

# Research Topic:



## OPEN ACCESS

EDITED AND REVIEWED BY  
Plamen Ch. Ivanov,  
Boston University, United States

\*CORRESPONDENCE  
Christoph Schmal,  
✉ christoph.schmal@hu-berlin.de  
Jihwan Myung,  
✉ jihwan@tmu.edu.tw

SPECIALTY SECTION  
This article was submitted to Systems  
Interactions and Organ Networks,  
a section of the journal  
Frontiers in Network Physiology

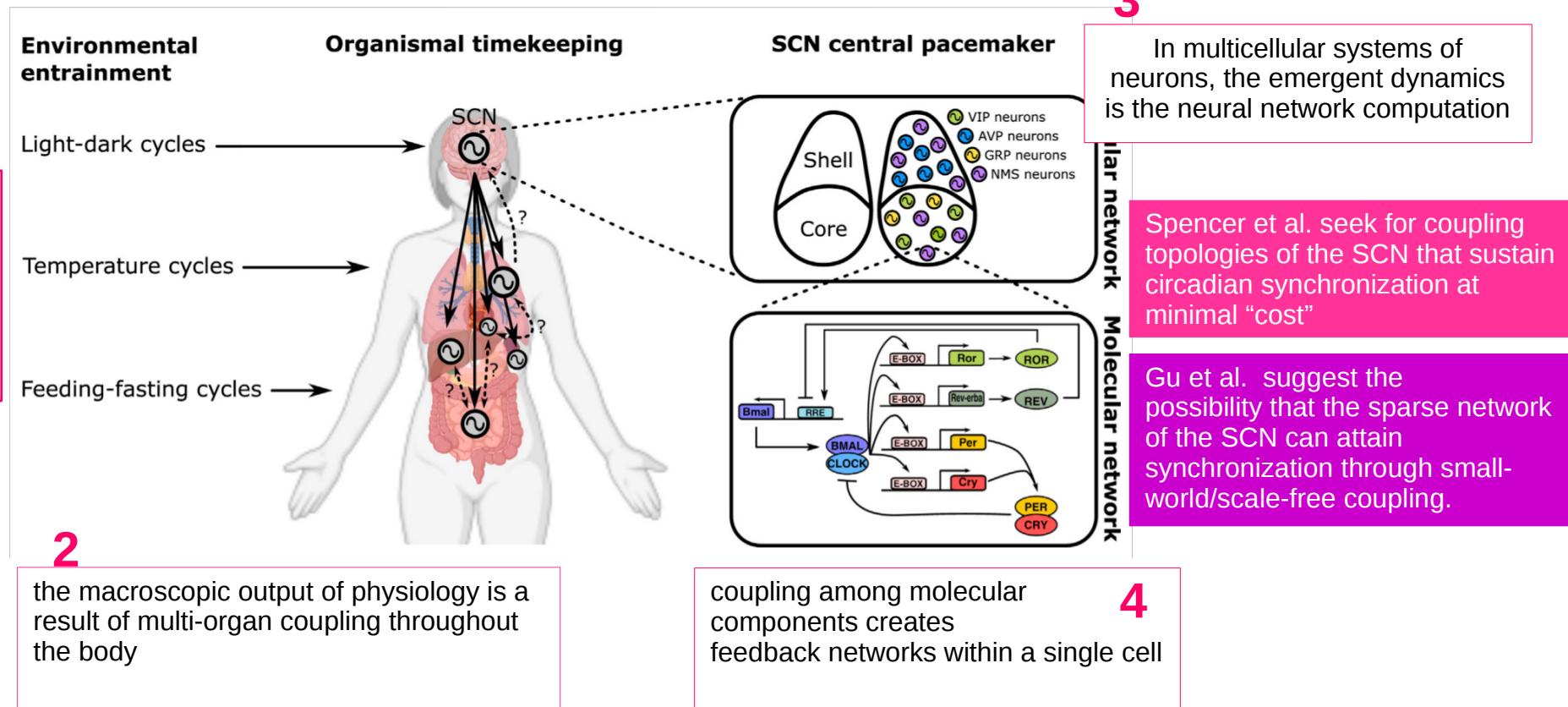
## Editorial: Coupling in biological systems: Definitions, mechanisms, and implications

Christoph Schmal<sup>1\*</sup>, Sungho Hong<sup>2</sup>, Isao T. Tokuda<sup>3</sup> and  
Jihwan Myung<sup>4,5\*</sup>

<sup>1</sup>Institute for Theoretical Biology, Humboldt University, Berlin, Germany, <sup>2</sup>Computational Neuroscience Unit, Okinawa Institute of Science and Technology, Okinawa, Japan, <sup>3</sup>Department of Mechanical Engineering, Ritsumeikan University, Shiga, Japan, <sup>4</sup>Graduate Institute of Mind, Brain and Consciousness (GIMBC), Taipei Medical University, Taipei, Taiwan, <sup>5</sup>Brain and Consciousness Research Centre (BCRC), TMU-Shuang Ho Hospital, New Taipei City, Taiwan

**Coupling:** The process of interaction or information exchange between two or more entities in a given physical, biological or chemical system is often referred to as “coupling”.

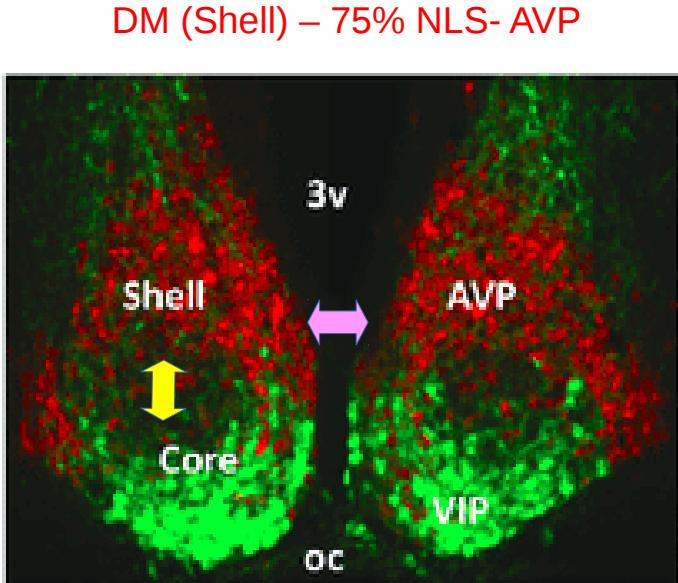
particularly interested in coupled biological oscillators



