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Introduction

Cardiopulmonary Coupling (CPC) is a patented technology that establishes Sleep Quality from the analysis of a continuous ECG signal to generate a Sleep Spectrogram, Sleep Quality and Sleep Pathology biomarkers as well as Sleep Latency and Sleep Duration. The ECG signal contains a convenient set of signals for extracting both heart rate variability (HRV) as a measure of autonomic drive and tidal volume fluctuations measured as R-wave amplitude fluctuations called electrocardiogram derived respiration (EDR).

Heart rate variability (HRV) is calculated from the R-R intervals on the ECG. Respiration activity is derived from the change in amplitude of the QRS complex that is directly related to tidal volume changes with inhalation and exhalation called electrocardiogram-derived respiration (EDR).

The algorithms utilize mathematical and frequency analysis to determine synchronization between modulations of heart rate and respiration and provides visualization of sleep states in the ECG-derived Sleep Spectrogram (Figure 1).

Cardiopulmonary Coupling analysis is based on patented algorithms developed and validated by sleep researchers, using continuous, evenly-sampled, normal sinus rhythm ECG as the only input requirement. To further enhance the value of the CPC technology, the SleepImage system additionally uses a high precision 3-axis accelerometer data to obtain snoring, and body position from actigraphy.

The validation of CPC utilized clinical Polysomnography (PSG) as the standard upon which it was compared. Simultaneous SleepImage and PSG recordings were performed, validated and published and the data shows periods of sleep identified by both systems were correlated. Please see our Publications Reference List which appears on the last few pages of this document.

The literature historically divided sleep into NREM-sleep and REM sleep, with NREM-sleep having four stages. Stage 1 happens for a very brief period as a person is falling asleep. It is very light sleep as the person is drifting in and out of sleep. Stage 2 is defined as when brain waves slow down with an occasional burst of faster brain waves and eye movement stops. Stages 3 and 4 were later combined (by eliminating Stage 4) to represent “deep sleep” or “slow wave sleep” a stage where the brain almost exclusively produces delta waves. How the biologic role of NREM sleep is associated with low delta power is unclear. Restricting such periods produces adverse consequences similar to those of total sleep deprivation including sleepiness and metabolic dysregulation. Electroencephalographic EEG delta frequency activity (usually 0.5-4 Hz) is considered a biomarker of homeostatic sleep drive. Delta power as a proportion of total EEG power is highest during the initial cycles of NREM sleep. It decreases across the biologic night and shows rebound effects after a period of sleep deprivation.
It is important to note that CPC does not rely on the same data input streams as PSG. Rather than a primary dependence on interpretation of EEG morphology, CPC utilizes the physiological changes that occur with sleep via the Autonomic Nervous System (ANS) through the “lower” brain centers and networks (including thalamus, hypothalamus, and hippocampus). It integrates information from brain electrical activity, respiration and autonomic drives, capturing the essence of sleep making a “sleep staging” comparison a misnomer. The metrics are independent of absolute EEG amplitudes and thus are not constrained by the “loss” of slow wave sleep with age.

CPC supports the bimodality (having only two distinct types) of non-rapid eye movement (NREM) sleep rather than the conventional graded classification. CPC is represented as High Frequency Coupling (HFC) or Stable sleep and Low Frequency Coupling (LFC) or Unstable sleep. HFC only occurs in stable NREM sleep and is thus equivalent to part of Stage 2 and all of Stage 3 when compared to “traditional sleep staging” and published research has proven the correlation between Stable sleep (HFC) and Delta Waves (deep sleep). In this stage, *desirable* sleep features dominate, including high vagal tone/sinus arrhythmia, blood pressure dipping, high slow wave power and stable breathing. LFC or Unstable sleep equates to the part of NREM sleep that is unstable, meaning all of Stage 1 sleep and part of Stage 2. In this stage generally *less desirable* features dominate, such as cyclic variation in heart rate, absence of blood pressure dipping, tidal volume fluctuations (with sleep apnea of a degree exceeding clinical thresholds) and lower delta power. CPC captures REM and Wake as Very Low Frequency Coupling (vLFC) differentiated by movement – vLFC with activity represents Wake and vLFC without activity represents REM sleep. Fragmented REM sleep takes on LFC characteristics.

The CPC technology has been validated against thousands of PSG studies and a high level of correlation with PSG sleep power mapping has been confirmed. The ebb and flow of slow wave power is the accepted marker of sleep drive in humans and in non-human species. Delta power measured from surface EEG correlates with ECG-derived Cardiopulmonary Coupling high-frequency power, further supporting a link between cortical EEG electrical activity and brainstem-related cardiorespiratory functions.

This correlation between delta power and high-frequency Cardiopulmonary Coupling is consistent with strong “top-down” modulation of autonomic and cardiorespiratory activity. The Spectrogram in Figure 2 shows the correlation between stable sleep (HFC) and normalized delta power (blue line) during simultaneous data collection using CPC and PSG.

Figure 2. The figure above reveals the relationship between HFC and normalized delta power (blue line) during simultaneous data collection using CPC and PSG as discussed in the paper “Relationship between delta power and the electrocardiogram-derived CPC Spectrogram: possible implications for assessing the effectiveness of sleep”. Dr. Robert Joseph Thomas et al. Sleep Med. 2014 Jan; 15(1); 125-131.

So although CPC and PSG come from different directions (ECG vs EEG) the difference between the two does not vary as much as it may seem at first, as shown in Figure 3 on the following page.
As such, both CPC and PSG are quite capable instruments that assess the same thing but with a different unit of measure. However, there are some important differences as well. In practicality PSG is a procedure, usually limited to a one night snapshot of sleep used to diagnose sleep disorders, while CPC is an objective sleep quality assessment tool to evaluate sleep disorders. CPC is intended to measure sleep quality and sleep duration that is useful to identify sleep pathology and track therapy efficacy. CPC offers a practical approach to trend sleep as a vital sign of good health over time, based on clinically validated measure of sleep physiology. The CPC Sleep Spectrogram and the sleep quality and pathology markers therefore provides a new way to look at sleep quality independent of the conventional electroencephalogram (EEG) that has been the conventional tool to measure sleep quality and identify sleep disorders.

