Understanding the limits of entrainment of circadian oscillator models using one-dimensional maps

Amitabha Bose
Department of Mathematical Sciences
New Jersey Institute of Technology

Joint work with Casey Diekman

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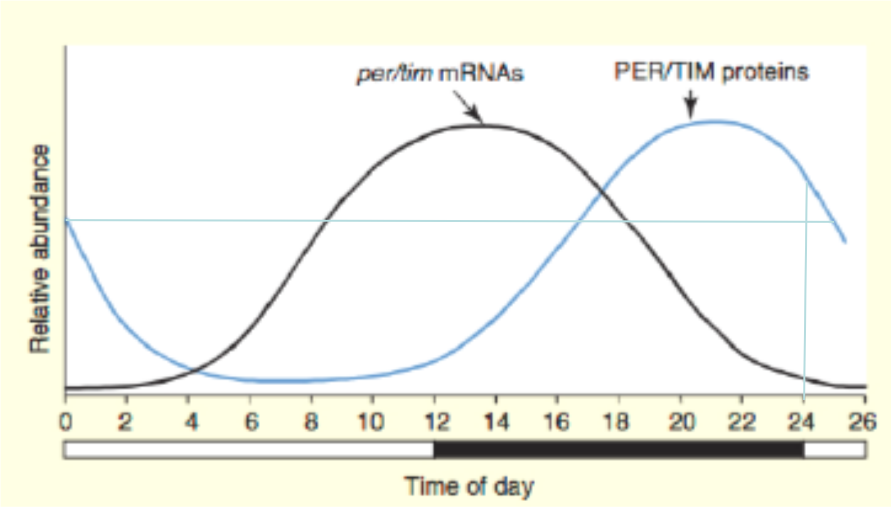
Outline

- New approach to studying entrainment using a one-dimensional map
- Analyze the Kronauer model for human circadian rhythm
- Application to jet lag: Why is there an asymmetry in recovery between east and west travel?
- Application to non-24 hour sleep wake disorder: non-entrainment and Bright Light Therapy
- Application to social jetlag: Can one engage in catch up sleep to minimize disruption?
- Timing matters!
- Mathematical modeling reveals some unexpected findings and leads to the exploration of new dynamic phenomenon.

A Nobel Prize winning example!

- Protein and mRNA levels in fly clock gene: 2017 Nobel prize winning work of Hall, Rosbash & Young (1984). schematic [Isaacson, 2013]

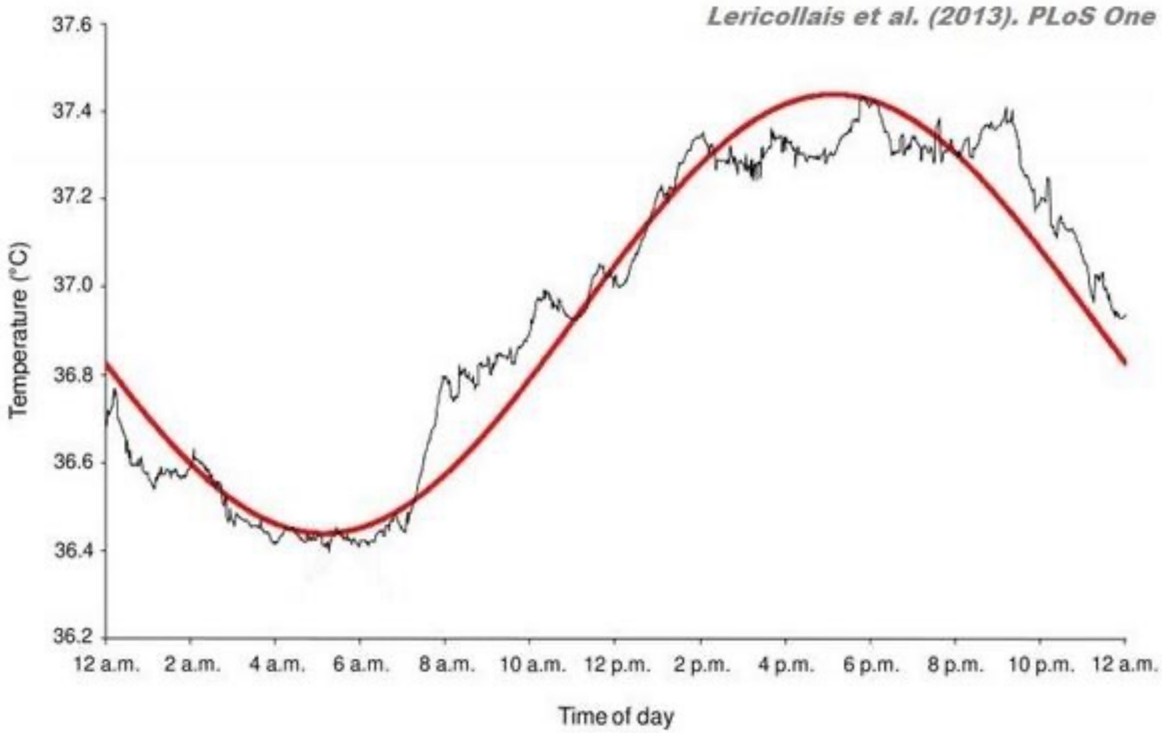


- Here the intrinsic or endogenous period of mRNAs and proteins is longer than 24 hours.

- How does this oscillation change as a function of light-dark input?

A whole body example

- Core body temperature rhythms [Lericollais et al, 2013]



- Note CBT-min occurs early in the morning and is a reliable maker of the phase of entrainment.

Central Questions

- How does entrainment of a circadian oscillator to a 24 hour light-dark cycle depend on intrinsic parameters of the oscillator and external parameters associated with the LD forcing?
- What determines the phase of locking?
- Is the East-West asymmetry of jet lag “generic”?
- How does the timing of bright light therapy affect the ability to entrain?
- Is “catch-up sleep” always beneficial?

Phase-locking due to periodic forcing

- This type of problem has been extensively studied in a variety of contexts; see work of Art Winfree who pioneered the study of biological clocks.
- 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)
- We will be interested in the existence and stability of 1:1 phase locked solutions, and how long it takes to <u>entrain</u> to them.

Circadian oscillators

Two "unforced" limit cycles (Petersen, 1980) and one LD entrained limit cycle

- Either in experiment or model, the oscillator can be subjected to 24 hours of constant darkness **DD**, constant light **LL**, or a combination of both **LD**, with a prescribed photoperiod

- These limit cycles will lie in different locations in phase space and presumably have different properties for attraction towards them (think: stable-unstable manifolds)

- Ultimately, it is attraction of (not necessarily nearby) initial conditions to the **LD** limit cycle we are interested in, and as such we need a method to assess "global" attraction.

Forger - Jewett - Kronauer (FJK) model

- fit to experimental data on how light affects human circadian rhythms
  - core body temperature (*C*)
  - auxiliary variable (*A*)
  - phototransduction pathway through which light drives the circadian system (*n*)

$$\frac{dC}{dt} = \frac{\pi}{12}(A + B)$$

$$\frac{dA}{dt} = \frac{\pi}{12}\left(\mu\left(A - \frac{4}{3}A^3\right) - C\left[\left(\frac{24}{0.99669\,\tau_c}\right)^2 + kB\right]\right)$$

