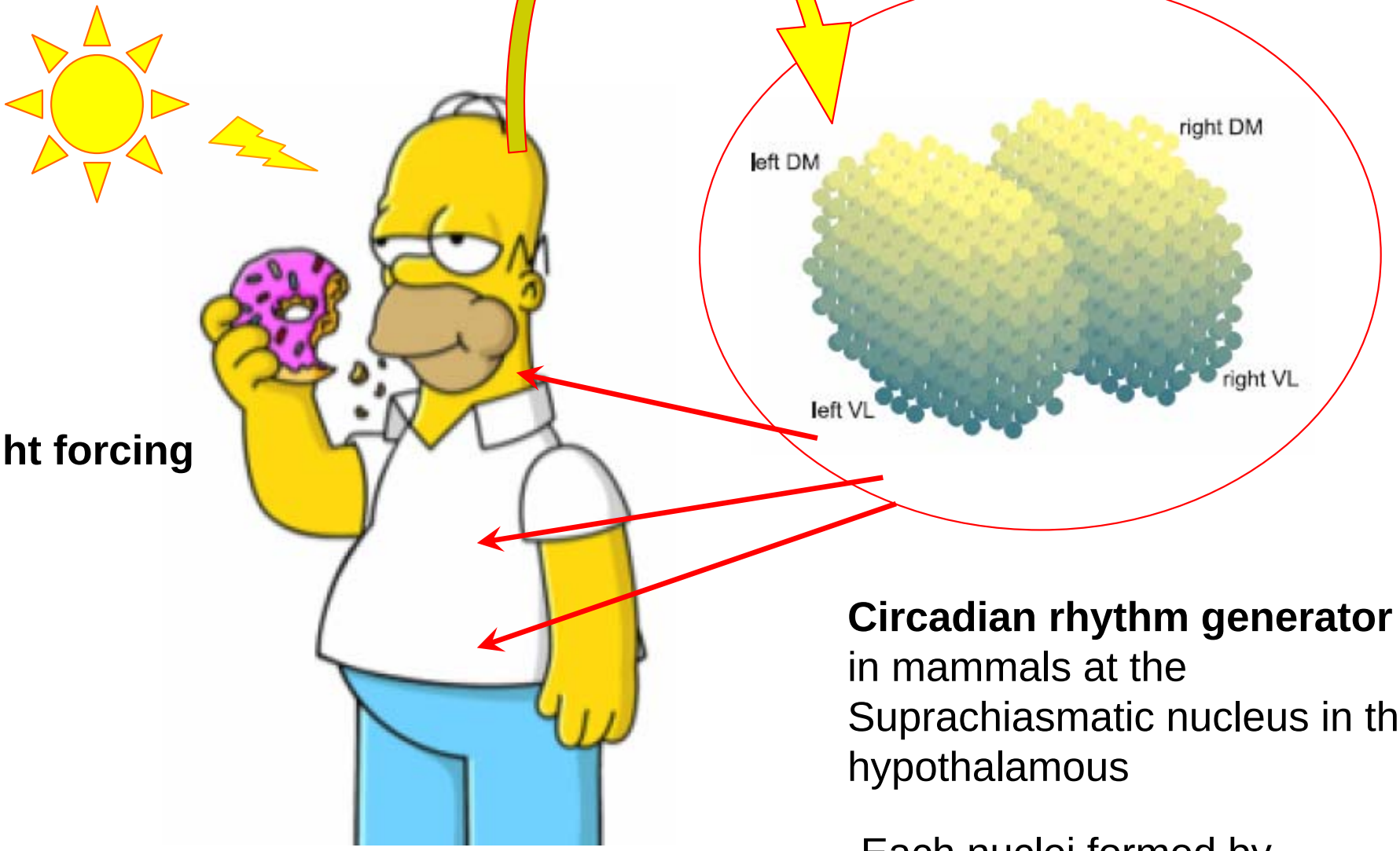
Synchronization and stochasticity in circadian oscillators ensembles

Niko Komin, Adrian Murza, Raúl Toral, Emilio Hernández-García

IFISC (Instituto de Física Interdisciplinar y Sistemas Complejos)
CSIC-University of the Balearic Islands
Palma de Mallorca, Spain



