Supporting Material
Robust entrainment of circadian oscillators requires specific phase response curves

Benjamin Pfeuty, Quentin Thommen and Marc Lefranc

April 26, 2011

This supplementary material presents the calculations and the procedures used to derive robustness quantities that measure how sensitive are circadian oscillators to daylight fluctuations. It contains three sections: (1) general expression of robustness quantities, (2) robustness quantities in the weak forcing limit, (3) robustness analysis of experimental PRCs.

1 General expression of robustness quantities

Let assume a non-linear oscillator subjected to a periodic and temporally-restricted forcing. If the forcing is not too strong or the limit cycle attracts nearby orbits sufficiently quickly, the dynamics of a periodically forced non-linear oscillator can be approximated by an unidimensional first-return map (Rand *et al*, 2006):

$$\phi_{n+1} = F(\phi_n) = \phi_n - \gamma + V(\phi_n) \tag{1}$$

where ϕ_n is the phase of the oscillator at dawn and the function $V(\phi)$ is equivalent to a phase response curve (PRC). A stable fixed point ϕ^* of the map satisfies $V(\phi^*) = \gamma$ and $-2 < \chi < 0$ with $\chi \equiv V'(\phi^*)$ (we use in the following prime notation for derivative of V with respect to the phase). We consider that forcing properties vary slightly among individuals with respect to some average daylight forcing $\epsilon_0 L_0(u)$:

$$\epsilon L(u) = \epsilon_0 (L_0(u) + \eta\, \tilde{L}(u)) \tag{2}$$

where L and L_0 are normalized with $1/\tau_D \int_0^{\tau_D} L(t)dt = 1$. This normalization must be preserved by an appropriate normalization of $\tilde{L}$ which depends on the type of fluctuations (amplitude or profile) considered (appendix B). We can now expand ϕ^* and χ up to first order in η :

$$\begin{cases} \phi^*(\eta) &= \phi^*(0) + \eta \frac{d\phi^*(0)}{d\eta} + 0(\eta^2) \\ \chi(\eta) &= \chi(0) + \eta \frac{d\chi(0)}{d\eta} + 0(\eta^2) \end{cases} \tag{3}$$

We introduce the sensitivity quantities Π and Σ that correspond to the squares of the linear variation of ϕ^* and of the relative variation of χ in response to small fluctuations η:

$$\begin{cases} \Pi & = [\frac{d\phi^*(0)}{d\eta}]^2 \\ \Sigma & = [\frac{1}{\chi(0)}\frac{d\chi(0)}{d\eta}]^2 \end{cases} \tag{4}$$

2 Robustness quantities in the weak forcing limit

2.1 Phase reduction method

Let us consider a forced circadian oscillator described by the deterministic differential equation:

$$d\mathbf{X}/dt = \mathbf{F}(\mathbf{X}, \mathbf{p_0} + \epsilon L(t)\mathbf{dp}) \tag{5}$$

where the light modulates the parameters with a T-periodic temporal profile $L(t)$. For small enough value of ϵ, Eq. 5 can be expanded and phase reduction method can be applied in the neighborhood of the free-running limit cycle trajectory $\mathbf{X}_\gamma$ of period T_0. If T and T_0 differ with an order of ϵ, the following differential equation for the evolution of the oscillator's phase at the leading order applies:

$$d\phi/dt = 1 + \epsilon L(\phi)Z(\phi) + \mathbf{0}(\epsilon^2) \tag{6}$$

where ϕ is the phase in time unit and $Z(\phi)$ is the infinitesimal impulse phase response curve (IPRC):

$$Z(\phi) \equiv \left(\frac{\partial\phi(\mathbf{X}_\gamma(\phi))}{\partial\mathbf{X}}\right)^T \left(\frac{\partial\mathbf{F}(\mathbf{X}_\gamma(\phi), \mathbf{p_0})}{\partial\mathbf{p}}\right)\mathbf{dp} \tag{7}$$

which indicates the steady-state phase-shift that results from an infinitesimal delta-impulse light stimulus and can be derived from the parametric or state impulse phase response function (Taylor *et al*, 2008). Using an averaging method (Kuramoto, 1984), one can predict the phase change $V(\phi)$ (defined by Eq. 1) induced by light during the day when the oscillator phase at dawn is ϕ:

$$V(\phi) = \epsilon\int_0^{T_0} L(u)Z(u+\phi)du \tag{8}$$

2.2 Π and Σ in the weak forcing limit

Decomposing the light temporal profile into an average and a fluctuating component (Eq. 2), Eq. 8 gives:

$$V(\phi) = V_0(\phi) + \eta\tilde{V}(\phi) \tag{9}$$

where $V_0(\phi)$ and $\tilde{V}(\phi)$ are the convolution of Z with $\epsilon_0 L_0$ and $\epsilon_0\tilde{L}$ respectively.

Expanding Eq. 9 up to first order in η using the expression of $\phi^*(\eta)$ in Eq. 3 and the property that $V(\phi^*(\eta)) = V_0(\phi^*(0)) = \gamma$ leads to:

$$\eta\big[V_0'(\phi^*(0))\frac{d\phi^*(0)}{d\eta} + \tilde{V}(\phi^*(0))\big] + 0(\eta^2) = 0 \tag{10}$$

In the following we use $\phi_0^* \equiv \phi^*(0)$. By neglecting higher-order terms and introducing the quantity Π (Eq. 4), we obtain:

$$\Pi = \left[\frac{\tilde{V}(\phi_0^*)}{V_0'(\phi_0^*)}\right]^2 \tag{11}$$

To compute Σ in the weak forcing limit, we begin with the expression derived from Eq. 4 and Eq. 3 in term of the first derivative of V:

$$\Sigma = \left[\frac{V'(\phi^*(\eta)) - V_0'(\phi_0^*)}{\eta V_0'(\phi_0^*)}\right]^2 \tag{12}$$

