Mathematical models and tools to understand coupled circadian oscillations and limit cycling systems

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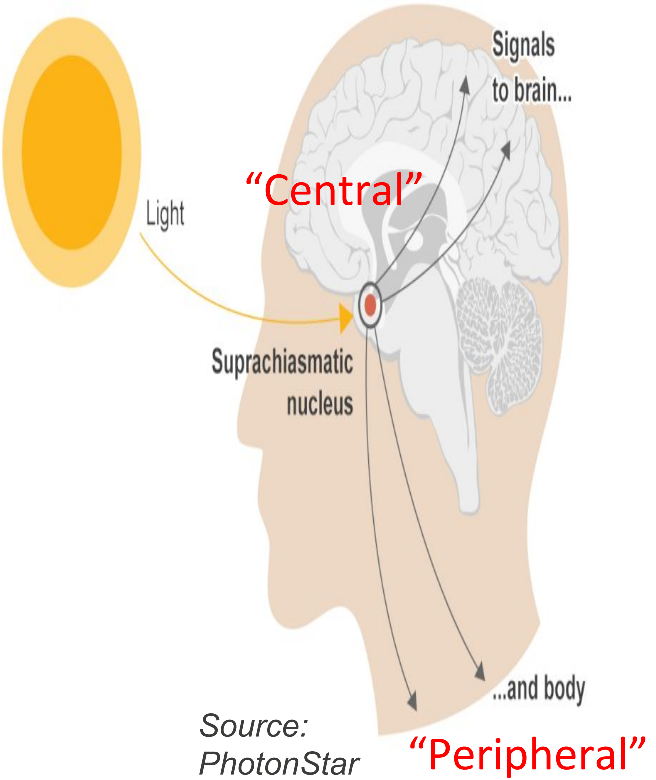
Introduction

- Circadian rhythm: an internal rhythm that regulates many body processes including the sleep-wake cycle, digestion and hormone release.
- Circadian rhythms exist across animal and plant species
- The ability of a circadian system to entrain its "central" and "peripheral" oscillators to the 24-hour light-dark cycle (LD) is one of the most important properties.



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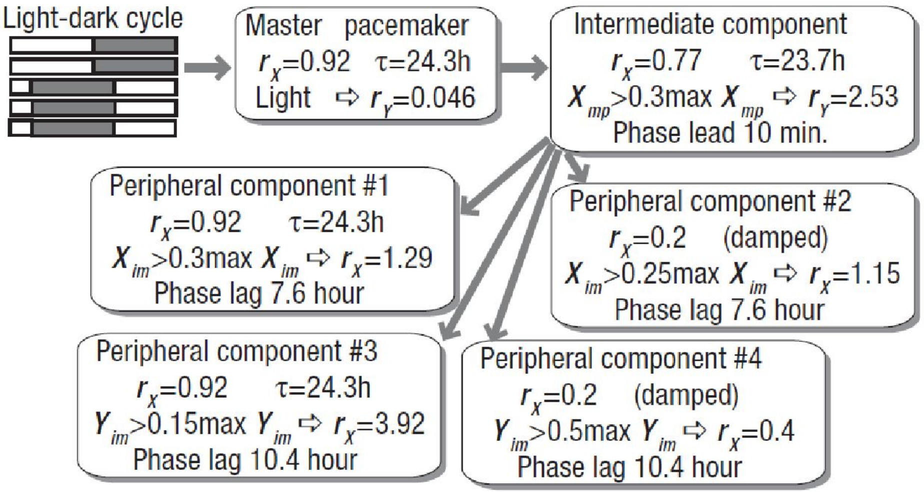
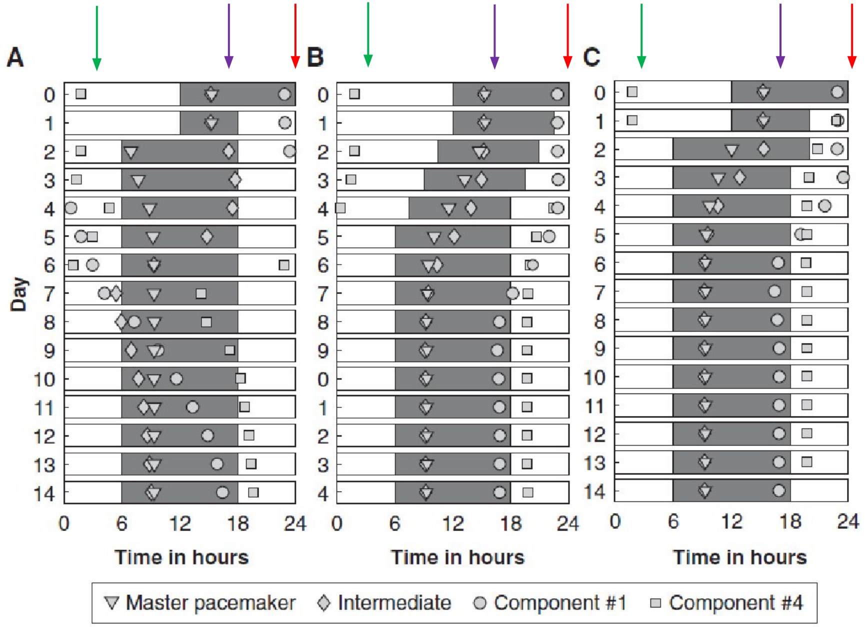
Dynamics of a Hierarchical Circadian System



Leise and Siegelmann, 2006 JBR



The nature of entrainment (advance vs delay) depends on how lights are shifted

Phase-locking due to periodic forcing

- This type of problem has been extensively studied in a variety of contexts
- Keener et al 1981, Bressloff 1992, Coombes & Owen 2003, Laing & Longtin 2003, Medvedev & Cisternas 2004 …. many more
- Circadian literature: Kronauer’s group 1990s-, Ronnenberg’s group 2000s-, Goldbeter’s group 2000s-, Herzel’s group 2000s-, Peskin and Forger 2003, 2004…many more
- Phase-locking described either through Arnold Tongue structure or Devil’s Staircase (Denjoy’s Theorem for Circle Maps)

Central Goals

- Derive an analytic/computational map-based method to assess the entrainment process as well as the effect of relevant parameters.

- Determine how the entrainment properties of central and peripheral oscillators may differ in a hierarchical circadian network.

- Identify important mathematical structures that help explain empirical observations. In fact, the map reveals the existence of saddle structures that organize the dynamics.

Main topics

- Part 1: Existing methods and some applications.
- Part 2: Entrainment map for coupled Kuramoto oscillators.
- Part 3: Entrainment map for coupled Novak-Tyson oscillators.

Part 1

Phase reduction

- A classical method (Winfree, 2001; Brown et al, 2004) that reduces a multi-dimensional limit cycle oscillator into a one-dimensional phase oscillator, which often relies on averaging.

- Many phenomena such as chemical reactions, electric circuits, mechanical vibrations, cardiac cells can be studied by this method.

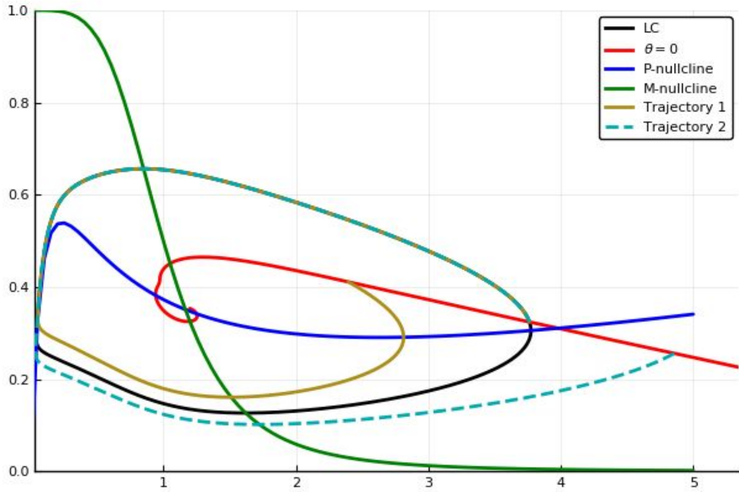
Parameterization

- Give a phase-amplitude coordinate system near the limit cycle.
- The parameterized space has simpler dynamics.
- It is often applied to find invariant manifolds (Castelli et al., 2015; Cabre, et al., 2005).
- For limit cycle, it can be applied to find the isochrones and isostable curves (Guillamon, 2020).

