SLEEP… ON THE TIP OF THE TONGUE?

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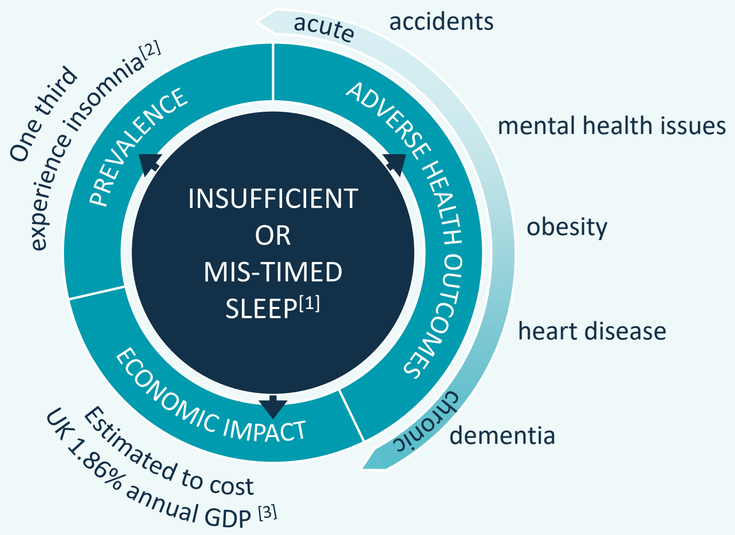
THE PROBLEM



WHAT CAN WE DO?

First, we must understand fundamental aspects of sleep timing:

1. Regulation by external and internal rhythms
2. Rhythms are observed to align very differently in different people

WHAT DO WE NEED?

We need a framework to understand the interaction, and alignment, of the internal rhythms that regulate sleep

CAN MATHS HELP?

Can a mathematical model (the two-process model)…

1. Reproduce observed differences in rhythm alignment between different people?
2. Give insight into possible mechanisms underlying differences?

CONCLUSIONS

- ✓ The fundamental 'tongue' structure of the two-process model can explain the large differences observed in internal rhythm alignment
- ✓ The model suggests that
  - a) variation in rhythm alignment is due to a number of different physiological mechanisms
  - b) the same alignment can be explained by multiple physiological mechanisms

OUTLOOK

Large differences in rhythm alignment between different people may mean a 'one-size-fits-all' treatment to improve sleep timing may be ineffective

Alongside future work to include the effect of external rhythms, the two-process model may act as a novel framework for designing personalised treatment interventions to improve sleep

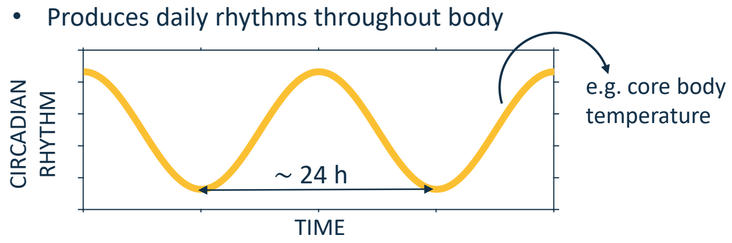
REGULATION: a combination of…

External rhythms

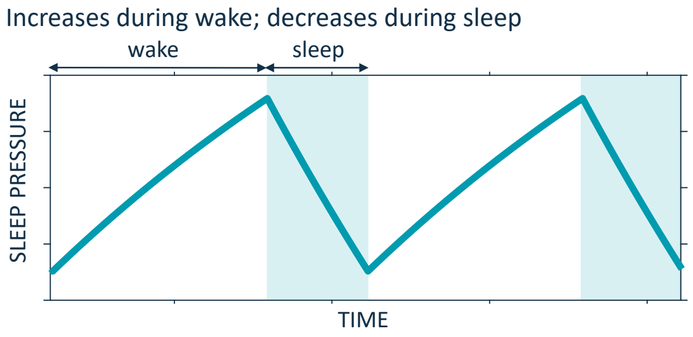
Day/night (light/dark) cycle, social life, work schedule…

Internal rhythms

'Circadian' rhythm
- Intrinsic, near-24 h body clock
- Aligns with external rhythms
- Produces daily rhythms throughout body



