Markov Analysis of Sleep Dynamics

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A new approach, based on a Markov transition matrix, is proposed to explain frequent sleep and wake transitions during sleep. The matrix is determined by analyzing hypnograms of 113 obstructive sleep apnea patients. Our approach shows that the statistics of sleep can be constructed via a single Markov process and that durations of all states have modified exponential distributions, in contrast to recent reports of a scale-free form for the wake stage and an exponential form for the sleep stage. Hypnograms of the same subjects, but treated with Continuous Positive Airway Pressure, are analyzed and compared quantitatively with the pretreatment ones, suggesting potential clinical applications.

Sleep is essential to maintain the physical condition of the body and probably to consolidate memories and learning [1]. Despite its importance, social pressure often leads to a perception that reducing sleep is advantageous. This causes widespread sleep deprivation. There is also a high prevalence of chronic sleep disorders, such as apnea, insomnia, excessive daytime sleepiness, and restless legs syndrome [2]. These sleep disorders pose public health issues with serious consequences for public safety [3]. For example, significant individual morbidity of shift workers is associated with disruptive nature of sleep, and a large number of automobile accidents are caused by drowsiness at the wheel [3]. Increased sleep disturbances and difficulty going to sleep are also important health problems, especially for the elderly [2].

Nocturnal sleep commonly shows frequent transitions between stages, such as rapid-eye-movement (REM), spontaneous awakening (wake), transitional periods from wake to sleep (S1), “stable” stage (S2), and deep sleep (S3 and S4) stages [4]. Time courses of these sleep stages (hypnograms) are commonly used to quantify sleep quality and diagnose sleep-related disorders. Some properties of hypnograms have been unveiled via statistical analysis recently [5–7]. For example, the probability distribution \( P(\tau) \) of wake durations \( \tau \) follows a power law and that of sleep (REM, S1, S2, S3, and S4) follows an exponential [5]. Although these studies of hypnograms focus on statistical properties of arousal patterns rather than underlying origins of sleep, they provide important constraints on neural-level experiments [8–12] and biophysical modeling [5,6,13–16].

In this Letter we propose a Markov approach that can simulate hypnograms [see Fig. 1(a)] and the statistics of sleep and wake transitions. In contrast to the previous reports, our approach shows that \( P(\tau) \) of all sleep and wake stages can be fitted by a modified exponential function. This result suggests that all arousal-state transitions can likely be understood in a unified framework.

To demonstrate a clinical application of our approach, we consider hypnograms of 113 subjects (54.0 \( \pm \) 11.7 yr, 16 female) diagnosed with obstructive sleep apnea (OSA) at the Center for Sleep and Chronobiology of Seoul National University Hospital. OSA is characterized by episodes of complete or partial pharyngeal obstruction during sleep that yield subsequent arousal and sleep fragmentation [17]. To obtain hypnograms, we analyze polysomnographic (PSG) signals recorded for nocturnal sleep (\( \sim 8 \) h), which include electroencephalography, electromyography, electrooculography, and electrocardiography. Each 0.5 min epoch is scored using standard criteria [4]. Since sleep stage 4 is relatively rare and very similar to stage 3, we group them together as slow-wave sleep (SS). Hypnograms are obtained twice for each subject, one without and one with Continuous Positive Airway Pressure (CPAP) treatment that is commonly used to improve sleep quality for OSA patients [18]. Hypnograms without CPAP serve as the controls, while ones with CPAP serve as the treated group. Informed consent of patients was obtained prior to PSG procedures.

