Systems Biology: A Personal View XXX. Oscillations, Waves and Synchronization in Uterine Tissue

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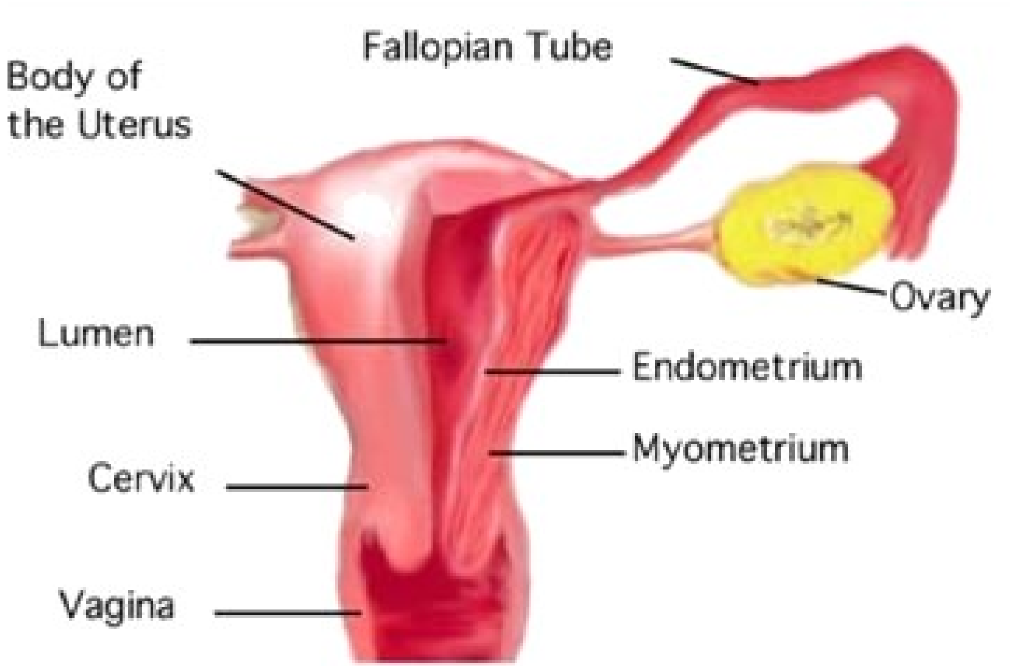
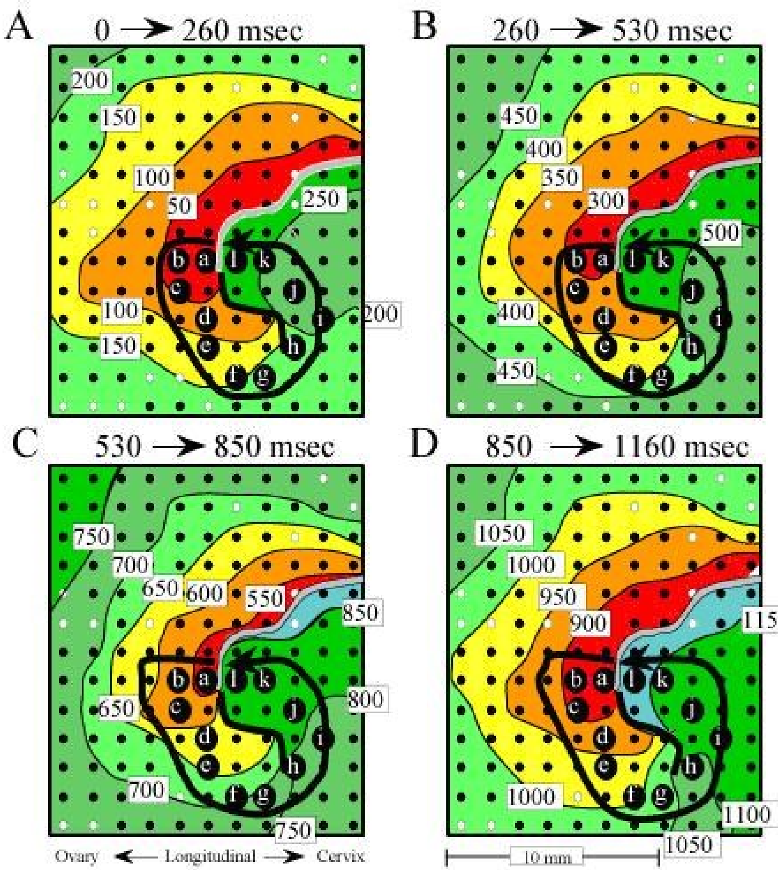
The uterus



Spiral waves in pregnant uterine tissue



Lammers Lab

Bulk of the uterus, myometrium, comprises primarily of excitable cells: the uterine myocytes

Excitation can travel through tissue via gap junctions; spiral waves have been observed in vitro

The Uterine Puzzle

How do coherent oscillations occur during pregnancy ?

• Usually the uterus does **not** show spontaneous periodic activity

• But during late stages of pregnancy, **sustained rhythmic excitations** – increasing in strength & duration over time

• **Global synchronization** leading to coherent contractions just before childbirth – results in ejection of the fetus

Puzzle: unlike the heart, there is no evidence of any pacemaker region in the uterus, nor do isolated cells exhibit oscillation

Solving the Uterine Puzzle

Self-organized emergence of coherence through interactions via coupling among neighboring elements

Understanding the mechanism of synchronization onset is important as premature initiation of rhythmic activity causing pre-term birth occurs in 10% of all pregnancies – responsible for > 1/3 of all infant deaths (USA)

Possible hint to solution : Throughout pregnancy, the number of gap junctions between cells increase significantly

- Can increased coupling among neighbors result in self-organized coherent activity ?

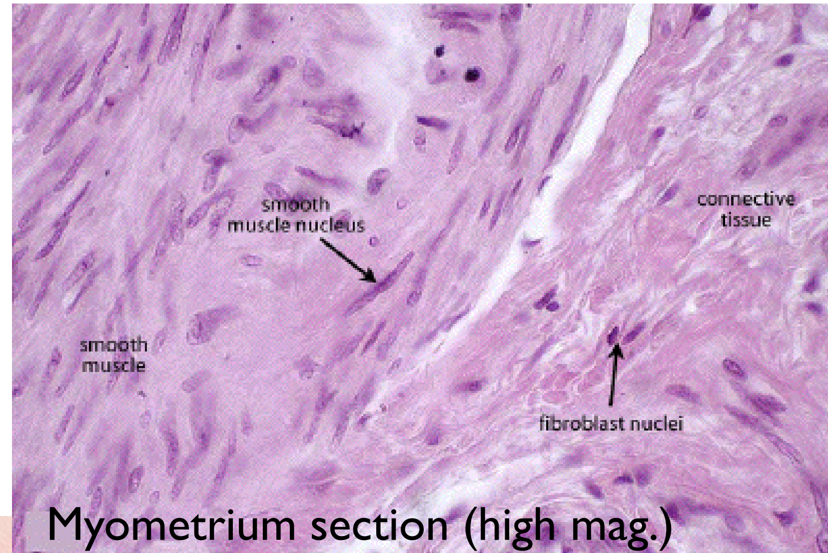
Uterine oscillations: a collective phenomenon?

The uterine tissue has a heterogeneous composition: electrically excitable smooth muscle cells (uterine myocytes) + electrically passive cells (fibroblasts and ICLC/telocytes)

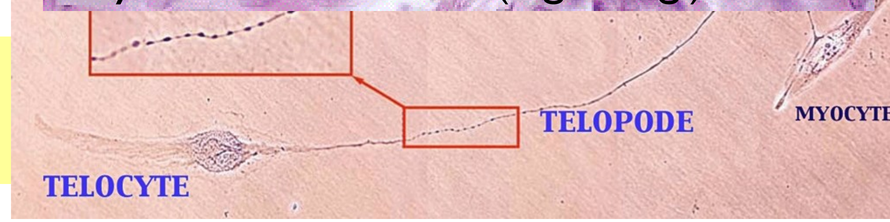
Neither can oscillate !

Shmygol et al Annals NYAS (2007): exptly verified isolated uterine cells do <u>not</u> oscillate

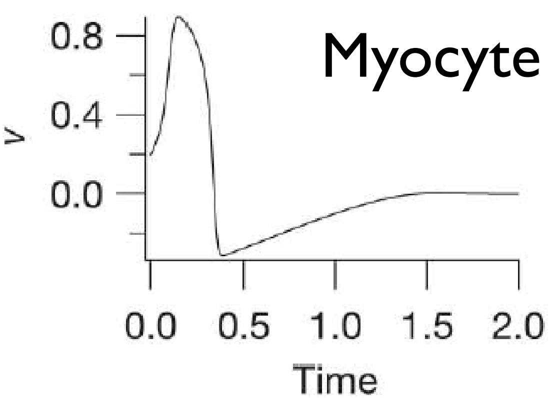
http://www.dartmouth.edu/~anatomy/Histo/muscle/muscle/DMS080/



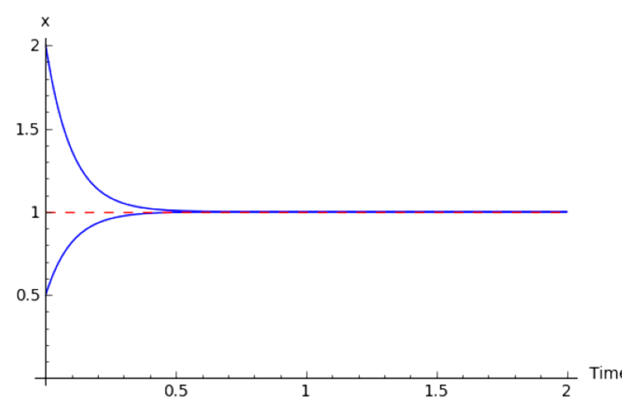
Myometrium section (high mag.)