$$\frac{dn}{dt} = (\alpha[I]f(t)\,(1-n) - \beta n)$$

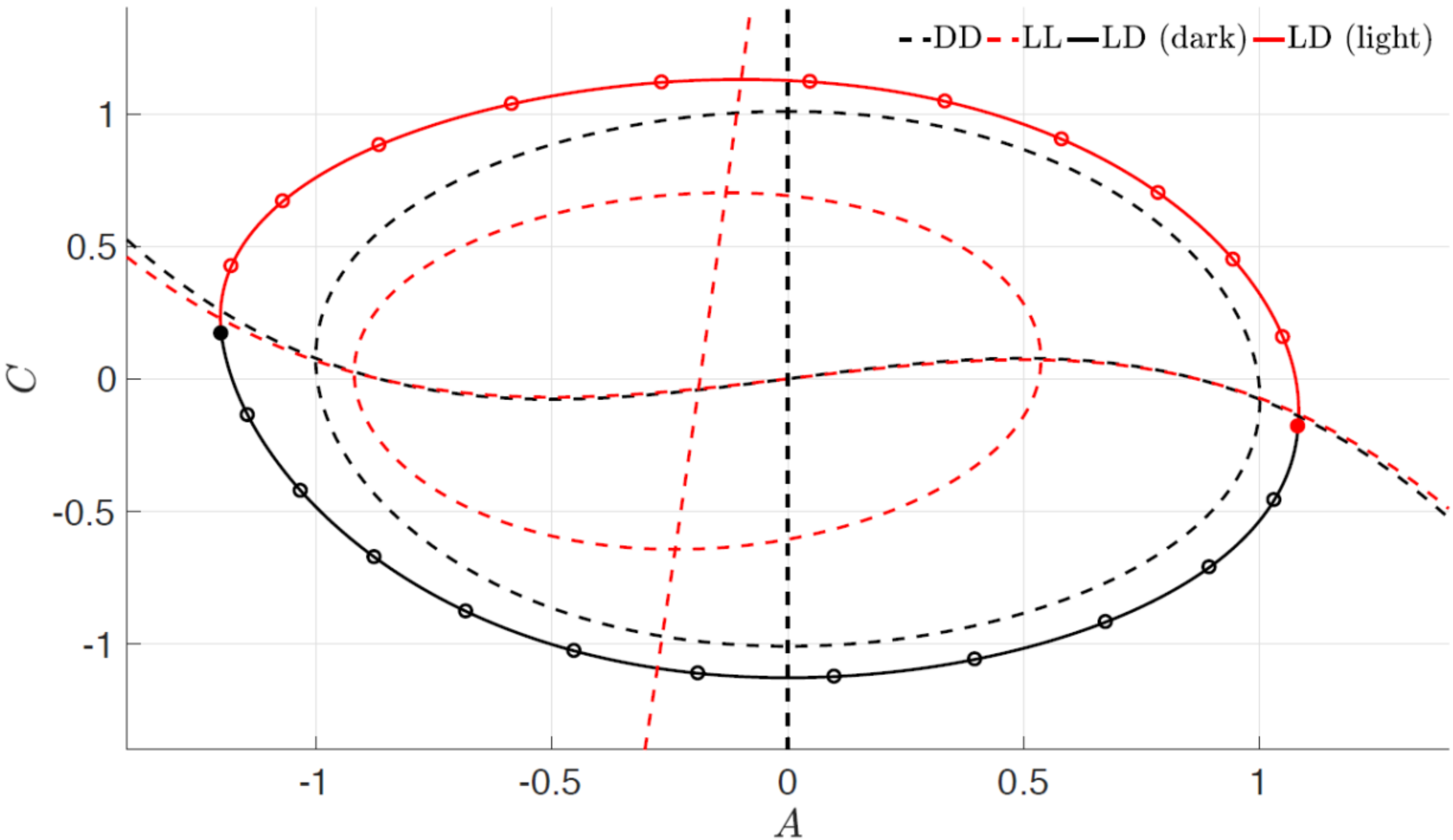
$$B = G\alpha[I]f(t)(1-n)(1-0.4C)(1-0.4A), \quad \alpha[I] = \alpha_0\left[\frac{I}{I_0}\right]^p$$

- *B* -- circadian modulation of the oscillator's sensitivity to light
- τ_c -- determines the period of the oscillator in constant darkness
- *I* -- intensity of light
- *p*– dose response exponent
- *f*(*t*) -- light stimulus

Forger, Jewett, and Kronauer (1999)

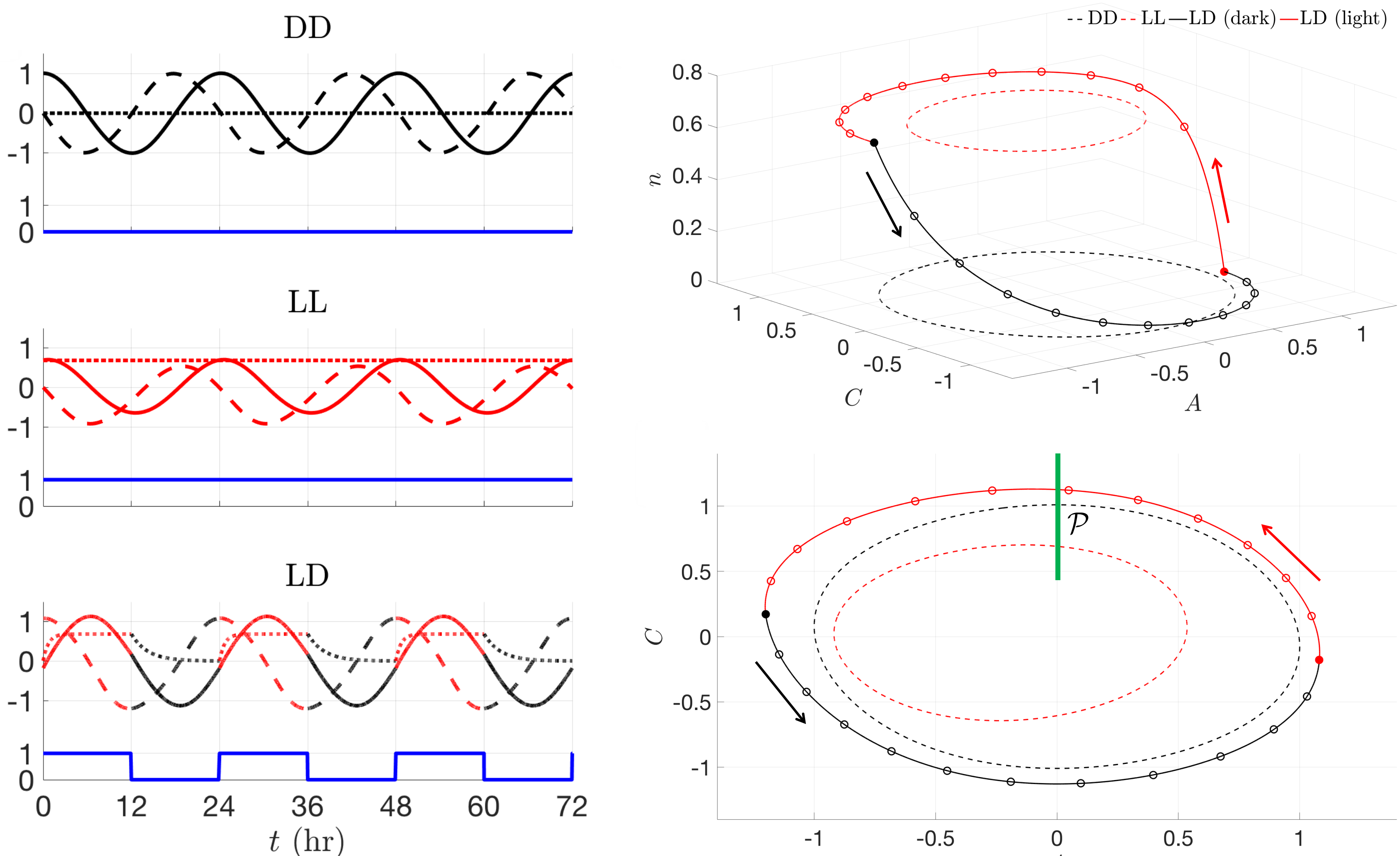
FJK phase plane for DD, LL and LD

- The DD limit cycle has a period of τ_c, the period of LL is less. The LD entrained solution has a period of 24 hours.