'Sleep pressure' rhythm
- Reflects level of sleep need across wake and sleep periods
- Increases during wake; decreases during sleep

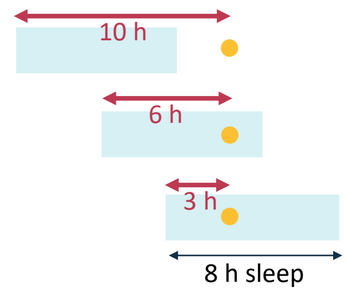


INDIVIDUAL DIFFERENCES in rhythm alignment

The rhythms that regulate sleep are timed relative to each other:

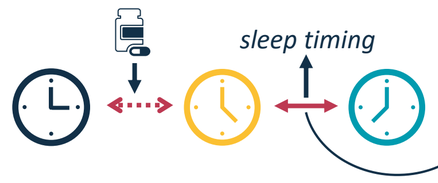
The alignment between each rhythm varies from person to person, even among healthy individuals:

The alignment between sleep onset time and the time of minimum core body temperature differs between healthy people (data adapted from [4])



IMPLICATIONS

Treatments for mis-timed sleep (e.g. melatonin supplements) target the alignment between external and circadian rhythms, but sleep timing also depends on circadian-sleep pressure alignment



Variation means that 'one-size-fits-all' treatments may be ineffective for some individuals

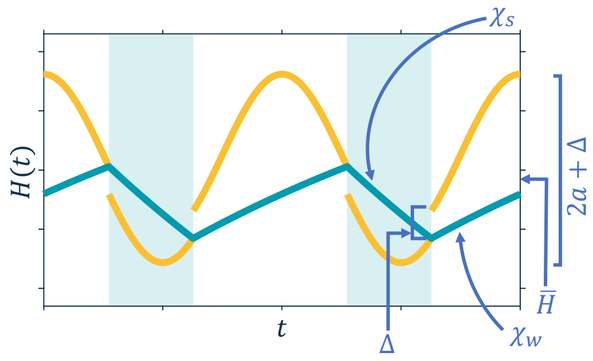
THE TWO-PROCESS MODEL[5,6]

The two-process model
- Is a phenomenological model, capturing the interaction of circadian and sleep pressure rhythms to maintain long term sleep function-related homeostasis
- Underlies other sleep models that capture neuronal activity during sleep and wake[7]

→ this means we can relate *physiological mechanisms controlling sleep* to the model parameters:

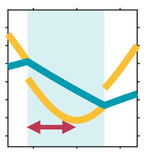
sensitivity to circadian drive → $a, \overline{H}, \Delta, \chi_w, \chi_s$ ← *rate of sleep pressure accumulation and decay*

$a, \overline{H}, \Delta$: *sensitivity to level of sleep pressure*



Parameters control model appearance

OUR WORK – *individual differences*



GOAL: Understand alignment in the two-process model
CHALLENGE: Alignment is not defined *a priori* in the model
SOLUTION: Use two strategies to study the structure of the model

