Reentrainment of the Circadian Pacemaker During Jet Lag: East-West Asymmetry and the Effects of North-South Travel

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Circadian Rhythms and Jet lag

- Central circadian pacemaker coordinates various physiological rhythms so that they peak at the appropriate time of the day
  - sleep-promoting hormone melatonin peaks in the evening
  - wake-promoting hormone cortisol peaks in the morning

- Endogenous period of human circadian clock is not exactly 24 hours
  - under normal circumstances, the oscillator is phase-locked or *entrained* to 24-hour environmental cycles
  - daily light-dark (LD) cycle is the strongest entraining signal

- Normal alignment of circadian rhythms with the LD cycle is disrupted after rapid travel across time zones
  - leads to sleep problems, indigestion, and other symptoms collectively known as *jet lag*

- We study the process of reentrainment to the LD cycle of the destination time zone
  - well-established ODE model of the human circadian pacemaker

Outline

- Construct one-dimensional *entrainment maps* and use them to explain several properties of jet lag

  - Why do most people experience more jet lag after traveling east than west?
    - endogenous period of the traveler’s circadian clock
    - daylength is also a factor

  - What trips (crossing how many time zones) will lead to the worst jet lag?
    - trips that put the traveler near the unstable fixed point of an entrainment map

  - Can strictly north-south travel cause jet lag even when no time zones are crossed?
    - yes, due to changes in daylength

- Traveling diplomat problem

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*)

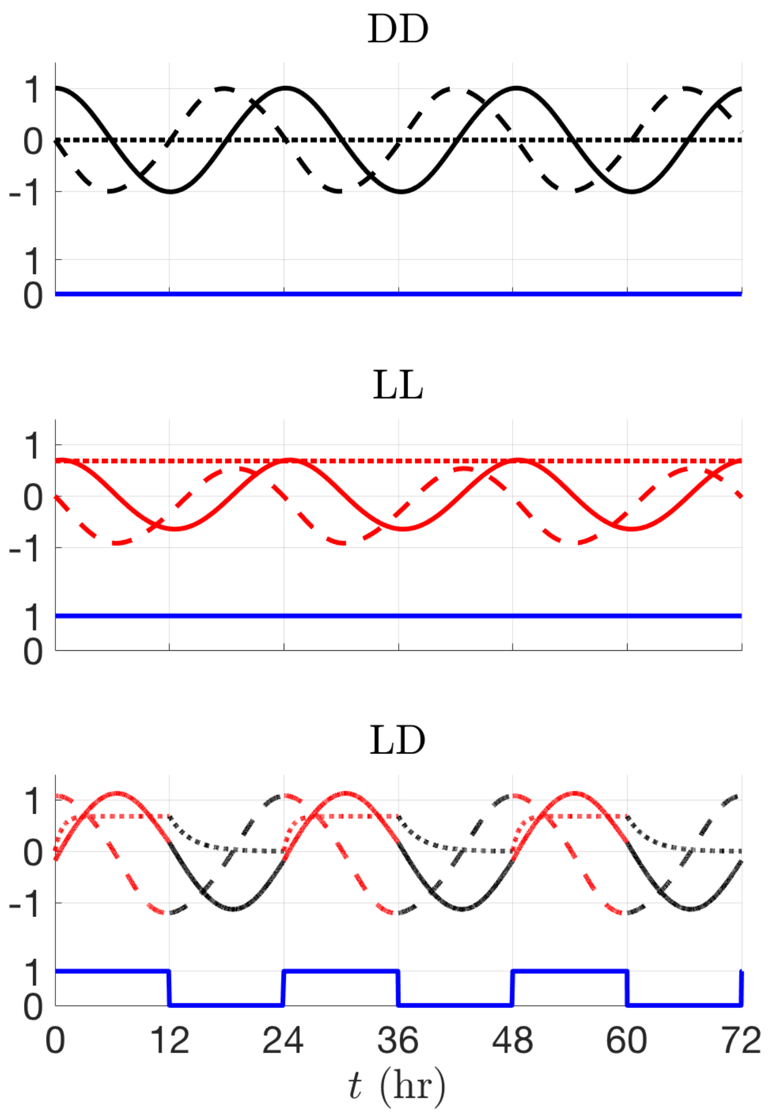
$$\begin{aligned}
\frac{dC}{dt} &= \frac{\pi}{12}(A+B) \\
\frac{dA}{dt} &= \frac{\pi}{12}\left(\mu\left(A-\frac{4}{3}A^3\right)-C\left[\left(\frac{24}{0.99669\,\tau_c}\right)^2+kB\right]\right) \\
\frac{dn}{dt} &= \left(\alpha[I]f(t)\,(1-n)-\beta n\right) \\
B &= G\alpha[I]f(t)(1-n)(1-0.4C)(1-0.4A), \quad \alpha[I]=\alpha_0\left[\frac{I}{I_0}\right]^p
\end{aligned}$$

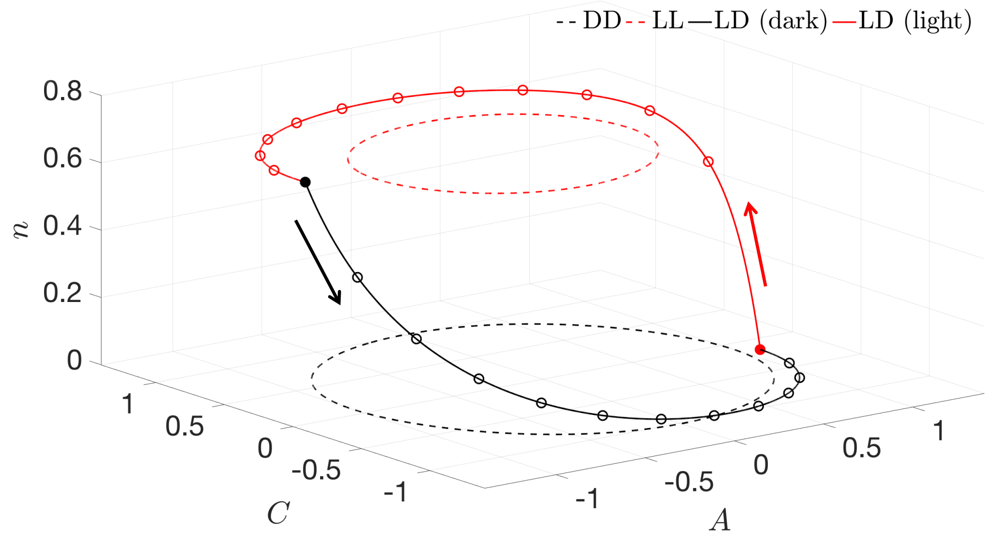
- *B* -- circadian modulation of the oscillator's sensitivity to light
- τ_c -- determines the period of the oscillator in constant darkness
- *I* -- intensity of light
- *μ* -- stiffness parameter that is related to the rate of amplitude growth or decay after the oscillator is perturbed off of its limit cycle
- *f*(*t*) -- light stimulus

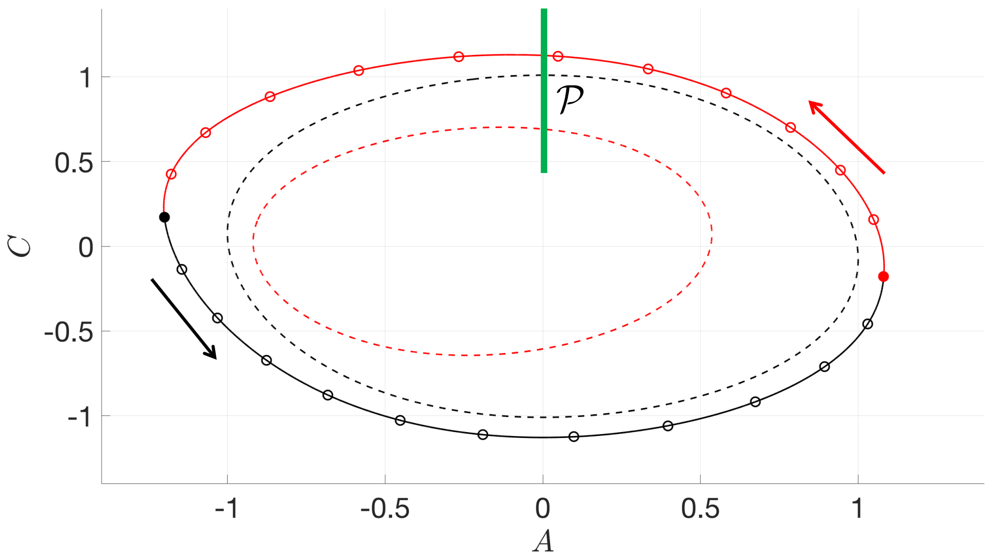
Forger, Jewett, and Kronauer (1999)

DD, LL, and LD limit cycles

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

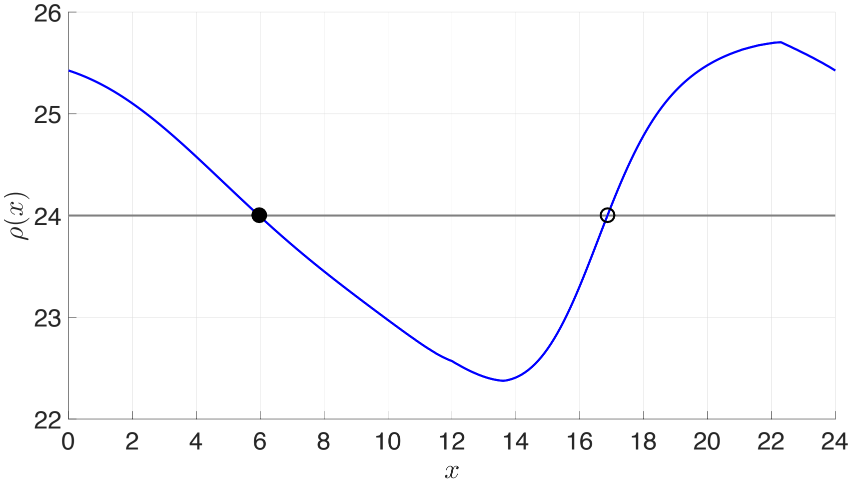


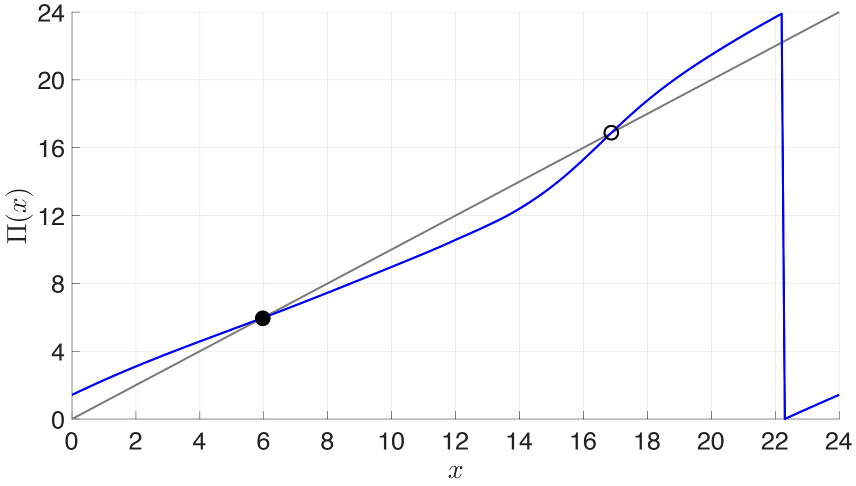




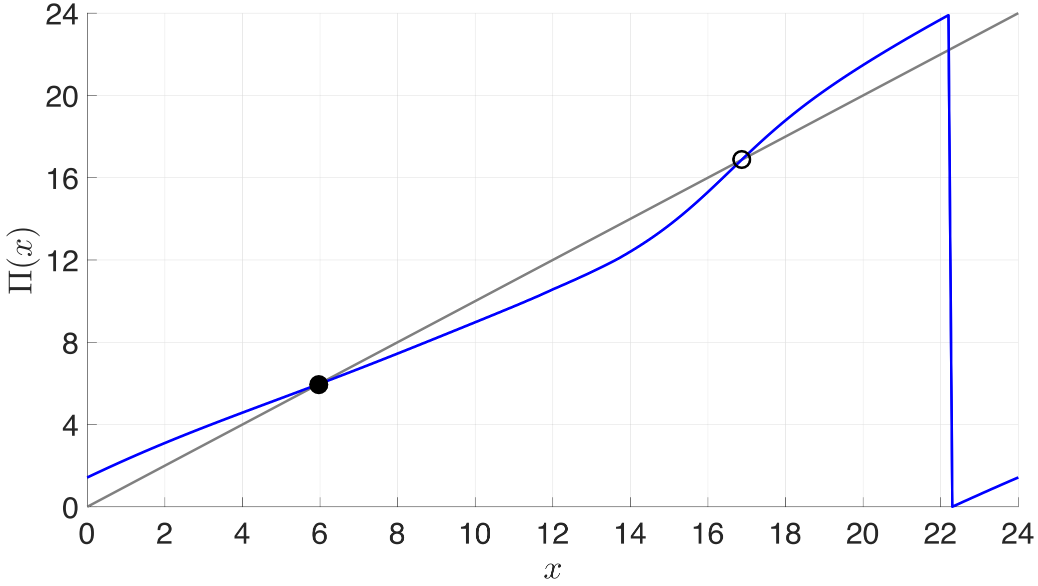
Definition of the entrainment map $\Pi(x)$

