Unobtrusive sleep state measurements in preterm infants - A review

Citation for published version (APA):

Document license:
TAVERNE

DOI:
10.1016/j.smrv.2016.03.005

Document status and date:
Published: 01/04/2017

Document Version:
Publisher’s PDF, also known as Version of Record (includes final page, issue and volume numbers)

Please check the document version of this publication:
• A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher’s website.
• The final author version and the galley proof are versions of the publication after peer review.
• The final published version features the final layout of the paper including the volume, issue and page numbers.

Link to publication

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

• Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
• You may not further distribute the material or use it for any profit-making activity or commercial gain
• You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the “Taverne” license above, please follow below link for the End User Agreement:
www.tue.nl/taverne

Take down policy
If you believe that this document breaches copyright please contact us at:
openaccess@tue.nl
providing details and we will investigate your claim.

Download date: 16. Sep. 2023
TECHNICAL REVIEW
Unobtrusive sleep state measurements in preterm infants – A review
Jan Werth a, b, *, Louis Atallah b, Peter Andriessen c, d, Xi Long a, b, *, Elly Zwartkruis-Pelgrim b, Ronald M. Aarts a, b
a Department of Electrical Engineering, University of Technology Eindhoven, De Zaale, 5612 AJ Eindhoven, The Netherlands
b Philips Research, High Tech Campus 34, 5656 AE Eindhoven, The Netherlands
c Neonatal Intensive Care Unit, Maxima Medical Center, De Run 4600, 5504 DB Veldhoven, The Netherlands
d Faculty of Health, Medicine, and Life Science, Maastricht University, Minderbroedersberg 4-6, 6211 LK Maastricht, The Netherlands

A R T I C L E  I N F O
Article history:
Received 12 August 2015
Received in revised form 25 March 2016
Accepted 29 March 2016
Available online 5 April 2016

Keywords:
Preterm infant sleep
Active sleep
Quiet sleep
Unobtrusive sleep measurement
Contactless vital sign measurement
Sleep monitoring

S U M M A R Y
Sleep is important for the development of preterm infants. During sleep, neural connections are formed and the development of brain regions is triggered. In general, various rudimentary sleep states can be identified in the preterm infant, namely active sleep (AS), quiet sleep (QS) and intermediate sleep (IS). As the infant develops, sleep states change in length and organization, with these changes as important indicators of brain development. As a result, several methods have been deployed to distinguish between the different preterm infant sleep states, among which polysomnography (PSG) is the most frequently used. However, this method is limited by the use of adhesive electrodes or patches that are attached to the body by numerous cables that can disturb sleep. Given the importance of sleep, this review explores more unobtrusive methods that can identify sleep states without disturbing the infant. To this end, after a brief introduction to preterm sleep states, an analysis of the physiological characteristics associated with the different sleep states is provided and various methods of measuring these physiological characteristics are explored. Finally, the advantages and disadvantages of each of these methods are evaluated and recommendations for neonatal sleep monitoring proposed.

Introduction
Sleep is one of the most important factors in the neural development of preterm infants [1], suggesting that its continuous monitoring could provide an indicator of such development over time. Today, monitoring is mainly performed with polysomnography (PSG) and/or behavioural observations to determine the quality of sleep and potentially detect pathological sleep events. PSG uses a number of measurements which require the attachment of sensors and electrodes to the body of the infant. The use of adhesive electrodes on preterm infants can cause damage to their fragile skin, making them more prone to infections [2,3], while the wires also form a barrier to direct skin-to-skin contact between parent and infant. The necessity of sleep monitoring and the obtrusiveness of these commonly used methods lead us to argue that unobtrusive sleep measurement methods are required to ensure a much more comfortable alternative, with a minimal burden on preterm infants.

Due to their unobtrusiveness, these techniques could also be used for long-term automated monitoring of sleep and development, leading to personalized sleep pattern identification, which could be implemented in the care plan for the preterm infant. Additionally, alarm sounds could be adapted to the sleep state of the preterm infant to reduce disturbance to the infant, as well as alarm fatigue in the caretaker, which can lead to a lapse or delay in attention to critical situations due to the desensitization of the caretaker to the alarm. Continuous sleep monitoring can also help to detect sleep-associated events such as central apnoea and may reveal the effects of medication on the sleep architecture and, thereby, the neuronal development of preterm infants. Sleep monitoring might also support the identification of discomfort or stress observable in an altered sleep architecture. In general, sleep monitoring can guide caretakers by integrating the moments of necessary neonatal (intensive) care without disturbing the indispensable sleep of the vulnerable preterm infant.

* Corresponding authors. Department of Electrical Engineering, University of Technology Eindhoven, De Zaale, 5612 AJ Eindhoven, The Netherlands. Tel.: +31 (0) 40 247 70 00.
E-mail addresses: jan.werth@philips.com, werth.jan@gmail.com (J. Werth), xi.long@philips.com (X. Long).
The goal of this paper is to review the methods or methodologies available to detect and distinguish sleep states while focusing on unobtrusiveness as an important requirement. We will first briefly introduce preterm infant sleep states. Subsequently, we will discuss the different measurement methods used to acquire signals connected to sleep states in preterm infants, before discussing some unobtrusive technical means for acquiring these signals.

Preterm infant sleep states

Five different states are commonly distinguished in preterm infants. These are active sleep (AS) (also identified as rapid eye movement [REM] sleep), quiet sleep (QS) (non REM or NREM), intermediate sleep (IS), arousal and the non-sleep state of wake [4,5]. More information on the role of each of these sleep states during development is available [6–8].

During the first month after birth, preterm infants spend up to 70% of their time sleeping. This contrasts with approximately 60% for term babies [9]. The change in total sleep time (TST) associated with neonatal development is accompanied by a change in sleep organization, with the length of AS decreasing as QS increases [9–15]. This change in sleep state organization is a strong indication of the maturation and consolidation process. By distinguishing each sleep state and determining its share of TST, it is possible to assess whether the developmental process is following the anticipated path or not [15]. These changes in sleep states over time can be seen in Fig. 1.

