

Simulation of Human Hypnograms Using a Markov Chain Model

Bob Kemp and Hilbert A. C. Kamphuisen

Department of Clinical Neurophysiology, Academic Hospital Leiden, Leiden, The Netherlands

Summary: A Markov chain model has been proposed as a mechanism that generates human sleep stages. A method for estimating the parameters of the model, i.e., the transition probabilities (rates) between sleep stages, has been introduced and applied to 95 hypnograms taken from 23 subjects. The rates characterize interindividual differences and nightly variations of the sleep mechanism, related to sleep-onset behavior, to the decreasing amount of slow wave sleep in the course of the night, and to the REM-NREM periodicity. The model simulates both probabilistic and the above-mentioned predictable dynamics of sleep, but only if these time-varying, individual rates are applied.
Key Words: Sleep—Models—Estimation—Simulation.

In the course of a night, human sleep seems to travel through various stages following a rather unpredictable pattern (Fig. 1). Despite the widely applied classification of sleep into a limited number of discrete stages [e.g., (1)], the precise definition and the functional significance of these stages is not clear, and other stages probably also exist (1-4). However, the classification is based upon clear electrophysiological events that occur during sleep, and many investigators have demonstrated the correlation between these stages and not only various somatic, autonomic, and biochemical sleep-related phenomena [e.g., (4)] but also pathological aspects of sleep [e.g., (3,5-8)]. Therefore, it may be useful to develop a model that can simulate hypnograms, since this may suggest a sleep mechanism, parameters to characterize sleep (9), and methods to analyze sleep [cf. this article and also (10)].

No comprehensive model of a hypnogram-generating mechanism is available, but several models describe various aspects of it. A physiological model of the REM-NREM sleep cycle mechanism in the cat (11-13) can also be used to simulate various human sleep characteristics (14). Several phenomenological models have been based upon reproducible, predictable aspects of human hypnograms. There are two categories of such models. (a) Deterministic models use time-varying functions to describe systematically occurring characteristics like the REM-NREM periodicity, the decreasing amount of slow wave sleep (stages 3 and 4) in the course of the night, and the relationship between sleep and the circadian rhythm (14-19). (b) Probabilistic models

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Address correspondence and reprint requests to ir. B. Kemp at Academisch Ziekenhuis, gebouw 20, Rijnsburgerweg 10, NL-2333AA Leiden, The Netherlands.

