Lecture 8: Neurons as Nonlinear Systems: FitzHugh-Nagumo and Collective Dynamics

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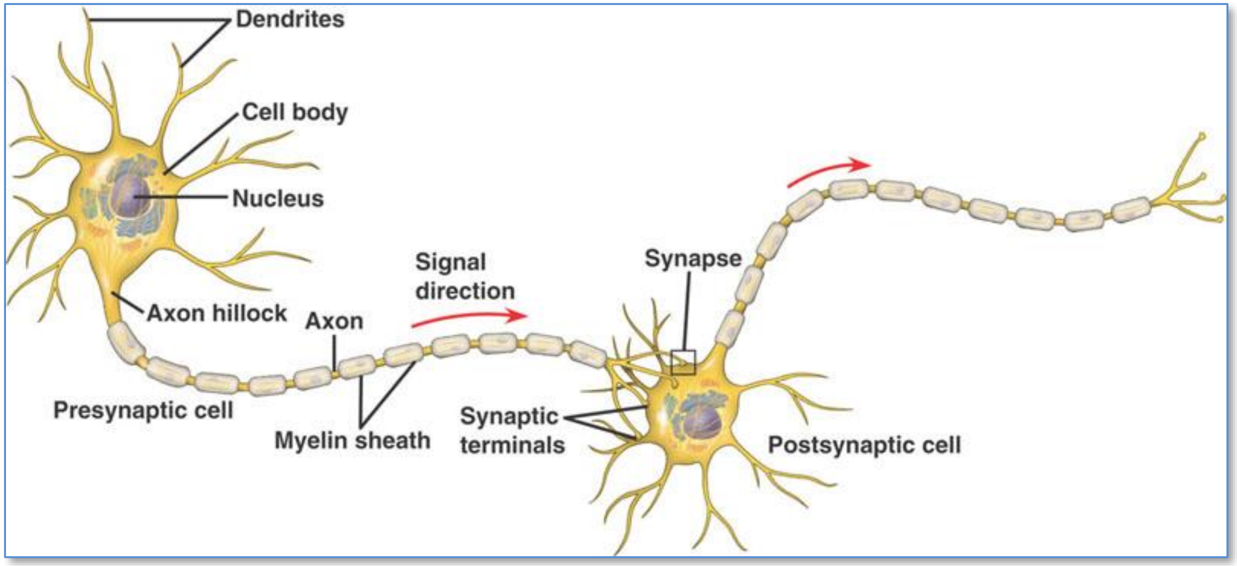
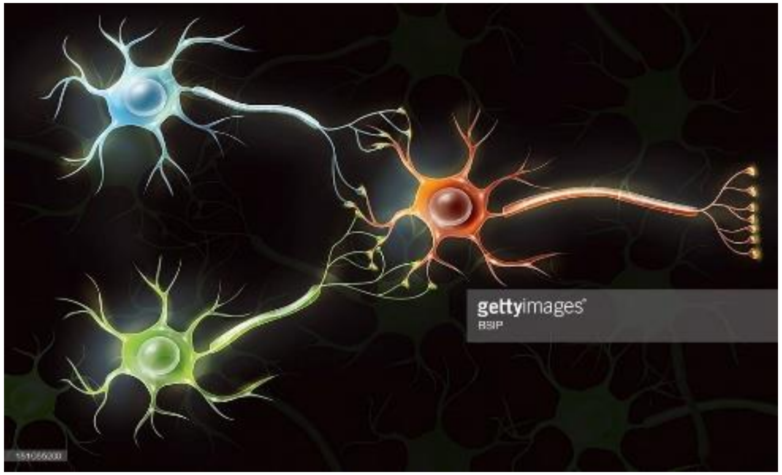
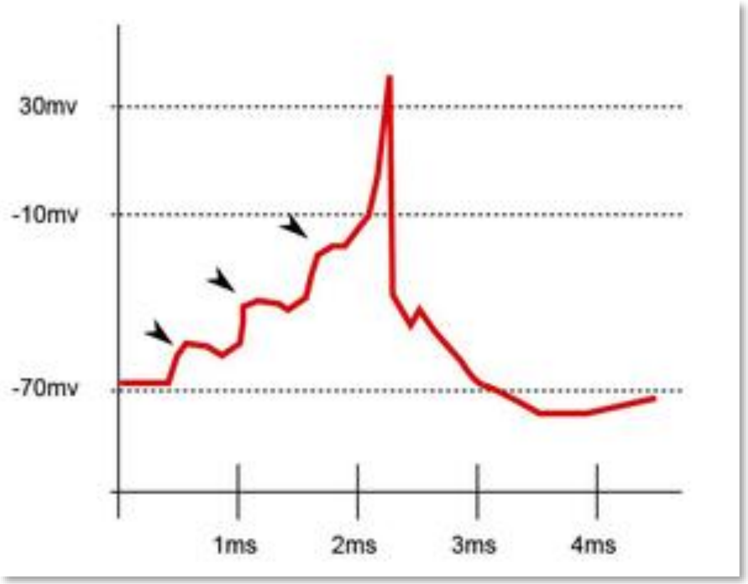
1. Reviewing neurons (and general modeling)



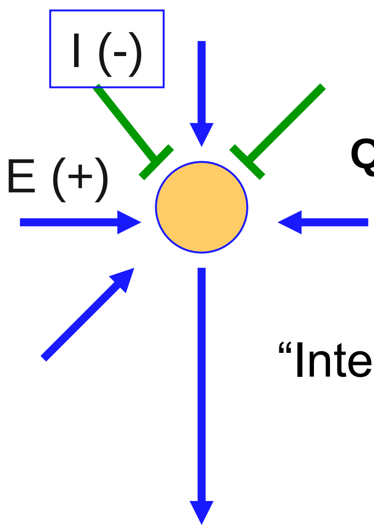




1. Reviewing neurons (and general modeling)

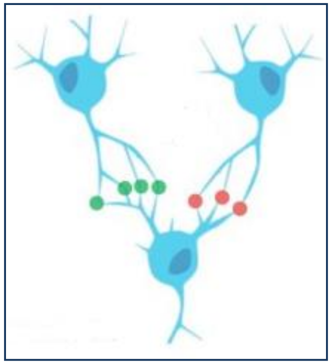
$$\tau \frac{du(t)}{dt} = -u(t) + \sum_k \sum_i g_k \Phi(t - t_i) + \xi(t)$$

Neuronal dynamics + connectivity + noise = complex collective behavior



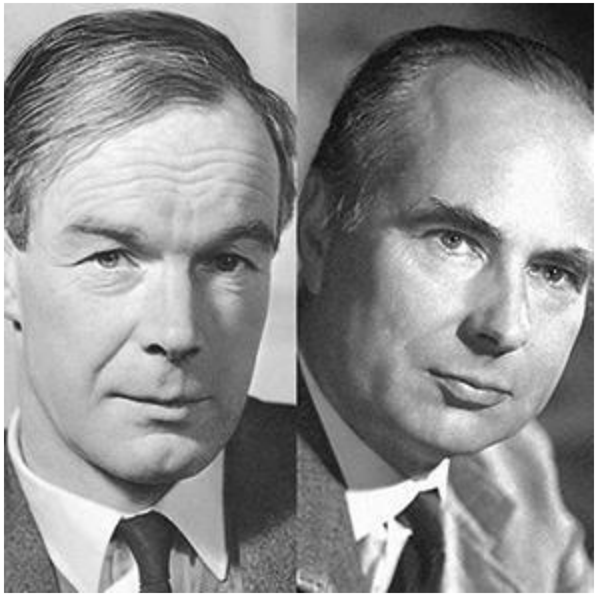
QUORUM OF INPUTS

"Integrate and fire"

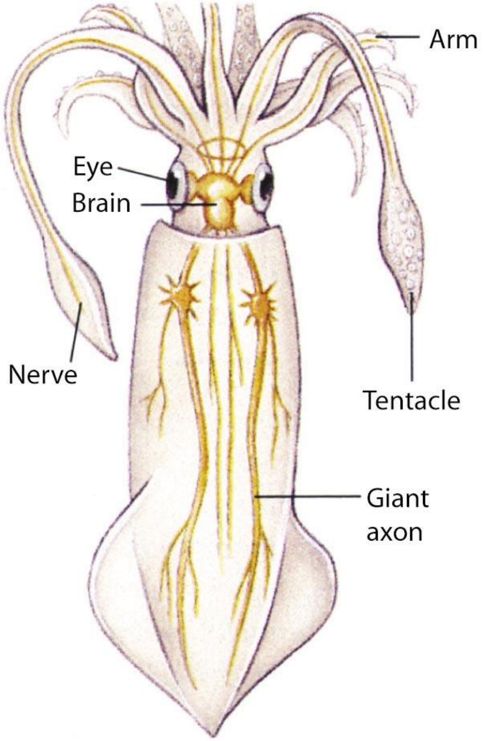


2. Accurate, Hodgkin-Huxley model

- FORMAL DESCRIPTION: **Hodgkin-Huxley** model (1952)



A. Hodgkin A. Huxley



The study of the electrical properties of the **giant axon of the squid** uncovered the working of a neuron: THE **ACTION POTENCIAL**.

$$
\begin{cases}
C_m \dfrac{dV}{dt} = -g_K n^4 (V - V_K) - g_{Na} m^3 h (V - V_{Na}) - g_L (V - V_L) + I_{appl}. \\
\tau_w(V) \dfrac{dw}{dt} = w_\infty(V) - w, \;\; w = n, m, h,
\end{cases}
$$

$$
\begin{cases}
\dfrac{dn}{dt} = \alpha_n(V_m)(1-n) - \beta_n(V_m)n \\
\dfrac{dm}{dt} = \alpha_m(V_m)(1-m) - \beta_m(V_m)m \\
\dfrac{dh}{dt} = \alpha_h(V_m)(1-h) - \beta_h(V_m)h
\end{cases}
$$

$$
\alpha_n(V_m) = \frac{0.01(V_m - 10)}{\exp\left(\frac{V_m - 10}{10}\right) - 1} \qquad \alpha_m(V_m) = \frac{0.1(V_m - 25)}{\exp\left(\frac{V_m - 25}{10}\right) - 1} \qquad \alpha_h(V_m) = 0.07 \exp\left(\frac{V_m}{20}\right)
$$

$$
\beta_n(V_m) = 0.125 \exp\left(\frac{V_m}{80}\right) \qquad \beta_m(V_m) = 4 \exp\left(\frac{V_m}{18}\right) \qquad \beta_h(V_m) = \frac{1}{\exp\left(\frac{V_m - 30}{10}\right) + 1}
$$

membrane potential

conductances

Input current

$$C_m \frac{dV}{dt} = -g_K n^4 (V - V_K) - g_{Na} m^3 h (V - V_{Na}) - g_L (V - V_L) + I_{appl}.$$

activation of ion gates (3 different)

$$\tau_w(V) \frac{dw}{dt} = w_\infty(V) - w, \; w = n, m, h,$$

membrane potential — conductances — Input current

$$C_m \frac{dV}{dt} = -g_K n^4 (V - V_K) - g_{Na} m^3 h (V - V_{Na}) - g_L (V - V_L) + I_{appl}.$$

activation of ion gates (3 different)

$$\tau_w(V) \frac{dw}{dt} = w_\infty(V) - w, \;\; w = n, m, h,$$

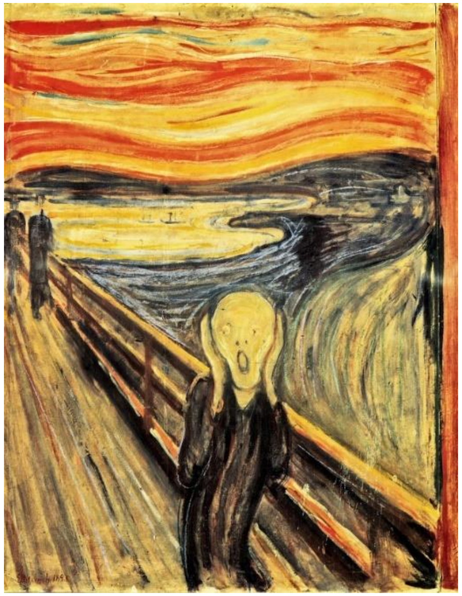
$$\frac{dn}{dt} = \alpha_n(V_m)(1-n) - \beta_n(V_m)n$$

$$\frac{dm}{dt} = \alpha_m(V_m)(1-m) - \beta_m(V_m)m$$

$$\frac{dh}{dt} = \alpha_h(V_m)(1-h) - \beta_h(V_m)h$$

$$\alpha_n(V_m) = \frac{0.01(V_m-10)}{\exp\left(\frac{V_m-10}{10}\right)-1} \quad \alpha_m(V_m) = \frac{0.1(V_m-25)}{\exp\left(\frac{V_m-25}{10}\right)-1} \quad \alpha_h(V_m) = 0.07\exp\left(\frac{V_m}{20}\right)$$

$$\beta_n(V_m) = 0.125\exp\left(\frac{V_m}{80}\right) \quad \beta_m(V_m) = 4\exp\left(\frac{V_m}{18}\right) \quad \beta_h(V_m) = \frac{1}{\exp\left(\frac{V_m-30}{10}\right)+1}$$



Nonlinear nightmare!

Reproduces accurately the behavior of excitable cells (neurons, cardiac)!
Umm…. but intractable if we want to study more than 10 coupled cells.

3. FitzHugh-Nagumo

- **FitzHugh-Nagumo** simplification (1960)

$$
\begin{cases}
C_m \dfrac{dV}{dt} = -g_K n^4 (V - V_K) - g_{Na} m^3 h (V - V_{Na}) - g_L (V - V_L) + I_{appl}. \\
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\end{cases}
$$

3. FitzHugh-Nagumo

- **FitzHugh-Nagumo** simplification (1960)

$$\begin{cases} C_m \frac{dV}{dt} = -g_K n^4 (V - V_K) - g_{Na} m^3 h (V - V_{Na}) - g_L (V - V_L) + I_{appl}. \\ \tau_w(V) \frac{dw}{dt} = w_\infty(V) - w, \;\; w = n, m, h, \end{cases}$$

very slow compared to *m.*

$$\begin{cases} \frac{dn}{dt} = \alpha_n(V_m)(1-n) - \beta_n(V_m)n \\ \frac{dm}{dt} = \alpha_m(V_m)(1-m) - \beta_m(V_m)m \\ \frac{dh}{dt} = \alpha_h(V_m)(1-h) - \beta_h(V_m)h \end{cases}$$

can be reduced to a much simpler form for (typical) biological parameters.

$$C_m \frac{dV}{dt} = -g_K n^4 (V - V_K) - g_{Na} m_\infty^3(V)(0.8 - n)(V - V_{Na}) - g_L (V - V_L) + I_{appl}$$

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

3. FitzHugh-Nagumo

Simplifying the notation:

$$\begin{cases} \dfrac{dv}{dt} = v(v-\alpha)(1-v) - w + I \\ \dfrac{dw}{dt} = \varepsilon(v - \gamma w). \end{cases}$$

fast variable (membrane potential)

slow variable (recovery)

Note the nonlinearity as v^3 !

How do we explore it? Nonlinear systems resources!
(nullclines, equilibrium points, orbits…)

- Can be analyzed in detail, and **works for most excitable cells**!
- Computationally better than HH, but still hard.
- Simple expansions allow to tackle richer scenarios.
- Coupling with other neurons through the current and potential.

