June 7th 2012

A hidden Markov model to assess drug-induced sleep fragmentation

Page meeting, Venice

Cheikh Diack , **Oliver Ackaert**, Bart Ploeger, Piet van der Graaf, Rachel Gurrell, Magnus Ivarsson, Dave Fairman

Sleep

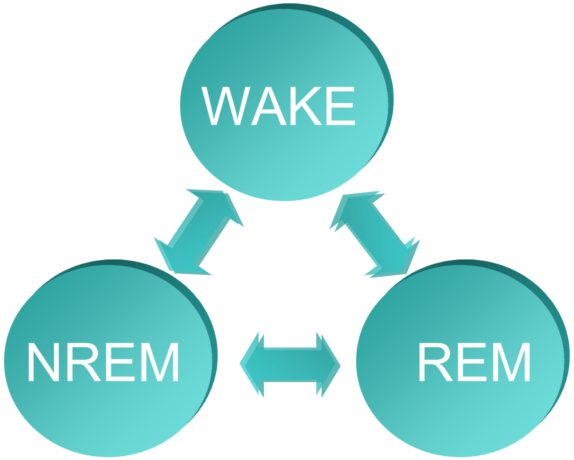
- Sleep is generally controlled by 2 opposing systems

Promotes wakefulness

↕

Promotes sleep

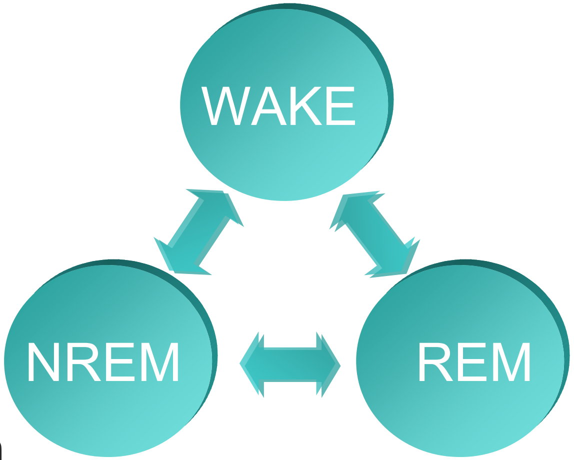
- Separated in 3 specific states



- Mammals cycle between the 3 different states
  - circadian pattern

Drug induced sleep fragmentation

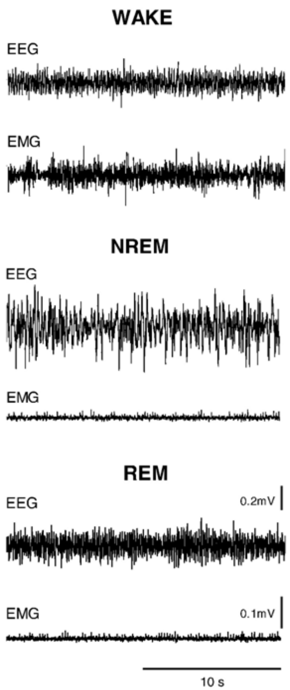
- Sleep fragmentation
  - Transitions between states increases
  - Causes sleep disturbances
    - Daytime sleepiness, insomnia, nightmares



- Drugs can induce sleep fragmentation
  - Intended pharmacological action
  - Side effect
- Characterisation of time course of transitions is important
  - understand mechanism
  - Screening of new compounds

Characterisation of sleep pattern

- 3 different vigilance states
  - Identified using electroencephalography (EEG) and electromyography (EMG) activity



Ref: [1]

- Circadian sleep pattern
  - shows frequent transitions between the 3 states
  - Likelihood of next state is function of current state

multiple correlated states

complex data analysis

[1]: Ivarsson et. al. European Journal of Pharmacology 522 (2005) 63–71

How to analyse this dense and highly correlated data?

Sleep fragmentation possess Markov property:

- present state depends on the past state
- given the present state, the future state is independent from the past state

Develop Markov model to assess sleep fragmentation

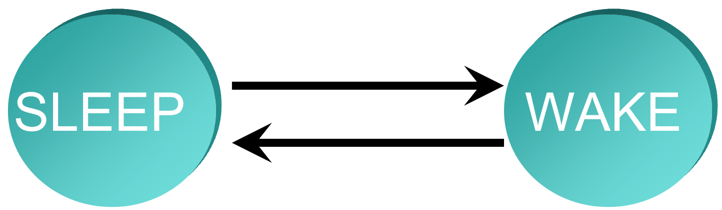
- Transition frequency, wake←→sleep
- Analyse this type of data in NONMEM
- Case study: compare drug effect on sleep
  - **methylphenidate** (powerful stimulant; Ritalin®)
  - **new chemical entity** (NCE)

