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Probing the Nonlinearity in Neural Systems Using Cross-frequency Coherence Framework

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Abstract: Neural systems can present various types of nonlinear input-output relationships, such as harmonic, subharmonic, and/or intermodulation coupling. This paper aims to introduce a general framework in frequency domain for detecting and characterizing nonlinear coupling in neural systems, called the cross-frequency coherence framework (CFCF). CFCF is an extension of classic coherence based on higher-order statistics. We demonstrate an application of CFCF for identifying nonlinear interactions in human motion control. Our results indicate that CFCF can effectively characterize nonlinear properties of the afferent sensory pathway. We conclude that CFCF contributes to identifying nonlinear transfer in neural systems.

Keywords: Biological Systems, Nonlinear System Identification, Frequency Domain Identification.

1. INTRODUCTION

Neural systems are highly nonlinear and can present various forms of nonlinear interaction between the input (stimulus) and the output (neural response) (Tass *et al*., 1998; Regan & Regan, 1988). The output of a linear system only contains spectral components at the same frequencies as the input stimulus, while a nonlinear system can include non-stimulated frequencies at the output, such as harmonic, subharmonic and/or intermodulation frequencies (see Fig. 1). Therefore, cross-frequency coupling between the input and the output is typically present in a nonlinear system (Chen *et al*, 2008).

In the nervous system, nonlinear interactions between the input and the output are often investigated using bicoherence (Nikias & Raghuveer, 1987). Bicoherence is an effective tool for analysing the second-order nonlinearities, such as $y(t) = x^2(t-\tau)$, and it is commonly used in neuroscience studies (Shils *et al*, 1996). Bicoherence can detect the second-order harmonic ($2f_i$) and intermodulation coupling ($f_i \pm f_j$); however, it cannot detect higher-order intermodulation between multiple input frequencies (such as $f_i \pm f_j \pm f_k$, $2f_i \pm 2f_j$) or subharmonic coupling ($4f_i/5$).

High-order harmonic and intermodulation coupling was first observed in the human visual system (Regan & Regan, 1988), and then also found in the human sensorimotor systems (Snyder, 1992; Yang *et al.*, 2015). Subharmonic coupling has been reported in bimanual execution of rhythmic movements (Daffertshofer *et al.*, 2000) and somatosensory responses to periodic vibrotactile stimulation (Langdon *et al.*, 2011). All these studies used dedicated and specific analysis techniques. There is a need for a general nonlinear coherence framework that can quantify the different types of cross-frequency coupling and therefore to identify the nonlinear characteristics of the system in a more comprehensive way.

The goal of this paper is to introduce a general framework in frequency domain for detecting and characterizing nonlinear interactions in neural systems, called the cross-frequency coherence framework (CFCF). CFCF can detect different types of nonlinear interactions, i.e. harmonic, subharmonic, and intermodulation coupling. We present two basic forms of CFCF: 1) the n:m coherence, for measuring harmonics and subharmonics related to individual input frequencies; 2) the multi-spectral coherence, for quantifying intermodulation among multiple (≥ 2) input frequencies. The full merits of CFCF is shown when the input signal consists of multiple frequencies, e.g. a multi-sine signal (sum of multiple sine waves) (Schouten et al, 2008), since the input with a single frequency can only excite (sub)harmonic coupling and not intermodulation coupling. We demonstrate the applications of CFCF for probing the nonlinear interactions in human motion

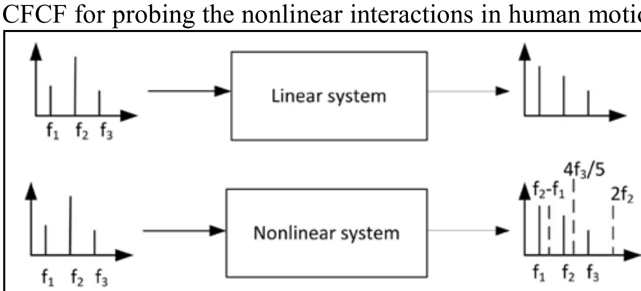

Fig. 1. Scheme of nonlinearities in the frequency domain. A linear system only generates the output at the same frequencies as the input stimulus (solid lines), while a nonlinear system can have the output at harmonic (e.g. $2f_2$), intermodulation (e.g.. f_2-f_1) and/or subharmonic (e.g., $4f_3/5$) frequencies (dash lines).

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control based on a "perturb-and-measure" approach; where periodic wrist movement (the external input) was imposed when the subject performed an isotonic wrist flexion task, and the cortical responses (the system output) were measured by electroencephalography (EEG).