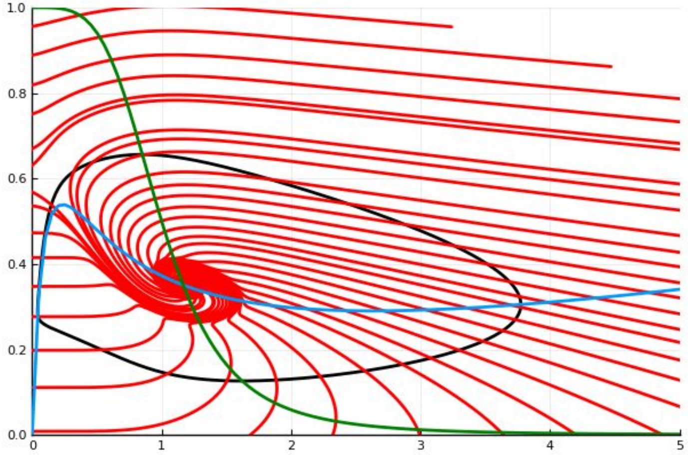
Application on computing isochrones

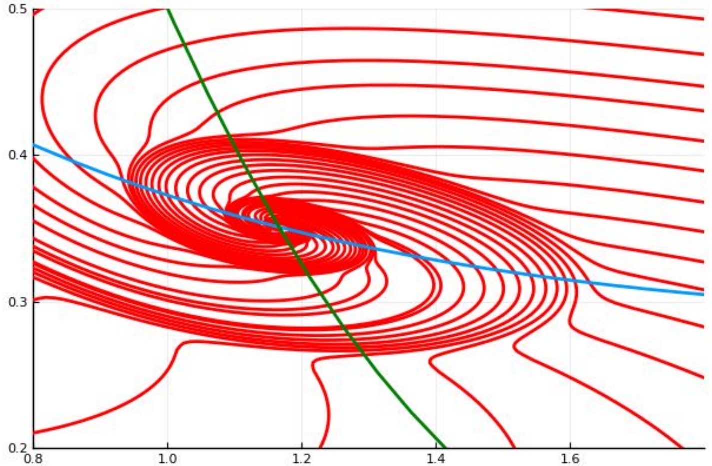
Unforced Novak-Tyson oscillator

$$\frac{1}{\phi}\frac{dP}{dt} = M - k_D P - k_f \frac{P}{0.1 + P + 2P^2}$$
$$\frac{1}{\phi}\frac{dM}{dt} = \epsilon\left(\frac{1}{1+P^4} - M\right)$$



- Isochrones are the invariant set for different initial conditions to have same phase.





Circadian oscillators: Two “unforced” limit cycles

- Either in experiment or model, the oscillator can be subjected to 24 hours of constant darkness **DD** or constant light **LL**
- In the presence of LD-periodic forcing, the trajectory will bounce back and forth between these two “unforced” limit cycles (Peterson, 1980).
- These oscillators will lie in different locations in phase space and presumably have different attractive structures (e.g. isochrons)
- We note that this attraction to either the LL or DD limit cycles is transient so the manifolds of either limit cycle are NOT invariant for the periodically forced flow.

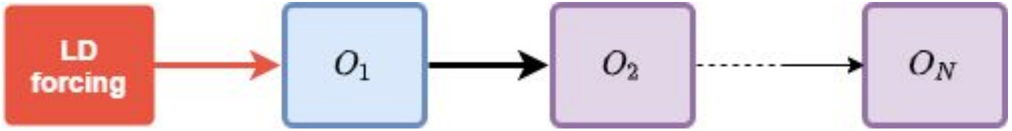
Part 2

- Hierarchical system modeled as Kuramoto oscillators
- Analysis on the entrainment map
- Numerical results

Hierarchical system modeled as Kuramoto oscillators

$$\frac{d\theta_0}{dt} = \omega$$
$$\frac{d\theta_1}{dt} = \omega_1 + kf(\theta_0)\sin(\theta_0 - \theta_1)$$
$$\frac{d\theta_i}{dt} = \omega_i + \alpha_{i-1}\sin(\theta_{i-1} - \theta_i),\ i = 2, \ldots, N.$$

$$f(\theta_0) = Heaviside(\sin(\theta_0))$$



Single oscillator case: 1-D entrainment map

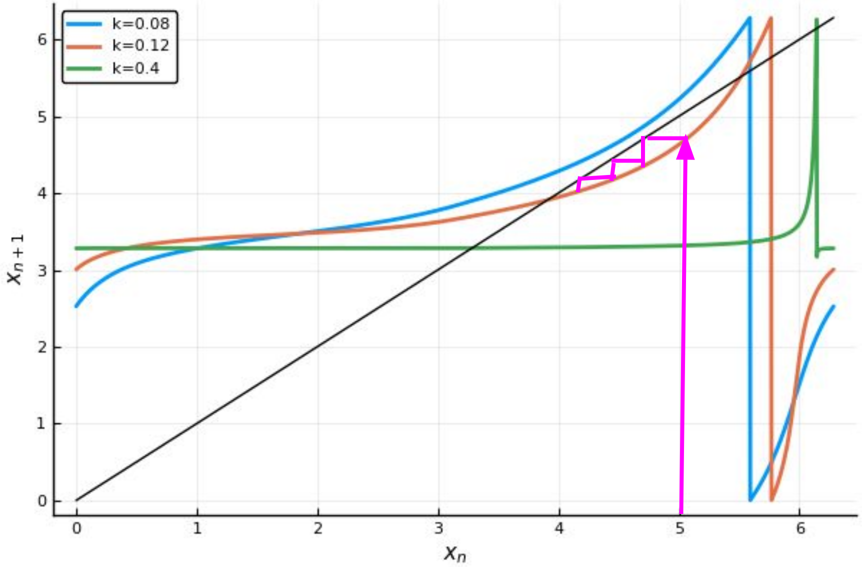
$$\frac{d\theta_0}{dt} = \omega$$
$$\frac{d\theta_1}{dt} = \omega_1 + kf(\theta_0)sin(\theta_0 - \theta_1)$$

$$x \mapsto F(x, k) = x + \omega\rho \, mod \, 2\pi$$

- x is defined to be the value of θ_0 , which is the phase of light-dark forcing.
- ρ measures the return time when the oscillator first returns to the chosen Poincare section: $\theta_1 = \pi$.

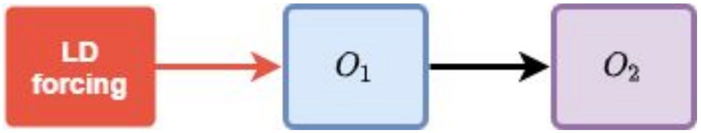
1-D entrainment map

- Easy to find the stable and unstable periodic orbits.
- Easy to calculate the entrainment time by iterating the map.
- Easy to see the direction of entrainment by cobwebbing (phase advance vs delay).
- Easy to show dependence on parameters.
- Discontinuity moves to the boundary as we increase k.



2-D entrainment map

$$\frac{d\theta_0}{dt} = \omega$$
$$\frac{d\theta_1}{dt} = \omega_1 + kf(\theta_0)sin(\theta_0 - \theta_1)$$
$$\frac{d\theta_2}{dt} = \omega_2 + \alpha_1 sin(\theta_1 - \theta_2)$$



Put a Poincare section at $\theta_2 = \pi$, and let $x = \theta_0, y = \theta_1$

$$x \mapsto F_1(x, y, k, \alpha) := x + \omega\rho \bmod 2\pi$$
$$y \mapsto F_2(x, y, k, \alpha) := y + \omega_1\rho + kI_1 \bmod 2\pi$$

$$I_1 = \int_0^\rho f(\theta_0)\sin(\theta_0 - \theta_1)dt$$

Necessary conditions on entrainment.

$$F_1(x, y, k, \alpha_1) - x = 0$$
$$F_2(x, y, k, \alpha_1) - y = 0.$$

Reduced to

$$\sin(\theta_1(s_1) - \theta_2(s_1)) = \frac{\omega - \omega_2}{\alpha_1}$$
$$\sin(\theta_0(s_2) - \theta_1(s_2)) = \frac{2(\omega - \omega_1)}{k}.$$