Wikipedia



Myocyte (excitable cell)



ive cell)

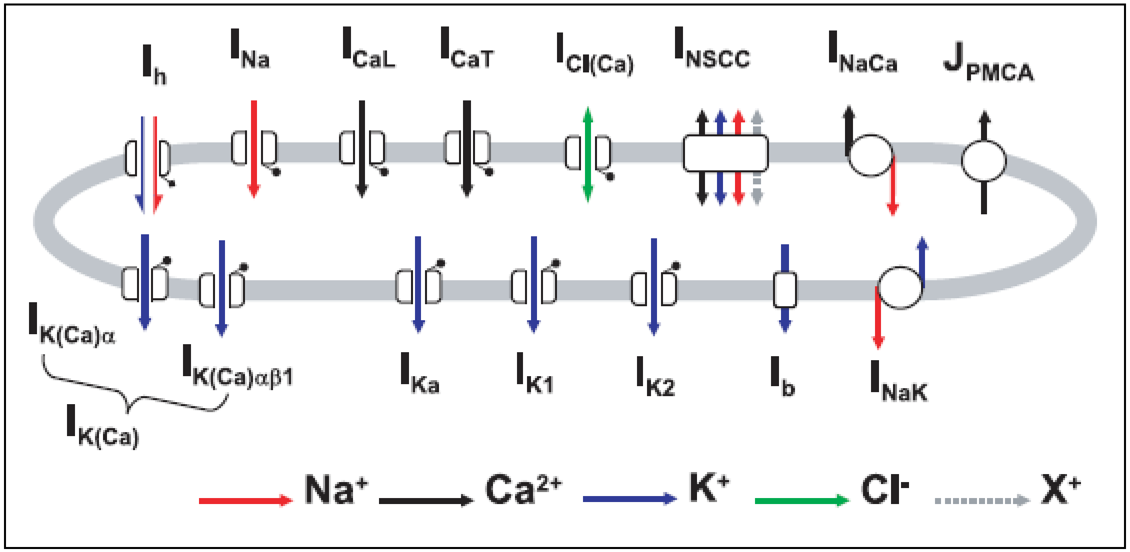
Modeling the myocytes in the uterus

OPEN ACCESS Freely available online PLoS one

A Computational Model of the Ionic Currents, Ca^{2+} Dynamics and Action Potentials Underlying Contraction of Isolated Uterine Smooth Muscle

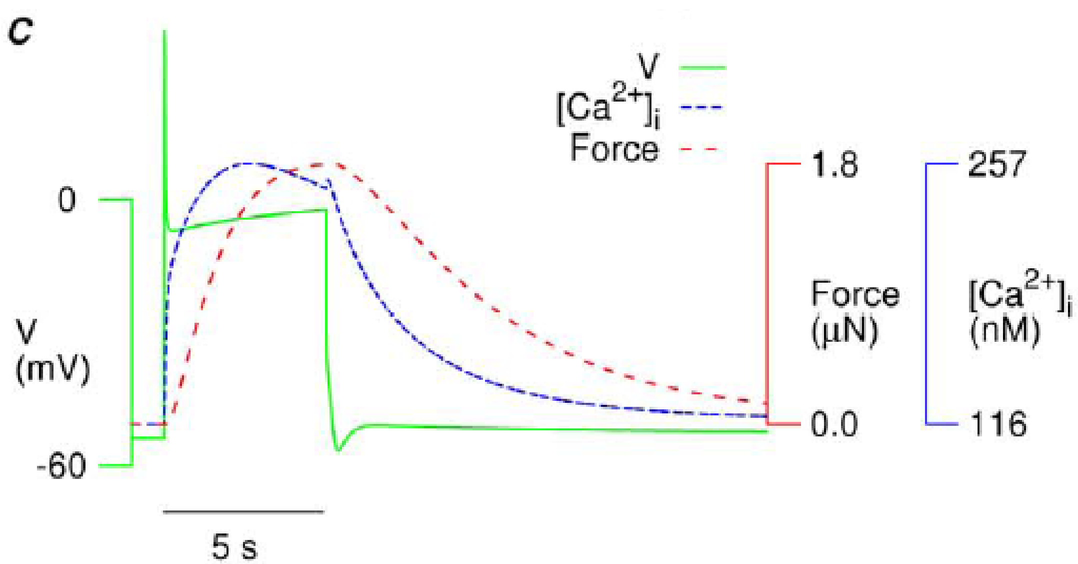
Wing-Chiu Tong[1,2], Cecilia Y. Choi[3], Sanjay Karche[3], Arun V. Holden[4], Henggui Zhang[3]*, Michael J. Taggart[1,2]*

PLoS ONE 6(4): e18685. (2011)

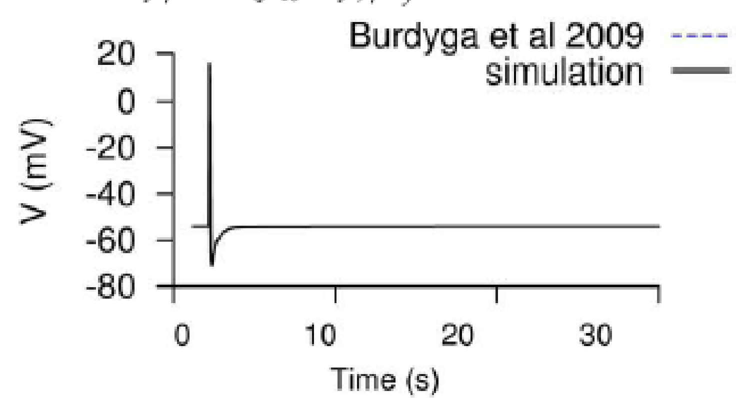


$$dV/dt = -\sum I_{tot}/C_m$$
$$d[Ca^{2+}]_i/dt = -\sum J$$
$$dForce/dt = f([Ca^{2+}]_i)$$

I_{tot} comprises 14 different membrane currents that are modeled using H-H formalism



$$I = \bar{g}y(V - E_{rev})$$
$$E_{rev} = (RT/F)\ln([X]_o/[X]_i)$$
$$dy/dt = (y_\infty - y)/\tau_y$$



Solving the Uterine Puzzle:
The first hint

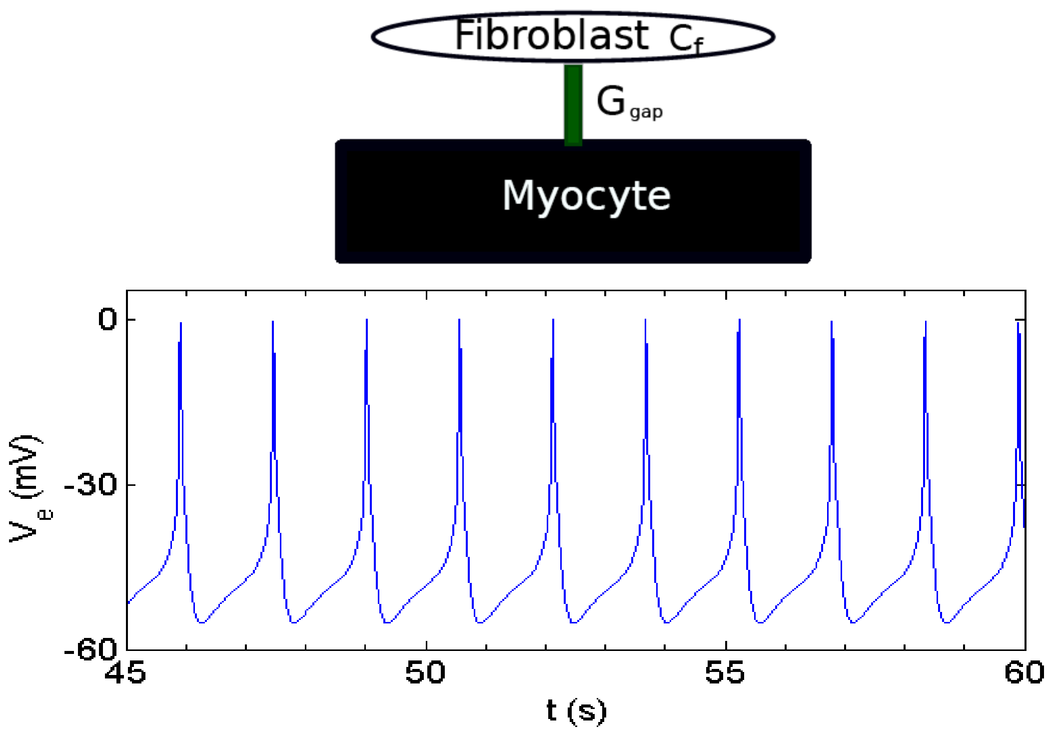
PHYSICAL REVIEW E 74, 011908 (2006)