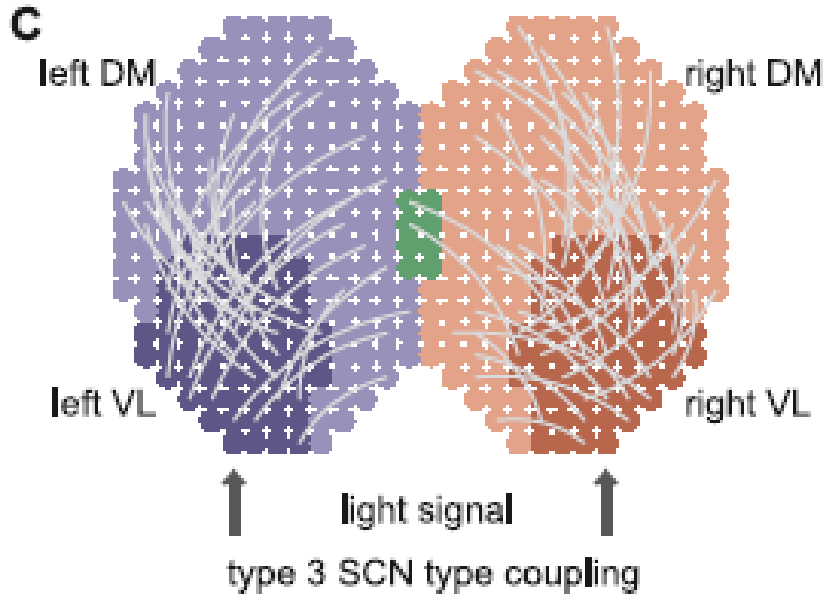
Light forcing

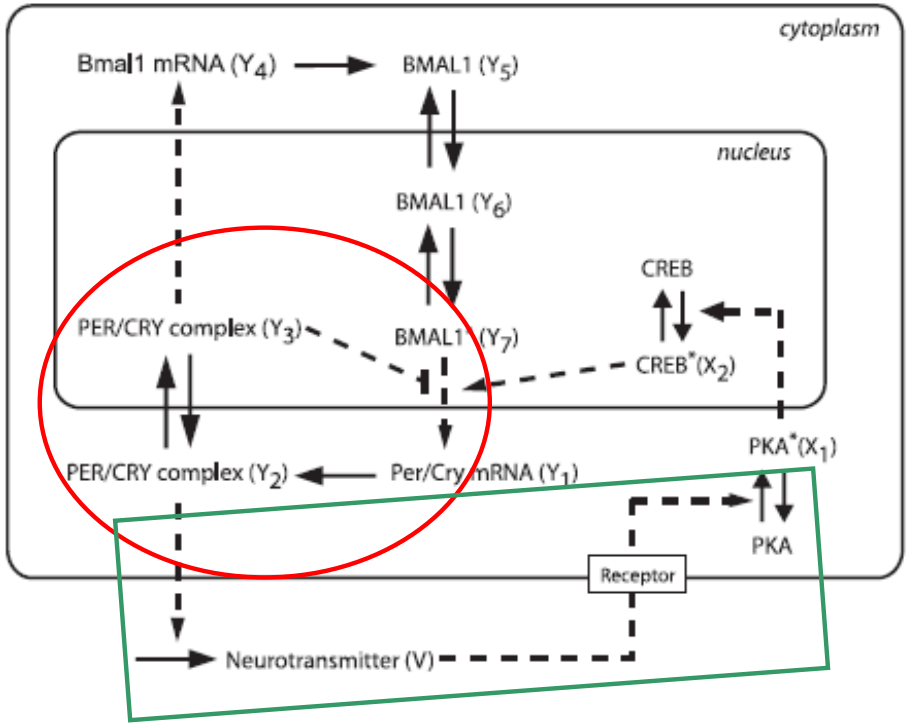
Circadian rhythm generator in mammals at the Suprachiasmatic nucleus in the hypothalamous

