Modeling of mathematical oscillators and the limit cycle

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Examples

**Mathematical Models**
- a) Circadian pacemaker
- b) Neurobehavioral Performance and Alertness
- c) Analytic techniques

**Applications**
- a) Adjustment of circadian system prior to shuttle launch
- b) Pilot flight schedules
- c) Shift work
- d) Extended duty schedules
- e) Jet lag

**Experiments**
- a) Forced desynchrony
- b) Phase response
- c) Simulated shift-work
- d) Field studies

**Effects on:**
- Work performance
- Worker safety
- Safety of others

Use mathematical models to predict effects and to test countermeasures
Box Modeling Paradigm:
How to do modeling
Note: is similar to designing experiments

Figure 1. Box modeling paradigm (reprinted with permission from Brown and Lathardt, 1999).
Why mathematical models?

- Identify key elements of system – organize facts
- Generate hypotheses to be tested
- Predict results under different, previously untested conditions
- Test experimental protocols or ideas without having to do the experiments, which may be very costly or time consuming
Analyses as subset of Modeling

• Any analysis of a system is an implicit modeling of the system
• The choice of analysis method (e.g., linear regression) contains assumptions about the underlying process.
• The choice of analysis method, therefore, will bias the results.
Outline

1. Oscillator systems
   - Limit cycle

2. Modeling the circadian oscillator
   - Modeling of the (whole organism) circadian system requires 2-dimensional system (e.g. Phase and amplitude)

3. Modeling the circadian oscillator
   - The equations used in different in mathematical models of circadian rhythms and in performances and alertness affect the results observed (sounds obvious, but frequently ignored)

4. Use of mathematical models
   - Predicting circadian phase after interventions
   - Predicting alertness or performance after interventions
   - Explaining unexpected results
   - Designing experimental protocols
1. Behavior of dynamic systems

• A stable system does not have to have constant levels
  – stable, recurring, or other patterns
    • Unforced pendulum -> stable point
    • Self-sustained oscillator -> periodic behavior

• If periodic behavior, can predict the long-term levels (“limits”) -> limit cycle
  – Even if there is perturbation, system returns (eventually) to the limit cycle

• Warning:
  – Can have more than one stable limit cycle
  – Not all systems have limit cycles. Also possible are:
    • attractors (to a point)
    • unstable, non periodic dynamics
Example: Two-process model of sleep

- Two-process model (Borbély 1983) is most influential. (do not confuse with 2-state system)
  - Originally derived to explain circadian and homeostatic influences on sleep timing and content
  - Also applied to subjective alertness or mood and objective performance measures

- Usually subdivide homeostasis into:
  - Sleep inertia (immediately after awakening)
  - Length of time awake or asleep
• Model
  • Note variation in C
  • S rises during wake
  • S declines during sleep
  • Are asleep when S exceeds C
  -> creates oscillation

• Testable if SWA is marker of process S
  • Increased S with increased wake
  • Decreased S after nap

Borbély *Hum. Neuro.* 1992
Behavior of dynamic systems

1. Take two variables from the 2-state system and plot on a x-y plot or a polar plot
2. How do these variables move in time? What can we expect will happen?
   - Use vectors to describe the trajectories and phase portrait of the system
   - Will they have stable, recurring, or other patterns?
     • Unforced pendulum -> stable point
     • Self-sustained oscillator -> periodic behavior
Limit cycles: predator and prey (1)

Regions: A – few rabbits and few foxes
B – many rabbits and few foxes
Etc.

Time is implicit in this graph

# foxes

# rabbits
Limit cycles: predator and prey (2)

Lotka-Volterra equations

\[
\begin{align*}
\frac{dx}{dt} &= x(\alpha - \beta y) \\
\frac{dy}{dt} &= -y(\gamma - \delta x)
\end{align*}
\]

Post-perturbation, return to limit cycle
Examples of phase portraits

Abraham and Shaw, *The visual mathematics library: Dynamics. The geometry of behavior* 1985
Why is this important?

• A stable system does not have to have constant levels
• System is periodic
• Can predict the long-term levels ("limits")
2. Key components of a mathematical model of circadian rhythms

- Self-sustained oscillator (doesn’t need input to oscillate)
- Limit cycle
- Can model at molecular or whole organism level
  - Molecular: Forger-Peskin and Leloup-Goldbatter models
  - Organism:
    - Multiple models
    - 2 state system (so can have both circadian Type 0 and Type 1 resetting)
- Dynamic, not static, representation

- Need marker of the model variables
2-state system

• Hands of a watch

vs.