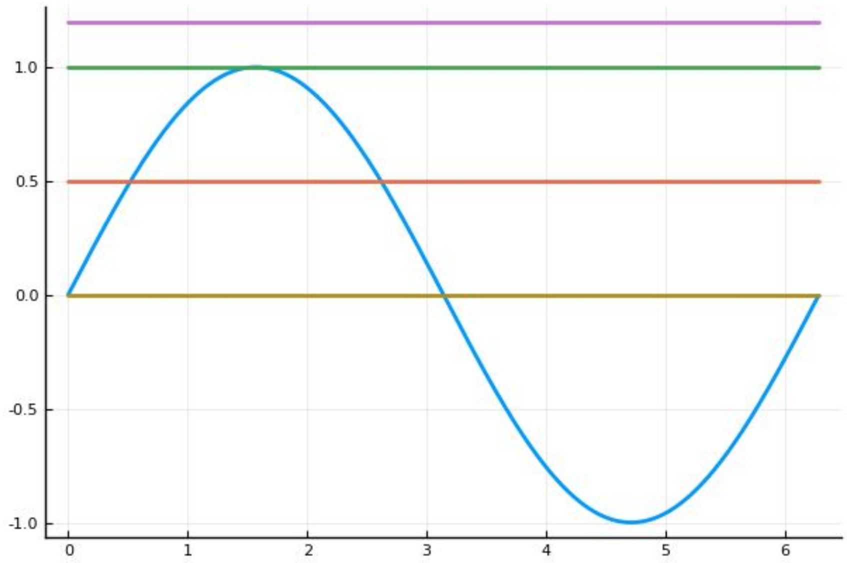
For entrainment, we need $k \geq 2(\omega - \omega_1), \alpha_1 \geq \omega - \omega_2.$

Number of fixed points (schematic explanation)

$$\sin(\theta_1(s_1) - \theta_2(s_1)) = \frac{\omega - \omega_2}{\alpha_1}$$

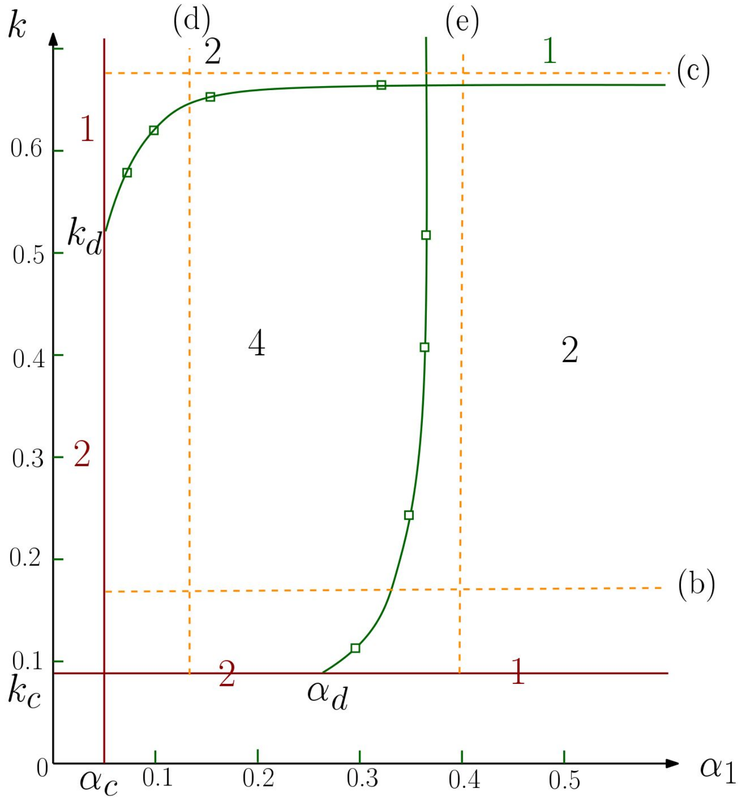
$$\sin(\theta_0(s_2) - \theta_1(s_2)) = \frac{2(\omega - \omega_1)}{k}.$$

- Number of fixed points depend on the number of intersections of the line and the sin function.
- The number of fixed points have four possibility: 0,1,2,4.
- Detailed proof is in the dissertation.



Numerical results of the fixed points analysis.

- No entrainment: $k < k_c, \alpha_1 < \alpha_c$
- Different number of fixed points are separated by the green curves.



Nullclines of the map for different parameters values.

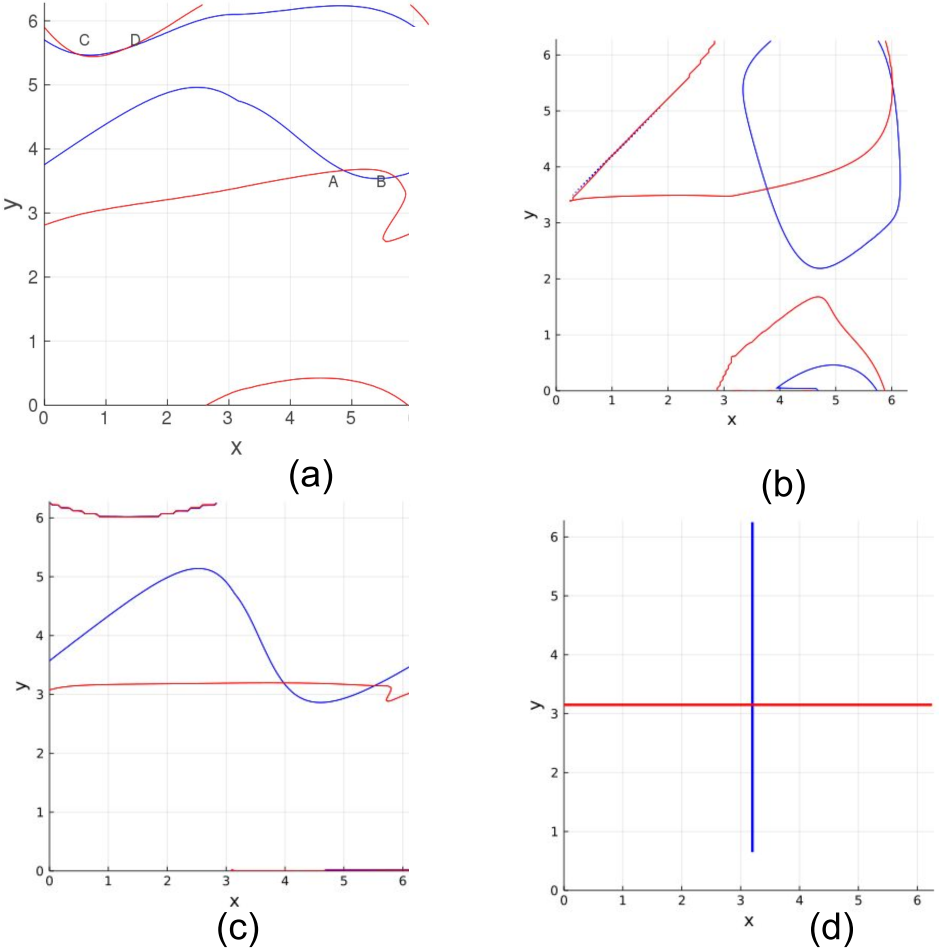
Red curve: x-nullcline
Blue curve: y-nullcline

(a) $k = 0.1, \alpha_1 = 0.1$

(b) Large k: $k = 2, \alpha_1 = 0.1$

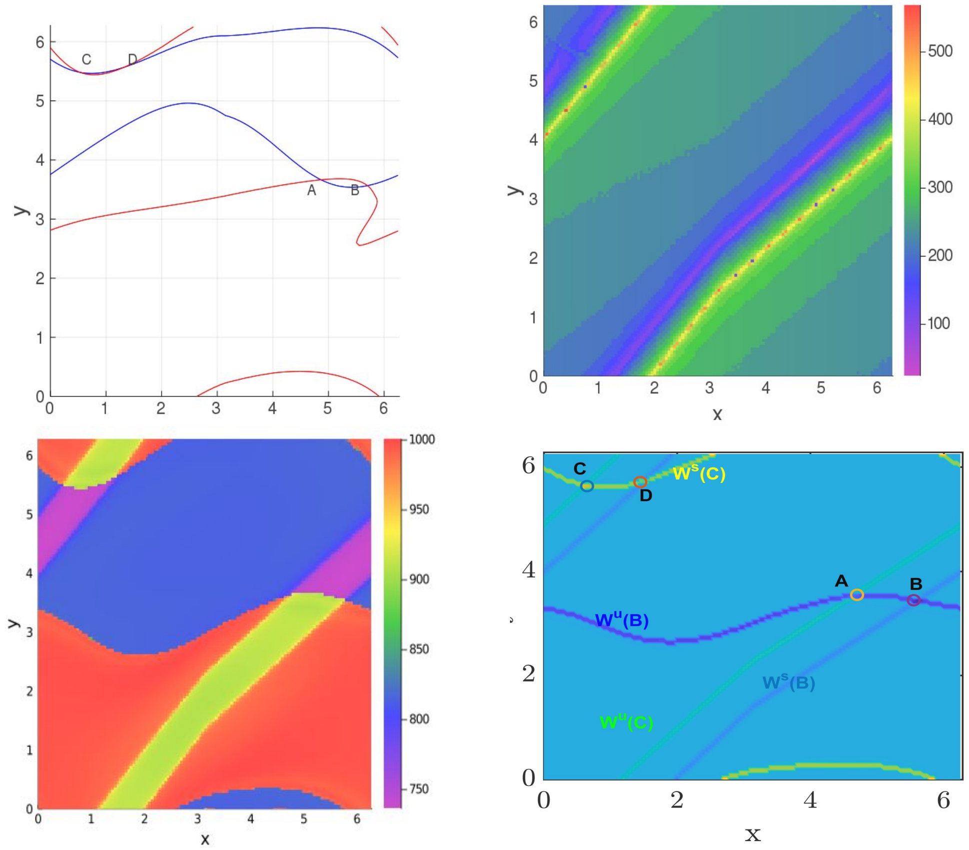
(c) Large **α**: $k = 0.12, \alpha_1 = 2$

(d) Both large: $k = 2, \alpha_1 = 2$



Numerical results for case (a)

- Stability of fixed points: A stable; B & C saddle; D unstable.
- Entrainment time is computed by iterating the map on each initial conditions.
- Manifolds visualization by Lagrangian descriptors method. (Lopesino et al., 2015).
- Discretized arclength plot and its gradient plot.