Each nuclei formed by 10,000 oscillating neurons

Networks appear at two levels:

a) which neuron interacts with which





b) The biochemical interaction network

One neuron

From Bernard, Gonze, Cajavec, Herzel and Kramer, PLoS Comp. Biol. 3, e68 (2007)

$$\tau_i \begin{cases} \dfrac{dX_i}{dt} = \nu_1 \dfrac{K_1^n}{K_1^n + Z_i^n} - \nu_2 \dfrac{X_i}{K_2 + X_i} + \nu_c \dfrac{KF}{K_c + KF} + L(t) \\ \dfrac{dY_i}{dt} = k_3 X_i - \nu_4 \dfrac{Y_i}{K_4 + Y_i} \end{cases}$$

$$\tau_i \begin{cases} \dfrac{dZ_i}{dt} = k_5 Y_i - \nu_6 \dfrac{Z_i}{K_6 + Z} \\ \dfrac{dV_i}{dt} = k_7 X_i - \nu_8 \dfrac{V_i}{K_8 + V_i} \end{cases}$$

Light forcing

Positive feedback from neurotransmitter

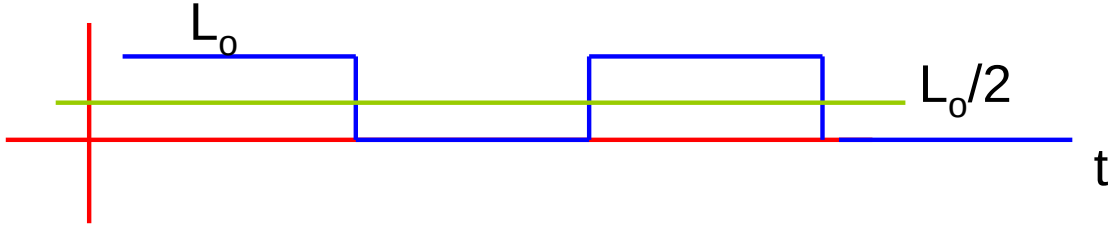
$$F = \frac{1}{Neigh} \sum_{i=1}^{Neigh} V_i$$

X: mRNA from clock gene(s)
Y: protein
Z: transcriptional inhibitor

V: neurotransmitter

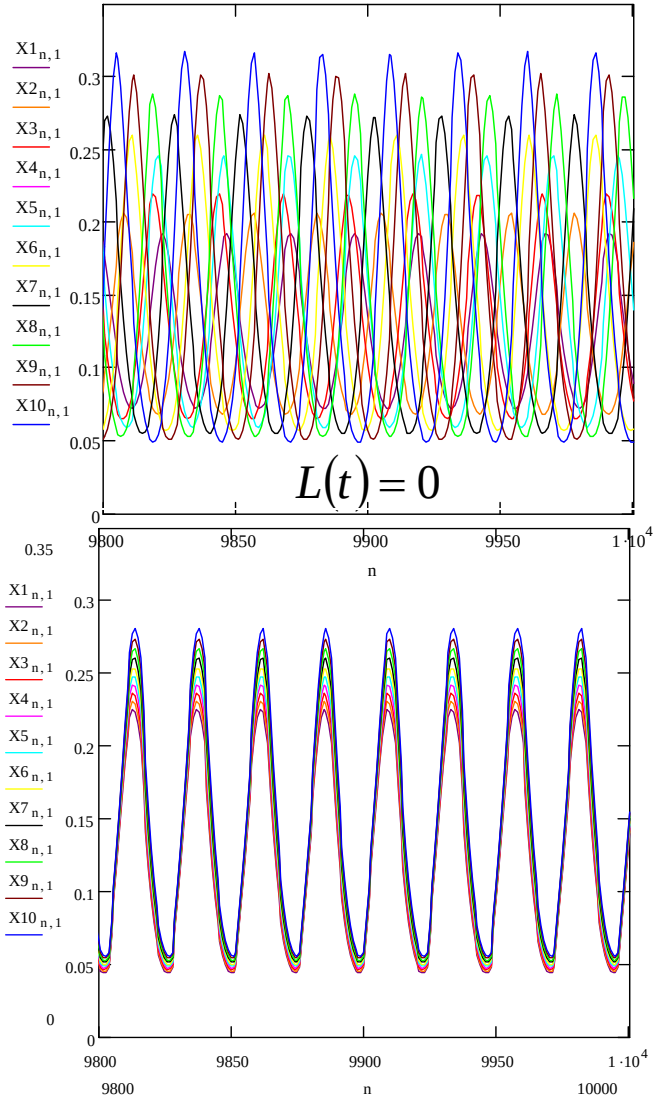
n=4

L(t)=24h-period square wave
(or sinusoidal)



Gonze D, Bernard S, Waltermann C, Kramer A, Herzel H. Spontaneous Synchronization of Coupled Circadian Oscillators. Biophys. J. 2005; 89: 120 - 129.