- return map for initial conditions lying on a Poincaré section $\mathcal{P}$
  - choose $\mathcal{P}$ at $A = 0$ with $A' < 0$
  - assume oscillator has an initial condition that lies on $\mathcal{P}$
  - let x denote the number of hours since the lights last turned on
  - evolve the trajectory under the flow until it again returns to $\mathcal{P}$, and call the elapsed time $\rho(x)$
  - the entrainment map $\Pi(x)$ is defined as the amount of time that has passed since the most recent onset of the lights
  - $\Pi(x) = [x + \rho(x)]$ mod 24, which yields a one-dimensional map



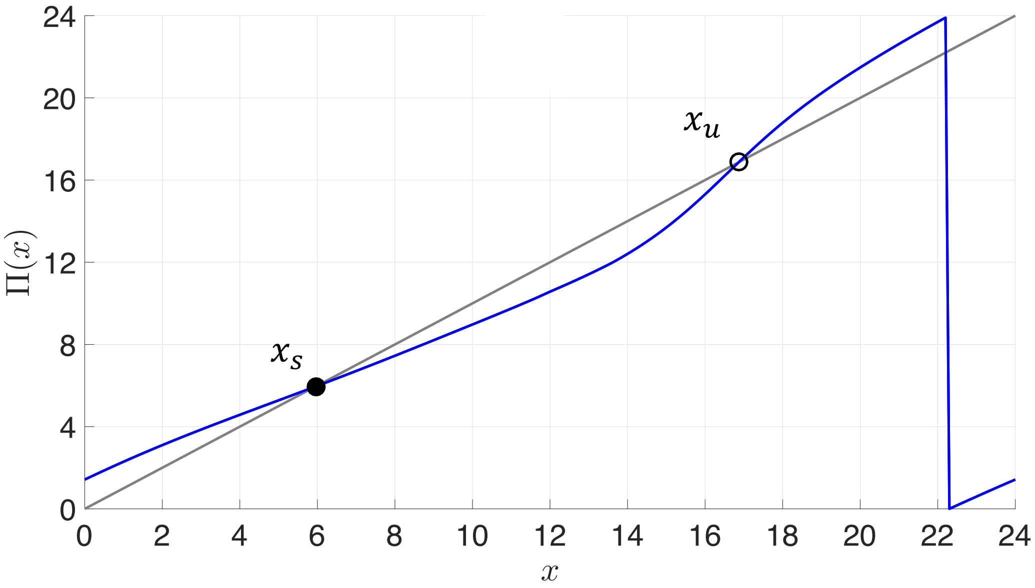


Properties of the entrainment map



- the map has certain generic properties
  - it maps the interval [0,24] onto itself
  - it has at most one point of discontinuity
  - it is increasing at each point of continuity
  - it is periodic in that $\Pi(0^+) = \Pi(24^-)$
  - it depends continuously on the important parameters of interest: τ_c, N, I

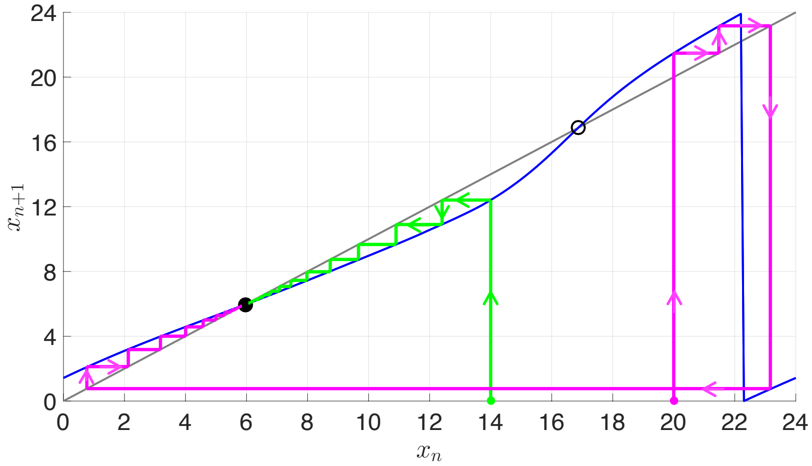
Fixed points of the entrainment map



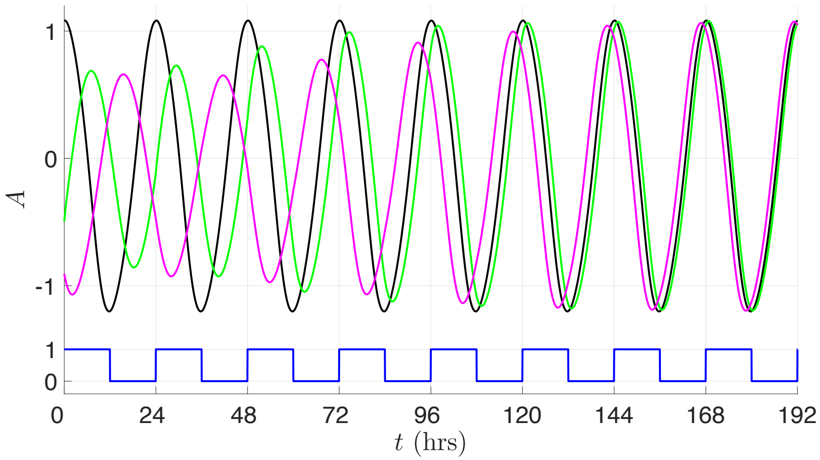
- a fixed point x^* of the entrainment map satisfies $\Pi(x^*) = x^*$
  - corresponds to the trajectory leaving $\mathcal{P}$ x^* hours after the lights turned on, and then returning to $\mathcal{P}$ exactly 24 hours later when the lights have again most recently turned on x^* hours ago
  - the fixed point is stable if $|\Pi'(x^*)| < 1$ and unstable otherwise
    - a stable fixed point x_s
    - an unstable fixed point x_u
  - a necessary, but not sufficient, condition for the existence of a periodic solution of the FJK model is the existence of a fixed point of the entrainment map

Dynamics of the entrainment map

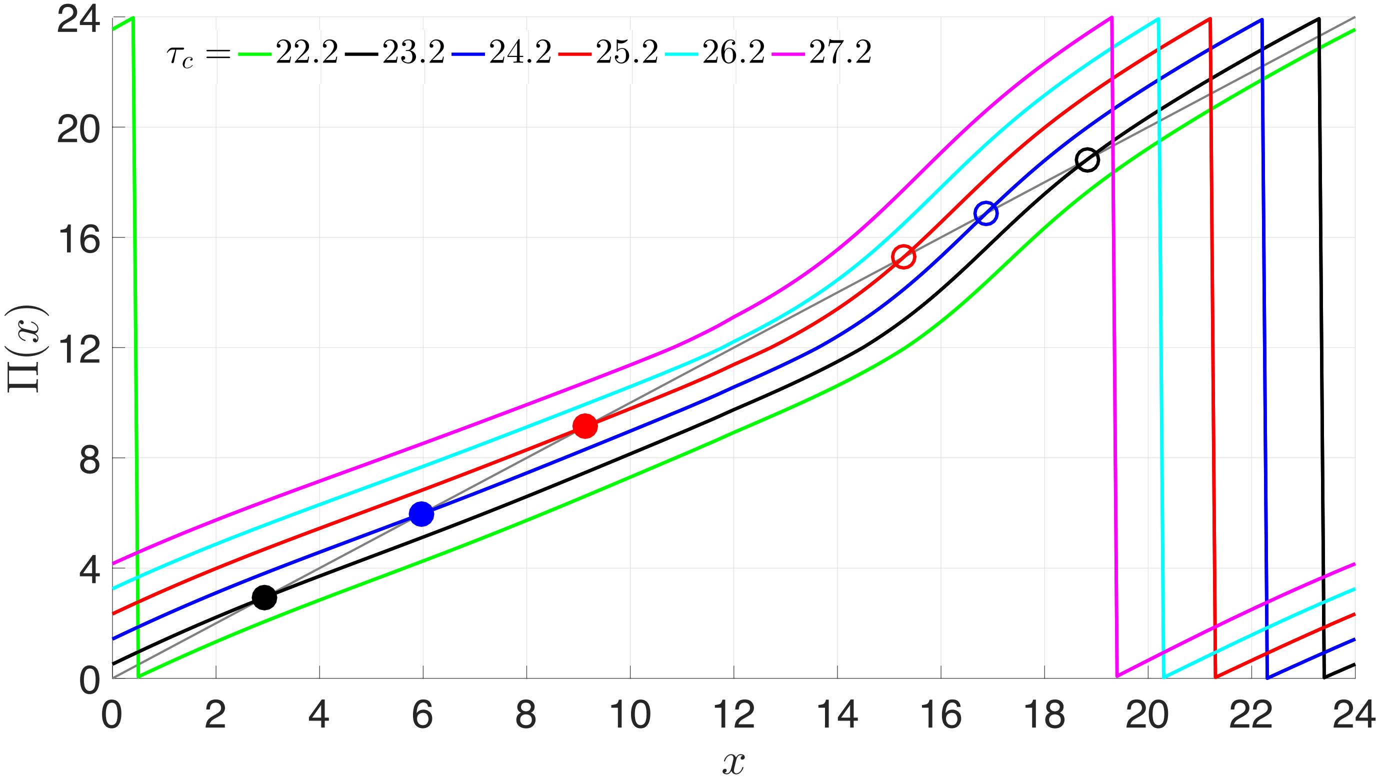
- Cobwebbing the entrainment map
  - x_u separates initial conditions that reentrain through **phase advance** and **phase delay**



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



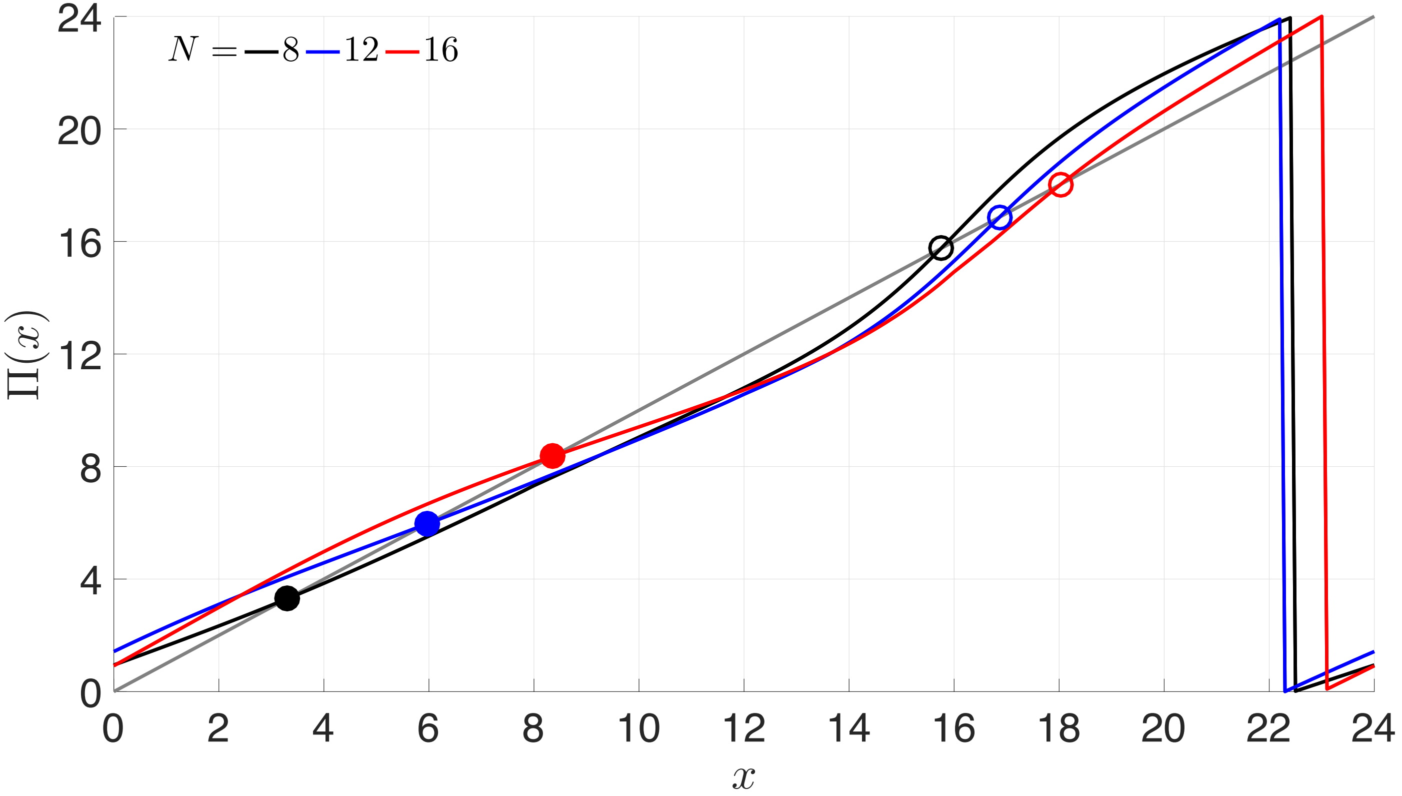
Dependence of $\Pi(x)$ on endogenous period