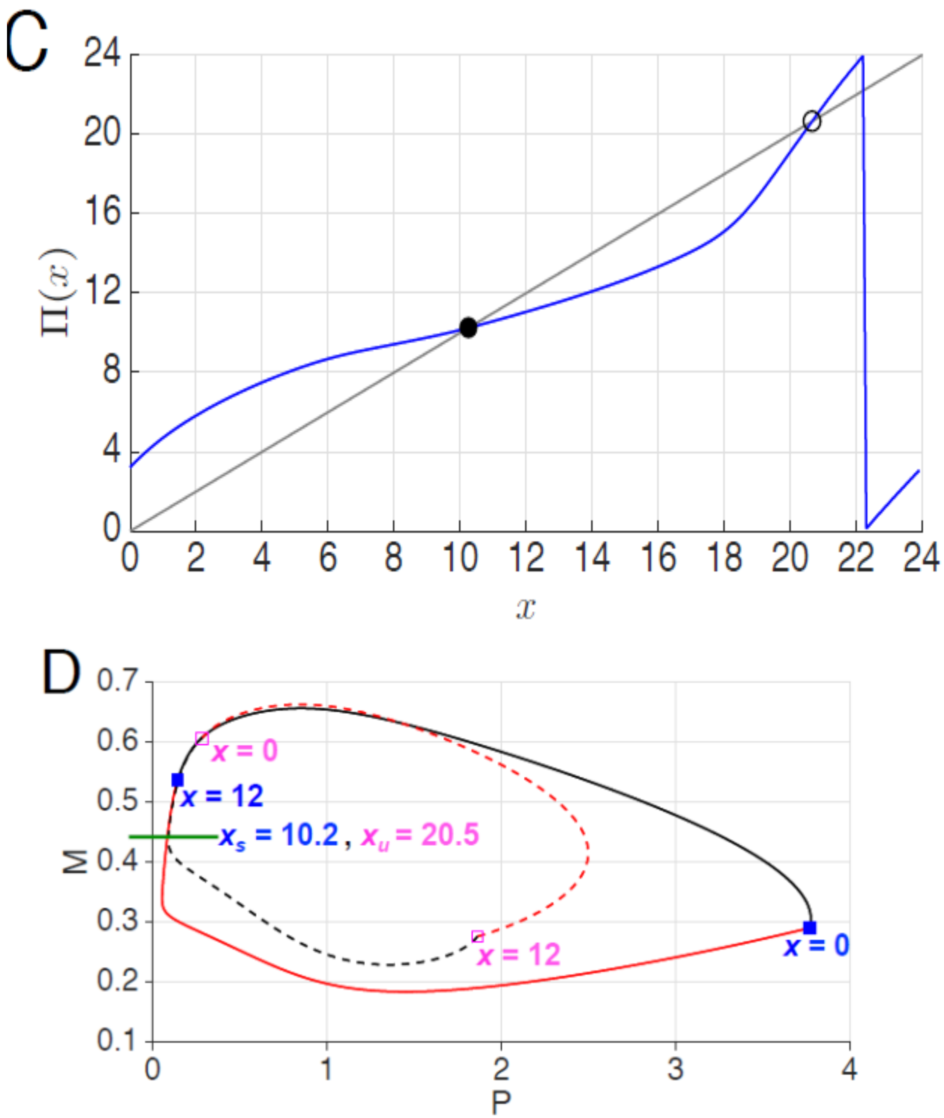


DD, LL, and LD limit cycles

$\tau_c = 24.2, N = 12, I = 1000$



The map and its properties



$\Pi(x)$ is piecewise increasing, piecewise continuous and periodic

It has a stable and unstable fixed point and at most one point of discontinuity

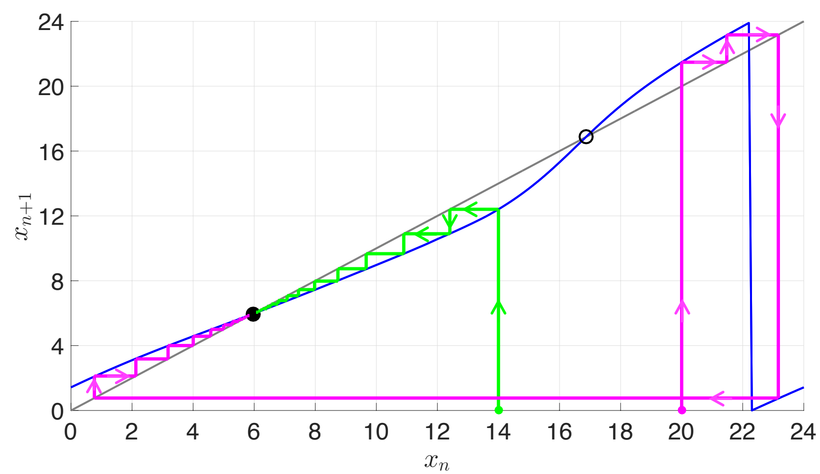
The map depends continuously on parameters

Mathematical Aside: Border collision bifurcations (Yorke et al, 90s)

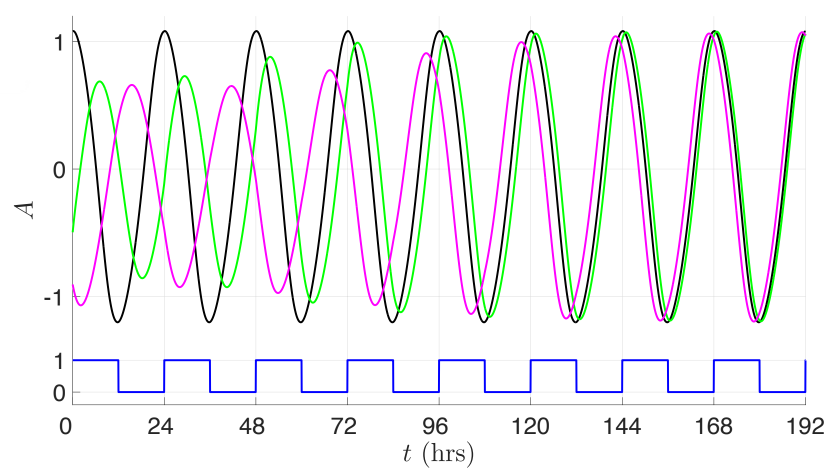
The corresponding stable and unstable periodic orbits from the Novak-Tyson model

Dynamics of the entrainment map

- Cobwebbing the entrainment map
  - x_u separates initial conditions that reentrain through **phase advance** and **phase delay**



- Direct simulations of the FJK model match predictions of the entrainment map

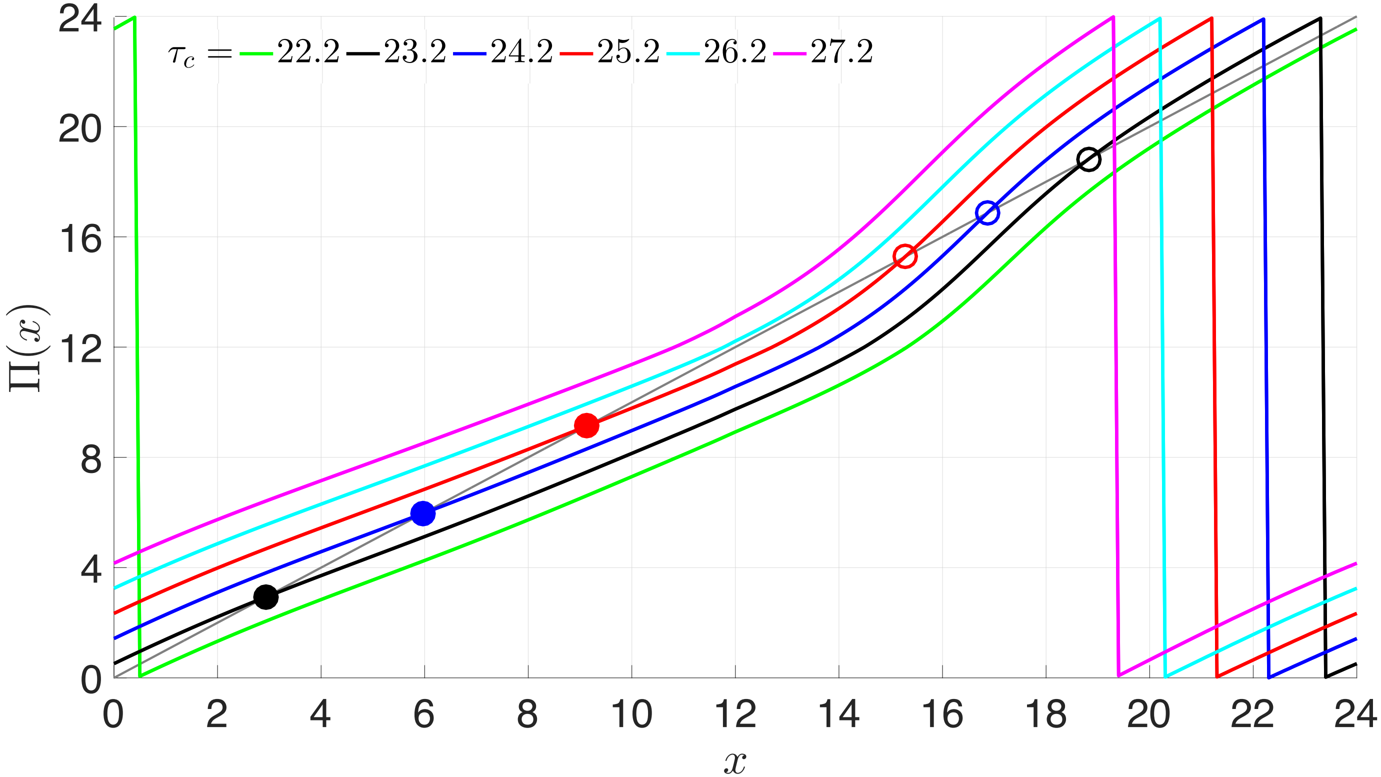


Entrainment: Dependence on parameters

- Four factors are critically important for determining the phase of entrainment of a circadian oscillator:
  - Endogenous period – the free running period of the oscillator in the absence of light input - τ_c
  - Light intensity – measured in lux – I
  - Photoperiod – the amount of light within a 24 hour day – N
  - Dose-response exponent - p

- It's reasonable to expect that the phase of entrainment should vary as any one of these parameters is varied.
- We shall show how these parameters affect the speed of entrainment and, consequently, their effect on jet lag and BLT

