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Thesis synopsis

Kinematic analysis of rhythmic motion: the cases of human hand tremor and fly wingbeat

Soma Chakraborty

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Prof. MUDr. RNDr. Jiří Beneš, CSc.

Školicí pracoviště
Fyziologický ústav AVČR

Autor: Mgr. Soma Chakraborty

Školitel: RNDr. Martin Zápotocký, Ph.D.

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Committee
Medical Biophysics

Committee head
Prof. MUDr. RNDr. Jiří Beneš, CSc.

Place of research work
Institute of Physiology, ASCR

Author: Mgr. Soma Chakraborty

Advisor: RNDr. Martin Zapotocky, Ph.D.

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The dissertation can be consulted at the dean's office of the 1st faculty of medicine of Charles University in Prague.

Contents

Abstract in Czech

V mé disertační práci prezentuji analýzu kinematiky rytmických pohybů a vyvozené závěry o řízení těchto pohybů. V první části práce jsem systematicky studovala bilaterální koherenci fyziologického třesu rukou (PT) u zdravých subjektů a esenciálního třesu (ET) u diagnostikovaných pacientů, za pomoci stacionárních a nestacionárních výpočetních metod. U většiny subjektů s PT i ET byla nalezena významná koherence mezi třesem levé a pravé ruky ve frekvenčním pásmu 1-10 Hz. V obou případech se koherence objevovala pouze přerušovaně. Analýza zahrnující pohyb hrudního koše ukázala, že u PT je bilaterální koherence na frekvencích 6-12 Hz důsledkem vazby mezi třesem rukou a vibracemi vyvolanými srdeční aktivitou.

V druhé časti disertace jsem studovala modulární řízení kmitu křídel v modelovém organizmu Drosophila melanogaster (octomilka obecná). Vyvinula jsem novou výpočetní metodu, založenou na modifikované analýze nezávislých komponent, a její pomocí identifikovala čtyři pohybové složky, které se navzájem neovlivňují. Tři z těchto pohybových komponent mají známé aerodynamické účinky. Čtvrtá komponenta překvapivě spočívala v modulaci amplitudy kmitu s periodou dvou mávnutí křídel, což vyžaduje řízení na velmi rychlé časové škále 5 msec. Tuto pohybovou složku jsem proto prostudovala podrobně.

Abstract in English

My dissertation presents analysis of the kinematics of rhythmic motion and inferences about its neuromuscular control. In the first part of my study I systematically assessed the bilateral coherence of physiological hand tremor (PT) in healthy subjects and essential tremor (ET) in diagnosed patients, using stationary as well as non-stationary analysis methods. The majority of both PT and ET subjects displayed significant bilateral coherence in the frequency range 1-10 Hz. In both cases strong coherence appeared only intermittently. Coherence of the hand tremors estimated after subtracting the coupling to the cardiac rhythm indicates that in PT, bilateral coherence in the range 6-12 Hz can largely be attributed to ballistocardiac forcing.

In the second part I studied the modular control of wing motion in the model organism *Drosophila melanogaster* (the fruit fly). I devised a novel method based on a variant of independent component analysis and identified four types of kinematic patterns that occur mutually independently. While three of these patterns could be associated with known flight maneuvers, the fourth comprised of stroke amplitude modulations with a period of 2 wingbeat cycles, extending for dozens of cycles. As the features of this novel kinematic pattern indicate the activity of a control system that operates at the very fast time scale of 5 msec, I studied it in detail.

1. Introduction

Rhythmic motions, regular or irregular, are an integral part of motor behavior both in health and in disease. Better understanding of the genesis of rhythmic motion is important for understanding the pathophysiology of diseases manifesting as rhythmic motions.

Bilateral coordination of tremors

Although mostly evident during diseased state, involuntary shaking of the limbs and other body parts, called tremors are present even in neurologically healthy subjects. This type of tremor called the physiological tremor (PT) is believed to have a multifactorial origin with both central and peripheral sources. Essential tremor (ET) on the other hand is the most common movement disorder in humans (Louis et al. 1998). ET is believed to be of central origin, with the cerebellum, thalamus and the motor cortex playing a prime role in the generation of the 4-12Hz tremor.

Similar fundamental frequencies of PT and ET in limbs on both the sides of the body raises the possibility that the contralateral tremors have a common source or are otherwise coupled. To confirm such coupling, however, it is necessary to systematically assess the dependence of the two tremor oscillations. A finding of significant coherence between the contralateral tremors points towards a common mechanism of tremor genesis. Also, understanding of bilateral tremor coherence is important for differential diagnosis of tremor diseases.

Modular control of the wing motion of fruit flies

Insect flight provides a powerful model system that aids in understanding the functionality of the analogous structures in the neuromuscular system of higher organisms (Dickinson et al. 2000).

