THE ROLE OF MECHANICAL RESONANCE IN PHYSIOLOGICAL TREMOR

by

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ABSTRACT

The origin of physiological tremor has been studied for many years. Several central and spinal mechanisms which provide an oscillatory input to the muscles have been proposed. Nevertheless, any neural control signal inevitably has to work upon a resonant peripheral system involving the series-coupled elastic muscle-tendon complex and the inertia of the limb.

In this thesis I look into the potential role for mechanical resonance to explain tremor. First, I show that the resonant component of hand tremor depends on the velocity of hand movement. Movement reduces muscle stiffness (a process called muscle thixotropy) and the tremor frequency falls. Second, I demonstrate that rhythmic tremor is abolished when eliminating resonance by recording tremor in isometric conditions. Third, I replaced EMG by an artificial drive. This generated tremor which behaved similarly to physiological postural and dynamic tremor. Finally, I studied the relationship between EMG and tremor in the transition from posture to movement. Muscle converts EMG into acceleration differently for static and moving limbs.

These findings suggest that there is a key role for mechanical resonance in the generation of physiological tremor. A frequency-specific neural input is not necessary to produce any of the characteristic peaks in postural or dynamic tremor.

DEDICATION

I dedicate this thesis to my parents Ries and Anja Vernooij
for their unconditional support, love and encouragement.

Lieve pap en mam,
Ik kan mijn dank voor jullie niet sterk genoeg uitdrukken.
Zonder jullie was ik niet geweest waar ik nu ben.
Wat is het toch fijn een stabiele, liefhebbende thuisbasis te hebben!

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Last but not least, I would like to thank the *Phoenix Coffee Club* for providing me with the essential liquid black gold that provided me fuel throughout the day.

LIST OF PAPERS AND ABSTRACTS

This thesis includes the following four papers, which correspond to the four experimental chapters:

Lakie M, **Vernooij CA**, Osborne TM & Reynolds RF (2012). The resonant component of human physiological hand tremor is altered by slow voluntary movements. *The Journal of Physiology* **590,** 2471–2483.

Vernooij CA, Reynolds RF & Lakie M (2013). A dominant role for mechanical resonance in physiological finger tremor revealed by selective minimisation of voluntary drive and movement. *Journal of neurophysiology* **109,** 2317–2326.

Vernooij CA, Lakie M & Reynolds RF. The complete frequency spectrum of physiological tremor can be recreated by broad-band mechanical or electrical drive *(submitted)*

Vernooij CA, Reynolds, RF & Lakie M. Muscle automatically adjusts to serve posture and movement *(in progress)*

Also, parts of this thesis have been previously presented at conferences and as a result published in abstract form:

Lakie M, Osler CJ, Reynolds RF, Scott JPR, Stevenson AT & **Vernooij CA** (2013). Increased gravitational force reveals the mechanical nature of physiological tremor. In *Abstracts of Progress in Motor Control IX*, pp. 107–108.

Lakie M, **Vernooij CA**, Osborne TM & Reynolds RF (2011). Human physiological hand tremor results mainly from resonance which changes during slow voluntary movements. In *Abstracts of the 6th international posture symposium*, p. 52.

Lakie M, **Vernooij CA** & Reynolds RF (2012). The role of resonance in physiological finger tremor. In *Proceedings of the Physiology Society 27*, p. C80.

Vernooij CA & Lakie M (2011). Human tremor size reduces with ischaemia due to decreased EMG to muscle gain. In *Proceedings of the Physiology Society 23*, p. PC297.

Vernooij CA, Lakie M & Reynolds RF (2013). Physiological finger tremor size reflects altered mechanical properties of muscle resulting from changes in neural control. In *Abstracts of Progress in Motor Control IX*, pp. 73–74.

Vernooij CA, Lakie M & Reynolds RF (2012). Voluntary vs electrical muscle activation reveals the resonant nature of physiological finger tremor. In *Proceedings of the Physiology Society 27*, p. PC322.

Vernooij CA, Reynolds RF & Lakie M (2011). A decrease in short-range elastic stiffness causes a drop in physiological finger tremor frequency. In *Abstracts of the 6th international posture symposium*, p. 91.

Vernooij CA, Reynolds RF & Lakie M (2013). Physiological finger tremor size mirrors speed of finger movement due to muscle thixotropy. In *Proceedings of the Physiology Society 31*, p. PCD252.

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CHAPTER 1.

GENERAL INTRODUCTION

1.1 Mechanical resonance

1.1.1 What is resonance?

Resonance is the predisposition of any system to vibrate with a certain regularity when exposed to a fluctuating force. The rate at which these oscillations occur is known as the natural frequency. For any sized fluctuating force input at the natural frequency, the system will generate a disproportionally large amplitude oscillation at this frequency. This is referred to as resonance. This resonance-phenomenon is attributable to the system's capacity to store energy and convert it to a different kind of energy. For instance, a spring stores potential energy when it is extended, and, when released, transfers it to kinetic energy. This accelerates an attached mass, which will overshoot its starting point and consequently compress the spring. Without frictional losses, this cycling of extension and compression will go on forever. Thus, in this system, at any time, force produced by the mass (according to Newton's second law) is in balance with force produced by the spring (Hooke's law) (Wikipedia):

$$F = ma = m\frac{d^2x}{dt^2} = -kx, \qquad (1)$$

where F is force, m is the inertial mass, a is acceleration, k is stiffness of the spring and x is displacement. The position of the mass over time t is then described as

$$x(t) = A\cos(\omega t + \varphi), \qquad (2)$$

where

$$\omega = \sqrt{\frac{k}{m}} = \frac{2\pi}{T}. \qquad (3)$$

These equations denote that the position of the mass at a certain time point *t* depends on the phase φ, signifying the starting position of the mass, and maximal displacement *A*. The frequency ω (which is proportional to 1/period *T*) at which the mass oscillates depends on the inertia of the mass and the stiffness of the spring.

If undamped, a system would oscillate perpetually. Any amount of damping in the system would result in a loss of energy and, without additional input, the oscillation transients would eventually die away. The green curve in figure 1.1 gives a typical example of the die-away oscillations of a mass-spring-damper system which is stretched to amplitude A and released. It takes several oscillations for the mass to reach the equilibrium point (x = 0). Damping is a resistive force that is opposite the motion. Often, damping is modelled as being viscous (i.e. proportional to velocity), in which

$$Fr = -cv, \qquad (4)$$

where *Fr* is the resistive force, *c* is the damping coefficient and *v* is the velocity of the mass. This is different from dry friction, which is a constant resistive force. The updated balance of forces is

$$F = ma = m\frac{d^2x}{dt^2} = -kx - c\frac{dx}{dt}. \qquad (5)$$

This can be rewritten to

$$\frac{d^2x}{dt^2} + 2\varsigma\omega_0\frac{dx}{dt} + {\omega_0}^2x = 0, \qquad (6)$$

where ω_0 is the damped frequency of oscillation and

$$\varsigma = \frac{c}{2\sqrt{mk}} \qquad (7)$$

is called the damping ratio (Wikipedia). The behaviour of the system is very much influenced by damping, as it affects the size of the oscillation and its frequency-range (see figure 1.1).

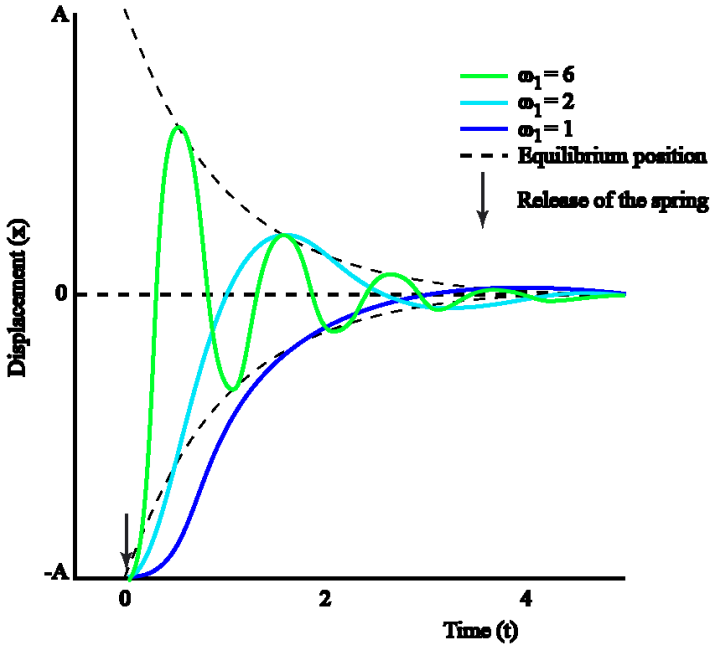


Figure 1.1. Displacement response of a damped oscillator

Displacement of a mass on a spring when released from maximal amplitude position A. Response curves are plotted for three damped systems. Adjusted from Wikipedia

The system is either:

Overdamped ($\zeta > 1$): After stressing the spring, the mass will return in an exponential fashion to the equilibrium position (where $x = 0$). Higher damping ratios generate slower movement to the equilibrium position.

Critically damped ($\zeta = 1$): After stressing the spring, the mass will return as fast as possible to the equilibrium position where it is stable after a single small overshoot.

Underdamped ($\zeta < 1$): After stressing the spring, the mass will accelerate to overshoot the equilibrium position and will start oscillating. The transients die away over time and the equilibrium position is eventually reached. Lower damping ratios lead to higher acceleration and require more oscillations before transients eventually cease. The frequency response of an underdamped system is given by $\omega_1 = \omega_0\sqrt{1-\zeta^2}$.

The sharpness of oscillatory tuning of a system is described by its Q-factor, which is defined as

$$Q = 2\pi \frac{energy\ stored}{energy\ lost\ per\ cycle}, \qquad (8)$$

and which is inversely related to the damping ratio; $Q = \frac{1}{2\zeta}$. The larger the damping ratio, the smaller the Q-factor, and thus the smaller the oscillation is in size and the wider the frequency response centred around the resonance frequency (Lakie et al., 1984).

Besides damping, the size of a resonance oscillation is dependent on the frequency content of its driving source (Knudsen & Hjorth, 2002). Equation 6 is then rewritten as

$$\frac{d^2x}{dt^2} + 2\zeta\omega_0 \frac{dx}{dt} + {\omega_0}^2 x = \frac{1}{m} F_0 \sin(\omega t) \qquad (9)$$

A system driven by a force F_0 solely at resonance frequency $\omega_r = \omega_0\sqrt{1-2\zeta^2}$ will generate an exceptionally large amplitude as the driving force is always in phase with the resonance movement. This is depicted in figure 1.2: the phase between the driving force and resulting velocity will shift by 180^o and runs through 0^o at the resonance frequency (Knudsen & Hjorth, 2002). At resonance, the inertia and spring stiffness cancel out and the only resistance is due to the damping, i.e. force depends entirely on velocity. Therefore, the slope of the phase shift is determined by damping. When damping is substantial the shift is gradual, whereas with zero damping the phase shift is instant. The lower the damping, the steeper the slope. When the deviation between the driving frequency and the resonance frequency increases the resulting amplitude will decrease; there are less time points when drive and resonance are in phase. A classical example of this driving mechanism is the timing of pushing a child on a swing. The relationship between damping, the driving frequency and resonance is given by figure 1.2.

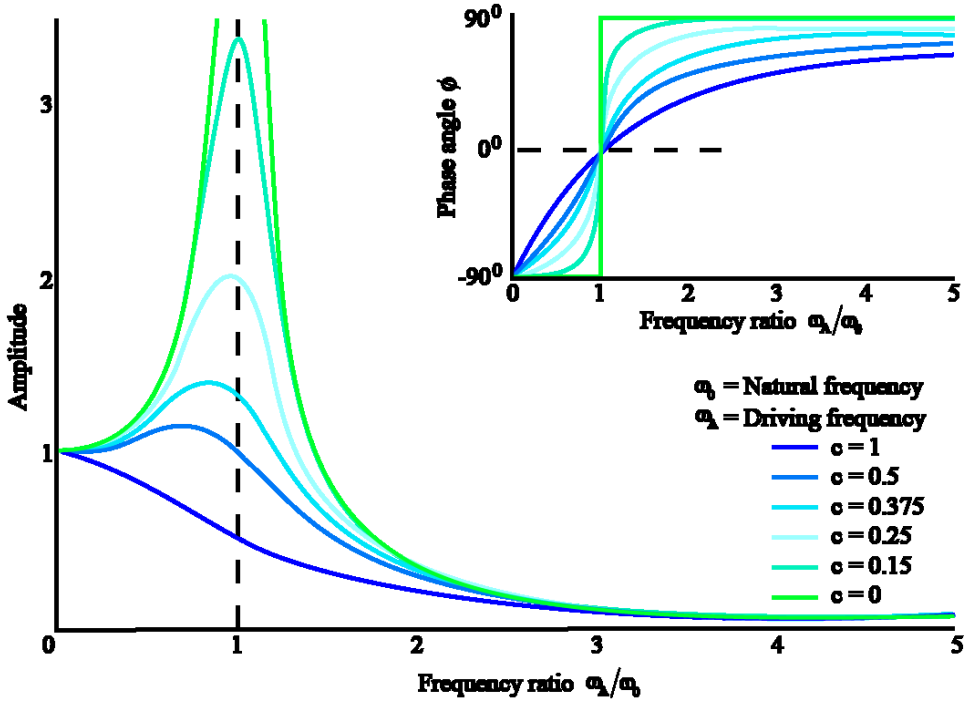


Figure 1.2. The effect of damping on the amplitude and phase of resonance

The relationship between the driving frequency (ω_A) and the resonance frequency (ω_0) is displayed on the x – axis, amplitude is shown on the y-axis. The larger the deviation between ω_A and ω_0, the smaller the amplitude. This relationship is affected by damping, c, in that larger damping leads to a decreased amplitude response. The inset shows the effect of damping on the force-velocity phase relationship between ω_A and ω_0 (Redrawn from Dr Chan http://personal.cityu.edu.hk/~bsapplec/forced.htm)

Resonance can occur in several forms. Some examples are: electromagnetic resonance (such as used in X-ray scans and microwaves), nuclear magnetic resonance (which is used in MRI scans), and optical resonance (used to produce laser beams). Probably the most familiar is mechanical resonance, which is the oscillation inherent to any physical body when it is given a tap or fluctuating input force. In this piece of work, I solely discuss mechanical resonance.

1.1.2 Mechanical resonance

Every physical object has a mechanical resonance. When a physical body is disturbed, it will (visibly or invisibly) oscillate at its natural frequency. This mechanical property is purposefully utilised in many devices like mechanical metronomes and watches. A special

type of mechanical resonance, acoustic resonance, forms the human voice and is used to produce (loud) sounds in musical instruments.

The magnitude and frequency of a mechanical resonance are dependent on three main parameters: stiffness, inertia and damping of the body. The mechanical resonance frequency (RF) is defined by:

$$RF = \frac{1}{2\pi}\sqrt{\frac{k}{J}} \qquad (10)$$

and the sharpness of tuning (Q-factor) is defined by:

$$Q = \frac{1}{c}\sqrt{kJ} \qquad (11)$$

where k is stiffness, J is inertia and c is damping. From these equations it can be deduced that

I. $RF^2 \sim k$

II. $RF^2 \sim -J$

III. $Q \sim c$

Avoiding mechanical resonance in engineering constructions can be crucial. Failing to do so can have disastrous consequences when the resonance amplitude gets too large. Resonance can start with a tiny periodic input, such as wind gusts, but the resulting vibration can grow drastically as with repeated input at the natural frequency of the mechanical body the resonance oscillation will increase in a similar fashion to positive velocity feedback. The Millennium Footbridge in London is a famous example of this kind of positive feedback oscillation (Strogatz et al., 2005). Walking on the bridge causes a slight lateral oscillation of the bridge, which in turn entrains walking steps, therefore increasingly amplifying the bridge's sway up to ~70 mm in the centre span (Dallard et al., 2001).

1.2 Mechanical resonance in the human body

As any physical body, the human body exhibits mechanical resonance. In fact, every body part and each limb resonates, and all have a different resonance frequency. The resonance frequency and size of the oscillations will depend upon the mechanical characteristics of the body part. If multiple series-coupled body parts are able to move freely, e.g. the arm, hand and finger segments, the resonances of the individual body parts will start interacting with each other and a more complicated overall resonance will be generated at the end point (e.g. fingertip).

1.2.1 Damping in the human body

Although not many mammals have been studied, it is generally believed that mammalian joints are naturally lightly damped (Lakie et al., 1984; Walsh, 1992). This is a useful survival mechanism, as light damping facilitates large and fast movement. Therefore, you can be fast when you want to be fast (e.g. flight/fight reactions or some reflexes). But this is not so useful when you want to be stationary, as any small perturbation elicited internally, like the fluctuating EMG drive or breathing movement, or by external causes will generate small die-away transients in the body. Limbs will therefore always show small resonance oscillations.

Any natural damping acting around joints reduces the amplitude of generated resonance oscillations (According to figure 1.2, e.g. Bach et al., 1983; Gielen & Houk, 1984; Harris & Wolpert, 1998; Lakie et al., 1984; Stiles, 1983). Mechanical damping in the human body acts to aid postural stability (Lakie et al., 1984), especially in limbs prone to resonance. Without damping, any (internal or external) input to limbs will inevitably make them oscillate uncontrollably until actively suppressed. High amounts of damping also have a slight reducing effect on the resonance frequency (see figure 1.2) as it makes responses to

an input slower, but this effect is negligible for lightly damped (c ~< 0.25 Nms/rad) structures.

While having a distinct meaning, the terms 'damping' and 'viscosity' are both used in literature to indicate a similar phenomenon. Viscosity is a type of mechanical damping which is dependent on the velocity of the oscillations. Besides viscosity, dry friction supplies a constant damping force. Lakie, Walsh & Wright (1984) drove the passive hand with different sizes of torque. They showed that the peak velocity of the hand in response to this drive increased linearly with larger torques (their figure 7). This implies that damping is mainly viscous in nature. It is noteworthy that the intercept of the relationship between peak velocity and torque did not project to zero. This means that there is some additional damping in the body for very small movements, potentially due to some static friction (stiction) in the muscle. Lakie and colleagues also demonstrated that damping can be counteracted by positive velocity feedback. This method makes the input to the system dependent on what the system does. Force is applied to the system in such a way as to increase its velocity. The system's natural damping is vitiated and it breaks into oscillation at its natural frequency. Together these observations by Lakie and colleagues led to the belief that damping in the human body is largely viscous, and thus the two terms are indistinguishable and interchangeable. I will use the term damping throughout this manuscript.

1.2.2 Stiffness in the human body

Limb joint stiffness is mainly determined by the combined stiffness of the series-coupled muscles and tendons associated with the wrist and fingers (e.g. Kistemaker et al., 2007). In addition, the capsule ligament complex provides some stability and rigidity to joints, but

this is minimal (Kuo & Deshpande, 2012). This latter complex will therefore not be discussed here.

1.2.2.1 Muscle stiffness and thixotropy

The basic structures of the muscle are shown in figure 1.3. It has been known for long that extrafusal muscle and muscle spindles do not have a constant stiffness (Denny-Brown, 1929). In static conditions muscular stiffness is high, whereas in dynamic conditions muscular stiffness is relatively low making stiffness highly non-linear. Denny-Brown (1929) discovered a history dependent character of this stiffness, which he called preliminary or stationary rigidity.

Hill (1968) looked into muscle non-linearity and showed that isolated muscle fibres display a small filamentary resting tension (FRT) and a high resistance to initial movements which he called the short range elastic component (SREC). He believed both of these features to be due to a small number of cross-bridges attached between actin and myosin filaments in the muscle. A small stretch of the muscle within the SREC-limit would initially stretch these cross-bridges and sharply increase the muscular tension. A continued stretch exceeding the SREC-limit would break the cross-bridge bonds and a cycle of detachment and reattachment of actin-myosin-bonds would evolve. This is associated with a drop (or at least a failure to rise) of tension, due to the reduced overall number of attached cross-bridges. This is shown in figure 1.4, where 2 successive stretches are applied to a muscle fibre. The first stretch of the muscle fibre leads to an initial sharp peak in the produced tension after which tension drops slightly and then changes much less with stretch.

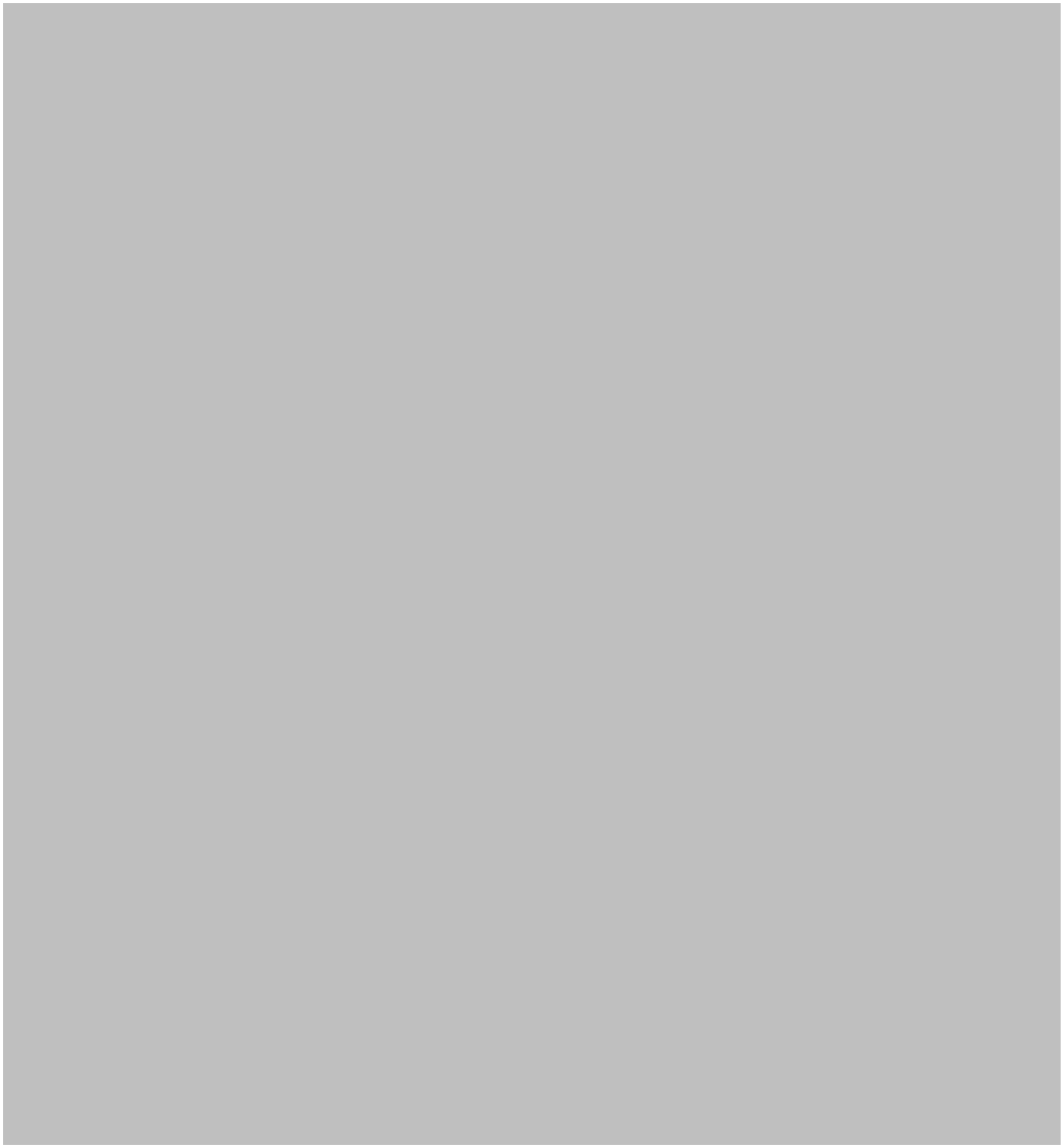


Figure 1.3. The main structures of the muscle

A diagrammatic representation of the main structures present in skeletal muscles. More detail, including the thick and thin filaments as well as the titin strings, is described in the lower figures (© 2004 Pearson Education, Inc., publishing as Benjamin Cummings).

The short-range elastic limit and recovery rate are very hard to determine, as it depends on several characteristics including the velocity of the stretch and the amount of free flowing Ca^{2+} (for an overview, see Campbell, 2010). It is shown in muscle fibre preparations that fibre stiffness drops with ~ 0.4% length change of the original resting length of the muscle fibre (Campbell & Lakie, 1998). If a subsequent rest is allowed, more cross-bridges will slowly be formed again (over many seconds) and stiffness will rise. If only a short rest period is allowed after which a second stretch is applied, muscle stiffness will still be low and a much smaller peak at the initial stages of the second stretch is apparent (see figure 1.4, second stretch).

The SREC and therefore the muscle fibre stiffness are thus dependent on the (recent) history of movement. They are thixotropic (e.g. Axelson & Hagbarth, 2001; Campbell & Lakie, 1996; Loram et al., 2007; Proske et al., 1993). The cross-bridge model is considered a scientific paradigm to explain the thixotropic behaviour of muscle fibres. Although it

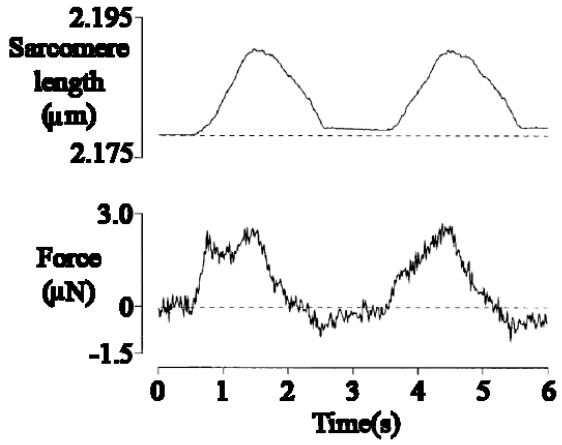


Figure 1.4. Effect of the short-range elastic component

The result of stretching a single relaxed frog leg muscle fibre in response to two triangular stretches of ~0.02µm (1% resting sarcomere length). The two stretches had a constant velocity (1% resting sarcomere length per second) and are separated by a 1s rest period. Resulting fibre length and force are shown. As the sarcomere length is altered, the tension produced by the muscle fibre does not follow in a linear way. There is a sharp increase in force at the initial stages of the first stretch, created by the short range elastic component (SREC) of cross bridge bonds. Any stretch surpassing this SREC will break the bonds and tension will change much less. The SREC is smaller for the second stretch (copied from Campbell & Lakie 1998)

implies cross-bridges reattach and produce force at different rates (Campbell & Lakie, 1998; 1996) and contentious alternatives exist e.g. non-linear contributions of titin (Bianco et al., 2007; Campbell, 2010; Proske & Morgan, 1999), the balance of evidence points towards a mechanism based on cross-bridges.

While it is easy to identify the mechanical characteristics of isolated muscle and muscle fibres, quantifying muscle responses in the intact system is less straight-forward because of interactions with diverse structures like the tendon and the uncertainty of an unchanging neural input. Consequently, conclusions on overall responses of the musculoskeletal system cannot solely be based on isolated muscle preparations. Early non-isolated experiments measured tension in tetanised cat soleus and gastrocnemius muscle during lengthening and shortening movements (Rack & Westbury, 1974). They found that, when stretching the muscle, tension rose sharply as a consequence of small amplitude stretches, but resistance decreased if the stretch continued. The cat's muscle thus showed a short-range elastic component very similar to what Hill described in isolated muscle fibres. They referred to this more generally as short range stiffness (SRS). The thixotropic properties seen in muscle fibres thus also arise from passive muscle and are a mechanical characteristic of intact muscle as well as isolated fibres.

When relaxed and passively stretched very slightly, the muscle will only produce a low tension (a few percent of maximal force, probably because of passively cycling cross-bridges (Campbell, 2010)). However, because the small tension change is produced by a very small length change this equates to a substantial stiffness. This stiffness will be significantly reduced when the muscle is passively stirred breaking all passive cross-bridge links. When voluntarily activated, many more cross-bridges form and the muscle tension levels go up. Muscle stiffness will be very high when the muscle is activated but not moving, like in position holding tasks.

But active muscle stiffness is also subjected to a dependence on the history of movement. Experiments in non-isolated human active muscles have shown that for small to intermediate movements, there is a considerable overall drop in muscle stiffness. Loram et al. (2007) used slow, low frequency rotations of the ankle while tracking length changes of the soleus and gastrocnemius muscle with ultrasound. They calculated that the muscle stiffness showed a non-linear reduction with slow movements to ~ one fifteenth of the static value. The high value when static was attributed to the series elastic component. The change in intermediate to large movement was only small, presumably due to cycling cross-bridges. Additionally, it has been shown that after movement, the muscular stiffness slowly increases again over several seconds (Lakie & Robson, 1988). This thixotropic behaviour of muscles is in line with the proposed cross-bridge model of muscle fibres, in which during movement the cross-bridges show a cycling behaviour (resulting in a relatively low muscle stiffness), while after movement and during posture more cross-bridges slowly become attached, stiffening the muscle up. Consequently, as resonance depends on stiffness (equation 10), the limb's mechanical resonance is dependent on past and present movement.

The thixotropy of muscles might be a useful mechanism of promoting *stability* during posture but *speed,* and thus *power,* during movement. During posture, muscles are stiff and thus will not be much affected by internal or externally provoked perturbations. With movement, muscular stiffness is decreased. The produced net force per unit input depends on the presence of passive fibres in the muscle and other muscles acting around the same joint. Active muscle fibres are shunted by these passive fibres. The net force produced is the total force minus the force required to deform these passive ('shunting') structures. With increased movement there are fewer stiff passive fibres and thus less shunting. As a result, the net force output per unit neural input increases, making the force production of

muscles dependent on movement (i.e. thixotropic). This increase in muscular gain thus allows for forceful contractions, producing larger and faster movements, thereby preventing a continuous fatigue of muscles during movement.

When the muscle produces force, it low-pass filters the neural input signal. Studies examining muscle properties of the cat (Bawa et al., 1976a; Mannard & Stein, 1973) and human (Bawa & Stein, 1976; Stein et al., 1972) show that muscles behave like a second-order low-pass filter. This is true for voluntarily activated muscle as well as when the muscle nerve is artificially activated by single or trains of electrical impulses. Consequently, muscular force fluctuations drop with higher frequencies. Where large force fluctuations can prevail at low frequencies, only small force fluctuations are possible at higher frequencies. At high frequencies, the size of force fluctuations falls off rapidly, and, independent of the overall level of force, the muscle contraction will take on the form of a semi-fused tetanus at frequencies > ~20 Hz (Bawa & Stein, 1976). As the muscle drives the limb resonance, the input to the resonance can be large at low frequencies, but will always be small at higher frequencies. Any higher frequency resonances would therefore be driven by a relatively small force input.

1.2.2.2 Tendon stiffness

Compared to the muscle, tendon has a relatively simple structure. Tendons are made of strands of fibrous connective tissue. At one end, they are connected to bone through the osteotendinous junction, at the other end they are connected to the muscle at the myotendinous junction. At this latter site, the force generated by muscular contractions is passed on to the tendon which will pull on the attached bone. Any tendon must thus bear an identical tension as its series-coupled muscle. Length changes in response to an applied stretch depend on the relative stiffness of the muscle and tendon. Proske & Morgan (1987)

present a few complex methods of measuring stiffness in isolated and intact tendon and the response to movement. More recently, it has also been possible to estimate the stiffness of tendinous tissue more simply and directly *in vivo* by ultrasonography (Fukashiro et al., 1995; Maganaris, 2002) and to measure interactions between muscle and tendon (Fukunaga et al., 2002).