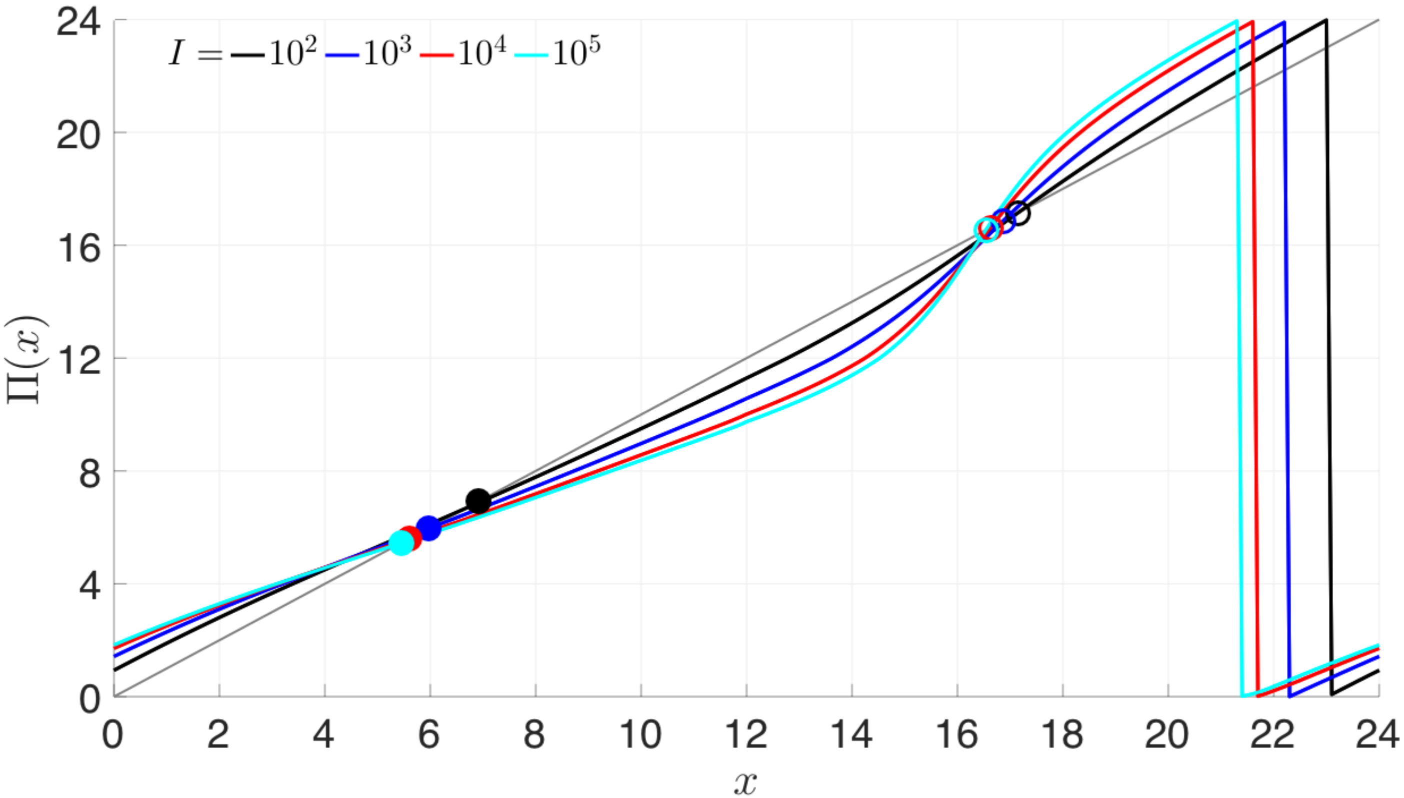
Dependence of $\Pi(x)$ on endogenous period



- as τ_c increases, $\Pi(x)$ shifts up and to the left
  - x_s moves to the right and x_u moves to the left
- as τ_c decreases the fixed points move in the opposite manner
- when τ_c becomes large or small enough, the fixed points merge at a saddle-node bifurcation
  - implies loss of entrainment

Dependence of $\Pi(x)$ on light intensity

- As I increases, concavity of the map increases
  - implies that higher light intensity reduces amount of time it takes oscillator to reentrain following a phase shift of the LD cycle

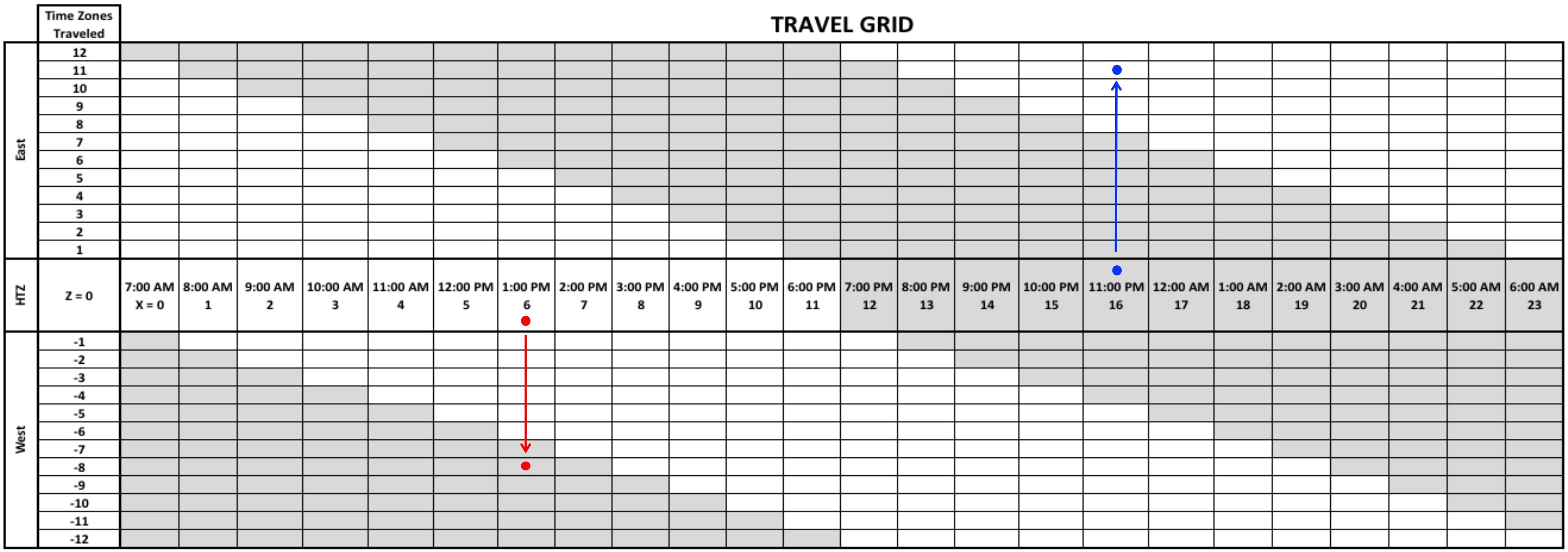


Jet lag due to east-west travel

- We computed, via direct simulation, reentrainment times for travelers making trips with all possible arrival times (X = 0 to 24) and number of time zones traveled (Z = -12 to 12)
  - $Z > 0$ corresponds to traveling east
  - $Z < 0$ corresponds to traveling west

Blue – NYC to Delhi arriving at 11PM HZT

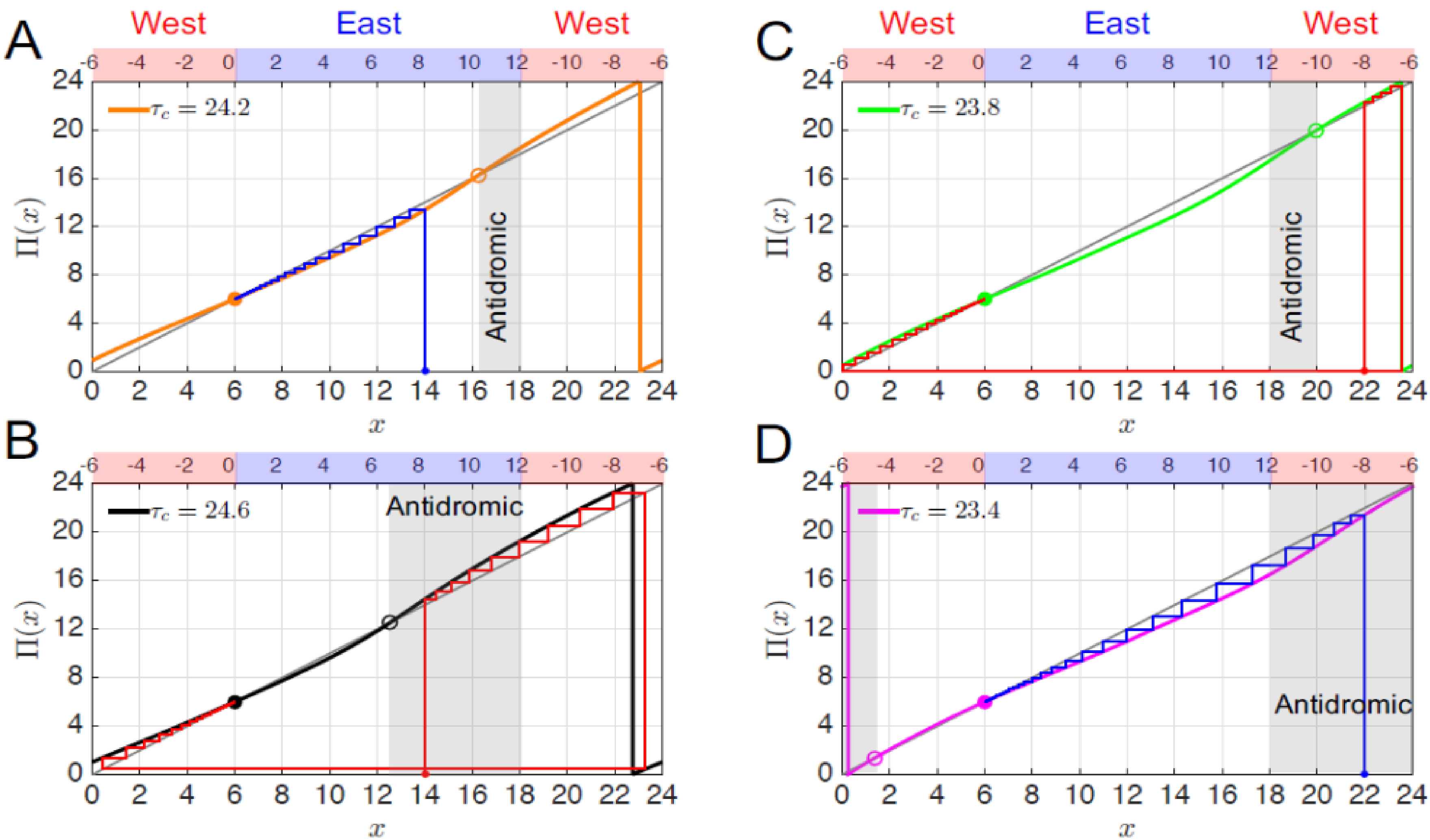
Red – London to Seattle arriving at 1PM HZT



