Designing a critical resetting protocol for achieving large phase shifts in humans

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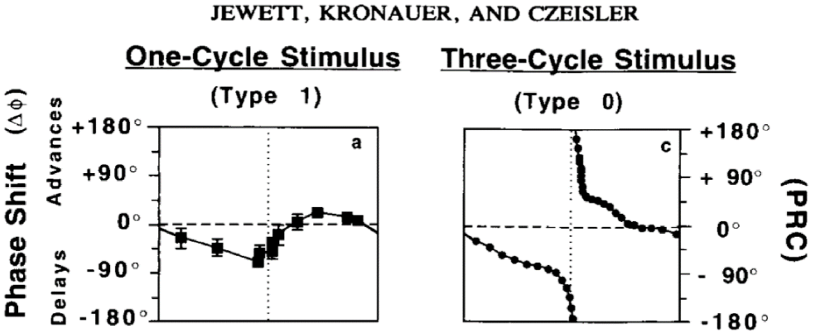
Outline

1. Introduction: circadian phase shifting
2. Intrinsic variability and critical phase resetting
3. Feedback control of critical resetting
4. Conclusions

Introduction: circadian phase shifting

Weak ("Type 1") and strong ("Type 0") phase response curves



PRC shape depends on perturbation strength, duration.

Jewett, Kronauer, Czeisler J Biol Rhythms 1994

A less commonly-observed response: critical resetting

Large magnitude or multiple light stimuli centered near core body temperature minimum is a critical stimulus.

Result:

Jewett, Kronauer, Czeisler Nature 1991

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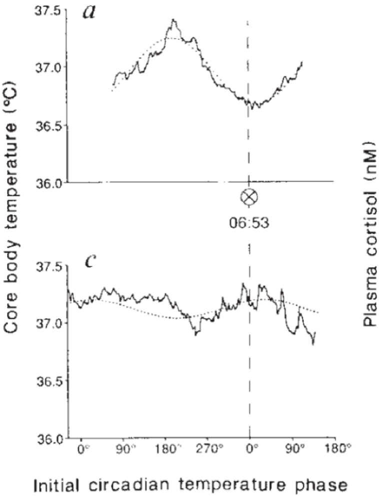

Jewett, Kronauer, Czeisler Nature 1991

Understanding oscillation explains phase responses

Biochemical states $x(t)$ represent are governed by dynamics:

$$\frac{dx}{dt} = f(x, p, u).$$

The system has an attractive limit cycle.

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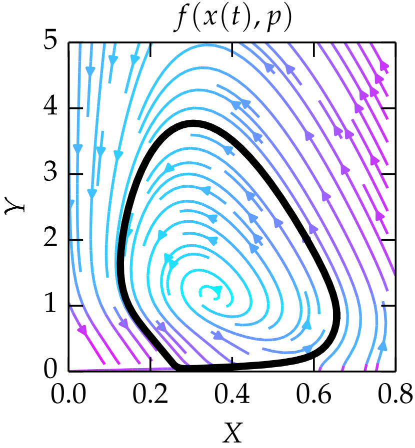

Fig: PC St. John

Type 1 phase response

A stimulus (e.g. light) shifts the oscillator from the limit cycle.

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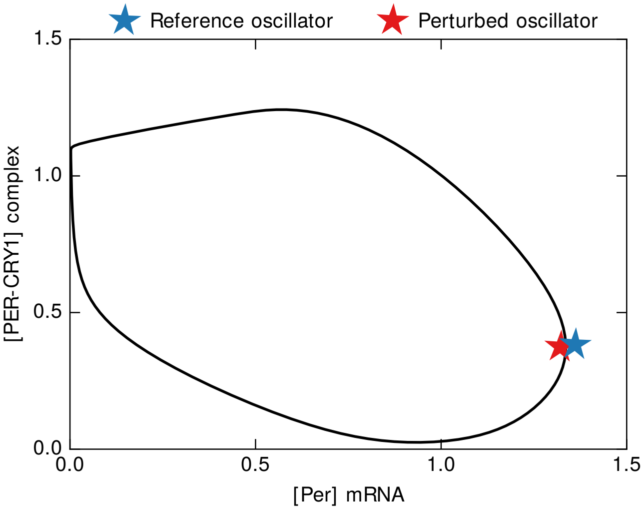

