- Out-degree: number of out-going connections

- Exponentially decaying degree distribution, not many highly connected ones





Connectivity of the somatic nervous system



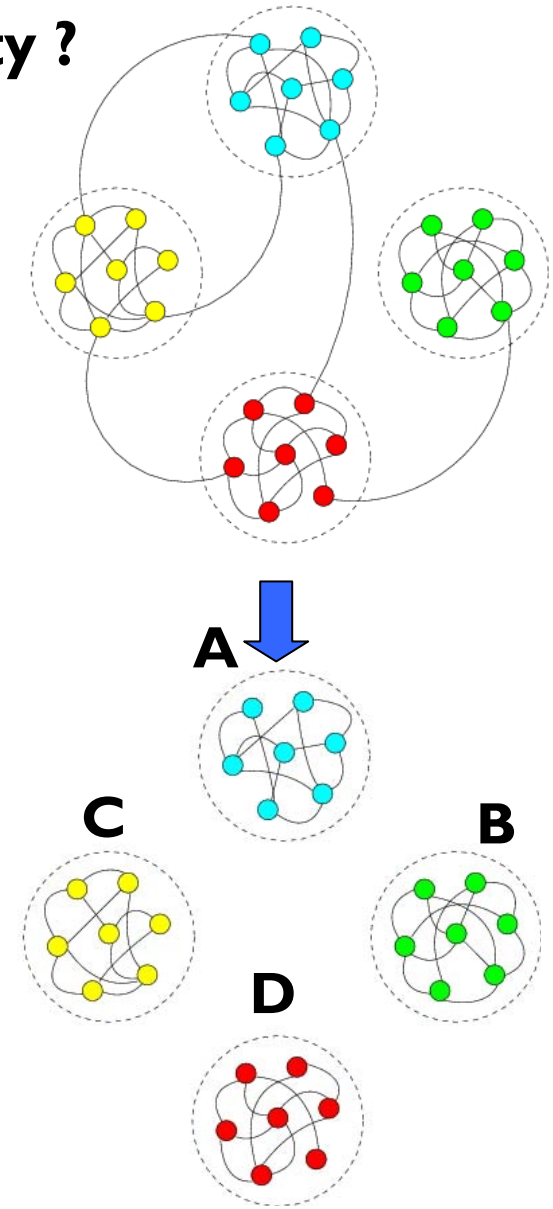
Observation:
Lateral ganglion *receives many connections from other ganglia and sends many connections*
Note that LG contains the "command" interneurons

Question:

Is the network modular ? How do you determine the modules if the connections are not localized within corresponding ganglia ?

Measuring modularity

How to quantify the degree of modularity ?



One suggested measure:

$$Q = \sum_s [(L_s / L) - (d_s / 2L)^2]$$

(Newman & Girvan, PRE, 2004)

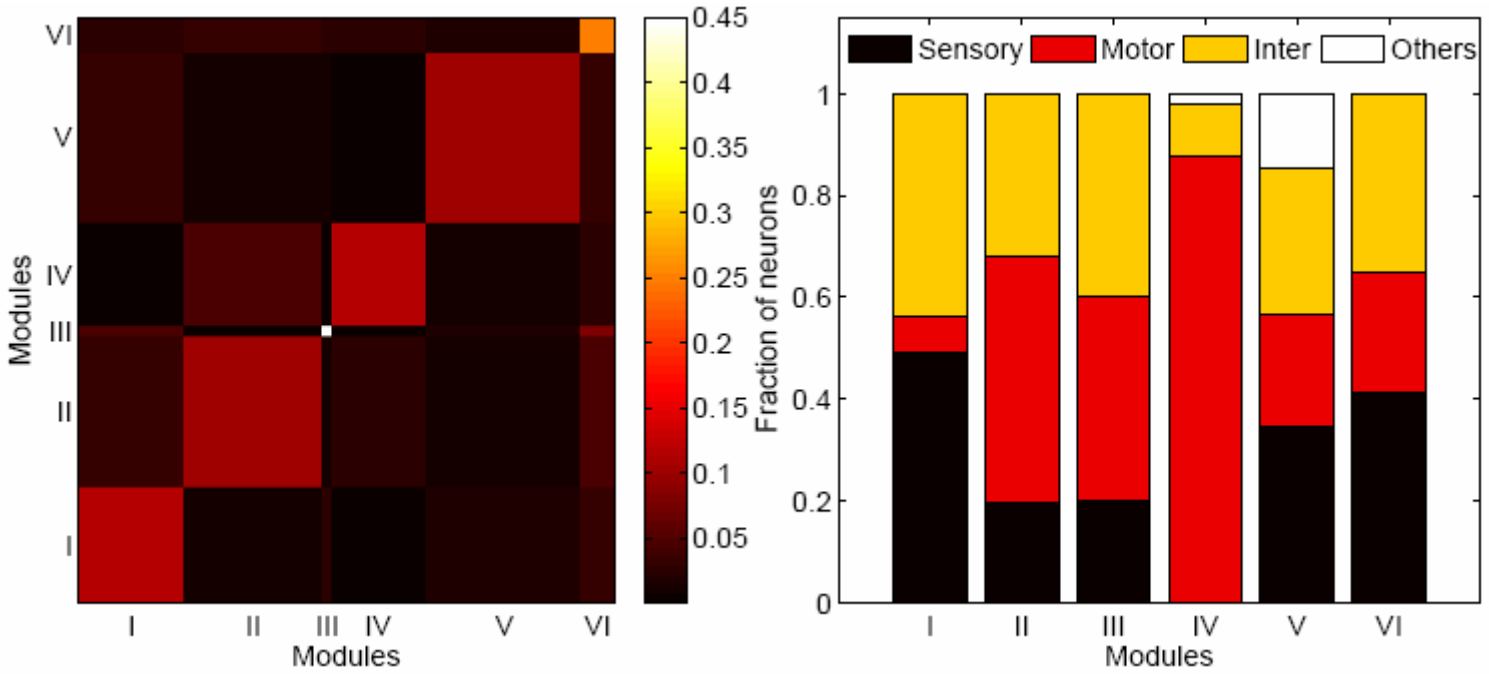
L : Total number of links
L_s : #links between nodes within module s
d_s : sum of degrees for nodes in module s

***Modules*: each node i belonging to module s has more links with nodes in s than rest of network (<u>strong</u> defn of community)**

Modules determined through stochastic optimization of Q

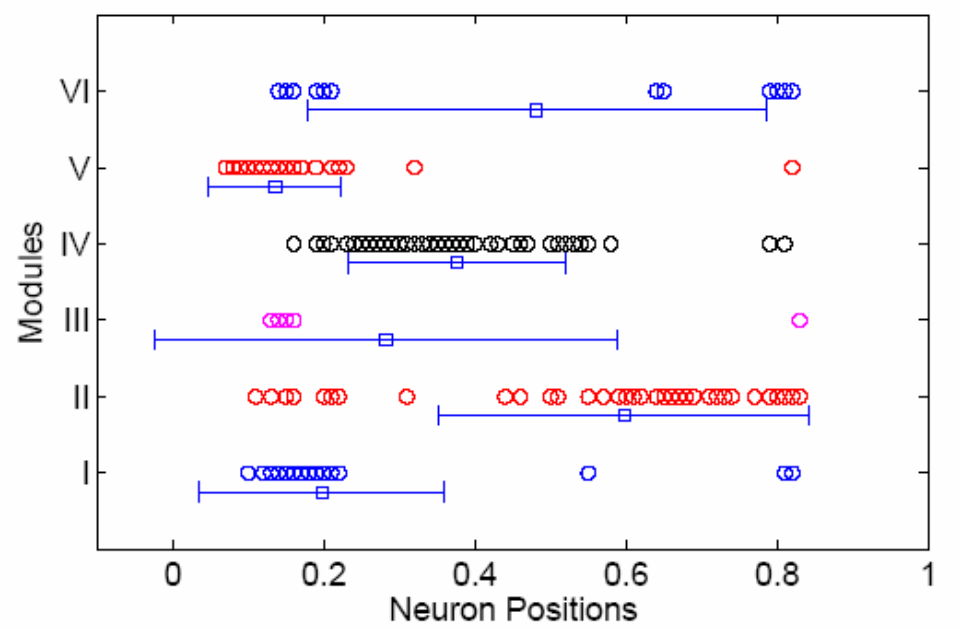
The Modular Structure of the Network

Optimal decomposition of the somatic nervous system into 6 modules



- Dense interconnectivity within neurons in a module, relative to connections between neurons in different modules
- The modules are not simply composed of one type of neurons (e.g., a purely sensory neuron or motor neuron or interneuron module does not exist)