Hypnograms record dynamical evolution of sleep as transitions between five stages (REM, wake, S1, S2, and SS) as in Fig. 1. To reproduce their statistics we consider a single Markov process that governs all these transitions, as follows: (i) Define \( \{x_n\} \) as a sleep stage at \( t = n \), where \( \{x_n\} = \{i\} \) \( (i = 1, \cdots, 5 \) for REM, wake, S1, S2, and SS stages, respectively) represents an orthonormal basis (i.e., \( \langle i|j\rangle = \delta_{ij} \), which is 1 for \( i = j \) and 0 otherwise) and \( n \) is a discrete time step in the unit of 0.5 min. (ii) \( \{x_{n+1}\} \) is randomly determined by the previous stage \( \{x_n\} \) with a transition probability from sleep stage \( j \) to \( i \), \( p_{ij} \) is obtained

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from statistics of clinical hypnograms (see Tables I and II; \( \sum_i p_{ij} = 1 \) because this is the total probability of exiting stage \( j \) or staying in it; whereas \( \sum_j p_{ij} \neq 1 \) in general because probabilities of all prior states must be incorporated to calculate the total flux into state \( i \)). (ii) Construct artificial hypnograms \( \{x_n\} \) for a long time (e.g., the number of epochs \( N = 1000 \) for 8 h sleep), as seen in Fig. 1(a). (iv) Repeat (i)–(iii) \( 10^5 \) times to obtain statistically reliable results. This process can be written as

\[
[x_n] = T[x_{n-1}] = T^n[x_0],
\]

(1)

where the operator \( T \) is the matrix of the \( p_{ij} \) and \( [x_0] \) is a column vector corresponding to an initial sleep stage [e.g., \( [x_0] = [2] = (0, 1, 0, 0)\) wake]. Note that this Markov process can easily be adapted to alternative rules, when and if proposed.

The probability density \( Q \) of each sleep stage is then proportional to the sum of all \( [x_n] \). We thus consider

\[
D = \lim_{N \to \infty} \frac{1}{N} \sum_{n=1}^{N} T^n.
\]

(2)

Since \( T \) can be written as \( VAV^{-1} \) [where the columns \( [v_i] \) of \( V \) are the eigenvectors of \( T \) associated with the eigenvalues \( \lambda_i \)], the operator (2) is further simplified to \( D = VRV^{-1} \), where the diagonal elements of \( R \) are

\[
r_{ii} = \lim_{N \to \infty} \frac{1}{N} \sum_{n=1}^{N} \lambda_i^n = \begin{cases} 1 & \text{for } |\lambda_i| = 1 \\ 0 & \text{for } |\lambda_i| < 1 \end{cases}.
\]

(3)

The Perron-Frobenius theorem [19] ensures \( |\lambda_i| \leq 1 \), so

\[
D = c([v_1], [v_1], [v_1], [v_1], [v_1]),
\]

(4)

where \( [v_i] \) is the eigenvector of \( T \) associated with \( \lambda_i = 1 \) and \( c \) is the normalization constant (i.e., \( 1/\sum v_{1i} \), where \( v_{1i} \) are the \( i \)th element of the vector \( [v_i] \)). The \( Q_i \) are thus obtained by applying (\( i \), the transpose of \( i \), to \( D[x_0] \));

\[
Q_i = \langle i \mid D[x_0] = cv_{i1},
\]

(5)

independent of the initial stage \( [x_0] \).

Figure 2 shows the \( Q_i \) of OSA patients with and without CPAP, and compares them with Eq. (5). Since OSA patients are often woken by disrupted breathing, the amount of stage \( S1 \) is significantly larger than with CPAP, so OSA patients often show less stage \( S2 \). We further investigate differences between the groups via a paired \( t \) test for each \( Q_i \), which shows that the probability densities of REM, S1, and S2 stages are statistically significantly different \( (p < 0.01) \), while the \( Q_i \) of the wake stage are not \( (p = 0.36) \). The figure also shows small differences in \( Q_i \) between the first and second half of nocturnal sleep periods. For example, the amount of REM increases slightly in the latter half, but this difference is not statistically significant. This indicates that the \( p_{ij} \) depend on the time of night, but we do not include this refinement in the present work because the differences are not significant.

