Are circadian amplitudes and periods correlated? A new *twist* in the story

Marta del Olmo[1], Christoph Schmal[1], Camillo Mizaikoff[1], Saskia Grabe[1], Christian Gabriel[2,3], Achim Kramer[3], and Hanspeter Herzel[1]

[1]**Institute for Theoretical Biology – Humboldt Universität zu Berlin and Charité Universitätsmedizin Berlin, Philippstraße 13, 10115 Berlin, Germany.**
[2]**Institute for Virology – Charité Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany.**
[3]**Institute for Medical Immunology – Laboratory of Chronobiology, Charité Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany.**

Study design and conceptualization: M.dO. and H.H.; Methodology: M.dO., C.S., and H.H.; Investigation: M.dO., C.S. and H.H.; Resources and data curation: M.dO., C.S., C.M., and H.H.; Writing (original draft): M.dO. and H.H.; Writing (review & editing): M.dO., C.S., S.G., C.G., A.K. and H.H.; Funding acquisition: A.K. and H.H.

Corresponding author: Marta del Olmo (marta.del-olmo@charite.de)

Supplementary Material

Table S1. Summary of parametric twist effects upon changes of model parameters in the Almeida model. Model parameters were changed individually around ±20% their default parameter value (see Table 2 in main text) to simulate oscillator heterogeneity and study amplitude-period correlations from all variables of the ensemble. Due to the synergies of feedback loops present in the Almeida model [1], different parametric twist effects can appear for variations of one particular parameter depending on the measured variable. If the default parameter variation resulted in an amplitude-period correlation where the range of ratio of amplitude variation (compared to the default amplitude) was < 0.1, that ensemble was considered to have no twist (twist = 0) for that particular control parameter. + and – signs refer to the sign of the correlations.

	±10% parameter change in											
effect on:	V_R	k_R	k_{Rr}	V_E	V_D	γ_{Ror}	γ_{Rev}	γ_P	γ_C	γ_{PC}	γ_{CP}	γ_{BP}
BMAL1	+	+	+	–	–	0	0	+	+	+	0	0
ROR	0	0	–	0	0	0	–	0	0	0	0	0
REV	+	+	0	+	0	0	+	+	+	0	0	0
DBP	+	+	+	0	0	+	+	+	0	+	0	0
E4BP4	0	0	0	0	+	+	0	0	0	0	0	0
CRY	0	0	0	0	0	0	0	0	0	0	0	0
PER	+	+	+	+	0	+	+	+	+	+	0	0
PERCRY	+	+	+	+	0	+	+	+	+	+	0	0

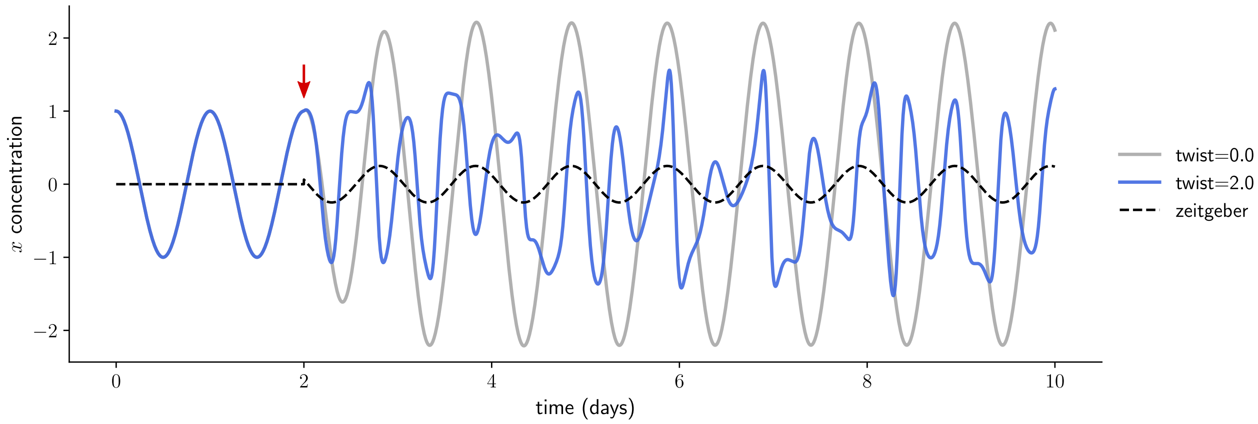

Figure S1. Large values of oscillator twist ϵ affect sync of individual oscillators to external zeitgeber inputs. An oscillator with no twist (shown in grey) entrains to the zeitgeber (indicated with a dashed line) when the periodic input is turned on (red arrow, $T = 24.5$ h, $F = 0.25$), but the oscillator with large positive twist (blue) does not entrain and loses its periodicity. Both oscillators, besides their twist value, are otherwise identical (same free running period $\tau = 24$ h, amplitude $A = 1$ and amplitude relaxation rate $\lambda = 0.05\,\text{h}^{-1}$).