Conclusions from Kuramoto model

- Number of fixed point is bounded by four.
- Entrainment time revealed structure of stable and unstable manifolds of the map.
- Dynamics of the map are organized by the manifolds of the two saddle points.
- Generalization to the N+1 oscillator case is discussed in the dissertation.

Part 3

- Coupled Novak-Tyson (CNT) oscillators.
- Entrainment map. (Liao, Diekman and Bose, 2020 SIADS)

Existing 1-D entrainment map

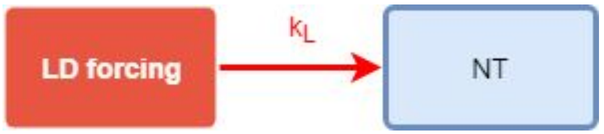
Novak-Tyson model:

$$\frac{1}{\phi}\frac{dP}{dt} = M - k_f h(P) - k_D P - k_L f(t) P$$

$$\frac{1}{\phi}\frac{dM}{dt} = \epsilon\left(g(P) - M\right)$$

$$g(P) = \frac{1}{1+P^4},\ h(P) = \frac{P}{0.1+P+2P^2}.$$

$$f(t) = Heaviside(sin(\frac{\pi}{12}t)).$$

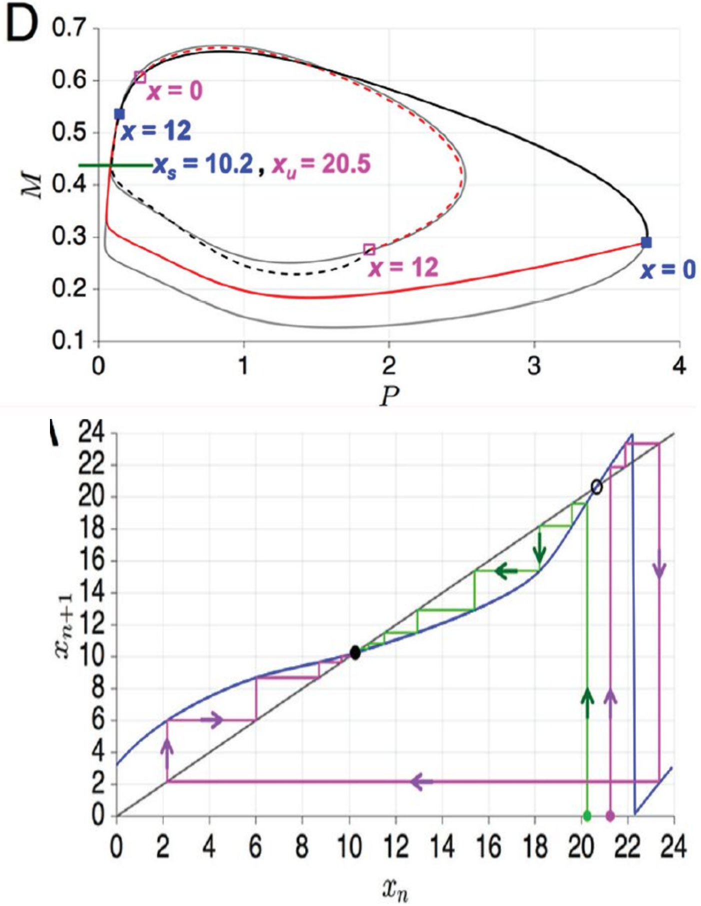


- Non-autonomous.
- Piecewise smooth periodic forcing.

Existing 1-D entrainment map

$$y_{n+1} = \Pi(y_n) = y_n + \rho(y_n) \; mod \; 24$$

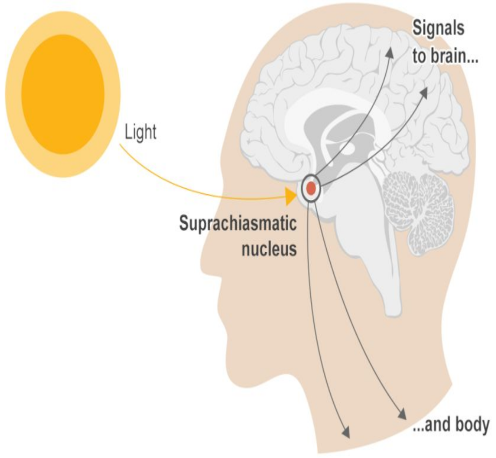
- **y** is defined to be the phase of light-dark forcing.
- **ρ(y)** measures the return time when the oscillator first returns to the chosen Poincare section.
- Structure of the map is similar to the one from the Kuramoto model.



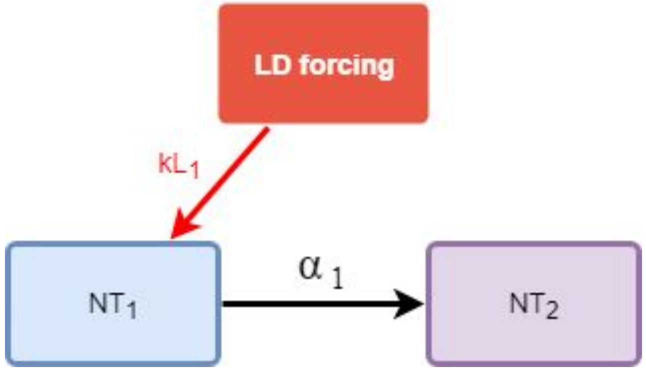
Diekman & Bose, 2016

The coupled Novak-Tyson model

$$\frac{1}{\phi_1}\frac{dP_1}{dt} = M_1 - k_f h(P_1) - k_D P_1 - k_{L_1} f(t) P_1$$
$$\frac{1}{\phi_1}\frac{dM_1}{dt} = \epsilon[g(P_1) - M_1]$$
$$\frac{1}{\phi_2}\frac{dP_2}{dt} = M_2 - k_f h(P_2) - k_D P_2$$
$$\frac{1}{\phi_2}\frac{dM_2}{dt} = \epsilon[g(P_2) - M_2 + (\alpha_1 M_1) g(P_2)]$$