Interestingly, the work of Curzi-Dascalova et al. [10,11] revealed results contrary to the generally accepted findings on AS and QS, with their work finding AS increasing and QS decreasing over time. These divergent results may have arisen due to a different annotation methodology, definition and/or signal quality. Moreover, the identification of sleep states at a very early age of 27 wk gestational age (GA), as in [11], is known to be very difficult.

Measurement methods

Infant sleep is scored using two main methods: PSG and behavioural sleep measurements. The scoring parameters of both methods can be found in the corresponding publications [16]. There are three ways to perform classification using the two methods: the use of PSG methods alone [1,17–20], the use of behavioural methods alone [13,14,21,22] and the use of both methods in combination [4,11,16,23–25]. However, sleep/wake states in electroencephalography (EEG) or PSG of preterm infants are typically scored manually.

Polysomnography

PSG combines several vital sign measurement methods to determine the sleep state of a patient, and is widely used in adults and infants. While there are already automated solutions for adults [26], annotations for preterm infant sleep monitoring using polysomnographic measurements are usually done manually. In the following section, we describe three of the methods used to determine preterm infant sleep states.

The main methods by which PSG distinguishes preterm infant sleep states are shown in Table 1.

---

**List of abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANS</td>
<td>autonomous nervous system</td>
</tr>
<tr>
<td>AS</td>
<td>active sleep</td>
</tr>
<tr>
<td>BCG</td>
<td>ballistocardiography</td>
</tr>
<tr>
<td>BR</td>
<td>breathing rate</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiography</td>
</tr>
<tr>
<td>EEG</td>
<td>electroencephalography</td>
</tr>
<tr>
<td>EMG</td>
<td>electromyography</td>
</tr>
<tr>
<td>EOG</td>
<td>electrooculography</td>
</tr>
<tr>
<td>GA</td>
<td>gestational age</td>
</tr>
<tr>
<td>HR</td>
<td>heart rate</td>
</tr>
<tr>
<td>HRV</td>
<td>heart rate variability</td>
</tr>
<tr>
<td>IBI</td>
<td>inter burst intervals</td>
</tr>
<tr>
<td>IR</td>
<td>infra-red</td>
</tr>
<tr>
<td>IS</td>
<td>intermediate sleep</td>
</tr>
<tr>
<td>NICU</td>
<td>neonatal intensive care unit</td>
</tr>
<tr>
<td>NIR</td>
<td>near infra-red</td>
</tr>
<tr>
<td>PPG</td>
<td>photoplethysmography</td>
</tr>
<tr>
<td>PSG</td>
<td>polysomnography</td>
</tr>
<tr>
<td>QS/NREM</td>
<td>quiet sleep/non rapid eye movement</td>
</tr>
<tr>
<td>REM</td>
<td>rapid eye movement</td>
</tr>
<tr>
<td>SNR</td>
<td>signal to noise ratio</td>
</tr>
<tr>
<td>TST</td>
<td>total sleep time</td>
</tr>
</tbody>
</table>

---

Fig. 1. Sleep state development over time. The graphic shows active sleep (AS) and quiet sleep (QS) across gestational age (GA). AS decreases, while QS increases. The data are compiled from ([4,12–14,25,38,94,95]).
EEG signals

EEG signal patterns can be used to distinguish sleep states. These signal patterns have been investigated in several publications [27–31]. The EEG pattern of preterm infants before 30 wk GA are discontinuous [32]. Niemarkt et al. [27] explained that during development, the inter burst intervals (IBI) of the discontinuous patterns shorten and the burst length increases, creating a more continuous pattern during AS [32]. With advancing development, this discontinuous pattern can then be separated into traces discontinuus and trace alternant. The latter is detectable from 34 GA onwards and is connected with QS [27].

Heart rate variability

Preterm infant heart rate (HR) is normally between 120 and 160 bpm [33,34]. HR and heart rate variability (HRV) change with the development of the preterm infant, with a decreasing HR and increase of R peak intervals [34,35].

HRV is closely related to the developmental stage [36,37], with development leading to a change in the absolute values of increased HRV and decreased HR, as well as their time response.

In addition to changes in their long-term trends, HR and HRV are also directly connected with changes in sleep states, resulting in immediate changes in HR and HRV. For example, HR decreases during QS and increases during AS [36], while HRV reflects the level of cardiovascular autonomic control and the functioning of the autonomous nervous system (ANS). Therefore, the different sleep states can be distinguished in the power spectrum and time domain features of HRV [35].

Respiration

A preterm infant breathes 40–80 times per minute [33,34]. As with HR and HRV, breathing patterns change over the course of the preterm infant’s development. The breathing/respiration rate (BR) becomes more regular in QS with maturation [13,38]. These breathing patterns can also be considered as indicators of sleep states, where the respiration depth can be used to estimate vagal activity and distinguish the sympathetic and parasympathetic dominance of AS and QS respectively [39]. Another way to identify sleep state changes is to use the above-mentioned regularity of BR.

These changes in regularity are reflected in both the frequency [13] and amplitude [38] of the BR signal, with BR relatively steady during QS, but more irregular during AS [4,13,24]. Holditch-Davis et al. [13] measured regularity in BR and divided it into three stages: very regular, regular and irregular. The criteria used to separate these categories are listed below:

- Regular respiration:
  - No more than one breath is between 20% and 50% of the height of the largest breath.
  - The narrowest peak to peak is at least 50% of the widest peak to peak interval.

- Very regular respiration:
  - During a 10 s epoch, the smallest breath is at least 80% of the height of the largest breath.
  - The narrowest peak to peak interval is at least 67% of the widest peak to peak interval.

- All other breathing patterns can be classified as irregular.

Methods of behavioural sleep classification

Behavioural measurements for sleep state analysis are also used to assist the PSG analysis and obtain a more robust annotation. However, they can also be used on their own to separate sleep states. Behavioural classification for sleep uses general body movements [4,11,20,23,24], specific body movements, such as face, eye, chin or limb movement [4,17,18,24,25], and BR [13,16,19]. General body movements (also referred to as motor activities) range from low activity in drowsy or alert states to high activity during periods of crying [38]. The sleep states can be behaviourally scored in the following manner:

- AS: The eyes are closed [5,40,41] or slightly opening and closing [22]. They might open during REM in AS [41]. A wide range of motor activity can be detected [38]. Motor activity is sporadic and appears in bursts of 5–60 s [41], but muscle tone is low between the movements [13,41]. The facial expressions include smiles, grimaces.

