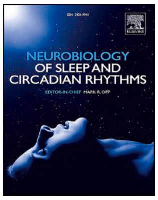
Neurobiology of Sleep and Circadian Rhythms 18 (2025) 100108

Contents lists available at ScienceDirect

Neurobiology of Sleep and Circadian Rhythms

journal homepage: www.elsevier.com/locate/



# One interesting and elusive two-coupled oscillator problem

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A R T I C L E  I N F O

Handling Editor: Mark R. Opp

*Keywords:*
Circadian rhythms
Entrainment
Coupled oscillators
Modeling
Phase jumps

A B S T R A C T

Chronobiology experiments often reveal intriguing non-linear phenomena, which require mathematical models and computer simulations for their interpretation. One example is shown here, where the two circadian oscillators located in the eyes of the mollusk *Bulla gouldiana* were isolated and measured *in vitro*. By maintaining one eye under control conditions and manipulating the period of the second eye, Page and Nalovic (1992) obtained a diversity of results, including synchronized and desynchronized eyes, associated to weak coupling and period differences. A subset of eye pairs, however, showed increasing phase angle followed by phase jumps. These occur and have been satisfactorily modeled in more complex systems where two zeitgebers play clear entraining roles. However, simulations of a simple model of free-running, two mutually coupled limit-cycle oscillators with unilateral change in oscillator period failed completely to reproduce these phase jumps. Here we explain how phase jumps arise in two-zeitgeber systems and then show the closest but unsatisfying, intermediate model that was fit to the *Bulla* system.

Chronobiology experiments often reveal intriguing non-linear phenomena, which require mathematical models and computer simulations for their interpretation. The diversity of mathematical modeling approaches that we have today is the mirror of the diversity of experimental techniques developed to approach the multiple levels of rhythmic phenomena, from behavioral to tissue, cell to molecular (Schmal et al., 2022). While we are now trying to understand the functioning of thousands of coupled clock circuits at several levels, our knowledge was largely built on the findings of conceptually simpler, emergent versions of coupled circadian oscillators, such as the iconic two bilaterally coupled oscillators closely associated to the two eyes in insects (optic lobes) (Nishiitsutsuji-Uwo and Pittendigh, 1968; Page et al., 1977; Page, 1982; Koehler and Fleissner, 1978; Tomioka and Chiba, 1986; Waddel et al., 1990) and mollusks (basal retinal neurons) (Jacklet, 1969; Hudson and Lickey, 1980; Block and Wallace, 1982; McMahon et al., 1984). These very pictorial “two-eye systems” paved the way to our understanding of coupling mechanisms, offering very concrete and didactic biological counterparts of the mechanical, coupled spring-mass systems. Several exciting experimental manipulations were performed in these two-oscillator systems (reviewed in Page, 1985), which keeps to this day igniting the imagination of newcomer students. These include experiments that verified sufficiency of one pacemaker to sustain daily synchronization of activity (Page et al., 1977) entrainment of one pacemaker through inputs to the contralateral optic lobe (Page, 1978, Page, 1981); resynchronization after phase shift in one eye (Roberts and Block, 1983), and experimental induction of desynchronization between the two eyes (Koehler and Fleissner, 1978; Hudson and Lickey, 1980; Wiedemann, 1983; Tomioka and Abdelsalam, 2004).

Among several intriguing dynamical responses arising in such experiments, a “phase jump” phenomenon was described, which corresponds to an abrupt change in phase of an oscillator in response to a slight change in one system parameter that otherwise causes a monotonic response. Although it sounds simple in this description, it makes quite a dramatic expression when appearing unexpectedly in circadian experiments. This phenomenon occurred, for instance, when the period of the pacemaker in one eye was experimentally manipulated while monitoring the dynamics of the two eyes (Page and Nalovic, 1992). In this *in vitro* experiment, the neurally connected eyes of the mollusk *Bulla gouldiana* were maintained under constant conditions and only one of the eyes was bathed in a medium that either lengthened (Lithium) or shortened (Chloride) the period of the oscillator, located in the retinal basal neurons. Period and phase were measured through the electric impulse rhythms recorded from the optic nerve of each eye. When the period of the Lithium or Chloride-treated eye was lengthened or shortened, respectively, by roughly 1h, most eye-pairs desynchronized or attained a new phase relationship, as expected from weakly coupled oscillators with different periods. However, in a few cases, the phase relationship between the eyes increased until an abrupt phase jump was shown, followed by a tight synchronization between them (Fig. 1). Interestingly, the authors tested, in a very clever way, whether the