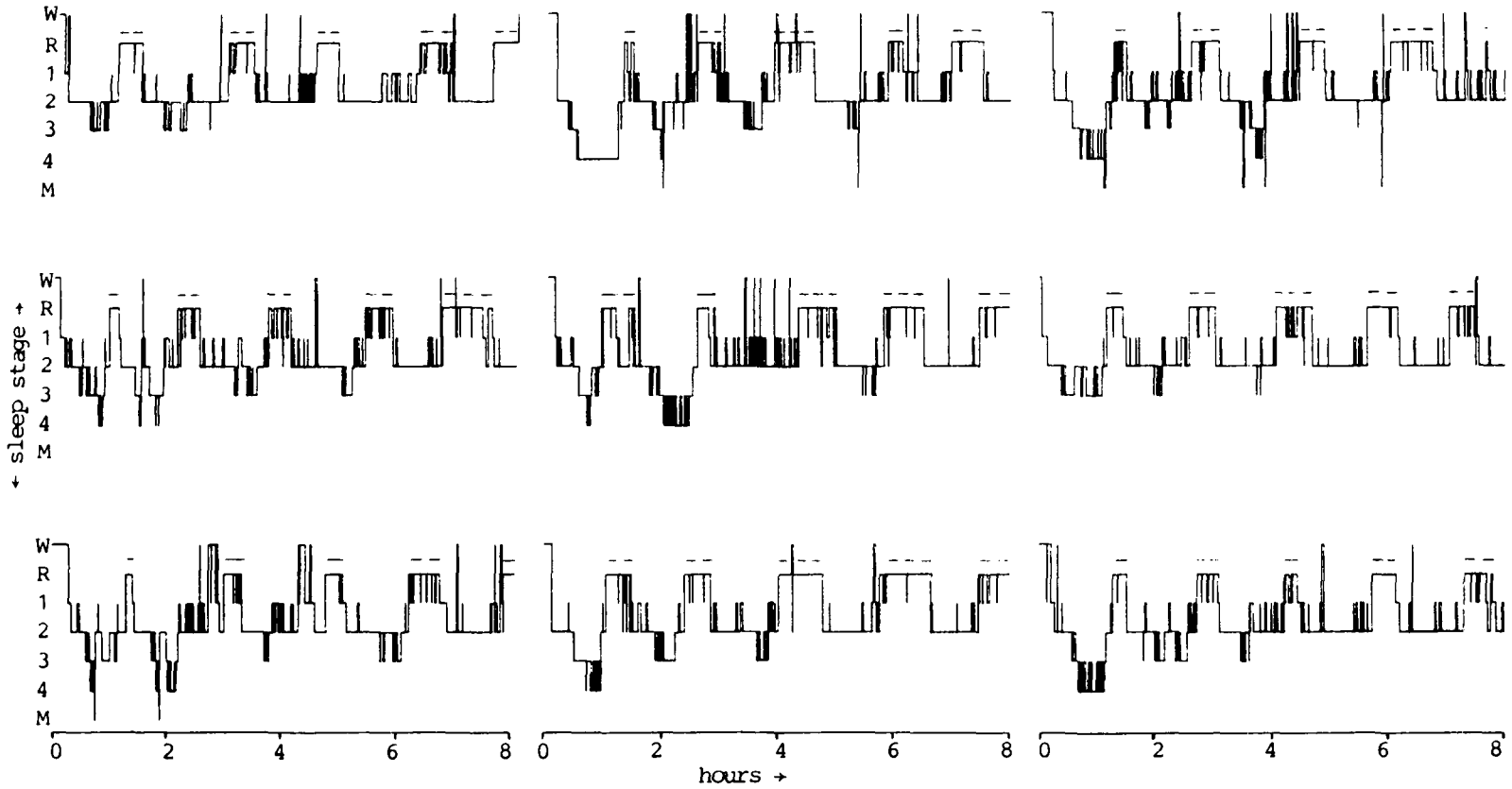


FIG. 1. Hypnograms of 9 nights of subject AD. Lights-off at 0 h. Sleep stages W, wakefulness; R, REM; 1, stage 1; 2, stage 2; 3, stage 3; 4, stage 4; and M, movement time. Note 90-min REM-NREM period and decreasing amount of stages 3 and 4 in the course of the nights. Dashes, REM "blocks."

use stochastic processes to describe statistical properties of hypnograms like the variability of the REM-NREM cycle, the short interruptions within REM "blocks" (Fig. 1), and the random (in time and in direction) transitions between stages (20-23).

Although some stochastic variation has been introduced into one of the deterministic models (19) and some time-varying functions into probabilistic models (21,23), the resulting mechanisms cannot, and were not intended to, simulate all probabilistic and deterministic aspects of hypnograms. To our knowledge, no simulated hypnograms have been reported.

In this article, we present a simple model that contains all the above-mentioned probabilistic and deterministic aspects of sleep. The model will be introduced in sufficient detail to enable, specify, and reproduce applications. We investigated its ability to characterize the nightly dynamics and the individuality of the sleep mechanism. Finally, we will show some simulated hypnograms.

MODEL

We will conform here to the standardized form of hypnograms (1), in which sleep is classified into a set of seven stages: wakefulness, REM, stage 1, stage 2, stage 3, stage 4, and movement time, abbreviated W, R, 1, 2, 3, 4, and M, respectively (Fig. 1).