# Network Structure of the Master Clock Is Important for Its Primary Function

Changgui Gu<sup>1\*</sup>, Jiahui Li<sup>1</sup>, Jian Zhou<sup>1</sup>, Huijie Yang<sup>1</sup> and Jos Rohling<sup>2\*</sup>

<sup>1</sup> Business School, University of Shanghai for Science and Technology, Shanghai, China, <sup>2</sup> Laboratory for Neurophysiology, Department of Cell and Chemical Biology, Leiden University Medical Center, Leiden, Netherlands



➡ Coupling asimetrico: DM-VL ( VIP/AVP)

➡ Coupling simétrico: entre lóbulos

## Cellular coupling:

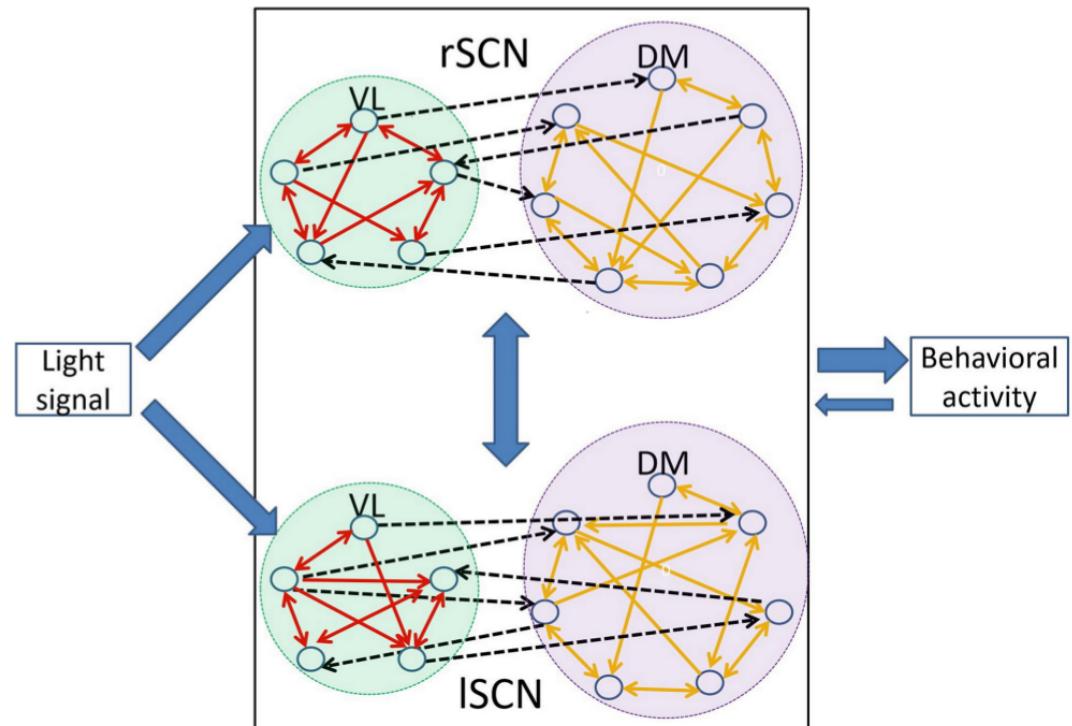
GABA

VIP

AVP

electrical gap junctions ( only 26%)

## Heterogeneidad en los nodos y arquitectura: Comunidades en el SCN



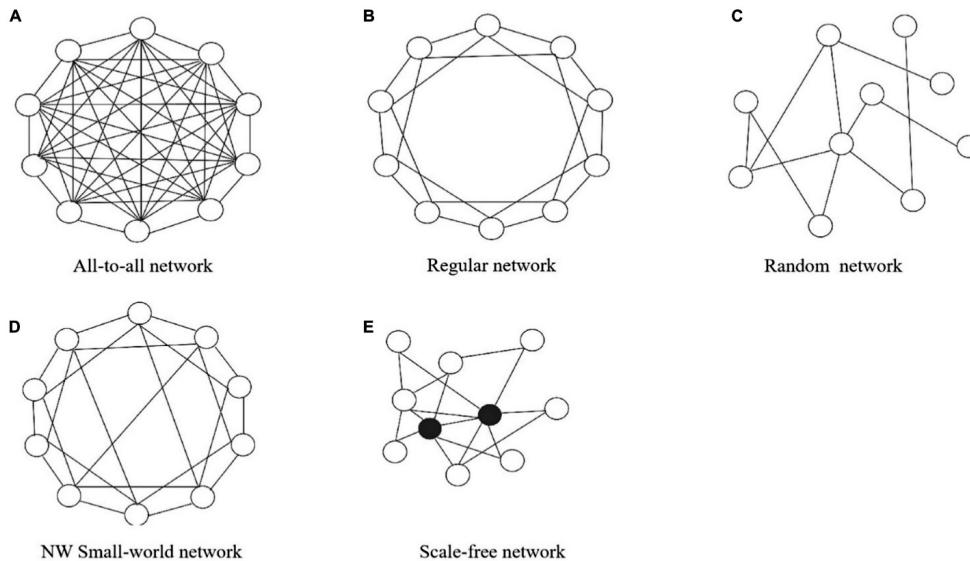
The heterogeneity of nodal properties lies in:

- the difference of the sensitivity to light between VL and DM neurons,
- the intrinsic neuronal periods
- the intrinsic neuronal amplitudes of the different SCN neurons

The heterogeneity of the network structure includes:

- the asymmetrical coupling between the VL and the DM
- the connectivity within these communities

# NETWORK PROPERTIES



NW small-world network: the average shortest path length is short and the cluster coefficient is large,

Scale-free network: the node degrees satisfy a power-law distribution and the average shortest path length is short.