An extreme functional dichotomy is seen in the flight musculature of flies, wherein the power muscles filling most of the thorax generate the necessary power for flight; and about a dozen small steering muscles at each wing base are responsible for the changes in wing kinematics that result in maneuvers. An important component of the flight control system is a pair of club shaped modified hind wings called halteres. Laced with the fastest sensorimotor loop, halteres are known to play a critical role in stabilizing flight at the face of perturbations.

In vertebrates there are evidences of simpler “motor primitives” combining linearly to generate a complicated motor activity. However, as the control system underlying voluntary motion is very complicated in humans, most of the studies were done on animals like frogs, cats, dogs etc. Finding a signature of this mode of motor control in the fruit flies is thus expected to provide a simpler system to understand the basic organization principles of motor primitives and can motivate studies in higher organisms.

Kinematic data analysis

Assessing the extent of involuntary motion of different body parts such as head, trunk, hands, arms, etc is a part of the general as well as disease specific tremor rating . However, all the tremor rating scales are to a large extent subjective to the examiner and difficult to standardize across subjects. Also, even the best clinical scale is not sensitive enough to allow detection of minimal abnormality or subtle changes in the progression of the disease (Hess and Pullman 2012). Hence, the present state of tremor diagnostics can benefit largely from an objective and accurate measure of tremor.

Flight maneuvers in fruit flies are generated by subtle variations in the wing stroke. Functional interpretion of observed variations in the wing kinematics has been clearly established using dynamically scaled robotic models (Sane and Dickinson 2001; Fry et al. 2005). Detailed measurement and analysis of wing kinematics therefore has the potential to reveal the functional organization of the flight control apparatus.

2. Hypotheses and objectives

Hypothesis I: Couplings between the left and the right hand oscillations in PT and ET are weak and posture dependent.

Hypothesis II: Fly wing motion is composed of mutually independent elementary kinematic patterns.

Objectives I: Analysis of human hand tremor

- Stationary and non-stationary analyses of bilateral coherence.
- Assess the possible contribution of blood-flow-generated mechanical vibrations in synchronizing the tremors of the two hands.

Objectives II: Analysis of *Drosophila* wing motion

- Measure wing motion for long durations (>1 min) with a sampling frequency high enough to record the subtle changes in the stroke angle of the wing.
- Develop suitable computational method to obtain the kinematic patterns that occur mutually independently.
- Interpret the significance and possible aerodynamic consequences of such kinematic patterns.

3. Experimental methods

Measuring physiological and essential hand tremor

Three groups of subjects were measured. Group I: 34 ET patients, Group II: 30 neurologically healthy subjects and Group III: 12 neurologically healthy subjects for control experiments and study of the effect of the cardiac mechanical impulse.

The hand tremor was recorded in three hand positions. Position I for rest tremor and the positions II and III for postural tremor. 3D acceleration was measured with integrated inertial measurement units placed on subjects' hand dorsa and the chest (in group III).

Measuring *Drosophila* wingbeat and data preprocessing

The wing kinematics of tethered flying flies (5-10 days old female flies fixated by their thorax to the tip of a steel tether) was measured using a computer vision system with real-time analysis functionality. The measurement procedure allows long duration (>1 min) flight recordings with a sampling frequency of 3125Hz for each wing.

In a batch of flies I surgically removed both the halteres using pointed tweezers and measured their flight post a recovery time of 12 Hrs.

4. Computational methods

Analyses of physiological and essential hand tremor

Magnitude squared coherence was estimated between the corresponding acceleration components of the two hands. Statistical significance of the estimates were assessed by comparing it to a threshold value estimated using primarily the criterion defined in (Wang et al. 2004). Partial coherence (Bendat and Piersol 1986) was estimated between the left and the right hand accelerations, subject to the chest acceleration (to account for the oscillations along the central axis of the body). Zero partial coherence at a particular frequency implies that either there is no linear relationship between the two hands at that frequency or the existing relation can be completely attributed to the coupling to chest motion (cardiac rhythm).

Wavelet coherence was estimated between the corresponding acceleration components of the two hands and the durations of the intermittent events of significant coherence were extracted. The threshold for significant wavelet coherence at each scale was obtained from the wavelet coherence estimates of 300 mutually independent pairs of surrogate time series having the same amplitude distribution and power spectral density as the hand acceleration components.

Analyses of wing motion of tethered flying fruit flies

A variant of independent component analysis based on minimization of mutual information (MILCA) was used to extract the least-dependent component (LDC) variations of wing stroke trajectory.