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https://doi.org/10.1016/j.nbscr.2024.100108
Received 21 June 2024; Received in revised form 15 November 2024; Accepted 23 November 2024

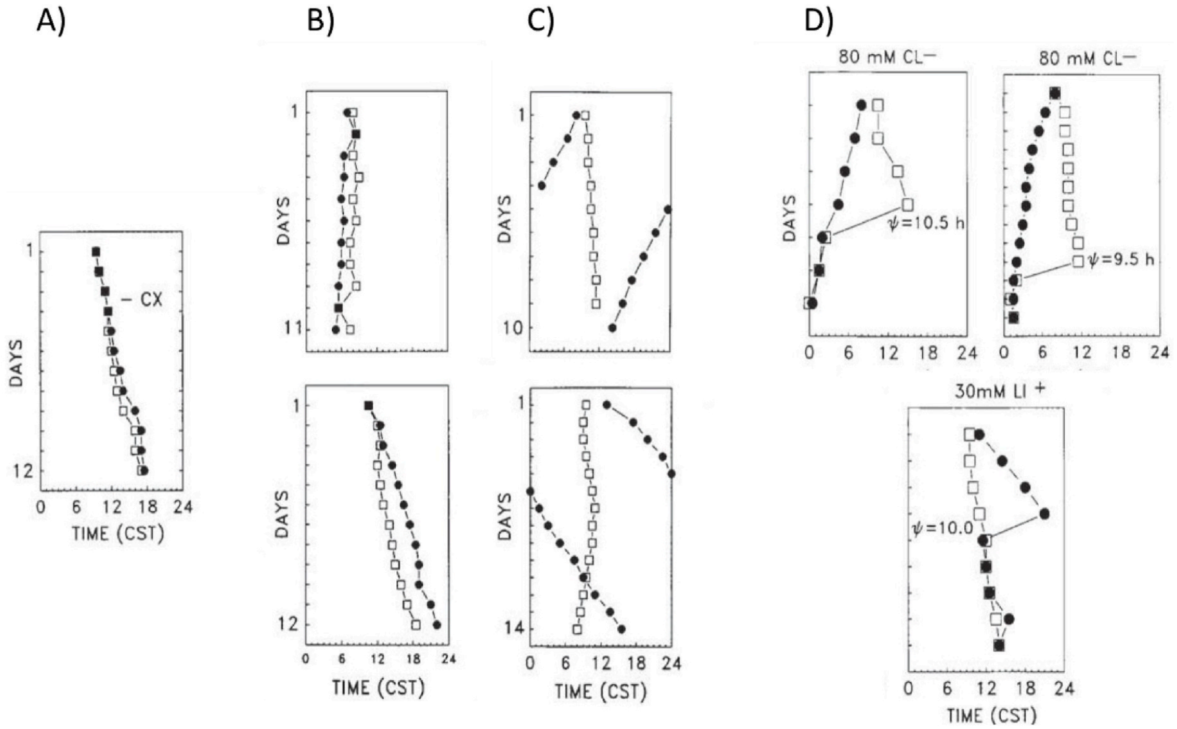

**Fig. 1.** Reference phases of CAP (compound action potential) frequency rhythms recorded from the optic nerves of isolated pairs of neurally connected eyes in *Bulla gouldiana*. Each eye was either bathed in filtered artificial seawater (control: 395 mM NaCl, 10 mM KCl, 50 mM MgCl, 28 mM NaS04, 10 mM CaCl2, 30 mM HEPES buffer, containing penicillin and streptomycin) or reducing the Chloride concentration to either 50 or 80 mM via substitution of sulfate (shortens period) or replacing a portion of the Sodium with Lithium (20 or 30 mM) (lengthens period) (Page and Nalovic, 1992). A) Two eyes in control medium. CX indicates the day when section of the cerebral and pedal comissures uncoupled the intact system, without generating period deviations; B) Pairs that maintained mutual synchronization with new phase angle after treatment of only one eye in either Chloride or Lithium medium; C) Pairs that exhibited desynchronization after treatment of only one eye in either Chloride or Lithium medium, corresponding to the majority of cases; D) Pairs that exhibited gradual increase in phase angle followed by a phase jump and resynchronization after treatment of only one eye in either Chloride or Lithium medium. In the experimental records, the filled circle plots data from the treated eye. (Modified from Page and Nalovic, 1992).

