Circadian Entrainment and Synchronization in Health and Disease: A Tail of Many Rhythms

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"I was close to a breakthrough when the grant money ran out."
Outline

Overarching question
Background work leads to interesting questions
A few stories
Concluding remarks
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Rhythms and health


Figure 5. Deaths (1962-71) from common heart disease (in hospital or out of hospital) in relation to sex and age group. The shaded area is to be interpreted as above and below the 95% mortality rate (1971). The horizontal line gives the values by months. The second half of each diagram repeats the first half to illustrate the pattern of seasonal variations more clearly.
Overarching question: Are the clock’s characteristics a “target”

Circadian PK/D

Target the circadian clock

Harmonious integration of internal and external rhythmic signals.


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A tail of two cities

Synthetic glucocorticoids (MPL)

Human endotoxemia (LPS)
Two different points of view

JPET, 326(3):700 (2008)
BMC Bionfo, 11:540 (2011)

Inn Imm, 20:774 (2013)
Some modeling

External signal
LPS +

Ligand-receptor interaction
R → mRNA_R

Intracellular signaling
IKK

(WKBr) → IkBa

Circadian Hormones
SCN

Cortisol signaling
FR → RFR

EPI → SNS

Epinephrine signaling

Intrinsic transcriptional responses

HRV

Cellular Level


Systemic Level

Maximum HRV depression

Strength of pro-inflammatory response

TNF (pg/ml)

IL-6 (pg/ml)

Hours from LPS


AJP Endo Met, 311:E310 (2016)
Certain mediators exhibit rhythmic patterns. Perturbing the system when the mediators exist at specific levels induces a “dose”-dependent response. Boring …
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Chronokinetics
Signaling

ADME

Toxicity

Figure 3.2. Rupatadine chronokinetics in mice (20 mg/kg IP) plasma levels according to time when the drug is injected at four different clock hours, that is, 1000h, 1600h, 2200h, and 0400h.

Cancer Causes Control, 17:611 (2006)
**Chronokinetics vs rhythm kinetics**

**Clock reprogramming**

- Reprogramming peripheral clock independently of pathology

**Toxicity**

- Comparable ultradian but different circadian
- Between strain differences
  - Female Fischer
  - Female Lewis

**Signaling**

**ADME**

**Rhythm dynamics**

**Cancer Res, 70:3351 (2010)**

**Endo, 139(10):4044 (1998)**

**Cancer Causes Control, 17:611 (2006)**
**Chronokinetics vs rhythm kinetics**

**Clock reprogramming**

**Signaling**  
*SHOCK, 41(3):214 (2014)*

**ADME**  
*PNAS, 106(50):21407 (2009)*

**Rhythm dynamics**  
*SHOCK, 41(3):214 (2014)*

**Toxicity**  
*Cancer Causes Control, 17:611 (2006)*

*Female Fischer  
Female Lewis*

Comparable ultradian  
but different circadian  
Between strain differences  
Within strain differences
Questions:

Is it only about magnitude?
What are the implications of altered patterns of rhythmic signals?
What happens if the rhythmic patterns are intentionally realigned?
If I were good at math...

An objective in this paper is thus to show that, when \( a \) is a periodic input, all solutions of system (12) converge to a (unique) limit cycle (Figure 3). The key tool in this analysis is to show that

\[
\dot{x} = a(t) - \delta x + k_1 y - k_2 (e^t - y) x
\]

\[
\dot{y} = -k_1 y + k_2 (e^t - y)
\]

The results will be valid for any mathematical model for the concentrations \( x \) of \( X \) and \( y \) of \( Y \) (the concentration of \( e \) is conserved) of the form of all needed results is given in the paper.
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Regulatory control of a rhythmic signal on a non-rhythmic target

Hypothalamic-pituitary-adrenal axis: Corticotropin-release hormone (CRH) released from the hypothalamus stimulates adrenocorticotropic hormone (ACTH) secretion in the pituitary gland provoking the production of cortisol by the adrenal gland.