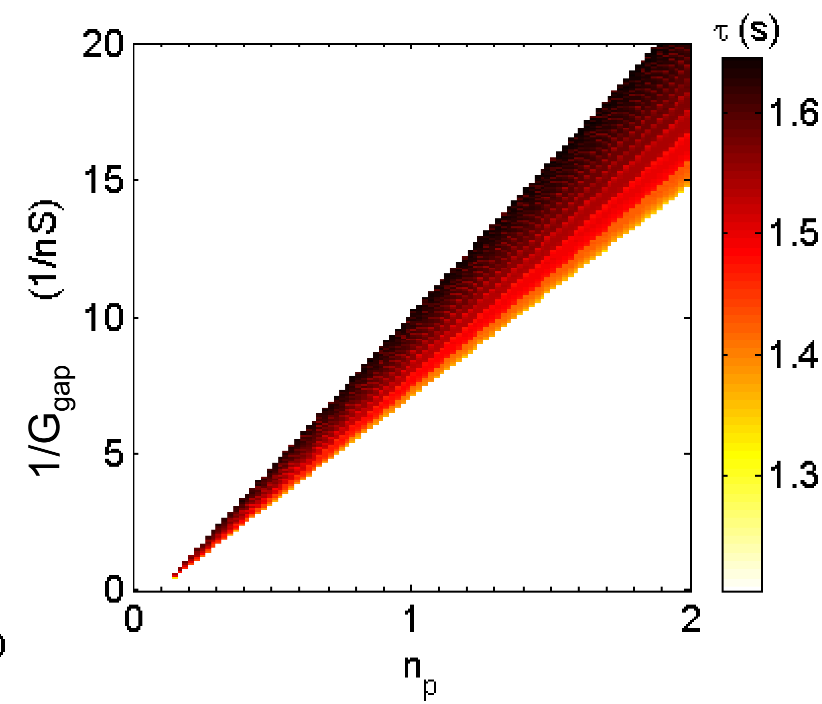
Pacemaker activity resulting from the coupling with nonexcitable cells

Vincent Jacquemet*

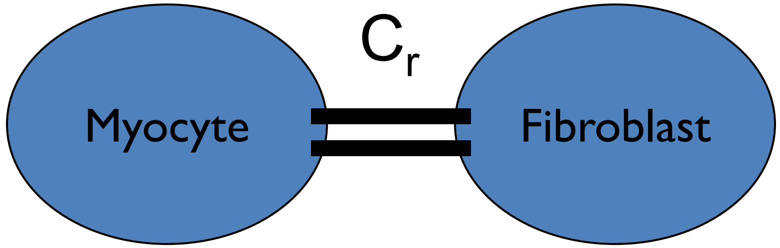
Excitable cell + Passive cell → Oscillations

Increased gap jn coupling between heterogeneous cell types lead to spontaneous periodic activity





Emergent oscillation via coupling in simpler models



Myocyte (FHN model):

$$C_m \dot{V}_e = -I_{ion}(V_e, g_i)$$
$$= AV_e(V_e - \alpha)(1 - V_e) - g,$$

$$\dot{g} = \epsilon(V_e - g),$$

Fibroblast (Kohl et al):

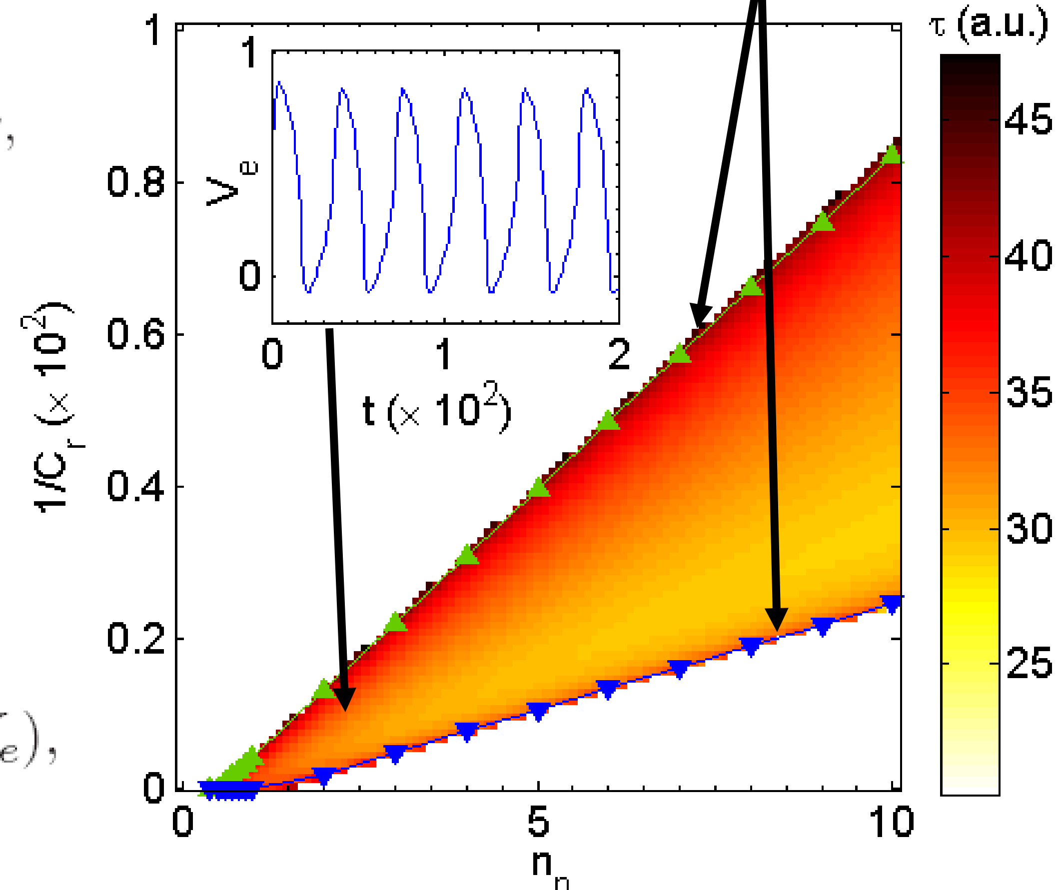
$$\dot{V}_p = F_p(V_p) = K(V_p^R - V_p)$$

A myocyte coupled to n_p fibroblasts :

$$\dot{V}_e = F_e(V_e, g) + n_p\, C_r(V_p - V_e),$$
$$\dot{V}_p = F_p(V_p) - C_r(V_p - V_e),$$

Linear stability analysis conditions for stability of fixed point solution

Oscillations



Solving the Uterine Puzzle:
Spatial Coupling

Excitable cell + Passive cell $\rightarrow$ Oscillations

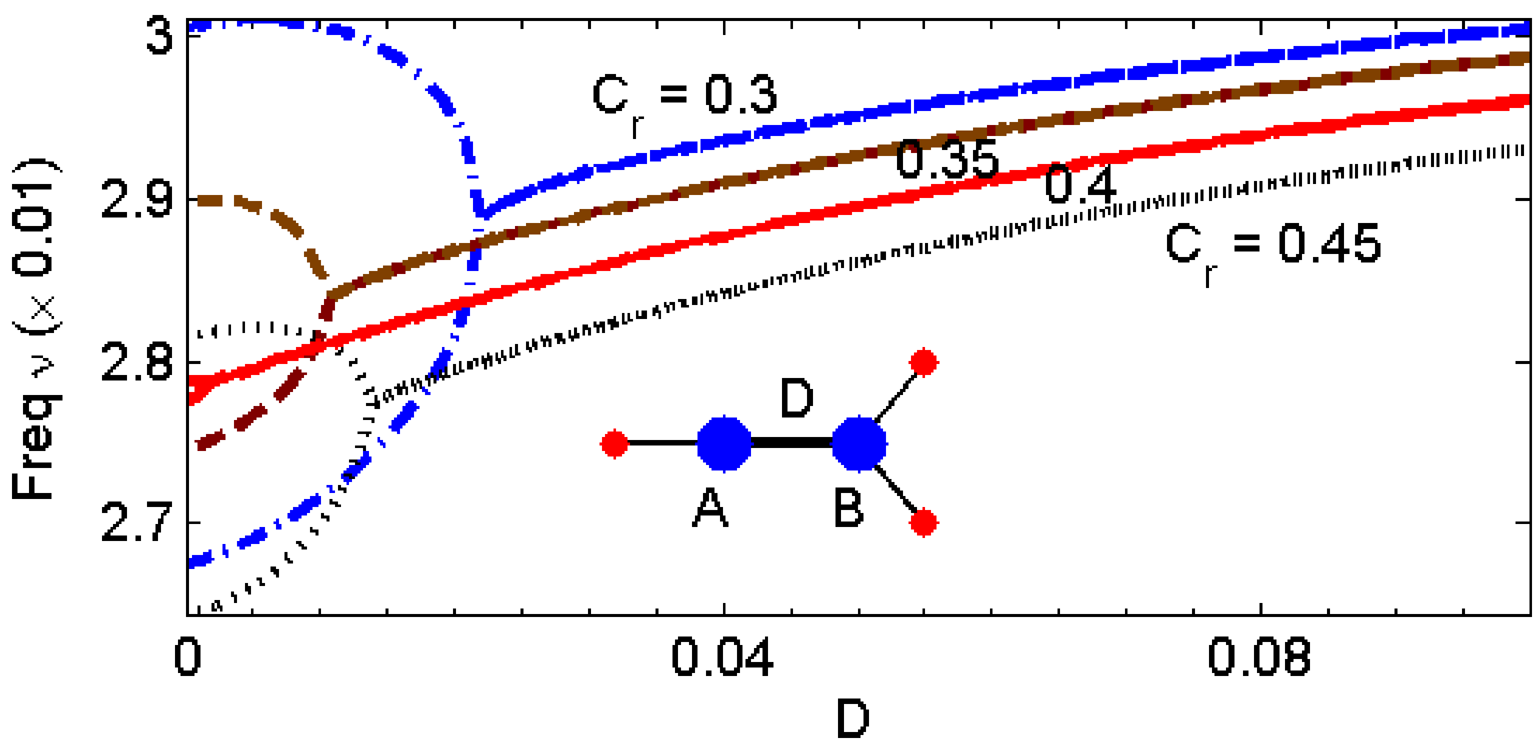
But possibility of conflict between regions oscillating at different frequencies & phase