The probability distribution \( P_\tau(\tau) \) of the duration \( \tau \) of the \( i \)th sleep stage is of interest due to recent reports of a scale-free distribution for the wake stage, in contrast to an exponential one for the sleep stage [5–7]. We thus also investigate \( P_\tau(\tau) \) averaged over 113 hypnograms of OSA patients, as seen in Fig. 3. Before \( P_\tau(\tau) \) is compared to our predictions from Eq. (1), we verify the statistical significance of \( P_\tau(\tau) \) by performing Kolmogorov-Smirnov (KS) tests for the \( P^k_\tau(\tau) \) of each subject \((k = 1, \ldots, 113)\). We find that the number of \( P^k_\tau(\tau) \) pairs showing inconsistency with the null hypothesis that the \( P^k_\tau(\tau) \) come from the same distribution (i.e., two subjects show similar sleep) at a

\[
\begin{array}{|c|c|c|c|c|}
\hline
\text{REM} & \text{Wake} & \text{S1} & \text{S2} & \text{SS} \\
\hline
\text{REM} & 0.86 \pm 0.01 & 0.04 \pm 0.05 & 0.04 \pm 0.00 & 0.01 \pm 0.00 & 0.00 \pm 0.00 \\
\text{Wake} & 0.06 \pm 0.01 & 0.55 \pm 0.02 & 0.12 \pm 0.01 & 0.06 \pm 0.01 & 0.01 \pm 0.00 \\
\text{S1} & 0.07 \pm 0.01 & 0.37 \pm 0.02 & 0.49 \pm 0.01 & 0.22 \pm 0.02 & 0.04 \pm 0.01 \\
\text{S2} & 0.01 \pm 0.00 & 0.04 \pm 0.01 & 0.35 \pm 0.01 & 0.69 \pm 0.02 & 0.56 \pm 0.03 \\
\text{SS} & 0.00 \pm 0.00 & 0.00 \pm 0.00 & 0.00 \pm 0.00 & 0.02 \pm 0.00 & 0.39 \pm 0.03 \\
\hline
\end{array}
\]

\text{TABLE I. Transition probabilities from a stage } j \text{ to } i \text{ in 0.5 min, } p_{ij} \text{ (mean } \pm \text{ root mean squared error) for OSA.}

\[
\begin{array}{|c|c|c|c|c|}
\hline
\text{REM} & \text{Wake} & \text{S1} & \text{S2} & \text{SS} \\
\hline
\text{REM} & 0.95 \pm 0.00 & 0.01 \pm 0.00 & 0.02 \pm 0.00 & 0.01 \pm 0.00 & 0.00 \pm 0.00 \\
\text{Wake} & 0.02 \pm 0.00 & 0.67 \pm 0.02 & 0.12 \pm 0.01 & 0.03 \pm 0.00 & 0.01 \pm 0.00 \\
\text{S1} & 0.02 \pm 0.00 & 0.30 \pm 0.02 & 0.55 \pm 0.01 & 0.06 \pm 0.01 & 0.00 \pm 0.00 \\
\text{S2} & 0.01 \pm 0.00 & 0.02 \pm 0.00 & 0.31 \pm 0.01 & 0.88 \pm 0.01 & 0.63 \pm 0.03 \\
\text{SS} & 0.00 \pm 0.00 & 0.00 \pm 0.00 & 0.00 \pm 0.00 & 0.02 \pm 0.00 & 0.36 \pm 0.03 \\
\hline
\end{array}
\]

\text{TABLE II. } p_{ij} \text{ in 0.5 min for OSA patients with CPAP.}
FIG. 2. Group average probability densities $Q_i$ of each sleep stage: (a) OSA patients and (b) OSA with CPAP treatment. White, gray, and black bars denote the $Q_i$ averaged over the entire, the first half, and the second half sleep periods, respectively. Open circles denote the $Q_i$ obtained from Eq. (5).

