Bioinformatic Approaches Used in Modelling Human Tremor

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Abstract: Bioinformatics is a field of information technology concerning the storage, retrieval, analysis, visualization, prediction and analysis of sets of data with biological or clinical significance. Tremor is a common movement disorder, for which pharmacological and neurophysiological models have been developed these last 3 decades, and which is at the frontier of biology, health sciences and computer technologies. Recently, new biomechanical modelling approaches of tremor have been proposed, based upon ambulatory systems and body area networks (BAN). Use of digital signal processing (DSP) techniques taking into account the non-linearity and non stationarity features of tremor time-series is reviewed in the present article. In particular, algorithms for instantaneous assessments of oscillations and direct online cancellations have been suggested. We discuss the advantages and drawbacks of the tremor detection algorithms, as well as prediction tools. In addition, promising models based upon neural networks, conductance studies and brain neurotransmitters are under development. These models will allow the accurate simulation of the behaviour of limbs. Their impact is outlined. The field of tremor research represents an excellent application of bioinformatics in medicine and rehabilitation.

Keywords: Tremor, bioinformatics, brain, animal models, time-series, Fast Fourier Transform, tremor detection algorithms, computational models.

1. DEFINITION OF TREMOR AND THE VARIOUS FORMS OF HUMAN TREMOR

Tremor is defined as a rapid back-and-forth movement of a body part [1]. Tremor is one of the most common movement disorders encountered in clinical practice and is readily apparent in most instances [2]. Tremor is a cause of social embarrassment in many patients. Many activities of daily life are contaminated, such as writing (Fig. **1**), eating, dressing…, resulting in poorer quality of life. Tremor occurs both in normal individuals (the so-called physiological tremor) and as a symptom of a disorder, most often of neurological origin.

1.1. Physiological Tremor

An example of physiological tremor is illustrated in Fig. (**2**). Physiological tremor is driven by a mechanical reflex and a central neurogenic oscillation, which are superimposed on a background of irregular fluctuations in muscle force and limb displacements [3].The mechanical reflex component is dependent upon the inertial and elastic properties of the body [4]. Pulsatile perturbations occurring in the human body as a result of irregularities in motor unit firings and blood ejection result in damped oscillations.

The frequency of these passive mechanical oscillations ω depends upon the stiffness K and are inversely related to the inertia I, according to the following equation:

$$\omega = (K/I)^{1/2}$$

Therefore, frequency of physiological tremor will increase from proximal to distal segments: the frequency is 3-5 Hz at the elbow, 7-10 Hz at the wrist and 12-30 Hz at the metacarpophalengeal joint [3]. Fig. (**3**) summarizes the main factors underlying physiological tremor.

1.2. Pathological Tremor

Pathological Tremor is usually a rhythmic and roughly sinusoidal oscillatory movement. However, tremor is a non linear and non stationary phenomenon which is distinct from other involuntary movement disorders such as chorea, athetosis, ballism, tics and myoclonus (Table **1**) by its repetitive and stereotyped feature [5]. The different pathological tremors are grouped according to their frequency, amplitude, topographical distribution and task or position-dependence. The most commonly used classification is to distinguish tremor into *rest tremor*, *postural tremor* and *kinetic tremor*. Action tremor designates any tremor produced by voluntary contraction of muscles, including postural, isometric and kinetic tremor [2]. Fig. (**4**) illustrates an example of action tremor of the wrist.

1.3. Rest Tremor

Rest tremor occurs while the body segment is maintained in a rest position. Rest tremor is typically in the 3-6 Hz frequency range. This form of tremor is assessed with the patient sitting with his arms supported against gravity. Tremor may disappear with action. For this reason, rest tremor is often a cause of social discomfort, rather than disability. Rest tremor is usually asymmetrical, starting distally in the arms. Lips and jaw can be affected. Typically, tremor in the upper

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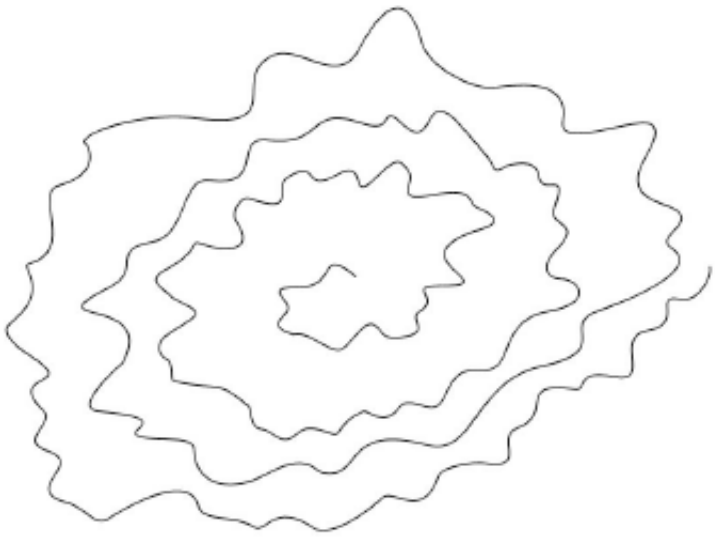

Fig. (1). Drawing of the Archimedes' spiral in a patient presenting essential tremor (ET).

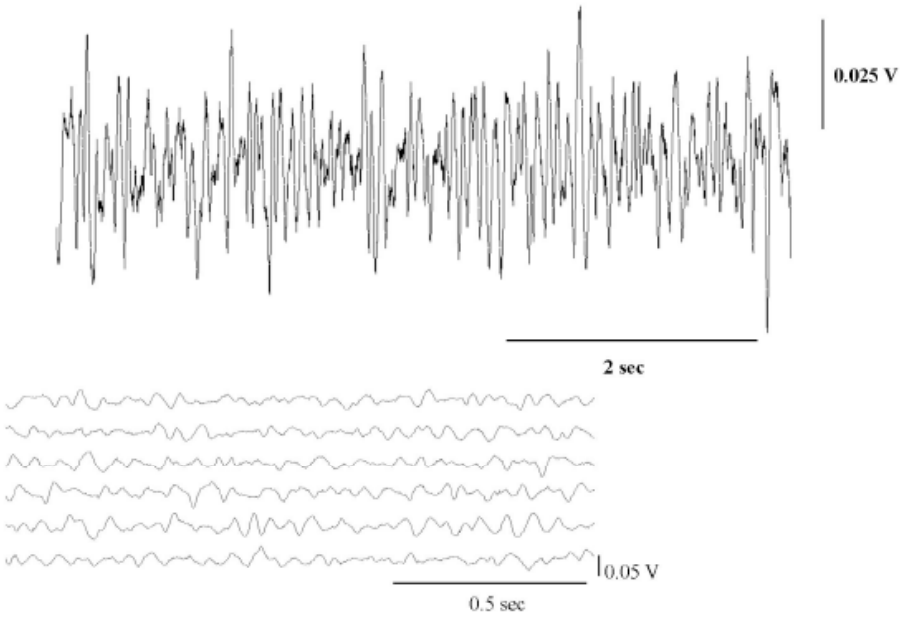

Fig. (2). Example of physiological tremor of the hand in a healthy subject. Recordings using monoaxial accelerometry. The subject is maintaining the upper limbs outstretched, parallel to the floor. Note the modulation in the amplitude of traces (upper panel). Frequencies in the range of 13-15 Hz are easily observed in time-series (bottom left).

limbs reminds the "pill rolling" movement. In some cases patients can reduce the tremor by holding one hand with the other or crossing the legs. Rest tremor often increases with mental stress (i.e. counting backwards) or contralateral movements.

1.4. Postural Tremor

Postural tremor occurs in body parts during the maintenance of a posture, such as holding a cup. Tremor is typically triggered by maintaining a position against gravity. Physiological tremor and enhanced physiological tremor have been considered as peculiar forms of postural tremor in the past. Postural tremor often causes a significant disability. The frequency of postural tremor is usually between 4 and 12 Hz.

1.5. Kinetic Tremor

Tremor appearing during limb movement and often worsening near the target is defined as a *kinetic tremor*. Tremorous movements are perpendicular to the main direction of the intended movement and tend to be predominant over proximal musculature. The terms "intention tremor" and "terminal tremor" have also been used. Kinetic tremor is classically tested during finger-to-nose (to put the finger on the nose) or heel-to-knee tests (to put the heel on the contralateral knee). The frequency is between 2 and 7 Hz in the large majority of cases. Addition of inertia tends to improve kinetic tremor. A recent study on the differences between smokers and non-smokers in terms of kinetic hand tremor

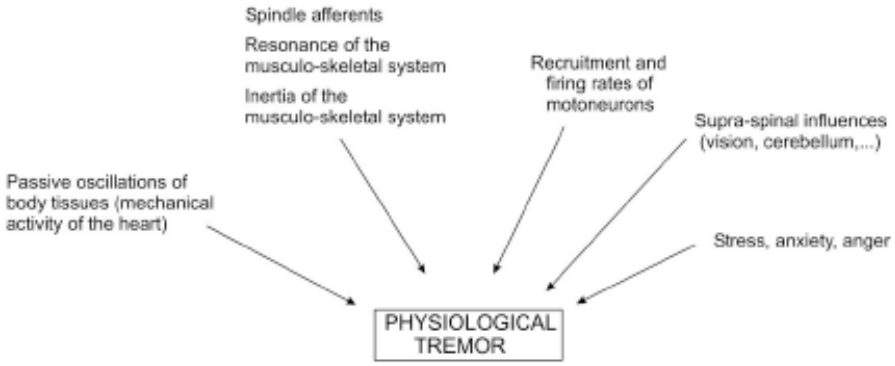

Fig. (3). Factors contributing to physiological tremor.