Transitions between these stages occur in unpredictable directions and at unpredictable moments. However, they seem to obey a probability law in which the sojourn times (i.e., the intervals between two successive transitions, during which sleep remains in the same stage) have an approximately exponential distribution (10,21,24,25). This observation suggests that the transitions may be generated by a continuous-time Markov chain process [e.g., (26) ch. 3.3]. Such a model was proposed briefly in 1965 by Zung et al. (20). Yang and Hirsch (21) concluded that the model is inadequate because the sojourn times in a group of individuals do not fit geometric (the discrete-time analogue of continuous-time exponential) distributions. However, different individuals show different sleep characteristics [e.g., (8)], that are also reflected by the model (as set forth in this article). Because of this and because the average of different (individual) geometric distributions is not geometric, the argument in (21) does not hold. Based on this argument, a semi-Markov model has been proposed (21), in which the sojourn times may have any (nonexponential) distribution function. These are two-dimensional functions, both of the clock time and of the sojourn time. Specification of the model is therefore almost impossible, and in all applications (21,22,27,28), only mean sojourn times (a function of clock time only) were considered. Because these are implicitly specified in the Markov model (26), all results obtained by these semi-Markov parameters can also be obtained by the Markov parameters. For the same reason, the attempt to validate the semi-Markov model (21), in fact, supports the Markov model. A continuous-time model is preferred because real sleep is not segmented into epochs (e.g., of 30 s), although hypnograms generally are.

The mechanism of the continuous-time Markov model is rather simple. If sleep, $h(t)$, at time, t , is in a certain stage, i , then there is for each $j \neq i$ a probability, $p\{h(t + \Delta) = j | h(t) = i\}$, that it will be in stage j after a time interval, Δ . The Markov property implies that this probability does not depend on sleep history. Because more than one transition may occur in one interval, Δ , one usually specifies the transition rates, $a_{ji}(t)$, over infinitely small intervals (which cannot contain more than one transition):

$$a_{ji}(t) = \lim_{\Delta \rightarrow 0} \{p[h(t + \Delta) = j | h(t) = i] / \Delta\} \quad (1)$$

This means that $a_{j|i}(t) \cdot \Delta$ is the probability that sleep jumps from i to j in the small interval, Δ . These transition rates specify completely the process that simulates sleep from wakefulness to the end of the night. The average sojourn times can be derived from the rates. In the section Simulations the process will be discussed in greater detail.

Time-dependent transition rates have been applied earlier to explain and to quantify the apparent, but variable, ultradian periodicities in the sleep of cats (29) and rats (23).

ESTIMATION OF TRANSITION RATES

The parameters of the model, i.e., the transition rates, have been estimated from 95 hypnograms taken from 23 healthy male volunteers, aged 18 to 30 years, with previous experience as subjects for polygraphic sleep recordings. Records were scored by two analysts according to the Rechtschaffen and Kales criteria (see Acknowledgment).

The maximum likelihood estimator for the transition rate, $a_{j|i}(t)$, reads [(30) ch. 2.4]

$$\hat{a}_{j|i}(t, \Delta) = [n_{j|i}(t, \Delta)]/[T_i(t, \Delta)] \quad (2)$$

where $T_i(t, \Delta)$ is the total time spent in stage i , and $n_{j|i}(t, \Delta)$ is the number of transitions from stage i to stage j . Both $T_i(t, \Delta)$ and $N_{j|i}(t, \Delta)$ are counted in an interval $[(t - \Delta/2), (t + \Delta/2)]$ of duration Δ around time t . The computation of $\hat{a}_{j|i}(t, \Delta)$ from more than one hypnogram, called averaging in the sequel, is performed by counting $T_i(t, \Delta)$ and $n_{j|i}(t, \Delta)$ from all the corresponding intervals around t . In the following, the arguments (t) and (t, Δ) will be omitted for brevity. Within small (relative to the nightly variations of the sleep mechanism, e.g., the REM-NREM periodicity) intervals, Δ , the process is assumed to be homogeneous, i.e., the transition rates are constant. In that case, the estimator is unbiased, and its variance depends on T_i and $a_{j|i}$ as follows [(28), example 2.4.8]:

$$\text{var}\{\hat{a}_{j|i}\} = a_{j|i}/T_i \quad (3)$$

A 70% confidence interval for $a_{j|i}$ can be approximated by ± 1 standard deviation, i.e.:

$$- \sqrt{a_{j|i}/T_i} \leq a_{j|i} - \hat{a}_{j|i} \leq \sqrt{a_{j|i}/T_i} \quad (4)$$