- Construct maps $\Pi_X(x)$ for each arrival time. By definition $\Pi_{16}(16)=16$, $\Pi_6(6)=6$
- Travel Z time zones (e.g. instantaneously)
- In the HTZ, with a new initial condition, entrain to the x_s of original map. $x_0 = X + Z \bmod 24$

Reentrainment: varying endogenous period

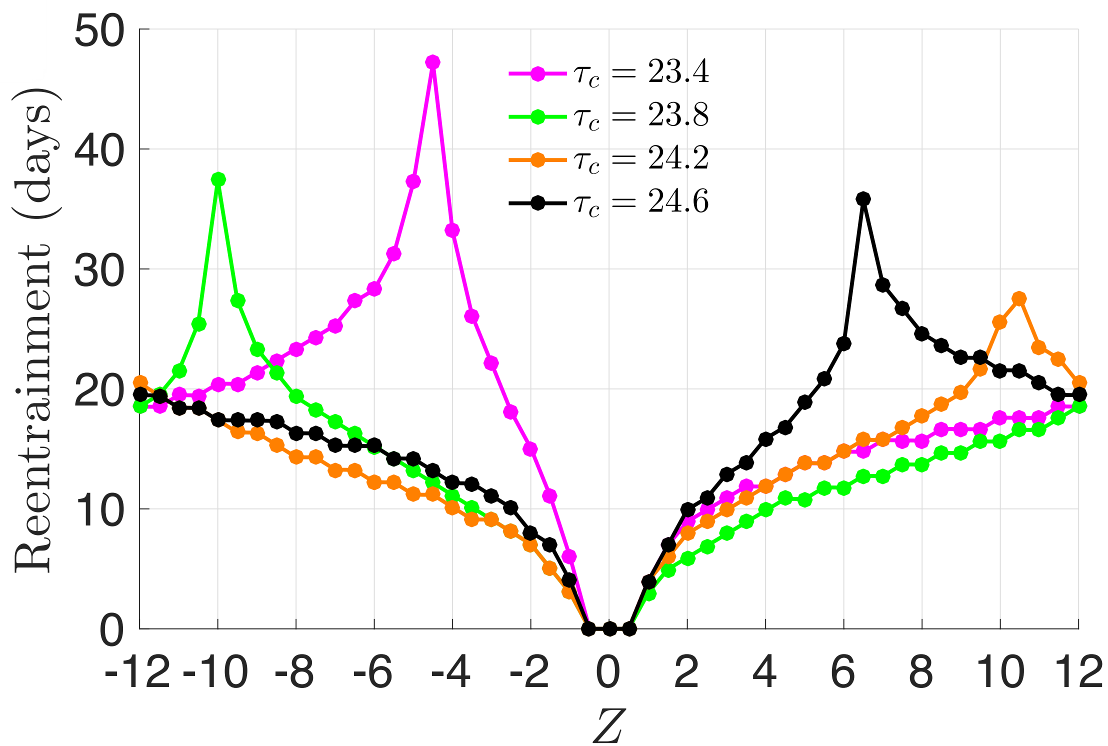
- HTZ arrival time of 1PM; x_s=6 after an 8 hour trips east or west.
- Note the role of the unstable fixed point x_u



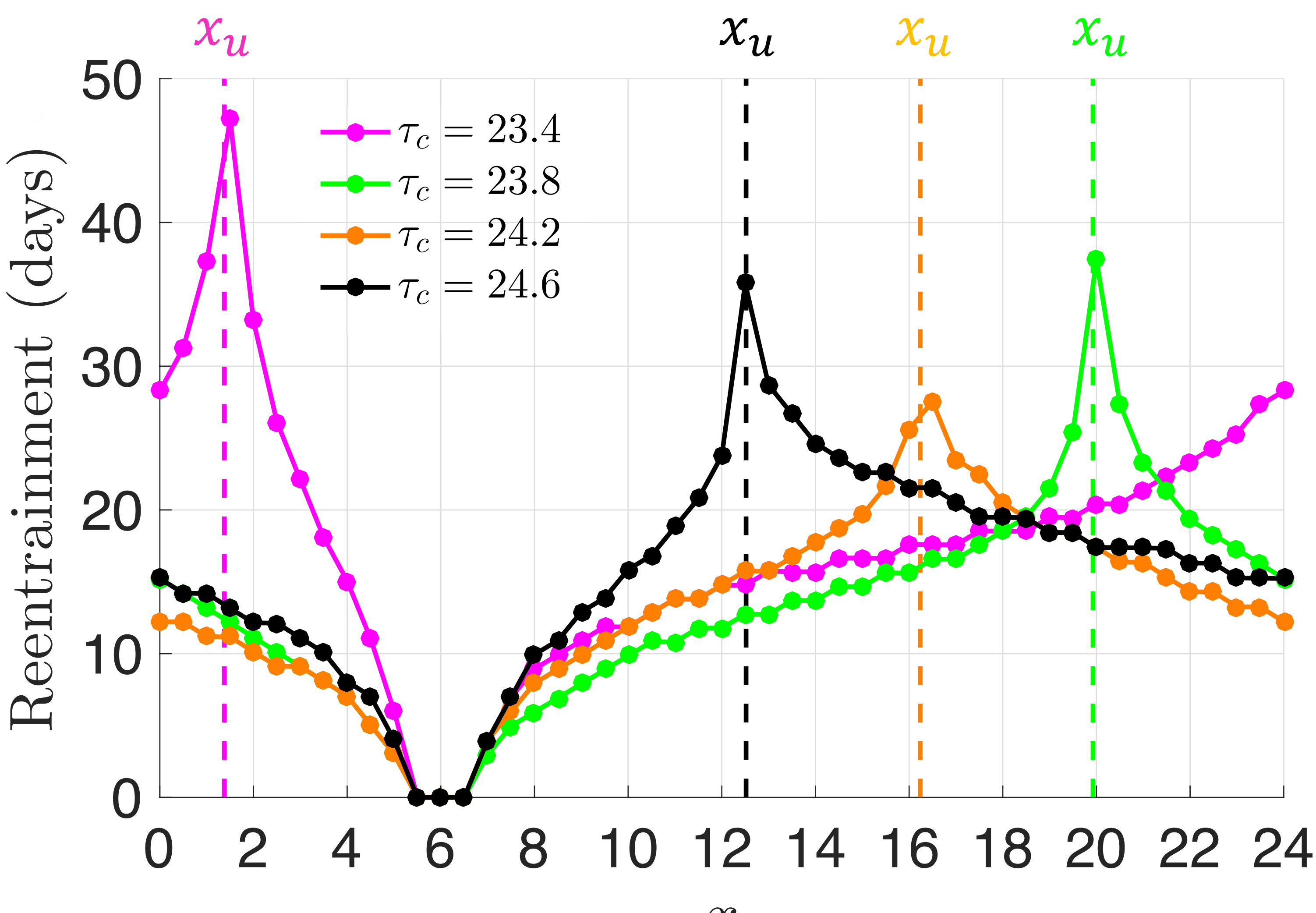
Worst-case travel depends on endogenous period