direction of phase jump - or which oscillator jumps - depended on which oscillator was manipulated. They showed that this direction depended, instead, on which of the oscillators was phase lagging after manipulation, jumping and being phase-caught by the leading oscillator.

These clean and simple experimental results invite a simple model explanation. However, the expected simple model of two mutually coupled, free-running limit-cycle oscillators with unilateral change in oscillator period failed completely to reproduce these phase jumps. As the period difference was monotonically increased, they attained monotonic variations in their phase relationships until loss of mutual synchrony after some critical value, which was higher for stronger coupling (Oda and Friesen, 2002).

Although it is desirable to use a simple system to describe and explain a complex phenomenon such as the emergence of “phase jumps”, the whole motivation of this letter is to highlight the paradoxic case in which a phenomenon could be satisfactorily computer simulated in a more complex but not in the “simpler” model, such as associated to the two-eye system of *Bulla*. The simple model can reproduce what was obtained in most eye-pairs (Fig. 1B and C) but left no room for phase jumps (Fig. 1D). This poses the question of what we are missing in the modeling of this system.

The phase jump phenomenon could be modeled and simulated in a much more complex system, where two zeitgebers were added to the two-oscillator system (Oda and Friesen, 2011; Flôres and Oda, 2020). This model was developed to understand the complex dynamics arising in two seemingly unrelated experiments, namely, that of *Drosophila* eclosion rhythm under conflicting Temperature and Light zeitgebers (Pittendrigh and Bruce, 1959) and of rodent activity patterns under different skeleton photoperiods (Pittendrigh and Daan, 1976). One of the advantages of modeling studies is to find connections between unrelated phenomena. The above mentioned modeling studies of two-zeitgeber systems revealed the deep connections between these two experiments that had at first just displayed one feature in common, namely the phase-jumps.

A brief explanation of how phase jumps arise in two-zeitgeber systems follows and then we return to the challenge of fitting some intermediate model to the *Bulla* system.

## 1. Phase jumps in two-zeitgeber systems

In the Pittendrigh and Bruce (1959) experiment, populations of fly pupae were raised under the cycling of two zeitgebers, namely the daily Light and Temperature cycles. To evaluate which zeitgeber was the stronger, their phase relationships were set at different values on different populations. In this sense, 12 fly pupae populations were raised under 12 different phase relationships between T and L cycles. The adult eclosion tracked the phase of the Temperature cycle, when viewing populations with increasing phase difference between T and L (Fig. 2A, lines 1–6). However, when T and L attained antiphase relation, a phase jump occurred (Fig. 2A, Line 7). For further increases in the phase difference between T and L, the phase of eclosion did not change anymore, independent of the phase of T, for the remaining populations (Fig. 2A, Lines 8–12). A model was proposed (Pittendrigh and Bruce, 1959) in which the timing of eclosion was regulated by a system of two coupled, A and B oscillators, each entrained by the T and L zeitgebers, respectively (Fig. 2B).

Our simulations of the simplest configuration of the two-zeitgeber/two-oscillator system helped to interpret those intriguing patterns,