Case study: dataset

- Male Sprague Dawley rats (n=6-8 per group)
- Placebo controlled cross-over design
  - Oral 3-30 mg methylphenidate
  - Oral 2-40 mg NCE
- PK determined in satellite animals
- EEG and EMG recordings for 12h after dosing
  - Sleep stage discriminator: allocate every 12 sec to state
  - 5 min epoch: residence time in each state reported

↳ data to be analyzed

Can we reduce computational burden?

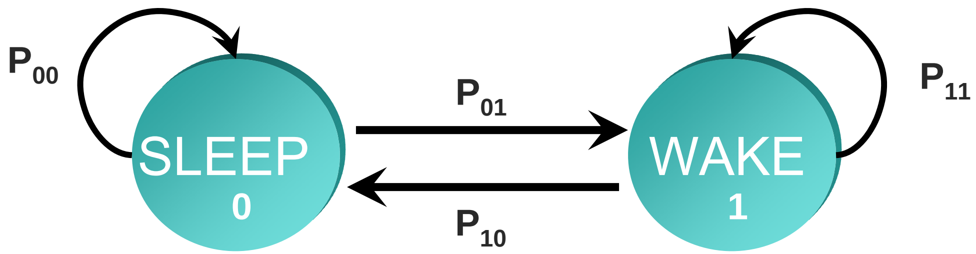


5 min epoch:
residence time in state

- Analysis can be computationally prohibitive
  - dense and continuous data
  - take into account the dependency between observations

1. 2 vigilance states were considered
2. Binarize data with 2.5 min as cut-off point
   - Length of time awake ≤ 2.5 min: animal in SLEEP state $\boxed{0}$
   - Length of time awake > 2.5 min: animal in WAKE state $\boxed{1}$

Markov model parameterisation



Parameterised by the intensities/rates of transition

u: rate of transitioning from WAKE → SLEEP ("falling asleep")

v: rate of transitioning from SLEEP → WAKE ("waking up")

Transition probabilities over time interval t:

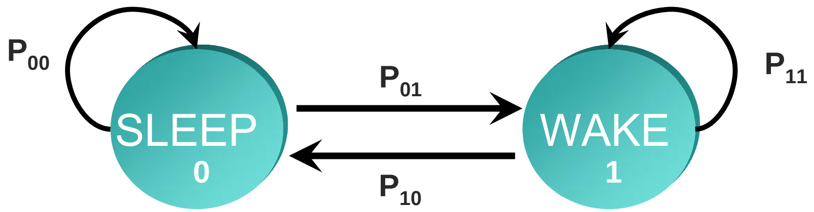
$$P_{01}(t) = \frac{v}{u+v}.(1-e^{-(u+v).t})$$

$$P_{10}(t) = \frac{u}{u+v}.(1-e^{-(u+v).t})$$

Drug effect

$$\boxed{\begin{aligned} u &= \exp(u_0 + Plac_u + Drg_u) \\ v &= \exp(v_0 + Plac_v + Drg_v) \end{aligned}}$$

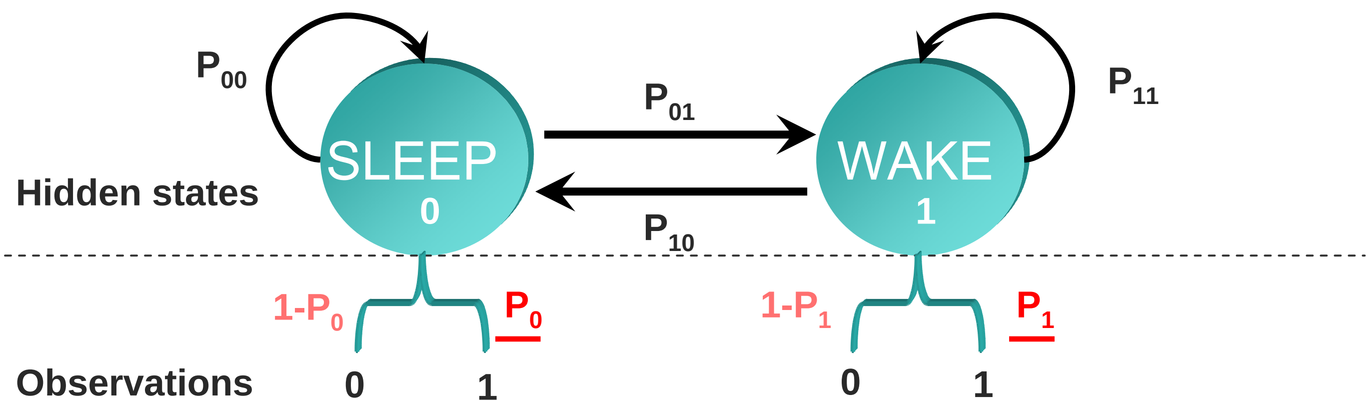
Regular Markov model towards hidden Markov model



