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Ontogenesis of sleep spindles in infants

Master Thesis by

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February – July 2008

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Contents

1. Summary

In human sleep, sleep spindles are a well known EEG pattern, an attribute commonly seen in stage 2 sleep. Sleep spindles first appear 6 to 8 weeks post term or at 45 to 46 weeks of conceptional age [1], [2], [3]. After their first appearance, they mature within two weeks, their frequency stabilizes and the duration increases [4]. Different groups investigated the ontogenesis of sleep spindles [5], [6], [7], [8] and reported age related changes in spindles. However, the results were inconsistent. Maximal values for sleep spindle duration were reported to occur at the age of 1-3 months [5], 3-4 months [8], 4-6 months [6], and 9 months [7]. The duration ranged from 1.5 – 3.7 s. Maximal sleep spindle density was found at the age of 3 to 9 months [5], [6], [7]. The Frequency of sleep spindles was observed to increase with age [5], [9] whereas asynchrony decreased [5], [6] and amplitude and symmetry increased [5]. Based on these findings of age related changes in sleep spindle development, maturational processes of the neuronal system underlying sleep spindle generation in infancy can be assumed.

Sleep spindles are generated in the thalamocortical system, in the reticular thalamic nucleus, which projects to the cortex. These thalamocortical projections are GABAergic [10], [11]. The rate of neuronal growth (dendritic density and length of dendrites) was found to reach a maximum in infants at the age of 6 months, which supports the hypothesis that spindle ontogenesis represents the formation of thalamocortical networks [10]. Therefore sleep spindle ontogenesis may be used as a marker for normal or delayed neuronal maturation.

In this study, existing polysomnographic recordings of 11 healthy full-term infants of a former study [2] were analyzed for sleep spindle ontogenesis with an automatic detection algorithm. In a first step, data was band-pass filtered (10 Hz-35 Hz) for the C3A2 derivation and sleep spindles were visually detected during

the first hour of non-REM sleep at the ages of two and nine months. The results of visual detection were compared with the output of automatic sleep spindle detection to determine specificity and sensitivity of the algorithm. Automatic sleep spindle detection was found to be more reliable for nights with a clear peak in the power spectra in the frequency range of sleep spindles (10 – 16 Hz) for derivation C3A2.

For the visually detected sleep spindles, significant age dependent changes for inter-spindle intervals ($p = 0.029$) and sleep spindle density ($p = 0.018$) were found. Sleep spindle density was found to be higher in nine month old infants compared to two month old infants, showing that inter-spindle intervals were shorter with increasing age. Sleep spindle duration was reduced at the age of nine months, but did not reach significance ($p = 0.241$).

For automatic sleep spindle detection, sleep spindle duration ($p = 0.0004$) and sleep spindle amplitude ($p < 0.0001$) were found to change significantly with age. Maximum sleep spindle duration was found at two and four months of age (2.1 s), decreasing afterwards and reaching minimal values at the age of 9 months (1.3 s). Sleep spindle amplitude was found to increase with progressing age, with values ranging from 4.75 ± 1.52 µV at the age of two months to 7.49 ± 2.76 µV at the age of nine months. Sleep spindle frequency ($p = 0.77$) and inter-spindle intervals ($p = 0.62$) did not change significantly with increasing age. Values ranging from 16.2 s (9 months) to 20.2 s (6 months) for inter-spindle intervals and 11.5 Hz (9 months) and 13.1 Hz (6 months) for frequency were observed.

So far, results regarding the ontogenesis of sleep spindles are inconsistent even within this study. However, there was little consistency in detection methods of sleep spindles in the previous studies. Here, an automatic sleep spindle detection was developed and therefore whole night analysis could be done, which is a new approach for sleep spindle detection in infants.

2. Introduction

We spend one third of our life sleeping. However, the function of sleep still remains to be elucidated, even if this state of quiescence is found in most organisms of the animal kingdom investigated [12], [13]. Sleeping behavior has evolved independently in a diverse spectrum of organisms. It is a rhythmic and regulated process, regulated by a circadian clock and a homeostatic sleep pressure, which is influenced by the time spent awake [12], [14]. For example, sleep pressure increases the longer we stay awake and dissipates during subsequent sleep. Thus, sleep is assumed to fulfill a crucial function. One of the most common assumptions of the purpose of sleep is recovery. However, other hypotheses claim that its function is energy conservation, immune system support, or memory consolidation [13], [12], [14], [15], [16].

In the sleeping state sensory information has reduced access to the brain. Usually eyes are closed and no communication with the external world occurs. Nevertheless, the brain remains very active, even if conciousness is fading during sleep [17]. This spontaneous activity is strongly associated with synaptic strength, as external influences are at a minimal level [14].

A tool to measure brain activity during sleep is the electroencephalogram (EEG). For that purpose electrodes, which measure potential differences on the scalp are attached to a subject's head. These potential differences represent summated activity of post-synaptic potentials [1].

2.1 Sleep stage scoring

Typical patterns of the EEG in conjunction with the electrooculogram (EOG) and the electromyogram (EMG) serve to discriminate the different sleep stages. In general, one can differentiate Rapid Eye Movement (REM) sleep from non-Rapid Eye Movement (non-REM) sleep. The latter is further subdivided into light sleep (stages 1 and 2) and deep sleep (stages 3 and 4). In each sleep stage different EEG waves are predominant (Table 2.1) [18], [13], [19].

A sleep cycle is defined as a period of non-REM sleep followed by a period of REM sleep. In humans a sleep cycle usually lasts about 90 to 110 minutes. Neonates usually have shorter sleep cycles with a duration of about 60 minutes [2], [13].

2.2. Sleep regulation

In adults a greater amount of slow-wave activity (SWA, spectral power in the 0.75-4.5 Hz range, Fig. 2.1.) is observed during the first sleep cycles, whereas REM sleep amount increases in the course of sleep. SWA also serves as a homeostatic marker for sleep intensity and sleep pressure. Slow waves (delta waves) are predominant in stages 3 and 4. Their occurrence increases as a function of the duration of prior wakefulness and decreases during sleep [18], [13], [12], [14]. Infants have no reduction of SWA in the course of the night. In contrast to this finding, theta activity (6.5-9 Hz) showed a decreasing trend during sleep and might be a marker of sleep homeostasis in infants [2], [13], [20].

Stage		Predominant frequency	Characteristic structures
Wakefulness (eyes closed)		Alpha (8-13 Hz)	
Non-REM sleep	Stage 1	Theta (4-7Hz)	Slow (rolling) eye movements
	Stage 2	mixed frequency	Sleep spindles, K-Complexes
	Stage 3	20-50% Delta (1-4 Hz)	Sleep spindles may be present, low frequency, high amplitude waves
	Stage 4	>50% Delta (1-4 Hz)	Low frequency, high amplitude waves
REM sleep		mixed frequency	Low muscle tone (atonia), rapid eye movements, absence of sleep spindles and K-Complexes

Table 2.1. Characteristics of sleep stages in adults

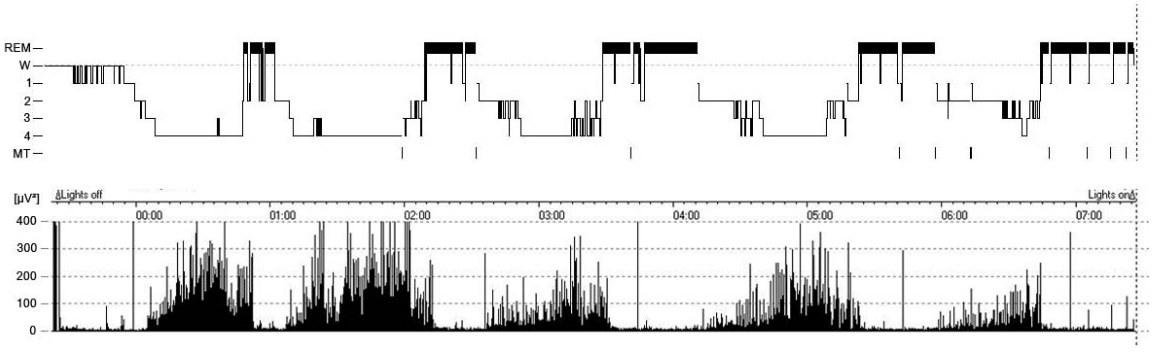


Figure 2.1. Hypnogram of a 25 year old male subject (upper panel) and the corresponding slow-wave activity (SWA; power in the 0.75 - 4.5 Hz range) (lower panel) with decreasing amounts of SWA in course of the night. A sleep cycle lasted from 90 to 110 minutes in this individual. X-Axis: Time [hours], Y-Axis: SWA in μV^2. X-axis: Abbreviations refer to W: Awake, 1 and 2: light sleep, 3 and 4: Slow wave sleep MT: Movements.

2.3. Sleep stage scoring in infants

In full term newborn infants REM sleep EEG patterns are very similar to the wake EEG. Furthermore, REM sleep in neonates is accompanied by intense movements, whereas in adults movements are reduced during REM sleep. In this early stage of development one distinguishes active sleep (corresponding to REM sleep) from quiet sleep (corresponding to non-REM sleep) with reduced eye and body movements. The term of indeterminate sleep refers to immature patterns of sleep, which occur most often at transitions between stages and are neither classifiable as active or quiet sleep (Table 2.2). In the neonates sleep, four patterns of EEG activity are observed: [21]

Low voltage irregular (LVI) pattern: Fast theta activity predominates the EEG, however, there is also SWA in the frequency range of 1-5 Hz. Amplitudes range from 14 to 35 µV in all scalp regions with little variation.
Trace alternant (TA) pattern: Consists of mixed frequency activity (duration of about 4-8 s) and bursts of high voltage slow waves (0.5-3 Hz). Bursts are occasionally superimposed by rapid low voltage waves and with sharp waves of 2-4 Hz. Usually these bursts last 3-8 s.
High voltage slow (HVS) pattern: Amplitudes are in the range of 50-150 µV whereas frequencies are between 0.5 and 4 Hz.
Mixed (M) pattern: Elements of HVS and LVI. The amplitude is usually lower than in HVS patterns.

For full term newborn infants to the age of three months, scoring the 3 different sleep stages (active, quiet and indeterminate sleep) occurs depending on the composition of the four EEG patterns (Table 2.2.) [21].

Stage / Event	Active sleep	Quiet sleep	Indeterminate sleep
EMG	Low muscle tone	Higher muscle tone	Criteria not corresponding to active and quiet sleep
EOG	REMs/ slow eye movements	No REMs	
Facial movements	Present	Not present	
Body movements	Present	Not present	
EEG patterns	LVI, M, HVS	HVS, TA, M	

Table 2.2. Characteristics of sleep stages in full term new born infants. Abbreviations (LVI, M, HVS and TA) refer to EEG patterns, which are explained in the text (page 8). (REMs = rapid eye movements)

Infants as well as newborns show different patterns in their sleep profiles compared to adults. Shortly after birth, sleep is polyphasic and circadian rhythms are barely existent. During the first year of life, daytime sleep decreases, whereas sleep during the nighttime increases and sleep finally becomes monophasic at the age of six years [2], [13]. Moreover, sleep composition varies with age. Younger subjects spend more time in REM sleep (Fig.2.2). In the first year after birth, REM sleep amounts up to 50% of sleep. Conversely, adults usually spend 20 - 25% in REM sleep. Moreover, infants have no reduction of SWA in the course of the night, the marker for sleep propensity in adults. In contrast to this finding as previously mentioned, theta activity (6.5-9 Hz) showed a decreasing trend during sleep and might be a marker of sleep homeostasis in infants [2], [13], [20].

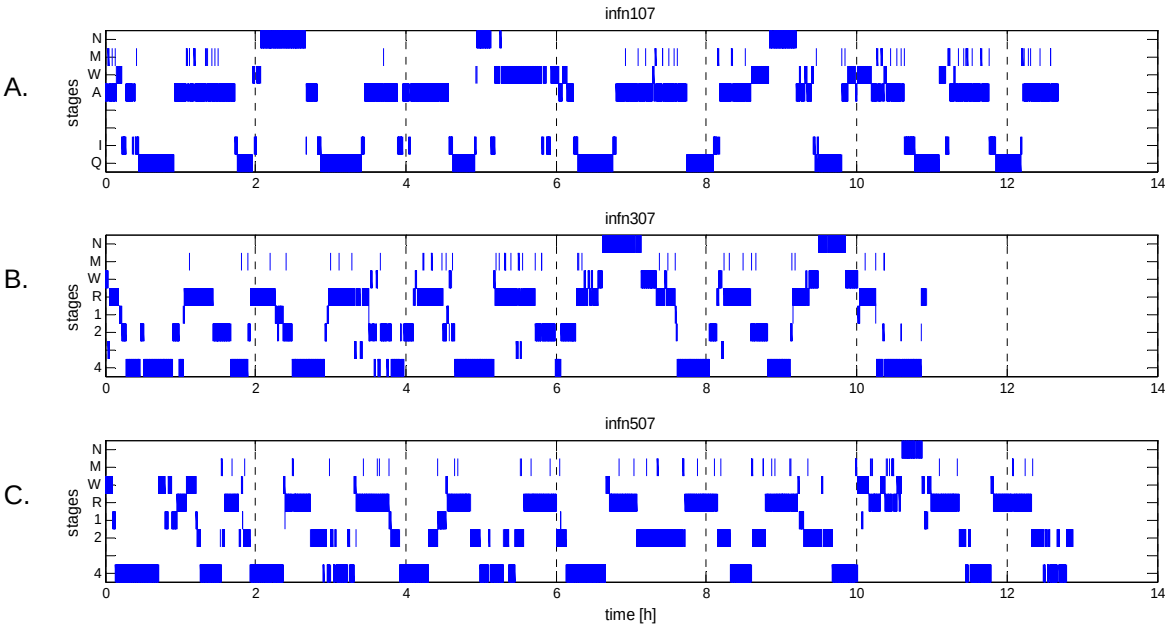


Fig. 2.2. Hypnograms of a healthy boy (Inf 07) A. at 2 weeks of age. B. at 4 months and C. at the age of 9 months. Sleep is polyphasic (not shown) and REM sleep accounts for approximately 50% of the night. X-axis: Time in hours, Y-axis: Abbreviations refer to N: Not scored, M: Movements, W: Awake, A: Active sleep, I: Indeterminate sleep, Q: Quiet sleep, R: REM sleep, 1 and 2: light sleep, 4: Slow wave sleep

Like the hypnograms, EEG patterns and sleep cycles of infants, sleep spindles, which are a marker for light sleep and a particular attribute of stage 2, also show age related changes in the EEG recordings [1], [2], [22]. According to these findings it can be concluded that infant's sleep is different compared to adults and sleep and sleep spindles in infants probably reflect different or additional functions. In the following part of this thesis the ontogenesis of sleep spindles in infants during development will be discussed.

2.4. Sleep spindles

2.4.1 Definition of sleep spindles

Sleep spindles, also known as sigma rhythm, are defined as oscillations in the frequency range of 12-14 Hz, with a duration of at least 0.5 s and with 7-8 waves within this period [19].

Gibbs and Gibbs [23] noted the frequency range of 12-14 Hz as too narrow and extended the defining frequency band to 10-16 Hz. In a recent approach, Schabus et al. [24] determined two different types of sleep spindles during adult slow wave sleep. Slow (11-13 Hz) and fast (13-15 Hz) spindle activity was distinguished and different scalp topography was found. Sleep spindles are usually most prominent at central derivations [25], [26], [27]. Thus, the strongest spindle signal may be measured with electrodes placed at C3 and C4 positions according to the 10-20 System [28]. Historically, the first description of sleep spindles refers to Loomis et al. [29], who defined the waves with an amplitude of 20-40 µV. Sleep spindles are generally a characteristic of non-REM sleep stage 2 [1].

2.4.2. Premature spindles

The first appearance of spindle-like activity is found mainly at ages 28 to 35 weeks past conception in the unborn child. These spindle-like bursts are known as ‘spindles of prematurity’ [30] or also as ‘brushes’ [31]. These comb-like trains are commonly associated with large 0.75-1.5 Hz waves and are found at a frequency around 16 Hz [1] or in the frequency range of 8-20 Hz. However, they are not comparable to sleep spindles in adults [30], [32]. The amplitudes range from 20 to 200 µV [32]. They are observed in all stages of the sleep - wake cycle with little

increase of brush activity during sleep. Oscillations disappear gradually with increasing age [32] and in full term newborns, brushes are no longer seen [30], [33]. The function of these premature spindles is not known.

2.4.3. Sleep spindles during development

Sleep spindles first appear between 6 to 8 weeks post term or at 45 to 46 weeks of conceptional age [1], [2], [3]. When they first appear they are weak and infrequent and not more than 3 or 4 per hour of slow wave sleep [30]. After their first appearance, they mature within two weeks, their frequency stabilizes and their duration increases [4]. Waveform and duration of sleep spindles in infants differ from those in adults: The spindles may be 2 to 4 s in duration and lack the typical fusiform amplitude modulation. The individual spindle may be sharply peaked in the surface-negative phase [1] followed by a rounded positive component [33]. These spindles of infancy and early childhood usually disappear between 18 and 24 months of age [33]. These specific features during development may indicate a different functional role of spindles in infant and adult sleep.

Sleep spindles arise in infants with their usual frequency of 12 to 14 Hz and are centered over the midline (Fz-Cz region, 10-20 System [28]), spreading to the neighbouring left or right central regions (C3 or C4) [1].

In a longitudinal study regarding sleep spindles in infants at age of 1.5 to 6 months, Louis et al. [5] reported an increased density and duration of sleep spindles with maximal values occuring at the age of 3 months. Afterwards they observed a downward trend to decreased sleep spindle density and shorter spindle duration. In their study, sleep spindles were visually detected in five consecutive minutes during non-consecutive stages 2 and delta sleep over 2 hour periods. The 5 min were selected from the middle of the stages in the most stable phases. Louis et al. [5] also reported an increased duration of sleep spindles

and higher frequencies at the beginning of the night at the age of 4.5 months. This suggests a process, which regulates the production and organization of slow wave sleep in infants. The percentage of spindles with higher frequencies increased in the course of the development, whereas asynchrony of sleep spindles decreased. Asynchrony refers to the time point of sleep spindle occurance. Amplitude and symmetry of sleep spindles increased with progressing age. Symmetry means that sleep spindle incidence has no predominance in one hemisphere.

In another study of sleep spindle ontogenesis [6] the maximal number of sleep spindles was found at 4-6 months of age (1 spindle/ 10 s). After 6 months, sleep spindle density decreased and reached a minimum at 27 months. Thereafter, the number of spindles remained constant up to 54 months and then rose again in older subjects. For spindle duration maximal values were also found at 4-6 months. At this age, duration ranged from 1.5 to 1.8 s. At the age of 25 months, the duration decreased to 0.5-0.6 s. Interhemispheric synchrony between spindles increased with age. As sleep spindles are considered as gate keepers for external stimuli, subjects were exposed to single and paired clicks throughout the night. However, no effect of this auditory stimulation could be shown. Sleep spindles were measured during whole night stage 2 sleep which occurred within 20 min preceding or following the first three REM sleep periods of the night. The set up was chosen to exclude influences of sleep cycles on spindle activity.

In the study of Scholle et al. [7], frontal sleep spindles of 120 subjects from 3 months to 16 years were visually determined. For that purpose, 10 min of non-REM sleep was analyzed at 2 a.m. Consistent with the findings of Tanguay et al. [6], their results divided spindle maturation in three distinct phases: up to 0.8 years long spindles (1.5 s) with a low density (<3/ min) and a short inter-spindle interval (20 s) were found. Afterwards spindles showed a decrease in duration (0.8 s) and an increase in the interspindle interval (111 s), with a lower spindle density (0.3-1.2/ min) up to 3 years. Thereafter, spindles were characterized by short

interspindle intervals (5-10 s), a high spindle density (4-10/ min), and long lasting spindles (0.9-1.5 s).

Lenard et al. [8] also reported age related changes in spindle ontogenesis in the first two years of life. Maximal values for spindle duration were found at the age of 3-4 months (1.8-3.4 s), decreasing afterwards to a minimal value of 0.5-0.7 s at the age of 2 years. The interspindle interval was found to increase from 9-11 s in the first half year of life to 19-28 s in the fourth half year of life.

An increase of the frequency of spindles in frontal and centroparietal spindles during puberty was found by Shinomiya et al. [9]. Thirty-two subjects were investigated in the age range from 4 to 24 years. Spectral power of frontal spindles showed an exponential decrease with increasing age, stabilizing at 13 years. This observation could not be made for centroparietal spindles. (For an overview see table 2.3.)

Another study of Metcalf et al. [34] supported the view that neurophysiological plasticity is influenced by ‘experience’ reflected in spindle ontogenesis. In this study, sleep spindle development of premature and full-term infants of the same conceptual age were compared and an earlier maturation of sleep spindles in premature infants was found. In a later study Metcalf et al. [4] could support these results of faster spindle maturation in premature infants. These findings suppose a faster maturation of the spindle generating system when exposed to an extra uterine environment.

Authors	Max. sleep spindle density	Max. sleep spindle duration	Min. sleep spindle density	Additional findings	Age of investigated subjects
Tanguay et al (1975)	4 - 6 months	4-6 months (1.5 - 1.8 s)	27 months Interspindle interval: (0.5 - 0.6 s)	Higher synchrony with progressing age	4 - 68 months
Louis et al (1992)	3 months	1.5-3 months (2.3 - 3.7 s)		Effect of beginning versus end of night at age of 4.5 months: increased duration and frequency at beginning of night. Higher amplitude and symmetry with progressing age. Percentage of fast spindle frequencies increasing, percentage of slow spindle frequencies decreasing with age	1.5 - 6 months
Scholle et al (2007)	0.8 years	0.8 years (1.5 s)	3 years (0.3 - 1.2 spindles/min)	After age of 3 years: short interspindle intervals and long duration	3 months - 16 years
Lenard et al (1970)		3-4 months (1.8 - 3.4 s)			2 months - 2 years

Table 2.3. Ontogenetic aspects of sleep spindles in early age. Age with maximal respective minimal values of sleep spindle variable with values found at these ages in brackets. Synchrony refers to the time point of sleep spindle occurrence whereas symmetry describes occurrence in brain hemispheres.

Based on these findings of sleep spindle development, a maturation of the system that produces sleep spindles in infants could be assumed. Therefore sleep spindle ontogenesis may be used as a marker for normal or delayed neuronal maturation.

In line with this hypothesis, Schultz et al. [35] reported a delayed development or decrease in incidence of sigma rhythm in hypothyroid cretin infants compared to healthy controls. After thyroid therapy all infants showed an increase of sigma rhythm. This delay in the bioelectric and neurophysiological development and the possible relationship to severity of retardation suggests that in some cases there is a continued deficit of neurological function.

Gross and Schulte [36] reported an increased spindle activity in infants with Phenylketonuria (Mongolism) compared to age-matched healthy controls. Phenylketonuria is a genetic disorder and leads, when untreated, to progressive mental retardation. Spindles were longer in duration and spindle incidence was significantly higher in infants with Phenylketonuria. Even if there was no sign of mental retardation, an increased spindle activity could be detected.

Shibagaki et al. [37] also reported abormal developmental changes in sleep spindle activtiy. They observed a decreased level of sleep spindle activity up to the age of 18 months, followed by increased sleep spindle activity at the age of 19 – 40 months in mentally retarded infants when compared to healthy controls.

2.4.4. Thalamocortical networks

The thalamus is the major gateway for relaying sensory information from the external world to the cortex. It is involved in auditory, somatic, visceral, gustatory and visual information processing. Therefore, it is the first station at which incoming signals can be modulated during sleep [38].

In 1985, Steriade et al. [10] studied the function of the reticular thalamic nucleus by lesions with kainic acid injections and found absence of sleep spindles on the ipsilateral side of reticular nucleus deprived thalamocortical neurons. In contrast, they found normal spindling rhythmicity in contralateral EEG leads. These findings suggest reticular thalamic neurons for the role as pacemakers for sleep spindles and for gate keepers of sensory information between the thalamus and cerebral cortex.

Reticular cells receive their input from collaterals of layer VI coritcothalamic cells and thalamic neurons that project to the cortex. These cells are exclusively inhibitory and project back to the thalamus [38]. Therefore they inhibit thalamocortical cells by their GABAergic projections and thus generate rhythmic inhibitory postsynaptic potentials (IPSP). IPSPs result in removal of inactivation of the low-threshold Ca^{2+} current in thalamocortical cells, and are followed by rebound spikes and associated bursts of action potentials. These bursts are then transferred to the cortex, where they induce excitatory postsynaptic potentials (EPSP) in cortical pyramidal cells, recognized in the EEG as spindle waves [10], [11], [38].

2.4.5. Sleep spindles as marker for neuronal maturation

The observed ontogenetic changes in sleep spindles and their thalamocortical network are in line with the results of Schadé and Meeter et al. [39]. In their study, they showed no increase in numbers of dendrites with age. However, growth and branching of dendrites and axons reached a maximum at the age of 6 months. Therefore it can be concluded that no mitosis but an alteration of the network occurs during this time of development. Steriade et al. [10] showed that thalamocortical structures and myelination show developmental changes. This was investigated by light microscopic measurements in Golgi-Cox stained tissues. The rate of neuronal growth (dendritic density and length of dendrites)

reached a maximum in newborn humans at the age of 6 months. Based on these results, one can assume that spindle maturation represents the formation of thalamocortical networks.

3.4.6. The role of sleep spindles

Sleep spindles were proposed to play an active role in inducing and maintaining sleep [33]. In line with the hypothesis of a sleep protecting function of sleep spindles, Cajochen et al. [22] found changes in spindle frequency in the course of the night. They proposed that circadian regulation in frequency could account for awakenings in elderly persons during early morning hours, compared to younger subjects.

Furthermore, it was proposed that sleep spindles are involved in long-term synaptic changes [38]. During spindle activity, Ca^{2+} enters in cells repeatedly and therefore provides conditions similar to the repeated tetanus used to induce long-term synaptic changes in slices. These synaptic changes are frequency sensitive. Supporting this hypothesis, Fuentealba and Steriade [40] also proposed memory consolidation as a hypothetical function of sleep spindles. As thalamocortical neurons are inhibited during spindle activity and disrupt the passing of sensory information from the thalamus to the cortex, this disconnection of the brain from the external world could underlie consolidation of memory traces acquired during the state of waking. Additonally, Steriade et al. [41] supposed that sleep spindles play a crucial role in synaptic plasticity of cortical and thalamic neurons.

Spindle-like patterns were also described in comatose patients [1], [33] (‘spindle coma’) and frontal spindling that is almost continuous can also result from drug intake [1]. These spindles have an unremitting character and lack reactivity to intense stimuli. Changed sleep spindle patterns were observed in patients after

barbiturate anesthesia relative to unmedicated conditions. They appear with a frequency of 15-25 Hz and must be distinguished from normal sleep spindles [33].

2.5. Aim of the project

Emergence of spindle activity is considered as an electrophysiological measurement of brain maturation and is thought to reflect developmental changes in thalamocortical structures, myelination and growth of dendrites [20]. The period of life in which an organism is maximally susceptible to lasting structural and functional changes is the one with fastest neuronal growth. The younger the individual, the faster is the neuronal growth and thus the more critical is the age factor. Therefore, spindle evolution during development could be used as a marker for normal or delayed neuronal maturation [30].

According to the hypothesis that sleep spindles play an active role in maintaining sleep, sleep instability could also be observed by abnormal spindle patterns. Additionally, a computational strategy to detect spindles could serve as a diagnostic tool for possible mental retardation in infants.

In this project sleep spindles in the first year of development were investigated to detect age related patterns of sleep spindle variables. For that purpose, infants recorded from two weeks to nine months were investigated with respect to sleep spindle evolution. Sleep spindle duration, inter-spindle interval, amplitude and frequency of spindles were analyzed. An algorithm for automatic sleep spindle detection was applied and compared with visually detected sleep spindles.

3. Methods

3.1. Subjects

Existing data from 11 healthy infants (5 boys and 6 girls) of a previously published study of Jenni and coworkers [2] were analyzed. Infant's birth weight ranged from 2.890 to 4.230 g (mean ± SE 3.724 ±138g). Length at birth varied from 48 to 56 cm (52.55 ± 0.69 cm) and gestational age from 38 to 42 weeks (40.0 ± 0.38 wk), whereas head circumference ranged from 34 to 37.5 cm (35.25 ± 0.44cm). All infants experienced a normal childbirth, were breastfed up to 2 (n=1) or 6 (n=10) months after birth and no infant had postnatal complications.

3.2. Polysomnographic recordings

Data were acquired at the age of 2 weeks, as well as 2, 4, 6 and 9 months after birth. EEG, EMG, EOG, electrocardiogram (ECG) and respiratory movements were recorded by a portable polygraphic amplifier system. (PS1, Institute of Pharmacology and Toxicology). The high-pass filter was set at 0.16 Hz (-3 dB), and the low-pass filter at 70 Hz (-3 dB), with a damping of at least -28 dB at 256 Hz. Data was sampled with 512 Hz, digitally filtered (EEG and EOG: low-pass filter at 30 Hz; EMG: band-pass filter between 20 and 50 Hz), and stored on a hard disc with a resolution of 128 Hz. Recordings were carried out at the infant's home in their habitual sleep environment with their usual bedtime routines. The

infants were unattended during the night. The electrode attachment took place before each recording session, between 18:00 and 21:00 h.

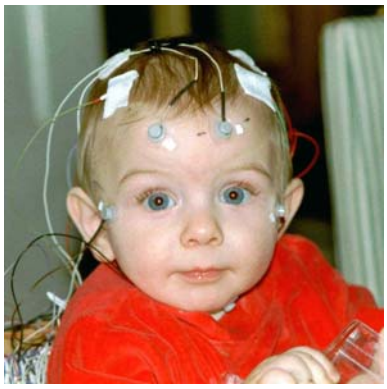


Fig. 3.1. Infant with attached gold electrodes on the scalp. Electrodes were applied with electrode paste. In the face self adhesive silver sliver-electrodes for EMG and EOG recording were used

Electrodes were placed according to the International 10-20 System, along the antero-posterior axis over both hemispheres [28] (Bipolar derivations: F3C3, F4C4, C3P3, C4P4, P3O1, P4O2; referential derivation: C3A2). For EEG recordings gold electrodes were attached with Grass EC-2 electrode paste (Grass Instrument Division, West Warwick, RI), whereas for EMG and ECG recordings self adhesive silver silver-chloride electrodes were used (Fig. 3.1.). The electrodes were secured with a tubular elastic net bandage.

3.3. Scoring of sleep stages

Scoring of sleep stages at the age of 2 weeks and 2 months was carried out according to Anders and coworkers [21], whereas subsequent recordings were scored according to Guillemiault and Soquet [42]. Sleep was visually scored for derivation C3A2 in 20-s epochs [2].

3.4. Sleep spindle detection

3.4.1. Visual sleep spindle detection

The aquired data were converted to European Data Fromat (EDF) for visual scoring of spindles. In a first step, data were filtered with a high-pass (10Hz) and a low-pass filter (35 Hz) in the Analysis Manager sofware environment (Analysis Manager 8.0, Embla Systems Inc., Rembrandt) for the C3A2 derivation (Fig. 3.2.). Thereafter, sleep spindles were visually detected and marked in the filtered signal during approximately the first hour of non-REM sleep for the nights recorded at two and nine months of age. Time analyzed was determined by the first hour of non-REM sleep plus the adjacent epochs until the next sleep stage change. Sleep spindles were defined as oscillations in the frequency range of 10 to 16 Hz for at least 0.5 s of duration. As baseline levels in EEG-signals in different nights ranged from 10-40 μV, the threshold for spindle amplitude had to be adjusted for each recording. Nights with high baseline signals (>30μV) and artefacts were excluded. Inter-spindle intervals were defined as the time interval from the start of one spindle to the beginning of

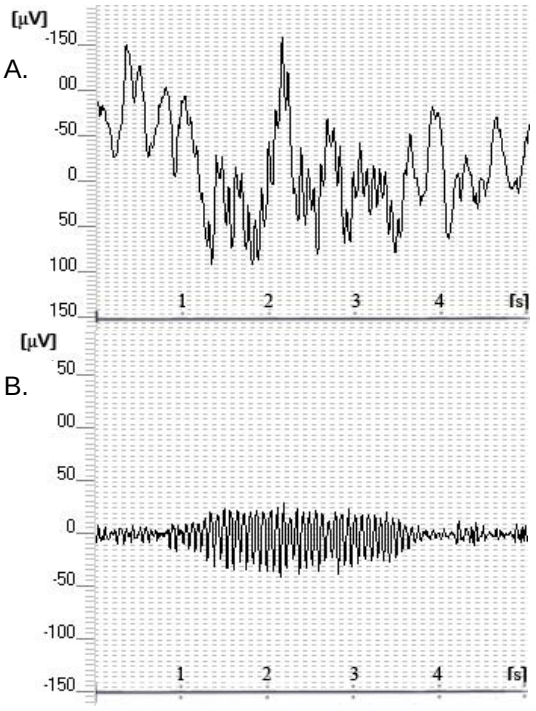


Fig.3.2. A. Sleep spindle in original EEG signal, superimposed on slow wave activity. B. Same sleep spindle filtered with high-pass filter at 10.0 Hz and low-pass filter at 35.0 Hz in Analysis Manager Software. Subject was a nine month old girl (Inf 16). X-axis: time [s], y-axis: Amplitude [μV]

the next spindle. Spindle activity separated for longer than 0.5 s was considered as two distinct spindles [19], [25].

Sleep spindle length and inter-spindle intervals of the first hour of non-REM sleep were exported as event traces into a text file for further processing.

3.4.2. Automatic sleep spindle detection

Besides visual scoring, an algorithm was developed which automatically detected sleep spindles in the band-pass filtered EEG signal. To evaluate the algorithm, the output of the first hour of non-REM sleep was compared to the output of the automatic detection. This method was chosen to determine specifity and sensitivity of the automatic sleep spindle detection. Epochs with artefacts were excluded. After evaluation of the algorithm, automatic sleep spindle detection was performed for the whole night recordings. Criteria for sleep spindles were the same as in visual detection. Namely, the signal had to be in the frequency range of 10 to 16 Hz for at least 0.5 s of duration. The threshold for the amplitude was adjusted for every night by measuring the standard deviation of data points from all stages in the filtered signal. Criteria for sleep spindle detection was 2x the standard deviation. Sleep spindle activity separated for longer than 0.5 s, was considered as two distinct spindles [19], [25]. Inter-spindle intervals were defined from the start point of one spindle to the beginning of the next spindle. As variables, spindle frequency, spindle duration, inter-spindle interval, maximal and mean spindle amplitude were investigated. On the basis of the time spent in non-REM sleep and the number of sleep spindles per night, sleep spindle density was calculated. For all subjects, the evolution of every variable for all available nights were plotted. As inter-spindle intervals in non-REM stages could be interrupted by REM sleep stages, intervals longer than 98 s were excluded from the analysis. The term of 98 s was determined by plotting the distribution of inter-spindle intervals, which revealed that values above bin 64 (>98 s) should be excluded (Fig. 4.10.). Distribution of sleep spindle parameters (inter-spindle intervals

corrected for intervals >98 s, frequency, duration, mean, and max amplitude) were plotted as well as hypnogramms reflecting the sleep spindle distribution across the night.

3.5. Statistics

3.5.1. Visual sleep spindle detection

Mean sleep spindle duration, mean inter-spindle interval and mean sleep spindle density from approximately the first hour of non-REM sleep were calculated and plotted for infants at the age of 2 and 9 months. Time analyzed was determined by the first hour of non-REM sleep plus the adjacent epochs until the next sleep stage change. Inter-spindle intervals were corrected for REM episodes between non-REM stages (exclusion criterion: > 98 s). A two-tailed paired t-test was performed for infants in which nights at both ages were available (n=6). Nights with high baseline signal and artefacts were excluded, as sleep spindles were hardly detectable. Therefore sample size was reduced to 6 infants with longitudinal data.

Infants with night 2 and 5 available	Number of visually detected spindles		Minutes of analyzed non-REM sleep	
	N 1	N 5	N 1	N 5
Inf 05	278	350	80.6	86.0
Inf 08	38	79	70.3	62.0
Inf 10	38	200	64.6	63.6
Inf 11	120	298	73.3	74.6
Inf 14	263	337	65.3	76.0
Inf 16	71	278	76	71.3

Table 3.1. Subjects analyzed in visual sleep spindle detection with both nights available for analysis. Number of detected spindles in respective nights and analyzed time spent in non-REM sleep in min. N2: 2 months and N5: 9 months of age.

3.5.2. Automatic sleep spindle detection

Statistical analysis was performed by means of linear mixed models (SAS 8.02; SAS Institute Inc., Cary, NC, USA) using a random intercept model presuming an identical intraclass correlation for all subjects. For every output (duration, inter-spindle interval, frequency, mean and maximal amplitude) a separate one-way mixed model analysis of variance (ANOVA) was calculated with the factor *Age* (0.5, 2, 4, 6 and 9 months). *Age* was modeled as a classed variable. Significance was reached when $p < 0.05$. Inter-spindle intervals > 98 s were excluded to correct intervals for interruptions of REM sleep episodes. It is known from the literature that first appearance of sleep spindles is at the age of 6 to 8 weeks. In our study, 2 (vp 09) to 269 (vp 11) sleep spindles were found for nights recorded at the age of two weeks and detected sleep spindles were not obviously mature sleep spindles. Thus, the first night was not included in the statistical analysis. For Inf 04 just one night was available, therefore the subject was excluded.

Subject	Nights with spindle detection	Number of detected spindles
Inf 04	N2	928
Inf 05	N2	675
	N4	953
	N5	1213
Inf 07	N2	508
	N3	1013
	N4	1086
	N5	1414
Inf 08	N2	385
	N3	544
	N4	481
	N5	476

Inf 09	N1	2
	N2	568
	N3	738
Inf 10	N1	134
	N2	509
	N3	274
	N4	172
	N5	295
Inf 11	N1	269
	N2	615
	N3	856
	N4	1108
	N5	820
Inf 12	N2	517
	N3	666
	N4	943
Inf 14	N1	233
	N2	814
	N3	1086
	N4	1222
	N5	1277
Inf 15	N1	30
	N2	243
	N3	949
	N4	1110
	N5	826
Inf 16	N1	120
	N2	627
	N3	109
	N4	1029

Table 3.2. Subjects and nights analyzed with automatic spindle detection. Number of detected sleep spindles for respective night. N1 = 2 weeks of age, N2 = 2 months of age, N3 = 4 months of age, N4 = 6 months of age, N5 = 9 months of age.

4. Results

4.1. Visually detected sleep spindles

Visual detection of band-pass filtered (10-35 Hz) sleep spindles was performed in the Analysis Manager environment for the first hour of non-REM sleep. After measurement of the two variables, 'sleep spindle duration' and 'inter-spindle interval', sleep spindle density was calculated. Mean sleep spindle duration at the age of two months ranged from 0.84 to 2.64 s, whereas at the age of nine months it ranged from 1.02 to 1.56 s. Inter-spindle interval values varying from 16.35 to 60.67 s at two months of age and from 10.92 to 23.46 s at nine months of age were found (Table 4.1). Intervals with REM sleep episodes between non-REM stages were excluded from analysis. A two-tailed paired t-test was used to compare the data of the two ages. Results were significant for inter-spindle intervals ($p=0.029$) and sleep spindle density ($p=0.018$) (Fig. 4.1. B. and C.). No significance was reached for sleep spindle duration ($p=0.241$). However, sleep spindle duration was shorter in nine month old infants (Fig. 4.1. A.). The statistics were performed only for 6 infants with both nights available, at the age of two and nine months.

Age [months]	Inter-spindle interval [s]	Sleep spindle duration [s]	Sleep spindle density [#/ min non-REM sleep]
2	38.51 ± 22.16 *	1.74 ± 0.90	1.86 ± 1.51 *
9	17.19 ± 6.27	1.29 ± 0.27	3.47 ± 1.16

Table 4.1. Mean inter-spindle interval, mean spindle duration and mean spindle density at two and nine month of age for visual detection with standard deviation. * indicates significance ($p < 0.05$; two-tailed paired t-test).

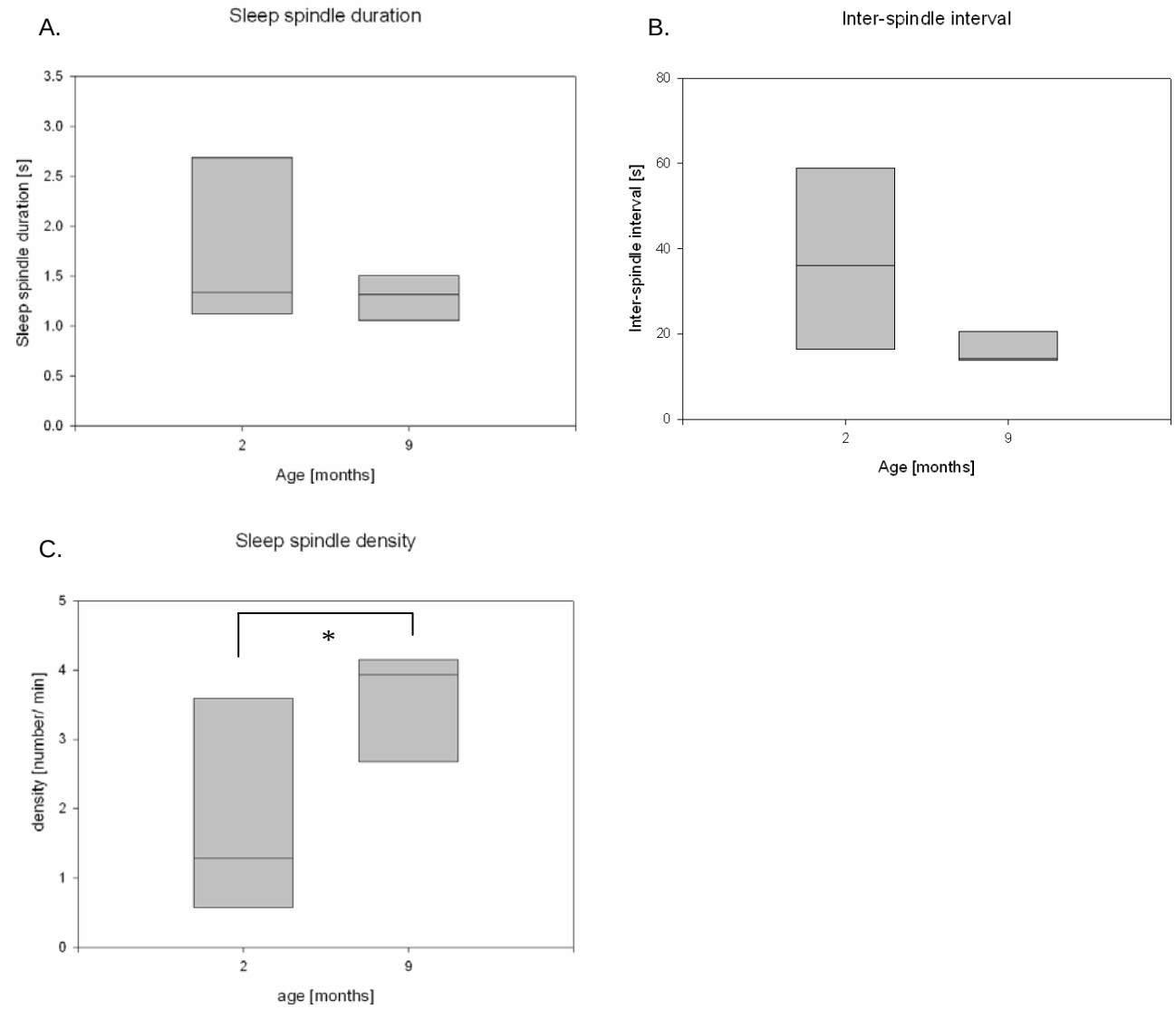


Fig. 4.1. Box plot of A. Sleep spindle duration, B. Inter-spindle intervals and C. Sleep spindle density at the age of 2 and 9 months of age (n=6) for visually detected sleep spindles. * indicates significance ($p < 0.05$; paired t-test). Median and 25- and 75 percentiles are illustrated.