High-frequency (0.1-0.4Hz) coupling (stable sleep) is a biomarker of integrated, stable NREM sleep, which is characterized by stable breathing, high vagal tone, a non-cyclic alternating pattern (n-CAP) on the electroencephalogram (generally), high relative delta power, and blood pressure dipping. This state may be considered to be “effective” NREM sleep. Effective sleep enables the normal functions of sleep, across multiple dimensions (e.g. neuronal network health, metabolic), such that spending periods in this state enables recovery and restoration processes.

Low-frequency (0.01-0.1Hz) coupling (unstable sleep) is a biomarker of integrated unstable NREM, with exactly opposite features: low-frequency tidal volume fluctuations, cyclic variation in heart rate, a cyclic alternating pattern (CAP), electroencephalogram low relative delta power and non-dipping blood pressure. This state may be considered “ineffective” NREM sleep. Ineffective sleep fails to accomplish the normal functions of healthy sleep. A subset of low-frequency coupling is termed Elevated Low-Frequency Coupling (eLFC); it is split into narrow band (e-LFCnb) which identifies sustained periods of central apnea and periodic breathing and broad band (e-LFCbb) which correlates with sleep fragmentation and sleep apnea (SA).

Very-Low Frequency (0.001-0.01 Hz) coupling identifies REM sleep and Wake. The SleepImage system uses accelerometer data (movement) to distinguish between these two states, VLFC with activity represents Wake and VLFC without activity represents REM sleep. Fragmented REM sleep has low-frequency coupling characteristics.

Sleep-fragmenting stimuli increase unstable sleep (low-frequency coupling), and sleep-consolidating stimuli increase stable sleep (high-frequency coupling) as a percentage of sleep, thereby allowing dynamic tracking of sleep physiology and pathology in health and disease. Further clinical information on the technology of Cardiopulmonary Coupling is described in a medical textbook on sleep medicine, Principles and Practice of Sleep Medicine, (Kryger – Roth=Dement) Sixth Edition, Chapter 166. Cardiopulmonary Coupling Sleep Spectrogram.
Glossary

**CAP:** Cyclic Alternating Pattern

**CPC:** Cardiopulmonary Coupling - the synchronization of heart rate variability and breathing activity

**CVHR:** Cyclic Variation of Heart Rate. Refers to characteristic heart rate pattern that happens during and at cessation of apnea events.

**e-LFCbb:** Elevated Low Frequency Coupling, Broad Band - an indicator of sleep pathology (e.g. pain) or airway disordered breathing patterns (e.g. Obstructive Sleep Apnea, Upper Airway Resistance. (see Understanding the CPC Spectrogram)

**e-LFCnb:** Elevated Low Frequency Coupling, Narrow Band - an indicator of periodic-type breathing patterns e.g. Central Sleep Apnea (see Understanding the CPC Spectrogram)

**ECG (EKG):** Electrocardiogram - recording the electrical activity of the heart over a period of time

**EDR:** Electrocardiogram Derived Respiration

**EEG:** Electroencephalogram - recording electrical activity of the brain along the scalp

**HFC:** High Frequency Coupling – an indicator of stable sleep (see Understanding the CPC Spectrogram)

**HRV:** Heart Rate Variability

**LFC:** Low Frequency Coupling – an indicator of unstable sleep (see Understanding the CPC Spectrogram)

**N-CAP:** Non Cyclic Alternating Pattern

**NREM:** Non-Rapid Eye Movement

**PSG:** Polysomnography – an in-laboratory sleep study where each 30 sec window (epoch) is manually scored.

**REM:** Rapid Eye Movement

**SA:** Sleep Apnea

**SAI:** Sleep Apnea Indicator. Displays “one number” for apnea events through the recording period by automatically detecting known changes that occur in the cardiovascular system during periods of sleep disordered breathing.

**SDB:** Sleep Disordered Breathing - refers to a wide range of sleep-related breathing abnormalities

**SQI:** Sleep Quality Index. Presents “one number” encompassing overall sleep health based on CPC metrics.

**Spectrogram:** Visual representation of the spectrum of the frequencies of Cardiopulmonary Coupling.

**UARS:** Upper Airway Resistance Syndrome

**vLFC:** Very Low Frequency Coupling – Wake/REM Sleep (see more in Understanding the CPC Spectrogram)
Understanding the SleepImage CPC Spectrogram
The CPC Spectrogram

The SleepImage System graphically displays the coupling of heart rate variability and respiration activity presented as a Sleep Spectrogram. In the front-view Spectrograms, time (hh:mm) is displayed on the horizontal axis, and frequency (Hz) is on the vertical axis. When both data streams are in-phase (coupled), peaks are generated on the graph to form a visual representation of the frequencies collected during the recording.

Stable Sleep or High Frequency Coupling - HFC

High frequency coupling is displayed on the Spectrogram as white peaks in the frequency range of 0.1 - 0.5Hz and represent Stable sleep. Most Stable sleep occurs during NREM-stage 2 and 3, especially with the EEG morphology called noncyclic alternating pattern (n-CAP) and delta waves. Stable sleep is a biomarker of integrated stable NREM sleep and is associated with periods of stable breathing, high vagal tone, generally a non-cyclic alternating pattern on the electroencephalogram, high relative delta power, physiologic blood pressure dipping, and stable arousal threshold.

Unstable Sleep or Low Frequency Coupling - LFC

Low frequency coupling is displayed on the Spectrogram as gray peaks in the frequency range of 0.0 - 0.1Hz and represents unstable sleep. Unstable sleep is a biomarker of integrated unstable NREM sleep, with opposite features to Stable sleep. Unstable sleep is associated with EEG activities called cyclic alternating pattern (CAP), periods of fluctuating breathing patterns (tidal volume fluctuations), cyclic variations in heart rate (CVHR), blood pressure non-dipping and variable arousal thresholds. Fragmented REM sleep has low-frequency coupling characteristics.