This can be transformed into two quadratic inequalities in $\hat{a}_{j|i}$ and $a_{j|i}$ [(31) ch. 1.4]. Their solutions express the confidence interval as a function of $n_{j|i}$ and T_i :

$$\hat{a}_{j|i} + \left(\frac{1}{2} - \sqrt{\hat{a}_{j|i} \cdot T_i + \frac{1}{4}}\right)/T_i \leq a_{j|i} \leq \hat{a}_{j|i} + \left(\frac{1}{2} + \sqrt{\hat{a}_{j|i} \cdot T_i + \frac{1}{4}}\right)/T_i \quad (5)$$

or, equivalently

$$(n_{j|i} + \frac{1}{2} - \sqrt{n_{j|i} + \frac{1}{4}})/T_i \leq a_{j|i} \leq (n_{j|i} + \frac{1}{2} + \sqrt{n_{j|i} + \frac{1}{4}})/T_i \quad (6)$$

If $n_{j|i} = 10$, the size of this 70% confidence interval is 60% of $\hat{a}_{j|i}$. If $n_{j|i} = 100$, it is 20% of $\hat{a}_{j|i}$.

A first impression of the absolute value of the rates has been obtained by estimating average whole-night transition rates (Table 1 and Fig. 2) over an interval, Δ , spanning the first 8 h of the hypnogram and by averaging over 46 hypnograms (23 subjects, 2 nights each). Although Fig. 2 allows a rapid inspection of some important sleep characteristics, it is biased because it neglects changes of the sleep mechanism that occur in the course of the night. Therefore, we investigated the time course of the transition rates of which the whole-night estimates were based upon at least 120 transitions (i.e.,

TABLE 1. Average whole-night transition rate estimates

i \ j	W	R	1	2	3	4	M
W	—	0.000149	0.007771	0.000130	0.000000	0.000000	0.000000
R	0.000221	—	0.001409	0.000338	0.000000	0.000003	0.000003
1	0.001363	0.003211	—	0.011243	0.000000	0.000000	0.000000
2	0.000249	0.000405	0.001069	—	0.001033	0.000000	0.000021
3	0.000137	0.000026	0.000231	0.005195	—	0.003734	0.000128
4	0.000028	0.000000	0.000028	0.000198	0.005777	—	0.000156
M	0.000000	0.000000	0.013492	0.017460	0.001587	0.000000	—

Estimates, \hat{a}_{ji} in s^{-1} (i.e., average number of transitions-to-stage-j per second-in-stage-i). See Model section for definition of abbreviations.

$n_{ji} \geq 120$). The 8-h interval has been divided into 32 intervals, Δ , of 15 min, each yielding an estimate if $T_i > 0$. Averaging has been performed over the same 46 hypnograms. Highly significant ($p < 0.0001$, i.e., >20 of the 32 confidence intervals did not include the whole-night average) inhomogeneities were present in five rates. In these cases, we proposed a subjectively smoothed (by hand) time course (Fig. 3). Besides some simple trends that seem to be related to sleep-onset and slow wave sleep, Fig. 3 shows periodicities in $\hat{a}_{R|2}$, $\hat{a}_{3|2}$, and $\hat{a}_{R|1}$ that may account for the REM-NREM periodicity. Because such periodicities may be obscured by interindividual differences, we have estimated these time courses separately for the eight subjects from whom at least six (maximum 10) hypnograms were available. Only within-subject averaging has been performed over these six to 10 hypnograms. These individual estimates indeed show more pronounced periodicities, especially in subjects ND, AD, and NS (Fig. 4). The three rates seem to be synchronized, $a_{3|2}$ being opposite to $a_{R|2}$ and $a_{R|1}$. They show clear interindividual differences.