3. FitzHugh-Nagumo

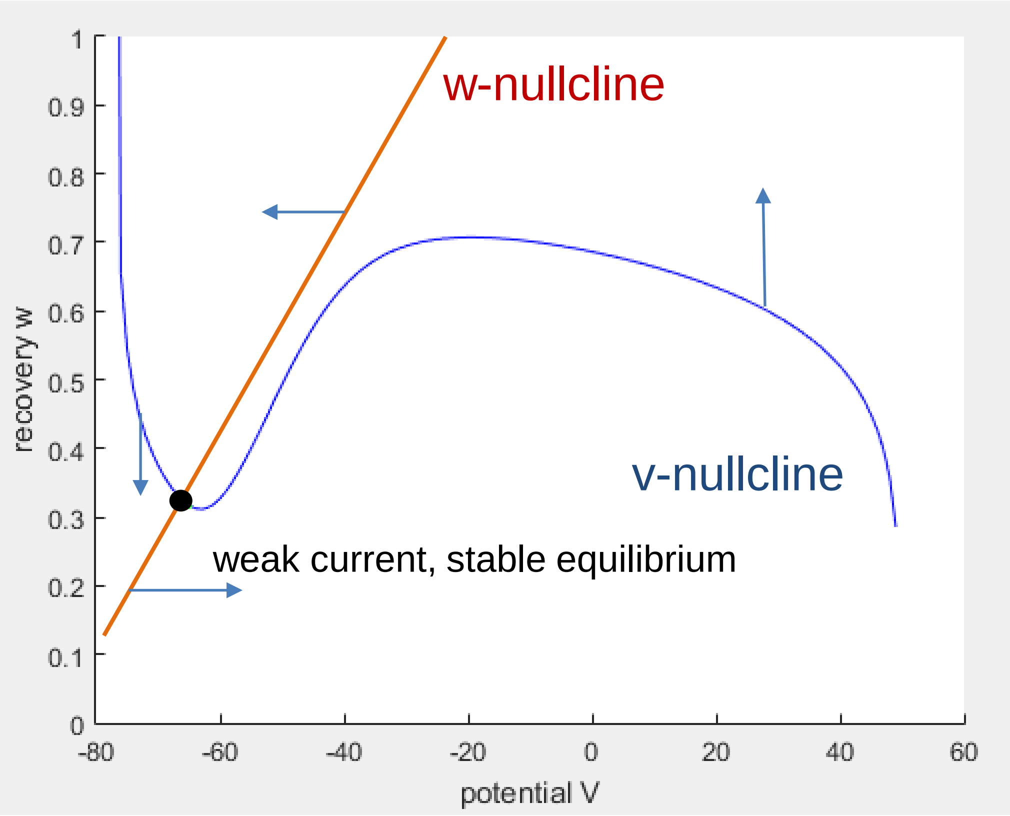
- **FitzHugh-Nagumo**: nullclines and dynamics

$$\begin{cases} \frac{dv}{dt} = v(v-\alpha)(1-v) - w + I \\ \frac{dw}{dt} = \varepsilon(v - \gamma w). \end{cases}$$

3. FitzHugh-Nagumo

- **FitzHugh-Nagumo**: nullclines and dynamics

$$\begin{cases} \frac{dv}{dt} = v(v-\alpha)(1-v) - w + I = 0 & \text{v-nullcline} \\ \frac{dw}{dt} = \varepsilon(v - \gamma w) = 0 & \text{w-nullcline} \end{cases}$$



3. FitzHugh-Nagumo

- **FitzHugh-Nagumo**: nullclines and dynamics

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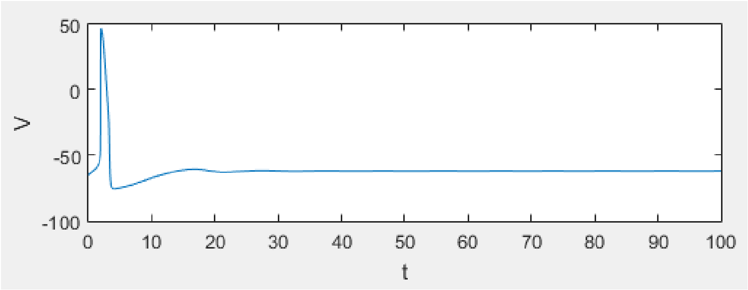
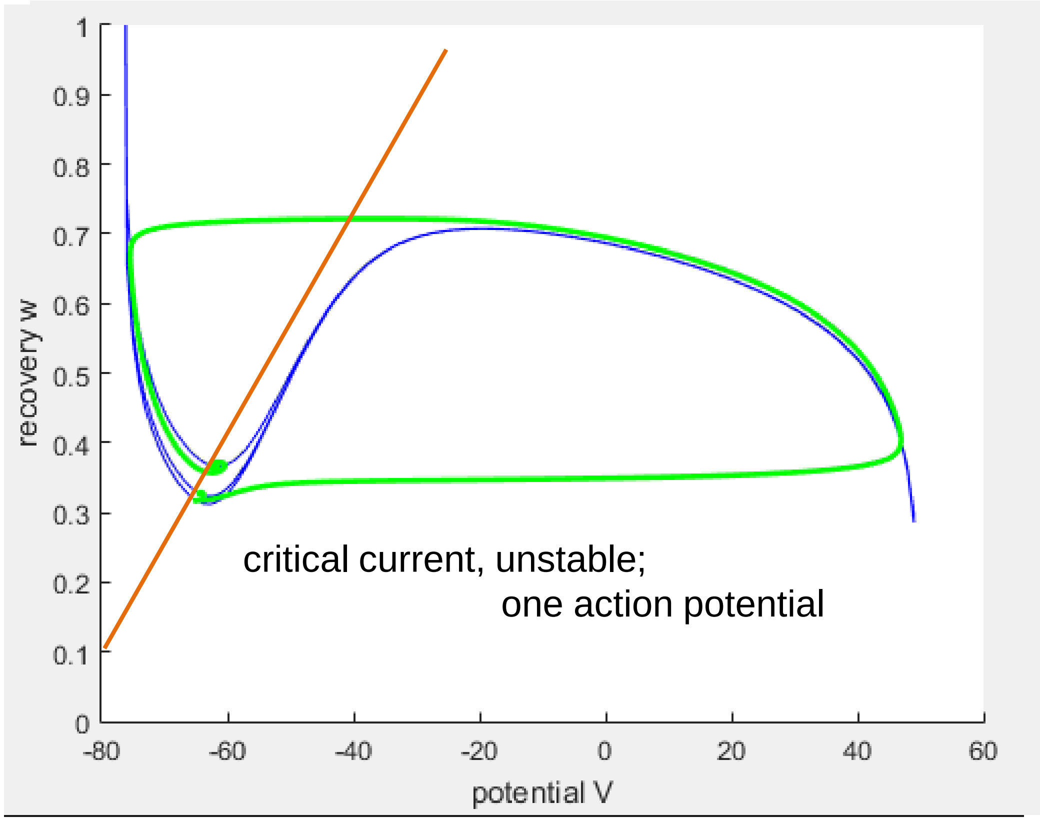
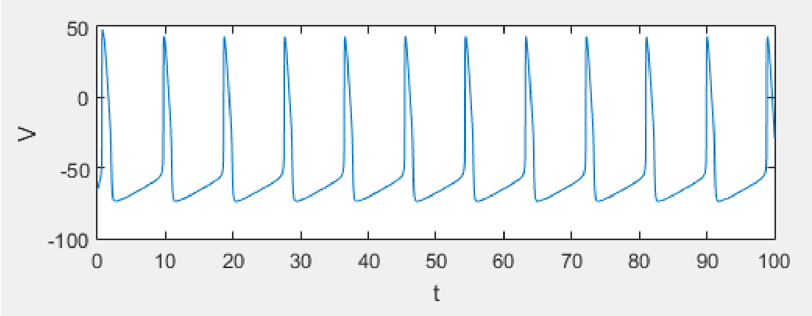




3. FitzHugh-Nagumo

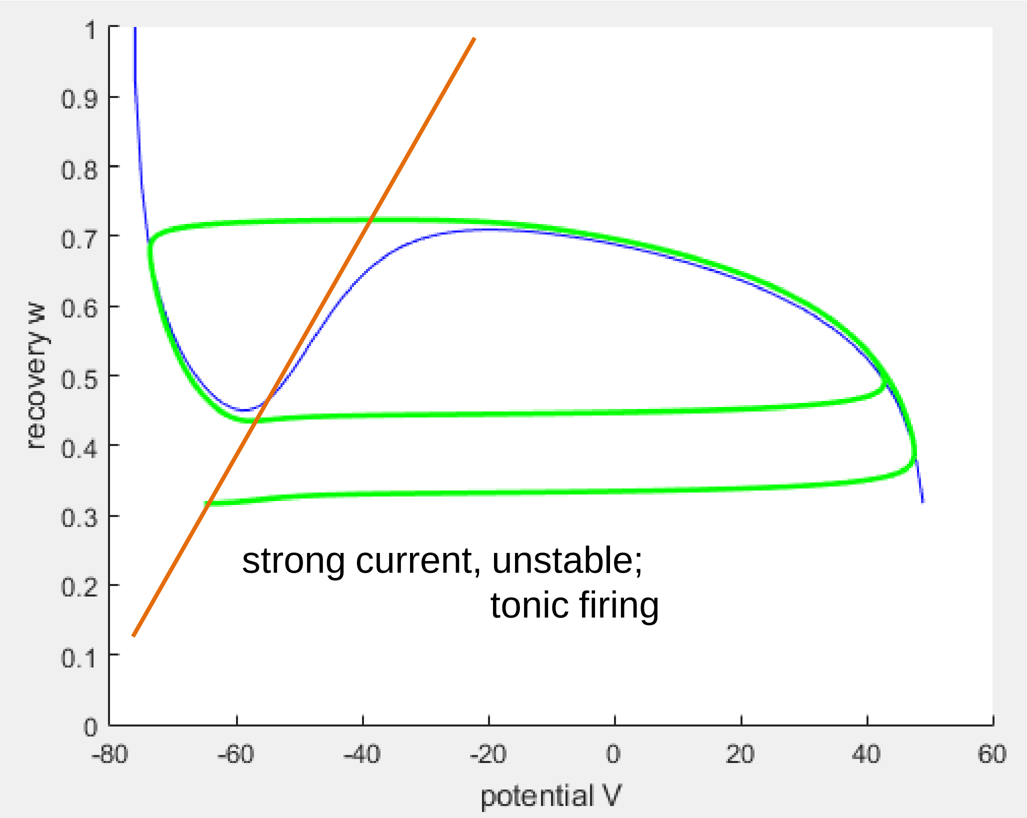
- **FitzHugh-Nagumo**: nullclines and dynamics

$$\begin{cases} \frac{dv}{dt} = v(v-\alpha)(1-v) - w + I = 0 \\ \frac{dw}{dt} = \varepsilon(v - \gamma w) = 0 \end{cases}$$



Oscillatory, but it is not an harmonic oscillator!

We will play with it in Matlab!



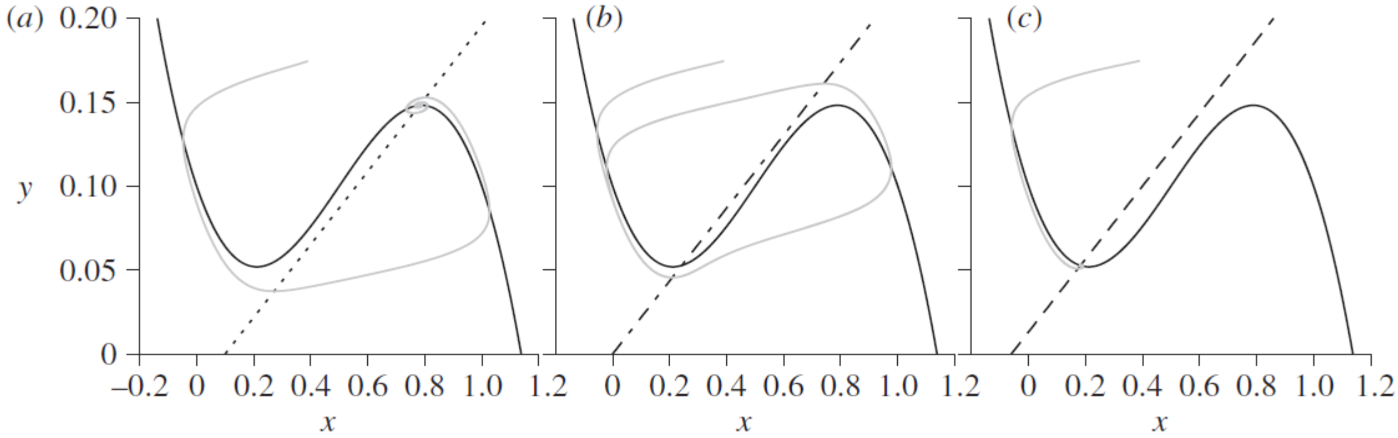
3. FitzHugh-Nagumo

- Extensions of FitzHugh-Nagumo

Neuronal variability

$$\begin{cases} \dfrac{dv}{dt} = v(v-\alpha)(1-v) - w + I \\ \dfrac{dw}{dt} = \varepsilon(v - \gamma w) + a \end{cases}$$

effectively shifts the w-nullcline left-right



stable (non-excited) oscillating stable (excited)

3. FitzHugh-Nagumo

■ Extensions of FitzHugh-Nagumo

Coupling among neurons:

Neurons receive (send) currents from (to) other neurons.

$$\begin{cases} \dfrac{dv_i}{dt} = v_i(v_i - \alpha)(1 - v_i) - w + \boxed{I_i^{SYN}} \\ \dfrac{dw_i}{dt} = \varepsilon(v_i - \gamma w_i) + \mathsf{a}_i \end{cases}$$

$$I_i^{\text{syn}}(t) = \frac{K}{N_c}\sum_{j=1}^{N_c}(v_j - v_i).$$ Linear, electric coupling

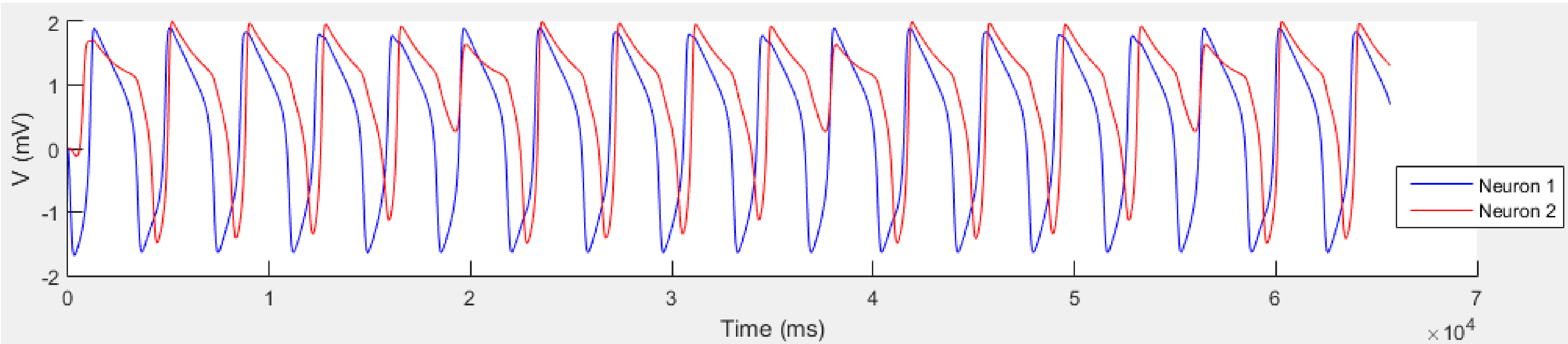
$$I_i^{\text{syn}}(t) = \frac{K}{N_c}\sum_{j=1}^{N_c} g_{ij} r_j(t)(E_i^{s} - v_i).$$ Nonlinear, chemical coupling

E_i^{s}: depends on neutronasmitters' nature

$r_j(t)$: accounts for neutronasmitters' depletion

3. FitzHugh-Nagumo

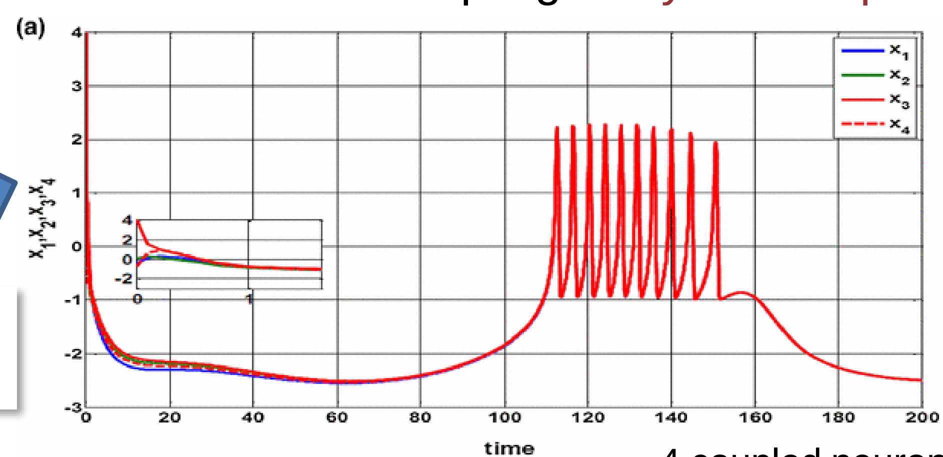
Coupling (here electrical) may change neuronal behavior



Recall Kuramoto: harmonic oscillators with nonlinear coupling.