2. MATERIALS & METHODS

2.1 Cross-frequency coherence framework

Cross-frequency coherence framework (CFCF) is a generalization of classical coherence based on high-order statistics. Let $X(f)$ and $Y(f)$ be the Fourier transforms of the input $x(t)$ and the output $y(t)$ signals. The nonlinear mapping from the input to the output in the frequency domain can be presented in two different ways:

1) n:m transfer: $Y^m(f_{out}) = H(n:m)X^n(f_{in})$, where $X^n \equiv \underbrace{X \bullet X \bullet \cdots \bullet X}_{n}$, the output frequencies (f_{out}) are related to the input frequencies (f_{in}) by the ratio n/m (n and m are coprime positive integers). The n:m transfer can generate harmonic (m = 1) and subharmonic coupling (m > 1) between the output and the input. The n:m transfer is typically present in a dynamic nonlinear system involving differential operations, such as the Lorenz system (Lorenz, 1963).

2) Integer multiplication: the output is the integer product of the input at frequencies $f_1, f_2, ...f_N$ ($f_1 < f_2 < ... < f_N$) with the integer powers $a_1, a_2, ..., a_n$:

$$Y(f_{out}) = H(f_1, f_2, ...f_N; a_1, a_2, ..., a_N)\prod_{i=1}^{N} M!X^{a_i}(f_i)$$

where $f_{out} = \sum_{i=1}^{N} a_i f_i > 0$; $H(f_1, f_2, ...f_N; a_1, a_2, ..., a_N)$ is the nonlinear transfer function; $X^0(f_i) \equiv 1$, $X^{-1}(f_i) \equiv X(-f_i) = X^*(f)$, and M is the number of non-zero a_i. The sum of the absolute values of integer powers is equal to the order of the integer multiplication: $d = \sum_{i=1}^{N} |a_i| \geq 2$. The integer multiplication mapping can generate harmonic and intermodulation coupling between the output and the input at the corresponding order. The integer multiplication can occur in a simple nonlinear system that does not contain differential operations, such as $y(t) = x^d(t-\tau)$; and the order of integer multiplication corresponds to the order of nonlinear system (d).

According to these two types of nonlinear mapping, the CFCF has two basic forms: *n:m coherence* and *multi-spectral coherence*.

1) n:m coherence quantifies the n:m coupling between the input and the output, where $f_{out} : f_{in} = n : m$:

$$nmc(n,m) = \frac{|S_{xy}(f_{in}, f_{out})|}{\sqrt{S_{xx}^n(f_{in})S_{yy}^m(f_{out})}} \tag{1}$$

where $S_{xy}(f_{in}, f_{out})$ is the *n:m cross-spectrum*:

$$S_{xy}(f_{in}, f_{out}) = \langle X^n(f_{in})Y^m(f_{out})\rangle$$

Thus n:m coherence can detect the harmonic and subharmonic coupling. Noteworthy n:m coherence is different from cross-frequency phase synchrony measures, which are time-dependent methods for detecting transient n:m *phase* coupling based on circular statistics or information theory (Young & Eggermont, 2009). Moreover, phase synchrony measures purely reflect the phase locking between time series independent of signal amplitude ratio; as a result, phase synchrony measures are not used for system identification.

2) Multi-spectral coherence measures the integer multiplication interactions between the input and the output, and is defined as:

$$msc(f_1, f_2, ...f_N; a_1, a_2, ..., a_N) = \frac{|S_{xy}(f_1, f_2, ...f_N; a_1, a_2, ..., a_N)|}{\sqrt{\prod_{i=1}^{N} S_{xx}^{|a_i|}(f_i)S_{yy}(f_{out})}} \tag{2}$$

where $S_{xx}(f_i)$ and $S_{yy}(f_{out})$ are the auto-spectra, and $S_{xy}(f_1, f_2, ...f_N; a_1, a_2, ..., a_N)$ is the *integer multiplication cross-spectrum*, which is the generalization of high-order cross-spectrum (Nikias & Mendel, 1993) by adding the parameters $a_1, a_2, ..., a_N$:

$$S_{xy}(f_1, f_2, ...f_N; a_1, a_2, ..., a_N) = \left\langle \prod_{i=1}^{N} X^{a_i}(f_i)Y(f_{out}) \right\rangle$$

According to the order of integer multiplication, we defined $d = \sum_{i=1}^{N} |a_i| \geq 2$ the order of multi-spectral coherence. The *d*-th order multi-spectral coherence can detect the *d*-th integer multiplication interactions, i.e. *d*-th harmonic and intermodulation coupling. Noteworthy a special case of multi-spectral coherence corresponding to bicoherence is the second-order multi-spectral coherence.