- How to get spatially extended coherent activity without an organizing center ?

Answer: by increasing the coupling between myocytes, in addition to, myocyte-telocyte coupling

Coupling the "oscillators" can result in <u>**higher**</u> frequencies for the combined system

Frequency of oscillation of a system of two myocytes (A & B) coupled to different number of passive cells ($n_A = 1, n_B = 2$) synchronizes on increasing inter-myocyte coupling D to a frequency <u>**higher**</u> than that of the component oscillators



Extending our model in space

To investigate onset of spatial organization of periodic activity

- 2-dimensional system of locally coupled excitable cells
- Each excitable cell coupled to n_p passive cells

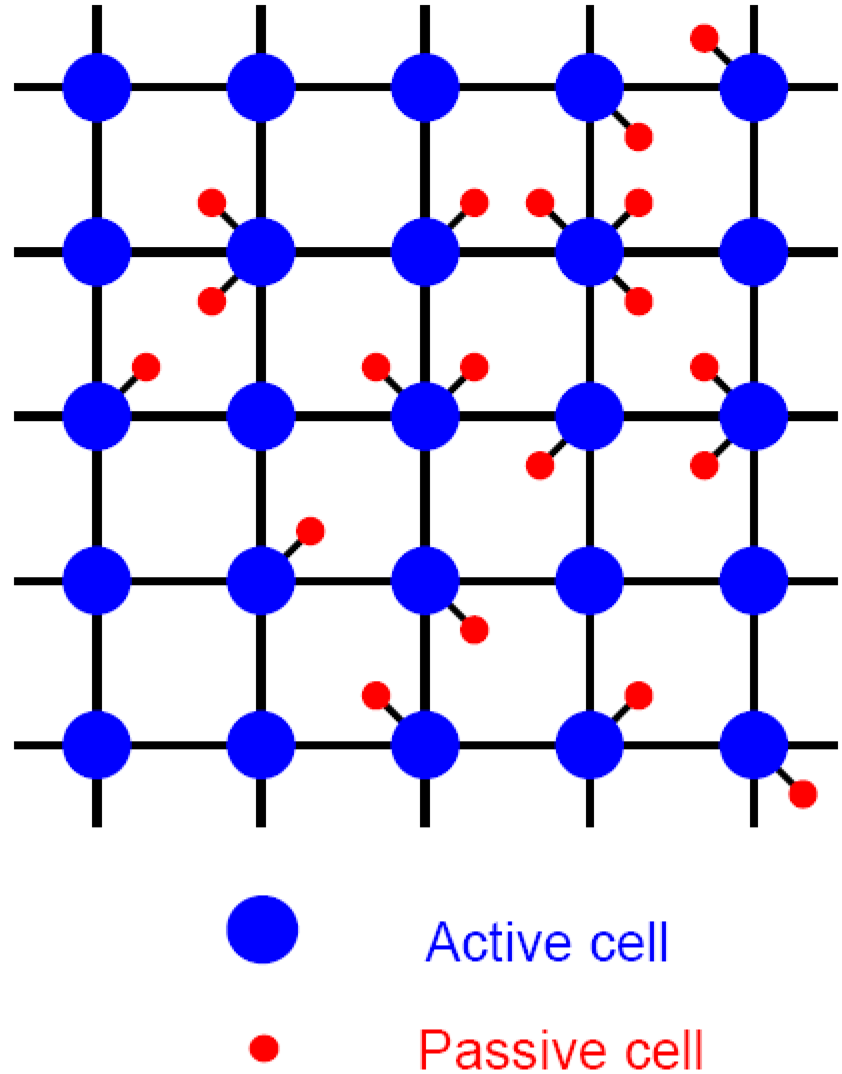
$$\frac{\partial V_e}{\partial t} = F_e(V_e, g) + n_p\, C_r(V_p - V_e) + D\nabla^2 V_e$$

- Distribution of n_p is Poisson(f)

$\Rightarrow$ f is a measure of the density of fibroblasts to myocytes

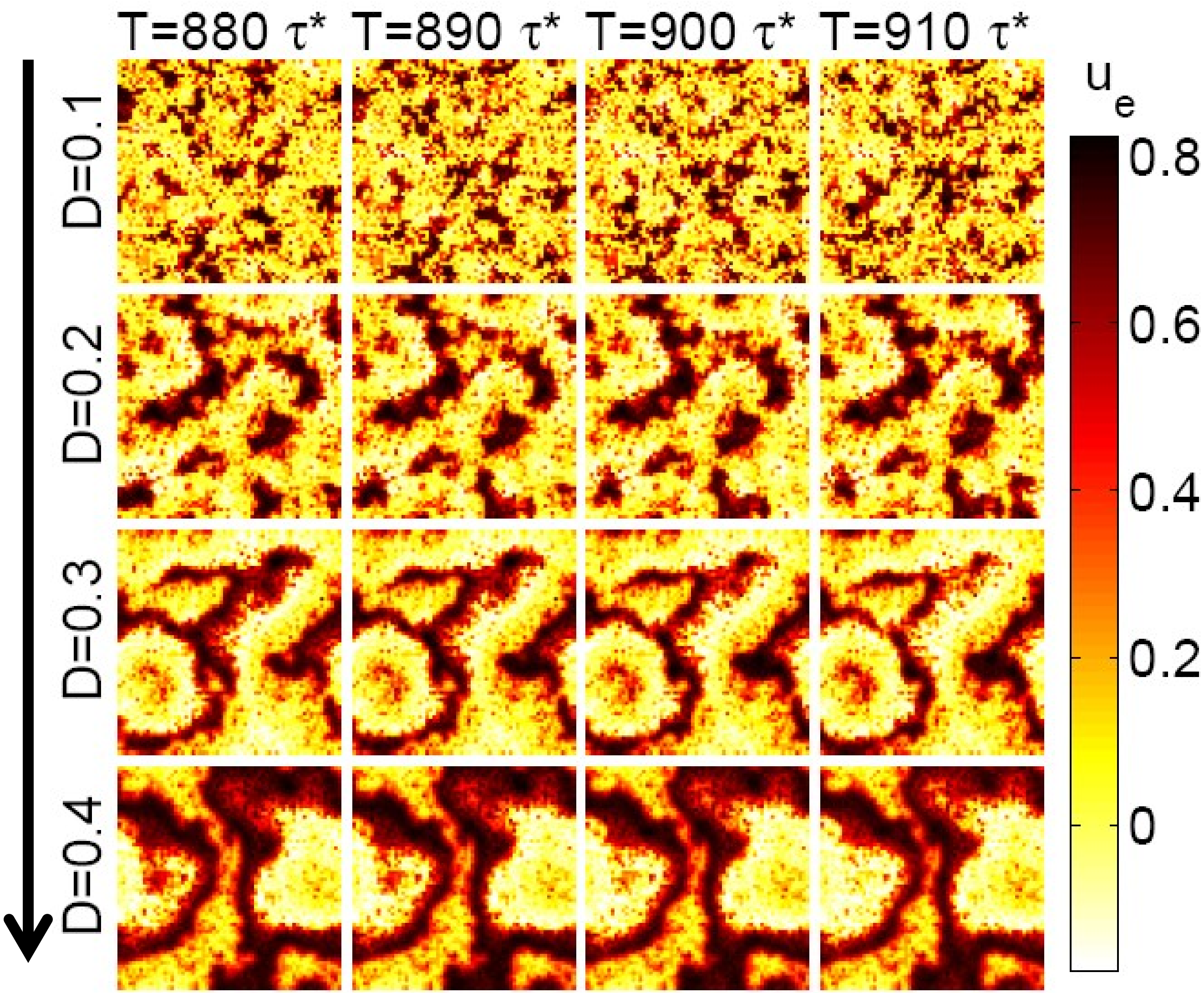
Results shown here for f = 0.7

- At large D, reduces to mean-field approximation of a single excitable element coupled to f passive cells.