- τ_c = 24.2 -- typical clock, worst jet lag is for eastward trips of 10.5 time zones
- τ_c = 24.6 -- slow clock, worst jet lag is for eastward trips of 7 time zones
- τ_c = 23.8 -- fast clock, worst jet lag is for westward trips of 10.5 time zones
- τ_c = 23.4 -- even faster clock, worst jet lag for is for westward trips of 6.5 time zones

we can explain these results using entrainment maps

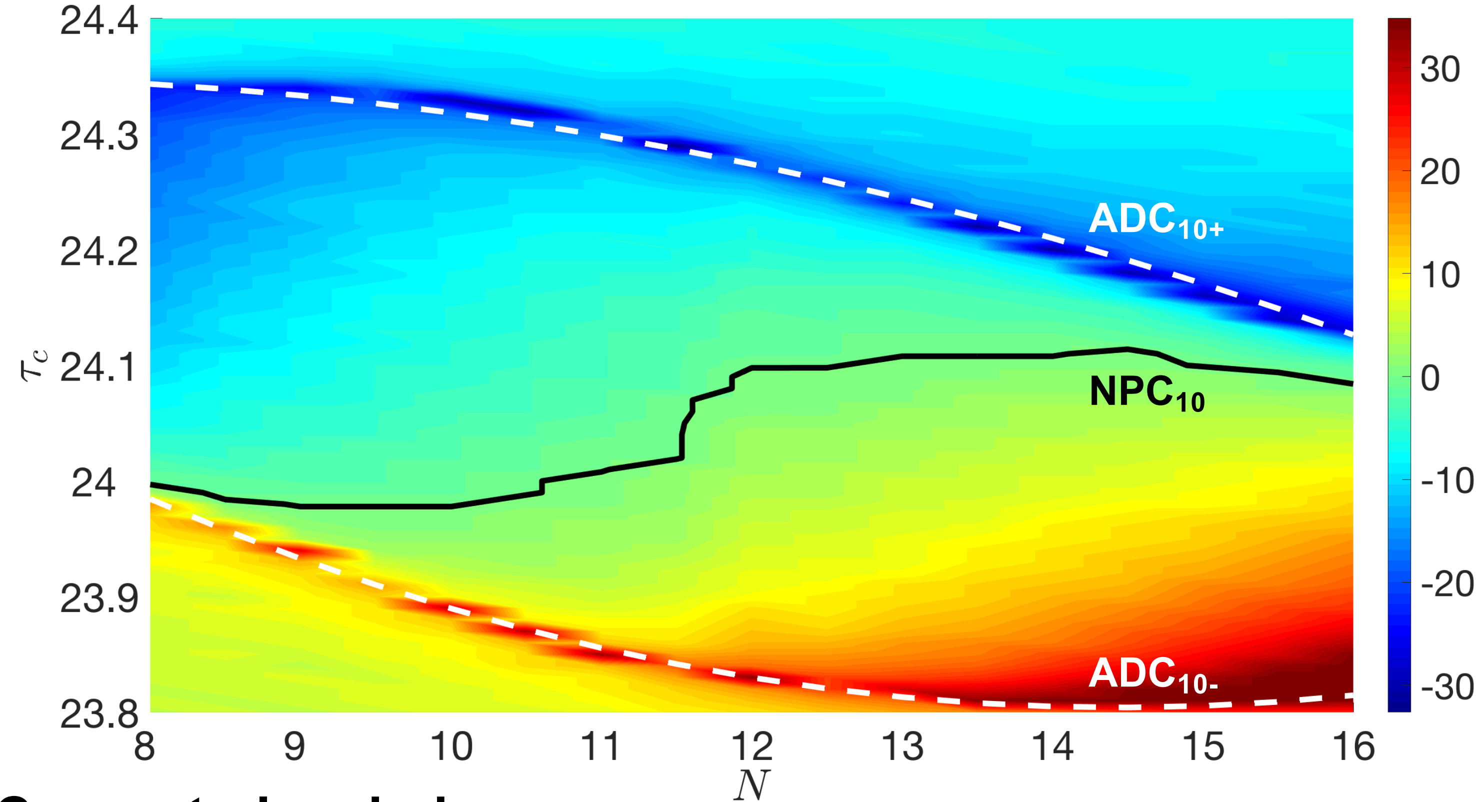


Worst-case travel is determined by location of x_u



East-West asymmetry also depends on daylength

- Calculated reentrainment times by cobwebbing maps for eastward and westward trips of 10 time zones
  - Colormap: (reentrainment time for Z = -10) – (reentrainment time for Z = 10)
  - East is worse, West is worse



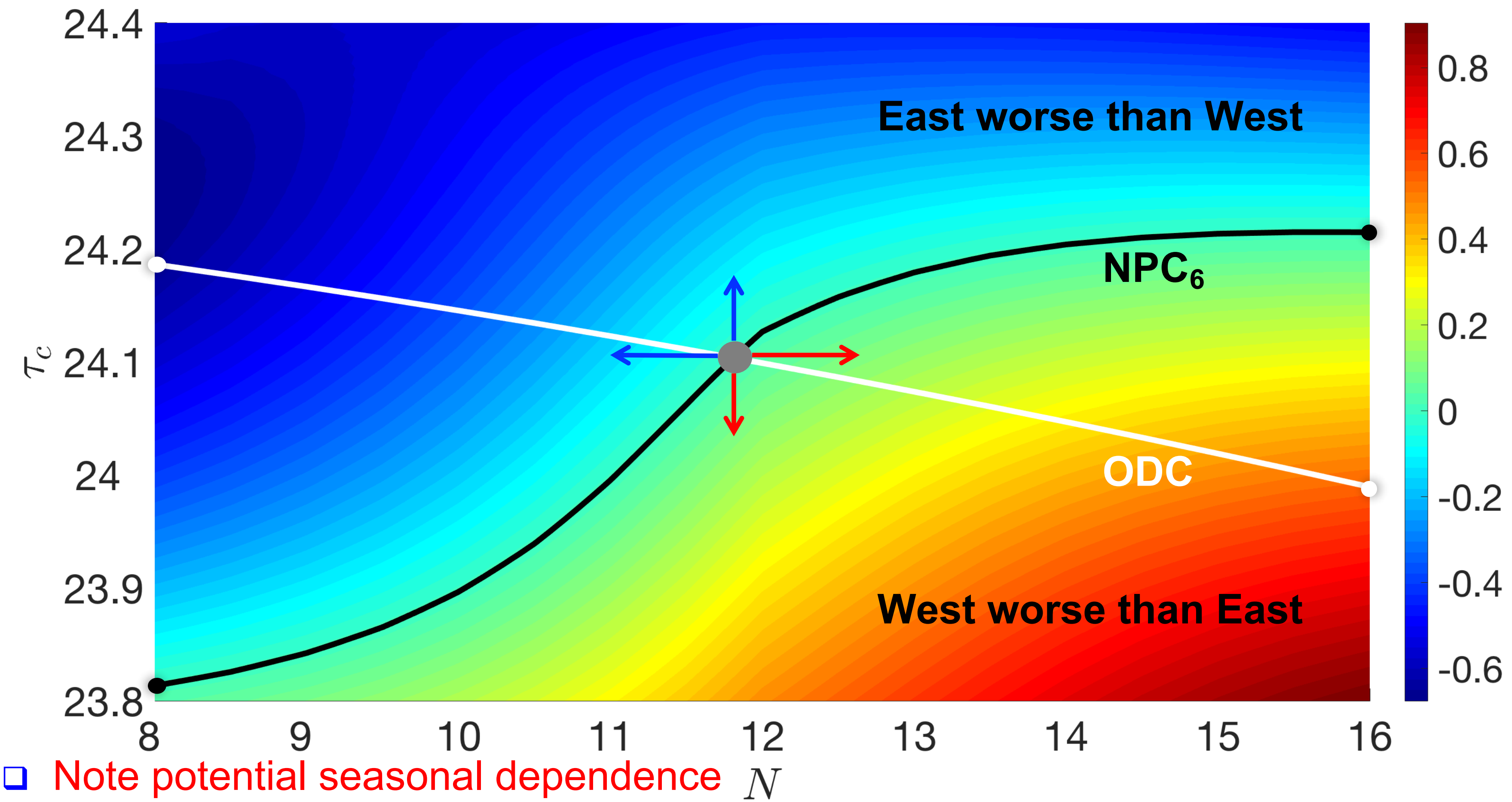
NPC = neutral period curve

generalizes Petersen (1980)

ADC = antidromy curve

East-west asymmetry is generic

- Approximated reentrainment times using first iterate of maps for eastward and westward trips of 6 time zones
  - ODC = orthodromy curve (x_s and x_u exactly 12 hours apart)