Table 1. Differential Diagnosis of Involuntary Movements

Sign	Definition/Features	Diseases Commonly Associated with the Movement Disorder
Tremor - rest - postural - kinetic	Tremor occurs in a rest position Tremor occurs during maintenance of a posture Tremor is enhanced at the end of a voluntary movement	Parkinson's disease Essential Tremor Cerebellar Tremor
Dystonia	Prolonged muscle contractions leading to abnormal postures. May be repetitive. Twisting movements.	Drug-induced Genetic Idiopathic
Chorea	Irregular; often hidden in voluntary movement; generates a dance-like movement.	Huntington's Disease
Athetosis	Continuous slow hyperkinesia of distal segments of limbs; causes an octopus-like movement.	Stroke
Ballism	Fast and ample movement of proximal segments of limbs; gives a "throw away"- like movement. More severe in upper limbs.	Stroke Inflammatory diseases
Tics	Fast and short hyperkinetic movements usually with a facial or head topography.	Gilles-De-La-Tourette Syndrome
Myoclonus	Sudden, short (20-150 msec) movement; may cause a pseudo-repetitive muscular contraction.	Essential Myoclonus Myoclonic Epilepsy Symptomatic myoclonus

showed a greater tremor intensity in smokers, even more apparent in women [6].

1.6. Principal Human Disorders Associated with Each Category of Tremor

Table **2** summarizes the main disorders associated with rest, postural and kinetic tremor. Some disorders combine these 3 forms of tremor to various extents.

The most common cause of rest tremor is idiopathic Parkinson's disease (IPD), a progressive neurodegenerative disorder with an estimated prevalence of 0.3% in the US population [7]. The prevalence might increase up to 4.5 % in subjects older than 85 years [8]. The majority of patients present a sporadic form, but familial cases have been reported, with a recessive or dominant inheritance pattern [9].

Many disorders are associated with a postural tremor. Essential Tremor (ET) is a typical example. ET is the most common movement disorder in the elderly, with a prevalence up to 4% in the population above 65 years [10]. A prospective population-based study in Spain of individuals aged 65 years and older has shown an adjusted incidence of 616 per 100.000 person-year [11]. ET is a familial disease in many cases, although a non familial sporadic form is recognized as well. Lesions in different anatomical locations of the cerebellar pathways result in different forms of postural tremor [12]. Acute or subacute postural tremor may result from supra-tentorial cortical lesions such as mass occupying lesions, ischemic lesions and arterio-venous malformations [13]. Postural tremor of the upper limbs is also a common manifestation of Wilson's disease, very likely generated within a synchronized cerebello-thalamo-cortical network [14].

Tremor occurring in cerebellar diseases is the typical example of a kinetic tremor, affecting especially the head and the upper part of the body. In case of cerebellar injury, kinetic tremor may increase secondarily, involving in particular in the proximal joints (shoulder).

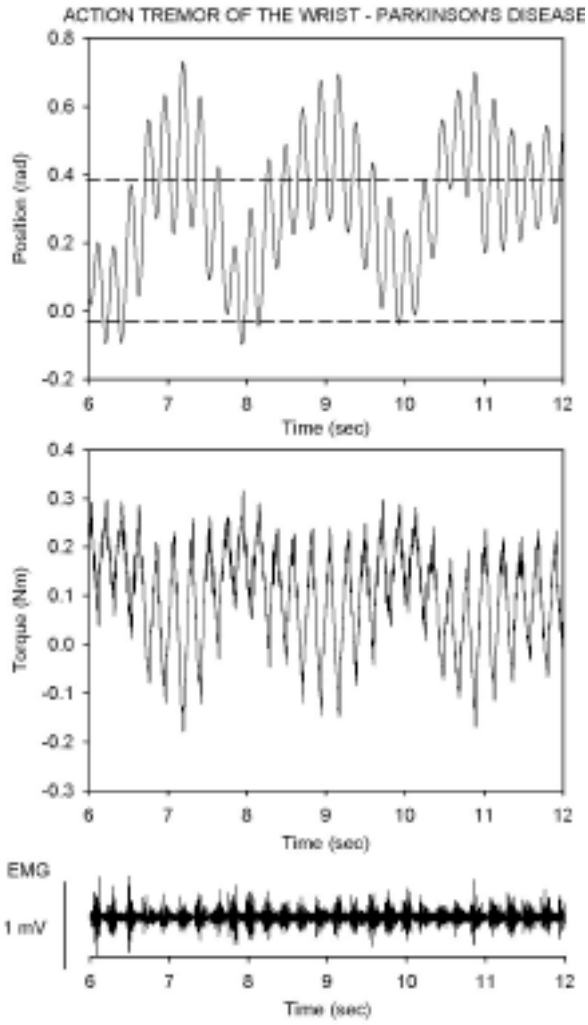

Fig. (4). Action tremor of the right wrist in a patient presenting a Parkinson's disease. Tremor is clearly present during successive movements between 2 targets (top panel). The associated torques are represented in the middle panel. Bottom panel: surface electromyographic (EMG) activities of the extensor carpi radialis (Gain: X 1000).

The group of tremor characterized by high-frequency discharges (> 14 Hz) includes orthostatic tremor (OT) and bilateral high-frequency synchronous discharges (BHFSD) [15]. OT is a rare disorder of middle-aged or elderly people, which is characterized by unsteadiness of standing and which remits when the patient sits or walks. Fig. (**5**) shows the high-frequency bursts typically recorded in lower limbs of a patient. BHFSD occurs in case of cerebellar degeneration and affects mainly the upper limbs.

1.7. Distinguishing the Various Forms of Tremor

Each category of tremor has its characteristics in terms of body segments involved, distribution (symmetry), enhancing/reducing effect of tasks or position, and associated disabilities [2]. A detailed neurological examination, blood studies and brain imaging are included in the work-up and follow-up. Tremors are often distinguished by analyzing their frequencies (see also section 2) and the durations of the electromyographic (EMG) bursts (Fig. **6**).

Table 2. Main Disorders Associated with Tremor

Type of Tremor	Diseases
Rest tremor	Parkinson's disease
	Drug-induced Parkinsonism
	Stroke
	Post-traumatic tremor
Postural tremor	Essential Tremor
	Enhanced Physiological tremor
	Cerebellar diseases
	Multiple Sclerosis
	Post-traumatic tremor
	Drug-induced postural tremor
	Metabolic diseases
Kinetic tremor	Cerebellar diseases
	Essential Tremor
	Multiple Sclerosis

1.8. Generators of Tremor and Anatomical Pathways

Several brain areas play a key-role in tremorgenesis (Fig. **7**). These regions are the key-elements of several loops controlling voluntary movement. Each of these loops has inherent time delays and interact with sensory feedback signals [16]:

-the loop between motor cortex and basal ganglia

-the loop between the cerebellum and the brainstem, in particular the Guillain-Mollaret triangle, which links dentate nucleus of the cerebellum with the contralateral red nucleus and the inferior olive (also called the dentate-rubro-olivary tract)

-the loop between the cerebellum, the thalamic nuclei and the motor cortex

-the peripheral loops, including the afferences from the muscle spindles to the alpha-motoneurons (spinal loop) and from the peripheral sensors to the motor cortex (transcortical loop).

Cerebellum is highly connected with the spinal cord, brainstem nuclei and projects to thalamic nuclei which relay the signals towards the sensorimotor cortex. It receives informations back from brain cortices mainly via the ponto-cerebellar tract and the olivo-cerebellar pathway. Cerebellum plays a major role in action control and motor learning [17]. Cerebellar lesions at the level of the afferent or efferent pathways are associated with a constellation of deficits including oculomotor disturbances, speech difficulties, tremor and dysmetria of the limbs, gait ataxia and learning difficulties [18-20].

Basal ganglia include 5 subcortical nuclei: caudate and putamen (forming the striatum), globus pallidus, subthalamic nucleus and substantia nigra. In each cerebral hemisphere, the basal ganglia receive information from the cerebral cortex and project to the thalamus, prefrontal, premotor and motor cortex. Patients presenting lesions of the basal ganglia exhibit various combinations of bradykinesia, rigidity of the limbs, tremor and impaired postural reflexes [2].