Neuronal models: nonlinear units with nonlinear coupling. Very difficult problem!!

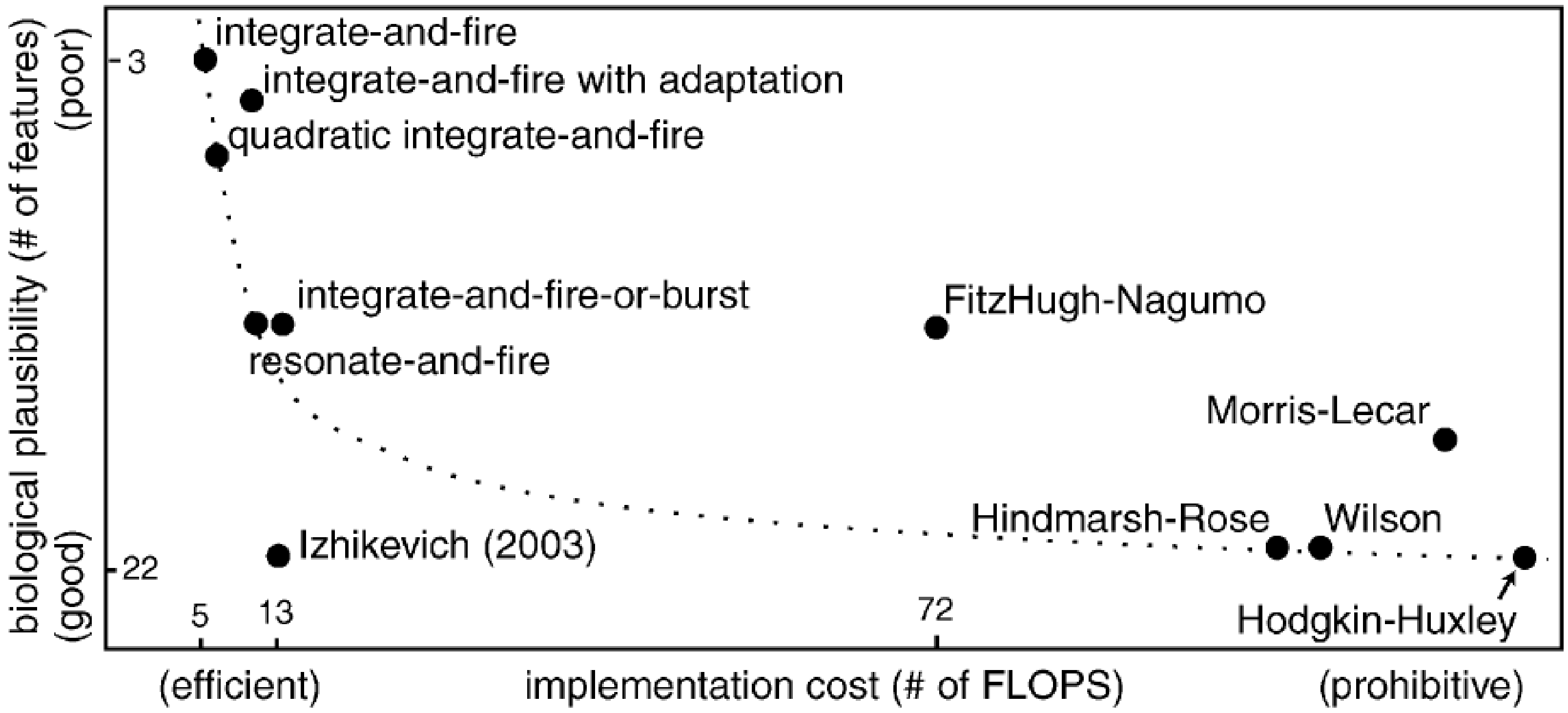
synchronization is much richer and complex!



4 coupled neurons

4. Izhikevich

- I want to study collective phenomena in neurons.
  Can I efficiently simulate N ~ 10^3-10^4 coupled neurons?



4. Izhikevich

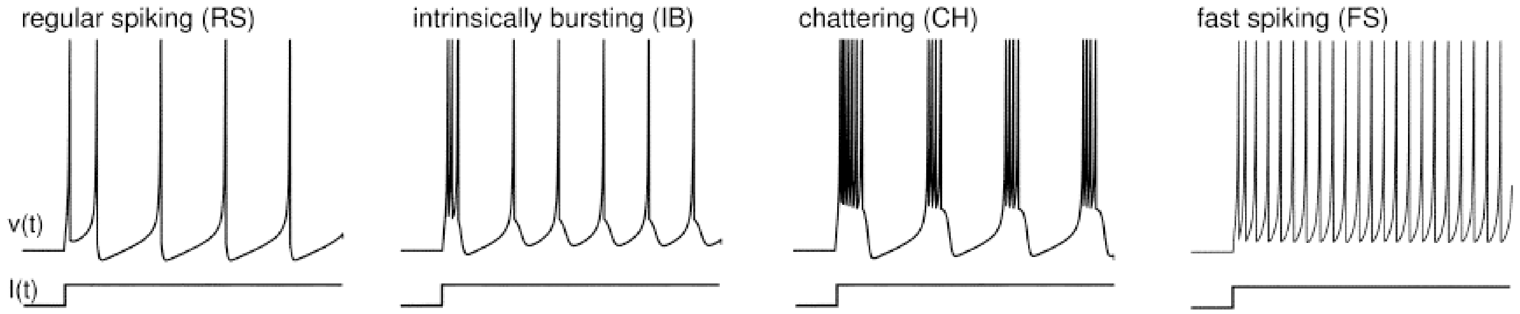
- Izhikevich model (2003) is optimized for computation

$$\begin{cases} v' = 0.04v^2 + 5v + 140 - u + I \\ u' = a(bv - u) \end{cases}$$

$$\text{if } v \geq 30\,\text{mV}, \text{ then } \begin{cases} v \leftarrow c \\ u \leftarrow u + d. \end{cases}$$

  - Rules out non-biologically relevant solutions in FHN.
  - Extremely fast and efficient computationally.
  - Used to compute large networks of N ~ 1000 coupled neurons.

  - Small variations in the parameters lead to all kind of **biologically observed behaviors** (in a much simpler way than HH or FHN).



5. Towards collective behavior

- What ingredients do I need to model collective behavior?

  - Experimental observations: repertoire of activity patterns,
    coherent behavior,
    response to forcing, …

  As experimental neuophysicist ➡ neuronal cultures

  - Network type: directed, weighted, …
  - Network topology: $p_k(k)$, metric embedding, correlations…
  - Dynamical model for neurons: Izhikevich?
  - Role of noise and fluctuations.
  - Neat characterization of observables (firing rate?, coherence?

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  - Experimental observations: repertoire of activity patterns,
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better description

  - Network type: directed, weighted, …
  - Network topology: $p_k(k)$, metric embedding, correlations…
  - Dynamical model for neurons: Izhikevich?
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5. Towards collective behavior

- What ingredients do I need to model collective behavior?
  - Experimental observations: repertoire of activity patterns,
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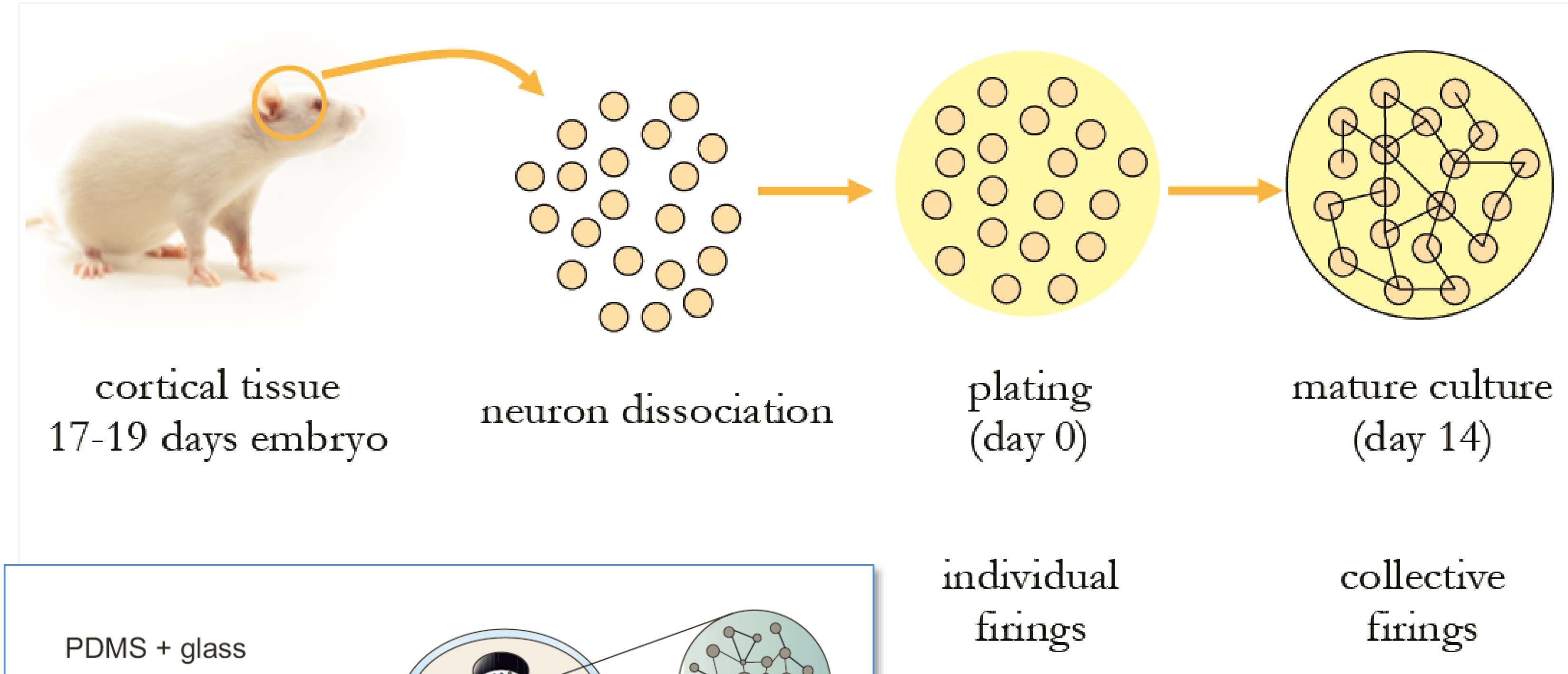
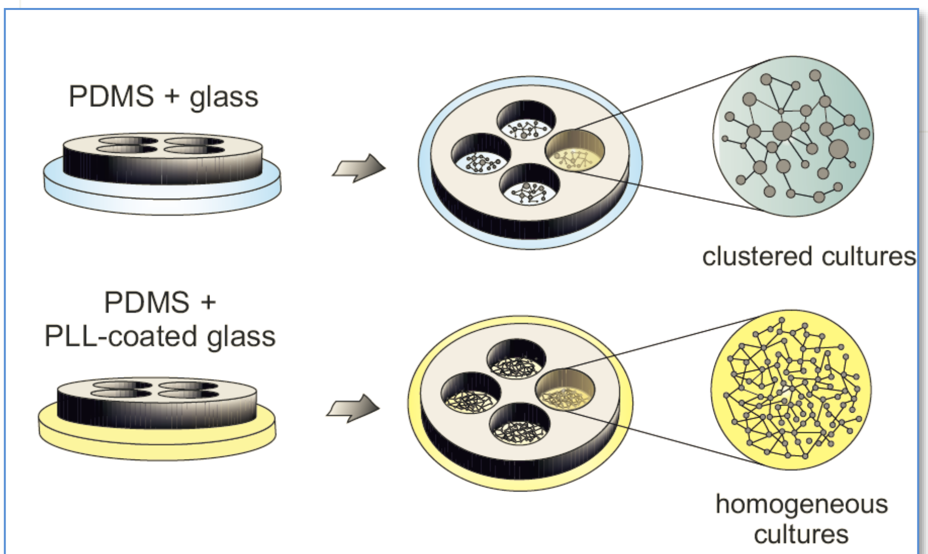
predictability, hidden mechanisms

  - Network type: directed, weighted, …
  - Network topology: $p_k(k)$, metric embedding, correlations…
  - Dynamical model for neurons: Izhikevich?
  - Role of noise and fluctuations.
  - Neat characterization of observables (firing rate?, coherence?

Examples ⇨ Predictability: more complex activity patterns
Hidden mechamisms: importance of noise, efficiency,…