- o: ACTH
- r: glucocorticoid receptor (pituitary)
- o: cortisol (adrenal)
Regulatory control of a rhythmic signal on a non-rhythmic target

\[
\frac{da}{dt} = \frac{p_1}{1 + p_2 \cdot r \cdot o} - p_3 \cdot a
\]

\[
\frac{dr}{dt} = \frac{(o \cdot r)^2}{p_4 + (o \cdot r)^2} + p_5 - p_6 \cdot r
\]

\[
\frac{do}{dt} = a(t - \tau) - o
\]

\[
D_p = \frac{o - o_{\min}}{o_{\max} - o_{\min}} \cdot A
\]

\[
D_c = \alpha \cdot D_p
\]

\[
DR = \frac{B_{\max}D_c}{K_d + D_c}
\]

\[
\frac{dDR_1}{dt} = \frac{1}{\tau_{DR}}(DR - DR_1)
\]

\[
\frac{dmRNA}{dt} = k_{prod}(1 + k_s \cdot DR_1) - k_{deg}mRNA
\]

Phys Genom, 44:121 (2012)
Rhythmic entrainment of a rhythmic target

\[
\frac{dF}{dt} = RF + k_{in,F} - k_{out,F} F
\]

\[
RF = \begin{cases} 
 k_{in,RF} & t_{F1} < \text{mod}(t, 24) < t_{F2} \\
 0 & t_{F2} < \text{mod}(t, 24) < t_{F1}
\end{cases}
\]

\[
\frac{dmRNA_R}{dt} = k_{syn,Rm} \left(1 - \frac{FR(N)}{IC_{50,Rm} + FR(N)}\right) - k_{dgr,Rm} \cdot mRNA_R
\]

\[
\frac{dR}{dt} = k_{syn,R} \cdot mRNA_R + R_f \cdot k_{re} \cdot FR(N) - k_{on} \cdot F \cdot R - k_{dgr,R} \cdot R
\]

\[
\frac{dFR}{dt} = k_{on} \cdot F \cdot R - k_T \cdot FR
\]

\[
\frac{dFR(N)}{dt} = k_T \cdot FR - k_{re} \cdot FR(N)
\]

\[
\frac{dy_1}{dt} = \frac{v_{1b} \cdot (y_3 + c)}{k_{1b} \cdot \left(1 + \left(\frac{y_3}{k_{1i}}\right)^p\right)} - k_{1d} \cdot y_1 + k_c \cdot \frac{FR(N)}{k_{ac} \cdot y_7}
\]

\[
\frac{dy_2}{dt} = k_{2b} \cdot y_1^2 - k_{2d} \cdot y_2 - k_{2l} \cdot y_2 + k_{3l} \cdot y_3
\]

\[
\frac{dy_3}{dt} = k_{2l} \cdot y_2 - k_{3l} \cdot y_3 - k_{3d} \cdot y_3
\]

\[
\frac{dy_4}{dt} = \frac{v_{4b} \cdot y_4^3}{k_{4b} + y_3} - k_{4d} \cdot y_4
\]

\[
\frac{dy_5}{dt} = k_{5b} \cdot y_4 - k_{5d} \cdot y_5 - k_{5l} \cdot y_5 + k_{6l} \cdot y_6
\]

\[
\frac{dy_6}{dt} = k_{5l} \cdot y_5 - k_{6d} \cdot y_6 - k_{6d} \cdot y_6 + k_{7a} \cdot y_7 - k_{6a} \cdot y_6
\]

\[
\frac{dy_7}{dt} = k_{6a} \cdot y_6 - k_{7a} \cdot y_7 - k_{7d} \cdot y_7
\]

"Serum shock"