Wake & REM sleep or Very Low Frequency Coupling - vLFC

Very low frequency coupling (vLFC) is displayed on the Spectrogram as dark blue peaks in the frequency range of 0.004 - 0.1Hz and represent REM sleep or wake.

During the course of a night’s sleep, there are spontaneous shifts between stable and unstable sleep. Oscillations between stable and unstable sleep are expected to modulate in 30-90 minute cycles that range from 4-8 cycles for an adult’s 8-hour healthy sleep and correspond to the alternating periods of NREM and REM sleep. Disease states negatively impact this pattern. Healthy, stable sleep, dominated by high vagal tone, results in characteristic heart rate variability, where the heart rate slows down and speeds up in synchrony with regular respiration. This is normal rhythm and is associated with stable NREM sleep (HFC).

![Figure 4](image-url)

**Figure 4.** Oscillations between stable and unstable sleep are expected to modulate in 30-90 minute cycles that range from 4-8 Cycles in an adult 8-hour healthy night’s sleep and correspond to the alternating periods of NREM and REM sleep.

When sleep is disrupted (from disrupted breathing pattern, stress, pain and a variety of other factors), the normal rhythm is disrupted and is associated with unstable NREM sleep (LFC).
**Full View Spectrogram - Healthy Sleep**

The full view Spectrogram displays the peaks and oscillation pattern of HFC, LFC and vLFC for the time series. The vertical axis uses frequency range 0.004Hz to 0.5Hz and time in hours on the horizontal axis.

![Spectrogram Front View](image)

*Figure 5. HFC peaks are present when stable sleep occurs and some coupling or synchronization between heart rate variability (HRV) and respiratory rate activity curves occur.*

HFC peak amplitude is in relation to the amount of coupling or synchronization between the curves generated by the heart rate variability (HRV) and respiratory rate activity.

Greater coupling results in higher amplitude peaks. Low amplitude peaks results from less overlap between the curves generated by heart rate variability and respiratory rate activity. A lack of coupling between these two input data streams (HRV and respiratory rate activity) will result in zero value and no peak generation.
3D View Spectrogram - Healthy Sleep

The SleepImage Spectrogram can be displayed in an interactive three dimensional view by rotating the image for a more detailed observation of the low frequency range. Using the 3D view helps to interpret sleep quality, sleep pathology and differentiate between Sleep-Disordered Breathing (SDB) phenotypes (Obstructive vs. Non-Obstructive SDB).

![3D Spectrogram](image)

Figure 6. The 3D Spectrogram shows distribution of the peaks in the LFC frequency range. The three axes show 1) time in hours, 2) the LFC frequency range 0.004Hz-0.10Hz and 3) CPC.

Strong LFC oscillations can correlate with apneas and hypopneas on the Polysomnogram. This subset of LFC is called elevated-LFC (e-LFC) and is seen in two different forms:

- Broad band e-LFC (e-LFCbb)
- Narrow band e-LFC (e-LFCnb)

### Expected Values (Percentage)

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<thead>
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<th>Variable</th>
<th>Adult</th>
<th>Pediatric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable Sleep - High Frequency Coupling (HFC)</td>
<td>&gt;50</td>
<td>&gt;65</td>
</tr>
<tr>
<td>Unstable Sleep - Low Frequency Coupling (LFC)</td>
<td>&lt;30</td>
<td>&lt;15</td>
</tr>
<tr>
<td>REM/Wake - Very Low Frequency Coupling (vLFC)</td>
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<td>&lt;20</td>
</tr>
<tr>
<td>Elevated Low Frequency Coupling, Broad Band (e-LFCbb)</td>
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<td>&lt;8</td>
</tr>
<tr>
<td>Elevated Low Frequency Coupling, Narrow Band (e-LFCnb)</td>
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<td>0</td>
</tr>
</tbody>
</table>

*Table 1. Expected values for CPC biomarkers*
Sleep Apnea Indicator & Sleep Quality Index

The **Sleep Apnea Indicator** is an automated measure of Cyclic Variation of Heart Rate during unstable breathing detecting oscillations in cardiac intervals often associated with prolonged cycles of sleep apnea. Bradycardia is seen at onset of sleep apnea, followed by abrupt tachycardia on resumption of breathing. The SAI is presented on a scale of 0-100 and is automatically calculated based on Cyclic Variation of Heart Rate during unstable sleep to help detect apneas through changes that occur in the cardiovascular system during sleep disordered breathing.

When SAI is presented with the Sleep Quality Index and e-LFC, separated by broad band and narrow band it is possible to use the SAI to not only help detect apneas, but also to differentiate between obstructive and central/complex sleep apnea.

- Adult SAI for healthy sleep is < 5
- Pediatric SAI for healthy sleep is < 2
- SAI for moderate to severe Sleep Apnea is > 15

Sleep Apnea is associated with significantly increased risk of cardiovascular morbidity and mortality. Autonomic dysfunction is now recognized to contribute to these cardiovascular consequences in SA patients who present decrease in heart rate variability and predominant cardiovascular sympathetic activity that persists during wakefulness.

Cardiac autonomic dysfunction ultimately leads to a fixed heart rate due to progressive dysfunction of the cardiac sympathetic nervous system. HRV is considered the earliest and most frequent indicator of symptomatic cardiovascular autonomic dysfunction. The Sleep Apnea Indicator is an ineffective tool to detect apneas in this subgroup of sleep apnea patients, as they do not exhibit the oscillatory heart rate dynamics, but the CPC e-LFC biomarkers are important additional biomarkers to aid in the diagnosis of Sleep Disordered Breathing in this patient population.

The **Sleep Quality Index** is a summary index of the CPC biomarkers: sleep duration, sleep stability, sleep fragmentation and sleep pathology. The SQI is displayed on a scale of 0-100 and is an overall measure of sleep health.