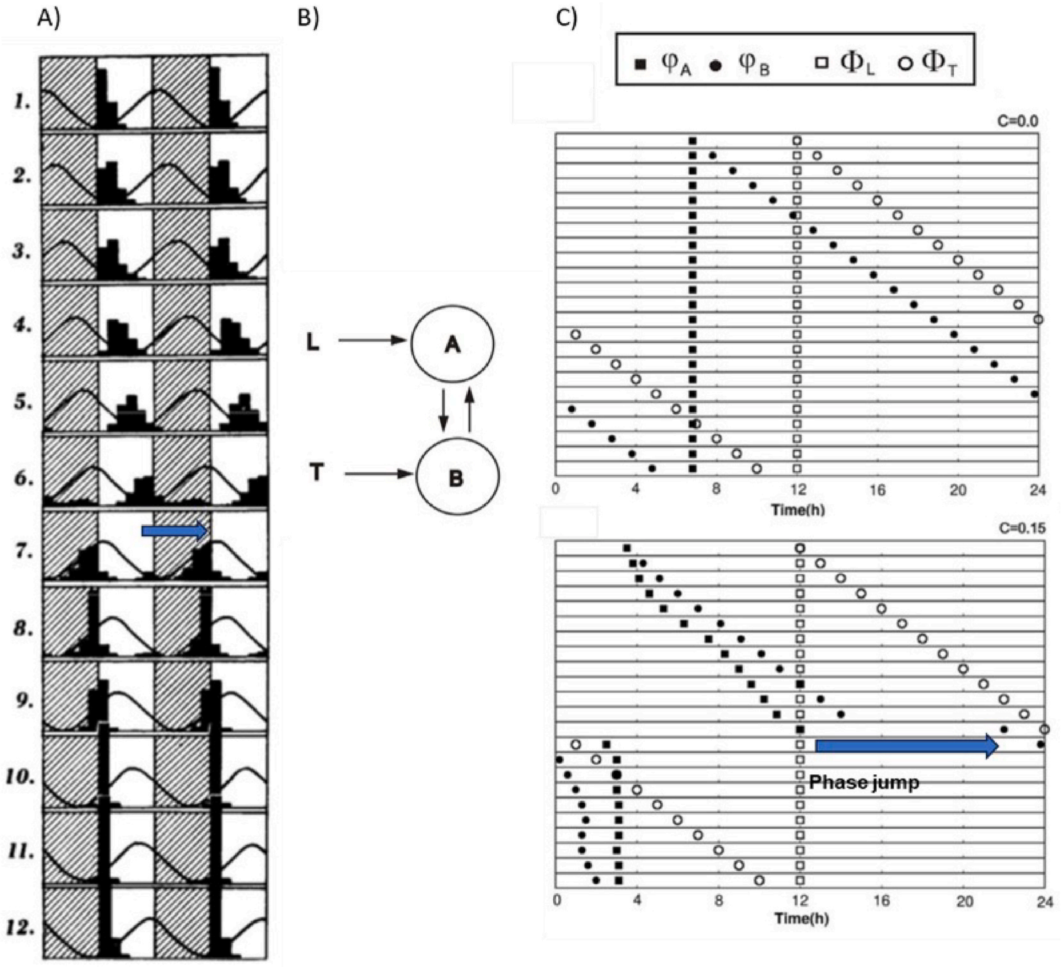

**Fig. 2.** Phase jumps in two-zeitgeber experiments. A) Eclosion rhythm of 12 Drosophila populations under different phase combinations between 24 h light/dark and temperature cycles. Each horizontal bar corresponds to two successive days. Light/dark cycles are shown by shaded areas and temperature cycles by a continuous curve. Dark bars indicate the number of flies that ecloded within a 2 h time window. The phase jump is indicated by blue arrow. Modified from Pittendrigh and Bruce (1959). B) Schematic diagram of two coupled A and B oscillators, entrained, respectively by zeitgebers L and T. C) Oscillator and zeitgeber reference phases at different coupling strengths C: Top: C = 0, Bottom: C = 0.15. Steady-state oscillator A and B phases are represented by filled squares and circles, respectively; zeitgeber L and T phases are represented by open squares and circles, respectively. In each of the 24 successive horizontal bars, the phase of zeitgeberT was increased by 1 h with respect to the phase of zeitgeber L, which was fixed at 12 h. Pittendrigh-Pavlidis equations, where R and S are the state variables of each oscillator: abcd are the oscillator parameters; L and T are Light and Temperature pulse zeitgeber amplitudes; C is the coupling intensity, indicated in the figures. Oscillator A and B equations: $dR_A/dt = R_A - cS_A^2 + (d\text{-}L) + K$; $dS_A/dt = R_A - aS_A + CS_B$; $dR_B/dt = R_B - cS_B^2 + (d\text{-}L) + K$; $dS_B/dt = R_B - aS_B + CS_A$; $K = 1/(1 + 100\ R^2)$; parameters: $a = 0.85$, $b = 0.3$, $c = 0.8$, $d = 0.5$. $T = L = 2$; L,T duration = 1,0. Simulations were performed with software *Neurodynamix* (Friesen and Friesen, 1994). Modified from Oda and Friesen (2011). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

