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Heterogeneity effects on the synchronization and entrainment of coupled circadian oscillators

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Abstract—Circadian rhythms in mammals are controlled by neurons in the suprachiasmatic nucleus of the hypothalamus, which are very efficiently entrained by the 24-hour light-dark cycle. Motivated by recent findings on the relevance of neuronal heterogeneity, we model neurons in the suprachiasmatic nucleus as chemically-coupled oscillators with non-negligible heterogeneity in their periods. The system response to the light-dark cycle is studied as a function of the coupling strength, forcing amplitude and neuronal heterogeneity. Our results indicate that neurons respond more coherently to external forcing when the right amount of heterogeneity is present.

1. Introduction

Circadian rhythms are cycles of roughly 24 hours, dependent on the dark-light ambient illumination, and present in the physiological processes of many living entities [1]. In mammals the main mediators between the illumination periodicity and the biological rhythms are the two suprachiasmatic nuclei (SCN), interconnected neural structures (they contain about 10.000 neurons each [1, 2]) located in the hypothalamus.

The activity of the SCN displays oscillations in synchrony with the external light-dark cycle. In vitro, individual neurons produce oscillations with a period ranging from 20 to 28 hours [3, 4], arising from a gene regulatory circuit with a negative feedback loop. Oscillations at the global nuclei level depend however on the interaction between the SCN neurons. Coupling between cells is achieved partly by neurotransmitters [3] such as the vasoactive intestinal polypeptide (VIP), which are also relevant to mediate the influence of the external light cycle onto the nuclei oscillations [5].

Our work builds on the proposal by Gonze et al. [6, 7] that synchronization to the external forcing is facilitated by the fact that interneuronal coupling transforms SCN into damped oscillators which can then be easily entrained. We show [8] that the presence of some level of heterogeneity or dispersion in the intrinsic periods of the oscillators can improve the response of the coupled neuronal system to the external light-dark forcing.

2. The circadian pacemaker

We model the SNC as an ensemble of coupled neurons subjected to a periodic forcing. Each of the neurons, when uncoupled from the others and from the external stimulus, acts as an oscillator with an intrinsic period. Heterogeneity is considered insofar the individual periods are not identical, but show some degree of dispersion around a mean value. For each one of the neurons i, $i = 1, ..., N$ in the SCN we use a four-variable model proposed by Gonze et al. [6], which is based originally on the Goodwin oscillator [9]. The variables (X_i, Y_i, Z_i, V_i) for each cell are as follows: The clock gene *mRNA* (at concentration X_i) produces a clock protein (Y_i), which activates a transcriptional inhibitor (Z_i) and this in turn inhibits the transcription of the clock gene, closing a negative feedback loop. The *mRNA* X_i also excites the production of neurotransmitter V_i, which in the coupled system will be then the responsible of an additional positive feedback loop.

Coupling between the neurons is assumed to depend on the concentration F of the synchronizing factor (the neurotransmitter) in the extracellular medium, which builds-up by contributions from all neurons. Under fast diffusion, the extracellular concentration is assumed to equilibrate to the average, mean-field, cellular neurotransmitter concentration, $F = \frac{1}{N}\sum_{i=1}^{N} V_i$. The resulting model is:

$$\tau_i \frac{dX_i}{dt} = \frac{\nu_1 K_1^4}{K_1^4 + Z_i^4} - \frac{\nu_2 X_i}{K_2 + X_i} + \frac{\nu_c K F}{K_c + K F} + L(t) \quad (1)$$

$$\tau_i \frac{dY_i}{dt} = k_3 X_i - \nu_4 \frac{Y_i}{K_4 + Y_i}, \quad (2)$$

$$\tau_i \frac{dZ_i}{dt} = k_5 Y_i - \nu_6 \frac{Z_i}{K_6 + Z_i}, \quad (3)$$

$$\tau_i \frac{dV_i}{dt} = k_7 X_i - \nu_8 \frac{V_i}{K_8 + V_i}, \quad (4)$$

$$F = \frac{1}{N}\sum_{i=1}^{N} V_i, \quad (5)$$

with $\nu_c = 0.4$ nM/h, $K_c = 1$ nM. Using the values $\nu_1 =$

0.7 nM/h, $\nu_2 = \nu_4 = \nu_6 = 0.35$ nM/h, $\nu_8 = 1$ nM/h, $K_1 = K_2 = K_4 = K_6 = K_8 = 1$ nM, $k_3 = k_5 = 0.7$/h, $k_7 = 0.35$/h, the period of the limit cycle oscillations in the uncoupled system for $\tau_i = 1$ is $T = 23.5$ h.