- 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

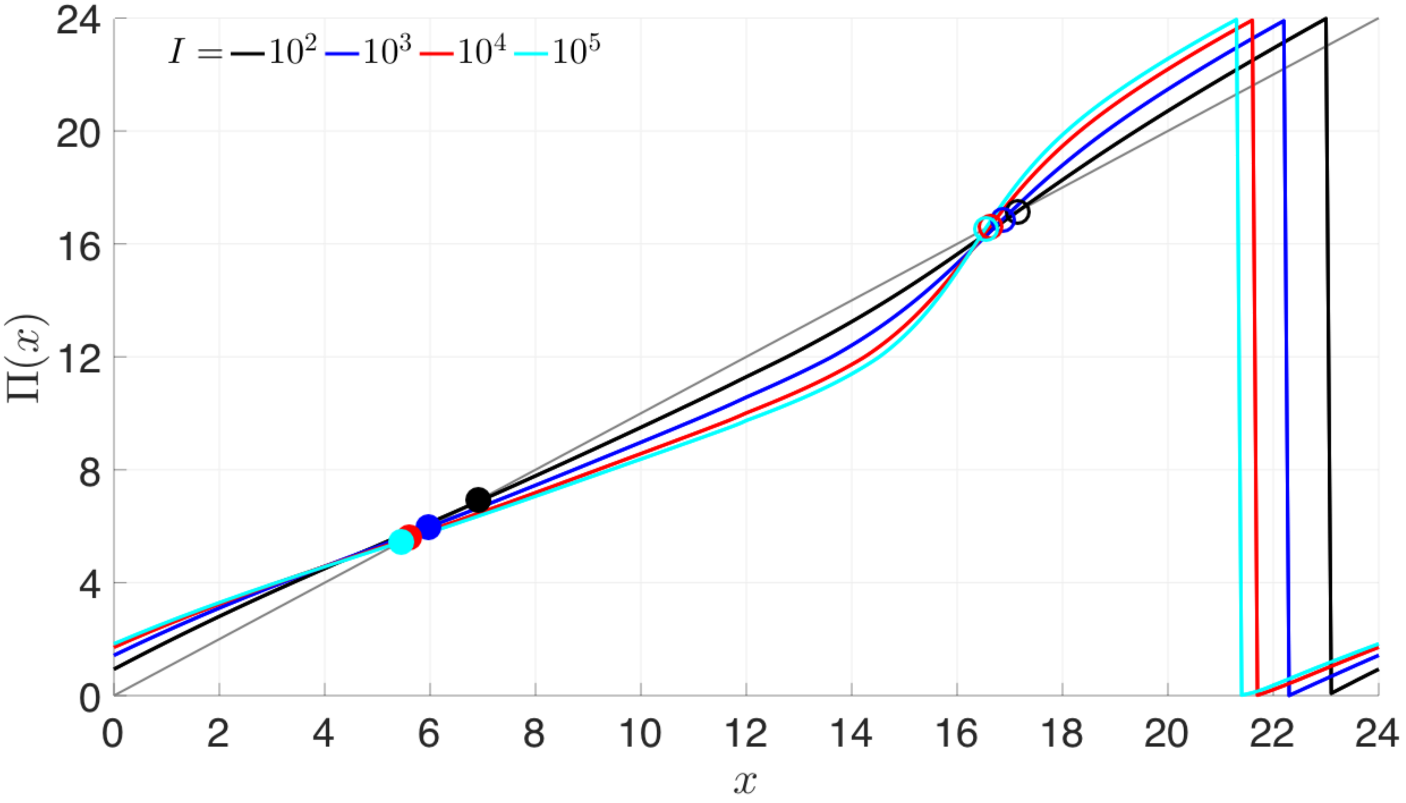
Dependence of $\Pi(x)$ on daylength

- As N increases, stable fixed point of map moves to the right
  - implies that as daylength increases phase of entrainment becomes more delayed



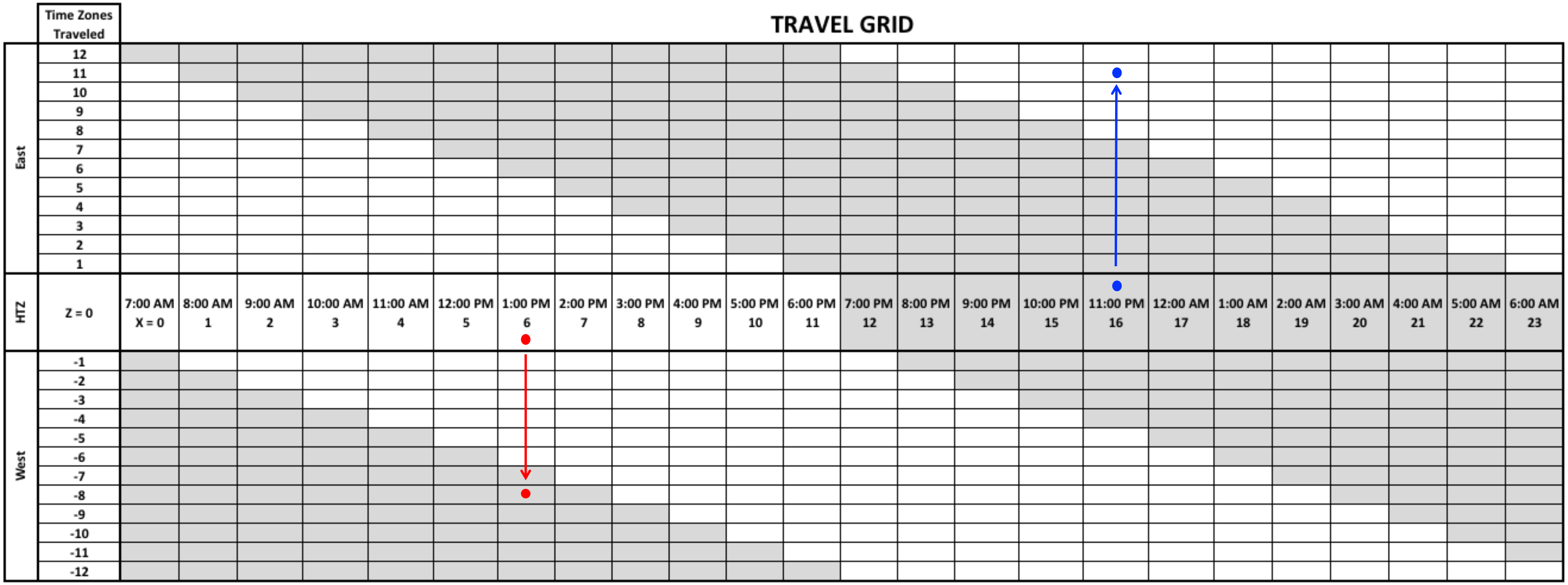
Dependence of $\Pi(x)$ on light intensity

- 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)
  - *X* = 0 corresponds to arrival time of 7 AM
  - *Z* > 0 corresponds to traveling east
  - *Z* < 0 corresponds to traveling west



TRAVEL GRID

	Time Zones Traveled																								
East	12	▨	▨	▨	▨	▨	▨	▨	▨	▨	▨	▨	▨												
	11		▨	▨	▨	▨	▨	▨	▨	▨	▨	▨	▨	▨				●							
	10			▨	▨	▨	▨	▨	▨	▨	▨	▨	▨	▨	▨										
	9				▨	▨	▨	▨	▨	▨	▨	▨	▨	▨	▨	▨									
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	7						▨	▨	▨	▨	▨	▨	▨	▨	▨	▨	▨	▨							
	6							▨	▨	▨	▨	▨	▨	▨	▨	▨	▨	▨	▨						
	5								▨	▨	▨	▨	▨	▨	▨	▨	▨	▨	▨	▨					
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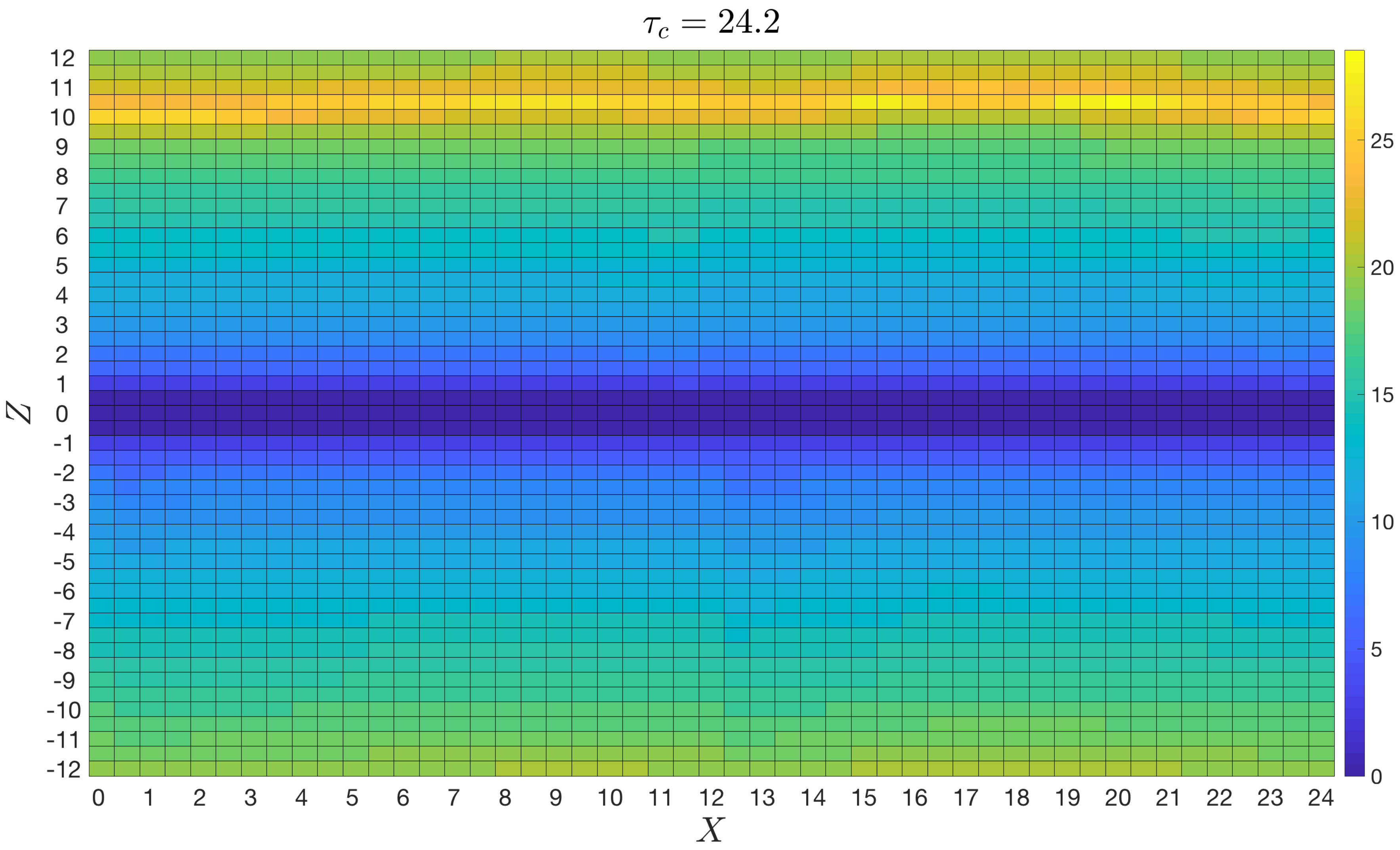
	2											▨	▨	▨	▨	▨	▨	▨	▨	▨	▨	▨	▨		
	1												▨	▨	▨	▨	▨	▨	▨	▨	▨	▨	▨	▨	
HTZ	Z = 0	7:00 AM X = 0	8:00 AM 1	9:00 AM 2	10:00 AM 3	11:00 AM 4	12:00 PM 5	1:00 PM 6 ●	2:00 PM 7	3:00 PM 8	4:00 PM 9	5:00 PM 10	6:00 PM 11	7:00 PM 12	8:00 PM 13	9:00 PM 14	10:00 PM 15	● 11:00 PM 16	12:00 AM 17	1:00 AM 18	2:00 AM 19	3:00 AM 20	4:00 AM 21	5:00 AM 22	6:00 AM 23
West	-1	▨													▨	▨	▨	▨	▨	▨	▨	▨	▨	▨	▨
	-2	▨	▨													▨	▨	▨	▨	▨	▨	▨	▨	▨	▨
	-3	▨	▨	▨													▨	▨	▨	▨	▨	▨	▨	▨	▨
	-4	▨	▨	▨	▨													▨	▨	▨	▨	▨	▨	▨	▨
	-5	▨	▨	▨	▨	▨													▨	▨	▨	▨	▨	▨	▨
	-6	▨	▨	▨	▨	▨	▨													▨	▨	▨	▨	▨	▨
	-7	▨	▨	▨	▨	▨	▨	▨													▨	▨	▨	▨	▨
	-8	▨	▨	▨	▨	▨	▨	▨ ●	▨													▨	▨	▨	▨
	-9	▨	▨	▨	▨	▨	▨	▨	▨	▨													▨	▨	▨
	-10	▨	▨	▨	▨	▨	▨	▨	▨	▨	▨													▨	▨
	-11	▨	▨	▨	▨	▨	▨	▨	▨	▨	▨	▨													▨
	-12	▨	▨	▨	▨	▨	▨	▨	▨	▨	▨	▨	▨												