significance level of 0.05 are 28%, 11%, 46%, 59%, and 5% for REM, wake, S1, S2, and SS stages, respectively. These relatively large numbers for REM, S1, and S2, compared to previous reports of 10–23% [5,7], suggest that we may need to consider subgroups of OSA patients, based on severity. However, we do not pursue this here because our data set is limited to 113 subjects. Since OSA severity is linked to frequencies of sleep-wake transitions, especially on short time scales, we compare the $P^i_1(\tau)$ for $\tau \geq 2$ min and find that fewer pairs (21%, 3%, 9%, 17%, and 15% for REM, wake, S1, S2, and SS stages, respectively) are inconsistent with the null hypothesis. The apparently contradictory increase in the number of pairs $P^i_1$ is statistically insignificant because SS is relatively rare.

Since the diagonal term $p_{ii}$ gives the probability of remaining in stage $i$ in the next epoch, $P^i_1(\tau)$ is roughly proportional to $p_{ii}^i$, where $\tau$ is discrete time in units of 0.5 min ($-1/\log p_{ii}$ corresponds to $\tau_m$ in the previous literature [5–7]). However, as in Fig. 3, $P^i_1(\tau)$ typically shows two scaling regions with the estimate, $P^i_1(\tau) \sim p_{ii}^i$, from fitting in good agreement for $\tau < \tau'_i$, where $\tau'_i$ denotes the breakpoint where the slope of $\log P(\tau)$ changes. This result strongly indicates existence of long-range correlations that reflect partial stability of the system against transitions; we discuss these below.

From Fig. 3, we estimate $\tau'_i = 8.5, 5.0, 7.0, 10.5,$ and 2.0 min for REM, wake, S1, S2, and SS stages, respectively. The diagonal elements $p_{ii}^i$ for the long-time scale ($\tau > \tau'_i$) are also estimated from the slopes of $P^i_1(\tau)$ vs $\tau$, with $p_{ii}^i = 0.96, 0.97, 0.96, 0.94,$ and 0.94 for REM, wake, S1, S2, and SS stages, respectively. We further assume that off-diagonal elements $p_{ij}$ ($j \neq i$) change in proportion to the diagonal elements $p_{ii}$. Thus, the time-dependent transition probability $p_{ij}(\tau)$ is

$$p_{ij}(\tau) = \begin{cases} p_{ii}^i + (p_{ii}^i - p_{ii})\tau/\tau'_i & \text{for } \tau \leq \tau'_i, \\ p_{ii}^i & \text{for } \tau > \tau'_i, \end{cases}$$

(6)

$$p_{ij}(\tau) = p_{ij}[1 - p_{ii}(\tau)]/(1 - p_{ii}) \quad (i \neq j).$$

(7)

Using (6) and (7), our Markov process produces artificial hypnograms, as seen in the bottom plot of Fig. 1(a), and the $P_i(\tau)$ from simulations show good agreement with the clinical ones (see Fig. 3). Note that $P_2(\tau)$ (wake) can also be fitted with a power law (not shown here), as reported previously [5–7], but this is not necessary as we have explained all the $P_i$ in a unified way. We also studied $P_i$ for longer epochs and found that the form of the probability distribution changed for epoch lengths $\geq 5$ min, analogously to rats [6].

To find the long-range correlations of sleep stages, we calculate autocorrelation functions for each stage,

$$C(\tau) = \langle x_{n+\tau}x_n \rangle/\langle x_n^2 \rangle,$$

(8)

where the bars denote averages over $n$ (discrete time) and all subjects. When $\tau \to \infty$, the probability of finding sleep stage $i$ is $Q_i$, independent of the current sleep stage, so $C_i(\tau) \to Q_i$, as seen in Fig. 4.