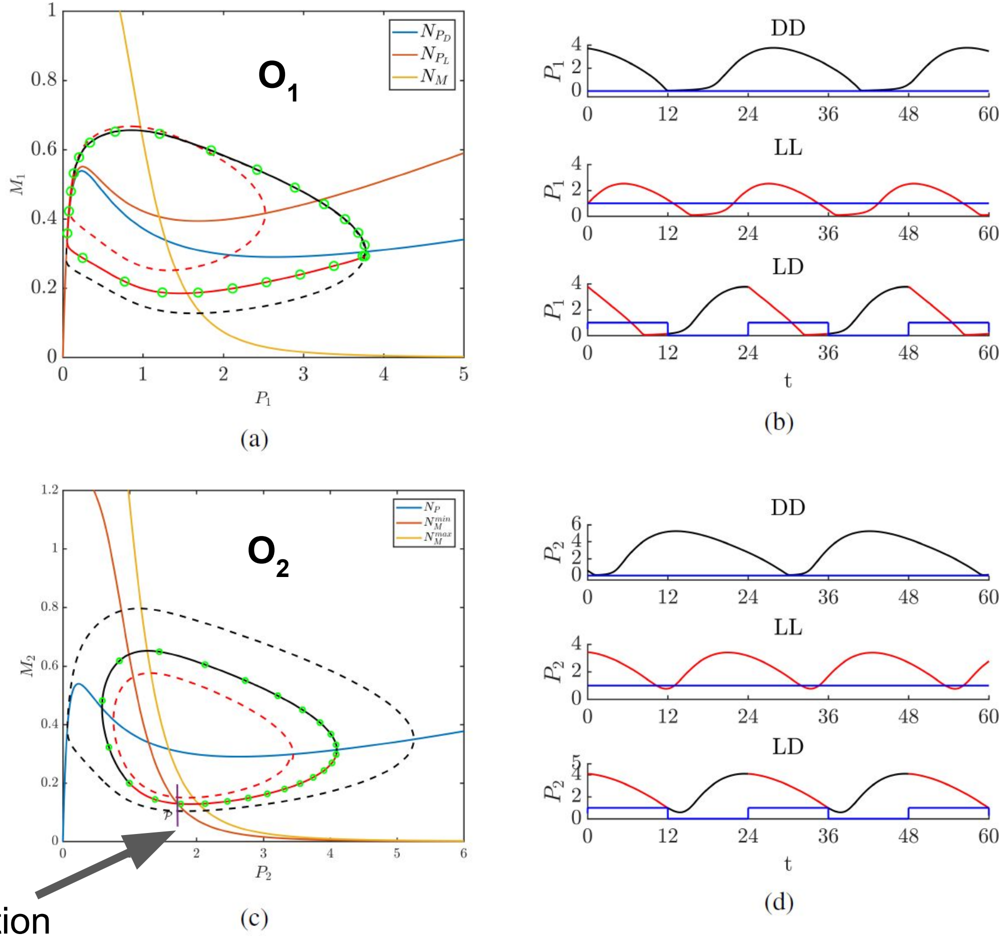


- This is a hierarchical network with oscillators at different levels of hierarchy.



Phase plane analysis

- The DD, LL and LD limit cycles of each oscillator.
- Poincare section is selected on the second oscillator.
- X = phase of O_1
- Y = phase of LD



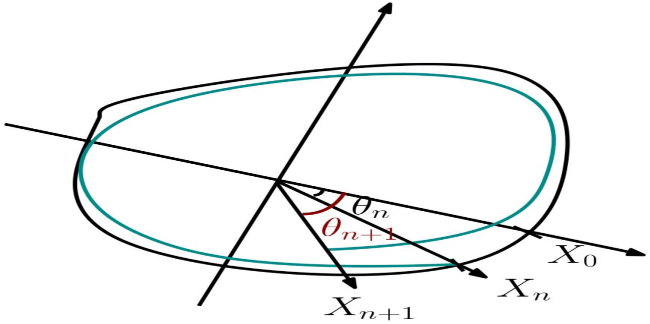
Poincare section

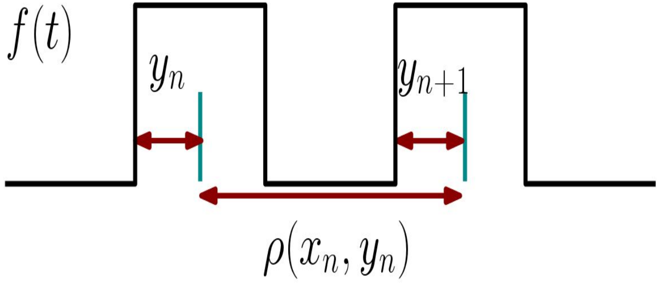
Construction of the 2-D entrainment map

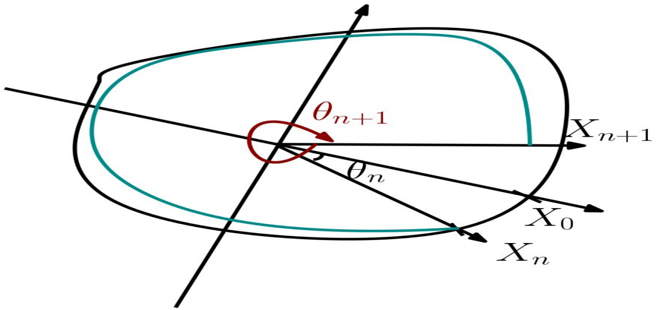
$$(x_{n+1}, y_{n+1}) = \Pi(x_n, y_n) = (\Pi_1(x_n, y_n), \Pi_2(x_n, y_n))$$

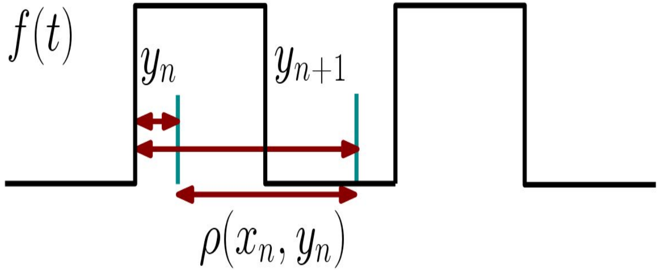
$$x_{n+1} = \Pi_1(x_n, y_n) = \min_{\forall x \in [0,24)} |Arg(\varphi_x(X_0)) - \theta_{n+1}|$$