Synchronization


Exploring dynamics

\[
\frac{d\text{MR}_c}{dt} = \frac{k_{\text{MR}}}{K_{\text{MR}} + \text{MR}_c} \left( 1 + \frac{k_{F_\text{MR}} + F_{\text{per}_c}}{K_{F_\text{MR}} + F_{\text{per}_c}} \right) (\text{MR}_T - \text{MR}_c^*) - \frac{k_{\text{MR.deg}} \cdot \text{MR}_c^*}{K_{\text{MR.deg}} + \text{MR}_c^*}
\]

(3)

\[
\frac{d\text{FMR}_c}{dt} = F_{\text{per}_c} \cdot \text{MR}_c - \text{FMR}_c
\]

(4)

\[
\frac{d\text{FMR}(N)_c}{dt} = \text{FMR}_c - \text{FMR}(N)_c
\]

(5)

**Glucocorticoid receptor:**

\[
\frac{d\text{GR}_c}{dt} = \frac{k_{\text{GR}}}{K_{\text{GR}} + \text{GR}_c} \left( 1 + \frac{k_{F_\text{GR}} + F_{\text{per}_c}}{K_{F_\text{GR}} + F_{\text{per}_c}} \right) (\text{GR}_T - \text{GR}_c^*) - \frac{k_{\text{GR.deg}} \cdot \text{GR}_c^*}{K_{\text{GR.deg}} + \text{GR}_c^*}
\]

(6)

\[
\frac{d\text{FGR}_c}{dt} = F_{\text{per}_c} \cdot \text{GR}_c - \text{FGR}_c
\]

(7)

\[
\frac{d\text{FGR}(N)_c}{dt} = \text{FGR}_c - \text{FGR}(N)_c
\]

(8)

\[
\frac{dmRNA_{\text{p.c}}}{dt} = k_{\text{mRNA}_{\text{p.c}}} \cdot (1 + k_{\text{p.LPSR}_{\text{max}}}) \cdot \text{LPSR}_c
\]

\[
\cdot \left( 1 + \frac{k_{F_\text{GR}} \cdot \text{FMR}(N)_c}{K_{F_\text{GR}} + \text{FMR}(N)_c} \right) \cdot (1 + k_{\text{PC.}\text{Per/Cry}} \cdot \text{mRNA}_{\text{Per/Cry}})
\]

(16)

\[
\frac{dP_c}{dt} = k_{\text{in}_P} \cdot \text{mRNA}_{P.c} - k_{\text{out}_P} \cdot P_c
\]

(17)

\[
\frac{dmRNA_{P_c}}{dt} = k_{\text{mRNA}_{P.c}} \cdot \left( 1 + \frac{k_{F_\text{MR}} \cdot \text{FMR}(N)_c}{K_{F_\text{MR}} + \text{FMR}(N)_c} \right)
\]

(18)

\[
\frac{d\text{R}_p}{dt} = k_{\text{in}_{\text{R}}_p} \cdot \text{mRNA}_{\text{R}_p} - k_{\text{out}_{\text{R}}_p} \cdot \text{R}_p
\]

(19)

\[
\frac{d\text{PR}_p}{dt} = k_{\text{d}} \cdot \text{P}_{\text{ens}} \cdot \text{R}_p - k_{\text{out}_{\text{PR}}_p} \cdot \text{PR}_p
\]

(20)

\[
\frac{d\text{P}_{\text{ens}}}{dt} = \text{mean}(P) - \text{P}_{\text{ens}}
\]

(21)