Emergence of synchronization

Onset of traveling waves with increased coupling that mediate the transition to synchronization



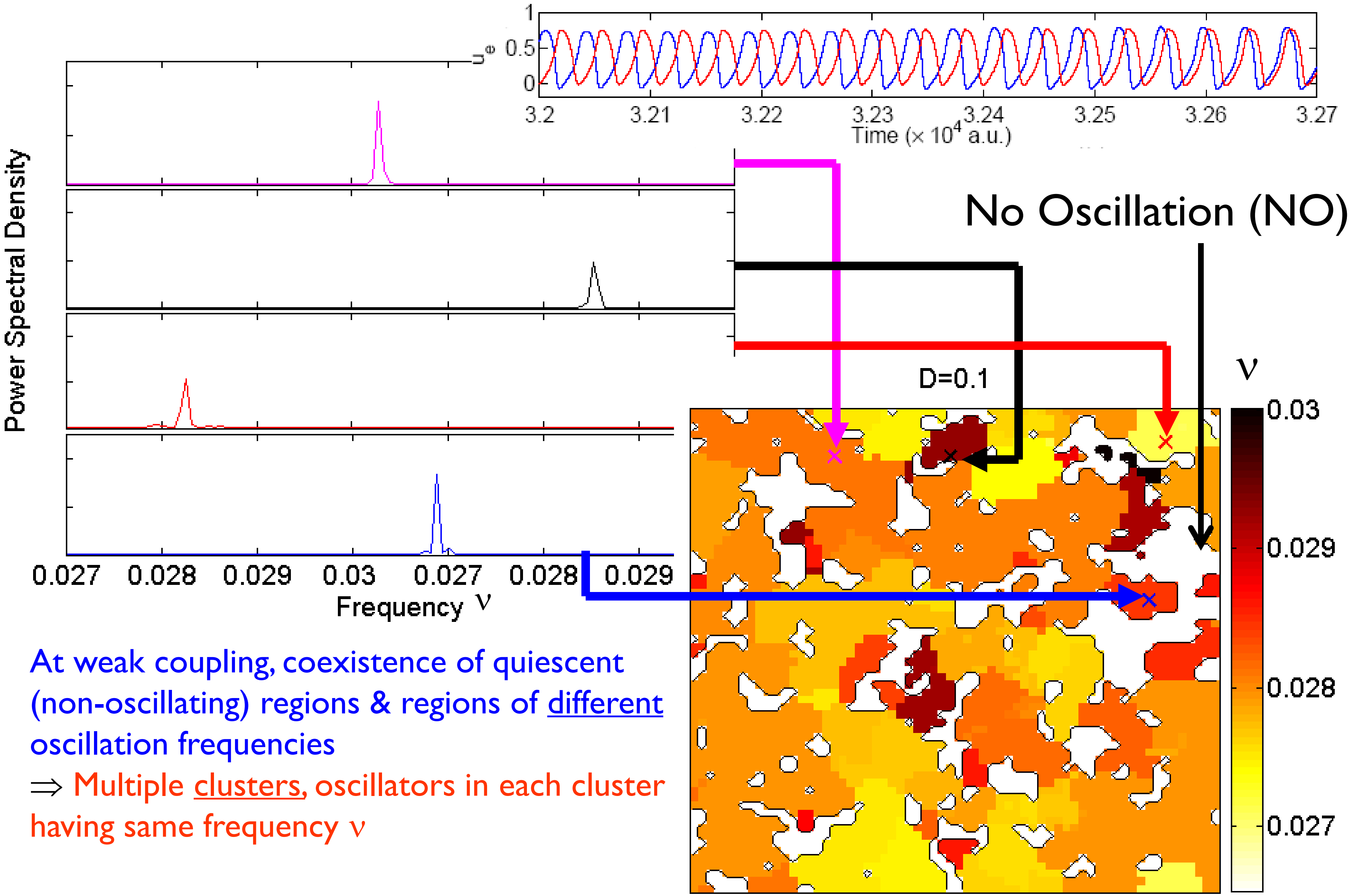
Intermittent excitations, no spatial correlation

Highly localized, asynchronous excitations

Formation of regions having coherent activity

Globally synchronized activity

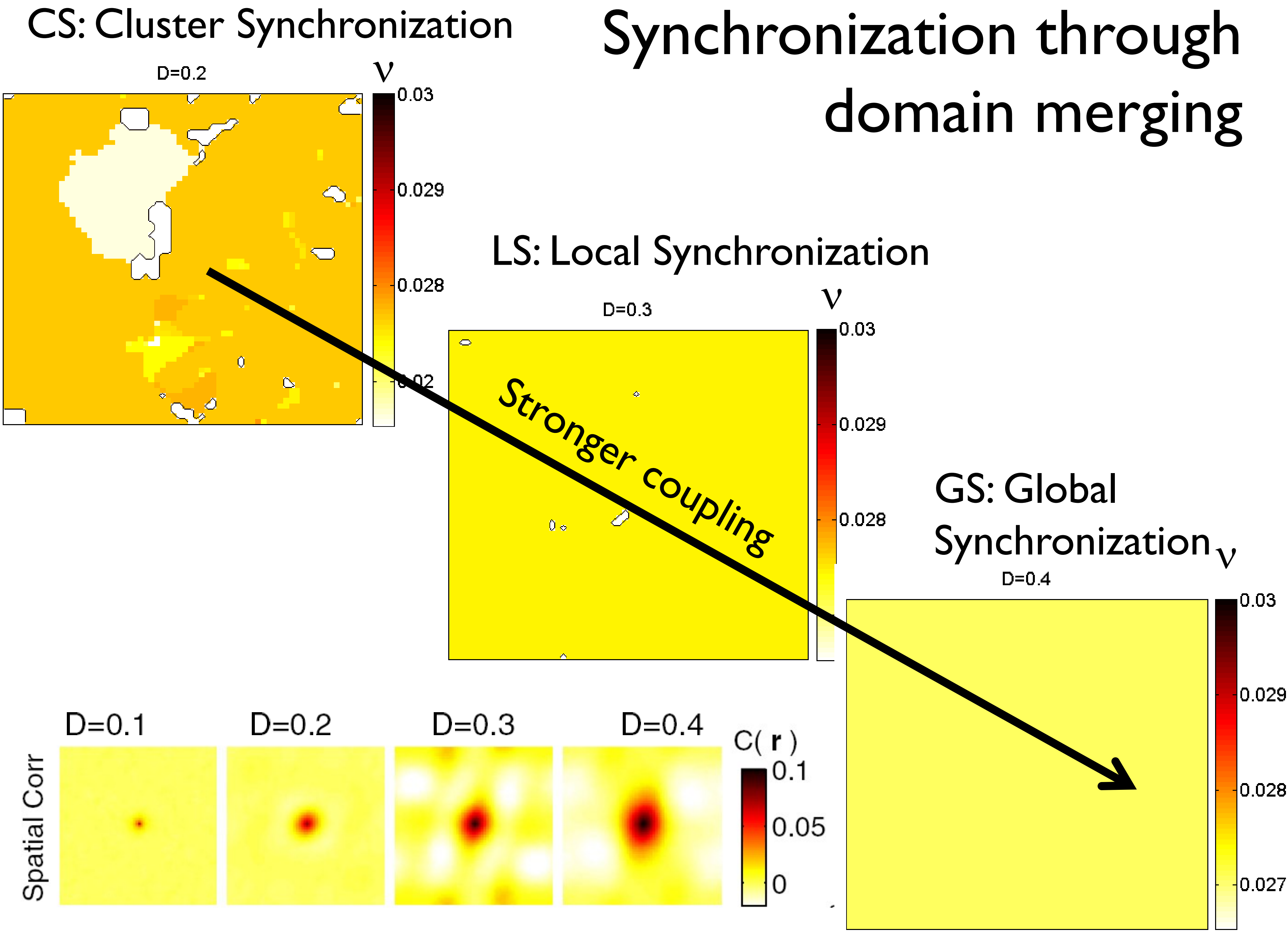
Existence of domains with different frequencies



At weak coupling, coexistence of quiescent (non-oscillating) regions & regions of <u>different</u> oscillation frequencies