- Note potential seasonal dependence

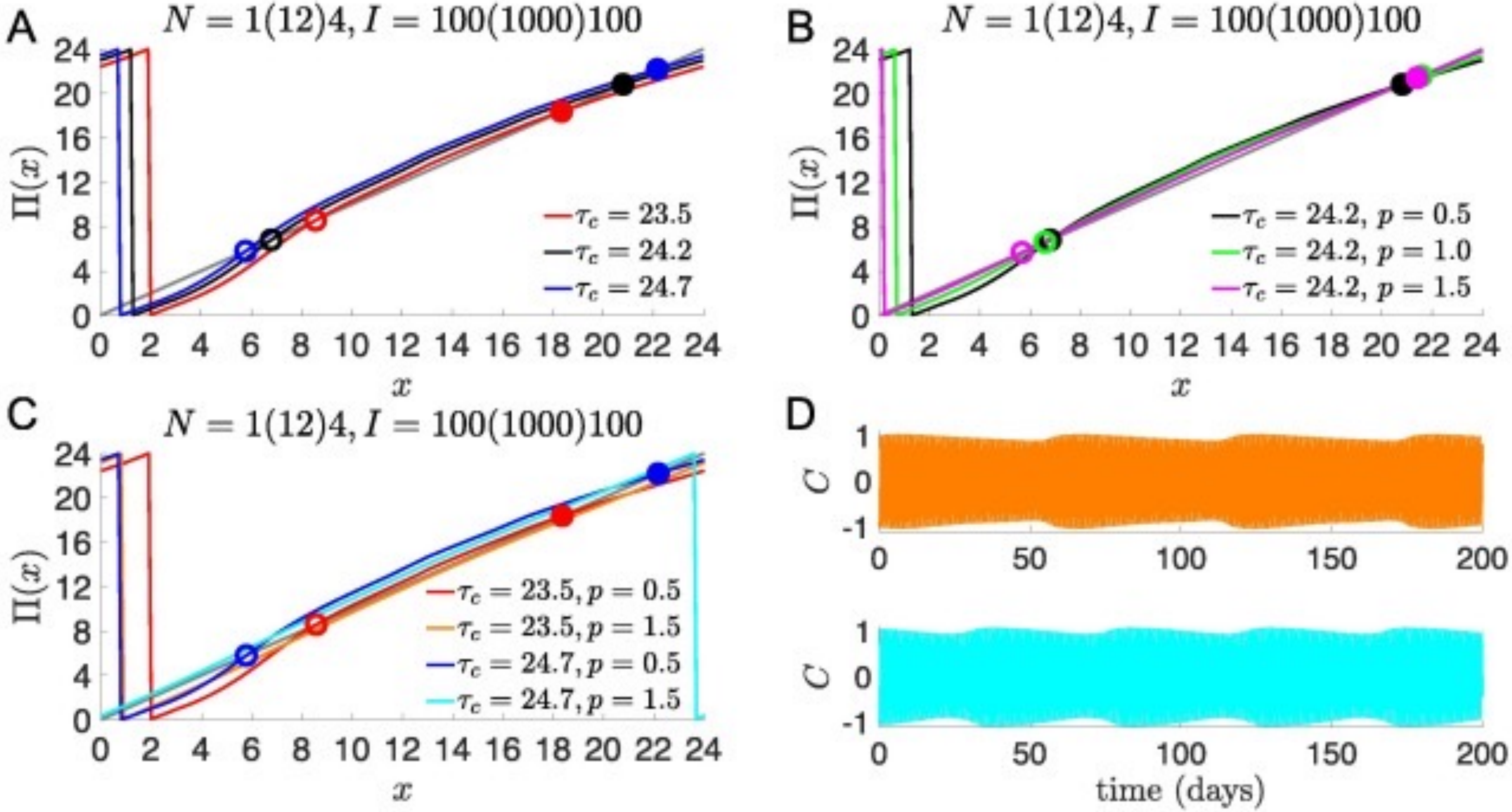
Conclusions about jetlag

- The extent of jetlag depends on one’s intrinsic clock, the time of year (photoperiod), light intensity and the direction of travel.
- Trips that place an individual in the neighborhood of the unstable fixed point, result in the worst jet lag, but….
- But, under high intensity light, those trips can result in very short jetlag due to the “phaseless set” (Guckenheimer 1973)
- East-west asymmetry is generic; it must exist.
- See our 2018 paper for a cute “traveling diplomat” problem

Non-24 hour sleep-wake disorder

- Patients with this disorder are not able to entrain to the 24-hour cycle.
- They can spend several days in a nearly entrained stated but then many days in which their phase advances or delays relative to the LD cycle.
- Bright light therapy: Exposure to high intensity light for short amount of time
- Now we will use multilux maps in which the light level is different at different times of the day
  - Lights on from 6AM to 11PM so N=17
  - N = 1 (12) 4, I= 100 (1000) 100
  - N= 1 (12) 4, I= **10,000** (1000) 100 Early morning BLT
  - N= 1 (12) 1 (3) , I= 100 (1000) **10,000** (100) Evening BLT

Reduction of light sensitivity causes non-entrainment

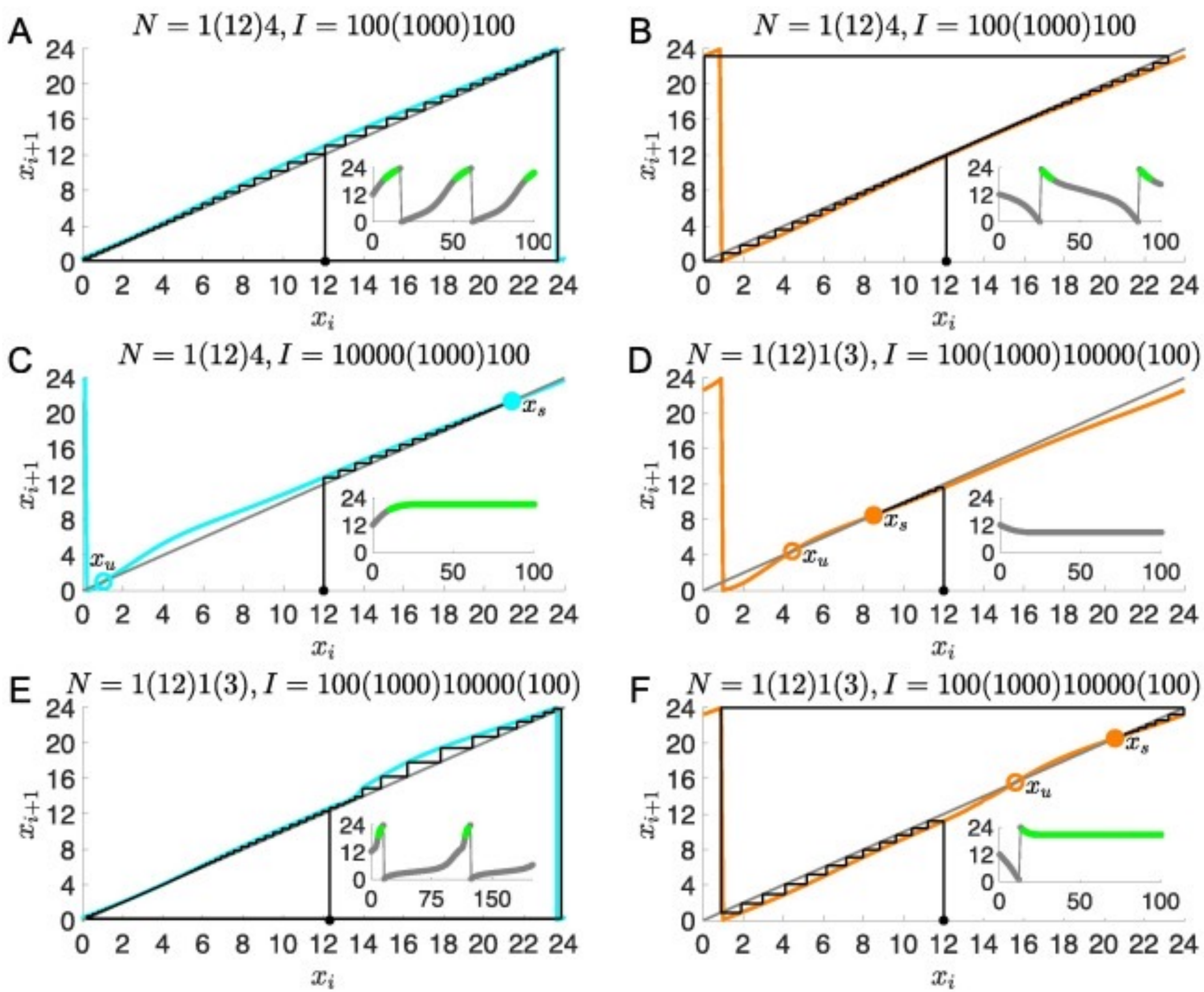


BLT works at different times for different endogenous periods

NO BLT

AM BLT

PM BLT



Slow clock τ_c =24.7

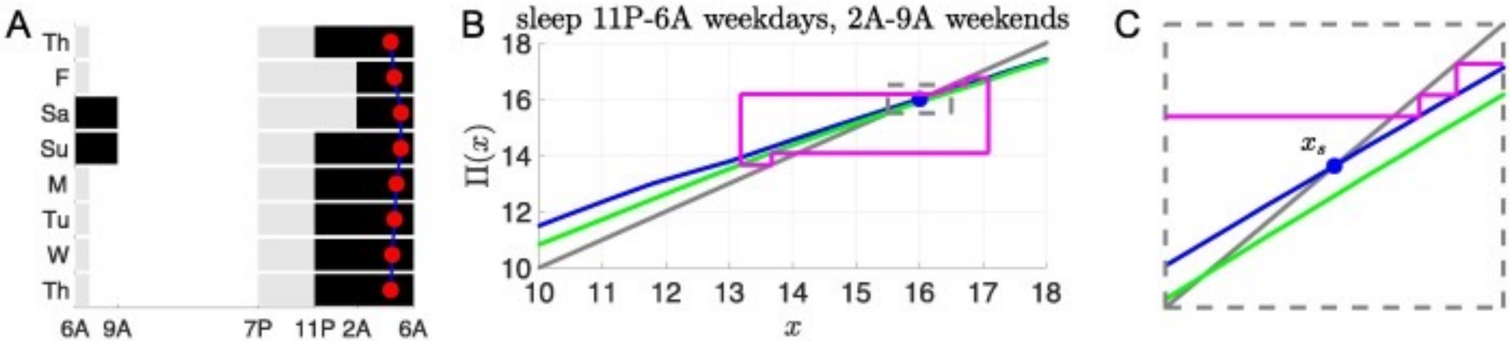
Fast clock τ_c =23.5

Conclusions about BLT

- For individuals with slow clocks,
  - BLT administered in the morning is beneficial.
  - BLT administered in the evening is non-effective
- For individuals with fast clocks,
  - BLT administered in the morning is partially effective but causes CBT_{min} to occur mid day.
  - BLT administered in the evening is beneficial
- Currently working on a model for BLT for depressive patients (Mainwaring, B, Diekman)