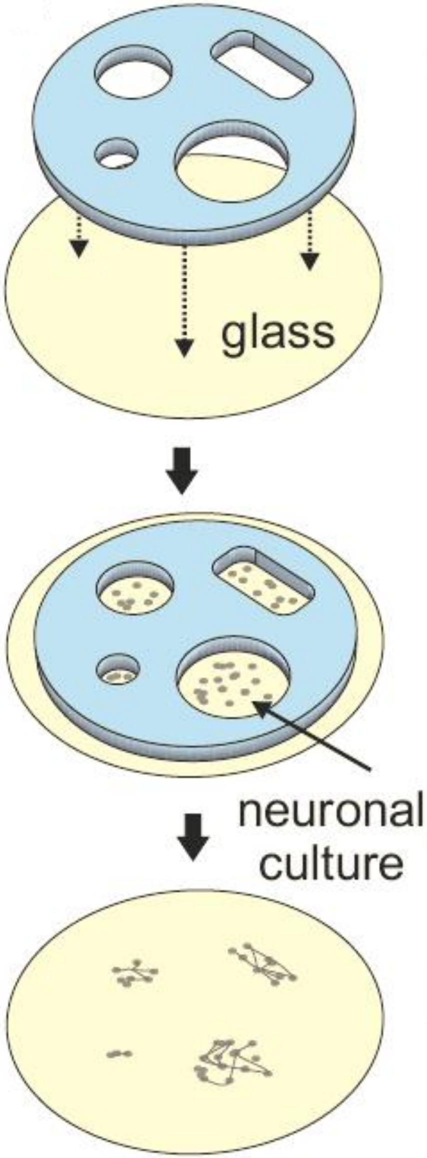
6. Neuronal cultures revisited

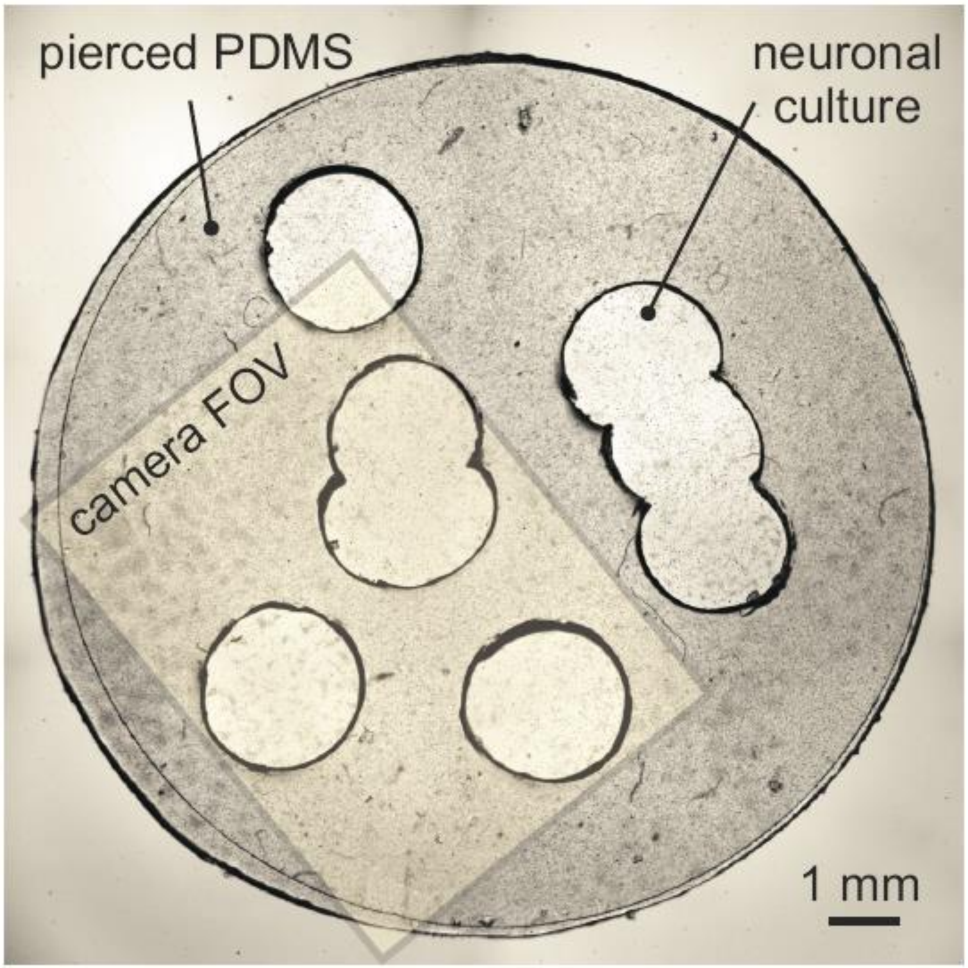




6. Neuronal cultures revisited

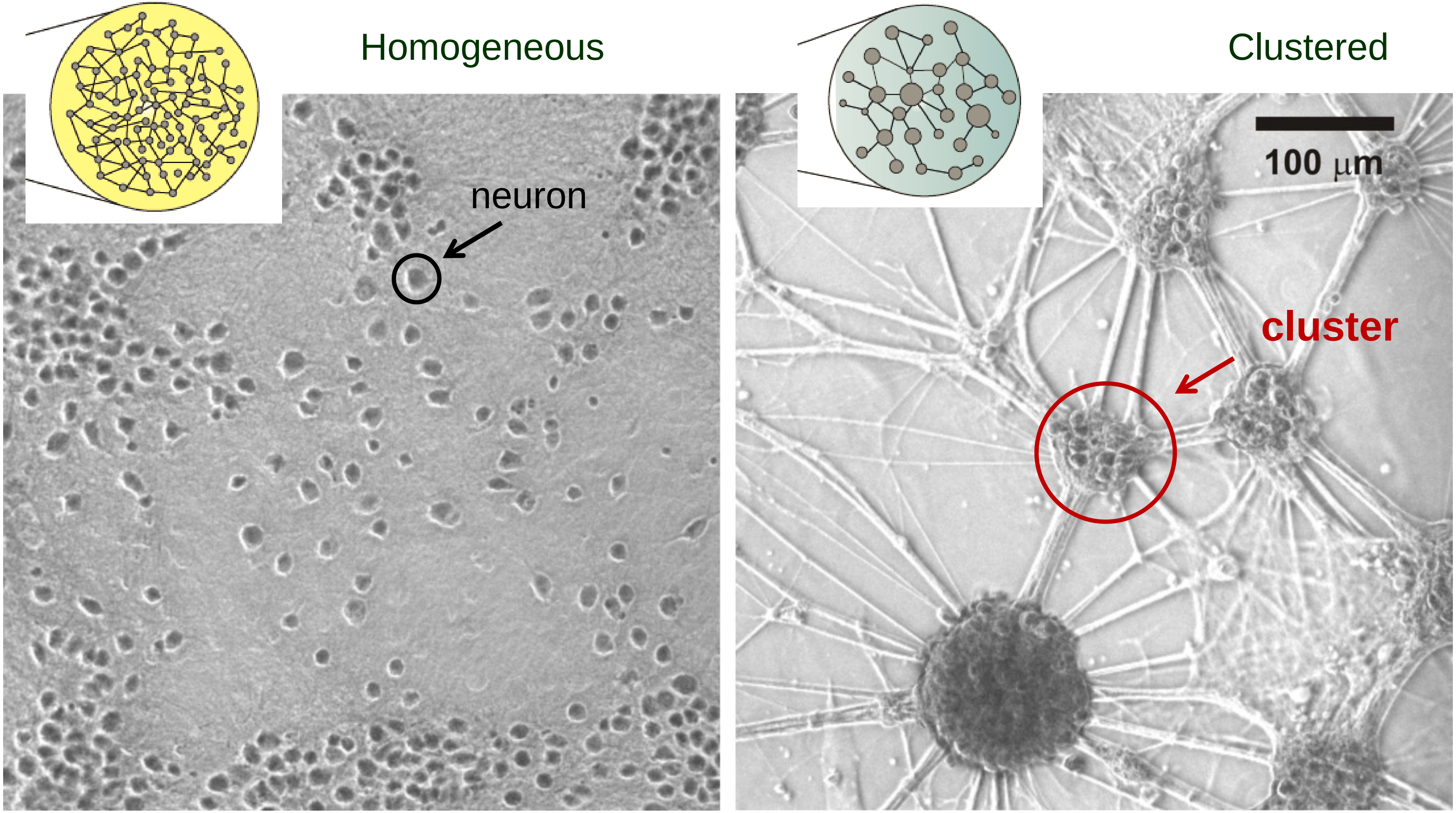
Orlandi et al., Nature Physics (2013)
Teller et al., PLOS Comput Biol (2014)





Allows the monitoring of all neurons!

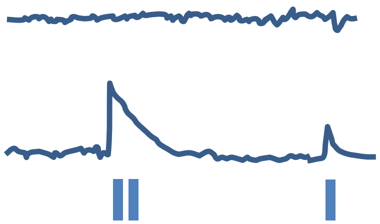
6. Neuronal cultures revisited

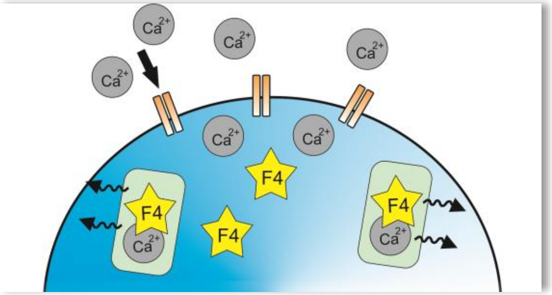


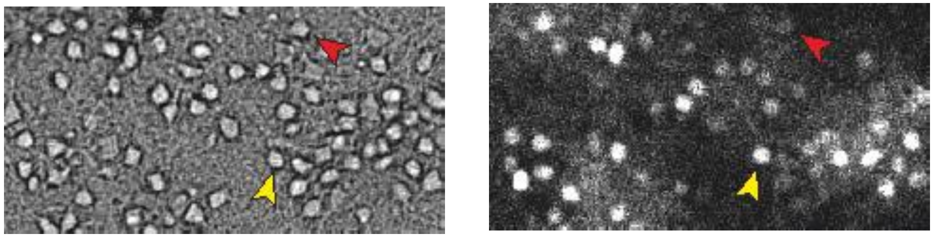
7. Experiments in homogeneous cultures

How do I measure?

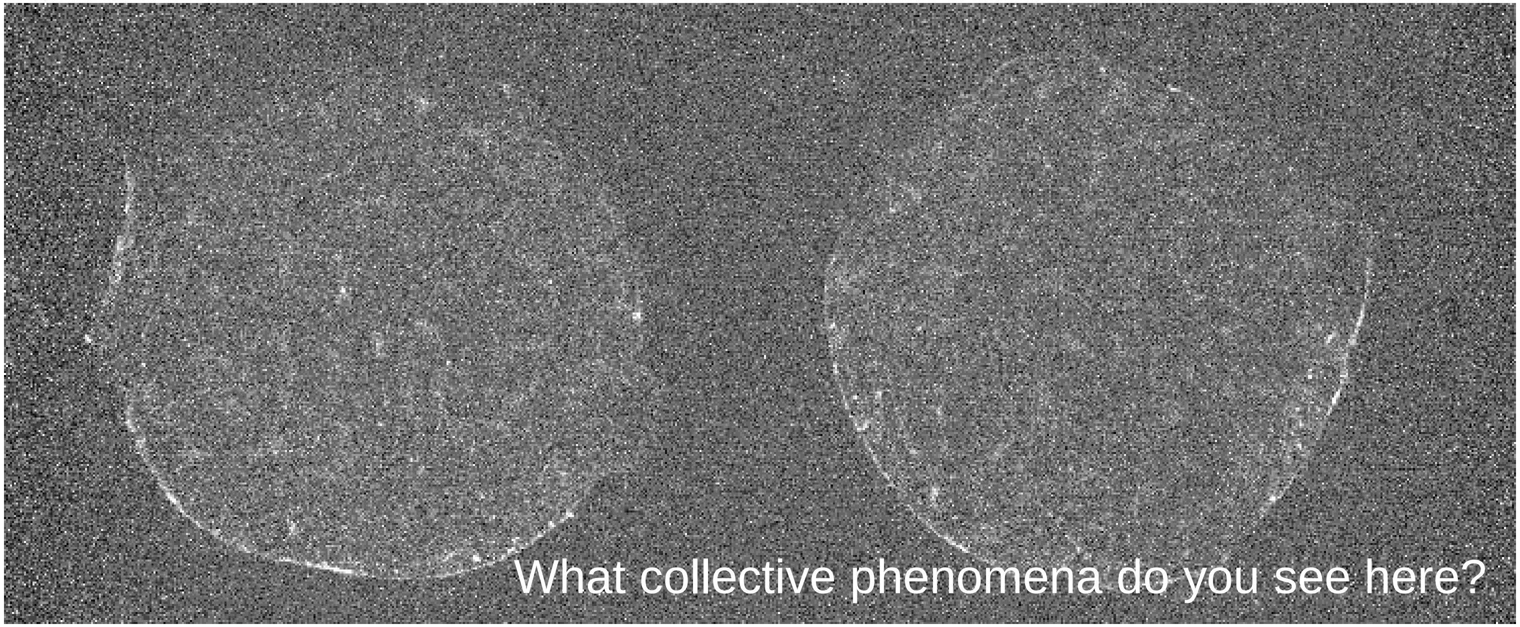
Detection of neuronal firing:
a fluorescent calcium probe + **camera.**