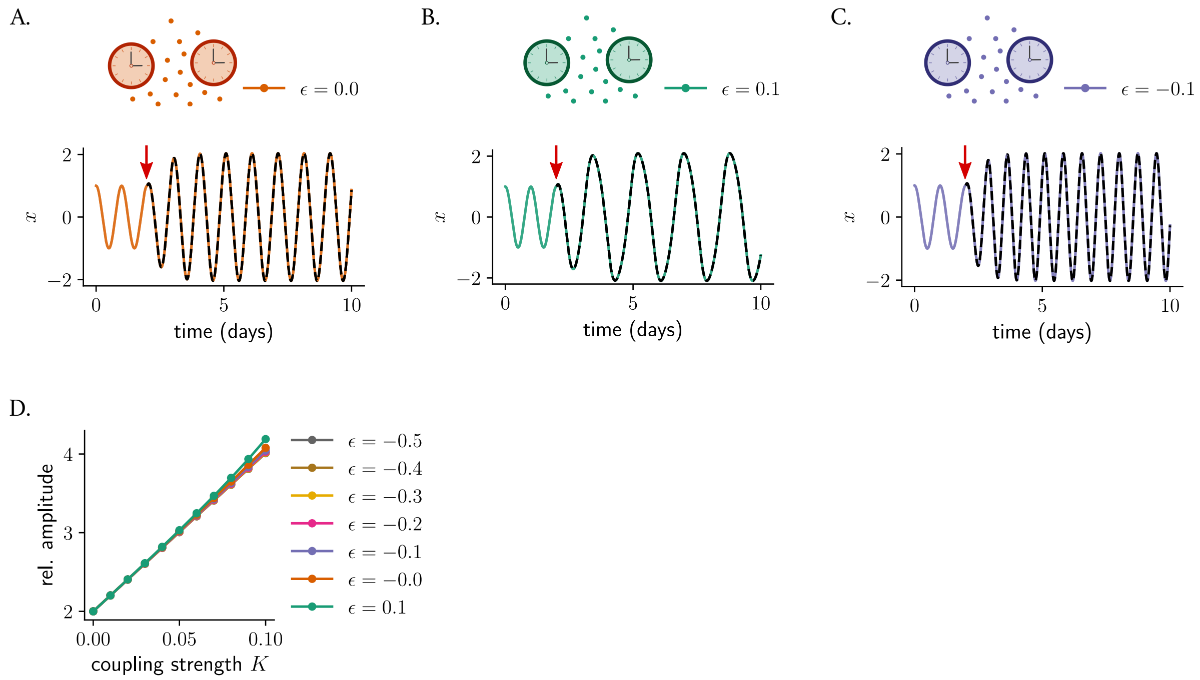

Figure S2. Coupling induces amplitude expansions and period changes that depend on the twist ϵ. Effect of mean-field coupling on two oscillators with (A) $\epsilon = 0$, (B) $\epsilon = 0.1$ or (C) $\epsilon = -0.1$ but otherwise identical (free running period $\tau = 24$ h, amplitude $A = 1$ and amplitude relaxation rate $\lambda = 0.05\,\text{h}^{-1}$). The time series show how the period of the coupled network depends on the twist parameter ϵ. The moment in which mean-field coupling is turned on, at a coupling strength $K = 0.1$, is shown with a red arrow; the mean-field is shown with a dashed black line. (D) The amplitude of the coupled network increases with coupling strength K, but with no major differences for networks with different twist values.

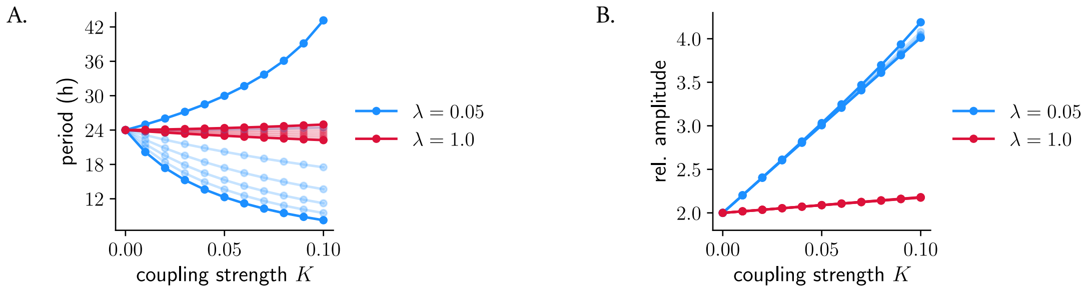

Figure S3. Role of amplitude relaxation rate on coupling-induced period and amplitude changes. More rigid clocks (higher λ values, red lines) are less sensitive to twist-induced effects and thus display less coupling-induced period changes (A) or amplitude expansions (B) than weaker clocks (in blue).