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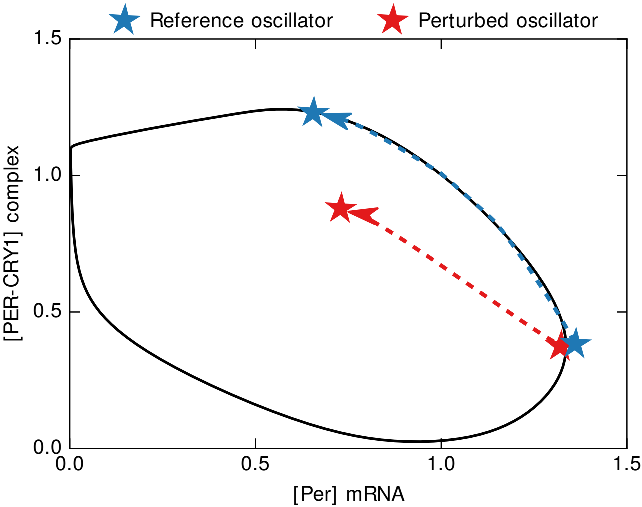
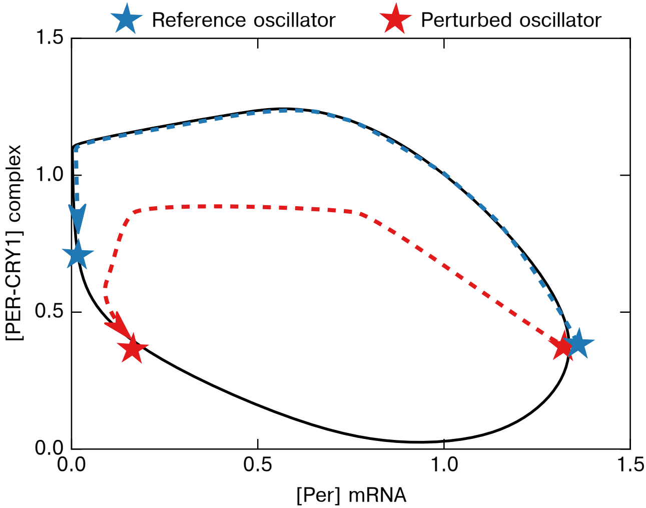


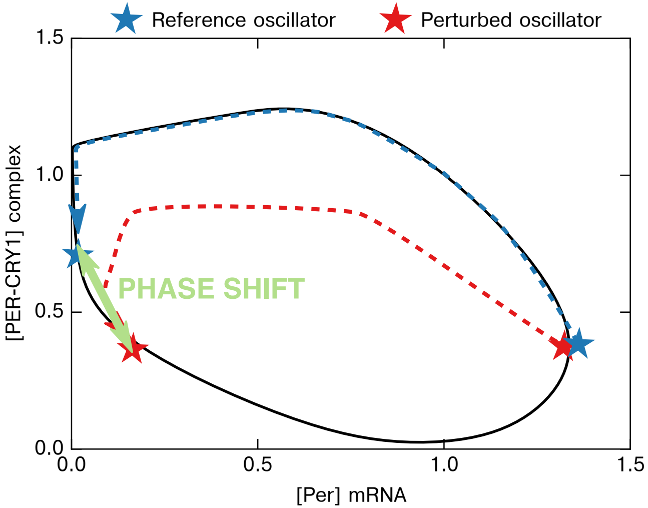
Type 1 phase response

System dynamics govern its eventual return.



