# Entrainment dynamics of forced hierarchical circadian systems.

Guangyuan Liao†, Casey Diekman† and Amitabha Bose†

†Department of Mathematical Science, New Jersey Institute of Technology

## Introduction

The ability of circadian oscillators to entrain to light-dark cycles is well known. The process of circadian entrainment has been studied by various methods from dynamical systems. Recently, a tool called the entrainment map was introduced to analyze the entrainment process [1]. We developed a 2-D entrainment map to study coupled circadian oscillators. The entrainment map is quite effective to study the time and direction of entrainment.

## Model

We first consider the situation in which a single central oscillator receives light-dark input. In turn, this central oscillator sends input to a single peripheral oscillator. To focus on the mathematical aspects of the derivation and analysis of the 2-D entrainment map, we will utilize the planar Novak-Tyson model [3] for both the central and peripheral oscillators.

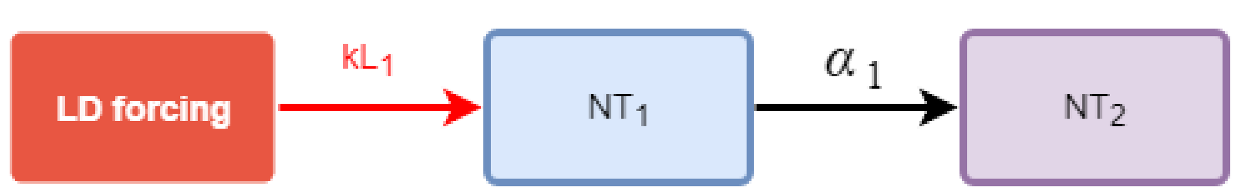


Fig. 1: Schematic figure of the model.

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

Where $g(P) = \frac{1}{1+P^4}$; $h(P) = \frac{P}{0.1+P+2P^2}$ and $f(t) = Heaviside(sin(\frac{\pi}{12}t))$

## Construction of the 2-D entrainment map

Instead of studying the original five dimensional model directly, we reduced the model as a two dimensional discrete phase model. The method is a combination of the Poincare map and phase reduction. The reduced system is written as a two dimensional map:

$$x_{n+1} = \Pi_1(x_n, y_n) = Arg[\varphi_{\rho(x_n,y_n)}(x_n, y_n)].$$
$$y_{n+1} = \Pi_2(x_n, y_n) = y_n + \rho(x_n, y_n) \; mod \; 24$$

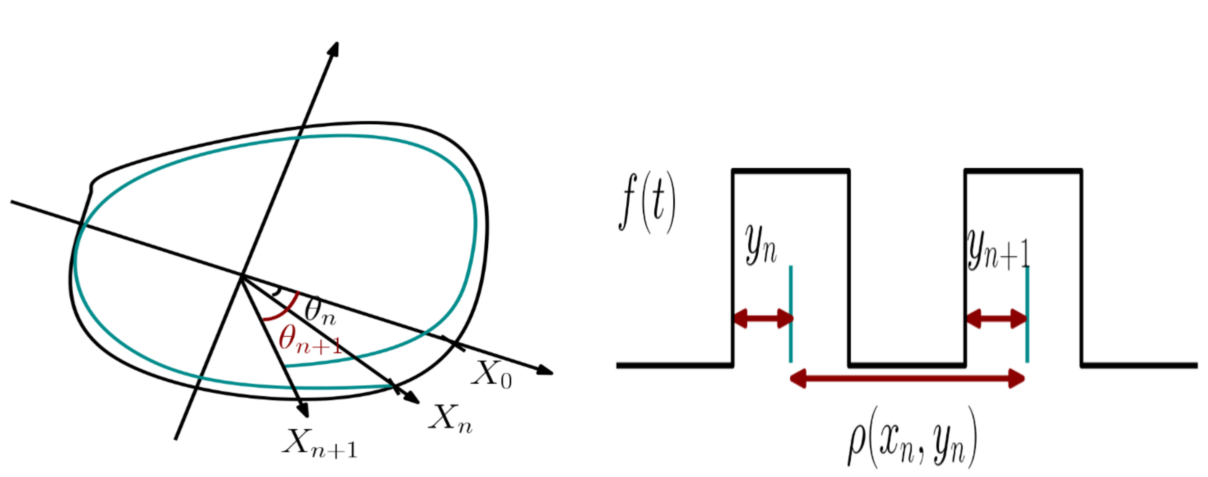


Fig. 2: Construct the map.

## Results

By studying the entrainment map, determining the nature of various fixed points, together with an understanding of their stable and unstable manifolds, leads to conditions for existence and stability of periodic orbits of the circadian system. We use the map to investigate how various properties of solutions depend on parameters and initial conditions including the time to and direction of entrainment. We show that the concepts of phase advance and phase delay need to be carefully assessed when considering hierarchical systems.