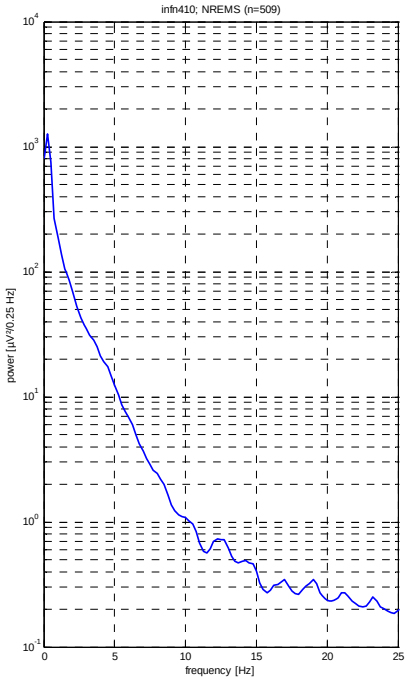
From Table 4.1 and Figure 4.1. a stabilisation of all three sleep spindle variables investigated can be assumed. Variance is much higher in younger than in older infants.

4.2. Automatic sleep spindle detection

4.2.1. Evaluation of automatic sleep spindle detection

A comparison of the visually detected sleep spindles of first hour non-REM sleep with the automatic sleep spindle detection revealed that the automatic and the human scoring were most consistent for nights with clear peaks in the frequency range of sleep spindles in the power spectra of derivation C3A2 (Fig. 4.2). A clear clustering of the results was observed by splitting the data in well and badly predicted sleep spindles. Average specificity of well detected spindles was 85.2% and average sensitivity 92.08%, whereas in badly predicted sleep spindles, average specificity was 37.32% and sensitivity 86.10%. Average non-REM sleep spectra of all infants are illustrated in the appendix.

A.



B.

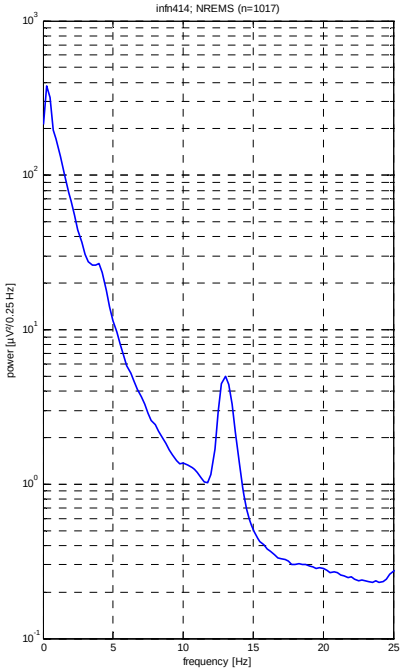


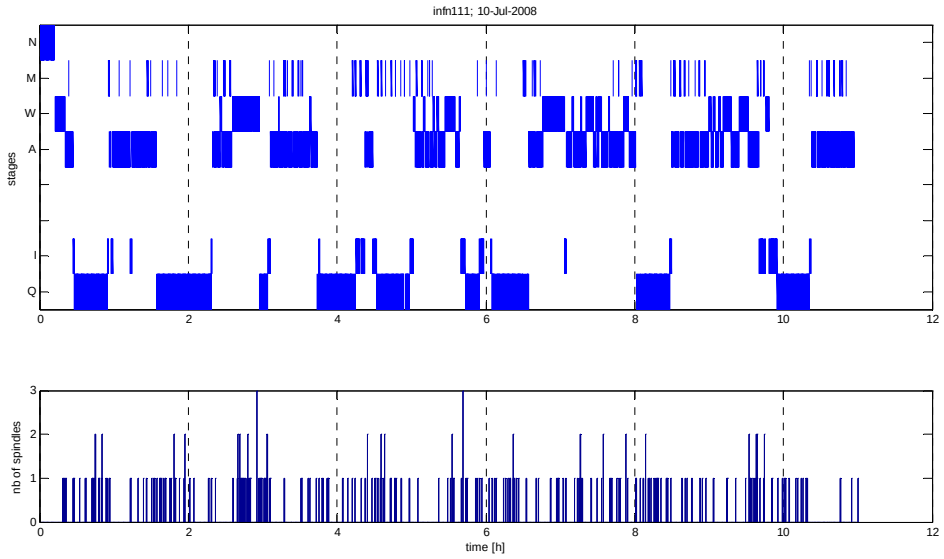
Fig. 4.2. Examples for a non-REM sleep EEG spectrum with a low and a clear peak in the sleep spindle frequency band. A. Infn410 at the age of 6 months with a low peak in the sleep spindle frequency band. B. Spectrum of Infn414 at the age of 6 months with a clear peak in the sleep spindle frequency band.

4.2.2. Illustration of data of a single infant (Inf 11)

Longitudinal data of a single individual are illustrated (Inf 11). Data of all individuals are compiled in the appendix. Figures 4.3 -4.5 illustrate the evolution of the occurrence of sleep spindles in the course of sleep. In the first recording, at the age of two weeks, sleep spindle incidence was distributed over the whole night and no clear pattern could be recognized. It is unclear whether the automatic detected spindles are mature spindles. This will further be discussed in chapter 4.2.4. At the age of two months, sleep spindles occur predominantly in quiet sleep episodes, and for ages four, six and nine months sleep spindles are most prominent in non-REM sleep. No trend in the occurrence of sleep spindles within the night is evident, as sleep spindles are distributed equally over the whole night.

Figures 4.6 - 4.9 illustrate the distribution of the investigated variables across the five recordings in one infant (Inf 11). The mode of the frequency of sleep spindles remained stable across age (2-9 months) at 13.5 Hz (Fig. 4.6). The duration of sleep spindles decreased from 2.4 to 1.4 s with increasing age (Fig. 4.7, see also appendix), while the amplitude (mean amplitude) increased from 3 to 8.5 µV (Fig. 4.8, mode). The mode of inter-spindle intervals (occurrence of spindles) remained stable across development at 12 s (Fig. 4.9).

A.



B.

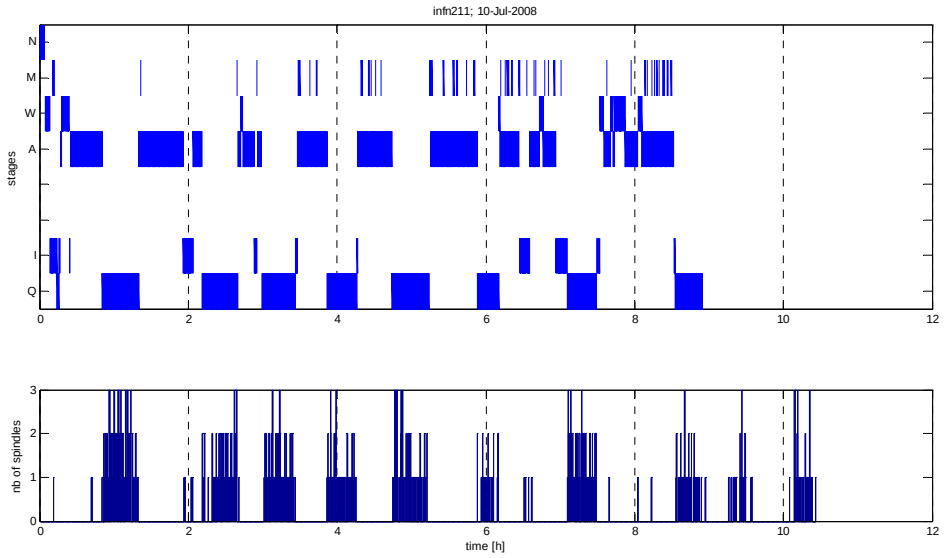
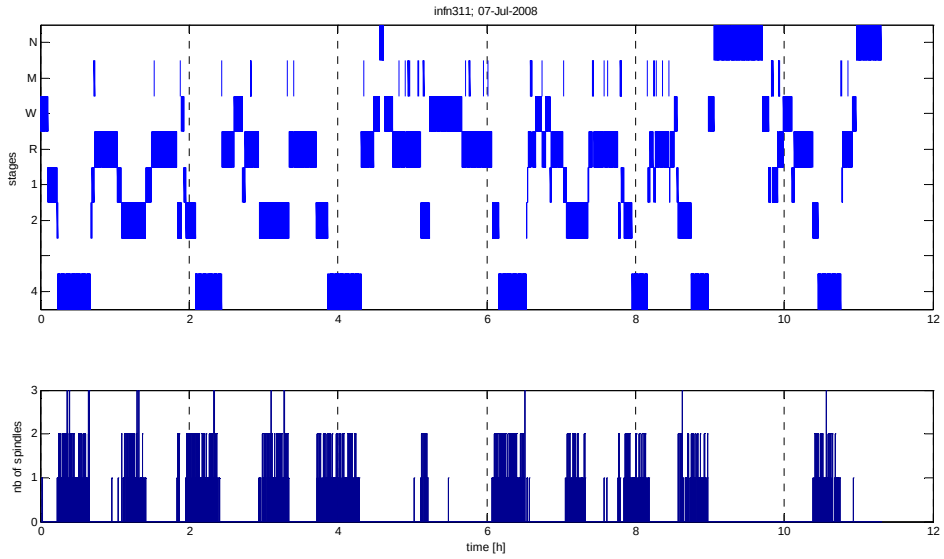


Fig. 4.3. Hypnograms and occurrence of sleep spindles of Inf 11 A. at the age of 2 weeks, and B. at the age of 2 months. N: Not scored, M: Movements, W: Awake, A: Active sleep, I: Indeterminate sleep, Q: Quiet sleep, R: REM sleep, 1 and 2: light sleep, 4: Slow wave sleep

A.



B.

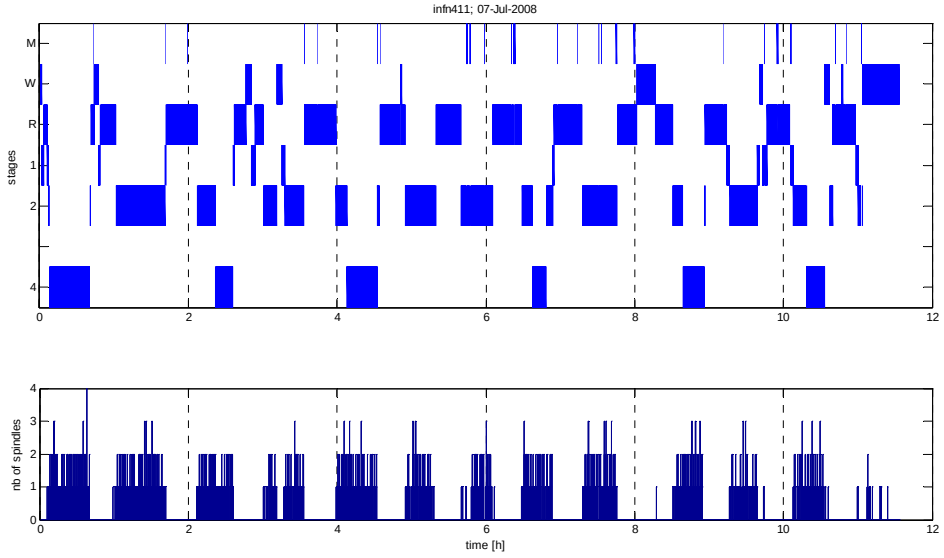


Fig. 4.4. Hypnograms and occurrence of sleep spindles of Inf 11 A. at the age of 4 months, and B. at the age of 6 months. N: Not scored, M: Movements, W: Awake, A: Active sleep, I: Indeterminate sleep, Q: Quiet sleep, R: REM sleep, 1 and 2: light sleep, 4: Slow wave sleep

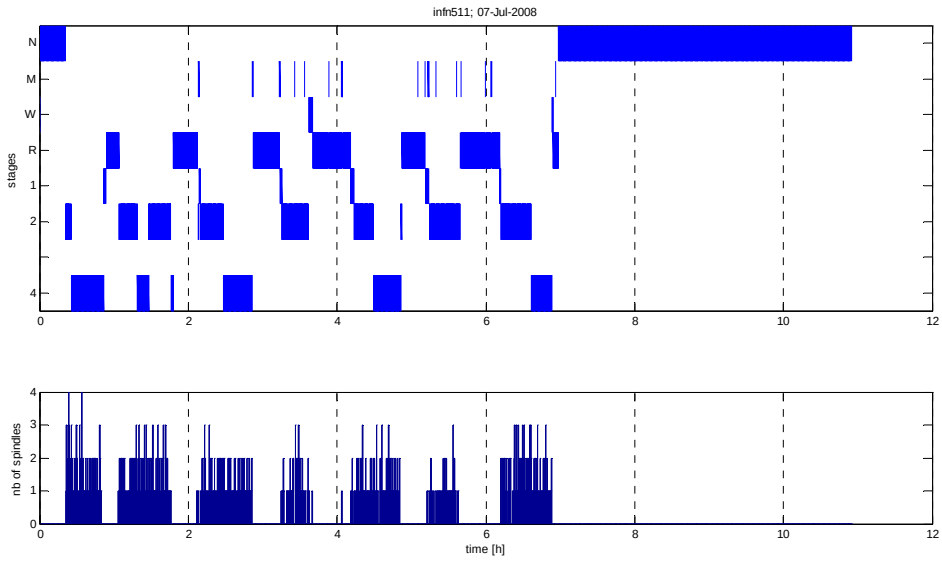


Fig. 4.5. Hypnogram and occurrence of sleep spindles of Inf 11 at the age of 9 months. N: Not scored, M: Movements, W: Awake, A: Active sleep, I: Indeterminate sleep, Q: Quiet sleep, R: REM sleep, 1 and 2: light sleep, 4: Slow wave sleep

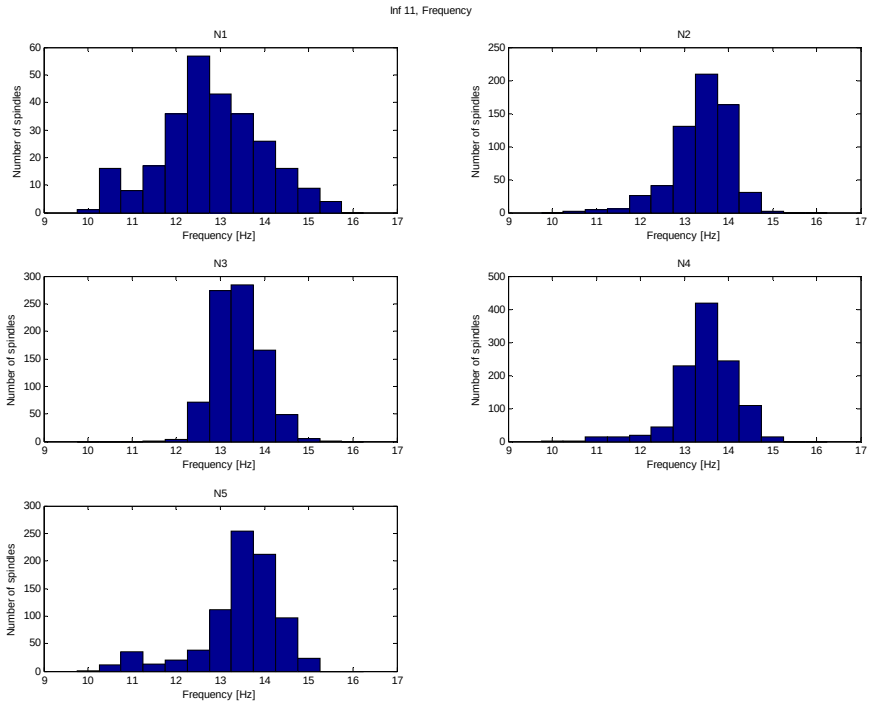


Fig. 4.6. Evolution of the distribution of sleep spindle frequency at ages two weeks (N1), two months (N2), four months (N3), six months (N4), and nine months (N5) of Inf 11

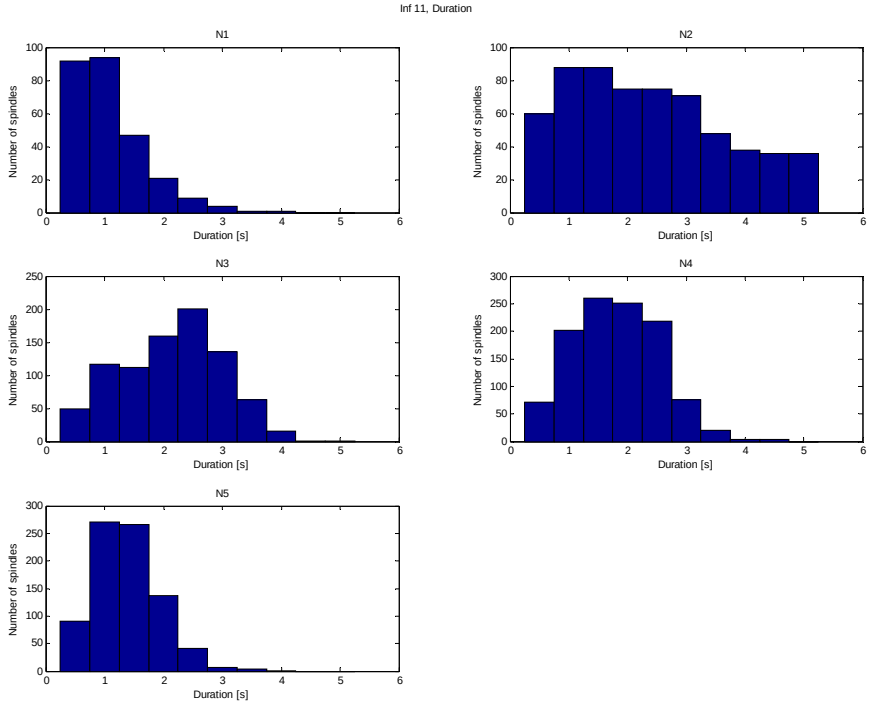


Fig. 4.7. Evolution of the distribution of sleep spindle duration at ages two weeks (N1), two months (N2), four months (N3), six months (N4), and nine months (N5) of Inf 11

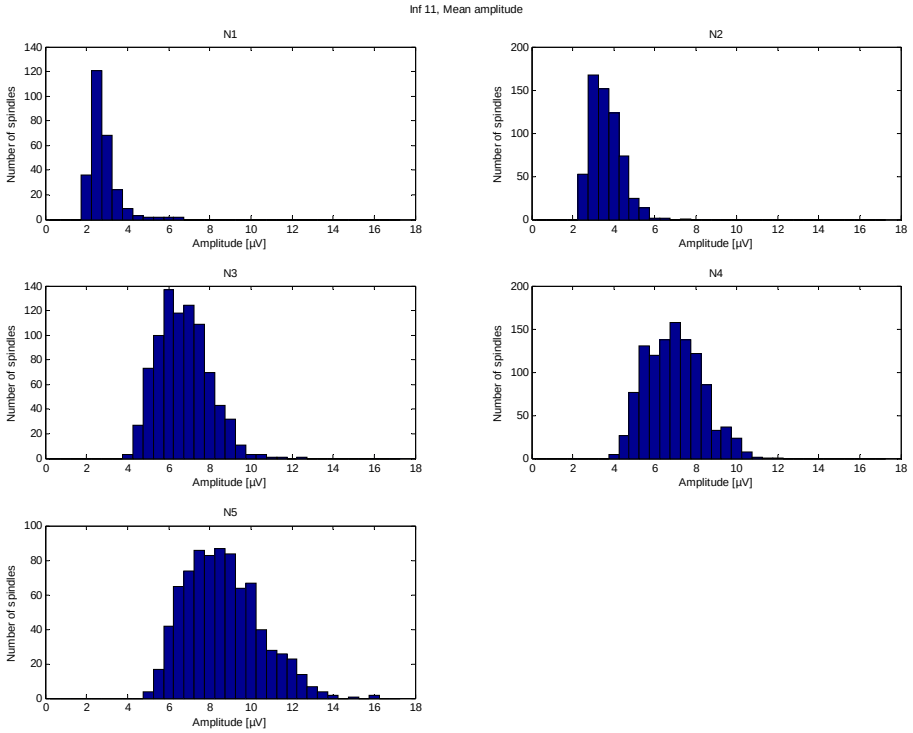


Fig. 4.8. Evolution of the distribution of sleep spindle amplitude at ages two weeks (N1), two months (N2), four months (N3), six months (N4), and nine months (N5) of Inf 11

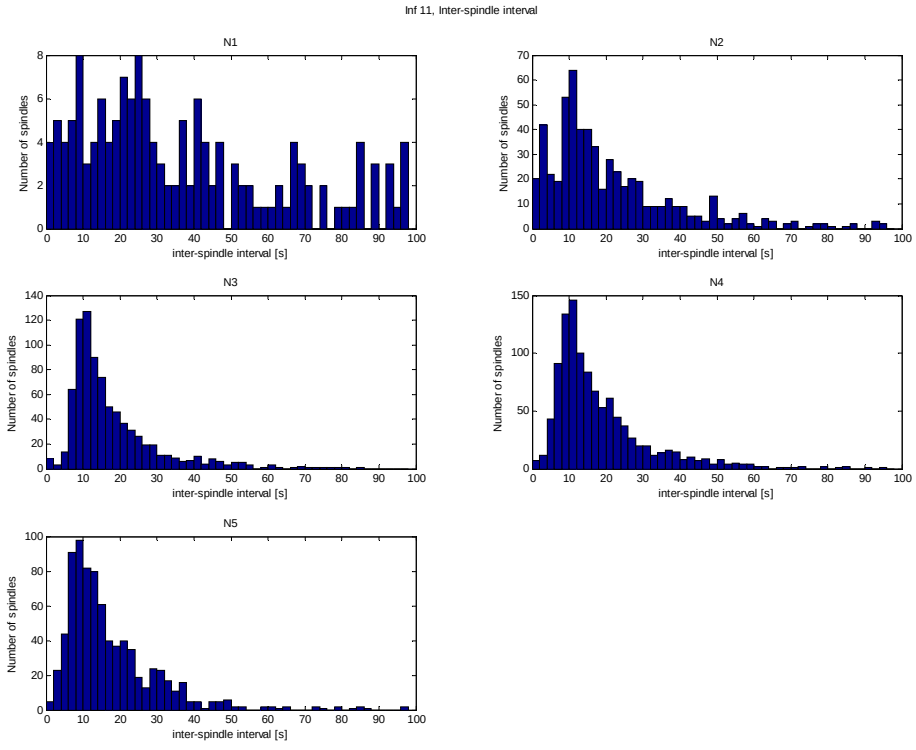


Fig. 4.9. Evolution of the distribution of inter-spindle interval at ages two weeks (N1), two months (N2), four months (N3), six months (N4), and nine months (N5) of Inf 11

4.2.3. Average data

Mean values and standard deviation for sleep spindle density, inter-spindle intervals, frequency, and sleep spindle duration are listed in Table 4.2. Inter-spindle intervals were corrected for intervals >98 s to exclude interruptions of intervals by stages other than non-REM sleep, e.g. REM sleep episodes. Plotting the distribution of inter-spindle intervals revealed that values above bin 64 (>98 s) should be excluded (Fig. 4.10). Inter-spindle intervals were plotted with log bin width.

Age [months]	Mean sleep spindle density [number/ min]	Mean inter-spindle interval [s]	Mean frequency [Hz] of detected sleep spindles	Mean sleep spindle duration [s]	Mean Amplitude [µV]	Sample size
0.5	0.62 ± 0.45	27.98 ± 4.65	11.25 ± 0.88	1.16 ± 0.24	3.02 ± 0.67	6
2	2.56 ± 0.56	19.85 ± 2.13	13.05 ± 0.32	2.08 ± 0.42	4.75 ± 1.52	11
4	2.83 ± 1.35	19.74 ± 4.10	13.05 ± 0.24	2.08 ± 0.41	7.14 ± 2.41	9
6	3.01 ± 1.03	20.23 ± 5.72	13.07 ± 0.39	1.78 ± 0.30	7.99 ± 2.17	9
9	2.64 ± 1.17	16.21 ± 3.56	11.49 ± 0.29	1.32 ± 0.19	7.49 ± 2.76	7

Table 4.2. Mean sleep spindle duration, inter-spindle interval, frequency and density of sleep spindles with standard deviation for automatic spindle detection. Inter-spindle intervals were corrected for intervals longer than 98 s to exclude interruptions by stages other than non-REM sleep.

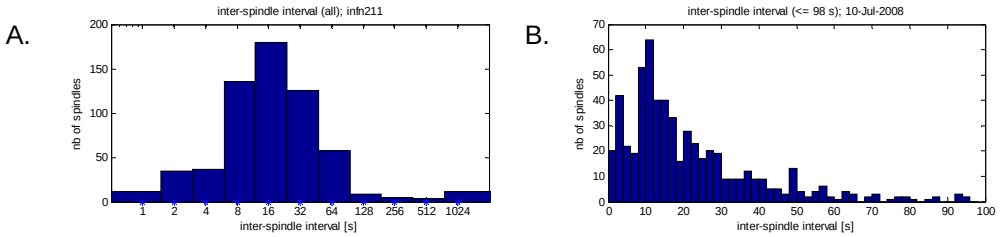


Fig. 4.10. A. Distribution of all detected inter-spindle intervals on a logarhithmic scale. B. Distribution of inter-spindle intervals with intervals >98 s excluded. Subject is Infn211 at the age of 2 months.

A mixed model ANOVA with factor *Age* was performed for all sleep spindle variables. Significance was reached for sleep spindle duration ($p = 0.0004$), maximal ($p < 0.0001$), and mean sleep spindle amplitude ($p < 0.0001$). No significance was observed for inter-spindle intervals ($p = 0.62$), sleep spindle frequency ($p = 0.77$) and sleep spindle density ($p = 0.26$). Complete longitudinal data was not available for all infants (Table 3.2). Nevertheless, all nights with available sleep spindle data were included.

Development across age for all variables is shown in Fig. 4.11. No significant age related changes were observed for sleep spindle density, inter-spindle intervals and frequency. For sleep spindle density (excluding values at the age of two weeks) values ranging from 2.56 spindles/ min (2 months) to 3.01 spindles/ min (4 months) were found. Inter-spindle intervals varied from 16.21 s (9 months) to 20.23 s (6 months). For frequency values between 11.49 Hz (9 months) and 13.07 Hz (6 months) were observed.

In contrast to these observations, significant age related changes for the variable sleep spindle duration was found. Sleep spindle duration remained stable from two to four months of age (2.08 ± 0.42 s at two months, 2.08± 0.41 s at four months) whereas afterwards a decrease was observed with shortest sleep spindle duration at 9 months (1.47 ± 0.12 s). Sleep spindle amplitude increased with progressing age from 4.75 ± 1.52 µV at the age of two months to 7.49 ± 2.76 µV at the age of nine months.

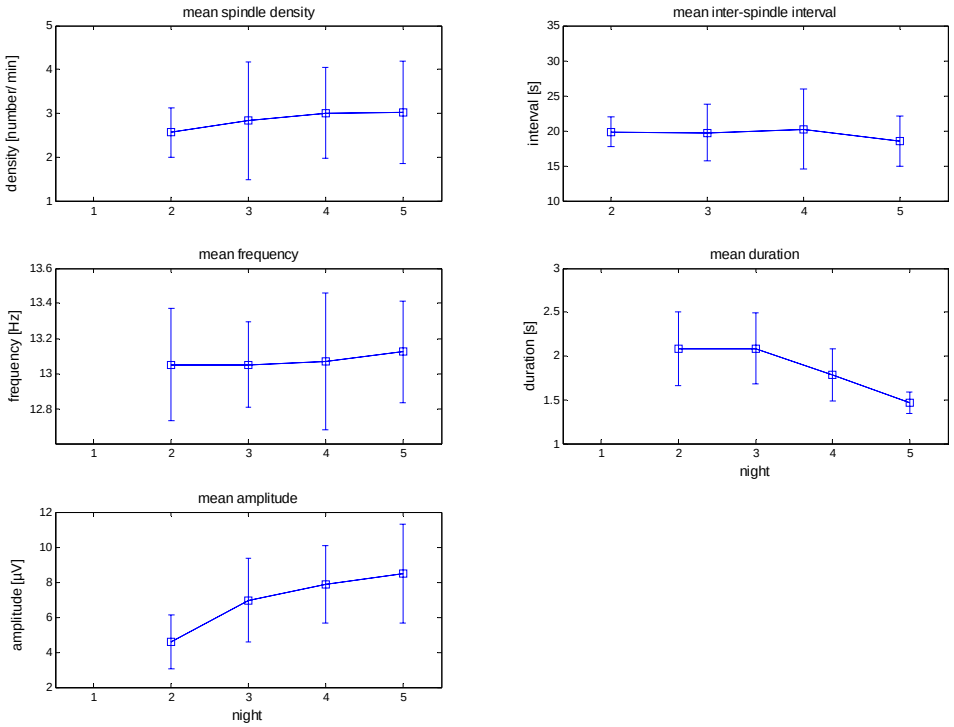


Fig. 4.10. Evolution of mean and standard derivation for A. sleep spindle density, B. inter-spindle interval, C. frequency D. duration, and E. mean amplitude of sleep spindles, averaged over all infants. Inter-spindle intervals >98 s were excluded. Mean values ± standard deviation are illustrated. Night 1-5 refers to ages N1 = 2 weeks, N2 = 2 months, N3 = 4 months, N4 = 6 months, N5 = 9 months

4.2.4. Sleep spindles at the age of two weeks

There is evidence from the literature that the first sleep spindles appear at an age of six to eight weeks [1], [2], [3]. In two week old infants the algorithm applied detected 2 – 269 spindles for first nights of available data (Table 4.3.). Frequency of detected spindles was in the sleep spindle frequency range and amplitude was low (see respective figures in appendix for distribution of frequency in first nights). So far it remains unclear if the detected spindles can be considered as mature sleep spindles. Therefore first nights were excluded from analysis. In recordings of first nights many ECG artefacts were visible and detected spindles sometimes may not be recognized as such (Fig. 4.12).

Subject	Number of detected spindles	Time spent in non-REM sleep [min]	Spindle density [number of spindles/ min]
Inf 09	2	182.00	0.01
Inf 10	134	166.00	0.81
Inf 11	269	239.67	1.12
Inf 14	233	182.67	1.28
Inf 15	30	52.00	0.58
Inf 16	120	213	0.56

Table 4.3. Number of detected sleep spindles in the first recording (age: 2 weeks). Epochs with artefacts in time spent in non-REM sleep were excluded.

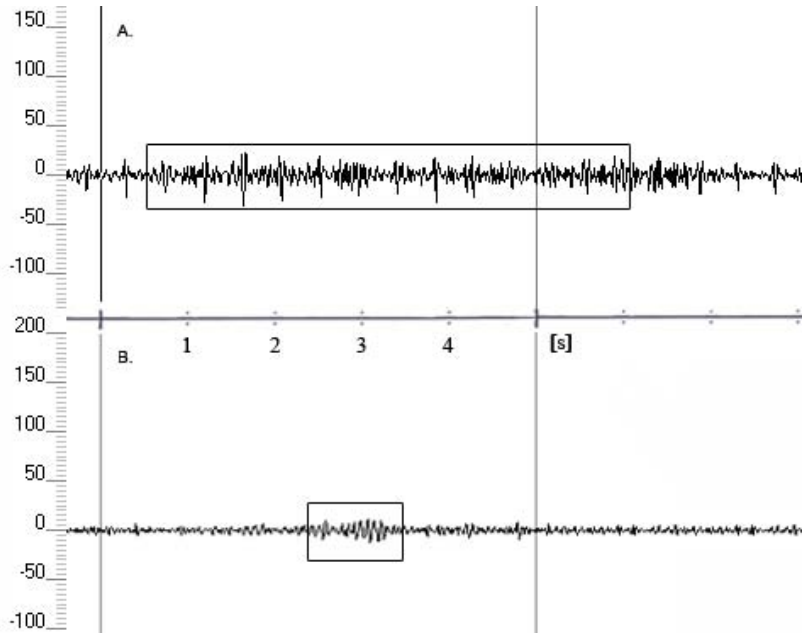


Fig. 4.12. Sleep spindles detected by algorithm at the age of two weeks. A. Baseline EEG signal contaminated with EKG artefacts of Inf 10. Frequency: 12.75 Hz, duration: 4.97 s. B. Inf 11, Frequency: 12.5, duration: 0.87 s. Frame indicates detected spindle.

5. Discussion

5.1. EEG maturity

Gestational age of infants used for the study ranged from 38 to 42 weeks. As the first recording occurred at 2 weeks of age, 4 weeks difference in gestational age could influence EEG maturity by some extent as is proposed by Ebersole et al. [1]. They suggest that EEG maturity is principally determined by the conceptional age, because neurological development is thought to proceed at the same rate during intra and extra uterine life. However, there are other studies with premature infants which propose that development of sleep spindles is influenced by extra uterine life [4], [34].

5.2. Visual sleep spindle detection

As the baseline signal varied in amplitude in different recordings even within the same infant, threshold criteria had to be adjusted for every night of visual scoring. Thus, the beginning and ending of a sleep spindle is very susceptible for setting the amplitude threshold. That is, if the threshold is set too high, detected spindles tend to be shorter for the whole recording and vice versa. Some of the recordings were also contaminated with ECG artefacts. Therefore baseline amplitude tended to be higher than without contamination and detection of a sleep spindle is more likely than without the artefacts. Nights with too many artefacts or high baseline signal (>30μV) were excluded from the analysis of visual detection as sleep spindles were hardly detectable. Accordingly, 2 nights were not available for every infant. The statistics were carried out for paired data (n=6). T-tests with

paired data was significant for inter-spindle intervals and sleep spindle density. No significance could be reached for sleep spindle duration. However, there was a tendency for decreased sleep spindle duration at the age of nine months. Possibly, statistical power with n=6 was too low. Furthermore, it has to be noted that visual detection of sleep spindles was performed only in the first hour of non-REM sleep of the recording night, which could influence the result. Moreover, the variable sleep spindle duration is very sensitive to the setting of amplitude threshold, therefore sleep spindle duration could interfere with threshold settings.

5.3. Automatic sleep spindle detection

The use of automatic detection of sleep spindles presents some problems because the computer does not distinguish between background noise, elevated baseline signal and artefacts even if epochs with moving artefacts were excluded from analysis. As the criteria for sleep spindle detection was 2x the standard deviation of the band-pass filtered EEG signal, this problem could be avoided. Moreover, comparison with visual sleep spindle detection verified automatic sleep spindle detection as reliable. However, algorithm detected sleep spindles better, when spectra showed a clear peak in the frequency range of sleep spindles. Therefore, a clustering of results was observed. In the cluster of well detected spindles, the average specificity was 85.2% and average sensitivity 92.08%, while in the cluster of badly predicted spindles specificity was 37.32% and sensitivity 86.10%. Sensitivity and specificity in the well predicted cluster are among the best published so far.

5.3.1. Distribution of sleep spindles in sleep stages

From the hypnograms and occurrence of sleep spindles across sleep it can be assumed that sleep spindles occurred mainly in non-REM sleep, for infants older than two months. At two weeks of age sleep spindles were distributed equally over the whole night. No statistic was performed for sleep spindle occurrence so far.

5.3.2. Sleep spindles in two week old infants

At the age of two weeks, the algorithm detected 2 – 269 sleep spindles in 6 individuals (Table 4.3.). Since from the literature it is known that the first appearance of sleep spindles occurs at the age of 6 – 8 weeks, it is unclear if these detected spindles can be considered as real or mature sleep spindles. From unborn infants it is known that premature sleep spindles or so called 'brushes' appear in EEG recordings [30], [31]. Therefore detected spindles at the age of 2 weeks could reflect remains of these 'brushes'. These premature spindles are dispersed in all sleep stages and do not occur predominantly in non-REM sleep, which could be shown by plotting sleep spindle occurrence across sleep (Hypnograms and occurrence of sleep spindles, appendix).

5.4. Visual detection compared to automatic detection

In visually detected sleep spindles significant differences in the variable sleep spindle density was found. Values ranged from 1.86 spindles/ min (2 months) to 3.47 spindles/ min (9 months), but no significant age related changes in inter-spindle intervals and sleep spindle duration were observed. In contrast to this finding, in automatic sleep spindle detection significance was reached for sleep

spindle duration with values ranging from 2.08 s (2 months) to 1.32 s (9 months). However, no significance was observed for the variables sleep spindle density and inter-spindle intervals. These different observations could be due to several reasons. For example sleep spindles could show circadian oscillations and therefore time point of sleep spindle detection plays an important role. However, this was not observed in hypnograms with sleep spindle occurrence in the course of the night. Amplitude threshold settings could also influence sleep spindle detection and particularly as sleep spindle duration is very sensitive to threshold settings. Additionally, sample size was small. In visual detection only paired data was analyzed, whereas in automatic sleep spindle detection all nights available were investigated. The observation of stabilizing sleep spindle variables from visually detected sleep spindles could not be confirmed with automatic sleep spindle detection for inter-spindle intervals and sleep spindle density. However, sleep spindle duration also seems to stabilize in automatic sleep spindle detection.

5.4. Statistics

Statistical analysis was performed by means of linear mixed model ANOVA with the factor *Age* (0.5, 2, 4, 6 and 9 months). *Age* was modeled as a classed variable, where no gradual changes are assumed. However, it is unknown so far if brain development proceeds gradually.

5.5. Summary and conclusions

From the literature, maximal values for sleep spindle duration were expected at the age of 1-3 months [5], 3-4 months [8], 4-6 months [6] or 9 months [7]. In this study, maximal sleep spindle values were found at the age of 2 and 4 months, thereafter sleep spindle duration decreased to a minimal value at the age of 9 months. These findings are in line with Louis et al. [5] and Lenard et al. [8].

For sleep spindle density maximal values were expected at the age of 3 to 9 months [5], [6], [7]. However, no significant differences in sleep spindle density could be shown with the automatic sleep spindle detection, yet there was a significant difference in sleep spindle density for the visually detected sleep spindle at the age of 2 and 9 months.

The frequency of sleep spindles was expected to increase with age [5], [9]. This result could not be confirmed, as frequency of spindles was stable across the recordings. Therefore it may be assumed that sleep spindle frequency shows an individual trait. However, further investigation is needed to demonstrate whether every individual has a typical spindling frequency. Amplitude was expected to increase with increasing age [5], and this relationship was confirmed by the results in this study.

So far, reported results are inconsistent but it can be concluded that sleep spindles change in relation to age. In the different studies sleep spindles were investigated at different times of the night and there was little consistency in detection methods of sleep spindles in the previous studies. It might be that a circadian factor in sleep spindle regulation contributed to the observed discrepancies. In this study an automatic sleep spindle detection was applied to the data which is a new approach for sleep spindle detection and therefore more data can be analyzed. Additionally, in this study a whole night analysis was done, whereas most studies investigated for a certain time point in course of the night.

6. Acknowledgements

I would like to thank Ana Jeroncic for developing the algorithm for automatic sleep spindle detection and for helping me with Matlab problems, Sanja Bratic, Sabine Regel, and Sarah Loughran for carefully reviewing the manuscript, Sabine Regel for her help with the statistics and Oskar Jenni for providing the data and the feedback on the manuscript.

Finally, I would like to thank Peter Achermann for enabling and supervising this master thesis.

7. References

1. Ebersole, J. S. Current practice of clinical electroencephalography (Lippincott Williams & Wilkins, Philadelphia, 2003).
2. Jenni, O. G., Borbely, A. A. & Achermann, P. Development of the nocturnal sleep electroencephalogram in human infants. American Journal of Physiology-Regulatory Integrative and Comparative Physiology 286, R528-38 (2004).
3. Dittrichova, J. Development of sleep in infancy. Journal of Applied Physiology 21, 1243-6 (1966).
4. Metcalf, D. R. EEG sleep spindle ontogenesis. Neuropadiatrie 1, 428-33 (1970).
5. Louis, J., Zhang, J. X., Revol, M., Debilly, G. & Challamel, M. J. Ontogenesis of nocturnal organization of sleep spindles: a longitudinal study during the first 6 months of life. Electroencephalography and Clinical Neurophysiology 83, 289-96 (1992).
6. Tanguay, P. E., Ornitz, E. M., Kaplan, A. & Bozzo, E. S. Evolution of sleep spindles in childhood. Electroencephalography and Clinical Neurophysiology 38, 175-81 (1975).
7. Scholle, S., Zwacka, G. & Scholle, H. C. Sleep spindle evolution from infancy to adolescence. Clinical Neurophysiology 118, 1525-1531 (2007).
8. Lenard, H. G. The development of sleep spindles during the first 2 years of life. Electroencephalography and Clinical Neurophysiology 29, 217 (1970).
9. Shinomiya, S., Nagata, K., Takahashi, K. & Masumura, T. Development of sleep spindles in young children and adolescents. Clinical Electroencephalography 30, 39-43 (1999).
10. Steriade, M., Deschenes, M., Domich, L. & Mulle, C. Abolition of spindle oscillations in thalamic neurons disconnected from nucleus reticularis thalami. Journal of Neurophysiology 54, 1473-97 (1985).
11. Steriade, M., McCormick, D. A. & Sejnowski, T. J. Thalamocortical oscillations in the sleeping and aroused brain. Science 262, 679-85 (1993).
12. Huber, R. Memory formation: sleep enough before learning. Current Biology 17, R367-8 (2007).

13. Borbély, A. Schlaf (Fischer Taschenbuch Verlag, Frankfurt am Main, Germany, 2004).
14. Tononi, G. & Cirelli, C. Steep function and synaptic homeostasis. Sleep Medicine Reviews 10, 49-62 (2006).
15. Hobson, J. A. Sleep is of the brain, by the brain and for the brain. Nature 437, 1254-6 (2005).
16. Stickgold, R. & Walker, M. P. Memory consolidation and reconsolidation: what is the role of sleep? Trends in Neurosciences 28, 408-15 (2005).
17. Massimini, M. et al. Breakdown of cortical effective connectivity during sleep. Science 309, 2228-2232 (2005).
18. Achermann, P. Sleep. In Wiley Encyclopedia of Biomedical Engineering (Metin Akay, ed.) Hoboken: John Wiley & Sons, Inc. (2006).
19. Rechtschaffen, A. & Kales, A. A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects (National Institutes of Health, Bethesda, Maryland, 1968).
20. Louis, J., Cannard, C., Bastuji, H. & Challamel, M. J. Sleep ontogenesis revisited: a longitudinal 24-hour home polygraphic study on 15 normal infants during the first two years of life. Sleep 20, 323-33 (1997).
21. Anders, T. F. Manual of Standardized Terminology, Techniques, and Criteria for Scoring of States of Sleep and Wakefulness in Newborn Infants (Mstni) Eds - Anders, Emde, Parmelee. Psychophysiology 9, 97-& (1972).
22. Cajochen, C., Munch, M., Knoblauch, V., Blatter, K. & Wirz-Justice, A. Age-related changes in the circadian and homeostatic regulation of human sleep. Chronobiology International 23, 461-74 (2006).
23. Gibbs F.A. and E. L. Atlas of Electroencephalography (2nd edn.) Addison-Wesley Press, Cambridge, 1950.
24. Schabus, M. et al. Hemodynamic cerebral correlates of sleep spindles during human non-rapid eye movement sleep. Proceedings of the National Academy of Sciences of the United States of America 104, 13164-13169 (2007).
25. Iber, C. & American Academy of Sleep Medicine. The AASM manual for the scoring of sleep and associated events rules, terminology and technical specifications (American Academy of Sleep Medicine, Westchester, Ill., 2007).