- Adult SQI for healthy sleep is > 55
- Pediatric SQI for healthy sleep is > 70

Using SQI and SAI together with e-LFCbb and e-LFCnb it is possible to identify the presence of sleep disordered breathing and categorize between obstructive or central sleep apnea and periodic breathing.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adult</th>
<th>Pediatric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Apnea Indicator (SAI)</td>
<td>&lt;5</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Sleep Quality Index (SQI)</td>
<td>&gt;55</td>
<td>&gt;70</td>
</tr>
</tbody>
</table>

*Table 2. Expected Values for Sleep Quality Index (SQI) and Sleep Apnea Indicator (SAI).*
Reviewing SleepImage Graphics & Reports
SleepImage Reports

Review the SleepImage report to study the patient’s Sleep metrics before studying the SleepImage Graphics.

1. Check **Signal Quality**. Only predominantly green signal quality should be considered for clinical decision-making.

2. Evaluate the **Sleep Quality Index** (SQI). Unhealthy sleep is indicated by SQI <55.

3. Evaluate the **Sleep Apnea Indicator** (SAI). Unhealthy sleep is indicated by SAI >15.

4. Evaluate percentages of **stable sleep** (HFC) and **unstable sleep** (LFC) compared to Expected Values.

5. Review Transition Counts. As SleepImage establishes sleep quality through SQI, seeing transitions between sleep states of can further enhance clinical investigation. Generally speaking, transitions from unstable to stable sleep are good, while transitions from stable to unstable sleep are less desirable.

6. Review sleep pathology biomarkers **e-LFCbb**, **e-LFCnb** & **SAI** in conjunction with the **Decision Assist** tool.
SleepImage Graphics

After reviewing the SleepImage Report, graphics should be reviewed for both Associations and Patterns.

1. Signal Quality: Evaluate the quality of the signal during the recording period. Red indicates signal loss and therefore the CPC algorithm is not able to produce accurate data during periods of poor signal detection.

2. Hypnogram: Observe the frequency of transitions between HFC (stable sleep), LFC (unstable sleep), and vLFC (wake, REM). A high number of transitions indicate more fragmented sleep.

3. Spectrogram: Review for HFC (stable sleep), LFC (unstable sleep) and vLFC (wake and REM sleep) distribution during the recording period in association with body position, movement, snoring and CVHR (cyclic variation of heart rate, presented as SAI (Sleep Apnea Indicator) on the report.

4. Sleep Disordered Breathing markers: Look for presence of thick and thin red lines. The e-LFC red line graphic gives an overview of areas of ‘elevated’ unstable sleep; thick lines represent events occurring in a ‘broad’ frequency range (e.g. OSA, pain). Thin lines reflect areas of metronomic activity occurring in a ‘narrow’ frequency range (e.g. central apnea, periodic breathing).

5. Body Position: Evaluate patterns during the recording time and look for association with stable and unstable sleep, snoring, activity and CVHR. Consider the presence of snoring in association with body position (i.e. supine and non-supine) and examine the snore trace for a crescendo pattern indicating upper airway resistance (the report displays snore count and duration).

6. Actigraphy: Associate level of Actigraphy with concurrent events, assess any patterns across the recording period and examine the actigraphy graph - see next page.

7. Sleep Apnea Indicator: Evaluate SAI (CVHR) in association with the Spectrogram, body position, snoring and movement. CVHR is a marker of changes in heart rate happening during and at the cessation of an apnea event.

8. Adjust the study period: Drag the green and red markers on the orange line at the top of the spectrogram to the desired beginning and end of the study and click the Recalculate button.

9. SleepImage Corporate Platform Users: Toggle HFC, LFC and vLFC peaks of the spectrogram on and off to isolate coupling types by clicking the labeled HFC, LFC and vLFC markers to hide/display the peaks by type.
Patterns

After an analysis for Associations, an overview of Patterns within the Traces below the Spectrogram in your SleepImage account should be considered. By reviewing the Spectrogram from Left (Start) to Right (End) and examining the Traces that coincide with the timeline of the recording, you can observe concurrent events.

1. Actigraphy Trace: Increased actigraphy associated with periods of unstable sleep

2. Snore Trace: Snoring with crescendo pattern during periods of unstable sleep
Decision Assist

The SleepImage Decision Assist for objective Sleep Disorder Evaluation diagram is a visual workflow tool to aid clinical evaluation of sleep disorders to inform or drive clinical management. It is recommended to take into consideration the results of multiple tests for clinical decision-making. The Decision Assist utilizes the following four key sleep metrics:

**Sleep Quality Index (SQI)** is an overall measure of sleep health on a scale of 0-100 which includes a measure of sleep stability, sleep fragmentation, sleep duration and sleep pathology. An SQI ≤55 indicates poor sleep quality.

**Sleep Apnea Indicator (SAI)** is a measure of Cyclic Variation of Heart Rate (CVHR) during unstable breathing, detecting oscillations in cardiac intervals that are often associated with prolonged cycles of sleep apnea. An SAI ≥15 indicates moderate to severe SDB.

**Elevated Low Frequency Coupling broad-band (e-LFCbb)** is a frequency band analysis which correlates with sleep fragmentation and Obstructive Sleep Apnea (OSA). An e-LFCbb ≥15% indicates Obstructive SDB.

**Elevated Low Frequency Coupling narrow-band (e-LFCnb)** is a frequency band analysis which correlates with periodic breathing or Central Sleep Apnea (CSA). An e-LFCnb >2% indicates Central SDB.

The Decision Assist will automatically tag each sleep study into one of four categories.

- **Clear Evidence of Sleep Disorder**
  - Review patient history for moderate to severe SDB symptoms.

- **Evidence of Sleep Disorder**
  - Review patient history for insomnia, mild SDB, Restless Legs or Periodic Limb Movement related symptoms.

- **No Evidence of Sleep Disorder**
  - Study does not indicate the presence of a sleep disorder.