Heterogeneity in the intrinsic periods has been introduced by multiplying the left-hand-side of each one of the equations (1–4) by a scale factor τ_i, so that the intrinsic period T_i of the isolated neuron i is $\tau_i T$. The variables τ_i are independently taken from a normal random distribution of mean 1 and standard deviation σ. In our numerical simulations we have explicitly checked that the τ_i have never taken a negative value for the values of σ considered here. The standard deviation σ is a measure of the diversity. A value of $\sigma = 0.1$ for example corresponds to a standard deviation of 10% in the individual periods of the uncoupled neurons, close to the observed variation of periods between 20 and 28 hours. Light is incorporated through a sinusoidal time-dependent function $L(t) = L_0\,(1 + \sin \omega t)\,/2$. The signal oscillates between the values $L(t) = 0$ and $L(t) = L_0$ with a period $2\pi/\omega = 24h$.

3. Synchronization quantifiers

Coupling and/or forcing might synchronize the neuronal oscillations. There are several possible measures of how good this synchronization is. The interneuronal synchronization will be quantified by the parameter of synchrony ρ, defined as

$$\rho = \sqrt{1 - \left\langle \frac{\sum_{i=1}^{N} [V_i(t) - F(t)]^2}{\sum_{i=1}^{N} V_i(t)^2} \right\rangle} = \sqrt{\left\langle \frac{F(t)^2}{\frac{1}{N}\sum_{i=1}^{N} V_i(t)^2} \right\rangle}, \tag{6}$$

where $\langle \ldots \rangle$ denotes a time average in the long-time asymptotic state. ρ varies between a value close to 0 (no synchronization) and 1 (perfect synchronization, with all neurons in phase, $V_i(t) = V_j(t), \forall i, j$).

Even if the neurons synchronize perfectly their oscillations, the period of those oscillations may not coincide with the mean period T of the individual oscillators or with the period $2\pi/\omega$ of the external forcing. In fact, in the unforced (no light) case, the period of the common oscillations (for the set of parameters given before, a dispersion of $\sigma = 0.05$ and a coupling $K = 0.5$) is approximately equal to 26.5 h whereas the period of the forcing is $2\pi/\omega = 24$ h and the mean period of the individual uncoupled oscillators is $T = 23.5$ h. Thus, we are also concerned about the quality of the global response of the neuronal ensemble to the external forcing $L(t)$. A suitable measure of this response can be defined from the time series of the average gene concentration,

$$\mathbf{X}(t) = \frac{1}{N} \sum_{i=1}^{N} X_i(t), \tag{7}$$

by computing the spectral amplification factor R [10],

$$R = \frac{4}{L_0^2} \left| \langle e^{-i\omega t} \mathbf{X}(t) \rangle \right|^2. \tag{8}$$

R is the normalized amplitude of the Fourier component at the forcing frequency ω of the time series $\mathbf{X}(t)$.

4. Results

Figure 1 shows the influence of the neuronal diversity σ on the different characteristics of the neural synchronization processes at a light level $L_0 = 0.0025$ and two values of the neuronal coupling. Results for additional parameter values can be found in [8].