providing a single narrative for the whole set (Fig. 2A, Lines 1–12) of results (Oda and Friesen, 2011). To have a complete picture, it is useful to view simulations in a range of coupling strengths, from independently responding oscillators in one extreme to the other, where they stick tightly to each other and respond as a single entity in often unexpected ways (Oda et al., 2000). When coupling between these two oscillators is loose (Fig. 2C, top), then each oscillator follows the phase of the corresponding zeitgeber, which would result, if that were the case, in eclosion events occurring twice a day at different times. On the other hand, when their mutual coupling is tight, as it is (Fig. 2C bottom), they establish a tight phase angle and respond to conflicting zeitgebers by tracking preferentially one. Throughout the whole range of phase relationships between T and L cycle, they first follow T until T and L become antiphasic. A phase jump of the phase of the coupled oscillators occurs and then they follow L. The tighter the inter-oscillator coupling, the more abrupt the phase jump.

The “phase jump” term was coined, in fact, in another set of experiments (Pittendrigh and Minis, 1964; Pittendrigh and Daan, 1976). Skeleton photoperiods consist of two light pulses that mimic dawn and dusk in a darkness background and they can entrain the circadian oscillator quite the same way as the full LD cycle. Interestingly, the circadian oscillator interprets one interval as L and the other as the D phase. If the activity rhythm of a rodent is measured under skeleton photoperiods, its activity duration is compressed between the two pulses as the distance between them is experimentally changed. This compression increases until a threshold distance between the pulses is attained. Then the oscillator phase jumps into the other interval, decompressing its daily duration on its way (Fig. 3A). The simplest model that explains phase jumps in fly eclosion rhythms under skeleton photoperiods is based on the phase response curve (Pittendrigh and Minis, 1964). To account for both phase jumps and activity compression/decompression of rodents, however, a two zeitgeber/two oscillator model is needed, where each light pulse of the skeleton photoperiod is interpreted as a separate zeitgeber, in analogy to the conflicting zeitgeber experiment (Flôres and Oda, 2020). In this case, changes in the distance between the two light pulses, representing