By inserting Eq. 9 into Eq. 12 and expanding for η small using Eq. 3, we obtain at the leading order:

$$\Sigma = \left[\frac{\tilde{V}'(\phi_0^*)}{V_0'(\phi^*)} - \frac{\tilde{V}(\phi_0^*)V_0''(\phi_0^*)}{V_0'(\phi_0^*)^2}\right]^2 \tag{13}$$

2.3 Fluctuations in the daylight intensities

The simplest example of fluctuation in the light driving cycle is when $\tilde{L}(u) = L_0(u)$, such that $\tilde{V} = V_0$. The general expression for Π and Σ in Eq. 11 and 13 becomes:

$$\Pi = \left[\frac{V_0(\phi_0^*)}{V_0'(\phi_0^*)}\right]^2 = \left[\frac{\gamma}{\chi}\right]^2 \tag{14}$$

and

$$\Sigma = \left[1 - \frac{V_0(\phi_0^*)V_0''(\phi_0^*)}{V_0'(\phi_0^*)^2}\right]^2 = \left[1 - \frac{V_0''(\phi_0^*)\,\gamma}{\chi^2}\right]^2 \tag{15}$$

2.4 Fluctuations in daylight profiles

Alternatively, one can also consider the case where only the temporal profile changes while the daily light intensity average remains unchanged:

$$\int_0^{\tau_D} \tilde{L}(u)\, du = 0.$$

We assume that the variance of the perturbation is normalized with $1/\tau_D \int_0^{\tau_D} \tilde{L}(u)^2\, du = 1$ so as to preserve the normalization of $L(u)$ given by $1/\tau_D \int_0^{\tau_D} L(t)dt = 1$.

For such type of fluctuations that is likely to vary from day to day, we only focus on the sensitivity Π. Rewritting Eq. 11 in term of the IPRC by using Eq. 8 leads to:

$$\Pi = \left[\frac{\int_0^{\tau_D} Z(u+\phi_0^*)\,\tilde{L}(u)\,du}{\int_0^{\tau_D} Z'(u+\phi_0^*)L_0(u)\,du} \right]^2 \tag{16}$$

One can also estimate the Π sensitivity in response to sinusoidal daylight fluctuations of period τ_D/k and phase ψ_k. Decomposing $\tilde{L}(u)$ as a Fourier series:

$$\tilde{L}(u,k,\psi) = \sum_k \tilde{l}_k \cos(k\,u/\tau_D + \psi_k) \tag{17}$$

and substituting Eq. 17 in Eq. 16 leads to:

$$\Pi(\psi) = \left[\frac{\sum_k \tilde{l}_k (a_k\,\cos(\psi_k) + b_k\,\sin(\psi_k))}{\int_0^{\tau_D} Z'(u+\phi_0^*)L_0(u)\,du} \right]^2 \tag{18}$$

where a_k and b_k as the kth cosine and sine Fourier coefficients of the IPRC truncated on the subinterval in which daylight perturbs the clock (usually daytime). Summing over ψ_k between 0 and 2π gives the averaged phase associated with a arbitrary fluctuations of zero mean ($\delta l_0 = 0$) and unitary norm ($\sum_k \tilde{l}_k^2 = 1$):

$$\Pi = < \Pi(\psi) >_\psi = 1/2\pi \int_0^{2\pi} \Pi(\psi) d\psi = \sum_k \tilde{l}_k^2\, \Pi_k \tag{19}$$

where Π_k are the phase-shift variances associated with sinusoidal fluctuations of period τ_D/k :

$$\Pi_k = \frac{\epsilon_0^2 (a_k^2 + b_k^2)}{2\,\chi^2} \tag{20}$$

Such quantities can be computed for instance in the case where Z is a decreasing linear function on the interval of coupling which leads to $\Pi_k = \tau_D^2/8\,k^2\,\pi^2$ for $L(u) = 1$ during daytime.

3 Robustness analysis of experimental PRCs

In this section, we briefly describe the procedure used to analyse the experimental PRCs. First, the fitting procedure adjusts the discrete experimental data t_j, y_j with $j = 1, N$ by a continuous function $f(t)$. It is based on the minimization of both the fitting error and the second derivative of f:

$$S_1 = \frac{k_1}{N} \sum_{j=1,N} (y_j - f(x_j))^2 + \frac{k_2}{T} \int_0^T [f''(t)]^2\,dt \tag{21}$$

The ratio k_2/k_1 is adjusted typically between 5 and 15 according to the data.

For experimental PRCs that are measured using relatively short light pulses of less than one hour, the estimated IPRC, z, is assumed to be roughly equal to f. Otherwise we perform a deconvolution operation to extract the estimated IPRCs, using a genetic algorithm to find the function, z, that minimizes the error:

$$S_2 = \int_0^T \left[f(t) - \int_t^{t+\tau_D} z(u)du \right]^2 dt \tag{22}$$

To estimate Π-values associated with experimental PRCs, we use Eq. 20 using the estimated IPRCs, z.

References

Kuramoto Y (1984) Chemical Oscillations, Waves, and Turbulence. Springer, Berlin.

Rand DA, Shulgin BV, Salazar D, Millar AJ. (2006) Uncovering the design principles of circadian clocks: mathematical analysis of flexibility and evolutionary goals. J Theor Biol, 238: 616-635.

Taylor SR, Gunawan R, Petzold LR, Doyle FJ 3rd (2008) Sensitivity Measures for Oscillating Systems: Application to Mammalian Circadian Gene Network. IEEE Trans Automat Contr, 53: 177-188.