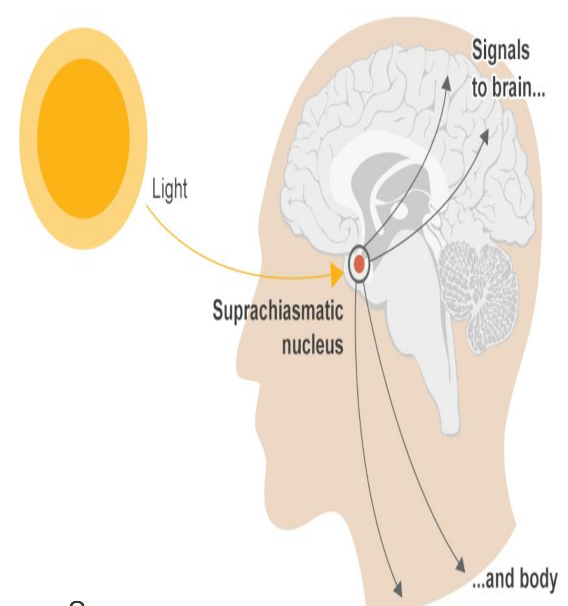
Mathematical Models and Tools for understanding the Entrainment of Hierarchical Circadian Systems

Guangyuan Liao, Casey Diekman, Amitabha Bose. Department of Mathematical Sciences, New Jersey Institute of Technology, Newark NJ 07102

Introduction

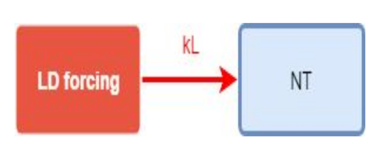
- The ability of circadian oscillators to entrain to light-dark cycles is well known.
- The process of circadian entrainment has been studied by various methods from dynamical systems.
- Recently, a tool called the entrainment map was introduced to analyze the entrainment process (Diekman & Bose, 2016).
- We develop a 2-D entrainment map to study coupled circadian oscillators.
- The entrainment map is quite effective to study the time and direction of entrainment.



Source: PhotonStar

1. Existing 1-D entrainment map

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

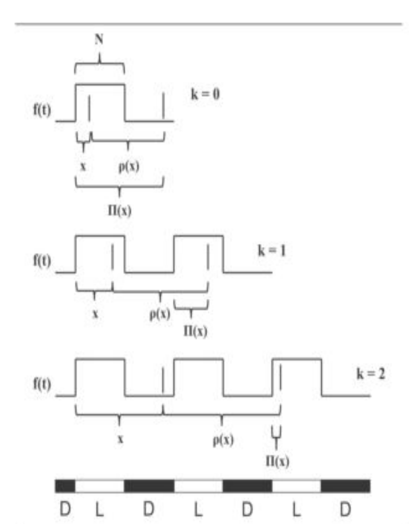


$$g(P) = \frac{1}{1+P^4},\ h(P) = \frac{P}{0.1+P+2P^2}.$$
$$f(t) = Heaviside(sin(\tfrac{\pi}{12}t)).$$

- This is a non-autonomous nonlinear system with piecewise smooth periodic forcing.

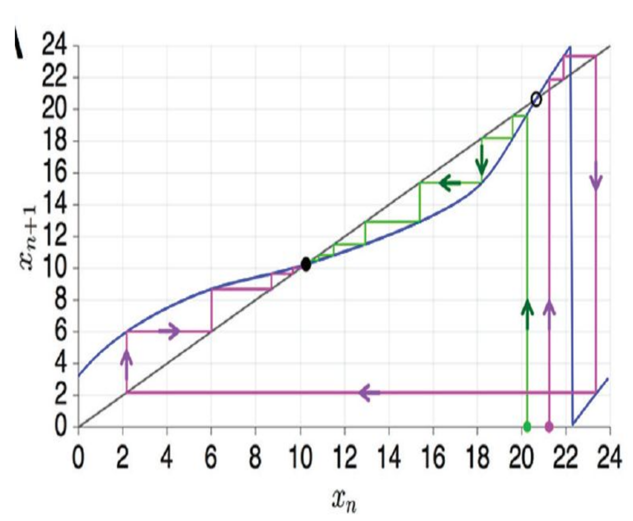
$$x_{n+1} = \Pi(x_n) = (\rho(x_n) + x_n)\ mod\ 24$$

- x is defined to be the phase of light-dark forcing.
- $\rho(x)$ measures the return time when the oscillator first returns to the chosen Poincare section.