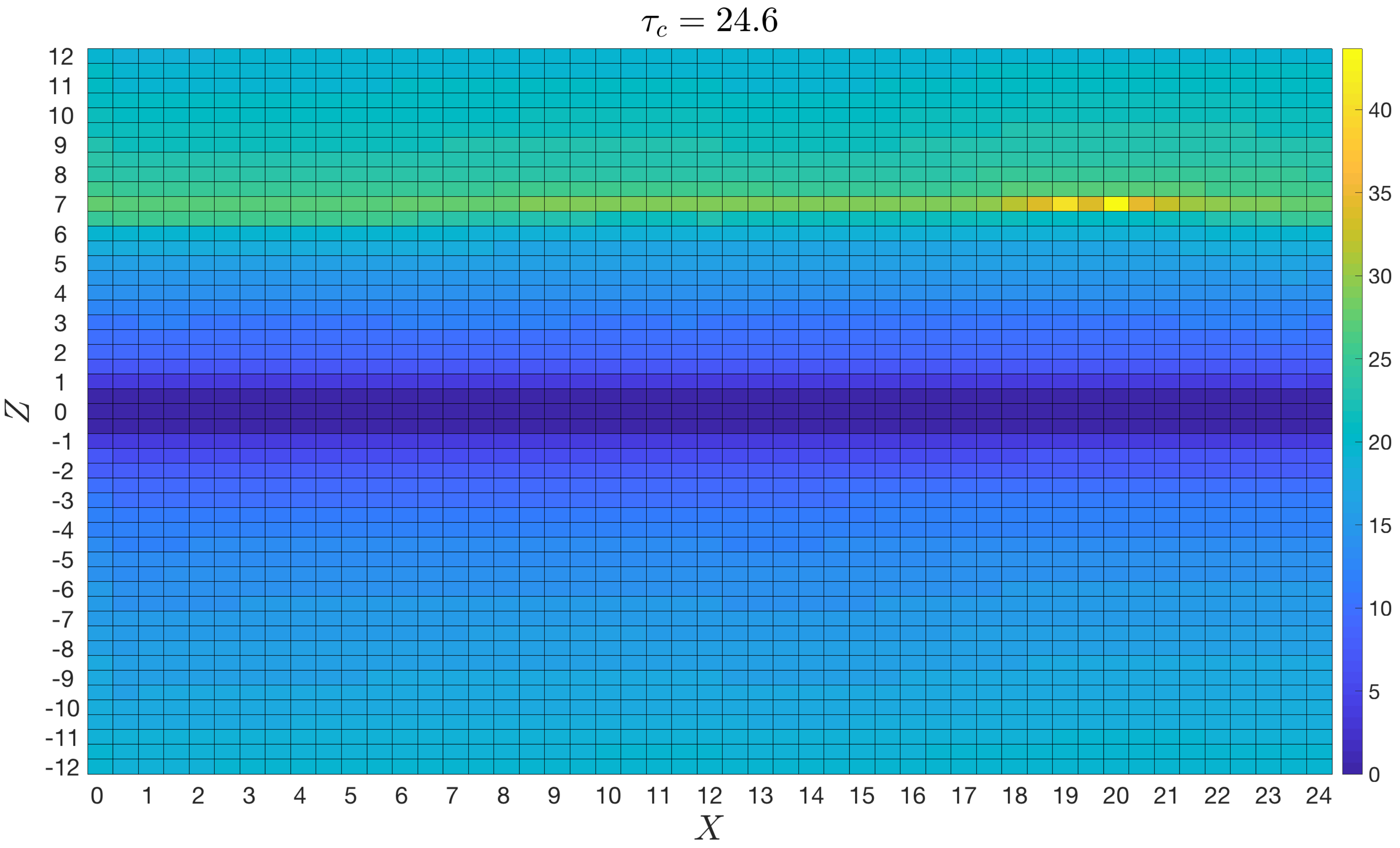
Days to reentrain with typical endogenous period



worst trip: traveling **East** 10.5 time zones

N = 12, *I* = 100

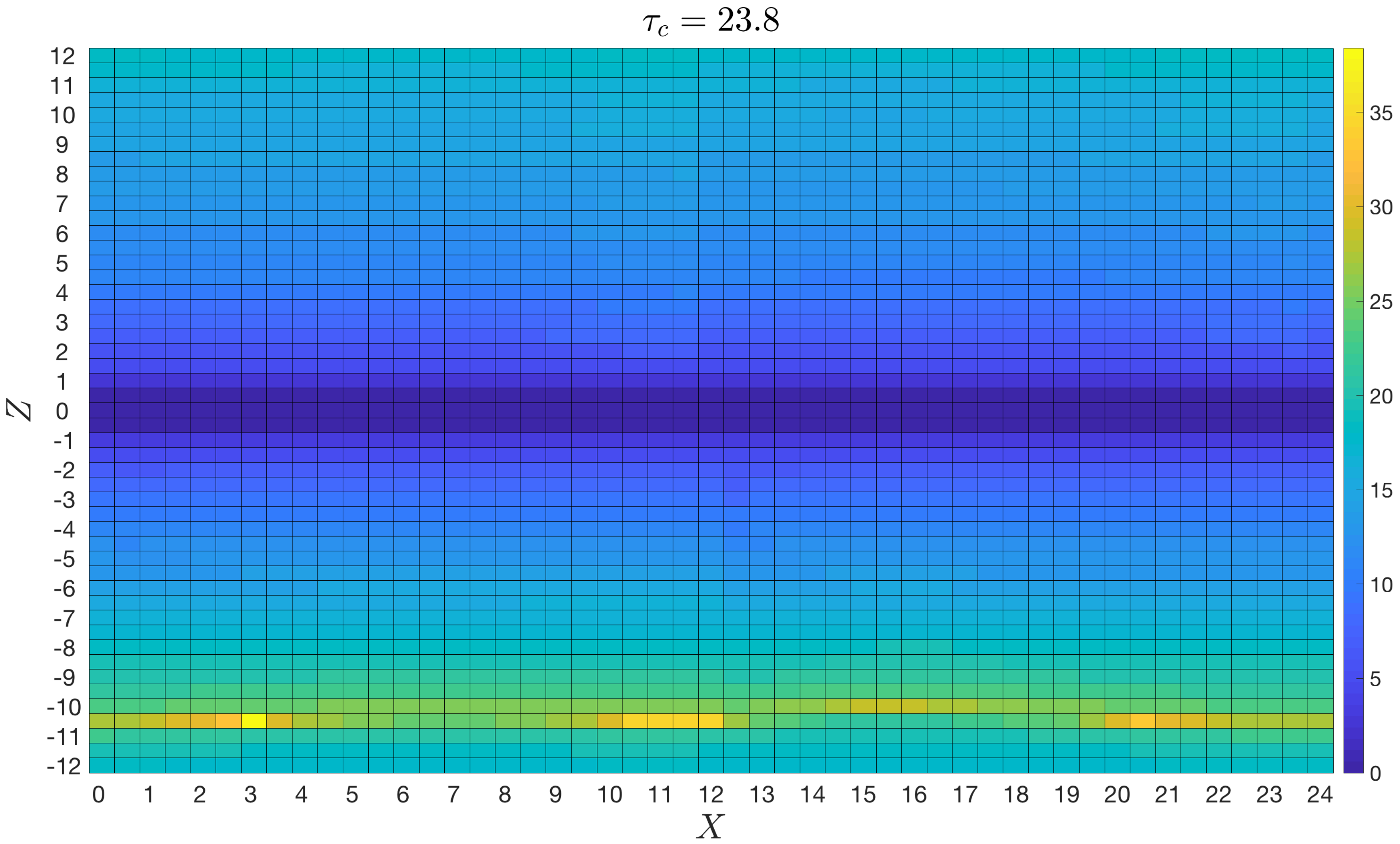
Days to reentrain with slow internal clock



worst trip: traveling **East** 7 time zones

$N = 12$, $I = 100$

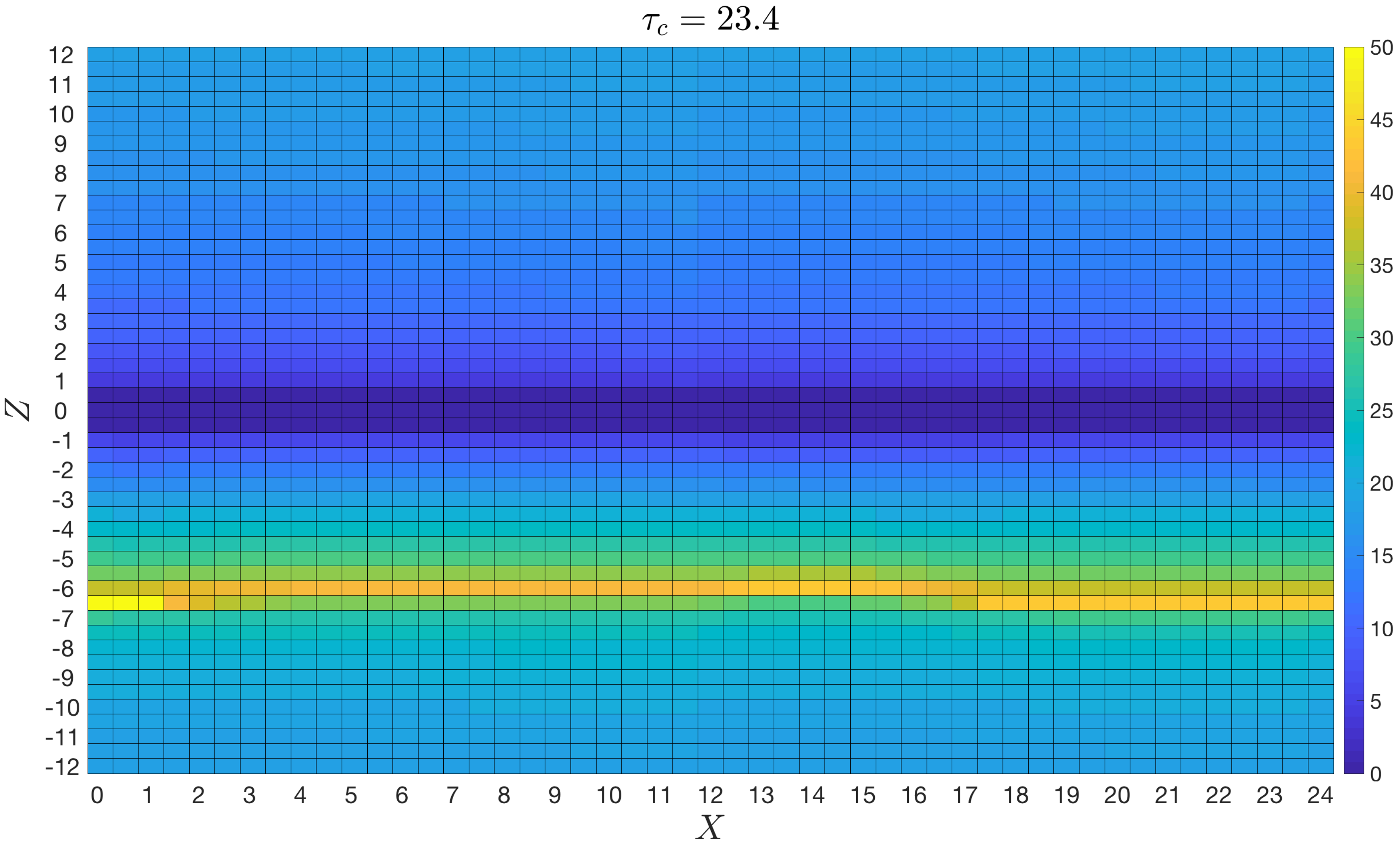
Days to reentrain with fast internal clock