Modules and Spatial Localization

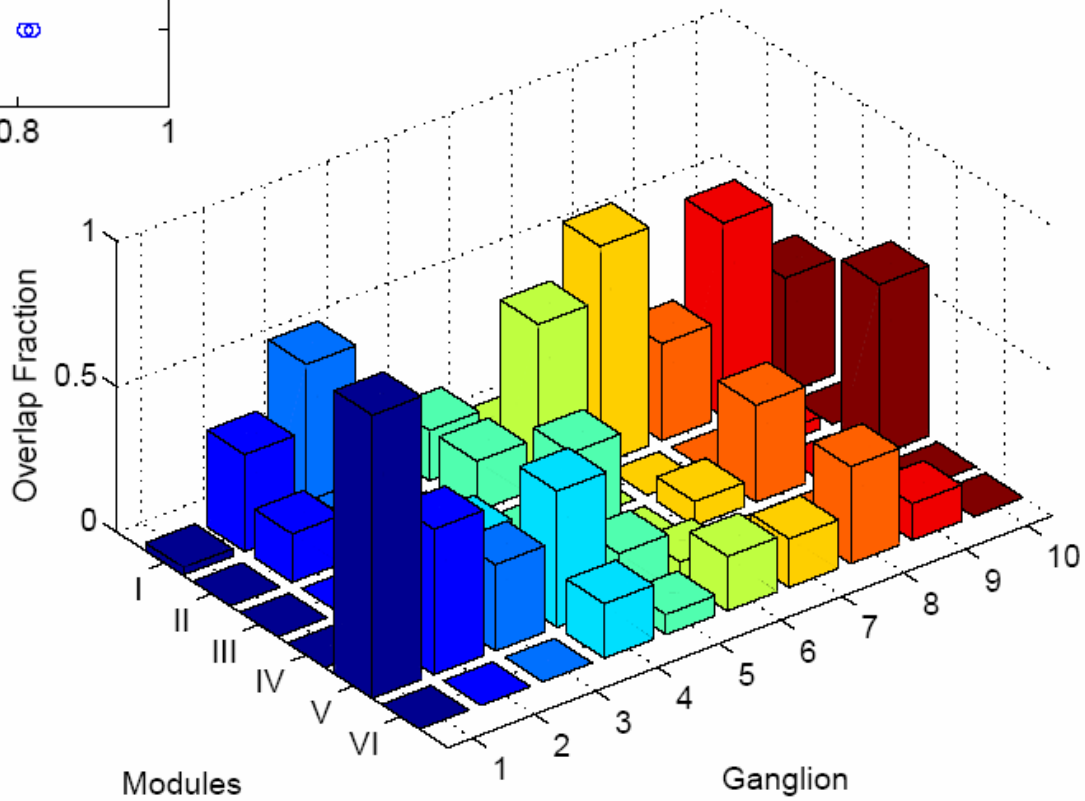


Q. Do constraints related to physical adjacency of neurons (e.g., minimization of wiring length) completely explain the modular organization ?

Ans. No

Q. How far does the existence of ganglia explain the modules ?

Ans. The overlap between modules and ganglia indicates that most ganglia are composed of neurons belonging to many different modules

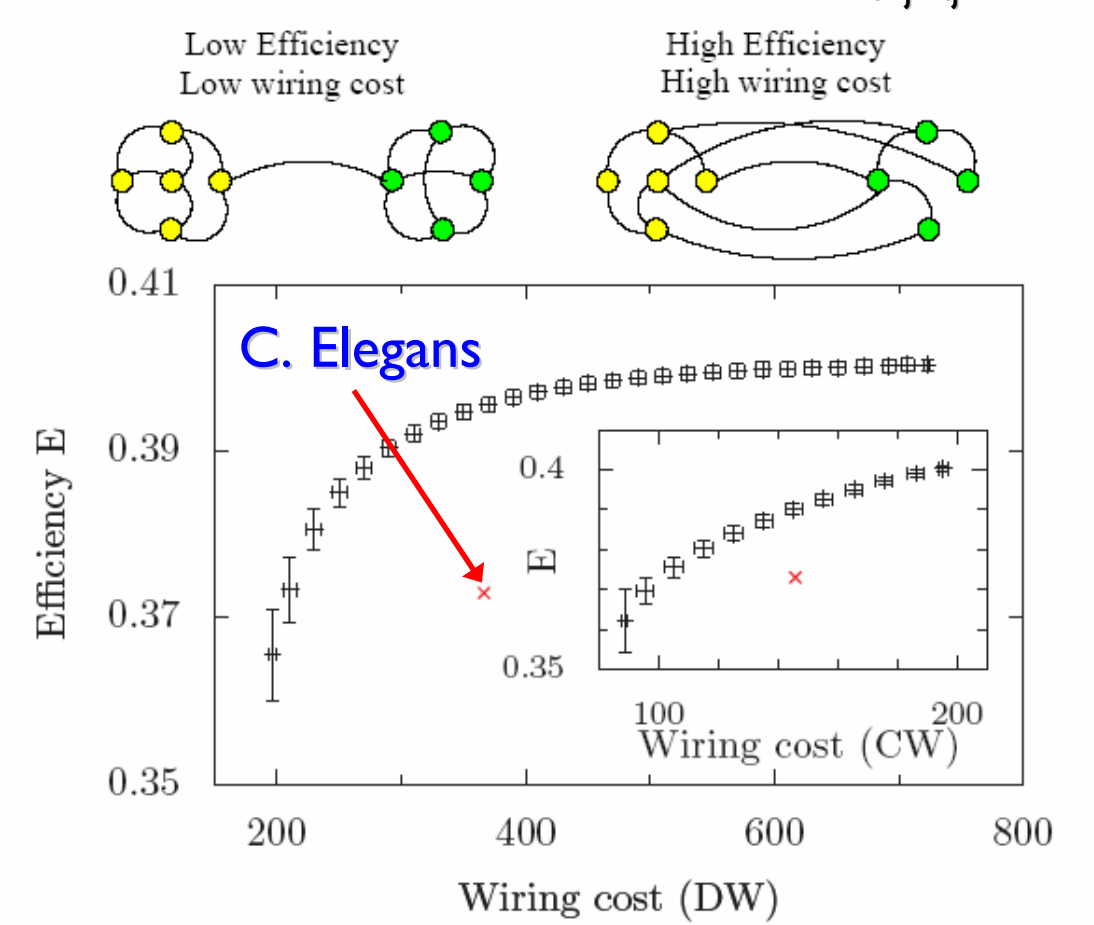


Optimizing for wiring cost and communication efficiency

Communication efficiency $E = 1 / \text{avg path length}, \ell = 2 / N(N-1) \sum_{i>j} d_{ij}$

Wiring cost $DW = \sum_{i>j} d_{ij}$ for all connected neurons

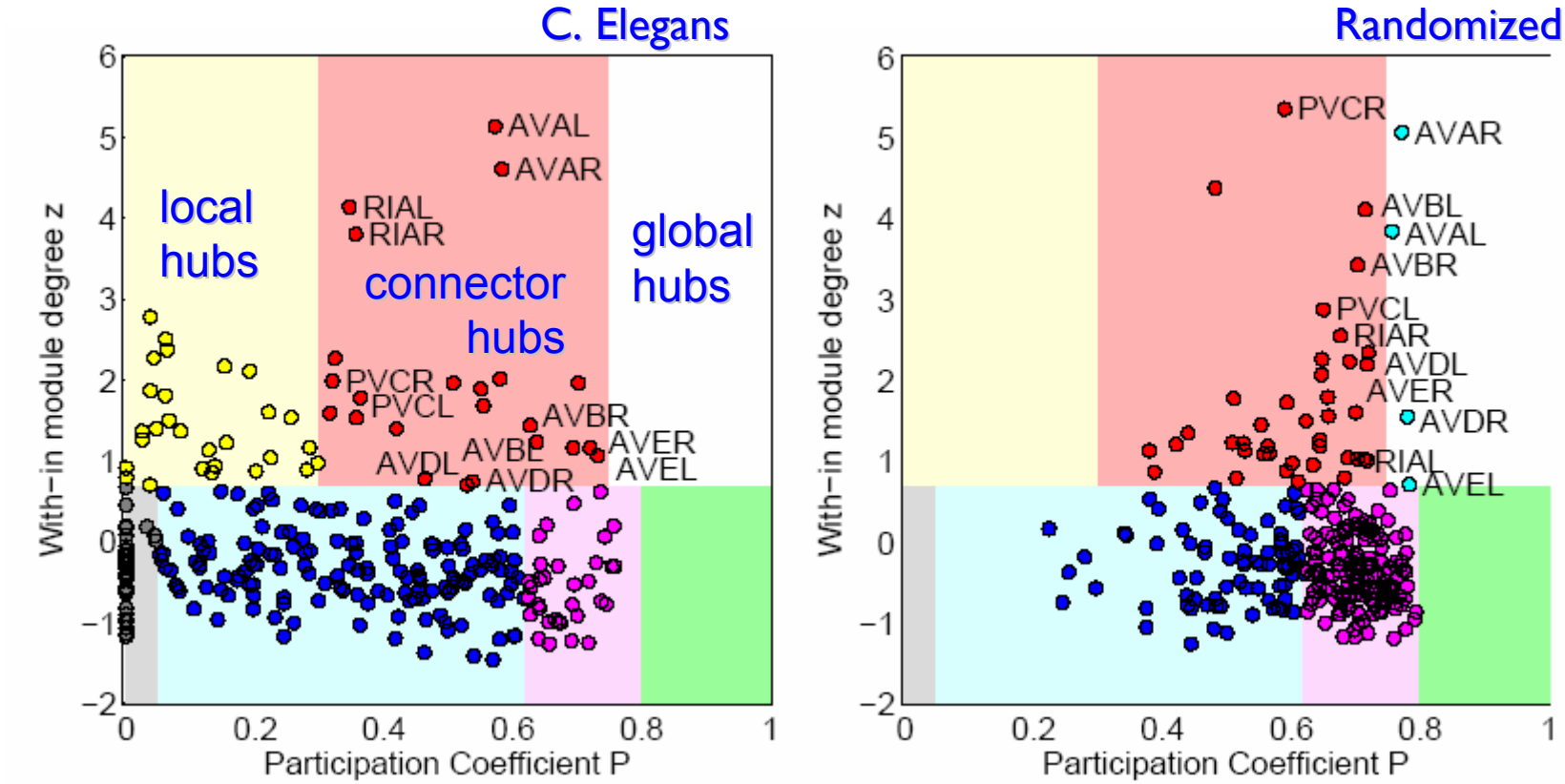
("dedicated wire" model)