With these two basic forms, the CFCF can detect different types of nonlinear coupling in the frequency domain. Although both the n:m coherence and the multi-spectral coherence can detect harmonic coupling, n:m coherence cannot detect the intermodulation coupling, while multi-spectral coherence is blind to the subharmonic coupling. So they are complementary forms of CFCF.

Similar to the classical coherence, both n:m coherence (1) and multi-spectral coherence (2) yield values between 0 and 1, and they are comprehensive measures incorporating phase and amplitude (gain) relationship between the input and the output (cf. Young & Eggermont, 2009). CFCF is more suitable for estimating the system properties (regarding both phase and amplitude) and effect of measurement noise in nonlinear system identification than cross-frequency phase synchrony measures. Neurophysiological signals, such as EEG, usually have poor signal-to-noise. Thus, it is important to have measures which can reflect the effect of SNR in the system.

2.2 *Perturb-and-measure approach and data collection*

To study the nonlinear interactions in human movement control, we used a wrist manipulator (Wristalyzer, Moog Inc., the Netherlands) to impose a wrist perturbation to the subjects' right wrists while they exerted an isotonic flexion torque (1 Nm). The perturbation signal consisted of a sum of three sine waves (different phases) with the frequencies 7, 13, and 29 Hz. These three frequencies are prime frequencies, and they are chosen to reduce the overlap of possible output frequencies. The period of the perturbation signal was 1 s, and peak-to-peak amplitude was 0.06 rad. The experiment consisted of 60 trials with a 17 s task period in each trial.

Fig.2 shows an overview of the human movement control system. Brain responses (EEG) were regarded as the output of the system. The EEG were recorded using a 128-channel cap (5/10 systems, WaveGuard, ANT Neuro, http://www.ant-neuro.com/) with Ag/AgCl electrodes, using common average reference. The EEG, the perturbation and torque signals were digitalized at 2048 Hz using a TMSi Refa amplifier (Oldenzaal, the Netherlands http://www.tmsi.com/) and stored for offline analysis.

To study the nonlinear interactions between the perturbation (the external input) and the EEG (the system output), all data were segmented into non-overlapping 1-s segments according to the period of the perturbation signal, yielding 1020 segments in total. Segments contaminated by the artefacts in the EEG (e.g. blinking) were removed after visual inspection. All data were transformed to the frequency domain by fast Fourier transform (Matlab R2013b). The n:m coherence (1) and multi-spectral coherence (2) were computed accordingly between the perturbation and the EEG.

3. RESULTS

To explore the relation between the brain response and the external perturbation we first used n:m coherence to quantify the harmonic and subharmonic coupling, and multi-spectral coherence to quantify the intermodulation coupling. We used the EEG signal at one electrode over the sensorimotor cortex representing the wrist area (C3) as the output. Significance of the coherence values was determined in a simulation using the approach introduced by Bortel & Sovka (2007). The confidence level was set to 0.95 ($\alpha = 0.05$).

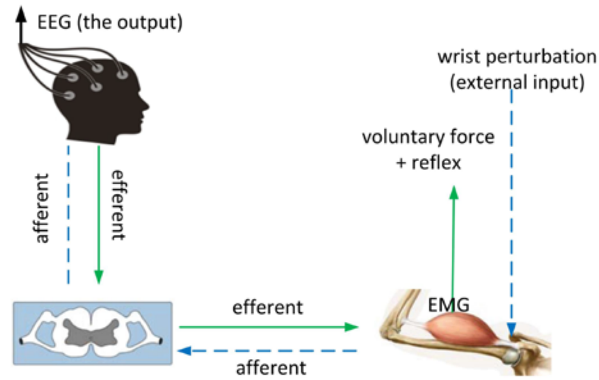

Fig.2. Overview of the human motion control system. The human motion control system is a closed-loop system involving efferent motor commands (solid lines) and afferent sensory feedback (dash lines). In the efferent pathway, motor commands are sent from the brain down through the spine to act on the muscles via the α-motor neurons. In the afferent pathway, the perturbation is encoded by mechanoreceptors (e.g. muscle spindles and tactile sensors), and transmitted through the spine to the brain.

3.1 *n:m coherence*

Fig. 3 shows the results of n:m coherence for one typical subject according to the input frequencies 7, 13 and 29 Hz, respectively. For all stimulated frequencies, the significant coherence values are mainly present in the harmonic frequencies. This result shows that high-order nonlinearities exist in the afferent pathway of human motion control from the periphery to the brain. We found that the highest order of the harmonics reduces with input frequency. Moreover, except the first order harmonic (the same as the input frequency), only even harmonics (the second, fourth and sixth order) are shown.