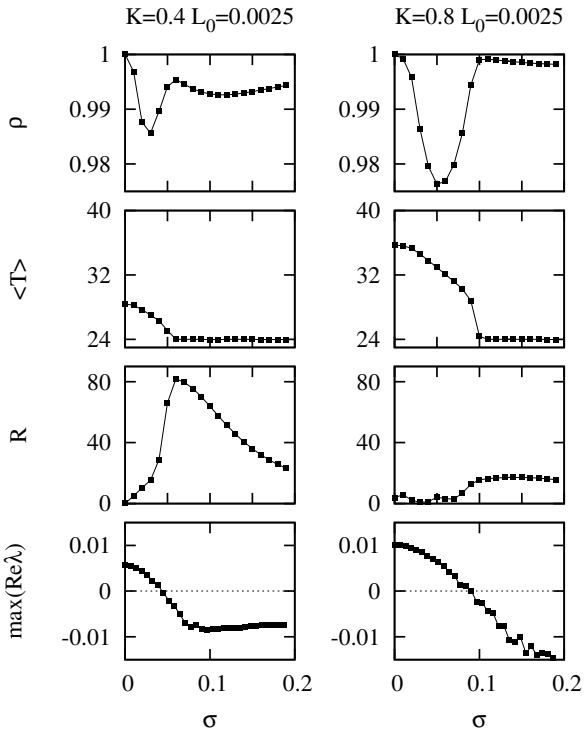

Figure 1: Synchronization characteristics as a function of diversity σ. The two columns correspond to two different values of the coupling constant K. Upper row: the synchrony parameter ρ; second row: the mean $\langle T \rangle$ of the individual periods T_i; third row: the response order parameter R; bottom row: the maximum real part of the eigenvalues of the linearized system.

The upper panels show ρ as a function of diversity σ. ρ first decreases by increasing σ until $\sigma \lesssim 0.04 - 0.05$, but then it develops a maximum. The range of values of L_0 for which this non-monotonous behavior is observed depends on the coupling constant K: the larger K, the larger the range of L_0.

As stated before, the fact that neurons synchronize amongst themselves does not mean that they synchronize to the forcing by light. To study this point, we have computed the individual periods T_i, $i = 1, \ldots, N$, of the oscillators in the ensemble (a mean period is used in cases of imperfect periodicity). The second row in Fig. 1 shows the mean value $\langle T \rangle = \frac{1}{N}\sum_{i=1}^{N} T_i$ as a function of σ for two values of K. Although, by construction, individual neurons have periods that fluctuate around $T = 23.5$ h, the period

of the resulting synchronized oscillations that occur in the unforced but coupled ($L_0 = 0$, $K > 0$) case, increases with increasing coupling K. For example, $\langle T \rangle \approx 29$ and 36 h for $K = 0.4$ and 0.8, respectively, mostly independent of the value of σ. As the forcing sets in, at low values of the coupling strength, the mean period is $\langle T \rangle = 24$ h for all values of L_0 and σ. As the coupling between neurons increases, larger values of L_0 and/or σ are needed in order for the mean period to coincide with that of the external forcing. The important feature is that for low light intensity it is possible to achieve a mean period of 24 h by increasing the neuronal diversity. For example, in Fig.1, while identical coupled neurons have periods close to 30 h, increasing σ induces an adjustment of the period to 24 h. The transition towards $\langle T \rangle = 24$ h is rather sharp, specially for large K. This is a clear manifestation that diversity indeed is able to improve the response to the external forcing. The same conclusion about the constructive role of diversity can be reached by looking at the measure of response R (third row in Fig. 1). These plots show that system response to the periodic light forcing displays a maximum value at an intermediate value of diversity σ. This indicates that it is possible to improve neuronal synchronization to the daily-varying light input by taking σ close to an optimal value. In fact this maximum can be very large as compared with the R value at zero diversity (see the case $K = 0.4$ in Fig. 1) so that one can say that one of the most noticeable effects of a non-vanishing neuronal diversity is to give the system the capacity to respond efficiently to the 24h forcing in situations of small or no response at this frequency in the absence of diversity (the non-diverse neuronal ensemble could be oscillating at a different frequency, as revealed by high values of ρ).

4.1. Diversity and oscillator death

As an explanation for the improved response to the external forcing with diversity we argue that the main effect of the increase of the diversity is to take the oscillators into a regime of oscillator death [11] in which they can be easily entrained by the varying part of the forcing. To understand this mechanism we first split the forcing into a constant (the mean) and a time varying part: $L(t) = (L_0/2) + (L_0/2)\sin(\omega t)$. Taking only the constant part, $L(t) = L_0/2$, Fig. 2 shows that the oscillators go from self-sustained oscillations to oscillator death, i.e. the amplitude of the self-sustained oscillations vanishes, as σ increases. Once oscillators are damped, they would respond quasi-linearly to periodic forcing, at least if this forcing is not too large, and linear oscillators always become synchronized to the external forcing, independently of their internal frequency. This is consistent with what is seen also in Fig. 2, where the neurons in the case of low heterogeneity oscillate synchronously with each other, but their common period is larger than the one of the light forcing. Only when diversity brings the neurons to oscillator death can all of them be entrained to the period of the forcing signal. The mechanism is related to the one discussed by [6, 7], but here we stress that neuron heterogeneity, as opposed to internal neuron parameters and couplings, is enough to damp the collective neuron oscillations and bring the system to a non-oscillating state where it can be more easily entrained.