$$y_{n+1} = \Pi_2(x_n, y_n) = y_n + \rho(x_n, y_n) \; mod \; 24$$

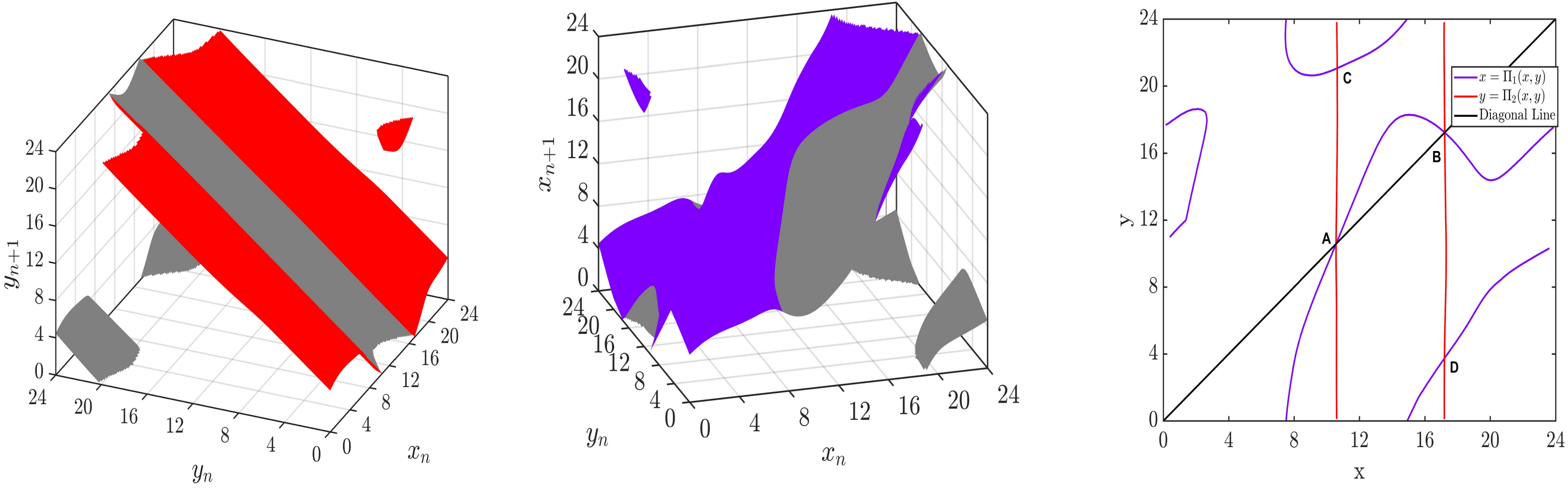






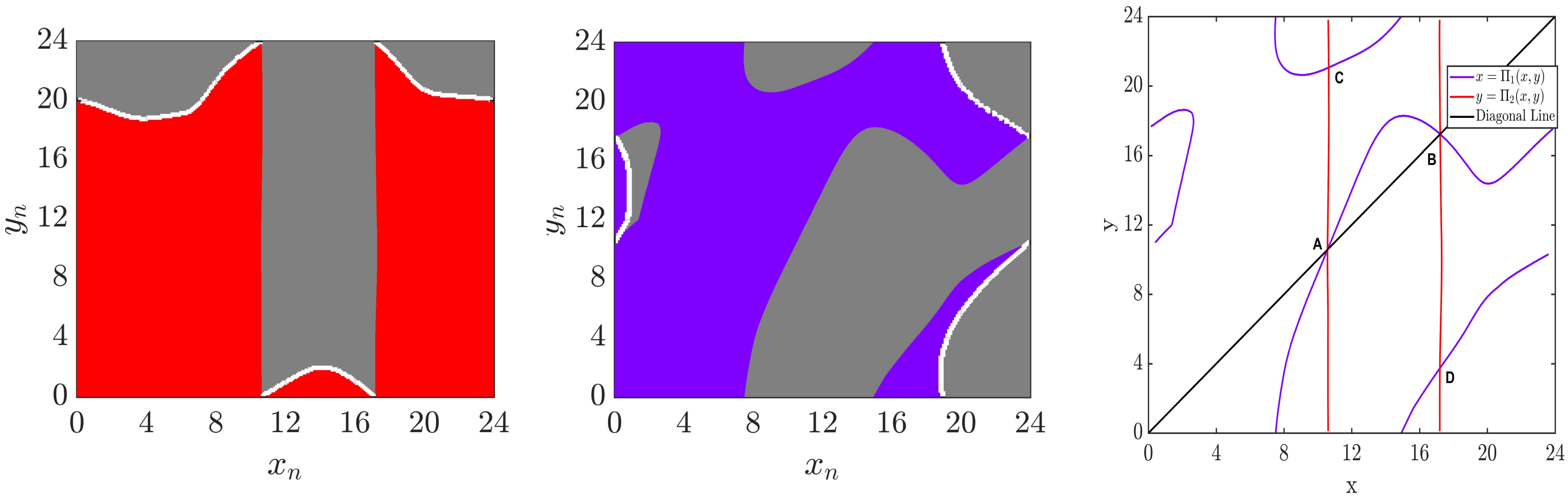


Surfaces and nullclines of the map



Geometrically find the fixed points of the map: use corresponding diagonal plane to intersect the surface of $\mathbf{\Pi}_1$ and $\mathbf{\Pi}_2$.

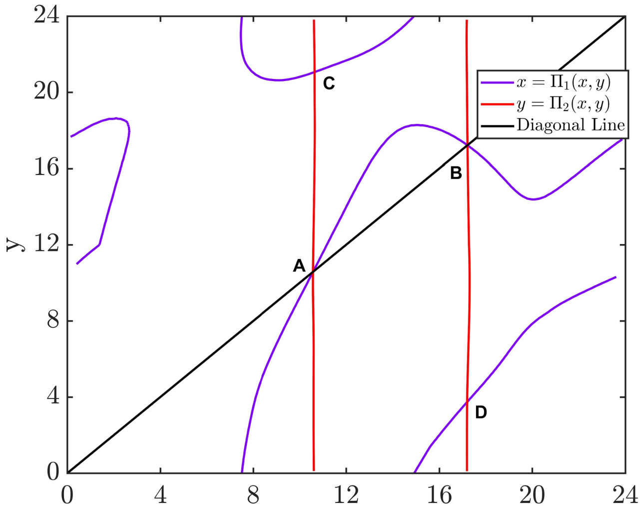
Surfaces and nullclines of the map (use top view)



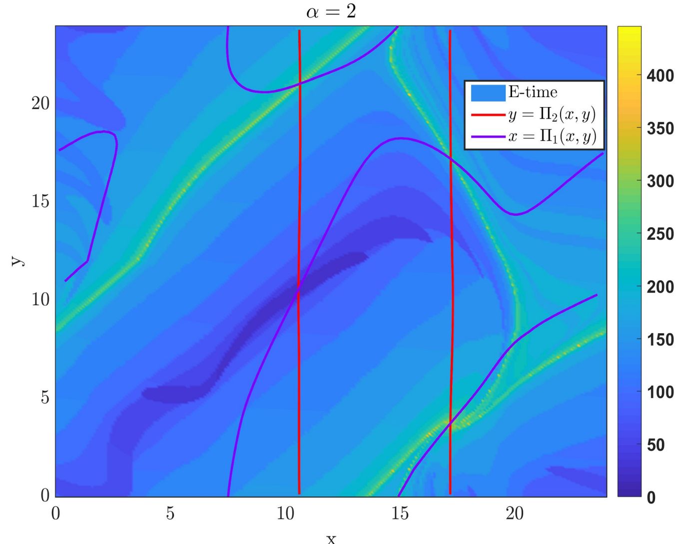
Geometrically find the fixed points of the map: use corresponding diagonal plane to intersect the surface of $\mathbf{\Pi}_1$ and $\mathbf{\Pi}_2$.

Stability and entrainment times

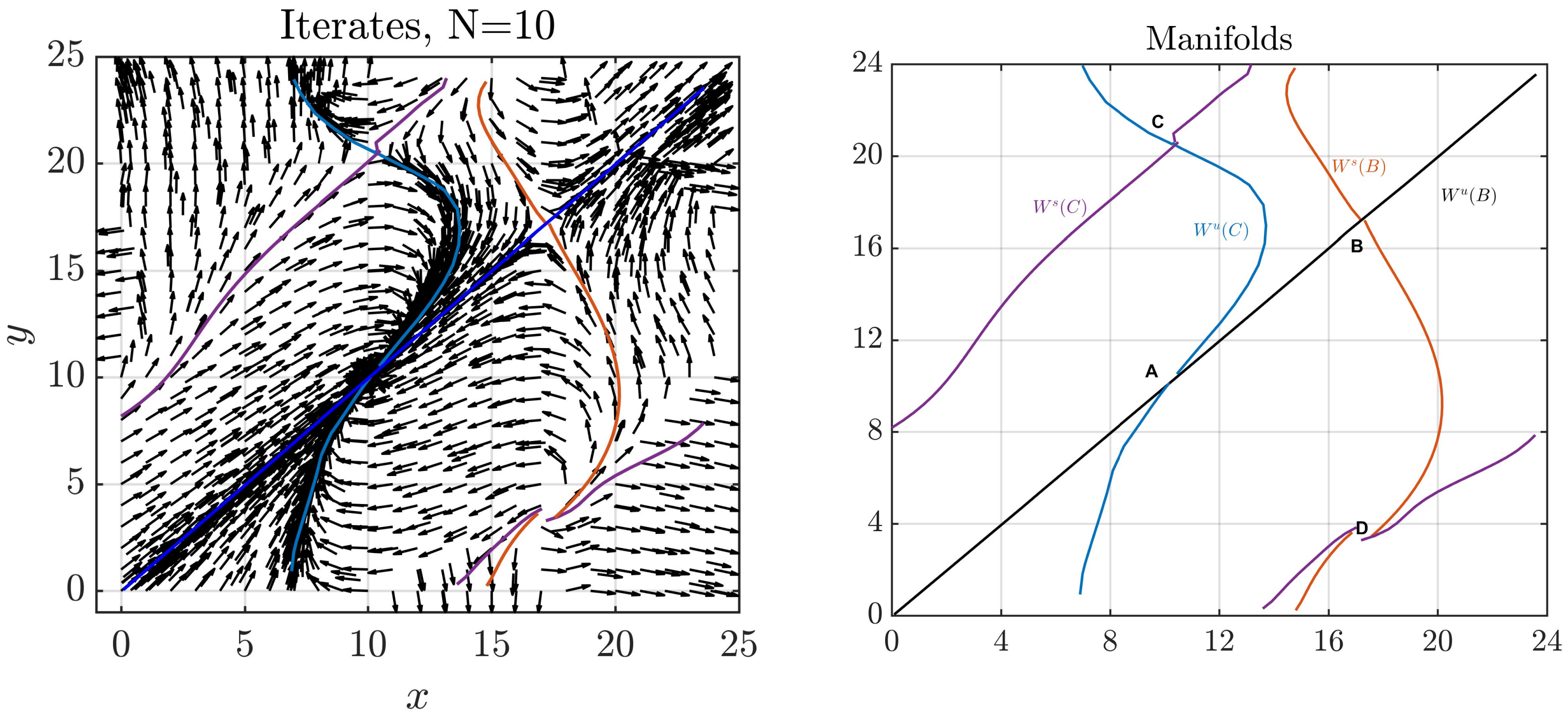
- The stability of the fixed points for the map reveal the properties of the original system under certain conditions.
- The entrainment time plot helps locating the stable manifolds.



	x	y	eigenvalue	stability
A	10.6	10.6	(0.1609,0.4453)	sink
B	17.2	17.2	(2.0858,0.4238)	saddle
C	10.6	21.1	(2.325,0.2734)	saddle
D	17.2	3.5	(1.595+0.77i,1.595-0.77i)	source