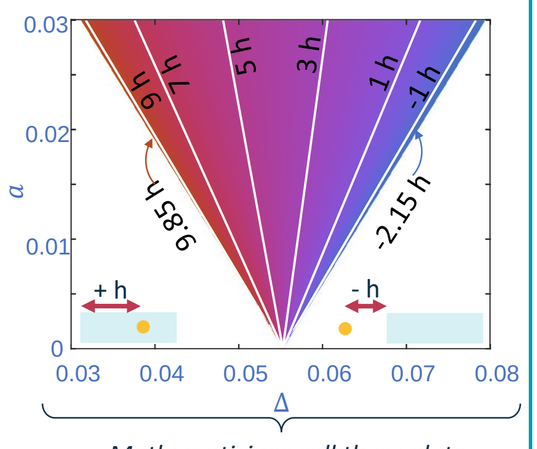
ANALYSIS

1. Make simplifying assumptions (small a)
2. Derive an equation for alignment, Φ

$$\Phi = \frac{12}{\pi}\arccos\left(\frac{f(\dots)}{a\rho}\right) - \theta$$

Replace with $\overline{H}, \Delta, \chi_w$ or χ_s

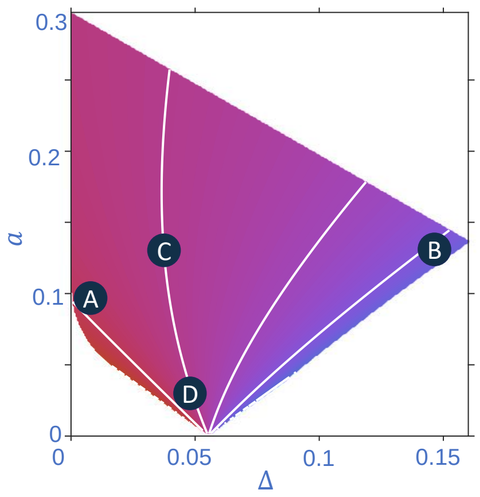
3. Draw conclusions
   - properties of the arccos function mean that alignment can vary by 12 hours
   - alignment can be varied by changing values assigned to a and any of $\overline{H}, \Delta, \chi_w$ or χ_s
4. Visualise structure as parameters (e.g. a, Δ) are changed
   - We find radiating contours of varying alignments



Mathematicians call these plots 'Arnold tongues'

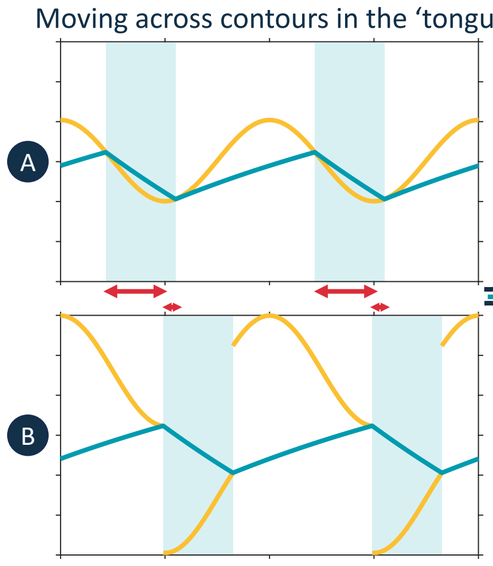
NUMERICS

1. Solve for alignment using MATLAB software
2. Visualise structure as parameters (e.g. a, Δ) are changed. We observe
   - how the 'tongue' extends for large a,
   - that the lower tip of the 'tongue' matches the prediction from Φ equation → numerical result has the same fundamental structure as analytical result



OUR WORK - *mechanisms*

Moving across contours in the 'tongue'



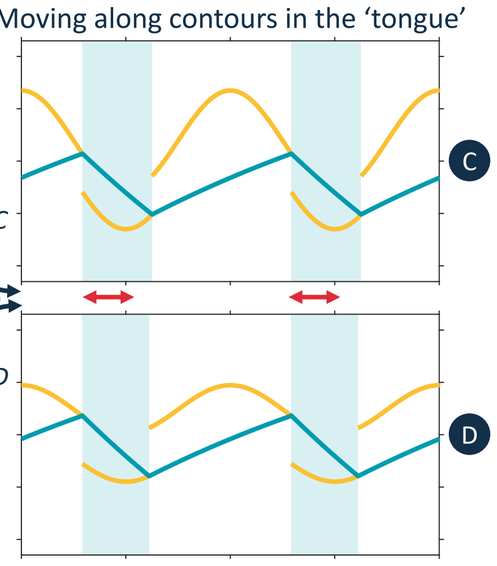
If alignments differ:
→ parameters differ
→ mechanisms differ
… different observed sleep timing requires different physiology

Mechanism A

Mechanism B

If alignments match:
→ parameters may differ
→ mechanisms may differ
… the same observed sleep timing does not require the same physiology

Moving along contours in the 'tongue'



Mechanism C

Mechanism D

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[1] Meyer, Dijk et al. 2022, *The Lancet.* [2] Bhaskar et al. 2016, *J Family Med Prim Care.* [3] Hafner et al. 2017, *RAND Health Q.* [4] Duffy, Dijk et al. 1998. *Am J Physiol.* [5] Borbély 1982, *Human Neurobiol.* [6] Daan et al. 1984, *Am J Physiol Regul*. [7] Skeldon et al. 2014, *PLoS ONE*.

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