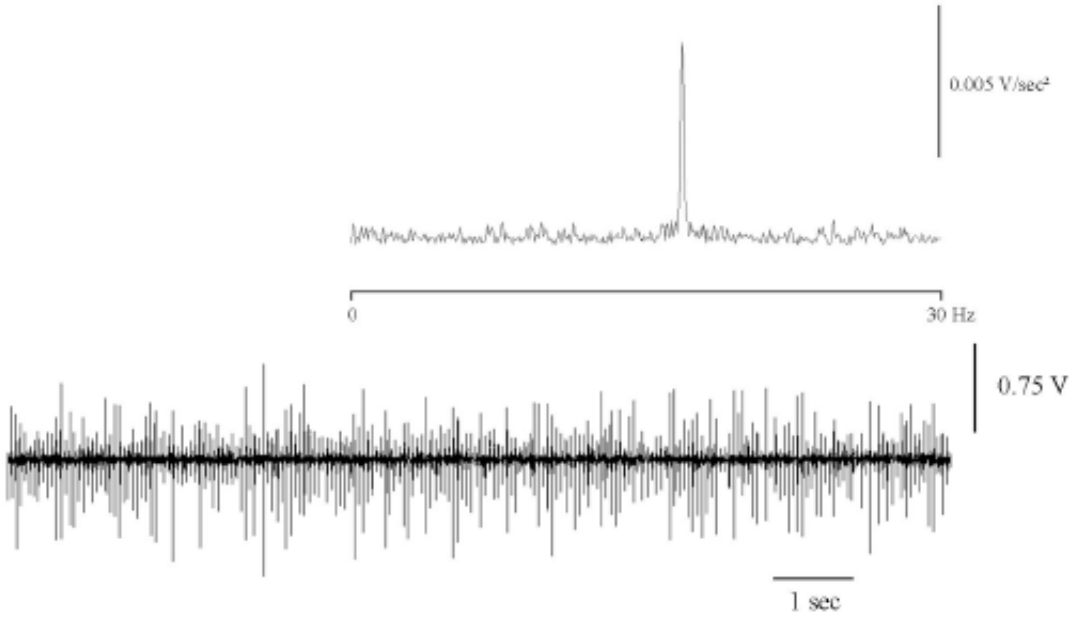

Fig. (5). Surface electromyographic (EMG) recordings in lower limb muscles during a standing task in orthostatic tremor (OT). Highly regular EMG bursts are recorded (lower trace). FFT (upper right) shows a clear peak of 17.5 Hz.

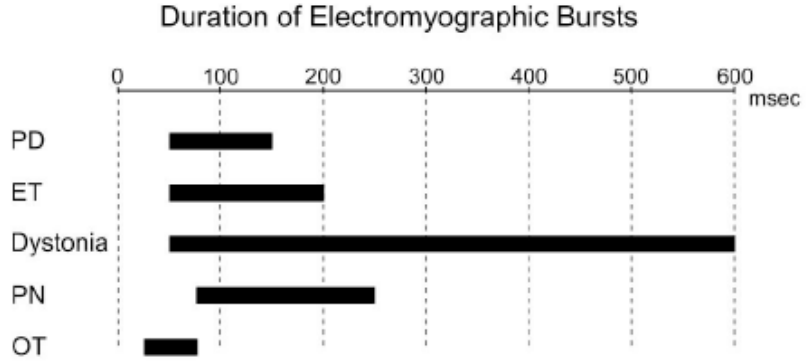

Fig. (6). Duration of EMG bursts in forearm muscles in various neurological disorders associated with tremor. Abbreviations: PD: Parkinson's disease, ET: essential tremor, PN: peripheral neuropathy, OT: orthostatic tremor. Adapted from Grimaldi and Manto, 2008.

Both cerebellar circuits and basal ganglia are highly connected by the pools of neurons in the spinal cord. The end effectors of the motor system are the motoneurons, whose discharges are responsible for the visible tremor. Motoneurons send their axons towards the agonist, antagonist and synergistic muscles of the limbs.

2. CONVENTIONAL SPECTRAL ANALYSIS OF TIME-SERIES

Tremor time-series are usually analyzed with concurrent recording of EMG activity and acceleration signals. In some cases, displacement sensors have also been used, such as pressure gauges [21], strain gauges [22-23], optical sensors [24], and more recently digitizing tablets [25-28]. Digitizing tablets, in particular, are applied for the conventional figure-copying task, i.e. drawing of the Archimedes spiral, and do not impose the need for the use of multiple sensors since the recording is only two-dimensional.

Surface EMG signals are usually high-pass filtered to remove undesired slow drifts and movement artifacts [29-32] and low-pass filtered for reducing large bandwidth noise and avoiding aliasing [29, 32-34]. These signals are sampled with frequencies of 1-2 kHz when the raw signals are stored or at lower rates when they are rectified and smoothed (envelope) by analog devices. Acceleration and displacement signals measured during tremor have smaller bandwidth and sampling rates around 40 Hz [35].

The analysis of human electrophysiological data of tremor has a long tradition. The earliest studies of tremor frequencies were made by visual inspection of the paper records of displacement data [21, 36]. Power spectral analysis was proposed in 1964 by Randall and Stiles as a new method of quantifying tremor waveforms . At that time spectral analysis was performed with analog computer devices. With the development of digital computers, tremor records have been more commonly analyzed off-line. Since the FFT algorithm for the computation of Fourier coefficients was reported by Cooley and Tukey [37], this technique has found increasing applications in the biomedical field (for review see [38]). At the same time, the widespread use of

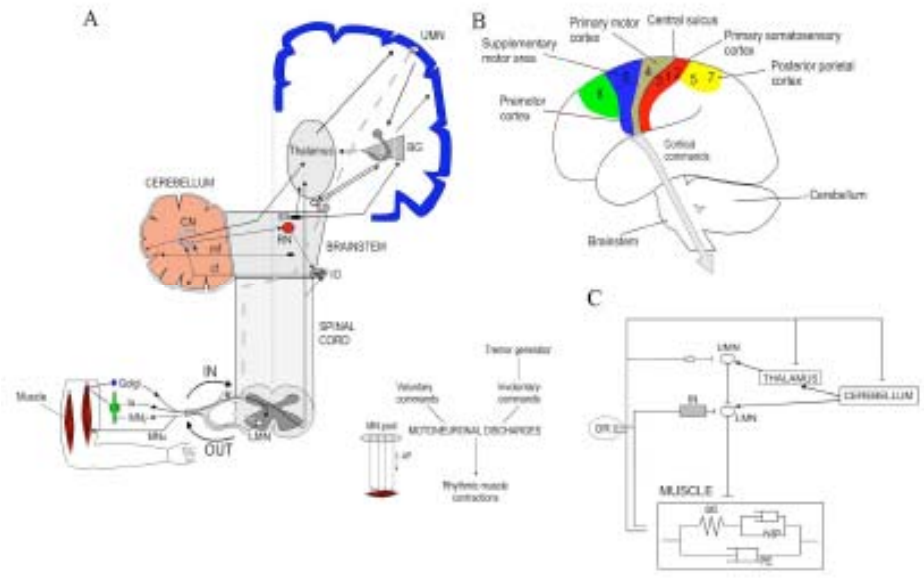

Fig. (7). Illustration of the main anatomical pathways involved in tremor genesis. A: representation of the central and peripheral nervous system. B: sensorimotor areas of the cerebral cortex with corresponding Brodmann's areas are drawn on the upper right panel. C: illustration of Hill's muscle model. Abbreviations: UMN: upper motor neurons, BG: basal ganglia, stn: subthalamic nucleus, sn: substantia nigra, RN: red nucleus, IO: inferior olivary complex, mf: mossy fibers, cf: climbing fibers, Ia: spindle afferents, MNγ: gamma-motoneuron, MNα: alpha-motoneuron. MN pool: motoneuronal pool, AP: action potential. DR: dorsal root ganglia, IN: interneurons of the spinal cord, SE: series elastic component, NIP: neural input processor, PE: viscous component. Adapted from Grimaldi and Manto, 2008.

accelerometers in automotive industry made these sensors inexpensive. Since then, tremor signals have been usually measured with piezoresistive accelerometers.

Currently, the Power Spectral Analysis is the most applied method for tremor analysis. Based on the rhythmic nature of tremor time-series and the assumption of wide-sense stationarity of this process, Power Spectral Density (PSD) is often used to obtain the distribution of power across frequencies. The PSD is usually averaged over epochs or smoothed over frequencies for reducing the variance of estimation [39-42] and the spectral content of the signal is presented in either linear or logarithmic scale (e.g.[42]). Interpretations of the tremor power spectra have been done differently by different authors. Based on the spectrum shape, single narrow, wide or multiple peaks and harmonics, various hypothesis about the tremor origins were proposed. Nevertheless, some basic guidelines for tremor spectral analysis have been provided [40, 42].

The amplitude of the signal is usually estimated as square root of the spectral peak value [43], under the assumption of a main peak in the power spectrum. According to this technique, however, amplitude may be underestimated in case of broad or multiple peaks. Another approach for quantifying the signal intensity consists in calculating the power for a fixed frequency range, usually –1 Hz to +1 Hz, around the peak frequency [39, 44]. Elble introduced the measure of the "EMG peak amplitude ratio" as the ratio between the square root of the power within the EMG peak and the total power from 0 to 15 Hz.

The frequency at which the power spectrum is maximum (peak frequency) is often used in the classification of the underlying pathology [45-47], although neither amplitude nor peak frequency provide a reliable discrimination of the type of pathological tremor. The diagnosis is also difficult with the clinical evaluation. For example, Meara *et al.* have reported that 103 out of 402 patients had been incorrectly diagnosed as having PD or parkinsonism when the diagnosis was based on clinical criteria [48].

The cross-spectral analysis has been widely used to investigate dependencies between signals and to determine signal pathways in the central nervous system. Phase and coherency spectra obtained from cross-spectral analysis have been extensively used to investigate the origin of tremor and its underlying mechanisms [23, 30-33, 49-52]. For example, cross-spectral analysis has been used to compare the spectral content of tremor between the left and right side in order to detect if contralateral limbs are driven by the same oscillator [34, 52]. In order to assess the involvement of brain structures in tremor generation, cross-spectral analysis has also been applied between EMG signals and rhythmic deep brain activity [51, 53-55], magnetoencephalography (MEG) [56], and electroencephalography (EEG) [32]. Moreover, for the purpose of investigating the contribution of reflexes and the mechanical properties of the limbs to tremor generation, EMG has been analyzed concurrently with mechanical measurements [23, 31, 33, 49, 57]. EMG has also been cross-analyzed between muscle pairs acting as antagonist at a joint [30, 39]. In some studies single motor unit activity has been analyzed along with surface EMG [23] and ACC [58]. Finally relationship between accelerometers and body Center of Pressure (COP) has also been suggested to study tremor with cross-spectral analysis [35].