During low to intermediate level voluntary contractions and steady state tensions, tendon stiffness is low compared to muscle stiffness (estimated to be ~one fifteenth during active stance (Loram et al., 2007)). This is due to the high compliance inherent in the tendon under these conditions (e.g. Fukashiro et al., 1995; Griffiths, 1991; Ito et al., 1998; Muramatsu et al., 2001). Because of its compliance, the tendon can 'absorb' large proportions of externally applied movement perturbation before the muscle gets stretched beyond its SREC (e.g. Morgan et al., 1978) as springs with a low stiffness store more energy. With stretch, tendon stiffness progressively increases (Maganaris, 2002). Where tendon stiffness is low during low strain, it becomes high at very large stretch lengths.

1.3 Physiological finger tremor

Resonance emerges most in distal limbs. This is due to their relative light mass and long tendinous and muscular connections to bone, which make the limb unstable and hard to control. The resonant frequency depends on both the limbs stiffness and mass (see equation 10). In effect, extra mass can be compensated by extra stiffness, so different limbs can have similar or very different resonance frequencies. When the limb is outstretched, the heavy forearm has a natural frequency of ~ 3 Hz (Fox & Randall, 1970), whereas the hand is thought to have a resonance frequency of ~ 8 Hz (Lakie et al., 1984), and the much lighter finger is estimated to resonate faster, at ~ 25-28 Hz (Lakie & Robson, 1988).

Interestingly, the resonance frequencies seem to correspond well to the physiological tremor frequencies of the limb. Physiological tremors are uncontrolled approximately sinusoidal limb oscillations with a peak at a limb specific frequency (see figure 1.5 for an example of finger tremor at ~ 26 Hz). In everyday activities these tremors are usually too small to perceive, but they can become more pronounced; e.g. when we are stressed or fatigued. Also, there is a large variation of tremor sizes. Some subjects display ~ 10 to 100 times more tremor than others (e.g. Lakie, 2010; Lakie, 1992). Tremor oscillations can be measured by their amplitude, velocity or acceleration. As the fluctuation frequency between these measures is identical, but is largest in size for acceleration (see figure 1.5), and it is very easy to measure acceleration with accelerometers which are now cheap and readily available, usually only acceleration spectra are displayed and used for analyses.

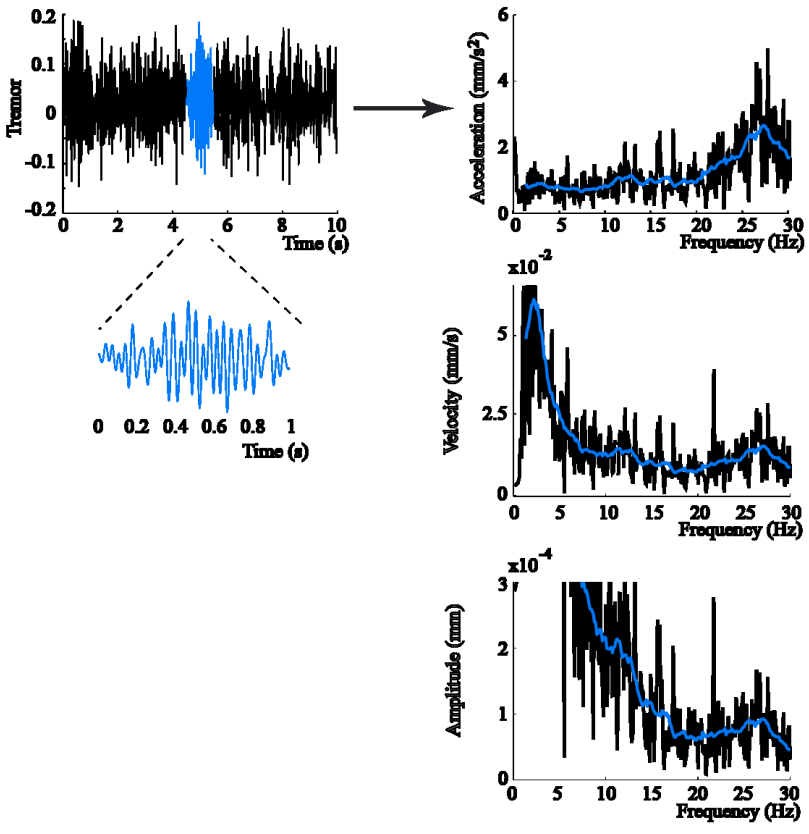


Figure 1.5. Raw tremor trace and its frequency spectra

A raw tremor acceleration trace of a static physiological finger tremor recording (left top), zoomed in to a 1 second period underneath. Clear almost sinusoidal oscillations can be seen in the bottom trace. The panels on the right show the associated frequency spectra of acceleration (top), velocity (middle) and position (bottom). In all of these spectra increased oscillations around 26 Hz are shown, but they are most prominent in the acceleration record because the 'DC offset' due to voluntary control < 5 Hz is filtered out. Additionally, a small bump ~11 Hz can be seen on all three records.

Besides these healthy tremors, some essential and pathological forms of tremors exist, of which Parkinsonian tremor is by far the most well-known. These tremors have a clear central degenerative cause with distinct characteristics. They are a few magnitudes larger than physiological tremor and display a lower peak frequency (e.g. Raethjen et al., 2000a). Although I will allude to pathological tremors sometimes, they are not the main topic of this piece of work. When referring to solely 'tremor', physiological tremor will be meant.

The cause of physiological tremors has been studied for many years, ever since Schäfer's impression that voluntary contractions in man seem to be produced by on average 10 nervous impulses per second (Schäfer, 1886). However, different views on the origin of tremor still exist in the literature. Several reviews have been written on the cause of physiological tremors, showing the widespread nature of central and peripheral explanations. Suggestions put forward cover central oscillations, spinal reflexes, Renshaw cell inhibition, motor unit synchronisation and peripheral resonance mechanisms (see for reviews e.g. Elble, 1996; McAuley & Marsden, 2000).

We have discussed above that limbs have an inherent resonance. This peripheral mechanism will impose small resonance oscillations on limb position and thus it will inevitably manifest in tremor records in some way. However, in general it is thought that at least some parts of the frequency spectrum of tremor are due to central or spinal neural oscillations. We control our body with some regularity, and positional adjustments are relatively large at < 5 Hz (see figure 1.5). Additionally, neural oscillations in the human body could arise, for instance through alpha rhythms in the primary motor cortex (e.g. Williams et al., 2009). It would therefore not be unreasonable to expect some neural influences on tremor at the frequency range which they work (usually suggested 8-10 Hz). Sometimes, increased tremor power around 8-12 Hz is attributed to a synchronous firing of individual motor units (Christakos et al., 2006; Halliday et al., 1999; Lippold, 1970). This

is in line with spinal feedback delays operating at ~ 50ms. Recently, more attention has been paid to the concept of a central oscillator (after Vallbo & Wessberg, 1993), actively and purposively controlling motor units at ~10 Hz (e.g. Bye et al., 2010). Where central or spinal synchronisation is involved, either mechanism would produce a characteristic peak at ~10 Hz in the EMG. This drive will inevitably produce synchronous tremor at this frequency. Such synchronous electrical and mechanical behaviour would be an expected hallmark of neural drive.

Where there is a peripheral resonating mechanism, any neural input to the muscles will have to work upon this resonance. For an input composed of a narrow band of frequencies (or a single frequency) at the limb's resonant frequency, driving will occur and the tremor will get very large (see figure 1.2). If the main frequency of the input force is at a different frequency, the peak at the limb's resonant frequency will be smaller. If the difference in frequencies is small, the peaks could merge and only a single peak frequency may be observed. Conversely, if the difference is large, two distinct oscillation frequencies may arise (e.g. one at the main frequency of the input force and one at the resonance frequency of the limb). For an input composed of a very broad band of frequencies or with equivalent power at all frequencies (as in the case of random noise), a specific tremor frequency will still be generated due to the mechanical resonance in the limb. Here, I look at the peripheral resonance mechanism and test what the effects are of different kinds of input and conditions.

1.4 The effect of different kinds of input and conditions on finger resonance

To illustrate the effect of different kinds of input and conditions on tremor, I choose to describe tremor of the finger. To consider the effects of different kinds of input and

conditions on tremor generation in a resonant limb, the limb can be modelled as a second order damped oscillator (e.g. Fox & Randall, 1970). When considering the effects of resonance mechanisms only, this model can be driven with a white noise input. This would be similar to broad-band EMG forcing of the finger by which any characteristic tremor would be generated by peripheral mechanical resonance properties of the muscle-tendon-limb complex. Alternatively, the model can be driven with an input which has a larger amplitude at certain frequencies. This would be representative for a finger in which the muscle receives a frequency-specific neural input.

In this section I will discuss different conditions under which finger tremor has been studied. In the final part of the section, these conditions will be tested in a computational model of a second order resonator.

1.4.1 Conventional postural tremor

Several studies have shown that 'normal' surface EMG corresponds to broad-band forcing. Especially at low intensity activation, like during the control of normal postural tremor, there is nothing 'special' about EMG. It contains no prominent component at the frequency of the tremor (e.g. Lakie et al., 2012; Raethjen et al., 2000b; Timmer et al., 1998b). Sometimes there is some synchronisation between motor units which causes an increased EMG size at a specific frequency-band. This is particularly seen when the tremor is very large. Possible reasons for such a rhythmicity are introduced in section 1.4.5 and section 1.4.6.

If the EMG shows no prominent peak at the tremor frequency, it can be conveniently regarded as white noise. This implies that there is also no frequency-specific neural drive of the muscles and any tremor peak is generated by resonant properties of the limb. This condition represents the easiest possible setting for the computational model, where the

input is white noise and typical physiological values are used to define the resonance. In section 1.4.7, this tremor is modelled. It will be seen as a default situation against which other conditions can be evaluated.

1.4.2 The effect of increased inertia

The first indication that tremor may have a resonant component rests on pioneering experiments investigating the effect of increased limb inertia by artificial loading. Added inertia will have an obvious decreasing effect on the frequency of the resonance oscillations (see equation 10), but will not influence a centrally generated tremor. Stiles & Randall (1967) added inertia to the distal phalanges of the index or middle finger and found the high tremor frequency to reduce from ~ 25 Hz to ~ 15 Hz when adding a weight of 25 g. Many studies since have shown that the tremor frequency of the finger readily decreases when inertia is added to it (from ~25 Hz variably to 7.6 or 15 Hz; e.g. Halliday et al., 1999; Hwang, 2011; Morrison & Newell, 2000). However, Halliday & Redfearn (1956) report that there is no drop in the frequency spectra when loading the finger up to 100 g, although their graph indicates differently. Elble & Randall (1976) report a *rise* in the 8-12 Hz component when masses of 200-500 g were suspended from the middle finger, but this excessive loading must have induced large changes in muscle activation. Overall, literature agrees that artificially adding inertia to the finger decreases the tremor frequency.

In section 1.4.7, the resonant effect of adding an artificial load to the finger is simulated. In common with all real experiments using this approach we ignore the associated likely changes in stiffness. When an increased load has to be held against gravity, a larger part of the muscle will be active. This will increase the muscular stiffness, which in turn will increase the resonant frequency. It is worth emphasising that the increased muscle stiffness may actually make little difference to the overall stiffness or to the resonance, because it is

in series with a compliant tendon (see section 1.4.3 and figure 1.6). Accordingly, for the model we disregard the effect which added load has on stiffness as it would complicate the interpretation of the results. The effect of increased stiffness is examined hereafter.

1.4.3 The effect of increased stiffness

The effect of a change in muscle stiffness on the overall stiffness, and thus the resonance frequency, is shown in figure 1.6. The typical tremor result was modelled with a muscle-to-tendon stiffness ratio of 15:2, leading to an overall stiffness of 1.76 Nm/rad (see appendix for reasoning for these values). This generated a resonance frequency of 19 Hz.

A large increase as well as a large decrease in muscle stiffness can be simulated. A reduction in muscle stiffness of a factor of 15 results in a large decrease in overall stiffness and resonant frequency. In contrast, increasing muscle stiffness by a factor of 15 has only a

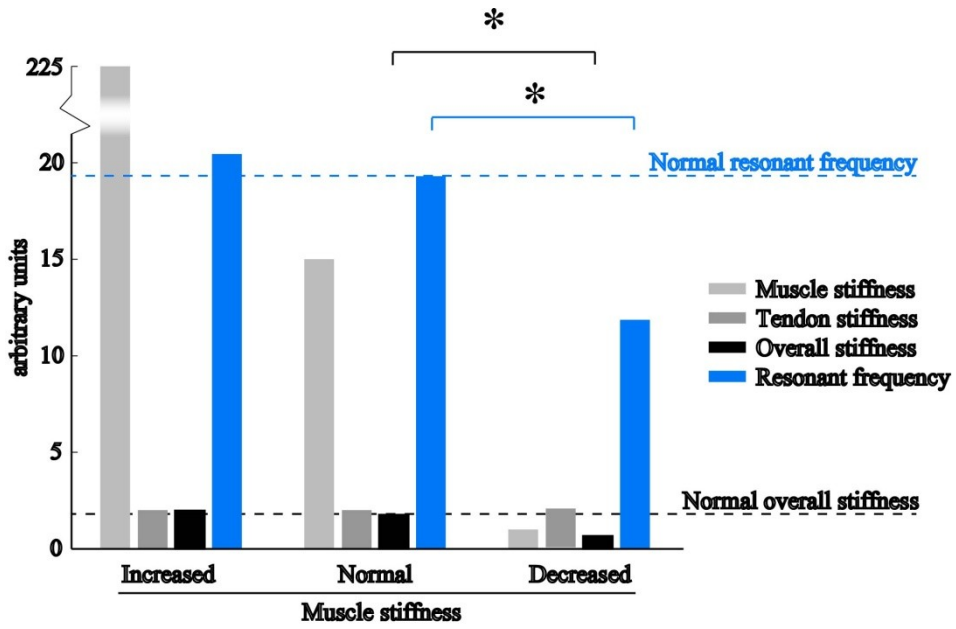


Figure 1.6 Illustration of the effect of increased and decreased muscular stiffness on the overall stiffness and on the resonant frequency.

Under normal finger settings, the muscle-to-tendon stiffness ratio was estimated to be 15:2 for the model. The overall stiffness of the system is very similar to the tendon stiffness, and the resonant frequency is ~19 Hz. Thixotropy would decrease the muscular stiffness ~15 times, but would not change tendon stiffness. This results in a decreased overall stiffness and resonant frequency. Muscle stiffness is increased when large forces are produced. When increasing the normal muscle stiffness by 15 times, the increase in overall stiffness is only minor because of the limiting effect of tendon compliance.

small effect on the stiffness. This is because a system is only as strong as its weakest component, and thus the overall stiffness is limited by the series coupled compliant tendon. Consequently, the resonant frequency does not change very much with increased stiffness. Only when high forces are used, which stretch the tendon to a region in which it is considerably stiffer, does the joint stiffness show a substantial increase. This is because the tendon is then stretched to a region where its stiffness increases dramatically in the same way as stretching a sock.

Increased joint stiffness arises when one applies co-contraction. Tendons and muscles provide stability and tension to the joints they are acting upon. It has been shown that joint stiffness goes up with co-contraction in the upper arm (Morrison & Newell, 2000), forearm (MacKay, 1984), hand (Milner & Cloutier, 1998) and finger (Daneault et al., 2011). This can be explained simply by activation of a larger cross-sectional area of the musculature (Schantz et al., 1983), which correlates with an increased muscle stiffness (Given et al., 1995).

In combination with the stiffer tendon described above, this increases the stiffness of the joint. Co-contraction is not commonly used in static postures as it is an inefficient control strategy. The only study that was found on co-contraction in finger tremor (Daneault et al., 2011) examined the subject's ability to reduce tremor amplitude with or without co-contraction. With co-contraction, an increase in tremor amplitude was found, and tremor frequency dropped. Unfortunately, their tremor records show large positional deviations during co-contraction, which has important consequences for the resonance produced by the limb (as discussed in the next paragraph). Therefore, conclusions on the effect of co-contraction from their results are not straightforward.

Joint stiffness also increases when a large external force has to be counteracted (e.g. Bawa et al., 1976b; Gallasch et al., 1997; Stein & Oğuztöreli, 1976b). The effect of increased stiffness due to an external force, but not inertia, was studied by examining forearm tremor under elastic loads (Joyce & Rack, 1974; Matthews & Muir, 1980). Subjects had to produce biceps force against springs which each had a different inherent stiffness. The tremor frequency of the forearm went up progressively with increasingly stiff springs. This result is predictable as these springs become part of the resonating system, which will inevitably have a higher stiffness with increased spring stiffness. McAuley et al (1997) applied a similar technique, but found different results for the index finger when abduction movements against an elastic band attached to a strain gauge were made. No less than three peak frequencies were discovered (at 10 Hz, 20 Hz and 40 Hz) in the power spectra of both tremor and EMG. None of the peaks changed in frequency when increasing force from 12.5% MVC to 50% MVC. They therefore concluded that all three peaks are central in origin. The ambiguity with their results is that the elastic bands might have an inherent resonance, which will make the interaction between the finger and band unclear. Additionally, there is the uncertainty of whether the frequencies are harmonics. Also, there have been similar experiments contradicting the appearance of three peaks (e.g. Conway et al., 1995; Taylor et al., 2003). This dispersion of results keeps matters inconclusive.

In section 1.4.7, the effect of increased stiffness in a resonant limb is examined. No distinction has been made between an increased force applied internally (by co-contraction with the antagonistic muscles) or externally (e.g. by counteracting springs or elastic bands). As said above, an increase in muscular stiffness will not have a large effect on the resonant frequency because the low stiffness of the series-coupled tendon puts a limit on the maximal stiffness of the system. Importantly, no such limit applies to a *decrease* in overall stiffness.

1.4.4 The effect of decreased stiffness

Decreasing muscular stiffness has a large effect on the overall stiffness, and thus on the resonant frequency. We have seen above that muscle activity *increases* its stiffness. How can muscular stiffness be reduced? When moving the limb actively or passively, the attached muscles will move. As described in section 1.2.2.1, muscles are thixotropic; their stiffness depends on movement. During, and for some time after, movement the muscle stiffness is low. This reduction with movement decreases the overall stiffness considerably (see figure 1.6). Consequently, this would greatly reduce the frequency of the resonance component of tremor. Such low frequency tremor is indeed observed during movement.

There are several studies published on finger tremor during movement (e.g. Bye & Neilson, 2010; McAuley et al., 1999; Vallbo & Wessberg, 1993), but there are only a few which directly compare this dynamic tremor with postural tremor in a systematic way (Daneault et al., 2011; Hwang et al., 2009a; Vernooij et al., 2013c). In general, it is shown that dynamic tremor is much larger and at a very much lower tremor frequency (8-12 Hz) than postural tremor (> 20 Hz). However, the low frequency tremor during movement is usually not attributed to resonance, but to a central oscillator.

1.4.5 Tremor as a consequence of a central oscillator

There has been an interest in the role of central oscillators in postural tremor for many years. This long-standing belief that oscillatory activity in the human cortex causes tremors started with suggestions that the alpha rhythm (at ~ 10 Hz) and beta rhythm (at ~ 15 Hz) closely corresponded to frequencies appearing in motor nerve discharges (Jasper & Andrews, 1938). This was directly opposed to the original observations of Horsley and Schäfer, who thought the 10 Hz rhythmicity was independent of the rate of cortical excitation (Horsley & Schäfer, 1886), which was indeed shown to be incorrect afterwards

(Lindqvist, 1941). Llinas and colleagues proposed a rebound excitation model of central oscillators (Jahnsen & Llinás, 1984; Llinás & Volkind, 1973). Based on *in vitro* slices on the guinea pig diencephalon and tetanised cat cortex, they suggested that central tremor is generated through a central control loop by oscillation properties of thalamic cells or afferent connections of the cerebellum (e.g. inferior olive). However, any reported coherences are small and the direction of causality is ambiguous (Williams et al., 2009). Although these regions might be involved in the generation of essential tremors (Raethjen & Deuschl, 2012), their involvement in physiological tremor is questionable as experiments are tenuous (e.g. comparison of in vitro guinea pig diencephalon vs in vivo human diencephalon).

One consequence of a central oscillator is that it should produce an inevitable interaction between the phase of postural tremor and voluntary movement initiation. There is evidence for and against such an interaction (Goodman & Kelso, 1983; Gross et al., 2000; Lakie & Combes, 2000; Riddle & Baker, 2006; Tiffin & Westhafer, 1940; Travis, 1929). Goodman and Kelso (1983) reiterated the results by Travis (1929) and Tiffin and Westhafer (1940), showing that voluntary movements are in phase with tremor. This could be advantageous for limb control as the tremor could be 'used' as part of the movement, and it could explain some of the variability in observed reaction times. Conversely, Lakie and Combes (2000) used modern techniques to study this subject and found no difference in reaction time when stimuli were presented at different phases of the tremor cycle. This latter study makes a strong case against the influence of a central oscillator on postural tremor.

While there is little evidence to support central oscillators in postural tremor or their involvement in the transition from static posture to movement, it has become common to regard central oscillators as causing tremor during movement. This would mean that when moving, the neural input to muscles contains an increased amount of power in a narrow

band of specific frequencies which drives the large and slow tremor that is observed. This kind of drive is believed to be absent during posture, causing a qualitative difference between tremor during posture and movement. This could explain why there is such a large difference in tremor characteristics between the conditions.

The belief that central oscillator produces the dynamic tremor frequencies is mainly based on work of the group of Vallbo, Wessberg & Kakuda. They found a clear rhythmicity in output to muscles (either EMG or individual motor units) 6-12 Hz with slow flexion and extension movements of the finger or hand (Kakuda et al., 1999; Vallbo & Wessberg, 1993; Wessberg & Kakuda, 1999; Wessberg & Vallbo, 1995, 1996). The rhythmicity was observed not only in the agonist, but also in the anti-phased activity pattern of the antagonistic muscle. This resulted in concomitant small jerks manifesting in the finger and hand at this frequency, but only when they were moving. Such discontinuities were virtually inexistent in postural conditions or only seen at the very start of a postural phase, suggesting this is a special feature of movement control. Based on this result, Vallbo & Wessberg (1993) concluded that there is a qualitative difference between postural tremor and the jerks seen during movement.

Recently, a study presented a computational model based on Vallbo's work which aimed to stress the necessity of this 10 Hz central-neurogenetic tremor peak (Bye & Neilson, 2010). In their model, purposive movements consist of small submovements of a fixed duration, which they call basic units of motor production (BUMP). BUMPs are produced by an intermittently operating response planning system, controlling daily life activities at 10 Hz. During posture, simulating a situation where the limb is held outstretched, the model does not produce 10 Hz oscillations. Critiques on this movement-specific intermittency in control lie in studies showing 10 Hz modulations during posture as well as movement (e.g. Carignan et al, 2010; Elble, 2003; Hwang et al., 2009b; McAuley et al., 1997; Stiles &

Randall, 1967), intermittent control at slower intervals (~200-500ms, Van der Kamp et al., 2013; Loram et al., 2011; Navas & Stark, 1968) and the appearance of a 10 Hz peak in tremor but not in the associated EMG (Lakie et al., 2012; Raethjen et al., 2000b).

The larger, slower tremor during movement can be alternatively explained by the thixotropic reduction in muscle stiffness and resonant frequency (see section 1.4.4) which is often not taken into account. Lakie and Robson (1988) have shown that transients, produced by a tap to the finger, are larger and slower close after movement than after rest. The resonant frequency of the finger thus increased with longer rest. Reynolds and Lakie (2010) have shown a similar effect for post-movement tremor of the hand, where hand tremor frequency slowly increased over several seconds after movement. How the influence of thixotropy on resonance relates to the difference in posture and movement is not clear. The two possibilities for the difference between postural and dynamic tremor, a central oscillator or a thixotropic reduction in muscle stiffness, are modelled in section 1.4.7.

1.4.6 The effect of reflexes on tremor

PBC Matthews (1997) observed *'The stretch reflex provides an inescapable contribution, whether for better or worse, by subjecting every contractile or other mechanical irregularity to regulation by negative feedback.'*. The role of stretch reflexes in tremor has been extensively studied. As Matthews said, an interaction between movement and EMG is inevitable. The problem is the nature of this interaction. Thus, EMG may be causative of the tremor or the tremor may be causative of the EMG. It remains unknown whether the modulation of the EMG is a minor consequence of the tremor or is necessary for its creation.

Researchers who believe the modulated EMG generates the low frequency peak seen in finger tremor find coherences between activity of motor units at 8-11 Hz (e.g. Allum et al., 1978; Christakos et al., 2006; Durbaba et al., 2005; Elble & Randall, 1976; Erimaki & Christakos, 2008; Freund et al., 1975; Hagbarth & Young, 1979; Halliday et al., 1999; Hammond et al., 1956; Lippold, 1970; Marshall & Walsh, 1956; Matthews & Muir, 1980). They variably attribute the modulation to being intrinsic to motor neurons, resulting from delayed spinal feedback drive from the limb or through Renshaw inhibition. Pulsatile motor unit firing may result in repetitive force input to the limb, generating small tremor oscillations at this frequency. This would suggest a peripheral neural control of low frequency tremor.

Still, there have been some unresolved issues with the theory.

1. It is unclear whether the stretch reflex is fast enough for the 8-12 Hz oscillations or not (Stein & Oğuztöreli, 1976a; Wessberg & Vallbo, 1995; 1996).

2. It is questionable whether such a stretch reflex mechanism would act as a self-sustaining and even self-*amplification* phenomenon, essentially acting as a positive feedback system. Oppositely, muscle spindle sensitivity might even *stabilize* the reflex oscillations (Matthews, 1997; Stein & Oğuztöreli, 1976a; Williams & Baker, 2009).

3. It is unclear whether the stretch reflex gain is strong enough to produce tremor (Vallbo & Wessberg, 1995;1996). It is possible that the effect of the stretch reflex is simply to produce an inevitable 1A afferent driven colouration of the EMG at the frequency where the velocity is highest – that is, the tremor frequency.

4. The tremor frequency does not change in response to cooling (Lakie et al., 1994), whereas the frequency of the spinal stretch reflex loop decreases as the loop delay increases with slower nerve conduction.

5. The tremor frequency does not change as people become bigger. Children should have faster tremor than adults because the reflex loop is shorter. However, there is no evidence of this.

The effects of feedback are complex and a model does not provide much physiological illumination. This is because they depend in a very critical way on the delay and gain, neither of which we know with certainty (e.g. Matthews, 1997). A very slight change in gain will change the behaviour from stable to uncontrolled oscillation at the resonant frequency. A change in feedback delay will not introduce new frequencies, but will lead to a different phase between drive and resonance at the resonance frequency. A small change in feedback delay therefore can also alter the system from being stable to being uncontrollable (in line with comment 2 above).

Accordingly I do not model feedback oscillation.

1.4.7 Modelled tremor

In the appendix, I present a computational model of a simple damped second order resonant system, which can be seen as a scientific paradigm for the influence of resonance on physiological tremor. It contains the low-pass filtering properties of the muscle for generating force (see Bawa & Stein, 1976), and has acceleration (tremor) as output. The resonance and muscle properties are computed by a Laplace transfer function. These computations assume that the system is linear. Technically, this is not true. As well as the fact that muscles have clear non-linear characteristics, limbs rotate around a joint and thus

possess *angular* characteristics. Practically, for small oscillations like those found in finger tremor, differences are trivial and the angular system can be treated as linear for each specific level of input. Therefore, the linear Laplace transformation can be considered valid for the angular system involved producing physiological tremor. A further underpinning for the correct use of this method here and details on non-linearity with larger movements are described by Stein & Oğuztöreli (1976a).

This is a very simplified model, but I wanted to test the effects on a resonant plant and explain the current literature in light of the resonant properties of the finger to illustrate their sensitivity to parameter changes. Note that only single values for stiffness and damping are used. This means that the model will inevitably produce a single resonant peak. Postural tremor measurements are often made over a relatively long period of time (over 30 seconds) and the single spectrum calculated has to account for the envelope of the whole record. Physiologically, it is not very likely that stiffness and damping will stay identical over long periods.

Conventional postural tremor modelled by a second order resonator

When driving the model with white noise, the estimated muscle force will become a low-pass filtered version of the EMG (see figure 1.7A and B). This force input drives the resonator, producing an acceleration signal with a peak frequency and power solely dependent on the resonance parameters of the system (i.e. inertia, stiffness and damping). With the chosen finger values, a tremor peak at 19.0 Hz is created (see figure 1.7C). Any changes to these parameters would modify the resonance frequency and amplitude, and thus the tremor, as per equation 10 and 11.

The effect of increased inertia on the model

To test the situation where inertia is added to the finger (comparable with Stiles & Randall, 1967), we increased the modelled finger weight from 37 g to 87 g in incremental steps of 10 g. Figure 1.7D shows the generated modelled tremor spectra. Adding weights of 10 to 50 g to the modelled finger brought about a considerable decrease in the resonance frequency (from 19.0 to 13.2 Hz). This decrease in resonance frequency is broadly comparable to values published in literature (e.g. Stiles & Randall, 1967). A small increase in tremor amplitude accompanies the gradual drop in tremor frequency. Note that only the effect of increased inertia on the resonance frequency is shown. Any concomitant changes in muscular stiffness or damping are not considered in this example.

The effect of increased stiffness of the model

Figure 1.7E shows the effect of increased force causing an *increased* muscular stiffness. With full co-contraction of the upper limb, Morrison & Newell (2000) found an increased arm stiffness of 11.6% to 31.5%. For the modelled results, overall stiffness was increased with 10%, 20%, 30% and 40% (k = 1.94, 2.12, 2.29 and 2.47 Nm/rad respectively). Such increments of muscle stiffness lead to a gradual increase in modelled tremor frequency, from 19.0 to 22.5 Hz. There does not seem to be a large effect on the amplitude of the tremor spectra with increases in stiffness. This is in line with a minimal decrease in damping-ratio with increased stiffness (equation 7).

However, these large increases in overall stiffness are not realistic for finger tremor. As discussed in section 1.4.3 and shown in figure 1.6, any increase in system stiffness will be due to an increase in muscular stiffness only, as the stiffness of the series-coupled tendon does not change much. This means that the maximal overall stiffness will be limited to the tendon stiffness of 2 Nm/rad. Its stiffness starts to increase only at very large forces when

the tendon is stretched extensively. A 40% increase in overall stiffness will therefore only be accomplished at these strong activations.

The effect of decreased stiffness of the model

Panel F shows the results for a thixotropic decrease in muscle stiffness. Loram et al. (2007) measured muscle and tendon stiffness in the calf and found that the stiffness ratio for muscle-to-tendon was 15:1 for static conditions. It has been suggested that the tendon controlling a single finger has a higher stiffness than when the tendons control the whole hand (Ward et al., 2006). This is necessary for the precise control and high sensitivity of the fingers. To adjust for this increased finger tendon stiffness, the static muscle-to-tendon stiffness ratio was estimated to 15:2 (equation 14; k = 1.76 Nm/rad). For dynamic conditions, Loram and colleagues estimated the muscle stiffness to decrease by ~15 times. As only small stretches are involved, any changes in tendon stiffness can be neglected, resulting in a muscle-to-tendon ratio of 1:2 under dynamic conditions. When applied to our model, this ratio results in an overall stiffness of (k = 0.67 Nm/rad). With movement, the model produces a tremor frequency that is reduced from 19.0 to 11.7 Hz. Also, an increase in amplitude can be seen. If the drop in joint damping with movement (Halaki et al., 2006; Lakie et al., 1984) was also included, this increase in amplitude would have been exaggerated (according to equation 11).

