A Method to Estimate Unbiased Partial Time-Frequency Spectra: Application to Repolarization Variability Changes Unrelated to Heart Rate Variability

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Dynamic interactions

Biological signals:
- Non-stationary
- Coupled to other signals

→ Dynamic interactions

- Insight into a specific physiological system
- Clinical applications
Time-frequency analysis

- **TF Spectra**: Amplitude of non-stationary oscillations.  
  Orini et al, MBEC 2010

- **TF Coherence**: Strength of linear coupling + similarity.  
  Orini et al, TBME 2012; Gil, Orini et al., Physio Meas, 2010

- **TF phase difference**: Degree of synchronization  
  Orini et al, EMBC 2011

- **TF Indices**: e.g. Baroreflex sensitivity  
  Orini et al, Physio Meas 2012

- **TF partial coherence**: Multivariate cardiovascular interactions  
  Orini et al, Eurasip 2012

- **TF partial spectra**: Separate coherent/residual components  
  Widjaja, Orini et al, CMMM 2013
Time-Frequency Partial Spectra

\[ x_1(t) \xrightarrow{} H_1 \xrightarrow{} x_{y:1}(t) \]
\[ x_2(t) \xrightarrow{} H_2 \xrightarrow{} x_{y:2}(t) \]
\[ y(t) = x_{y:1}(t) + x_{y:2}(t) \]
Time-Frequency Partial Spectra

\[ y(t) = x_{y:1}(t) + x_{y:2}(t) \]

If \( x_{y:1}(t) \) and \( x_{y:2}(t) \) are uncorrelated:

\[ S_y(f) = S_{y:1}(f) + S_{y:2}(f) = S_y(f) - S_{y:2}(f) + S_{y:2}(f) \]

- **Residual Spectrum**
- **Coherent Spectrum**

\[ S_{y:1}(f) = S_y(f) - S_{y:2}(f) = (1 - |\gamma_{y,2}(f)|^2) S_y(f) \]

\[ S_{y:1}(t,f) = S_{y:1}(t,f) - S_{y:2}(t,f) = (1 - |\gamma_{y,2}(t,f)|^2) S_y(t,f) \]** TF Extension
Time-frequency coherence

\[ \gamma_{xy}(t, f) = \frac{|S_{xy}(t, f)|}{\sqrt{S_{xx}(t, f) + S_{yy}(t, f)}} \]

\[ S_{xy}(t, f) = \iint \phi(t, f)W_{xy}(\tau - t, \nu - f) d\nu d\tau \]  
(Cross) Spectrum

\[ W(t, f) = \int x(t + \tau/2)y^*(t - \tau/2)e^{-i2\pi f \tau} d\tau \]  
Wigner-Ville Distribution
Time-frequency coherence

TFC quantifies the **strength of local linear coupling** between 2 non-stationary signals

- TFC = 1 → Perfect local linear coupling
- TFC = 0 → Uncoupled
Time-frequency coherence

TF spectrum

Frequency [Hz]

Time [s]
Time-frequency coherence

TF spectrum

TF spectrum

Frequency [Hz]

Time [s]
Time-frequency coherence

![Time-frequency coherence diagram](image)
Biased Estimators

- Coherence estimators are biased ($\hat{\gamma} \neq \gamma_0$)
- Bias depends on estimator’s parameters
  → Partial Spectra are Biased

Coherence by TFD

Coherence by CWT

Orini et al, CinC 2009

Keissar et al, Phil Trans R Soc A 2009
Biased Estimators

- Coherence estimators are biased \( (\hat{\gamma} \neq \gamma_0) \)
- Bias depends on estimator’s parameters
  \[ \rightarrow \text{Partial Spectra are Biased} \]

Proposed solution

- Assess the bias (theoretical – estimated)
- Estimate a correction function
- Map estimated coherence into unbiased coherence
Unbiased Time-Frequency Coherence

\[ \hat{\gamma}(t, f) = h(\gamma^0(t, f)) \]
Unbiased Time-Frequency Coherence

\[ \hat{\gamma}(t, f) = h(\gamma^0(t, f)) \Rightarrow g(\cdot) \approx h^{-1}(\cdot) \]
Unbiased Time-Frequency Coherence

\[ \hat{\gamma}(t, f) = h(\gamma^0(t, f)) \Rightarrow g(\cdot) \approx h^{-1}(\cdot) \Rightarrow \hat{\gamma}_c(t, f) = g(\hat{\gamma}(t, f)) \approx \gamma^0(t, f) \]
Unbiased Time-Frequency Coherence

\[ \gamma^2 \]