26. De Gennaro, L., Ferrara, M. & Bertini, M. Topographical distribution of spindles: variations between and within nrem sleep cycles. Sleep Research Online 3, 155-60 (2000).
27. McCormick, L., Nielsen, T., Nicolas, A., Ptito, M. & Montplaisir, J. Topographical distribution of spindles and K-complexes in normal subjects. Sleep 20, 939-41 (1997).
28. Jasper, H. H. The ten-twenty electrode system of the International Federation of Societies for Electroencephalography: Appendix to report of the committee on methods of clinical examination in electroencephalography. Electroencephalography and Clinical Neurophysiology 10, 370-375 (1958).
29. Loomis, A. L., Harvey, E. N. & Hobart, G. Further Observations on the Potential Rhythms of the Cerebral Cortex During Sleep. Science 82, 198-200 (1935).
30. Ellingson, R. J. Development of Sleep Spindle Bursts during the 1St Year of Life. Sleep 5, 39-46 (1982).
31. Lombroso, C. T. Neurophysiological Observations in Diseased Newborns. Biological Psychiatry 10, 527-558 (1975).
32. Watanabe, K. & Iwase, K. Spindle-like fast rhythms in the EEGs of low-birth weight infants. Developmental Medicine & Child Neurology 14, 373-81 (1972).
33. Jankel, W. R. & Niedermeyer, E. Sleep spindles. Journal of Clinical Neurophysiology 2, 1-35 (1985).
34. Metcalf, D. R. The effect of extrauterine experience on the ontogenesis of EEG sleep spindles. Psychosomatic Medicine 31, 393-9 (1969).
35. Schultz, M. A., Schulte, F. J., Akiyama, Y. & Parmelee, A. H., Jr. Development of electroencephalographic sleep phenomena in hypothayroid infants. Electroencephalography and Clinical Neurophysiology 25, 351-8 (1968).
36. Gross, H. P. & Schulte, F. J. Increased Spindle Activity in Sleep Eeg of Infants with Phenylketonuria. Zeitschrift Fur Kinderheilkunde 105, 324-& (1969).
37. Shibagaki, M., Kiyono, S. & Watanabe, K. Spindle evolution in normal and mentally retarded children: a review. Sleep 5, 47-57 (1982).
38. Sejnowski, T. J. & Destexhe, A. Why do we sleep? Brain Research 886, 208-223 (2000).
39. Schadé, J. P. & Meeter, K. Neuronal and Dendritic Patterns in the Uncinate Area of the Human Hippocampus. Progress in Brain Research 3, 89-110 (1963).

40. Fuentealba, P. & Steriade, M. The reticular nucleus revisited: intrinsic and network properties of a thalamic pacemaker. Progress in Neurobiology 75, 125-41 (2005).
41. Steriade, M. Sleep, epilepsy and thalamic reticular inhibitory neurons. Trends in Neurosciences 28, 317-24 (2005).
42. Guilleminault, C. & Soquet, M. in Advances in perinatal neurology (eds. Korobkin, R. & Guilleminault, C.) 225-247 (SP Medical & Scientific Books, New York, 1979).

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9. Appendix

Spectra

Spectra were plotted for non-REM sleep stages. y-Axis: power density in μV^2/0.25 Hz, x-axis: frequency in Hz.

Hypnograms and occurrence of sleep spindles during the night

Hypnograms and sleep spindle occurrence was plotted for all nights. Abbreviations: N: Not scored, M: Movements, W: Awake, A: Active sleep, I: Indeterminate sleep, Q: Quiet sleep, R: REM sleep, 1 and 2: light sleep, 4: Slow wave sleep.

Distributions of sleep spindle variables

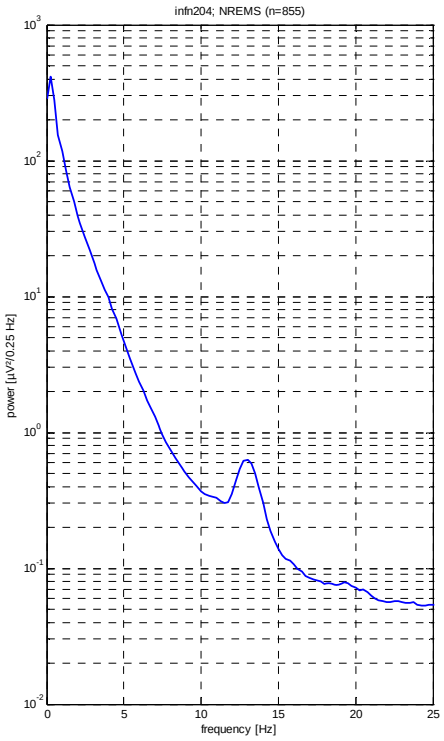
Distributions for all sleep spindle variables (inter-spindle intervals, frequency, mean amplitude, sleep spindle duration and maximal amplitude) were plotted for every individual for all recorded night. Inter-spindle intervals were plotted uncorrected and corrected for intervals > 98 s to exclude interrupts by other stages than Non-REM sleep.

Individual development of sleep spindle variables across age

Age related changes for all sleep spindle variables (sleep spindle density, mean/ median inter-spindle interval, mean/ median frequency, mean/ median sleep spindle duration, mean/ median sleep spindle amplitude) were plotted for every individual. 1-5 refers to age at recording night (N1: 2 weeks, N2: 2 months, N3: 4 months, N4: 6 months, N5: 9 months).

Spectra

Inf 04



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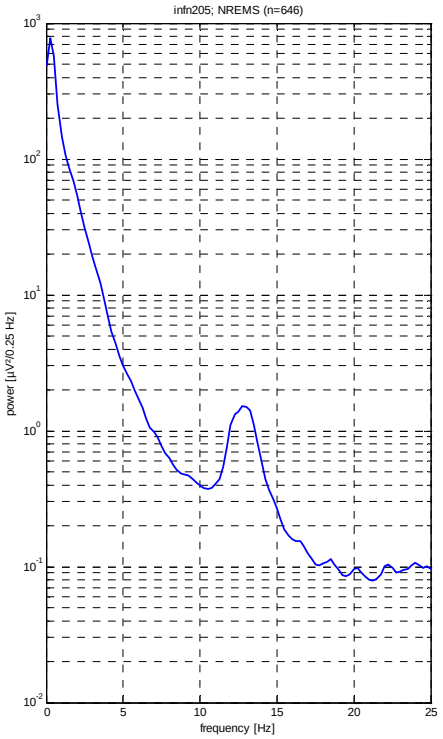
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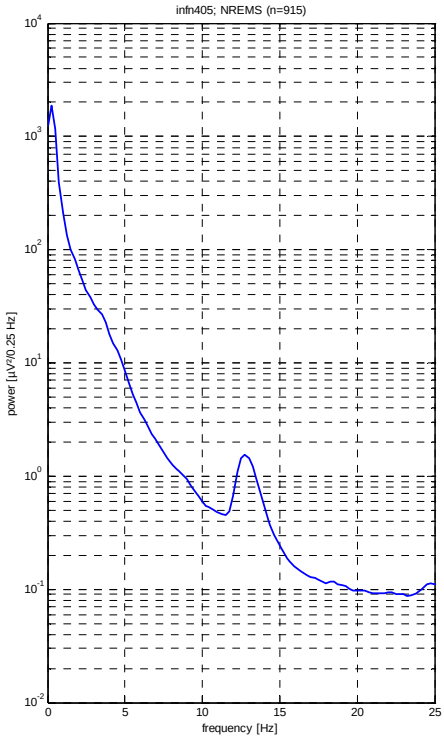
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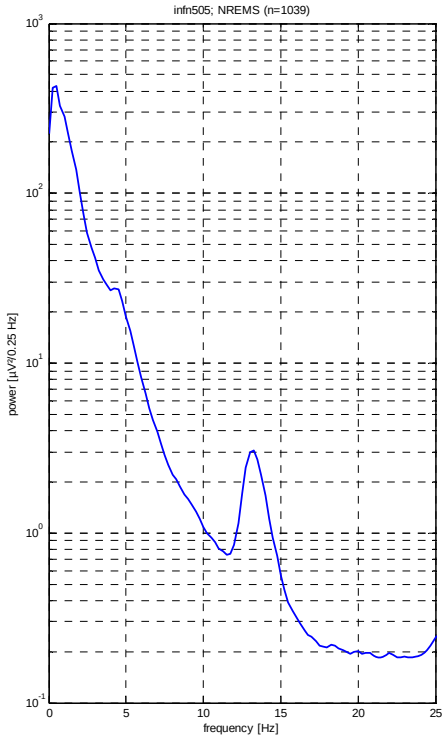
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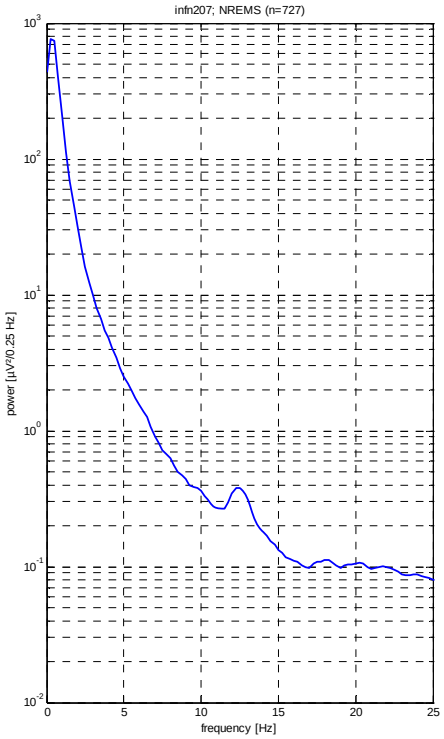
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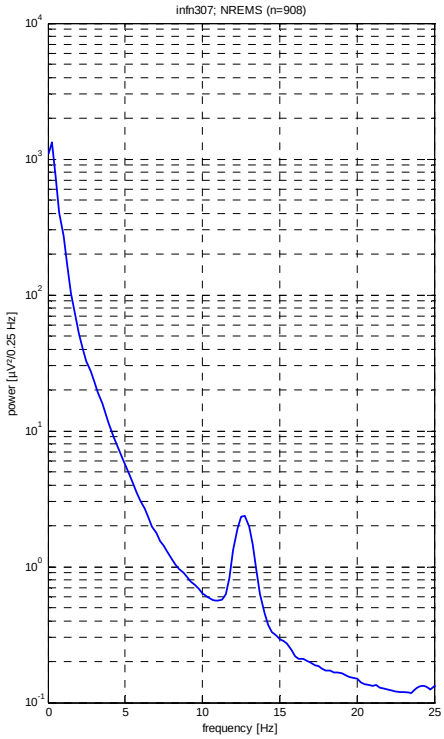
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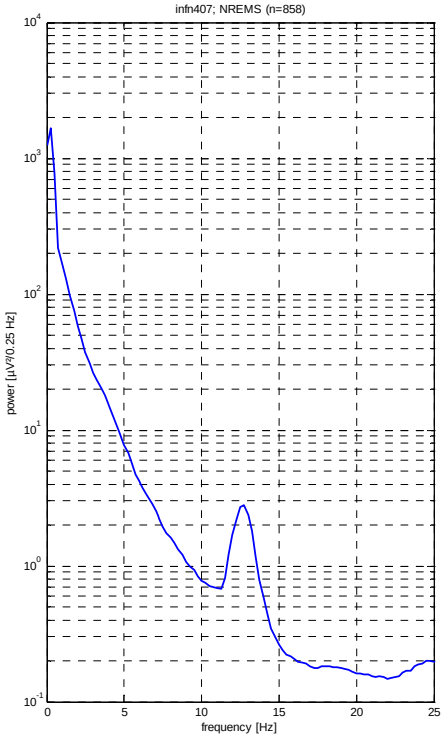
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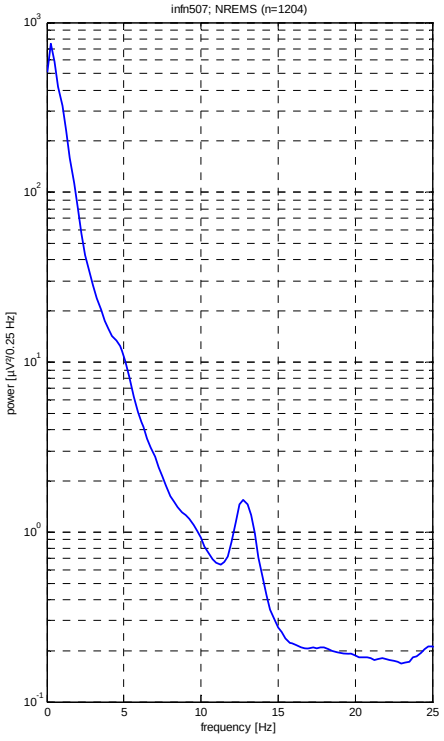
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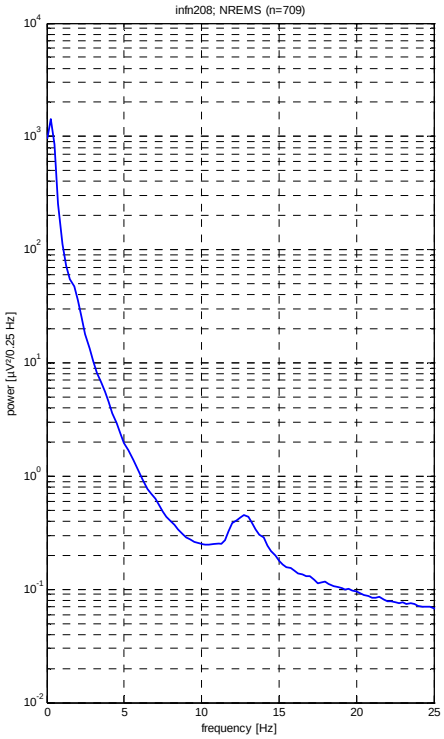
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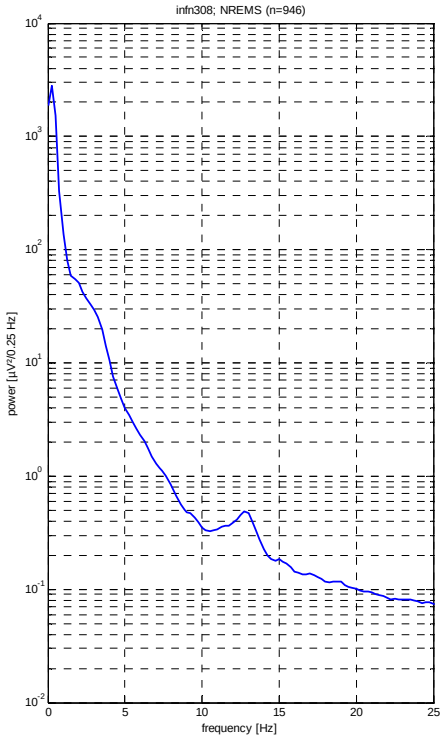
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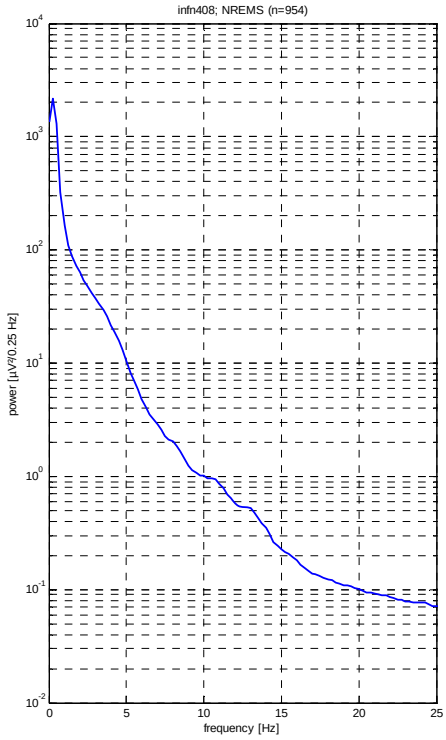
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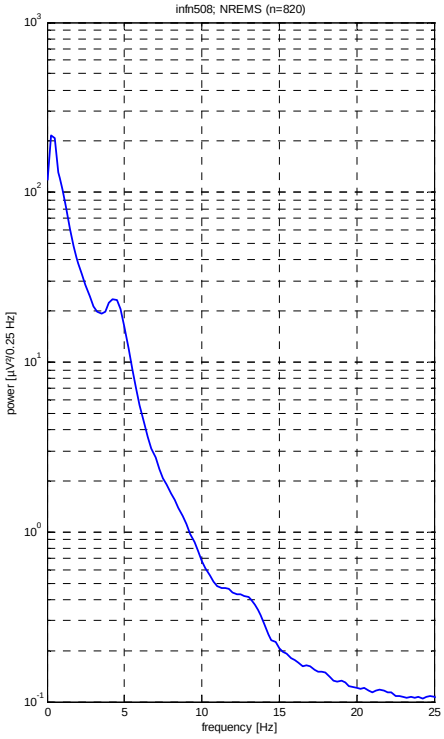
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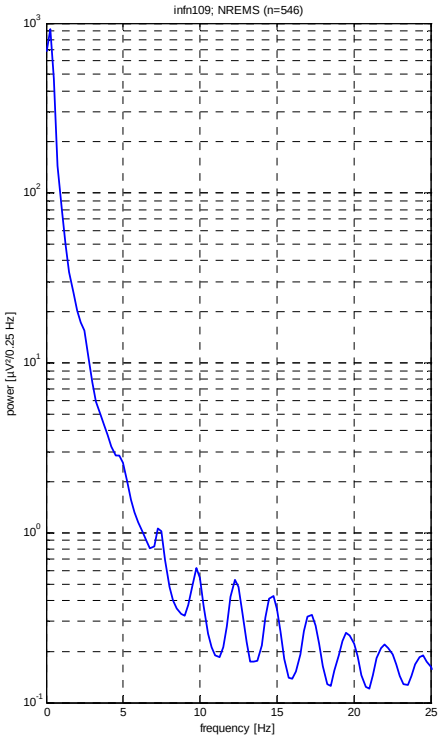
Inf 09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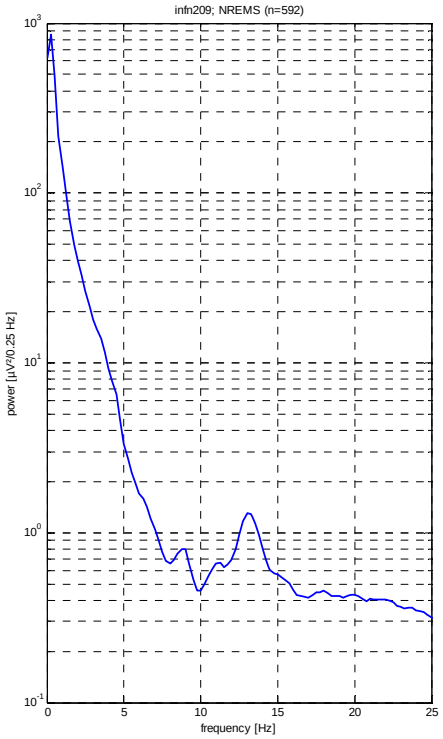
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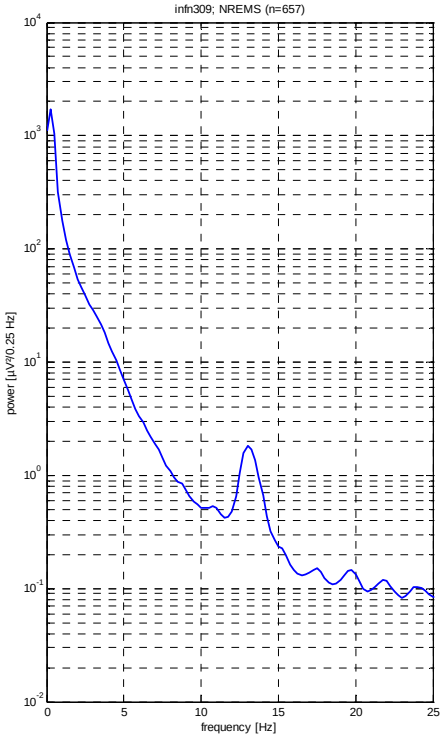
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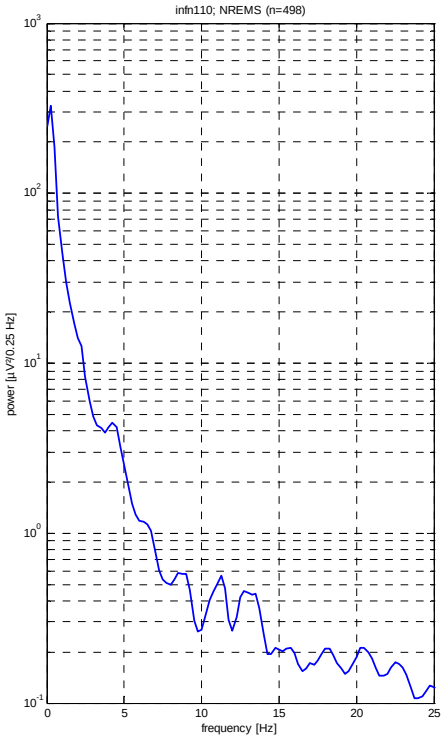
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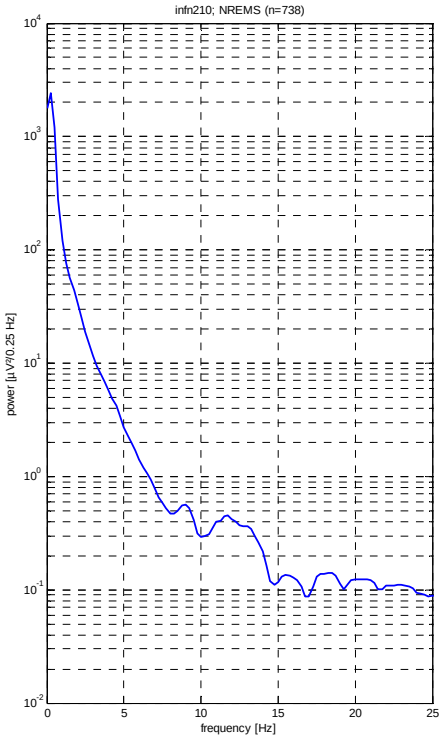
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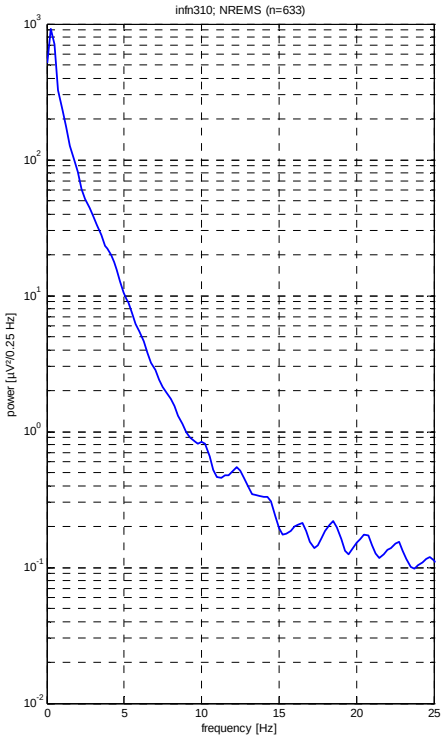
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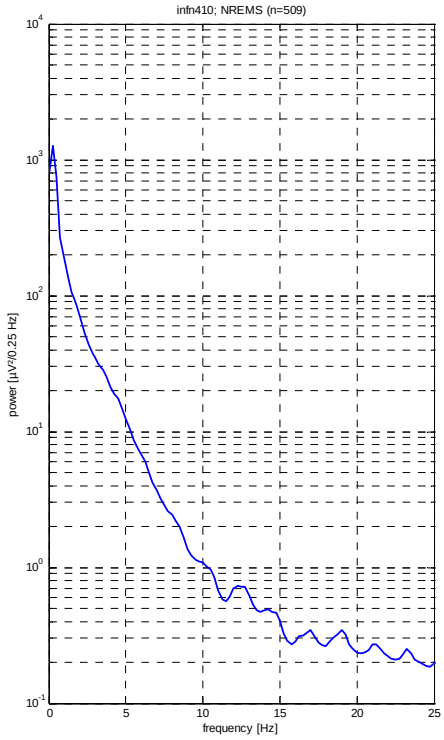
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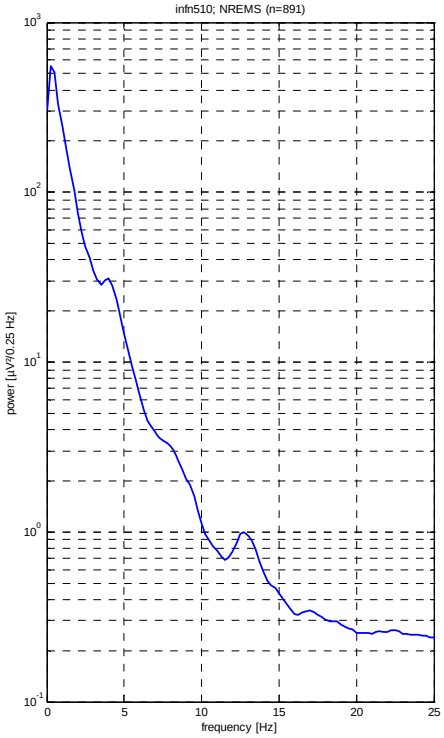
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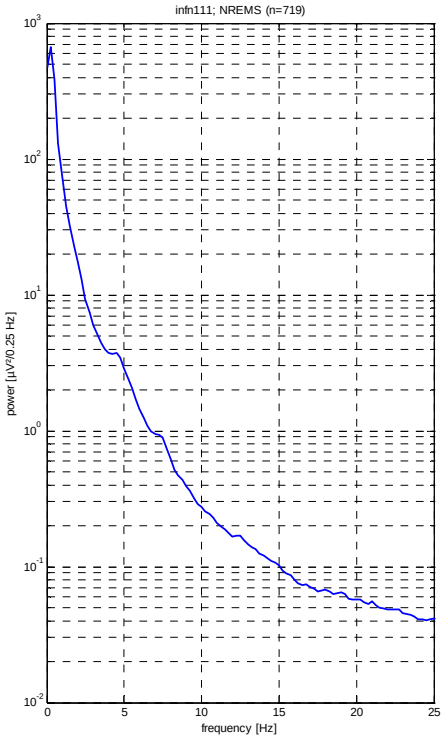
5
10
15
20
25

Inf 11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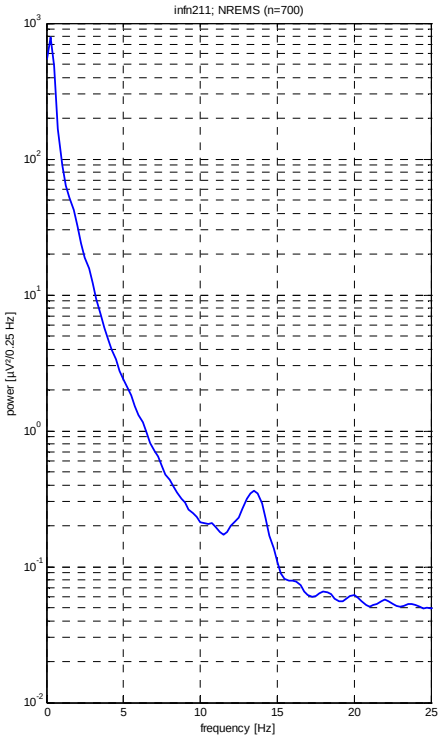
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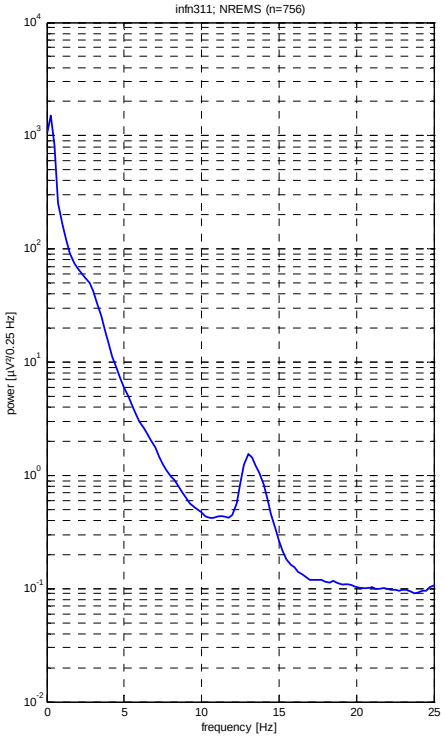
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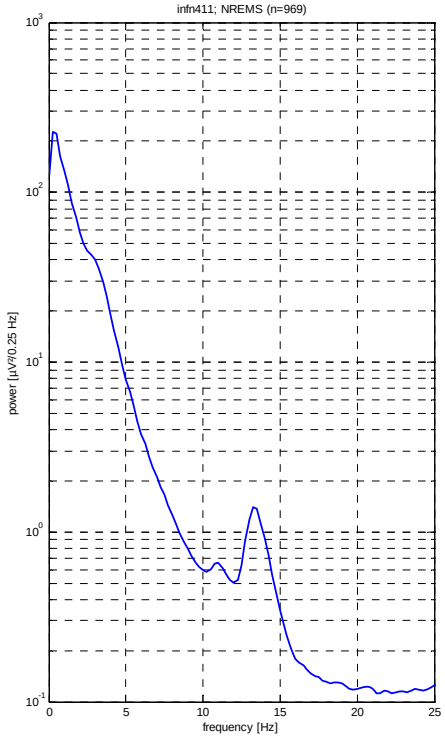
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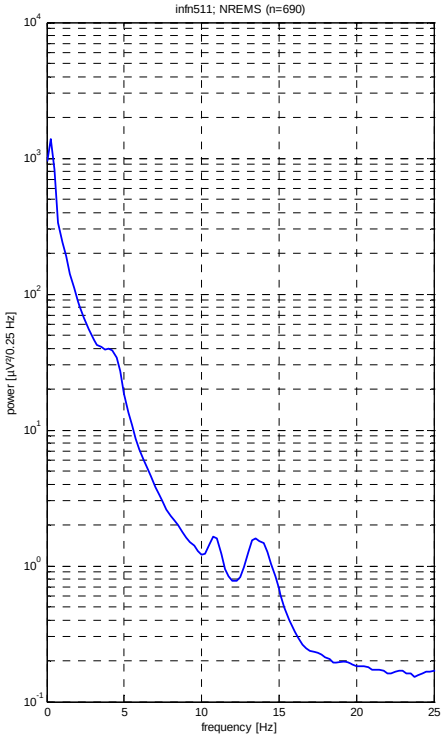
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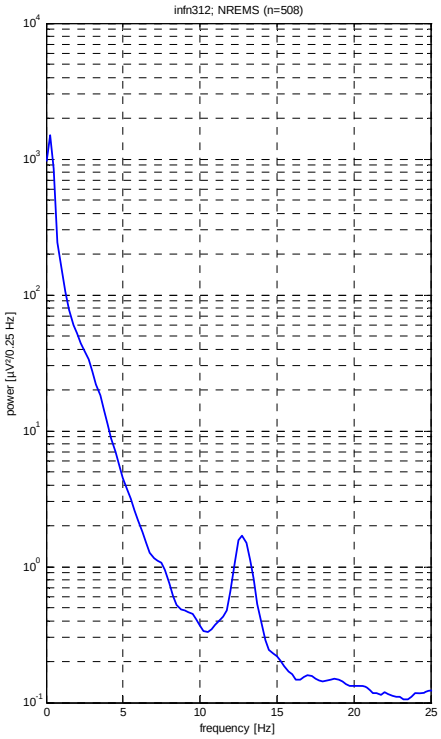
10
15
20
25

Inf 12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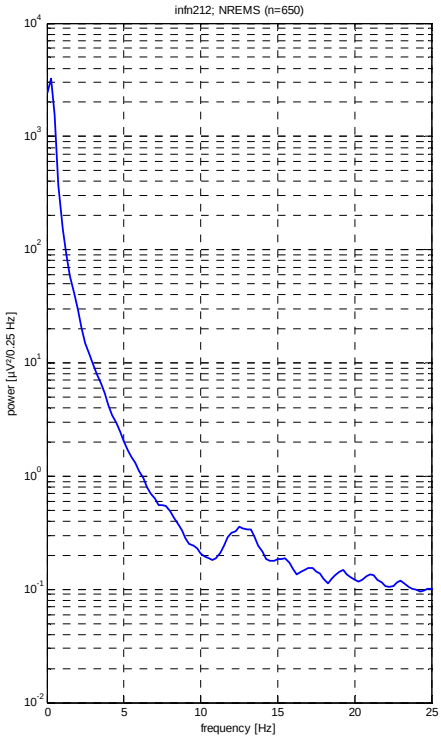
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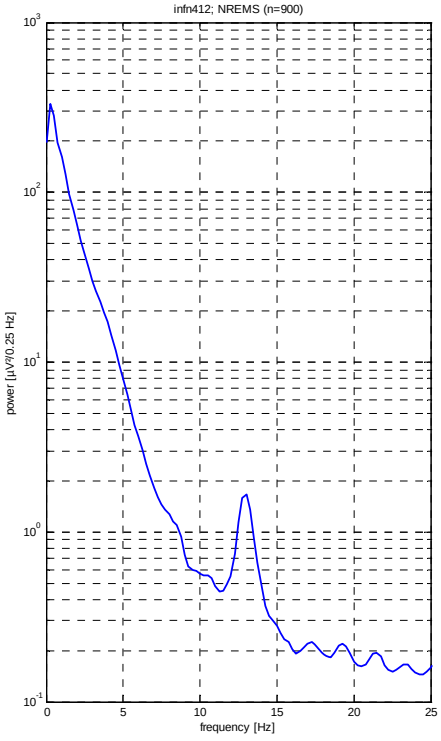
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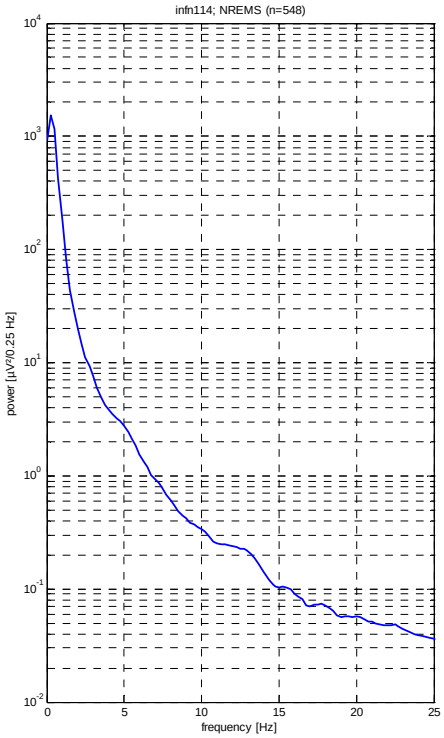
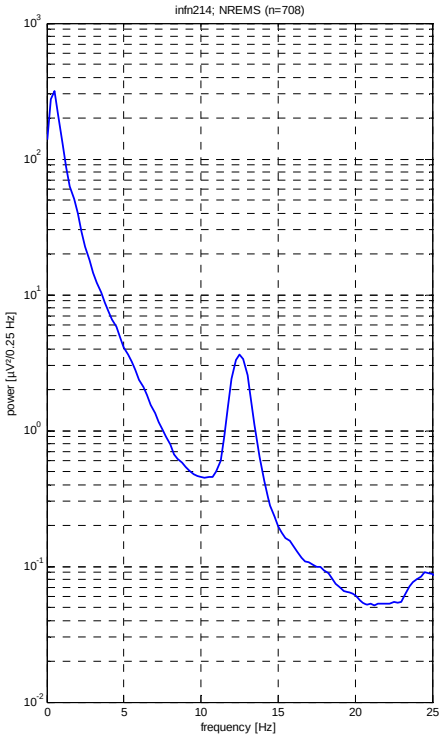
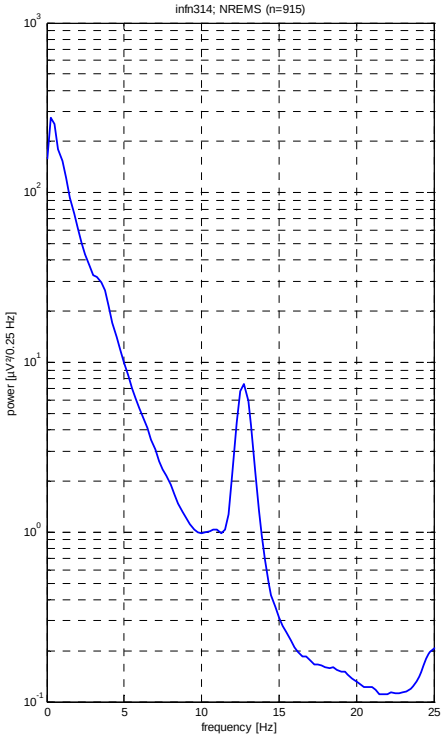
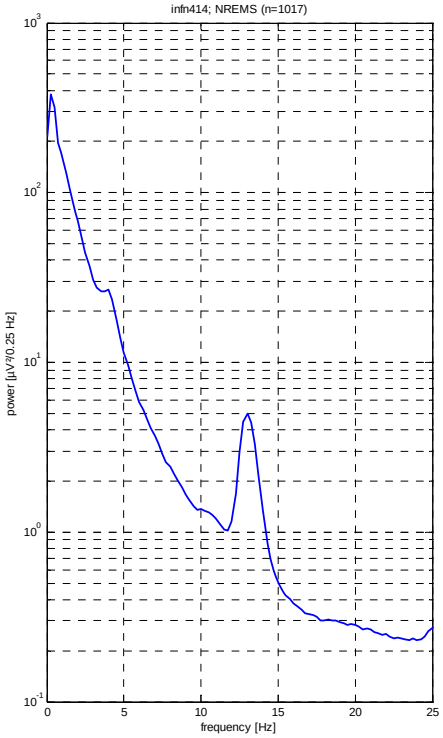
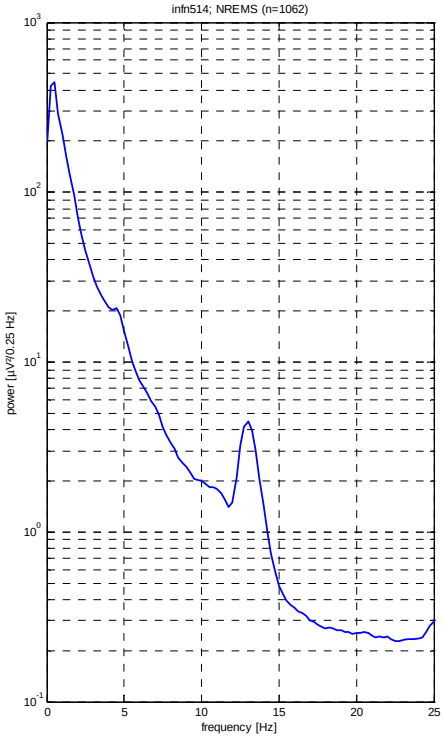
Inf 14


infn114; NREMS (n=548)
power [µV²/0.25 Hz]
frequency [Hz]

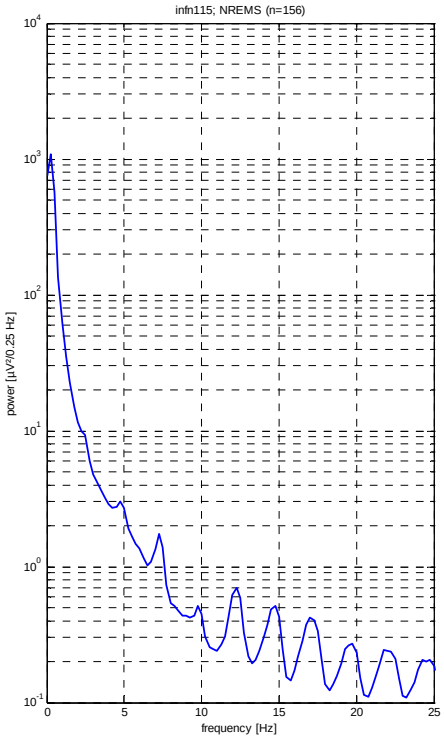

infn214; NREMS (n=708)
power [µV²/0.25 Hz]
frequency [Hz]

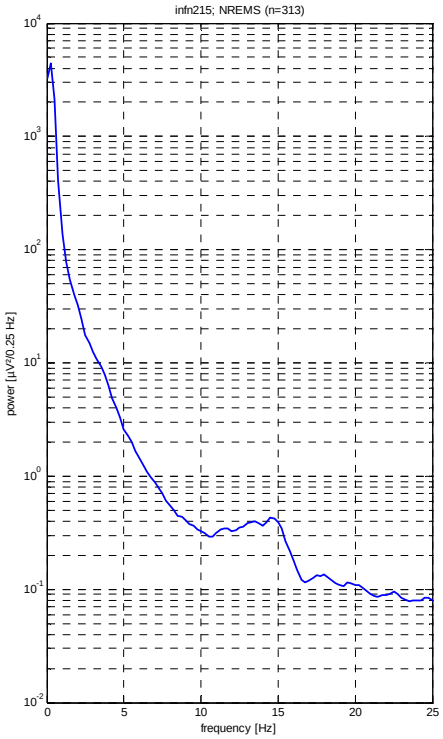

infn314; NREMS (n=915)
power [µV²/0.25 Hz]
frequency [Hz]

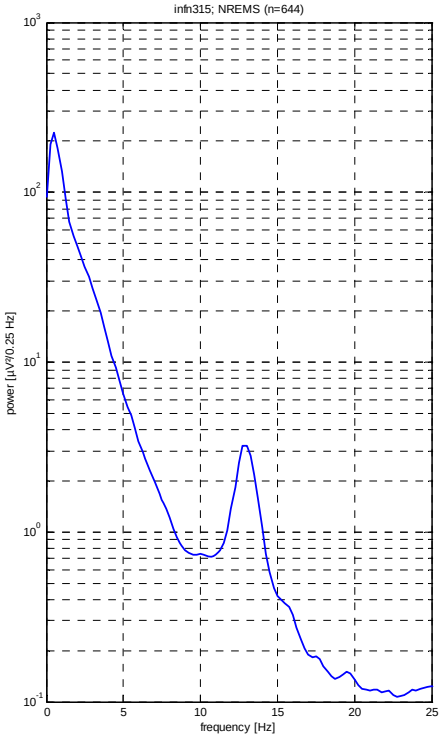

infn414; NREMS (n=1017)
power [µV²/0.25 Hz]
frequency [Hz]

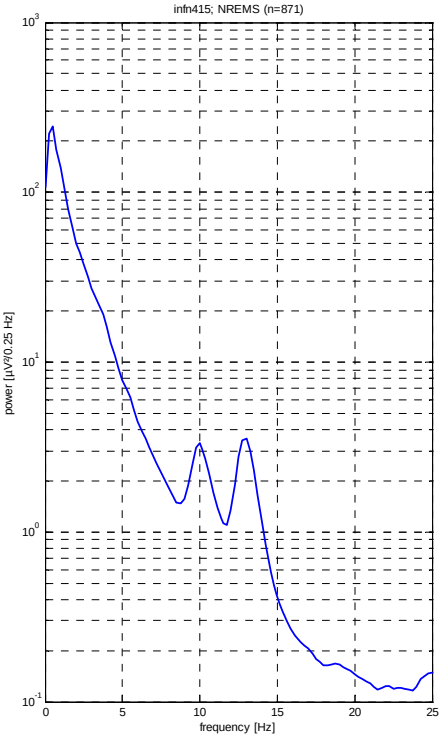

infn514; NREMS (n=1062)
power [µV²/0.25 Hz]
frequency [Hz]
10^3
10^2
10^1
10^0
10^-1
0
5
10
15
20
25