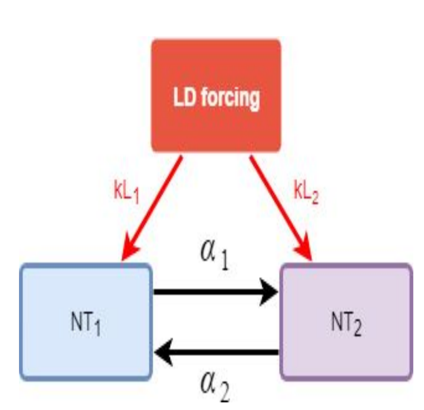
Diekman & Bose, 2016

- It's equivalent to a circle 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).

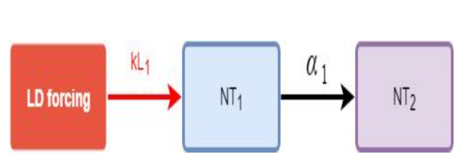


2. The coupled Novak-Tyson Model

$$\frac{1}{\phi_1}\frac{dP_1}{dt} = M_1 - k_f h(P_1) - k_D P_1 - k_{L_1} f(t) P_1$$
$$\frac{1}{\phi_1}\frac{dM_1}{dt} = \epsilon_1 (g(P_1) - M_1) + \epsilon_1(\alpha_2 M_2) g(P_1)$$
$$\frac{1}{\phi_2}\frac{dP_2}{dt} = M_2 - k_f h(P_2) - k_D P_2 - k_{L_2} f(t) P_2$$
$$\frac{1}{\phi_2}\frac{dM_2}{dt} = \epsilon_2 (g(P_2) - M_2) + \epsilon_2(\alpha_1 M_1) g(P_2)$$

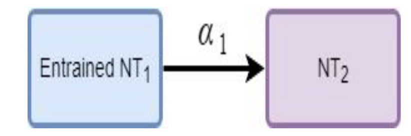


- This is a hierarchical network with oscillators at different levels of hierarchy.
- Here we study a reduced model with uni-directional connection, where kL_2=0 and α_2=0.