We note that S2 and REM stages show strong periodic behavior, in contrast to other sleep stages (see Fig. 4). To determine the period, we fit $C_i(\tau)$ to

$$(C_i - Q_i)e^{-\tau/\tau'_i} \cos \omega_i \tau + Q'_i,$$

(9)

FIG. 3. Distribution $P(\tau)$ of the durations of sleep stages of OSA patients: (a) REM, (b) wake, (c) S2, (d) S1, and (e) SS. $P(\tau)$ from clinical data (circles, averaged over 113 subjects) are compared with those from the model (dotted lines, averaged over $10^5$ simulations). Dotted vertical lines denote $\tau'$ (see text).

FIG. 4. Autocorrelation $C(\tau)$ of each sleep stage for OSA. Here, $C(0) = 1$, but is not clearly seen due to the time scale.
with $C_i = C_i(0.5)$, and we set $\omega_j = 0$ for wake, S1, and SS stages. The estimated $Q_j$ are 0.15, 0.16, 0.28, 0.36, 0.02 for REM, wake, S1, S2, and SS stages, respectively, which show good agreement with $Q_j$ obtained from the hypnograms directly. Large $\tau_j^f = 21, 14, 7.0, 21, 11$ min (REM, wake, S1, S2, and SS stages, respectively) indicate that the sleep stages have strong correlations on long-time scales. Here, $\tau_j^f$ is roughly proportional to the modeled cutoff time scale $\tau_j^f$ (Fig. 2), and $\gamma_j = 1.0$ except for REM ($\gamma_j = 0.64$, which explains its longer durations). The period $(2\pi/\omega_j)$ is 108 min for REM and 125 min for S2, comparable with the known periodicity of REM behavior [13].

As a clinical application of our approach, we analyze hypnograms of the same subjects with CPAP treatment. To quantify sleep quality, we process the hypnograms of OSA with CPAP treatment as for previous cases. Table II shows the transition probability $p_{ij}$ of OSA patients with CPAP. Compared with untreated OSA patients (Table I), we find $p_{44}$ (S2) increases significantly by 28%. This implies that S2 becomes more stable under CPAP, yielding better quality sleep. We note that $p_{22}$ (wake) also increases by 18%. The smaller $p_{22}$ without CPAP implies that the wake stage is less stable, causing more frequent sleep-wake transitions, in accord with typical OSA symptoms. Paired t tests on each $p_{ij}$ show that OSA subjects with CPAP are statistically different from ones without CPAP ($p < 0.01$, except for $p_{55}$ where $p = 0.16$). To further verify that CPAP treatment improves sleep, we perform KS tests pairing two $P_i(\tau)$ of the same subject, with and without CPAP. We find that 70% of subjects show that $P_i(\tau)$ of S2 with CPAP is statistically different from one without CPAP. KS tests for other stages show that the number of subjects rejecting the null hypothesis (i.e., that CPAP does not affect sleep), is relatively small (46%, 12%, 29%, and 8% for REM, wake, S1, and SS stages, respectively). Since the S2 stage is the largest component of sleep, its difference is most significant.

Differences of sleep quality between OSA patients and the same subjects with CPAP treatment are often reported by comparing the $Q_j$ directly (see Fig. 2). From our statistical results, we find that the amount of S2 increases by 26% under CPAP, while that of S1 decreases by 47%. Although both measures can quantify the quality of sleep, additional features of dynamical evolution of sleep, such as the duration probabilities of each sleep stage, can be further explored via the transition matrix.

In summary, we have provided a new description for sleep statistics based on the Markov transition matrix $p_{ij}$, which is verified by statistical analysis of clinical data. Our approach shows that all $P_i$ follow a modified exponential distribution, in contrast to previous reports of different forms for wake and sleep states. This provides a strong constraint on the underlying physiology and dynamics, implying that a common mechanism can likely account for all sleep transitions. Periodic behavior of REM and S2 ($\sim 120$ min) is also seen and the effects of CPAP treatment on OSA subjects are statistically analyzed via our Markov process. We thus argue that our method can potentially be used to monitor treatment progress and to diagnose various sleep-related disorders via statistical analysis of relevant hypnograms.

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