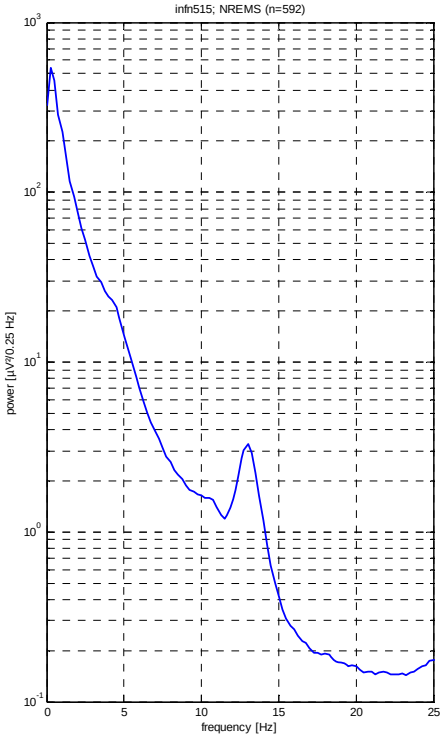
Inf 15


infn115; NREMS (n=156)
power [µV²/0.25 Hz]
frequency [Hz]

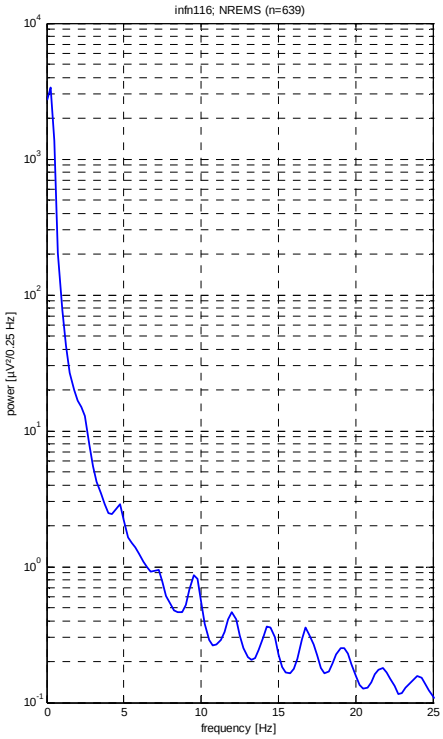

infn215; NREMS (n=313)
power [µV²/0.25 Hz]
frequency [Hz]

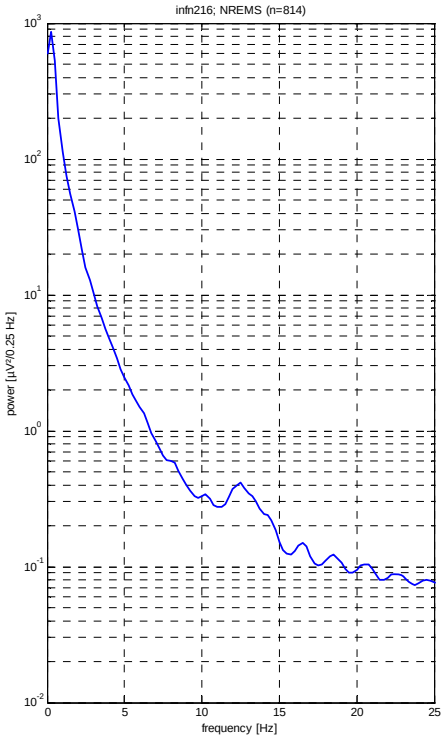

infn315; NREMS (n=644)
power [µV²/0.25 Hz]
frequency [Hz]

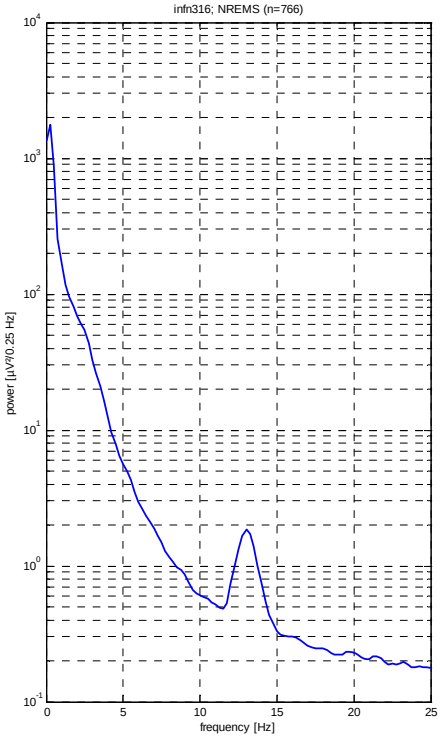

infn415; NREMS (n=871)
power [µV²/0.25 Hz]
frequency [Hz]

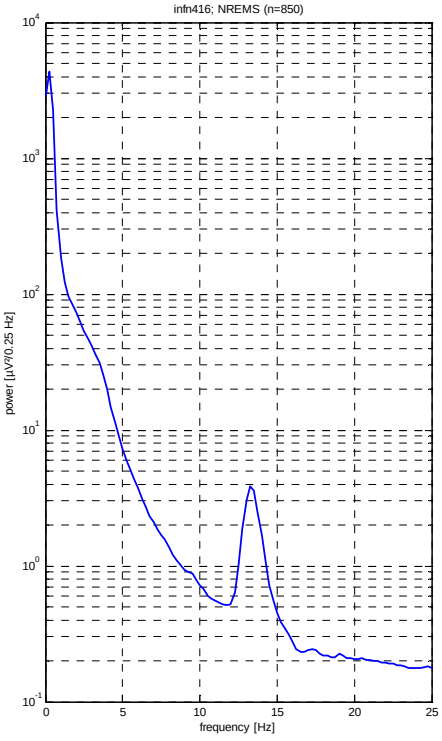

infn515; NREMS (n=592)
power [µV²/0.25 Hz]
frequency [Hz]
10^3
10^2
10^1
10^0
10^-1
0
5
10
15
20
25

Inf 16


infn116; NREMS (n=639)
power [µV²/0.25 Hz]
frequency [Hz]

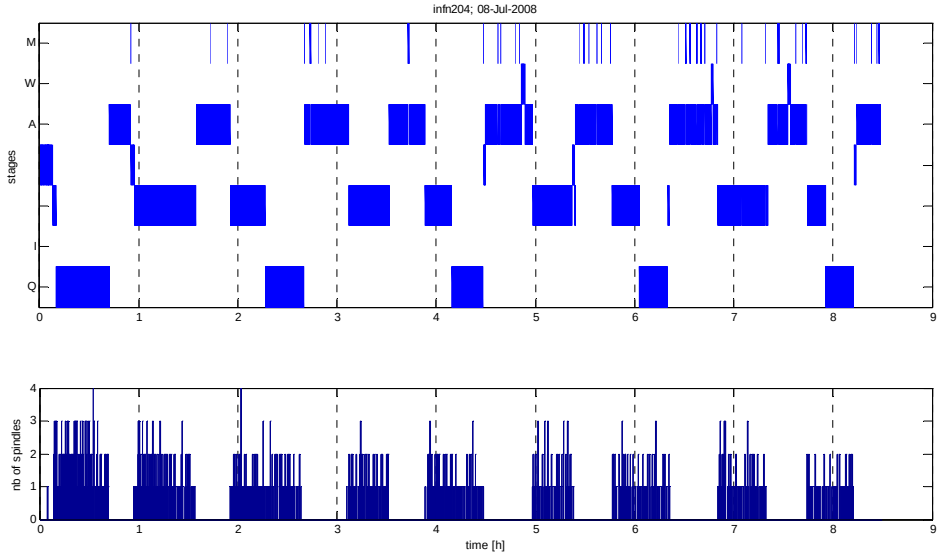

infn216; NREMS (n=814)
power [µV²/0.25 Hz]
frequency [Hz]


infn316; NREMS (n=766)
power [µV²/0.25 Hz]
frequency [Hz]

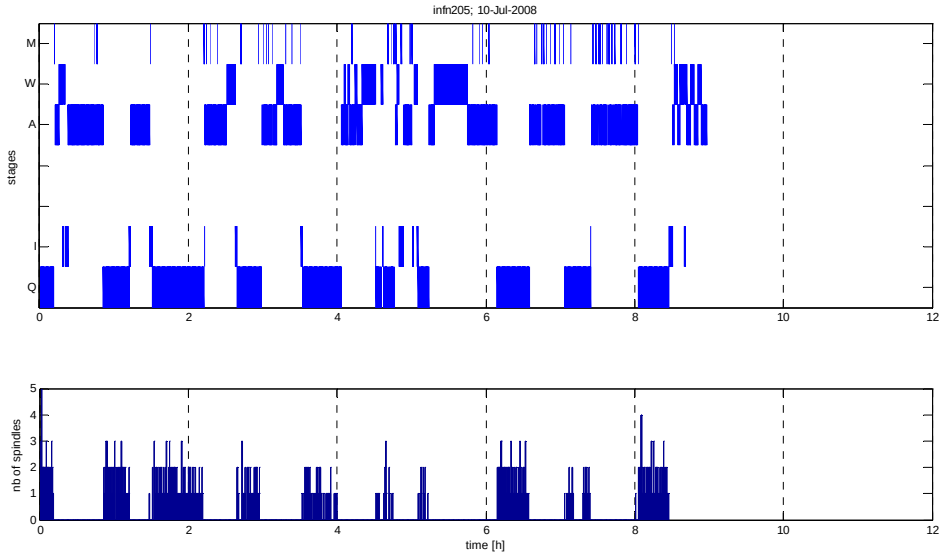

infn416; NREMS (n=850)
power [µV²/0.25 Hz]
frequency [Hz]

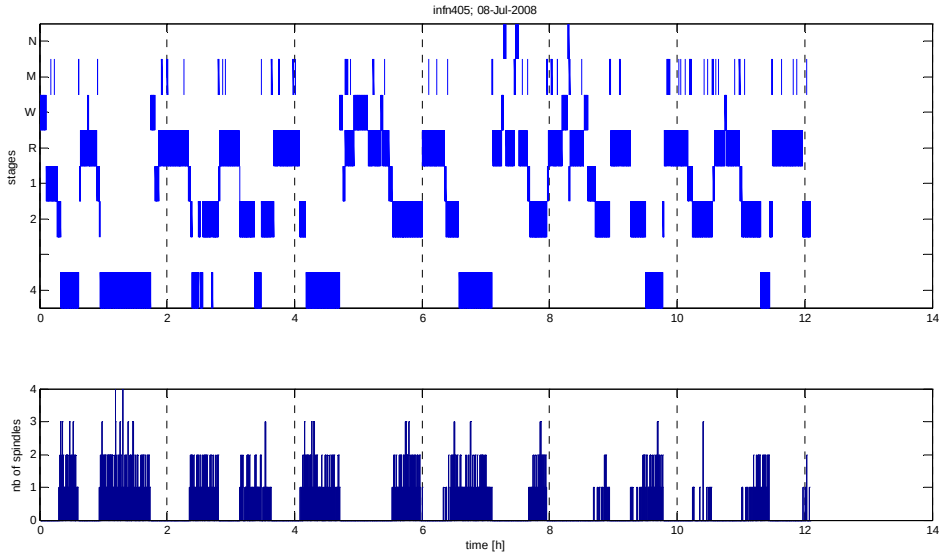
Hypnograms and occurrence of sleep spindles during the night

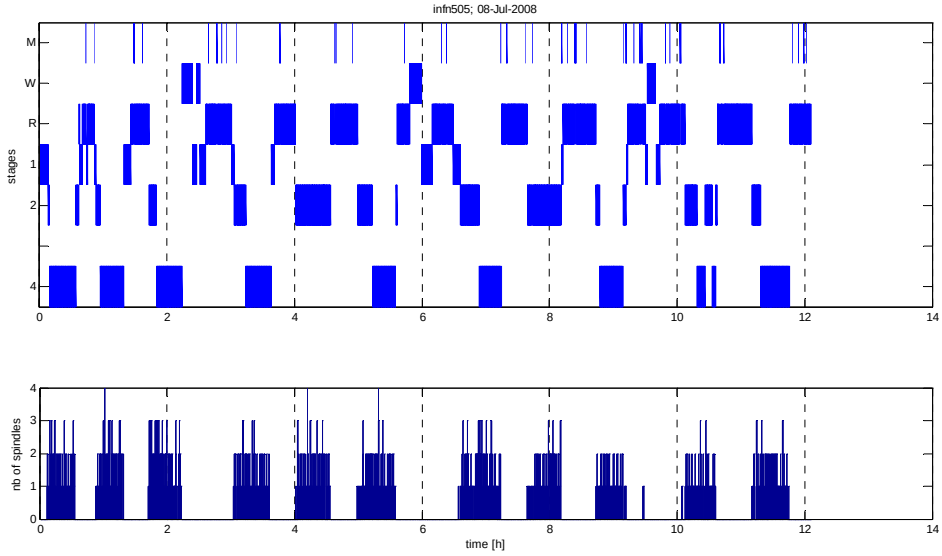
Inf 04



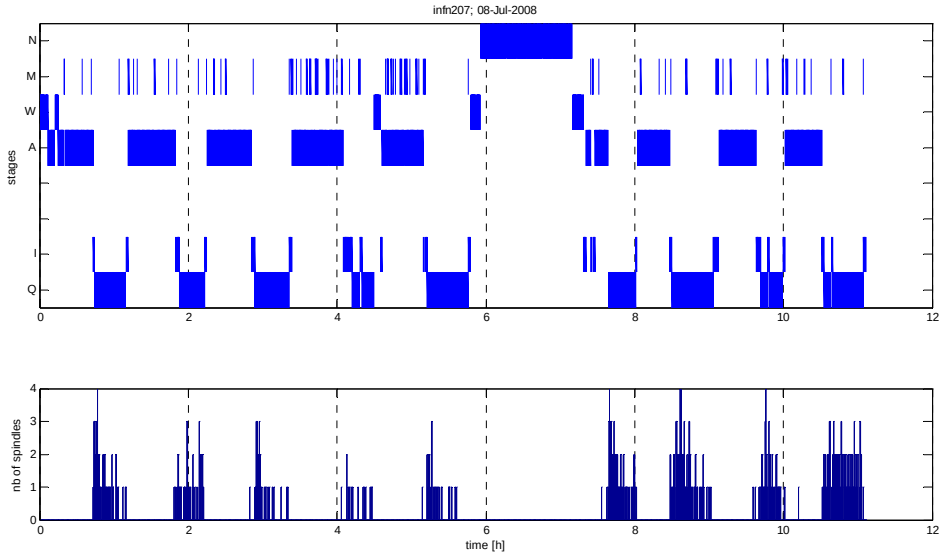
Inf 05

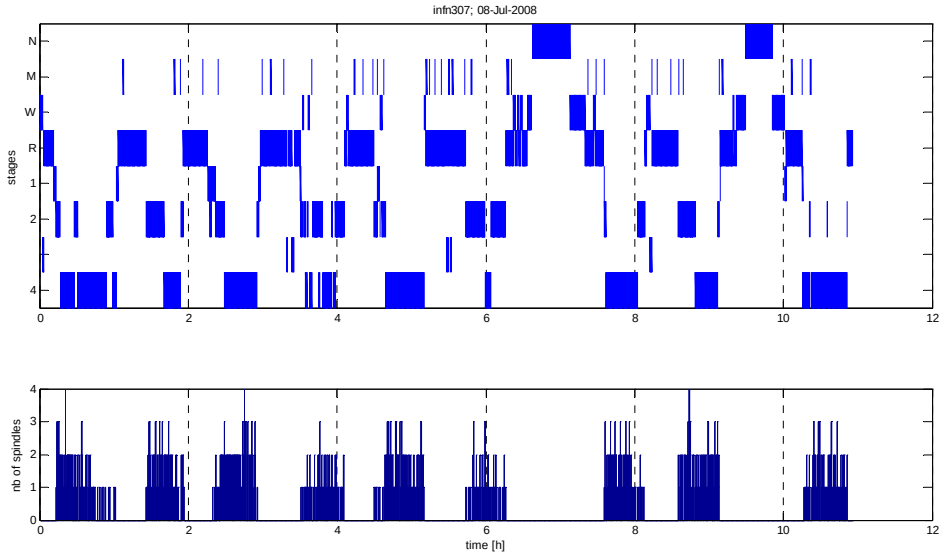

infn205; 10-Jul-2008
M
W
A
I
Q
stages
0
2
4
6
8
10
12
nb of spindles
0
1
2
3
4
5
time [h]

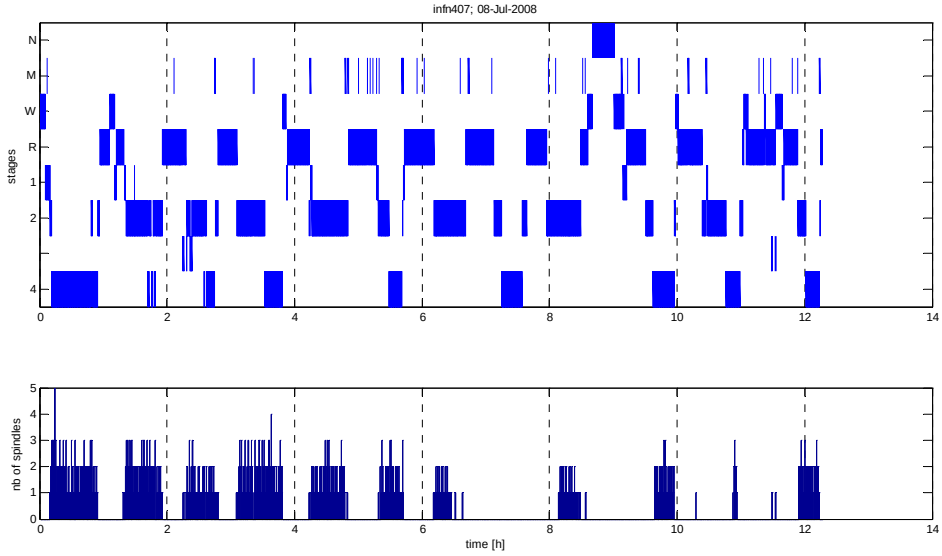

infn405; 08-Jul-2008
N
M
W
R
1
2
4
stages
0
2
4
6
8
10
12
14
nb of spindles
0
1
2
3
4
time [h]

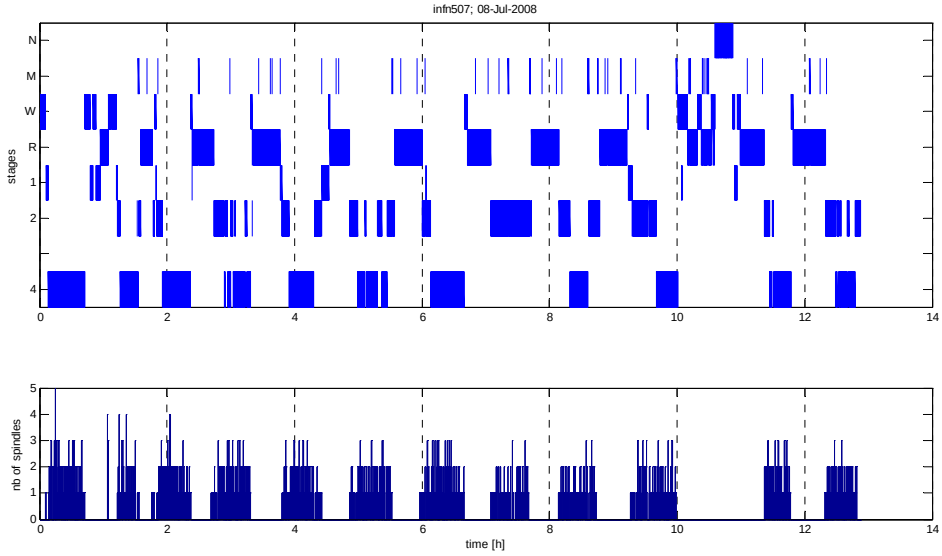

infn505; 08-Jul-2008
stages
M
W
R
1
2
4
0
2
4
6
8
10
12
14
nb of spindles
0
1
2
3
4
time [h]

Inf 07

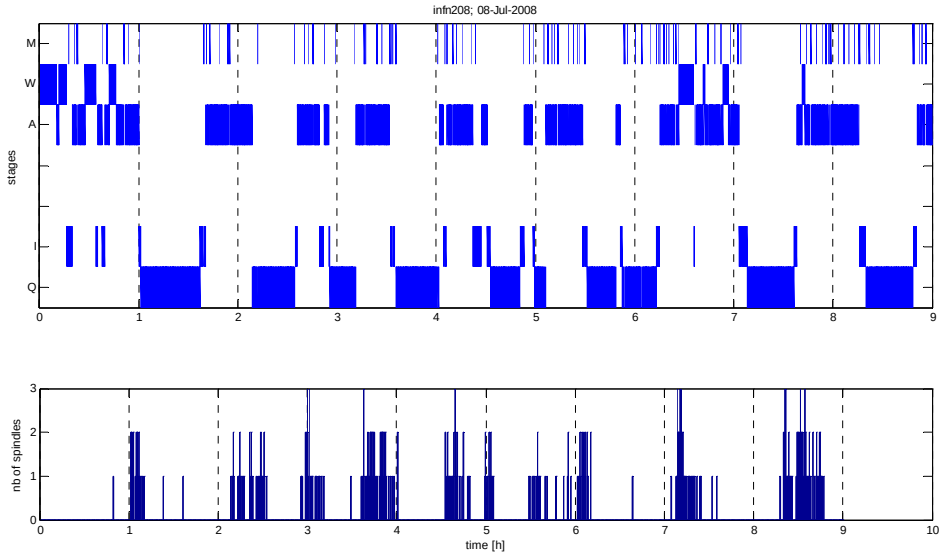

infn207; 08-Jul-2008
stages
N
M
W
A
I
Q
nb of spindles
time [h]

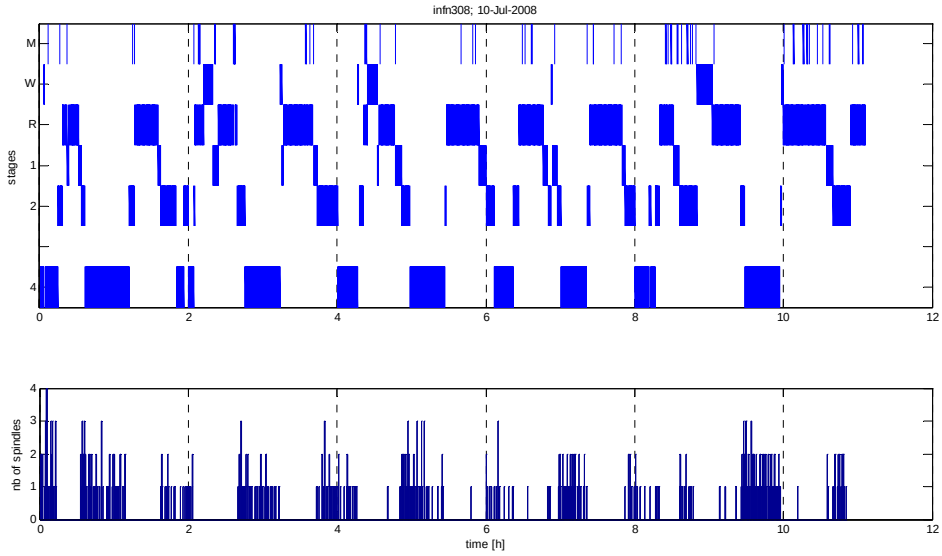

infn307; 08-Jul-2008
stages
N
M
W
R
1
2
4
nb of spindles
time [h]

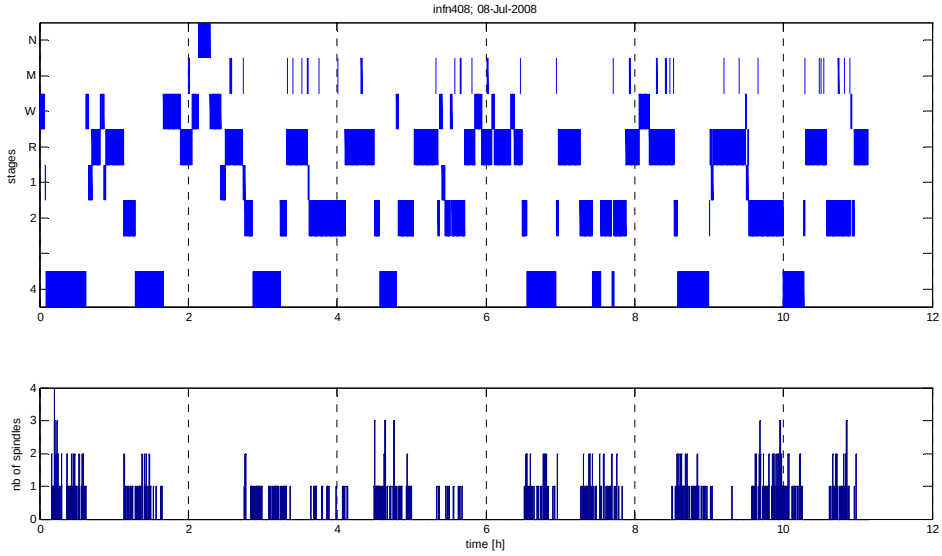

infn407; 08-Jul-2008
stages
N
M
W
R
1
2
4
0
2
4
6
8
10
12
14
nb of spindles
5
4
3
2
1
0
time [h]

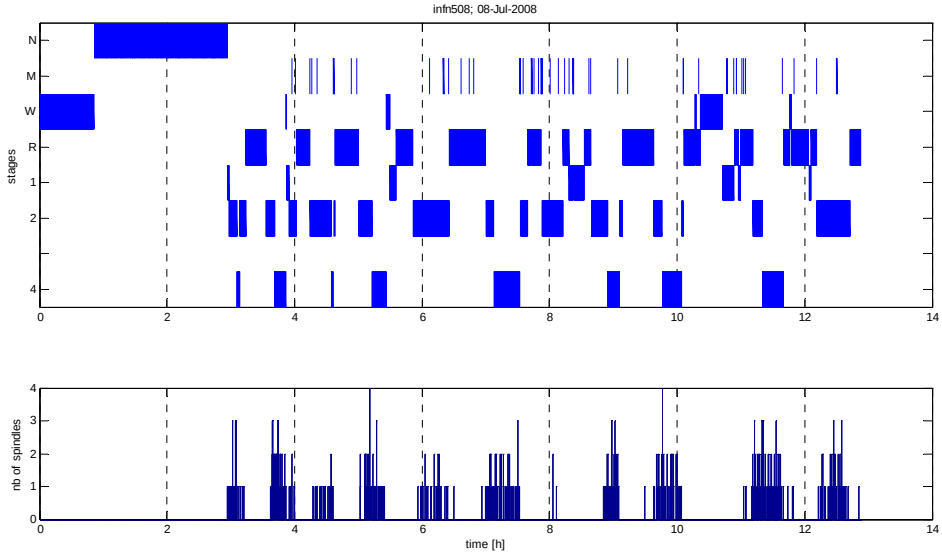

infn507; 08-Jul-2008
stages
N
M
W
R
1
2
4
0
2
4
6
8
10
12
14
nb of spindles
5
4
3
2
1
0
time [h]

Inf 08

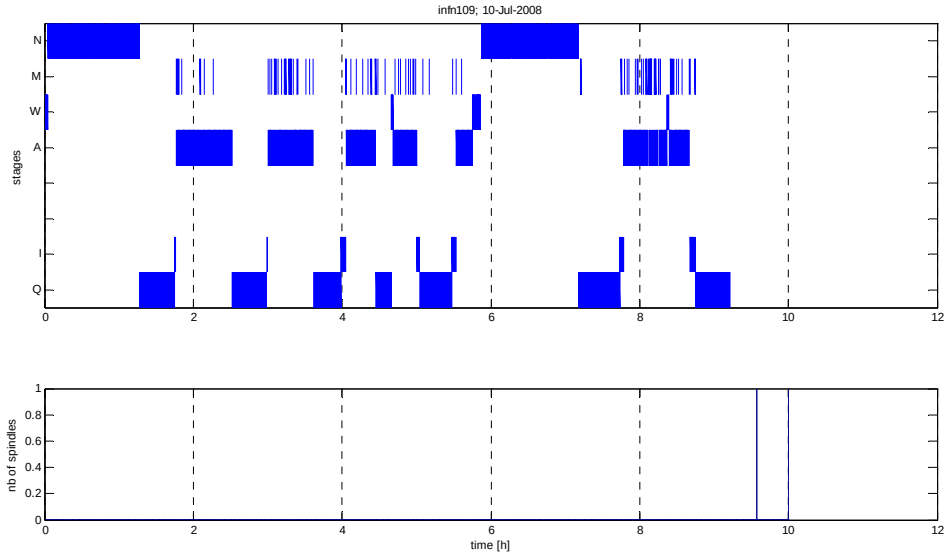

infn208; 08-Jul-2008
M
W
A
I
Q
stages
nb of spindles
time [h]

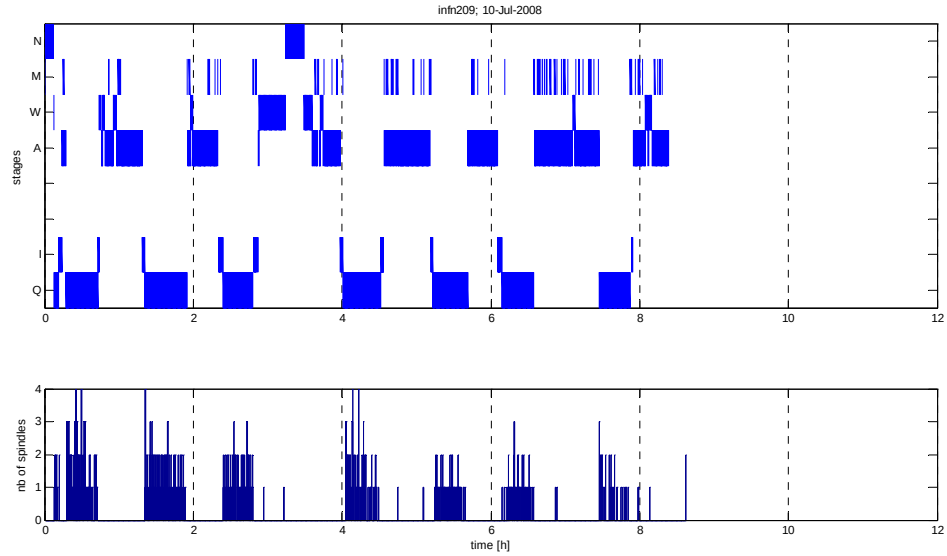

infn308; 10-Jul-2008
M
W
R
1
2
4
stages
nb of spindles
time [h]

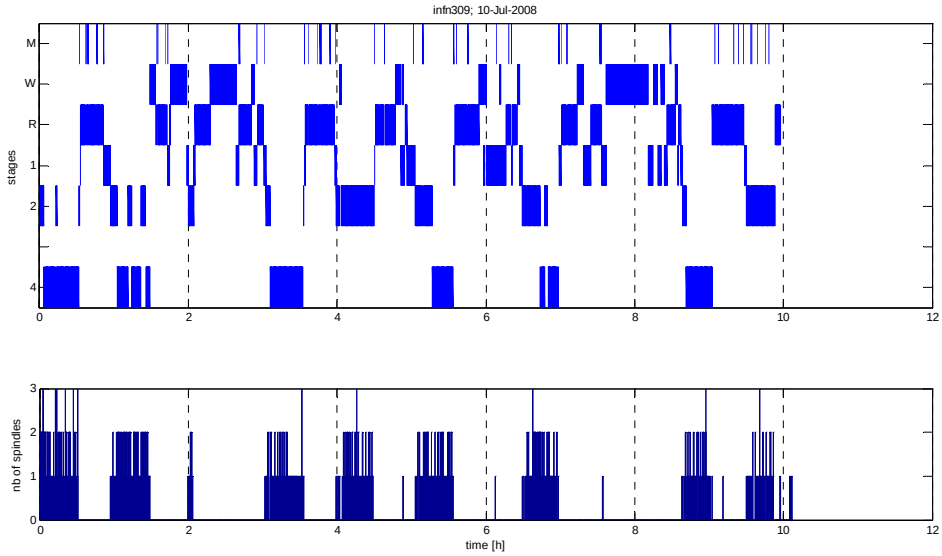

infn408; 08-Jul-2008
stages
N
M
W
R
1
2
4
0
2
4
6
8
10
12
nb of spindles
0
1
2
3
4
time [h]


infn508; 08-Jul-2008
stages
N
M
W
R
1
2
4
0
2
4
6
8
10
12
14
nb of spindles
0
1
2
3
4
time [h]

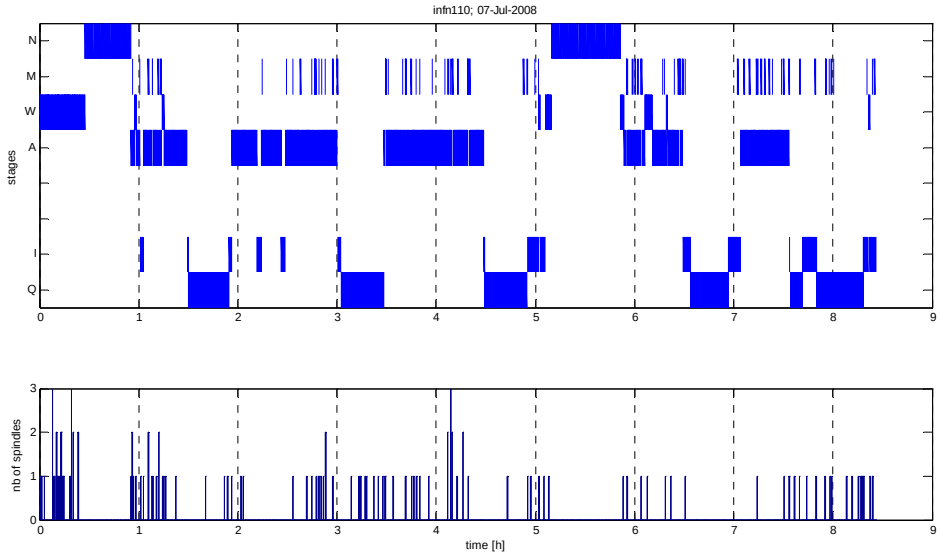
Inf 09

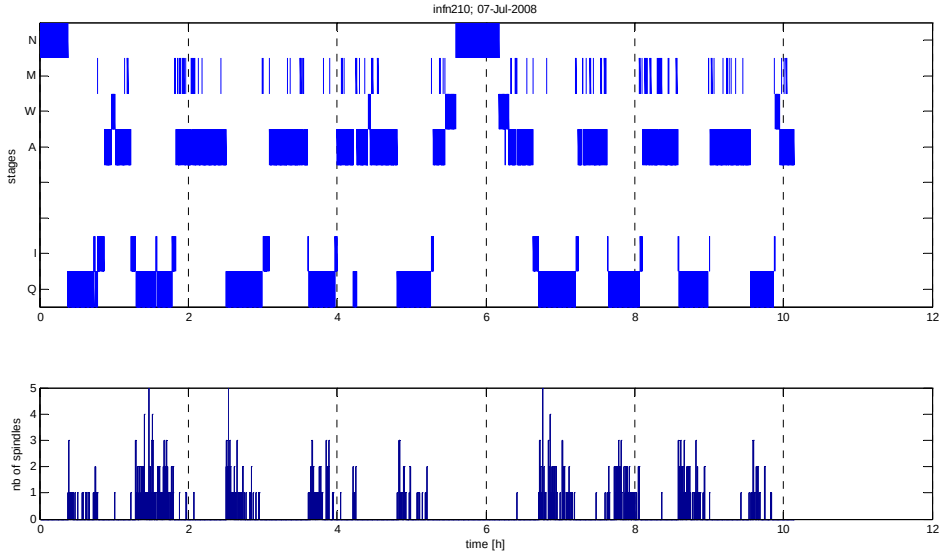

infn109; 10-Jul-2008
stages
N
M
W
A
I
Q
0
2
4
6
8
10
12
nb of spindles
1
0.8
0.6
0.4
0.2
0
time [h]

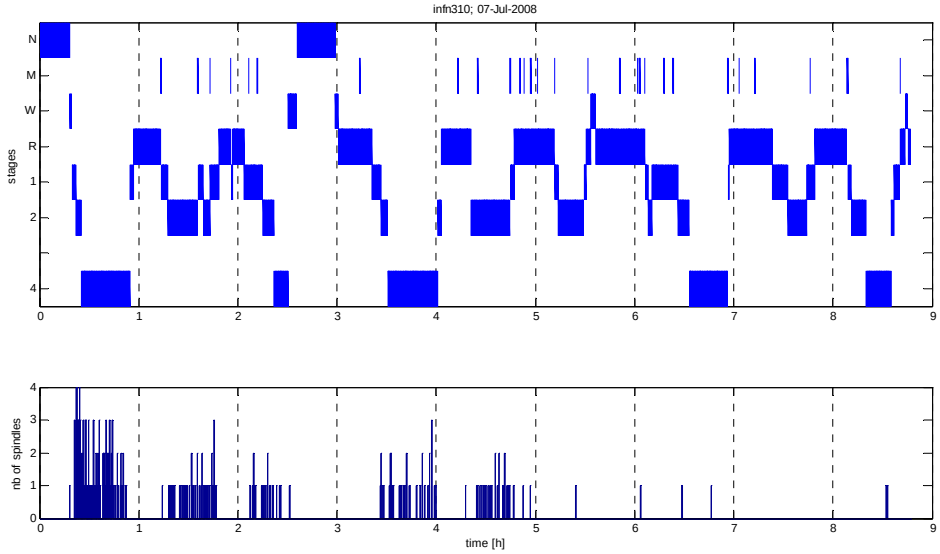

infn209; 10-Jul-2008
stages
N
M
W
A
I
Q
0
2
4
6
8
10
12
nb of spindles
4
3
2
1
0
time [h]

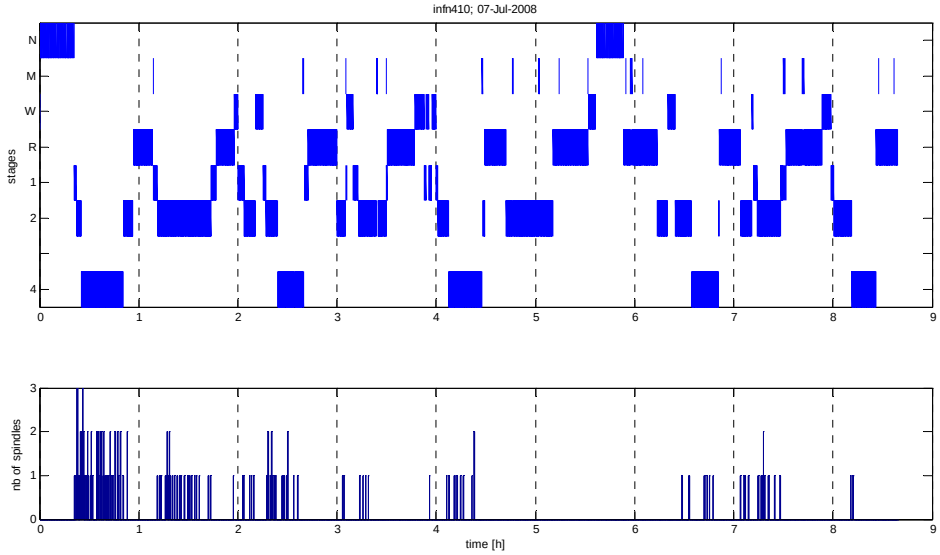

infn309; 10-Jul-2008
stages
M
W
R
1
2
4
0
2
4
6
8
10
12
nb of spindles
3
2
1
0
time [h]

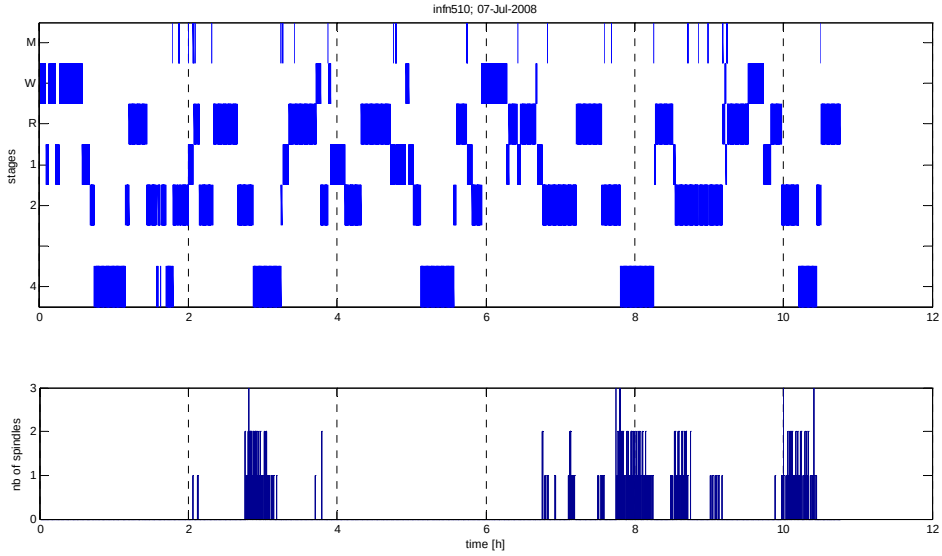
Inf 10


infn110; 07-Jul-2008
stages
N
M
W
A
I
Q
nb of spindles
time [h]

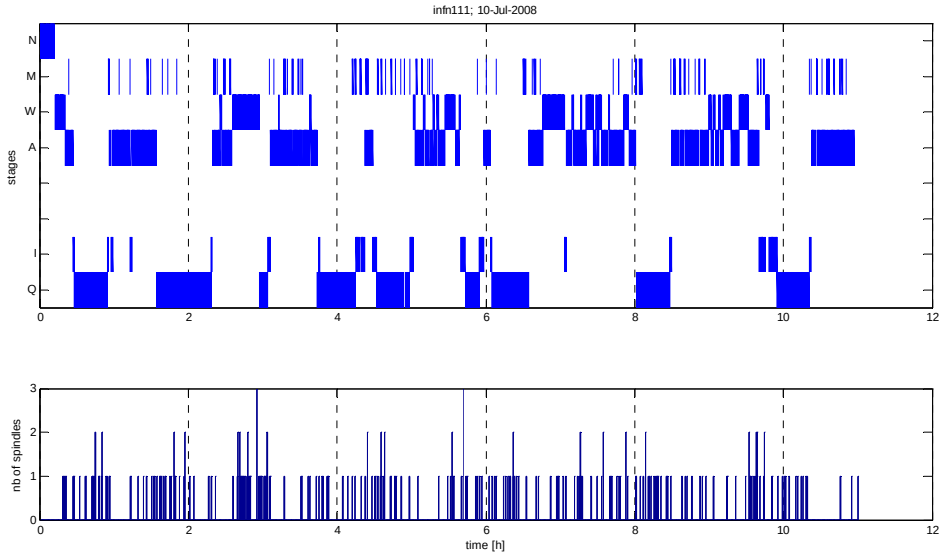

infn210; 07-Jul-2008
stages
N
M
W
A
I
Q
nb of spindles
time [h]