• Longitude and Latitude
**PRC vs. PTC**

Type 1

PRC: initial phase vs. phase shift

Type 0

PTC: initial phase vs. final phase

Note: “Break in Type 0 PRC is not present in PTC

Jewett et al., *JBR* 1994 Figure 2
Make a torus

Winfree, Timing of biological clocks 1986

Mosquito resetting curve. Colored line is old=new phase

Type 1: encloses the donut “hole” winding # = 1
Type 0: does not traverse include the donut “hole” winding # = 0
Type 0

Type 1

Type 2

Note: Type “number” refers to both slope in PTC and number of times trajectory passes through center of torus.

Type "number" refers to both slope in PTC and number of times trajectory passes through center of torus.
Type 0 and Type 1 resetting

• Type 0 resetting requires 2-state system (proof not shown)
• A 2-state system can produce either Type 0 and Type 1 resetting. But a 1-state system can NEVER have Type 0 resetting.
• Similar magnitude phase shifts observed for Type 0 and Type 1, except in critical region (0° in these plots).
• Difference is whether resetting occurs via changes in amplitude near the singular point
In a 2 state system, there must be a singularity

- Equivalent to:
  - North or south pole
  - Pencil standing straight
  - Pendulum hanging straight down

- No amplitude, ambiguous phase
- Easy to make large changes in phase
- May be stable or unstable
  - If unstable, it is difficult to reach and remain at singular point (singularity). System “defends” it.

- Required or will have problems at boundaries (e.g., date line)
- Sometimes called “fixed point” even though it is not “fixed”
Polar and x-y plots

Pure sinusoid of amplitude 2
Smoothed phase-amplitude resetting map (PARM) to 3-cycle bright light stimulus (after 1\textsuperscript{st} pulse)

After 1\textsuperscript{st} pulse at different initial phases, wide range of new phases

Note: light stimuli drive in this graph

Jewett et al., \textit{JBR} 1994 Figure 5
Smoothed phase-amplitude resetting map (PARM) to 3-cycle bright light stimulus (after pulses 2 & 3)

Note:
- results only shown for stimuli given only in critical region for 2 pulses
- decreased amplitude of system for stimuli near phase 0°
- all post-3 pulse phases are shown. Limited range of phases

Jewett et al., JBR 1994
Figure 4
Smoothed phase-amplitude resetting map (PARM) to 3-cycle bright light stimulus (3)

Note:
- limited range of final phases
- restoration of amplitude

Jewett et al., *JBR* 1994
Figure 3
Why only limited number of phases after at singularity?

- One answer - is that system moves away from stimulus. For example, if a pencil is standing on its tip, it will fall away from the direction of stimulus and therefore there will be limited area (“phase”) in which it will fall.
- Next slide shows alternate explanation, which is that have stopped the clock and are now restarting it. So initially, only limited phases are possible.
What happens at the singularity in humans? (1)

Shanahan *J. Biol. Rhythms* 1999

Jewett *Nature* 1991
What happens at the singularity in humans? (2)

Data from a CR after exposure to critical stimulus (red line) vs. normative data (dotted line).

Note loss of circadian rhythmicity in alertness but retained length-of-time-awake decay. Loss of rhythm in CBT also seen.

Jewett
Sleep Res.
1992
Example of “stopped” clock

Eclosion rhythm of flesh-fly *Sarcophaga argyrostoma*. White triangle represents time of light exposure. Each point is the median eclosion time for the culture from the end of the light exposure. Note that the duration between end of light exposure and eclosion is constant (11.5 hrs, dotted line), as if the clock is stopped and restarts when the stimulus ends. This can also be represented as shift to a different limit cycle (within the previous limit cycle) – NOT as movement to singular point. Note the slight ~24 hr oscillation around the dotted line.