Permissive / suppressive
Rhythmic environment, rhythmic regulator, rhythmic target

\[
\begin{align*}
\frac{dCRH}{dt} &= \frac{k_{p1}}{K_{p1} + FR(N)_{HPA}} - V_{a1} \cdot \frac{CRH \cdot \left(1 + \frac{\text{light}}{1 + \text{light}}\right)}{K_{d1} + CRH} \\
\frac{dACTH}{dt} &= \frac{k_{p2} \cdot CRH}{K_{p1} + FR(N)_{HPA}} - V_{a2} \cdot \frac{ACTH}{K_{d2} + ACTH} \\
\frac{dF_{HPA}}{dt} &= k_{p3} \cdot ACTH - V_{d3} \cdot \frac{F_{HPA}}{K_{d3} + F_{HPA}} \\
\frac{dmRNA_{R,HPA}}{dt} &= k_{syn,Rm} \cdot \left(1 - \frac{FR(N)_{HPA}}{IC_{50,Rm} + FR(N)_{HPA}}\right) - k_{deg} \cdot mRNA_{R,HPA} \\
\frac{dR_{HPA}}{dt} &= k_{syn,R} \cdot mRNA_{R,HPA} + r_f \cdot k_re \cdot FR(N)_{HPA} \\
&\quad - k_{on} \cdot (F_{HPA} - 1) \cdot R_{HPA} - k_{dgr,R} \cdot R_{HPA} \\
\frac{dFR_{HPA}}{dt} &= k_{on} \cdot (F_{HPA} - 1) \cdot R_F - k_{T} \cdot FR_{HPA} \\
\frac{dFR(N)_{HPA}}{dt} &= k_{T} \cdot FR_{HPA} - k_{re} \cdot FR(N)_{HPA} \quad \text{ light } = \begin{cases} 
1, & 6AM \leq t < 6PM \\
0, & 6PM \leq t < 6AM
\end{cases}
\end{align*}
\]
Connecting the oscillators

From days to seasons

\[
\frac{d\text{CRH}}{dt} = \frac{k_{p1} \cdot \text{InCRH}}{K_{p1} + \text{FR(N)}_{\text{HPA}}} - \frac{V_{d1} \cdot \text{CRH}(1 + \frac{V_{\text{season}} \cdot \text{light}}{1 + \text{light}})}{K_{d1} + \text{CRH}}
\]

\[
\frac{d\text{ACTH}}{dt} = \frac{k_{p2} \cdot \text{CRH}}{K_{p2} + \text{FR(N)}_{\text{HPA}}} \left(1 + \frac{k_{tp} \cdot \text{P}_{\text{HPA}}}{K_{tp} + \text{ACTH}}\right) - \frac{V_{d2} \cdot \text{ACTH}}{K_{d2} + \text{ACTH}}
\]

\[
\frac{dF_{\text{HPA}}}{dt} = \frac{k_{p3} \cdot \text{ACTH}}{c_{\text{season}} \cdot K_{p3} + \text{ACTH}} \left(1 + \frac{k_{tp} \cdot \text{P}_{\text{HPA}}}{K_{tp} + \text{F}_{\text{HPA}}}\right) - \frac{V_{d3} \cdot F_{\text{HPA}}}{K_{d3} + F_{\text{HPA}}}
\]

**Physiol. Genom.,** 48:719 (2016)
From days to seasons
From an individual to a population

Weaker CRH inhibition \( (K_{p1} F > K_{p1} M) \)
Higher adrenal sensitivity \( (k_{p3} F > k_{p3} M) \)
Balance between the two inhibitory arms
Acute and chronic stress

Graph showing differences in AUC for 4h with CORT level over time for different groups. 3D graph indicating changes in parameters $k_p_1$. 

Legend: 
- Female: ♂
- Male: ♀
Adaptation and allostatic load: The price of adaptation and loss of flexibility
(non)pharmacologic entrainment of cell cycle

In our proposed model for glucocorticoid efficacy in asthma, intermittent glucocorticoid dosing simultaneously mediates antiinflammation in injured asthmatic epithelium and increases the ability of asthmatic epithelium to synchronize its mitosis. This leads to more effective regeneration of injured regions”, Am. J. Respir Cell Mol Biol, 44:863 (2011)
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Underlying hypothesis: synchronizing and entraining implications of cascades of oscillators

The discussion was primarily about
- describing design principles
- building models that predict trends