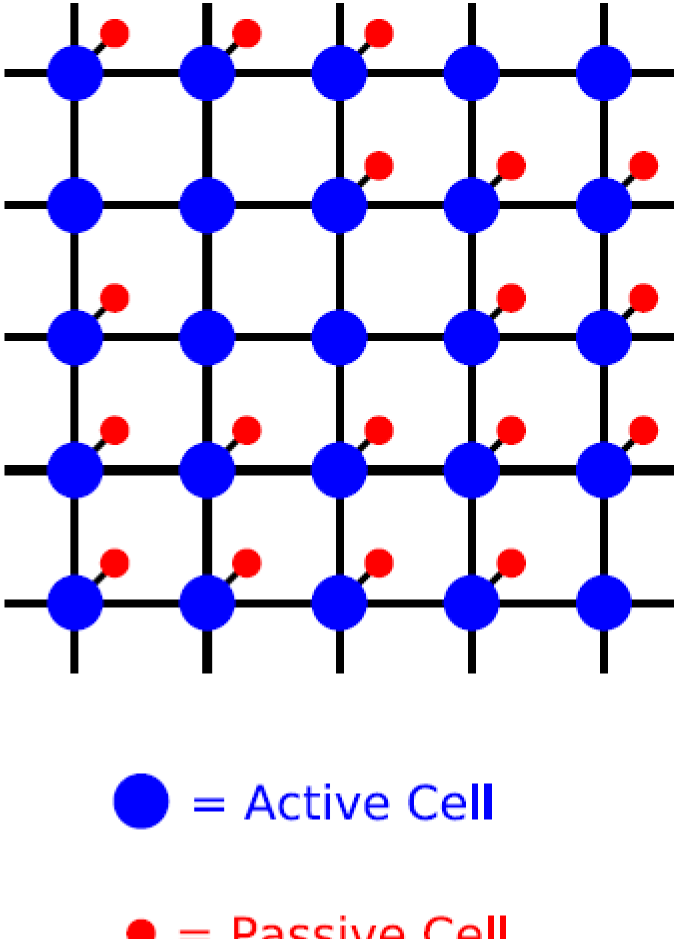
⇒ Multiple <u>clusters</u>, oscillators in each cluster having same frequency ν

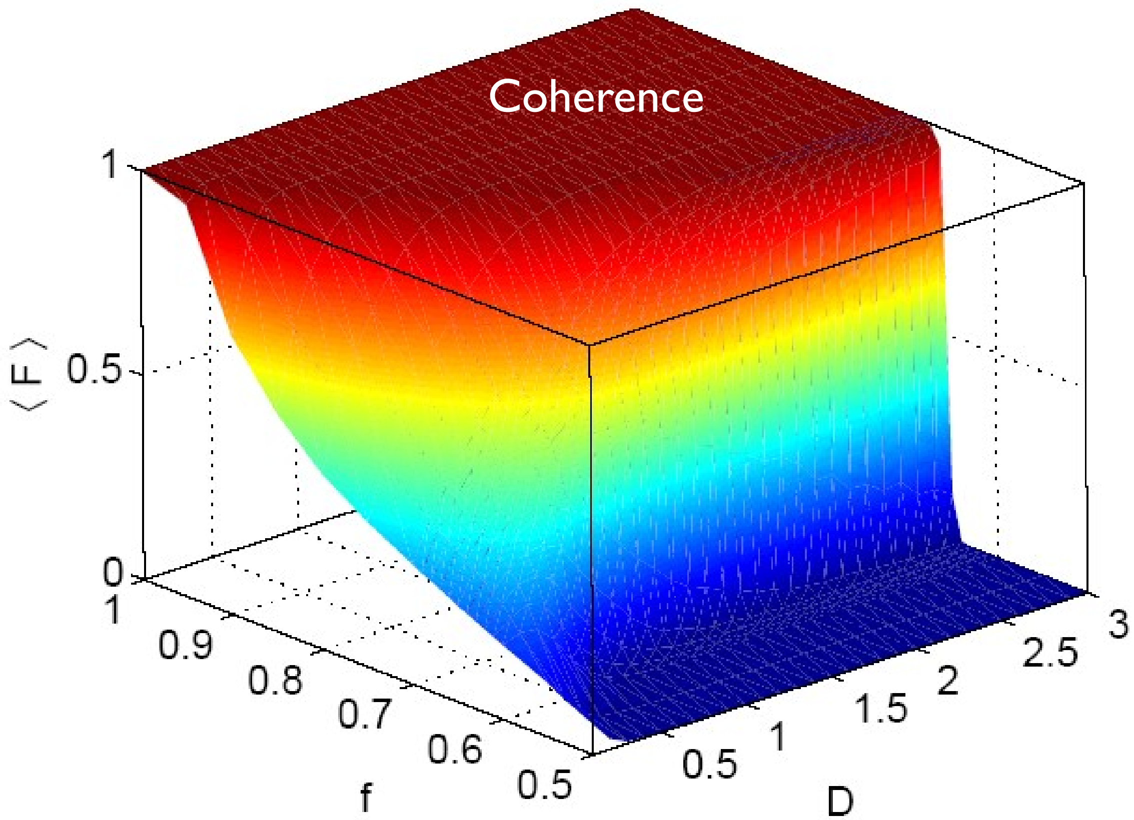
Synchronization through domain merging



The emergence of coherence

When <u>all</u> oscillators have the same <u>phase</u> as well as <u>frequency</u>, we term it coherence identified by order parameter $F \equiv \max_t[f_{act}(t)] \to 1$ where $f_{act}(t)$ is the fraction of elements active $(u_e > \alpha)$ at time t

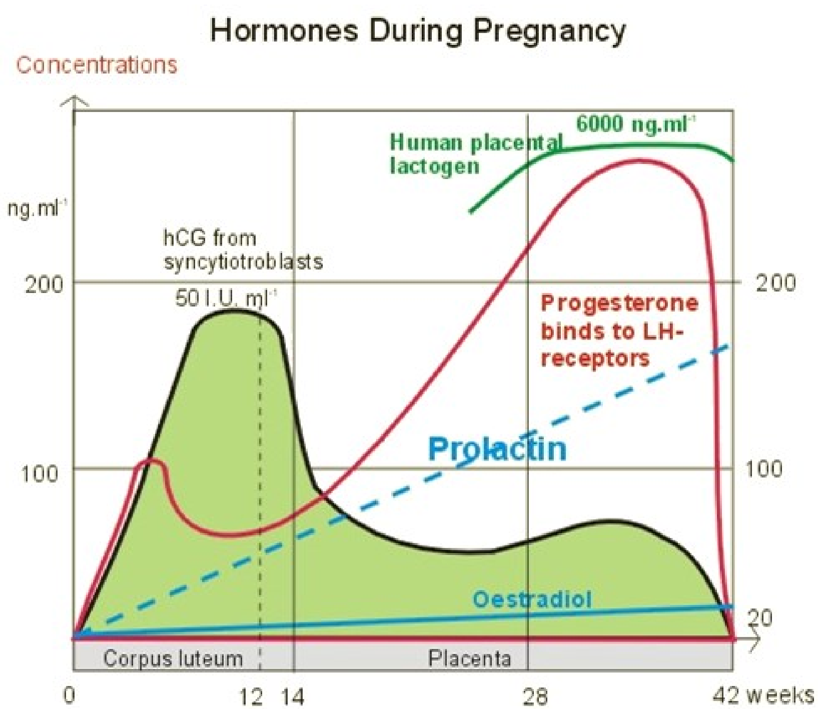




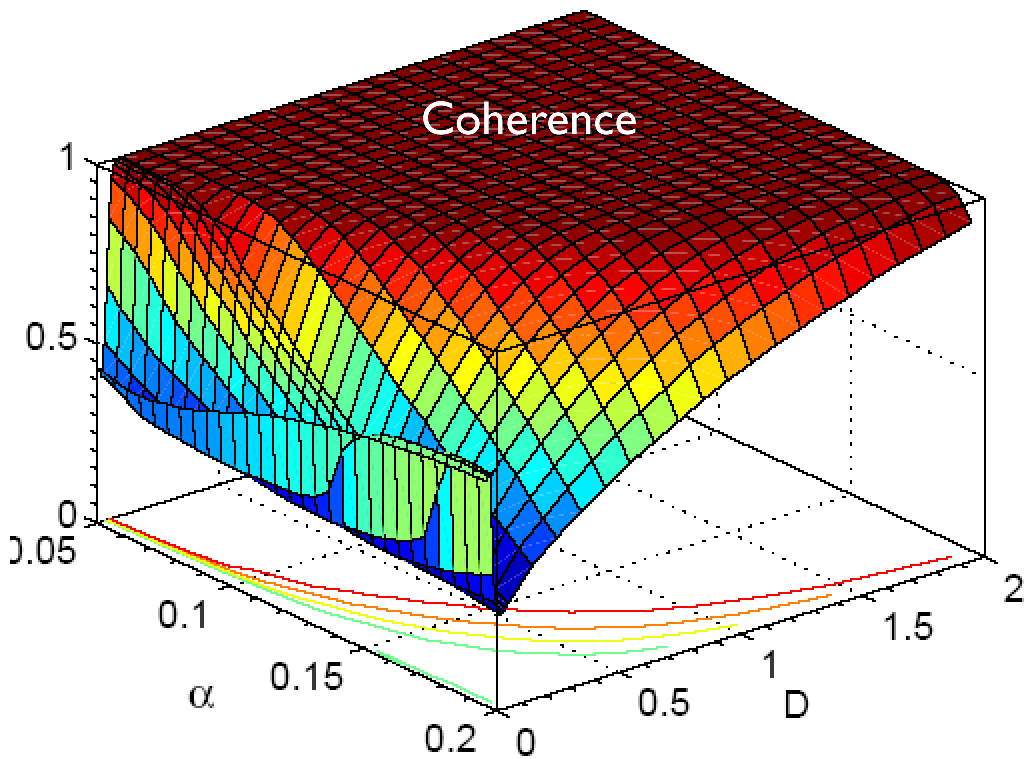
$$f = \frac{\text{no. of passive cells}}{\text{no. of active cells}}$$