Social Jetlag

- Social jetlag refers to situations where individuals have very different sleep patterns on a few days of the week
- Most common one is to stay up late on weekends and sleep in late
- Another form is high school students who stay up late during the week and try to engage in “catch up sleep” on the weekends
- To model this cases, we need maps for each of the different sleep patterns



Focus on high school students
Slow clock τ_c =24.6

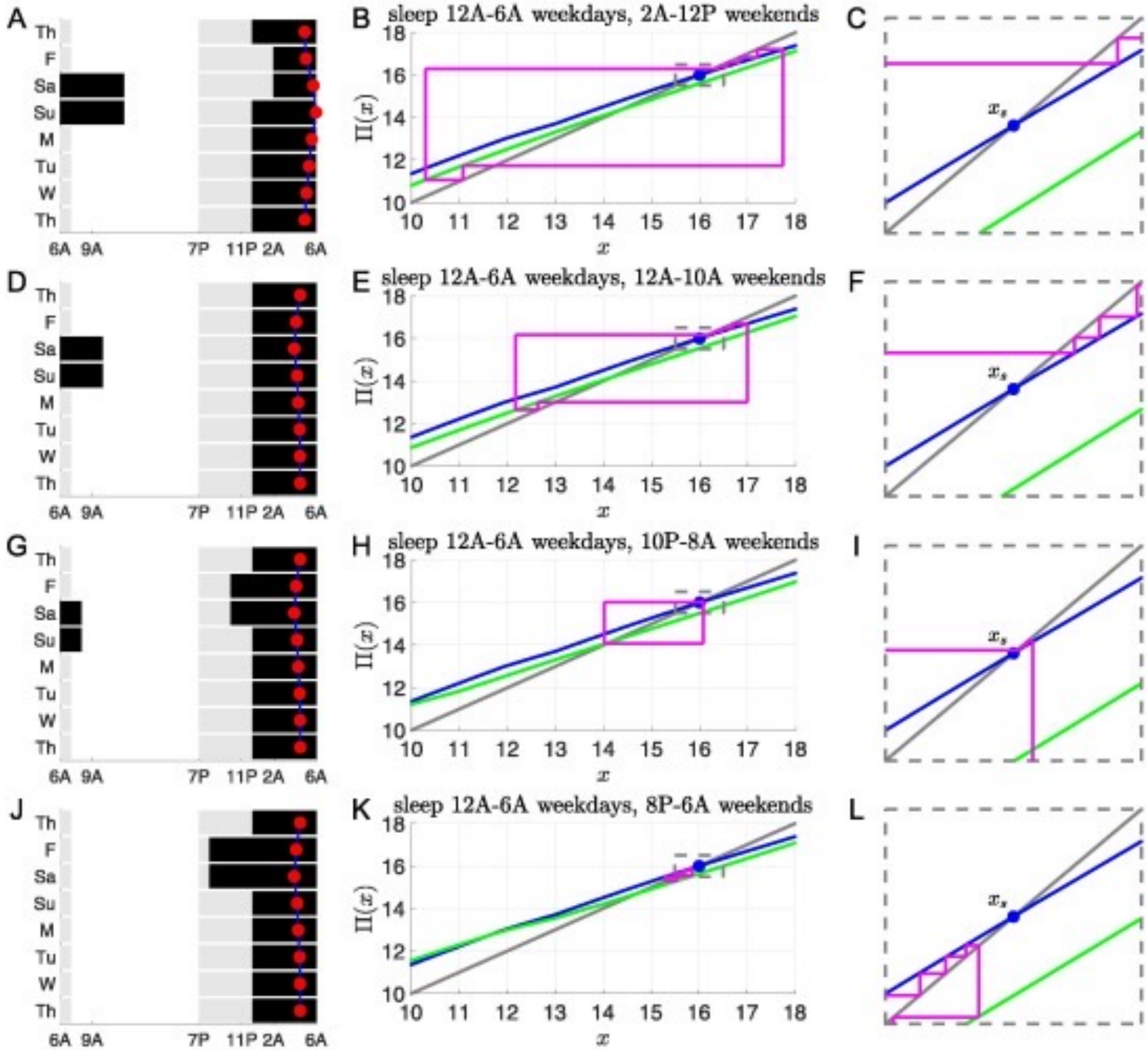
- Teenagers should be sleeping 8-10 hours a night.

- Suppose teenagers sleep 6 hours 12AM-6AM Sunday-Thursday
- Assume 8 hours is normal, so loss of 10 hours of sleep
- Catch up sleep on Friday and Saturday of 10 hours (still -6)

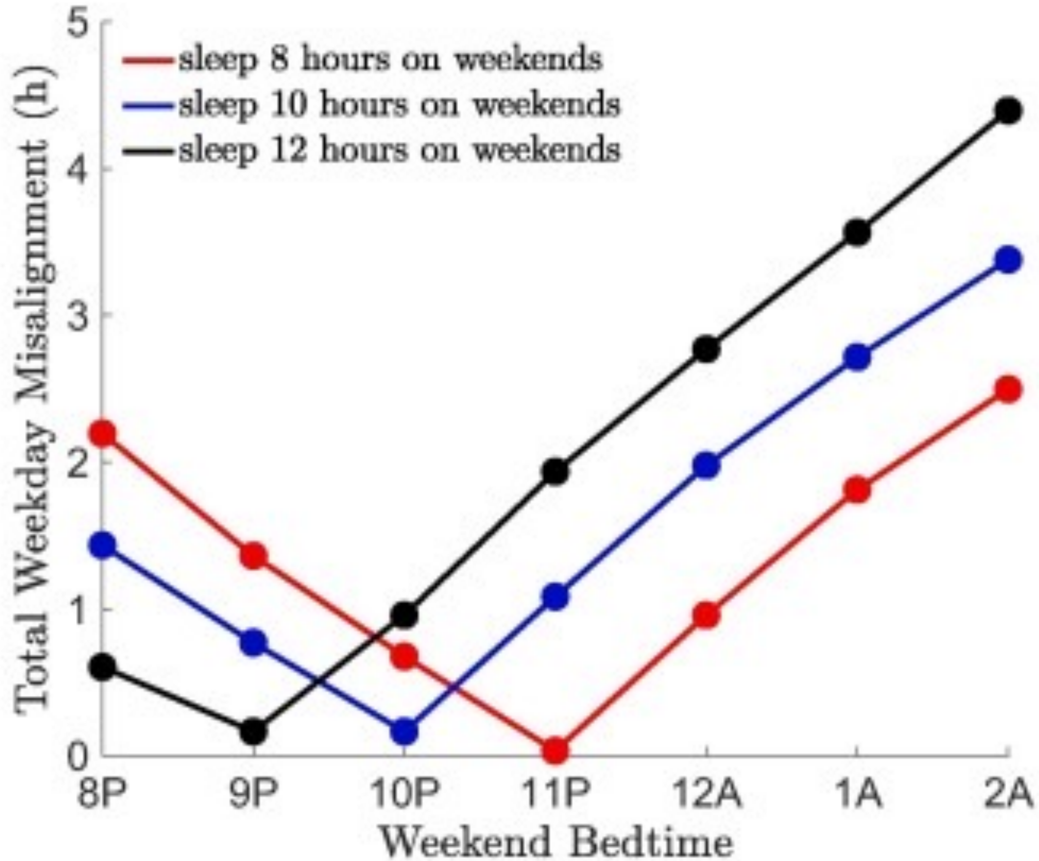
- Does the timing of the catch up sleep matter?
- Should teenager go to sleep at 12AM and sleep to until 10AM?
- Or sleep at 8PM and wake up at 6AM, or something in between?

- Circadian misalignment: When weekday iterates of the map fall more than 0.5 hours away from the stable fixed point of the weekday map.

10 hours catch up sleep with different onset times



Rule of thumb for minimizing misalignment



- Shift sleep and wake times forward and backward by $(N_{wd} - N_{we})/2$
- Mathematical reason has to do with distance between stable fixed points of the different maps

Conclusions about catch up sleep

- Getting more sleep on weekends in and of itself is not sufficient.
- Too much sleep at the wrong times does not help
- Shifting the sleep and wake times appropriately is critical

- Korean school kids seem to follow the appropriate strategy compared to North American kids (Carskadon, 2011)

Summary

- Entrainment maps can **explain** and **predict** several features of reentrainment
  - East/West jetlag asymmetry depends on both endogenous period and daylength
    - whether endogenous period is > or < 24 hours is not the critical factor
  - Appropriately timed Bright Light Therapy can be therapeutic for non-24 sleep-wake disorder or Seasonal Affective Disorder
  - Catch up sleep can be timed to minimize circadian disruption

- Several open mathematical questions exist regarding the role of unstable objects in the phase space and how they organize dynamics

- Future Work
  - BLT for depression patients (ongoing with Mainwairing and Diekman)
  - Incorporate sleep/wake dynamics (see work by Booth, Diniz-Behn)
  - Peripheral oscillators in other organs and phase tumbling (ongoing with Liao and Diekman)