Trade-off between increasing communication efficiency and decreasing wiring cost

The network is sub-optimal !
⇒ presence of other constraints governing network organization

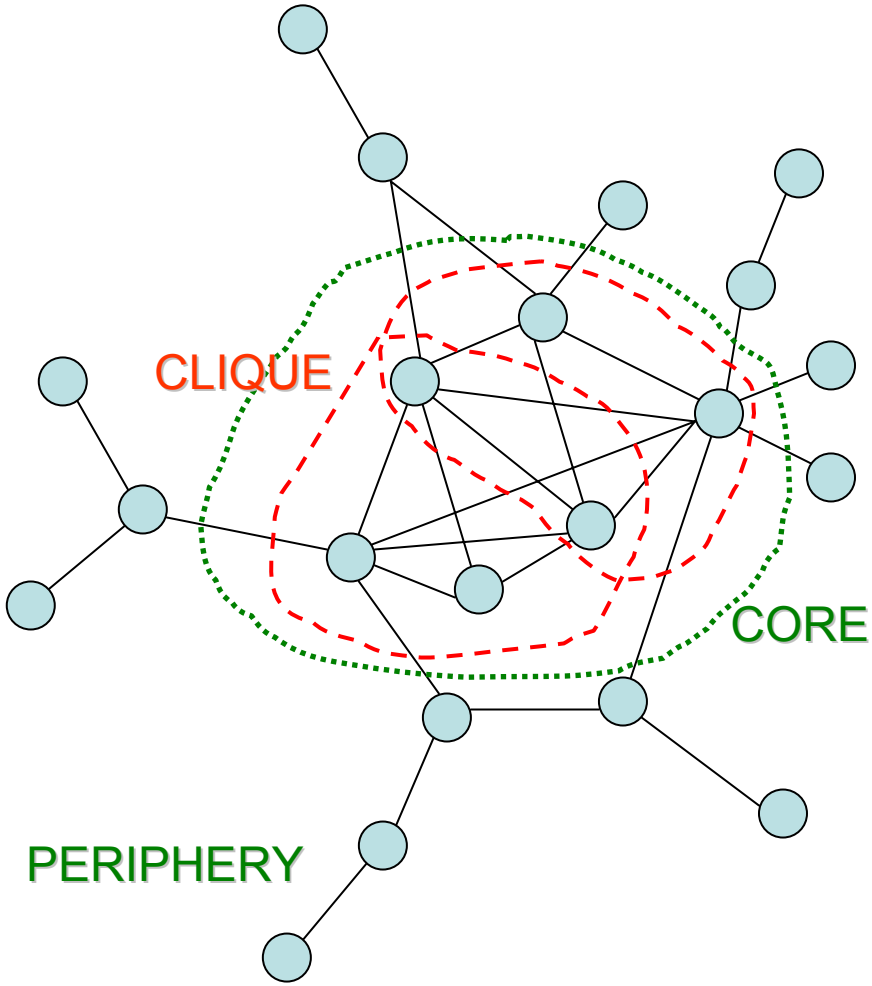
How mesoscopic network structure can alert us to critical functional role of neurons

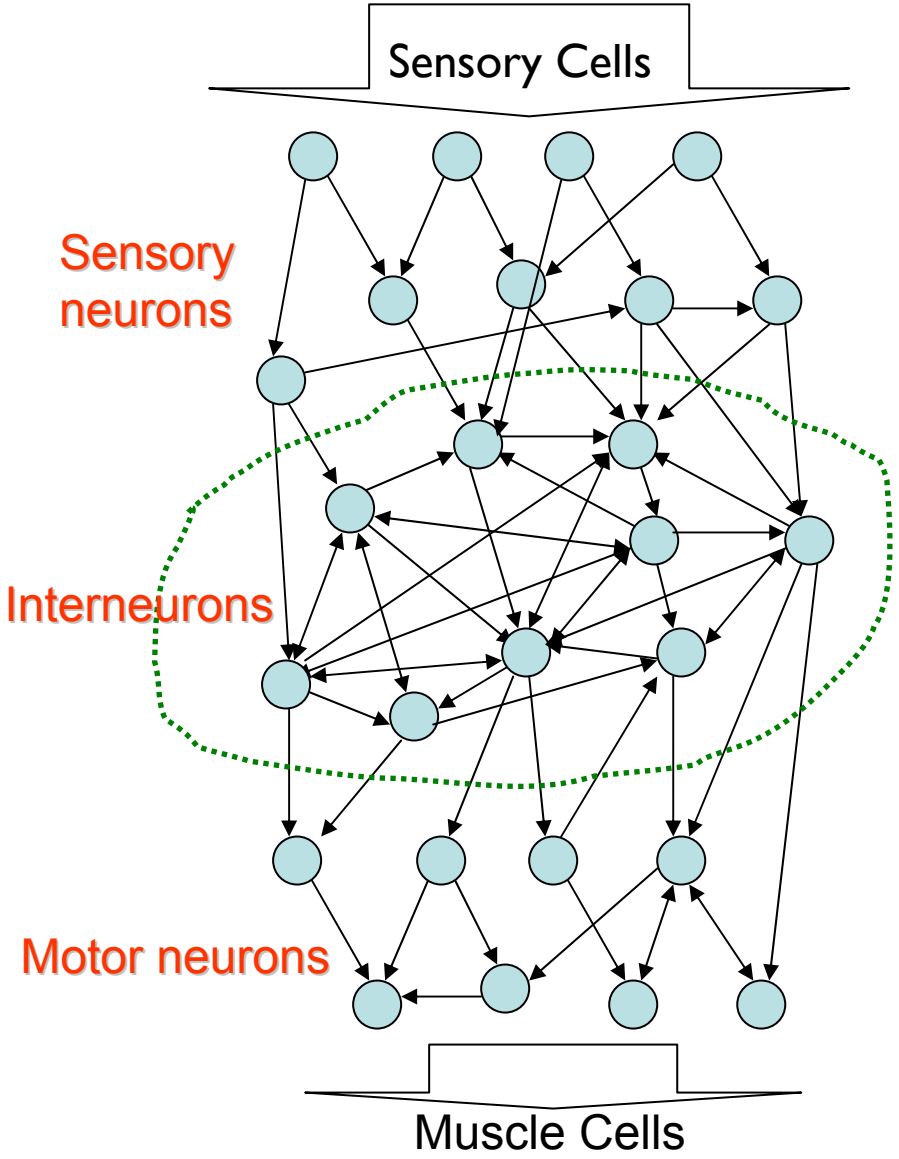


Importance of connector hubs: possibly integrating local activity to produce coherent response, 21 out of the 23 already implicated in critical functions