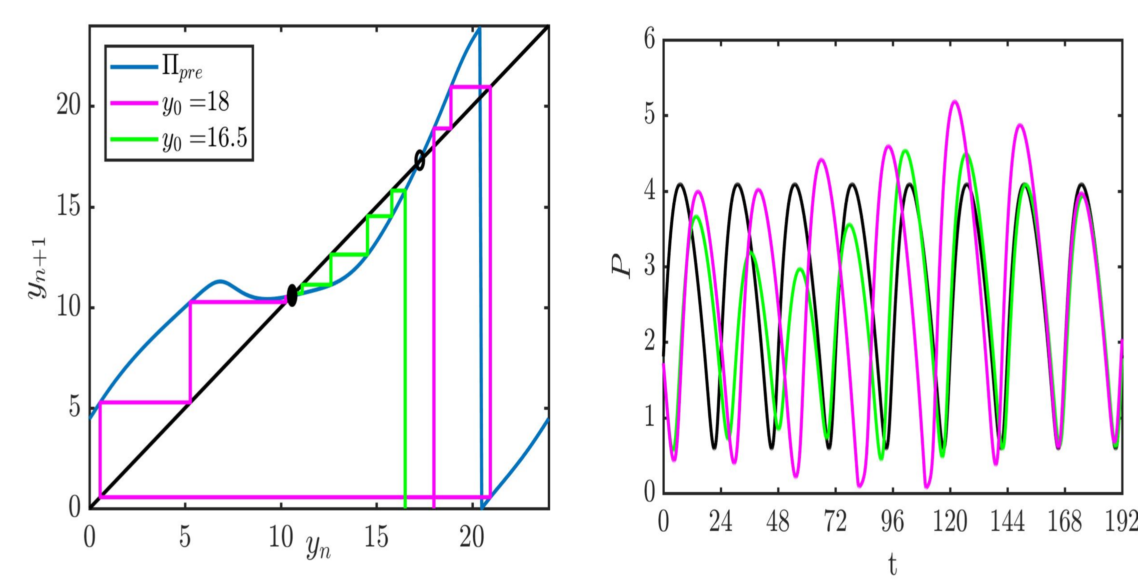
3. The 1-D pre-entrained map

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

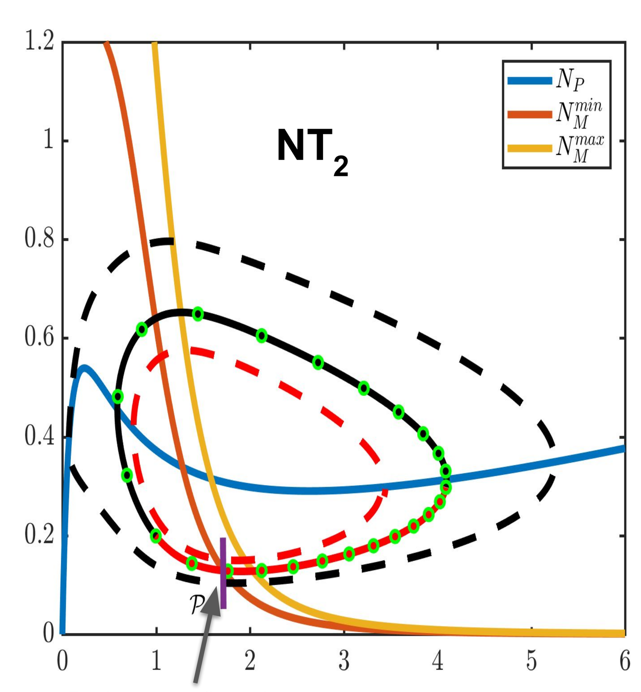


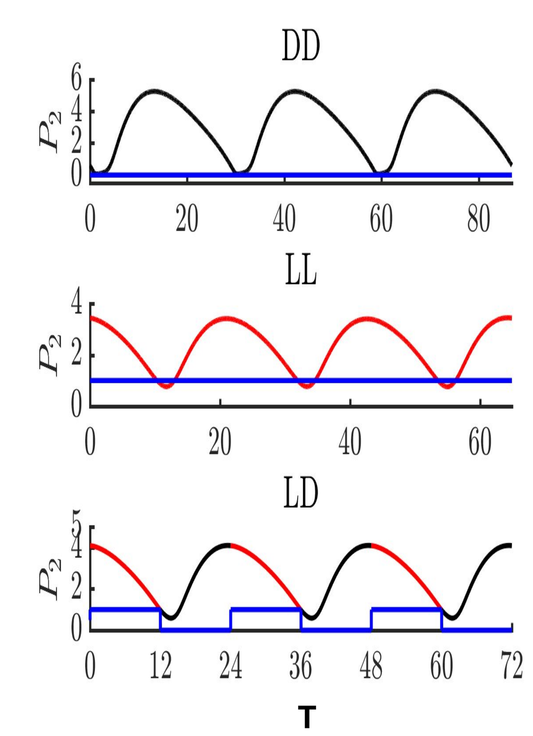
$$y_{n+1} = \Pi_{pre}(\varphi_{y_n}(X_0), y_n) = (y_n + \rho(\varphi_{y_n}(X_0), y_n))\ mod\ 24$$

$\varphi_{y_n}(X_0)$: Denotes the flow of NT_1, starting at X_0, y_n hours later.