In a regular network: both average shortest path length and cluster coefficient are large

## Network types

All-to-all network (Albert and Barabasi, 2002; Newman, 2003)

Regular network (Albert and Barabasi, 2002; Newman, 2003)

Random network (Bollobás, 2001)

NW Small-world network (Newman, 2002)

Scale-free network (Dorogovtsev et al., 2000; Cohen and Havlin, 2003; Fronczak et al., 2003)

## Network properties

### Degree distribution

$$k = N - 1$$

$$k = K$$

$$P(k) = C_N^k p^k (1-p)^{N-k}$$

$$P(k) = C_N^{k-K} \left(\frac{Kp}{N}\right)^k \left(1 - \frac{Kp}{N}\right)^{N-k+K}$$

$$k \geq K$$

$$P(k) = \frac{2m(m+1)}{k(k+1)(k+2)}$$

$$L = 1$$

$$L \approx \frac{N}{2K}$$

$$L \propto \frac{\ln N}{\ln p(N-1)}$$

$$L = \frac{N}{2db} F(pbN^d), N = \xi$$

$$L \propto \frac{\log N}{\log \log N}$$

$$C = 1$$

$$C = \frac{3(K-2)}{4(K-1)}$$

$$C = p$$

$$C = \frac{3(K-2)}{4(K-1)+4Kp(p+2)}$$

$$C = \frac{m^2(m+1)^2}{4(m-1)} [\ln(\frac{m+1}{m}) - \frac{1}{m+1}] \frac{|\ln t|^2}{t}$$

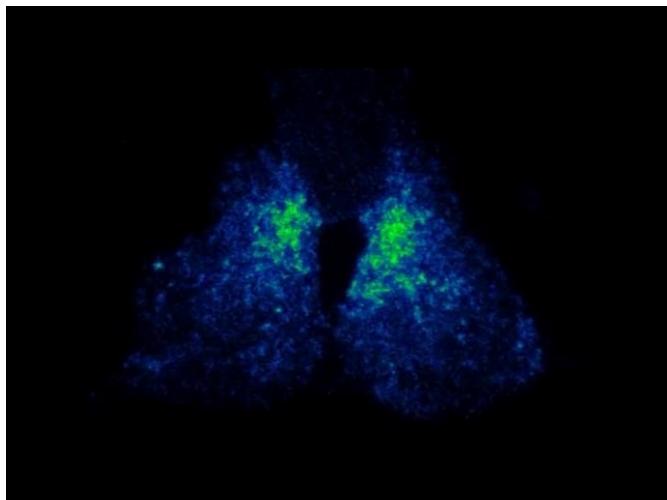
$N$  is the number of nodes,  $k$  is the degree of the node,  $K$  is the degree of the node in random network and is a fixed value in NW small-world network,  $p$  is the probability of two nodes connected,  $\xi$  is Characteristic length unit,  $b$  is the number of network edges,  $d$  is degree of separation, and  $\xi = \begin{cases} \frac{1}{pd}, & d = 1 \\ \frac{1}{pb^{\frac{1}{d}}}, & d > 2 \end{cases}$ ,  $F$  is an universal computing function and  $F(x) = \begin{cases} \frac{1}{4}, & x < 1 \\ \frac{\log 2x}{4x}, & x \geq 1 \end{cases}$ ,  $m$  is the number of existing nodes and  $t$  is the step size in building a scale-free network.

$$\xi = \begin{cases} \frac{1}{pd}, & d = 1 \\ \frac{1}{pb^{\frac{1}{d}}}, & d > 2 \end{cases}$$