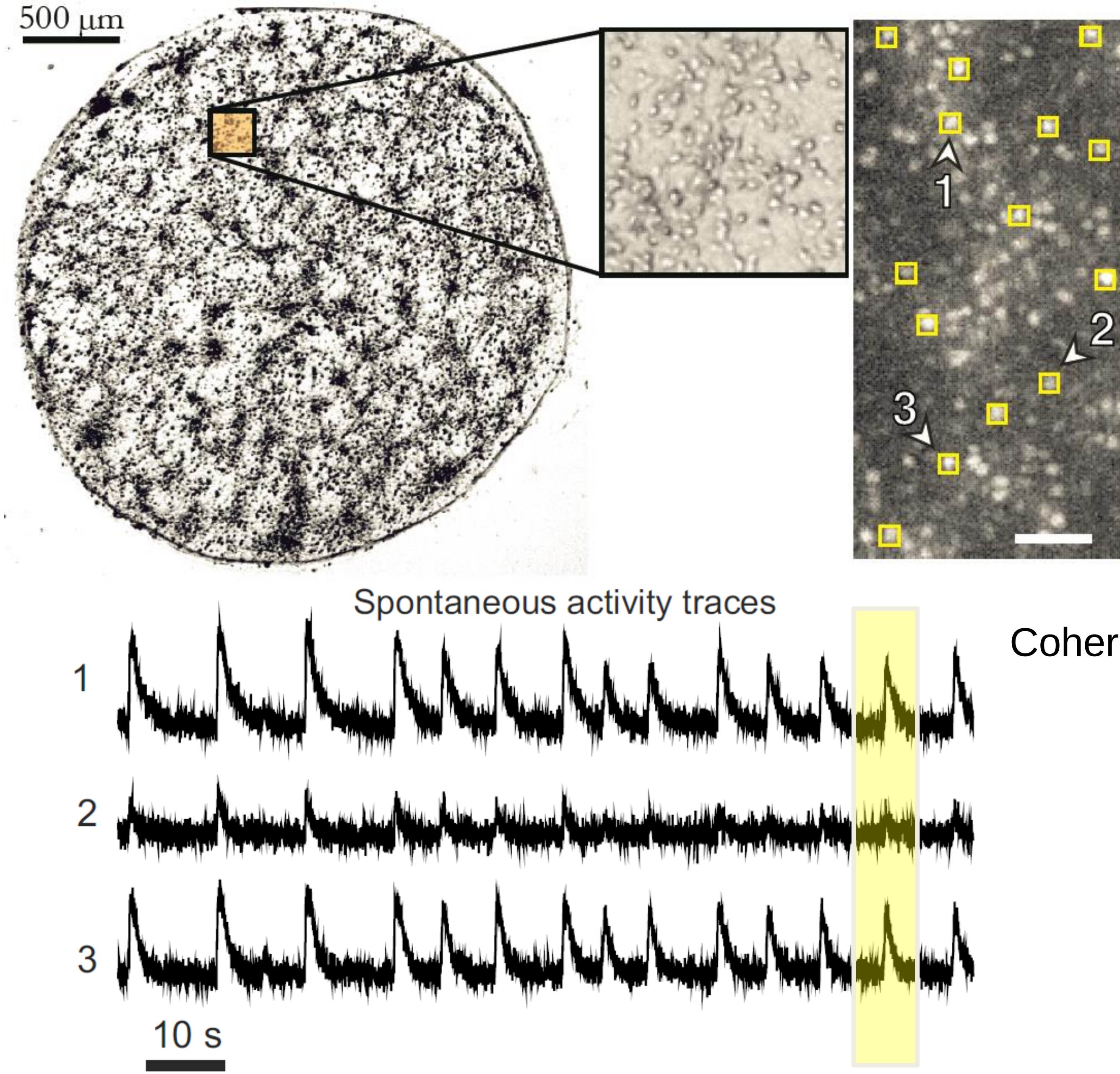






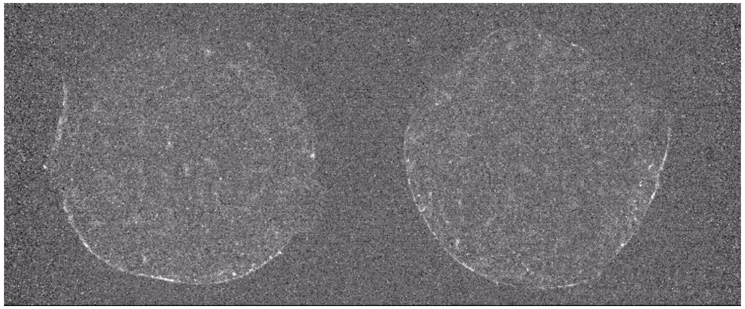
2 cultures, 3 mm diameter each

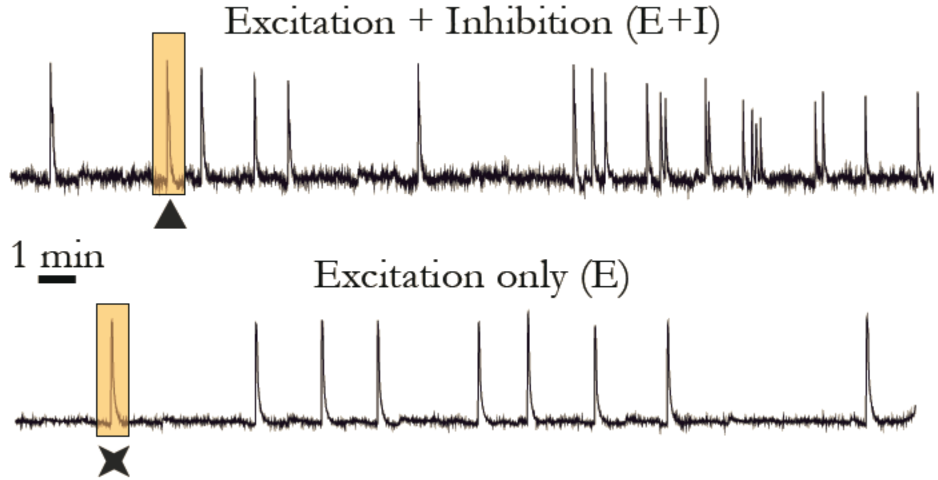




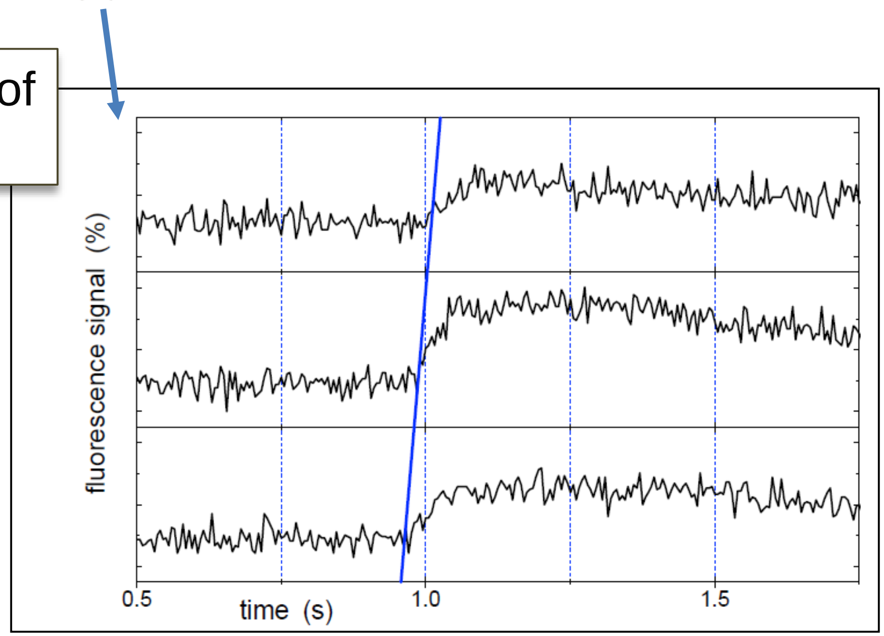
Coherent activity

7. Experiments in homogeneous cultures

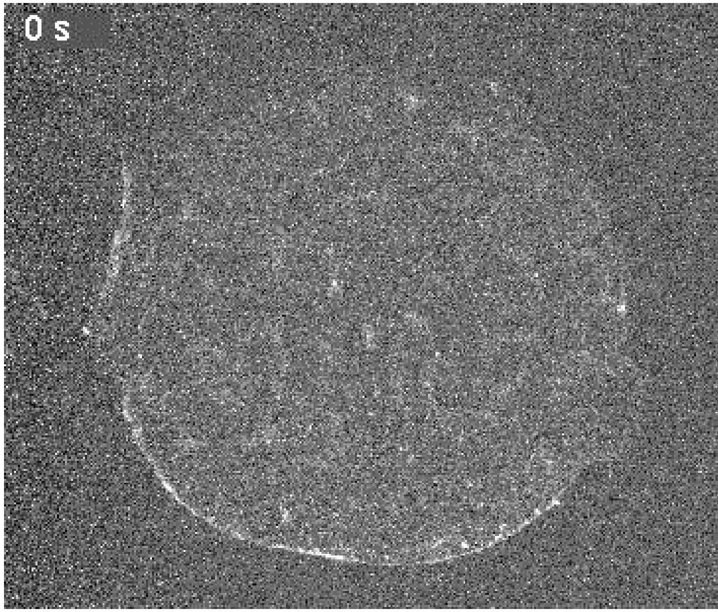


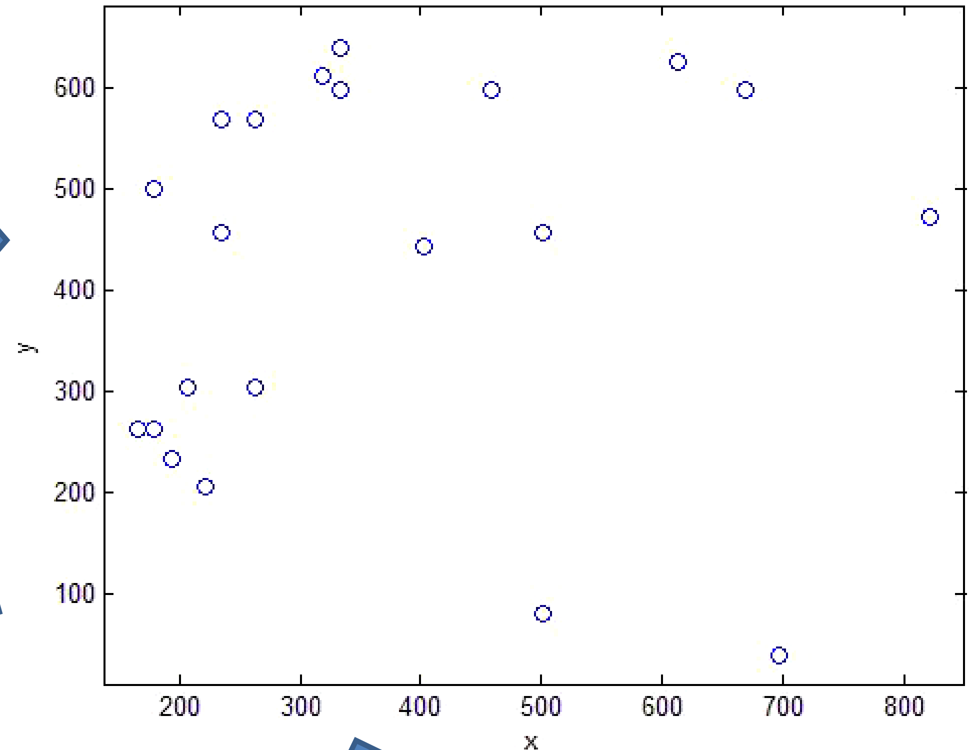


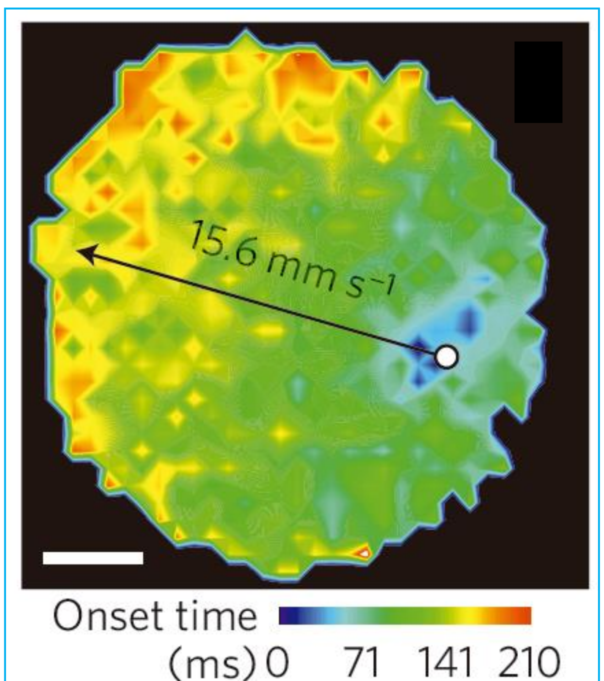
Computation of time delays

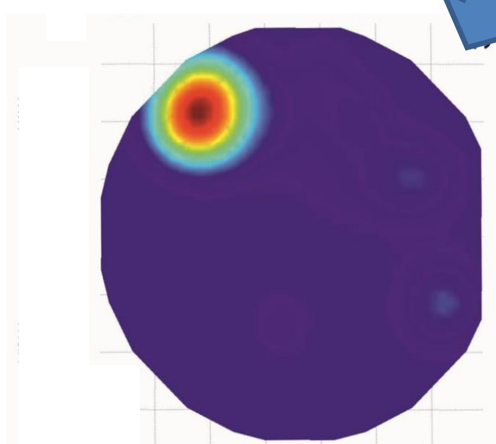


Propagating pulses









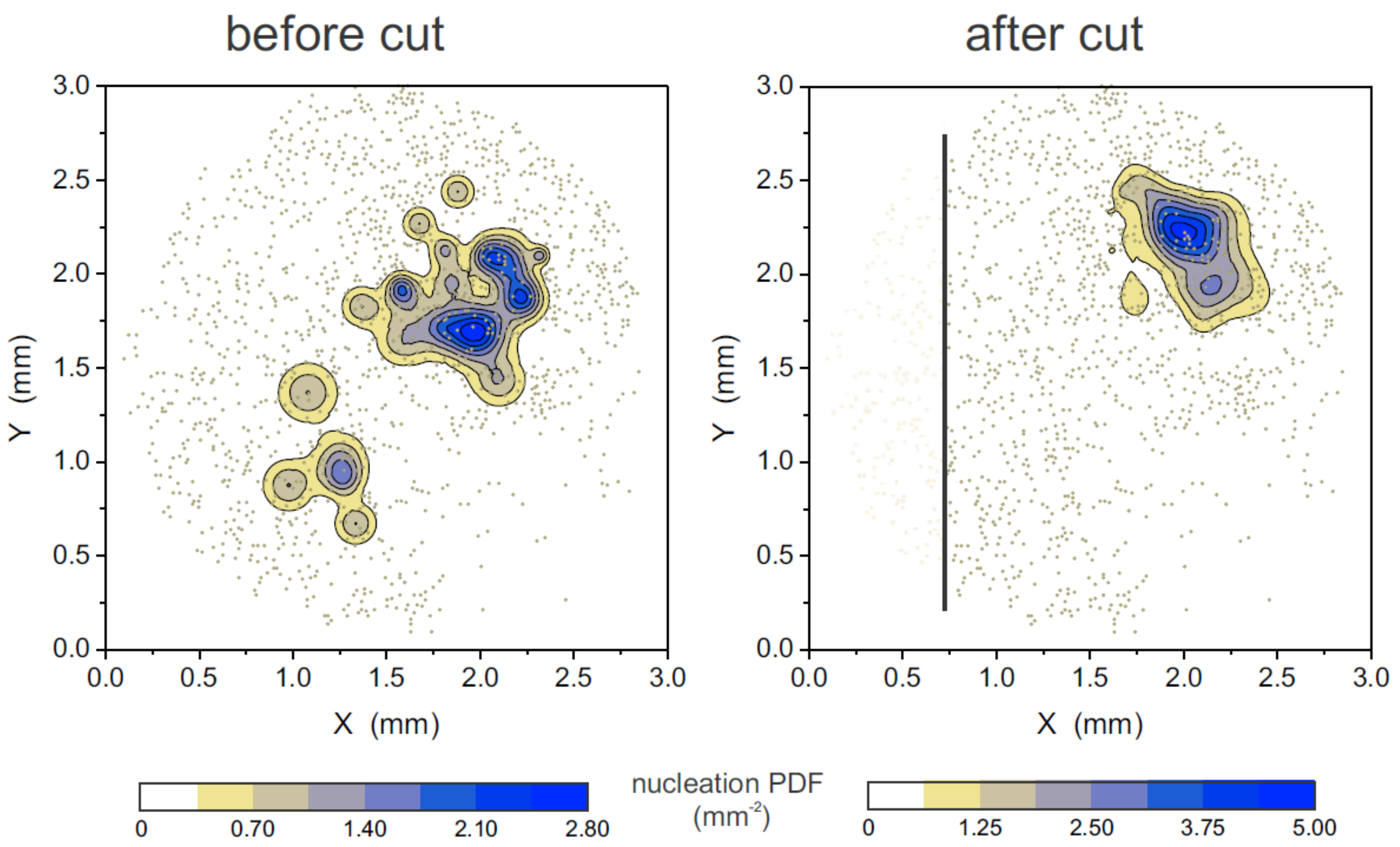
Why here?
What's more important?
- Topology?
- Neuronal dynamics?

7. Experiments in homogeneous cultures

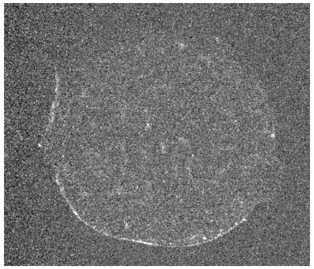
Manipulating cultures to test dynamical changes.

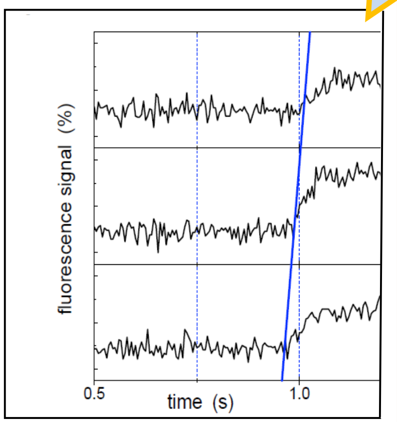
Example: **cutting** experiment.

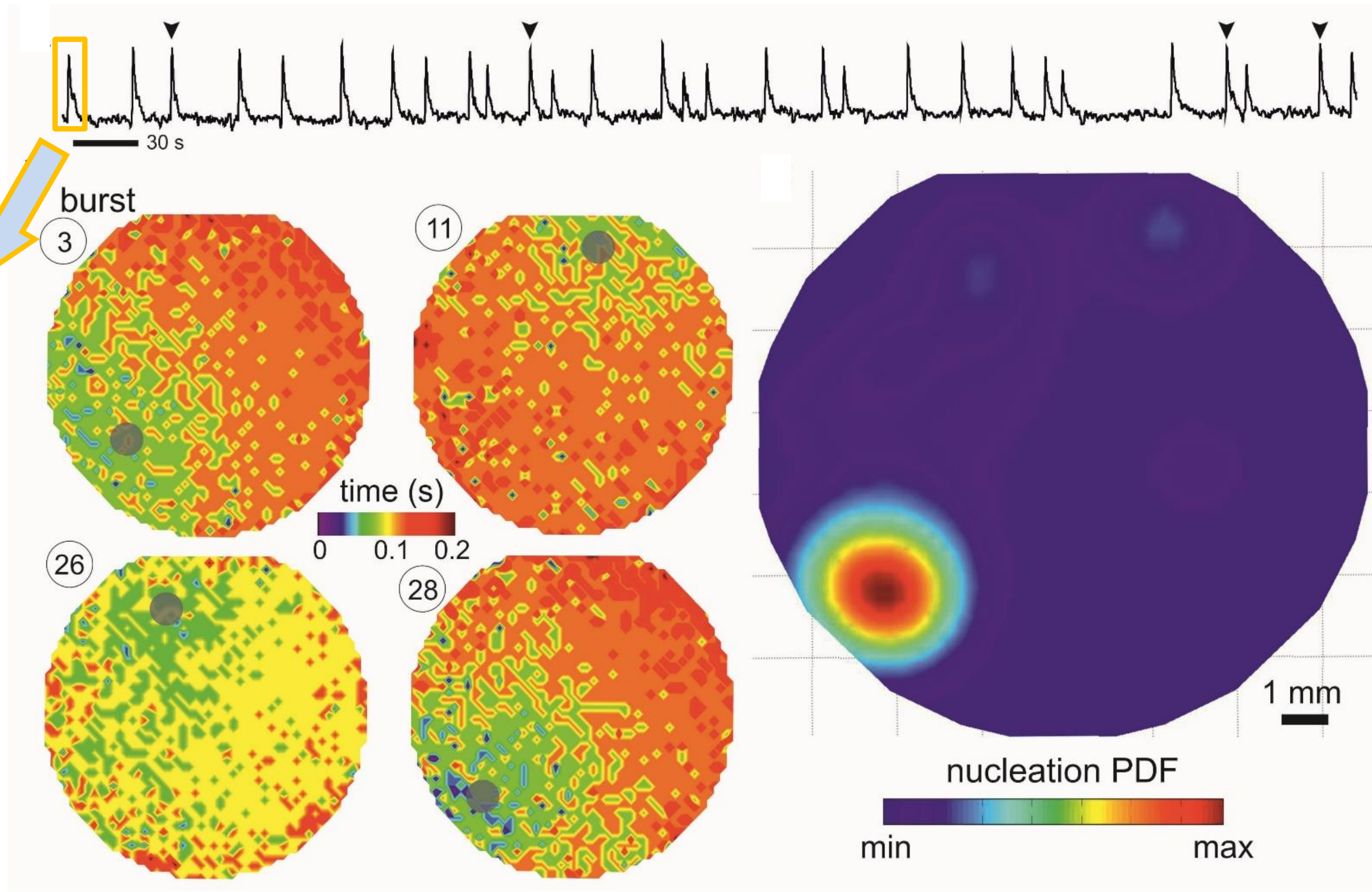
J.G. Orlandi et al, Nature Phys. (2013)