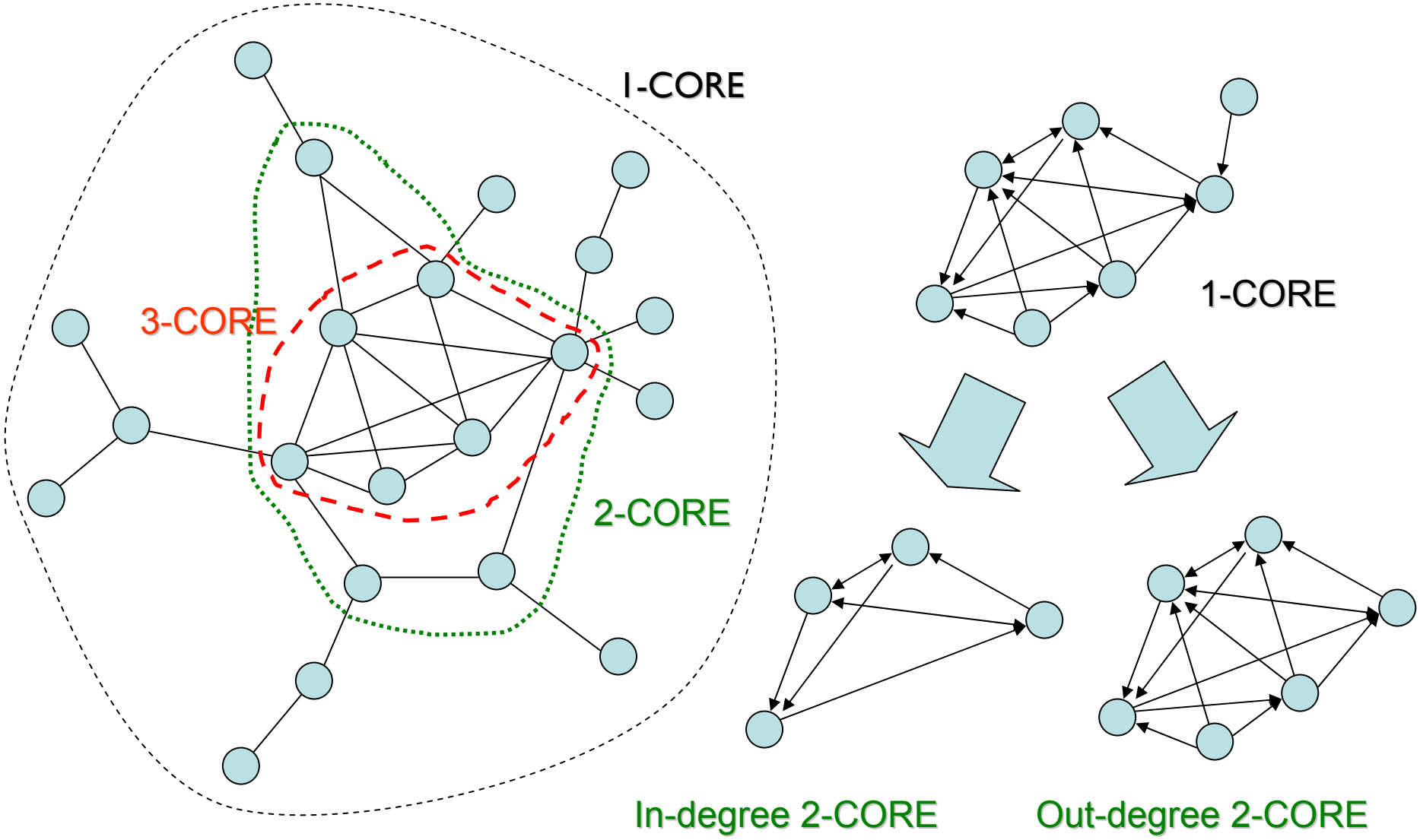
Prediction: AVKL and SMBVL are likely important for some as yet undetermined function