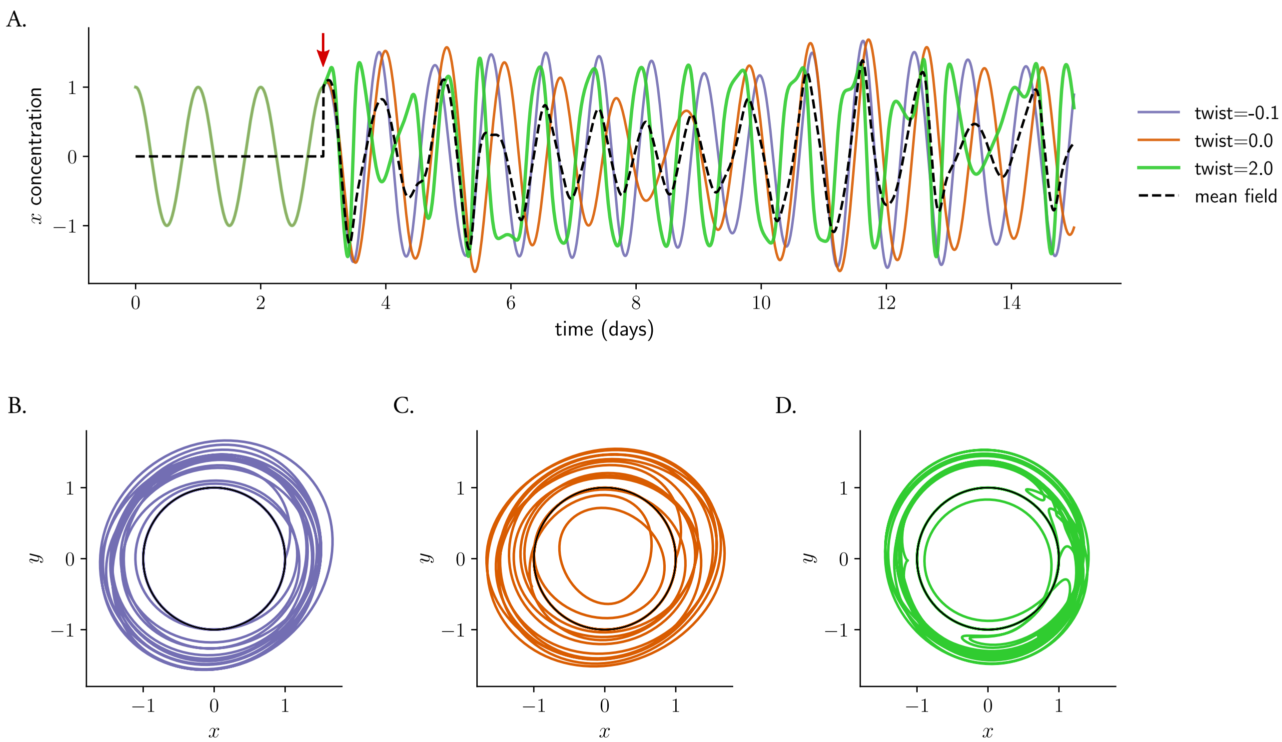

Figure S4. Twist-induced chaos upon mean-field coupling. (A) Oscillators with $\epsilon = -0.1, 0, 2$ oscillate in a self-sustained manner in the absence of coupling, but when mean-field coupling at $K = 0.1$ is turned on (red arrow), periodicity is lost. The oscillator with $\epsilon = 2$ (green line) cannot synchronize due to its large twist and thus affects the rest of the network (purple and orange lines become arrhythmic too). As a result, the mean-field (shown in black and with dashed line) also becomes arrhythmic. (B–D) Twist-induced chaotic trajectories of the oscillators from (A) shown in phase space. The limit cycles from the uncoupled clocks are shown in black.

References

[1] Almeida, S., Chaves, M. & Delaunay, F. Transcription-based circadian mechanism controls the duration of molecular clock states in response to signaling inputs. *J Theor Biol* **484**, 110015 (2020).