7. Experiments in homogeneous cultures







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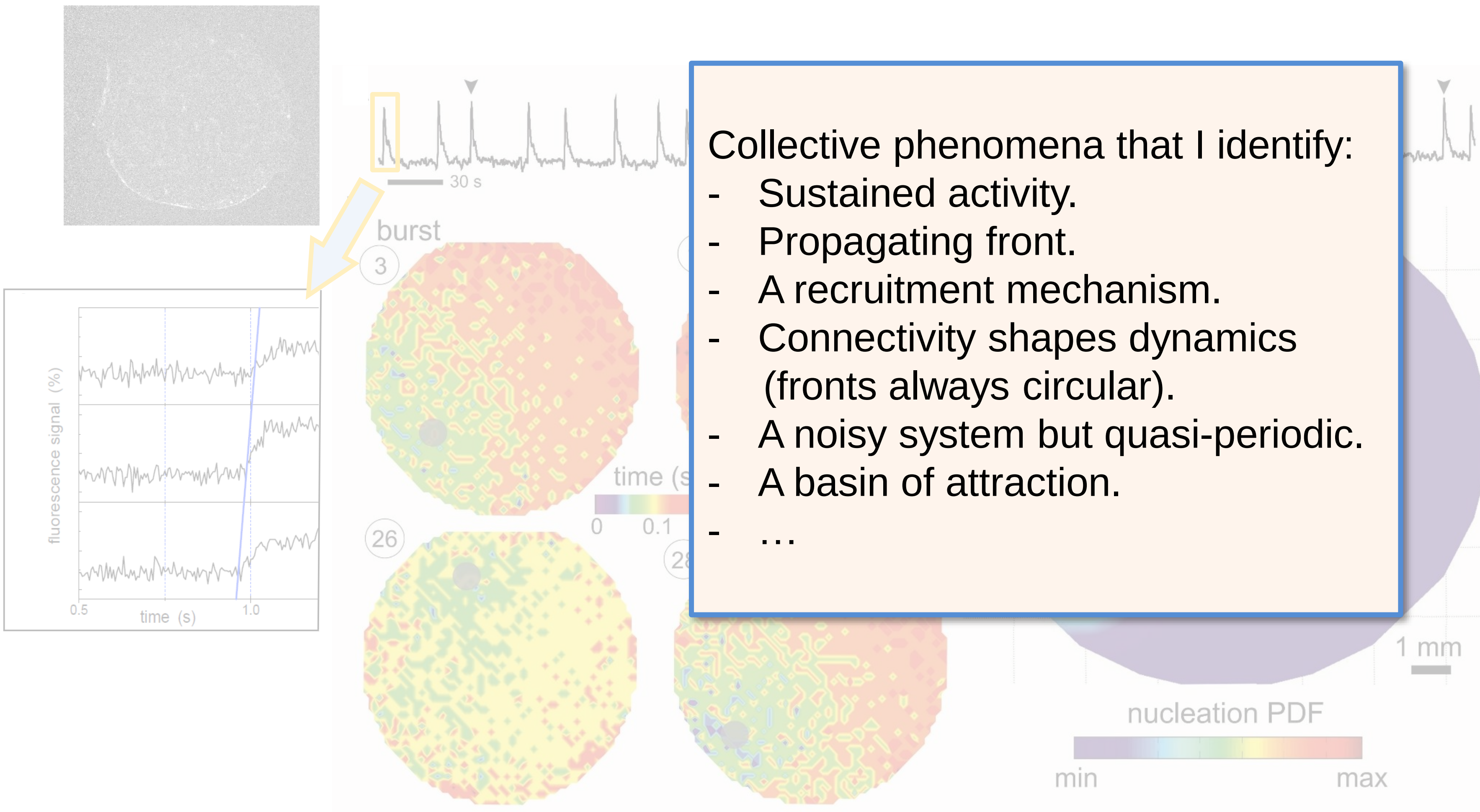
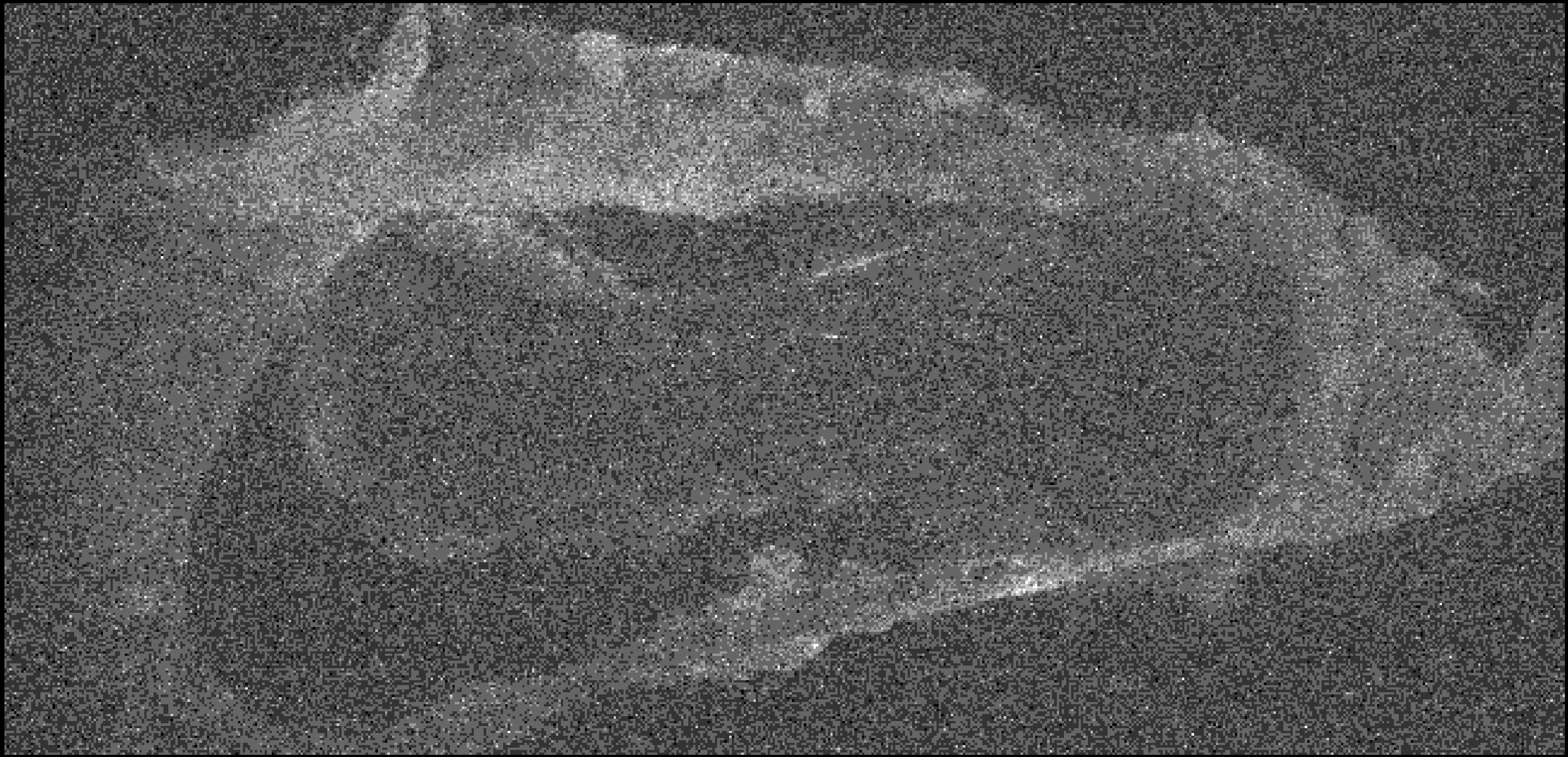


Collective phenomena that I identify:

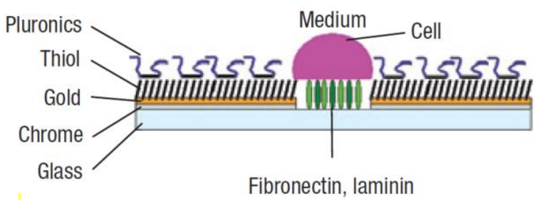
- Sustained activity.
- Propagating front.
- A recruitment mechanism.
- Connectivity shapes dynamics (fronts always circular).
- A noisy system but quasi-periodic.
- A basin of attraction.
- …

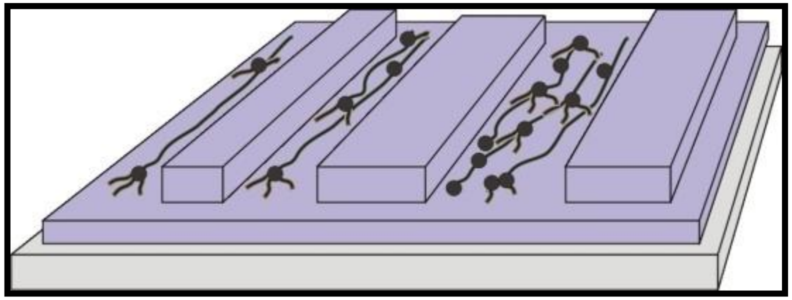
Quasi one-dimensional culture



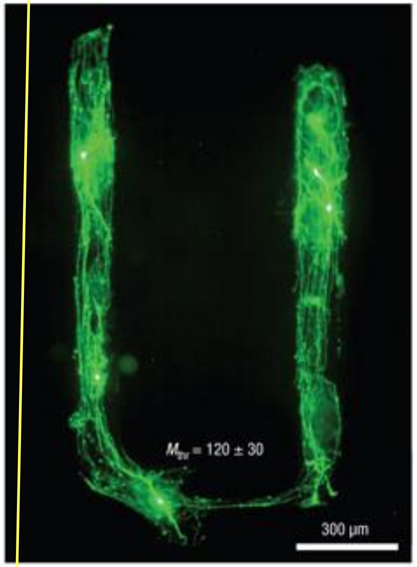
8. Experiments in patterned cultures

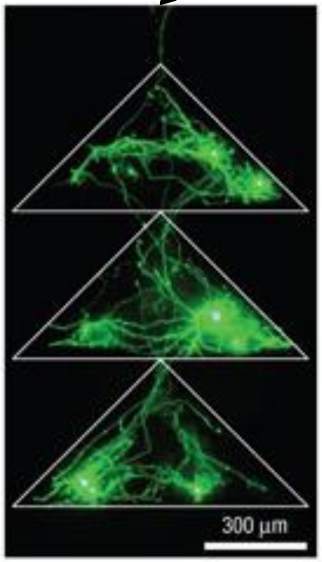
Chemical patterning

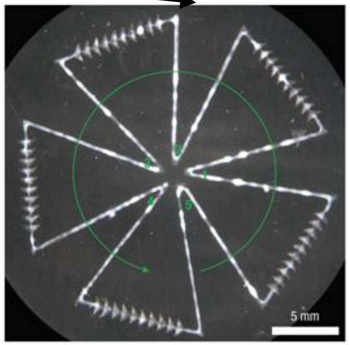


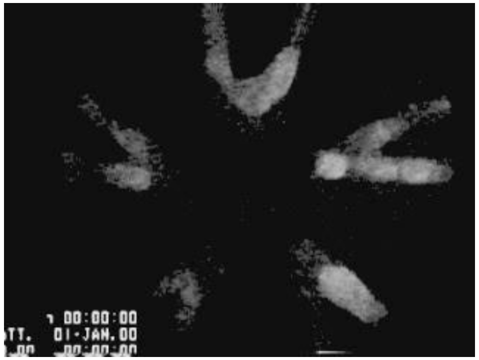


Topographical patterning

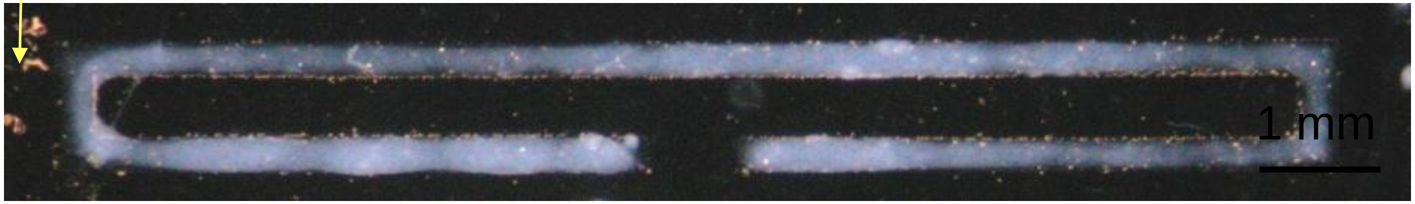




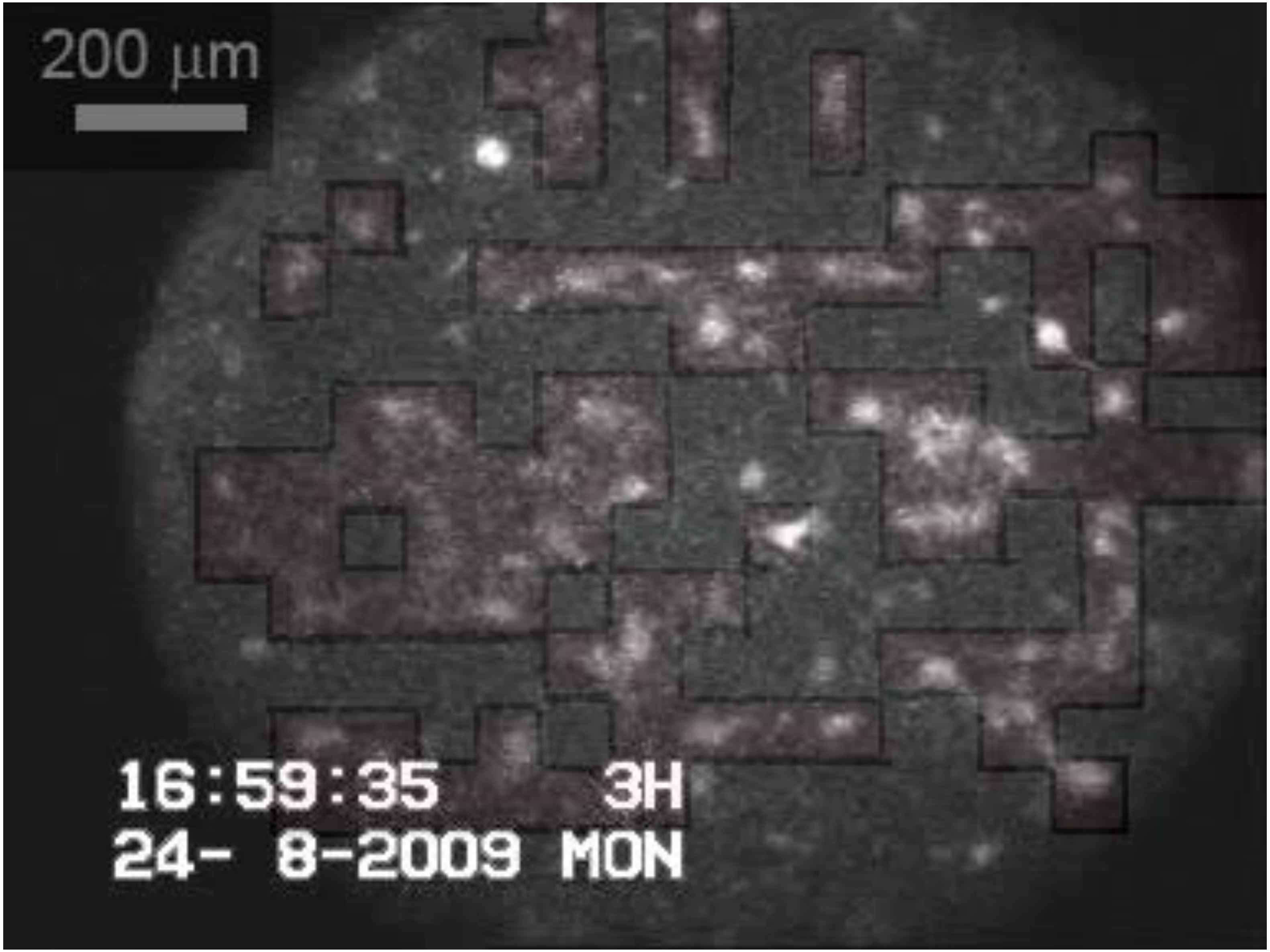




Feinerman et al, Nature Phys. (2008)