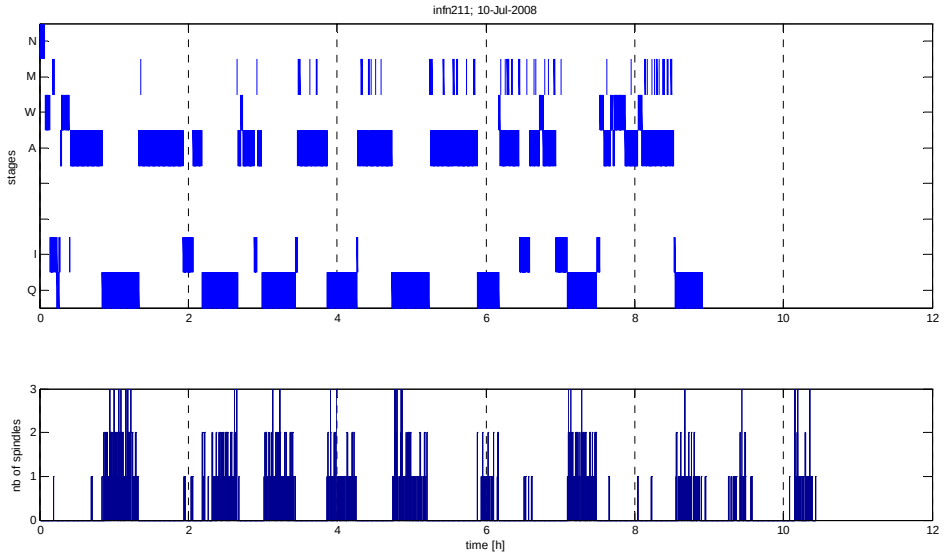

infn310; 07-Jul-2008
stages
N
M
W
R
1
2
4
nb of spindles
time [h]

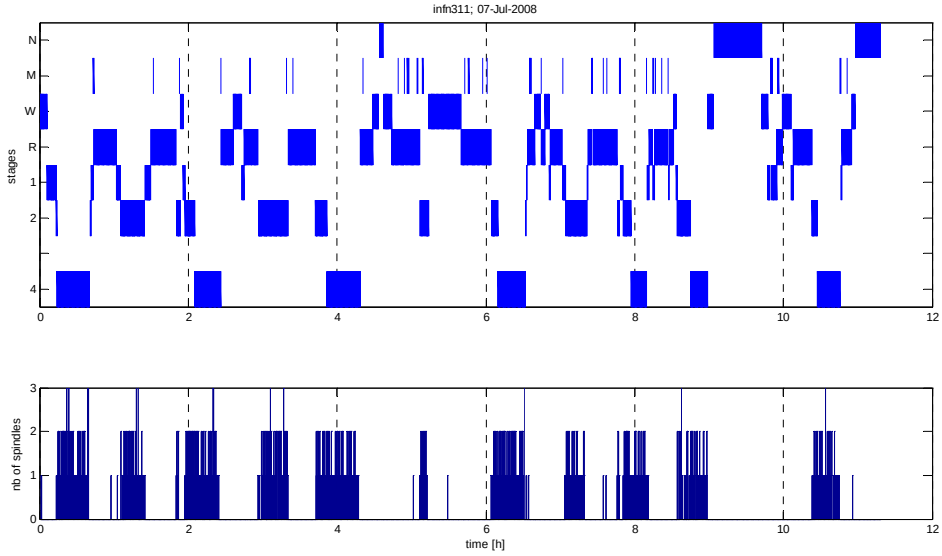

infn410; 07-Jul-2008
stages
N
M
W
R
1
2
4
nb of spindles
time [h]

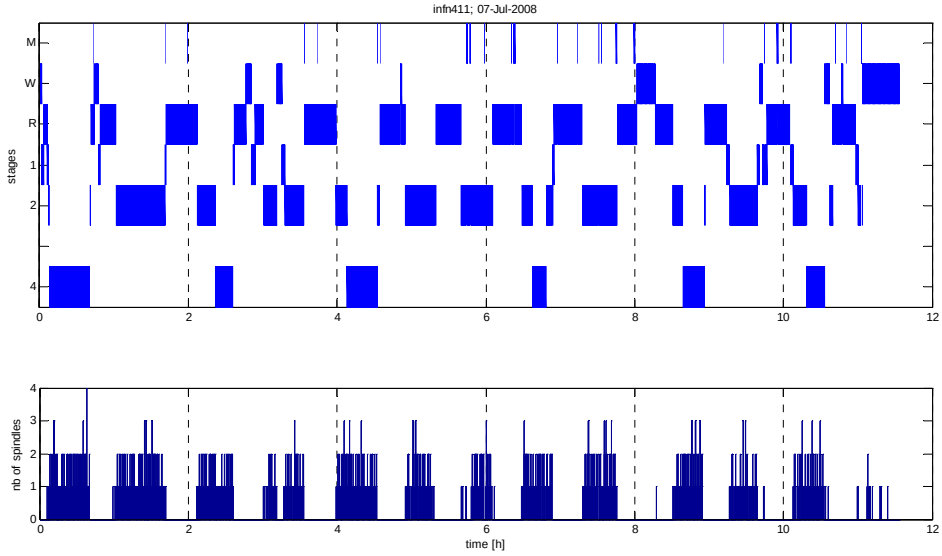

infn510; 07-Jul-2008
stages
M
W
R
1
2
4
0
2
4
6
8
10
12
nb of spindles
3
2
1
0
time [h]

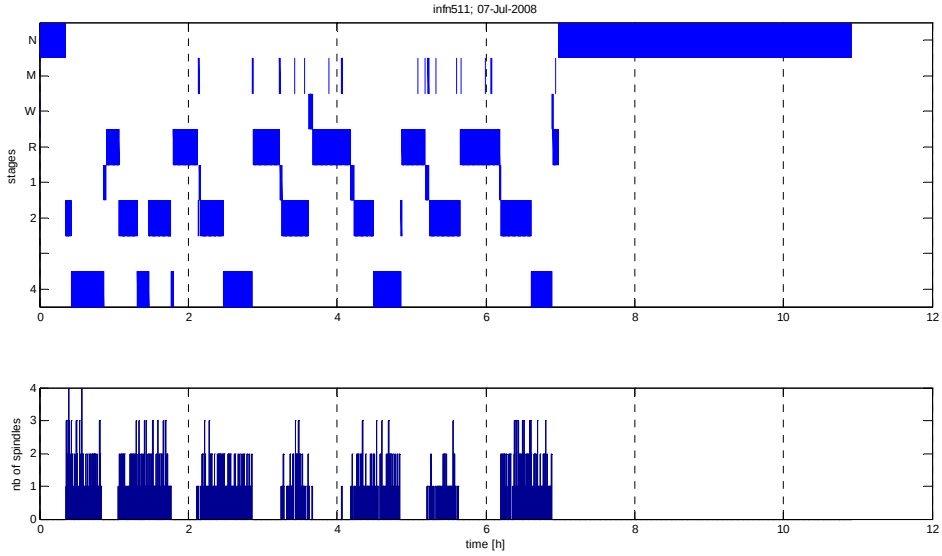
Inf 11


infn111; 10-Jul-2008
N
M
W
A
I
Q
stages
0
2
4
6
8
10
12
3
2
1
0
nb of spindles
time [h]

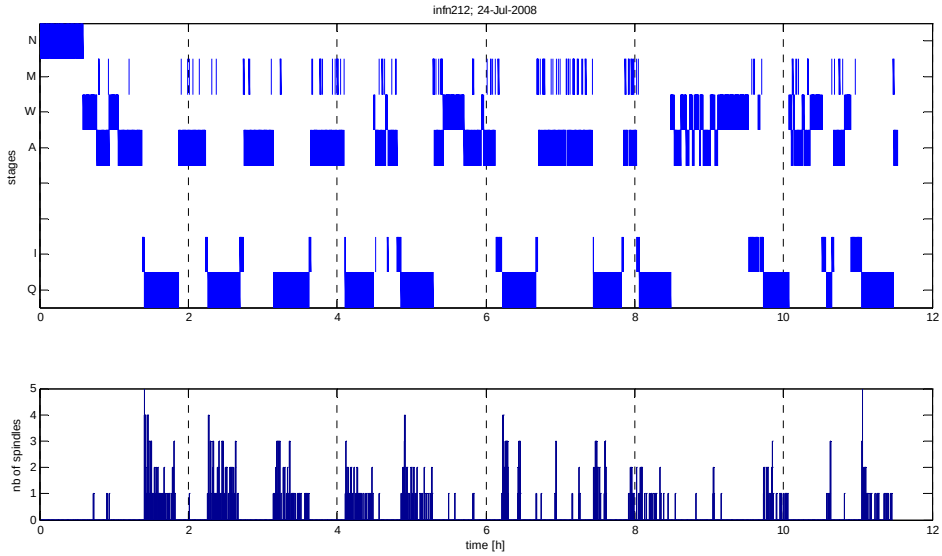

infn211; 10-Jul-2008
N
M
W
A
I
Q
stages
0
2
4
6
8
10
12
3
2
1
0
nb of spindles
time [h]

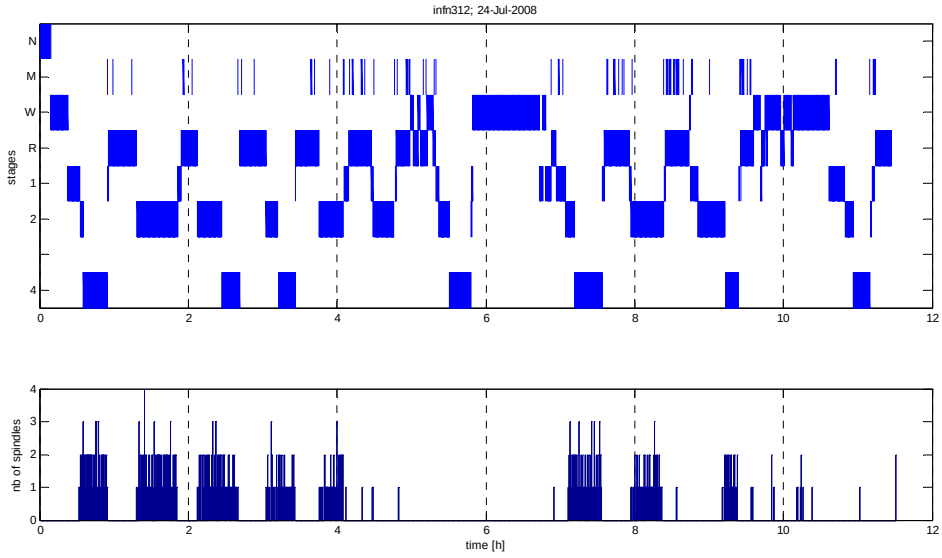

infn311; 07-Jul-2008
stages
N
M
W
R
1
2
4
nb of spindles
time [h]
0
2
4
6
8
10
12
1
3

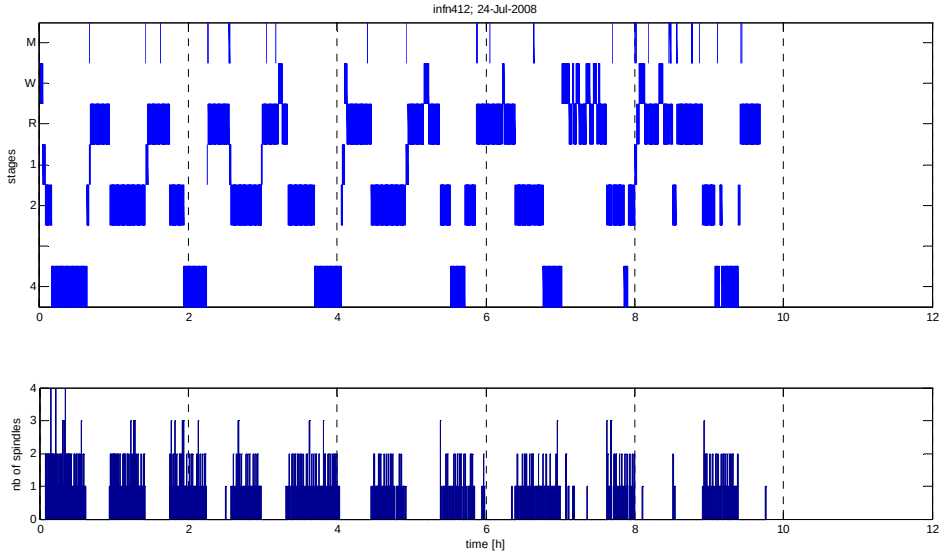

infn411; 07-Jul-2008
stages
M
W
R
1
2
4
nb of spindles
time [h]
0
2
4
6
8
10
12
3


infn511; 07-Jul-2008
stages
N
M
W
R
1
2
4
0
2
4
6
8
10
12
nb of spindles
0
1
2
3
4
time [h]

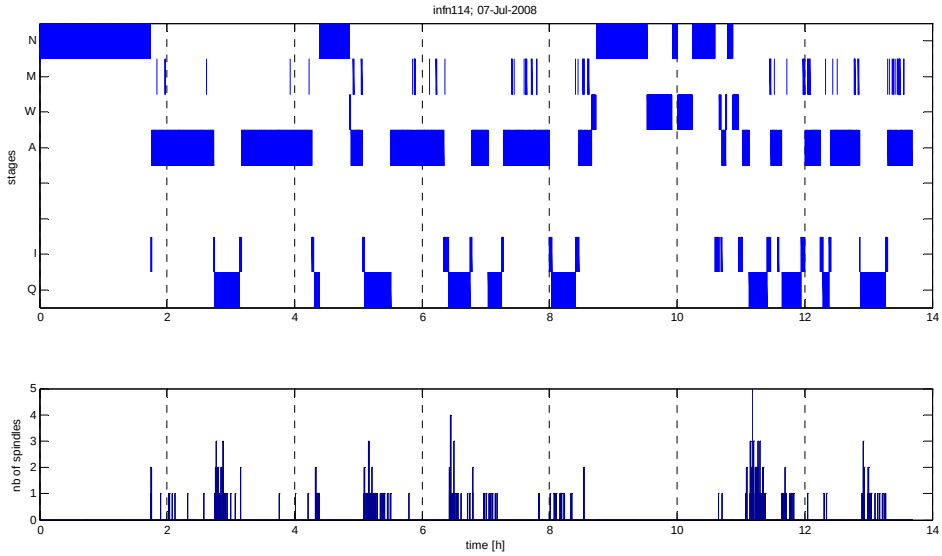
Inf 12

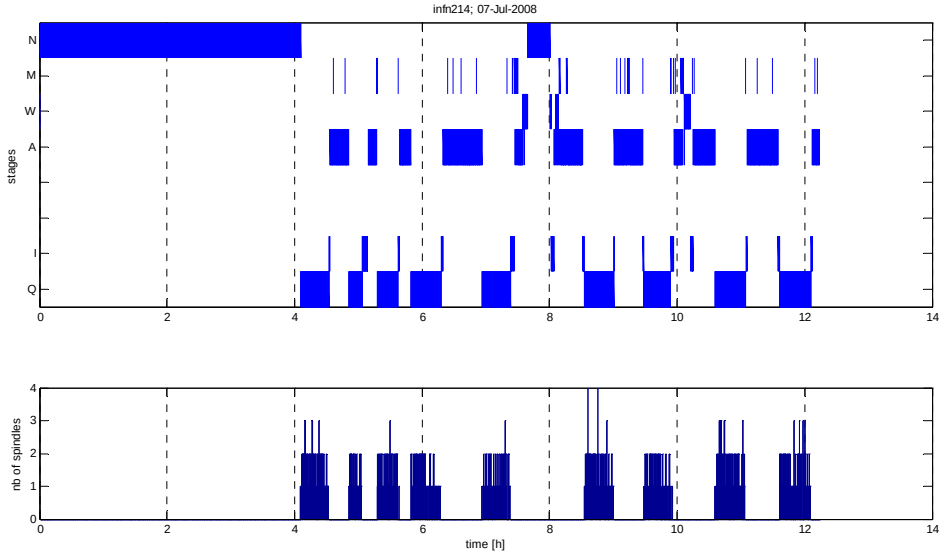

infn212; 24-Jul-2008
stages
N
M
W
A
I
Q
0
2
4
6
8
10
12
nb of spindles
0
1
2
3
4
5
time [h]

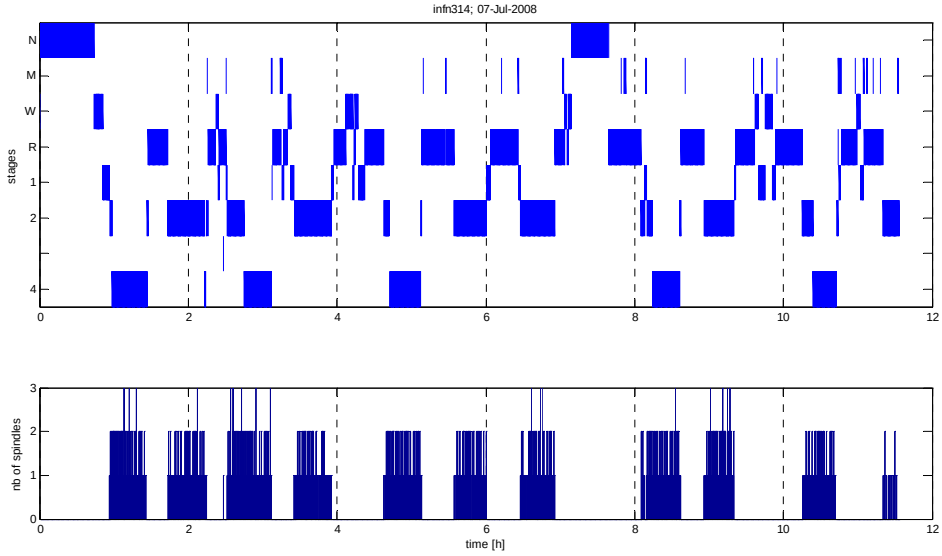

infn312; 24-Jul-2008
stages
N
M
W
R
1
2
4
0
2
4
6
8
10
12
nb of spindles
0
1
2
3
4
time [h]

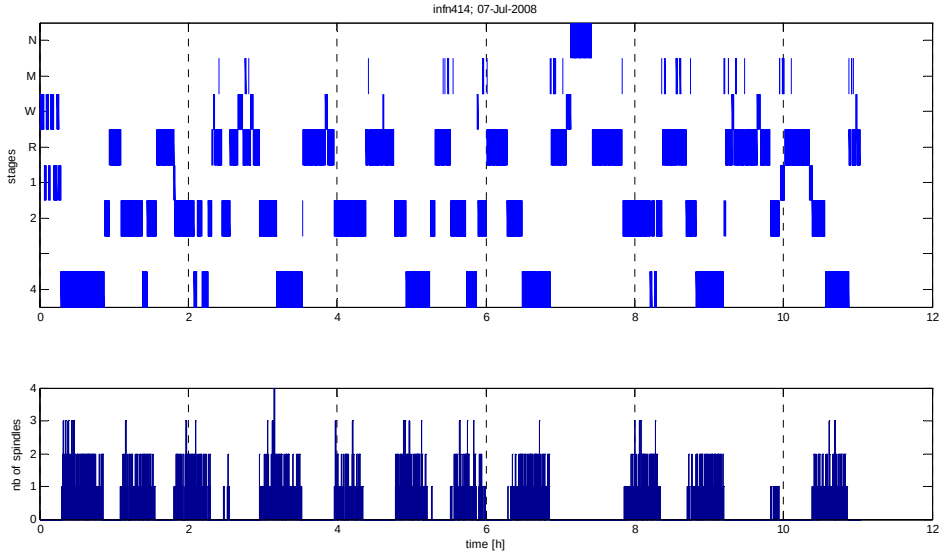

infn412; 24-Jul-2008
stages
M
W
R
1
2
4
0
2
4
6
8
10
12
nb of spindles
0
1
2
3
4
time [h]

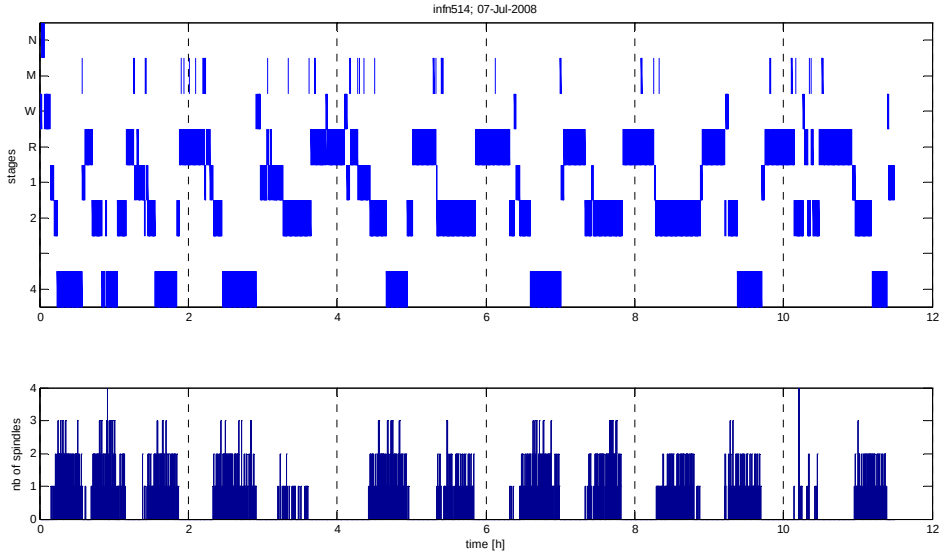
Inf 14


infn114; 07-Jul-2008
stages
N
M
W
A
I
Q
0
2
4
6
8
10
12
14
nb of spindles
0
1
2
3
4
5
time [h]

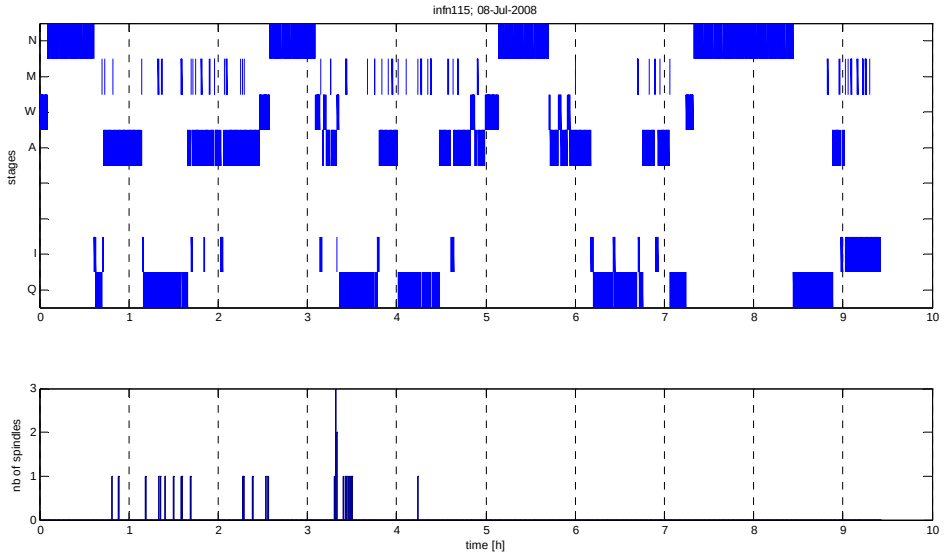

infn214; 07-Jul-2008
stages
N
M
W
A
I
Q
0
2
4
6
8
10
12
14
nb of spindles
0
1
2
3
4
time [h]

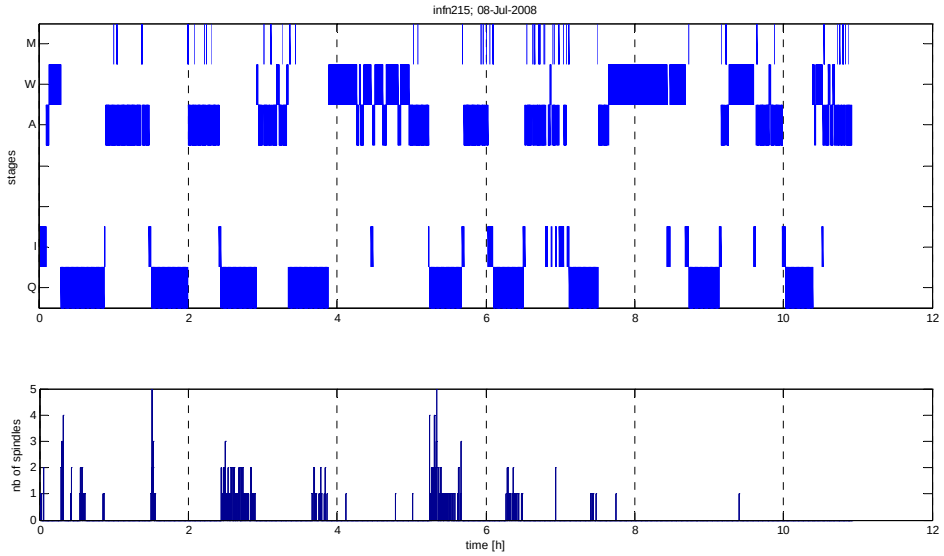

infn314; 07-Jul-2008
stages
N
M
W
R
1
2
4
0
2
4
6
8
10
12
nb of spindles
3
2
1
0
time [h]

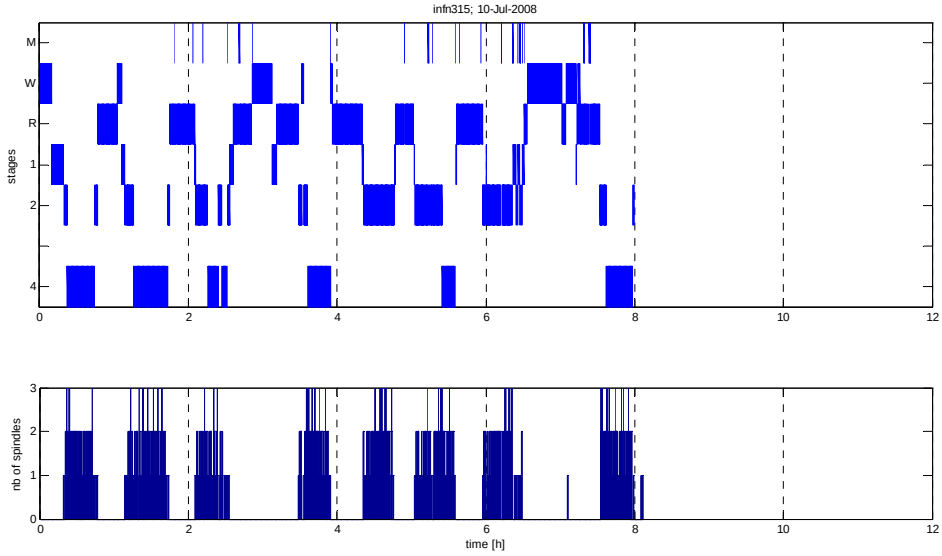

infn414; 07-Jul-2008
stages
N
M
W
R
1
2
4
0
2
4
6
8
10
12
nb of spindles
4
3
2
1
0
time [h]

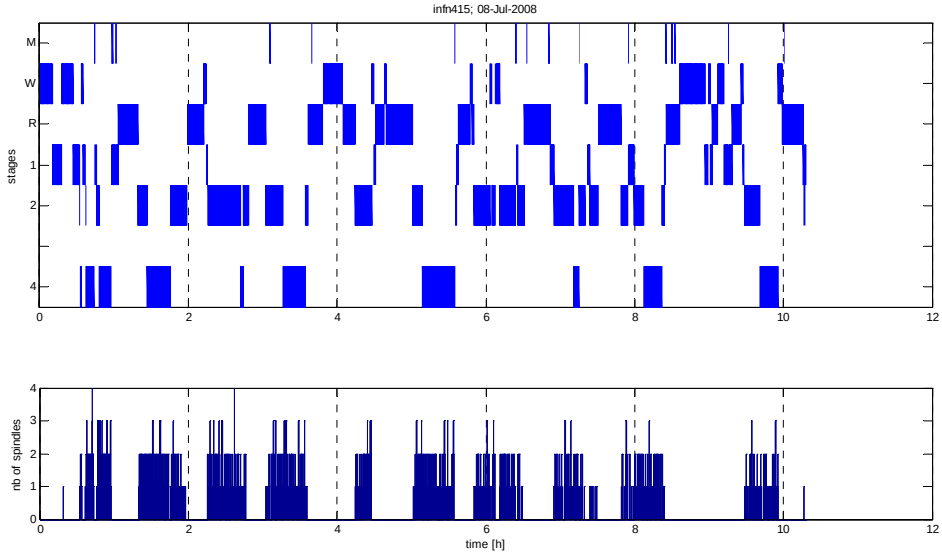

infn514; 07-Jul-2008
stages
N
M
W
R
1
2
4
0
2
4
6
8
10
12
nb of spindles
0
1
2
3
4
time [h]

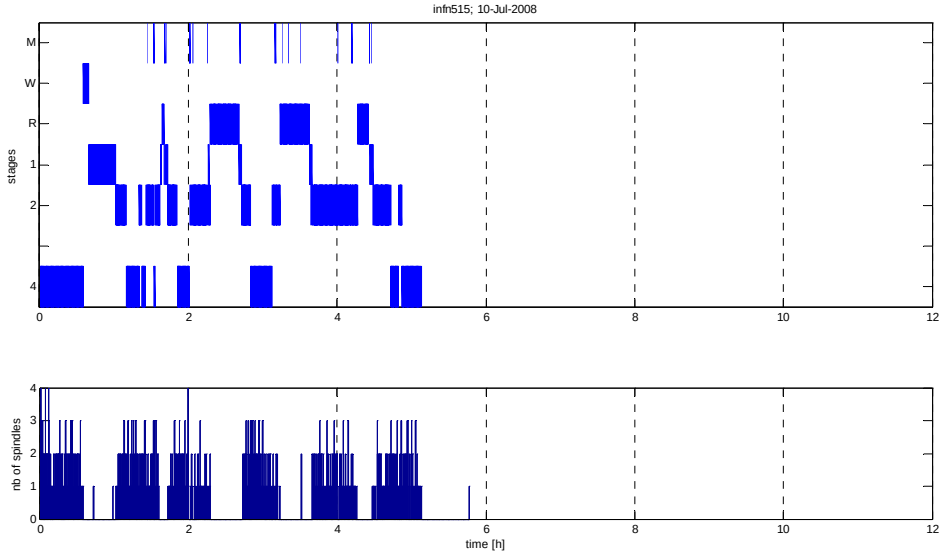
Inf 15


infn115; 08-Jul-2008
N
M
W
A
I
Q
stages
0
1
2
3
4
5
6
7
8
9
10
nb of spindles
time [h]

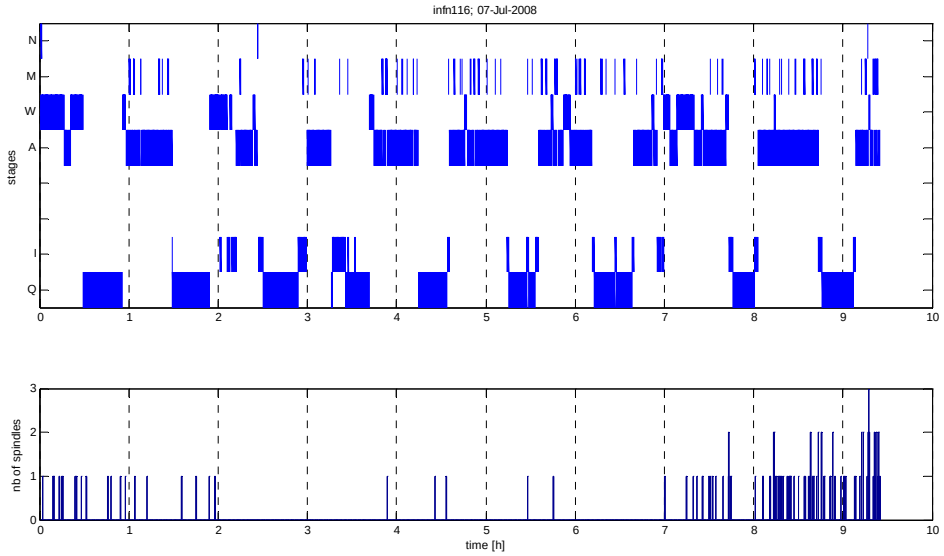

infn215; 08-Jul-2008
M
W
A
I
Q
stages
0
2
4
6
8
10
12
nb of spindles
time [h]

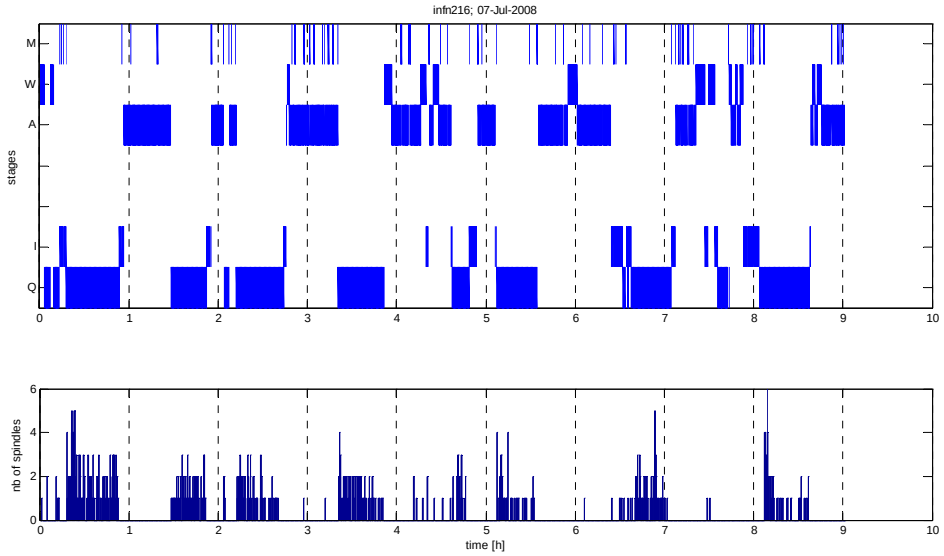

infn315; 10-Jul-2008
stages
M
W
R
1
2
4
nb of spindles
0
1
2
3
0
2
4
6
8
10
12
time [h]

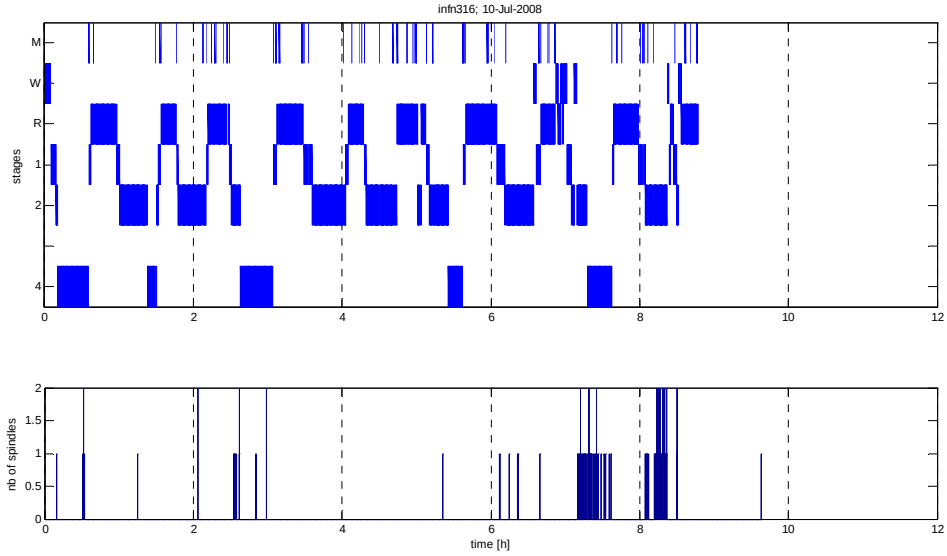

infn415; 08-Jul-2008
stages
M
W
R
1
2
4
nb of spindles
0
1
2
3
4
0
2
4
6
8
10
12
time [h]

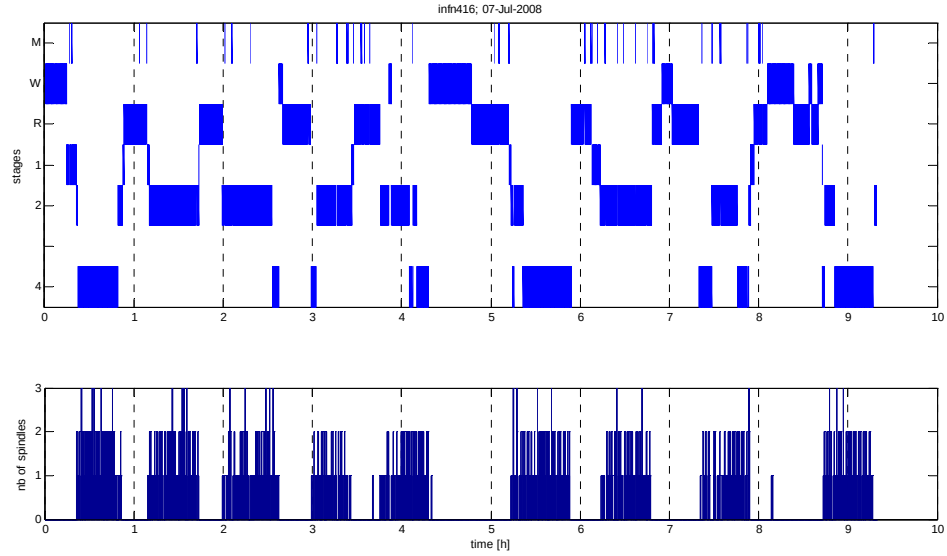

infn515; 10-Jul-2008
stages
M
W
R
1
2
4
0
2
4
6
8
10
12
nb of spindles
0
1
2
3
4
time [h]

Inf 16


infn116; 07-Jul-2008
stages
N
M
W
A
I
Q
nb of spindles
time [h]

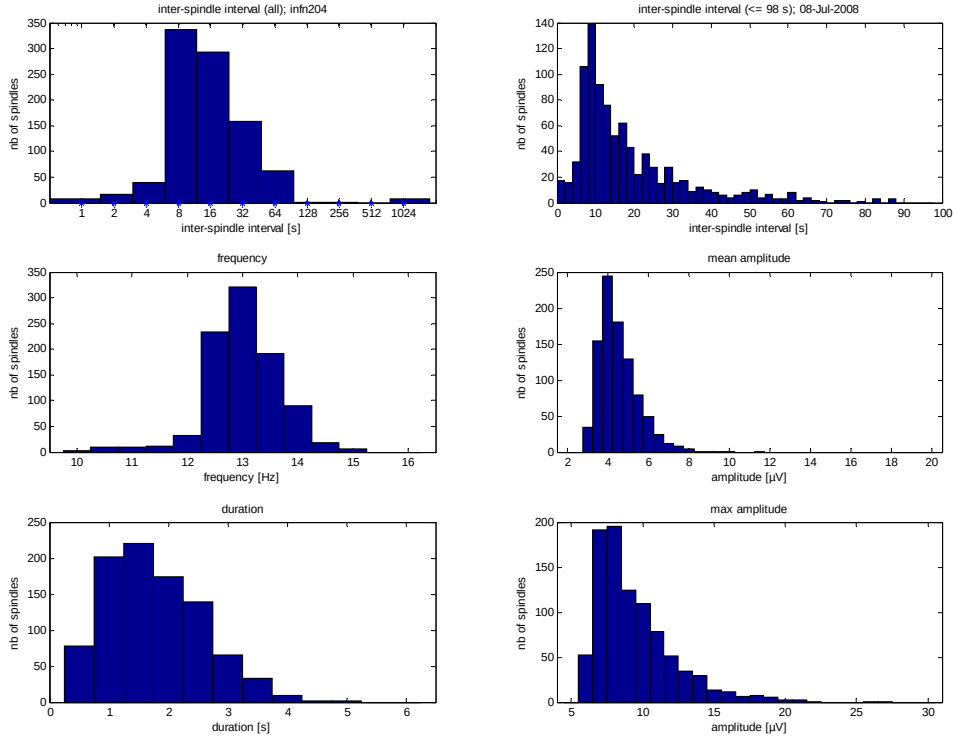

infn216; 07-Jul-2008
stages
M
W
A
I
Q
nb of spindles
time [h]


infn316; 10-Jul-2008
M
W
R
1
2
4
stages
0
2
4
6
8
10
12
2
1.5
1
0.5
0
nb of spindles
time [h]

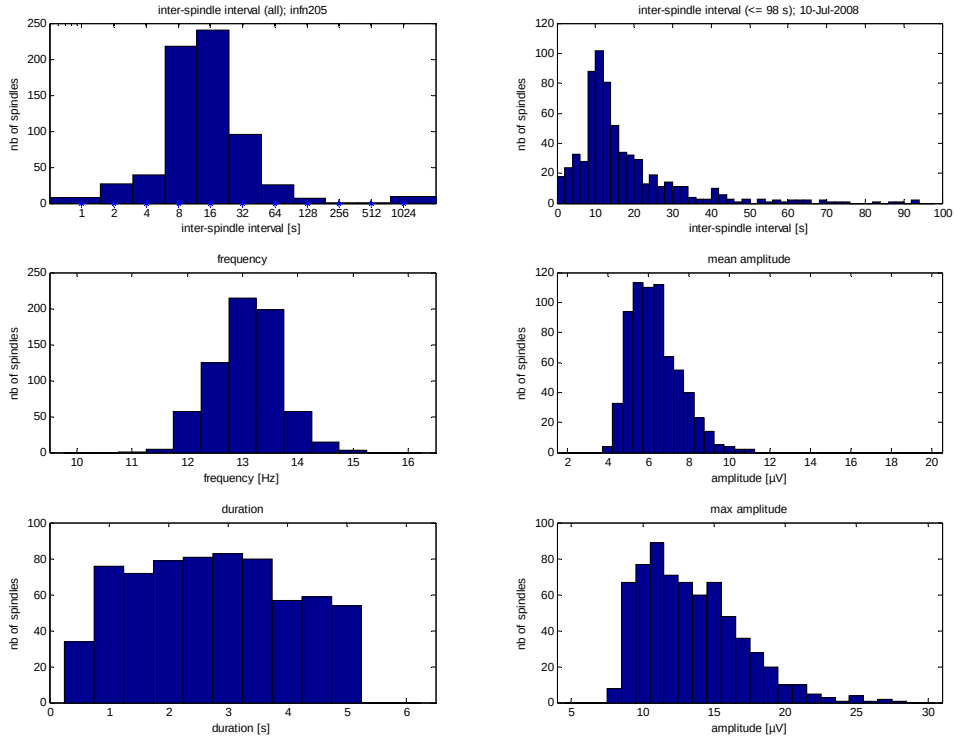

infn416; 07-Jul-2008
M
W
R
1
2
4
stages
0
1
2
3
4
5
6
7
8
9
10
3
2
1
0
nb of spindles
time [h]