- “Regular” Markov model
  - states can be directly observed from data (0,1)
  - “what you see is what you get”
- In our case we binarized the data by selecting a cut-off point of 2.5 min
  - Cut-off point selection → classification may be incorrect
  - observation might be set to 0 (sleep), while animal is truly awake

⇨ Hidden layer
  - The true state can not be directly observed from data (0,1)
  - We can guess in which true state the animal is → states are hidden

Hidden Markov model



Markov model transition probabilities

$$P_{01}(t) = \frac{v}{u+v}.(1-e^{-(u+v).t})$$

$$P_{10}(t) = \frac{u}{u+v}.(1-e^{-(u+v).t})$$

+

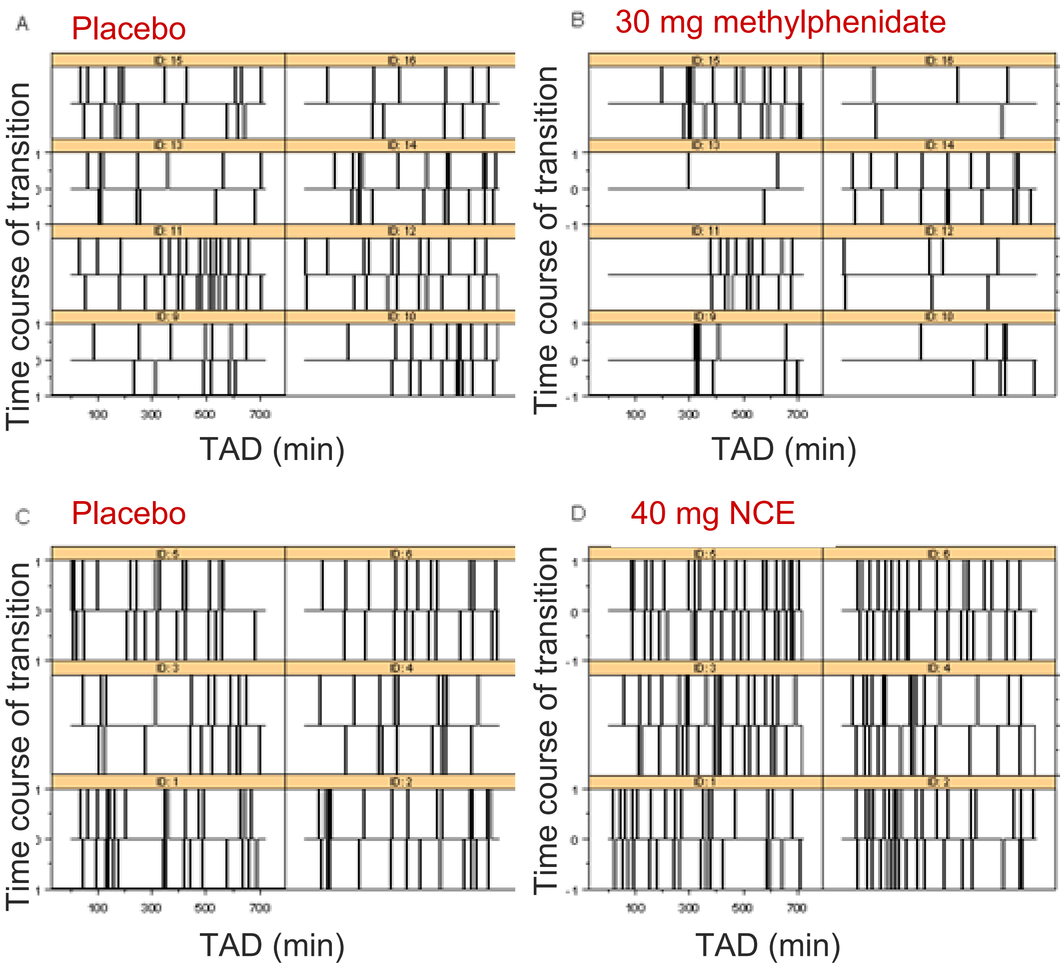
Hidden component observation probabilities