Peterson and Saunders J. Theor Biol 1980 Figs 1&2c
PRC vs. PTC

Type 1       Type 0

PRC

PTC

PRC: initial phase vs. phase shift

PTC: initial phase vs. final phase

Jewett et al., *JBR* 1994 Figure 2
## Summary Table

<table>
<thead>
<tr>
<th></th>
<th>Type 1</th>
<th>Type 0</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PRC</strong></td>
<td>Crosses old=new phase (phase shift = 0) twice</td>
<td>Crosses old=new line (phase shift = 0) near 180° “Break” near 180°</td>
</tr>
<tr>
<td></td>
<td>One cross is in critical region, one near 180°</td>
<td></td>
</tr>
<tr>
<td><strong>PTC</strong></td>
<td>Overall slope of 1</td>
<td>Overall slope of 0</td>
</tr>
<tr>
<td></td>
<td>Positive slope in critical region</td>
<td>Negative slope in critical region</td>
</tr>
<tr>
<td><strong>PARM</strong></td>
<td>Encloses the singularity</td>
<td>Does not enclose the singularity</td>
</tr>
<tr>
<td><strong>Final phases</strong></td>
<td>All possible</td>
<td>Limited</td>
</tr>
<tr>
<td><strong>Winding number</strong></td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Winding #: # passes through center of torus, or # of rises through one cycle of PTC

from Jewett et al., *JBR* 1994
Simulated Type 0 and Type 1 resetting

- Light pulses were 5 hours long
- Use mathematical model to simulate phase and amplitude after 1, 2, or 3 days with 5-hours of light centered at different circadian phases are on next slide. Note amplitude is so low near 0 degrees after 2 pulses, that it is difficult to “determine phase”, so there are some “missing” points.
Strength of appropriate stimulus causes Type 0 or Type 1 resetting (PRC)

Klerman et al., AJP 1996
Drosophila eclosion rhythm

Winfree, *Timing of biological clocks* 1986
Winfree, *Timing of biological clocks* 1986

PTC with differing stimulus intensities
Note: Winding number is 0 for Type 0 and 1 for Type 1.
Summary

• Circadian system is a two-state system
  – Mammals, mosquito, *drosophila*
  – Is it two interacting physical oscillators (e.g., morning, evening) or some other physical configuration?

• Same stimulus can cause Type 0 or Type 1 resetting
  – Depends on strength of stimulus
  – Same mechanism for both
  – Differentiate only by stimuli at critical region
  – Only happens in two-state system
To be discussed

- Beersma and Daan work and Kronauer et al. rebuttal
- Key point: the structure of the model determines the outputs. Therefore, chose the structure wisely.
  - A phase only system can not produce Type 0 resetting
  - A sinusoid–based representation of the circadian pacemaker can not change shape in response to stimuli
  - A sinusoid-based analytic tool can not be fit to interventions in the data
3. Model the outputs or observable rhythms of the circadian system

Derive equations for:

• Circadian oscillator
  – Self-sustained with period approximately 24 hrs
  – Capable of entrainment
  – Has limit cycle

• Homeostatic component
  – Length of time awake or asleep
    • Includes Sleep inertia (time since awakening)
  – Long term (many days)

• Interaction of these inputs

• Outputs: circadian phase and amplitude, neurobehavioral performance, alertness, sleep
Example: Our (Kronauer-Jewett) current mathematical model

- Components:
  - Circadian system affected by light timing and intensity and by non-photic stimuli
  - Circadian, homeostatic, and sleep inertia inputs
  - Subjective alertness and neurobehavioral (cognitive) performance outputs
Differences among circadian models

• Circadian equations
  – 1- or 2-state system (pure sinusoid is 1-state)
  – Dynamic or static (pure sinusoid is static)
• Homeostatic component
  – Shape of decline (exponential, linear, etc.)
• Sleep inertia
  – Length of time sleep inertia is present
• Output of model
  – Subjective alertness
  – Objective performance – what specifically?

Similarities: Most have same input of sleep/wake times and assume light levels
Homeostatic component

Jewett J. Biol. Rhythms 1999
Recent evidence of circadian rhythm in sleep inertia duration and/or amplitude (not shown)
4. What to do with these models (1)

- Test possible explanations for results
  - Examples: observed period is 24.2 hours under Forced Desynchrony conditions. Can this be produced by intrinsic $\tau$ of 25.0 hours? And, can observed period of 24.9 hours be generated by intrinsic period of 24.3 hours?

- Test experimental conditions
  - Example: what lighting conditions and sleep-wake schedule should be used to achieve desired results of maximum differences between control and treatment groups?
Is tau \( \sim 24.2 \) or \( \sim 25 \) hours?