Core-periphery organization

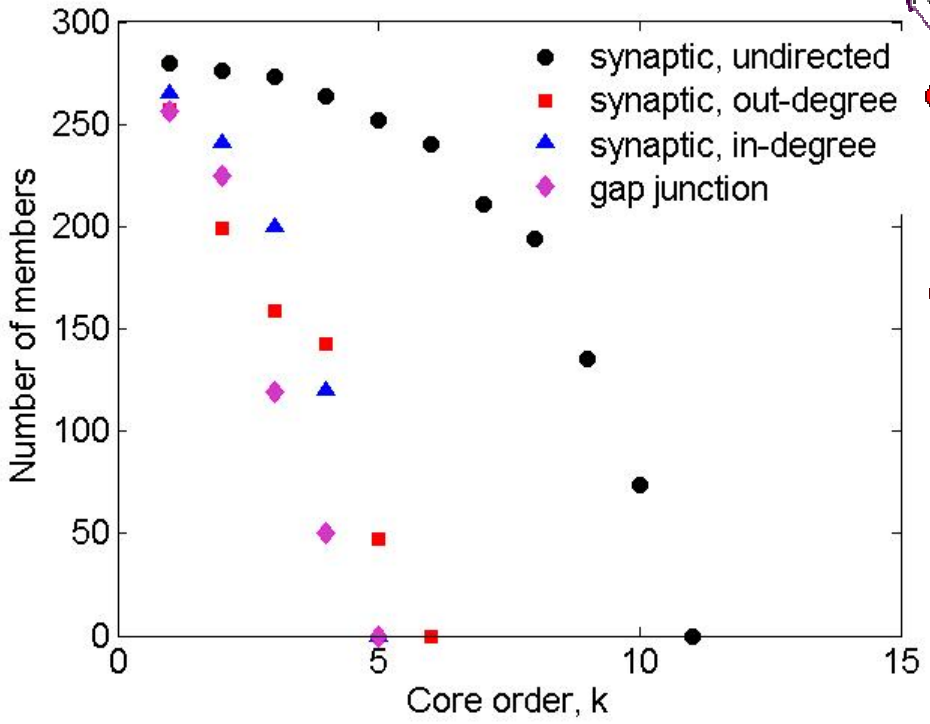


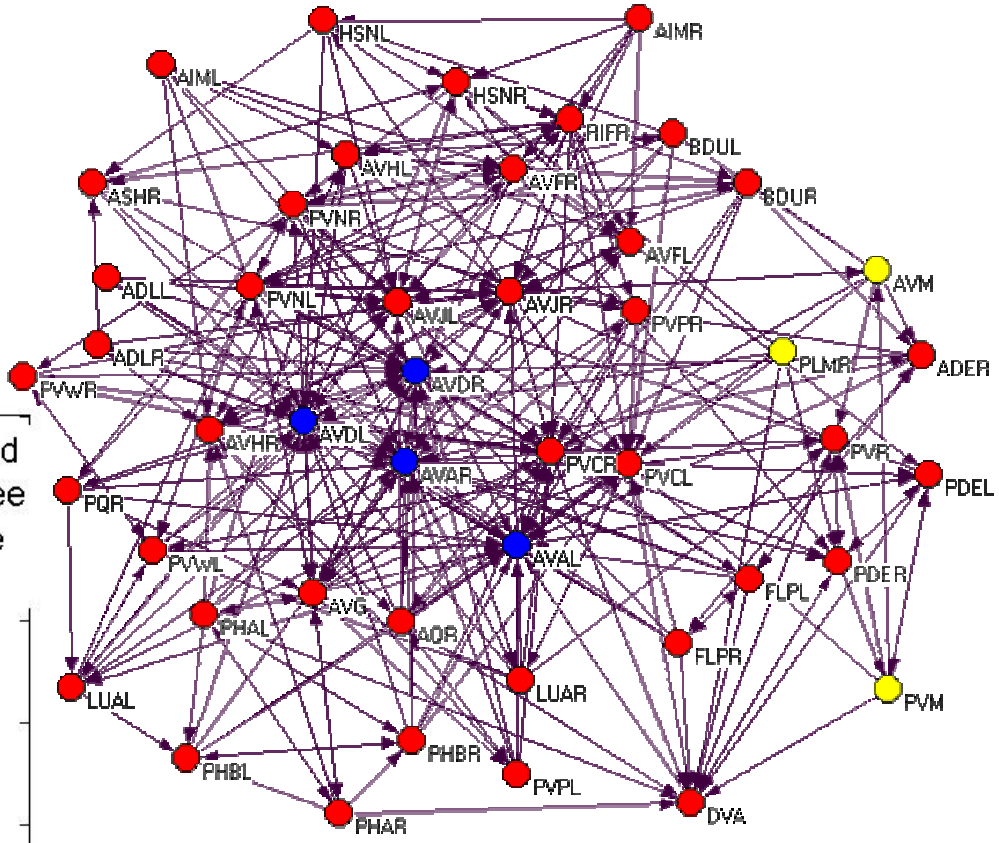


k-Core: Undirected & Directed



k-Core of *C Elegans* neural net



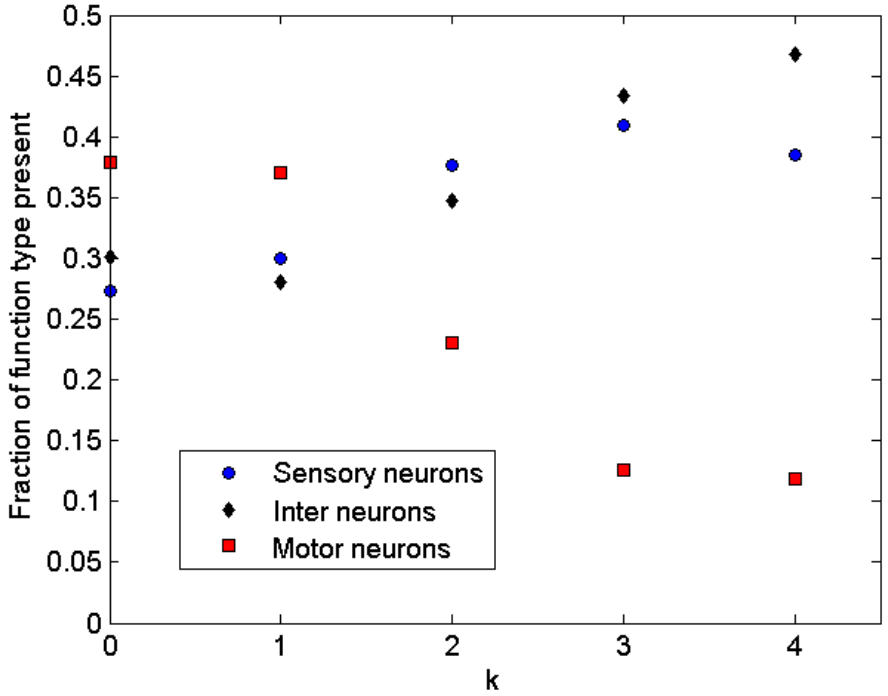


Out-degree 5-core of synaptic network

Composition of k-Cores

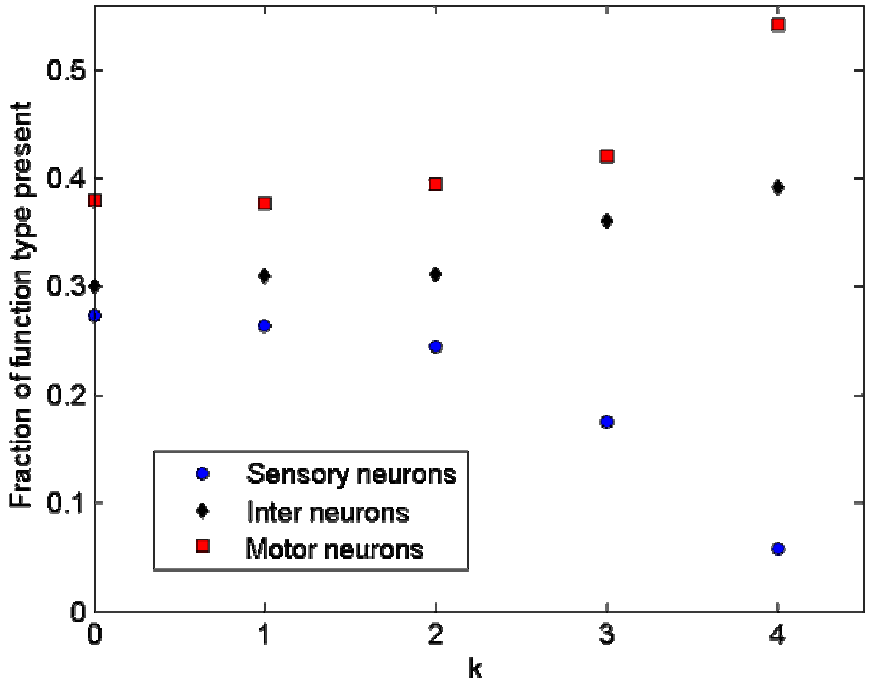
Out-degree cores

Mostly sensory & interneurons



Over-representation of Lumbar & Lateral Ganglia neurons

Over-representation of Lateral Ganglion & Ventral Cord Neural Group

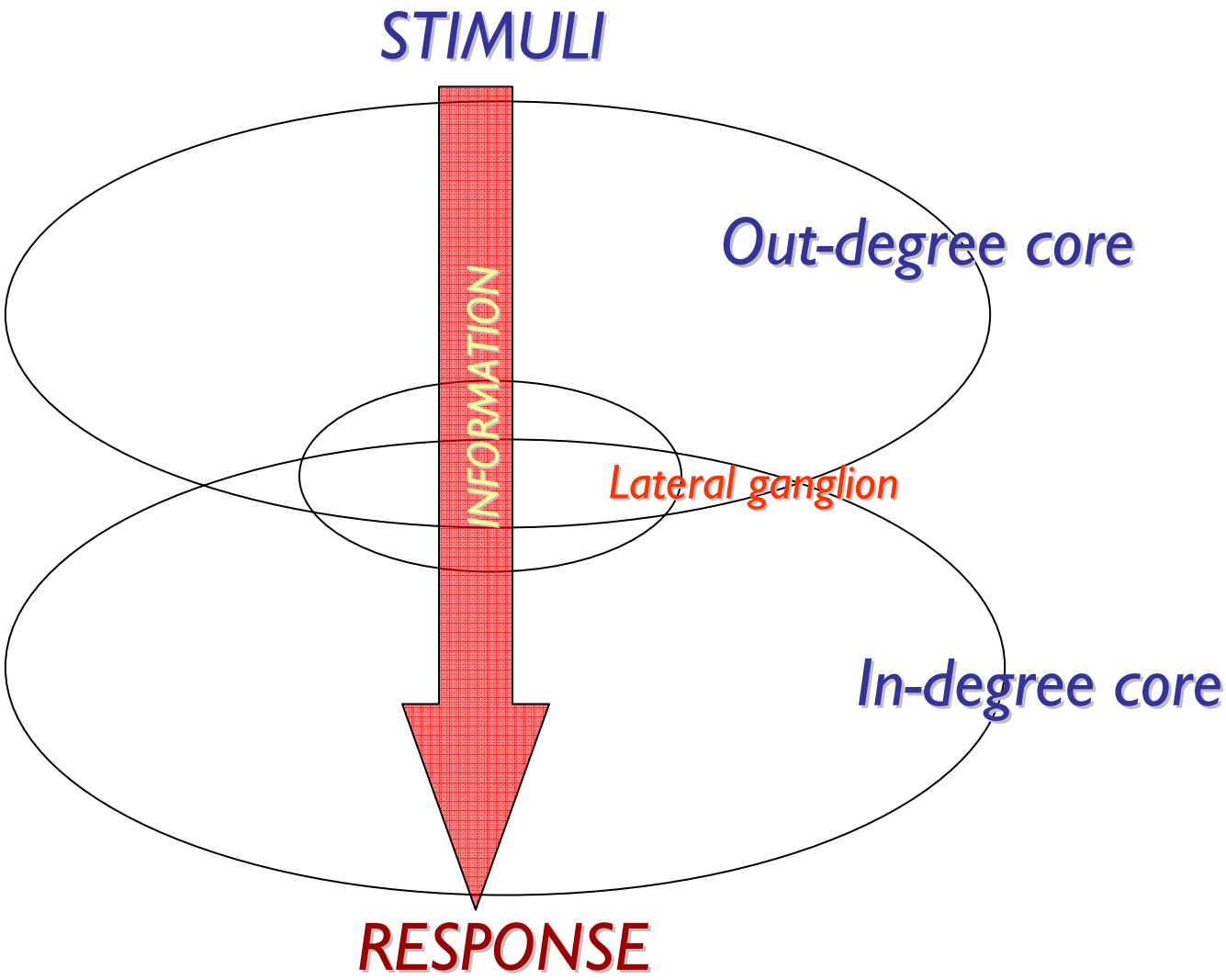


In-degree cores

Mostly motor & interneurons

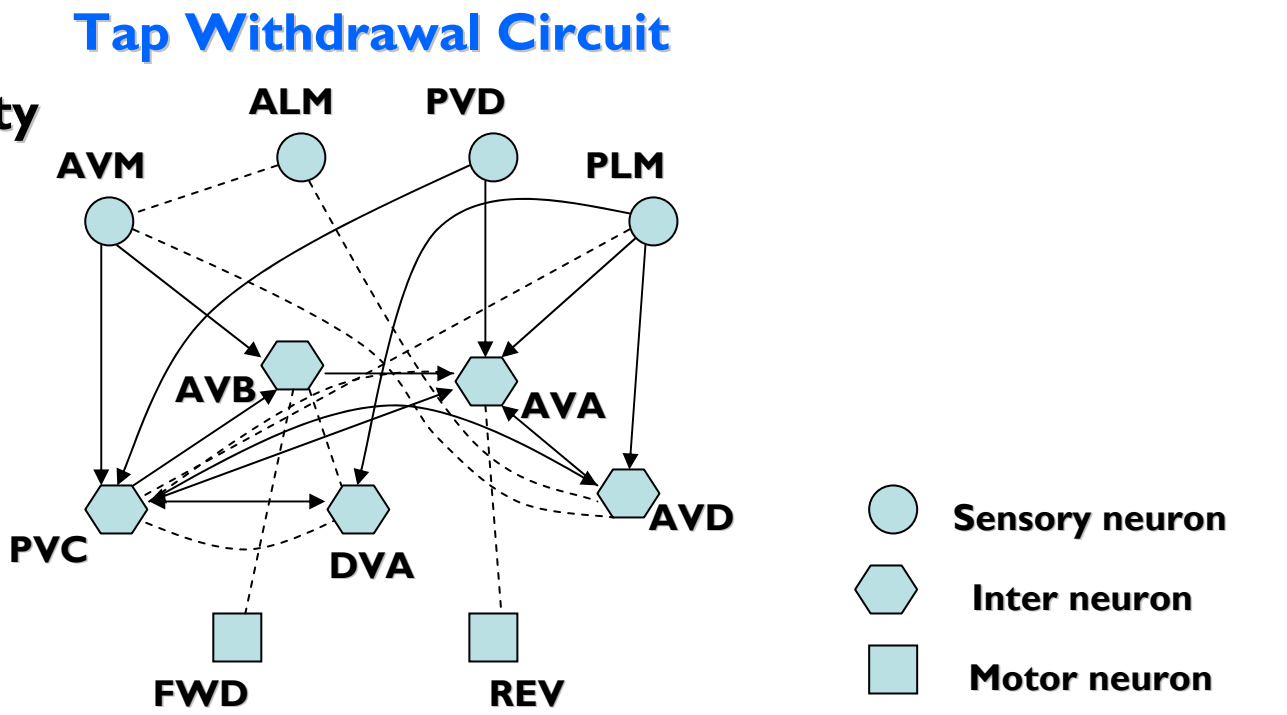
Lateral Ganglion: the information highway of *C Elegans*