- QS: Continuous mix of EEG patterns 40–80 μV in amplitude
- Defined if no other state fits
- Mixed EEG pattern with movement artifacts
- Decreased amplitude and increased frequency

- IS: Defined if no other state fits
- Open and moving eyes; No REMs; Eyes can be closed during crying
- Open and fixed eyes

- Wake: Open and moving eyes; No REMs; Eyes can be closed during crying
- High and irregular HR

- Arousal: Increased heat to beat variability

Table 1

Polysomnography (PSG) attributes. This table shows how the different preterm infant sleep states are observed using different features. The states are active sleep (AS), quiet sleep (QS) intermediate sleep (IS), wake and arousal. The vital signs/movements are: brain activity, heart rate (HR), eye movements, heart rate variability (HRV), muscle activity and respiration. Additional abbreviations: electroencephalography (EEG), gestational age (GA), rapid eye movement (REM).

<table>
<thead>
<tr>
<th>Brain activity</th>
<th>Eye movements</th>
<th>HR</th>
<th>HRV</th>
<th>Muscle activity</th>
<th>Respiration</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS</td>
<td>Continuous mix of EEG patterns 40–80 μV in amplitude</td>
<td>Slow and rapid bursts and isolated eye movement; 20 s epochs of REM bursts</td>
<td>Mostly irregular</td>
<td>Low frequencies are dominant 0.03 to 0.39 Hz</td>
<td>Low amplitudes superimposed with twitches and phasic saccadic movements; Low tone between movements</td>
</tr>
<tr>
<td>QS</td>
<td>&lt;34 GA</td>
<td>Discontinuous with delta bursts &gt;32 &lt; 46 GA traced alternant 50–150 μV in amplitude</td>
<td>No eye movement (infrequent eye movement can be seen)</td>
<td>Mostly regular with some acceleration during startles</td>
<td>High frequencies are dominant 0.4 to 1 Hz</td>
</tr>
<tr>
<td>IS</td>
<td>Defined if no other state fits</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>Wake</td>
<td>Open and moving eyes; No REMs; Eyes can be closed during crying</td>
<td>High and irregular HR</td>
<td>Variable</td>
<td>High muscle tone superimposed with general body movements</td>
<td>Regular; Tracking motor activity</td>
</tr>
<tr>
<td>Arousal</td>
<td>Decreased amplitude and increased frequency</td>
<td>Open and fixed eyes</td>
<td>HR acceleration</td>
<td>Increased heat to beat variability</td>
<td>General body movement incl. startle &gt;1 min – awakening</td>
</tr>
</tbody>
</table>
and frowns, and bursts of sucking movements can also be seen [5,40] as well as small twitches. Sighs and sosms might be heard [40].

QS: The eyes are closed [5,40,41]. Little or no motor activity is detectable [38], only appearing as occasional startles, sighs or other brief discharges. A tonic motor level is maintained [13,40]. Mouth movements or sucking can be seen [5,41].

An overview of behavioural observations related to the sleep states can be found in Table 2.

Preterm infant behavioural patterns are often considered static over time. However, Holditch-Davis et al. [13] found decreasing body movement with maturation. They realized that their finding contradicted other publications and suggested this was due to the longer follow-up period used in their trial [13]. If body movements are used to annotate sleep, and sleep organization changes with maturation, it can be assumed that body movements will undergo change as well. Therefore, age should also be considered as a factor in behavioural annotation.

Unobtrusive measurement methods of sleep state monitoring

Unlike behavioural observations, other sleep monitoring methods based on vital signs require the attachment of adhesive electrodes, including cables, which can be obtrusive and create additional burdens for fragile preterm infants. In the following sections, we describe unobtrusive methods of vital sign and movement measurements that can distinguish preterm infant sleep states. An overview of these methods is given in Table 3. It is difficult to undertake a direct comparison of the results obtained by different groups, as the statistical analyses used to compare the performance of their method with the specific reference are quite different. However, the following section will highlight some of the most promising methods, giving an indication of their performance in comparison with the standards of currently used methods.

The methods are clustered into the following groups:

- PSG with electrical origin
  - EEG, electrocardiography (ECG) and electrooculography (EOG)
- Polygraphy with mechanical origin
  - HR, BR
- Behavioural signals
  - Body movement, facial expression

Unobtrusive EEG/ECG/EOG signal measurement

This section presents an overview of unobtrusive measurement methods using signals of electrical origin from dry electrodes and capacitive electrodes. Normal gel electrodes are not useful for long-term monitoring of preterm infants because of impedance changes due to drying gel [42]. Additionally, there are inflammation risks at the electrode-skin contact [3]. In some rare cases, toxicological concerns about the gel electrodes have been reported.

In preterm infants under 34 wk GA, the epidermis is 2–3 layers thick with barely no protective outer skin layer (the stratum corneum) [2]. Therefore, all electrodes in contact with the fragile skin are considered obtrusive.

Dry electrodes

Dry electrodes create contact with the skin without the need for skin abrading to reduce skin resistance or any application of conductive gel to ensure correct electrode contact. There are several types of dry electrodes, including various metal disks, conductive rubber, spring-loaded fingers and conductive foam. The principle is that in most cases the material follows the skin contour without leaving any high impedance air gap, as shown in Fig. 2. The interface impedance with dry electrodes is higher than with gel electrodes, as only the skin moisture/sweat is used as a conductive bridge, which has a lower ion conductivity than conductive gel [3]. Lower impedance means that smaller signal amplitudes can be measured (e.g., low EEG amplitudes). Also, the thermal noise (Johnson noise) of the electrode itself is lower, leading to a higher signal-to-noise ratio (SNR).