Halliday *et al.*, 1995 and Timmer *et al.*, 1997 highlighted the need for introducing confidence regions for spectral peak frequencies [59-60]. This was a necessary condition for the development of a software for recording and analyzing hu-

man tremor signal [34]. This software is a standardized tool for tremor analysis currently available and it has been used in clinical studies.

Even though conventional spectral analysis is a simple mean to obtain useful information on the characteristics of tremor, it has important limitations. For example, tremor signals are non-stationary (i.e., their statistical and spectral properties change over time), therefore their distribution of energy should be jointly analyzed in the time and frequency domain, which poses a compromise between resolutions in the two domains.

2.L Imits in the Current Characterization and Understanding of Tremor

Wireless techniques, in the emerging field of body sensor networks (BSN) and body area networks (BAN), offer new perspectives for remote tracking of tremor. Indeed, tremor is a movement disorder occurring in numerous situations during daily life and these situations often differ from laboratory environments. It is widely accepted that there is a large gap between these laboratory recordings and tremor occurring at home, for instance. Therefore, tremor evaluation in freely moving patients during their ambulatory activities is one of the most interesting and promising aspects in novel monitoring systems. Development of low-cost, reliable and wearable unobtrusive sensors appears as a key-step for the next decade.

Current techniques do not allow the grasping of the activity of the brain networks at a cellular level and there is a lack of knowledge regarding the neurochemical events occurring at the beginning or throughout the course of a neurological disease manifesting with tremor. Surprisingly, several drugs currently administered for the management of tremor have been assessed in human in absence of clear definition of their mechanism of action in terms of regulation of neuronal discharges related to tremor. For instance, it is unclear how primidone –widely administered for essential tremor- affects the neurophysiological and neurochemical properties of brain networks. The effects of the main neurotransmitters involved in tremor genesis (GABA, Glutamate, acetylcholine, serotonin, nitric oxide) on the behaviour of central and peripheral oscillators are very complex. This complexity is even greater when the heterogeneity of the intrinsic properties of each network and the multiple reciprocal connections are taken into account. The translation of the neuronal discharges generated centrally into oscillatory activities in peripheral effectors cannot be understood without attempting to extract the rules governing the neurochemical cascades. It is currently assumed that most kinds of tremor are associated with an overexcitability of neurons, rendering the neurons prone to discharge in a rhythmic way. Therefore the initial events leading to an increase of excitability require attention.

Approaching the analysis of tremor some crucial factors should be taken into account. Unfortunately, they have been underestimated in many studies:

- the appropriate placement of the sensor on the body; the choice of relevant sensors, sensor packaging, type of communication, power consumption, autonomy, integration and ergonomic aspects. Comfort during recordings has often been completely ignored;

- the analysis set-up: recordings need to be performed in a quiet room, free of vibrations or electrical interferences;

- the regular calibration of the instrumentation system: using standardized recording procedures is essential for intra- and inter-patients comparisons.

Regarding surface EMG, the SENIAM project (Surface Electromyography for the Non-Invasive Assessment of Muscles – **www.seniam.org**) illustrates an effort of standardization for measurements based on surface EMG. This European concerted action has resulted in the following recommendations:

-for electrode shapes: the consortium has not identified clear recommendations

-for electrode size: the size of the electrodes in the direction of the muscle fibers should be 10 mm maximum

-for the inter-electrode distance: the inter-electrode distance should be 20 mm; for small muscles, the inter-electrode distance should not exceed 25 % of the muscle fiber length

-for the electrode material: pre-gelled Ag/AgCl electrodes are preferred

-for sensor construction: a construction with fixed inter-electrode distance is recommended, with cables fixed in order to avoid pulling artefacts

-for preparation of the skin: the patient should be shaved in case of presence of hair, and the skin should be cleaned with alcohol

-for sensor location: with respect to the longitudinal location of the sensor on the muscle, the recommendation is to place the sensor halfway the most distal motor end-plate zone and the distal zone; with respect to the transversal location of the sensor on the muscle, it is recommended to place the sensor at the surface away from the edge with other subdivisions or muscles so that the geometrical distance of the muscle to these subdivisions and other muscles is maximised

-for fixation on the skin: the use of elastic band or tape/rings is preferred

-for testing the connection: a clinical test for each individual muscle should be performed.

The contribution of brain imaging in the characterization of tremor remains an important step. Computerized Tomography (CT) and Magnetic Resonance Imaging (MRI) -more sensitive and specific than CT- provide a morphological assessment of brain structures. They are especially useful for the diagnosis of tremors associated with neurodegenerative diseases, vascular diseases or in case of post-traumatic tremor. Spatial resolution is crucial in MRI identification of morphological features. At least a 3 tesla MR is required if a detailed anatomical description is looked for in order to perform an anatomo-clinical correlation [61]. Positron emission tomography (PET), with specific tracers to measure Dopamine Transporter binding (DAT; SPECT), provide *in vivo* analysis of neurochemical, hemodynamic, or metabolic processes that underlie movement disorders [62]. Functional imaging is also employed to monitor disease progression. Nevertheless, concordance between clinical outcome and

imaging measures after therapeutic interventions is not consistent, precluding the use of functional imaging as surrogate end points in clinical trials [63].

3. ANIMAL MODELS OF TREMOR

Development of animal models is an essential step for the understanding of the pathophysiological mechanisms underlying tremors [64]. In addition, they represent a precious tool for the screening of drugs [65]. However, it is crucial to use valid models to avoid erroneous conclusions. Three aspects of validity should be taken into consideration by experimenters [66]. Construct validity implies that factors underlying the phenomenon of interest in animal, such as neurobiological or genetic factors, are similar to those described in human. As exemplified below, this criterion can be satisfied by using neurotoxins which provoke discrete neurodegenerations comparable to those found in patients. Predictive validity is reached when the manipulation of an independent variable (typically a pharmacological agent) has closely related consequences in human and animal. Lastly, face validity requires isomorphism between the behavioural or physiological expressions of the original process and those observed in the model. Concerning this latter, the specificities of the animal used as model should not be overlooked. For instance, the frequency as well the amplitudes of tremors in rodents differ from those found in human, partly because of distinct biomechanical properties [67].

3.1. Scoring Tremor in Animal Models

Several techniques are used to characterize tremors in animals. The simplest method consists in scoring the shaking of the whole body or part of it. In many studies dealing with the rodent model of essential tremor, an experienced observer scores the trembling by using a rating scale comprising 5 grades: no tremor = 0, mild tremor = 1, moderate intermittent tremor = 2, moderate persistent tremor = 3 and pronounced severe tremor = 4 [68-69]. This grading system has the advantage of simplicity, but remains very subjective and relatively imprecise. Some objective alternatives exist. EMG is sometimes used to record the oscillatory discharges of muscles following administration of tremorogenic compounds, generally as a complementary method of the subjective assessment [68-70]. In a study aiming at quantifying harmaline-induced tremor in cerebellar mutant mice, Milner and his collaborators also coupled EMG analysis with accelerometer-based device [71]. In this case, the shaking measurement was indirect since accelerometer was attached to a platform. Few studies, published in the 1980's, reported the use of accelerometers affixed directly on the back of rats [72]. Since then, only one work has proposed the use of a miniaturized accelerometer combined with a video system as an efficient mean to analyse vibratory behaviours in rats [73]. Another method consists of assessing rodents on a surface where they can freely move [74-75]. The signal resulting from the pressure exerted by animals on the floor is analyzed to characterize locomotor movements and tremor.

3.2. Neurotoxic-Induced Tremors and Mutants Exhibiting Tremor

Most animal models of tremor-related diseases are based upon chemical-induced neuronal degeneration. Among the compounds available, harmaline, 6-OHDA (6-hydroxydopamine) and MPTP (1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine) are the most used (Fig. **8**)..

Harmaline is an indole alkaloid and β-carboline derivative extracted from *Peganum harmala* [76-77]. The harma-

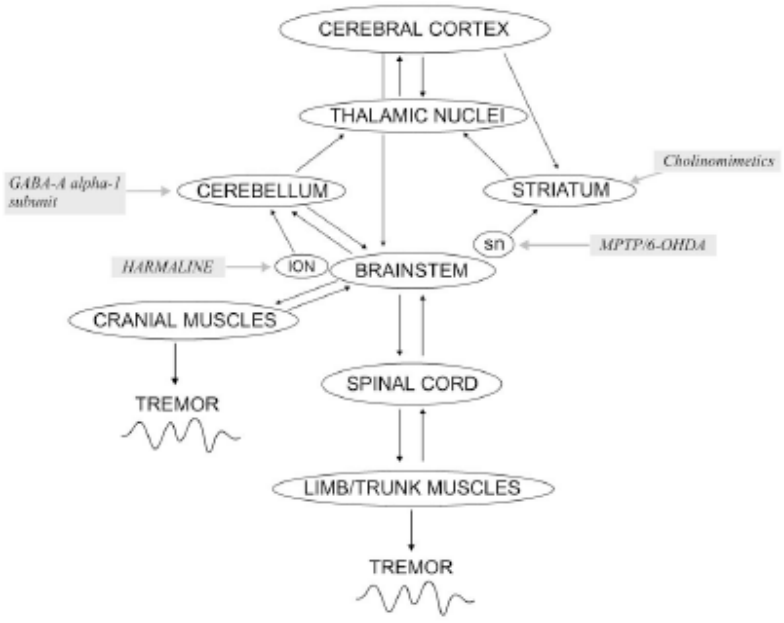

Fig. (8). Sites of action of pharmacological agents used to generate tremor in animals. Most studies have been performed in rodents and monkeys. Cholinomimetics target the muscarinic receptors of striatal neurons. MPTP is a potent neurotoxic for dopaminergic neurons of the substantia nigra (sn). Cathecholaminergic fibers are damaged by 6-OHDA. Harmaline is a beta-carboline alkaloid (BCA) which increases the rhythmic discharges of the olivo-cerebellar pathway by enhancing the electrotonic coupling of inferior olivary neurons (ION). The drug affects also directly cerebellar networks, including glutamatergic transmission in cerebellar nuclei. Knockout mice for the GABA-A receptor alpha-1 subunit display a high-frequency action tremor. Adapted from Miwa, 2007.