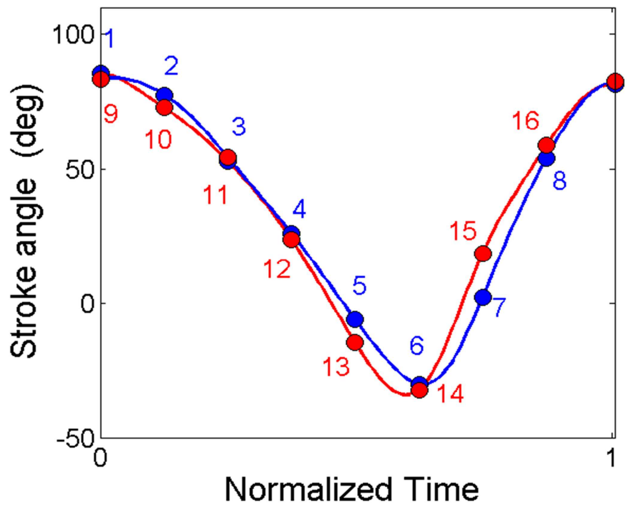

Figure 4.1: Definition of phase points. A) A cycle of the stroke trajectory of left (blue) and right (red) wing. The cycle is divided into 8 phase points sampled at equal time intervals.

I divided each stroke cycle into 8 temporally equidistant phase points (Fig.4.1). For each phase point, the stroke angles from all consecutive stroke cycles defined a time series. The set of 16 time series so extracted were analyzed in segments of 2500 wingbeat cycles. The value of each LDC in a given cycle gives the weight of a particular stroke deformation mode in the overall wing stroke trajectory. Together, the activation time course and the stroke deformation mode constitute a least-dependent kinematic pattern. An algorithm has been devised to visualize the stroke deformation mode corresponding to each LDC. The extent of temporal structure in each LDC was quantified by its Wiener entropy (WE), defined as the ratio of the geometric mean to the arithmetic mean of the spectral density and ranges from 0-1.

Wavelet analysis was used to study the pattern of occurrences of a characteristic sub-harmonic variation of the wing stroke. Morlet wavelet transform of the ventral amplitude time series of each wing was estimated to identify transiently occurring episodes of 2, 3 and 4 cycle periodic variations.

5. Results and discussion I

Intermittent bilateral coherence in physiological and essential tremor

Results I

- **Bilateral coherence of wrist kinematics:** In cases of PT, significant bilateral coherence was obtained in nearly all subjects for the rest position and at a lower fraction of subjects in position 2 (hands extended) and position 3 (arms extended). The coherence peaks were largely located in the frequency range 1-12 Hz. High coherence values were reached more often in ET patients. In this case, the peaks of particularly high coherence (above 0.7) were restricted to the frequency range 3 to 5 Hz, which coincides with the main frequency band of ET.

- **Intermittent character of bilateral coherence:** Using wavelet based analysis I found the bilateral coherence to be distributed highly non-uniformly within the recorded interval of 20s, for both healthy subjects and ET patients. Typically, patches of high coherence lasting for several seconds are separated by time intervals with low coherence. I systematically extracted intervals of transiently occurring significant coherence, for both PT and ET subjects, in all three studied positions, and found long episodes of intermittent coherence to be more dominant in ET than in PT in case of the postural tremors.

- **Dependence of bilateral coherence on ballisto-cardiac forcing in healthy subjects:** Partial coherence analysis of bilateral PT subject to chest motion revealed that, while at the frequency range 1-8 Hz partial coherence frequently persists, at frequencies above 8 Hz significant bilateral coherence is typically not accompanied by significant partial coherence. This implies that at frequencies above 8 Hz, including the range 8-12 Hz corresponding to the main frequency band of PT, bilaterally coherent hand motion is usually coupled to cardiac activity.

Discussion I

- **Bilaterally coherent tremor is not limited to the resting hand position:** Consistent with previous literature on PT (Marsden et al. 1969), I found bilateral coherence to be highly prevalent for resting tremor. In addition I also found a considerable number of healthy subjects (73%) with significant bilateral coherence of postural tremor (at least one acceleration component).

  Unlike previous studies on ET, I found significant bilateral coherence during rest as well as the postural tremors. In case of ET rest tremor, a positive correlation between the coherence magnitude and the hand displacement amplitude suggests a fundamentally bilateral origin.

- **Ballistocardiac forcing contributes to the bilateral coherence of physiological tremor:** While the results show a relation between the bilateral coherence in the main frequency band of PT and the ballistocardiac forcing, it is unlikely that the coherent motion of the hands arises directly and solely by the mechanical action of this force. There are several lines of evidence that speak against such direct mechanism.