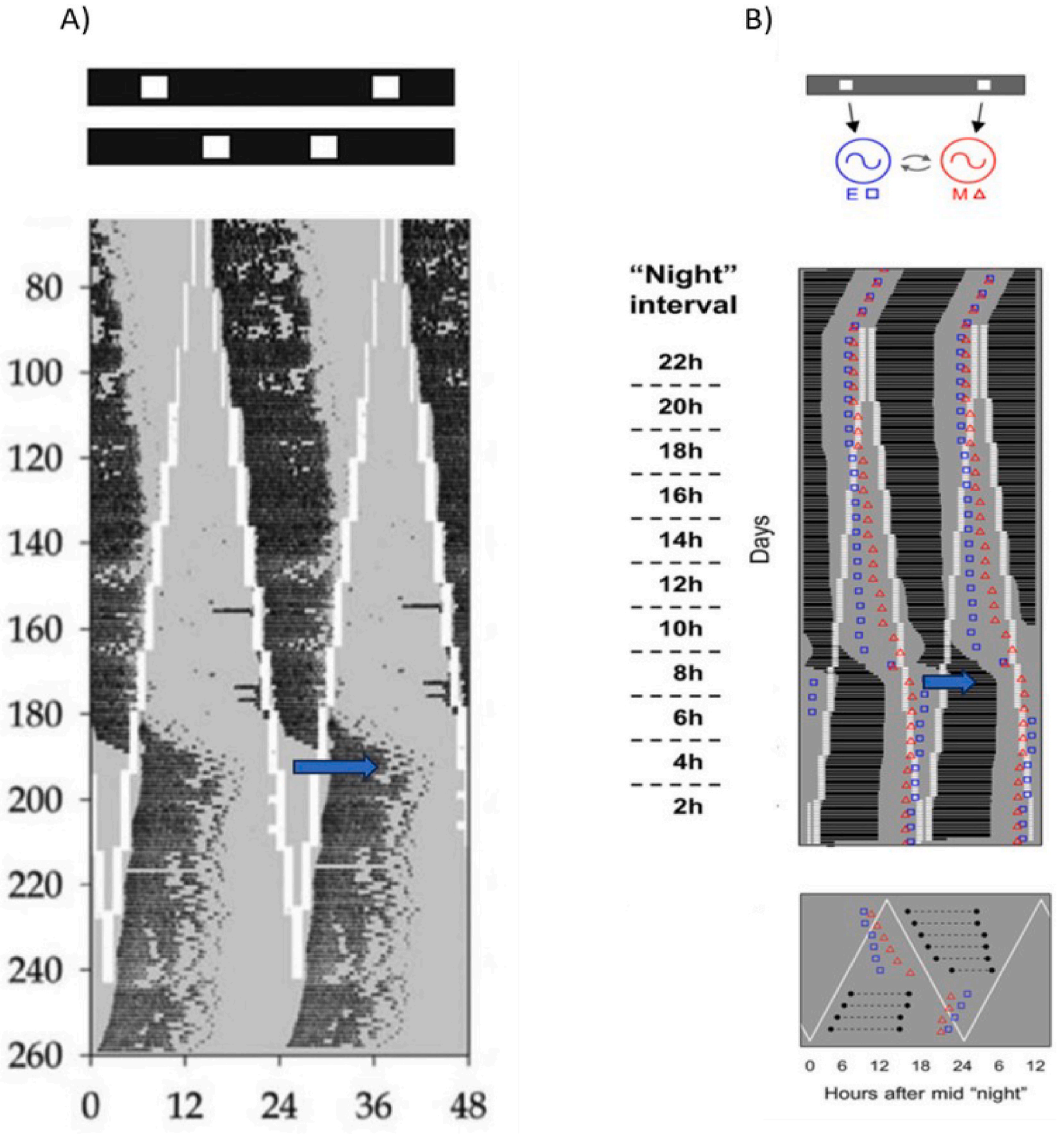

**Fig. 3.** Phase jumps in two-zeitgeber experiments. A) Double-plotted actogram depicting the activity record (black marks) of a mouse exposed to varying skeleton photoperiods, as schematized on top, in which 2 light pulses (white) occur daily on a darkness background (gray). The interpulse interval ("night" interval) that contains the activity phase is progressively shortened through the days. Daily activity duration is gradually compressed on days 140–180. Thereafter, the phase of entrainment is reversed to the complementary interpulse interval after a phase jump (indicated by blue arrow), and daily activity duration is decompressed. Modified from Spoelstra et al. (2014). B) Top: Schematic representation of model configurations depicting the skeleton photoperiods (gray-white bars), the oscillators (circular symbols), and the effects of the light pulses on the oscillators (arrows). Curved arrows indicate coupling between them. Mid: Double-plotted actograms illustrating the activity rhythm of the model organism. The phase jump is indicated by the blue arrow. Bottom: Phase of entrainment and activity duration under different skeleton photoperiods. Onset and offset points (black filled circles) are connected by a black dashed line. Diagonal white lines indicate the times of the pulses, as the skeleton photoperiod changes in the y-axis. Peaks of the state variables are indicated for the evening (squares) and morning (triangles) oscillators in each photoperiod. Pittendrigh-Pavlidis equations, where R and S are the state variables of each oscillator: abcd are the oscillator parameters; L is Light pulse zeitgeber amplitude; C is the coupling strength. Oscillator E and M equations: $dR_E/dt = R_E - cS_E^2 + (d\text{-}L) + K$; $dS_E/dt = R_E - aS_E + CS_M$; $dR_M/dt = R_M - cS_M^2 + (d\text{-}L) + K$; $dS_M/dt = R_M - aS_M + CS_E$; $K = 1/(1 + 100\ R^2)$; model parameters: $a = 0.85$, $b = 0.3$, $c = 0.8$, $d = 0.5$; $L = 1,1$; $Lduration = 1,0$; $C = 0.07$. Simulations were performed with software *Neurodynamix* (Friesen and Friesen, 1994). Modified from Flôres and Oda (2020). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