- **No Studies/Insufficient Data**
  - No study has been uploaded or the study does not contain sufficient data for Decision Assist analysis.
Decision Assist Flowchart

Disclaimer: This Flowchart is intended to assist clinicians to evaluate sleep disorders to inform or drive clinical management; it is not a diagnosis of a sleep disorder. Sleepimage is not responsible for any use of this information.
Distinguishing Sleep Disordered Breathing Types

Sleep Disordered Breathing (SDB) comprises a wide spectrum of sleep-related breathing abnormalities. There are three major types of SDB:

1. **Obstructive Sleep Apnea (OSA)** is the most common one and is related to increased upper airway resistance and includes snoring, upper airway resistance syndrome (UARS) and obstructive sleep apnea (OSA). Patients who suffer from OSA periodically struggle to breathe and are unable to inhale effectively because the airway has collapsed.

2. **Central Sleep Apnea (CSA)** happens when the brain temporarily stops sending signals to the muscles that control breathing. This condition often occurs in people who have certain medical problems when this is not associated with another disease it is called idiopathic central sleep apnea. A condition called Cheyne-Stokes respiration can mimic CSA.

3. **Complex/Mixed Sleep Apnea** is most often seen in patients who have been diagnosed with OSA and treated with positive airway pressure, but fail to breathe normally after the airway has been opened and their sleep apnea assumes the characteristics of central sleep apnea, they make no effort to breathe during apneic episodes.

An exceptional feature of SleepImage’s CPC analysis is its capacity to easily distinguish between SDB types. Each SDB type has a visually discernable Spectrogram pattern that makes identification simple.

The CPC algorithms identify Obstructive Sleep Apnea pathology as increased elevated LFC ‘broad band’ (e-LFCbb). Periodic-type breathing pattern (i.e. Central Sleep Apnea) is identified by elevated LFC ‘narrow band’ (e-LFCnb). Complex Sleep Apnea, a combination with both Obstructive and Central components is an alternating pattern of elevated LFC broad and narrow bands.

To aid the clinician in identifying individuals with SDB, the SleepImage system offers the Sleep Apnea Indicator (SAI). A normal SAI value for adults is <5. SAI is automatically calculated from known changes in heart rate that occur during apneas, called Cyclic Variation of Heart Rate (CVHR). A simple way to explain CVHR is that it consists of bradycardia during apnea followed by abrupt tachycardia near the end of the apnea.

After reviewing the CPC biomarkers for sleep pathology (SQI, SAI, e-LFCbb and e-LFCnb), look at the 3D Spectrogram. Examples representing the different types of SDB are below.

**3D Spectrogram - Obstructive Sleep Apnea**

The presence of a broad band of peaks indicates that the upper airway is the primary pathophysiological contributor to the patient’s Sleep-Disordered Breathing. E-LFCbb is presented by broad gray peaks on the 3D Spectrogram.
3D Spectrogram - Central Sleep Apnea

Central Sleep Apnea or periodic breathing is represented by narrow red colored peaks as e-LFCnb on the 3D Spectrogram view and identifies patterns of breathing or movement having a "narrow band" LFC profile.

![3D Spectrogram - Central Sleep Apnea](image)

Figure 8. 3D Spectrogram - Central Sleep Apnea is presented as a line of narrow peaks. The system colors these peaks red to make it easier for users to identify the periodicity.

3D Spectrogram - Complex Sleep Apnea

A combination of both obstructive and central components showing narrow band e-LFC (e-LFCnb) and broad band e-LFC (e-LFCbb).

![3D Spectrogram - Complex Sleep Apnea](image)

Figure 9. 3D Spectrogram - Complex Sleep Apnea is a combination of both obstructive and central components.
Sleep Architecture

Over the last decades, Polysomnography (PSG) has been the most widely used clinical measure of sleep where sleep is divided into two major types, NREM sleep and REM sleep based on Electroencephalogram (EEG) morphology. NREM sleep is presented in 3 sleep stages and REM sleep is also often referred to as dream sleep.

Cardiopulmonary Coupling (CPC) is based on the physiological changes of the autonomic nervous system that occur during sleep. It integrates information from the brain electrical activity through the autonomic nervous system. Analyzing heart rate variability (HRV) coupled with respiration, captures the essence of sleep by looking at the ebb and flow of slow wave power that is the accepted marker of sleep drive in humans and in non-human species. CPC does not rely on the same data streams that PSG relies on and the output is not meant to match PSG; it however complements conventional sleep staging, albeit with a different method of categorizing sleep. Rather than being dependent on manual interpretation, primarily of EEG morphology, the automated output reveals that NREM sleep has a distinct bimodal-type structure marked by distinct alternating and abruptly varying periods of high and low frequency Cardiopulmonary Coupling. High frequency coupling (HFC) or stable sleep occurs during stage N2 and N3 and is associated with periods of stable breathing, non-cyclic alternating pattern (non-CAP) EEG, increased absolute and relative delta power, strong sinus arrhythmia and blood pressure dipping. Conversely, low frequency coupling (LFC) or unstable sleep has opposite features and is characterized by temporal variability of tidal volumes, cyclic alternating pattern (CAP) EEG and non-dipping of blood pressure, lower frequency cyclic variation in heart rate. Fragmented REM sleep has an LFC signature, while normal REM sleep and wake show very low frequency coupling (VLFC).

In a healthy sleep pattern, cycles between Stable, Unstable and REM sleep (Stage 1, 2 and 3 NREM – REM sleep cycles in PSG) occur every 30-90 minutes and approximately 4-8 cycles occur during an 8-hour healthy sleep. The ratio of NREM sleep to REM sleep in each cycle varies during the course of the sleep. The first episode of REM sleep may last only a few minutes, but time-period spent in REM sleep increases progressively over the sleep period, with the final period of REM sleep lasting up to 30 minutes. In summary, Stable sleep (NREM slow-wave sleep) is prominent in the first third of the night and REM sleep is prominent in the last third of the night.

Stable & Unstable Sleep (NREM sleep)

NREM Sleep accounts for 75-80% of sleep time. During this phase, thinking and most physiological activities slow down, but movement can still occur.