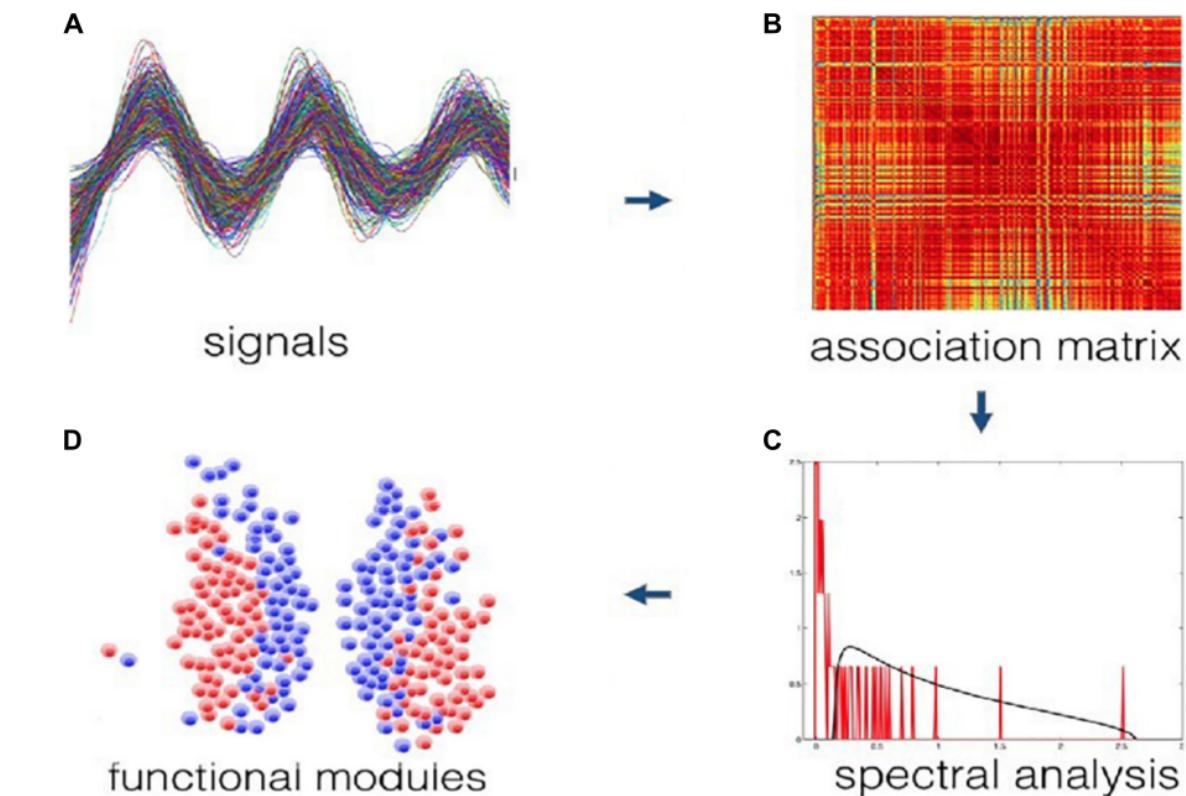
# NETWOEK STRUCTURE EXPLORED BY TIME-SERIES ANALYSIS

The method is purely data-driven, and does not have any knowledge on locations of the neurons that are recorded It also does not use arbitrary thresholds to identify communities.

It guarantees to find a partition of the data into communities that are positively correlated internally and negatively correlated between the communities (Almog et al., 2019).



The communities that were found not always exactly overlapped with the anatomical VL/DM distinction, but they are comparable to the regions described in other literature.

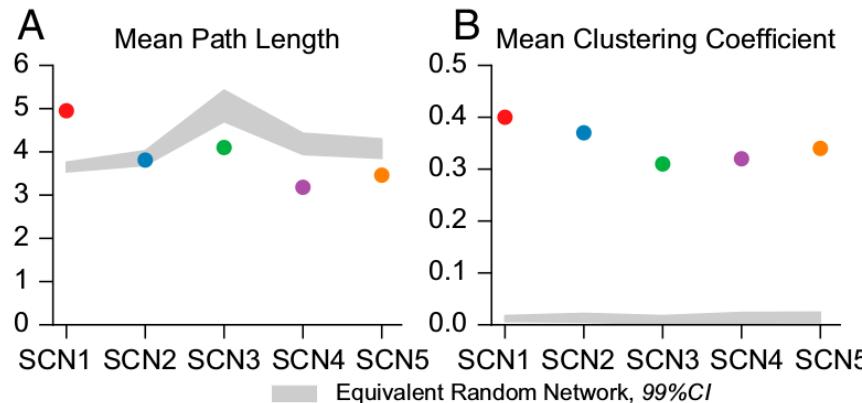


network of the SCN is modular, and contains different communities of neurons

# Properties in the Undirected SCN Network

## SCN network satisfied small-world characteristics

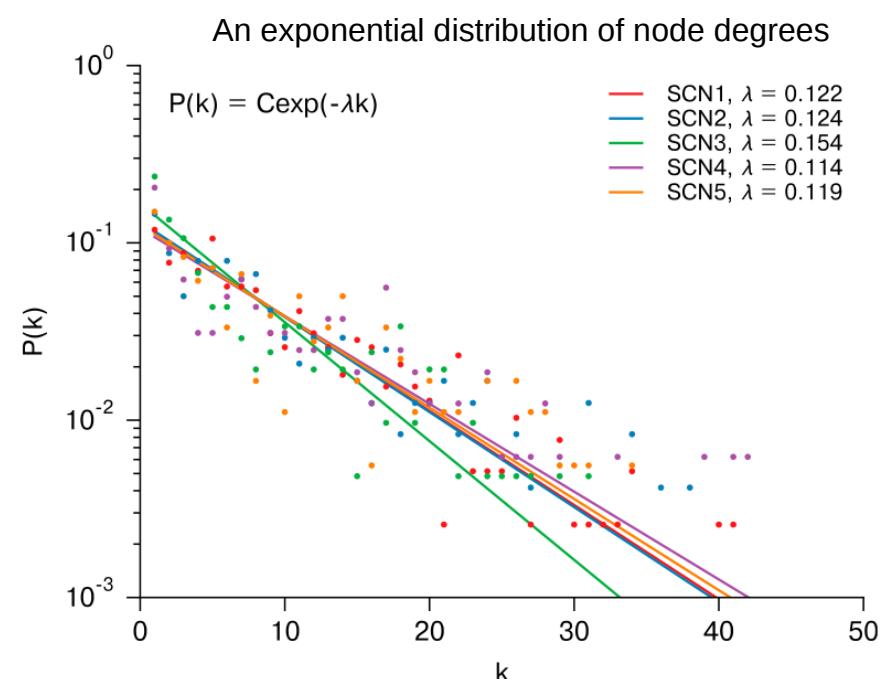
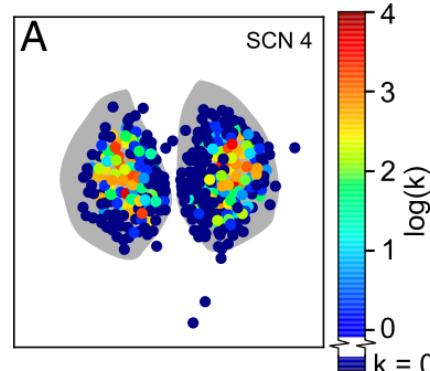
a small average shortest path length



large average clustering coefficient (around 0.35)

**Fig. 3.** SCN functional networks display small-world structure. (A) Average path length is on the same order of magnitude of an equivalent random (Erdos-Renyi) network. (B) Clustering coefficient is a magnitude greater than that of equivalent randomly generated networks. CIs are determined by generation of 10,000 equivalent Erdos-Renyi networks for each SCN.

there were also hubs in this small-world network, and these are preferentially located in the central SCN, with sparsely connected shell-regions surrounding the core. This indicates that the network might also contain some scale-free properties.