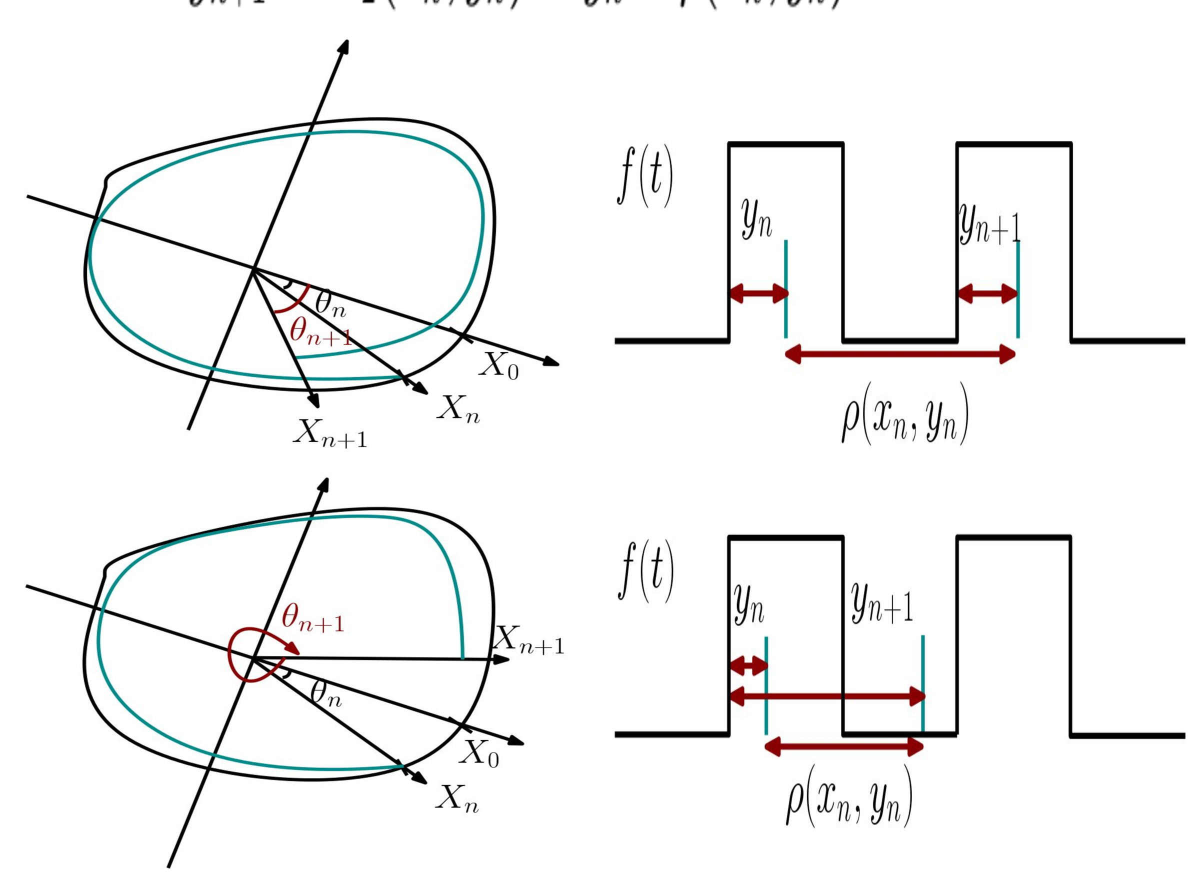


4. Construction of the 2-D entrainment map

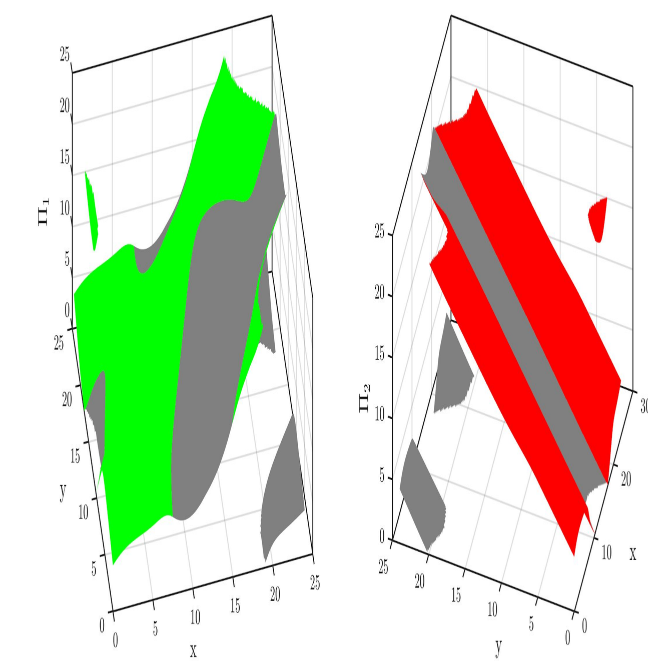




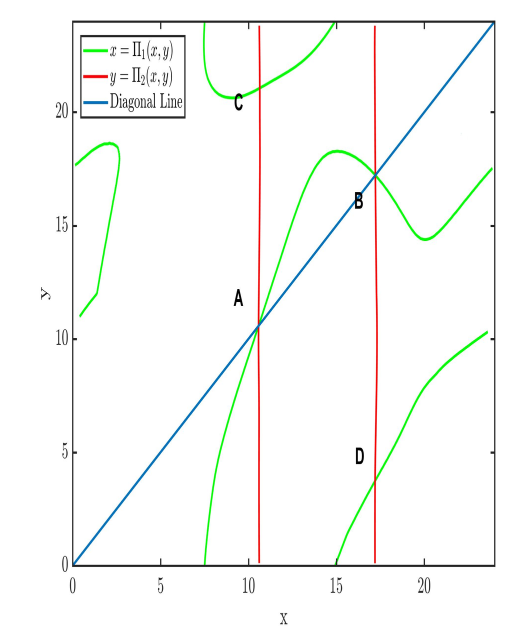
$$(x_{n+1}, y_{n+1}) = \Pi(x_n, y_n) = (\Pi_1(x_n, y_n), \Pi_2(x_n, y_n))$$
$$x_{n+1} = \Pi_1(x_n, y_n) = \min_{\forall x \in [0,24)} |Arg(\varphi_x(X_0)) - \theta_{n+1}|$$
$$y_{n+1} = \Pi_2(x_n, y_n) = y_n + \rho(x_n, y_n)\ mod\ 24$$