Stage 1 NREM sleep = Unstable Sleep – accounts for 3-8% of total sleep time and each period is about 5-10 minutes long and occurs most frequently in the transition from wakefulness to the other sleep stages or following arousal during sleep. In stage 1 NREM sleep, alpha activity, which is characteristic of calm wakefulness, diminishes and low-voltage theta waves appear on EEG. While in stage 1 sleep, people lose awareness of their surroundings, but they are easy to wake up.

Stage 2 NREM sleep = Unstable & Stable Sleep – accounts for 45-55% of total sleep time. This is the first stage of true sleep and each period lasts about 10-25 minutes. The characteristic EEG findings of this stage are sleep spindles believed to occur when the brain disconnects from outside sensory input and begins the process of memory consolidation and K complexes that are sort of built-in vigilance system that keep you poised to awake if necessary. Delta waves first appear during this period of sleep but are present in small amounts. Most people spend about half of the night in this stage, where eyes are still, and heart rate & breathing gradually slows down.
Stage 3 NREM sleep = Stable Sleep – accounts for 15-20% of total sleep time. The characteristic EEG findings of this stage are that slow-brainwaves or Delta waves become dominant. The brain becomes less responsive to external stimuli, making it difficult to wake up the sleeper. Slow-wave sleep is the time for the body to renew and repair. During this sleep stage muscle tone decreases, breathing becomes more regular, blood pressure falls and pulse rate slows. Blood flow is directed less toward the brain and at the beginning of this stage the pituitary gland releases a pulse of growth hormone (GH) that stimulates tissue growth. When a sleep deprived person gets some sleep, he or she will pass quickly through the lighter sleep stages, into the deeper sleep stages and spend a greater proportion of sleep time there. This is believed to indicate that slow-wave sleep has an essential role in a person’s optimal functioning.

REM Sleep

REM sleep accounts for about 20% of the sleep time. Dreaming occurs during REM sleep. The first REM sleep episode occurs 60-90 minutes after the onset of NREM sleep. Characteristics of REM sleep is atonic of skeletal muscle groups but the brain is active thinking and dreaming as the eyes move back and forth behind closed eye lids, hence the name Rapid Eye Movements (REM). During this stage heart rate and blood pressure increase and respiration becomes irregular. Despite all this brain and eye activity, the body hardly moves, the motor function becomes “paralyzed”. Like Stable sleep (slow-wave sleep) restores the body, REM sleep or dream sleep restores the mind by facilitating learning and consolidating memories. When a person deprived of REM sleep falls asleep, he or she will enter REM sleep stage earlier and spend a higher proportion of sleep time in REM sleep.
Healthy Sleep - Pediatric

The Spectrogram shows dominant stable sleep (HFC) with an expected high percentage of HFC or stable sleep, in a child. The time to sleep onset defined by the occurrence of HFC is about 10 minutes.

Periods of stable sleep are consolidated and good oscillations between stable (HFC) and unstable (LFC)/wake vs. REM/Wake (vLFC) episodes are seen. A minimal amount of unstable sleep is present as expected in healthy sleep. The pattern of HFC consolidation and oscillation would correspond to the expected high amount of slow wave, healthy sleep at this age.

The number of oscillations between stable sleep and unstable sleep vs. REM/Wake are 6 (expected 4-8) with duration from 30-120 minutes.
Healthy Sleep - Adult

Stable sleep dominates the Spectrogram with an expected high percentage of stable sleep (HFC). Long consolidated stable sleep periods (30-60 minutes) with intermittent periods of unstable sleep (LFC) and periods of REM sleep / Wake (vLFC) episodes are present in the approximately 8 hour sleep recording. Periods of stable sleep are consolidated and good oscillations between stable and unstable sleep is seen. A minimal amount of unstable sleep is present as is expected for healthy sleep.

Figure 12. Spectrogram - front view, presenting healthy sleep in an adult person. The sleep recording is approximately 7 hours, SQI = 84 (expected >55), SAI = 0 (expected <5); HFC = 85% (expected >50%); LFC = 7% (expected <30%); e-LFCbb = 0% (expected <15%); e-LFCnb = 0% (expected <2%). All parameters are in the normal range.

Figure 13. 3D Spectrogram, Healthy Adult.
Insomnia
Insomnia

The subject is a 60 year old female describing her sleep issues as "It is easy to fall asleep, but having a chronic difficulty staying asleep", wakes up a few times every night. The sleep recording shows lack of stable sleep periods and fragmented sleep dominates the Spectrogram.

Figure 14. Approximately 8 hours and 20 minutes of sleep was recorded. Sleep is fragmented. SQI = 48, HFC= 43% is decreased, (HFC, stable sleep expected >50%) LFC = 38% is increased (unstable sleep expected <30%), SAI=9, e-LFDbb = 14% (a marker of sleep pathology, expected <15%).
Caffeine
Caffeine - Adult

The subject is a 27 year old healthy male with no sleep complaint or history of known sleep disorders, and a BMI of 22. Sleep quality assessment with CPC analysis demonstrates baseline conditions as a healthy adult sleep, SQI=80. The Spectrogram in Figure 15 is the baseline night with no caffeine consumption. Figure 16 presents the sleep spectrogram after the subject consumed one cup of strong coffee containing approximately 150 mg of caffeine at 7:00pm.

Baseline night

Figure 15. The Spectrogram is of the baseline night: no caffeine consumption. SQI=80, Sleep Latency=0 min, Sleep Interruptions=34 and Stable Sleep=78%.

Caffeine night

Figure 16. The Spectrogram was recorded after the subject consumed approximately 150 mg of caffeine at 7:00pm. SQI=66, Sleep Latency=6 min, Sleep Interruptions=82 and Stable Sleep=62%.
The subject’s sleep quality during the night upon which caffeine was consumed approaching bedtime was significantly decreased as demonstrated by CPC values. Table 3, below, shows the CPC-parameters for the baseline night, when no caffeine was consumed compared to the following consecutive night where one cup of strong coffee was consumed at 07:00PM.

On the baseline night, the sleep pattern is healthy; the subject had no issues falling asleep and good stable sleep consolidation is seen through the night.