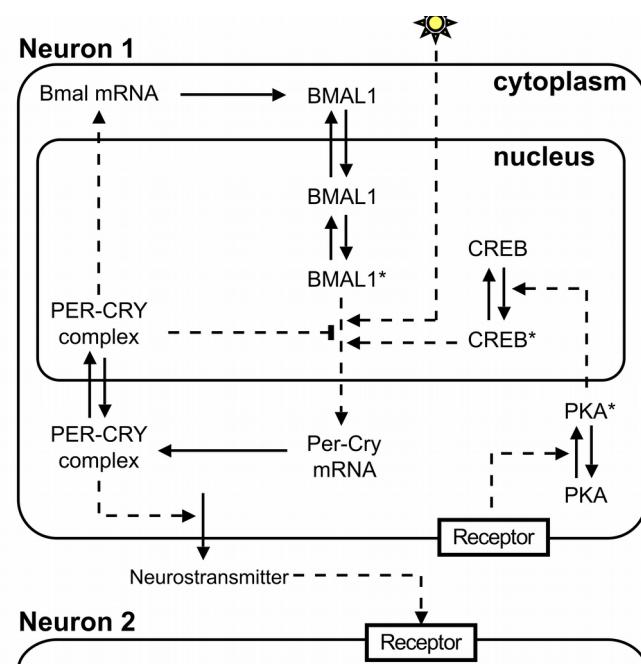


**Fig. 4.** Node degree ( $k$ ) distributions for SCNs 1–5 plotted on a semilog scale. The resulting discrete exponential distributions  $P(k) = C \exp(-\lambda k)$  were fit via numerical optimization of the maximum likelihood, resulting in distribution parameters  $\lambda$  for each network. Each SCN is better fit by a discrete exponential distribution than a discrete power law distribution (likelihood-ratio test,  $P < 0.0005$  for each SCN). The strong agreement between  $\lambda$  shows a consistent network structure across SCNs. This agreement exists for a range of node degrees (Fig. S5).

# NETWORK STRUCTURE EXPLORED BY MATHEMATICAL MODELLING

## Networked Goodwin Model

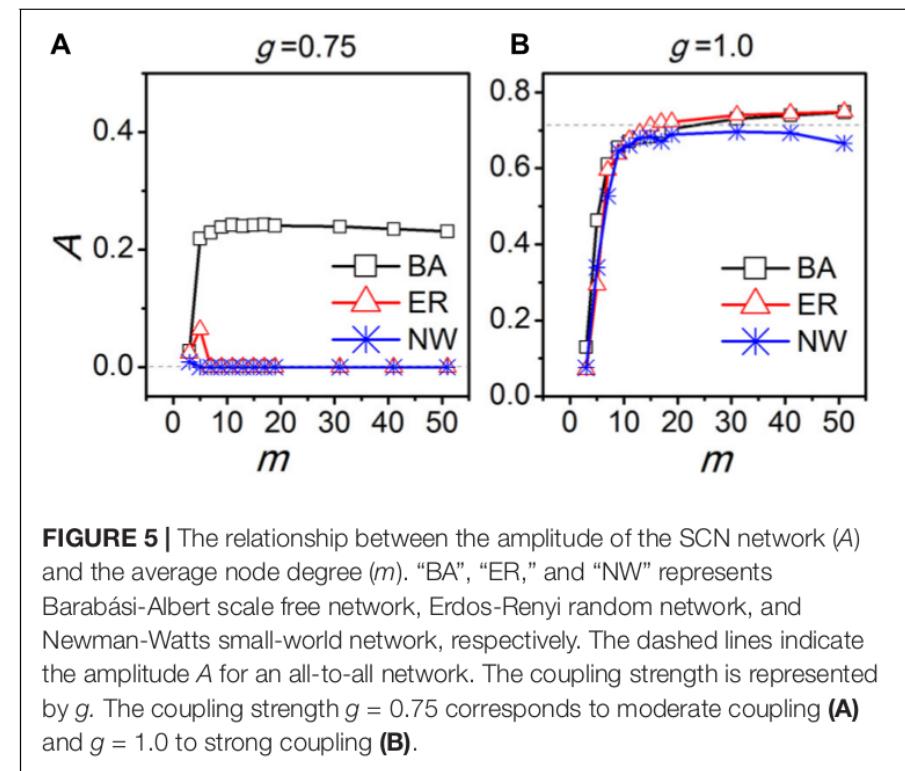
$$\begin{aligned} \dot{x}_i &= \alpha_1 \frac{k_1^n}{k_1^n + z_i^n} - \alpha_2 \frac{x_i}{k_2 + x_i} + \alpha_c \frac{gF_i}{k_c + gF_i} + L_i, \\ \dot{y}_i &= k_3 x_i - \alpha_4 \frac{y_i}{k_4 + y_i}, \\ \dot{z}_i &= k_5 y_i - \alpha_6 \frac{z_i}{k_6 + z_i}, \\ \dot{V}_i &= k_7 x_i - \alpha_8 \frac{V_i}{k_8 + V_i}, \quad i = 1, 2, \dots, N \\ F_i &= \frac{1}{\sum_{j=1}^N e_{ji}} \sum_{j=1}^N V_j e_{ji}, \end{aligned} \quad (2)$$



A single SCN neuron is represented by three variables:

- clock gene mRNA ( $x$ )
- clock protein ( $y$ )
- transcriptional inhibitor ( $z$ )
- neurotransmitter ( $V$ )