different photoperiods, are analogous to the changes in the phase relationships between T and L zeitgebers, while the A and B oscillators are analogous to the Evening and Morning oscillators that comprise the rodent circadian oscillator (Fig. 3B). When this link between the two experiments is established, we interpret the results as follows: for tight coupling between E and M oscillators, they remain tightly synchronized to each other and activity onset of the coupled system tracks the dusk light pulses until an antiphasic relationship between the pulses is attained. Further small increases in the distance between pulses cause a phase-jump followed by a switch in the phase preference of the system, where activity offset now tracks the dawn light pulse (Fig. 3B). The analogy between the two experimental results is highlighted.

## 2. Phase jumps in free-running systems?

The two zeitgeber system indicates that phase jumps occur when each one holds the phase of each oscillator and stretches the spring-like coupling between them like in a tug-of-war. In free-running systems, there is no external zeitgeber and each oscillator responds primarily to the other oscillator, leaving no room for stretching phase relationships.

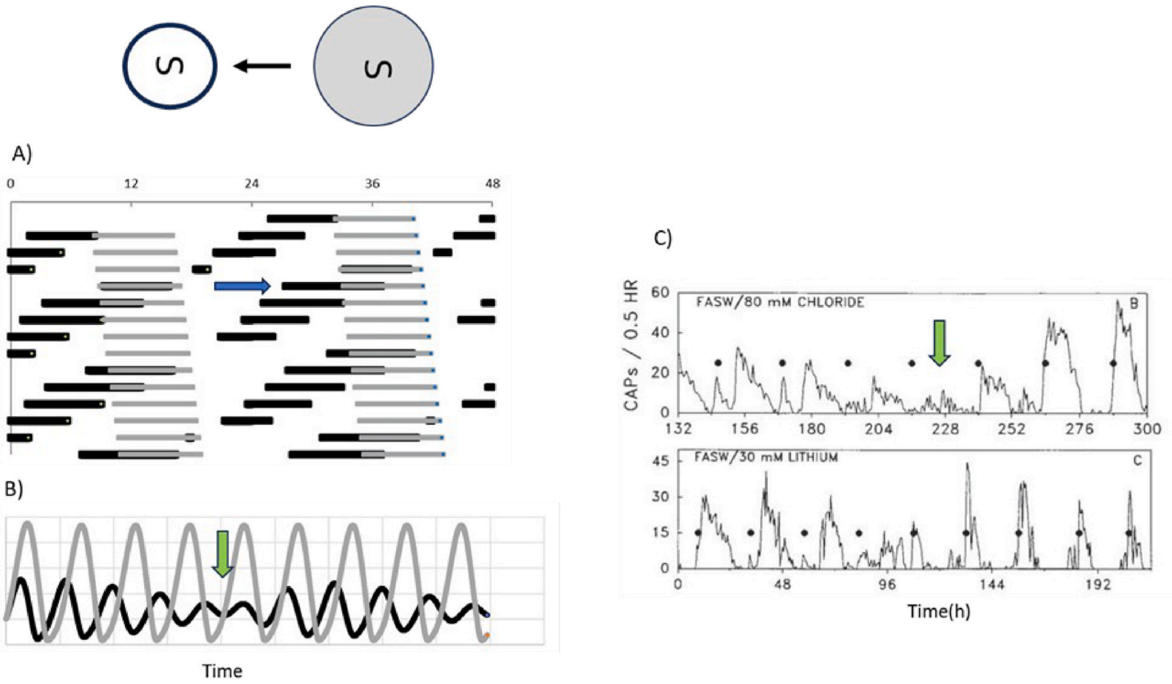

**Fig. 4.** Modeling attempt of the dynamics behind phase jumps in the two-oscillator system of *Bulla*. The schematic figure on top indicates the model system of two oscillators, where coupling is excitatory and its direction is from the longer to the shorter period/amplitude oscillator. When their periods are different, they remain synchronized for a range of period differences, with the shorter period oscillator phase leading. When the period difference attains a limit (inversely proportional to the coupling strength), relative coordination occurs, as depicted in A), where the driven oscillator (black) phase jumps (blue arrow). B) Time series showing the waveform of the state variable S(t) of the two oscillators. While the amplitude of the longer period oscillator (gray) does not change, the amplitude of the shorter period oscillator (black) damps (green arrow) when the phase jump occurs. C) Similar to the pattern in B, here the data of Fig. 1D is displayed in time series format (Modified from Page and Nalovic, 1992). Pittendrigh-Pavlidis equations, where R and S are the state variables of each oscillator: abcd are the oscillator parameters; C is the coupling strength. Oscillator equations: $dR_1/dt = R_1 - cS_1^2 + (d\text{-}L) + K$; $dS_1/dt = R_1 - aS_1 + CS_2$; $dR_2/dt = R_2 - cS_2^2 + (d\text{-}L) + K$; $dS_2/dt = R_2 - aS_2 + CS_1$; $K = 1/(1 + 100\ R^2)$. model parameters: Shorter period (black): $a = 0.85$, $b = 0.7$, $c = 0.8$, $d = 0.5$; Longer period (gray):$a = 0.85$, $b = 0.3$, $c = 0.8$, $d = 0.5$. Coupling strength $C = 0.05$, from the longer to the shorter period oscillator. Simulations were performed with software *Neurodynamix* (Friesen and Friesen, 1994). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

However, the manifestation of this phenomenon in a free-running system is not restricted to the two-eye experiment of *Bulla*, as indicated by a similar occurrence in the locomotor rhythm of free-running mice lacking functional CaMKIIα (Ca2+/calmodulin-dependent protein kinase IIα). Activity duration displays "spontaneous" compression or decompression in free-running individuals, associated to a jump in phase of activity onset or offset (Yoshikawa et al., 2024).