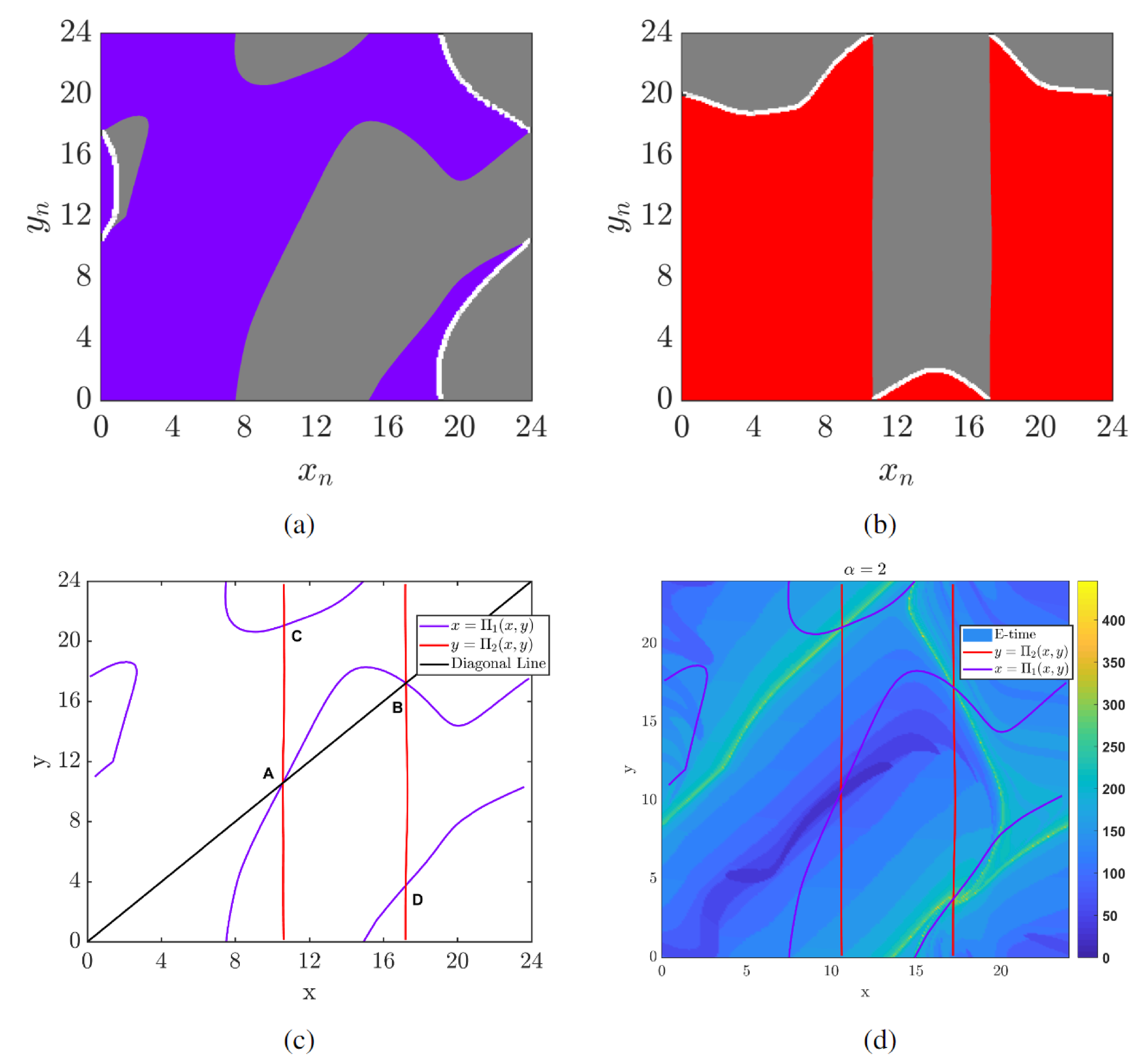


Fig. 3: Finding fixed points and computing entrainment time

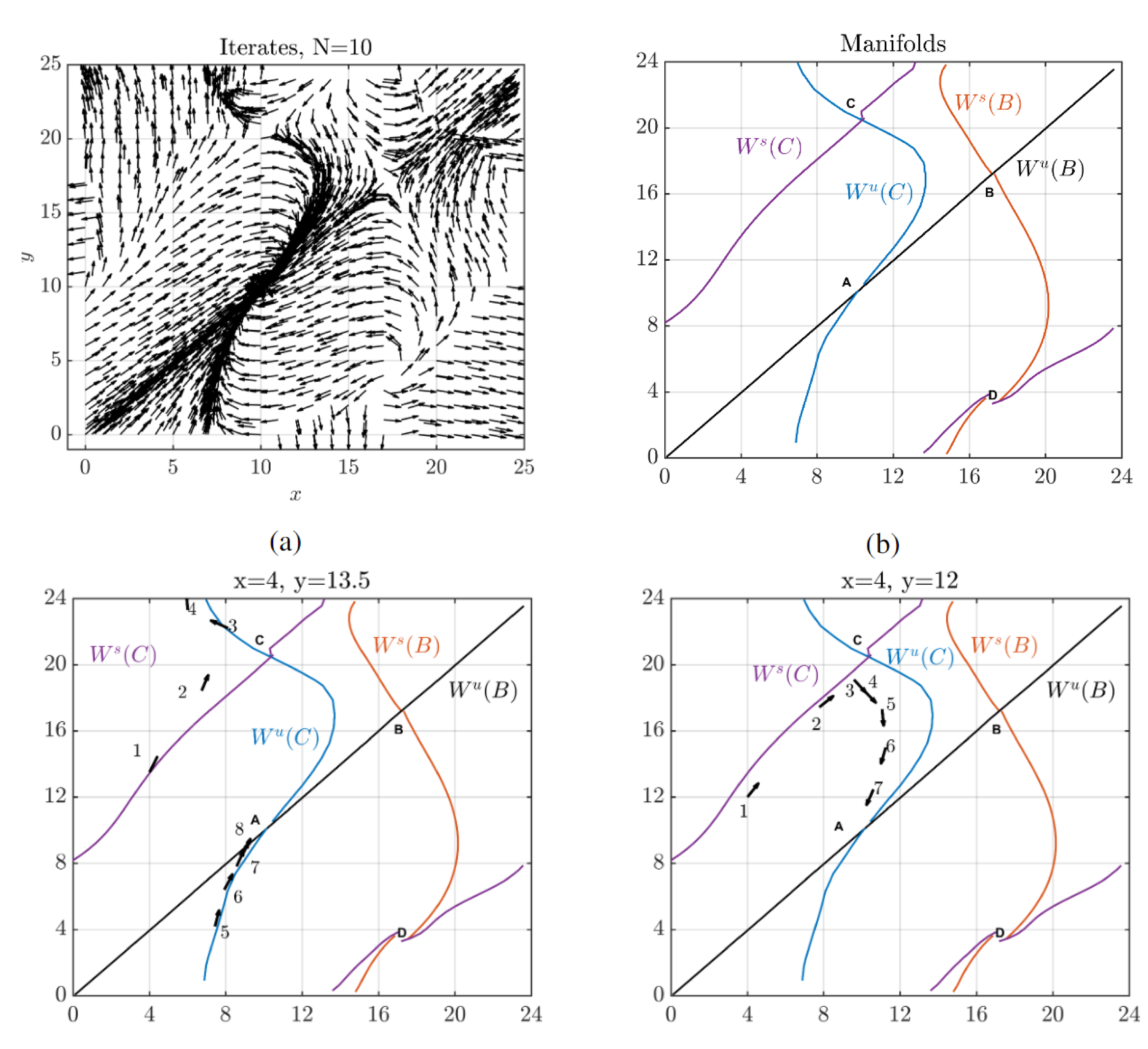


Fig. 4: Iterates and manifolds.

## Parameter dependance and bifurcations

we calculate the 2-D map at different values of $\alpha_1$ to see how the fixed points and the entrainment time depend on $\alpha_1$. In Fig. (a) (b), we show the $x$ and $y$ nullclines for three different $\alpha_1$ values; the points with solid circle are the stable fixed points, the points with open circles are the unstable fixed points, and the starred points are saddle points. In Fig. (c), we show the heatmap of entrainment times for $\alpha_1 = 1.52$. In Fig. (d), we show the heatmap of entrainment times for $\alpha_1 = 2.5$. Note that $\alpha_1 = 2$ is our canonical case, and was presented before. Increasing $\alpha_1$, in general, decreases the entrainment time as can be observed from the color scale values (yellow max value $\approx 700$ for $\alpha_1 = 1.52$) verus 400 for $\alpha_1 = 2.5$. In other words, stronger coupling between the central to peripheral oscillator speeds up entrainment.