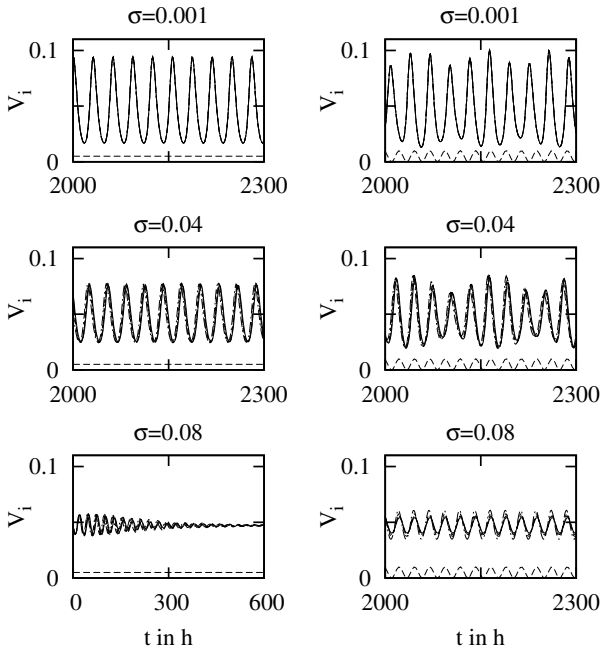

Figure 2: Left panels: time-dependent amplitude of the V_i variable for a few selected neurons in the presence of constant light and increasing σ. Right panels: amplitude of the same neurons with sinusoidal light and increasing σ. The thin line on the bottom of the graphs is the external light signal. $K = 0.6$. Diversity increases from top to bottom.

An alternative way of checking this mechanism based on *diversity-induced oscillator death* is by analyzing the stability of the steady state of the system of Eqs. (1–5) when considering a constant forcing $L(t) = L_0/2$. The fixed point solution of the model can be calculated, Eqs. (1–5) linearized around such steady state, and the eigenvalues of the stability matrix computed for several realizations of diversity parameters τ_i. In each case, the positive or negative character of the real part of the eigenvalue with the largest real part indicates the instability or stability, respectively, of the fixed point solution. Fig.1 shows the mean of that maximum real part of the eigenvalues averaged over various realizations of the time scales τ_i, for $N = 200$ coupled neurons, as a function of σ. In every diagram we can see that low diversity yields an unstable steady state. This is where self-sustained oscillations are observed. The eigenvalue becomes negative precisely at the σ value for which the other indicators identify the onset of the 24h-entrainment.

A qualitative argument explaining the diversity-induced oscillator death in our system of coupled neurons goes as follows: We know from [6] that a single oscillator can switch from a limit cycle to a stable steady state by adding

a constant light forcing (i.e. replacing F in Eq. (1) by a time-independent constant in the single-oscillator case) of sufficient strength. Furthermore we have observed that the amplitude of the oscillations decreases with rising diversity (see Fig. 2), but the mean does not change. In a system with low diversity we have large oscillations of F around that mean value. If this value, taken as a constant, determines a stable steady state, then we argue that the large oscillations lead the system into unstable regions, whereas, by increasing σ the amplitude is decreased and the concentrations do not leave the neighborhood of the stable fixed point, thus finding themselves damped all the time. This is a possible mechanism for the *diversity-induced oscillator death* phenomenon.

5. Conclusion

In this work we have analyzed the role of diversity in favoring the entrainment of a system of coupled circadian oscillators. We introduce non-negligible heterogeneity in the periods of all neurons in the form of quenched noise. This is achieved by rescaling the individual neuronal periods by a scaling factor drawn from a normal distribution. The system response to the light-dark cycle periodicity has been studied as a function of the interneuronal coupling strength and neuronal heterogeneity.