Before correction

\[ \gamma_0^2 \]

\[ \hat{\gamma}^2 \]

\[ P^0_{y:1} \]

\[ P^0_{y:2} \]

\[ \hat{P}_{y:1} \]

\[ \hat{P}_{y:2} \]
Unbiased Time-Frequency Coherence

Before correction

\[ \gamma^2 \]

\[ \hat{\gamma}^2 \]

\[ P^0_{y:1} \]

\[ P^0_{y:2} \]

\[ \hat{P}_{y:1} \]

\[ \hat{P}_{y:2} \]
Unbiased Time-Frequency Coherence

Before correction

After correction

Partial power

$\gamma_{\text{teo}}$
Unbiased Time-Frequency Coherence

Before correction:

\[ \gamma^2 \]

After correction:

\[ \gamma^2 \]

Partial power:

\[ P^0_{y:1}, P^0_{y:2}, \hat{P}_{y:1}, \hat{P}_{y:2} \]

\[ \gamma_{teo} \]
Application: Examples

Before correction

Actual

After correction

Actual

Partial power

Time (s)
Application: Examples

Before correction

After correction

Coherence

Partial power

Time (s)

\( \hat{\gamma}^2_{y,1} \)

\( \tilde{\gamma}^2_{y,1} \)

\( \hat{P}_{y,1} \)

\( \hat{P}_{y,2} \)

\( \tilde{P}_{y,1} \)

\( \tilde{P}_{y,2} \)
Application: Examples

**Before correction**

- Coherence
  - $\hat{\gamma}_{y,1}^2$
  - $\tilde{\gamma}_{y,1}^2$

**After correction**

- Partial power
  - $\hat{P}_{y,1}$
  - $\hat{P}_{y,2}$
  - $\tilde{P}_{y,1}$
  - $\tilde{P}_{y,2}$

Time (s)
Application : Examples

Before correction

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After correction

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Coherence

Partial power

Time (s)
RRV-Unrelated QT Variability

\[ x_{QTV}(t) = x_{QTV:RRV}(t) + x_{QTV:VRV}(t) \]
RRV-Unrelated QT Variability

\[ x_{QTV}(t) = x_{QTV:RRV}(t) + x_{QTV:VRV}(t) \]

Sinus Node ~ Parasympathetic

Ventricles ~ Sympathetic

\[ x_{RRV}(t) \rightarrow H_{RR} \rightarrow x_{QTV:RRV}(t) \]

\[ x_{VRV}(t) \rightarrow H_{VR} \rightarrow x_{QTV:VRV}(t) \]
## Short term QT variability

<table>
<thead>
<tr>
<th>Condition</th>
<th>QTV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>↑</td>
</tr>
<tr>
<td>Gender</td>
<td>=</td>
</tr>
<tr>
<td>Exercise</td>
<td>↑</td>
</tr>
<tr>
<td>Cardiac abnormalities (LQTS)</td>
<td>↑</td>
</tr>
<tr>
<td>VT/VF, SCD, Cardiovascular mortality</td>
<td>↑(10) /= (3)</td>
</tr>
<tr>
<td>Cardiomyopathies, CAD, Hypertension</td>
<td>↑</td>
</tr>
<tr>
<td>Increased sympathetic activity</td>
<td>↑(3)</td>
</tr>
<tr>
<td>Disturbed cardiac autonomous regulation</td>
<td>↑(6)</td>
</tr>
<tr>
<td>Sympathomimetic drugs</td>
<td>↑</td>
</tr>
<tr>
<td>β-blockers</td>
<td>↓</td>
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Niemeijer et al. “Short-term QT variability markers…”, *Heart*, 2014

Baumert, M. et al., “QT interval variability in body surface ECG…” Europace, 2016, -
Short term QT variability

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“QT variability markers are potentially useful determinants of ventricular arrhythmias, (sudden) cardiac death and total mortality, both in the context of risk stratification and drug safety. Also, results suggest that the QTV may be used as a marker of neural regulation of cardiac function.”

QT variability unrelated to HRV may be a better predictor and a better marker of sympathetic activation …

Niemeijer et al. “Short-term QT variability markers…”, Heart, 2014

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RRV-Unrelated QT Variability

Tilt table test: orthostatic stress -> sympathetic activation

17 healthy subjects Age: 28.2±2.7
• ECG: 1000 Hz
RRV-Unrelated QT Variability

![Graph showing Coherence (QTV, RRV) and \( P_{QTV} / RRV \) before and after with significance levels of (0.0004).]
Summary

• (TF) Coherence estimators biased → Partial spectra biased

• We propose a simple method for correcting coherence bias and to improve TF partial spectra accuracy.

• QTV unrelated to RRV estimated by means of unbiased TF partial spectra was about 20% higher than that estimated without correcting for the bias.

• The proposed methodology improves the accuracy of cardio-respiratory and cardiovascular markers, and can provide a better tracking of changes of QTV unrelated to RRV.
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