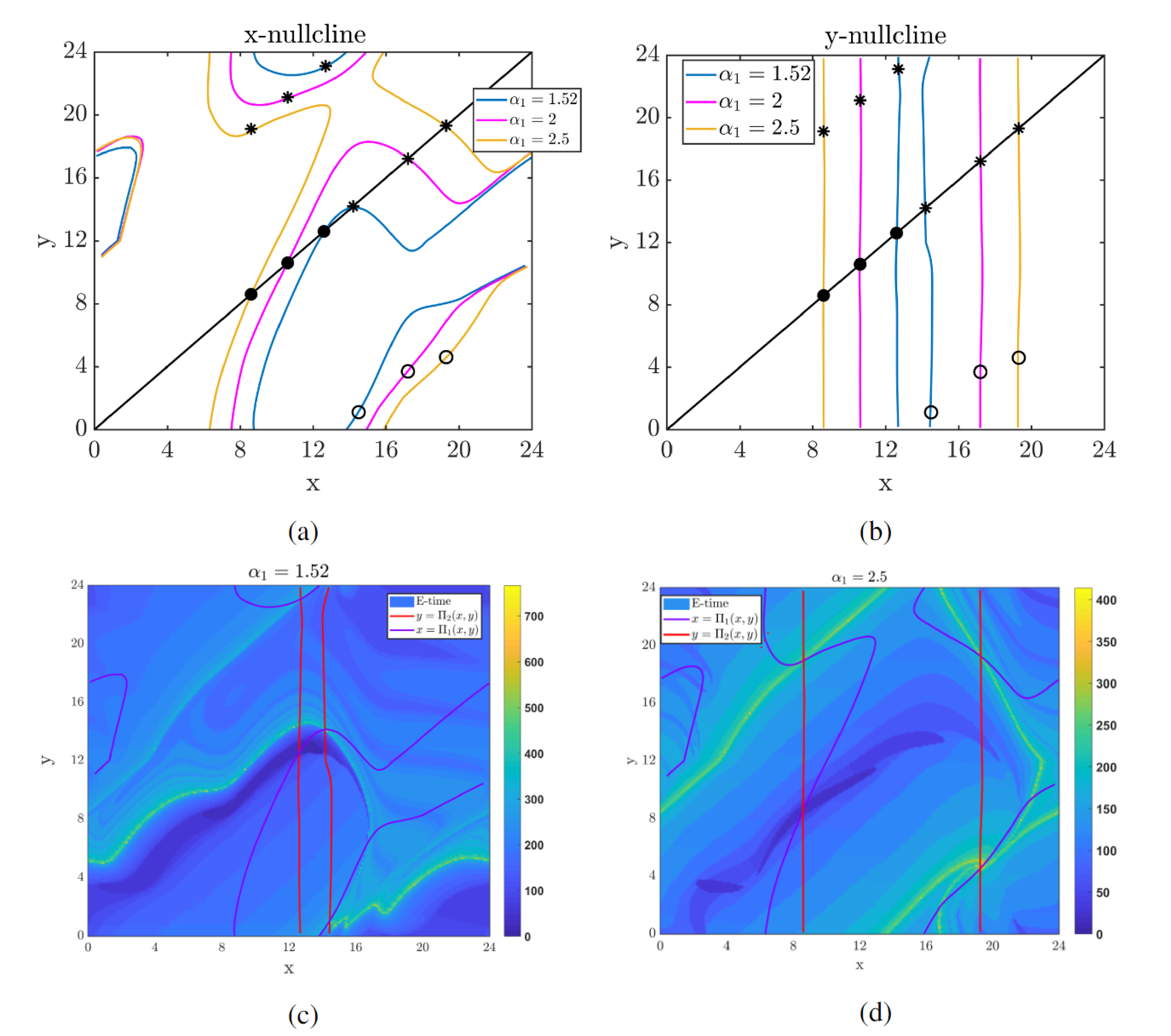


Fig. 5: Parameter dependence.

## Conclusion

We generalized the entrainment map to two dimensions by introducing the phase angle. Analyzed the time of entrainment and the direction of entrainment by studying the properties of the map. The direction of entrainment is not necessarily monotonic. Entrainment time calculations provide a way to locate and approximate stable and unstable manifolds. We then computed the stable and unstable manifolds by growing method and search circle method [2].

## Future work

Apply the entrainment map to other kinds of coupled network. Develop entrainment maps for more general models of periodic forced oscillators. Apply Floquet theory to derive the entrainment map under phase-amplitude coordinate system. Study the bifurcation of the entrainment map.

## References

[1] Casey O Diekman and Amitabha Bose. "Entrainment maps: A new tool for understanding properties of circadian oscillator models". In: *J. Biol. Rhythms* 31.6 (2016), pp. 598–616.

[2] James P England, Bernd Krauskopf, and Hinke M Osinga. "Computing one-dimensional stable manifolds and stable sets of planar maps without the inverse". In: *SIADS* 3.2 (2004), pp. 161–190.

[3] Béla Novák and John J Tyson. "Design principles of biochemical oscillators". In: *Nat. Rev. Mol. Cell Biol.* 9.12 (2008), p. 981.