The drop in tremor frequency with movement to ~10 Hz (Daneault et al., 2011; Hwang et al., 2009a; Vernooij et al., 2013c) was not completely reached by the simple change in muscle-to-tendon ratio copied from Loram et al (2007). This is most likely due to the fact that Loram's study involved calf muscles and tendons which have different characteristics than the finger described here. Relative to the calf finger tendons are not very compliant, probably so they can produce precise control (Ward et al., 2006). Based on this study, we

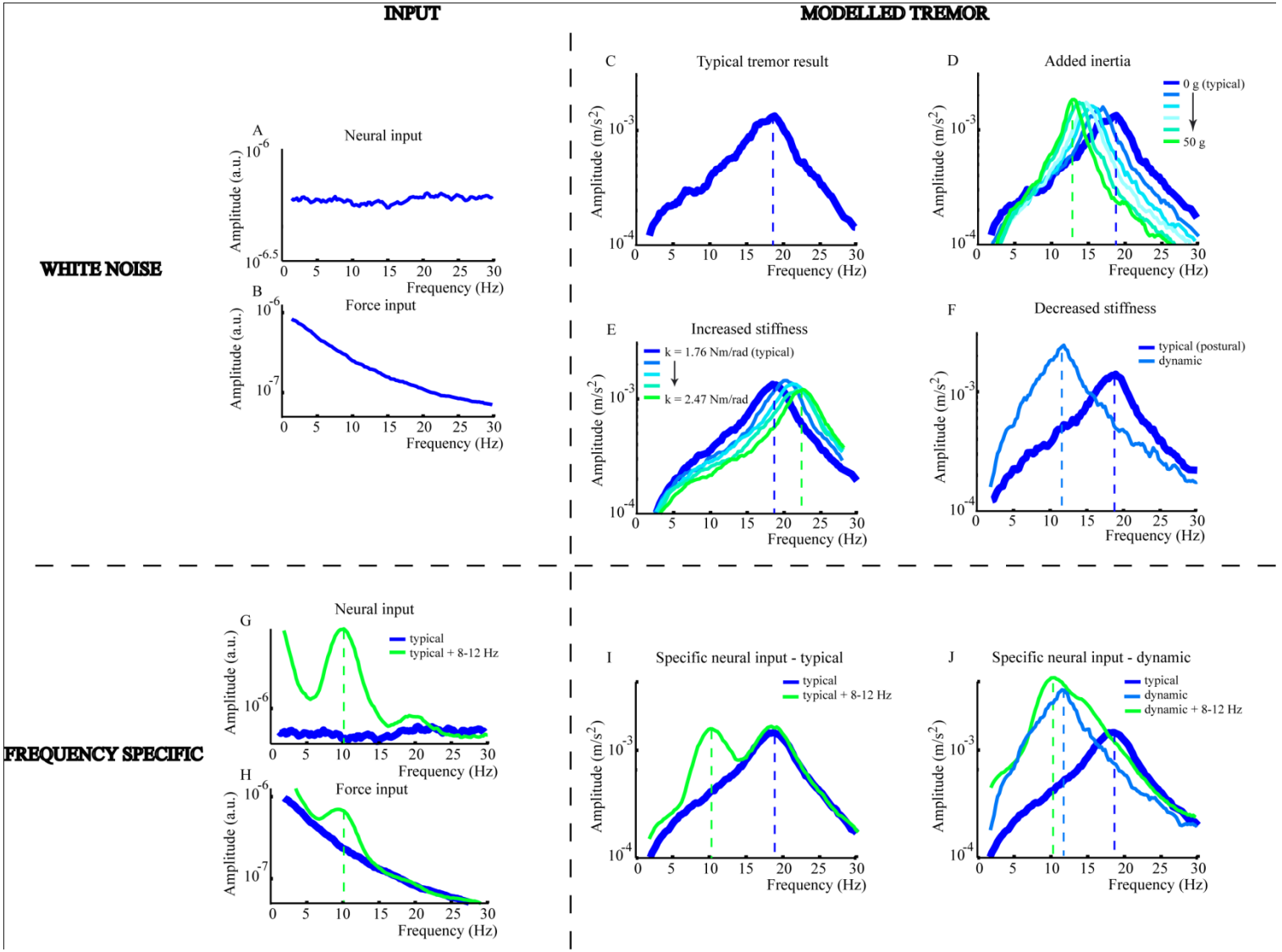


Figure 1.7 Frequency spectra of modelled typical finger tremor
Modelled finger frequency spectra. *A)* White noise input spectrum; *B)* Generated force input spectrum after low-pass filtering the white noise input signal; *C-F)* Generated finger tremor spectra with a white noise input signal; *G)* frequency-specific input spectrum; *H)* Generated force spectrum after low-pass filtering the frequency-specific input signal; *I-J)* Generated finger tremor spectra with a frequency-specific input signal.

estimated here that the tendon stiffness is twice as high for the finger as for the hand, but this might be an underestimation. A stiffer tendon could transfer more resonance oscillations generated by the muscle and consequently allow for a larger drop in resonant frequency.

The effect of a central oscillator driving the model

Driving our resonator model with a white noise signal combined with increased amplitude at specific frequencies would be comparable to driving the muscle with a frequency-specific centrally generated input. The frequency and size of the modelled tremor created with this drive depend on the combined characteristics of the resonance and the specific neural control (see figure 1.2 and page 18).

A broad 8-12 Hz peak was introduced to the white noise input signal to the model. The peak is a filtered white noise signal (1st order Butterworth, dual band pass 4-6 Hz) which was rectified (to create a peak 8-12 Hz) and added to the white noise signal. Figure 1.7G shows the input spectrum, which has a clear peak around 10 Hz. This input generated a force spectrum decaying with higher frequencies, but with a peak ~10 Hz (figure 1.7H). These input and force spectra are similar to previous studies who find a synchronised neural input (compare figure 1.7G and H with e.g. Christakos et al., 2006; Halliday et al., 1999).

Panel I and J show the modelled finger tremor spectra resulting from this frequency-specific drive, representing a postural and a dynamic condition respectively. When postural finger tremor was created with the typical resonance properties, the 'normal' peak at 19.0 Hz was joined by a second peak around 10 Hz (figure 1.7I). When conditions other than normal postural tremor are studied, this 10 Hz peak would not change in frequency. For instance, figure 1.7J displays tremor generated under moving conditions. This dynamic

tremor can be compared when generated with a white noise input (identical to figure 1.7F) and with a frequency-specific input. Both modelled dynamic tremor spectra display a single peak at a low frequency (10-11 Hz). Besides a minor difference in peak frequency, no clear distinction can be made between the two spectra. The peak generated by the neural input has merged with the resonance peak and the influences of the separate components is unclear. A specific neural input therefore does not seem to have a clear influence on the modelled dynamic finger tremor spectra.

1.4.8 Concluding remarks

As discussed in this chapter, there is still a debate on the effect of resonance on physiological tremor and firm evidence is lacking. Some authors attribute the entire spectrum to resonance, while others argue it only has a secondary or even minimal role in generating tremor. Here, with the use of a simple model, it was simulated that mechanical resonance could potentially take up a major role in tremor generation and has the capability to explain the complete range of frequencies found in finger tremor. With some very simple, physiologically justifiable adjustments to muscle properties the computational model of a resonator was able to more or less replicate characteristics of tremor spectra under several conditions. On the other hand, only single aspects of muscle properties were modified at one time here whereas usually parameters may alter simultaneously. If there is a specific neural drive, this will enhance or add to the spectra generated by pure resonance.

1.5 Side notes

1.5.1 Interactions between resonances

Every body part contains its specific resonance amplitude and frequency. As daily life activities often comprise multiple body parts, for instance the upper arm, forearm, hand and fingers are involved when pointing to a target, the envelope of the combined resonances will emerge in the endpoint, e.g. the pointing fingertip. Series-coupled non-linear systems give complex interactions that cannot be predicted by the sum of their individual behaviours.

1.5.2 Does the brain know about and compensate for resonance?

It is questionable whether we control our body in such a way to reduce resonances. Especially since we have seen that the size and frequency of resonances in the human body vary under different conditions. And if it does know how to control these phenomena, it is unclear how it knows which resonances are dominating at which circumstances and how it can calculate the hugely complicated interaction patterns amongst resonances described above. Muscle spindles send out afferent feedback on muscle contractions, but, as discussed above, it is not sure whether this sensory feedback is even fast enough to account for simple spinal control $\geq$ 10 Hz. Note that Axelson and Hagbarth (2001) believe the central nervous system does take control of and compensates for the short-range elastic component. Additionally, the compliant tendon might not transfer all finger oscillations to the muscle, and so the 'external perturbation' signal that is passed onto the muscle is filtered. An active voluntary control of complex interactions thus seems ruled out. Potentially, the most economic and safe regulation of resonances is control through a broad-band activation pattern, ensuring none of the resonance components is exacerbated.

1.5.3 Practical implications

There are a number of practical implications on the appearance of resonance in tremor spectra. Resonance is a mechanical, peripheral issue, which can be reduced or exacerbated under certain circumstances.

First, although tremor is usually minor, in the case of essential or pathological (e.g. Parkinsonian) tremor it interferes with daily life activities. These forms of tremor are caused by a central deficit causing a large tremulous control around 4-5 Hz (Raethjen et al., 2000a). As Reynolds & Lakie (2010) suggested, these large tremors may cause the muscle to be in a constant 'dynamic' stiffness state, preventing muscles from stiffening up when attempting to hold the limb still and keeping the system's damping low. The resonance oscillations of these subjects will thus always be large in size and slow in frequency. This leads to a continuous relatively large and slow *physiological* tremor on top of the *pathological* tremor movements.

Second, the effect of any tremor is amplified when the lever arm is artificially extended. Small oscillations in the hand and fingers are significantly larger at the endpoint of a hand-held rod or pointer. This same effect of tremor transmission applies to holding surgical tools and prosthetics. It is therefore of importance to control for these tremulous effects when building these 'extensions' of the human body. Moreover, if resonance contributes to some tremor components some of its tremulous effects in limb-extending tools could potentially be diminished, e.g. by incorporating frequency-cancelling mechanisms around the resonance band or adapting stiffness or inertia components.

Third, there may be some applications for increasing our understanding of resonance effects on tremor when it concerns sports. If unmoved for a period of time, muscles become very stiff since a large number of cross bridges will be attached between the two

filaments. Initial movements will change the produced muscle tension, which inevitably makes control less precise. Stretching before commencing exercise will break all 'permanent' cross bridge bonds and will not only generate a more consistent force to control, but could also increases flexibility. This might have beneficial effects for performance in sports like Tai Chi. Conversely, precise sports like target shooting could benefit from stiff muscle connections (e.g. Lakie, 2010).

1.6 Summary, thesis objectives and contributions

In this introduction, mechanical resonance is described and introduced as a mechanism acting in the human body. Springy structures like tendon and muscle act upon the inertial limb by which producing a resonance as any spring-load combination would. Interestingly, the resonance of the hand and finger occur at a similar frequency as physiological tremor in these limbs. Although it is sometimes argued there is a neural origin of tremor, any input (whether frequency specific or not) will have to act upon the peripheral resonance mechanism. This introduction has attempted to illustrate the potential of mechanical resonance to be responsible for the majority of physiological tremor manifestations. Different kinds of input were fed to a simple spring-mass-damper model, representing the resonating features of the fingers, and physiologically justifiable modifications to the spring characteristics were applied. From these simulations there seems to be a possible large role for mechanical resonance in generating physiological tremor.

This thesis aims to examine and specify the role of mechanical resonance in the generation of physiological hand and finger tremor.

It has a few specific objectives:

- Objective 1: To study the influence of mechanical resonance on hand tremor by comparing postural hand tremor to tremor when under slow voluntary movements (Chapter 2).

- Objective 2: To verify the computational model presented in the current chapter by applying it to recorded tremor data of the hand (Chapter 2) and finger (Chapter 4).

- Objective 3: To examine the effect of minimising, as far as possible, the effect of mechanical resonance on physiological finger tremor by comparing isometric and isotonic tremor (Chapter 3).

- Objective 4: To examine the effect of minimising, as far as possible, the effect of neural input on physiological finger tremor by artificially (electrically and mechanically) generating tremor (Chapter 3 and 4) and by studying deafferented subjects (Chapter 4).

- Objective 5: To study the effect of altered levels of muscle activity on tremor and mechanical resonance by applying a range of artificial inputs to the finger muscle whereby tracking the cross-spectral gain and phase (Chapter 3 and 4).

- Objective 6: To investigate how finger tremor and neural control are related to everyday motor tasks by examining EMG and tremor during the transition between posture and movement (Chapter 5).

Chapter 2 was devised by ML, who also collected the data. However, with the help of ML and RR, I performed the data analyses. I made all figures and, together with TO, I constructed a working resonance model. I also had a large contribution in drafting the manuscript. All authors contributed to the final version of the paper. Chapter 3 was jointly devised by all three authors. ML and I gathered the data for the experiments. Again, I performed all data analyses and made all figures. Together with ML and RR, I drafted the manuscript. All three authors jointly devised the idea for the study presented in Chapter 4. I conducted the experiment, performed all data analyses and made the figures. I additionally devised two new analyses, i.e. the comparison of subjects showing active vs. passive EMG activity and reanalysing the data based on produced tremor size (instead of preset levels). Together with ML and RR, I drafted the manuscript. For Chapter 5, I gathered all data, undertook data analyses and made the figures. I drafted the manuscript with input from ML and RR.

CHAPTER 2.

THE RESONANT COMPONENT OF HAND TREMOR IS ALTERED BY SLOW VOLUNTARY MOVEMENT

Limb resonance imparts a characteristic spectrum to hand tremor. Movement will alter the resonance. We have examined the consequences of this change. Rectified forearm extensor muscle EMG and physiological hand tremor were recorded. In postural conditions the EMG spectrum is relatively flat whereas the acceleration spectrum is sharply peaked. Consequently, the gain between EMG and acceleration is maximal at the frequency where the tremor is largest (~ 8 Hz). The shape of the gain curve implies mechanical resonance. Substantial alterations in static posture do not significantly change the characteristics of the tremor or the shape or size of the gain curve. By contrast, slow or moderately paced voluntary wrist flexion-extension movements dramatically increase the hand tremor size and lower its peak frequency. These changes in size and frequency of the tremor cannot be attributed to changes in the EMG. Instead they reflect a very large change in the size and shape of the gain curve relating EMG to acceleration. The gain becomes larger and the peak moves to a lower frequency (~ 6 Hz). We suggest that a movement related (thixotropic) alteration in resonant properties of the wrist provides a simple explanation for these changes. The mechanism is illustrated by a model. Our new findings confirm that resonance plays a major role in hand tremor. We also demonstrate that muscles operate very differently under postural and dynamic conditions. The different coupling between EMG and movement in posture and when moving must pose a considerable challenge for neural predictive control of skeletal muscles.

2.1 Introduction

When any limb is maintained in a postural configuration it is not perfectly static. The small movements that it exhibits occur at a range of frequencies. When it is recorded, most of the fluctuation in position is seen at low frequencies and probably represents the small slow adjustments which are the best efforts of the nervous system to maintain a posture. If, instead, velocity or acceleration are recorded the higher frequency involuntary components are greatly emphasized. This behaviour is clearly demonstrated by the hand when held in an outstretched position. There is a prominent frequency peak in the acceleration spectrum of the hand. Tremor is commonly recorded as an acceleration signal and most investigators agree that the central frequency of this peak lies somewhere between 7 – 11 Hz (Stiles & Randall, 1967; Marsden et al., 1969a; Elble & Randall, 1978; Hömberg et al., 1987; Lakie, 1992; Raethjen et al., 2000b) and it is commonly described as "10 Hz tremor" although in fact a figure of 8 Hz would better describe the mean frequency for the hand. Although people tend to have similar hand tremor frequencies there is a very wide range of tremor size in different subjects (Lakie, 1992).

Considerable attention has focused on 10 Hz tremor since it was first clearly described in the thumb by Schäfer (1886). Schäfer believed this rhythm to be associated with what would now be known as sub-tetanic motor unit firing and therefore to be ubiquitous in skeletal muscle. However, extensive subsequent work has shown that there might be other causative factors. It has been held to result from oscillation in a reflex loop (Lippold, 1970; Durbaba et al., 2005) or to result from a central oscillatory process (Elble, 1996).

In addition to central oscillators or feedback oscillation, one definite component of tremor is mechanical. Force produced by the motor units is filtered by the muscle itself and by the viscoelastic and inertial load of the tendons and limbs. Marshall & Walsh (1957) first

suggested that tremor might be a consequence of the imperfect low pass filtering properties of muscles which allowed significant sub-tetanic ripple in force output. Subsequently, Lakie, Walsh & Wright (1986) showed that the ripple was combined with the mechanical properties of the hand which behaved as a resonator. The combination of the inertia and stiffness of the limb produced a resonance and the frequency of the tremor could be altered systematically by artificially changing the inertia of the hand. Resonance was also found to be the dominating mechanism in shaping the tremor of the hand by Raethjen et al., (2000b). Also, recent work (Reynolds & Lakie, 2010) showed changes in the frequency of hand tremor which they attributed to alteration in the resonant frequency which was related to the history of movement. Hand tremor frequency increases as muscles progressively stiffen following voluntary movement and this rise in tremor frequency is not associated with a rise in frequency of the EMG responsible.

It is not presently known what happens to hand tremor during slow movements when a large thixotropic reduction in stiffness occurs. Interestingly, large, tremor like, oscillations have been commonly observed during finger movements (for example Vallbo et al., 1993). These oscillations have been attributed to a central organization of motor output during movement and the same claim has been made for hand movements (Kakuda et al., 1999). Daneault et al. (2011) have very recently shown that finger tremor size greatly increases during slow movement. However, none of these papers considered the possibility that muscle properties will be greatly altered during movement and that this mechanical change, rather than a change in the pattern of neural firing, may be responsible for the large tremors that occur in dynamic conditions. In addition, there has been no systematic study of the relationship between tremor recorded posturally and in slow movement, although they have been said to be different (Vallbo et al., 1993, Kakuda et al., 1999).

In the present study hand acceleration (tremor) was examined under three postural conditions and four of voluntary movement at different velocities. The gain that relates EMG to acceleration of the hand was calculated. The results were clear. The EMG spectrum is relatively flat and not greatly different in postural and moving conditions. The acceleration spectrum is sharply peaked (at ~ 8 Hz in static, and ~ 6 Hz in slow movement). The fact that acceleration is particularly large at a certain frequency in the absence of any corresponding large EMG activity is a clear indication that resonance is occurring. We found that the resonance was very different in postural and moving conditions and we suggest that thixotropic changes in muscle stiffness are responsible. To illustrate this we describe a simple model. We used previously determined values for hand inertia and wrist stiffness and existing estimates of the way in which stiffness is partitioned between muscle and tendon. In order to demonstrate the effect of movement we made two suppositions based on experimental evidence obtained from in vitro preparations and other limb – muscle combinations.

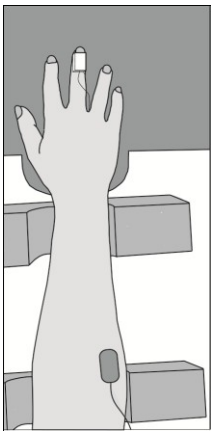
Other limbs have tremor spectra which can show a peak around 10 Hz. However they may also have additional peaks. For example, tremor of the finger usually shows two components. One is at a broadly similar frequency to hand tremor but the other is at a higher frequency (20 – 25 Hz). (Stiles & Randall, 1967; Lakie, 1992). The presence of an additional peak is clearly a complication and for this reason the present chapter is restricted to hand tremor.

2.2 Methods

Subjects

These experiments were carried out on 10 subjects (9 male). The age of the subjects ranged from 19 – 55, mean 23. All subjects were, as far as they knew, free from neuromuscular disorder. Subjects were asked to abstain from alcohol for 12 hours before the experiments. Ethical permission was obtained from the School's ethics committee and experiments were performed in accordance with the declaration of Helsinki and with the subjects' written, informed consent.

Apparatus



Tremor was recorded using a purpose-built apparatus. Subjects sat in a comfortable adjustable chair with a headrest. The forearm was supported in a foam moulding at waist height and a padded support surrounded the pronated wrist. The hand was free to move in the vertical plane. A miniature single axis accelerometer (ICS 3021, EuroSensor, UK) was attached to the dorsum of the hand. A retro-reflective laser rangefinder (YP11MGV80, Wenglor Sensoric, Germany) was positioned so that it reflected from a white label attached to the upper surface of the accelerometer. Thus vertical displacement and acceleration of the hand could be simultaneously recorded. Hand position was displayed to the subjects as a spot on a screen 1.5 m in front of them. Computer generated targets were presented to the subject as a short bar on the screen.

The subject was instructed to match the spot and bar as accurately as possible by tracking the bar. The static positions were "up, middle and down". "Middle" was adjusted so that the central screen position suited the subject who held the hand in a neutral position,

somewhat below horizontal. "Up" was a 15 degree upward (extension) and "down" was 15 deg downwards (flexion). These were postural changes of a substantial size without approaching the limits of joint rotation. The compatible vertical shifts on the screen were 7.5 cm. In the dynamic conditions the target alternated from the predetermined "bottom" position to the "top". The target moved at one of four preselected constant velocities which were triangular waveforms at 0.1, 0.2, 0.5 and 1.0 Hz. The corresponding maximal angular velocities of the wrist were approximately 6, 12, 30 and 60 degrees per second. Subjectively, these hand movements were of moderate size and ranged from very slow (0.1 Hz) to moderate (1.0 Hz). Faster movements were not studied because they are difficult to pace successfully and it was desired to maintain a wide gap between the tremor frequency and the movement frequency.

All recording sessions lasted 60 s and the order was randomized. Subjects were told which condition to expect and a short period of practice was allowed before each recording was started. Each task was very easy to perform and was not physically or mentally demanding but rest periods were allowed between each recording. Surface EMG was recorded by a 2 channel Bagnoli system (Delsys Inc, USA) with electrodes positioned above the muscle belly (determined by palpation) of the extensor digitorum communis muscle.

Analysis

Tremor was recorded as a filtered acceleration signal. The signal was band pass filtered between 0.05 Hz and 45 Hz to reduce DC offsets caused by tilt and high frequency noise. It was amplified so that 1 volt = 0.05 g (50 cm s^{-2}). The position signal was recorded at a sensitivity of 1 Volt = 1 cm. The frequency response of the position sensor was flat up to 100 Hz. EMG was amplified by a factor of 1000 with a pass band of 20 – 300 Hz. The resulting waveform was rectified to obtain an amplitude modulated signal. All signals were

sampled at 1000 Hz using a MC 6043 PCI card and PC. Analysis was carried out offline on recorded signals using Matlab software (MathWorks Matlab 2011a, Natick, Massachusetts, U.S.A.). Frequency domain calculations were performed on each measured acceleration signal and rectified EMG signal using NeuroSpec-software for Matlab (NeuroSpec, Version 2.0, 2008. For a theoretical framework see Halliday et al., 1995). In addition, the cross spectral gain response between the rectified EMG and acceleration was obtained with NeuroSpec. The denominator in the gain calculation was the auto spectrum of the input and this approach has been commonly used for tremor analysis (e.g. Halliday et al., 1995).

The frequency spectra were all calculated with a resolution of 0.06 Hz. The mean frequency spectra per condition were computed and smoothed using a running average of 0.003 s. Mean peak frequencies of acceleration and gain spectra were determined by establishing the maximum amplitude of heavily low-pass filtered individual spectra (4^{th} order Butterworth-filter, cut-off frequency: 20 Hz). Differences in the peak frequencies of all conditions were studied using a repeated measures ANOVA for both acceleration and gain with each of the seven conditions as the within subjects factor. A Bonferroni correction was used to adjust the main effects to compensate for multiple observations. In addition, to compare the peak frequencies between acceleration and gain, we used paired samples T-tests between each of the conditions. To compare all static conditions with all dynamic conditions each subjects mean (of the three static conditions and of four dynamic conditions) was compared by a paired samples t-test. Gain ratios were additionally calculated by dividing the gain of separate dynamic conditions by the mean static gain.

Modelling

The limb was modelled using Simulink (MathWorks, U.S.A.). The model was a second order damped torsional oscillator. The hand was regarded as a moment of inertia *J*

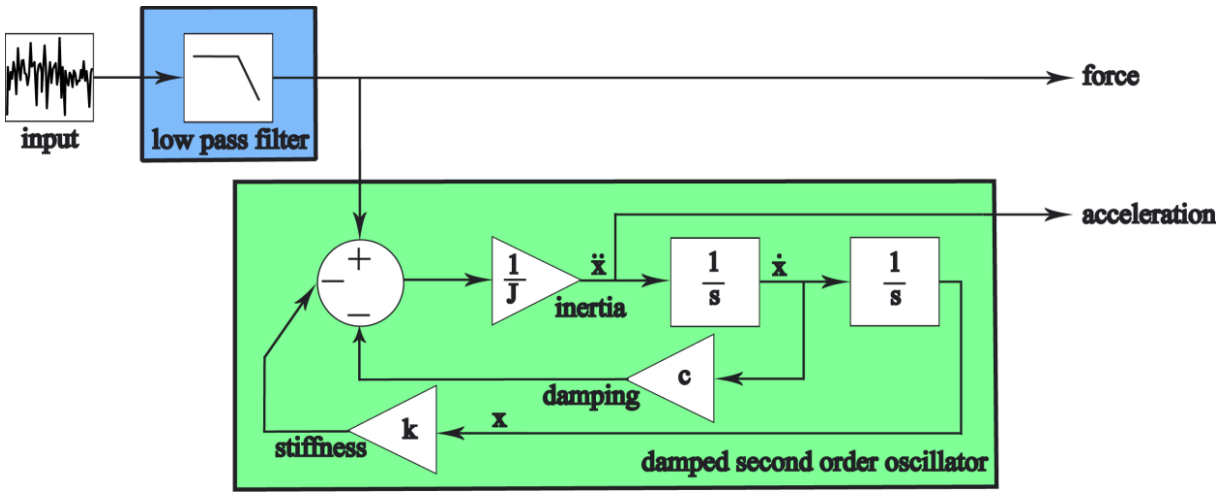
connected to a muscle-tendon complex. The angular stiffness of the complex is *k*. The damping is *c*. The input was either white noise or a pre-recorded extensor EMG signal. Both were put through a low pass filter which simulated muscle force generation. The output of the model is acceleration, but we also recorded force.

k is composed of the series combination of muscle stiffness (kM) and tendon stiffness (kT).

Accordingly,

$$k = \frac{1}{\frac{1}{kM} + \frac{1}{kT}}$$

In the model we used a single set of values for *kM*, *kT*, *c* and *J* to represent postural conditions. When moving, muscle stiffness and damping are known to decrease (Lakie et al., 1984, Bennett et al., 1992). Therefore to model the dynamic conditions we used a different value for *kM* and *c*. We did not change the values for the other parameters.



For computational convenience we used the transfer function form where (*s)* is the complex Laplace variable. For the muscle (low pass filter):

$$H(s) = \frac{1}{(1 + s\tau)^2}$$

And for the damped oscillator:

$$H(s) = \frac{1}{Js^2 + cs + k}$$

Our intention in developing this model was not to produce a perfect fit to the data that we recorded. We wanted to show that it was possible to produce a realistic tremor acceleration spectrum with a very simple model involving nothing more than a spring, mass and damper. We further wanted to show that by making a plausible alteration to two values (muscle stiffness and damping) we could mimic the changes that occur in the acceleration spectrum during movement. We used recorded EMG as an input but we also used white noise in order to show that there is nothing "special" about the EMG waveform.

Choice of values. We used angular units for the model as these are common in the literature because they are easier to measure directly.

Moment of inertia of the hand (J). Estimates range between 0.001 and 0.004 kg m^2. (Milner & Cloutier, 1998; Lakie et al., 1986; Lehman & Calhoun, 1990). We used 0.0025 kg m^2 .

Angular stiffness of the wrist (k). Estimates are 6 – 7.5 Nm rad^{-1} (Lakie et al., 1984), 5 – 13 Nm rad -1 (Milner & Cloutier, 1993) and an average value of 6.3 Nm rad^{-1} (Grey, 1997). We used 7.5 Nm rad^{-1}.

Damping of the wrist (c). The natural viscosity of the relaxed wrist was estimated to be 0.02– 0.03 Nms rad^{-1} (Gielen & Houk, 1984) and 0.03 Nms rad^{-1} (Grey, 1997). We used 0.03 Nms rad^{-1}.

We made two assumptions about the change from static to moving conditions.

First, when muscle moves there is a considerable change in the ratio of muscle stiffness to tendon stiffness. This results from a thixotropic decrease in muscle stiffness. We used values from Loram et al. (2007) obtained from the calf muscles. In this work it was shown that under static conditions the muscle was ~ 15 times as stiff as the tendon (15:1 ratio). When ankle rotation exceeded ~ 0.5 degree this ratio changed rather abruptly to 1:1 because of a reduction in muscle stiffness. Note that these ratios are slightly different from the ones used for the finger in Chapter 1 due to the finger's higher tendon stiffness. Accordingly, when we modelled dynamic conditions we reduced muscle stiffness by a factor of 15. Second, when muscle moves there is a decrease in limb damping. Halaki et al. (2006) found a reduction of 73 % in larger movements. We reduced damping by a factor of three.

The input to the model was either recorded extensor EMG or white noise of a matched RMS size. The filter which simulated the muscle had a time constant of 120 ms.

2.3 Results.

All subjects found the experiments easy to perform. Results from a representative subject are shown in figure 2.1 (left) and the mean from all subjects in figure 2.1 (right).

In all conditions the rectified extensor EMG spectra (top row) are fairly flat. Most subjects had a small peak somewhere between 10 and 20 Hz. This is visible in the case of the representative subject who has a peak at ~ 15 Hz in the postural conditions. When all subjects are averaged, the peak becomes very indistinct. The dynamic recordings additionally show a specific peak at the frequency of movement (0.1, 0.2, 0.5 and 1.0 Hz)

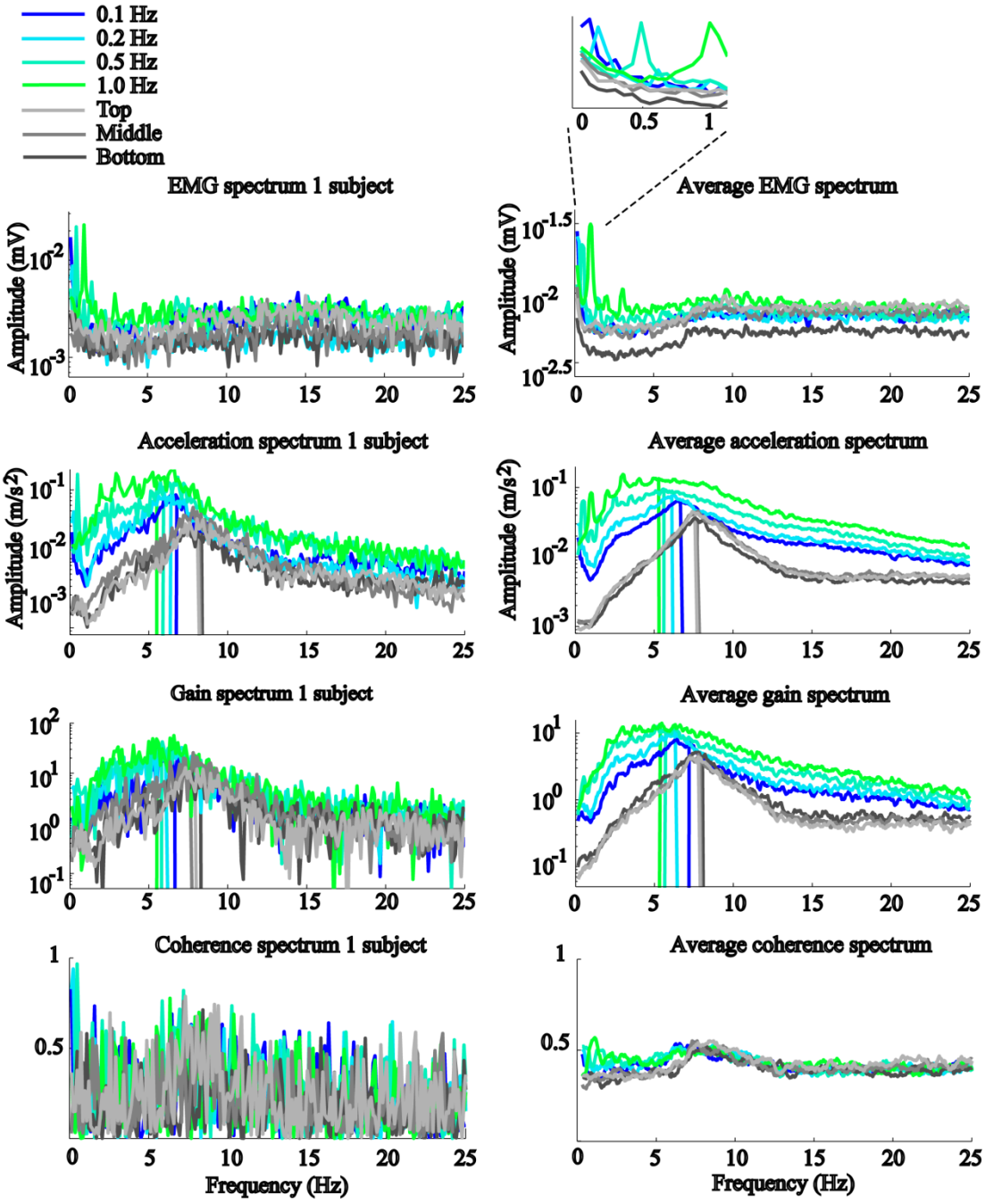


Figure 2.1 Results from a representative subject (left) and all subjects (right).