THIS WORK (in fact work in progress)



Group (~100 cells) of similar but not identical oscillators (mean period 24h, but some variance) sharing a global coupling

Look at the response to the external light forcing, and to the response periods

Look at the degree of synchronization among the oscillators

Focus on the effect of the cell diversity on the results

Measuring synchronization

We quantify the resonance effect by the spectral amplification factor R for the MEAN FIELD X

$$X = \frac{1}{N}\sum_{i=1}^{N} X_i \qquad L(t) = \frac{L_0}{2}\left[1+\sin(\omega t)\right] \qquad R = \frac{4}{L_0^2}\left|\left\langle e^{-i\omega t} X(t)\right\rangle\right|$$

<...> = average over time

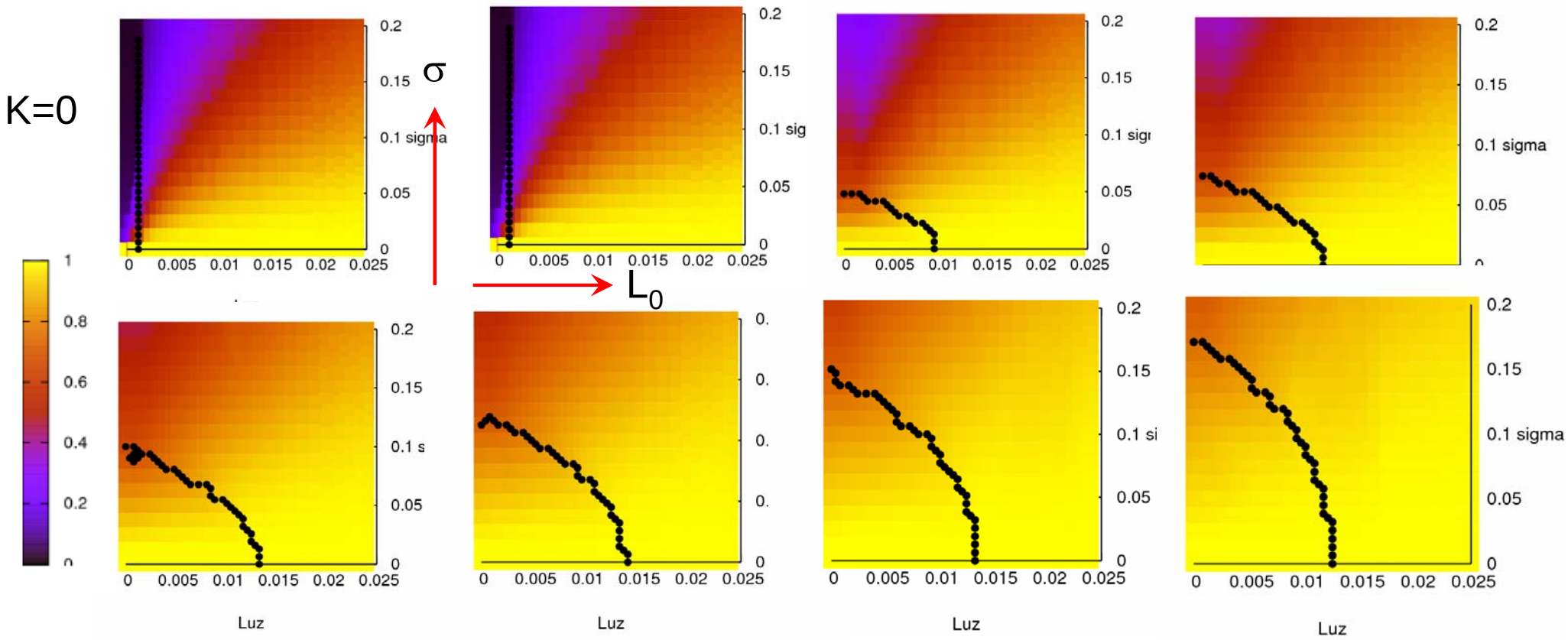
RESPONSE of the **MEAN FIELD**

$$R_G = \frac{\left\langle F^2\right\rangle - \left\langle F\right\rangle^2}{\frac{1}{N}\sum_{i=1}^{N}\left(\left\langle V_i^2\right\rangle - \left\langle V_i\right\rangle^2\right)} = \frac{Variance_t(F)}{Mean_i\left(Var_t(V_i)\right)}, \qquad F = \frac{1}{N}\sum_{i=1}^{N} V_i$$

ORDER PARAMETER or **SINCHRONY**

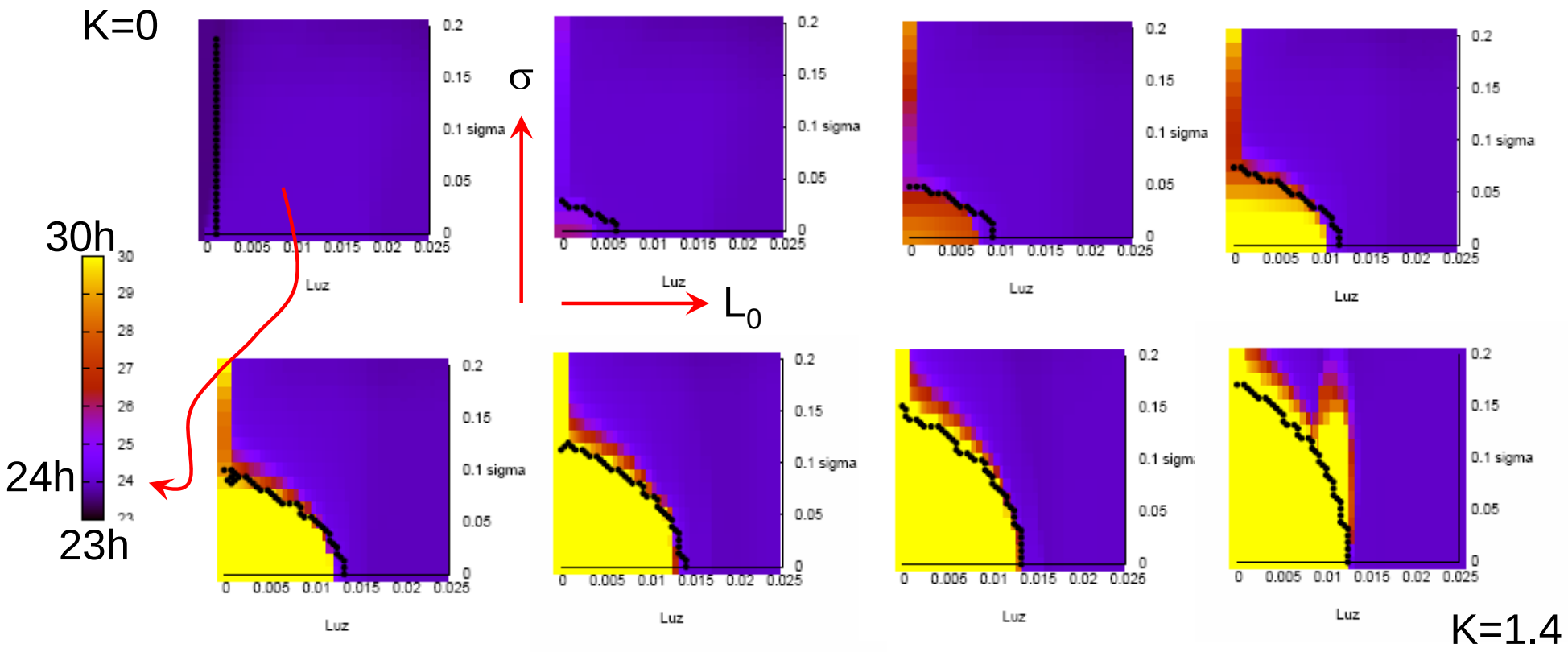
R_G measures the distribution of phases of the neurons.
It is ranging between 0 (no synchronization) and 1 (perfect synchronization, with all neurons in phase)