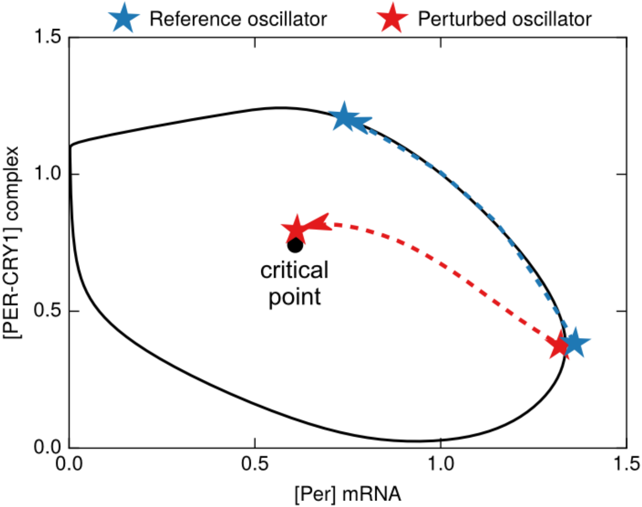
Type 1 phase response

The oscillator returns to the cycle with a new phase (advance).



Critical circadian resetting

Oscillator shifted to the center of the limit cycle, result in loss of amplitude and/or loss of oscillation.



Critical circadian resetting

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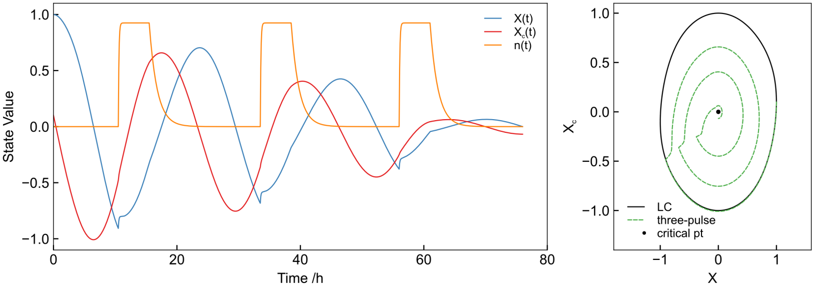
Critical circadian resetting *in silico*

A multi-cycle critical stimulus reproduces critical phenotype using an established model of human light responses.



Model formulation from Kronauer, Forger, Jewett J Biol Rhythms 1999

Critical resetting is unreliable

A "critical stimulus" application led to wide variability in phase/amplitude responses.

TABLE 1 Responses of temperature and cortisol rhythms to near-critical stimuli

Group I: Substantial loss of rhythmicity in both variables

Subject	T	S	$q(t)$	$q(c)$	$\Delta\phi(t)$	$\sim\Delta\phi(c)$
642	+0.2	5.0×2	0.30	0.45	—	—
703 (trial 2)	+0.5	5.5×2	0.02	0.10	—	—
917	−0.4	5.6×2	0.24	0.38	—	—

Group II: Partial amplitude reduction and phase shift in both variables

Subject	T	S	$q(t)$	$q(c)$	$\Delta\phi(t)$	$\sim\Delta\phi(c)$
724 (trial 1)	+1.8	5.5×2	0.48	0.50	−4.9	+1
724 (trial 3)	+1.1	6.0×2	0.85	0.44	−9.9	−11
724 (trial 4)	+1.2	6.0×2	0.44	0.59	+6.8	+7
910	+0.6	6.2×2	1.22	0.53	+7.7	+8
911	−0.1	9.0×1	0.83	0.44	−3.3	−4
914	+0.7	6.2×2	0.36	0.97	+8.8	+7
922	+0.8	5.6×2	0.95	0.52	−4.7	−5

Group III: Substantial loss of rhythmicity in one variable; partial reduction and phase shift in the other variable

Subject	T	S	$q(t)$	$q(c)$	$\Delta\phi(t)$	$\sim\Delta\phi(c)$
831	+0.4	8.0×1	0.16	0.69	—	0
913	−0.1	9.0×1	0.32	0.84	—	+5
916	+0.7	6.2×2	0.31	0.82	—	+6
919	+0.6	5.6×2	0.28	0.80	—	+5
926	+0.6	5.6×2	0.59	0.32	+5.5	—

Trials in which cortisol data are not available:

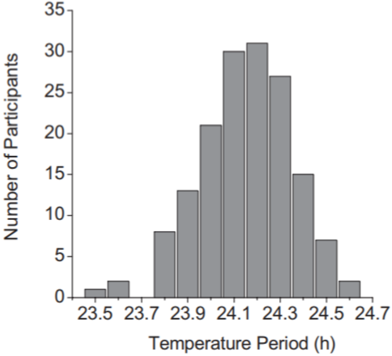
Subject	T	S	$q(t)$	$\Delta\phi(t)$
703 (trial 1)	+0.2	5.4×2	0.60	−7.2
724 (trial 2)	+1.2	5.5×2	0.30	—
1027	0.0	5.5×2	0.15	—