Grey - postural trials; green-blue - dynamic trials. Top row shows the rectified EMG spectrum of the extensor muscle in the seven different conditions. Second row shows the acceleration spectrum of the hand in the different conditions. Third row shows the gain between rectified EMG and acceleration in the different conditions. The cross coherence (bottom row) between EMG and acceleration is generally moderate with very high coherence only at the frequency of the voluntary movement in the dynamic conditions. There is slightly elevated coherence in all conditions in a frequency range of approximately 7 – 13 Hz. The inset shows the clear peaks in rectified EMG at the frequency of voluntary movement in the dynamic conditions. These can also be seen in the dynamic acceleration spectra. The vertical axis is logarithmic except for coherence.

as would be expected (inset). Because the waveform being tracked was triangular, low frequency harmonics of the movement frequency are also visible in the EMG spectrum. These are particularly visible in the 1.0 Hz record.

In all conditions there is a clear peak in the acceleration spectrum (second row). In the representative subject it is impossible to distinguish clearly between the three static conditions (where the hand was held in a bottom, middle or top position). However, there is an obvious difference between the static conditions and the dynamic conditions. Under dynamic conditions the size of the peak was considerably bigger and the frequency of the peak was lower than under static conditions. The mean results from all subjects show these differences more clearly. The three static acceleration spectra remain almost indistinguishable. However the four acceleration spectra under dynamic conditions are clearly different from the static conditions and from each other.

With movement at the lowest speed (0.1 Hz) the acceleration spectra become considerably larger and the peak of the spectrum shifts to a lower frequency. There is a further increase in size and decrease in frequency as the movement is made faster. There are small peaks visible in the dynamic spectrum at the low frequencies of movement that were used in tracking which are a consequence of the tilt or acceleration at the frequency of the tracking task. The gain between rectified extensor EMG and acceleration is shown in figure 2.1 (third row). As may be anticipated from the shape of the EMG and acceleration spectra, these results show a gain which is sharply peaked at the tremor frequency. Results for all subjects show that, during movements of increasing speed, the mean gain has increased by a factor that ranges from approximately two to five and the frequency at which the gain is maximal has dropped from ~ 8 Hz to 6 Hz. The cross coherence between rectified EMG and acceleration is shown (bottom row). This shows that there is moderate coherence (~ 0.4) between EMG and acceleration at most frequencies. In all conditions this is enhanced

where the acceleration is largest (between approximately 7 and 13 Hz). In the moving conditions there is also very high coherence at the frequency of the movement.

The consequence of the changes in EMG and acceleration is a very clear increase in gain under dynamic conditions. As the gain in the three static conditions is very similar it seemed sensible to combine these into a single set of representative values for postural conditions. Using these values, the ratio between the mean static gain and dynamic gain has been calculated for each of the dynamic conditions. This ratio signifies whether the shape of the gain curves is altered between static and the different dynamic conditions. If the ratio between two conditions (e.g. static vs. 0.1 Hz) is not 1 over all frequencies, it indicates a change in shape of the gain curves between those conditions, in which higher ratios imply increased gain in the dynamic condition. Results are shown in figure 2.2.

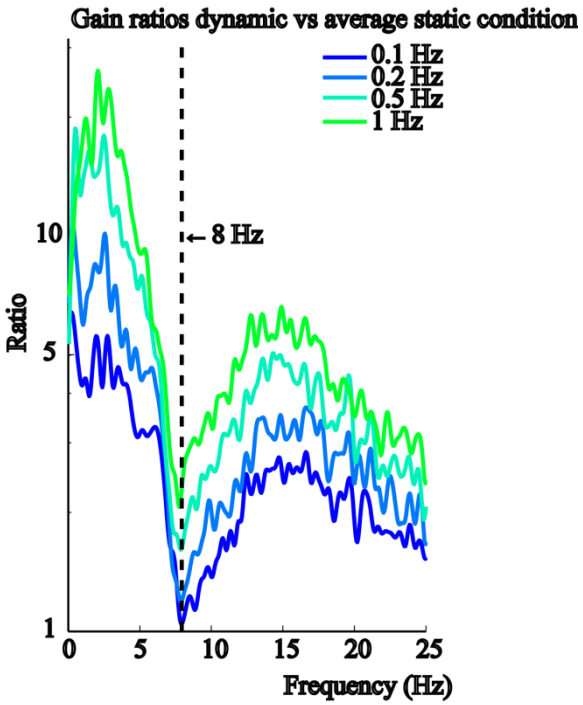


Figure 2.2 Gain ratios.

The gain for each of the four dynamic conditions is compared with the mean gain of the three static conditions. The gain is ratio is always greater than unity and is highest with the fastest movements. The gain ratios show a local minimum at approximately 7 – 8 Hz.

This figure shows that the gain is higher at every frequency in the dynamic state compared to postural tremor although the difference becomes small around the frequency of tremor (approximately 8 Hz). This figure also shows that the gain ratio becomes greater as speed of movement increases. However, each increase represents an approximate doubling of speed and the last increase (from 0.5 Hz to 1.0 Hz) produces a relatively modest increase in gain ratio which suggests a saturating response.

For the gain measurements to be meaningful it is necessary to show that the EMG is being recorded from an appropriate muscle – that is one that is involved in the postural and dynamic task. Figure 2.3 shows the mean level of rectified EMG from the extensor digitorum communis muscle in all of the static tasks and in one of the dynamic tasks. It can be seen that the level of EMG correlates with the demand of maintaining the different

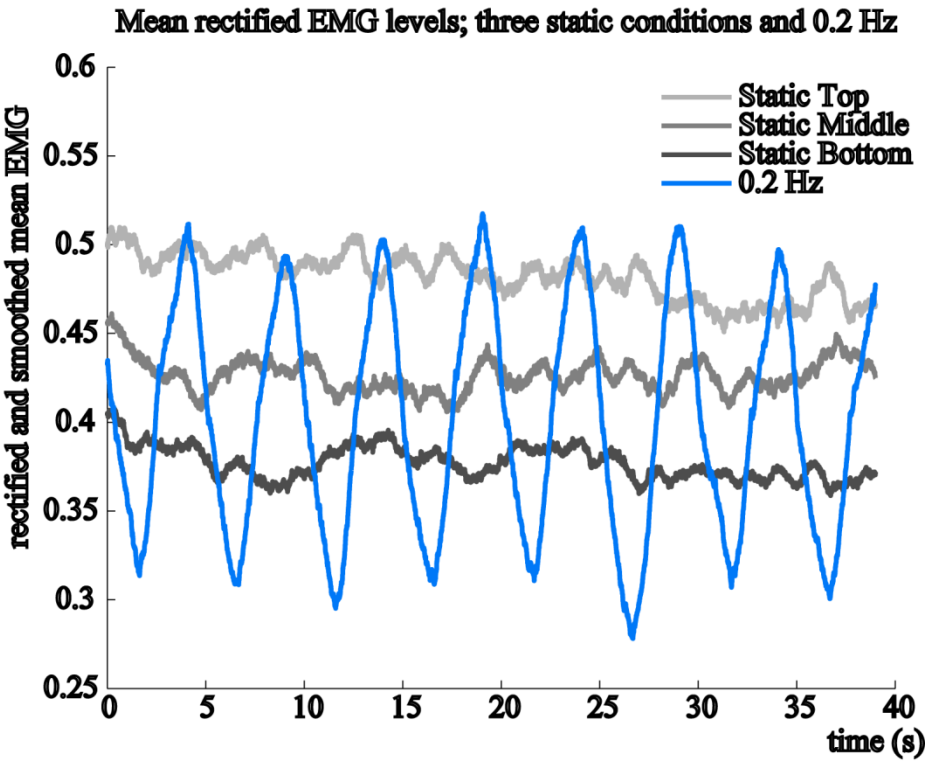


Figure 2.3 The mean rectified EMG (all subjects) of the extensor muscle

Presented in all 3 static conditions and in one of the dynamic conditions (0.2 Hz). The other 3 dynamic ones show a similar range of modulation but are omitted for clarity. EMG has been smoothed by a 50 point moving averaging

postures. Under dynamic conditions the depth of EMG modulation is revealed showing that the EMG variation slightly more than encompasses the range of bottom to top static EMG levels. The muscle from which the EMG is recorded is intimately concerned with the postural and dynamic regulation of hand position, a fact which was also shown by observation and palpation of the forearm.

It was clear from figure 2.2 that the peak tremor frequency was different in static and dynamic conditions and this is explored more fully in figure 2.4. This figure shows the frequency at which the acceleration spectrum was maximal (± sd) and the frequency at which the gain was maximal (± sd) in every condition. In effect these values describe the frequency of the tremor. The principal findings of the statistical tests are:

a) The peak frequencies between acceleration and gain in all conditions except for the 1.0 Hz and static bottom condition are not significantly different (t -1.000 to .181; p .331 to .932). For 1.0 Hz and static bottom condition, acceleration and gain peaks were slightly but significantly different (1.0 Hz, t = -2.413; p = .027: static bottom, t = -2.650; p = .017). These two conditions were considered the least constant since the movement speed was rather high and variable (1.0 Hz) or there was very little EMG present (static bottom).

b) The average static peak frequency of both acceleration and gain was significantly different from the average dynamic peak frequency (respectively t = -9.856, p <.001; t = -8.713, p < .001).

c) None of the static peak frequencies were significantly different from any of the other static peak frequencies (all p >.99).

d) The acceleration and gain peaks for the dynamic conditions ranged from statistically different (p < .001 for acceleration peaks between 0.1 Hz and 1.0 Hz) to not significant

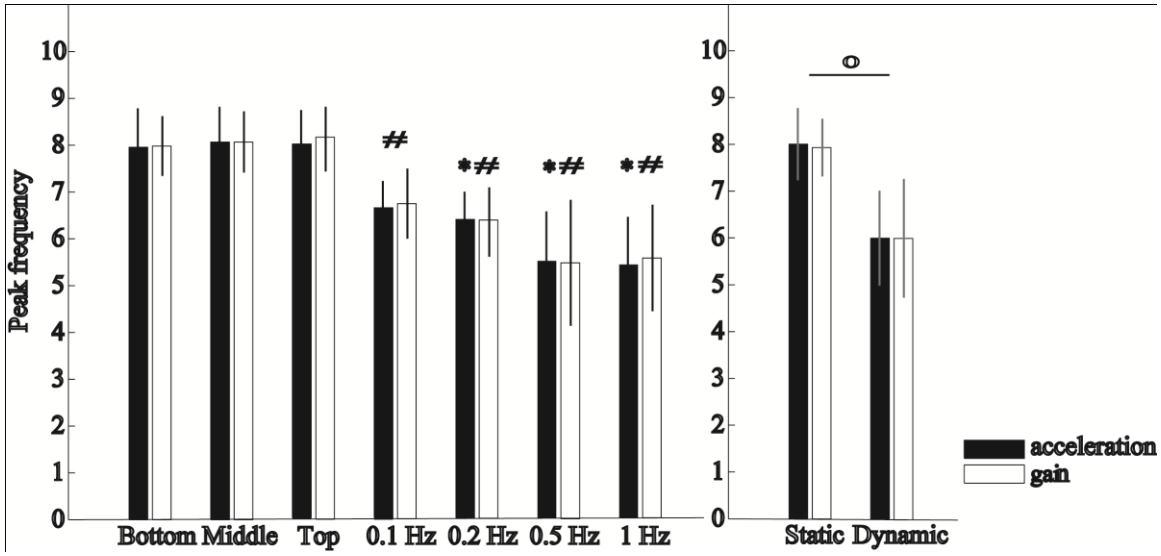


Figure 2.4 The frequency at which the acceleration spectrum and the gain spectrum are maximal in size

Left, results are pooled from all subjects in each condition. The mean and sd are shown for each condition. Right, the mean (± sd) of all static and all dynamic conditions is also displayed. * = significantly different from 0.1 Hz, # = significantly different from static, o = significant group difference.

(acceleration and gain peaks between 0.5 Hz and 1.0 Hz). This, in combination with figure 2.4, shows that tremor frequency is reduced by movement, reducing a little more as movement speed increases.

There is some variability in peak tremor frequencies within each condition, which you can assume to be due to between-subject variability. Is there a systematic relationship between the tremor during posture and the tremor during movement? This question is addressed in figure 2.5. This figure compares the frequency of tremor in postural and dynamic conditions. For simplicity the values plotted for each subject are the mean of their three postural measurements and the mean of their four dynamic measurements. There is a range in static and dynamic tremor frequencies between subjects, but none of the values are considered as outliers as all fall within the physiological range. The dynamic tremor frequency is consistently lower for dynamic than for static conditions. There is a moderate correlation ($r^2 = 0.38$) between postural and dynamic frequencies. The equation of the best

fit linear regression suggests that on average the frequency of dynamic tremor is 2 Hz lower than of postural tremor.

We aimed to produce a simple model which would recreate the acceleration spectra from the EMG that we recorded. This model and its results are shown in figure 2.6. The top left panel shows the recorded EMG under a postural ("static middle") and dynamic condition (0.2 Hz) for a representative subject. The corresponding recorded tremor acceleration spectra are shown in the right middle panel. It was these acceleration spectra that we aimed to recreate. First, the recorded EMG was used as an input to the model. The acceleration spectra that it produced is shown in the top right panel – the resemblance to the real data is obvious. Second, a simpler input was used. This took the form of white noise, with a flat spectrum. Fed into the same model, it too produced a good approximation of the experimentally recorded acceleration spectrum (bottom right panel). The force spectra

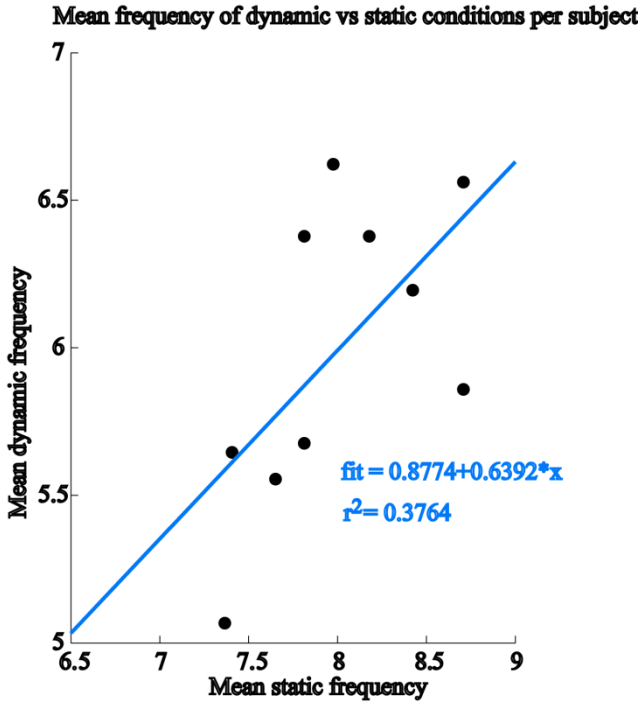


Figure 2.5 Frequency of the tremor peak under static and dynamic conditions

The static values are the mean of the three static measurements and the dynamic measurements are the mean of the four dynamic measurements.

show (top) the force that results from passing the recorded EMG through a filter which resembles a muscle and (bottom) the force resulting from similarly filtering a white noise input.

The model used published estimates for limb stiffness and inertia. Because it represents an under-damped second order oscillator its resonant frequency is proportional to the square root of these parameters. Therefore the effect of changing either of these values is relatively slight and a broad range of realistic inertia and stiffness values will give a satisfactory match for a representative subject. The effect of changing the damping is almost exclusively an alteration of the height of the resonant peak. The most striking feature of the model was that it successfully produced a realistic small reduction in resonance frequency with movement.

The stiffness of skeletal muscle is known to change very considerably with movement and this might have been expected to produce a much larger reduction in resonant frequency. The reason that this does not occur is because of the relatively low and constant stiffness of the series coupled tendon. We employed results from experiments on the ankle. It may be that in the wrist the ratios are different. Accordingly we carried out a form of sensitivity analysis to examine this question (figure 2.7). This figure shows the resonant frequency of the model at different values of stiffness ratio. It shows clearly that a reduction of approximately 2 Hz results from a change in stiffness ratio of 15:1 to 1:1. The upper level of this ratio is not very critical; a completely rigid muscle would produce only a slight elevation in resonant frequency. Furthermore, the muscle stiffness would have to decrease to extremely low values to produce a larger reduction in resonant frequency.

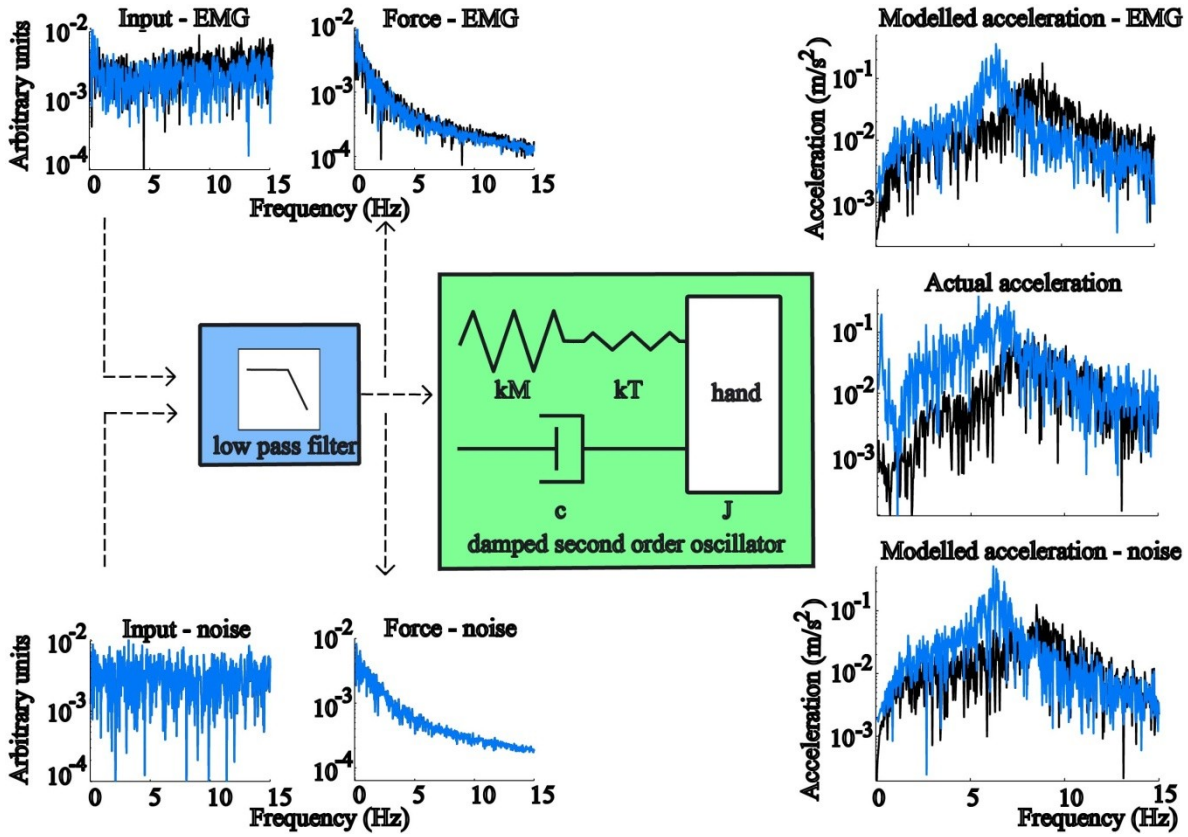


Figure 2.6 Model results

Black = static conditions; blue = dynamic conditions. Left shows the input signals; real EMG (top, black static middle, blue 0.2 Hz), or white noise (bottom). Middle shows the force spectra that are produced by the model "muscle". Right shows the acceleration spectra produced by the oscillator model (top and bottom). These are compared with the actual tremor acceleration spectrum (centre). Reducing muscle stiffness by a factor of 15 and damping by a factor of 3 has produced an resonance (acceleration peak) that is ~ 2 Hz lower and ~10 times bigger. The model does not recreate the low frequency (0.2 Hz) peak in the acceleration spectrum. This peak results mainly from accelerometer tilt in the real data and is accordingly not reproduced by the model.

2.4 Discussion.

The results show the following main features. 1) The rectified EMG spectrum is broad-band and has no distinguishable peak at the tremor frequency. 2) The gain between rectified extensor EMG and acceleration of the hand shows a pronounced peak which coincides with the frequency of the tremor. 3) When posture is replaced by slow movement there are two very clear changes. First, tremor size is greatly increased and this is attributable to an increase in gain not to an increase in EMG at the tremor frequency.

Second, the peak frequency of hand tremor is reduced 2 Hz by movement. These features are reproduced by a simple model. Finally, 4) the relationship of these results to central oscillators is considered and 5) the implications are discussed.

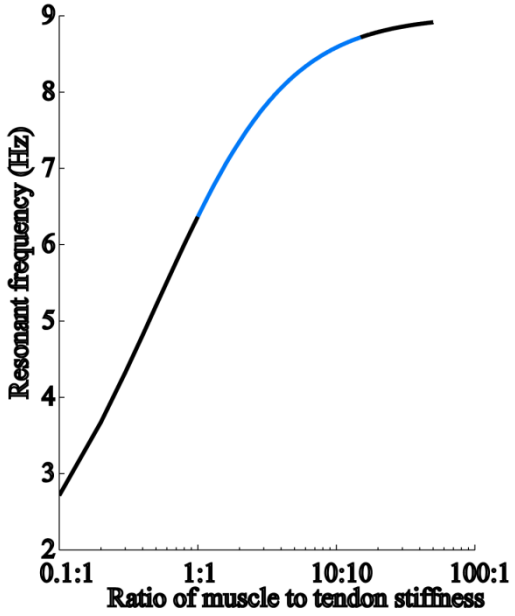


Figure 2.7 Stiffness ratio sensitivity analysis.

This shows the effect on the resonant frequency of the model of adjusting the ratio; muscle stiffness: tendon stiffness. In postural conditions we have estimated this ratio as 15:1 and in movement we estimate it as 1:1. These limits are indicated by the blue area.

The rectified EMG spectrum is broad-band and has no distinguishable peak at the tremor frequency

In all conditions the average rectified extensor EMG spectra (figure 2.1) are fairly flat. This average does mask a degree of inter-individual variation with some subjects having a broad peak between 10 and 20 Hz. Using an unsophisticated frequency analyser, we previously estimated this mean peak frequency at 14 Hz (Lakie et al., 1986) and more recently using wavelet analysis at 12 Hz (Reynolds & Lakie, 2010). Others report very

similar wrist tremor EMG spectra; for example Timmer et al. (1998b) show a slight peak at ~ 15 Hz. Raethjen et al. (2000b) describe a similar spectrum with an EMG peak normally distributed within a frequency range between 8 and 18 Hz for the hand. These values are generally higher than that of hand tremor. It is probable that the EMG peak represents the firing of individual motor units at these frequencies which are strongly picked up by the surface EMG as it coincides with the likely rate of motor neuronal discharge in these minor postural tasks (Erimaki & Christakos, 2008). Kakuda et al. (1999) report firing rates of ~ 8 – 16 Hz. If hand tremor resulted largely from modulated EMG activity there would be a clear peak in the EMG at the frequency of the tremor.

For the hand tremor that we have studied this makes it very unlikely that any substantial part of the tremor results from a neural oscillator of central or peripheral (reflex or Renshaw cell) origin. These results do not exclude the possibility that some part of the EMG at the tremor frequency comes from an oscillator of central or other origin. Interestingly, if a neural oscillator were to start operating at an appropriate frequency (perhaps due to a tremor pathology) its mechanical consequences would be magnified by the gain at that frequency.

The inference of the present experiments seems robust. For all of our subjects the large acceleration of tremor is produced by broad band forcing with no particularly large amount of neural drive at the characteristic tremor frequency. A number of studies have shown that there is a degree of synchronization between tremor and EMG at frequencies around the tremor frequency. However these studies have employed cross coherence or cross correlation of EMG and tremor (discussed in Gantert et al., 1992; Timmer et al., 1998a). The cross coherence that we show in figure 2.1 is moderate at all frequencies. As the EMG "drives" the acceleration the result is inevitable. The slight elevation in cross coherence that occurs around 7- 13 Hz in all conditions and at the frequency of movement in the

dynamic conditions is almost certainly a feature of the improved signal to noise ratio at these frequencies. While cross coherence will measure the linear relationship between EMG and mechanical output it cannot express the effect of this correlation in terms of explaining how much of the tremor is due to EMG activity at different frequencies.

The gain between rectified extensor EMG and acceleration of the hand shows a pronounced peak which coincides with the frequency of the tremor

The gain between EMG and isometric force is well established (Bawa & Stein, 1976) It conforms to that of a second-order, low-pass filter so that as excitation frequency increases the size of the force fluctuations decreases until full fusion of the response occurs and the muscle cannot produce any pulsatile output. However, the gain between rectified EMG and acceleration does not appear to have been previously described. From Newton's second law, acceleration is proportional to force and it might therefore be expected that hand acceleration would behave in exactly the same way as muscle force. The present results show that that is not the case (figure 2.1, third row).

Gain is low at low frequencies and high frequencies, and has a pronounced peak at approximately 8 Hz in postural conditions, whether the hand was held in a bottom, middle or top position. This occurs because the hand to which the accelerometer is fastened acts as a resonant load. The load is susceptible to forcing. Small fluctuations in force close to the resonant frequency will produce exaggerated excursions of the limb at that frequency. The acceleration is the second derivative of that excursion and because the acceleration signal increases with the square of the frequency the acceleration will be very large at resonance. Thus the shape of the gain spectrum reflects the resonant properties of the hand, muscle and tendon.

It is possible to recreate this behaviour using an under-damped second order oscillator model (figure 2.6). The model consists of an inertial load which represents the hand and a spring which reflects the series combination of muscle and tendon. The model produces a realistic "tremor" spectrum when its input is either extensor muscle EMG or pure white noise.

The gain spectra are not statistically distinguishable under bottom, middle or top postural conditions all of which show a peak at approximately 8 Hz. This value is similar to those typically reported for hand tremor (Marsden et al., 1969a; Lakie, 1992; Raethjen et al., 2000b; Reynolds & Lakie 2010). Changes in static posture are not sufficient to alter tremor frequency. The inertia reflects the mass of the moving parts and is unlikely to change. The stiffness represents primarily the elasticity of the muscles, tendons and ligaments which cross the joint because the stiffness of the joint itself is trivial (Johns & Wright, 1962). The main cause of the stiffness lies in the series combination of the muscles and tendons (Loram et al., 2007). For the differences in degree of activation of the muscle required to maintain a "top", "middle" or "bottom" posture (figure 2.4) by counteracting gravitational forces the stiffness differences are negligible and the tremor frequency does not change.

The effect of slow movement on tremor

The relationship between postural tremor and tremor during movement has not been very extensively studied. Examining the discontinuities that occurred during slow movements of the finger, Vallbo et al. (1993) concluded that although there was a resemblance to tremor the discontinuities represented something different. However, these authors did not carry out a direct comparison of the postural tremor and dynamic tremor of their subjects. Kakuda et al. (1999) observed that the size of hand tremor was considerably larger during movement than when stationary and they predicted that the frequency would be lower.

Recently, Daneault et al. (2011) showed that during slow random tracking movements finger tremor amplitude increased by a factor of 4. They also showed that the median power frequency of the tremor reduced from 9.70 Hz in the static condition to 6.45 in the tracking condition.

Here we confirm that tremor size is greatly increased during slow movements. As the movement velocity increases up to a certain limit, the tremor size increases further. We studied slow movements; 0.1 Hz corresponds to a target velocity of only 6 degrees per second. Naturally, in performing the task, the subject's hand velocity will sometimes exceed this value and sometimes lag behind it. Figure 2.1 strongly suggests that there is a critical zone in which gain increases as movement speed increases. In maintaining a posture a limb is never perfectly still so the velocity is only transiently zero. We suggest that as the mean speed increases there is a rapid and progressive increase in gain coupling EMG to acceleration until a velocity of approximately 30 degrees per second is attained (0.5 Hz) when no further large increase in gain occurs.

Why does this increase in gain occur? In making these slow and low force movements only a small number of motor units will be required. Figure 2.3 shows that the range of EMG is comparable in dynamic and static conditions. In order to move, muscle must overcome its own stiffness and the stiffness of the surrounding passive muscle fibres. In the case of the hand there are also numerous relaxed synergistic and antagonistic muscles to consider. During (and for some time after) movement, the resistance to movement of these muscles is considerably reduced, a phenomenon known as muscular thixotropy which has been demonstrated in a range of human limb muscles (Axelson & Hagbarth, 2001; Hufschmidt & Schwaller, 1987; Lakie & Robson, 1988; Lakie et al., 1986; Proske et al., 1993; De Serres & Milner, 1991). We suggest that, during movement, muscle stiffness decreases,

producing both the considerable increase in size and the modest drop in frequency that is observed during movement.

The modest drop in frequency is of particular interest because the stiffness decrease of muscle during movement is very large. This has been shown by numerous studies in a range of in vitro and in vivo preparations. In the model we used a reduction factor of 15, derived from ultrasound calf muscle measurements (Loram et al., 2007). Resonant frequency is proportional to the square root of stiffness so it might seem that this would produce a frequency reduction of close to fourfold rather than the ~ 25% reduction which is observed. The reason for this is the unchanging and relatively low value of tendon stiffness which mitigates the overall stiffness decrease that occurs. The effect of altering the reduction factor is shown in figure 2.7. The increase in size and decrease in frequency of tremor during movement are similar to, but more pronounced than, the changes described immediately following movement (Reynolds & Lakie, 2010). This is because thixotropic muscle effects begin to reduce very rapidly immediately movement ceases (Lakie & Robson, 1988).

We have correlated tremor frequencies in postural and moving conditions (figure 2.5). The correlation suggests that there is a shift in frequency in each individual so that his or her tremor frequency drops by ~ 2 Hz during movement. The imperfection of the correlation is no surprise. Small variations in the spectrum from trial to trial introduce a degree of variability in the frequency of maximal oscillation. However, the systematic shift resulting from movement strongly suggests that hand tremor arises from a single process which is systematically altered by movement. The model that we demonstrate in figure 2.6 produces rather sharp frequency peaks as would be expected for a lightly damped second order oscillator driven by a random input. Real tremor is less sharply tuned. The reason is straightforward – the model uses a single fixed value of stiffness for static conditions and a

single fixed value of stiffness for moving conditions. The reality must be an ever shifting value of stiffness which reflects a parameter such as the mean muscle speed. More sophisticated models would work on this basis and would create broader and more variable frequency peaks.

There is nothing in the EMG spectrum during movement that suggests the emergence of a neural oscillator acting at the frequency of the tremor. The EMG spectrum is very similar to the spectrum in postural conditions. As the EMG does not change much and the acceleration changes considerably the simplest explanation is an alteration in the way in which muscle transduces EMG into acceleration.