A recently introduced dry electrode type with minimal skin contact is the nano needle array (Fig. 3). This electrode consists of 50 nm wide and 10–15 μm long carbon tubes [43] which can puncture through the high-impedance, 10–15 μm thick stratum corneum [44] to reach the underlying low-impedance layers. Although the nano needle arrays can be considered invasive, Lopez-Gordo et al. [42] state that, due to the minimal diameter of the needles, the infection risk is minimal. Due to their minimal penetration depth, the nano and needle arrays are painless (thus far only shown in adults). The underlying nerves are not stimulated enough to trigger pain [45]; however, their application in preterm infants remains to be investigated. These attributes make them less harmful, while exhibiting similar or more stable long-term impedance [46] and fewer motion artefacts than classic wet electrodes. Ruffini et al. [43] tested their nano needle array for one hour in a laboratory environment on a single adult subject (confirmed by author). Visual inspection comparing them to the gold-standard, commercial wet EEG electrodes, revealed similar results for adults in both the time and frequency domains. Forvi et al. [47], demonstrated that their measurements are on par with the gold standard for EEG, ECG and electromyography (EMG). Similar test, showing comparable results to the gold standard,

| Table 2 | Behavioural attributes. This table shows behavioural attributes that are used to identify sleep/wake states. These states are: active sleep (AS), quiet sleep (QS), intermediate sleep (IS), wake and arousal. Additional abbreviations: rapid eye movement (REM). |
|---|---|---|---|
| | Audio | Eyes | Face | Movement/Motor activity |
| AS | Sighs; Sobs | Closed or slightly opening and closing eyes; REM | Smiles; Grimaces; Frowns; Bursts of sucking Episodes of rhythmic mouth movements; Sucking | Wide range; Small twitches; Sporadic motor burst of 5–60 s; Low muscle tone in-between |
| QS | Sighs | Closed eyes | In quiet wake relaxed; No smile or frown | Little or none startles; Continuous tonic levels; Motion low |
| IS | Crying; Fussing | Open eyes; Focused eyes; No REM; Scanning | Defined if no other state fits | Head and arm movements; Orientation response; Motor high or low |
| Wake | Open eyes; Focused eyes; No REM; Scanning | In quiet wake relaxed; No smile or frown | Head and hand movements; Motion shows different intensity |
| Arousal | Open eyes; Fixed and focused | Mouth movement | | |
where recently performed by Stavrinidis et al. [48], and Hsu et al. [49]. Nevertheless, all these tests were done in laboratory settings with limited subject numbers. Therefore, further validation is needed, especially for preterm infants.

**Capacitive electrodes**

Another unobtrusive vital sign measurement method is capacitive coupling. This method allows the skin to couple capacitively to the measurement electrode without any contact with the skin of the preterm infant. However, the biggest problem with these electrodes is their sensitivity to movement and the production of dielectric artefacts. The coupling capacitance is altered by every movement [50,51], producing artefacts. One problem is the small amplitude of signals and the highly resistive elements of capacitive electrodes [51]. Therefore, the attached amplifier circuits need to have very low noise [52] so as not to mask the EEG signal, which makes the measurement unit more complex. Chi et al. [53] and Sullivan et al. [52] created contactless EEG/ECG electrodes for adults with signal and noise amplitudes in the same range as classic gel electrodes.

Serteyn et al. [54] used an estimation of artefacts to lower their effect on data obtained by capacitive electrodes. For ECG monitoring alone, the electrodes can also be placed under the preterm infant, for example, in a mattress, to detect HR or HRV. Atallah et al. [2] used a sensor array (shown in Fig. 4), which also takes into account that the preterm infant is not always in the same position. They developed a mattress with eight capacitive sensors and adaptive channel selection allowing contactless ECG and HR measurements in the neonatal intensive care unit (NICU). Using this method they were able to achieve results equivalent to standard ECG recorded with gel electrodes on preterm infants. They also showed that results improve with fewer layers of fabric between the infant and electrodes [2].

Fig. 5 presents levels of obtrusiveness, resistance, noise coupling and infection risk for the electrodes discussed in this section. Capacitive sensors offer several advantages compared to gel electrodes. This is due to their unobtrusiveness and low infection risk. From a technical point of view, gel electrodes perform well with respect to resistance and noise coupling; however, their obtrusiveness is problematic for preterm infants. Despite the negative psychological association with pain, the nano needle patches are a

## Table 3

Unobtrusive methods. The measurement methods are listed in relation to the vital signs and movement measurements. The methods are merged for several vital signs or movement. The degree of unobtrusiveness of the methods is indicated with colors and plus/minus indicators black & white. Red (minus indicators) indicates high to medium obtrusiveness and green (plus indicators) indicates minimal obtrusiveness. The methods are explained in Sections Unobtrusive EEG/ECG/EOG signal measurement to Unobtrusive behavioural measurements. Additional abbreviations: electrocardiography (ECG), electroencephalography (EEG), heart rate (HR).

<table>
<thead>
<tr>
<th>Method</th>
<th>Unobtrusiveness</th>
<th>EEG-signal</th>
<th>ECG-signal</th>
<th>Eye movement</th>
<th>HR</th>
<th>Respiration</th>
<th>Movement</th>
<th>Facial expressions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry electrodes</td>
<td>- -</td>
<td>No conductive gel needed;</td>
<td>Low impedance;</td>
<td>Low movement artifacts;</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Needle patch</td>
<td>-</td>
<td>Minimal invasive skin penetration;</td>
<td>Very low impedance;</td>
<td>Suitable for long term monitoring;</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Capacitive electrodes</td>
<td>+ +</td>
<td>Unobtrusive;</td>
<td>Prone to motion artifacts</td>
<td>Unobtrusive;</td>
<td>HR, respiration and movement has to be separated;</td>
<td>Need clear field of view</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Laser Doppler vibrometry</td>
<td>+ +</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ballistocardiogram</td>
<td>+ +</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accelerometry [behavioural]</td>
<td>+ +</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doppler radar</td>
<td>+ +</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Camera</td>
<td>+ +</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
good trade-off between good technical properties and minimal harm to the skin. However, their use for the neonatal population needs to be carefully assessed.

**Unobtrusive heart rate and respiration measurements**

In addition to electrodes, the measurement of signals of mechanical origin, for example, simple HR measurement, can be achieved using other methods.