$$\underline{P_0} = \frac{1}{1+\exp(-\delta.\theta_0)} \quad \text{Type I error}$$

$$\underline{P_1} = \frac{1}{1+\exp(-\delta.\theta_1)} \quad \text{Power}$$

δ ~distance from cut-off point

Time course of transitions
sleep ←→ wake



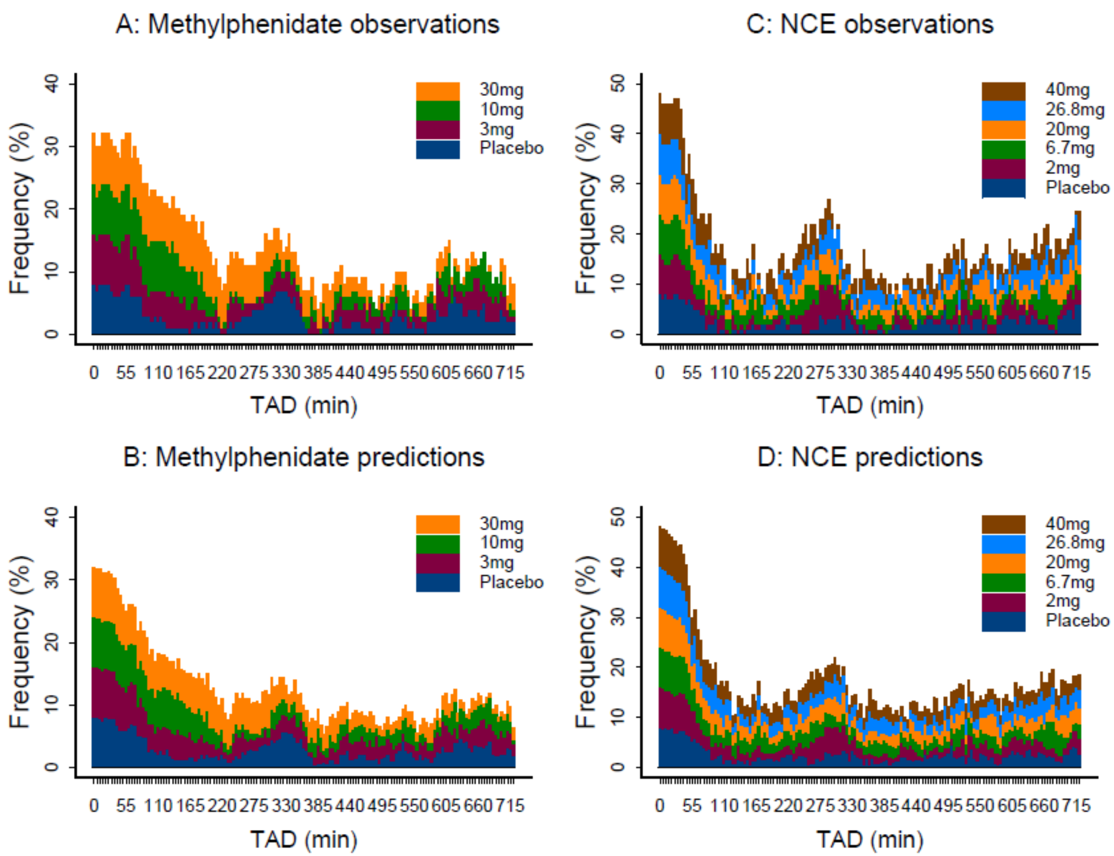
- Observed individual time course
- Spike represents transition
  - Spike up: wake → sleep
  - Spike down: sleep → wake
  - Flat line: no transition
- Different drug effect compared to placebo
  - Methylphenidate:
    less spikes → transitions ↘
  - NCE:
    more spikes → transitions ↗

Drug effect
Potency and efficacy

Transition	Compound	EC_{50} (RSE) nM	E_{max} (RSE)	$T_{eq,drug}$ (RSE) min	Type I and Power
Wake→Sleep	NCE	**12** (2)	**0.37** (0.06)	**29** (2)	$P_0 = 0.05$
	Methylphenidate	**41** (4)	**-2.59** (0.37)	**24** (5)	$P_0 = 0.04$
Sleep→Wake	NCE	**2.6** (1.0)	**0.55** (0.07)		$P_1 = 0.92$
	Methylphenidate	**288** (9)	**-0.71** (0.91)		$P_1 = 0.95$