There is a big complexity difference between the two-zeitgeber/two-oscillator systems in the cited examples and the two-oscillator system under constant conditions. The first possibility is that the phase jumps observed experimentally in each system are based on totally distinct mechanisms and the apparently similar dynamics have nothing to add in the understanding of each other. However, there is also the possibility that there is a hidden component that we are missing in the simple system. One possibility of getting a phase jump-like dynamics in the free-running, two-oscillator system is through unidirectional coupling (Fig. 4). Starting from two identical oscillators, if the period/amplitude of the first oscillator is shortened, the phase angle as well as the elastic force relative to the second oscillator can be stretched much more than on mutually coupled oscillators, because while in the former the second oscillator does not care about the first, in the latter it responds to the first in an attempt to synchronize, resulting in small phase differences. When the period of the first oscillator attains the limit of entrainment of the second oscillator for that coupling strength, it enters relative coordination with phase jump-like dynamics. These phase jumps arising in relative coordination can be explained through the phase response curve. Relative coordination entails temporal patterns of amplitude variations (Schwartz et al., 2009, Suppl Mat) that were observed in the *Bulla* eye-pairs that displayed phase jumps (Fig. 4). This is so far the closest we got to a phase jump-like dynamics that could be computer simulated in two free-running, coupled limit-cycle oscillators. However, it is not satisfying in relation to the results of *Bulla* in several aspects, such as the unidirectional coupling and on the phase jump occurring in the direction of the shorter to the longer period oscillator. Page and Nalovic (1992) had insightfully made further experiments showing that the oscillator that jumps is the one that phase lags, independently of being the treated or the non-treated one.

In sum, this is an intriguing example where a mathematical modeling approach can reproduce an interesting dynamical phenomenon in complex systems, but finds resistance in a simpler counterpart. It also shows the importance of well conceived experiments to properly establish minimum conditions that modeling approaches need to fulfill. Finally, while coupled circadian systems are being investigated by experimental and modeling approaches of increasing complexity (Buhr et al., 2010; Yamaguchi et al., 2013; Schmal et al., 2022), the iconic two-eye system still offers unresolved dynamic problems that are especially challenging due to their very simplicity.

## Funding agency

FAPESP – Fundação de Amparo à Pesquisa do Estado de São Paulo.

## Declaration of competing interest

The author declare no conflict of interest.

## Acknowledgements

The author thanks André Chiara and two anonymous referees for their kind attention and very good suggestions; Prof. Otto Friesen for the Neurodynamix software and Danilo Flôres for the simulation program.

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