- $F_i$ : a local mean-field which is the mean value of the transmitters

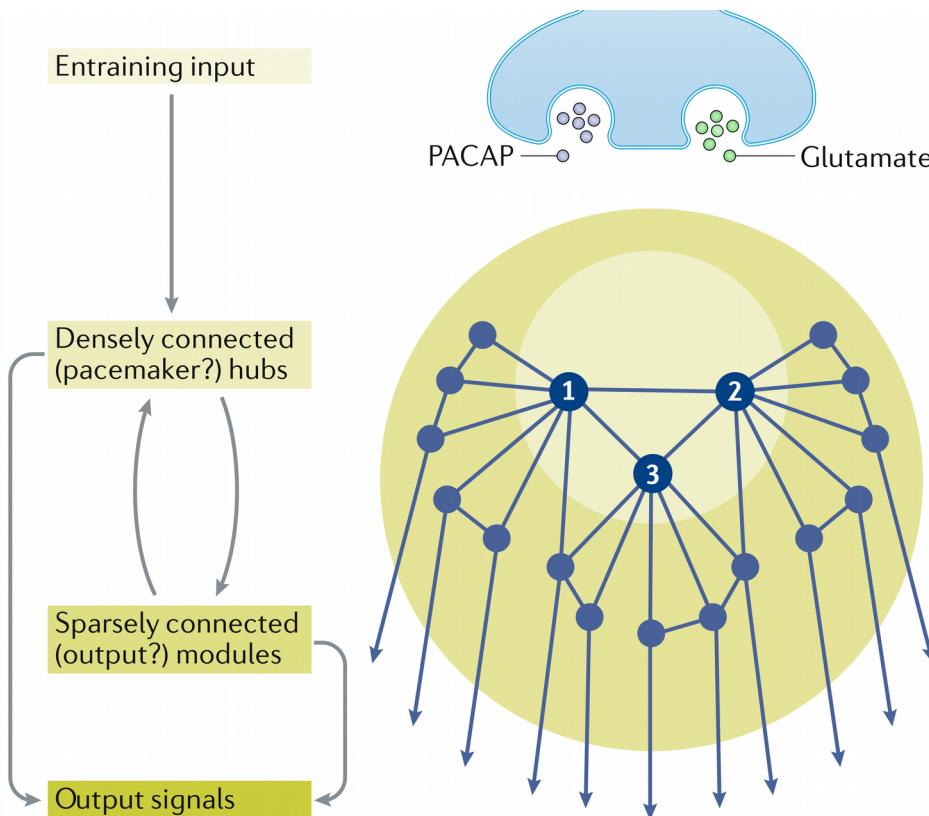


## Future:

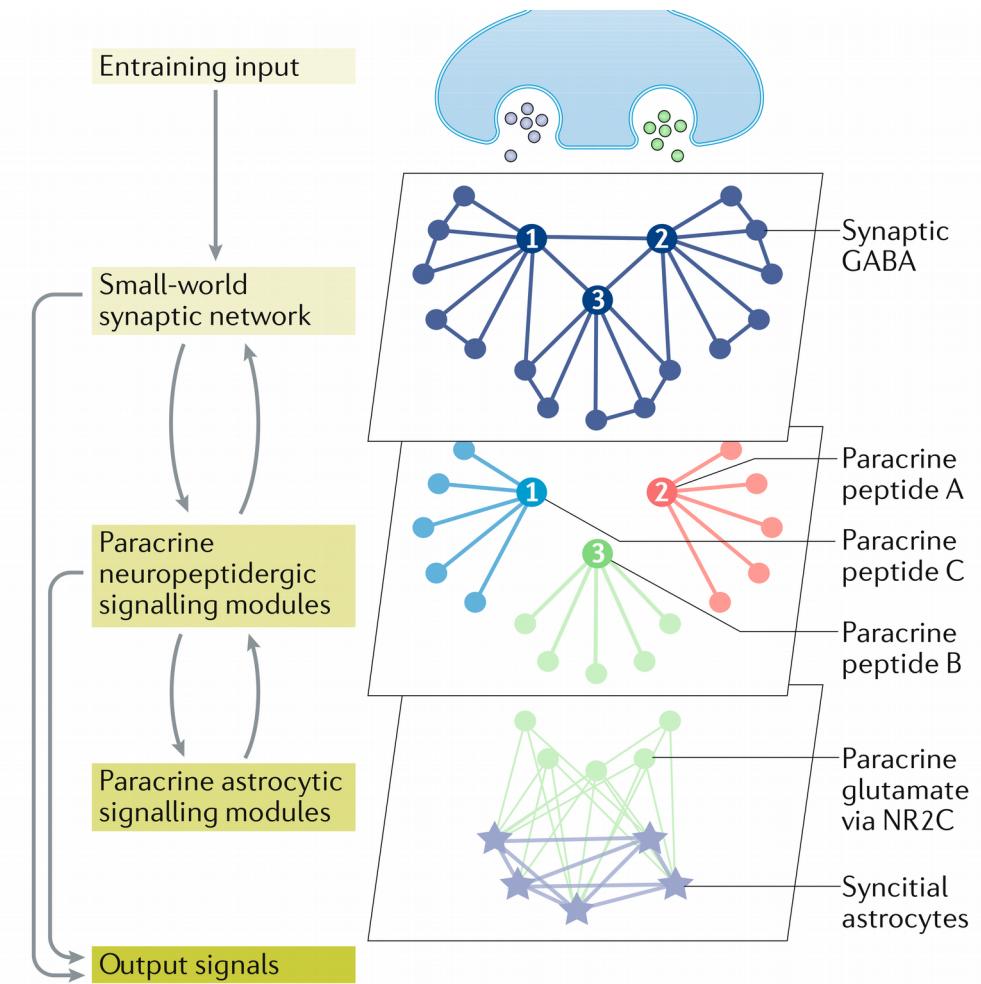
Connections between neurons do not necessarily lead to synchronization in the network. To extend our knowledge on the SCN network, future work should consider a more realistic network structure for the SCN, taking into account the multilayer network for different timescales, including electrical processes and the glial cells, and the attractive links and the repulsive links (Deoskin et al., 2015; Myung et al., 2015; Pauls et al., 2016; Sueviriyan et al., 2020).