line model is considered as the reference experimental model for essential tremor [64, 78]. Indeed, harmaline is closely related to harmane, a substance endogenously produced which could constitute an environmental risk factor for essential tremor when present in the diet [79-80]. Moreover, administration of harmaline to rodents results in tremor with frequencies comparable to that observed in patients with respect to the relative size of species. These frequencies range from 6 to 25 Hz in rats (generally around a 10 - 12 Hz band frequency) and from 11 to 14 Hz in mice depending on the method of quantification and the dose used [67, 74]. Furthermore, drugs effective in the treatment of the essential tremor such as propranolol, primidone or ethanol have been shown to reduce the harmaline-induced tremor in rodents [81-82]. Finally, the main neurophysiological modification caused by the neurotoxin is the increase of synchronization of discharges in the olivocerebellar system and this might represent one mechanism involved in essential tremor [46, 83]. Although the harmaline model is widely used, there are several concerns about the pertinence of this model. First, harmaline is a small molecule with a wide range of effects which make interpretation of data potentially difficult. Harmaline acts as a modulator of voltage-gated channel currents [84], an inhibitor of phosphodiesterase [77] and monoamine oxidases [85] or a weak or partial agonist at benzodiazepines receptors [86]. In addition, recent evidence suggest that harmaline has a direct toxic effect upon skeletal muscles (unpublished data). Second, the harmaline model is a very acute model of tremor (tremor appears after a few minutes), whereas essential tremor is a disease evolving ovser several years. Third, from a behavioural point of view, it was noticed that this compound causes spatial learning deficiencies [87], strong ataxia (unpublished data) as well as suppression of locomotor activity [88], deficits which are seldom encountered in patients, although some patients exhibit an ataxic gait. Fourth, some significant differences have been reported between species, including microgliosis in the inferior olive nucleus in mice and death of some Purkinje cells combined with microgliosis in the cerebellar cortex in rats [83].

MPTP was discovered as a neurotoxin inducing parkinsonian-like effects accidental injection. The drug induces symptoms of Parkinson's disease (PD) such as bradykinesia, rigidity or rest tremor [89-90]. These deleterious effects have been attributed to the action of MPP+ (1-methyl-4-phenyl-2,3-dihydropyridinium ion), a metabolite of MPTP resulting from its metabolization in astrocytes and serotinergic neurons [91-92]. MPP+ would inhibit the activity of the complex I of the mitochondrial electron transport chain in dopaminergic cells [91]. This inhibition leads to severe degeneration of the nigrostriatal pathway, probably by a mechanism of oxidative stress. MPTP injection induces massive loss of neurons located in substantia nigra pars compacta mimicking lesions observed in PD patients. Non-human primates and mice are the most commonly used species for this model [92]. Curiously, the molecule fails to exert its full neurotoxic effects in rats [91-93]. Although typical PD-related motor deficiencies such as akinesia or tremor have been described in mice [95-96], some limitations include strain-dependent effects [97-99] and rapid recovery. For these reasons and due to the proximity of the motor repertoire [91], MPTP-injected monkeys are thought to be of a greater interest to model PD. Occasional postural whole body tremor and resting/postural tremors were respectively reported in marmosets [100] and vervet monkeys [101]. Action tremor was also noticed in the latter and in rhesus monkeys [90, 102]. Unfortunately, MPTP-induced tremors is hardly reproducible. Moreover, even if α-synuclein aggregations are sometimes observed in MPTP-treated monkeys, true Lewy bodies characteristic of human PD are lacking [91, 103-104].

6-OHDA is the second neurotoxin commonly used to induce a PD-like syndrome in different species. Its toxicity, which results in the selective death of catecholaminergic neurons, lies in several mechanisms but one of the most important involves the inhibition of mitochondrial complex I [92, 105]. Given that 6-OHDA is unable to cross the blood-brain barrier, one has to inject it stereotactically into the brain [91-92]. This kind of injection is usually achieved in the striatum, substantia nigra or medial forebrain bundle [106-107]. This is needed to avoid degeneration of other catecholaminergic neurons. As in MPTP model [90], the unilateral lesions are preferred to the bilateral lesions because the latter leads to so severe motor impairments than animals have some difficulties to feed and require nursing care [108]. The behavioural consequences of 6-OHDA in rodents comprise akinesia and parkinsonian rigidity-like catalepsy [109-110]. Nevertheless, the rotation induced by dopaminergic agonists like amphetamines or apomorphine in unilaterally 6-OHDA injected rodents is considered as a valuable behavioural clue [111-112]. Rotational behaviour is used to screen potential antiparkinsonian drugs [91]. Although a proper tremor is rarely observed (e.g. 113-114), tremulous jaw movements (TJMs, that is purposeless chewing) in rats injected with 6-OHDA are reported [110]. Some authors consider these movements as related to tremor [67, 115]. Moreover, tacrine-induced TJMs in rats were showed to be a reliable model of PD [116]. Indeed, these movements are within the 3-7 Hz frequency range which is characteristic of the tremor present in the human disease and are reversed by well-known anti-parkinsonian drugs such as scopolamine, apomorphine or levodopa [115]. TJMs as well as "real" tremors can be also provoked by cholinomimetics [67]. The latter group includes tremorine, oxotremorine and carbachol. Unfortunately, the mechanisms underlying their tremorgenic action are poorly understood and do not involve the degeneration described in trembling patients. Although a muscarinergic mediation is suspected, a nicotine-induced tail tremor has been demonstrated [67, 117]. Finally, injection of cholinomimetics in animal is not considered as a "good model" of human tremor.

While some chemical-induced lesions mentioned above allow to test anti-parkinsonism potency of drugs like levodopa [92], zonisamide (a sulphonamide anticonvulsant with anti-epileptic properties) [118] or adenosine A2A antagonists [119], they generally fail to reproduce progressive onset of the human PD [89, 91-92, 103]. In this respect, we have to mention the pesticide intoxication-based models. The most used compound is rotenone, a potent inhibitor of mitochondrial complex I leading to a selective and progressive destruction of nigro-striatal pathway [91]. In addition to formation of α-synuclein inclusions in nigral cells, rotenone administration in rat results in behavioural symptoms including rigidity, hypokinesia and, occasionally, shaking of forepaws considered by some authors as similar to rest tremor

[120]. Nevertheless, once again rotenone-model remains controversial [121].

Apart from chemical-induced neurodegenerations, spontaneous or directed mutations have been used to mimic pathologies associated with tremor (e.g. [9], [67], [91], [122]). Given their diversity, we will not catalogue here all these genetic models available but we will just mention the most important ones. The species commonly used in this kind of modelling are mice, rats and drosophila. The latter help, above all, to identify the cellular and biochemical mechanisms involved in modelled diseases, but no behavioural equivalent of tremor seems to be present in these flies. They have permitted to demonstrate that transcribed premutation CGG-repeats presents in fragile X-associated tremor / ataxia syndrome are sufficient to provoke neurodegeneration [123]. Moreover, a mutant drosophila overexpressing α-synuclein has been generated to elucidate the formation of Lewy bodies-related cytoplasmic inclusions and their impact in PD [124]. Interestingly, this mutant exhibits locomotor dysfunction. Motor impairments and cytoplasmic inclusions have also been found in mice expressing a mutated form of α-synuclein [125]. On the other hand, most of the mice null for parkin, a gene determining autosomal juvenile parkinsonism, do not exhibit any substantial phenotypic change except for deficiencies of dopamine metabolism [122].By contrast, strong postural and kinetic tremors and motor coordination deficits have been highlighted in gamma-aminobutyric acid A receptor α-1 subunit knockout mice, which have been proposed as a model of essential tremor [126]. However, the tremor frequency recorded in the mutant mice (19 Hz) exceeds by far that observed in human disease (4-8 Hz) [67]. A lot of supplementary mutant rodents exhibiting shaking such as trembler, shiverer, vibrator, wobler or jimpy mice, and zitter or shaker rats have been described. In these mutants, tremor is associated with some alterations such as demyelination or cerebellar Purkinje cells degeneration. We can't detail here the behavioural and biological features expressed by these mutant rodents (see [67]). Among the other species used as genetic models of tremor, pigs affected by the "Campus syndrome" constitute a particularly interesting case [127-128]. Indeed, they are characterized by a 14 – 15 Hz tremor occurring only when they are standing and walking, but which disappears when they are lying. These features make the Campus syndrome a promising model of orthostatic tremor.