worst trip: traveling **West** 10.5 time zones

N = 12, *I* = 100

Days to reentrain with even faster internal clock



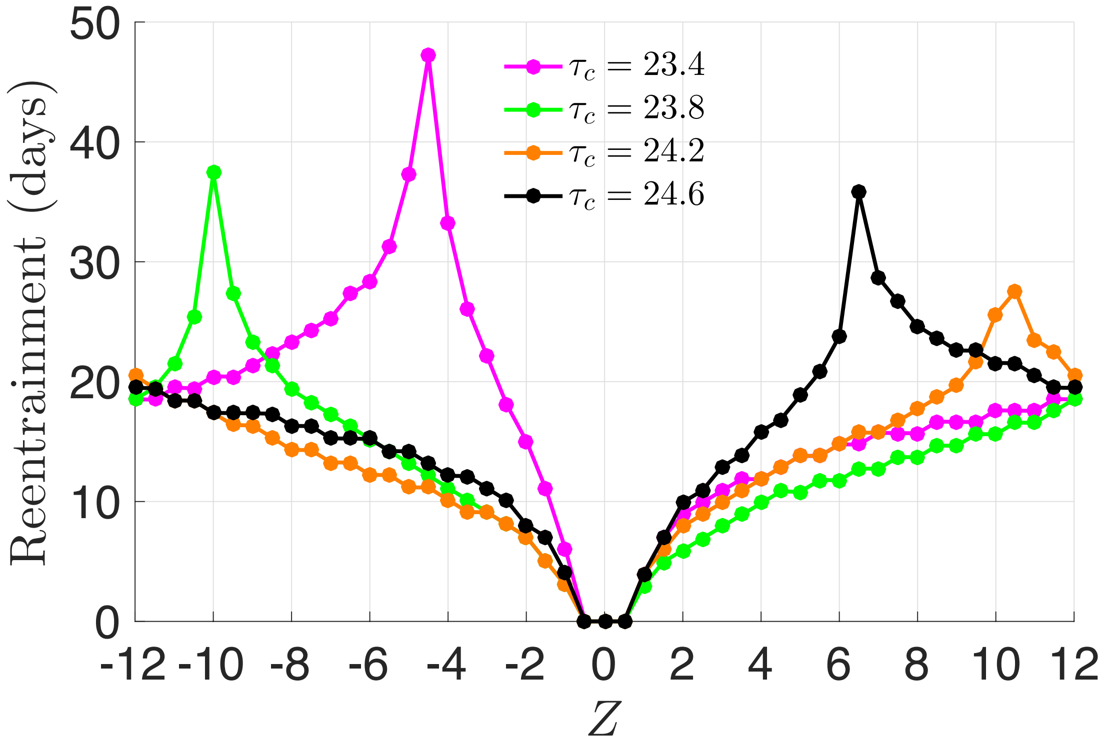
N = 12, *I* = 100

worst trip: traveling **West** 6.5 time zones

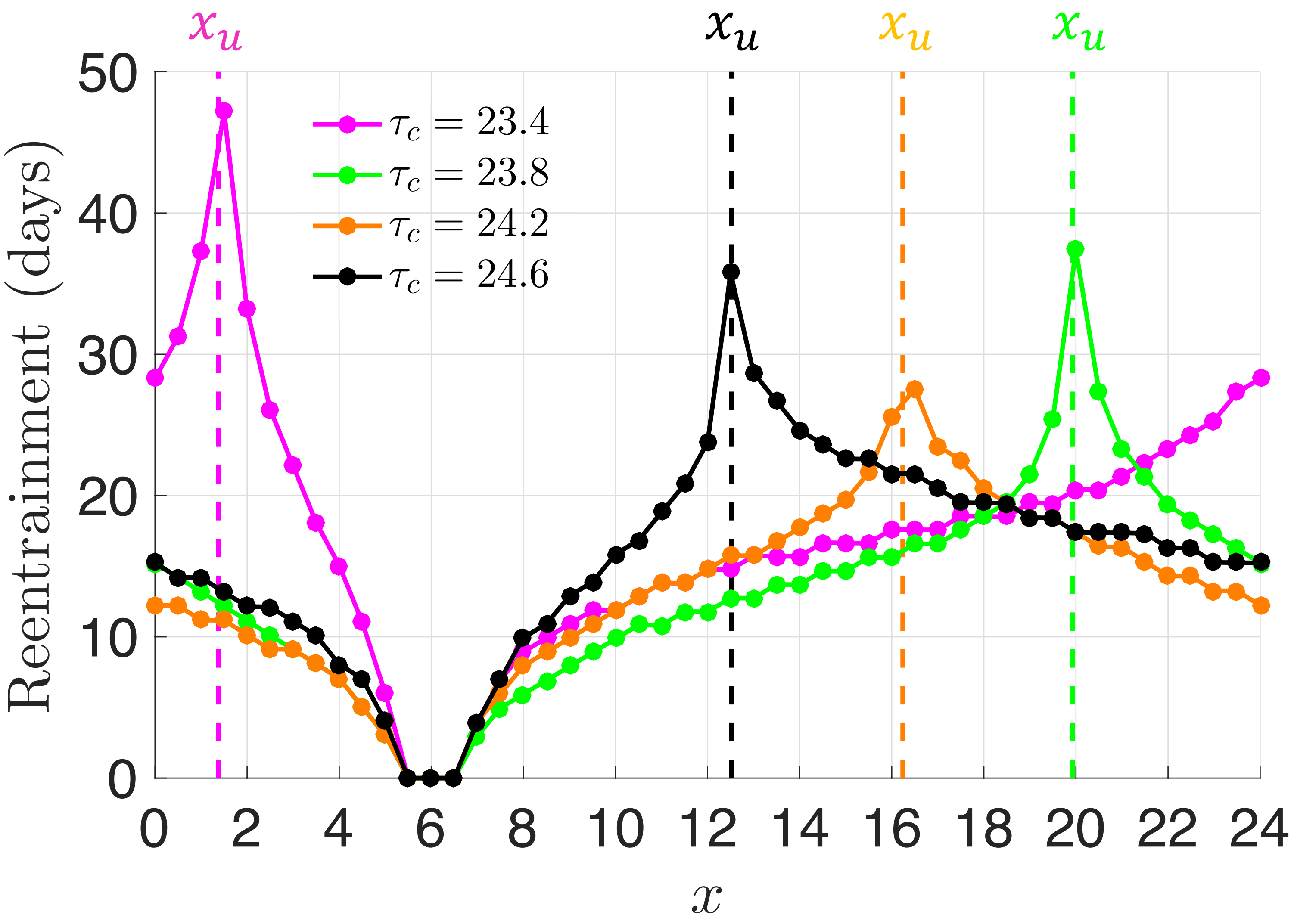
Worst-case travel depends on endogenous period

- ☐ **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



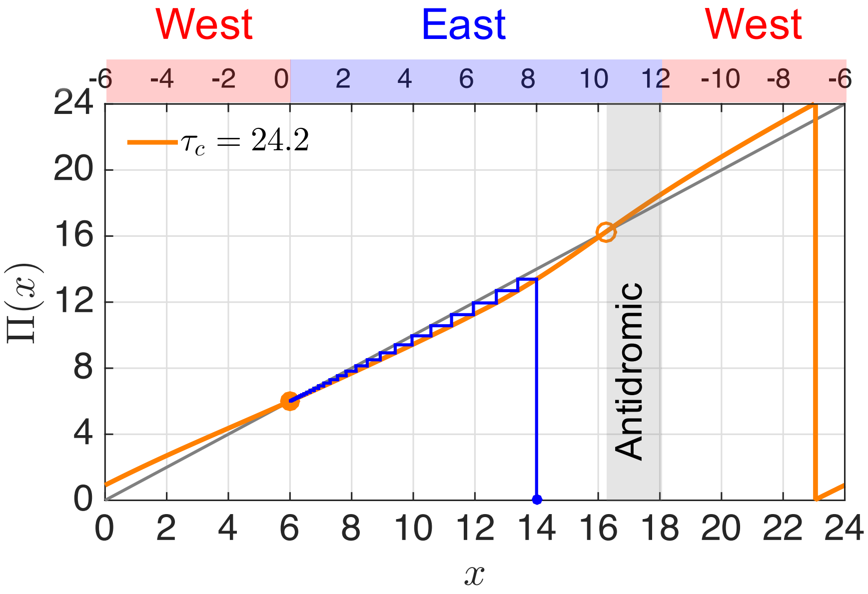
Worst-case travel is determined by location of x_u

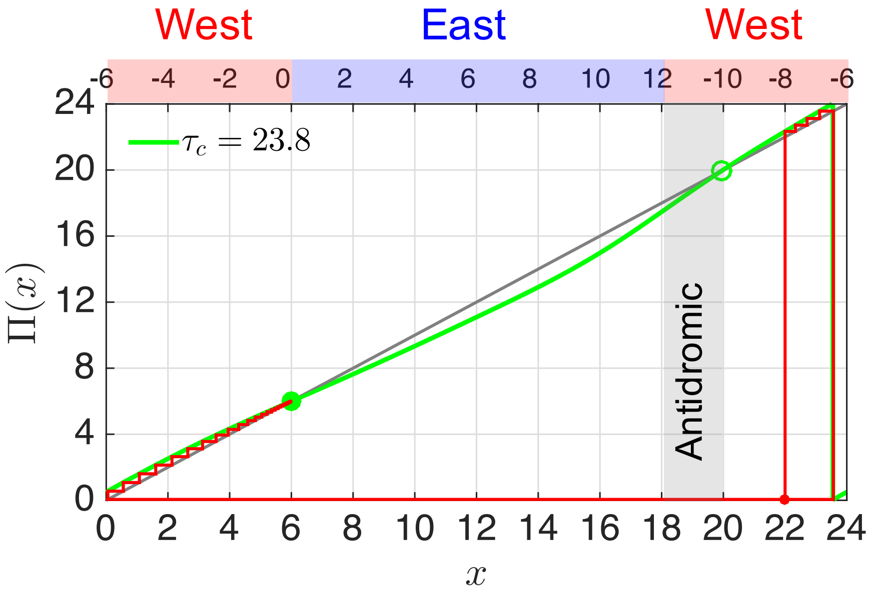


x_u also controls mode of reentrainment

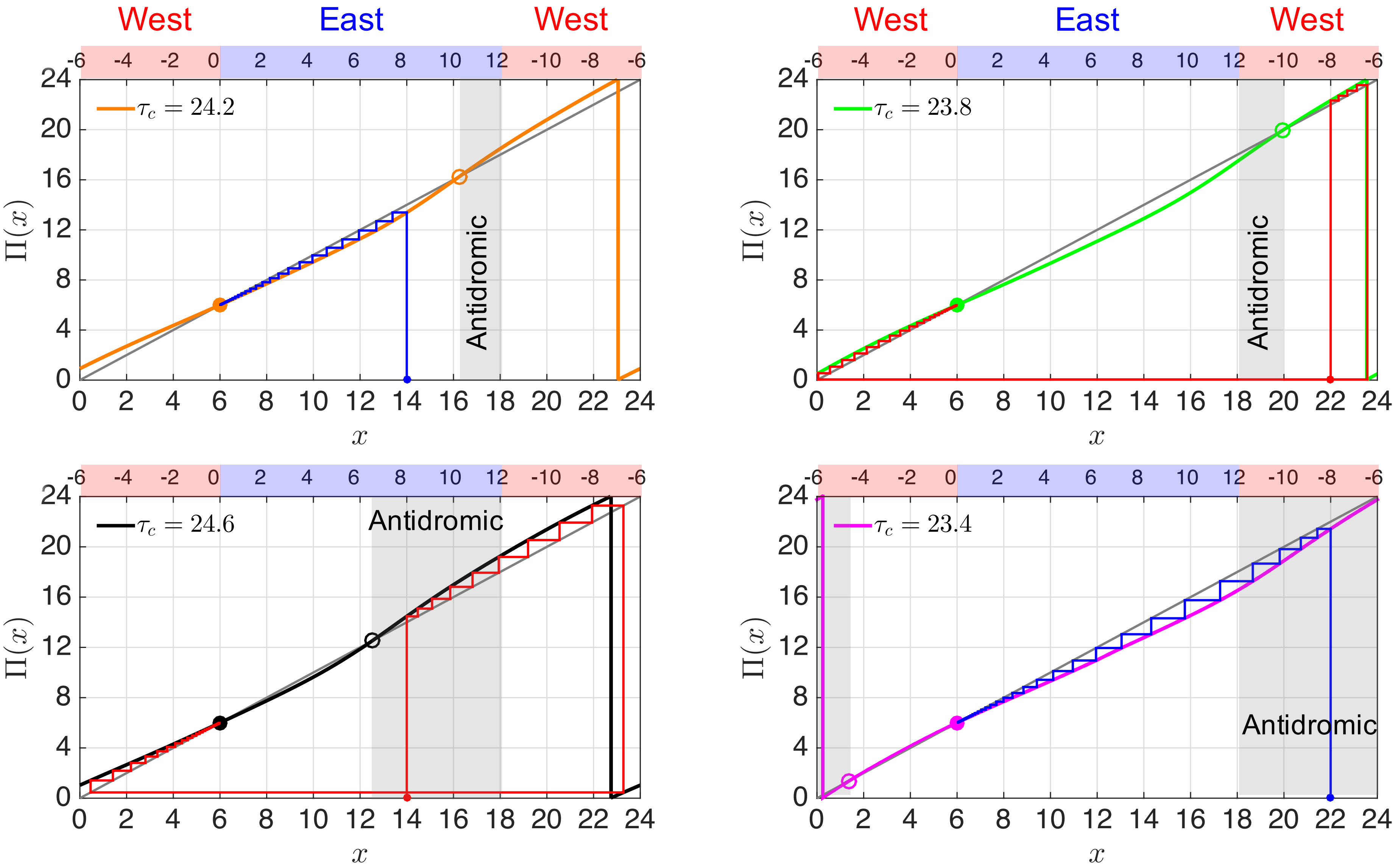
- Orthodromic: reentrainment in same direction as the shift in the LD cycle
  - through phase advances after traveling East, or phase delays after traveling West

- Antidromic: reentrainment in opposite direction as the shift in the LD cycle
  - through phase delays after traveling East, or phase advances after traveling West