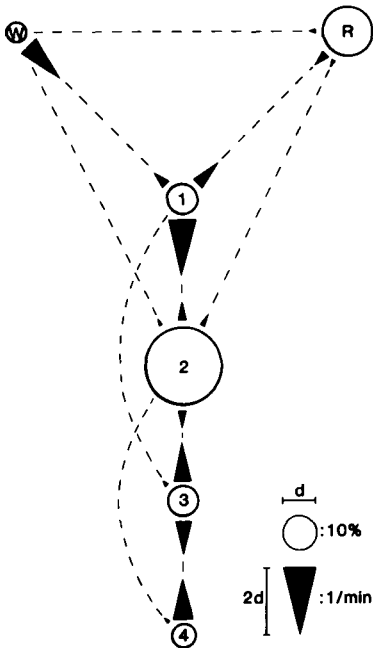


FIG. 2. Average whole-night sleep structure as estimated from 46 hypnograms of 23 subjects. Circle areas are proportional to the percentage of time spent in the corresponding stage (W, wakefulness; R, REM; 1, stage 1; 2, stage 2; 3, stage 3; 4, stage 4). Arrows indicate the directions of possible stage transitions. Arrow areas are proportional to the corresponding transition probabilities, i.e., rates (from Table 1). Calibrations (lower right) of circles and arrows have areas $\pi d^2/4$ and d^2 , which correspond to 10% and 1/min, respectively. Stage M ($<0.1\%$) and some very unlikely transition possibilities ($<1/100$ min) are too small to be reproduced. Note, for example, that in stage 1, the most likely transition is to stage 2.

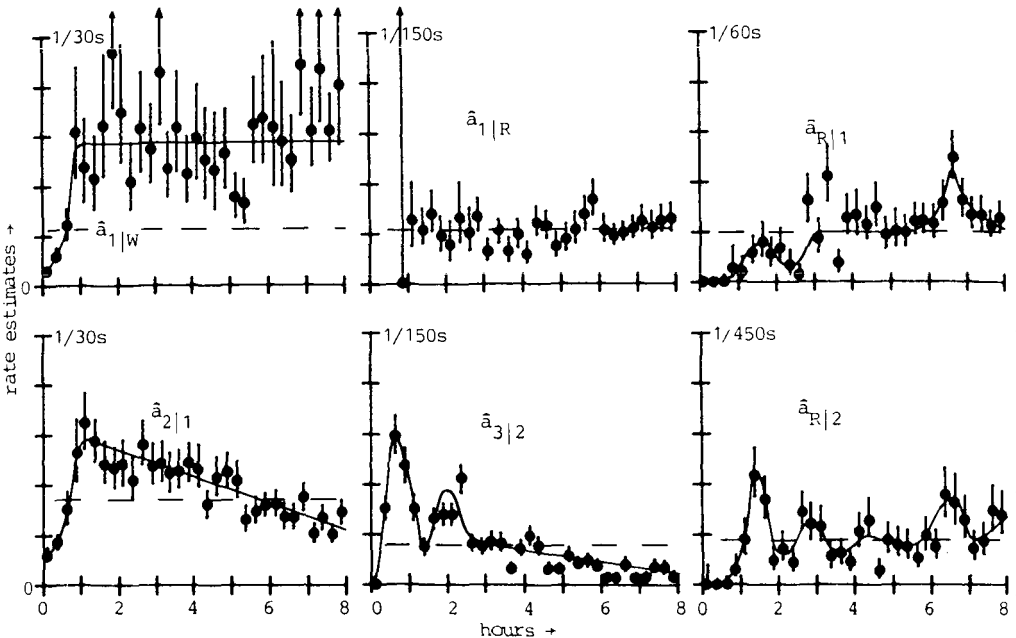


FIG. 3. Nightly variations of average (23 subjects) transition rates. Circles, estimated rate, \hat{a}_{ji} , from stage i to stage j . Vertical bars, approximate 70% confidence interval. Dashes, whole-night average of Table 1 and Fig. 2. Solid line, smoothed (by hand) time course. Note the increasing tendency to fall asleep in $\hat{a}_{1|w}$ and $\hat{a}_{2|1}$ in the first hour and the periodicities in $\hat{a}_{R|1}$, $\hat{a}_{R|2}$, and $\hat{a}_{3|2}$ in the first 3 hours. Note the decreasing tendency, $\hat{a}_{3|2}$, to reach stage 3 in the second half of the night. $\hat{a}_{1|R}$ serves as an example of a very constant rate.