**Ballistocardiogram**

A ballistocardiogram (BCG) presents a measurement of cardiac activity by retrieving the mechanical signal from the platform the patient is lying on. This could be a mattress inside an incubator or the incubator rack itself [55]. The signal is created by the force of the heart pumping blood through the body. The propagation to the outside depends on blood pressure and blood vessel elasticity [56]. The generated pulse wave can be monitored electrically with piezo elements (e.g., bed film sensors, Fig. 6) [57], mechanically with load cells [58,59], or with accelerometers, known in this form of application as a kinetocardiography [60]. The difference between the
methods is that the use of accelerometers needs time-varying pressure, while piezo and load sensors can also measure a constant pressure. The BCG can be used for both HR monitoring and BR monitoring [58,59].

These methods have been successfully used in adult patients [57–60] and even tested in the NICU [61]. In adult patients, BCG showed almost the same results as classic PSG for sleep classification [62]. The test on a preterm infant showed a very high correlation between an ECG reference and a BCG of 0.91, and a BR reference and a BCG of 0.74, proving BCG to be a suitable alternative for detecting HR and BR in preterm infants [61]. There are commercial products for infants using BCG, for example, AngelCare (www.angelcare.de) or NannyCare (www.nannycare.nl), but they are mostly used as sudden infant death syndrome alarm systems rather than continuous monitoring devices.

BCG methods pose a difficulty in designing algorithms to separate HR and BR from motion and noise. Brink et al. [58] found that in adults even the resonance frequency of the mattress could lead to the misinterpretation of signals. This might not be relevant to preterm infants but does emphasize that even slight movements can affect the signal. These problems may be resolved by adaptive signal processing, as done by Liu et al. [63], who presented a new method to separate BR in adults from other movements. Using a pressure-sensitive textile, they detected body position, movement and BR during sleep, matching the results of the reference method with a correlation of $r = 0.96$ to $r = 0.98$ (see Table 4). Another problem in the NICU is the signal amplitude. The small body of a preterm infant does not produce large mechanical waves. Therefore, the sensors need to be placed as close as possible to the body and should not be shielded by damping material. However, during sleep, preterm infants move in a smaller range than adults, which results in fewer motion artefacts.

Radar

Unobtrusive monitoring of HR and BR is also possible using radar. The heart wave and the respiratory movements are propagated to the surface and can therefore be detected by a non-contact system. A radar signal is directed towards the body of the preterm infant, where it is reflected in a frequency shift. The moving body surface modulates the phase due to the Doppler effect (see Fig. 7). This phase shift can be further transformed into HR and BR signals [64]. Different materials reflect the radar signals in different amounts, depending on the permittivity of the material. This is an advantage of radar technology over other non-contact methods, as the radar signal will be reflected by the preterm infant body (water permittivity = 50–88), but almost not at all by the clothing (cotton permittivity = 1–3) or the incubator shield (acrylic glass (PMMA) permittivity = 5), meaning it does not require a clear field of view (e.g., it can lie under the incubator mattress). With an adult patient in the optimal position, the method can deliver reliable HR, comparable to that obtained from standard ECG, with a correlation factor of $r = 1$ and $r = 0.827$ for different frequency windows (see Table 5) [65]. A preterm infant can easily be placed in the optimal position, without a great range of random movements, making this method more viable for the NICU than for adults. The use of radar for vital sign measurement suffers from similar problems to the methods already mentioned above: noise, movement and even background movement from several metres away [66] can affect its accuracy [64]. Recently, however, several algorithms have been proposed to deal with these problems. Solutions to the common radar problem of offset recalibration due to unwanted reflections from static objects have also been proposed [65]. Despite its advantages, the method has not been used in NICUs thus far due to being in the experimental stage.

Laser Doppler vibrometer

A similar method to the Doppler radar is the Doppler laser vibrometer. Here, a laser beam is sent to the chest of the preterm infant, where it is reflected by a shift in the phase due to the

<table>
<thead>
<tr>
<th></th>
<th>Gel electrode</th>
<th>Dry electrode</th>
<th>Needle patch</th>
<th>Capacitive electrode</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obtrusiveness</td>
<td>+</td>
<td>+</td>
<td>-/+</td>
<td>+ + +</td>
</tr>
<tr>
<td>Resistance</td>
<td>+++</td>
<td>-/+</td>
<td>+</td>
<td>- - -</td>
</tr>
<tr>
<td>Noise coupling</td>
<td>+ +</td>
<td>-</td>
<td>+</td>
<td>- - -</td>
</tr>
<tr>
<td>Infection risk</td>
<td>- - -</td>
<td>+ +</td>
<td>+ + +</td>
<td>+ + +</td>
</tr>
</tbody>
</table>

Fig. 5. Comparing electrodes. The obtrusiveness, resistance, noise coupling and infection risk of four different electrode types, gel, dry, capacitive and needle patches, are described. The gel electrodes show poor results for unobtrusiveness and infection risk compared to capacitive electrodes. Dry electrodes and needle patches share a medium level of obtrusiveness, while the needle patch has almost no infection risk. On the technical side, gel electrodes and needle patches show low resistance and noise coupling compared to dry and capacitive electrodes.

Fig. 6. Bed film sensors. The Sensor-mat by TEKSCAN (www.tekscan.com) is made from numerous piezoelectric sensors and is placed between the mattress and the sheets to record movement (Courtesy of Mohammed Meftah).
Validation of heart beat detection via Doppler radar. Gu et al. [65] presented a pressure sensitive sheet, covering a foam mattress to detect the BR in adult patients. They validated this with 12 adult subjects in different positions. The results show very high correlation with the ground truth which was obtained from video recording in a laboratory setting.

Table 4
Validation of breathing rate (BR) detection via pressure sensitive bed sheets. Liu et al. [63] presented a pressure sensitive sheet, covering a foam mattress to detect the BR in adult patients. They validated this with 12 adult subjects in different positions. The results show very high correlation with the ground truth which was obtained from video recording in a laboratory setting.