The emergence of coherence

Coherence can also be promoted by increasing the excitability of the medium through application of hormones or drugs (implemented in our simulations by decreasing threshold α)



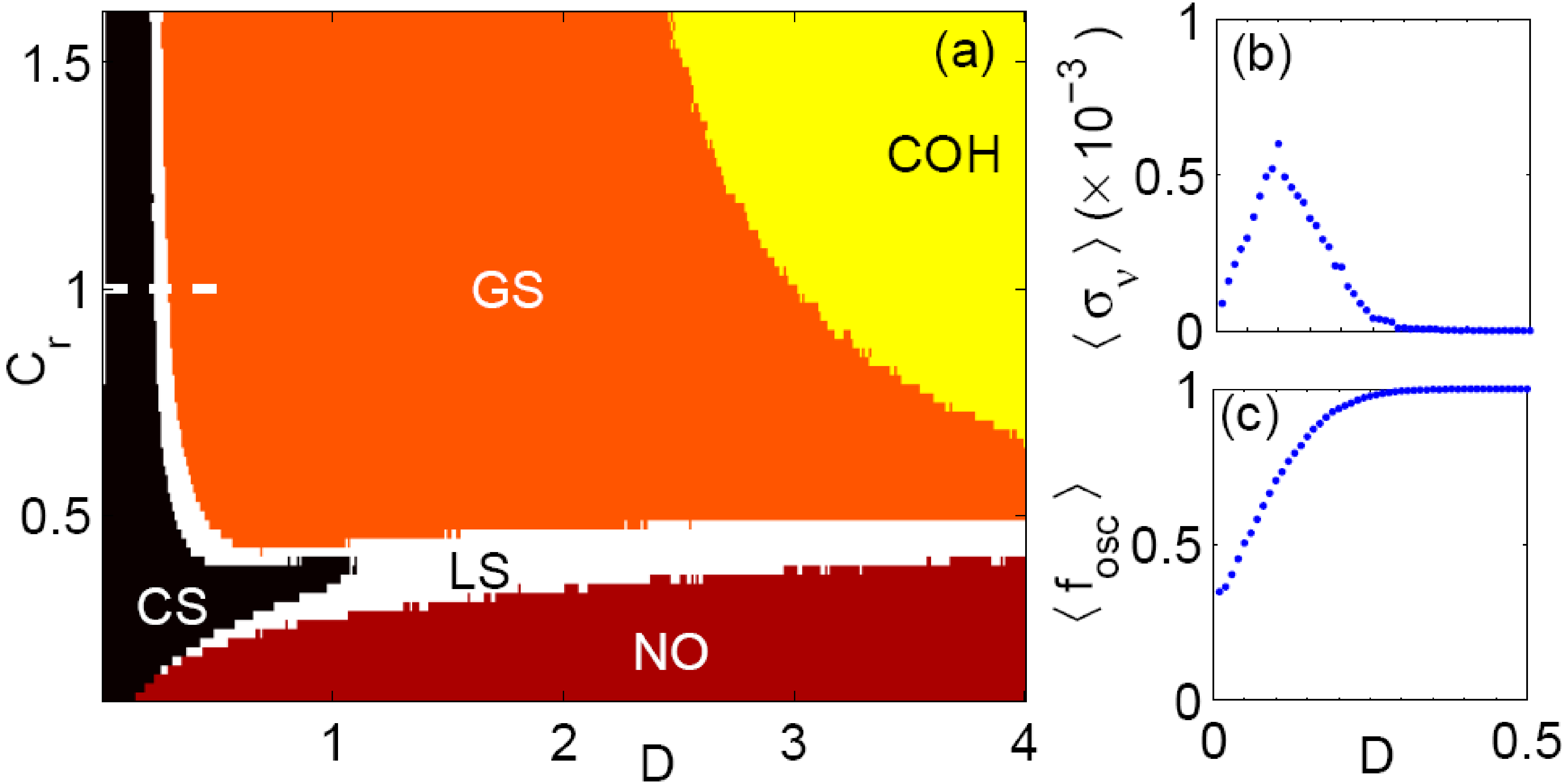
http://www.1cro.com/MedicalPhysiology/chap29



Different dynamical regimes of the model

Characterized by the order parameters:

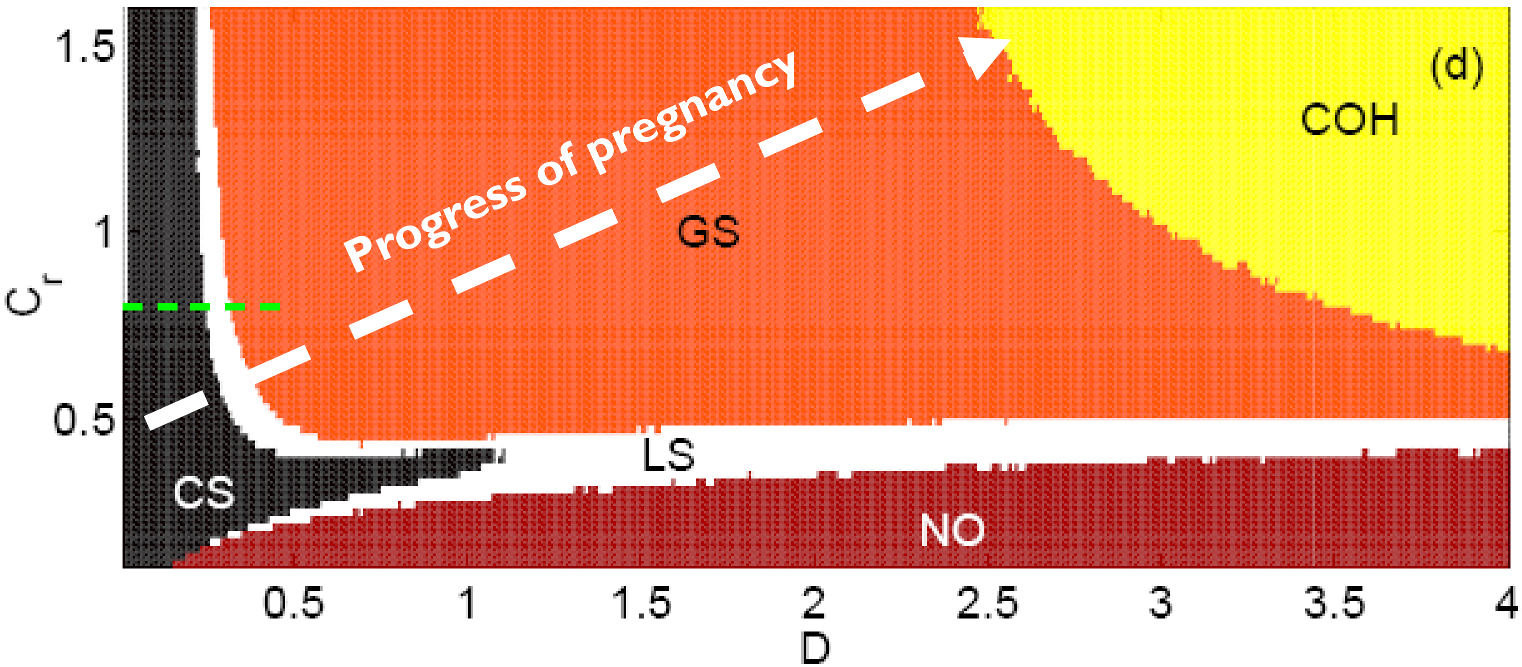
- Width of the frequency distribution, $\langle \sigma_\nu \rangle$
- Fraction of oscillating cells, $\langle f_{osc} \rangle$