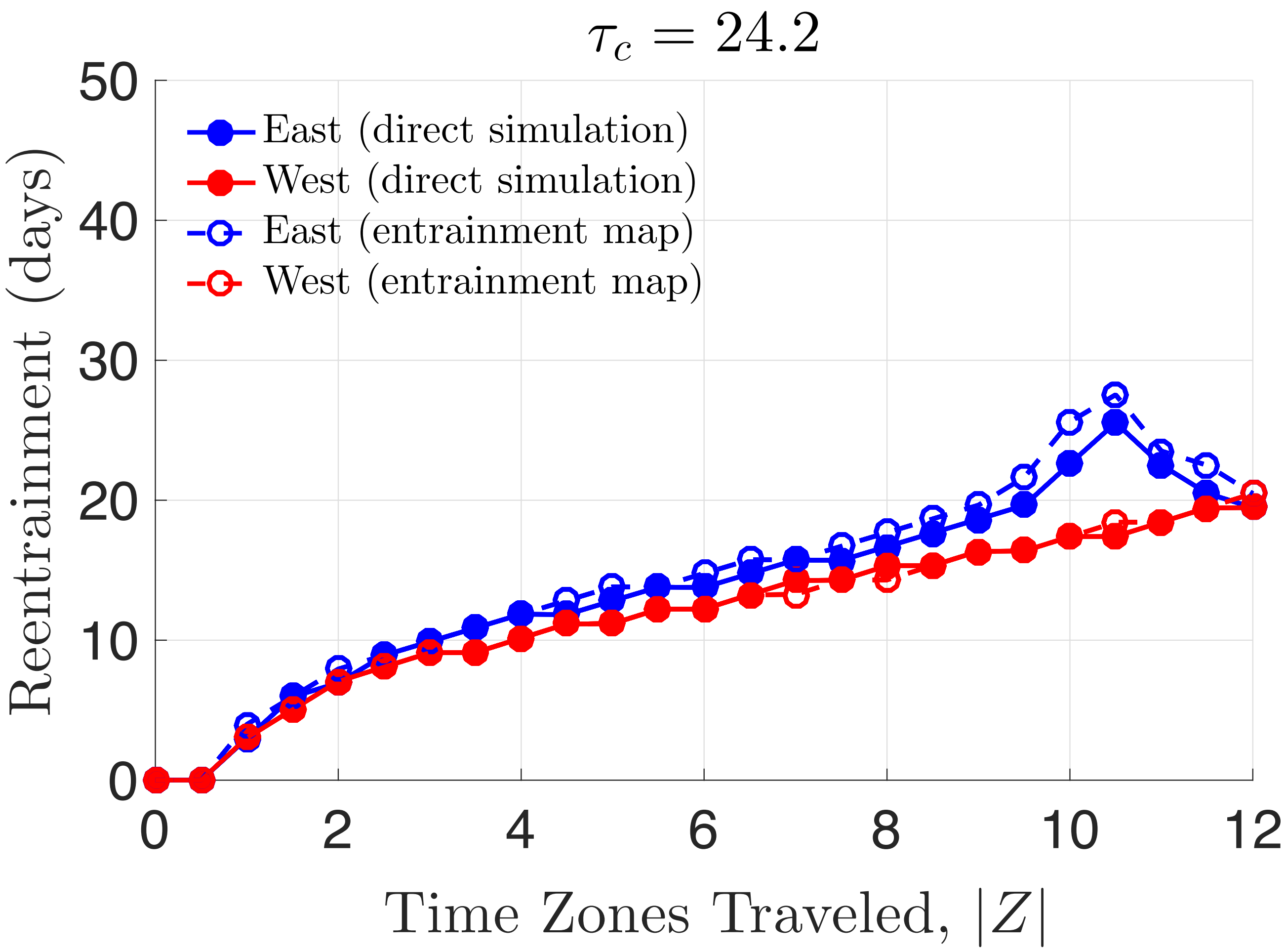




x_u also controls mode of reentrainment

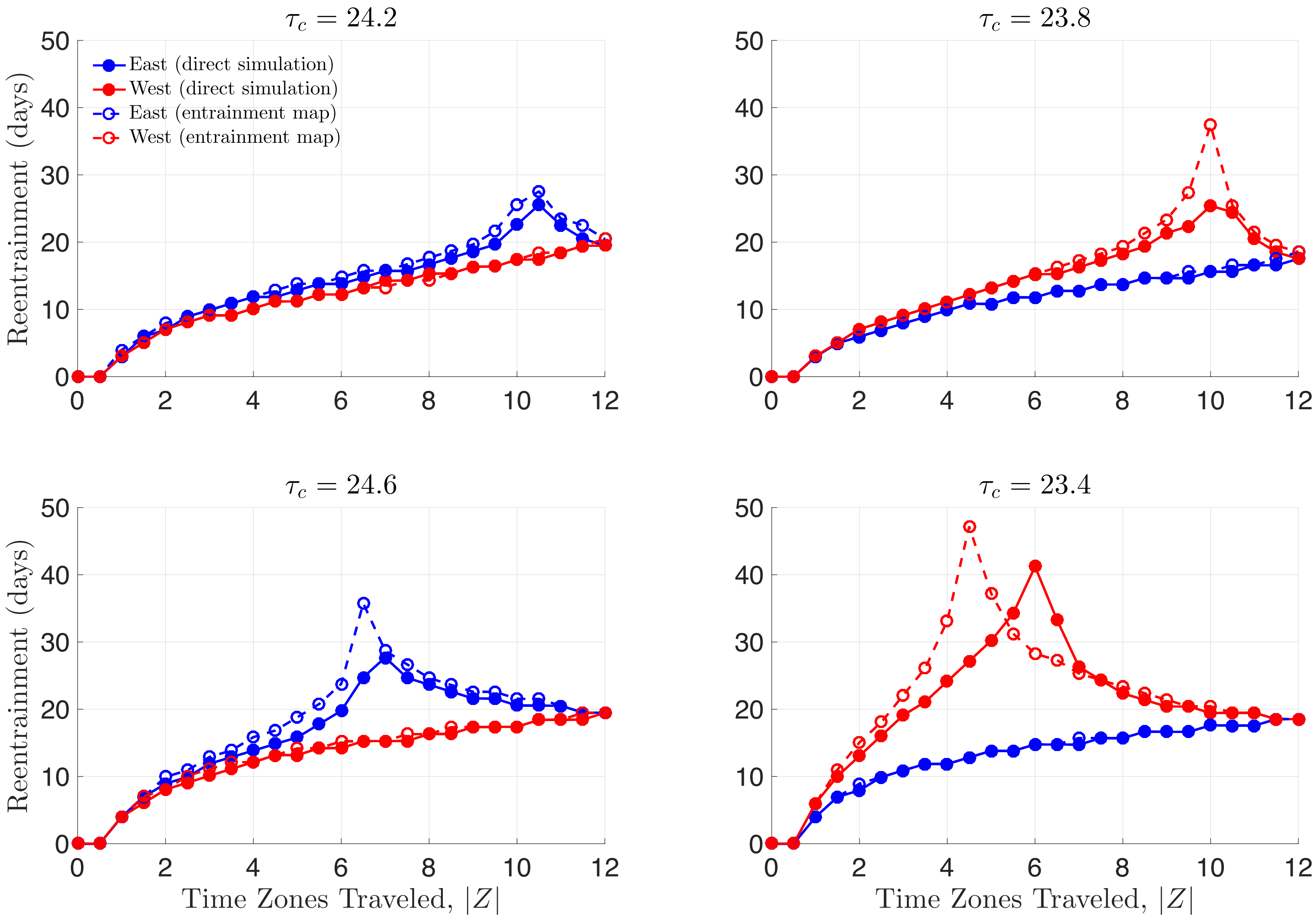


East-West asymmetry of reentrainment times



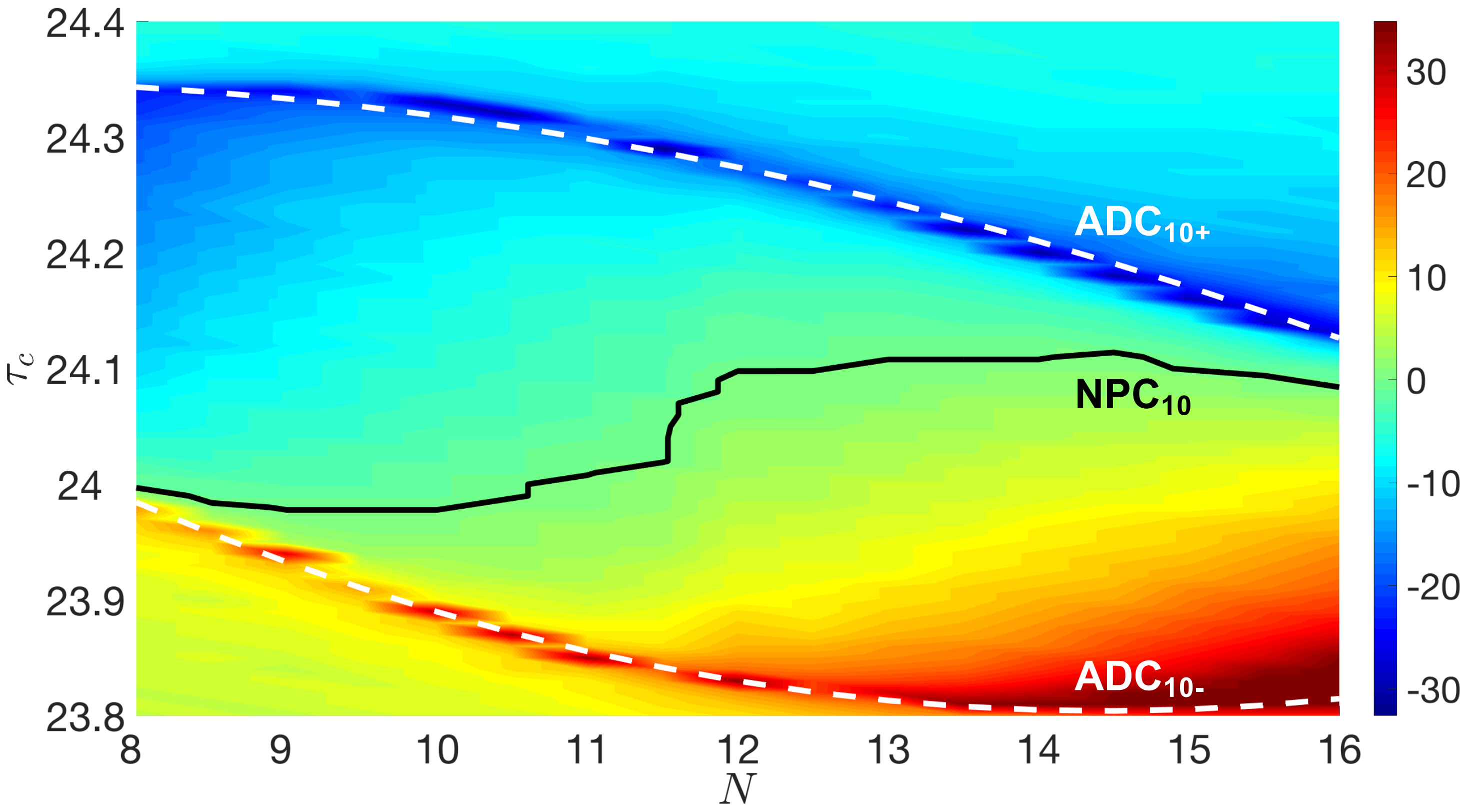
- East-west asymmetry depends on endogenous period
  - Lu, Klein-Cardena, Lee, Girvan, Antonsen, and Ott. *Chaos* (2016)