Jewett 1991

Intrinsic variability and critical phase resetting

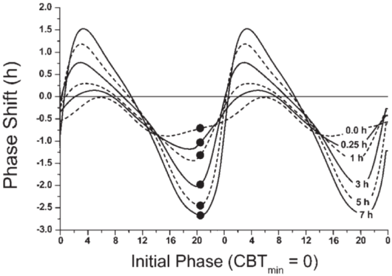
Humans have a range of intrinsic periods

Could this explain some of the variability in response?
How would we correct for this?



Duffy *et al.* PNAS 2011

Intrinsic period influences critical responses



The PRC region targeted by critical resetting experiments is very sensitive.

Fig: Kronauer, Forger, Jewett J Biol Rhythms 1999

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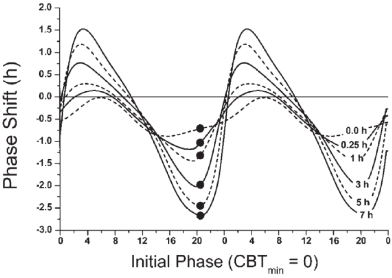


The PRC region targeted by critical resetting experiments is very sensitive.

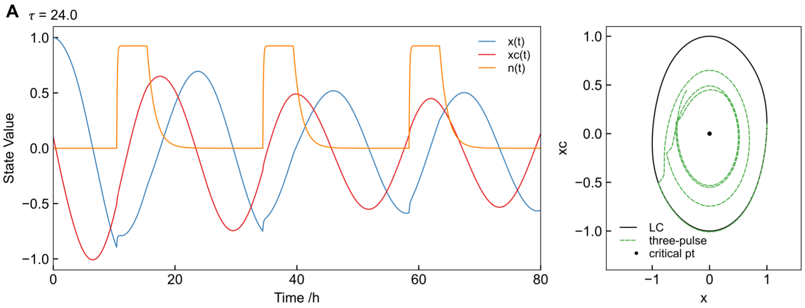
Prediction: This affects ability to critically reset.

Pulse too early (long period): phase delays.

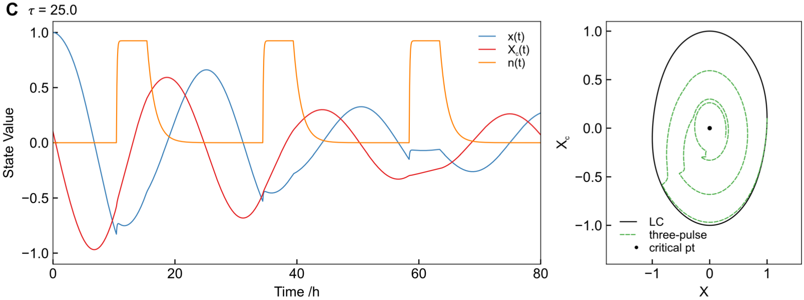
Pulse too late (short period): phase advances.

Fig: Kronauer, Forger, Jewett J Biol Rhythms 1999

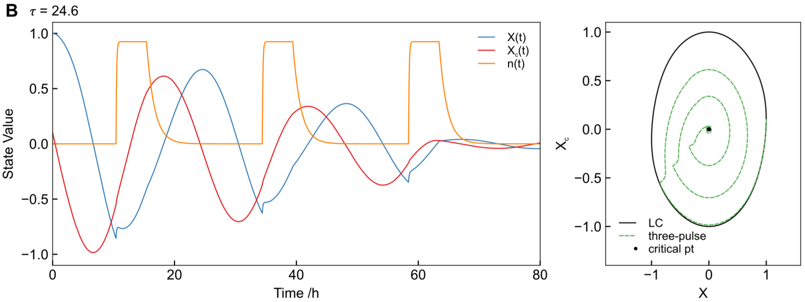
Simulation: short period (24.0h)



Simulation: long period (25.0h)



"Goldilocks" period (24.6h)



Feedback control of critical resetting

Feedback control paradigm

Use observations from the system to determine control (light) input for a range of periods.