On the caffeine consumption night, approximately 2hr and 30 minutes elapsed until the first period of consolidated stable sleep lasting more than 30 minutes is seen. Movements are increased during this time and, for the rest of the night, sleep is noticeably more fragmented than during the baseline night.

The response is likely attributable to caffeine increasing EEG arousals through known inhibition of adenosine metabolic pathways. The result of this experiment supports previous work showing that utilization of heart rate variability is a sensitive measure for evaluating the effects of caffeine on the autonomic nervous system. CPC analysis mathematically integrates heart rate variability and respiration, which is responsive in capturing the caffeine effect during sleep.

This example is indicative of the value of repeated sleep measures to test the effect of lifestyle changes that may be important and helpful to identify and administer the most effective treatment method for patients who suffer from sleep disruption, regardless of the presence of sleep disorders.

<table>
<thead>
<tr>
<th></th>
<th>Baseline night</th>
<th>Caffeine Night</th>
<th>Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total sleep time</strong></td>
<td>8 hrs 25 min</td>
<td>8 hrs 6 min</td>
<td>19 min decrease</td>
</tr>
<tr>
<td><strong>SQI</strong></td>
<td>80</td>
<td>66</td>
<td>14 pt decrease</td>
</tr>
<tr>
<td><strong>Stable sleep</strong></td>
<td>78%</td>
<td>62%</td>
<td>16%pt decrease</td>
</tr>
<tr>
<td><strong>Unstable sleep</strong></td>
<td>12%</td>
<td>16%</td>
<td>4%pt increase</td>
</tr>
<tr>
<td><strong>e-LFCbb</strong></td>
<td>3%</td>
<td>7%</td>
<td>4%pt increase</td>
</tr>
<tr>
<td><strong>Sleep Interruptions</strong></td>
<td>34</td>
<td>82</td>
<td>+48</td>
</tr>
<tr>
<td><strong>Wake during sleep</strong></td>
<td>5min</td>
<td>15 min</td>
<td>+10 min</td>
</tr>
</tbody>
</table>

Table 3. Comparing the CPC biomarkers to track how consuming caffeine few hours before sleep affects sleep quality.
Obstructive Sleep Apnea
Obstructive Sleep Apnea - Adult

The subject is a 42 year old male with BMI of 46 who underwent a diagnostic Polysomnogram (PSG) study. SleepImage algorithms analyzed the ECG data stream from the PSG study. The result from the PSG study was an AHI (Apnea Hypopnea) score of 80. All CPC biomarkers except e-LFCnb are pathological and the SAI number is high, 35.

![Graph 1](image1.png)

**Figure 17.** The sleep recording is approximately 8 hours, SQI = 37 (expected >55); SAI = 35 (SAI >15 indicates moderate to severe Sleep Disordered Breathing); HFC = 23% (expected >50%); LFC = 46% (expected <30%); e-LFCbb = 35% (expected <15%); e-LFCnb = 0% (expected <2%).

![Graph 2](image2.png)

**Figure 18.** Looking at the 3D Spectrogram, the peaks have a broad band distribution indicative of Obstructive Sleep Apnea which correlates with the prevalence of e-LFCbb at 35%.
Central Sleep Apnea
Central Sleep Apnea – Adult

The subject, a 70 year old female with a BMI of 22, underwent a Polysomnogram (PSG) study and simultaneously recorded sleep with the SleepImage Sleep Data Recorder. Epworth sleepiness score was 19/24 and AHI was 102.

Figure 19. The sleep recording is approximately 6 hours, SQI = 10 (expected >55); SAI = 77 (SAI > 15 indicates moderate to severe Sleep Disordered Breathing); HFC = 0 % (expected > 50%); LFC = 96% (expected < 30%); e-LFCbb = 18% (expected < 15%); e-LFCnb = 73% (expected <2%). All CPC parameters are pathological.

Figure 20. When looking at the 3D Spectrogram where the narrow red colored peaks line up representing the pattern of periodicity indicating that this patient has Central Sleep Apnea.
Complex Sleep Apnea
Complex Sleep Apnea – Adult

The subject is a 61 year old male with BMI of 33 who underwent a Polysomnogram (PSG) study while simultaneously recording with the SleepImage Sleep Data Recorder. The PSG showed an AHI of 52.

Figure 21. The sleep recording is approximately 7 hours, SQI = 20 (expected >55); SAI = 63 (SAI >15 indicates moderate to Severe Sleep Disordered Breathing). HFC = 9% (expected >50%); LFC = 85% (expected <30%), e-LFCbb = 37% (expected < 15%), e-LFCnb = 23% (expected <2%). All CPC parameters are pathological.

Figure 22. The 3D Spectrogram shows a combination of peaks. A broad-band pattern mixed with narrow red-colored peaks (representing the pattern of periodicity) indicates that this patient has Complex Sleep Apnea.
Fibromyalgia / Pain
Fibromyalgia – Adult

Non-restorative sleep associated with sleep disruption and fragmentation is a recognized symptom of patients with chronic pain conditions, such as Fibromyalgia Syndrome (FMS), where 75% of patients complain of non-refreshing sleep. This is a sleep recording of a 47 year old female diagnosed with fibromyalgia syndrome with complaints of waking up tired in the morning, daytime fatigue and somnolence. Her sleep data shows fragmented sleep with a lack of consolidated stable sleep.

Figure 23. Approximately 9 hours and 30 minutes of sleep was recorded. Sleep is fragmented and lacking stable sleep consolidation. In this case, periods of stable sleep last from 5-30 minutes (expected 30-90) minutes. Other sleep parameters also indicate sleep pathology: Time to sleep onset, defined by the occurrence of HFC, is > 10 minutes. SQI=46 (expected >55), SAI=0 (expected <5), Stable sleep is 37% (expected >50%), Unstable Sleep is 40% (expected <30%) and e-LFCbb = 20% (expected <15%).