- **Possible mechanisms of bilateral coherence:** In the case of PT a possible explanation is a simultaneous entrainment of both the upper limbs by the afferent signal modulation by ballistocardiac impulses. In case of ET it is more likely that the observed intermittent bilateral coherence arose due to a mutual neural coupling between the left and right tremor oscillators. The possibility of a weak interaction between the central tremor generators of ET in the right and left brain has been already proposed in literature (Hellwig et al. 2003).

6. Results and discussion II

Modular control of wing kinematics of the fruit fly *Drosophila melanogaster*

Results II

- **Events with distinct time courses are separated into distinct least-dependent components:** The 16 signals encoding wing stroke variations contain a variety of temporal structures. MILCA (see sec.4) separates events of distinct types into distinct components. Mutual information (measure of statistical dependence) estimated between the least-dependent components (LDCs) testify that MILCA produces the maximally mutually independent set of linear combinations of the 16 input signals.

- **Statistical analysis decomposes complex stroke trajectories into elementary kinematic patterns:** The events in distinct kinematic patterns occasionally overlap in time. Based on the statistical analysis over 2500 wingbeat cycles, in the course of which distinct stroke deformations occur simultaneously, the conclusion was made that the complex deformation of the original stroke trajectory is a composite of the elementary stroke deformations separated in the least-dependent kinematic patterns.

- **Classification of frequently obtained least-dependent kinematic patterns:** Kinematic patterns with certain features were found to occur repeatedly. I could classify these recurring components into 7 well-defined types of kinematic patterns; out of which four showed strong evidence of being elementary kinematic patterns.

- **Effect of haltere ablation on the kinematic pattern controlled at the time scale of a single wing stroke:** The elementary kinematic patterns that comprised of a periodically recurring characteristic single cycle stroke deformations, was considerably affected in absence of haltere feedback. The main affects being: a) an increase in the recurrence duration of the characteristic stroke deformation and, b) development of a weak coupling between the ventral amplitudes and the ventral-to-ventral stroke durations.

Discussion II

- **Implications of the least-dependent kinematic patterns for flight control:** The stroke deformation modes associated with the 7 types of least-dependent kinematic patterns were studied. Two of these stroke deformations can be associated with the control of yaw torque and total flight force. A third deformation involves a change in the downstroke-to-upstroke duration ratio, which is expected to alter the pitch torque. A fourth kinematic pattern consists in the alteration of stroke amplitude with a period of 2 wingbeat cycles, extending for dozens of cycles. It is plausible that this kinematic pattern is caused by some steering muscle(s) becoming active in every other wingbeat cycle.

- **Physiological interpretation of the periodic single cycle ventral amplitude jumps:** One group of muscles known to be associated with sudden increase in wingbeat amplitude is the one inserting in the basalare sclerite. The characteristic features of the subharmonic events strongly indicate a principal role of a particular muscle (M.b2) in their generation, both in the untreated and the haltere ablated flies. The increased recurrence time of the characteristic stroke deformation on haltere ablation can be explained by the hypothesis of temporal summation of the excitatory postsynaptic potentials (EPSP). This hypothesis would mean that the summed EPSP generated by the haltere and the wing is strong enough to activate the muscle synergy every other cycle. But the wing-driven EPSP alone would more often require the cumulative effect over at least two cycles to activate the post synaptic neuromuscular junction.

7. Conclusions

i. Bilateral coherence in physiological and essential tremor expressed in the two hands is more common than has previously been reported. In both the cases the oscillations of the two hands are intermittently synchronized. I proposed that in postural physiological tremor, bilateral coherence at the main tremor frequency arises from transient simultaneous entrainment of the left and right hand oscillations to ballistocardiac forcing. The hand acceleration data from ET patients that I analyzed did not enable us to clarify the mechanisms for ET, additional studies are needed in this front.

ii. Complicated wing movements during insect flight, such as that during a banked turn, can be generated from linear superposition of elementary kinematic patterns that are controlled mutually independently. This provides strong evidence for the presence of modular motor control of rhythmic motion in invertebrates.

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- Chakraborty,S., Kalisova,J., Sprdlik, O., Hoskovcova, M., Ulmanova, O., Ruzicka,E., Zapotocky,M. (2017) Intermittent bilateral coherence in physiological and essential hand tremor. (Accepted for publication in Clinical Neurophysiology)
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- Chakraborty, S., Bartussek, J., Fry, S. N., Zapotocky, M. (2013) Independent components of wing kinematics in the fruit y Drosophila. Proceedings of Twenty Second Annual Computational Neuroscience Meeting: CNS 2013, Paris 2013. BMC Neuroscience 2013, 14(Suppl 1):P429
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Published Matlab codes and data

- Chakraborty, S., Bartussek, J., Fry, S. N. and Zapotocky, M. (2015). Wing stroke kinematics and its independent components in Drosophila melanogaster. Figshare. https://dx.doi.org/10.6084/m9.figshare.1244993.v1