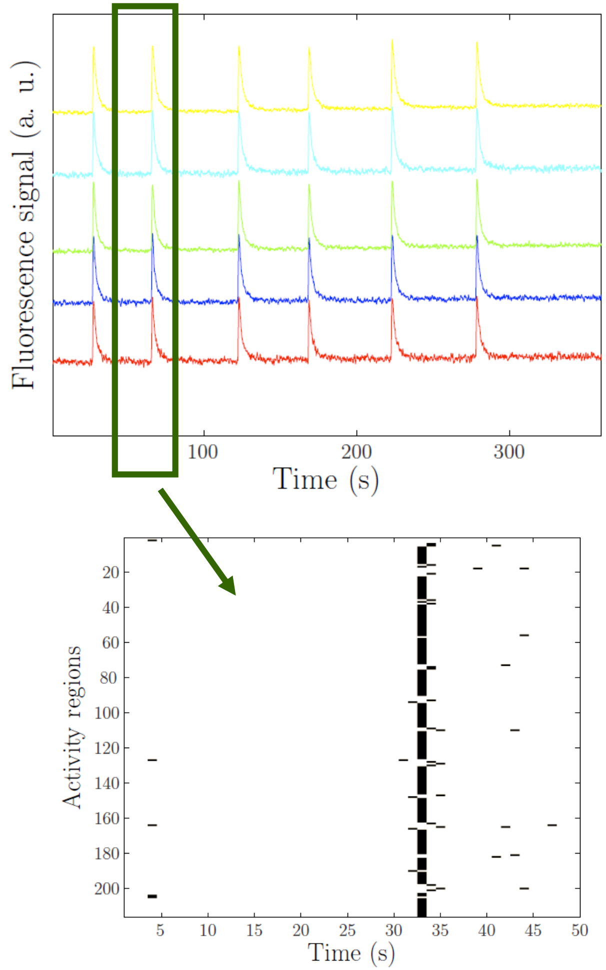


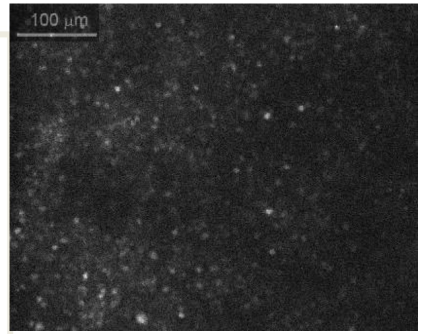
8. Experiments in patterned cultures

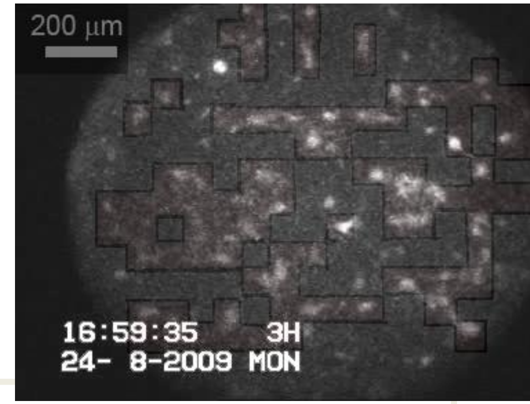


8. Experiments in patterned cultures

Homogeneous

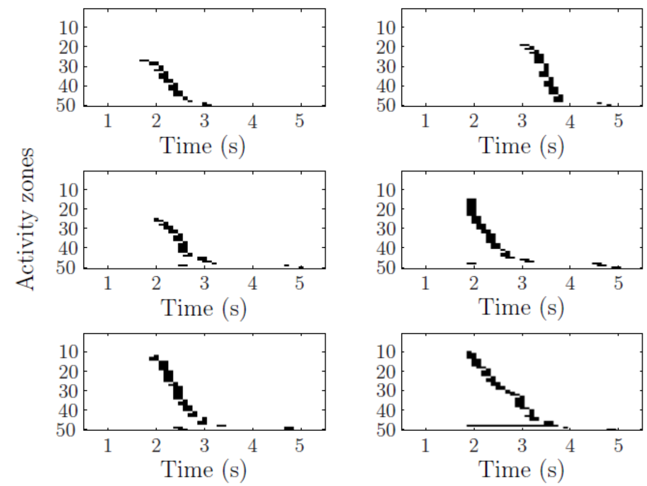






"Strongly" synchronous.

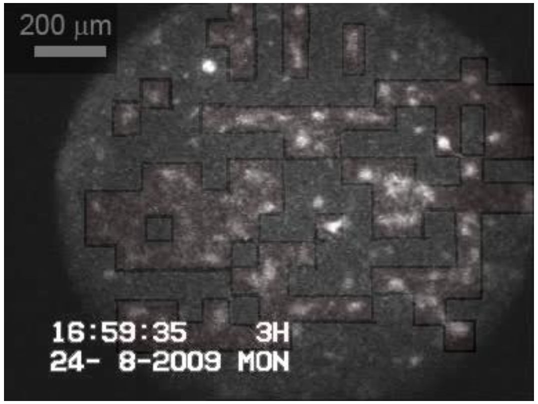
Patterned



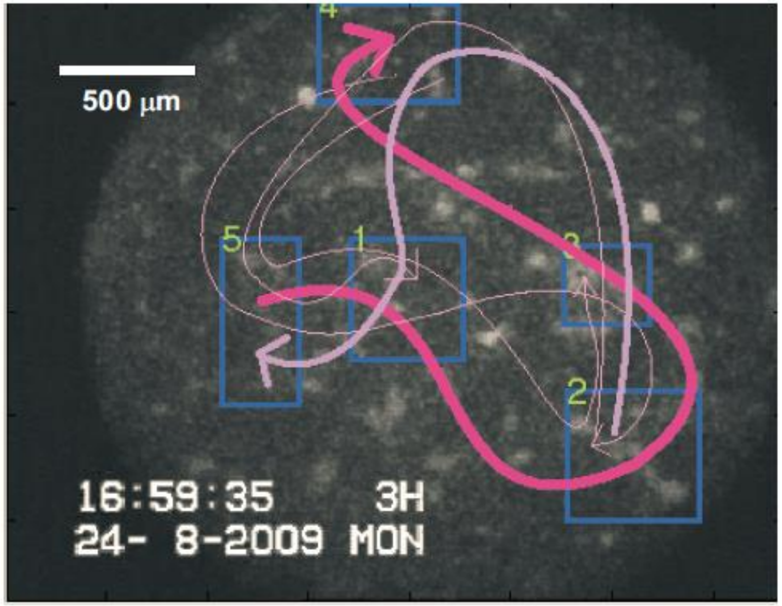
"Weakly" synchronous.

Richer repertoire of activity!

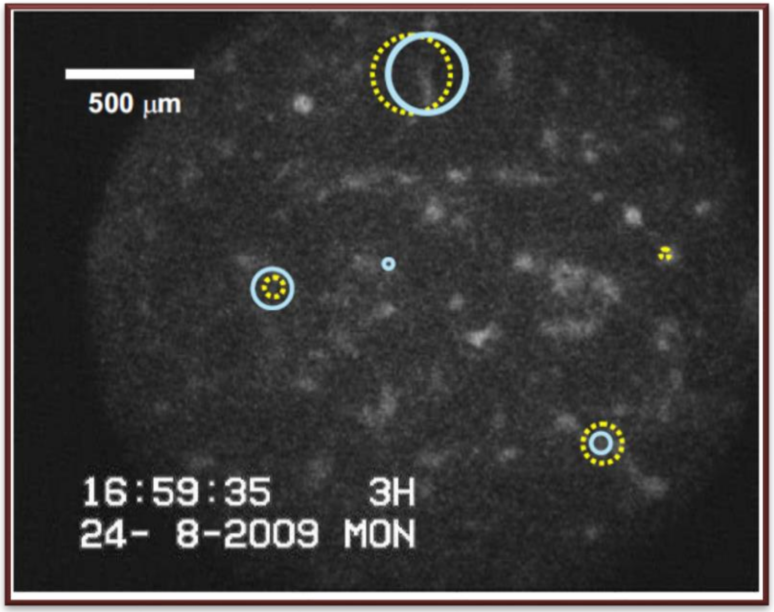
8. Experiments in patterned cultures



Complex propagation paths:



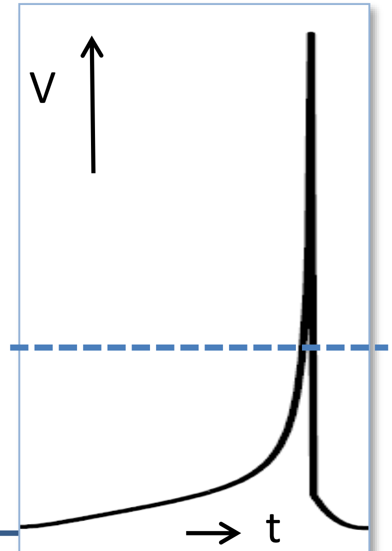
Bursts initiation zones:



Very different collective behavior!

9. Modelling ingredients

▶ ■ Dynamics



v = membrane potential
u = recovery variable

soma

$$C\dot{v} = k(v - v_r)(v - v_t) - u + I$$
$$\dot{u} = a(b(v - v_r) - u)$$

$$\text{if } v \geq v_p \Rightarrow$$
$$v = c,\ u = u + d$$

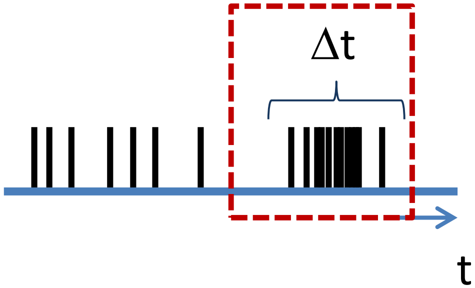
synapse

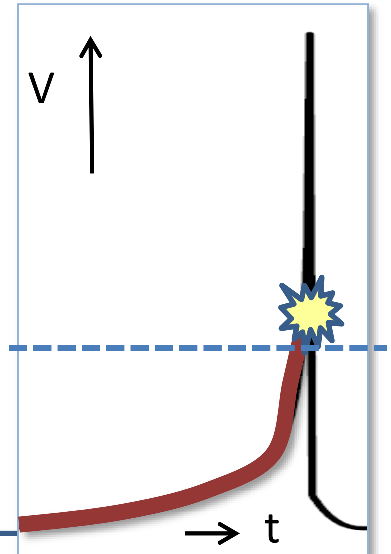
$$I_s = gD(t_0)\exp\left(-\frac{t - t_0}{\tau_s}\right)\theta(t - t_0)$$

$$\dot{D} = \frac{1}{\tau_D}(1 - D) \qquad \text{at } t_m \Rightarrow D = \beta D$$

9. Modelling ingredients

▶ ■ Dynamics





QUORUM:
~ 15 inputs in Δt for firing

soma

$$C\dot{v} = k(v - v_r)(v - v_t) - u + I$$
$$\dot{u} = a(b(v - v_r) - u)$$

$$\text{if } v \geq v_p \Rightarrow$$
$$v = c, \; u = u + d$$

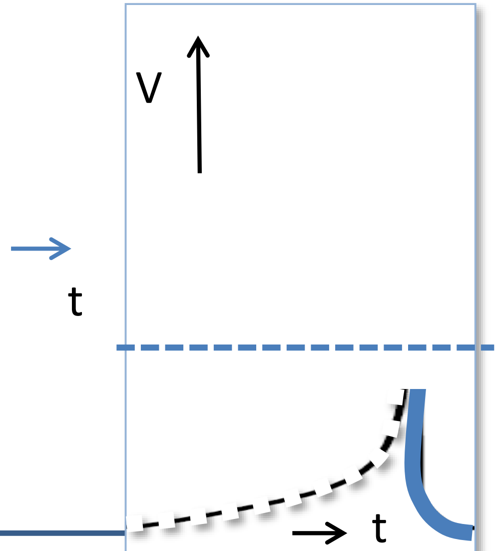
synapse

$$I_s = gD(t_0)\exp\left(-\frac{t - t_0}{\tau_s}\right)\theta(t - t_0)$$

$$\dot{D} = \frac{1}{\tau_D}(1 - D) \qquad \text{at } t_m \Rightarrow D = \beta D$$

9. Modelling ingredients

■ Dynamics



soma

$$C\dot{v} = k(v - v_r)(v - v_t) - u + I$$
$$\dot{u} = a(b(v - v_r) - u)$$

$$\text{if } v \geq v_p \Rightarrow$$
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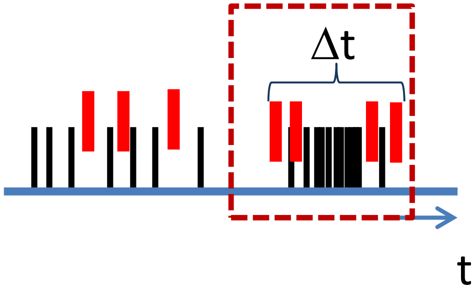
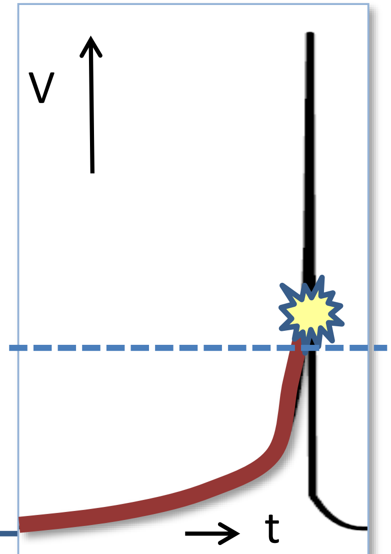
$$\dot{D} = \frac{1}{\tau_D}(1 - D) \qquad \text{at } t_m \Rightarrow D = \beta D$$

9. Modelling ingredients

- Dynamics
- Noise





QUORUM may be effectively reduced, and may trigger activity in silent neurons.

~ 15 inputs for firing { other neurons; **noise** }

soma

$$
\begin{aligned}
C\dot{v} &= k(v - v_r)(v - v_t) - u + I + \xi(t) \\
\dot{u} &= a(b(v - v_r) - u)
\end{aligned}
$$

$$
\text{if } v \geq v_p \Rightarrow \\
v = c,\ u = u + d
$$

synapse

$$
I_s = gD(t_0)\exp\left(-\frac{t - t_0}{\tau_s}\right)\theta(t - t_0)
$$

$$
\dot{D} = \frac{1}{\tau_D}(1 - D) \qquad \text{at } t_m \Rightarrow D = \beta D
$$

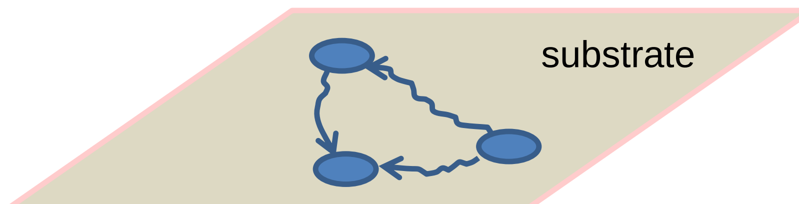
9. Modelling ingredients

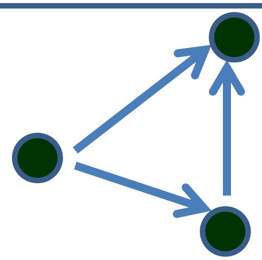
- Dynamics
- Noise
- Network

- Spatially (2D) embedded network:
  (arbitrary connectivity **forbidden**)
  - Long range connections rare.
  - Metric correlations!
  - High clustering at short distance.
  - Loops ⇒ amplification mechanisms.