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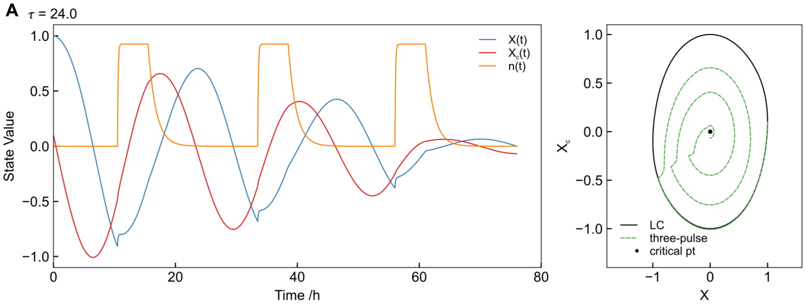
5. Repeat for three cycles.

Feedback control is predicted to allow resetting regardless of intrinsic period



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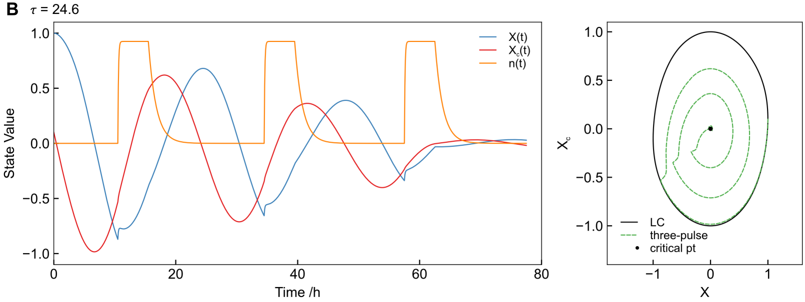

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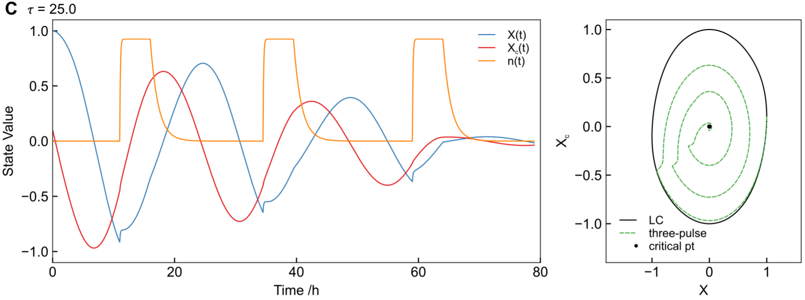

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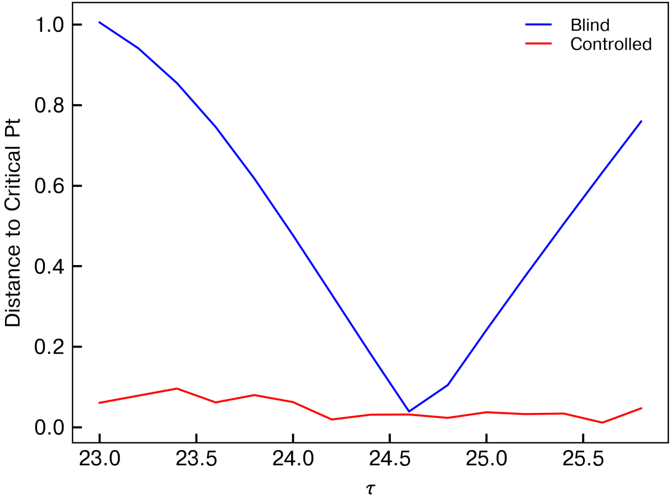

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Feedback control is necessary for precise circadian manipulation.

As such, accurate, real-time *in vivo* phase sensing is essential. (See: Lindsey Brown (T60), Yitong Huang (15 minutes!).)

Acknowledgments

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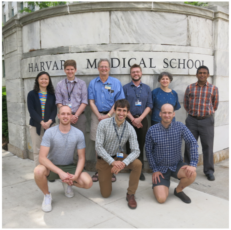

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Open questions?