5. Graph and fixed points of the 2-D entrainment map



Intersection with diagonal planes

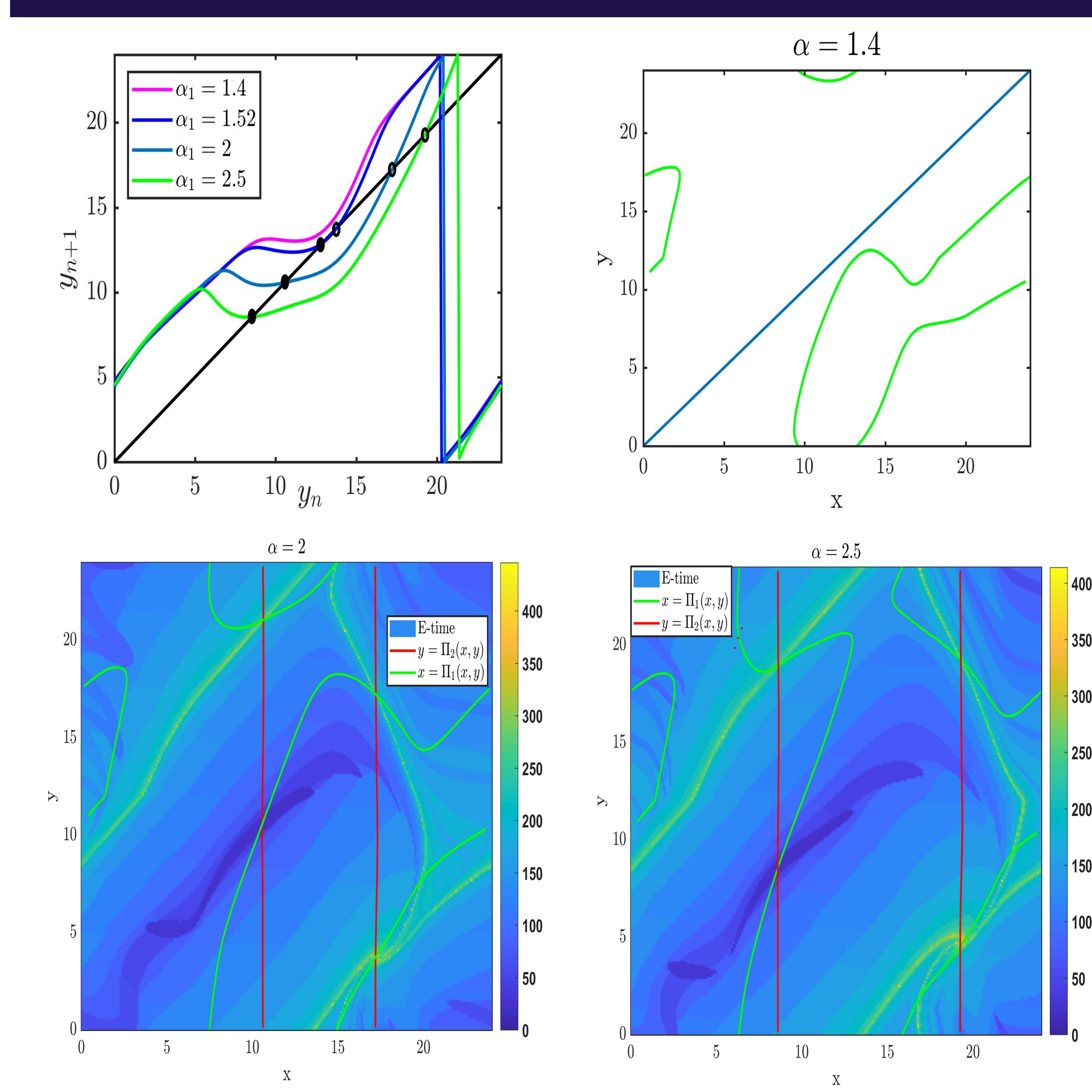


Projection onto x-y plane

Numerically calculate Jacobian matrix at A,B,C,D.

	x	y	eigenvalue	stability
A	10.6	10.6	(0.1609,0.4453)	sink; $NT_1, S; NT_2, S$
B	17.2	17.2	(2.0858,0.4238)	saddle; $NT_1, S; NT_2, U$
C	10.6	21.1	(2.325,0.2734)	saddle; $NT_1, U; NT_2, S$
D	17.2	3.5	(1.595+0.77i,1.595-0.77i)	source; $NT_1, U; NT_2, U$