We want to point out that the animal models never reproduce identically the human impairments [64]. Nevertheless, some of them sufficiently mimic lesions exhibited by patients (construct validity) to provide a good tool in screening drugs able to counteract pathophysiological mechanisms (predictive validity). In fact, it seems that the face validity, that is shaking, is the most hardly reached criterion of pertinence in modelling tremor. In addition, a special attention should be given to the anatomical features of the animals used and the biomechanical implications in regard to the tremor-related motor phenomena. As Miwa judiciously pointed out, rodents, which remains commonly used, are quadruped, implicating postural adjustments very different from those of human beings [67]. For instance, one could wonder whether it is possible to really model resting tremor in such species. On the other hand, the use of animals more closely related to humans like monkeys raises ethical issues [108].

Although they have contributed to a better understanding of shaking-related diseases and to the development of treatments, animal models of tremor clearly need to be refined. Improvements are necessary in the absence of reliable alternatives permitting to elucidate mechanisms underlying the complex and integrated tremor phenomenon.

4. BIOMECHANICAL MODELLING: A CRITICAL REVIEW

There is a lack of studies in the literature centred on the analysis of biomechanics of tremor in human upper limb. This section introduces an estimation of tremor kinematic parameters, by reproducing upper limb kinematics based on a biomechanical model. The method used for analysis of tremorous movements is based on a combination of solid modelling techniques with anthropometric models of the upper limb, from which a kinematic and dynamic upper limb model can be developed. This model of upper limb musculoskeletal system can be used to estimate the force contribution of each muscle component during motion, to experiment with modifications of musculoskeletal topology and to devise complex motion coordination strategies. The input in the model is the angular position, velocity and acceleration of each joint, measured by gyroscopes placed on the upper limbs of patients suffering from tremor [129].

Given the respective material properties, bones may be regarded as rigid bodies in contrast to soft tissues, with respect to the relevant physiological ranges of motion and force handling. This allows the isolation of the skeletal subsystem from the soft tissues by converting their relations with the bones into external actions. The upper limb kinematics and dynamics may then be analyzed and modelled in considering the skeletal components only [130]. Neglecting the hand, the human upper limb may be described as composed of five bones, the clavicle, the scapula, the humerus, the ulna and the radius, forming two mechanisms, the shoulder and the elbow. Their association allows a wide range of combined motions, and confers to the human arm the highest mobility in the human body. In our study we are considering the joints in which tremor is more disabling: elbow flexion-extension, forearm pronation-supination, and wrist flexion-extension [131].

The forearm movements are independent from each other [132]. Physiologically, no fixed axis or rotation centre can be recognized in a real joint. For most joints, the relative motion between bones is a combination of rolling and gliding with pressure on the contact areas. An accurate joint model should account for all these movements as well as the forces and torques induced on the bones. A 2-D theoretical analysis was performed in this direction by Engin in 1984 [133]. The model described the relative motion between two bones, including both geometrical and material non-linearities as well as the ligament and contact, forces and torques. Chao *et al.* presented another approach towards joint dynamics simulation [134]. The technique, named Rigid Body Spring Model, consisted of modelling the articular surface pressure with distributed compressive springs. When subjected to tensile forces, the compressive springs were removed from the model. An iterative scheme was thus used to solve the

system for the equilibrium, whereas the spring redundancy was handled by energy optimization. It was applied to static analysis of the wrist and hand biomechanics.

In most cases, translations appear negligible with respect to rotations, so that the model development and analysis may be simplified using idealized joints. The general procedure is to individually consider the true functional mobility of each joint before considering the inter-dependencies induced by loops. In most analysis [133], the upper limb joints were idealized in the form of 3-DOF (degree-of-freedom) Ball & Socket 3-DOF Ball & Socket 2-DOF Hinge or 1-DOF Hinge rotational joints. Regarding dynamics, the upper limb has been assumed to be composed of rigid bodies in most approaches, including the bones and the soft tissues attached to them, connected by ideal (frictionless) kinematic joints. The rigid bodies have been assumed to possess fixed centres of gravity, and the joints, fixed axes or centres of rotation [135]).

The biomechanical model proposed has been build taking into account the de Leva [136] and Zatsiorsky and Seluyanov tables [137]. These tables are the most widely accepted within the field of biomechanics in order to perform dynamic analysis. Especially in sports and medical biomechanics, De Leva adjustments have been made in order to define accurately the anthropometric measurements required to obtain inertial parameters from Zatsiorsky tables.

A solid rigid model of the forearm was built with the information from the above-mentioned tables and parameterized following the Denavit-Hartenberg approach. In addition, a library was created to permit dynamic analysis of the system. This analysis was performed using the recursive algorithm [138], so that the libraries have been built on a modular basis.

4.1. Denavit–Hartenberg Parametrization

The model considers the upper limb as a chain composed of three rigid bodies – the arm, the forearm and the hand – articulated on the rigid base formed by the trunk and linked by ideal rotational joints. This representation relies on three assumptions: 1) the mechanical behaviour of the upper limb with respect to the trunk is independent of the rest of the human body; 2) each segment, including bones and soft tissues, has similar rigid body motions; and 3) the deformation of the soft tissues does not significantly affect the mechanical properties of a segment as a whole. The hand was considered as a rigid extension of the forearm on the assumption that hand motion has a negligible effect on the broad motion dynamics of the upper limb. This was necessary to determine a rigid body equivalent to the hand and forearm assembly to be substituted in the rigid body dynamic analysis. As a result, four rigid segments were defined in order to be able to analyse all the recorded degrees of freedom. Each segment is responsible for a degree of freedom: 1) elbow flexion-extension; 2) pronation-supination; 3) wrist flexion-extension; 4) wrist deviation.

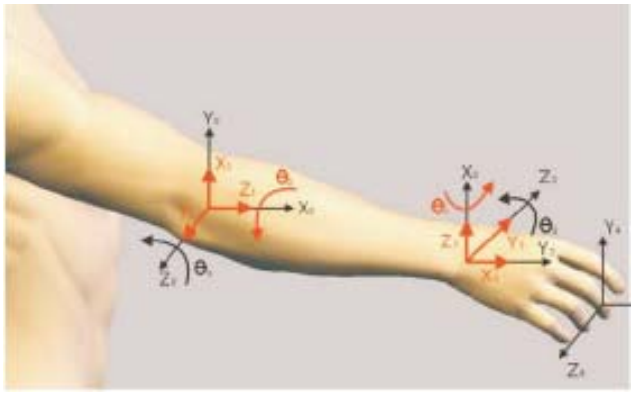

Fig. (9). Solid model representation of the forearm.

Two of these segments are virtual (no mass and no length). Each segment has its own reference system (plus a coordinate frame for the all of them) attached. Fig. (**9**) shows the coordinate frames defined and the degree of freedom represented for each system.

The Denavit-Hartenberg parameters can be seen in Table **3**. For rotary elements, the parameter θ determines the position of the joint. The table indicates the relationship between the parameter and the physiological measured angle represented by βi for each segment i. F_L means forearm length and H_L corresponds to hand length.

Biomechanical parameters per segment were obtained from De Leva *et al*. [136]. Segment 1 and Segment 3 are virtual. They are only defined to cope with the degrees of freedom of elbow flexion-extension and wrist flexion-extension respectively. However, when these segments are moved, the masses of the "real" segments are moved. All the inertial and mass parameters of a segment are defined below, using the following symbols: BM, body mass, FL, forearm length, FM, forearm mass, HL, hand length, HM, hand mass, CoGM, centre of gravity of each segment and M_I inertia matrix.

The computational algorithm used is based on the Newton-Euler equations of motion described in [138]. Thanks to their recursive implementation, these equations of motion are the most efficient set of computational equations for running on a uniprocessor computer, so that implementation in real-time is possible. This analysis is intended to estimate the

Table 3. Denavit-Hartenberg Parameters

Segment	d	a	θ	α
1.Elbow F/E	0	0	$\beta_1 + \pi/2$	$\pi/2$
2.Pronation	F_L	0	β_2	$\pi/2$
3.Wrist F/E	0	0	$\beta_3 + \pi/2$	$\pi/2$
4.Elbow Dev.	0	H_L	β_4	$\pi/2$

torque and power of the tremorous movement in each joint of the upper limb based on the information provided by gyroscopes placed on the upper limb.

Active orthoses have been developed to counteract tremor by applying controlled forces. Torque is an essential parameter in the choice of the actuator technology that will be used by powered orthoses. Special care should be taken with this parameter since it presents a dynamic behaviour. As shown in Fig. (**10**), this parameter presents a dynamic behavior. The actuator technology that will drive the orthosis must have the capacity to apply the same torque characteristics. (Table **4**) summarizes the mean value of torque estimated in each joint of the upper limb for the tasks of stretching out the arm and putting finger to nose. These tasks are shown because they are the ones in which maximum values of tremor activity were registered.

One of the critical aspects in the design of wearable devices is energy, because this factor determines the choice of the capacities of the batteries of the device (and subsequently the size and the weight of the batteries, and the design of the device). The amount of energy required by the system should be calculated on the basis of (1) the energy required to suppress tremor, and (2) the loss of energy due to the inefficiencies of the system. The energy required to suppress tremor corresponds to the power associated with the tremorous movement. The key parameter is the power related to the oscillations themselves. The estimated values of power for each movement of the elbow and the wrist during 2 classical clinical tasks are given in Table **5**. For the analysis of the power, the gravitational component of the movement has been removed from the estimations because this work is performed by the voluntary component of movement: tremor is considered as a stationary component in every point of the voluntary movement. Leaving aside the viscous coefficient of joint braking, there is no effective work done on the joint.