3.2 *Multi-spectral coherence*

For the input frequencies 7, 13 and 29 Hz, there is no overlap between the second and third order harmonic and their intermodulation frequencies (see Table 1). Thus, Fig. 4. shows the second and third order multi-spectral coherence values in the corresponding output frequencies for the same subject as in Fig. 3. All second-order multi-spectral coherence values are significant, whereas only a few significant values (6 out of 19) occur in third-order intermodulation. The majority of significant third-order intermodulation coherence (4 out of 6) are related to 29 Hz. The intermodulation coupling between the output and input, indicating integer multiplication, may be linked to the capability of multi-frequency sensory integration in the sensorimotor system (Chen *et al.*, 2013). Furthermore, our results suggest a frequency-sensitive processing in the system.

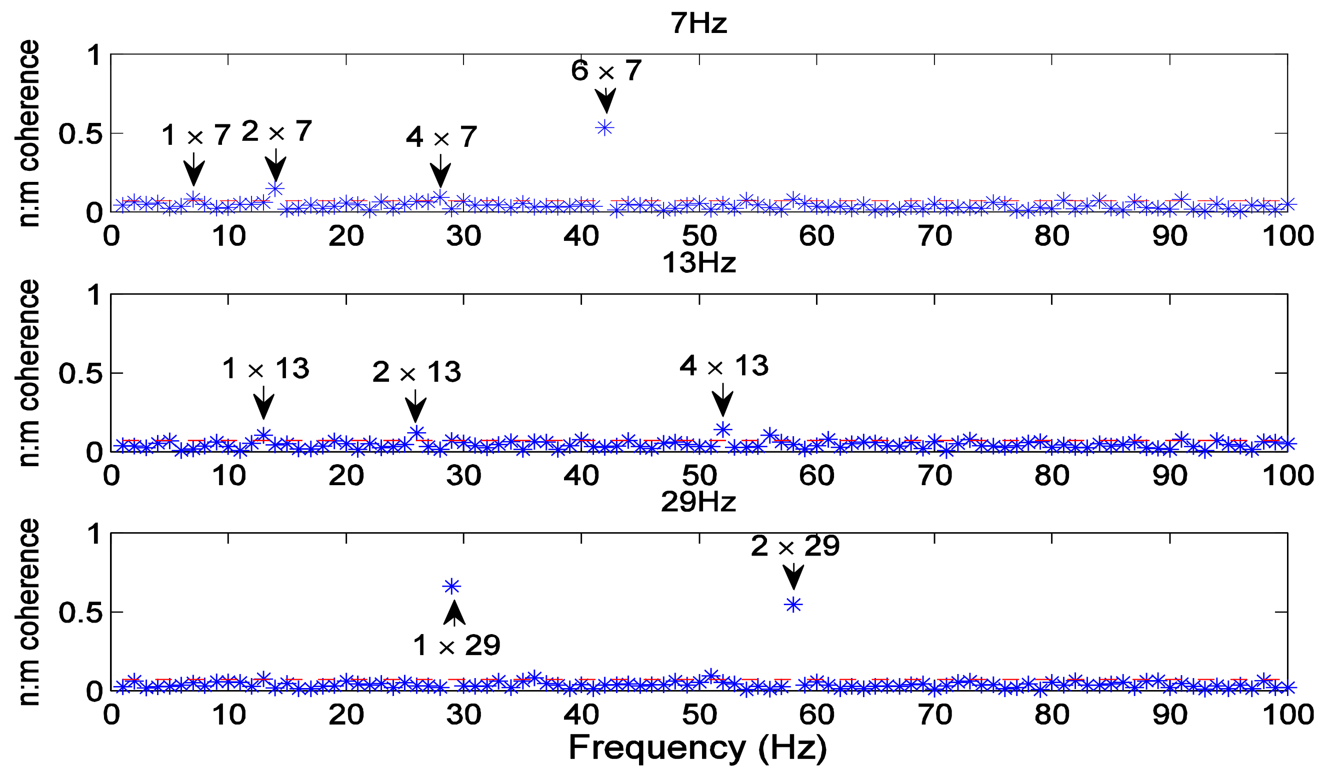

Fig. 3 The n:m coherence for the input frequencies 7, 13, 29 Hz, respectively. The output frequencies are scanned by varying the ratio of n:m with the frequency resolution 1 Hz. The horizontal dash line indicates the significant level (α = 0.05). Significant coherence values at harmonics are marked by the arrows.