SYNCHRONY ORDER PARAMETER

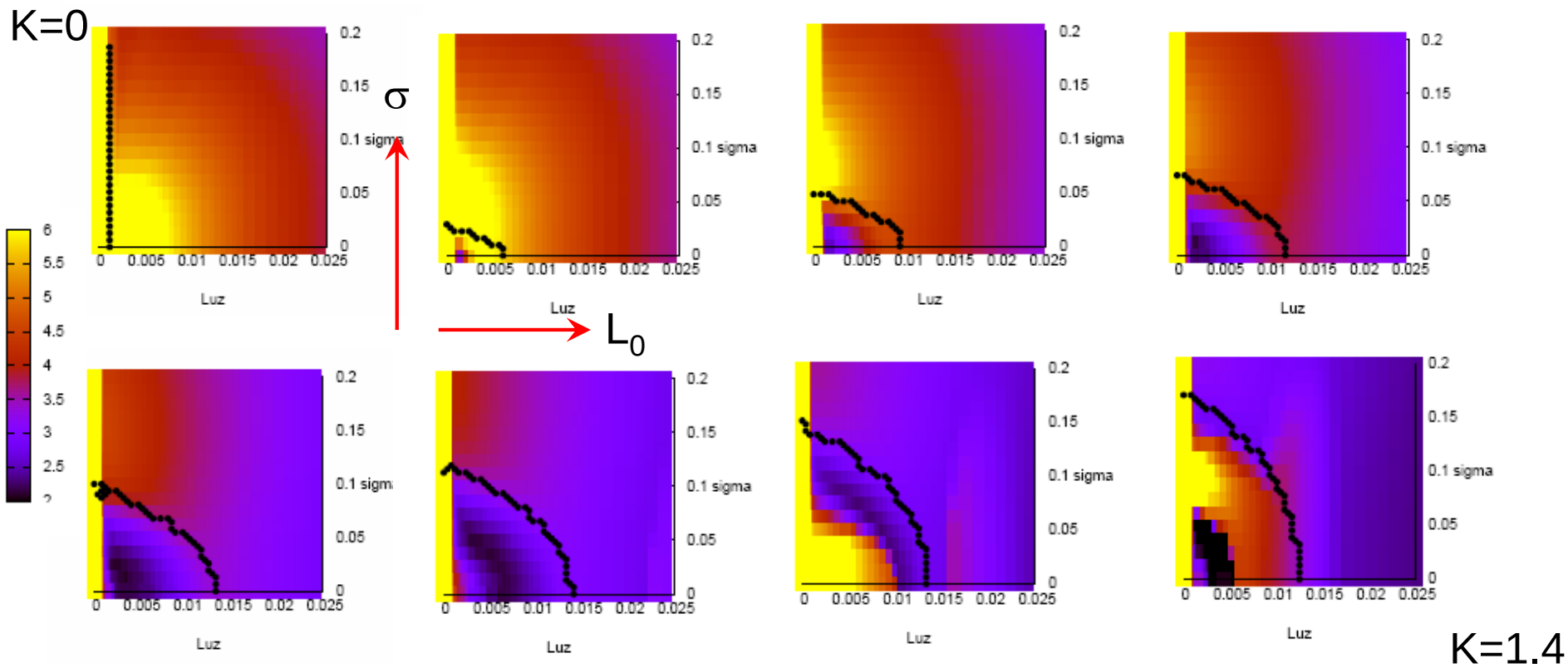


Synchrony is favored by strong light intensity, low diversity, and large coupling

Mean of the individual periods under forcing at 24h cycle



BUT THE SYNCHRONY IS NOT ALWAYS AT THE 24H-PERIOD OF THE FORCING: individual periods take-off. The 24h cycle is respected for strong light and LARGE DIVERSITY (and small internal coupling)