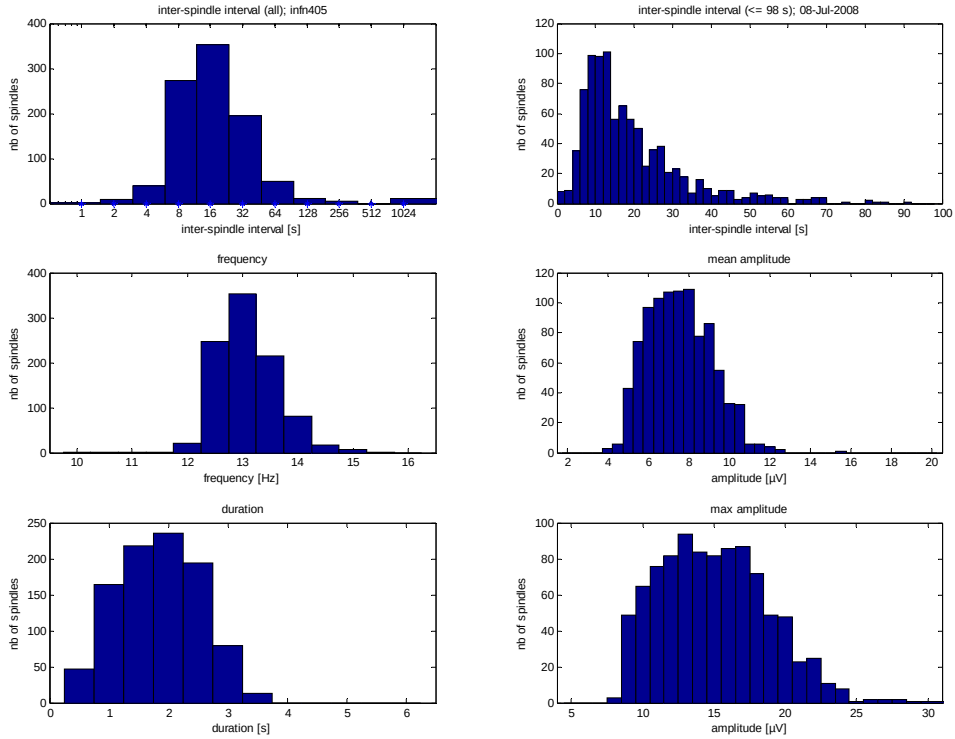
Distributions of sleep spindle variables

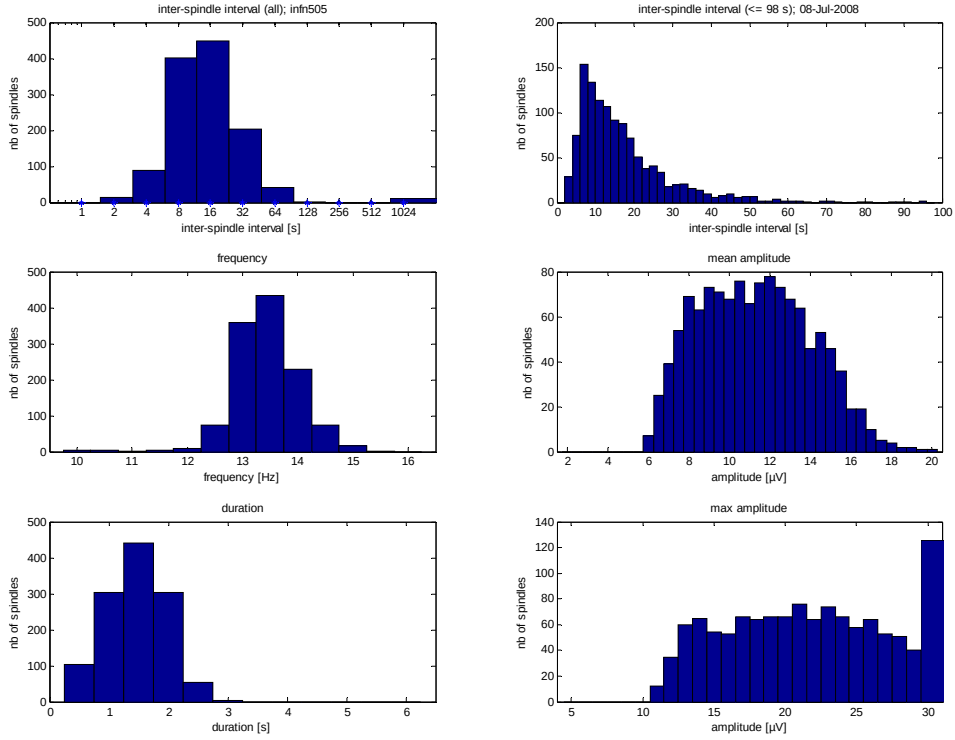
Inf 04



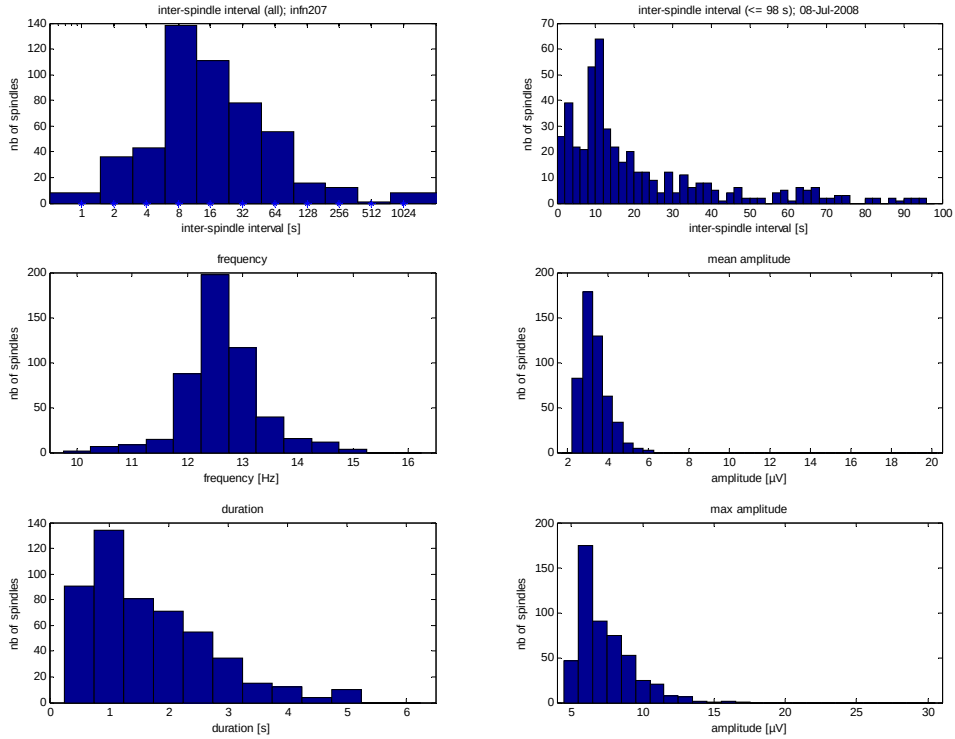
Inf 05

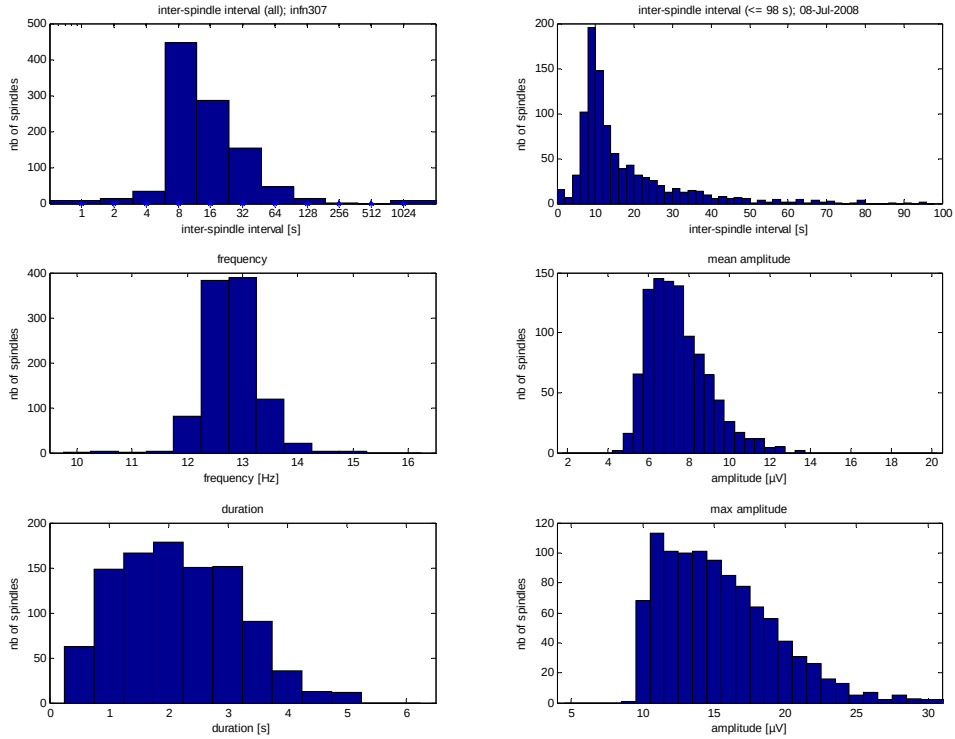

inter-spindle interval (all); infn205
nb of spindles
inter-spindle interval [s]
inter-spindle interval (<= 98 s); 10-Jul-2008
nb of spindles
inter-spindle interval [s]
frequency
nb of spindles
frequency [Hz]
mean amplitude
nb of spindles
amplitude [µV]
duration
nb of spindles
duration [s]
max amplitude
nb of spindles
amplitude [µV]

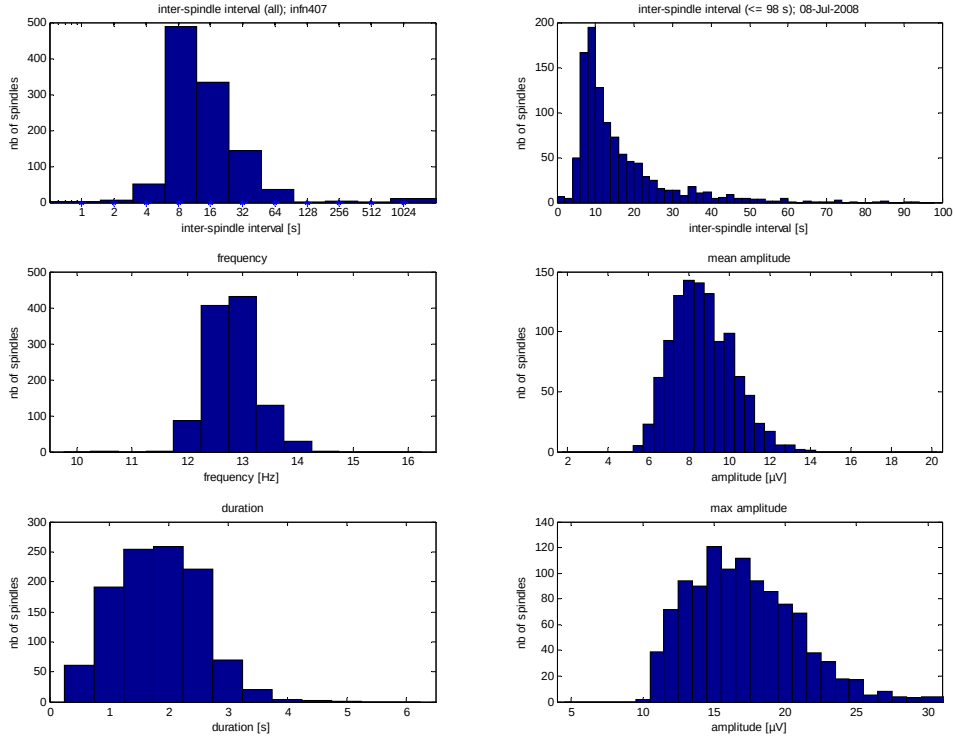

inter-spindle interval (all); infn405
nb of spindles
inter-spindle interval [s]
inter-spindle interval (<= 98 s); 08-Jul-2008
nb of spindles
inter-spindle interval [s]
frequency
nb of spindles
frequency [Hz]
mean amplitude
nb of spindles
amplitude [µV]
duration
nb of spindles
duration [s]
max amplitude
nb of spindles
amplitude [µV]

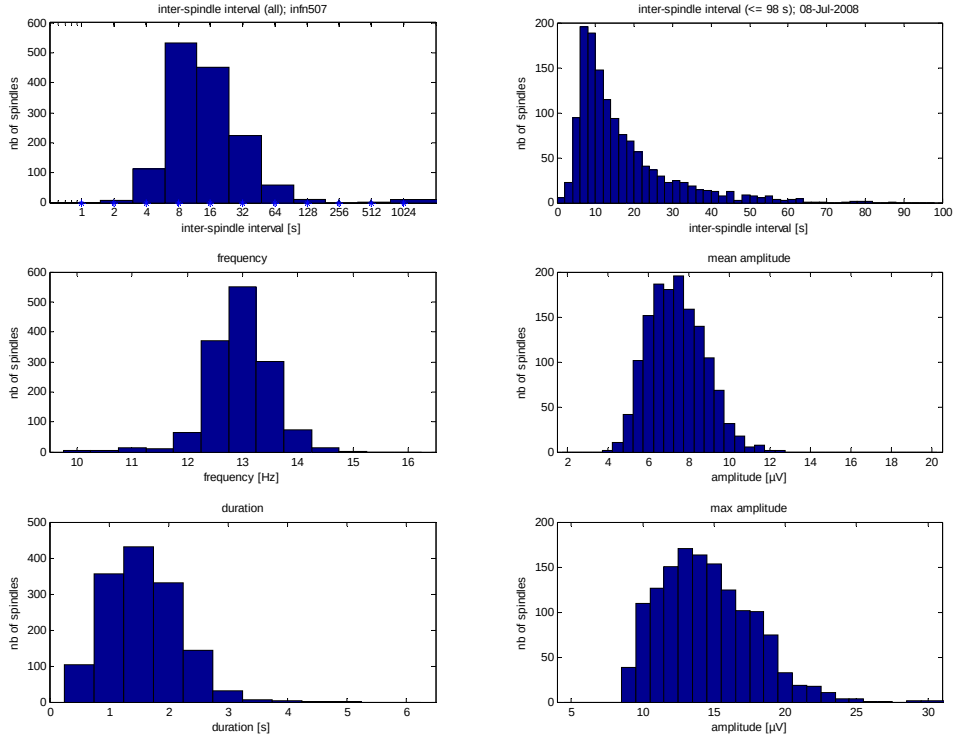

inter-spindle interval (all); infn505
nb of spindles
inter-spindle interval [s]
inter-spindle interval (<= 98 s); 08-Jul-2008
nb of spindles
inter-spindle interval [s]
frequency
nb of spindles
frequency [Hz]
mean amplitude
nb of spindles
amplitude [µV]
duration
nb of spindles
duration [s]
max amplitude
nb of spindles
amplitude [µV]

Inf 07

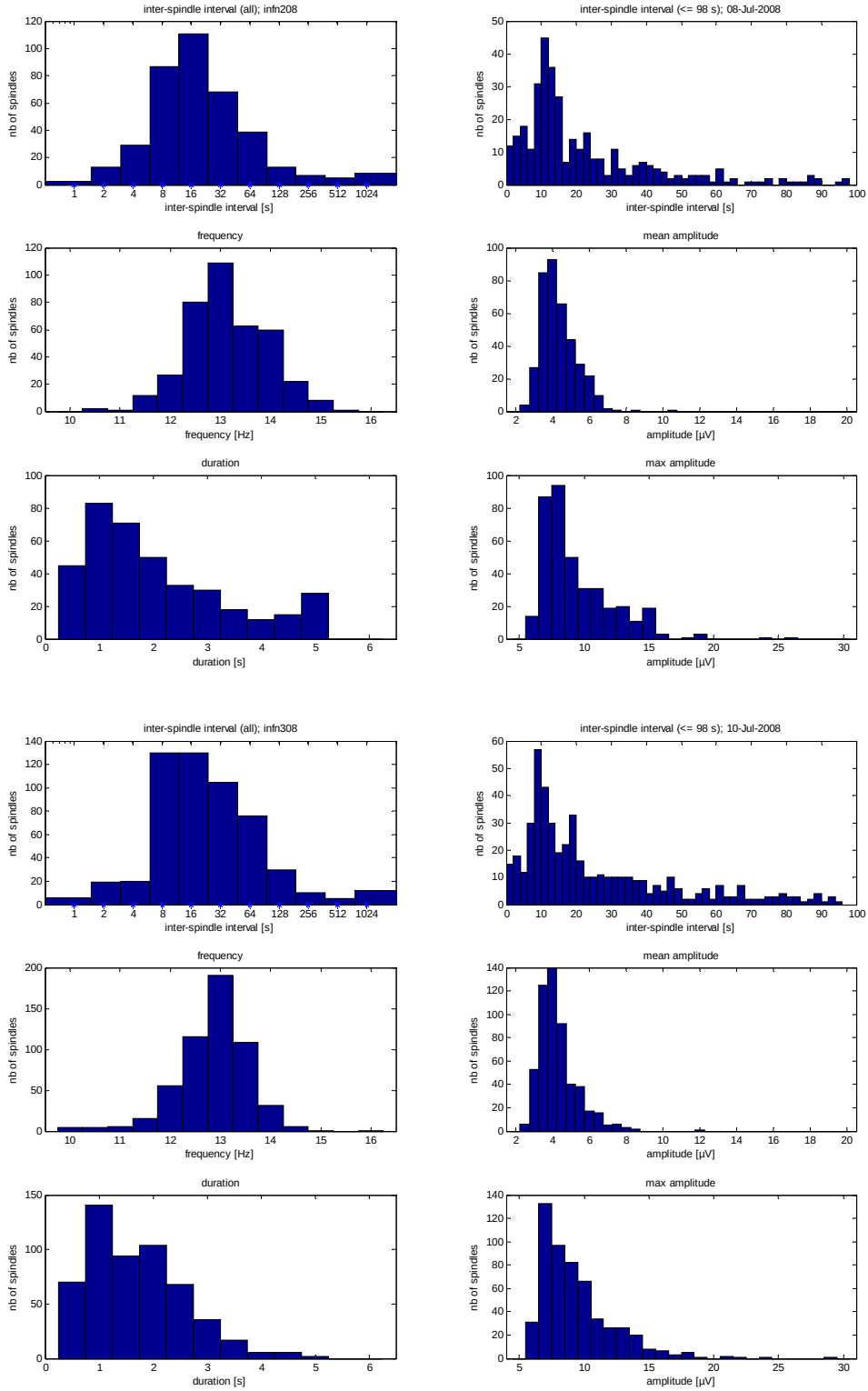

inter-spindle interval (all); infn207
nb of spindles
inter-spindle interval [s]
inter-spindle interval (<= 98 s); 08-Jul-2008
nb of spindles
inter-spindle interval [s]
frequency
nb of spindles
frequency [Hz]
mean amplitude
nb of spindles
amplitude [µV]
duration
nb of spindles
duration [s]
max amplitude
nb of spindles
amplitude [µV]

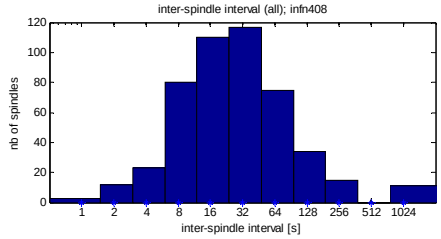

inter-spindle interval (all); infn307
nb of spindles
inter-spindle interval [s]
inter-spindle interval (<= 98 s); 08-Jul-2008
nb of spindles
inter-spindle interval [s]
frequency
nb of spindles
frequency [Hz]
mean amplitude
nb of spindles
amplitude [µV]
duration
nb of spindles
duration [s]
max amplitude
nb of spindles
amplitude [µV]

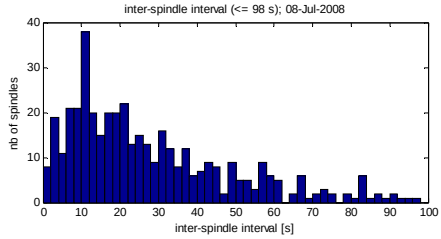

inter-spindle interval (all); infn407
nb of spindles
inter-spindle interval [s]
inter-spindle interval (<= 98 s); 08-Jul-2008
nb of spindles
inter-spindle interval [s]
frequency
nb of spindles
frequency [Hz]
mean amplitude
nb of spindles
amplitude [µV]
duration
nb of spindles
duration [s]
max amplitude
nb of spindles
amplitude [µV]

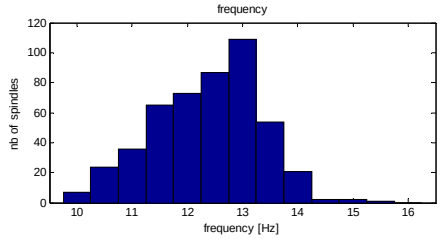

inter-spindle interval (all); infn507
nb of spindles
inter-spindle interval [s]
inter-spindle interval (<= 98 s); 08-Jul-2008
nb of spindles
inter-spindle interval [s]
frequency
nb of spindles
frequency [Hz]
mean amplitude
nb of spindles
amplitude [µV]
duration
nb of spindles
duration [s]
max amplitude
nb of spindles
amplitude [µV]

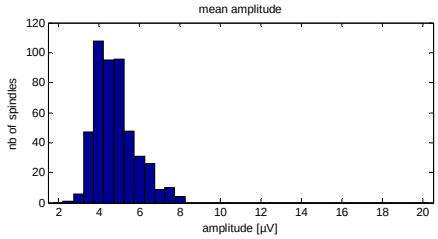
Inf 08

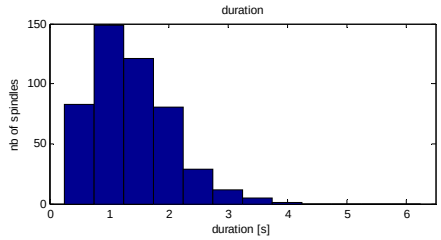

inter-spindle interval (all); infn208
nb of spindles
inter-spindle interval [s]
inter-spindle interval (<= 98 s); 08-Jul-2008
nb of spindles
inter-spindle interval [s]
frequency
nb of spindles
frequency [Hz]
mean amplitude
nb of spindles
amplitude [µV]
duration
nb of spindles
duration [s]
max amplitude
nb of spindles
amplitude [µV]
inter-spindle interval (all); infn308
nb of spindles
inter-spindle interval [s]
inter-spindle interval (<= 98 s); 10-Jul-2008
nb of spindles
inter-spindle interval [s]
frequency
nb of spindles
frequency [Hz]
mean amplitude
nb of spindles
amplitude [µV]
duration
nb of spindles
duration [s]
max amplitude
nb of spindles
amplitude [µV]

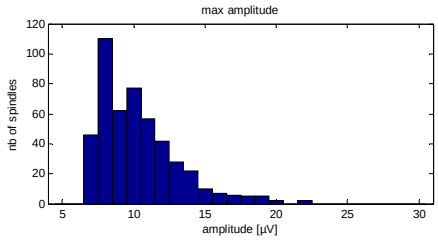

inter-spindle interval (all); infn408
nb of spindles
inter-spindle interval [s]

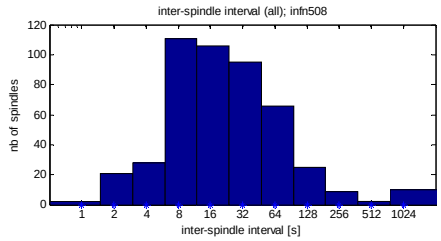

inter-spindle interval (<= 98 s); 08-Jul-2008
nb of spindles
inter-spindle interval [s]

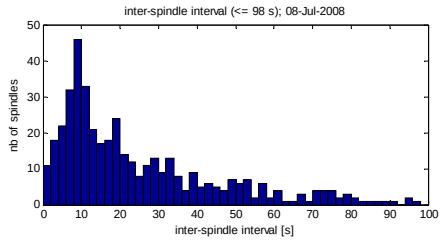

frequency
nb of spindles
frequency [Hz]

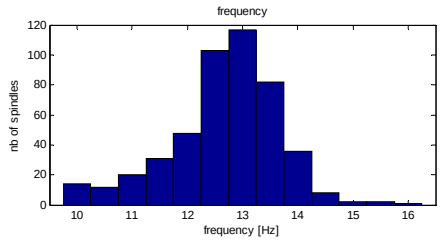

mean amplitude
nb of spindles
amplitude [µV]

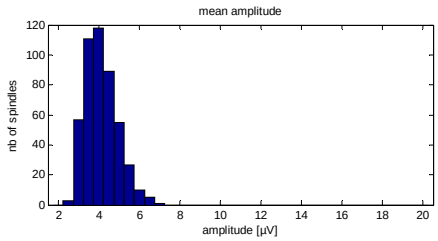

duration
nb of spindles
duration [s]

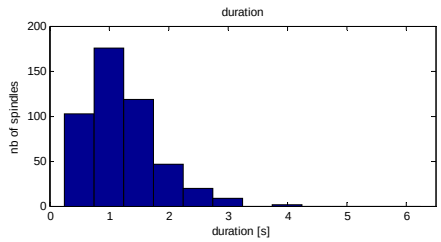

max amplitude
nb of spindles
amplitude [µV]

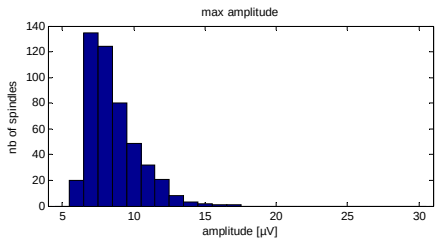

inter-spindle interval (all); infn508
nb of spindles
inter-spindle interval [s]


inter-spindle interval (<= 98 s); 08-Jul-2008
nb of spindles
inter-spindle interval [s]

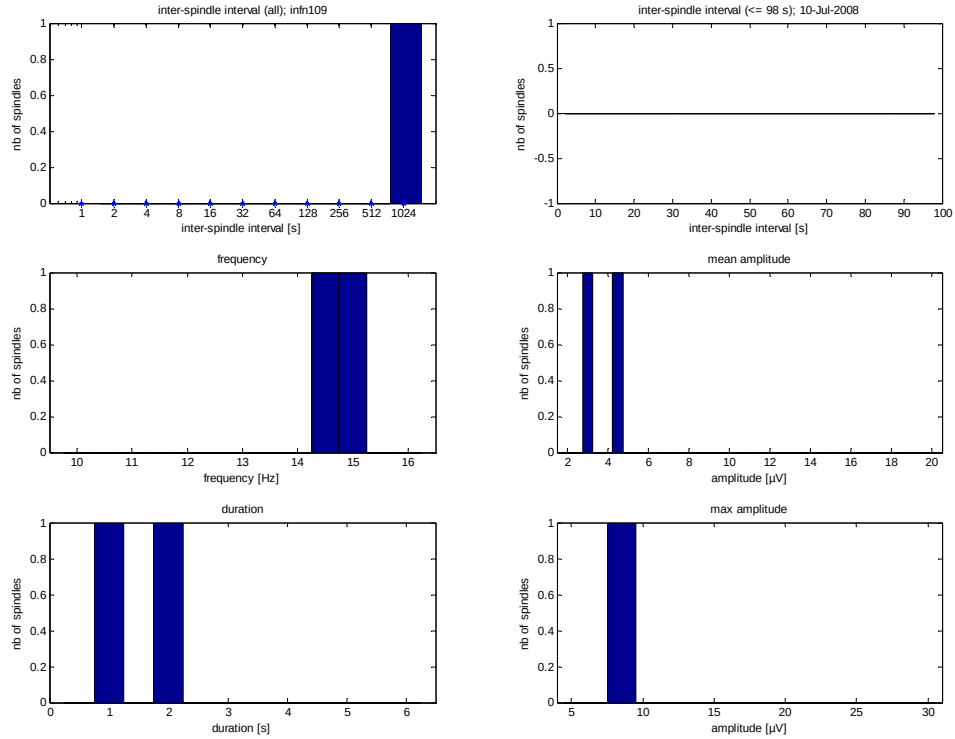

frequency
nb of spindles
frequency [Hz]

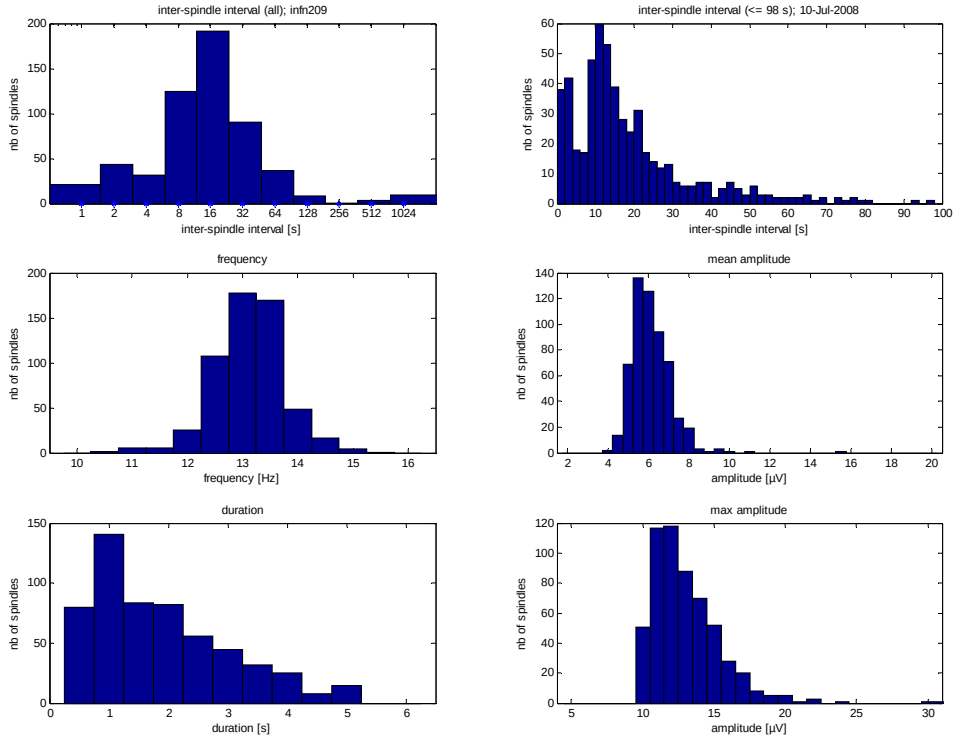

mean amplitude
nb of spindles
amplitude [µV]

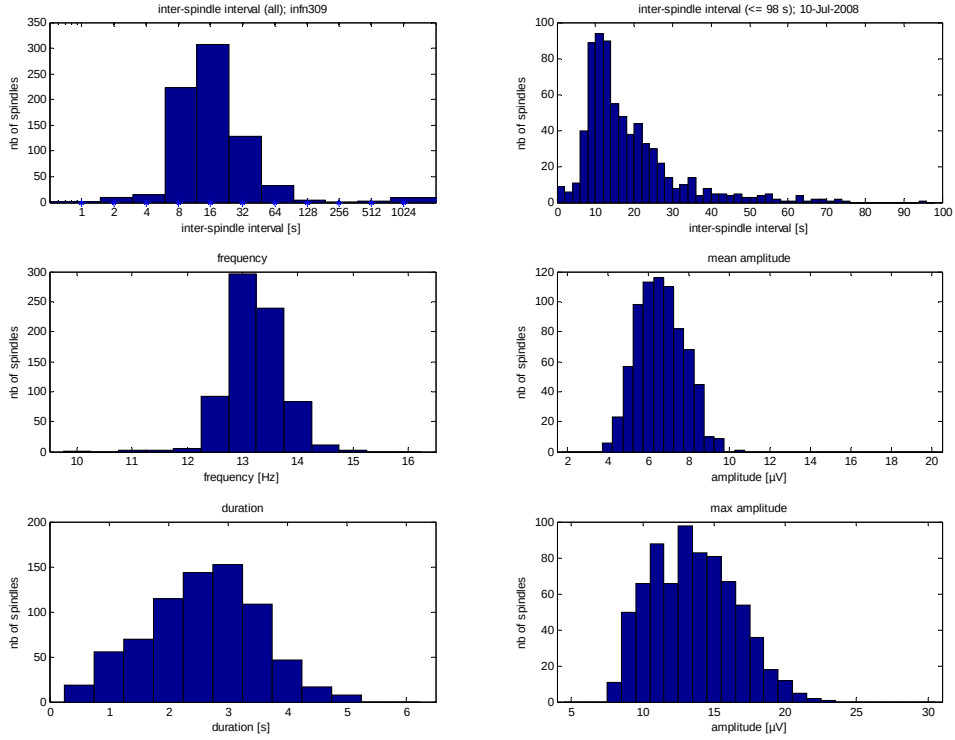

duration
nb of spindles
duration [s]


max amplitude
nb of spindles
amplitude [µV]

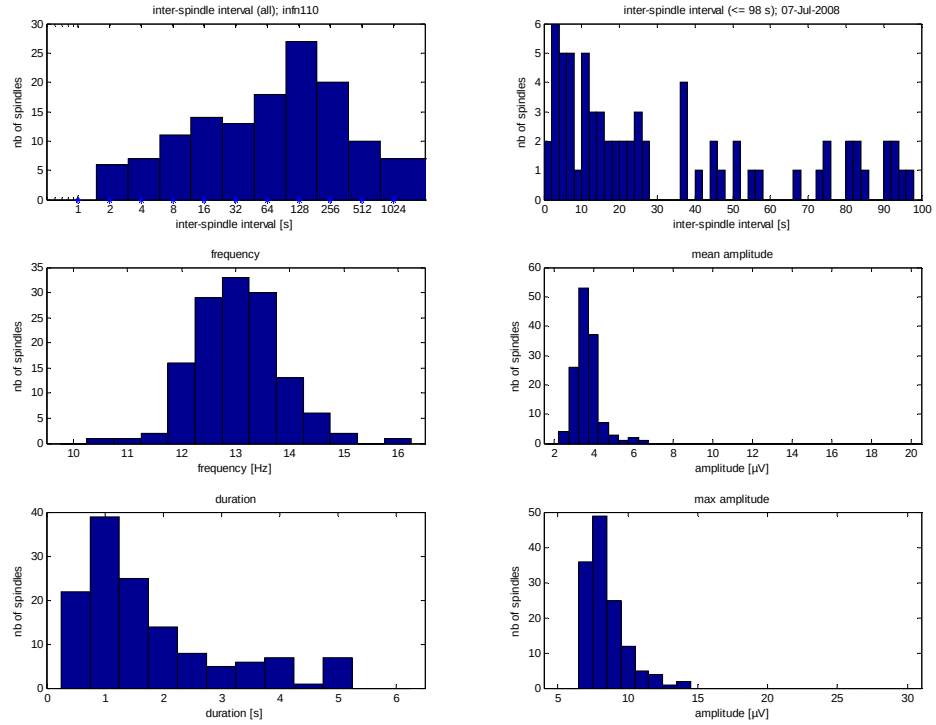
Inf 09

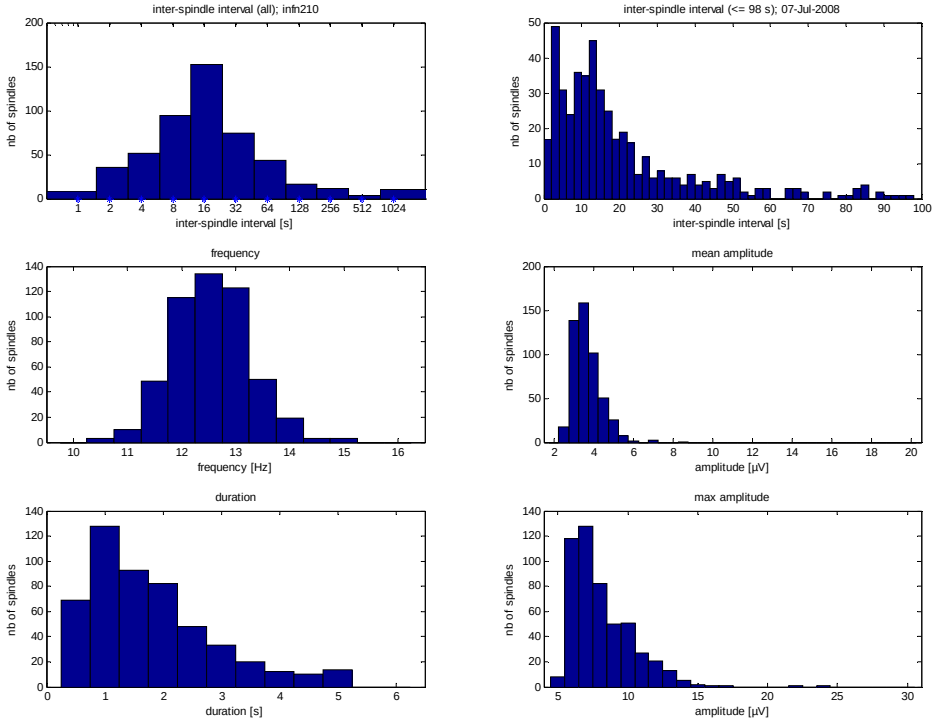

inter-spindle interval (all); infn109
nb of spindles
inter-spindle interval [s]
inter-spindle interval (<= 98 s); 10-Jul-2008
nb of spindles
inter-spindle interval [s]
frequency
nb of spindles
frequency [Hz]
mean amplitude
nb of spindles
amplitude [µV]
duration
nb of spindles
duration [s]
max amplitude
nb of spindles
amplitude [µV]

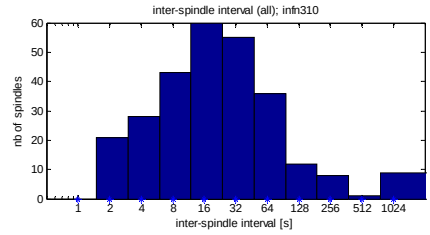

inter-spindle interval (all); infn209
nb of spindles
inter-spindle interval [s]
inter-spindle interval (<= 98 s); 10-Jul-2008
nb of spindles
inter-spindle interval [s]
frequency
nb of spindles
frequency [Hz]
mean amplitude
nb of spindles
amplitude [µV]
duration
nb of spindles
duration [s]
max amplitude
nb of spindles
amplitude [µV]

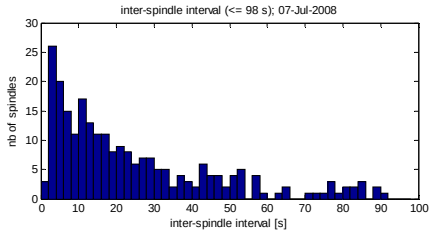

inter-spindle interval (all); infn309
nb of spindles
inter-spindle interval [s]
inter-spindle interval (<= 98 s); 10-Jul-2008
nb of spindles
inter-spindle interval [s]
frequency
nb of spindles
frequency [Hz]
mean amplitude
nb of spindles
amplitude [µV]
duration
nb of spindles
duration [s]
max amplitude
nb of spindles
amplitude [µV]

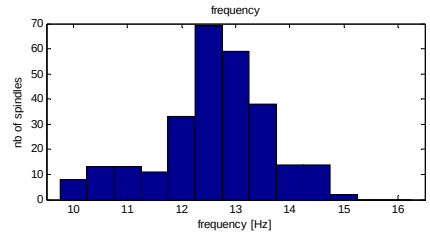
Inf 10

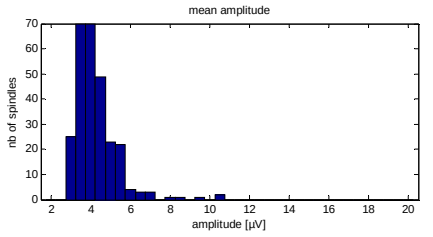

inter-spindle interval (all); infn110
nb of spindles
inter-spindle interval [s]
inter-spindle interval (<= 98 s); 07-Jul-2008
nb of spindles
inter-spindle interval [s]
frequency
nb of spindles
frequency [Hz]
mean amplitude
nb of spindles
amplitude [µV]
duration
nb of spindles
duration [s]
max amplitude
nb of spindles
amplitude [µV]

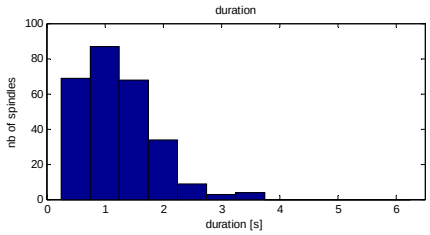

inter-spindle interval (all); infn210
nb of spindles
inter-spindle interval [s]
inter-spindle interval (<= 98 s); 07-Jul-2008
nb of spindles
inter-spindle interval [s]
frequency
nb of spindles
frequency [Hz]
mean amplitude
nb of spindles
amplitude [µV]
duration
nb of spindles
duration [s]
max amplitude
nb of spindles
amplitude [µV]

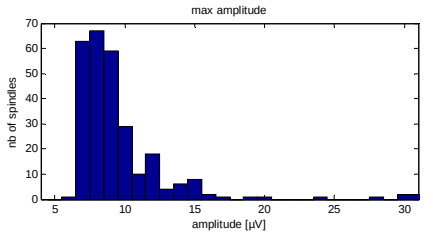

inter-spindle interval (all); infn310
nb of spindles
inter-spindle interval [s]

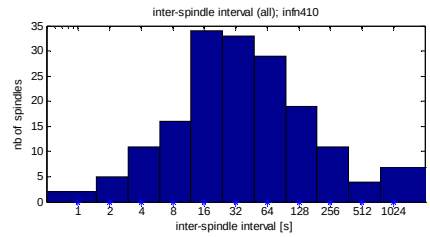

inter-spindle interval (<= 98 s); 07-Jul-2008
nb of spindles
inter-spindle interval [s]

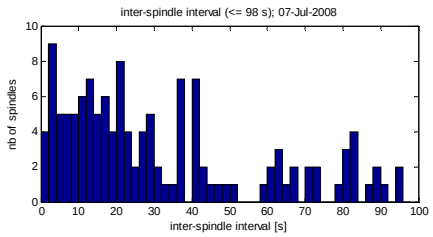

frequency
nb of spindles
frequency [Hz]

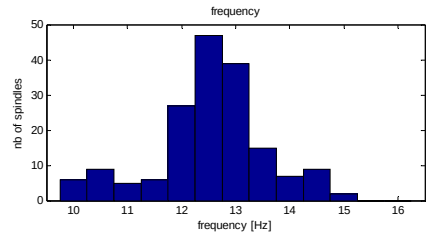

mean amplitude
nb of spindles
amplitude [µV]

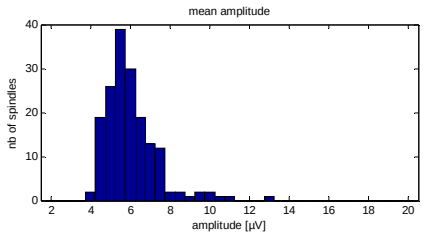

duration
nb of spindles
duration [s]

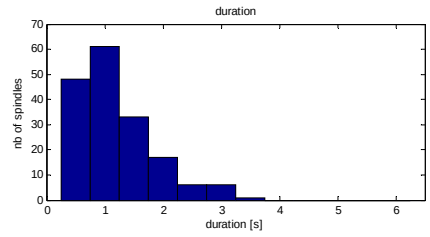

max amplitude
nb of spindles
amplitude [µV]

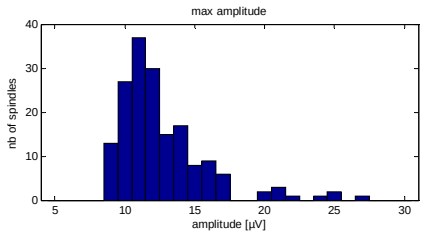

inter-spindle interval (all); infn410
nb of spindles
inter-spindle interval [s]