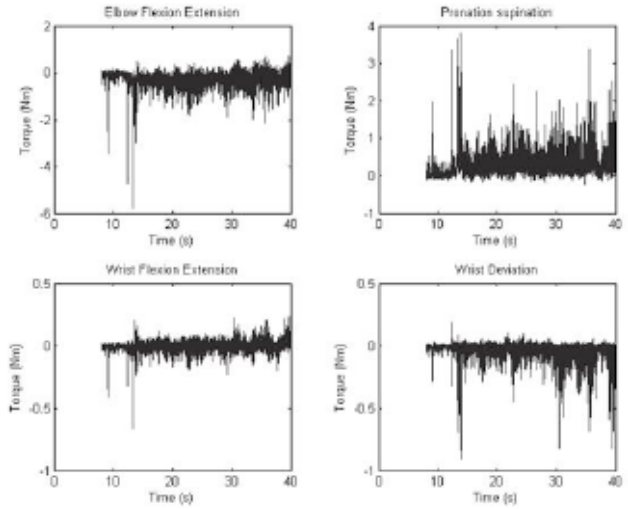

Fig. (10). Torques in upper limbs.

5. ADVANTAGES AND DRAWBACKS OF TREMOR DETECTION ALGORITHMS DEVELOPED RECENTLY

Human physiological tremor is surrounded by a long history of controversy and general interest [139]. Most of the interest is based on the beliefs that (1) tremor offers some clue to the mechanisms of neuromuscular control in man and (2) the clarification of physiological tremor will help to elucidate the origins of many pathological action tremors.

Timmer is one of the researchers paying more attention into modelling tremor. Initially, the standard methods of stochastic and deterministic time series analysis were used to analyse data of various physiological and pathological forms of tremor. Timmer *et al.* have shown that the physiological tremor can be described as a linear stochastic process whereas pathological forms of tremor represent non-linear

Table 4. Mean Values of the Torques Estimated During Finger to Nose and Outstretched Arm Tasks

Movement	Finger-to-nose	Outstreched Arm
Elbow Flexion-extension	1.9 Nm	1.2 Nm
Forearm Prono-supination	3.7 Nm	1.9 Nm
Wrist Flexo-extension	0.4 Nm	0.2 Nm
Wrist Deviation	1.1 Nm	0.5 Nm

Table 5. RMS (Root-Mean-Square) Values of the Power Estimated in Each Joint During Execution of Finger to Nose and Outstretched Arm Tasks

Movement	Finger-to-nose	Outstreched Arm
Elbow Flexion-extension	0.2 W	0.01 W
Forearm Prono-supination	1.8 W	0.2 W
Wrist Flexo-extension	0.08 W	0.03 W
Wrist Deviation	0.4 W	0.04 W

processes [140]. The authors used a stochastic feedback system which applies a sigmoidal non-linearity describing the activation function of the motoneurons that was introduced by Stein [141]. In this work, Timmer and colleagues provide evidence for the contribution of the reflexes to the tremor. However, there is no proof from data that reflex loops primarily cause the tremor, although they modulate the oscillations. Reflex loops alter the frequency, relaxation time, and amplitude of existing oscillation to some degree. Therefore, Timmer suggests that the primary cause of physiological tremor is the resonant behaviour of the hand and a synchronised EMG activity that is either generated centrally or due to the recruitment strategy of motoneurons.

Pathological tremor exhibits a non-linear oscillation that is not strictly periodic [142]. In order to investigate whether the deviation from periodicity is due to non-linear deterministic chaotic dynamics or due to non-linear stochastic dynamics, various methods from linear and non-linear time series analysis have been applied to tremor time series. The results of the different methods suggest that the considered types of pathological tremors represent non-linear stochastic second order processes. Finally, Timmer *et al*. investigated whether two earlier proposed features capturing non-linear effects in the time series allow for discrimination between two pathological forms of tremor for a much larger sample of time series than previously investigated. Tremor time series might span a large range of different behaviours. The physiological tremor of healthy subjects represents a linear second order stochastic process driven by white noise originating from uncorrelated firing of motoneurons [142]. The enhanced physiological tremor can either be described by a stochastic linear second order process driven by colored noise or non-linear stochastic delay differential equation depending on the degree of the contribution of a central pacemaker or of reflexes [142]. Pathological tremor like essential, Parkinson, and kinetic tremor might exhibit a non-linear oscillation. The oscillation is not strictly periodic. The possible reasons for the deviation from a strictly periodic have been looked for. The affirmation that a non-linear stochastic second order process best describes the oscillations of the pathological tremors contradicts the suggestion of Gresty and Buckwell [143], according which the variability observed in the pathological tremors should be interpreted as caused by frequency and/or amplitude modulated harmonic oscillators.

As stated above, tremorous activity is composed of deterministic and stochastic components [142]. The detection and quantification of tremor are of clinical interest for diagnosis of neurological disorders and objective evaluation of their treatment [144]. Furthermore, the estimation of tremor is an important stage in systems that aim to control limb oscillations, and also in biofeedback studies. In this regard, estimation techniques have been developed for tremor suppression. Methods based on the Fourier transform (FT) are commonly employed for this purpose, especially because of the similarity between tremor and a sine wave [139].

Estimation techniques have been developed for tremor suppression. Different techniques have been used in order to separate the voluntary and involuntary motion [145], among others, have investigated low pass filtering. Most of this work involves either finite impulse response linear equalizers trained on tremor recordings, or linear low-pass or band-stop filtering approaches, which aim to attenuate the full frequency band of tremor, while passing frequencies below 1 or 2 Hz, which are assumed to be voluntary. Linear filters are successful in attenuating tremor in many applications, but their inherent time delay is a drawback in active noise control, with its demand for zero-phase compensation. Furthermore, low-pass filtering is not sufficiently selective to form an explicit tremor model for use as an actuator command. Effective active tremor compensation requires a zero-phase system which generates a specific tremor estimate to be used as an opposing vibration.

A different approach is proposed by Gonzalez *et al*. [146] who address the problem of smoothing the tracking signal through the optimal design of a signal equaliser. Designing an optimal equaliser is a mathematical optimisation problem in which a filter of a given class is optimised according to the maximisation of a measure of closeness between reference and tracking signal. The author defines and uses the F-MSEd index as the closeness indicator. They developed a digital filtering algorithm that utilised an optimal equaliser to equilibrate a tremor contaminated input signal and a target signal that the subject attempted to follow on a computer screen [147]. Most attempts to develop such systems have involved teleoperative approaches [148-149].

The most used algorithm to estimate tremor is the weighted-frequency Fourier linear combiner (WFLC) developed by Riviere in the context of actively counteracting physiological tremor in microsurgery. The WFLC is an adaptive algorithm that estimates tremor using a sinusoidal model, estimating its time-varying frequency, amplitude, and phase [150]. Riviere also investigated the application of neural networks to augment manual precision by cancelling involuntary motion [151]. The main disadvantage of the WFLC is the need for a preliminary filtering stage to eliminate the voluntary component of the movement [150]. This filtering stage introduces an undesired time lag for our system when estimating tremor movement, this time lag introduces a time delay that could considerably affect the implementation of the control strategies for tremor suppression.

Recently, a new algorithm based on based on a two-stage algorithm has been used [131]. In the first stage, the Benedict-Bordner filter estimates the voluntary component of the movements. In the second stage, the estimated voluntary motion is removed from the overall motion and it is assumed that the remaining movement is tremor. After this, the WFLC was used in order to estimate tremor parameters. In this stage, the algorithm estimates both the amplitude and the time-varying frequency of the tremorous movement. The algorithm proposed was evaluated with data obtained from the patients measured in our experiments. The estimation error of the first stage was smaller than 2 degrees. The second stage algorithm has a convergence time always smaller than 2 s for all signals evaluated and the Mean Square Error (MSE) between the estimated tremor and the real tremor, after the convergence, is smaller than 1 degree. The combination of both techniques resulted in a very efficient algorithm with small processing cost for estimating in real time the voluntary and the tremorous components of the overall motion.

A novel technique for the study of tremor was presented. The technique, called Empirical Mode Decomposition, is a high-resolution technique that solves most of limitations of the Fourier Analysis (the standard technique to the study of tremor time series). This technique was proposed by Rocon *et al.* [152]. This technique was identified as a very useful tool for an automatic decomposition of the signal into tremor and voluntary signal. Moreover, this technique enables the representation of the amplitude and the instantaneous frequency of the input signal as function of time in which the amplitude could be contoured on the time-frequency plane. This technique provides, in a time-frequency energy plot, a clear visualization of local activities of tremor energy over the time (Fig. **11**). The application of this technique introduces new attributes to the tremorous signal such as instantaneous amplitude, instantaneous phase and instantaneous frequency.

6. NEURAL NETWORKS: POTENTIAL IMPACTS

Computational models, that is computer programs able to simulate the behaviour of complex systems by using computational resources, are often used when dealing with neuroscience and motor control studies. Motor control mechanisms have a high rank of complexity, because they are generated by the integration of contributions coming from several neuronal structures, such as those devoted to perceptive, associative, cognitive and motor functions. It is difficult, if not even impossible, to represent such a complexity by a "deterministic" simulation approach where every instruction has to be clearly defined. Instead, soft computing offers the most viable solution to this problem by moving the rationale of the modelling from the mathematic description of a behaviour to the understanding of the fundamental concepts behind this behaviour. Soft criteria [153] accept statistically varying results if they lie in a range of acceptable solutions. In these terms, soft computing appears as the most plausible implementation of biological mechanisms.