The relationship of these results to central oscillators

Could the large tremor during movement represent something different from postural tremor? Looking at finger movements, Vallbo and colleagues (Vallbo & Wessberg, 1993; Wessberg & Vallbo, 1996) have determined that the discontinuities represent purposive intermittent adjustments in the neural drive to finger muscles that occur during slow movement. Kakuda et al. (1999) have extended this idea to hand movement. They have shown that during hand movement, but not posture, there is increased coherence between simultaneously sampled motor units in the hand extensor muscles and also between individual motor units and acceleration.

There has been a tendency to attribute the coherence to common descending central drive of motor neurones and there is an ongoing search for central oscillators operating at the appropriate frequency(ies) during movement. Our results for the wrist suggest an alternative interpretation. The fact that, during movement, there is a large resonant, asynchronously driven tremor implies that some common input to the motor units of reflex origin is perhaps more likely, with synchronising volleys of spindle activity perhaps

inevitably produced at the tremor frequency during movement but not in posture. Thus any coherence close to the tremor frequency may be a consequence of the tremor oscillation rather than its cause. In this respect, arguments about the phase shift or loop delay of such feedback pathways are not very relevant. Driving of the EMG as a consequence of movement may be destabilising or stabilising, but so long as the reflex gain is low it will not sustain an oscillation on its own (for example as proposed by Durbaba et al., 2005; Lippold, 1970). It is possible that the slight coherence between motor neurones or between motor neurones and tremor is a general phenomenon produced by resonance and spindle drive rather than by a central oscillator. Christakos et al. (2006) have shown that coherence might result from very small fluctuations in spindle length even in pseudo- isometric conditions. Such coherence would naturally be enhanced during movement when, as seen here, the resonance becomes much larger.

What are the implications of these new findings?

Tremor size increases and its frequency decreases even during very slow movement. This may provide an explanation for the wide range of tremor sizes observed in healthy subjects (Lakie, 1992). It is a testable hypothesis that larger physiological tremors are observed in subjects who are less able to keep still, and who are therefore at a physiological disadvantage when considering tremor. The reduction of tremor frequency as tremor size increases is consistent with observations of normal physiological tremor where it is a general finding that as tremor size increases its frequency decreases (Lakie, 1992). There is also the possibility of a form of positive feedback where movement caused by tremor might generate further tremor thus giving rise to an enhanced or possibly essential tremor. The results also have more general implications for motor control. They show that even slow movements have a very large effect on the effectiveness of coupling EMG activity to output. It has been previously suggested that muscle thixotropy produces a situation where

the nervous system is confronted by mechanical behaviour which is very difficult or perhaps impossible to predict because it depends on the history of movement and the presence or absence of other unassociated small limb movements (Lakie & Robson, 1988; Axelson & Hagbarth, 2001). A neural control system can compensate by using feedback. If feedback is too slow then predictive (internal model based) mechanisms can be used. The fickle nature of muscle must make such prediction very difficult and may favour a form of control such as "bang-bang" (where the initial input is a doublet, making this initial movement relatively large thereby surpassing the SREC) or trial and error in order to overcome this severe non-linearity in response.

CHAPTER 3.

MINIMISATION OF NEURAL INPUT OR RESONANCE REVEAL A KEY ROLE FOR RESONANCE IN FINGER TREMOR

There is a debate in the literature about whether the low and high frequency peaks of physiological finger tremor are caused by resonance or central drive. One way to address this issue is to examine the consequences of eliminating, as far as possible, the resonant properties or the voluntary drive. To study the effect of minimising resonance, finger tremor was recorded under isometric conditions and compared to normal isotonic tremor. To minimise central drive, finger tremor was generated artificially by broad-band electrical stimulation. When resonance was minimised, tremor size declined almost monotonically with increasing frequency. There was no consistent large peak at a frequency characteristic of tremor. Although there was sometimes a peak around the tremor frequency during some isometric conditions, it was extremely small and variable; therefore any contribution of central drive was minimal. In contrast, there was always a prominent peak in the *isotonic* frequency spectra. Resonance was therefore necessary to produce the characteristic tremor peaks. When central drive was minimised by replacing voluntary muscle activation with artificial stimulation, a realistic tremor spectrum was observed. Central drive is therefore not required to generate a characteristic physiological tremor spectrum. In addition, regardless of the nature of the driving input (voluntary or artificial), increasing the size of the input considerably reduced isotonic tremor frequency. We attribute the frequency reduction to a movement related thixotropic change in muscle stiffness. From these results we conclude that physiological finger tremor across a large range of frequencies is produced by natural broad-band forcing of a non-linear resonant system, and that synchronous central input is not required.

3.1 Introduction

Humans are unable to hold their fingers completely still; some trembling will always be present. This physiological finger tremor during posture is generally described as semi-regular oscillations of the limb with distinct acceleration peaks at one or two frequencies, around 8-12 Hz and/or over 15 Hz (e.g. Daneault et al., 2011; Elble, 1996; Raethjen et al., 2000b; Stiles & Randall, 1967). There is a long-standing debate on the origin of physiological finger tremor. Physiological tremor inevitably involves the resonant properties of the limb, possibly with some synchronisation of motor units through central and/or peripheral neural oscillations. In chapter 2 we have observed that all of the characteristics of *hand* tremor and pulsation during movement can be satisfactorily reproduced by a resonator driven by a noisy EMG input (Lakie et al., 2012). The evidence for relevant central oscillators is therefore tenuous and here we test the idea that the distinguishing features of physiological finger tremor do not require any central drive.

A prerequisite for any mechanical resonance is that a body must be able to move. Applying this principle to the origin of finger tremor, resonance should be revealed by a systematic comparison of isotonic and isometric tremor, measured by acceleration and force fluctuation, respectively. To our knowledge, this has not been done before in finger tremor. We know of only one study which has made this comparison, but this was for *hand* tremor. Hand tremor is different from finger tremor because its frequency spectrum is a single sharply tuned peak usually below 10 Hz, rather than the wide range (8 – 40 Hz) and somewhat broader tuning frequently observed in finger tremor. Burne and colleagues compared hand tremor in a ‘hand free’ and ‘hand fixed’ condition (Burne et al., 1984). They observed a sharply tuned peak in the EMG power spectrum, but only when the hand was free to move. This corresponded to the peak frequency of isotonic hand acceleration, leading the authors to conclude that the primary cause of tremor was the stretch reflex.

However, other studies have shown that the peak frequency of hand tremor does not match the peak frequency of the demodulated EMG (e.g. Raethjen et al., 2000b; Timmer et al., 1998b), which has been confirmed by our laboratory (Chapter 2; Reynolds & Lakie, 2010).

In the present study we systematically examine physiological *finger* tremor when the finger is fixed or free to move. We compare the relationship between EMG and either acceleration (isotonic) or force fluctuations (isometric). In particular, we examine the gain between EMG and acceleration or force to determine how the musculo-skeletal system acts at different frequencies. Since our recently published study (Lakie et al., 2012) suggests that tremor frequency and amplitude is altered by movement, we also incorporate different levels of muscular activation and movement.

A prerequisite for centrally generated finger tremor is input from the brain. In our second approach to resolving the debate, we minimise central input by studying artificially-evoked finger tremor using electrical stimulation of the relaxed extensor muscle. The technique is conceptually similar to the use of broad-band "stochastic" stimulation to probe the response of the vestibular system (Dakin et al., 2007; Reynolds, 2011; Scinicariello et al., 2002). We use random broad-band noise stimulation to ensure that what we observe is not the response to a frequency-specific component of the input signal. Just as we study various levels of muscle activation in the voluntary experiment, we systematically apply different RMS amplitudes of electrical stimulation.

Using these two experimental approaches, we address the following questions:

1) What is the effect on tremor of eliminating resonance?
2) What is the effect on tremor of minimising central drive?
3) What is the effect on tremor of altered levels of muscle activity?
4) What are the implications for physiological and pathological finger tremor?

3.2 Methods

Subjects

Six healthy right-handed subjects (age 20-56y, mean 21.6y, 3 male) participated in a voluntary muscular control study. Eight healthy right-handed volunteers from the same subject pool (age 21-58y, mean 29.3y; 7 male) participated in an artificial muscular control study. All showed typical tremor characteristics and gave their informed consent. Ethical permission was received from the University of Birmingham, and the experiment was carried out in accordance with the Declaration of Helsinki.

Apparatus and procedures

Subjects sat in a comfortable chair with their pronated right forearm supported in a foam rest situated at waist height. The hand was secured to a horizontal support with a central slot. This permitted unconstrained flexion-extension movements at the metacarpophalangeal joint of the splinted middle finger in the vertical plane.

There were two separate experiments, each with two conditions. In one condition, a small accelerometer (Model SCA3000, Active Robots, UK, 12.7x20.32mm) was attached to the nail plate of the middle finger to measure vertical tremor acceleration. This will be referred to as the *isotonic* condition. In a second condition, the splinted middle finger was attached to a very stiff steel bar instrumented with strain gauges (Model 632-124, RS Components Ltd, UK) to record exerted vertical tremor force. This will be referred to as the *isometric* condition.

Experiment 1: Preventing mechanical resonance (voluntary control)

In this experiment, participants voluntarily activated their extensor muscle. The activation they generated was therefore subject to central control. Muscle activation was recorded as

surface EMG from the belly of the extensor digitorum communis muscle (m. EDC, determined by palpation) using a Delsys Bagnoli system. A computer controlled bar target was displayed on a large screen oscilloscope (Model 1910, Wavetek, USA) 1.2 m in front of the subject. There were three trials in which the target was stationary (top, middle or bottom) and two trials in which it moved sinusoidally between the static top and static bottom positions at 0.1 Hz or 0.2 Hz.

For the isotonic condition, a retroflective laser (Model YP11MGV80, Wenglor Sensoric, Germany) pointed at a white reflector placed on the finger. The laser measured vertical finger movement, which was displayed to the subject on the oscilloscope. The participants' task was to align their displayed position with the target. Consequently, increasing amounts of activation were required respectively for a static bottom, middle and top posture and a slow and faster dynamic movement. The stationary middle position of the target was individually adjusted to a comfortable middle position of the finger. The top and bottom position (+10 cm and -10 cm from the middle position on the screen) corresponded to a finger angle of approximately 15 degrees upward or downward, spanning a total finger displacement of 30 degrees. The dynamic trials corresponded to a mean angular speed of approximately 6 or 12 degrees per second.

For the isometric condition, the force signal from the strain gauge was low pass filtered (time constant 2.0 s) and displayed to the subject on the oscilloscope. Participants were asked to align their generated force signal with the target. Thus the subject's task was to produce one of three levels of continuous force or to track alternately from the lower to the higher value at one of two different rates. Note that the trials involved the control of a steady or dynamically changing amount of generated force. There was never any actual finger *movement* in the isometric condition and thus never any thixotropic effects. Equal amounts of activation are desirable to be able to compare the isotonic and isometric

condition. Accordingly, the static top and static bottom positions of the target in the isometric condition were set in such a way that the EMG activation was comparable in the isometric and isotonic conditions. The mean levels of force ranged from 0.25 N (bottom) to 1.0 N (top), which were subjectively considered to be very low force levels.

All trials were performed for 60 s and rest periods were allotted between trials. Hardly any fatiguing was present during or between each trial Adequate practice was allowed so that the subjects could carry out each trial easily.

Experiment 2: Minimising central input (artificial control)

In this experiment, we artificially activated the subject's m. EDC by electrical stimulation. The activation that was generated did not require central control. Two aluminium electrodes (~1 cm^2 each), coated with electrode paste, were attached by tape to the skin over the muscle belly of the m. EDC. A neuromuscular stimulator (Model DS7A, Digitimer Ltd, UK), controlled by a pc, was connected to these electrodes.

Subjects were asked to sit as still as possible and to keep their arm and fingers relaxed during the entire experiment. Pseudo-random stimulus trains of small electrical currents were applied to the electrodes on the extensor muscle (duration of a single stimulus 50μs, duration of stimulus train 60 sec, frequency range 2 – 30 Hz). We wished to encompass the acceleration magnitudes produced in each of the five voluntary trials (static top, middle, bottom, dynamic 0.1 Hz and 0.2 Hz). Accordingly, we predetermined five stimulus intensities for each subject so that the range of tremor sizes was generously encompassed. Note that finger *position* during these trials does not correspond to the voluntary control experiments but their acceleration profiles do overlap. For each subject we adjusted the intensity so that a single shock produced a twitch with peak acceleration of 0.25 m s^{-2} and called this intensity 1. We then established the shock intensity required to produce a twitch

of 7.5 m s^{-2} and called this intensity 5. We used an empirically derived algorithm to set the intermediate intensities so that an approximately linear progression of response sizes resulted. The mean stimulus currents were 28mA, 33mA, 38mA, 42mA and 47mA (range 20-70mA). A single stimulus train at each of the five intensities was presented to the subjects in both the isotonic and isometric condition.

Data analysis

EMG signals were amplified by 1000 and band-pass filtered between 20 Hz and 300 Hz. Acceleration, force and EMG were sampled at 1000Hz and digitized using a MC 6026 PCI card. For all trials, the appropriate input signal (either stimulus train or EMG) and output signal (either force or acceleration) were processed using Matlab (MathWorks Matlab 2011a, Natick, Massachusetts, U.S.A.). Fast Fourier Transforms, resolution 0.12 Hz, were calculated for the input and output signals using neurospec-software for Matlab (Version 2.0, 2008. For a theoretical framework see Halliday et al 1995). The cross-coherence between rectified EMG and output signals was determined. In addition, the cross-spectral gain between the input and output signals was calculated. For the *artificial* control experiment it is not possible to record EMG during continuous stimulation. Accordingly, we computed stimulus-to-output gain for experiment 2 which does not provide the same unambiguous information about muscle properties as the use of EMG because the electrical stimulus may not be the sole input to the muscles. However we included the gain calculation because it provides a simple correction for differences in the level of stimulation and thus allows some degree of size comparison with the EMG-to-output gain in the *voluntary* experiments. For graphical purposes, individual frequency spectra were pooled together and smoothed (running average 0.015 sec). Finally, the mean level was subtracted from the average EMG spectra to compare the shape of the EMG spectra in the isotonic and isometric conditions for each trial.

To quantify the effect of increased muscular activity (both voluntary and artificial) on frequency changes, frequency spectra were split into five bins (0.25-5 Hz, 5-10 Hz, 10-15 Hz, 15-20 Hz, and 20-25 Hz) and the mean amplitude within each bin was calculated. We excluded frequencies below 0.25 Hz to exclude movement related components in the dynamic trials. A repeated measures ANOVA was used to examine mean EMG, acceleration, force and gains for each bin. Since the use of post hoc tests in a repeated measures ANOVA is controversial (Howell, 2010) and the results are clear, we decided not to check post hoc differences between frequency bins. In addition, paired samples t-tests were used to examine the frequency bins in which the outputs and gains were maximal per condition. Statistics were calculated using SPSS (v.18, Chicago, Illinois, U.S.A.) and all tests were considered significant with an alpha of $\leq 5\%$.

3.3 Results

Figure 3.1, left panel, displays the frequency spectra of the EMG averaged from all subjects measured in the isotonic and isometric condition. Shaded areas represent standard error. Mean EMG power is slightly greater in isometric conditions. As expected, it also increases slightly when more activation is required. To enable a direct comparison of spectral shape, the right panels show the same spectra with their mean subtracted. The EMG spectra all have a broad peak between 10 and 18 Hz. The shape of the spectra of isometric and isotonic conditions is remarkably similar in almost all trials, suggesting qualitatively similar neural input to the muscle. The biggest difference can be seen in the static top trial where the isometric condition shows more power at ~ 18 Hz. In the dynamic trials, there is inevitably a sharp peak at the frequency of movement (0.1 or 0.2 Hz). This

confirms that the EMG was recorded from the appropriate section of muscle controlling the finger.

Figure 3.2 displays the average frequency spectra for all subjects in the *voluntary* control experiment. The top panels illustrate the isotonic condition; the bottom panels illustrate the isometric condition. Shaded areas represent standard error. The left panels show the input spectra (EMG from figure 3.1 re-plotted), the middle panels show the output spectra (acceleration or force) and the right panels show the input-output gain. The acceleration spectra (top middle panel) all show a peak. For the static postural trials, this peak is quite broad, with power concentrated between 10 and 20 Hz. The mean level of acceleration increases with increasing levels of static activation and the peak becomes more pronounced and moves closer to 10 Hz. For the dynamic trials, mean acceleration increases further and

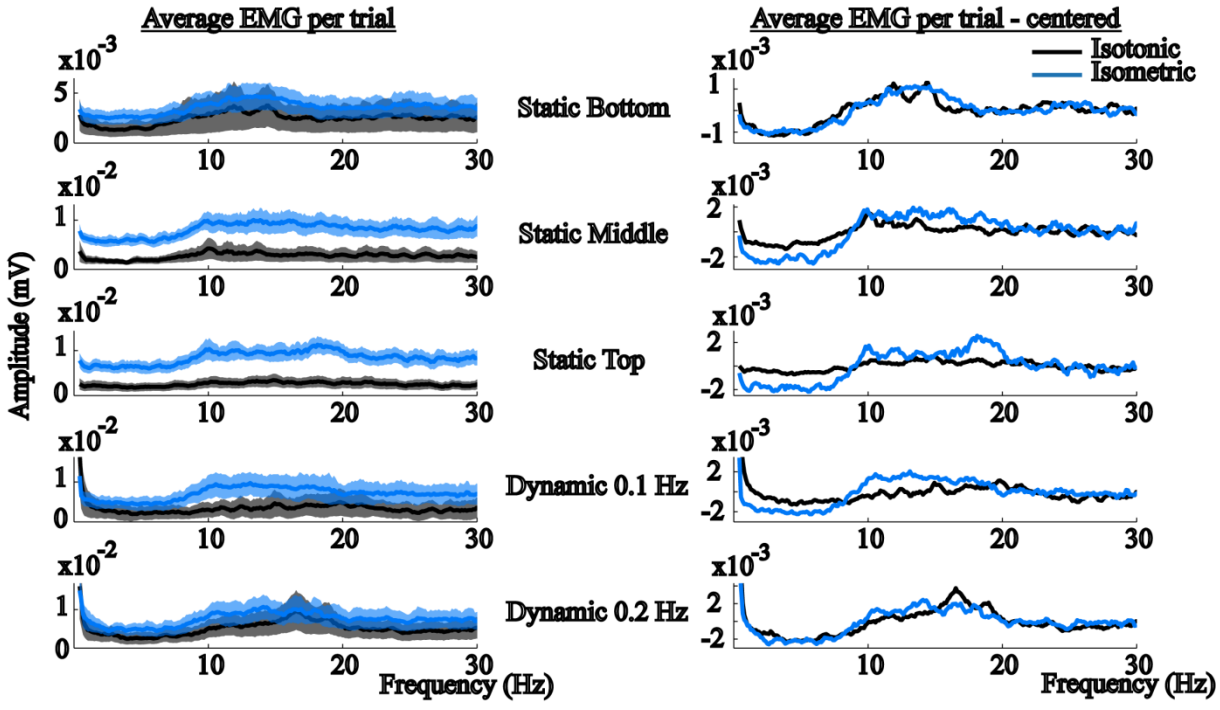


Figure 3.1 Frequency spectra of the EMG averaged per trial over all subjects

Isotonic condition (black traces) and isometric condition (red traces). Shaded areas represent standard error. Left: amplitude spectra; right: amplitude spectra with mean subtracted for a direct comparison of shape. In general slightly more EMG is generated in the isometric condition of all trials. The shape of the spectra is similar for isometric and isotonic conditions. The spectra all have a small peak 10-18 Hz.

the peak becomes sharply tuned at ~ 10 Hz. Additionally, there is a barely visible peak at the frequency of movement (0.1 or 0.2 Hz) which is probably due to tilt of the accelerometer. Interestingly, within each condition, the peak frequencies of acceleration and EMG do not coincide. For example, in the dynamic 0.2 Hz condition, peak acceleration and EMG frequencies occur at ~ 11 and 18 Hz, respectively. Furthermore, across conditions, acceleration peak frequency reduces with greater activation levels whereas there is a tendency for peak EMG frequency to increase (albeit non-significant). The relationship between EMG and acceleration is formally quantified by the cross-spectral gain (top right panel). Gain for static trials has a distinct peak at low (~ 10 Hz) and high (20 – 25 Hz) frequencies. The low frequency peak becomes more prominent as activation increases.

The force spectra, obtained in the isometric condition, are shown in the bottom middle panel. The force spectrum declines at a decreasing rate at higher frequencies. This holds for all trials. As activation increases, the amplitude of the force spectrum becomes larger at all frequencies and, on the semi-logarithmic plots shown here, forms a series of approximately parallel curves. In some of the static spectra there is a small peak or inflection around 10 Hz. The EMG-force gain plots (bottom right panel) are quite similar to the force spectra, and mainly decreases in amplitude with higher frequencies. Again, a small modulation can be seen ~ 10 Hz, indicating this locally increased amplitude is not due to specific EMG activity at that frequency. The difference between static and dynamic trials, while clear, is much smaller than under the isotonic condition.

Cross-coherence was calculated between rectified EMG and the output signals (acceleration for isotonic tremor and force for isometric tremor). As the EMG drives the acceleration and force there was, as expected, a moderately high degree of coherence between EMG and the output signals at all frequencies (see figure 3.3). The dashed line

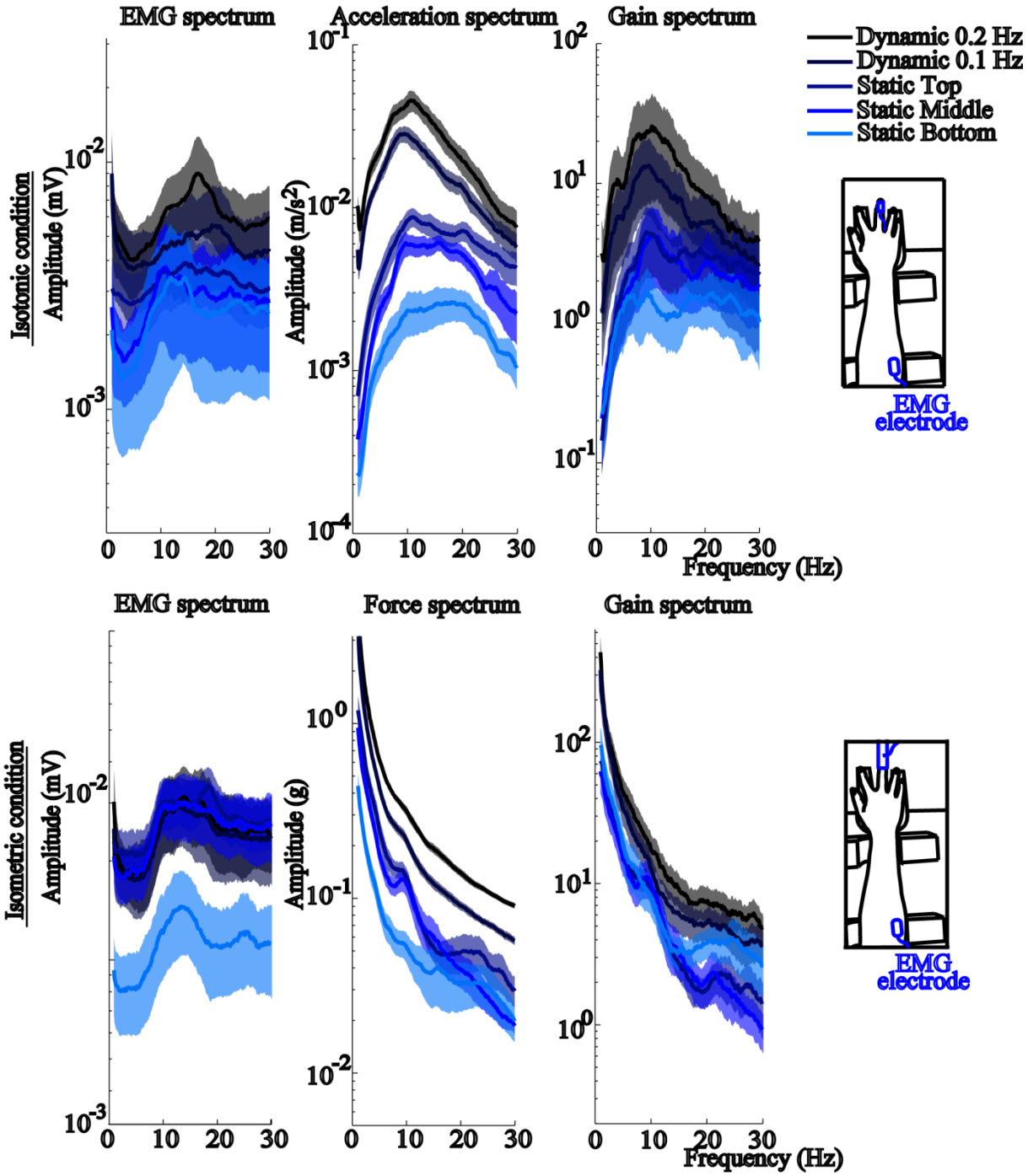


Figure 3.2 Frequency spectra averaged per trial over all subjects in the *voluntary* control experiment.

Top panel: isotonic condition; Bottom panel: isometric condition. Shaded areas represent standard error. Left: input (EMG); middle: output (acceleration or force); right: cross-spectral gain. The isotonic acceleration always shows a peak. Acceleration amplitude rises and frequency drops with increased level of activation. The isotonic gain shows a broad spectrum with a small peak ~20Hz for lower activation trials. Gain size is increased and sharply peaked at ~10Hz for dynamic trials. Isometric force and isometric gain show a decay in amplitude with higher frequencies, and show an overall rise in amplitude with increased level of activation.

shows the upper level of the 95% confidence interval for the hypothesis that the two processes are independent. In almost every case, in both isotonic and isometric conditions, coherence is highest between 8 and 15 Hz. The magnified inset shows the very high degree of coherence between rectified EMG and force or acceleration at the low frequencies of voluntary activation (0.1 or 0.2 Hz) in the dynamic conditions.

Figure 3.4 displays the frequency spectra averaged from all subjects in the *artificial* control experiment. This figure strikingly resembles figure 2. The top panels illustrate the isotonic condition; the bottom panels illustrate the isometric condition. Shaded areas represent the standard error. The left panels show the input spectra (stimulations), which confirm an equal distribution of frequencies. The middle panels show the output spectra (acceleration or force) and the right panels show the input-output gain. The acceleration spectra (top middle panel) all show a peak. At low stimulus intensities, the acceleration spectrum has a

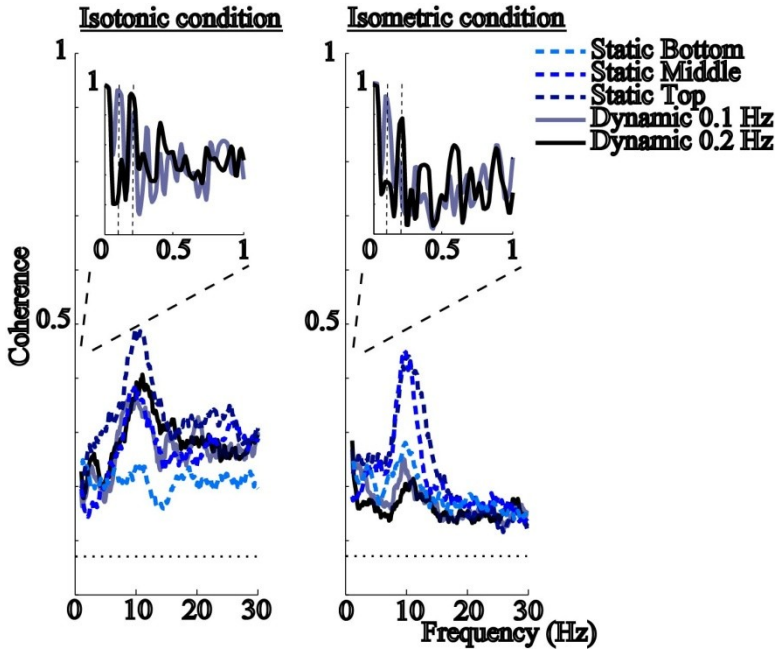


Figure 3.3 Coherence spectra averaged per trial over all subjects in the *voluntary* control experiment. Left: isotonic condition; right: isometric condition. The horizontal dashed line represents the upper level of the approximate 95% confidence interval for the hypothesis that the two processes are independent. The coherence spectra are quite similar for all trials and both conditions. The coherence has a mean level of 0.3 at all frequencies. In nearly all trials, coherence is higher 8-15 Hz. The inset displays a magnified 0-1Hz range of the two dynamic spectra, showing a very high coherence at the frequencies of movement.

peak at approximately 18 Hz. At higher stimulus intensities, acceleration levels rise, become sharply tuned and the peak frequency decreases to ~ 10 Hz. The cross-spectral gain between the stimuli and the acceleration is shown in the top right panel. The gain is largest at ~ 18 Hz. With higher stimulus intensities, the overall gain increases and the peak shifts to ~ 10 Hz.

The frequency spectra of the force measured during the isometric condition are shown in the bottom middle panel. The force shows a fall-off in amplitude with higher frequencies. With increasing stimulus intensities, there is an overall increase in force and this increase leads to almost parallel spectra. The stimulus-to-force gain (shown in the bottom right panel) also decreases with higher frequencies, in an almost linear fashion on the semi-logarithmic plot. Increased stimulus intensities produce elevated gain. In the isometric condition, there are no identifiable frequency peaks, in stark contrast to the isotonic gain.

We wanted to examine shifts in frequency that occurred with increasing muscular activation, and also to compare voluntary with stimulated activation. Accordingly, the input, output and gain data were reduced to frequency bins for statistical evaluation.

Figure 3.5 shows the mean acceleration (top two plots) and force (bottom two plots) within each of five frequency bins (0.25-5 Hz, 5-10 Hz, 10-15 Hz, 15-20 Hz, 20-25 Hz). The left and right plots resulted from the *voluntary* and *artificial* control experiments, respectively. Asterisks represent frequency bins where power was greatest. We chose to plot output size rather than gain since for the *artificial* control experiment the gain provides less clear information and for both experiments the paired samples t-tests showed output and gain would provide similar graphs. For all levels of activation, in both *voluntary* and *artificial* control experiments, the generated isometric force is highest in the lowest frequency bin (0.25-5 Hz, indicated by *) and declines with increasing frequency. ANOVA showed

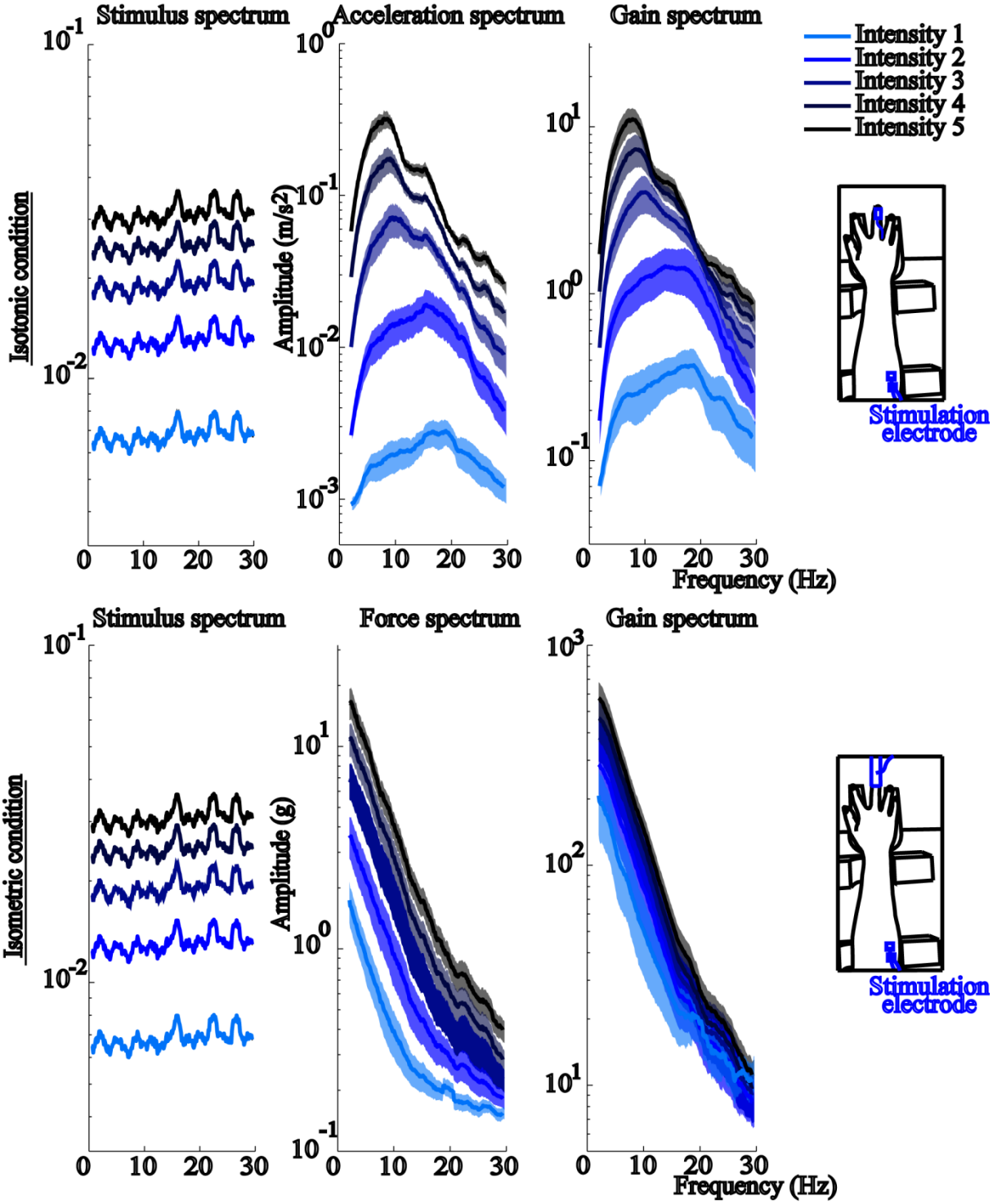


Figure 3.4 Frequency spectra averaged per trial over all subjects in the *artificial* control experiment.