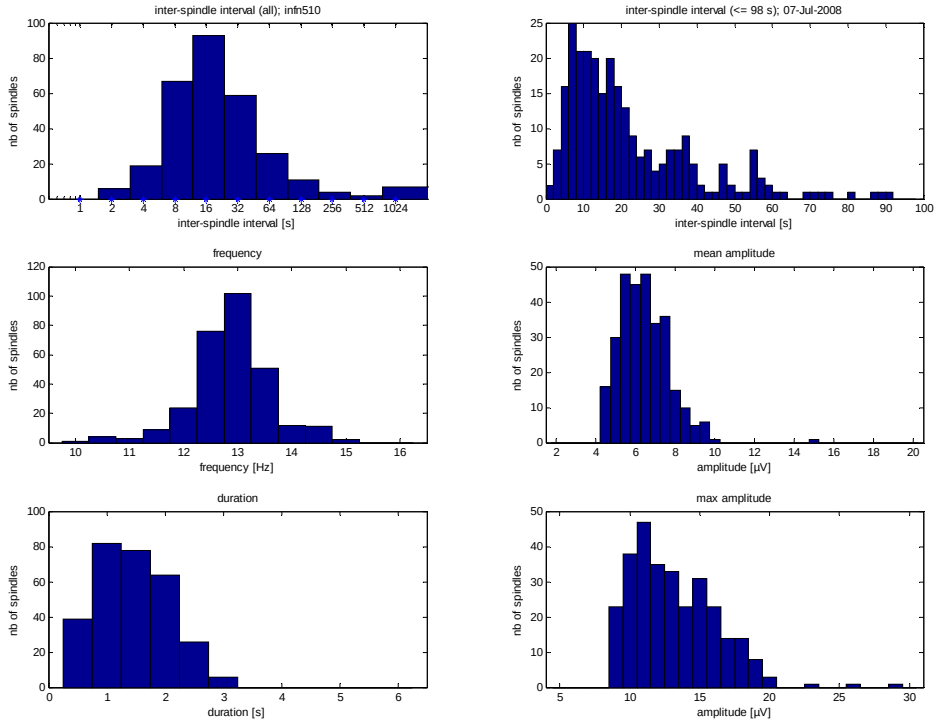

inter-spindle interval (<= 98 s); 07-Jul-2008
nb of spindles
inter-spindle interval [s]


frequency
nb of spindles
frequency [Hz]

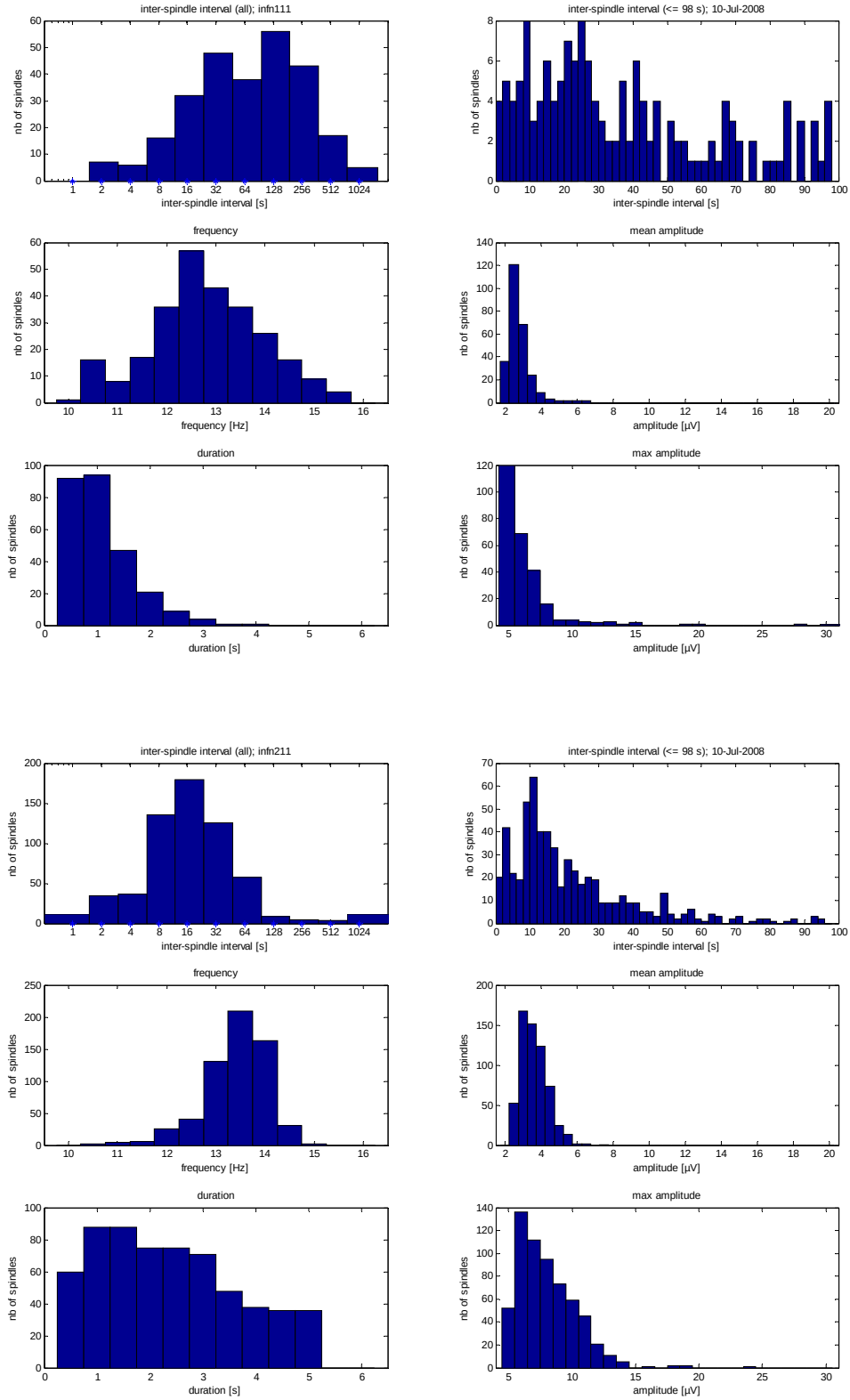

mean amplitude
nb of spindles
amplitude [µV]

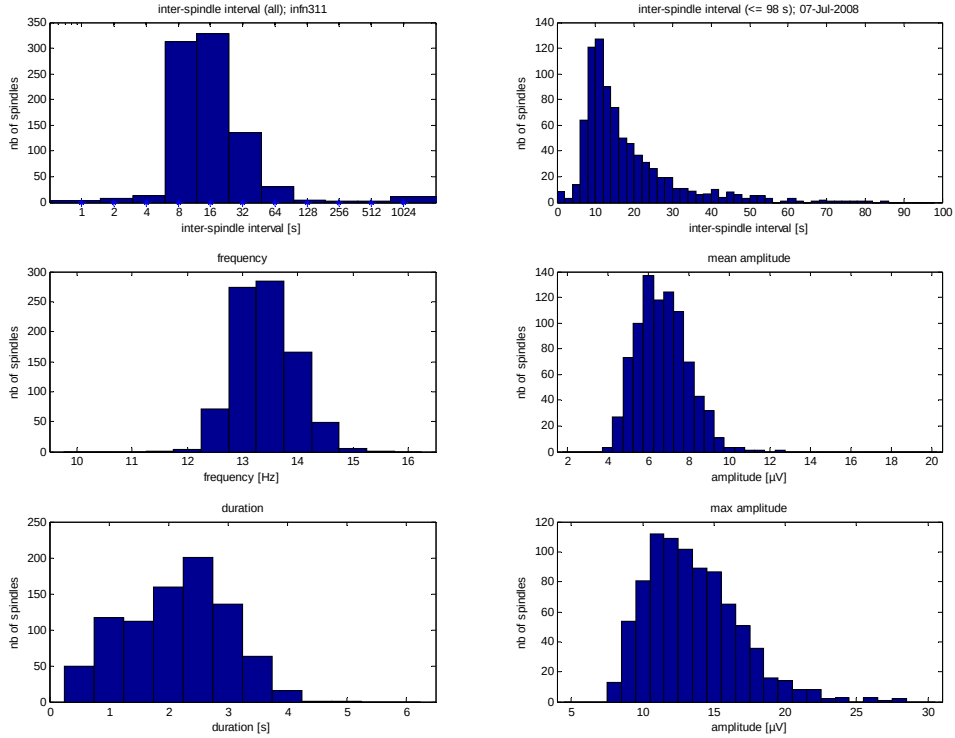

duration
nb of spindles
duration [s]

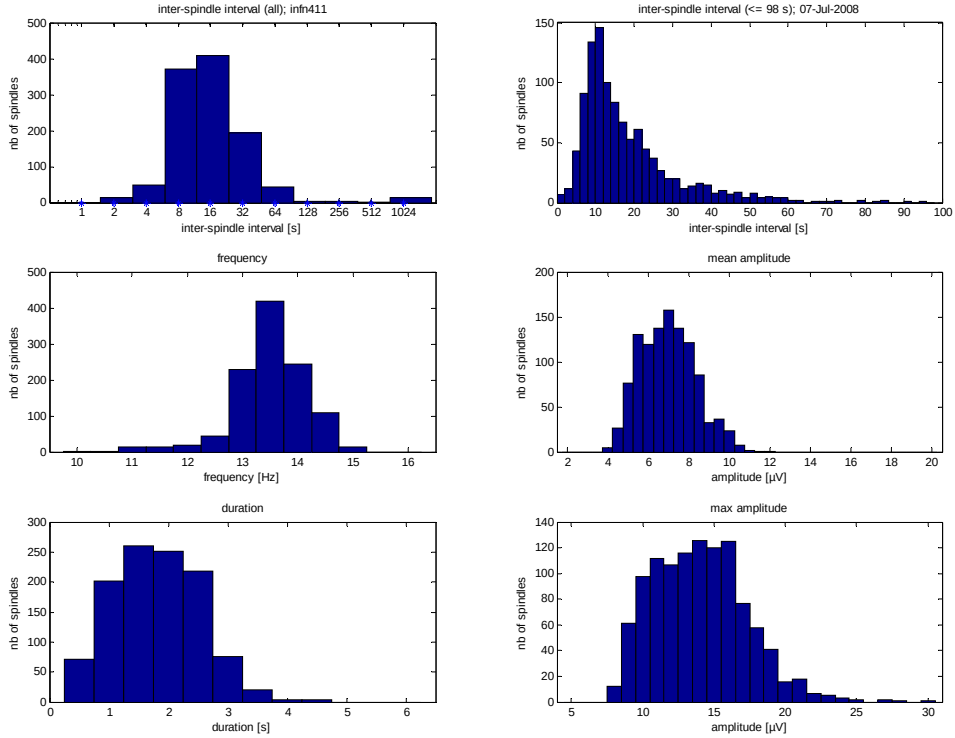

max amplitude
nb of spindles
amplitude [µV]

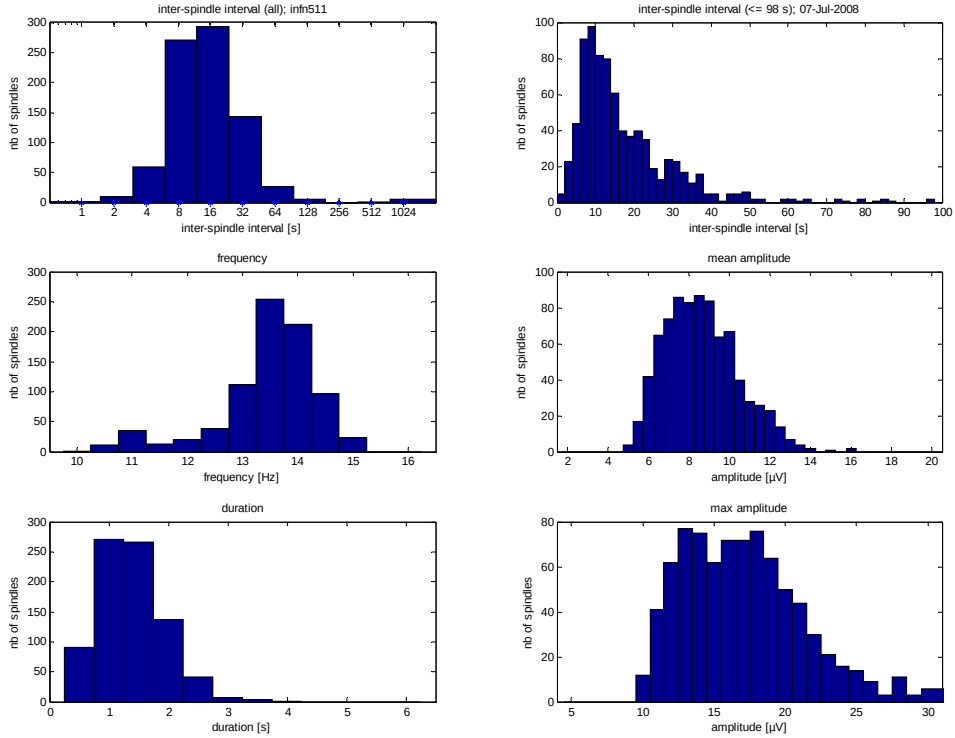

inter-spindle interval (all); infn510
nb of spindles
inter-spindle interval [s]
inter-spindle interval (<= 98 s); 07-Jul-2008
nb of spindles
inter-spindle interval [s]
frequency
nb of spindles
frequency [Hz]
mean amplitude
nb of spindles
amplitude [µV]
duration
nb of spindles
duration [s]
max amplitude
nb of spindles
amplitude [µV]

Inf 11

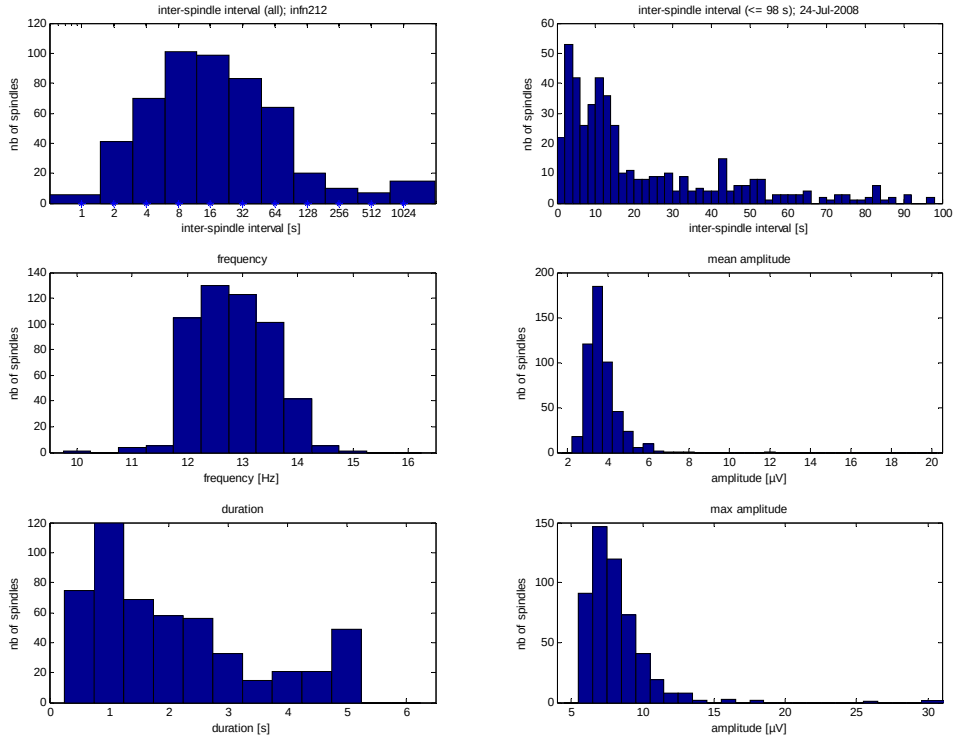

inter-spindle interval (all); infn111
nb of spindles
inter-spindle interval [s]
inter-spindle interval (<= 98 s); 10-Jul-2008
nb of spindles
inter-spindle interval [s]
frequency
nb of spindles
frequency [Hz]
mean amplitude
nb of spindles
amplitude [µV]
duration
nb of spindles
duration [s]
max amplitude
nb of spindles
amplitude [µV]
inter-spindle interval (all); infn211
nb of spindles
inter-spindle interval [s]
inter-spindle interval (<= 98 s); 10-Jul-2008
nb of spindles
inter-spindle interval [s]
frequency
nb of spindles
frequency [Hz]
mean amplitude
nb of spindles
amplitude [µV]
duration
nb of spindles
duration [s]
max amplitude
nb of spindles
amplitude [µV]

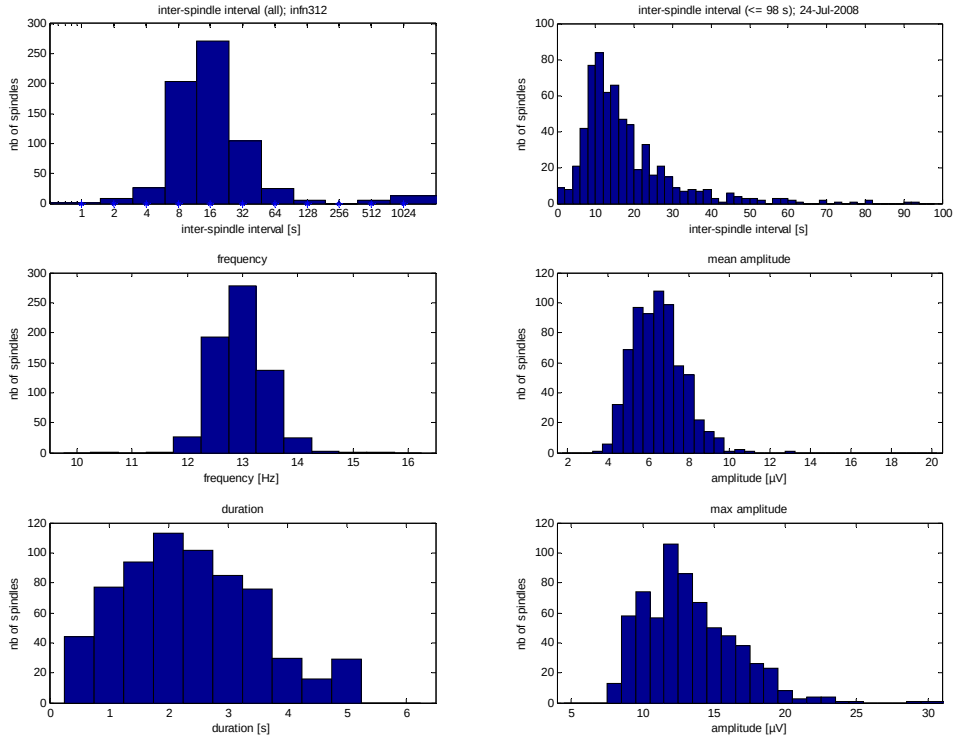

inter-spindle interval (all); infn311
nb of spindles
inter-spindle interval [s]
inter-spindle interval (<= 98 s); 07-Jul-2008
nb of spindles
inter-spindle interval [s]
frequency
nb of spindles
frequency [Hz]
mean amplitude
nb of spindles
amplitude [µV]
duration
nb of spindles
duration [s]
max amplitude
nb of spindles
amplitude [µV]

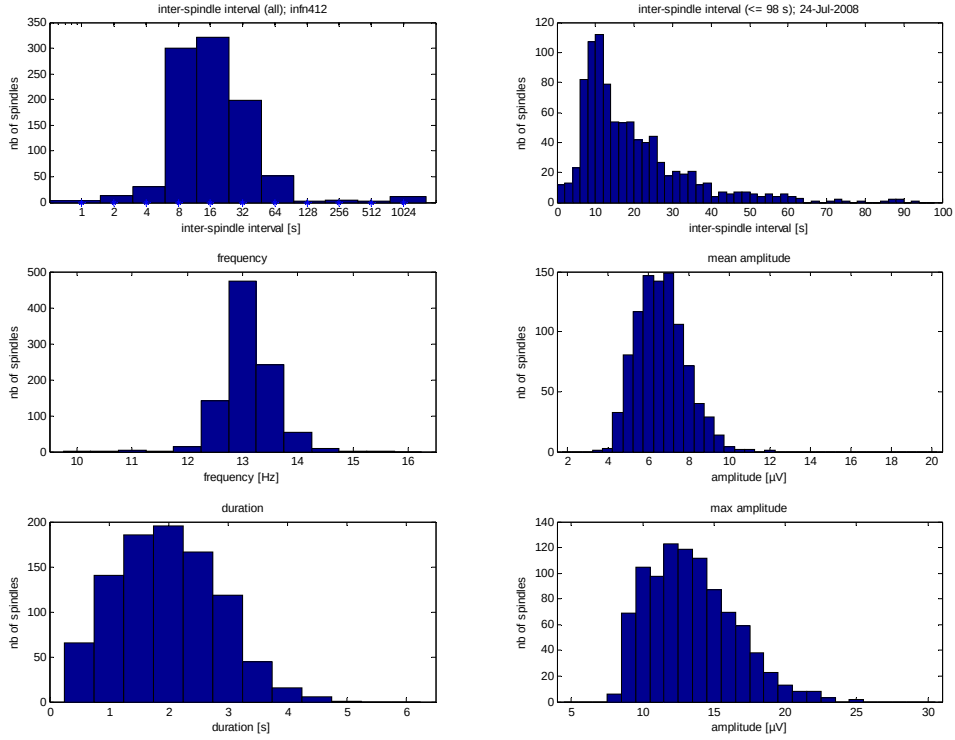

inter-spindle interval (all); infn411
nb of spindles
inter-spindle interval [s]
inter-spindle interval (<= 98 s); 07-Jul-2008
nb of spindles
inter-spindle interval [s]
frequency
nb of spindles
frequency [Hz]
mean amplitude
nb of spindles
amplitude [µV]
duration
nb of spindles
duration [s]
max amplitude
nb of spindles
amplitude [µV]


inter-spindle interval (all); infn511
nb of spindles
inter-spindle interval [s]
inter-spindle interval (<= 98 s); 07-Jul-2008
nb of spindles
inter-spindle interval [s]
frequency
nb of spindles
frequency [Hz]
mean amplitude
nb of spindles
amplitude [µV]
duration
nb of spindles
duration [s]
max amplitude
nb of spindles
amplitude [µV]

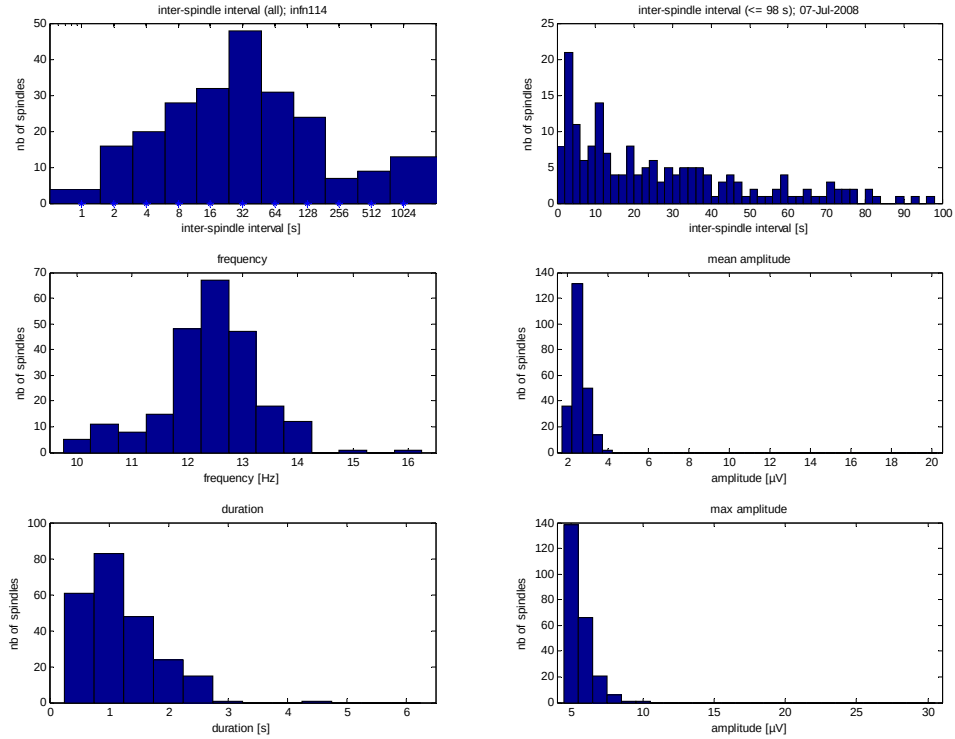
Inf 12

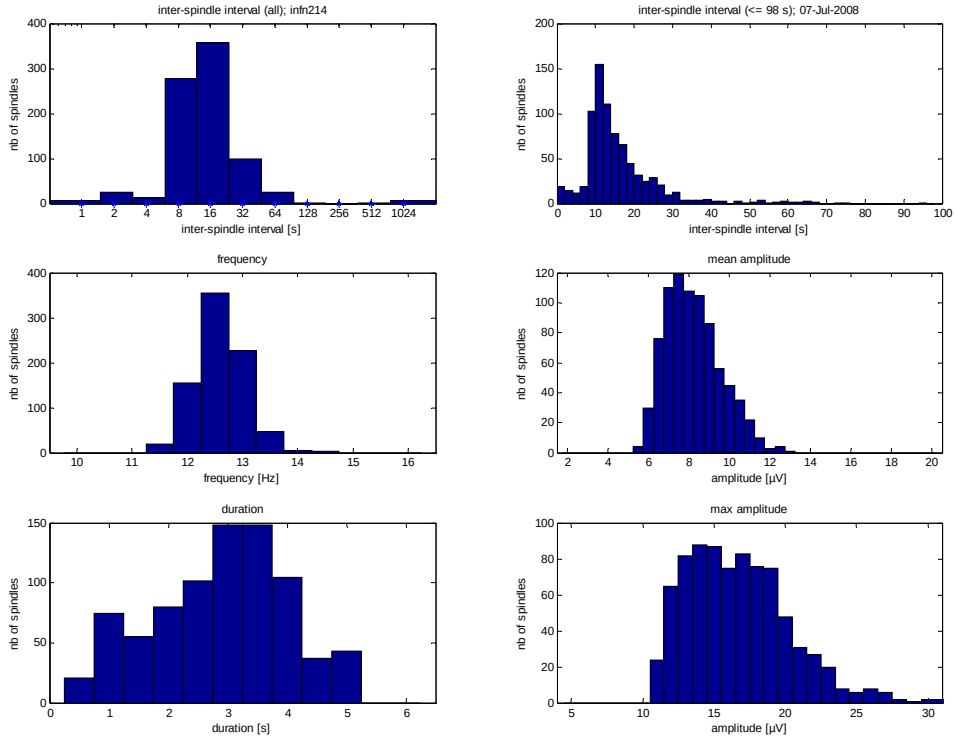

inter-spindle interval (all); infn212
nb of spindles
inter-spindle interval [s]
inter-spindle interval (<= 98 s); 24-Jul-2008
nb of spindles
inter-spindle interval [s]
frequency
nb of spindles
frequency [Hz]
mean amplitude
nb of spindles
amplitude [µV]
duration
nb of spindles
duration [s]
max amplitude
nb of spindles
amplitude [µV]

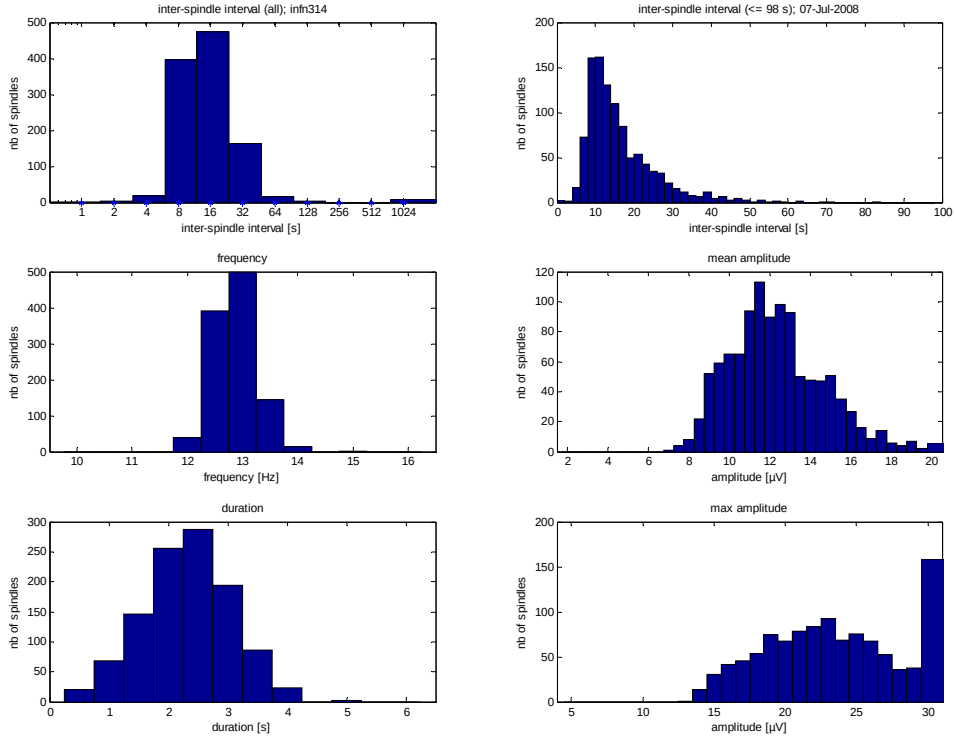

inter-spindle interval (all); infn312
nb of spindles
inter-spindle interval [s]
inter-spindle interval (<= 98 s); 24-Jul-2008
nb of spindles
inter-spindle interval [s]
frequency
nb of spindles
frequency [Hz]
mean amplitude
nb of spindles
amplitude [µV]
duration
nb of spindles
duration [s]
max amplitude
nb of spindles
amplitude [µV]

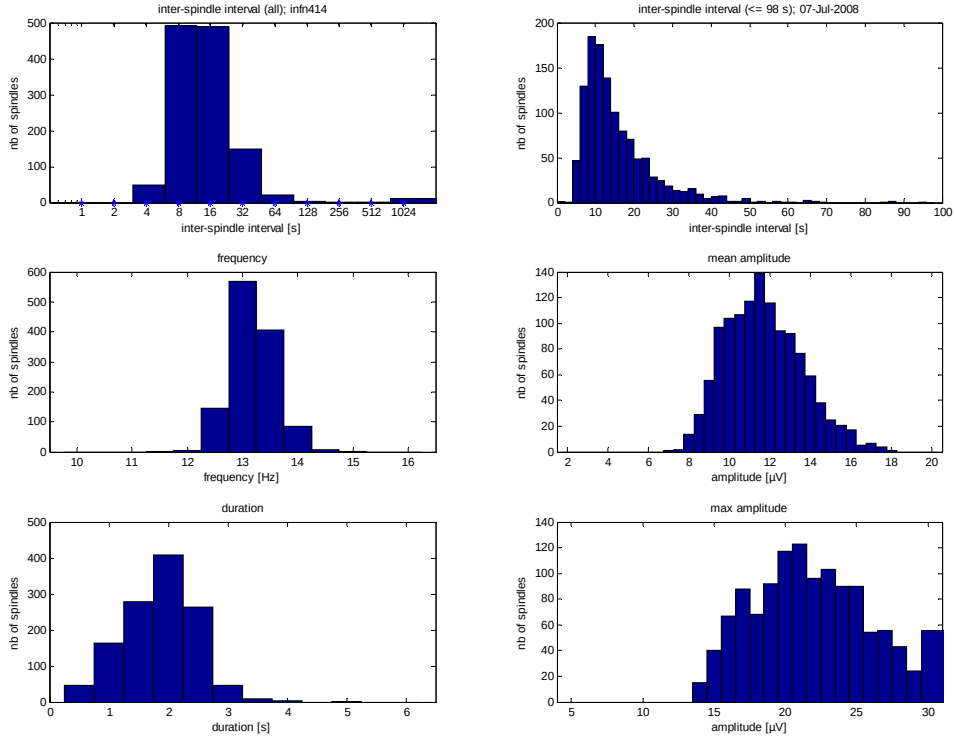

inter-spindle interval (all); infn412
nb of spindles
inter-spindle interval [s]
inter-spindle interval (<= 98 s); 24-Jul-2008
nb of spindles
inter-spindle interval [s]
frequency
nb of spindles
frequency [Hz]
mean amplitude
nb of spindles
amplitude [µV]
duration
nb of spindles
duration [s]
max amplitude
nb of spindles
amplitude [µV]

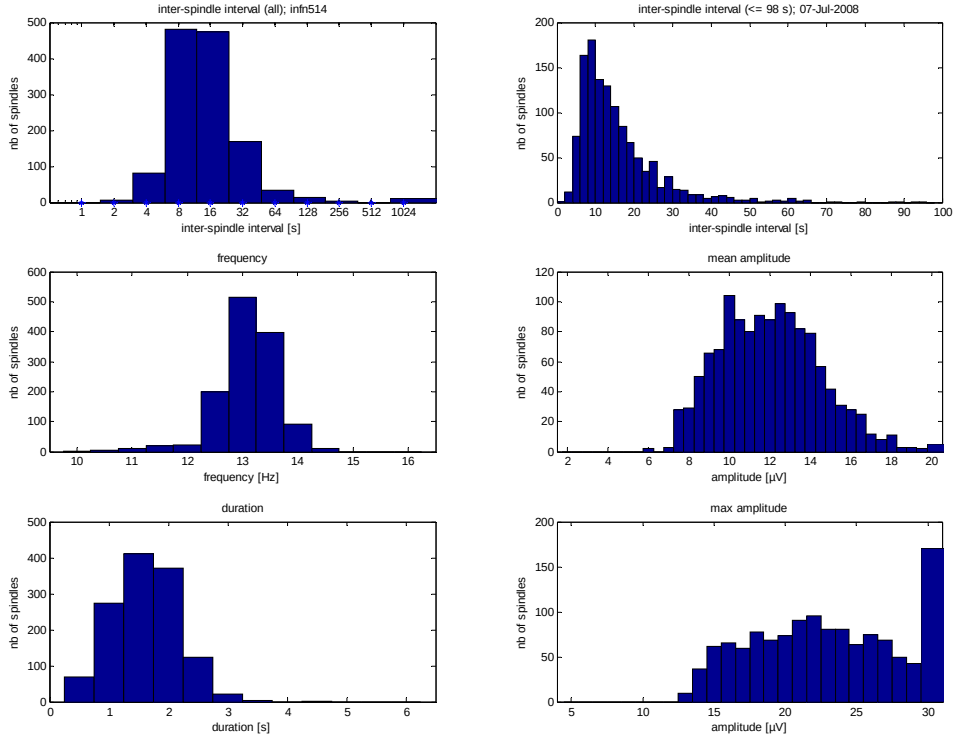
Inf 14


inter-spindle interval (all); infn114
nb of spindles
inter-spindle interval [s]
inter-spindle interval (<= 98 s); 07-Jul-2008
nb of spindles
inter-spindle interval [s]
frequency
nb of spindles
frequency [Hz]
mean amplitude
nb of spindles
amplitude [µV]
duration
nb of spindles
duration [s]
max amplitude
nb of spindles
amplitude [µV]

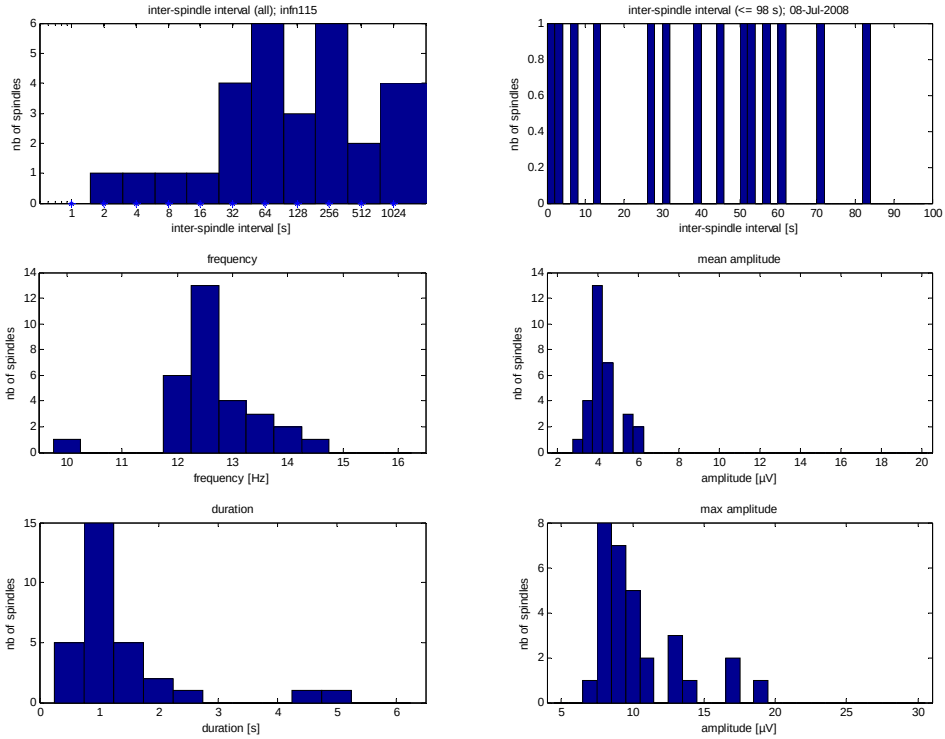

inter-spindle interval (all); infn214
nb of spindles
inter-spindle interval [s]
inter-spindle interval (<= 98 s); 07-Jul-2008
nb of spindles
inter-spindle interval [s]
frequency
nb of spindles
frequency [Hz]
mean amplitude
nb of spindles
amplitude [µV]
duration
nb of spindles
duration [s]
max amplitude
nb of spindles
amplitude [µV]

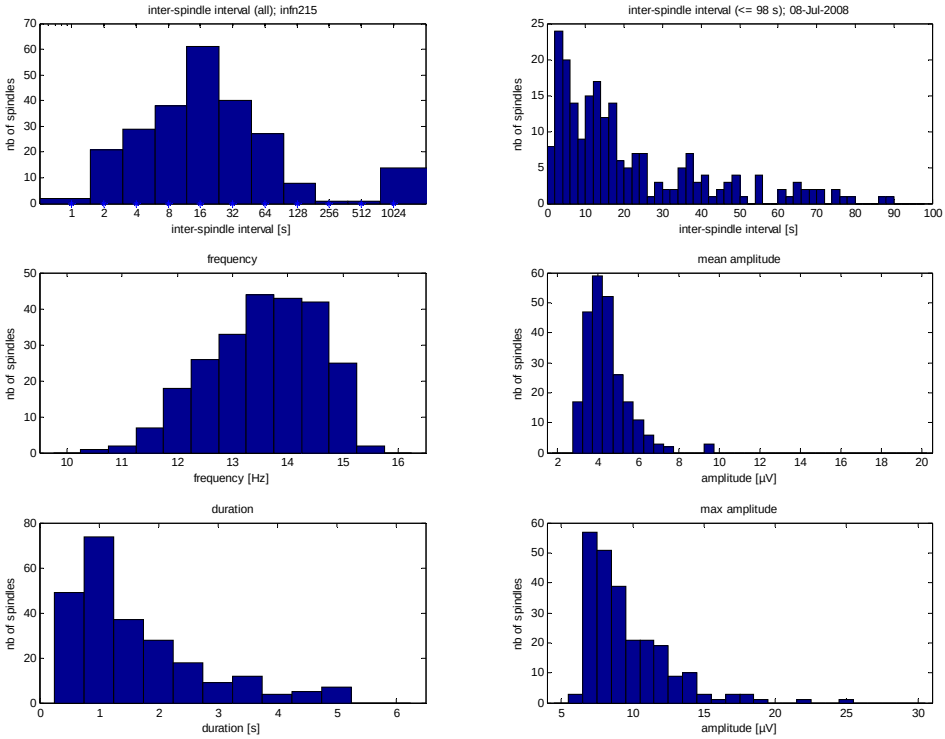

inter-spindle interval (all); infn314
nb of spindles
inter-spindle interval [s]
inter-spindle interval (<= 98 s); 07-Jul-2008
nb of spindles
inter-spindle interval [s]
frequency
nb of spindles
frequency [Hz]
mean amplitude
nb of spindles
amplitude [µV]
duration
nb of spindles
duration [s]
max amplitude
nb of spindles
amplitude [µV]

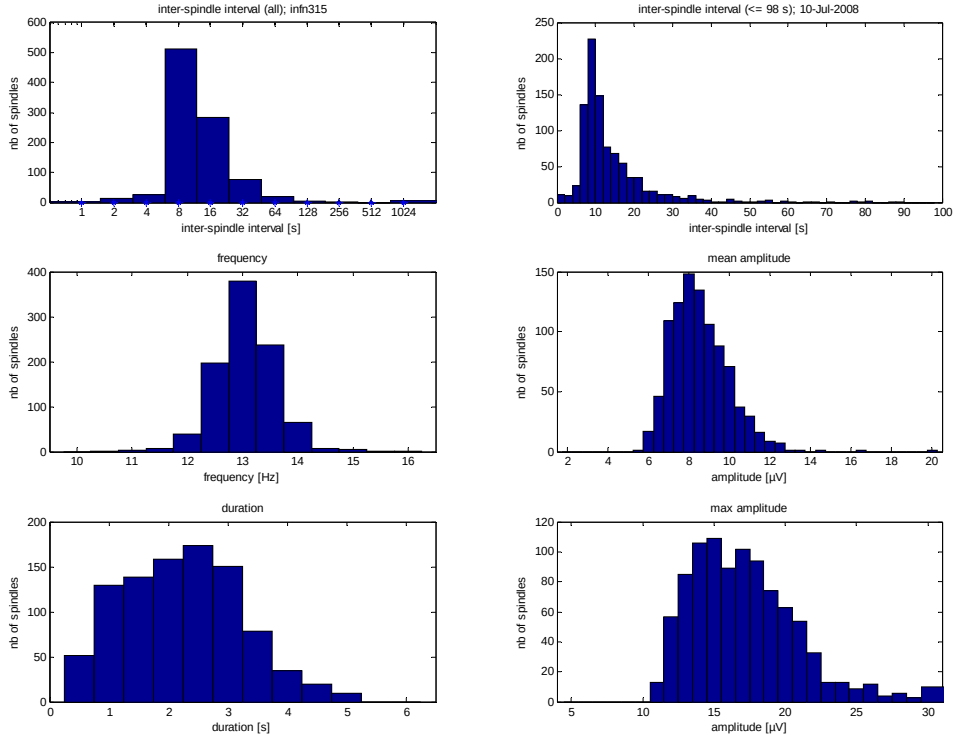

inter-spindle interval (all); infn414
nb of spindles
inter-spindle interval [s]
inter-spindle interval (<= 98 s); 07-Jul-2008
nb of spindles
inter-spindle interval [s]
frequency
nb of spindles
frequency [Hz]
mean amplitude
nb of spindles
amplitude [µV]
duration
nb of spindles
duration [s]
max amplitude
nb of spindles
amplitude [µV]