SIMULATIONS

In this section we describe how to generate simulations by the model. These enable both a general qualitative impression of its performance and statistical testing of any particular aspect. Some examples are given.

When sleep resides in stage i , there are six possible transitions to the other six stages, $j \neq i$. Each transition may occur with a certain probability, as specified by the transition rates, $a_{j|i}$. This corresponds to the transitions being generated by Poisson point processes (28, ch. 2) with the same rates. As soon as one of these six Poisson processes generates a point, the corresponding transition, e.g., to stage $k \neq i$, occurs. Sleep now resides in stage k , and the process starts anew.

The simulation based on Poisson point processes runs as follows. We start at time t at stage i . Six Poisson processes (with rates $a_{j|i}$) are active, and they are simulated simultaneously as follows. A random number generator is used to obtain six independent variables, x_j , that are uniformly distributed in the interval $[0,1]$. A logarithmic transformation yields the variables, $-\ln(x_j)$, that are exponentially distributed. These would equal the six waiting times, $W_{j|i}$, for the first transitions to the six possible stages, $j \neq i$, if the Poisson processes were homogeneous with rates $a_{j|i} = 1$. The correct waiting times for our inhomogeneous processes are obtained by a transformation of the time axis. These are the times, $W_{j|i}$, for which [(28), ch. 2]:

$$\int_t^{t + W_{j|i}} a_{j|i}(\tau) d\tau = -\ln(x_j) \tag{7}$$

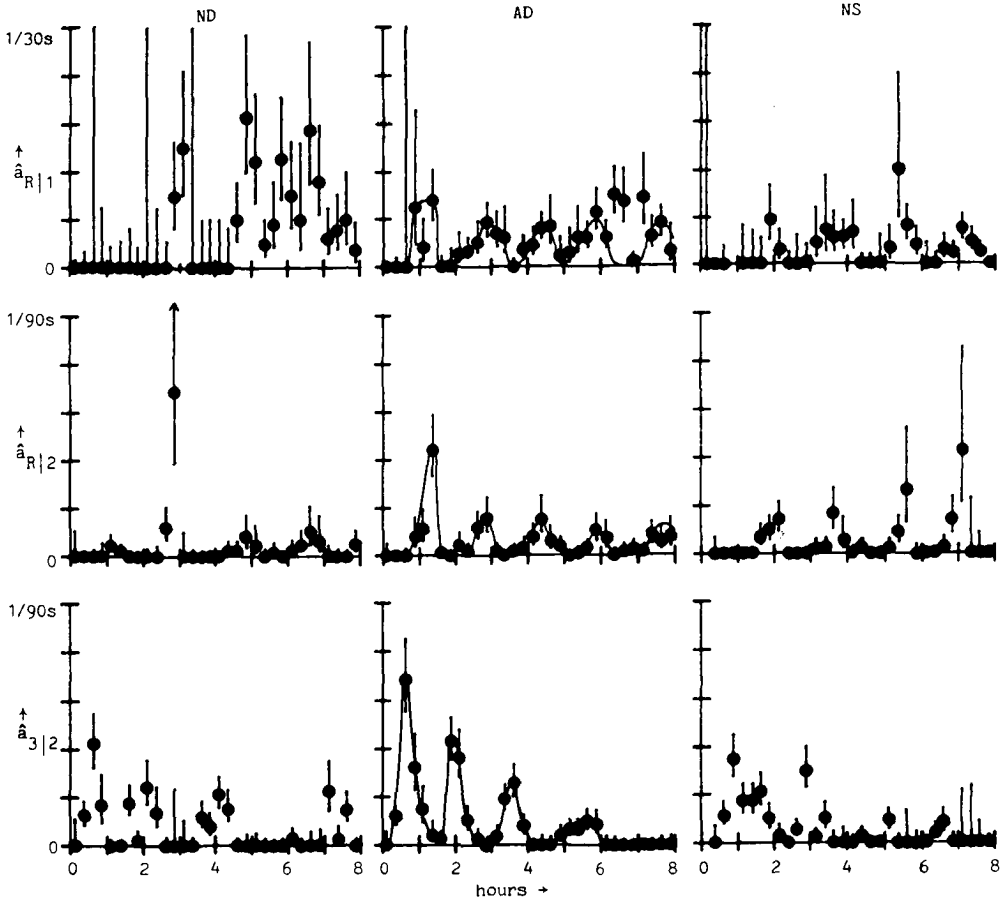


FIG. 4. Individual time courses of transition rate estimates for subjects ND, AD, and NS. Solid line, smoothed time course (by hand, AD only). Note the constant, synchronized periodicities in AD and NS with periods of ~ 93 and 101 min, respectively.

After the shortest, W_{kji} , of these six waiting times, a transition at time $t + W_{kji}$ to stage k occurs. Thereafter, the simulation of the next transition starts.

Figure 5 shows three types of simulation. The first two merely serve as a further illustration, besides Figs. 3 and 4, to the experienced hypnogram reader (others may use Fig. 1 as a reference) of the importance of time variability and individuality in the model. Simulations that neglect these (Fig. 5a and b, respectively) can be seen, even at first glance, to differ clearly from real hypnograms. Only the "individual" simulations in Fig. 5c show a nightly trend in the amount of slow wave sleep and a REM-NREM periodicity comparable with real sleep.

DISCUSSION

The proposed model suggests transition rates, a_{jij} , as parameters that characterize the sleep mechanism. The rates reflect the well-known trends and periodicities in sleep as well as some interindividual differences. Simulations resemble real hypnograms. The arguments (21) against the model have been disproved. Therefore, the Markov