East-West asymmetry depends on τ_c



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

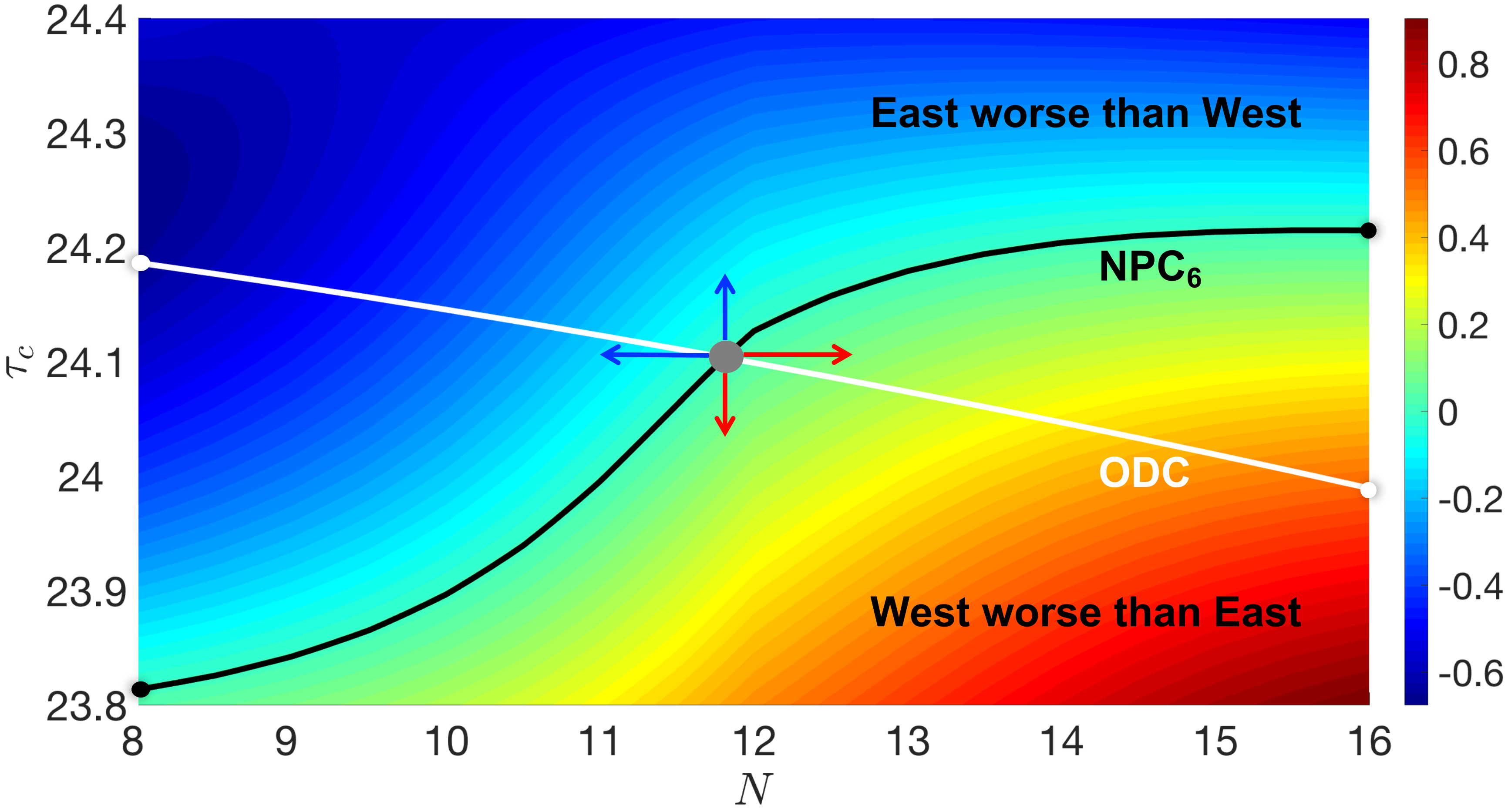


NPC = neutral period curve

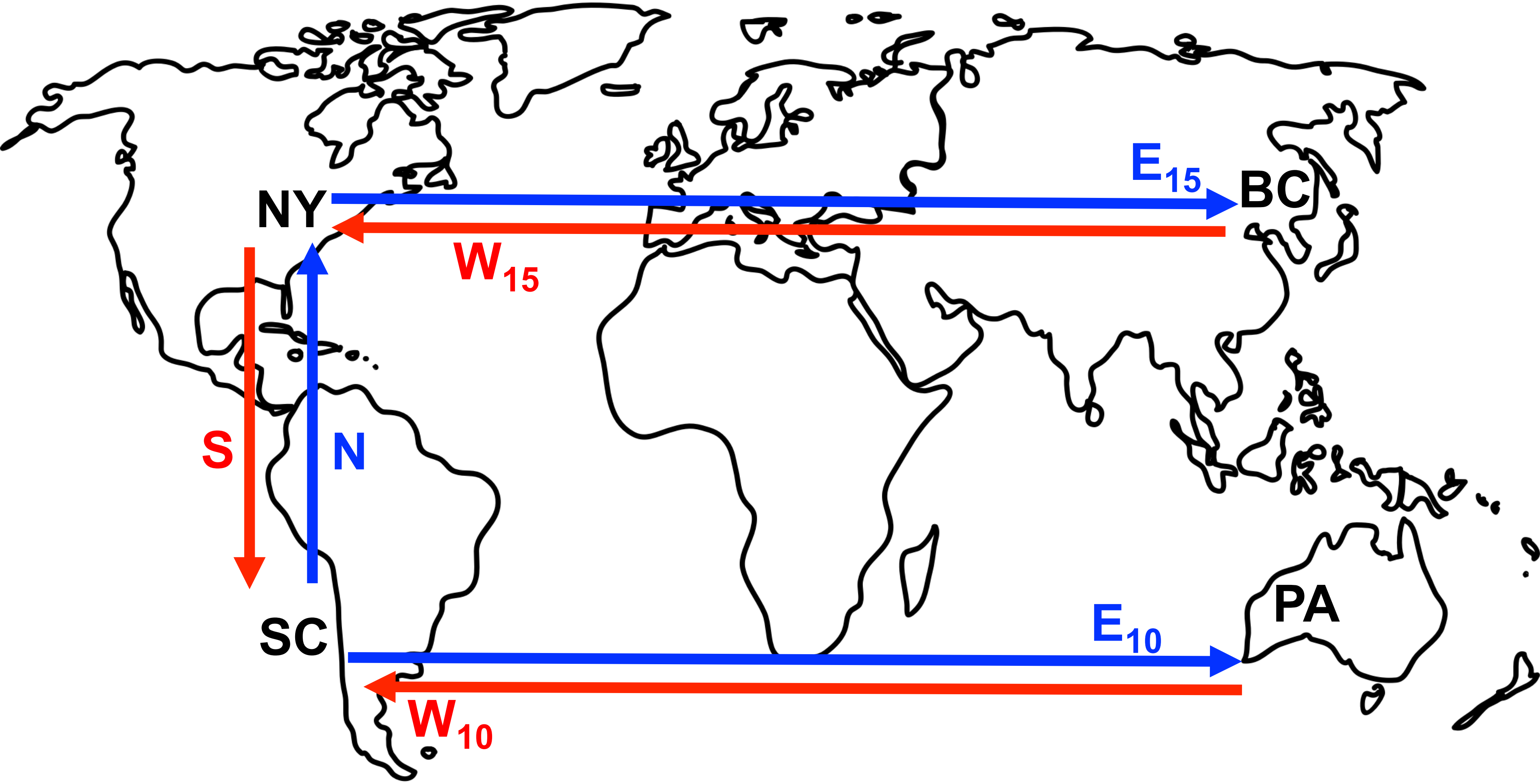
ADC = antidromy curve

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)



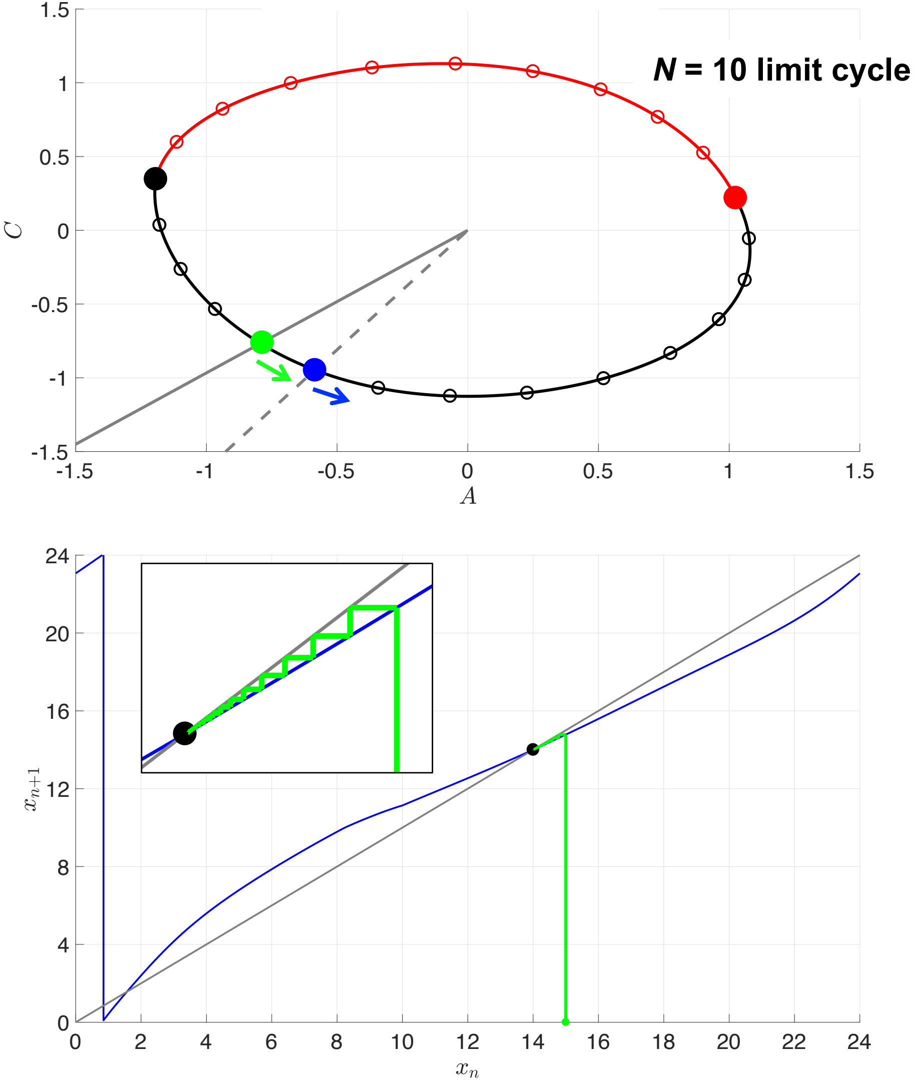
Effects of daylength



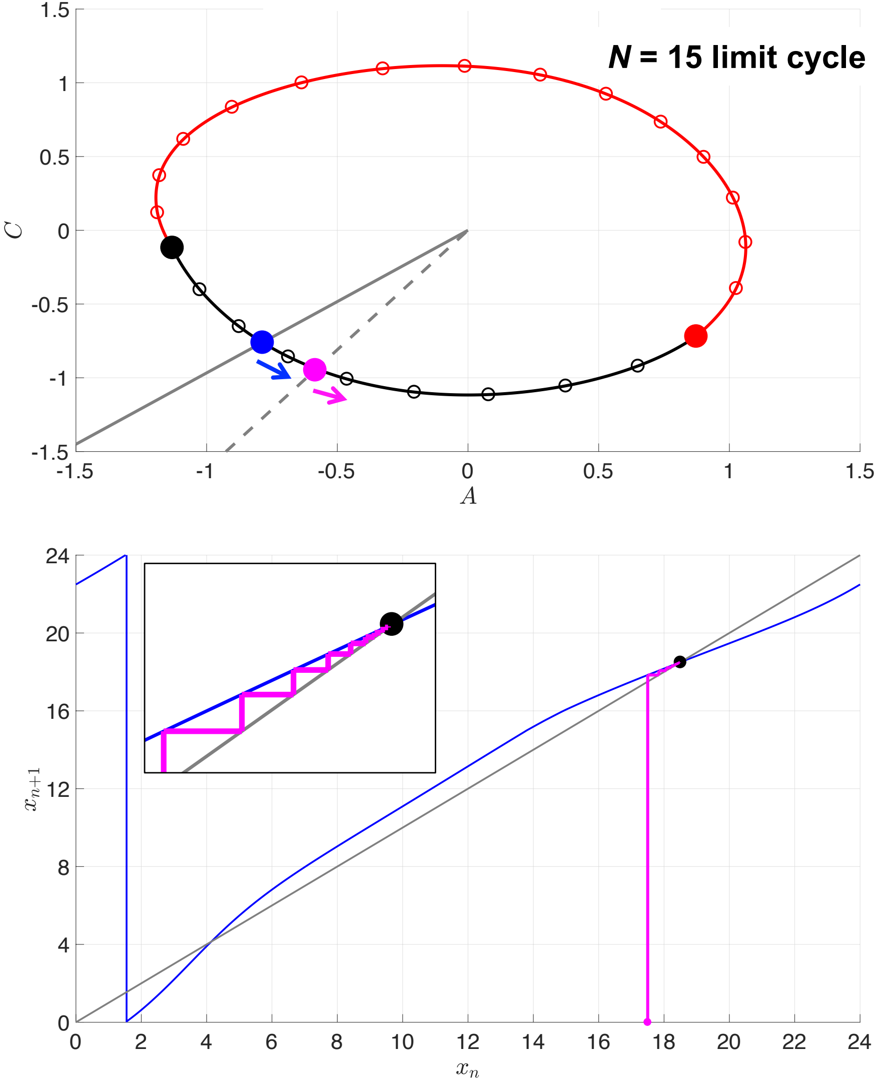
- In June, New York City has 15 hours of daylight while Sanitago, Chile has 10 hours