Top panel: isotonic condition; Bottom panel: isometric condition. Shaded areas represent standard error. Left: input (stimulations); middle: output (acceleration or force); right: cross-spectral gain. Stimulations confirm white noise input, which means output and gain are similarly shaped. The isotonic acceleration and gain always shows a peak. Amplitude rises and frequency drops (~20Hz to ~10Hz) with increased level of activation. Isometric force and isometric gain show a decay in amplitude with higher frequencies, and show an overall rise in amplitude with increased level of activation.

significant main and interaction effects of frequency bin and activation for both force and gain (All $p < 0$ .01, F-value range: $F_{(1.533,10.729)} = 9.417$ to $F_{(2.074,10.371)} = 638.483$). For low levels of *voluntary* and *artificial* muscle activation, isotonic acceleration and gain is peaked in the 15-20 Hz bin. With increasing muscular activation, acceleration and gain level significantly increase, while the peak frequency significantly reduces to 10-15 Hz (*voluntary*) and 5-10 Hz (*artificial*) (indicated by *, all $p < 0.001$). Importantly, there was also a significant interaction between frequency bin and intensity for acceleration and stimulus-to-acceleration gain (both $p < 0.001$), demonstrating that the peak frequency shifted with higher levels of muscular activation. Unfortunately, EMG-to-acceleration gain did not show these significances, possibly due to large variability in EMG bins. Frequency and intensity had no significant effect upon *EMG* input ($p > .05$). Crucially, there was no interaction between frequency and intensity ($p > .05$), indicating that the distribution of EMG did not change with higher levels of muscular activation.

3.4 Discussion

We now consider the questions we posed.

What is the effect on tremor of eliminating resonance?

EMG spectra always showed a broad peak for both isometric and isotonic finger tremor, but this peak frequency was variable over trials and participants. This is in agreement with other studies reporting frequency-specific, broadly tuned extensor EMG spectra when the finger is outstretched (e.g. Halliday et al., 1999; Raethjen et al., 2000b; Wessberg & Kakuda, 1999). Most likely, the peak in the EMG reflects some fluctuating synchronization of individual motor unit firing (Christakos et al., 2009; Halliday et al., 1999). Figure 3.2 shows that with increasing activation the EMG peak frequency increases

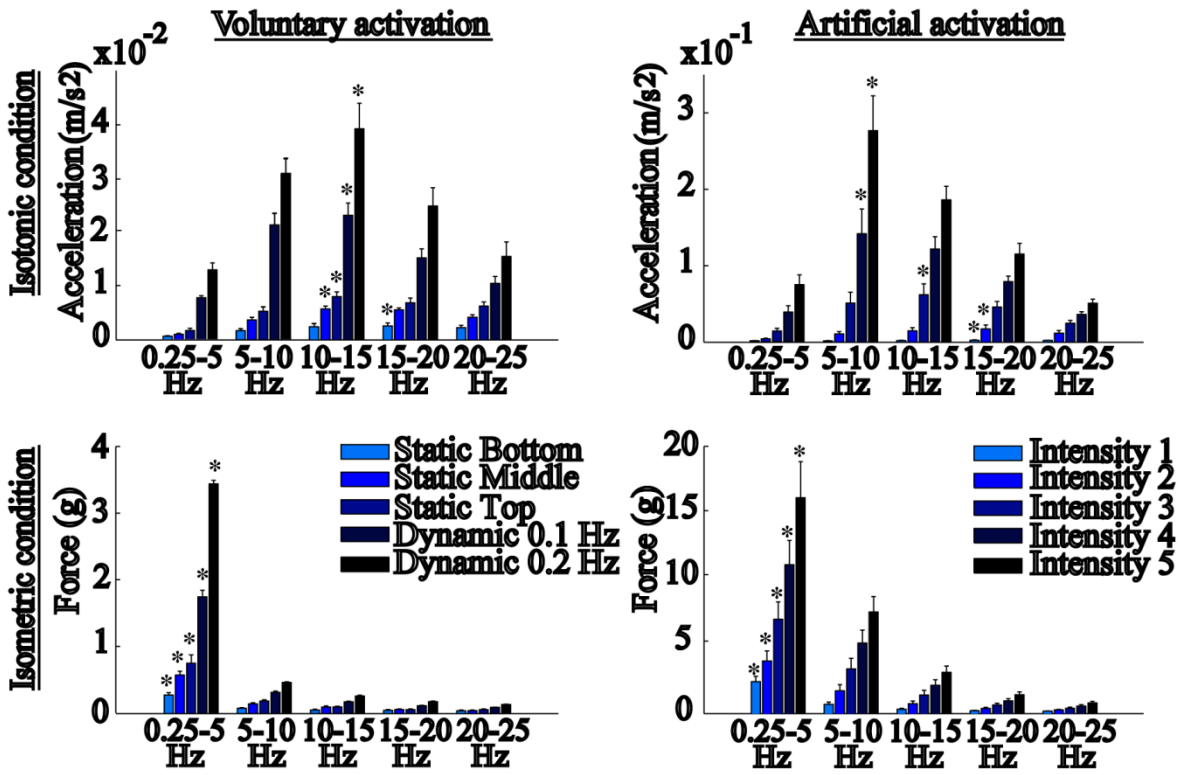


Figure 3.5 Mean acceleration (top) and force (bottom) within each of five frequency bins.

Left: *voluntary* muscular activation experiment; right: *artificial* control muscular activation experiment. Asterisks (*) represent the bins in which the maximal amount of acceleration and force per level of muscular activation was found. For all levels of activation, in both experiments, the generated force is highest in the lowest frequency bin (0.25-5 Hz) and declines over frequencies. Acceleration is peaked in the 15-20 Hz bin (indicated by *) for low levels of activation. With increasing muscular activation, the frequency bin containing most acceleration decreases to the 10-15 Hz bin (*voluntary*) and the 5-10 Hz bin (*artificial*).

\slightly, as might be expected based on a higher discharge frequency of motor units (Henneman, 1956; Wessberg & Kakuda, 1999).

As far as we are aware, only Burne et al. (1984) have studied the origin of tremor by comparing isotonic and isometric tremor. In their study on *hand* tremor they found an acceleration peak at 9 Hz exclusively in isotonic conditions. However, unlike the present study, they also found a large sharply tuned peak at 9 Hz in EMG under isotonic conditions, which they interpreted as part of a self-sustaining, neurally generated, mechano-reflex oscillation. The reason for this different result is not clear. In contrast to

the current research, they studied the hand. Hand tremor can be represented by a single sharply tuned peak in the acceleration spectrum and therefore shows a different behaviour to finger tremor. However other studies do not show a sharply tuned peak at a corresponding frequency in the associated EMG (e.g. Deutsch et al., 2011; Halliday et al., 1995; Lakie et al., 2012; Reathjen et al., 2000). It is possible that the sharp peak they observed is due to increased synchronization of EMG activity due to fatigue (e.g. Hagbarth & Young, 1979). Addition of extra motor fibres firing in synchrony will increase the coherence between EMG and acceleration or force. In our results for the finger there was no simple relationship between the frequency of the tremor and the EMG. For example, in figure 3.2 as activation increases and tremor frequency decreases, there is no corresponding reduction in the peak frequency of the EMG.

Unlike the input spectra (EMG), the output spectra (force and acceleration) were not similar across conditions. For all levels of activation, isometric force decayed with increasing frequency in an approximately exponential fashion. This is a well-known phenomenon of force production in muscle tissue. Several studies on the properties of soleus muscle in cat (Bawa et al., 1976a; Mannard & Stein, 1973) and human (Bawa & Stein, 1976; Stein et al., 1972) confirm that a muscle acts like a second-order low-pass filter when it is voluntarily activated or when the muscle nerve is stimulated with either single pulses or a random pulse train. If there is a synchronization of motor units at a specific frequency, the amplitude of force fluctuation increases at that frequency (Christakos et al., 2006; Elble & Randall, 1976; Allum et al., 1978). Christakos et al. showed a variable degree of motor unit synchronisation and the effect was a localised peak around 10 Hz in the force spectrum of the FDI muscle of some subjects. To a degree this was also observed in our data. This is considered in more detail below.

In contrast to force, acceleration always displayed an obvious peak in the spectrum. For low levels of activation, this peak was ~20 Hz. With increasing amounts of activation, it dropped to ~10 Hz and the overall amplitude of acceleration increased. In general, when the finger is held outstretched, i.e. a postural configuration, its tremor is described as acceleration with two main components in its spectrum: one between 8-12 Hz and one between 15 - 30 Hz (e.g. Daneault et al., 2011; Elble, 1996; Lakie et al., 1992; Raethjen et al., 2000b; Stiles & Randall, 1967). Most studies show an altered frequency spectrum when inertia is added to the finger or during slow movements of the finger. It seems to be a general finding that under postural conditions tremor tends to be dominated by high frequencies (Daneault et al., 2011) whereas when increased level of activation is required, as in loading (Stiles & Randall, 1967) or tracking conditions (Vallbo & Wessberg, 1993; Wessberg & Vallbo, 1995, 1996), the high frequency peak drops to a lower frequency or the low frequency greatly predominates. Our results (see figure 3.2) reflect these findings.

What is the effect on tremor of minimising central drive?

In our hand tremor study (Chapter 2), we found that a model of the limb generated life-like tremor whether the input was pre-recorded EMG or white noise. Here we used random per-cutaneous electrical stimulations to implement this in a real physiological system. This procedure eliminated central input as far as possible. Conveniently, the amplitude of the electrical stimulus could be tailored to generate comparably sized tremor in all subjects. This also allowed us to explore a larger range of movements than in the voluntary control experiments. We used five levels in each experiment, so there is considerable overlap between tremor sizes under *artificial* and *voluntary* control. As expected, experiments using *artificial* control generated congruent results to *voluntary* control and the changes between trials became much clearer because of the reduction in inter-subject variability in tremor size. It is of particular interest that with artificial input of appropriate size, the low

frequency acceleration peak (8-12 Hz), previously attributed to neural causes, is clearly apparent. Eliminating the central input does not seem to have a large influence on the tremor spectra, which depend almost entirely on the size of the input spectrum (whether artificial or voluntary) rather than its shape.

Because the gain spectra were calculated from the applied stimulation they are virtually identical to the output spectra (see Methods). The precise input to the muscle cannot be known, because we were unable to record EMG simultaneously during stimulation. Theoretically, the EMG may have included reflex or voluntary components that might affect our interpretation of the gain calculation. *Voluntarily* generated activation is likely to be minimal since subjects were instructed to stay relaxed, and is not likely to increase systematically with increased stimulation. The role of *reflex* activation in tremor generation is unclear; previous studies are contradictory or fail to include the effect of their experiment on muscle properties (e.g. Marsden et al., 1969b; Lakie et al., 2004). Reflex activation might increase with activation level. However, the output spectra are very similar with *voluntary* and *artificial* control and overlap in amplitude. This implies that the pattern of EMG driving both is likely to be similar. As there was no EMG peak at the tremor frequency in the voluntary control experiment there is no reason to expect that stimulation would generate a peak at that particular frequency. So, although we cannot rule out stretch reflex mechanisms during artificial control, it is not a likely explanation for the clear difference between isotonic and isometric tremor.

What is the effect on tremor of altered levels of muscle activity?

The cross-coherence describes the *strength* of the relationship between the input (EMG) and output (acceleration or force). It is a correlative measure. Unlike the transfer function, describing gain and phase, the nature of a system cannot be inferred from the coherence.

The meaning of a low coherence is that there is a substantial amount of noise (uncorrelated with the input) present in the output. The very high degree of coherence at the frequency of voluntary dynamic activation (0.1 or 0.2 Hz) is a strong indication that the EMG we recorded is intimately involved in the generation of the output. The power of the EMG is maximal at this frequency of voluntary modulation. In nearly all conditions there is a local peak in the coherence between 8 and 15 Hz. Coherence is likely to be greater at these frequencies because the majority of spontaneous EMG power, and thus relatively the least amount of uncorrelated noise, is found there (figure 3.1). It is particularly interesting that the coherence spectra are very similar in isotonic and isometric conditions. A possible cause of the increased coherence between 8 and 15 Hz could be synchronisation of motor unit firing at these frequencies. However, much larger afferent activity from the muscle produced under *isotonic* conditions would be expected to greatly increase the amount of synchronisation. Since our results indicate that the extent of any such synchronisation is similar in the isotonic and isometric conditions substantial motor unit synchronisation seems unlikely.

In contrast to coherence, the cross-spectral gain shows the *quantitative* relationship between input and output at each frequency and thus provides information about the system under investigation. The distinction between coherence and gain is very clear when comparing figure 3.2 and 3.3. In our study, the gain reflects the properties of the muscle and limb and it is therefore ideal for examining changes in the muscle's properties that occur with altered activation levels.

For the isometric condition, with EMG as input and force as output, we found that the gain dropped almost exponentially at higher frequencies and is negligible at frequencies over ~15 Hz. It increased slightly with activation level, which possibly reflects progressive recruitment of larger motor units. Bawa & Stein (1976) studied the properties of human

soleus muscle and calculated the gain between single or random trains of electrical nerve stimulation and muscle force. They found a declining stimulus-to-force gain at higher frequencies reflecting increasing twitch fusion. Therefore, the decay in gain in our results was expected. Additionally, there is a small inflection at ~ 10 Hz visible in the static isometric gain spectra, which reflects those seen in the force spectra (figure 3.2). The cause of these minor peaks in the force and gain is unclear. The absence of corresponding peaks in our measured EMG strongly suggests that synchronisation of motor neuronal firing is not responsible. A possibility is that there is some force generated by activity of one or more motor units, firing at < 10 Hz, which did not register because contributions of individual motor units cannot always be detected in an EMG signal. However, when subjects voluntarily modulated their force in the dynamic conditions there was very strong coherence between EMG and force at the low frequency of voluntary modulation. This suggests that we were recording from a part of the muscle closely involved with driving the finger. Certainly, the force peaks, while superficially similar in frequency to the isotonic tremor, were miniscule, variable within and between subjects, and nothing like the very large peaks seen under isotonic conditions. We do not think that our study shows *tremor* under isometric conditions. We think it is a small component of force fluctuation due to poorly fused motor unit activity at firing frequency (Dideriksen et al., 2012). However we cannot say categorically that a central oscillator never operates in isometric conditions.

The gain for the isotonic condition was very different from the isometric gain. The results show that the EMG-to-acceleration gain always had a peak. The broadband nature of the EMG and the peak in gain show that isotonic tremor is a consequence of resonance produced by the mechanical properties of the muscle-limb rather than anything specific in the EMG input. The peak in the gain spectrum became clearer and dropped from ~ 20 to 10

Hz with increased activation. Even though EMG displayed more overall power with increased activation, this drop in frequency of the peak gain shows that the tremor at low frequency results from an altered frequency-specific *amplification* of the EMG input, rather than an *increase* in EMG power. The peaked gain in isotonic trials, and its absence in isometric trials, suggests a strong influence of a mechanical resonance. With increased activation, amplitude increased as expected but the frequency of the resonance decreased. This behaviour is not due to the firing frequency of motor units; which rises with increased activation (voluntary) or stays the same (artificial). Neither is it a consequence of recruiting different motor units. As voluntary activation increases, progressively larger and faster motor units are recruited. This will not be true for artificial activation which tends to stimulate the largest motor units first. However resonant frequency decreases similarly as both modes of activation are increased. Our results are consistent with a resonant system driven by largely random noise. It is possible that there is some minor peripherally generated synchronisation of EMG activity that we fail to detect produced by the very small muscle movements in the isometric condition. However, under isotonic conditions where muscle movement is much larger, and when electrically stimulated where motor unit firing is more synchronised, entrainment should be very obvious. Yet it does not occur.

What are the implications for physiological and pathological finger tremor?

These results are qualitatively similar to the behaviour of hand tremor which we recently reported (Chapter 2; Reynolds & Lakie., 2010). We reported that hand tremor decreased in frequency from 8 Hz when postural to 6 Hz when moving. We proposed an explanation based on resonance of the inertia of hand and stiffness of tendon and muscle. We suggested that a substantial reduction in muscle stiffness accompanied movement and reduced resonant frequency (muscle thixotropy). However, the reduction in resonant frequency was relatively modest because the relative compliance of the tendon caused the overall stiffness

to drop only ~ 2-fold. In the case of finger tremor the change in frequency from 20 Hz to 10 Hz is much greater. How can this be explained? We can suggest two possibilities. Possibly, because the finger has a smaller inertia than the hand, its resonant frequency will be altered more by any change in stiffness. Alternatively, perhaps a switch between different modes of oscillation occurs. During low levels of activation the muscle will be very stiff and the tendon and finger may resonate as a unit at high frequency. When activation is large, the muscle stiffness starts to drop due to its thixotropic nature (Axelson & Hagbarth, 2001; Lakie & Robson, 1988; Proske et al., 1993). Consequently, more of the muscle resonates with the tendon and finger causing a substantially lower resonant frequency. This second possibility implies that tremor can coexist as two modes of oscillation, so that, as muscular activation and movement increase, a growing low frequency peak becomes superimposed upon the high frequency peak. These alternatives are studied in the next chapters.

Our results show that isotonic physiological finger tremor as generally recorded is mainly a consequence of mechanical resonance. During movement, the finger resonates at ~ 10 Hz and when there is little movement (static posture) the finger trembles at ~ 20 Hz. When a finger is held outstretched the amount of muscle movement will naturally vary. As tremor is always recorded over a period of many seconds it is therefore likely that both frequency peaks will appear in the spectrum. In finger tremor it is never certain which peak *(high or low frequency)* would be larger, sometimes consecutive recordings from a single subject could be different (Lakie et al., 1992). Possibly, different resonant mechanisms predominate at different instants. Furthermore, long periods of immobility have been shown to raise the resonant frequency of the relaxed finger driven by impulses from 13 ± 8 to 20 ± 9 Hz (mean ± sd) (Lakie and Robson, 1988). On this basis, the high frequency tremor will occur at times when the subject is most purely postural, to be replaced by low

frequency tremor when muscle movement occurs. The observations that we make are confined to physiological tremor. Certainly it is a fact that essential tremor and Parkinsonian tremor, which have a larger size, have low frequencies. However, in Parkinsons disease and in some cases of essential tremor there is no doubt that central oscillation is involved.

CHAPTER 4.

FINGER TREMOR CAN BE RECREATED BY BROAD-BAND MECHANICAL OR ELECTRICAL DRIVE

Physiological finger tremor has two frequency peaks of variable preponderance. High frequency spectral peaks (> 15 Hz, predominating in postural tremor) are thought to be due to mechanical resonance, whereas lower frequency peak (8-12 Hz, dominating dynamic tremor) is usually explained by synchronous central or reflexive neural drive. Here, we determine the contribution of mechanical resonance to both high and low frequencies. Artificial finger tremors were produced by random torque or muscle stimulation in relaxed subjects. Resonant frequency (inferred from gain and phase) always varied inversely with the size of the input, from > 20 Hz at the lowest level, down to ~ 10 Hz at the highest. The high and the low physiological tremor frequencies can both be produced by entirely random inputs of appropriate size. We wished to show that the size/frequency relationship was mechanically caused and not due to altered central or spinal neural drive. First, finger extensor EMG, recordable only with torque inputs, showed some activity in four subjects, but these 'active' subjects had almost identical tremor spectra to the eleven 'passive' subjects. Second, muscle stimulation applied to 2 clinically deafferented controls produced similar results to our typical subjects, thus excluding stretch reflexes. Our results suggest that mechanical resonance can explain the full spectral range of postural and dynamic physiological finger tremor. A specific neural input of central or spinal origin is not necessary to produce any of the tremor frequencies. The inverse relationship between the intensity of the driving input and the peak frequency of the resulting tremor can be explained by a movement-dependent reduction in muscle stiffness, a conjecture we support using a simple computational model.

4.1 Introduction

When holding a hand in a static posture, its physiological tremor is characterised by a single prominent peak in the acceleration spectrum at a frequency between 7 and 11 Hz (Lakie, 1992; Wade et al., 1982). It is known that the precise frequency of this single peak depends on the contemporaneous (Stiles, 1976, Lakie et al., 2012), and preceding (Reynolds & Lakie, 2010) amount of movement of the hand. Movement causes a moderate drop in frequency. This transition from postural to dynamic tremor has been successfully reproduced by a very simple model of the hand, muscles and tendons as a resonator with the key feature that the stiffness of the controlling muscles falls during movement (Lakie et al., 2012). The input to the resonator is the random noise of muscle activity. More recently, we have shown corresponding effects in finger tremor. Here the drop in frequency of the peak from postural to dynamic tremor is much more obvious (Vernooij et al., 2013c). Although the finger tremor frequency reduced very markedly, there were no corresponding alterations in EMG. Furthermore, EMG never showed distinct peaks at the tremor frequency in postural or dynamic conditions.

These findings are interesting because it is well known that in normal postural physiological finger tremor there are two peaks of variable preponderance (Lakie, 1992). The high frequency peak (typically > 15 Hz) *is* generally thought to be mechanical resonance, because the finger is believed to resonate only at these high frequencies (e.g. Elble, 1996). Consequently, the lower frequency peak (usually described as 8 - 12 Hz, or often simply 10 Hz tremor) *is not* generally attributed to resonance. Instead, it is usually attributed to synchronous neural drive. This phrase commonly implies not the sub-tetanic ripple in muscle force output caused by individual motor unit firing, but rather a synchronised modulation of the envelope of neural firing of all contributing motor units produced by reflex or central mechanisms (reviewed by McAuley & Marsden,

2000). However, our results suggested the new possibility that *all* frequencies (including the 10 Hz component) of finger tremor might be produced by a resonant mechanism. A fact that has not usually been thoroughly considered is that the natural resonant frequency of the finger is not fixed (Lakie & Robson, 1988) since muscle, and hence joint, stiffness depends strongly on its history of movement. Muscle stiffness decreases dramatically during movement and recovers progressively over a period of seconds. This movement dependence is called thixotropy (Lakie et al., 1984; Proske et al, 1993; Reynolds & Lakie, 2010; Campbell, 2010). Reflecting Lakie and Robson's finding, our study on finger tremor suggested that thixotropic changes in muscle stiffness when the finger is moving produce a large drop in physiological tremor frequency so that dynamic tremor is dominated by the 10 Hz peak and the 20 Hz peak vanishes (Vernooij et al., 2013c). Consistent with this suggestion, we were able to create a comparable range of artificial tremor frequencies by the use of appropriately sized purely random electrical stimulation of the relaxed finger extensor muscle. We therefore proposed that mechanical resonance could shape the low, as well as high, frequencies of the tremor spectra. However, a limitation of generating artificial tremor by electrical stimulation was that a possible contribution of spinal neural input (motor unit synchronisation due to stretch or other reflexes induced by our stimulation) could not be excluded, because we were unable to record EMG during muscle stimulation.

Here, we study the influence of mechanical limb resonance on finger tremor while excluding any possible central or reflexive components. We employ a novel type of artificially evoked finger tremor that enables the recording of EMG activity. To this end, we generate small finger movements by applying random mechanical perturbations directly to the middle finger using a miniature torque motor. Synchronisation due to central drive or peripheral reflex mechanisms can then be detected by analysis of

EMG. Specifically, we look at the effect of thixotropic changes of muscle stiffness to explain the different tremor frequencies seen during posture and movement. As thixotropy is related to velocity of movement (amount of movement over time), we generate artificial tremor with movement velocities comparable to those prevailing in postural and dynamic conditions. The resultant mechanically generated tremor can then be compared with physiological postural and dynamic tremor and with an electrically evoked analogue (as used in Vernooij et al., 2013c). Furthermore, we applied our method of randomised electrical stimulation to two patients with a profound large fibre sensory neuronopathy in whom reflexes are absent. We additionally employ our spring-mass model (Lakie et al., 2012), tuned to finger properties, to test whether the observed tremor spectra can be recreated solely by mechanical resonance.

4.2 Methods

Fifteen healthy, right-handed subjects (aged 24.7±10.1 (mean±sd); 8 male) volunteered to participate in this study. All gave their informed consent. Two control subjects suffering from extensive large fibre sensory neuronopathy participated in one of the experiments. Ethical permission was received from the University of Birmingham, and the experiments were carried out in accordance with the Declaration of Helsinki.

Apparatus and procedures

Subjects sat in a comfortable chair with their pronated right forearm supported in a horizontal foam rest placed at waist height. The ring finger and index finger, as well as the knuckles and wrist, were very firmly strapped to a rigid U-shaped aluminium rest (see figure 4.1) that permitted unrestrained vertical movement of the middle finger. No other

movements of the hand or fingers were possible. Subjects were asked to sit as still as possible and to keep their middle finger relaxed.

A small accelerometer (Model SCA3000, Active Robots, UK, 12.7x20.32mm) encased in epoxy resin was attached on top of the distal phalanx of the middle finger to measure its vertical acceleration. A light duraluminium bar strapped to the finger acted as a splint to restrict movements to the metacarpophalangeal (MCP) joint. A thin (diameter 2.5 mm) titanium crank extending from a miniature servomotor (Maxon Type D, Switzerland) was attached to the distal end of the middle finger. The rotary axis of this low-inertia motor was aligned with the MCP joint. The motor was connected as a torque servo (Type 201583 Maxon amplifier, Switzerland) which converted an input voltage to torque. As well as imposing any desired torque perturbations, the motor supplied a minor offset torque to counteract the weight of the titanium linkage. For five subjects, a miniature strain gauge (Model 632-124, RS Components Ltd, UK) was cemented to the titanium linkage to directly measure the force, and therefore torque, applied to the finger. Analysis of this torque confirmed that it faithfully recreated the voltage signal supplied to the motor.

We studied three conditions. In the first condition we measured voluntary physiological postural tremor and dynamic tremor during slow approximately sinusoidal movement. In the second condition, an artificial tremor was generated by random mechanical perturbation. In the third condition, an artificial tremor was generated by random electrical stimulation. We wanted to compare the two types of artificial tremor with physiological postural tremor and dynamic tremor during slow movement. Because it is impossible to recreate slow movement by random electrical stimulation we adopted a different approach. We employed six different preset levels of torque and stimulation input. The effect was to produce six distinct amounts of finger motion. With the smallest inputs there was a barely visible movement of the finger. This was the analogue of postural tremor. As the inputs

increased, finger movement also increased, becoming comparable to movements associated with dynamic tremor. In all cases we used RMS velocity as our measure of movement. We used six increasing levels of input so that we could be sure of encompassing the postural and dynamic range. Each trial lasted 60 seconds and each stimulus train was presented once to each subject. Rest periods were obligatory between trials to minimise muscular fatigue.

Voluntary physiological finger tremor

We measured the subject's normal physiological finger tremor during static posture and dynamic tremor during movement. In the postural trial, subjects were asked to actively hold their middle finger at a comfortable middle position, which was midway between flexion and extension at MCP. In the movement trial, subjects were asked to sinusoidally flex and extend the finger through a range of ~ 50 degrees at 0.1 Hz using pursuit tracking. A laser range-finder (Model YP11MGV80, Wenglor Sensoric, Germany) was used to measure finger position, and visual feedback was provided on a computer screen along with the target position. Surface EMG of the extensor digitorum communis muscle (EDC) was recorded (Bagnoli system, Delsys Inc, USA).

Tremor evoked by mechanically applied torque

Random signals with a flat spectrum between approximately 5 and 25 Hz were generated by applying a band-pass filter to white noise (4^{th} order Butterworth, cut-off frequencies 2 Hz and 30 Hz). These produced randomly varying torque which were applied to the distal part of the relaxed, splinted middle finger by the linkage connected to the miniature servomotor. The range of torque sizes was predetermined on an individual basis, according to the magnitude of the evoked finger acceleration. The lowest (1) and highest (6) level of torque were those that generated a peak acceleration that was hardly visible (~0.01 ms^{-2})

and ~0.1 ms^{-2} respectively when it was applied to the finger as a random torque signal. Torques 2 to 5 were set at intermediate torque levels between torque 1 and 6. When applied as a random train these produced an artificial tremor size which ranged from barely visible to movements of a few degrees. Surface EMG was recorded from the EDC, as above.

Tremor evoked by muscle stimulation

Random electrical stimuli were applied to the relaxed EDC. This allowed us to examine resonance of the finger when it moved as a result of artificial activation of its muscle. Two aluminium electrodes (~1 cm^2 each) were placed over the belly of the EDC. A computer-controlled constant current stimulator (Model DS7A, Digitimer Ltd, UK; 50 μs pulse duration) supplied trains of stimuli. The 60-second stimuli trains had a flat spectrum between 5 and 25 Hz and on average contained 10 stimuli per second. Each stimulus caused a brief contraction of the EDC and therefore a small upward movement of the finger. Current intensities were individually preset based on the acceleration response to a single electrical stimulus in exactly the same way as for the *mechanical* condition.

On two separate occasions, we measured electrically evoked tremor in two patients suffering from long-standing large fibre sensory neuronopathy. Subject GL (55 years old, female) has lost all muscular and cutaneous sense below the nose (Sarlegna et al., 2006) and subject IW (59 years old, male) has lost all muscular and cutaneous sense below the neck (level C3) (Cole & Sedgwick, 1992). Neither subject exhibits stretch reflexes. If the stretch reflex does contribute to physiological tremor, it would be expected to generate a frequency of approximately 10 Hz (Lippold, 1970; Durbaba et al., 2005). Our previous results (Vernooij et al., 2013c) show that this frequency of artificial tremor occurs with high intensities of electrical stimulation. Therefore, to determine the effect of an absent

stretch reflex upon this particular frequency, we stimulated both patients at a level comparable to highest intensity applied to the healthy volunteers. Three repeats at this level were applied per patient.