Among soft computing approaches, Artificial Neural Networks (ANN) have been widely used in neuroscience, especially in the motor control field, because of their ability to mimic the behaviour of biological neuronal networks. Moreover, they offer the possibility to take into account the mechanisms of motor learning and all the procedures aiming at acquiring novel motor skills.

An ANN is composed by a number of units linked through weighted connections, just as the human neuronal structures. Historically, the development of ANN derived from the attempt to simulate the neuronal structures of the brain tissue: the original idea undoubtedly derives from the studies on the central nervous system, and still today most of the research activities follow that direction. It is possible to assert that ANN can be considered as 'computational models' characterised by skills such as training (either supervised or unsupervised), adaptation, learning, generalization, clustering, self-organization and parallel processing.

Starting from the link between neuronal and neural networks, in this paragraph the authors would like to explore mainly the potential impact that artificial controllers, modelled by ANN and then biologically inspired, could have on the simulation of limbs motor behaviour. ANN, mimicking the biological neuronal networks, can help in the simulation of limbs' behaviour because they can be efficiently used to implement motor control strategies. In particular they have been used as controllers for the generation of those dynamic models representing the interaction of a limb with the environment, and for the definition of motor commands driving the execution of the movement.

Scientific literature offers important contributions starting with the work by Kawato [154] where a hierarchical ANN was proposed to generate motor commands for a voluntary movement. The neural network receives as input the information derived from transformation processes such as the determination of the desired trajectory in the visual coordinates space and the transformation of trajectory coordinates to the body coordinates space. Both the control and the learning performance of the model were investigated by computer simulation.

This work put the basis for the use of ANN in the simulation of internal models that, originating in the field of control theory and robotics, were introduced in the pioneristic work by Ito [155] who proposed that the cerebellum contains forward models of the limb. In a mathematical view, internal models have been defined as the mechanisms able to simu-

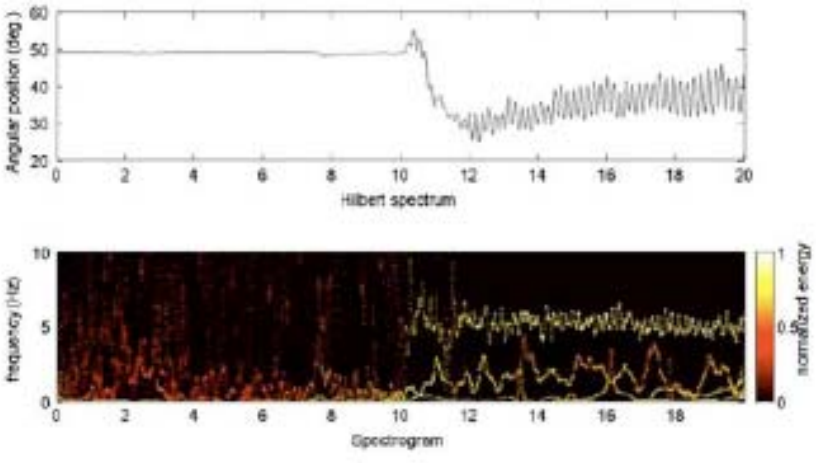

Fig. (11). Hilbert Spectrum of data obtained in patient presenting essential tremor and performing a postural task (keeping the arms outstretched). The high levels of energy activities are perceived when the patient is performing the task.

late the transfer function of the motor apparatus [154] and have been classified into: *forward internal models* driven by motor commands to generate movement [156], and *inverse internal models* driven by trajectory information to calculate feed-forward motor commands [157-158]. This is the implementation of the so called internal model hypothesis by which motor learning allows the acquisition of an inverse dynamics model of objects to be controlled, and after which motor control can be executed in a pure feed-forward manner.

The original model by Kawato [159] is based on a feedback-error learning paradigm, that is while an inverse model is tuned to provide accurate feed-forward control, simultaneously the feedback control is used to correct errors. This hypothesis about motor learning, which has been developed according to a combination of psychophysical observations and engineering considerations, predicts that once the tuning of the inverse model is complete, the role of feedback control is limited to the correction of disturbances. The neural model by Kawato, after test with a robotic manipulator, demonstrated to have the following characteristics: 1) acquisition, during training, of both the dynamic models of the control, that is forward and inverse-dynamics models; 2) ability to control movements quite different and faster than those used during learning; 3) generalization skills allowing the neural network model to work well even when only very limited information about the dynamical structure of the controlled system was available.

Leaving away the discussion about the physiological validity of the internal model hypothesis, that is not in the aims of this contribution, it is worth to outline that ANN after the work of Kawato *et al*. [159] have been used for the simulation of mechanisms such as internal model learning and voluntary movement control [160-164].

A comprehensive neural-based model of the human arm has been implemented by Karniel and Inbar [160]. It includes a 2DOF manipulator driven by three muscle pairs for the biomechanical arm modelling, while an ANN and a Pulse Generator transform the neural outputs into representative motor commands. The results obtained are consistent with physiology although the movements are restricted to a limited region of the entire workspace and the learning algorithm is not biologically inspired.

Fagg presented in 1997 [161] a computational model that learns motor programs simply by bringing an arm to the target, thus producing biologically plausible movements, since they are characterised by bell-shaped tangential velocity profiles.

Stroeve proposes a multi-layer perceptron to simulate a properly tuned internal model of environmental dynamics to guide the selection of motor commands for a given task of the limb [162]. The work tested the system performance showing a good control of the non-linear musculoskeletal model, producing neural control signals which resulted similar to real electromyographic data. Moreover, the response of the arm to external forces has been studied and compared with experimental data on arm impedance, in order to study the adaptivity of the model to environmental disturbances.

The work by Ebadzadeh [163] studied a computational approach to control limb movements by modelling the cerebellar and reflex pathways by means of a circuit whose structure is derived from functional constraints. In particular, motor signals are processed by means of two neural networks, the first trained by an error signal to model the direct function of the biomechanics, and the second trained by the output signal of the first one, in order to learn the inverse function [156, 159, 165]. These two processing steps aim at modelling two functionally different parts of the cerebellum, one to compute direct functions and another to compute inverse functions. After learning, the model is able to drive accurately, that is both in velocity and in position, angular movements of a rod actuated by two pneumatic McKibben muscles.

An ANN controller for ballistic movements has also been proposed in by Bernabucci *et al*. [164] with the aim of presenting a biologically inspired controller. The model and the learning algorithm have been developed with the aim of being as much biologically plausible as possible. The system is able to generate muscular activations knowing only the starting and arrival points of each movement, giving rise to a solution for the inverse dynamics problem, that is determining muscular forces on the basis of kinematic information. This biologically inspired model integrates an ANN, together with a biomechanical arm model, considered as a 2 DOF system, to perform in-silico test. The model gives rise to biologically plausible movements in the sense that muscular activations generating ballistic movements have characteristics similar to human movements, and all the kinematic invariants reported in experimental studies [166-167] are maintained.

The good results obtained by using ANN to model the limb controller and to represent motor learning and its connections with visual, associative and mirror neurons areas are transmigrating toward different research fields such as cognitive robotics [168], or rehabilitation and development of devices to support the disability [169-170].

Goffredo and co-workers in 2008 presented the rationale for a novel Functional Electrical Stimulation (FES)-assisted rehabilitation system for the upper limb driven by a biologically inspired ANN controller such as the one reported in [164]. The system is envisioned to help in the rehabilitation of post stroke hemiparetic patients, by assisting the movement of the paretic upper limb, once trained with a set of movements performed by the therapist or in virtual/augmented reality. The ANN controller, fed by kinematic data extracted by a markerless algorithm working on video images of the limb's movement, has been implemented to provide the stimulation patterns that could be used to drive a smart FES system (called sFES by the authors).

After this overview a question arises, that is: is there a way of using the ANN controller to deal with anomalous motor behaviours dealing with impairment and disability? And with more specific reference to the tremor, that is the main topic of this contribution: how is it possible to use ANN controllers to counteract tremor effects on the limbs?

Recently various tremor control strategies based on FES have been investigated and developed [171-172]: the driving of FES systems by biologically inspired ANN controllers could represent a general answer to the question about limb tremor management. The strategies implemented by FES

systems try to control the tremor by determining the muscle activation patterns needed for active tremor reduction (out of phase muscle activation) and/or semi-active tremor reduction (muscle impedance modification).

The authors would like to enlarge the answer to the question above, by proposing the idea of a novel philosophy for the tremor control therapy. The proposed answer includes a smart controller based on ANN, able to adaptively drive the electrical stimulator device in order to promote the voluntary movement and to concurrently decrease the tremor. In particular, the system should be able to produce the correct electrical stimulus that allows the arm to execute the desired movement without tremor, by implementing either active or semi-active control strategies. This approach, whose preliminary in-silico results are encouraging [173], offers enormous potential impacts on rehabilitation field, and opens a wide span of possibilities for the development of smart protheses and the improvement of quality of life for patients affected by tremor.

CONCLUSION

Tremor is en emerging field in the domain of bioinformatics. Tremor is attracting the attention of scientists from various disciplines, because of the high prevalence of neurological disorders associated with tremor and thanks to the significant progress made these last years in terms of characterization of trembling movements. It appears obvious that advances in signal processing and development of unobtrusive wearable sensors will greatly improve our knowledge of the phenomena which lead to tremorgenesis in the coming decade. Bioinformatic approaches will play a key-role since these events cannot be unravelled without an integrated study based on computer technologies and analysis of neurobiological processes. This will impact directly on the therapies proposed worldwide.

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