Most of the cases of order induced by heterogeneity or noise carried out so far [10, 12, 13, 14, 15], emphasize the fact the diversity directly improves oscillator synchronization. In our case the mechanism is rather different. Diversity does not improve system synchronization directly. This is achieved indirectly, by leading first to a diversity-induced stabilization of the fixed points of the neurons forming the system. Once steady concentrations are asymptotically stable, it is much better entrainable by the external forcing, so that the damped neurons adapt easily to the external forcing (and then, in addition, they appear as synchronized between them).

Of course, it is an open question whether the observed diversity in the periods of the neurons of the SCN has been tuned by evolution in order to display a maximum response to the 24 h dark-light natural cycle. A detailed experimental check of our predictions would require to be able to vary the amount of diversity in the neuronal ensemble.

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References

[1] S. Reppert, D. Weaver. "Coordination of circadian timing in mammals." *Nature*, vol. 418, pp. 935–941, 2002.

[2] R. Moore, J. Speh, R. Leak. "Suprachiasmatic nucleus organization." *Cell and Tissue Research*, vol. 309, pp. 89–98, 2002.

[3] S. Honma, W. Nakamura, T. Shirakawa, K. Honma. "Diversity in the circadian periods of single neurons of the rat suprachiasmatic nucleus depends on nuclear structure and intrinsic period." *Neuroscience Letters*, vol. 358, pp. 173–176, 2004.

[4] D. Welsh, D. Logothetis, M. Meister, R. S.M. "Individual neurons dissociated from rat suprachiasmatic nucleus express independently phased circadian firing rhythms." *Neuron*, vol. 14, pp. 697–706, 1995.

[5] S. J. Aton, C. S. Colwell, A. J. Harmar, J. Waschek, E. D. Herzog. "Vasoactive intestinal polypeptide mediates circadian rhythmicity and synchrony in mammalian clock neurons." *Nature Neuroscience*, vol. 8, pp. 476–483, 2005.

[6] D. Gonze, S. Bernard, C. Waltermann, A. Kramer, H. Herzel. "Spontaneous Synchronization of Coupled Circadian Oscillators." *Biophys. J.*, vol. 89, pp. 120–129, 2005.

[7] S. Bernard, D. Gonze, B. Čajavec, H. Herzel, A. Kramer. "Synchronization-induced rhythmicity of circadian oscillators in the suprachiasmatic nucleus." *PLoS Comput. Biol.*, vol. 3, p. e68, 2007.

[8] N. Komin, A. C. Murza, E. Hernández-García, R. Toral. "Synchronization and entrainment of coupled circadian oscillators." *Interface Focus*, vol. 1, pp. 167–176, 2011.

[9] B. C. Goodwin. "Oscillatory behavior in enzymatic control processes." *Adv. Enzyme Regul.*, vol. 3, pp. 425–438, 1965.

[10] L. Gammaitoni, P. Hänggi, P. Jung, F. Marchesoni. "Stochastic resonance." *Rev. Mod. Phys.*, vol. 70, pp. 223–287, 1998.

[11] G. Ermentrout. "Oscillator death in populations of 'all to all' coupled nonlinear oscillators." *Physica D*, vol. 41, pp. 219–231, 1990.

[12] L. Gammaitoni, P. Hänggi, P. Jung, F. Marchesoni. "Stochastic resonance: A remarkable idea that changed our perception of noise." *Eur. Phys. J. B*, vol. 69, pp. 1–3, 2009.

[13] C. J. Tessone, C. R. Mirasso, R. Toral, J. D. Gunton. "Diversity-induced resonance." *Phys. Rev. Lett.*, vol. 97, 194101, 2006.

[14] A. Pikovsky, J. Kurths. "Coherence resonance in a noise-driven excitable system." *Phys. Rev. Lett.*, vol. 78, pp. 775–778, 1997.

[15] E. Ullner, J. Buceta, A. Diez-Noguera, J. García-Ojalvo. "Noise-induced coherence in multicellular circadian clocks." *Biophys. J.*, vol. 96, p. 3573, 2009.