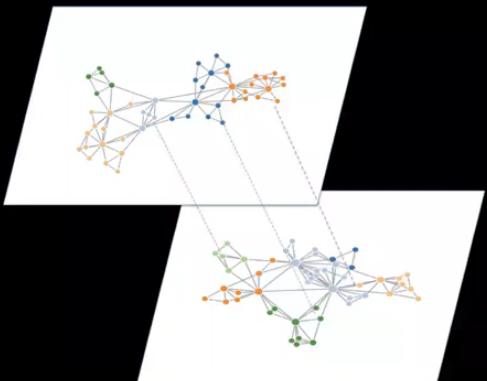
## Multilayer Networks

Hafner et al 2020, Plos Computational Biol



Hastings et al 2018, Nature Reviews





ECMI 2021  
13 April 2021

## MULTILAYER NETWORKS

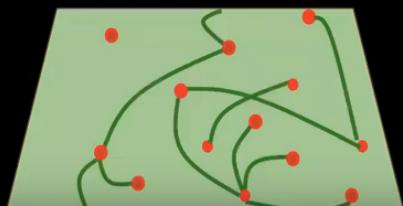
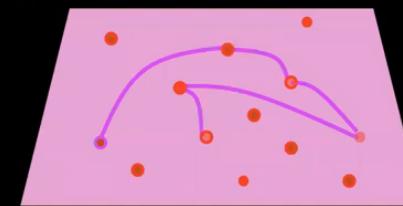
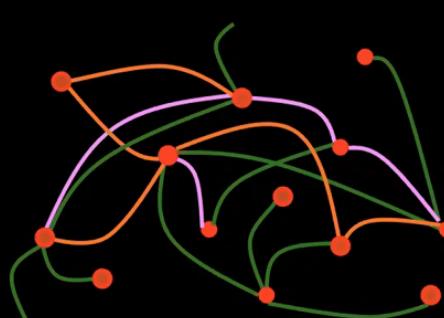
**Ginestra Bianconi**

*School of Mathematical Sciences,  
Queen Mary University of London, UK  
Alan Turing Institute*

The

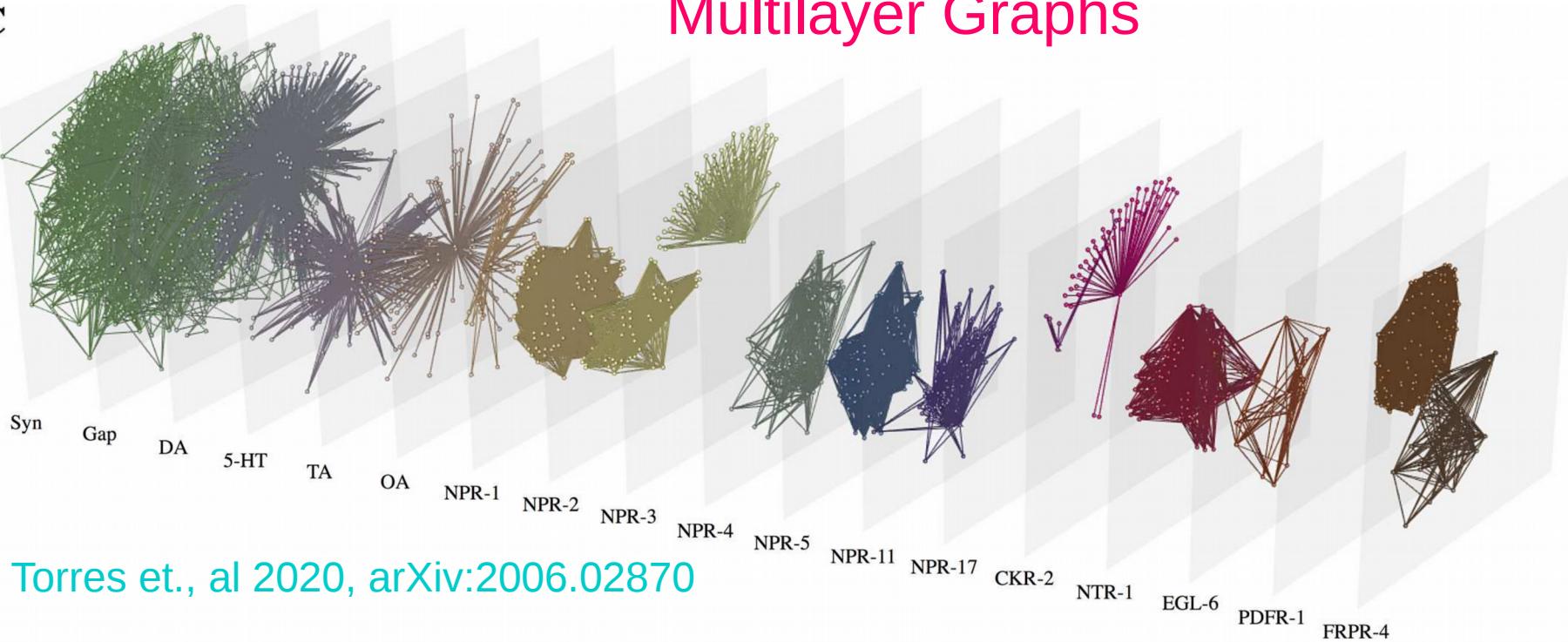


## Multiplex Network



**C**

## Multilayer Graphs



Generally, multilayer graphs consist of a set of graphs that may (or may not) involve the same nodes; each graph in the set comprises a layer. The graph in a given layer contains relations of exactly one type.

when all layers contain the same set of nodes, the representation is called a multiplex graph.

# Evolutionary Constraints on Connectivity Patterns in the Mammalian Suprachiasmatic Nucleus

Connor Spencer <sup>1</sup>, Elizabeth Tripp <sup>2</sup>, Feng Fu <sup>1,3</sup> and Scott Pauls <sup>1\*</sup>

<sup>1</sup>Department of Mathematics, Dartmouth College, Hanover, NH, United States, <sup>2</sup>Department of Mathematics, Sacred Heart University, Fairfield, CT, United States, <sup>3</sup>Department of Biomedical Data Science, Geisel School of Medicine, Dartmouth College, Hanover, NH, United States

Our basic model represents the SCN as a network of agents each with two properties:

- a phase
- a flag (determines if it communicates with its neighbors or not).

Communication comes at a **cost** to the agent  
Synchronization of phases with its neighbors bears a **benefit**.