- Drug effect on falling asleep and waking up
- Delay in drug effect on falling asleep
- Different drug effects
  - Methylphenidate : negative E_{max} →inhibition transitioning
  - NCE : positive E_{max} →stimulation transitioning
- Type I error (P_0) ≤ 0.05 and power (P_1) ≥ 0.92

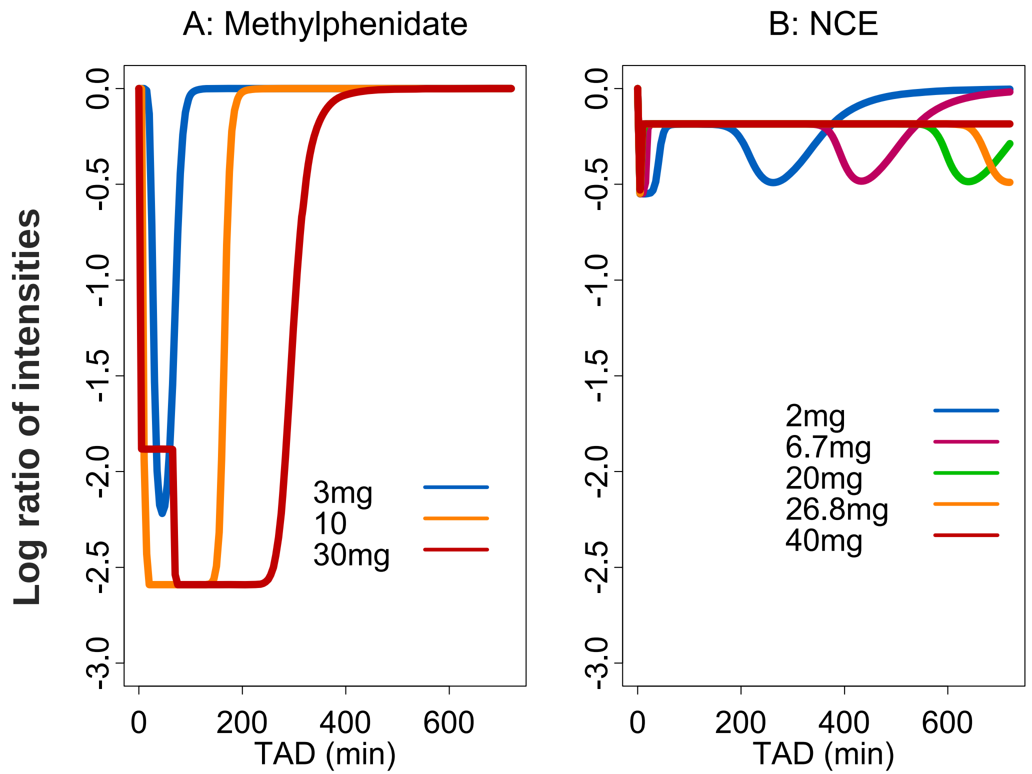
Model evaluation
Predictive check



- Frequency over time of animals in the WAKE state
- Plots are stacked

Adequate description of the sleep fragmentation

Is the drug promoting sleep or wakefulness?



Log ratio of intensities, corrected for placebo

$$\log(\frac{u}{v})_{drug} - \log(\frac{u}{v})_{placebo}$$

pos ratio: promote sleep

neg ratio: promote wakefulness

- Both drugs show negative ratio → promote wakefulness
  - Dose dependency
  - Max ratio methylphenidate (-2.6) = ± 5x max ratio NCE (-0.55)

Summary

- A 2-state hidden Markov model was developed to assess drug-induced sleep disturbance
  - Analysis of dense and correlated data in NONMEM
  - Computational less prohibitive
  - Misclassification errors were acceptable

- The complex sleep pattern was well captured
  - Quantify differences in sleep fragmentation
    - Methylphenidate: promote wake + increases residence time in a state
    - NCE: promote wake + increases transitioning
  - Provide insight underlying mechanism

→ Applied for screening NCE's early in development

Further reading

J Pharmacokinet Pharmacodyn (2011) 38:697–711
DOI 10.1007/s10928-011-9215-3

A hidden Markov model to assess drug-induced sleep fragmentation in the telemetered rat

C. Diack · O. Ackaert · B. A. Ploeger ·
P. H. van der Graaf · R. Gurrell · M. Ivarsson ·
D. Fairman

NM code is included in this paper as supplementary material!