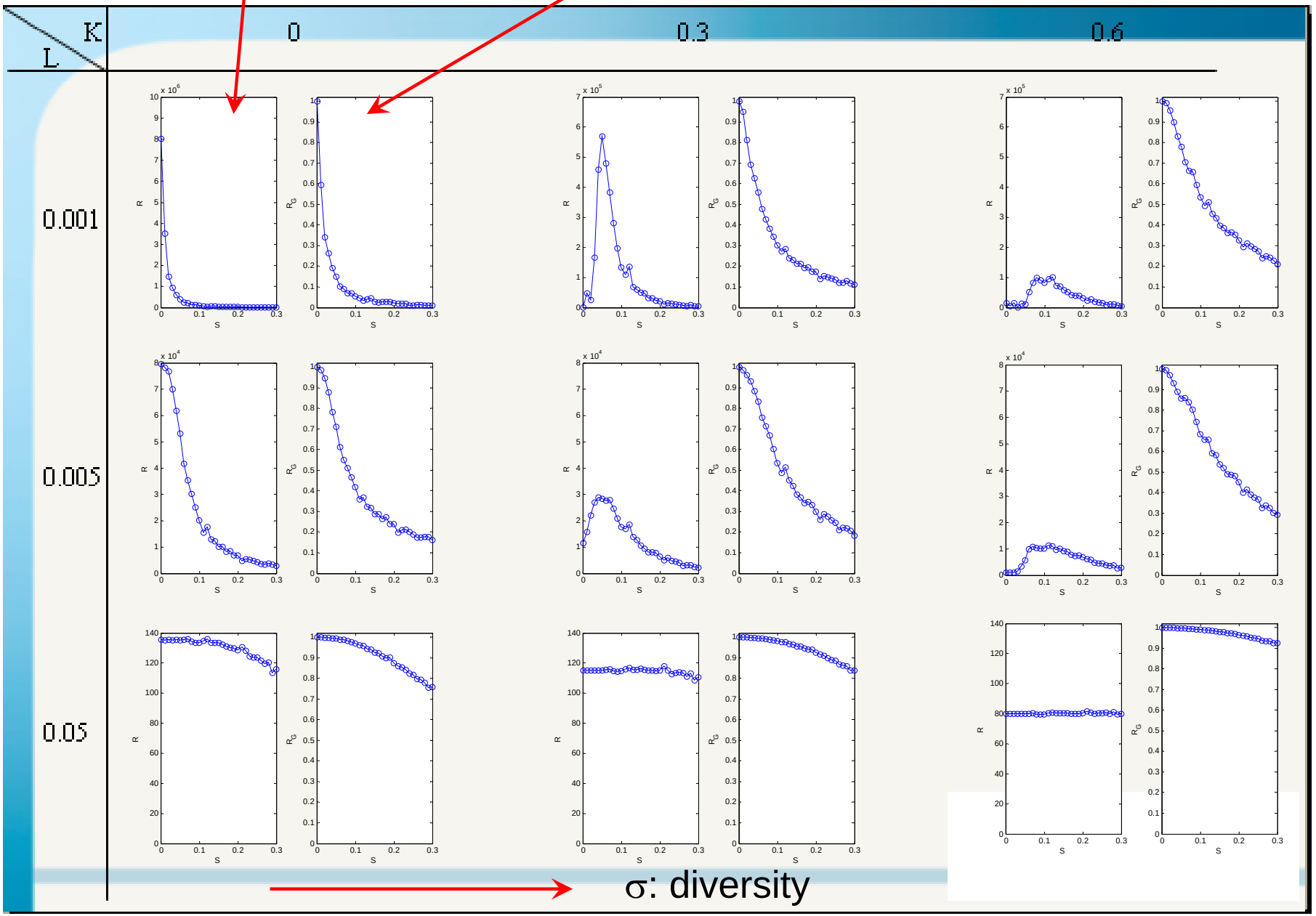


log(RESPONSE) to 24h forcing larger for weak light
and INTERMEDIATE DIVERSITY

Optimal diversity to give maximum response at 24h

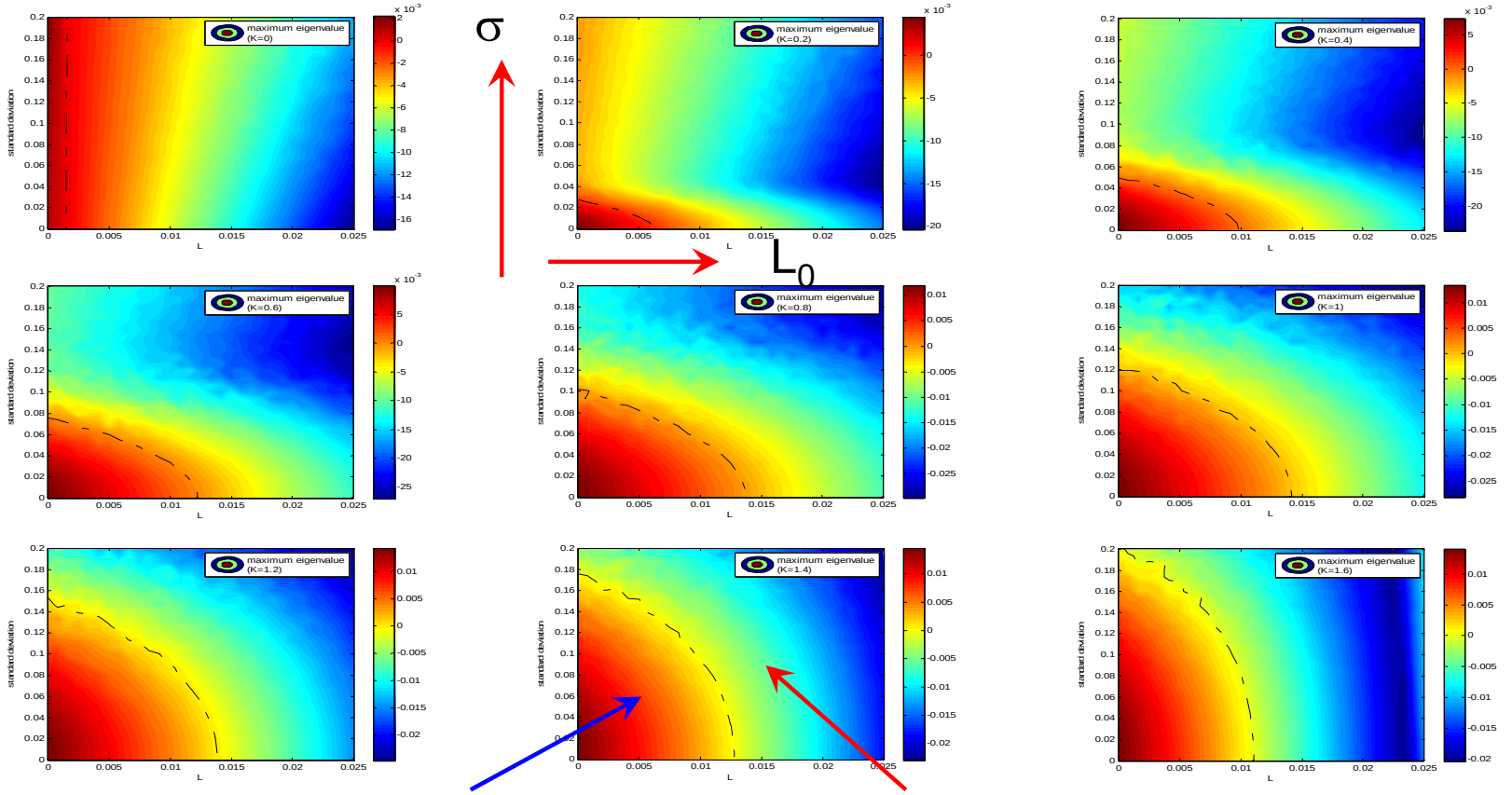
RESPOSE

SYNCHRONY



Maximum eigenvalue of fixed point of 100 coupled oscillators (averaged 10 times) under constant light $L_0/2$

K=0



increasig coupling

Fixed point Hopf unstable

Fixed point stable

K=1.6

Diversity (and light) induces oscillator death: stabilizes the fixed point

Diversity (at optimal levels; not too large, not too small) is able to improve the collective response of the neuron ensemble to the 24h cycle

The mechanism is related to the oscillator death it produces: the damped oscillators follow better the external signal than the ones self-oscillating with different periods (which in the strong coupling regime lead to fast oscillations).

Inhomogeneous link topology is also a type of diversity worth to be also considered