Here, we use an **evolutionary game theoretic framework to explore how evolutionary constraints can influence the synchronization of the system** under various assumptions on the connection topology,

## Kuramoto oscillator model

$$\dot{\theta}_i = \omega_i + \lambda \sum_{j=1}^n h_{ij} \sin(\theta_j - \theta_i), \quad (1)$$

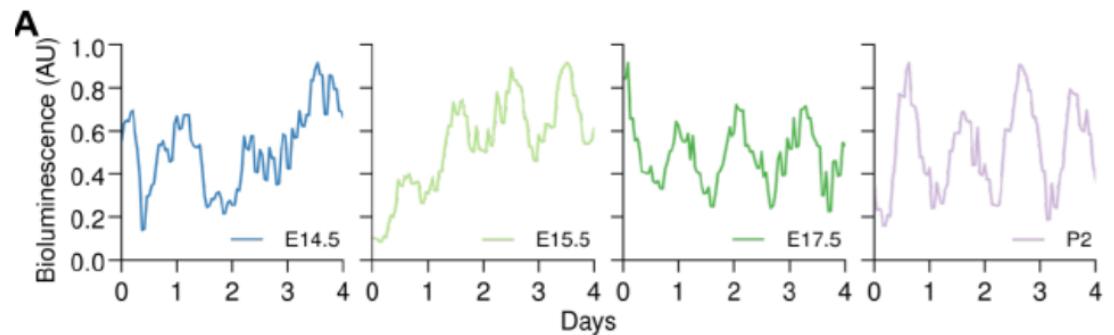
## Kuramoto oscillator model with a strategy attribute

$$\dot{\theta}_i = \omega_i + s_i \lambda \sum_{j=1}^n h_{ij} \sin(\theta_j - \theta_i), \quad (2)$$

Sj

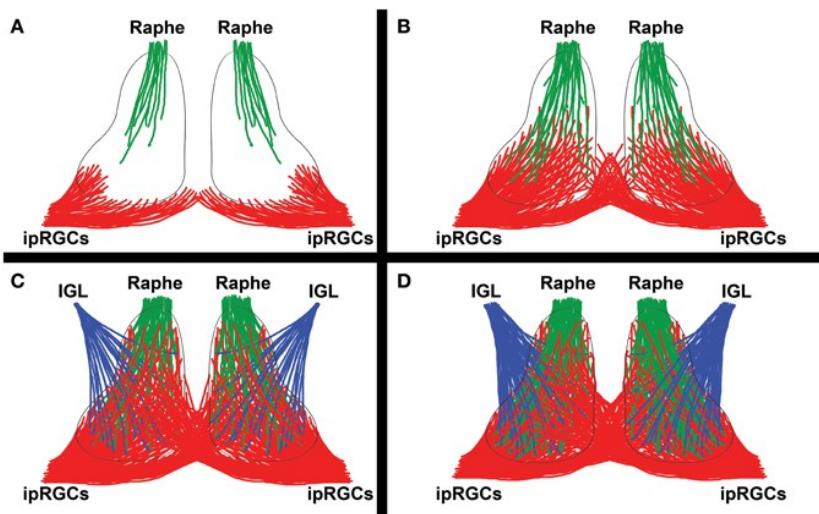
$$A = \begin{bmatrix} B(0) - c & B(1) - c & \dots & B(1) - c & \beta(0) - c & \beta(1) - c & \dots & \beta(1) - c \\ B(1) - c & B(0) - c & \dots & B(2) - c & \beta(1) - c & \beta(0) - c & \dots & \beta(2) - c \\ \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \ddots & \vdots \\ B(1) - c & B(2) - c & \dots & B(0) - c & \beta(1) - c & \beta(2) - c & \dots & \beta(0) - c \\ \beta(0) & \beta(1) & \dots & \beta(1) & 0 & 0 & \dots & 0 \\ \beta(1) & \beta(0) & \dots & \beta(2) & 0 & 0 & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \ddots & \vdots \\ \beta(1) & \beta(2) & \dots & \beta(0) & 0 & 0 & \dots & 0 \end{bmatrix}. \quad (3)$$

# Desarrollo del NSQ

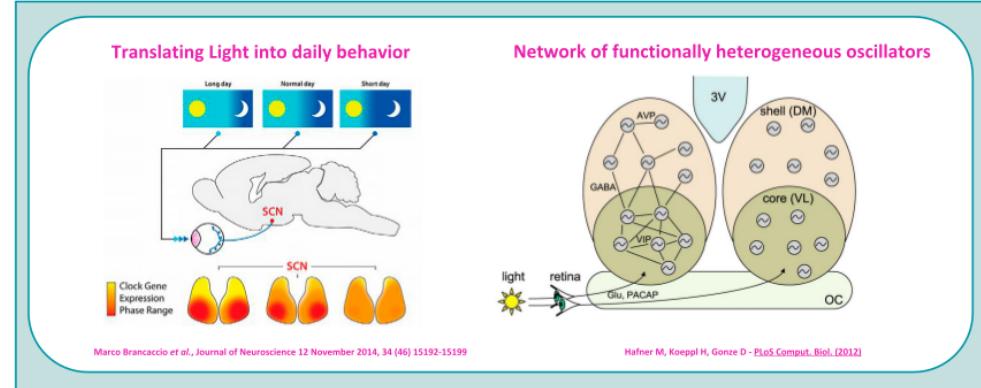


- ✓ Between E14.5 and E15.5 increases the % of rhythmic cells and decreases variability in cycle-to-cycle period.

## Aferentes del SCN



## Introduction



## Mathematical Model

External stimulus

$$\frac{d\theta_{1c}}{dt} = w_{1c} - B \sin(\theta_{1c} - w_f t) - K \sum_{\theta_n \in \text{neighbors}} \sin(\theta_{1c} - \theta_n)$$

$$\frac{d\theta_{rc}}{dt} = w_{rc} - K \sum_{\theta_n \in \text{neighbors}} \sin(\theta_{rc} - \theta_n) \quad \bar{w} = \frac{1}{L^2} \sum_{r=1}^L \sum_{c=1}^L w_{rc}$$

**Global Order Parameter**      **Local Order Parameter**      **Detuning**

$$R = \frac{1}{L^2} \left| \sum_{r=1}^L \sum_{c=1}^L \exp(i\theta_{rc}) \right| \quad R(r) = \frac{1}{L} \left| \sum_{c=1}^L \exp(i\theta_{rc}) \right| \quad |w_f - \bar{w}|$$