Data analysis

EMG signals were amplified x1000. Artificial input signals (torque & electrical stimuli), acceleration and EMG were sampled at 1000 Hz and digitized using a MC6026 PCI card. EMG signals were then band-pass filtered between 40 Hz and 300 Hz and rectified. As it could not be directly measured, the torque generated by stimulation was calculated by using an appropriate filter (see appendix).

All signals were processed using Matlab (MathWorks Matlab 2011a, Natick, Massachusetts, USA). Fast Fourier Transforms (FFTs) were calculated for torque, acceleration and rectified EMG (voluntary and mechanical conditions only) at a resolution of 0.12 Hz using NeuroSpec-software for Matlab (Version 2.0, 2008. For a theoretical framework, see Halliday et al., 1995). Cross-spectral analysis was used to determine gain and phase between input and output signals. This provided two accepted indicators of mechanical resonance (e.g. Bach et al., 1983); a peak in the gain spectrum between torque and finger acceleration, and a 0^o phase angle between torque and finger *velocity* (see Knudsen & Hjorth, 2002). Velocity was obtained by integrating the acceleration signal. For both the *stimulation* and *mechanical* conditions, the frequencies of peak gain and phase crossing points were analysed using repeated-measures ANOVA. Since the use of post hoc tests in a repeated measures ANOVA is controversial (Howell, 2010) we decided not to check post hoc differences between frequency bins.

Our interest in these experiments was the systematic variation of tremor frequency with tremor size. It is known that muscular thixotropy makes muscle stiffness dependent on the

change in muscle length (e.g. Lakie et al., 1984; Loram et al., 2007). We believe that this thixotropy is what separates postural and dynamic trials. Velocity is thus a more appropriate criterion of 'movement' than position or acceleration. We calculated RMS finger velocity for each artificial and voluntary trial to compare the artificial tremors with the voluntary counterparts. Also, we reanalysed the artificial data by ranking all trials based on the velocity of finger movement. We allocated each trial to one of 15 exponentially increasing bins of RMS velocity. We chose exponentially increasing bins as this gave the most equal distribution. This reallocation had the additional advantage of permitting a direct comparison between the *mechanical* and *stimulation* conditions for specific RMS finger movements. Unfortunately, an empty bin at one of the intermediate bins of the *mechanical* condition was unavoidable (Figure 4.6A) due to an unanticipated difference between the two conditions (see section 4.4 Discussion).

For the *mechanical* condition, we found that some subjects displayed a level of EMG activity larger than expected for passive musculature. This may have been caused by incomplete relaxation or by reflex components. This provided a serendipitous opportunity to evaluate the effect of adding neural colouration of central or spinal origin to passive resonance. We grouped trials based on the average amplitude of the EMG spectrum. EMG spectra with an amplitude clearly larger than during the rest trial ($> 10^{-3}$ mV), which also often contained a peak, were considered 'active' and were split from the spectra showing an amplitude $< 10^{-3}$ mV ('passive'). We found that four out of 15 subjects were consistently active, whereas 11 were consistently passive. We analysed tremor spectra separately for these two groups. EMG-to-acceleration coherence was also calculated separately for both groups. This was calculated at a resolution of 0.98 Hz to obtain a reliable statistical estimate.

Tremor model

In a previous study, we used a single spring-mass-damper model to support our suggestion that physiological *hand* tremor is mainly caused by resonance (Lakie et al., 2012). This simplified model represented the hand as a mass connected to an underdamped torsional spring, which represented the muscle-tendon complex. Driven by white noise, the model successfully recreated the main characteristics of hand tremor. A substantial reduction in muscle stiffness and a slight reduction in damping were sufficient to reproduce the change from tremor during posture to tremor during movement. Here, we use the same model, adjusted for finger properties, to test our supposition that the observed finger tremor spectra generated in both the *mechanical* and *stimulation* condition can be recreated by a single resonator. The difference between these two conditions is that during electrical stimulation the muscle is active and thus the signal driving the model is a low-pass filtered version of the input (Bawa & Stein, 1976). Details of the model are attached in the appendix.

4.3 Results

Characteristics of physiological postural and dynamic finger tremor

Figure 4.1 shows the relevant spectra from the two voluntary conditions. All figures show the mean from all subjects and the S.E.M. is indicated. Figure 4.1A shows the postural tremor acceleration on a conventional linear scale. As is commonly reported, postural tremor shows two peaks, in this case one at 26 Hz and one at 9 Hz. This was not true of every subject and the considerable variation is evident from the standard error. Dynamic tremor (Figure 4.1B) has a different shape. It has a single large peak at ~ 9 Hz and is an

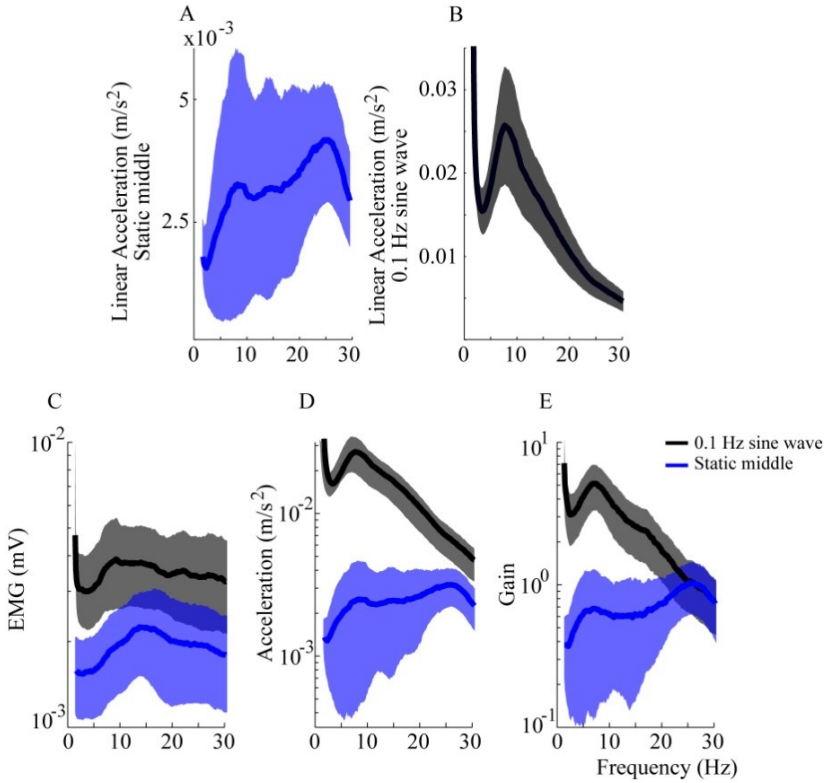


Figure 4.1. Physiological finger tremor: Frequency spectra averaged per trial over all subjects

A: Postural tremor acceleration plotted on a conventional linear scale. The anticipated twin peaks in postural tremor acceleration at ~ 9 and ~ 26 Hz are very evident. B: Dynamic tremor acceleration plotted on a conventional linear scale (an order of magnitude larger than A). The dynamic tremor acceleration spectrum displays a single sharp peak at ~ 9 Hz. C: Surface EMG of EDC. The EMG in the dynamic trials has a frequency peak at the frequency of movement (0.1 Hz). The dynamic EMG spectrum is larger than the postural spectrum; both show most activity at frequencies from ~ 8-20 Hz. D: Tremor acceleration from (A) and (B) on a logarithmic scale. E: Cross-spectral gain from EMG (C) to acceleration (D). The gain spectra (between C and D) strongly resemble the acceleration spectra because the EMG spectra (C) are fairly flat. Shaded areas represent standard error (S.E.M.).

order of magnitude larger than postural tremor, making it impossible to show both clearly on a single linear scale. Accordingly, all results are henceforth plotted with a logarithmic vertical axis. Figure 4.1C shows the spectrum of the rectified EMG in the postural and dynamic trials. There is a sharp peak in the EMG spectrum at the frequency of movement (0.1 Hz) for the dynamic trial, but not for the postural trial. This confirms that we were measuring EMG from a part of the muscle controlling finger extension. The dynamic EMG spectrum is two to three times larger than the postural one but they are otherwise similar in that they show a broad range of activity from ~ 8-20 Hz. Figure 4.1D displays the tremor

acceleration from figure 4.1A and B plotted on a logarithmic scale. The peak frequencies of tremor appear less sharp. An increased amount of acceleration at the frequency of movement in the dynamic tremor trial (0.1 Hz), probably due to accelerometer tilt, can also be seen. As a result of the relatively flat EMG spectrum (Figure 4.1C), the shapes of the cross-spectral gain spectra (Figure 4.1E) are very similar to the acceleration spectra. For the postural trial, a peak ~ 9 Hz and a larger peak ~ 26 Hz are shown. The gain for the dynamic tremor is peaked at ~ 9 Hz.

Characteristics of artificially evoked finger tremor

Table 4.1 displays the mean RMS velocities of finger movement that prevailed during the voluntary postural and voluntary dynamic trials and during the six levels of the *mechanical* and *stimulation* conditions. It also includes the prevailing finger velocity during voluntary postural and *stimulation* trials of the two deafferented patients. The lowest level of mechanically generated tremors produced movement velocities that were very similar in

Table 4.1. RMS velocities for each level of each condition

RMS velocity / *Condition*	*Voluntary*	*Stimulation*	*Mechanical*	*Deafferented subjects*
Postural	0.0011	N/A	N/A	0.0113
Tracking	0.0124	N/A	N/A	N/A
Artificial tremor level 1	N/A	0.0025	0.0012	N/A
Artificial tremor level 2	N/A	0.0038	0.0096	N/A
Artificial tremor level 3	N/A	0.0065	0.0207	N/A
Artificial tremor level 4	N/A	0.0165	0.0427	N/A
Artificial tremor level 5	N/A	0.0303	0.0608	N/A
Artificial tremor level 6	N/A	0.0416	0.0925	0.0494

size to those during postural tremor, whereas electrically stimulating the muscle at even the lowest level resulted on average in slightly larger movement velocities. Tremor velocity during voluntary dynamic trials was within the range of velocities that we generated by artificial methods. The two deafferented patients show a very similar artificially generated tremor size to healthy subjects. Their velocity during postural tremor is an order of magnitude larger than normal, because their posture was less well controlled resulting from a degree of sensory ataxia.

Figure 4.2 displays the artificial tremor spectra from a representative subject. It shows the frequency spectra of the applied or generated torque (left panels), finger acceleration (middle panels) and cross-spectral gain (right panels) when tremor was evoked artificially at six different levels. The top and bottom graphs represent the *mechanical* and *stimulation* conditions, respectively. For the *mechanical* condition (top panels), all applied torque spectra were flat up to approximately 25 Hz, subsequently tailing off. With the lowest amplitude of driving torque, the finger acceleration spectrum (top middle panel) shows a defined peak at ~ 26 Hz. Increasing torque level produces a systematic increase in acceleration magnitude, and a drop in peak frequency to ~ 10 Hz at the highest level. Consequently, the gain (top right panel) between torque and acceleration also displays a peak at 26 Hz for low torque inputs, steadily dropping to ~ 10 Hz with increased torque. Gain increases substantially with the first increment in torque, probably as the SREC was not surpassed with the smallest input size, but begins to plateau with further increases.

For the *stimulation* condition (lower panels), we estimated the muscle generated torque by multiplying the white noise stimulation spectrum by the muscle filtering characteristics (see methods). This process results in an applied torque which decreases with frequency (Figure 4.2; bottom left panel). Increasing current levels generated a systematic increase in estimated torque across all frequencies. At low levels, the finger acceleration spectrum

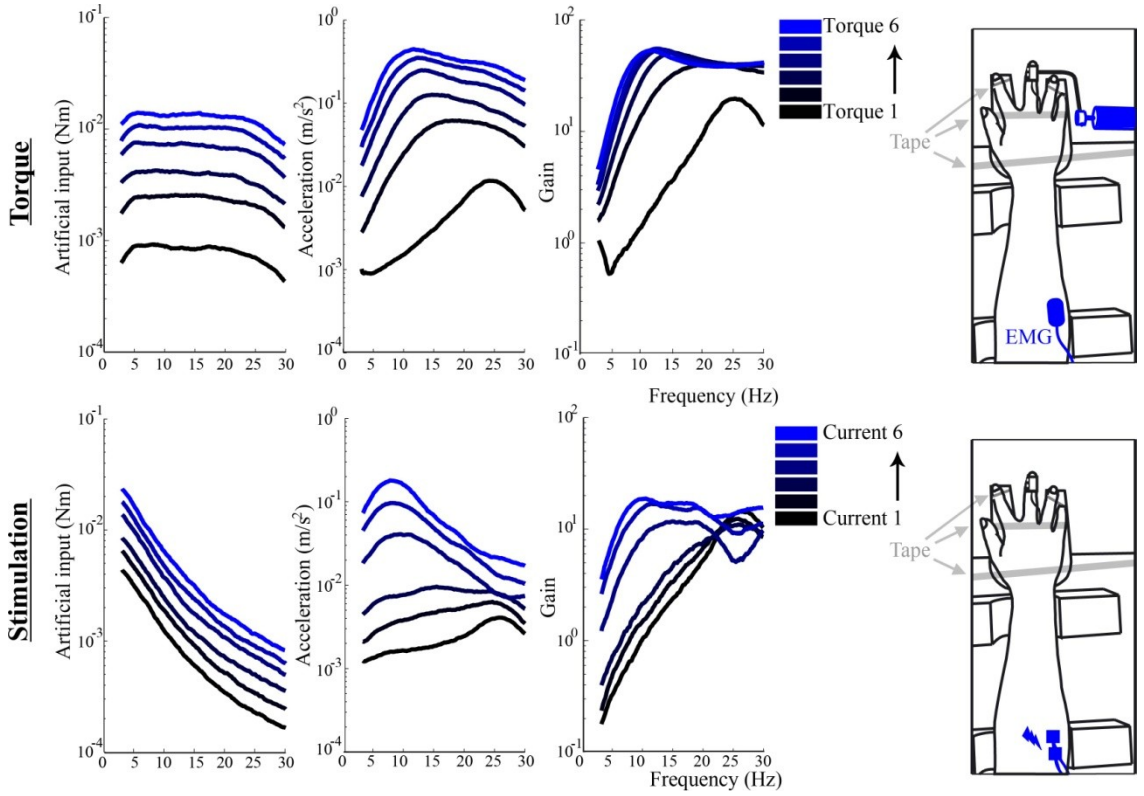


Figure 4.2. Artificially evoked finger tremor: Frequency spectra per trial for a representative subject

Top panel: Mechanical condition; bottom panel: stimulation condition. Left: artificial torque input (mechanical torque or estimated muscular torque); middle: Tremor acceleration; right: cross-spectral gain. Shaded area represents standard error. The mechanical torque (top left) is almost equal over all frequencies. The estimated muscular torque (bottom left) shows an almost exponential drop as frequency rises. The acceleration spectra always have a peak, which drops in frequency with increased levels of artificial input for both conditions. Consequently, the gain also shows a decrease in frequency of the peak with increased intensity of input.

(lower middle panel) is peaked at ~ 26 Hz. With increasing levels, it becomes more sharply tuned, at ~ 9 Hz, and increases in amplitude. Therefore, the gain (lower right panel) is peaked at ~ 26 Hz for low intensities and the frequency peak progressively decreases to ~ 9 Hz with increased current. There is a slight increase in gain with higher stimulation level. Three repeats at the highest level of electrical stimulation were applied to two deafferented patients. Their average acceleration spectra are plotted in Figure 4.3, alongside the average spectrum from the healthy subjects (in black) elicited at a comparable intensity. The tremor spectra are almost identical in shape, peak frequency and size between subjects.

Resonance inferred from gain and force-velocity phase

At resonance, the velocity of a moving body will be in phase with the applied force (or torque) and there will be a peak in the gain between input and output (measured here as acceleration) (Knudsen & Horth, 2002; Timmer et al., 1998ab). Figure 4.4A illustrates representative phase and gain graphs for levels 2 and 6 in both conditions. The frequencies at which torque and velocity are in phase (0^o phase crossing) are marked with a vertical dashed line. The crossing frequencies are similar for electrical stimulation and mechanical torque input. The 0^o phase crossing points correspond well to the gain peaks. Figure 4.4B shows the average frequencies of peak gain and phase crossing points for both conditions. We found no significant difference between these two methods for estimating the point of resonance ($F_{(1,140)} \leq 3.95$; $p \geq 0.06$). However, there was a small interaction between frequency and method for the *mechanical* condition ($p < 0.001$, $F_{(5,140)} = 6.23$). ANOVA confirms a significant decrease in the peak frequency of both gain and phase shift ($F_{(5,70)} \geq 27.16$; $p < 0.001$) as the input size increased. Although both mechanical torque and electrical stimulation produced a progressive decline in frequency, the shape of the curves was clearly different.

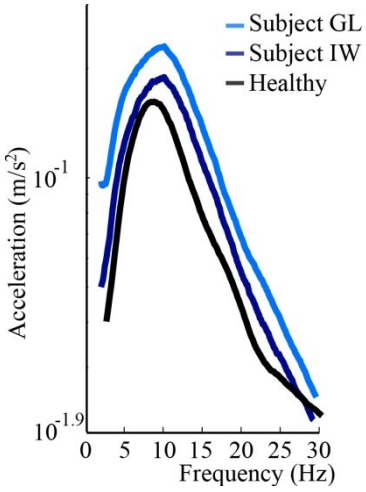


Figure 4.3. Tremor frequency spectra of two deafferented subjects and healthy subject

The average acceleration spectra recorded from high-intensity stimulation of the extensor muscle of two deafferented subjects, with the corresponding average tremor spectrum of the healthy subjects (black) superimposed. The tremor spectra are very similar in shape, size and peak frequency.

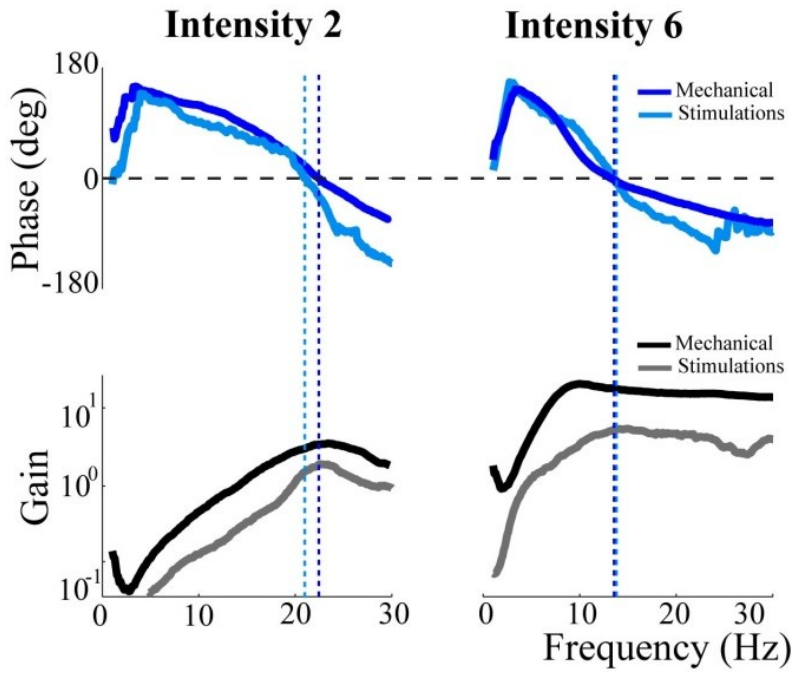


Figure 4.4. Comparison of phase and gain in the mechanical and stimulation conditions

A) Phase (top) and gain (bottom) graphs at intensity 2 (left) and 6 (right) for a representative subject. The frequencies where the phase crosses 0^o are marked with a vertical dashed line. The crossing frequencies are similar for the stimulation and torque input. The zero phase crossing points correspond to the gain peaks. B) Average and SD of the gain peak and 0^o phase crossing for the mechanical condition (left) and the stimulation condition (right). There is no significant difference between these two methods for estimating the point of resonance.

Comparison of mechanically evoked tremor in subjects with passive and active muscle

In the *mechanical* condition, four out of fifteen subjects displayed a level of EMG activity that was larger than their passive rest level (average spectral amplitude > 10^{-3}mV), caused either by subjects not being completely relaxed or by some form of reflex activity. This provided an opportunity to compare acceleration spectra in truly relaxed subjects and those with central or reflexively induced EMG. In figure 4.5, we plot the average EMG and acceleration spectra produced by the four 'active' subjects, and compare them to the spectra of the 11 'passive' subjects who showed an EMG level typical for passive muscle. Frequency spectra of this passive group confirmed a flat and low level of EMG (left panel). In those subjects exhibiting EMG, a variable peak can be seen between 12 and 18 Hz.

Despite this group-difference in EMG, the acceleration spectra of the artificial tremor for both groups of subjects are strikingly similar (middle panel). While the peak frequency occurs at slightly lower frequency and is somewhat more sharply tuned in the passive subjects, the overall shape and amplitude of the spectra are almost identical between the active and passive subject groups. In physiological tremor, coherence between EMG and acceleration is cited as supporting evidence for a neural contribution to tremor causation (e.g. Halliday et al., 1999; Kakuda et al., 1999; Williams et al., 2009; 2010). We calculated coherence between EMG and acceleration in both passive and active subjects (right panel). For passive subjects, coherence is minimal (~0.03) and flat for all intensities (right panel). In contrast, active subjects show a peak in coherence where acceleration is largest. However, the presence or absence of coherence made no obvious difference to the artificial tremor that was produced.

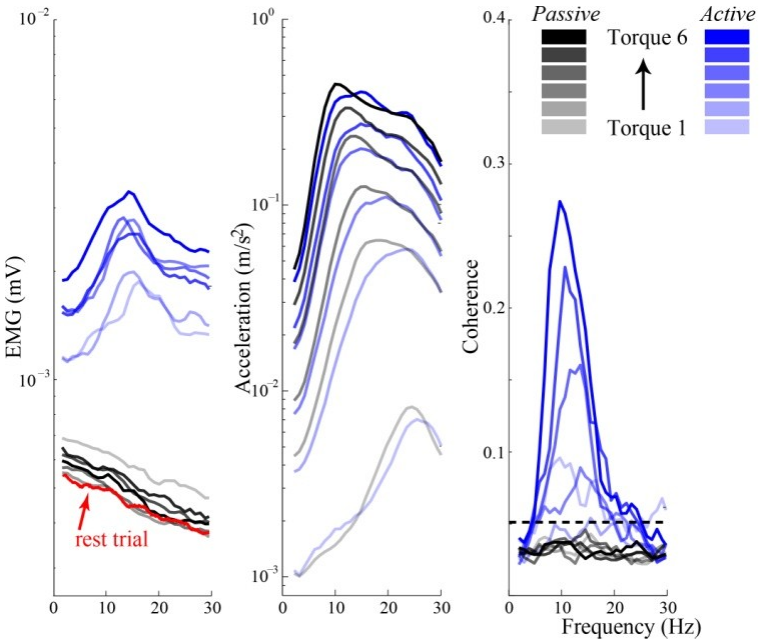


Figure 4.5. Average frequency spectra and coherence compared for active and passive subjects

Left: EMG, middle: acceleration, right: coherence. The EMG spectra of the passive subjects show a flat spectrum over frequencies. Active subjects show a variable EMG peak at 12 – 18 Hz. The acceleration spectra all show a peak, which drops from ~ 25 Hz to ~ 10 Hz in frequency with increased input. The acceleration spectra between passive and active subjects are very similar. The coherence spectra for passive subjects is flat, whereas coherence for active subjects shows a peak where the acceleration is largest. Coherence confidence limits are indicated by the dashed lines.

Effect of amount of movement upon tremor frequency

Although the mechanically and electrically stimulated tremors were generated differently, they produced amounts of movement that overlapped (see methods for rationale for assessing movement as velocity). Therefore, to examine this relationship in more detail, to compare mechanical and stimulation conditions and to provide a direct comparison between artificial tremors and physiological postural and dynamic tremor, we binned all individual trials based on their RMS velocity.

Figure 4.6A shows the binned acceleration wavelets (time-frequency graphs) for the *mechanical* condition (top plot) and the *stimulation* condition (bottom plot). In the wavelet plots of figure 4.6A only, the power at the peak frequency for each velocity bin was set to 1. This enabled a clear comparison of peak frequency and spectral shape between bins. For the lowest velocity bins, both conditions show acceleration peaks at high frequencies (25-30 Hz). With higher velocity bins, the peak frequency drops: to 10 Hz (mechanical) and 9 Hz (stimulation). At intermediate velocities, the acceleration peak is broader and more variable, particularly in the stimulation condition. Figure 4.6B shows a superimposition of physiological and artificial tremor. Postural and dynamic tremors (as indicated in table 1) are compared with the most appropriate artificial tremor velocity bins (0.0011 and 0.0132 deg/s respectively). There is good correspondence between spectral size and shape of artificial and physiological tremor with the exception of the dynamic tremor / mechanical input condition. This is further examined in Figure 4.6C which illustrates how the peak frequency within each bin changes with movement velocity. From this is can be seen that although peak frequency decreases progressively with increasing movement velocity in both artificial conditions, mechanical inputs are less effective in causing a reduction in frequency. Thus, to produce a reduction in frequency to physiological dynamic tremor values, disproportionately more mechanical input is required.

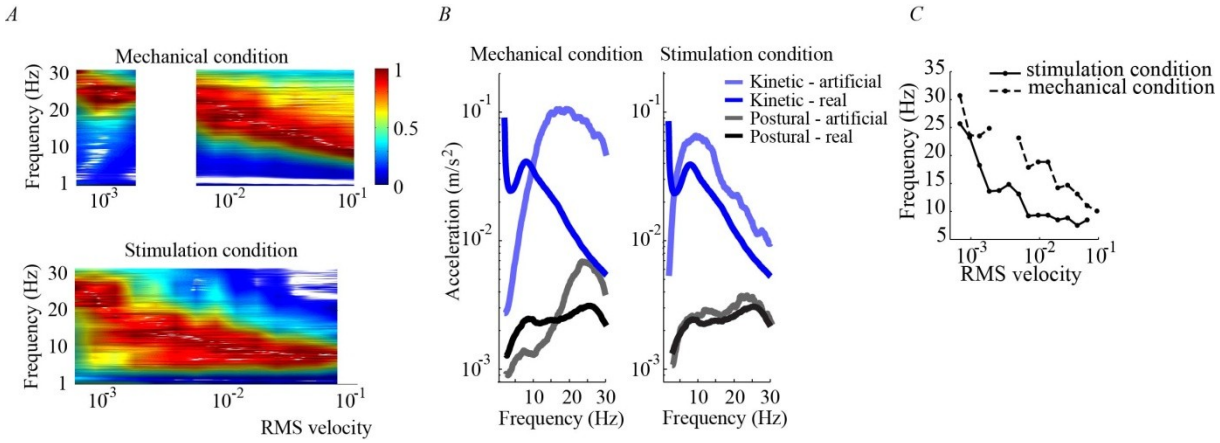


Figure 4.6. The relationship between frequency and amplitude of the evoked tremor

A) Time-frequency plots of the acceleration spectra binned based on RMS velocity. Top: mechanical condition, bottom: stimulation condition. B) cross-sections of time-frequency plots at the bin-levels comparable to postural and dynamic tremor. C) Peak frequency within each bin. With increased RMS velocity, there is a gradual decrease in peak tremor frequency, > 20 Hz to ~ 10 Hz for both conditions.

Resonance model

Using a simple computational model (see appendix), we generated the tremor spectra that would result from a pure resonant system driven by artificial (mechanical or electrical) white noise. Tremor was modelled at low and high levels of input. Joint stiffness decreases systematically with movement velocity. To account for these thixotropic effects, the modelled joint stiffness also decreased with the higher level of input. We made the simplest possible change to the model to account for the difference between the *mechanical* and *stimulation* conditions. That was to low-pass filter the input in *stimulation* conditions to reproduce the properties of the muscle.

Figure 4.7 shows the modelled tremor (right panel) and equivalent measured tremor (left panel). With white noise input, the model produced a good approximation of the recorded acceleration spectra. At low input levels, the measured tremor spectra show a high frequency peak (~ 26 Hz) in the acceleration whether electrically or mechanically energised. The modelled equivalents show a peak at a slightly lower frequency, namely ~

24 Hz. The shape of the spectra between measured and modelled acceleration is very similar. At high levels of artificial input, some difference between conditions becomes apparent in the measured tremor spectra. While in both conditions tremor frequency drops substantially (to ~ 9 Hz) and amplitude increases, the electrical stimulation condition shows a larger decay at higher frequencies. The modelled tremor reproduces the drop in frequency and increase in tremor amplitude, and strikingly also replicates the difference between the *mechanical* and *stimulation* condition. The model is able to produce this difference simply by including low-pass filtering of muscle activity.

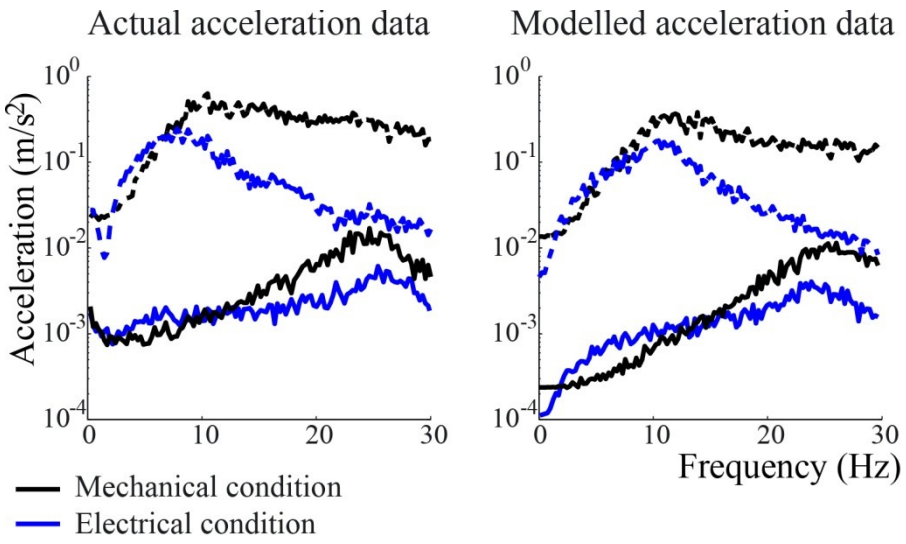


Figure 4.7. Illustration of the effect of changes in model parameters on tremor spectra

Left: Measured acceleration data, right: modelled acceleration data. Solid lines represent a response to a low artificial input intensity ('static tremor'), dashed lines represent the tremor modelled for a high level of input ('dynamic tremor'). The modelled data results from a white noise input to an underdamped 2nd order resonator. The main features of the measured tremor data can be reproduced with the model. Addition of a low-pass filter, characterising the muscle in electrical stimulation conditions, can explain the difference between the two conditions. Accommodating for a thixotropic drop in muscle stiffness with higher input levels (like during movement), the model results in a large drop in frequency and increase in amplitude (solid vs dashed lines).

4.4 Discussion

We discuss five main results

First, we demonstrated that the frequency peaks found in the spectra of postural and dynamic physiological finger tremor can be reproduced when tremor is artificially generated by applying appropriately sized white noise inputs to relaxed subjects. Second, we confirmed that modulated EMG is not necessary to generate tremor-like behaviour. Third, we confirmed that artificial tremor is due to mechanical resonance and suggest that the difference between *mechanical* and *stimulation* conditions is a reflection of the contribution of muscle. Fourth, we reproduce this behaviour with a very simple computational model which requires only one change reflecting muscle engagement to simulate both conditions. Finally, based on the resonant properties of the finger that we describe, we suggest a novel explanation for the long-known presence of two peaks in postural finger tremor and for the large, low frequency tremor which accompanies voluntary movement.