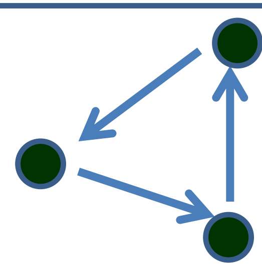
Connection probability decays with distance r:

$$P(r) \sim r^{-\delta}$$

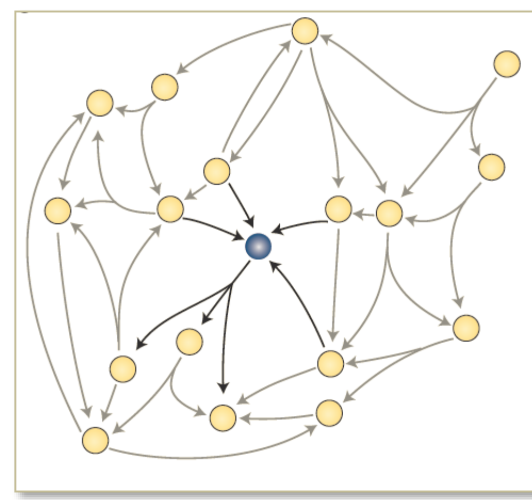




Feed forward loop
(**facilitates propagation**)



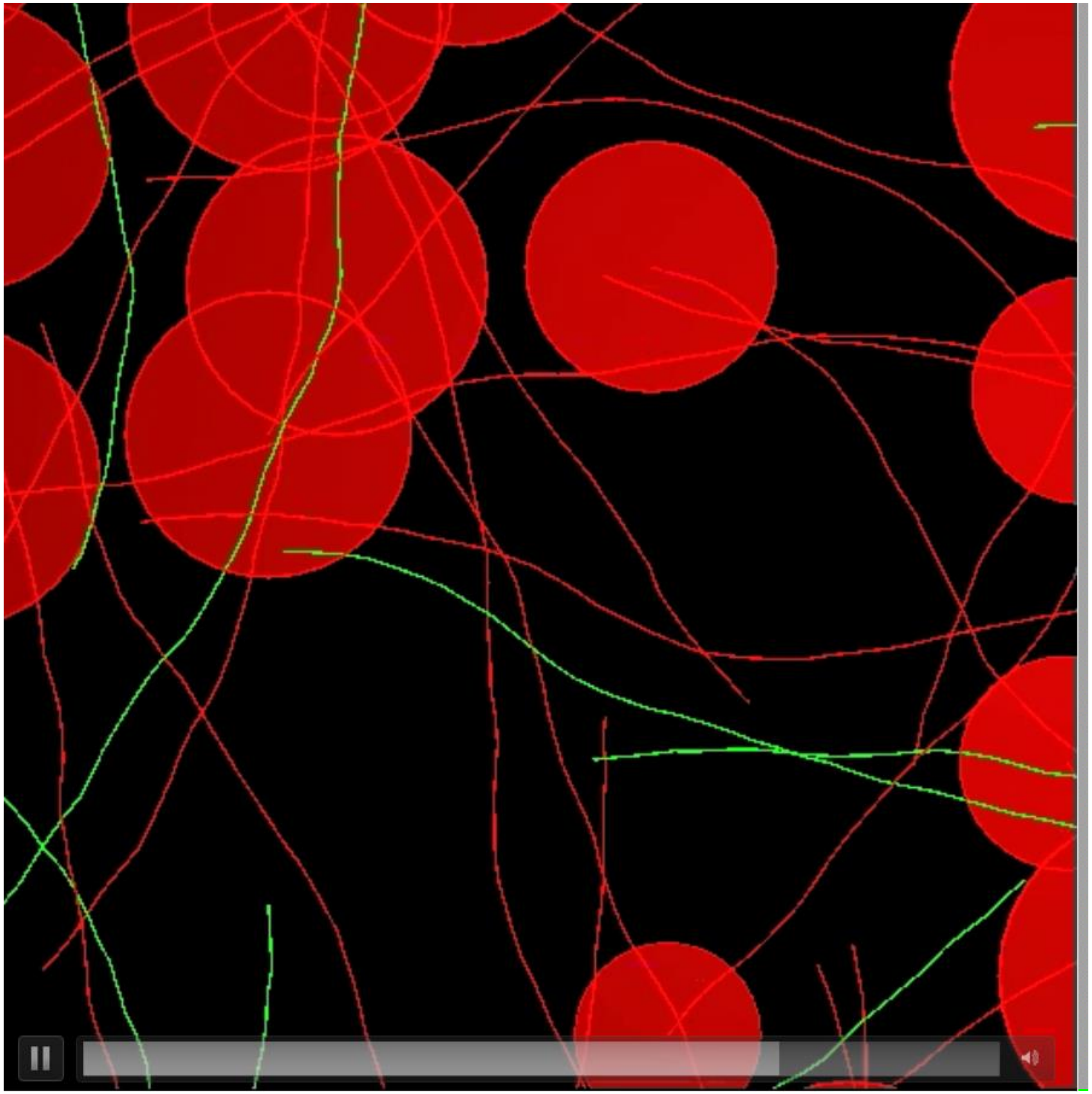
Feed backward loop
(retains propagation)



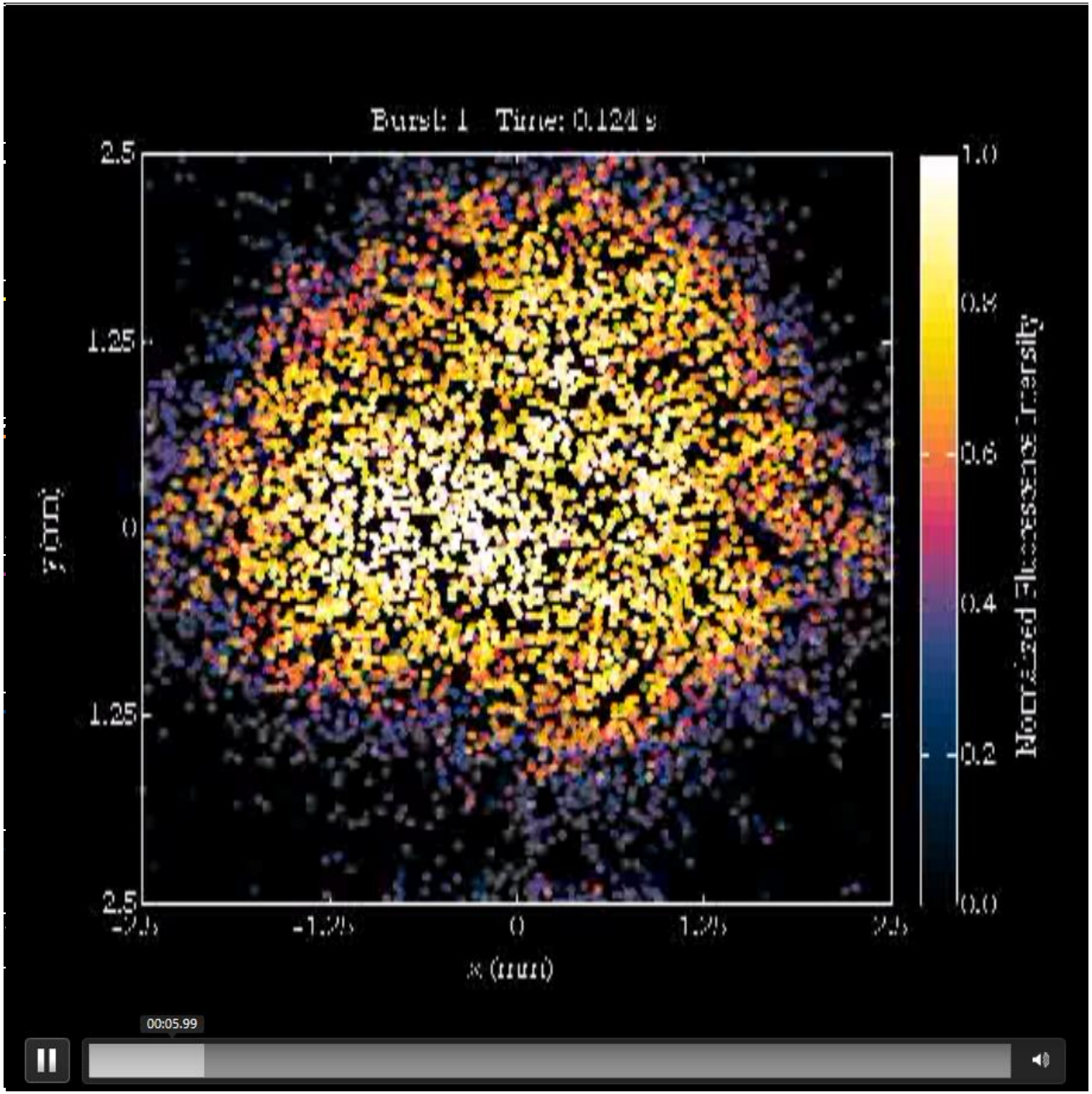
- Connections are **directed** and **weighted**.

- Excitatory and inhibitory neurons.

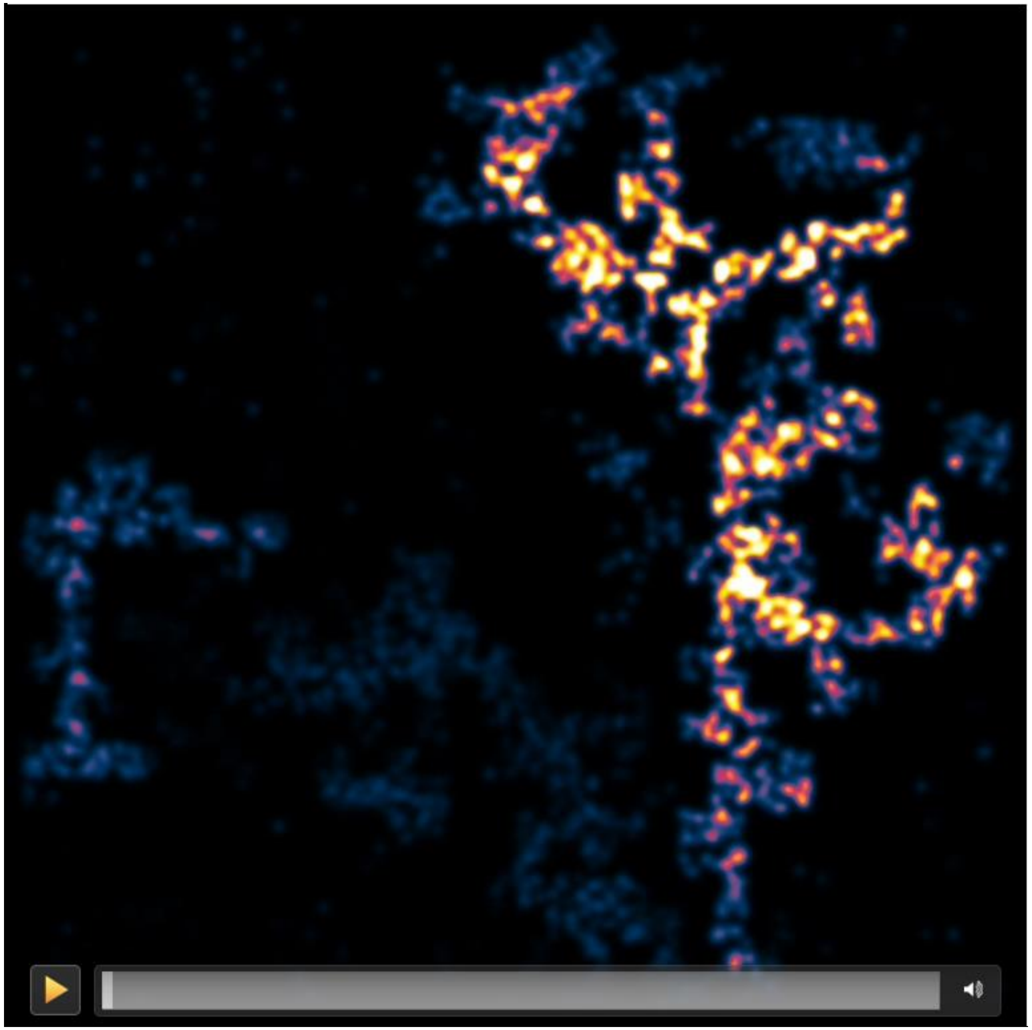
Example of network construction

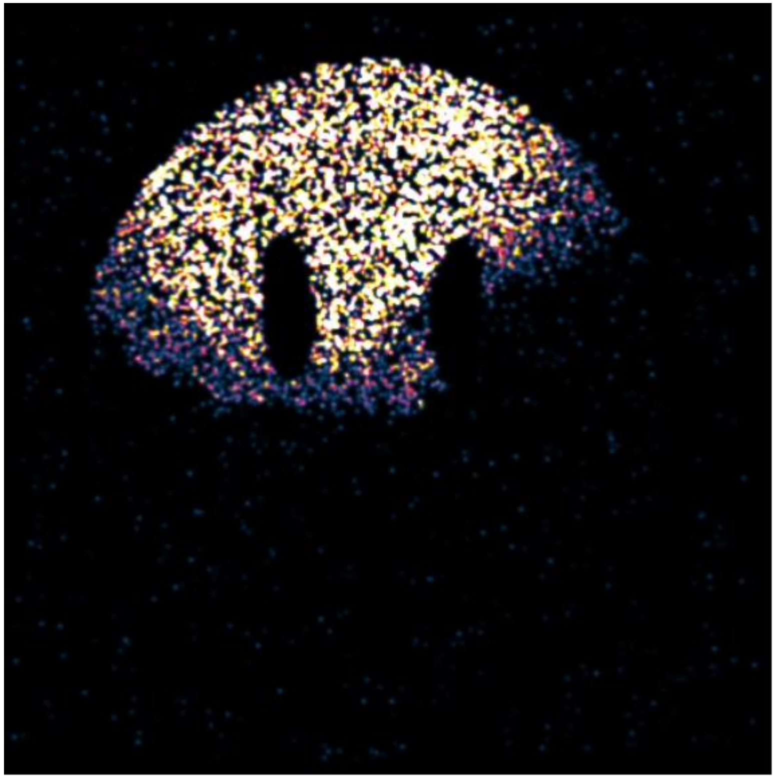


Network dynamics

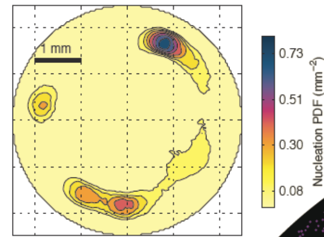


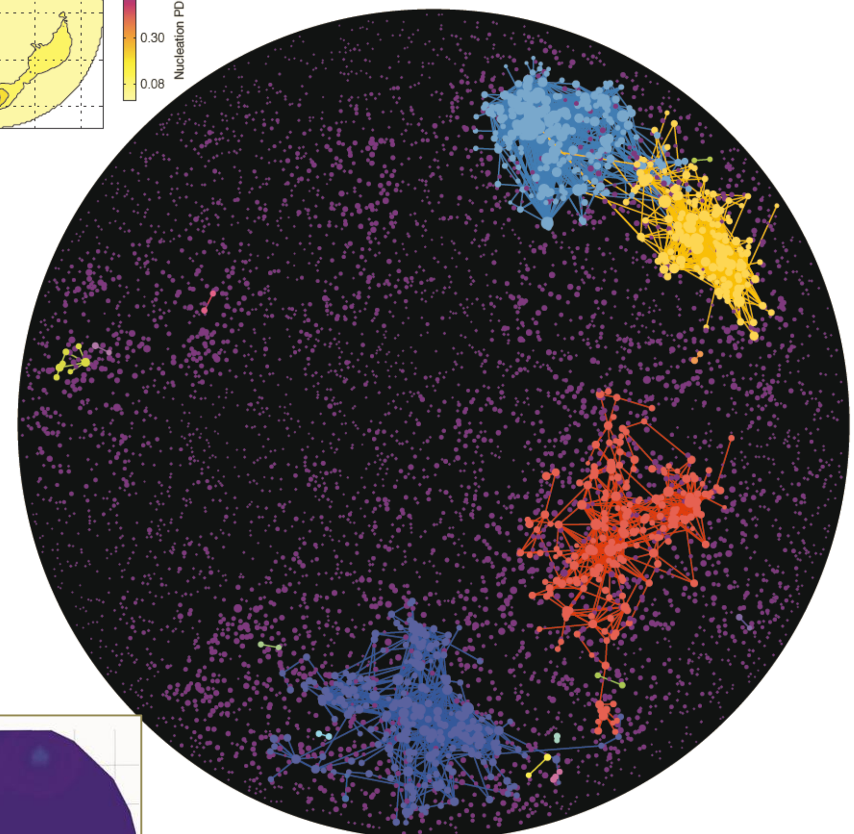
Incorporation of spatial features



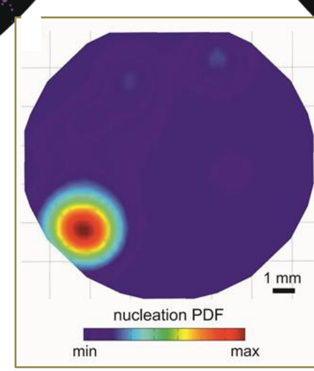


The model naturally captures the **initiation zones**





Effective network of **background** activity



Effective network of **ignition** activity

End of lecture 8

TAKE HOME MESSAGE:

- Neurons are nonlinear elements with nonlinear coupling.
- Neuronal cultures a versatile experimental platform to develop models and explore actual biological complexity.
- Noise is a fundamental player in neuronal networks.
- Realistic connectivity is crucial to reproduce biological results.

Questions and discussion aspects:

- The nonlinear paradigm: coherence, reproducible behavior
- Can we think of a continuum model?
- What ingredients are necessary for a mean-field description?
- What is more important: dynamics or connectivity layout?

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