<table>
<thead>
<tr>
<th>Position</th>
<th>Lateral</th>
<th>Prone</th>
<th>Supine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Detected respiration rate</td>
<td>Reference</td>
<td>Detected respiration rate</td>
</tr>
<tr>
<td>Patients 1</td>
<td>169</td>
<td>172</td>
<td>174</td>
</tr>
<tr>
<td>2</td>
<td>137</td>
<td>154</td>
<td>147</td>
</tr>
<tr>
<td>3</td>
<td>162</td>
<td>173</td>
<td>171</td>
</tr>
<tr>
<td>4</td>
<td>184</td>
<td>186</td>
<td>184</td>
</tr>
<tr>
<td>5</td>
<td>125</td>
<td>133</td>
<td>127</td>
</tr>
<tr>
<td>6</td>
<td>138</td>
<td>144</td>
<td>136</td>
</tr>
<tr>
<td>7</td>
<td>162</td>
<td>162</td>
<td>155</td>
</tr>
<tr>
<td>8</td>
<td>174</td>
<td>176</td>
<td>179</td>
</tr>
<tr>
<td>9</td>
<td>158</td>
<td>167</td>
<td>160</td>
</tr>
<tr>
<td>10</td>
<td>137</td>
<td>142</td>
<td>138</td>
</tr>
<tr>
<td>11</td>
<td>170</td>
<td>172</td>
<td>164</td>
</tr>
<tr>
<td>12</td>
<td>147</td>
<td>146</td>
<td>152</td>
</tr>
<tr>
<td>Correlation factor</td>
<td>0.960</td>
<td>0.985</td>
<td>0.984</td>
</tr>
</tbody>
</table>

Photoplethysmography

Another unobtrusive way of monitoring HR and BR is through photoplethysmography (PPG), which is a common, simple and low-cost optical technique that can be used to detect blood volume changes in the skin [68]. The PPG sensor emits light onto the skin using LEDs and detects the reflected light. The determination of HR using PPG is based on the different level of absorption of light by haemoglobin and the surrounding tissue. The blood volume change in the veins, due to the pumping heart, changes the amount of absorbed light and consequently the amount of reflected light detected. Thereby, the blood volume change can be measured and translated into HR and, subsequently, BR. In addition to HR and BR assessment, PPG can detect respiratory sinus arrhythmias, which can be used to normalize HR with respect to respiration-induced variations, making it easier to determine HRV [68–70].

To date, the detection of HR and BR by PPG has mostly been applied to adult patients, with many different algorithms having been proposed [71–74]. Although they have not been tested on preterm infants, they have been used for newborn term infants [71,75,76] and term infants in the NICU [69,71], with very high correlations of \( r = 0.99 \) between the reference ECG and PPG, as well as between a reference BR and PPG. The possible problems with this method for preterm and/or term infants concern uncontrolled movements leading to artefacts [69] and the complicated realization of a breathing protocol to calibrate the analysis. The calibration helps to separate the BR from other variations in the PPG around the same frequency range, such as temperature fluctuations, vasomotion and/or baroreceptor oscillations (Mayer waves).

Classic PPG is performed with a light source and photo detector placed directly on the skin (Fig. 8), where it is usually wrapped around the foot of the preterm infant. It does not need any abrading of the skin and is thereby only slightly obtrusive. As described in the next section, a more recent and advanced method is the use of non-contact video PPG analysis.

Camera

The PPG camera measurement method uses the same basic principles as classic ankle/foot PPG, described in the previous subsection, but avoids the use of any attached sensors. Another difference between the methods is that the camera measures the ambient light emitted from the skin of the patients, instead of LED light. One example of its use can be found in the work of Verkruysse et al. [77], who used a simple inexpensive camera to detect BR and HR for adults, using ambient light for illumination. A simple
webcam is sufficient and achieves comparable results to a high-end camera system [78].

Koolen et al. [79] showed that it is possible to use a camera for an analysis of HR in preterm infants. A pilot study on preterm infants in the NICU by Aarts et al. [80] resulted in very high correlations of the HR measurements with those derived from standard ECG, even with added noise from rocking during kangaroo care and high-frequency oscillation from ventilation. However, they used a camera that required good illumination in the visible spectrum. With an improved camera technique, the results in a laboratory setting can reach perfect correlation values of $r = 1.0$ for HR, $r = 0.91$ for BR and $r = 0.97$ for HRV [81]. Their results confirm that this method lies close to the gold standard.

These studies reveal that an important factor in camera-based approaches is illumination. This is especially important with respect to monitoring preterm infants in an incubator, as the light is usually dimmed in the patient room, and the incubator is covered to avoid disturbing the preterm infant. The light intensity is 3–6 lux (a candle at a distance of one metre has 1 lux) in a covered incubator and 60–120 lux in an uncovered incubator with dimmed lights. Recently, van Gastel et al. [82] showed that for HR measurement, cameras operating in the IR spectrum perform just as well as cameras operating in the visible spectrum, enabling analysis in pitch-dark incubator settings, and making continuous and less obtrusive measurements possible. In this case, the camera has to be equipped with a near infra-red (NIR) light source. To protect the preterm infant’s eyes, the maximum NIR radiation must be limited to 10 mW/cm² and the maximum total infra-red (IR) radiation to 60 mW/cm² [83]. When using an artificial light source, the light amplitude and the modulation of the light source must also be considered, because they can desynchronize the signal. However, Tarrasenko et al. [84] showed very recently that this artificial light-flicker noise can be eliminated with auto-regressive methods.

An additional problem is that of movement artefacts [85]. However, these can be removed with an algorithm that synchronizes frames [77] or cross correlates several frames, increasing the SNR for BR and HR [85].

Unobtrusive behavioural measurements

Video analysis can also offer a solution for behavioural sleep analysis. Limb movements, face twitches and REM can all be detected visually. The illumination problem is the same as that discussed in the camera section above. Camera systems have been used to annotate sleep in premature infants [86]. However, no automated algorithms were used in most of the cases. Instead, time-lapsed video analysis was used to annotate the videos manually [14]. One of the few exceptions is the work of Scatena et al. [87], in which the open-source video analysis tool Zone-Minder was used to automate the video analysis of sleep in adults. However, the correlations between the software and reference PSG and the software and reference actigraphy were only fair. To date, no automated video analysis has been conducted on preterm infants. Due to the similar body/circular-system composition of preterm infants and adults, adaptations to the video analysis and actigraphy software might enable an automated analysis for preterm infants.