Table 1. Second and third order harmonic and intermodulation frequencies of 7, 13 and 29 Hz

Order	Harmonics/Intermodulation	Frequencies (Hz)
2	$2f_i$	14 26 58
	$f_i \pm f_j > 0, i \neq j$	6 16 20 22 36 42
3	$3f_i$	21 39 87
	$2f_i \pm f_j > 0; i \neq j$	1 19 27 33 43 45 51 55 65 71
	f_i □ $2f_j > 0; i \neq j$	3 15
	$f_3 \pm f_2 \pm f_1 > 0$	9 23 35 49

4. CONCLUSION

We introduced the cross-frequency coherence framework as a general tool for assessing nonlinear coupling between the input and the output of neural systems. CFCF can detect different types of nonlinearity in frequency domain including harmonic, subharmonic and intermodulation coupling.

Two forms of CFCF, i.e. n:m coherence and multi-spectral coherence, reflect two different transformations in nonlinear systems, i.e. n:m transfer and integer multiplication. The CFCF can identify different nonlinear transformations in a system, and as such it is useful for probing the nonlinearities in a given system.

We demonstrated an application of the CFCF in characterizing the nonlinear interactions in the afferent pathway of human motor control. Based on the results, we suggest that: 1) integer multiplication might be an important mapping in the sensorimotor system, therefore the system may be described by single-input-and-single-output Volterra model (Billings, 1980); 2) high-order nonlinearities exist in the afferent pathway and show a frequency-sensitive property, e.g. the highest order of harmonics reduces with input frequency and most of the third intermodulation links to 29 Hz; and 3) even nonlinearities are dominant in the human somatosensory system.

In conclusion, the cross-frequency coherence framework (CFCF) provides a general framework in frequency domain for detecting and characterizing nonlinear interactions in neural systems.

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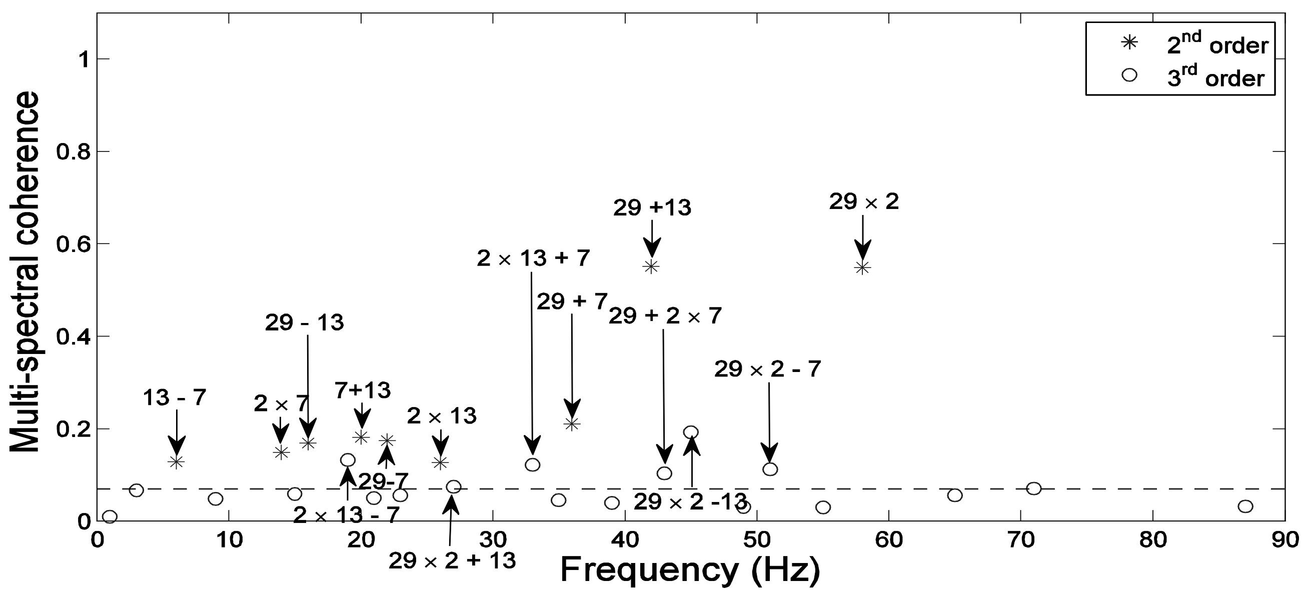

Fig.4. Second (asterisks) and third (circles) order multi-spectral coherence. The horizontal dash line indicates the significance level (α = 0.05). The arrows mark significant coherence values and the corresponding input frequency combinations are indicated.

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