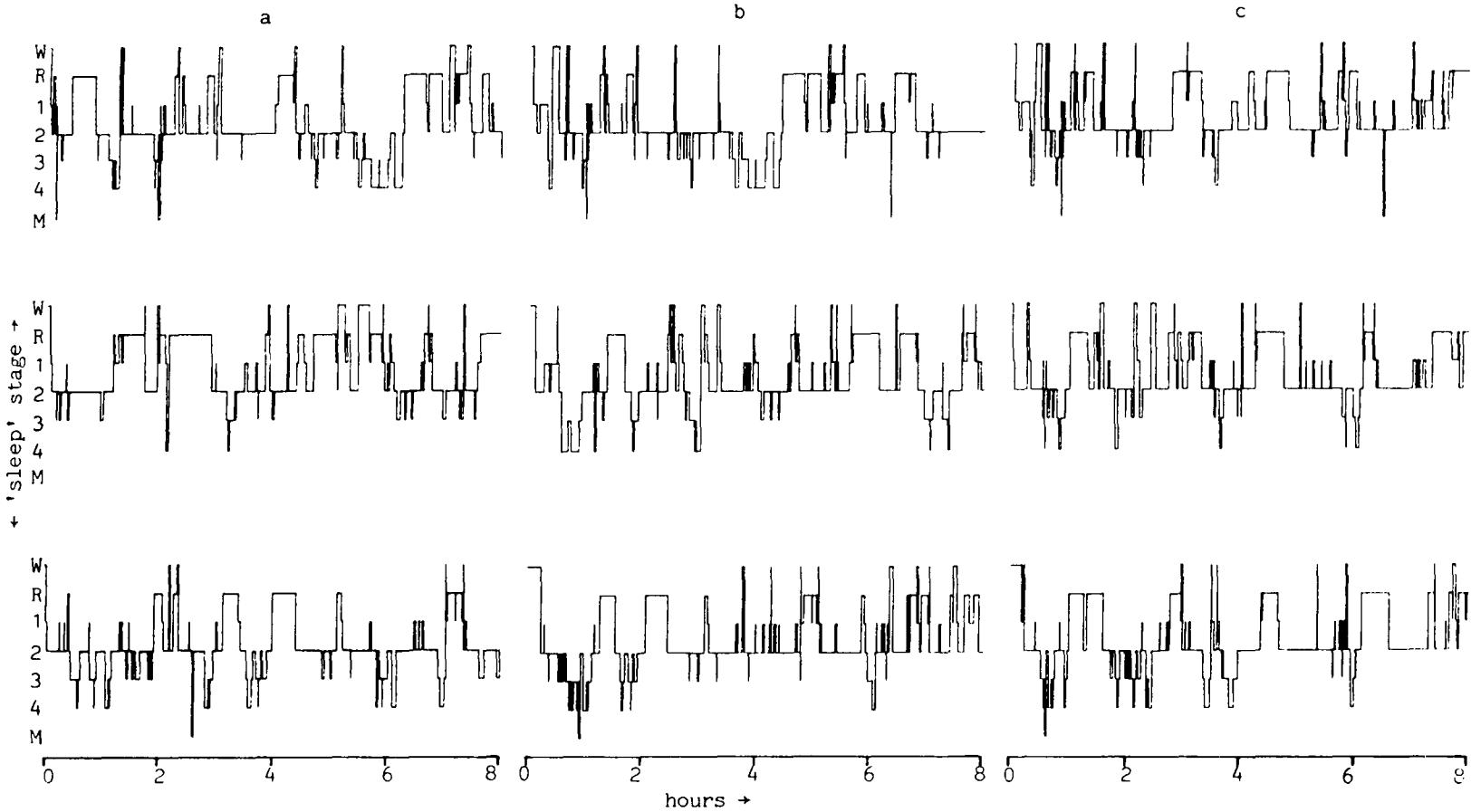


FIG. 5. Simulated hypnograms, based on (a) constant whole-group rates of Table 1; (b) as (a), but with the five smoothed time-varying whole-group rates of Fig. 3. (c) as (b), but with the three individual smoothed rates of Fig. 4, subject AD. Note the absent, weak, and comparable (to the real hypnograms of Fig. 1) REM-NREM periodicity in a, b, and c, respectively.

model deserves reconsideration, and this article provides the methods for its specification, application, and simulation.

The transition rates in our simulations can have any time course, and they are set a priori and independent of each other, thus offering a very large degree of freedom. In fact, if the estimation interval, Δ , becomes infinitely small, the model will exactly reproduce the one hypnogram to which it has been adapted. Validation of the Markov, and of any more complex, model is therefore difficult. Although it may be possible to apply statistics individually, based on many nights per subject, this would still account for only some aspects. Therefore, simulated hypnograms should also be subjected to the more comprehensive judgment of experienced sleep researchers.

The model can probably be simplified, because the rates seem to be generated by mechanisms that impose simple time courses (e.g., $a_{2|1}$, $a_{1|W}$ and $a_{3|2}$), interdependencies between rates (e.g., $a_{R|2}$, $a_{R|1}$, and $a_{3|2}$ seem to be synchronized to each other), or sleep dependencies. Such mechanisms are also suggested by the deterministic sleep models mentioned in the introduction. It is possible to combine the Markov model and some deterministic models by interpreting the deterministic models as mechanisms that generate the rates for the Markov model. The result might be a model with few parameters that still simulates most probabilistic and deterministic aspects of sleep.

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RÉSUMÉ

Un processus de Markov a été proposé comme modèle pour le mécanisme qui produit les phases de sommeil humaines. Une méthode a été introduite pour l'estimation des paramètres du modèle, i.e., les probabilités de la transition (taux) entre les phases du sommeil, et a été appliquée aux 95 hypnogrammes chez 23 sujets. Les taux caractérisent des différences interindividuelles et des variations nocturnes du mécanisme du sommeil, lié au nombre diminuant du "slow wave sleep" (vague lente de sommeil) dans le cours de la nuit, et la périodicité REM-NREM. Le modèle simule les deux, le dynamisme probable, ainsi que le dynamisme prédit sus-mentionné, mais seulement si ces taux individuels, variant en temps, sont appliqués.