Similar to HR and BR with BCG, actigraphy can be acquired by the use of pressure sensors or accelerometry embedded in, for example, the neonatal mattress [41,88], detecting sleep, wake or activity patterns [89]. Pressure sensors can detect slight changes in the g force (>0.05 g) [40,87], making it suitable for measuring the less intense movements of preterm infants. The signals given by the movements are stronger than those of HR and BR, which implies easier monitoring.

Limb movement measurement for preterm infants can be obtained by an accelerometer worn on the wrist or ankle [10]. In this case, the signal that was previously considered as noise, can now be used for sleep state distinction. However, this method must be combined with other measurements if small motion patterns are to be registered.

To conclude this section, Fig. 9 illustrates a possible future NICU, including some of the measurement features discussed. The vital signs measured with these methods can lead to a monitoring system, as in Figs. 9 and 10, presenting, for example:

- Actual and past sleep states
- Estimated time of state change
- A recommended time slot for optimal caretaking
- Long-term display of sleep states with boundaries of ‘normal/expected’ changes
- Display of sleep-related events (e.g., possible sleep apnoea event)

Modality fusion

Modality fusion combines the various input information that can be collected through different sensors. This can be done in three different ways: data fusion, feature fusion or classifier fusion (see Fig. 11). Data fusion merges data from different sensors before the feature extraction stage. Feature fusion, also called early fusion, involves fusing features that are used as an input set for an algorithm; for example, a classifier such as a neural network. Classifier fusion, also called late or semantic fusion, involves combining the results of classifiers in the post-analysis stage.

Data and feature fusion are usually used on synchronized and closely linked data. An example would be HRV and EEG waveforms which are both instantaneously and simultaneously steered via the ANS and are approximately synchronal in adapting to sleep state change. Classifier fusion is preferred for modalities that exhibit a larger time-shift, such as temperature change and BR. Here, the various inputs are processed independently beforehand and, therefore, as an advantage over feature fusion, they do not need to occur simultaneously or be synchronized. The disadvantage of classifier fusion is the possibility of overlooking cross-modality interactions, which occur frequently, particularly in the human body. Thus, feature fusion is favoured for biological systems [90].

It may appear logical that modality fusion will always improve the information gain. Nevertheless, Wu et al. [91] took an in-depth
statistical look into the improvement due to modality fusion by using classifier fusion on a test dataset. Their test set was not related to sleep, but the general conclusion was that the performance of modality fusion can vary greatly. This variability is often due to the misconception that the fusion input signals are equal in accuracy, as well as due to the different impact of different fusion inputs on the results. Normalization and weighing the input beforehand can be used to compensate for this.

Peng et al. [92] used feature and classifier fusion for adult sleep monitoring, showing that classifier fusion of HR and motion resulted in an improvement in the performance of adult sleep monitoring in comparison to a single modality analysis (see Table 6). However, their feature fusion performance was inferior compared to a sleep analysis on the basis of motion alone. This confirms the findings of Wu et al. on performance variations, despite the use of a generally favourable method.

Modality fusion for a single sensor (e.g., EEG) is already in use for preterm infants to improve monitoring robustness and also specifically for preterm infant sleep analysis; for example, by using classic feature extraction and machine learning tools [93]. To date, extensive modality fusion on the sensor level, for example, the fusion of EEG and body movement information, has not been performed in preterm infant sleep analysis. This probably stems from the circumstance that each research group, as a matter of course, focus mainly on their field of expertise. Thus, collaboration between groups with different specializations could further improve the performance of preterm infant sleep analysis.

Conclusions and recommendations

- Sleep plays a very important role in the development of preterm infants. Its disturbance can lead to negative long-term effects.
- The variation of the sleep states of AS and QS over time is an indicator of development.
- The sleep states can be distinguished in various ways. The classic method is EEG. However, EEG can distinguish sleep-wake at an early age of around 24 wk GA, while the more specific sleep states of AS, QS and IS only at later stages of development

Fig. 9. Visual illustration of a neonatal intensive care unit (NICU) summarizing the in this review mentioned unobtrusive vital sign measurement methods (Monitor graphic with courtesy of Mine Danisman-Tasar). The vital signs could lead to a sleep state monitoring system reflecting the actual sleep state and additional information such as state development over longer periods, short-term estimations and/or warnings about sleep abnormalities.

Fig. 10. Detail of sleep monitoring visualization (Courtesy of Mine Danisman-Tasar). The sleep states are visualized over a number of hours to obtain an overview of the state patterns of the preterm infant. Additionally, care, feeding or other interventions can be highlighted, and optimal timeslots for caring can be suggested. Thereby, caregivers can plan and coordinate their shifts according to the preterm infant sleep patterns and maintain an overview of changes and incidents.
There are several approaches possible for unobtrusive PSG and behavioural sleep state monitoring, such as EEG/ECG measurements using capacitive electrodes or dry electrodes, as well as HR, HRV, BR and movement monitoring using BCG, Doppler radar, Doppler laser or camera monitoring.

Sleep state distinction should be performed using HR, HRV, BR and/or movement as multiple unobtrusive methods are available to measure these signals.

The obtrusiveness of the methods used to obtain the vital signs for sleep state distinction can vary. The methods described differ in the way they come into contact with the preterm infant. Classic adhesive electrodes and cables are a burden for the preterm infant.

In order to rank the methods introduced above and present our suggestions for future implementations, we classified them according to the origin of the signal: electrical (EEG, ECG, EOG) or mechanical origin (HR, BR), and behavioural signals (body movement, facial expression).