Transequatorial (north-south) travel

NYC to Santiago



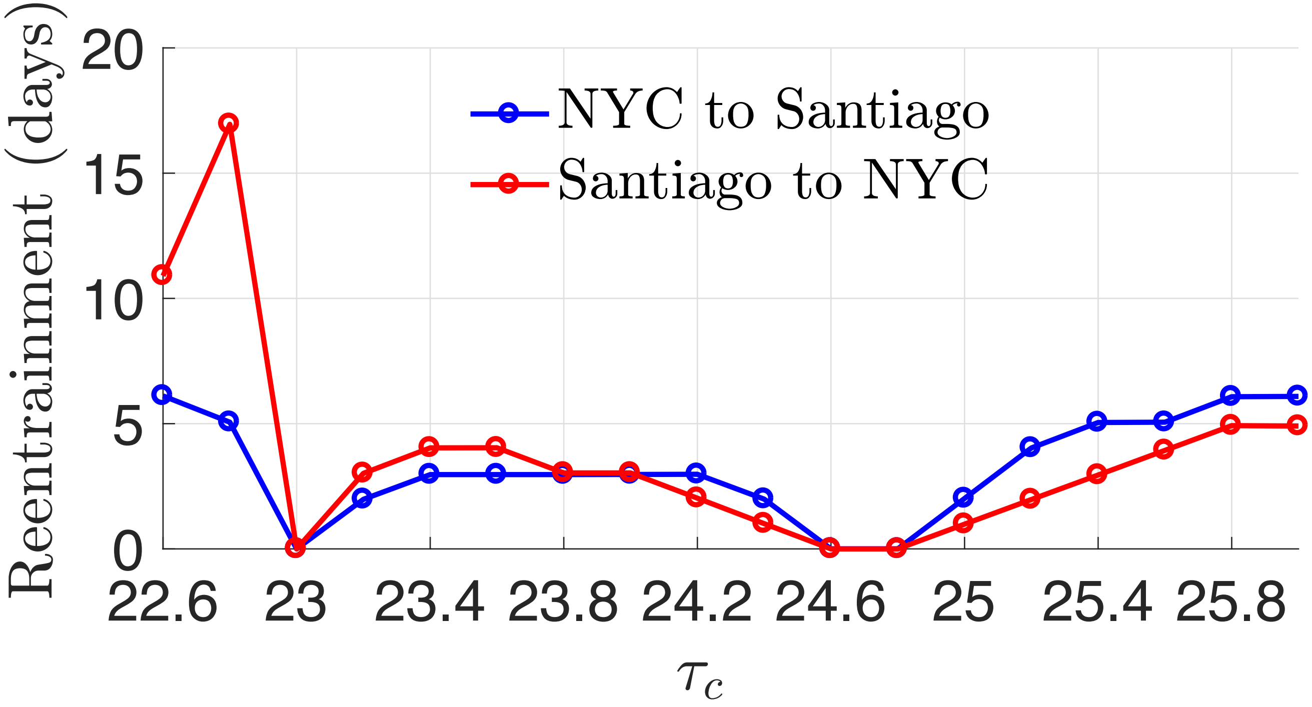
Santiago to NYC



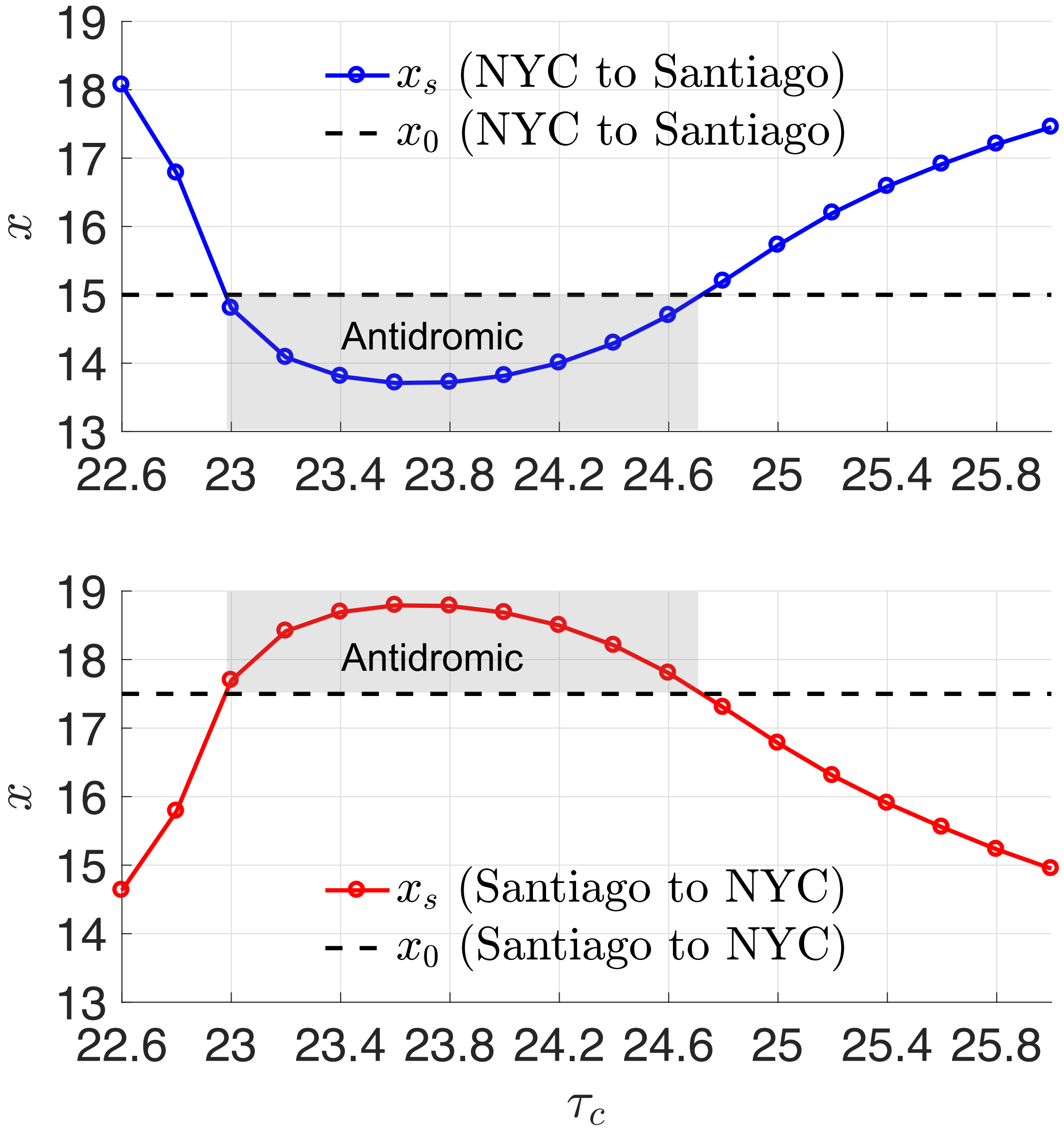
North-south travel can cause jet lag

	Direct simulation			Entrainment map				
	t	t_{ref}	$t_{ref} - t$	x_n	x_{n+1}	$x_s - x_{n+1}$	$\rho(x_n)$	$\sum \rho(x_n)$
NYC to Santiago	23.776	23.005	-0.772	15	14.780	-0.775	23.780	23.779
	47.598	47.005	-0.593	14.780	14.622	-0.617	23.842	47.621
	71.459*	71.005	-0.454	14.622	14.465	-0.460	23.843	71.465**
Santiago to NYC	24.3444	24.9960	0.6516	17.5	17.841	0.655	24.341	24.341
	48.5594*	48.9960	0.4366	17.841	18.040	0.456	24.199	48.540**

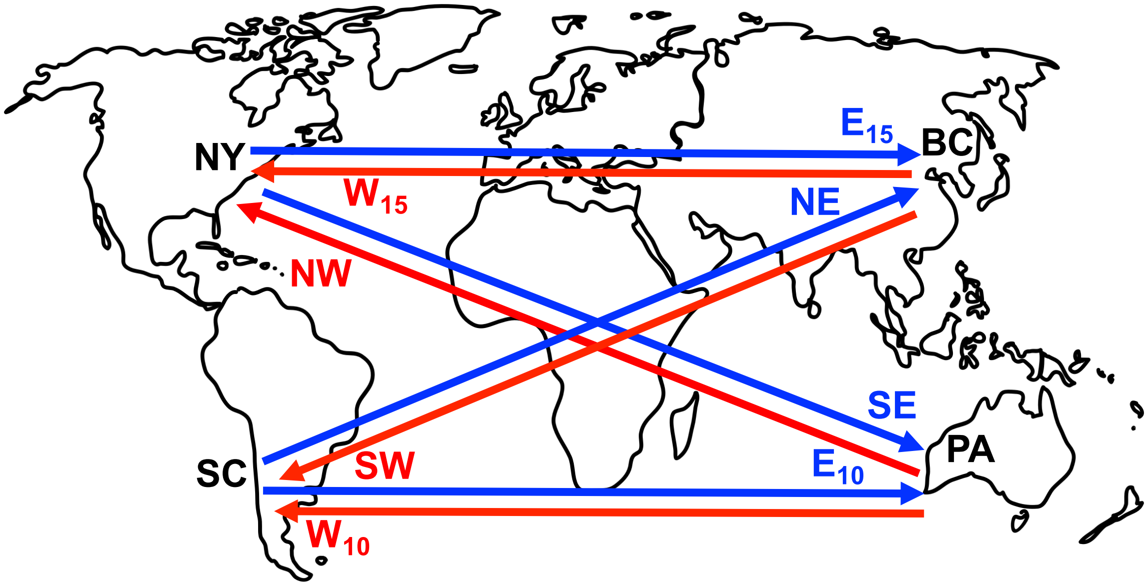
Table 1. Reentrainment times for southward and northward travel with $\tau_c = 24.2$.

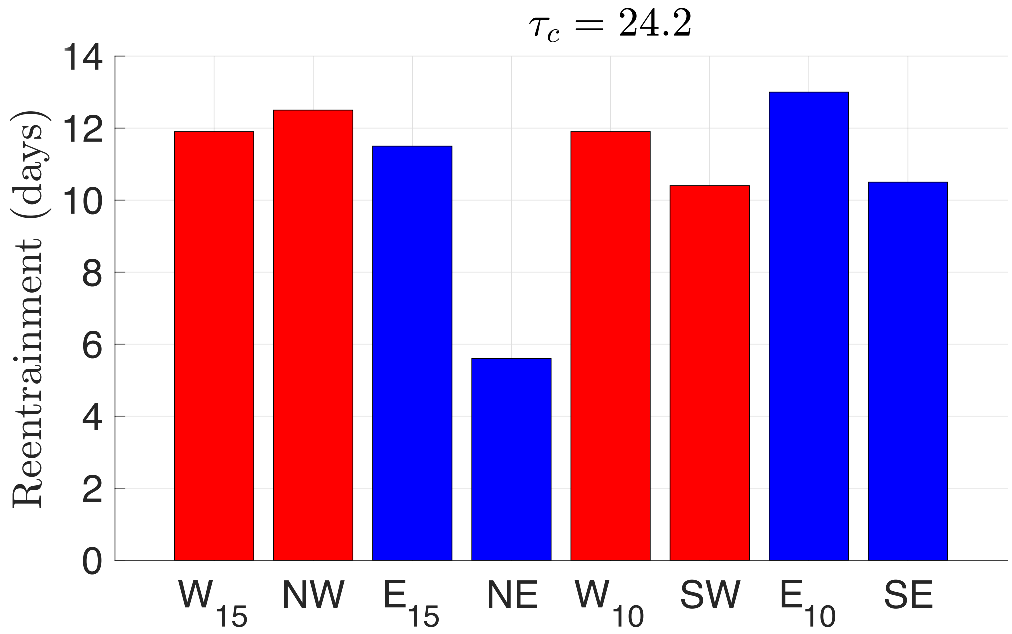


Natural mode of reentrainment is antidromic



Transmeridian + transequatorial travel





Traveling diplomat problem

- Traveling salesman problem involves arranging travel to several locations to minimize total travel distance

- If a diplomat wished to visit a certain number of countries, could they arrange their schedule to minimize the total amount of jet lag?

  - NYC → Santiago → Perth → Beijing → NYC : 28 days
  - NYC → Beijing → Perth → Santiago → NYC : 28 days
  - NYC → Perth → Beijing → Santiago → NYC : 24 days
  - NYC → Santiago → Beijing → Perth → NYC : 23 days

Summary

- ☐ Entrainment maps can explain several features of jet lag
  - East/West asymmetry depends on both endogenous period and daylength
    - whether endogenous period is > or < 24 hours is not the critical factor
  - Unstable fixed point of map separates orthodromic and antidromic reentrainment
  - North-south travel can cause significant jet lag

- ☐ Future Work
  - Social jet lag
  - Shift work
  - Seasonal affective disorder

  - Incorporate sleep
  - Peripheral oscillators in other organs

Acknowledgements

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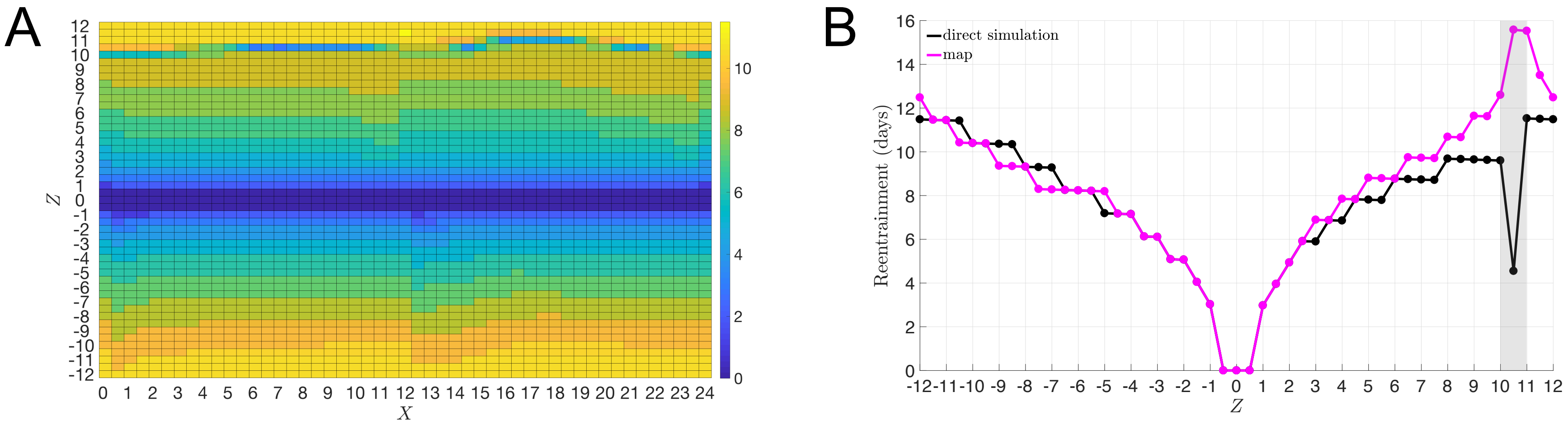
Reference

Diekman and Bose, *Journal of Biological Rhythms,* Volume 31, December 2016

Phaseless set



Phaseless set