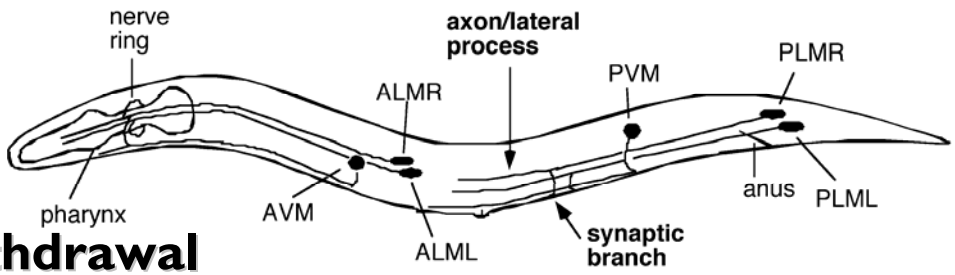
Bridging the sensory & motor neurons



Functional circuits of C Elegans

- Touch sensitivity
- Egg laying
- Thermotaxis
- Chemosensory
- Defecation
- Locomotion
  when
  - Satiated: Feeding
  - Hungry: Exploration
  - Escape behavior: Tap withdrawal

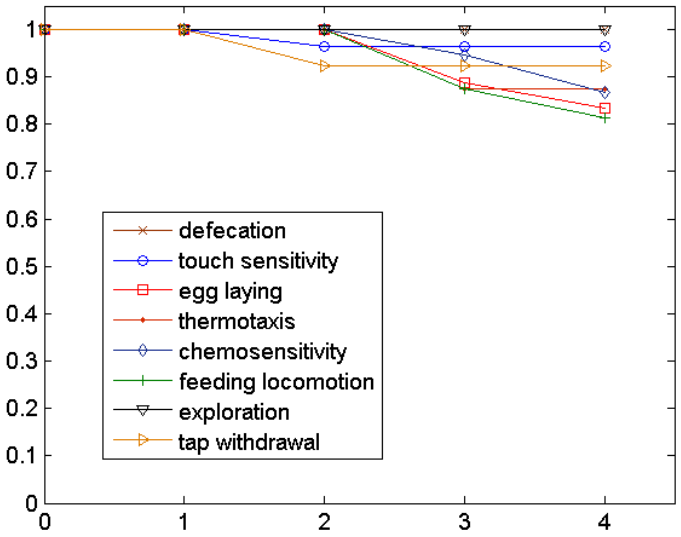




Functional ckts & k-Core

Most k-core neurons are the neurons involved in different functional circuits and…

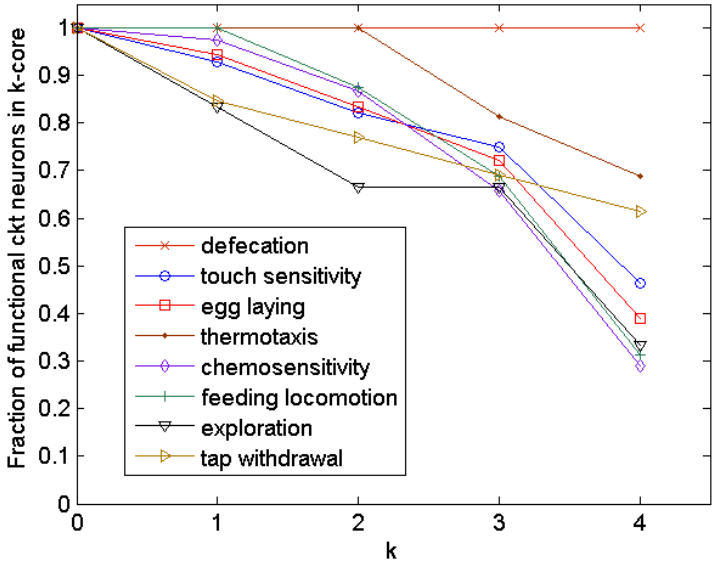
… large fraction of the functional circuit neurons are present in the inner cores !



Out-degree core

In-degree core

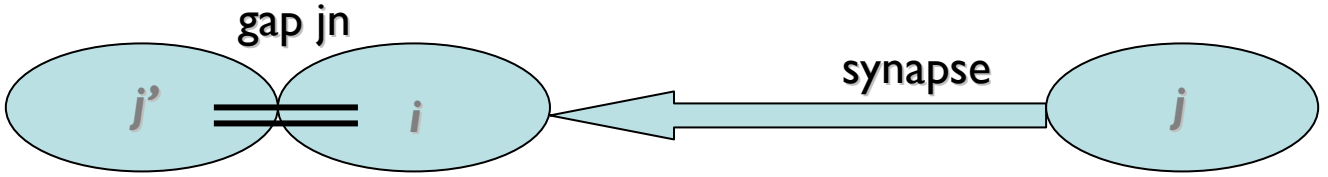
***Reason:* eliminating inner core neurons more likely to result in behavioral anomaly**



k-Core: *Relating structure & functional importance*

So far we talked about structure… What about dynamics ?

Let's look at how the *i*-th neuron's potential (which represents its activity) belonging to the network evolves with time



$$R_m C_m dV_i/dt = V_{leak} - V_i + R_{mi} \Sigma (I_{ij} + I'_{ij}) + I_{ext}$$ Potential V_i

$$I'_{ij} = \omega'_{ij} g'_{ij} (V_j - V_i)$$ Gap jnl current: Input through gap junctions

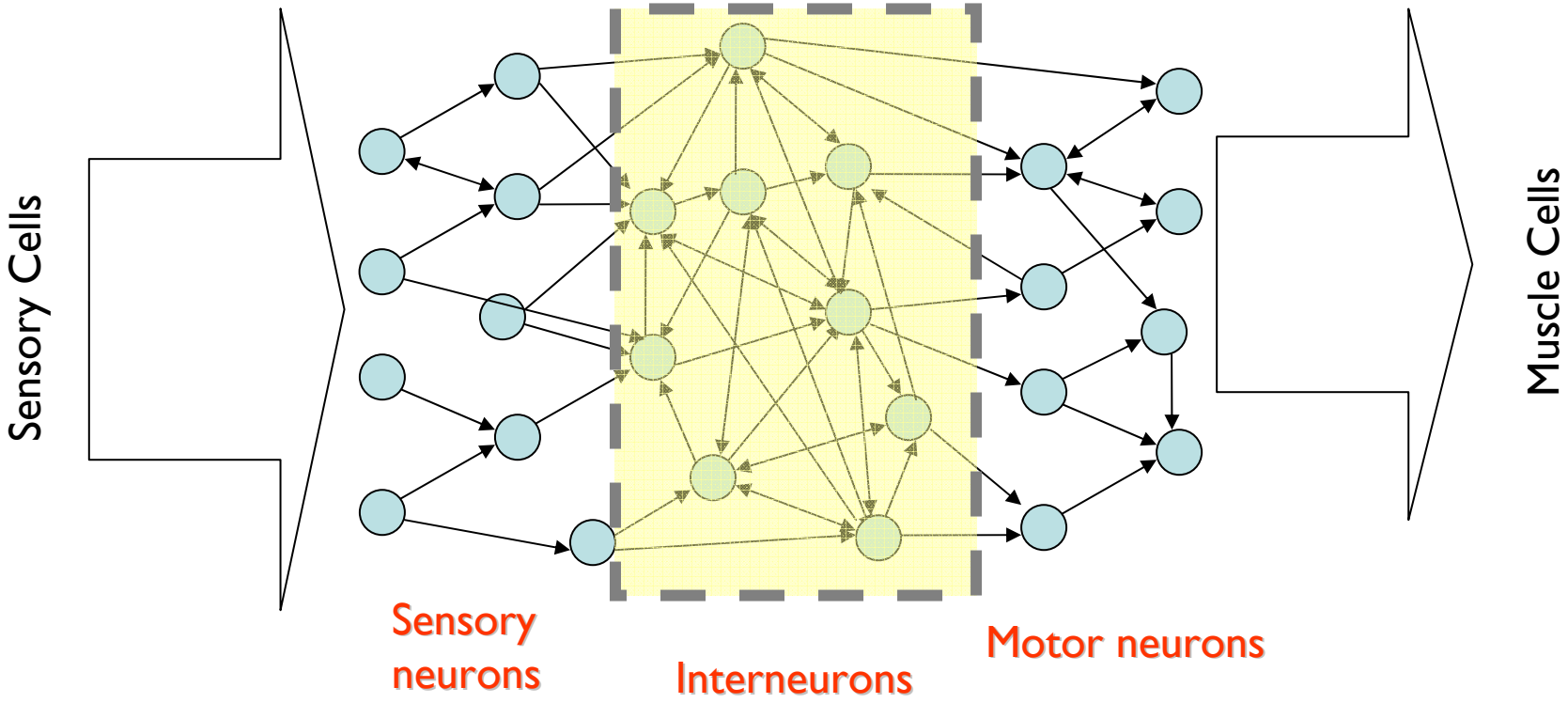
$$I_{ij} = \omega_{ij} g_{ij} (E_{ij} - V_i)$$ Synaptic current: Input through synapses