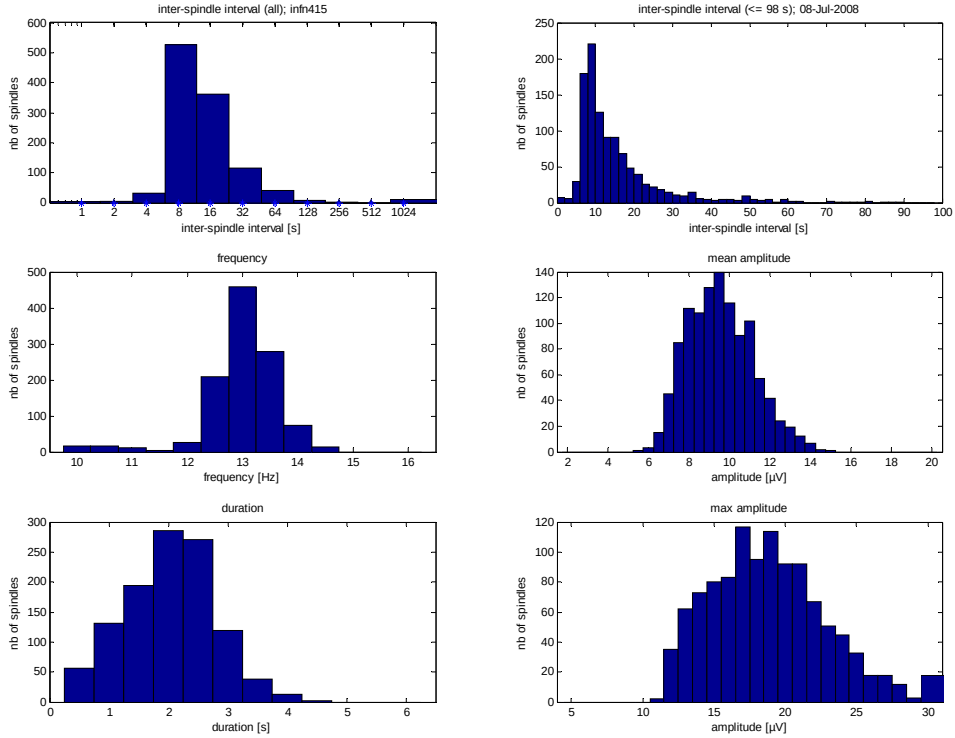

inter-spindle interval (all); infn514
nb of spindles
inter-spindle interval [s]
inter-spindle interval (<= 98 s); 07-Jul-2008
nb of spindles
inter-spindle interval [s]
frequency
nb of spindles
frequency [Hz]
mean amplitude
nb of spindles
amplitude [µV]
duration
nb of spindles
duration [s]
max amplitude
nb of spindles
amplitude [µV]

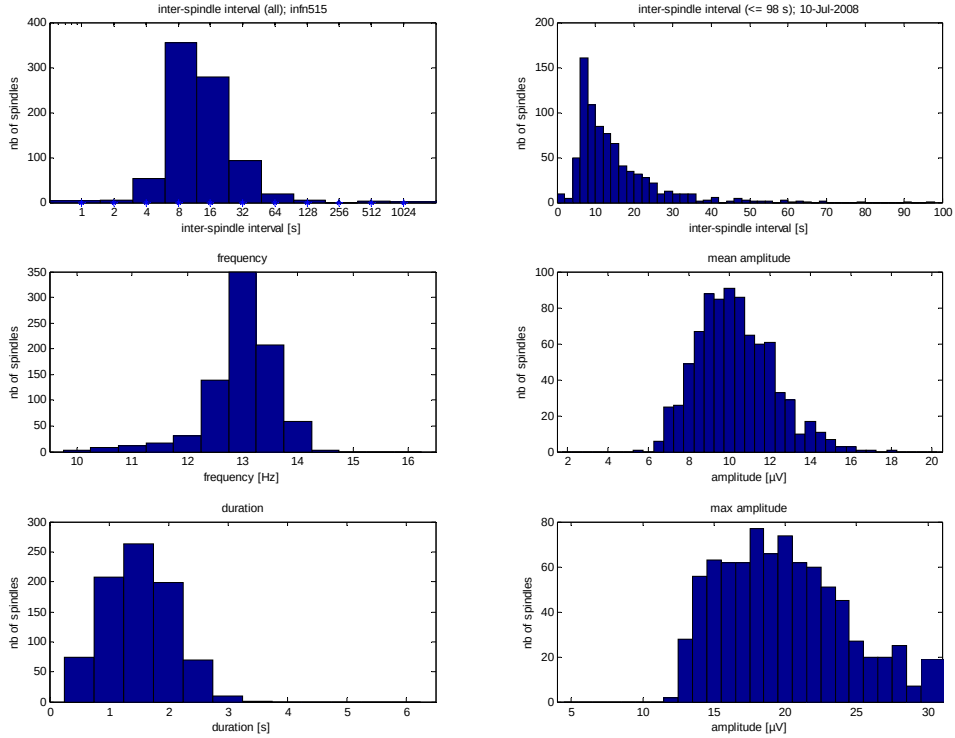
Inf 15


inter-spindle interval (all); infn115
nb of spindles
inter-spindle interval [s]
inter-spindle interval (<= 98 s); 08-Jul-2008
nb of spindles
inter-spindle interval [s]
frequency
nb of spindles
frequency [Hz]
mean amplitude
nb of spindles
amplitude [µV]
duration
nb of spindles
duration [s]
max amplitude
nb of spindles
amplitude [µV]

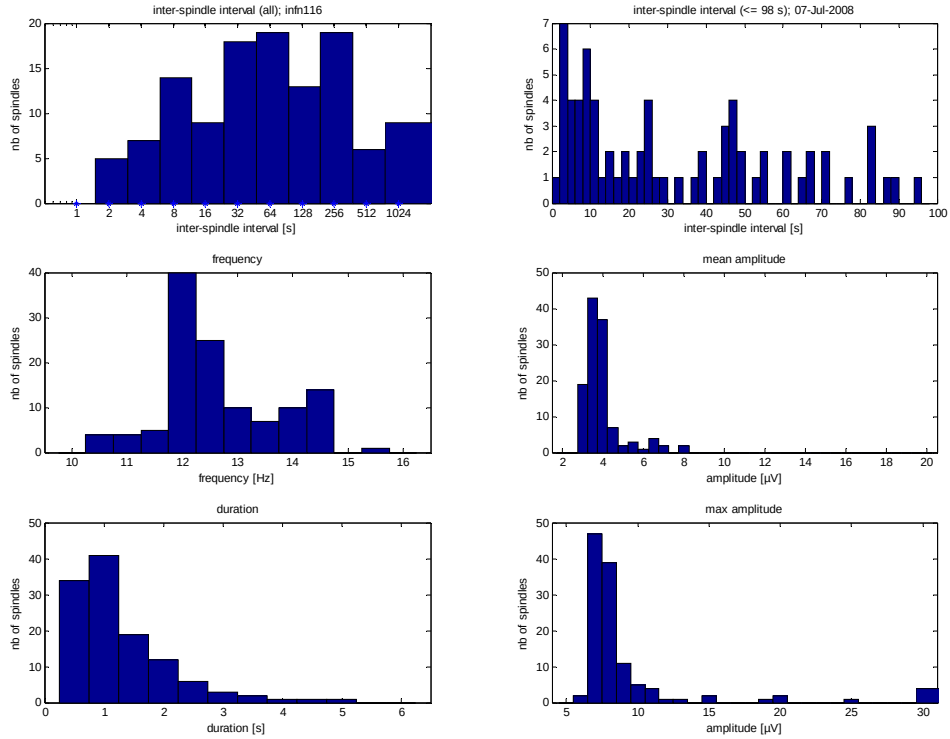

inter-spindle interval (all); infn215
nb of spindles
inter-spindle interval [s]
inter-spindle interval (<= 98 s); 08-Jul-2008
nb of spindles
inter-spindle interval [s]
frequency
nb of spindles
frequency [Hz]
mean amplitude
nb of spindles
amplitude [µV]
duration
nb of spindles
duration [s]
max amplitude
nb of spindles
amplitude [µV]

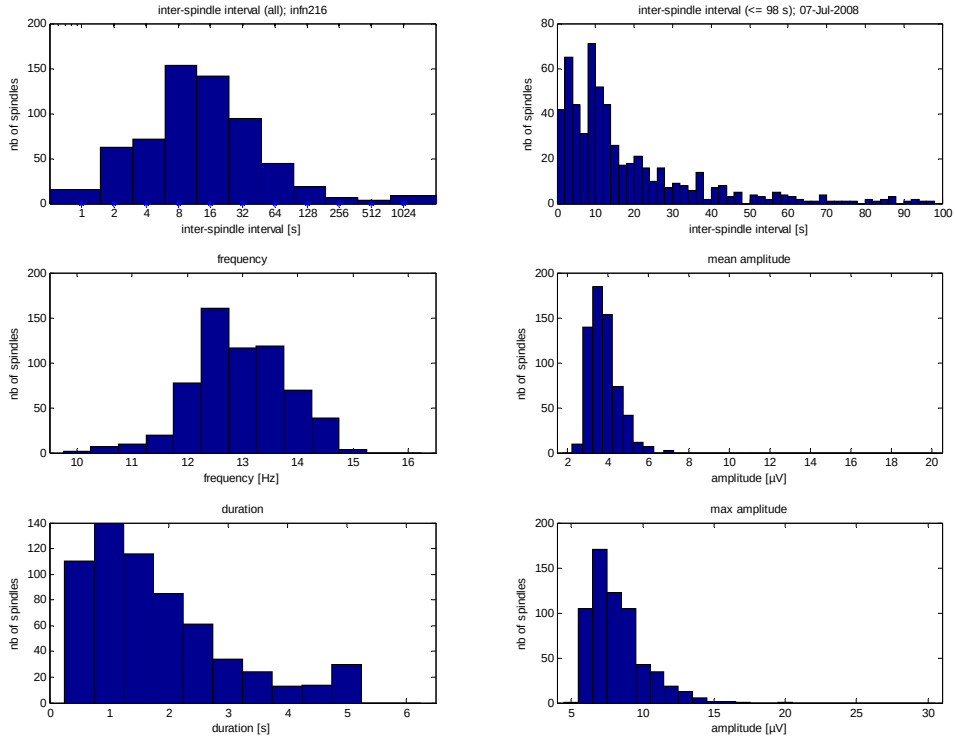

inter-spindle interval (all); infn315
nb of spindles
inter-spindle interval [s]
inter-spindle interval (<= 98 s); 10-Jul-2008
nb of spindles
inter-spindle interval [s]
frequency
nb of spindles
frequency [Hz]
mean amplitude
nb of spindles
amplitude [µV]
duration
nb of spindles
duration [s]
max amplitude
nb of spindles
amplitude [µV]

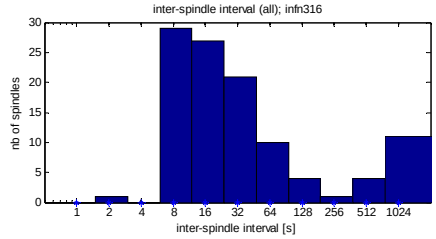

inter-spindle interval (all); infn415
nb of spindles
inter-spindle interval [s]
inter-spindle interval (<= 98 s); 08-Jul-2008
nb of spindles
inter-spindle interval [s]
frequency
nb of spindles
frequency [Hz]
mean amplitude
nb of spindles
amplitude [µV]
duration
nb of spindles
duration [s]
max amplitude
nb of spindles
amplitude [µV]

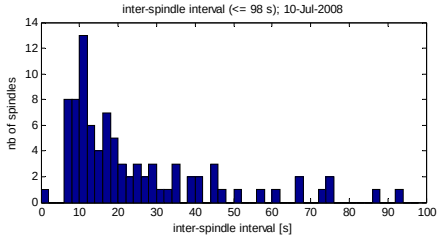

inter-spindle interval (all); infn515
nb of spindles
inter-spindle interval [s]
inter-spindle interval (<= 98 s); 10-Jul-2008
nb of spindles
inter-spindle interval [s]
frequency
nb of spindles
frequency [Hz]
mean amplitude
nb of spindles
amplitude [µV]
duration
nb of spindles
duration [s]
max amplitude
nb of spindles
amplitude [µV]

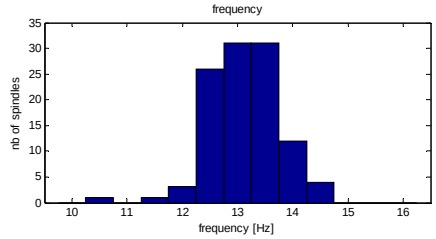
Inf 16

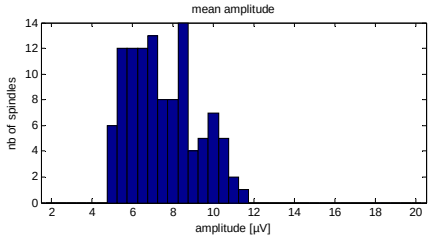

inter-spindle interval (all); infn116
nb of spindles
inter-spindle interval [s]
inter-spindle interval (<= 98 s); 07-Jul-2008
nb of spindles
inter-spindle interval [s]
frequency
nb of spindles
frequency [Hz]
mean amplitude
nb of spindles
amplitude [µV]
duration
nb of spindles
duration [s]
max amplitude
nb of spindles
amplitude [µV]

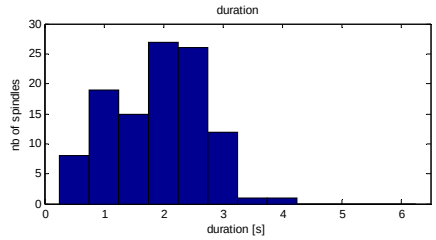

inter-spindle interval (all); infn216
nb of spindles
inter-spindle interval [s]
inter-spindle interval (<= 98 s); 07-Jul-2008
nb of spindles
inter-spindle interval [s]
frequency
nb of spindles
frequency [Hz]
mean amplitude
nb of spindles
amplitude [µV]
duration
nb of spindles
duration [s]
max amplitude
nb of spindles
amplitude [µV]

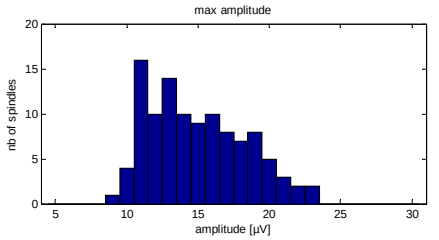

inter-spindle interval (all); infn316
nb of spindles
inter-spindle interval [s]

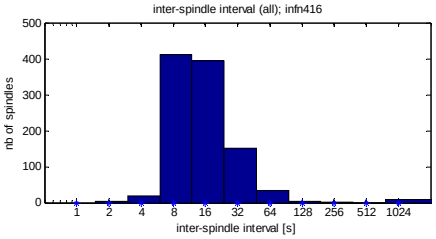

inter-spindle interval (<= 98 s); 10-Jul-2008
nb of spindles
inter-spindle interval [s]

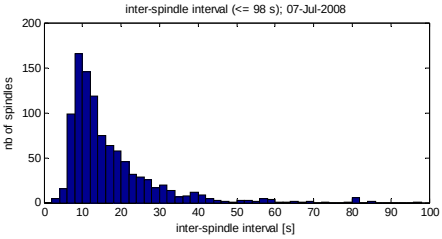

frequency
nb of spindles
frequency [Hz]

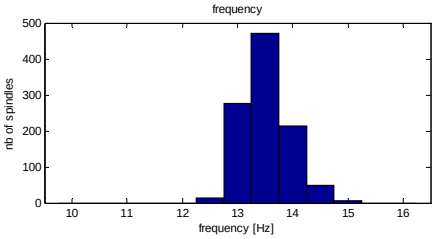

mean amplitude
nb of spindles
amplitude [µV]

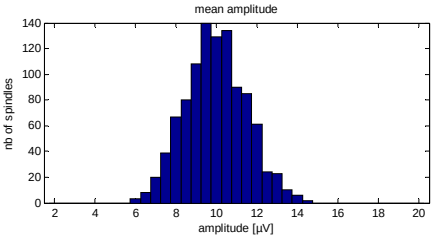

duration
nb of spindles
duration [s]

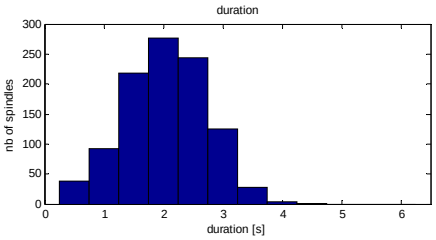

max amplitude
nb of spindles
amplitude [µV]

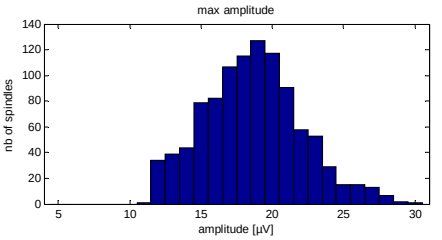

inter-spindle interval (all); infn416
nb of spindles
inter-spindle interval [s]


inter-spindle interval (<= 98 s); 07-Jul-2008
nb of spindles
inter-spindle interval [s]


frequency
nb of spindles
frequency [Hz]

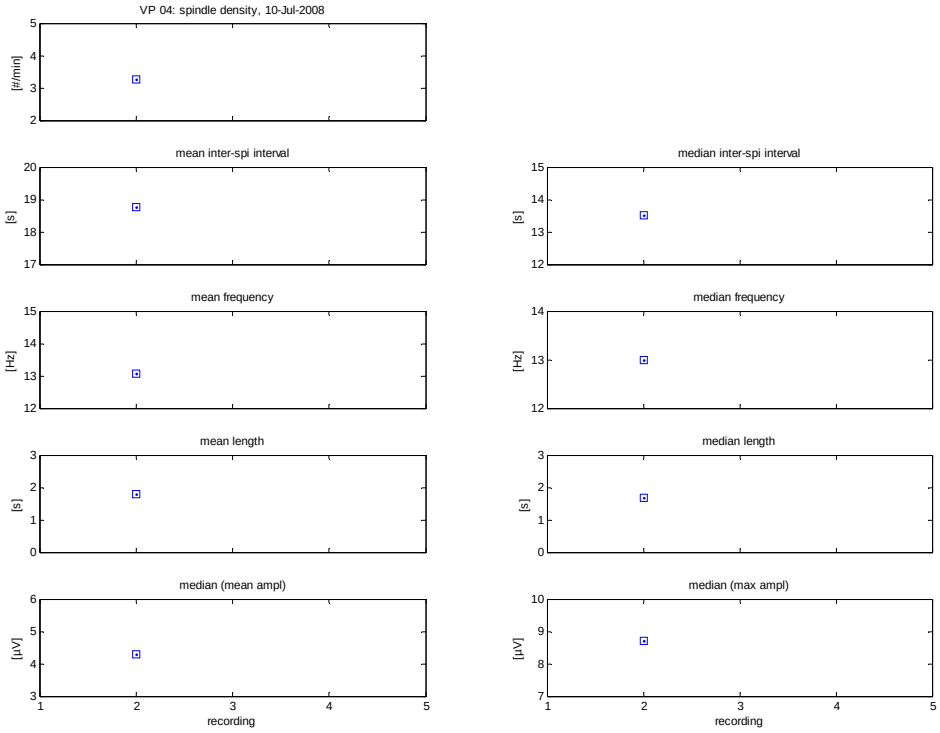

mean amplitude
nb of spindles
amplitude [µV]


duration
nb of spindles
duration [s]

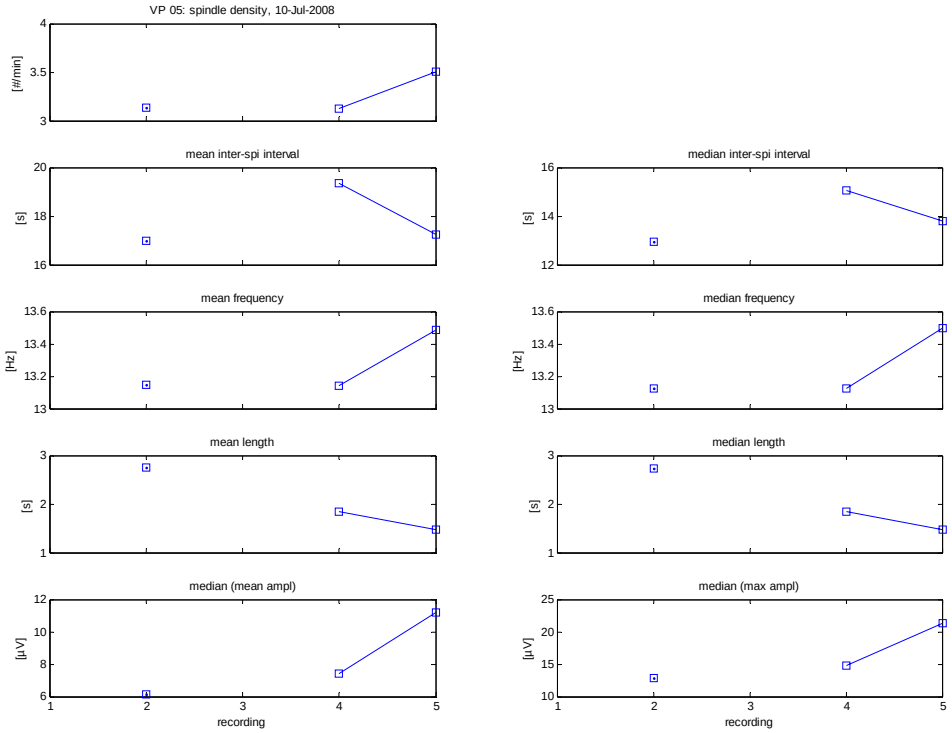

max amplitude
nb of spindles
amplitude [µV]

Individual development of sleep spindle variables across age

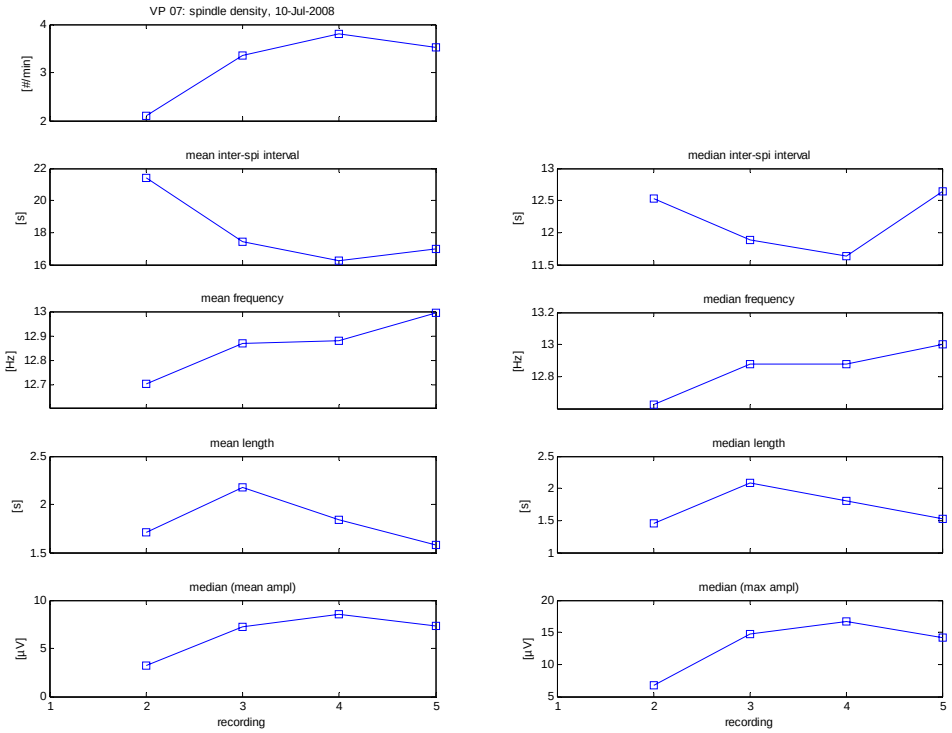
Inf 04



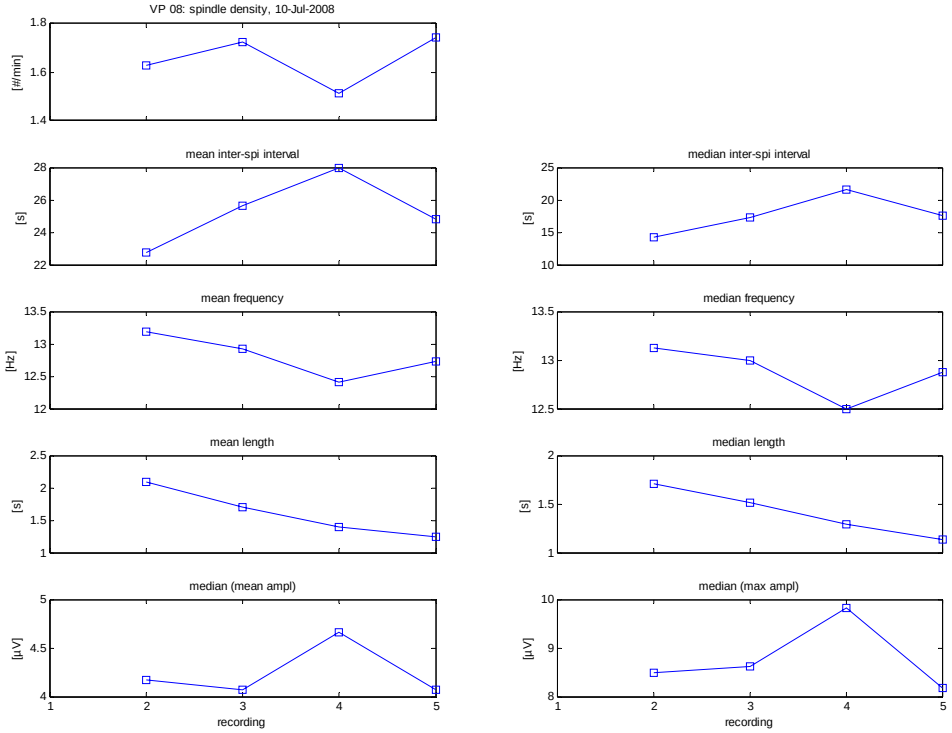
Inf 05


VP 05: spindle density, 10-Jul-2008
[#/min]
mean inter-spi interval
median inter-spi interval
[s]
mean frequency
median frequency
[Hz]
mean length
median length
[s]
median (mean ampl)
median (max ampl)
[µV]
recording

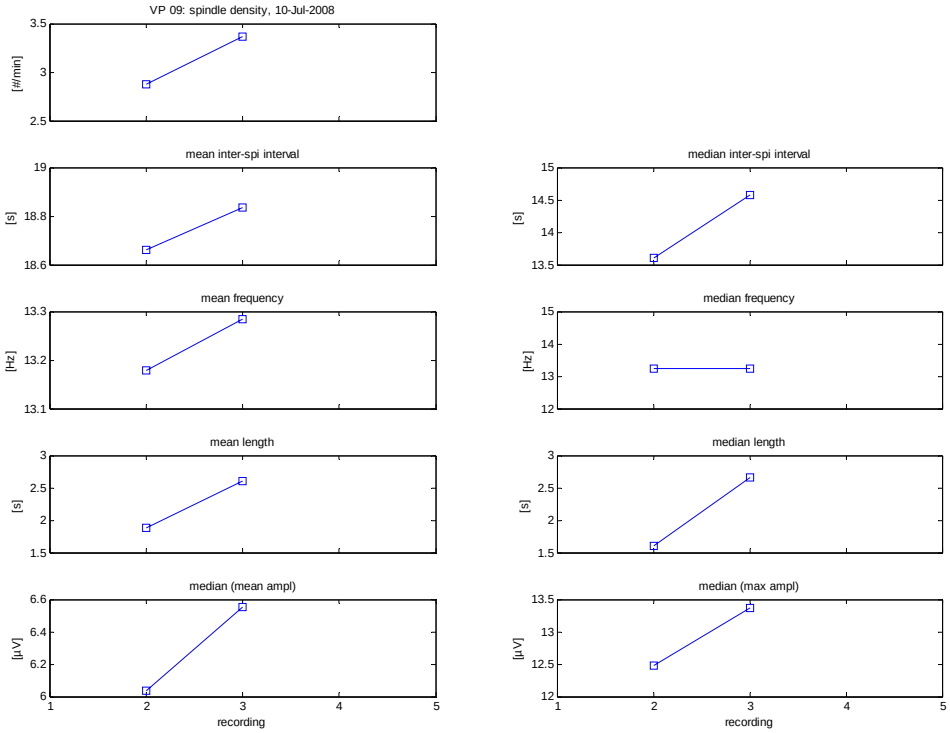
Inf 07


VP 07: spindle density, 10-Jul-2008
[#/min]
mean inter-spi interval
[s]
median inter-spi interval
[s]
mean frequency
[Hz]
median frequency
[Hz]
mean length
[s]
median length
[s]
median (mean ampl)
[µV]
median (max ampl)
[µV]
recording
recording

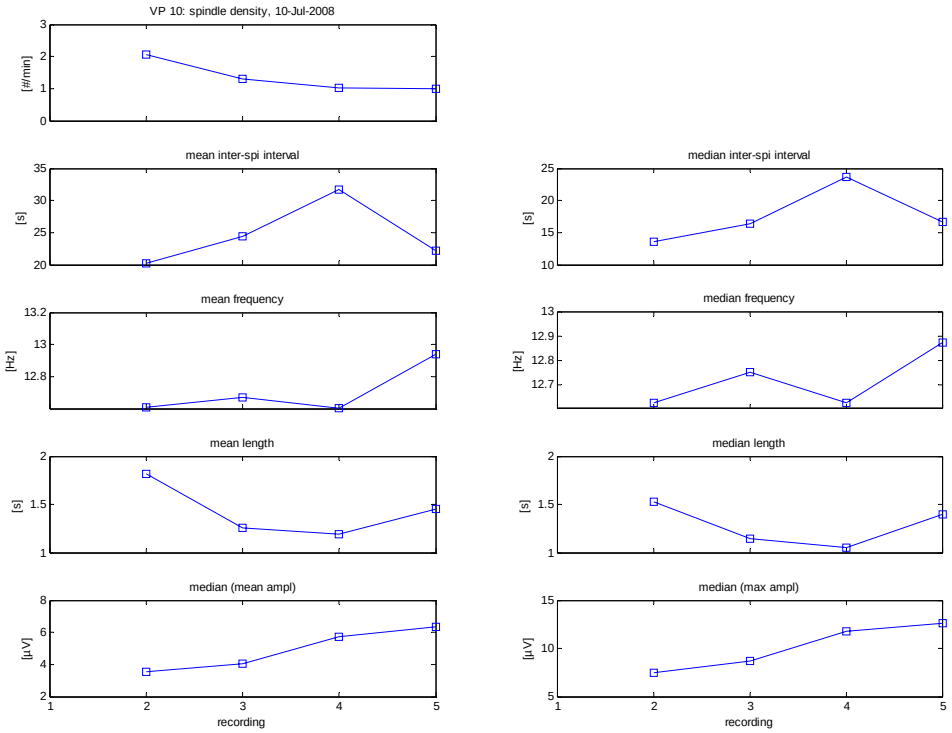
Inf 08


VP 08: spindle density, 10-Jul-2008
[#/min]
mean inter-spi interval
median inter-spi interval
[s]
mean frequency
median frequency
[Hz]
mean length
median length
[s]
median (mean ampl)
median (max ampl)
[µV]
recording
recording

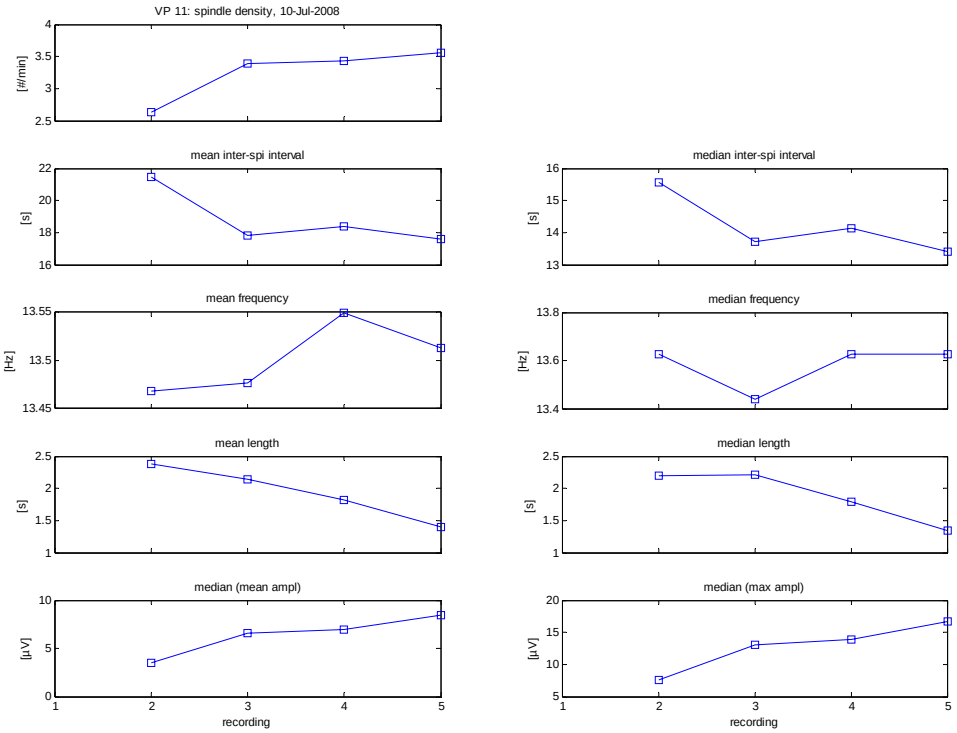
Inf 09


VP 09: spindle density, 10-Jul-2008
[#/min]
mean inter-spi interval
[s]
median inter-spi interval
[s]
mean frequency
[Hz]
median frequency
[Hz]
mean length
[s]
median length
[s]
median (mean ampl)
[µV]
median (max ampl)
[µV]
recording
recording

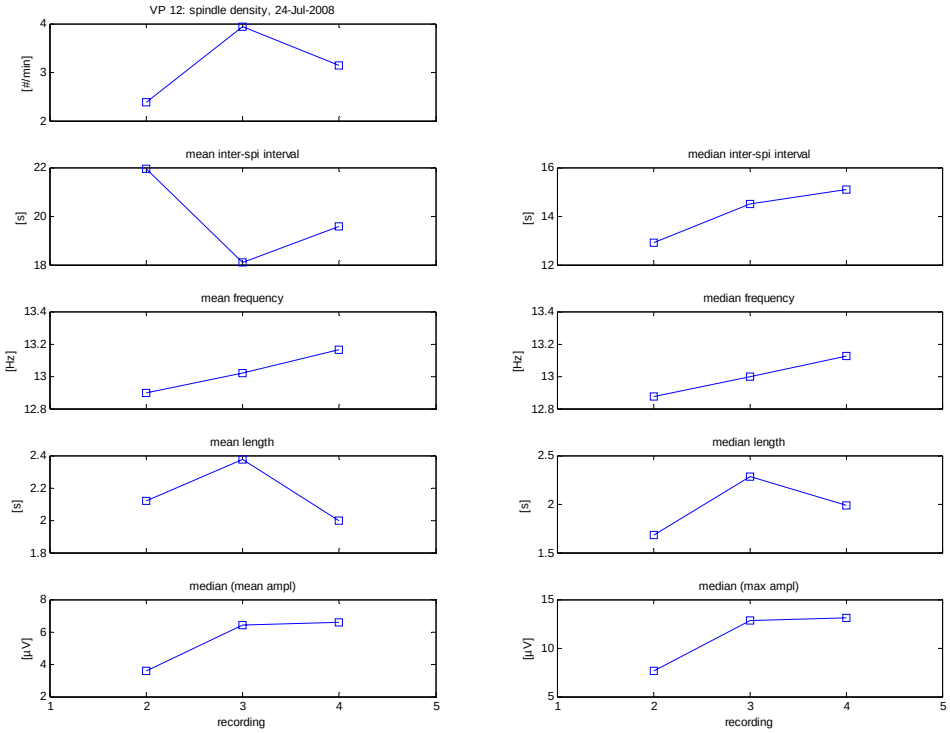
Inf 10


VP 10: spindle density, 10-Jul-2008
[#/min]
mean inter-spi interval
median inter-spi interval
[s]
mean frequency
median frequency
[Hz]
mean length
median length
[s]
median (mean ampl)
median (max ampl)
[µV]
recording
recording

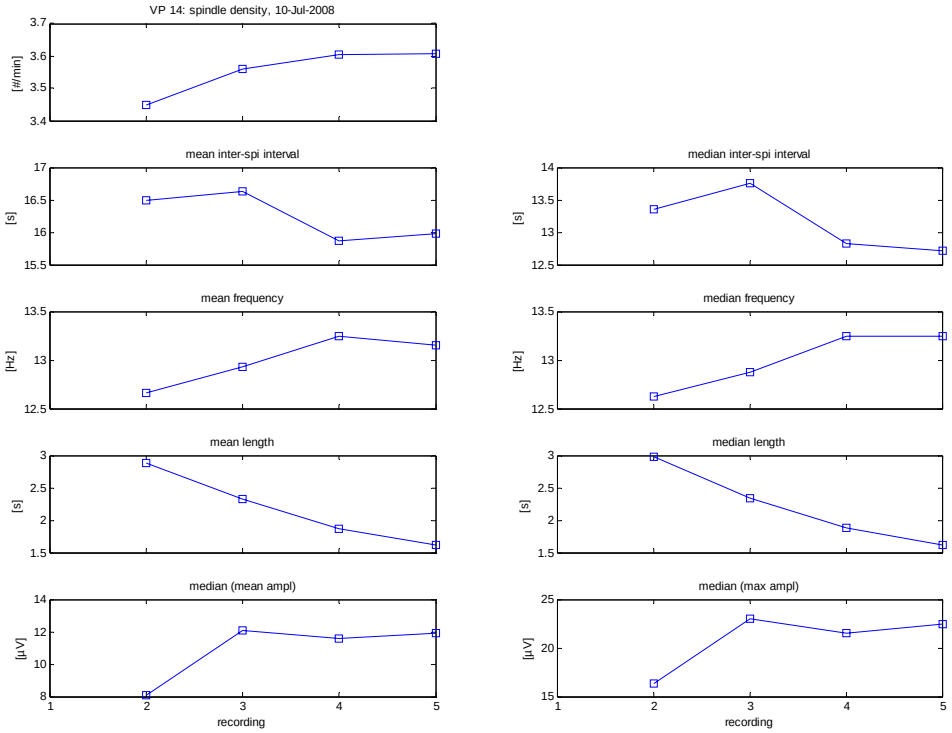
Inf 11


VP 11: spindle density, 10-Jul-2008
[#/min]
mean inter-spi interval
median inter-spi interval
[s]
mean frequency
median frequency
[Hz]
mean length
median length
[s]
median (mean ampl)
median (max ampl)
[µV]
recording
recording

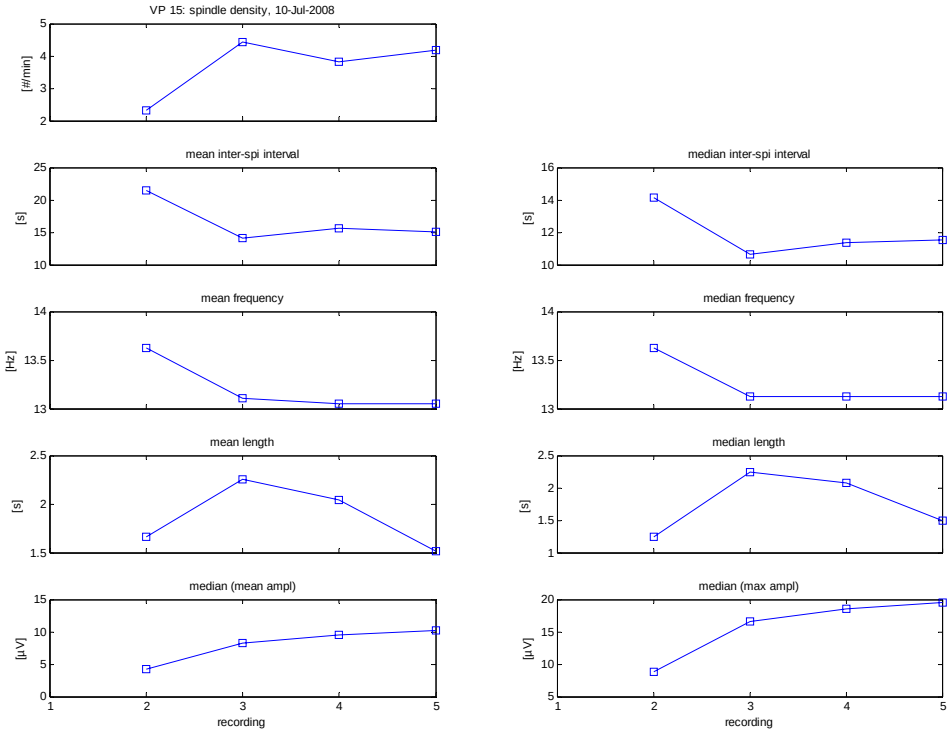
Inf 12


VP 12: spindle density, 24-Jul-2008
[#/min]
mean inter-spi interval
[s]
median inter-spi interval
[s]
mean frequency
[Hz]
median frequency
[Hz]
mean length
[s]
median length
[s]
median (mean ampl)
[µV]
median (max ampl)
[µV]
recording
recording

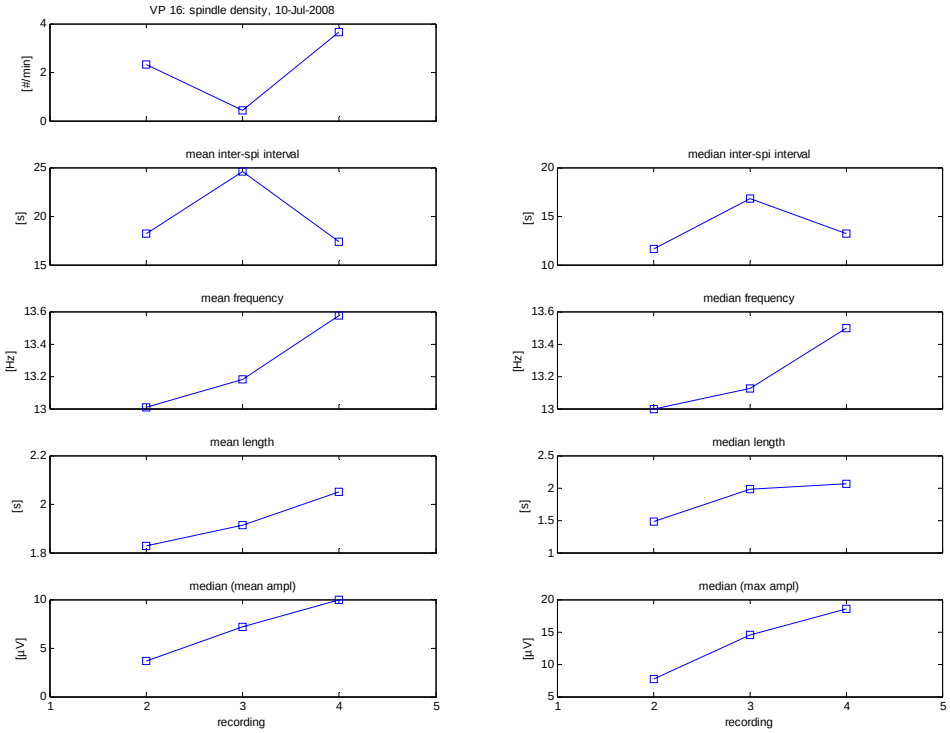
Inf 14


VP 14: spindle density, 10-Jul-2008
[#/min]
mean inter-spi interval
median inter-spi interval
[s]
mean frequency
median frequency
[Hz]
mean length
median length
[s]
median (mean ampl)
median (max ampl)
[µV]
recording

Inf 15


VP 15: spindle density, 10-Jul-2008
[#/min]
mean inter-spi interval
median inter-spi interval
[s]
mean frequency
median frequency
[Hz]
mean length
median length
[s]
median (mean ampl)
median (max ampl)
[µV]
recording

Inf 16


VP 16: spindle density, 10-Jul-2008
[#/min]
mean inter-spi interval
median inter-spi interval
[s]
mean frequency
median frequency
[Hz]
mean length
median length
[s]
median (mean ampl)
median (max ampl)
[µV]
recording
recording