6. Entrainment time and parameter dependence

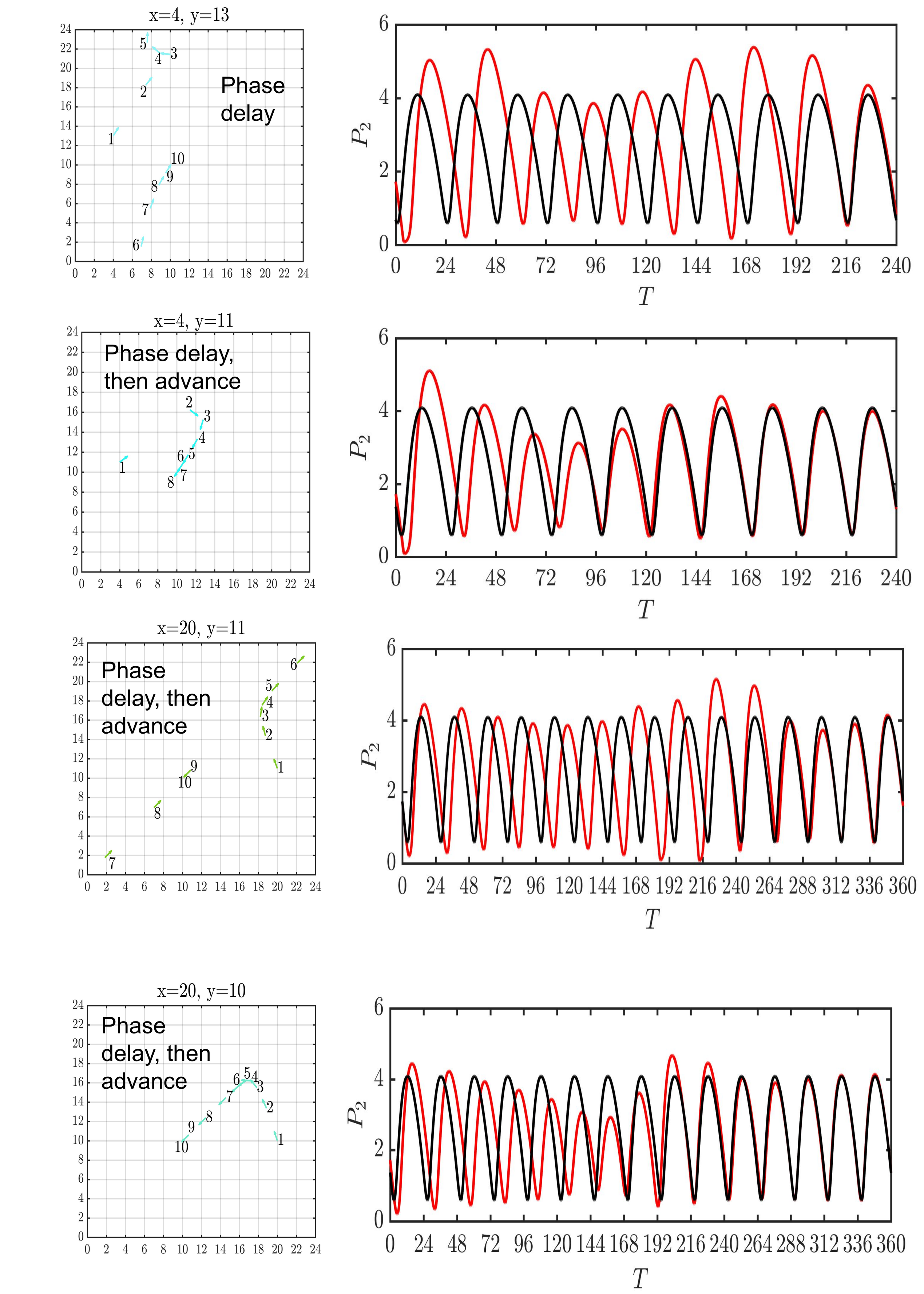


The light colored curves denote longer entrainment time, and also help to locate $W^S(C)$ & $W^S(D)$.

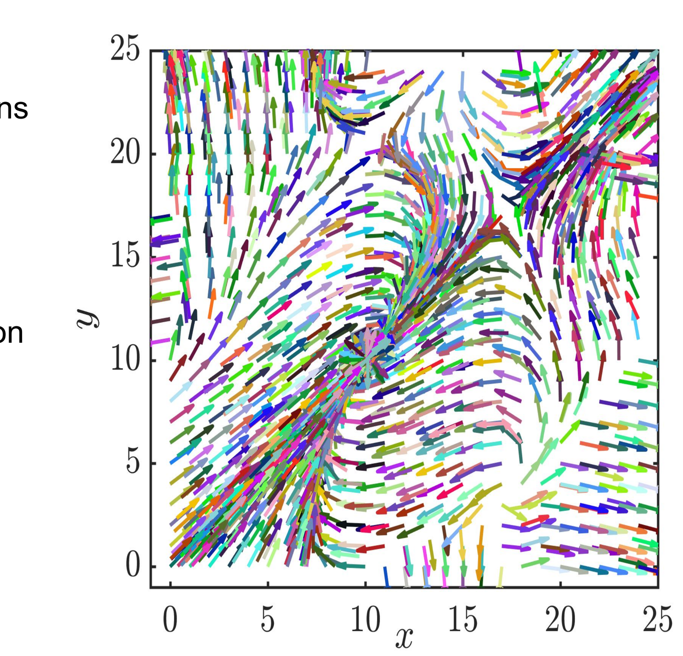
References

[1] Diekman, C.O. and Bose, A., 2016. Entrainment maps: a new tool for understanding properties of circadian oscillator models. *Journal of Biological Rhythms*, 31 (6), pp. 598–616 .
[2] Diekman, C.O. and Bose, A., 2018. Reentrainment of the circadian pacemaker during jet lag: East-west asymmetry and the effects of north-south travel. *Journal of Theoretical Biology*, *437*, pp.261-285.
[3] England, J.P., Krauskopf, B. and Osinga, H.M., 2005. Computing one-dimensional global manifolds of Poincaré maps by continuation. *SIAM Journal on Applied Dynamical Systems*, *4*(4), pp.1008-1041.
[4] Brown, E., Moehlis, J. and Holmes, P., 2004. On the phase reduction and response dynamics of neural oscillator populations. *Neural computation*, *16*(4), pp.673-715.

7. Direction of entrainment and compare with simulations



- Four different initial conditions near the stable manifold of saddle point C and D.
- Agrees with the simulation.
- The full iterates are shown on the right.



Conclusions & Future work

Conclusions

- 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.

Future work

- Apply the entrainment map to other cases of the coupled network with feedback.
- Compute the invariant manifolds of the entrainment map.
- Develop entrainment maps for more general models of periodic forced oscillators.
- Develop phase models for weakly coupled networks with piecewise continuous forcing.