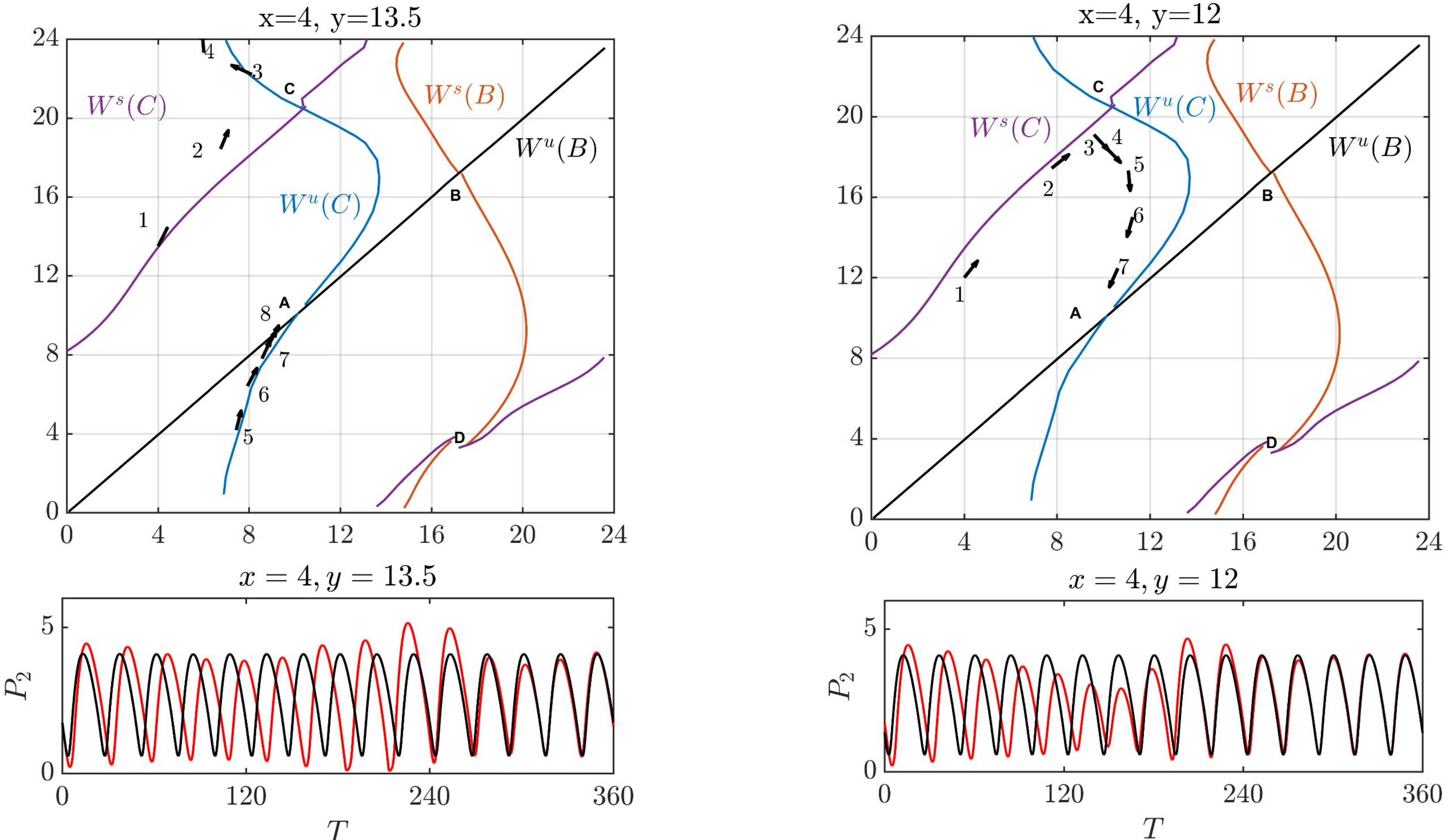


Iterates and manifolds

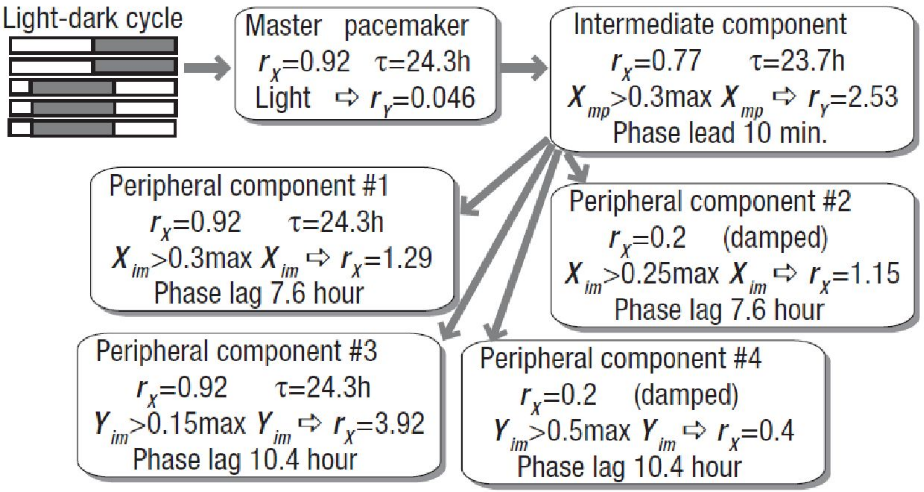


- The phase portrait with 10 iterates of each point.
- The unstable and stable manifolds of the saddle points B and C are calculated by growing method and Search Circle (SC) method. (Krauskopf, B. & Osinga, H., 1997; England, J.P., Krauskopf, B. & Osinga, H.M., 2004.)

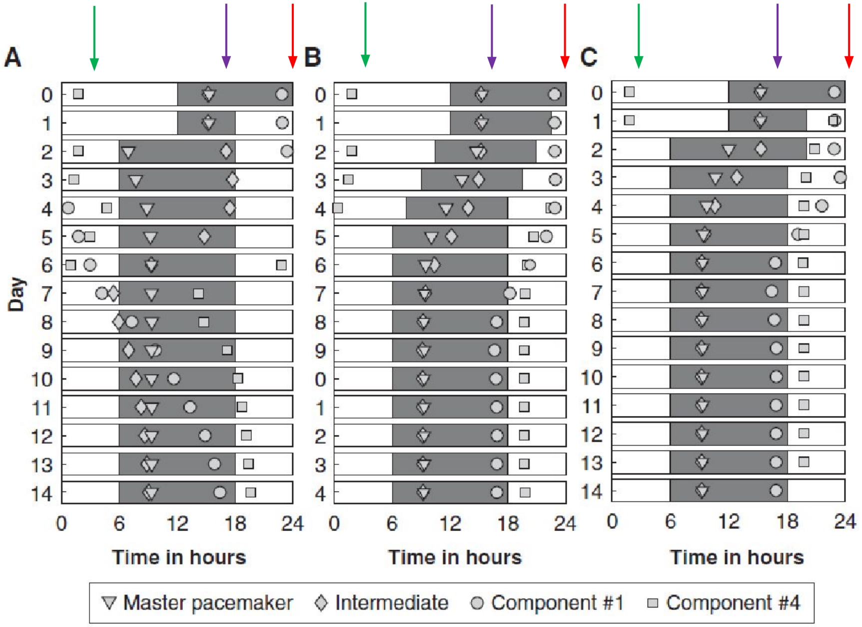
Different directions of entrainment



Dynamics of a Hierarchical Circadian System



Leise and Siegelmann, 2006 JBR



Our results suggest that the saddle structures exist for this model.

Conclusions

- The 2-dimensional entrainment map reveals the mathematical structures underlying the different types of entrainment behaviors.
  - The saddle points and their manifolds organize how iterates approach the stable LD-entrained solution.
  - Though not discussed, the entrainment time plots can be used to calculate jet lag recovery (see Diekman & Bose 2018, JTB)
- The map behaves in stereotypical ways across different circadian models making it easy to understand or predict parameter dependencies.
- Though not discussed here, the entrainment map should still “be applicable” in the presence of modest stochasticity and/or noise
- The map does not give us a proof of the existence of periodic orbits for the CNT model that correspond to the fixed points B, C and D.
- The map does not give complete information, however, as it is constructed only in a neighborhood of the LD entrained solution.