To measure the signals of electrical origin, such as EEG, ECG and EOG, capacitive electrodes and nano needle array seem to be optimal solutions. Capacitive electrodes have good signal properties for ECG; however, in comparison to both ECG and EEG, the nano needle array seems to be the better alternative regarding signal quality. There is minimal harm involved in nano needle arrays, contrary to the skin damage caused by classic adhesive electrodes. However, the acceptance of needle patches for preterm infants by parents or legal guardians could be problematic due to the negative associations of needles with pain and discomfort. Also, at present, nano needle electrodes are still in the development phase and require further research to validate their applicability in preterm infants.

Regarding signals of mechanical origin, the methods are quite similar in their degree of obtrusiveness/unobtrusiveness and performance. BCG and radar are non-contact methods and do not need a free field of view. Radar has the drawback that, currently, in most cases, recalibration is needed for each individual change in the measurement setup; however, recently proposed algorithms can deal with this problem. In relation to BCG, the small signal amplitude of preterm infant HR and HRV might be a problem, and it produced lower performance values in clinical trials than the other methods. Vital sign measurement using laser needs a free field of view of the (blanketed) preterm infant to operate. This is a drawback compared to radar, despite their similarities, favouring radar over BCG and laser. It remains to be investigated which of the methods deals best with the problem of motion artefacts.

With the inclusion of behavioural observation for sleep state

<table>
<thead>
<tr>
<th>Classifier</th>
<th>Classifier fusion (average)</th>
<th>Classifier fusion (maxima)</th>
<th>Feature fusion</th>
<th>Motion only</th>
<th>Heart rate only</th>
</tr>
</thead>
<tbody>
<tr>
<td>False positive rate</td>
<td>0.194</td>
<td>0.142</td>
<td>0.210</td>
<td>0.181</td>
<td>0.2</td>
</tr>
<tr>
<td>False negative rate</td>
<td>0.190</td>
<td>0.092</td>
<td>0.275</td>
<td>0.230</td>
<td>0.316</td>
</tr>
<tr>
<td>Accuracy of wake detection</td>
<td>0.806</td>
<td>0.857</td>
<td>0.779</td>
<td>0.818</td>
<td>0.8</td>
</tr>
<tr>
<td>Accuracy of sleep detection</td>
<td>0.810</td>
<td>0.907</td>
<td>0.724</td>
<td>0.770</td>
<td>0.682</td>
</tr>
<tr>
<td>Overall accuracy</td>
<td>0.810</td>
<td>0.903</td>
<td>0.728</td>
<td>0.773</td>
<td>0.692</td>
</tr>
</tbody>
</table>

Fig. 11. Modality fusion. There are three different ways of modality fusion: data fusion, feature fusion or classifier fusion. Data and feature fusion are optimal for close connected and synchronized signals, while classifier fusion is optimal for non-synchronized data. The classifier fusion has several advantages over the other methods but tend to miss cross modality interconnections, which appear especially in biological systems.
distinction, the camera seems to be the optimal solution, allowing simultaneous HR, BR and behavioural measurements, while additionally providing general visual surveillance. However, a free field of view is always required. If the camera is repositioned or blocked by the staff, sleep monitoring is not possible. The incubator is often covered and the lights in the NICU are frequently dimmed to minimize disturbance of the preterm infant. Therefore, IR illumination is needed to obtain a clear video image with sufficient resolution for a sleep state annotation algorithm or to be annotated manually.

In terms of costs, it is difficult to make any judgements about the above techniques, as most are still in the research phase and are not commercially available. Nevertheless, in most cases, the reusability (versus that of using disposables) will reduce overall expenses.

Most of the methods mentioned are currently not used in the NICU or are only in the stage of initial trials in relation to preterm infants, this could be due to the long development and approval time for medical devices as well as the coherent, cautious implementation of new approaches, especially in the sensitive and high-risk environment of the NICU.

Finally, each measurement method has its own advantages and disadvantages, but the use of nano needle patches, BCG, Doppler laser, Doppler radar and/or cameras enables the noninvasive measurement of the vital signs of HR and BR for the purpose of preterm infant sleep monitoring. The performance of the methods compared to the reference signals were very good, making them suitable candidates for use in the NICU. Furthermore, modality fusion is already in use for adults, increasing the performance of sleep detection methods. Nevertheless, further optimization can be achieved if the impact of single modalities is compensated by weighted and modified fusion methods. Modality fusion on the sensor level, meaning the fusion of different vital signs or movement, could further enhance the performance of preterm infant sleep monitoring. Therefore, further cooperation between different specialized research groups is needed.

practice points

Relying only on EEG, sleep-wake distinction is possible at 24 wk GA, while the more specific sleep state distinction sleep state distinction is not possible before 32 wk GA. Combining several methods, such as EEG and HR and/or BR, allows sleep state distinction at an earlier age. Behavioural observations have achieved the earliest sleep state distinction at around 26 wk GA.

Several modern techniques have recently been proposed to continuously measure vital signs and/or behaviour unobtrusively or even without contact. They have been shown to match the gold standards, with very high correlation factors and/or accuracy. Video analysis, for example, is capable of measuring vital signs and behaviour in the NICU, showing a high correlation (r = 0.91 to r = 1.0) with the control group. All of the methods described have the problem of motion artefacts. Nevertheless, modern signal-processing algorithms have been proposed to address this problem.

Modality fusion can enhance the performance of sleep-state distinction if common misconception of the input signal attributes are considered and compensated for. So far, modality fusion of different monitoring methods is not put into practice for preterm infant sleep analysis.

Research agenda

1. The research on automated vital sign analysis should be broadened more extensively within preterm infants. At the moment, the focus in automated preterm infant sleep analysis lies on the use of EEG.
2. Existing algorithms for adults should be enhanced/adapted for automated preterm infant sleep-state monitoring using HRV and BR.
3. The here introduced unobtrusive methods of obtaining vital signs should be studied in detail, and on this basis the most promising features with respect to an automated sleep-state monitoring system should be derived.
4. The collaboration between groups with different fields of knowledge should be fostered to reach the next research stage for preterm infant sleep.

Conflicts of interest

Jan Werth is part of a Philips Research and Maxima Medical Center funded project. Xi Long and Ronald Aarts are partly employed at Philips Research. Louis Atallah and Elly Zwartkruis-Pelgrim are fully employed at Philips Research.

References


* The most important references are denoted by an asterisk.