$$dg_{ij}/dt = (g_{ij}(V_j) - g_{ij})/\tau_{ij}$$ Synaptic conductance: graded potential synapse

$$g(V_j) = g_{ij}/(1 + e^{(K_{ij}(V_j - V_{eqj})/V_{rangeij})})$$ sigmoid function of pre-synaptic potential

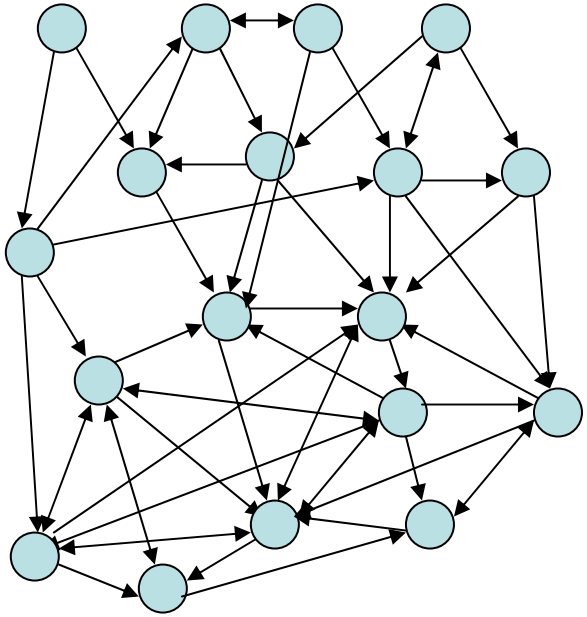
But why look at dynamics ?

- Because dynamics is the key behind how the nervous system does its job
- How to design the network (especially the "control box" of interneurons) so as to have a large number of possible input-output relations?

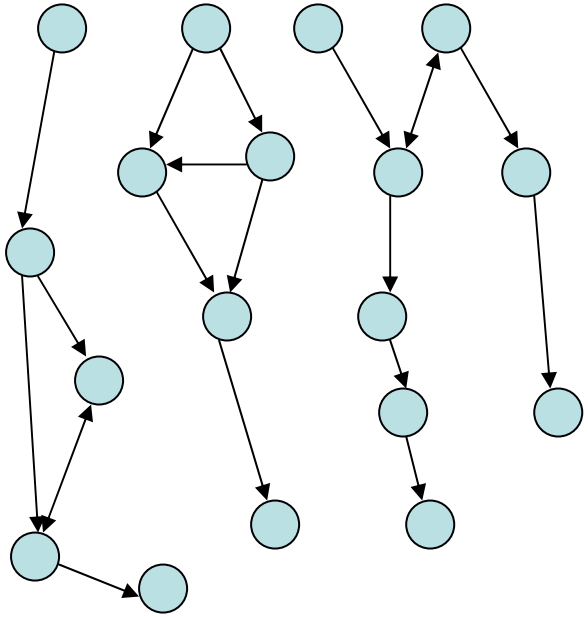


The Central Question

- Why central nervous system (brain) evolved at all instead of a nervous system equivalent to a collection of reflex arcs ?
- Why networks rather than parallel pathways ?



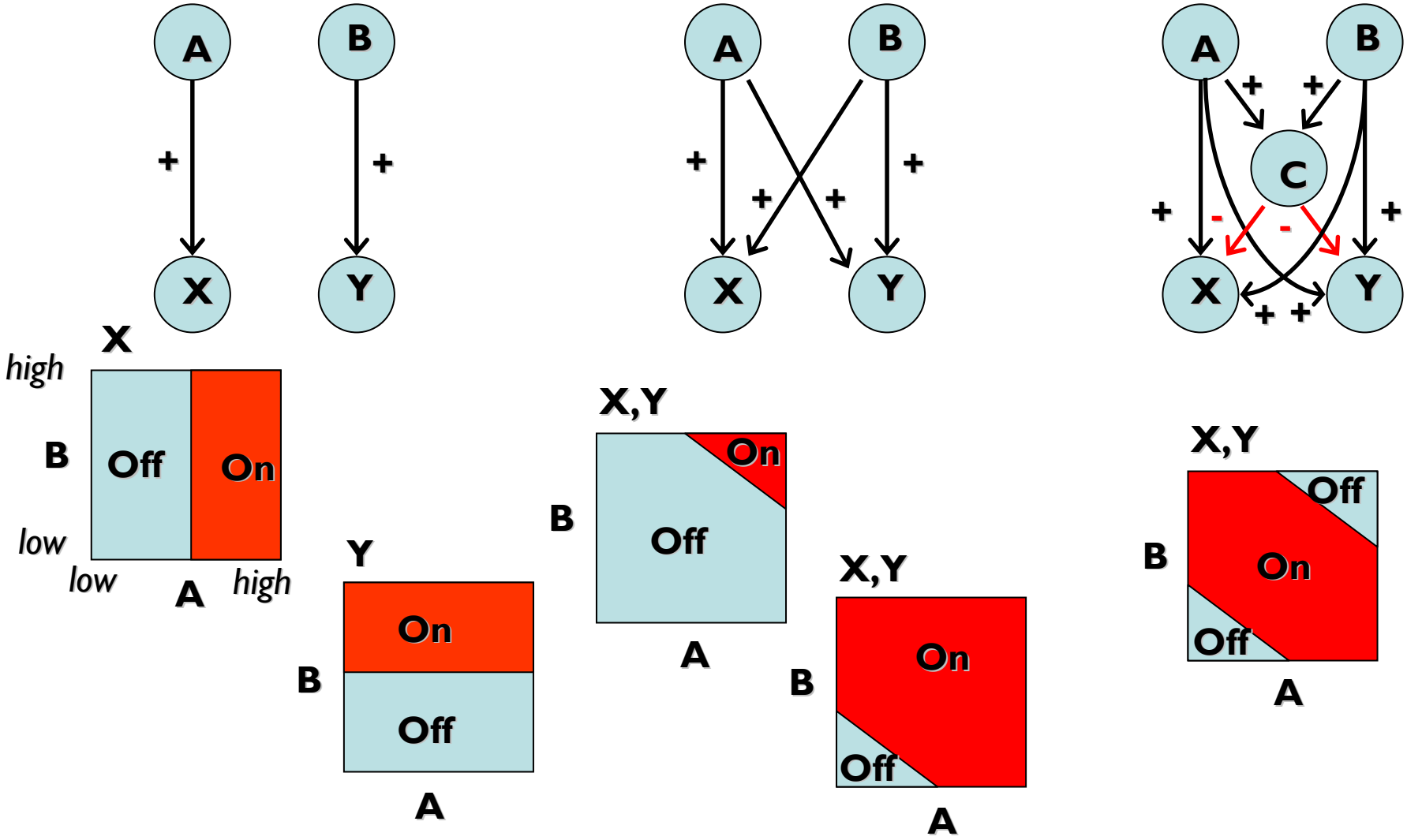
versus



Also relevant for intra-cellular signaling networks (protein kinase instead of neurons)