- Model protocols with different taus
  - Can simulate all results with \( \tau = 24.2 \) hours, even those with observed period of 25.0 hrs
  - Can not simulate all results with \( \tau = 25 \) hours.

- How can this happen?
Using mathematical simulations to explain results

How can intrinsic period of 24.3 hrs (during Forced Desynchrony) produce observed period of 24.9 hrs (during self-selected)? Via differential light exposure.

Lines = self-selected sleep episodes; circles = predicted circadian phase from model

Klerman *Am. J. Physiol.* 1999
Use model to show that:
1) Changing only the strength of an appropriate stimulus causes Type 0 or Type 1 resetting
2) Difference between Type 0 and Type 1 is observed only at some phases

Klerman Am. J. Physiol. 1996
Using mathematical simulations to plan protocols

What light level and forced period should be used to find tau?

**Intrinsic period**

- **A:** Intrinsic: 23.8 hours
- **B:** Intrinsic: 24.2 hours
- **C:** Intrinsic: 24.6 hours
- **D:** Intrinsic: 25.0 hours

**Forced (scheduled) period**

- 10 lux
- 150 lux
- 1000 lux
Use mathematical model to highlight unknown physiology (1)

Observed phase shift disproportionate to light duration when intermittent light stimulus -> add component to model

Gronfier *Am. J. Physiol.* 2004
Use mathematical model to highlight unknown physiology (2)

Observed phase shift disproportionate to light duration when intermittent light stimulus -> add component to model -> new anatomical results that relevant cells remain “on” even after stimulus ends

Hattar et al Science 2002
Use mathematical model to force re-evaluation of data and new experiments

*In vitro* data: decreased PER phosphorylation

Model prediction: tau mutation would cause increased (not decreased PER phosphorylation) as explanation for short phenotype

New experiments -> tau mutation increased phosphorylation of PER2 *in vivo*
What to do with these models (2)

• Predict results
  – What will alertness and performance be after different activity:rest and light:dark conditions?
  – What are limits of entrainment of the circadian system under different conditions (e.g., Mars day)?
  – What activity:rest and light:dark interventions would increase performance of pilots or shift-workers or astronauts
Circadian Performance Simulation Software

New version of software will be available soon at http://sleep.med.harvard.edu/people/faculty/225/Elizabeth+B+Klerman+MD+PhD
Astronaut pre-launch schedule

Triangle is launch time; thin pink lines are times of minimal alertness; Black bars are scheduled sleep; red bars are time of bright light exposure

Dean, unpublished work
Shifter demonstration
Comparing models

1. Problem
   what metric used to compare models?

2. However can:
   • Compare models to results
   OR
   • Find a condition under which two models predict very different results. Then conduct an experiment
How quick is return to a limit cycle?

Test 2 models: Forger 1999 (rapid) vs. Jewett 1998 (slower)

From P. Indic
See Indic Chronobiol. Int. 2005

-> Experiments supported the Jewett model
Compare results of 2-dimension model (Kronauer-Jewett, □) with 1-dimension model (SAFTE, ● AND Three Process △) & with experimental data (EXP, ★)

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<th>BL2</th>
<th>BL3</th>
<th>CR1</th>
<th>IN1</th>
<th>IN2</th>
<th>IN3</th>
<th>CR2</th>
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</table>

The 1-dimensional model cannot predict the large phase shift observed.

Note: IN1, IN2 and IN3 days include 5 hours of 10,000 lux light exposure

Klerman J. Biol. Rhythms 2007
Model hormone pulses

• If model using physiologic information, can use *physiologic* marker (e.g., time of Synthesis Onset and Offset) rather than curve fitting marker (e.g., DLMO or mid-point).
• Example of dynamic vs. static modeling
• Analytic method always includes implicit or explicit modeling

Solid line = with melatonin suppression included. Dashed line = without melatonin suppression

St Hilaire *J. Pineal Res.* 2007
Unsolved modeling problem: splitting

Biochronometry 1971
Other mathematical modeling gaps

• Sleep restriction: time course of buildup and of dissipation over many days
• Better equations for homeostasis that reflect underlying homeostasis
• More output measures
• Testing under field conditions, not just lab conditions
• Inter-individual differences, not group means
• Rate of risk
• Effect of different interventions: pharmacologic (caffeine and other stimulants, sleep inducing) or naps
References


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