Figure 24. Broad-band e-LFC (e-LFCbb) is seen on the 3D Spectrogram as broad peaks (on the frequency axis) and is an indicator of sleep pathology.
Signal Quality & Abnormal ECG Rhythms
**Signal Quality**

Signal Quality is presented below the spectrogram. If the input data is of high quality a green indicator is presented on the Signal Quality, if the ECG signal has some interruption but still most of the data has good signal quality, the color indicator turns to yellow. If the ECG signal is fully compromised the signal quality bar turns red. It is recommended that a minimum of 4 hours of predominantly green signal quality should be used for clinical decision-making. Red signal affects the output metrics causing it to be invalid. A red signal quality report section should not be used for any clinical decision-making.

**Abnormal ECG Rhythms**

Disconnection or interruption of the ECG signal is detected and displayed by the Signal Quality. A red bar is a sign of poor or no data collection. Since the Cardiopulmonary Coupling (CPC) algorithm is based on normal sinus-to-sinus beat rhythm, application in the presence of continuous atrial fibrillation or presence of atrial or ventricular bigeminy is not feasible and is presented in the Signal Quality as a yellow and red in color.

**Atrial Fibrillation**

This data is from a patient with known atrial fibrillation. The bar shows poor signal quality (yellow and red). The irregularity in the heartbeat causes the ECG-derived respiration (EDR) signal to be ‘noisy’ and provides poor data for coupling, does not represent actual respiration and is therefore of no clinical value for the purpose of a sleep measure.

![ECG screenshot](image)

**Figure 25.** The ECG-screenshot presents lack of the p-wave in a patient with Atrial Fibrillation causing the CPC algorithm to fail analyzing the data.
Premature Atrial Contractions (PACs)

PACs are a common cardiac dysrhythmia characterized by premature heartbeats originating in the atria. They are most often asymptomatic and are not considered an abnormal finding but as they cause irregular heartbeat, they can interfere with the CPC algorithm and cause the Signal Quality to turn from green to yellow or red. The result on the Spectrogram is “noisy” causing the clear separation between stable and unstable sleep to disappear during periods when the ECG signal is compromised causing deteriorated signal quality with LFC dominating the picture during periods of irregular heartbeat. (see also PVCs/VECs, next page)

Figure 26. Presents sections of “noisy” spectrogram where clear separation between stable and unstable sleep disappears during periods when the ECG recording has a compromised signal quality. The total amount of recording time demonstrating PACs will determine the usability of the recording for sleep analysis.
Irregular Heartbeat (PVC/VES)

PVC/VES (Premature Ventricular Contraction / Ventricular Extra Systole), as with PACs (previous page) are most often asymptomatic and are not considered an abnormal finding but, as they cause irregular heartbeat, they can interfere with CPC analysis and cause the Signal Quality to turn from green to yellow or red.

These ECG and Spectrogram examples are from a patient with known PVCs. The Signal Quality bar shows poor signal quality periods (yellow and red) during this sleep recording. The irregularity in the heartbeat causes the ECG-derived respiration (EDR) signal to be inaccurate respiration data for coupling and the result in the Spectrogram is 'noisy' or the data is lost and the recording for that period therefore of limited clinical value.

Figure 27. CPC signal quality is compromised due to irregular heart rhythm caused by PVC's.
The following examples are from the same recording demonstrating that the subject’s irregular heartbeat causes the variability in CPCs detection of signal quality during the night.

**ECG**

**Signal Quality Green: period of good signal detection: 01:08am**

![ECG Signal Quality Green: period of good signal detection: 01:08am](image)

**Signal Quality Green: some PVCs but not affecting results: 01:10am**

![ECG Signal Quality Green: some PVCs but not affecting results: 01:10am](image)

**Signal Quality Yellow: period of compromised signal detection: 01:43am**

![ECG Signal Quality Yellow: period of compromised signal detection: 01:43am](image)

**Signal Quality Red: period of data loss due to frequent VES: 06:08am**

![ECG Signal Quality Red: period of data loss due to frequent VES: 06:08am](image)

Figure 28. ECG periods of good signal quality (green), periods of partially compromised signal quality (yellow) and fully compromised signal (data loss) due to frequent VES (red).

PVC/VES may be perceived as a “skipped beat” or felt as palpitations in the chest and is a relatively common event where the heartbeat is initiated by Purkinje fibers in the ventricles rather than by the Sinoatrial node, the normal heartbeat initiator. The electrical events of the heart detected by the electrocardiogram (ECG) allow PVC/VES to be easily distinguished from a normal heartbeat. Most often, PVC/VES are benign and may even be found in otherwise healthy hearts but can also be a sign of decreased oxygenation to the heart muscle.
ECG Artifact - Distorted Baseline

An irregular ECG pattern causes the ECG-derived respiration (EDR) signal to be ‘noisy’ and provides poor data for coupling and the Spectrogram shows dominant LFC during this period. In this case, the LFC has little influence from actual respiration and is therefore of limited clinical value.

Figure 29. ECG artifact due to distorted baseline is presented on the spectrogram compared with a quality signal.
Compromised ECG Signal

CPC is based on analyzing normal sinus rhythm ECG signals. CPC analysis should be constrained to areas of good ECG signal quality to ensure meaningful data interpretation and it is recommended to base clinical decisions on studies containing at least 4 hours of green signal. ECG signal quality is shown on the Signal bar presented below the spectrogram.

A compromised signal is shown as yellow (when there is some noise, but the signal has still mostly normal sinus rhythm) or red (when the signal has lost sinus rhythm or there is no signal). When there is no data, there is a gap in the spectrogram and the area is excluded from sleep analysis. As shown in the following example, at 4:23am Signal Quality is red and the Spectrogram shows a corresponding loss of data.

Figure 30. Compromised ECG signal due to signal loss is shown in the red color of the Signal bar and a corresponding gap in the Spectrogram.
CPC Publications

I. Books

II. Published Papers
I. Technique

II. Relationship between CPC and PSG

III. Before and after therapy
IV. Pediatric

V. Sleep Disordered Breathing

VI. Insomnia/Mental Health

VII. Other