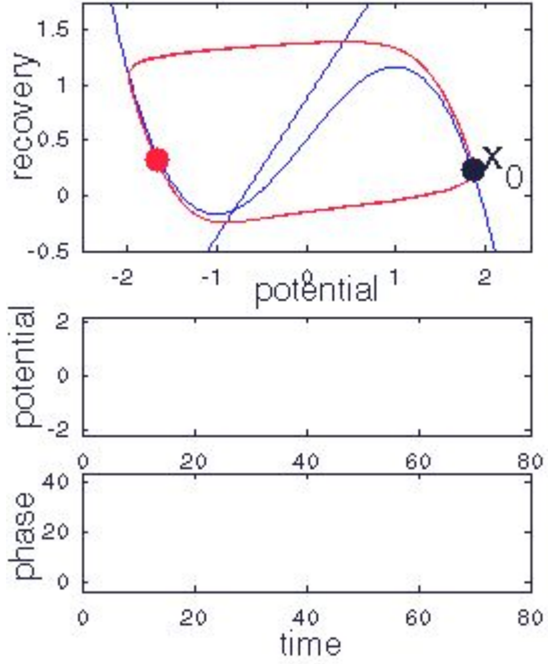
Appendix

Example of phase reduction

1. Periodic orbit of FitzHugh-Nagumo model.

2. The zero-phase point x_0 is chosen to correspond to the peak of the potential.

3. The dynamics near the periodic orbit are well described by the phase model.



Scholarpedia.org

Application

- The linear approximation of $P(\theta, \sigma)$ is applied for computing isochrons of some biological oscillators.

$$x = P(\theta, \sigma) = \gamma(\theta) + \sigma e^{-\mu\theta}\Phi(\theta)\vec{u} + o(\sigma^2)$$

- Isochrons are the level sets of the function θ(x) defined in the phase reduction method.

Number of fixed points is bounded above by four.

$$\sin(\theta_1(s_1) - \theta_2(s_1)) = \frac{\omega - \omega_2}{\alpha_1}$$
$$\sin(\theta_0(s_2) - \theta_1(s_2)) = \frac{2(\omega - \omega_1)}{k}.$$

Choose k and $\boldsymbol{\alpha}_1$, such that the value of the right hand side is between 0 and 1. Hence,

$$\theta_1(s_1) - \theta_2(s_1) = \beta_i(s_1), i = 1, 2.$$
$$\theta_1(0) - \theta_2(0) = \beta_i(0).$$

Since $\theta_2(0) = \pi$

$$y_0 = \theta_1(0) = \beta_i(0) + \pi.$$

Similarly, we can show

$$x_0 = \theta_0(0) = \zeta_j(0) + \theta_1(0) = \zeta_j(0) + \beta_i(0) + \pi.$$

Change in the number of fixed points for large values of parameters.

Let $\tau = \alpha_1 t$, we obtained the fast equations.

θ_2 becomes synchronized to $y = \theta_1(0)$.

$$\frac{d\theta_0}{d\tau} = 0$$
$$\frac{d\theta_1}{d\tau} = 0$$
$$\frac{d\theta_2}{d\tau} = \sin(\theta_1 - \theta_2)$$

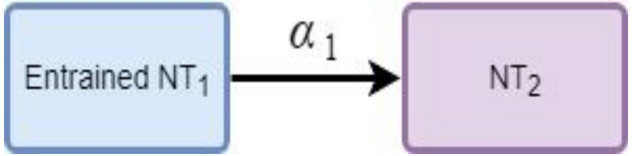
Let $\epsilon = 1/\alpha_1$, the equations on original time scale becomes

$$\frac{d\theta_0}{dt} = \omega$$
$$\frac{d\theta_1}{dt} = \omega_1 + kf(\theta_0)\sin(\theta_0 - \theta_1)$$
$$\epsilon\frac{d\theta_2}{dt} = \epsilon\omega_2 + \sin(\theta_1 - \theta_2),$$

On the original time scale, $\theta_1 = \theta_2$ remains. Thus when θ_1 returns to the Poincar\'e section again, $y = \pi$.

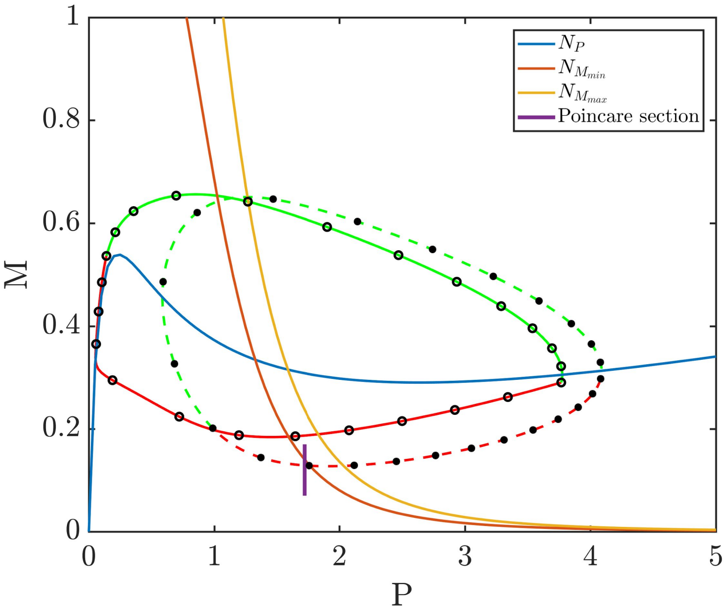
The 1-D pre-entrained map

$$\frac{1}{\phi_2}\frac{dP_2}{dt} = M_2 - k_f h(P_2) - k_D P_2$$
$$\frac{1}{\phi_2}\frac{dM_2}{dt} = \epsilon_2[(g(P_2) - M_2) + (\alpha_1 M_1)g(P_2)]$$



Poincare section is selected at

$$\mathcal{P} : P_2 = 1.72, |M_2 - 0.1289| < \delta$$

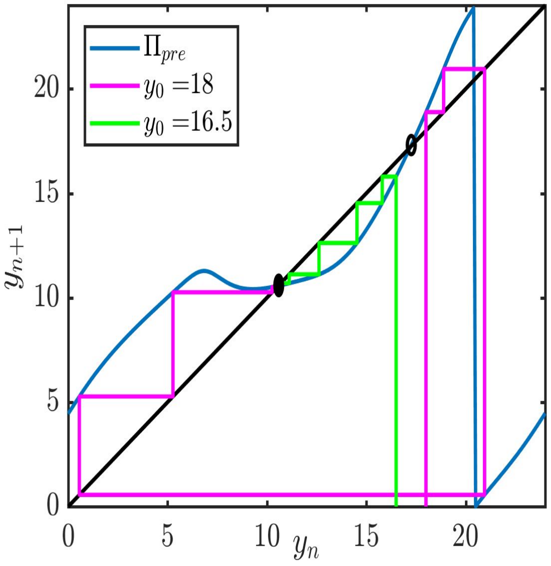


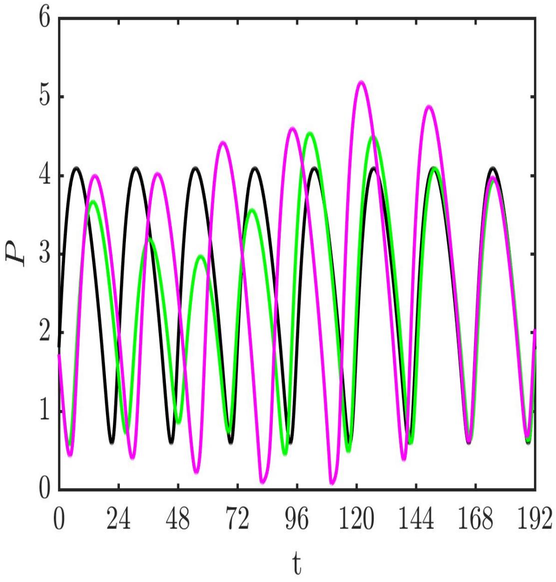
In the pre-entrained case, oscillator 1 is a periodic forcing into oscillator 2.

The 1-D pre-entrained map

$$y_{n+1} = \Pi_{pre}(y_n) = (y_n + \rho(y_n; \gamma(y_n)))\ mod\ 24$$

- $\mathbf{y}$ has the same definition as before.
- The return time $\boldsymbol{\rho}(\mathbf{y})$ is evaluated for oscillator 1 at a certain location which is determined by $\mathbf{y}$.
- $\gamma(y) = \varphi_y(X_0)$ is a point on oscillator 1's limit cycle





Construction of the 2-D entrainment map

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\begin{tikzcd}
(x, y) \arrow[r, "f_1\text{: map x to its limit cycle}"] \arrow[d, "\Pi"'] & (P_1(x), M_1(x), y) \arrow[d, "S\text{: apply Poincaré map}"] \\
(x', y') & (P', M', y + \rho(x, y)) \arrow[l, "f_2\text{: phase angle projection}"']
\end{tikzcd}
$$

The map is written as

$$\Pi(x, y) = f_2 \circ S \circ f_1(x, y)$$

Parameter dependance.

- The x & y nullclines change systematically as we vary the value of α_1.
- The entrainment time plot under different value of coupling strength (α_1).