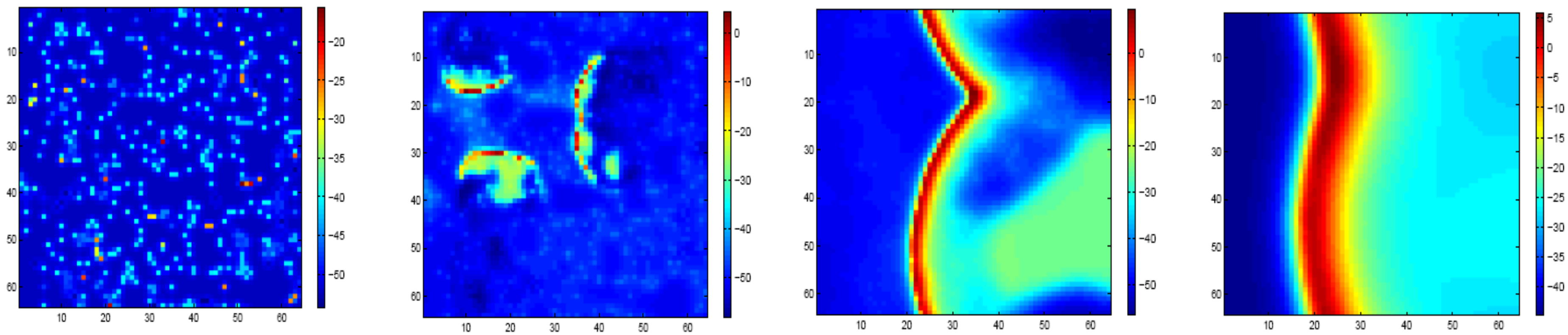
Correspondence to physiology

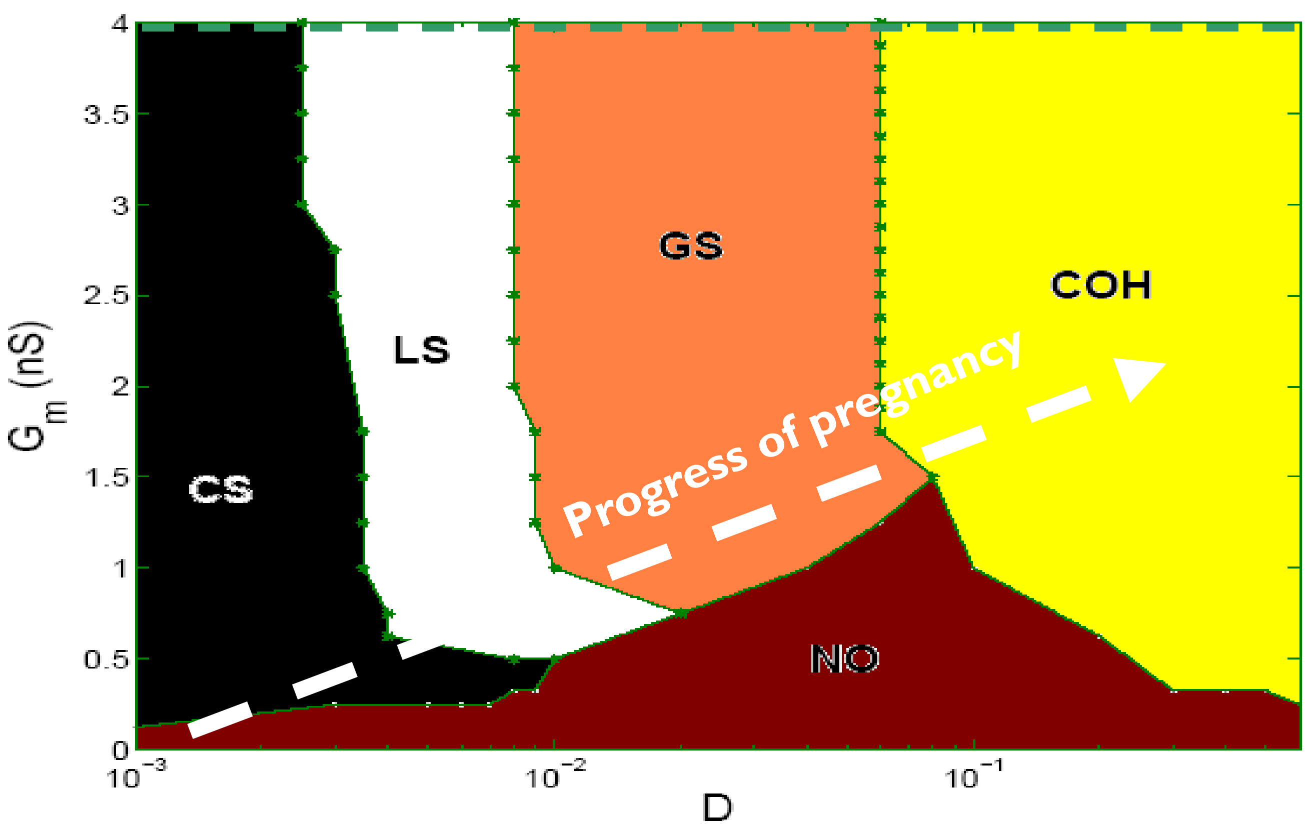
Our results help in causally connecting two well-known observations about electrical activity in the pregnant uterus:

- a remarkable increase in the number of myometrium gap-junctions close to onset of labor, and,
- excitations are initially infrequent & irregular, but gradually become sustained and coherent towards the end of labor



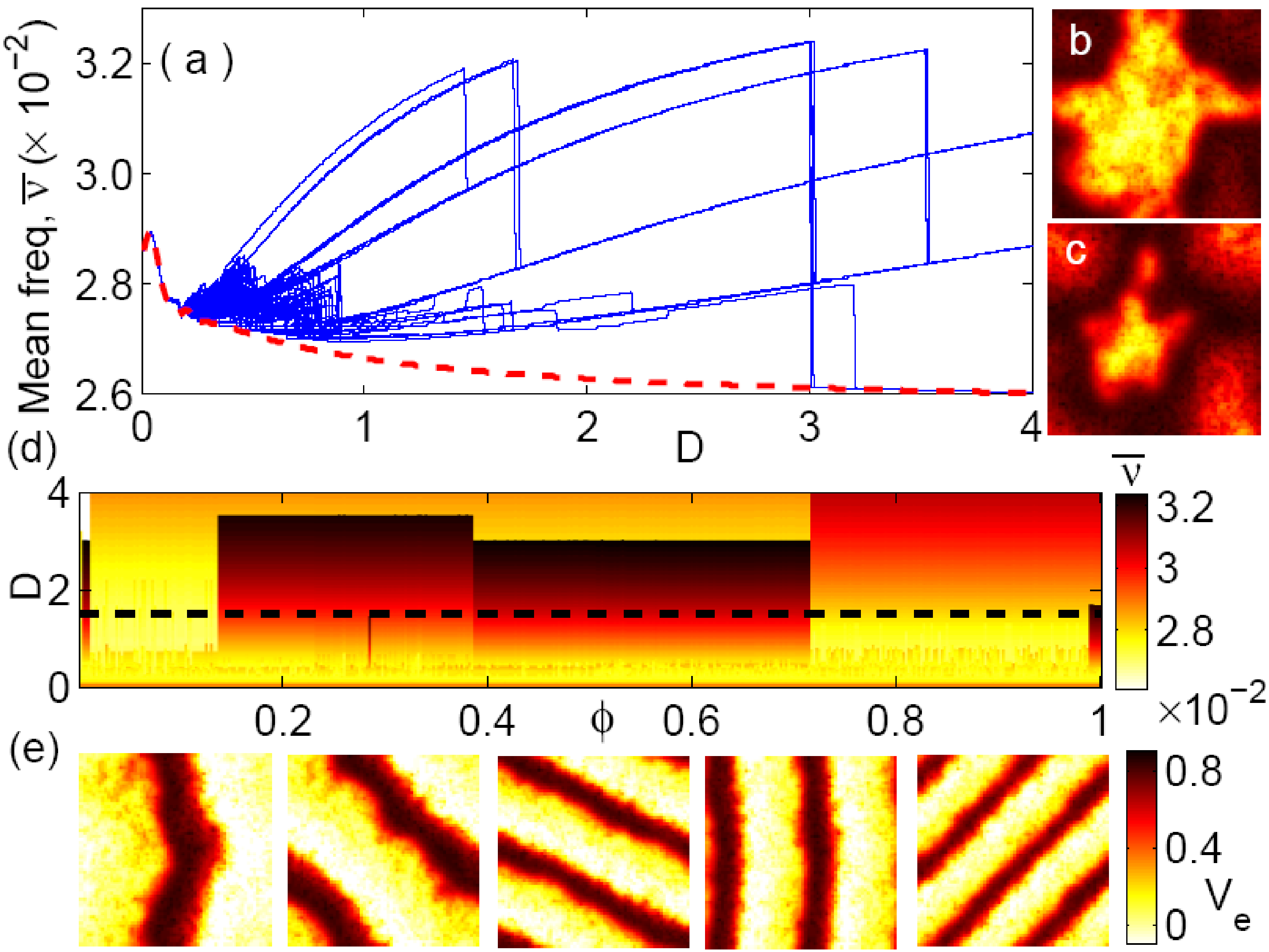
Reproducing the results in a realistic model





2-D lattice of 64 x 64 uterine myocytes modeled by Tong et al eqns, coupled to n_p passive cells having Poisson distr with mean f=0.1

Many coexisting dynamical attractors having different mean oscillation frequencies



Depending on choice of initial state as the coupling strength is varied, the frequency variation with coupling shows contrasting behavior

For adiabatic increase of D, frequency <u>increases</u> with coupling

- Emergence of coherent activity: a question of central importance complex systems; in particular, is crucial for many biological functions
- How does coordinated rhythmic behavior emerge without an organizing center (pacemaker) ?
- Coupling leads to coherence through different dynamical regimes: clustered, local & global synchronization
- Onset of traveling waves accompany synchronization
- Consistent with physiological observations about the uterus: gap junctions increase significantly during pregnancy