Advantage of Networks: Flexibility

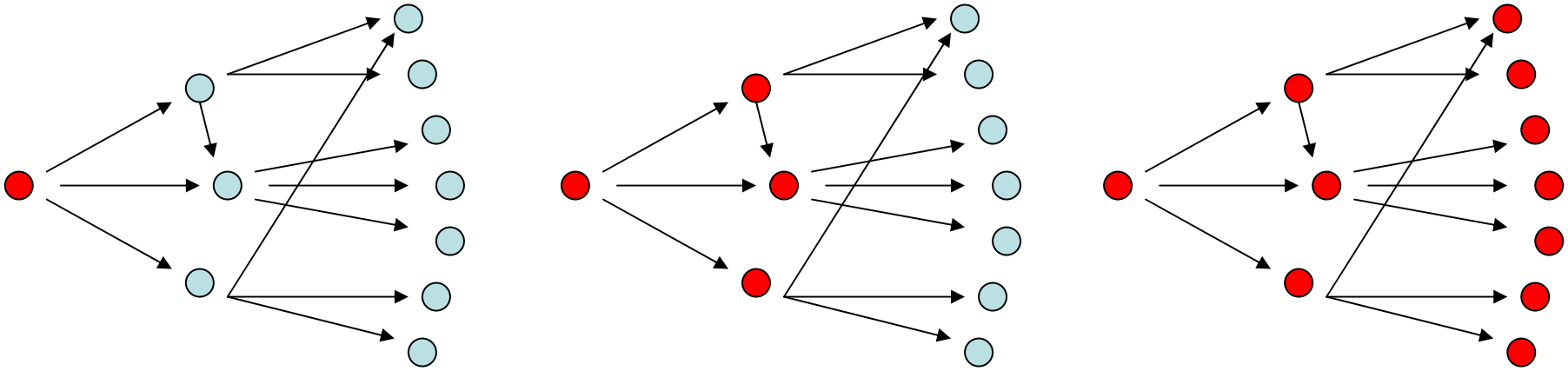
Logic Gates out of Threshold Element Networks



Disadvantage of Networks: Necessity for complex control mechanisms

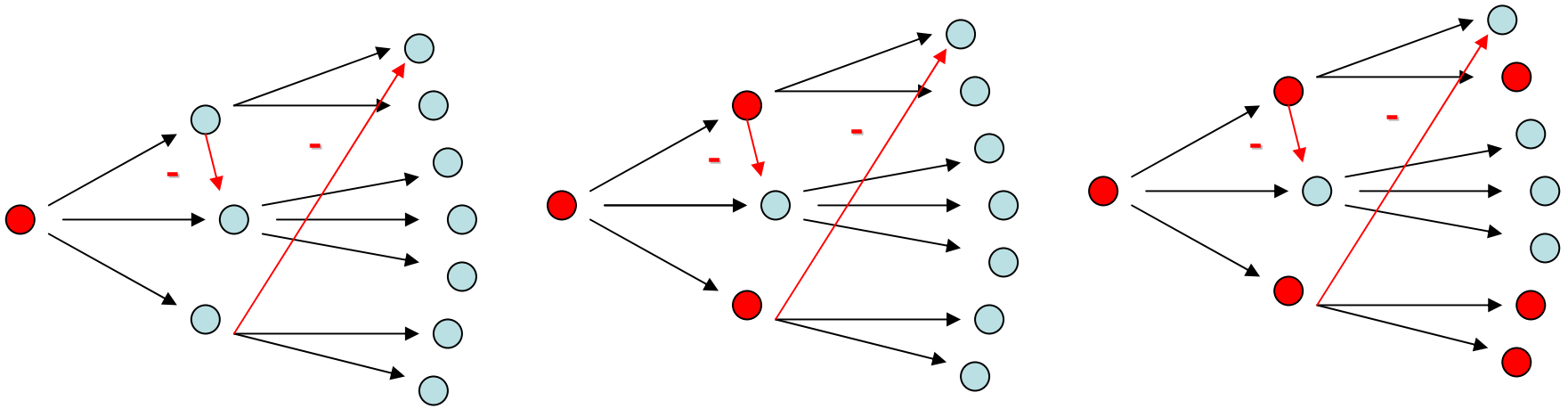
- The price to be paid for this flexibility: *Control overheads*

  Need to introduce additional control machinery to segregate different functional circuits
- E.g., stimulation of a mechano-sensitive neuron should lead only to tap withdrawal and NOT to egg-laying !
- Problem: In a structurally connected network, stimulating any neuron will lead eventually to stimulation of all neurons through cascading activation signals



Solution: Segregation of functional ckts through excitation/inhibition

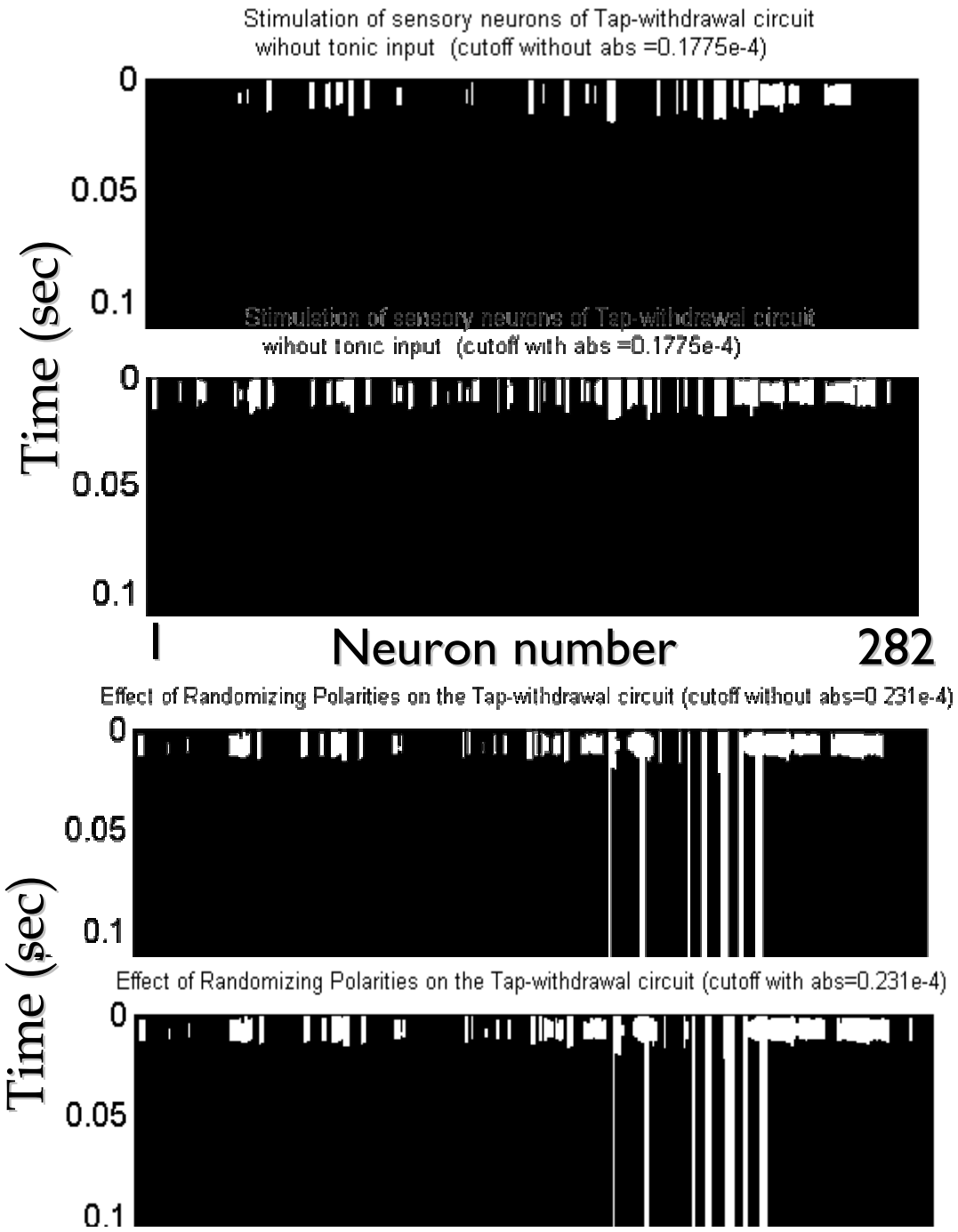
- The problem of runaway excitation can be controlled by introducing negative links (inhibition)



- To determine the actual network of positive & negative links, need to identify excitatory & inhibitory neurons
- Problem: *C. elegans* is too small to do electropysiology
- So we are determining polarities of neurons by comparing output of our dynamical network model with experimental data
- cross-validation through indirect methods (e.g., comparison with *Ascaris*)

Control

Effect of randomized polarities



In lieu of conclusion

- Modular analysis may help spot functionally critical neurons
- k-Core analysis indicates role of lateral ganglion as information highway between the sensory and motor components (stimulus-response path)
- Almost all functional circuit neurons are present in the inner cores: relating structure and functional importance
- Differing behavior of in-degree core and out-degree core indicates different organization in the sensory-interneuron and inter-motor neuron sections of the network
- Ongoing work: using neuronal dynamics to study the logic circuits of the nervous system
- Network maybe using polarity and the attenuation of graded potentials over long network distances to localize activity within different regions