1) Physiological and artificial tremor

Our 15 subjects demonstrated very typical physiological tremor spectra. The average result for postural tremor, when the finger was held against gravity, (Figure 4.1) showed two peaks, one at ~ 9 Hz and one at ~ 26 Hz. The standard error of this figure gives some idea of the considerable variability in absolute and relative size of these peaks amongst subjects. These features have been known for a considerable time (e.g. Stiles & Randall, 1967; Lakie, 1992). One aspect which has been only more recently noted is that during movement there is a shift to a much larger and slower form of tremor. This is also shown clearly in figure 4.1. This large tremor was attributed by Vallbo and colleagues to a shift to an intermittent or discrete form of neural control during movement (Vallbo & Wessberg,

1993). However, we have recently suggested an alternative explanation (Vernooij et al., 2013c). We believe that the low frequency peak is produced by a thixotropic reduction in muscle stiffness and damping. Consequently, the postural resonance shifts systematically to a lower frequency and becomes much larger during movement (Lakie et al., 2012, Vernooij et al., 2013c). Thus, our suggestion is that the alteration in size and shape of the spectrum going from posture to movement has a mechanical rather than a neural explanation.

It is a simple matter to record real postural tremor (while holding the finger as still as possible) and real dynamic tremor (while carrying out a movement using an appropriate tracking task). It is less trivial to artificially mimic these conditions in relaxed subjects. Our solution was to use entirely random electrical muscle stimulation and mechanically applied torque at a range of intensities. The smallest intensities produced a barely visible dither of the digit. This approximated to postural tremor. As the level increased, the size of the movement increased until, with the largest intensities, the finger's movement became a random dance of considerable amplitude. This approximated to dynamic tremor.

The thixotropic properties of the muscle are a reflection of its velocity (that is, movement over time) so we categorised all our different conditions in terms of the RMS velocity of the finger. These velocities are summarised in Table 1, which enables a comparison of our artificial conditions with postural and dynamic trials. The smallest levels of input created velocities almost as low as those seen in postural conditions and the largest produced velocities greater than those seen in the tracking task that we employed. It was particularly difficult to mimic postural tremor sizes during electrical stimulation due to the twitch summation properties of the muscle. Therefore, some subjects had a somewhat larger tremor velocity for the lowest electrical stimulus intensity, leading to a slightly larger average tremor size. Most importantly, we show that the *frequencies* found in the spectra

of postural and dynamic finger tremor can also be reproduced by artificially evoking finger movement by appropriately sized random inputs. The elicited frequency peaks occurred at frequencies very similar to the subjects' physiological tremor both in static posture and dynamic conditions (i.e. ~9 Hz and ~26 Hz) as can be seen in Figs 2, 4 and 6.

2) Modulated EMG is not necessary to generate tremor-like behaviour.

We have previously demonstrated that both the high and low frequency peaks of finger tremor can be reproduced by entirely random electrical stimulation of the appropriate extensor muscle (Vernooij et al., 2013c). Although the artificial tremor spectra were identical to voluntary generated tremor, a drawback of this approach is that EMG is impossible to record satisfactorily because of the inevitable recording of the stimulus itself. Therefore, we were unable to rule out some contribution of reflex driving to shaping the tremor.

Here we have excluded this possibility in two ways. First, we used mechanical perturbations which permit us to record EMG activity associated with the movement. Second, we used electrical stimulation in two patients with a very rare neurological disorder which renders them a-reflexive. In mechanically driven artificial tremor, extensor EMG was insignificant and displayed a flat spectrum in the majority of our relaxed subjects. Neural input therefore was not implicated in their artificial tremor spectrum. Some subjects did exhibit some EMG, either because they were not well relaxed or because the movement caused some driving of the EMG. However, in this group there was no systematic relationship between peak frequency of EMG and the tremor that was generated (figure 4.5). This suggests that spinal and/or central neural input was not necessary to produce the physiological characteristics of finger tremor.

Several studies have cited coherence between neural activity (motor cortex activity, motor unit firing or EMG) and tremor as evidence in favour of a specific neural drive causing the observed movement (e.g. Halliday et al., 1999; Kakuda et al., 1999; Williams et al., 2009; 2010). Such logic would imply that the EMG-to-acceleration coherence peaks that we observed at 10-15 Hz in active subjects only (Figure 4.5) would also indicate neural driving of tremor at these frequencies. However, any effect of this colouration is so subtle as to be invisible, because as shown in Figure 4.5, the acceleration spectra were indistinguishable in the subjects who showed, and did not show, EMG. Thus, although the coherence peaks *could* mean that an element of tremor is dependent on EMG, this cannot explain the acceleration spectra observed in passive subjects who show a negligible coherence. It seems more likely that in some, but not all subjects the resonant tremor may drive the EMG to some extent, inevitably producing a degree of coherence that is greatest where the signal-to-noise ratio is largest – that is at resonance. The application of random stimulation to two patients with widespread sensory neuronopathy supported these observations because their tremor was indistinguishable from our healthy subjects.

3) Gain and phase shift plots suggest a resonance is involved

In the literature, generally only the high frequency (> 15 Hz) component of finger tremor is attributed to mechanical resonance. The usually cited evidence is that only this peak decreases in frequency when finger inertia is artificially increased (e.g. Stiles & Randall, 1967; Halliday et al., 1999). However, recent work suggested a main role for mechanical resonance in shaping the *complete* finger tremor spectrum (Raethjen et al., 2000b; Vernooij et al., 2013c). In our study (Vernooij et al., 2013c), we compared isotonic finger tremor to its isometric counterpart, where movement, and thus resonance, was prevented. In the isometric condition, tremor and gain declined almost exponentially as frequency increased. In comparison, isotonic tremor and gain always showed a peak which systematically

decreased in frequency with increased drive. This suggests that movement has a main role in producing *any* characteristic frequency peak in tremor. We attributed this to resonance.

Here, we employed a secondary corroborative technique to indicate resonance; the phase relationship between torque and velocity. For any mechanical system, the applied force (or torque) and resulting velocity will be in phase precisely at the point of resonance (Knudsen & Hjorth, 2002; Timmer et al., 1998ab). Here, we observed that the frequency at which this occurred corresponded well to the peaks in gain. In both cases, the estimated resonant frequencies ranged from ~ 10 Hz to > 20 Hz, depending upon the level of the driving input (figure 4.4). The gain and phase data showed a systematic decrease in peak frequency with increasing stimulus amplitude, for both artificial inputs. The low frequency ~10 Hz is quite similar to the resonance frequency of the hand. Nevertheless, we are convinced this low frequency is not due to hand oscillations as the wrist and all other digits were strapped to a rigid device and were unable to move. Additionally, Lakie & Robson (1988) have previously reported a similar range of relaxed finger resonance frequencies using entirely different apparatus.

Why does resonant frequency of the finger decrease as it moves more? Figure 4.6 suggests that tremor amplitude is linearly related to finger *velocity*. We propose that the resonant frequency drops with movement due to muscle thixotropy. Only minimal muscle movement is required to greatly reduce muscle stiffness (Lakie et al., 2012; Loram et al., 2007; Proske et al., 1993). The precise mechanism of this phenomenon is not fully established, but is likely to be due to a decrease in the number of attached actin-myosin cross-bridges following movement or activity (Campbell, 2010; Campbell & Lakie, 1998). When the muscle subsequently remains still, bonds reform, the muscle becomes stiff again and the resonant frequency rises. This would explain why, with increasing intensity of artificial input (and therefore more muscle movement), we observed a systematic drop in

resonant frequency. The relationship between thixotropy and finger velocity or position is studied in the next chapter (Chapter 5).

Thixotropy may also explain an observed difference between the two methods of artificial input. Specifically, for a particular movement velocity bin, why was there was a tendency for peak frequency to be lower during electrical stimulation compared with mechanical torque (figure 4.6B and C)? When stimulating muscle electrically, the evoked finger movement must be a consequence of muscle contraction. In contrast, when driving the finger with mechanical torque, the muscle is not directly coupled to the perturbation. In this case, the compliant tendon will not transmit all movement to the muscle. Because the muscle moves less for a given finger movement, it is relatively stiffer and the resonance frequency higher. Consequently, a larger level of mechanical input will be required to produce an amount of muscle movement comparable to electrical stimulation and a corresponding reduction in stiffness and frequency.

4) A simple model reproduces the main findings

We have previously described a model of a simple underdamped spring-mass-damper resonator which reproduces physiological hand tremor. Here, we have adjusted the parameters of this model to match finger mechanics. As for the hand, this model was able to reproduce the effect of increased artificial input (and thus movement) by imposing a reduction in muscle stiffness. The finger model was also able to reproduce a second key difference between the two artificial techniques. Electrical stimulation and mechanical torque produced finger acceleration spectra with somewhat different tuning properties (figure 4.6B). Specifically, electrical stimulation produced spectra with greater attenuation at higher frequencies. Just as the difference in artificial tremor frequency varies slightly due to muscle stiffness differences (see paragraph above), the tuning difference can also be

explained in terms of muscle properties. The torque produced by the muscle when it is activated is a low-pass filtered version of the white noise input (see figure 4.2). In contrast, the mechanical perturbations were applied directly to the finger, so were not low pass filtered. To reproduce this difference, it was only necessary to add a physiologically realistic low-pass filter to the input in order to mimic the known EMG-to-force transfer properties of muscle tissue (e.g. Bawa & Stein, 1976; see figure 4.7). This single change to the model reproduced the difference in tuning properties in tremor between the *electrical* and *mechanical* conditions remarkably well.

5) A new explanation for the low frequency peak of postural physiological tremor.

The spectrum of physiological tremor has long been known to have two peaks of variable preponderance (e.g. Lakie, 1992). These are seen in frequency domain transforms of time domain data typically lasting 30 to 60 seconds. There has always been an assumption that the high and low frequency tremor peaks are simultaneously present. We propose an alternative explanation. The nearly static postural state of muscle generates considerable stiffness and the frequency of the tremor is high. Any appreciable movement produces a considerable temporary reduction in stiffness and the resonant frequency drops rapidly towards its lower ~ 10 Hz frequency. Any normal postural state is a mixture of periods of near stillness interspersed by minor movements. We suggest the resulting 30 to 60 second finger tremor record is an alternation of high and low frequency oscillations, with the high frequency occurring during the stationary periods and bursts of low frequencies occurring when positional adjustments are made. Thus brief periods of dynamic tremor occur in an otherwise postural condition. Conventional frequency analysis combines this tremor time record into a composite spectral signature with two peaks. Inevitably during movement the record is dominated by low frequency dynamic tremor. Many everyday motor tasks must involve repeated transitions between movement and posture. Our results imply that, during

such tasks, the mechanical responsiveness of a muscle to a given neural input will also continuously change. This may pose accuracy constraints upon fine manual motor tasks, as well as increasing tremor during movement. In the next chapter (Chapter 5) we investigate the consequences for human motor control.

CHAPTER 5.

MUSCLE AUTOMATICALLY ADJUSTS TO SERVE POSTURE AND MOVEMENT

Every day we execute innumerable fine motor tasks that subsequently involve periods of static posture and movement. This generates a conflict between succeeding stability and flexibility. Here we suggest that this is resolved by the mechanical characteristics of the muscle, which are dependent on the current and recent history of movement. This adjusts the muscle's mechanical responsiveness to neural input. We examined muscle activity (EMG) during a manual tracking task involving the transition between posture and movement. We took physiological finger tremor (acceleration) as a measure of performance. We found no simple relationship between EMG and acceleration, not in size, nor in frequency. Instead, we observed the size and the frequency of the tremor acceleration to be directly related to the speed of the movement, in which larger movement led to larger, slower tremor. In contrast, the associated EMG input increased when higher vertical finger positions had to be held, but its frequency did not change. This means that there is an increase in the electro-mechanical gain of the muscle when moving, which resulted in a larger acceleration for a given amount of muscle activity. Gain decreased when nearly stationary, so that fluctuating neural drive was less likely to disturb posture. This suggests the characteristics of the acceleration were dependent on the thixotropic muscle properties. This economically promotes flexibility and speed during movement, and stability and accuracy when trying to stay still. Conversely, this means that the nervous system has an inherently less stable load to control in the transition to movement. Controlling even the simplest of these tasks must inevitably involve the complicated control of continuously changing muscle properties.

5.1 Introduction

Every day we execute innumerable fine motor tasks that involve transitions between static posture and movement. However, muscles behave very differently during posture and movement. Their thixotropic character makes muscle stiffness dependent on the recent history of movement, thereby changing the muscle's mechanical responsiveness to neural input (Lakie et al., 1988; Proske et al, 1993; Reynolds & Lakie, 2010). The mechanical resonance of a limb is strongly affected by this change in muscle stiffness, even though the series-coupled compliant tendon will blunt the large (~ 15 times) decrease somewhat (see figure 1.6). Accordingly, the resonance will alter its frequency and amplitude during the transition between posture and movement.

We have previously studied the role of mechanical resonance and the effect of movement on physiological finger tremor (Chapter 3). This research suggested that resonance shapes the tremor frequency spectrum. As demonstrated before (e.g. Chapter 2; Daneault et al., 2011; Stiles & Randall, 1967; Vallbo & Wessberg, 1993; Lakie et al., 2012), an increase in the drive to the controlling muscle (either EMG or artificial noise input) led to an increase in tremor amplitude and a drop in frequency. But, in contrast to popular belief (e.g. Bye & Neilson, 2010; Hagbarth & Young, 1979; Vaillancourt & Newell, 2000; Vallbo & Wessberg, 1993), a frequency specific muscular drive was not necessary to produce the lower tremor frequency ~10 Hz which dominates when the finger is moving. This component could simply be explained by a lower resonance frequency due to a thixotropic reduction in stiffness. However, all these studies examine tremor *either* during posture or during movement. Reynolds & Lakie (2010) have examined tremor during and directly post-movement, but this study was done in the hand, not the finger. As hand tremor covers only a small range of frequencies, no direct conclusion on finger tremor can be made based on this study. How physiological finger tremor behaves during the transition between

posture and movement has never been directly studied. Furthermore, its behaviour during slow movement has been claimed to be different from its behaviour while stationary (Vallbo & Wessberg, 1993), but a formal comparison is lacking.

The purpose of this chapter is to study the effect of a gradual shift from posture to movement on physiological finger tremor and EMG. We look at changes in amplitude and frequency of tremor over time while subjects track a target that evolves from a static posture into a very slow vertical sinusoidal movement. We record surface EMG from the extensor muscle to examine changes in neural input. We demonstrate that both tremor amplitude and frequency are directly related to the *speed* of the finger movement. In contrast, the associated EMG amplitude is related to the vertical *position* of the finger which reflects the force demand. The shape of the demodulated EMG frequency spectrum does not undergo large changes. Some of these findings have been briefly reported elsewhere (Vernooij et al., 2013ab).

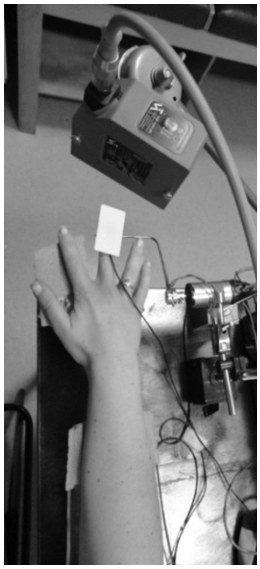
5.2 Method

Subjects

The experiment was carried out on fifteen healthy, right-handed volunteers (3 female, 23.7 ± 9.9 years old). None of the subjects suffered from known neurological or physiological disorders. Subjects were asked to withhold from exercising and not to consume alcohol or caffeine 24 hours before participation. All signed an informed consent form before the experiment started. The experiment was carried out in accordance with the Declaration of Helsinki. Permission was obtained from the ethics committee of the University of Birmingham.

Apparatus

Subjects sat in a comfortable chair with their right arm pronated and supported by a plastic curved rest. The hand as well as the index and ring finger were taped to a u-shaped support with an adjustable gap to fit individual subjects (similar to figure 3.2, top). This allowed for unhindered flexion-extension of the middle finger around metacarpophalangeal joint 3 (MCP-3). A light duraluminium splint underneath the middle finger prevented movement at interphalangeal joints. The arm and the hand rest were individually connected to a heavy steel table by magnetic supports, so they could be adjusted to the optimal configuration.



A miniature 3-axis accelerometer (Model SCA3000, Active Robots, UK, 12.7x20.32 mm) was attached to the top of the nail of the middle finger to measure tremor. A retro-reflective laser rangefinder (YP11MGV80, Wenglor Sensoric,Germany) was pointed at a white plastic reflective surface (~2x3 cm) placed on top of the accelerometer to record vertical finger position, which was projected as a white cross on a computer screen ~1 m in front of the subject. In addition, a computer controlled target in the form of a red ball was displayed.

The target was initially static at an individually determined comfortable middle position of the finger. After 10 s the target moved into a vertically orientated sinusoidal chirp linearly rising in frequency from 0 Hz to 0.05 Hz over 50 s. The target then decelerated as a mirror image of this chirp and ended stationary in the middle position for 10 s (see figure 5.1A). The entire sequence occupied 120 s. The peak amplitude of the waveform was ~ 15 deg of finger movement. Subjects were asked to track the target by keeping the white cross and red ball on the computer screen aligned as accurately as possible. Note that in figure 5.1

top, the position of the target and finger precisely overlap. The maximum angular velocity required to track was 3 deg/s (see figure 5.1 bottom). Subjectively, this seemed a very slow movement. Each subject repeated the trial 10 times. Surface EMG was recorded from the belly of the extensor digitorum communis muscle (m. EDC) with a Bagnoli system (Delsys Inc, USA).

Data analysis

EMG signals were amplified x1000. EMG, acceleration and positional data were sampled at 1000 Hz and digitized by a MC 6026 PCI card. Further analysis was carried out offline using custom Matlab scripts (Mathworks Matlab 2011a, USA). EMG was band-pass filtered between 35 and 200 Hz by a 4th order Butterworth dual filter and rectified.

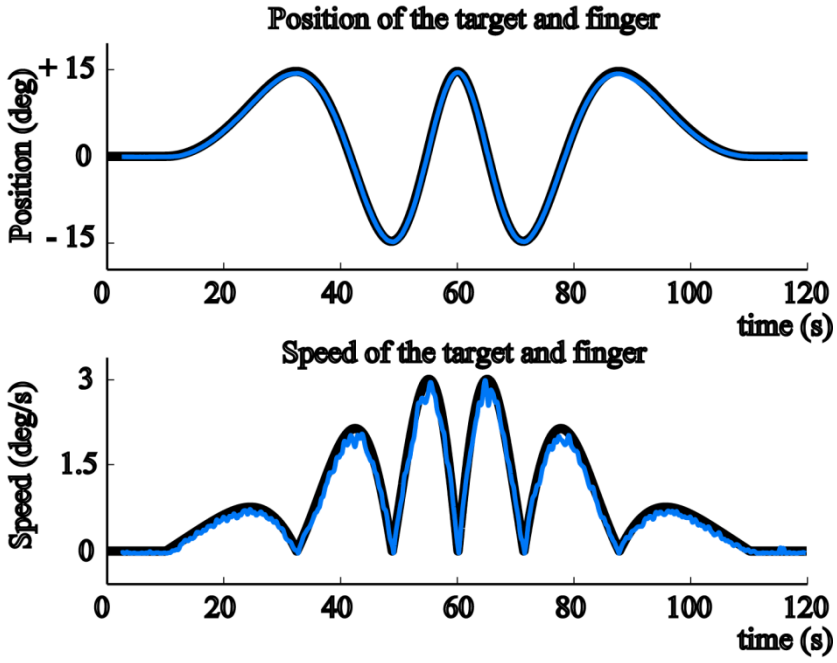


Figure 5.1 Position and speed of the target and finger

Top: the position of the target (black) following a vertical chirp ranging from 0 to 0.05 m/s and back. The average position of the finger (blue) is superimposed and precisely overlaps the target. Bottom: The associated speed of the target and finger superimposed.

Acceleration signals were high-pass filtered at 0.1 Hz by a 4th order Butterworth dual filter to correct for artefactual modulation within the range of target frequencies. EMG and acceleration were downsampled to 100 Hz and a time-frequency coefficient was calculated for frequencies between 5 Hz and 37.5 Hz using a continuous wavelet transform (cwt). Details on the wavelet and its parameter settings are explained in an earlier study by Reynolds & Lakie (2010). The peak wavelet frequency and size (power) over time were derived for each trial. Absolute velocity (speed) of the finger was obtained by filtering the acceleration signal (0.2 Hz low-pass, 2nd order Butterworth dual filter), which was then differentiated and rectified.

We were interested in the relationship between the finger movement (position and speed) and the wavelet characteristics of EMG and acceleration (size and frequency). Accordingly, for every individual trial we computed a Pearson's correlation coefficient between each pair of finger and wavelet properties for EMG and acceleration. Correlations were then averaged over trials and subjects. The Pearson's correlations between the *averaged* variables was also calculated. We determined the strongest correlation per pair.

In further investigation, we examined the properties of the average wavelets and finger movements over time at intervals of 0.5 s. For both EMG and acceleration, we separately plotted the peak wavelet size and frequency at each interval against the movement variable with which it correlated most strongly. This was always finger position for EMG and finger speed for tremor. Then, a curve was fitted to signify the relationship between wavelet and movement variable. Additionally, the size-frequency relationships of acceleration and EMG were determined.

We wanted to know whether, and at which time point, the frequency of tremor and its neural drive would significantly change. Therefore, the 95% confidence interval (CI) was

calculated for the peak frequency of acceleration and EMG over time. For both variables, the frequencies covered by the CI over the last 5 seconds of the two static periods (at the start and end of the movement) was called the postural frequency range. We then defined when the limits of the CI during the tracking movement would exceed this postural frequency range. For tremor, this is the time when the upper limit of the confidence limit during movement was smaller than the lower confidence limit during posture. The first and last time point were used to signify a borderline finger velocity that signifies a change in frequency. Wavelet data as well as finger position and finger velocity were averaged over trials and subjects and finally smoothed (0.4 s).

5.3 Results

Relationship between acceleration, EMG and finger movement

Figure 5.2 illustrates how wavelet size (figure 5.2A) and frequency (figure 5.2C) of tremor evolve over time during the tracking task. The speed of the finger is superimposed in blue. There is a striking resemblance between the finger speed and the two variables. The modifications of size and frequency are gradual and show an increase in size and decrease in frequency almost immediately after initial movement onset. The acceleration covers a wide range of frequencies. The postural frequency bands (CI = 16.6 – 20.6 Hz) are exceeded when the speed exceeds 0.15 deg/s. At the fastest speed (3 deg/s), the frequency is reduced to 7.8 Hz. The right two panels of figure 5.2 display the finger speed plotted against the tremor wavelet size (figure 5.2B) and frequency (figure 5.2D). There is a positive linear relationship between size and speed (average individual $r^2 = 0.64$ or $r^2 = 0.87$ for mean signals) and negative power-relationship between frequency and speed (average individual $r^2 = -0.41$ or $r^2 = 0.92$ for mean signals).

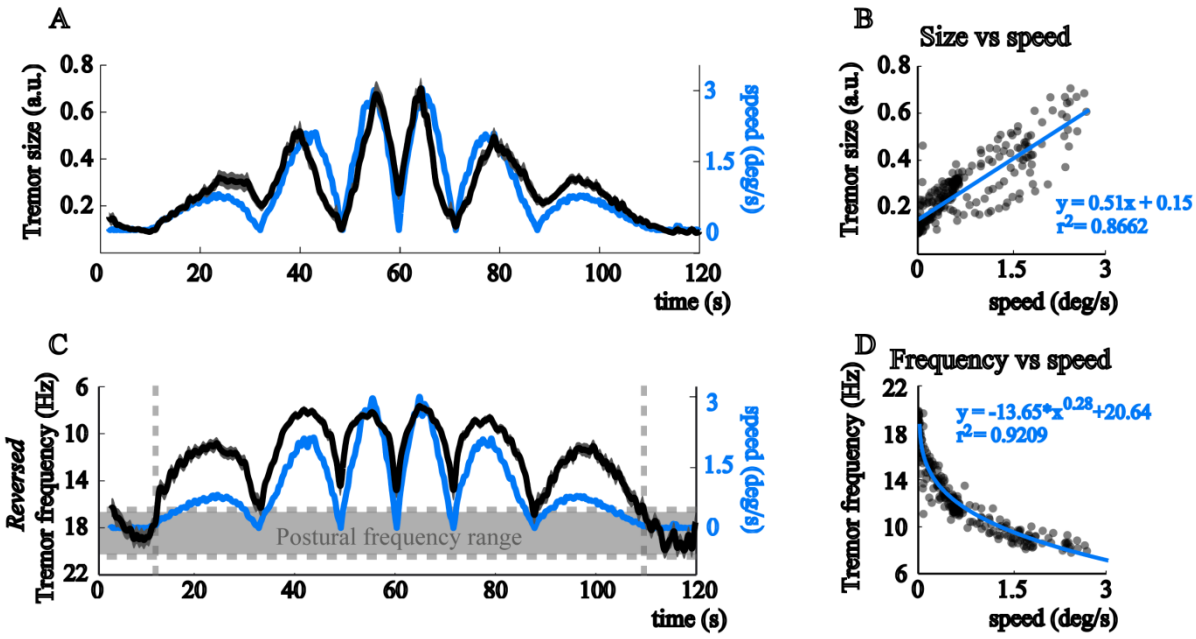


Figure 5.2 Tremor size and frequency over time

Tremor size and frequency when under the transition between posture and movement. Grey area denotes SE. A) The tremor size (black) over time superimposed on the speed of the finger (blue). The size of the tremor increased with higher speeds of the finger. B) Tremor size plotted against finger speed at intervals of 0.5 s. A strong size-speed linear relationship is shown (r^2 = 0.8662). C) Frequency of the tremor (black) over time superimposed on the speed of the finger (blue). Note the reversed frequency axis. Tremor frequency increased with higher speeds of the finger and exceeds the postural frequency almost immediately after movement onset. D) Tremor frequency plotted against finger speed. A negative power relationship is displayed (p=0.9209), in which the largest drop in frequency occurs at the initial stages of movement increases.

There is a stark contrast between acceleration and EMG in the response to movement and the range of frequencies covered. Figure 5.3A shows the average wavelet size over time for EMG. The EMG size is almost exactly superimposed upon the position of the finger following the target (average individual r^2 = 0.69 or r^2 = 0.93 for mean signals). When plotted against each other, the strong correlation between EMG size and finger position is signified by a linear relationship (figure 5.3B). Not surprisingly, more EMG in the extensor muscle is required to move the finger to a correspondingly higher position. Figure 5.3C shows that, completely dissimilar to peak acceleration frequency described above, the EMG frequency during movement remains within the postural frequency range (CI = 12.5

– 15.1 Hz). Compared to the range of frequencies covered by the acceleration, i.e. 7.8 to 20.6 Hz, this postural band only covers a relatively small band of the frequencies that form the acceleration spectrum. Relatively steep drops in EMG frequency occur when the finger moves downwards, but only once is there a short period where the frequency slightly decreases below the postural range. Overall, there is a slight increase in EMG frequency with higher finger positions (figure 5.3D). Pearson's correlation between EMG frequency and position shows an average individual $r^2 = 0.07$ or $r^2 = 0.35$ for mean signals.

Size-frequency relationship within EMG and acceleration

The relationship between size and frequency for EMG and for acceleration is shown in Figure 5.4. For each plot, we use one of two colour scales to signify the association of the

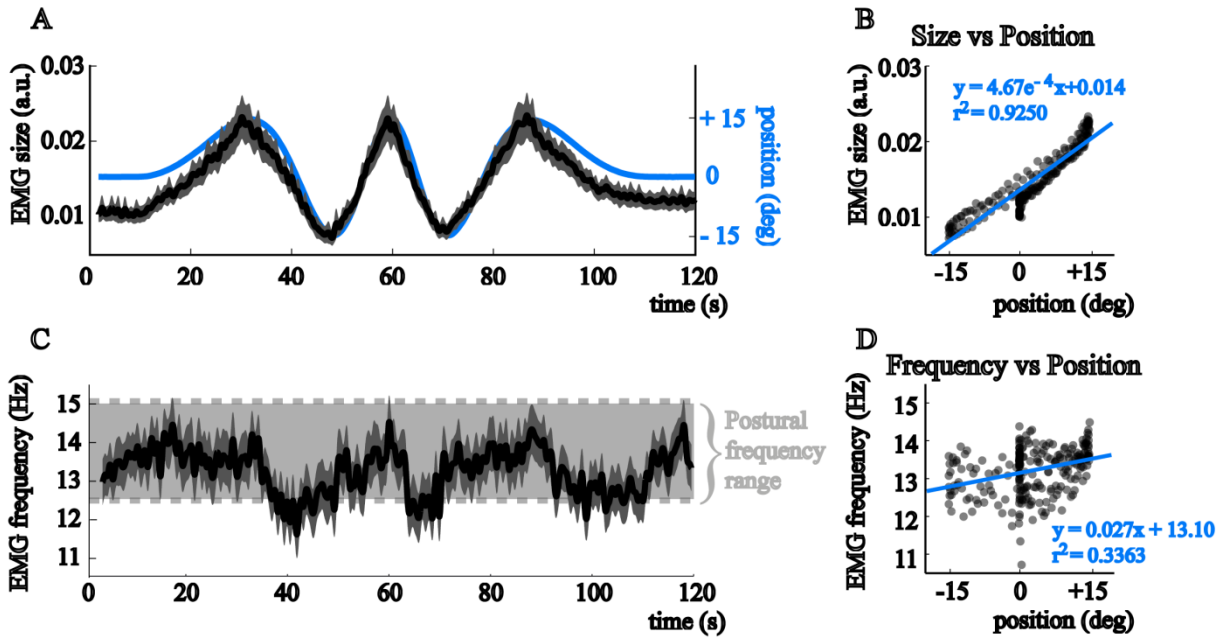


Figure 5.3 EMG size and frequency over time

EMG size and frequency when under the transition between posture and movement. Grey area denotes SE. A) The EMG size (black) over time superimposed on the position of the finger (blue).The size of the EMG increased with higher finger position. B) EMG size plotted against finger position at intervals of 0.5 s. A strong size-speed linear relationship is shown ($r^2 = 0.9250$). C) Frequency of the EMG (black) over time. EMG frequency is not significantly modulated in the transition between posture and movement. D) EMG frequency plotted against finger position. A weak positive linear relationship is displayed (p=0.3363), but variability is high at all finger positions.

plotted relationship with the movement of the finger. A red colour scale denotes finger position and a blue colour scale denotes finger speed, in which black always implies low values. Panel A displays the value of the average wavelet size re-plotted against frequency at 0.5 s intervals for EMG. Panel B shows the same for acceleration. There is a significant positive linear relationship between EMG frequency and size. In general, as more EMG is produced the EMG frequency increases, but there is considerable variability ($r^2 = 0.13$, $p < 0.01$). The red colour scale reiterates the much stronger relationship between finger position and EMG size. Quite the reverse is shown for the size-frequency relationship of tremor. There is a significant *negative* linear relationship between tremor frequency and size. As tremor size goes up, its frequency always greatly decreases. The largest drop in frequency occurs when the finger is just moving – that is at low finger speeds where the tremor is small, signified by the colour scale. A power-curve fit gave a strong correlation of $r^2 = 0.78$ ($p < 0.01$).

As any tremor *has* to be a consequence of some neural input, whether it is broad-band or a frequency specific input, the size and frequency between EMG and acceleration were also correlated (see figure 5.4C and D). As expected, there was a little more acceleration with increased EMG size, but this was relatively small ($r^2 = 0.18$, $p < 0.01$) and the relationship is complicated. For clarity, we chose to use a colour scale based on finger speed. There also did not seem to be a strong systematic modulation of acceleration frequency with EMG frequency ($r^2 = 0.13$, $p < 0.01$). Although a positive linear relationship is shown (solid line), this line is very different from the line of unity (dashed line) indicating that the frequency behaviour does not show a causal relationship as such. Again the strong negative relationship between tremor frequency and finger speed is obvious.

5.4 Discussion

Results show that the size and frequency of physiological finger tremor are modulated by the *speed* of finger movement, whereby faster movements lead to progressively larger and slower tremor oscillations. Tremor holds a strong negative size-frequency relationship: as tremor size increases, it undergoes a substantial drop in frequency. The decrease is largest

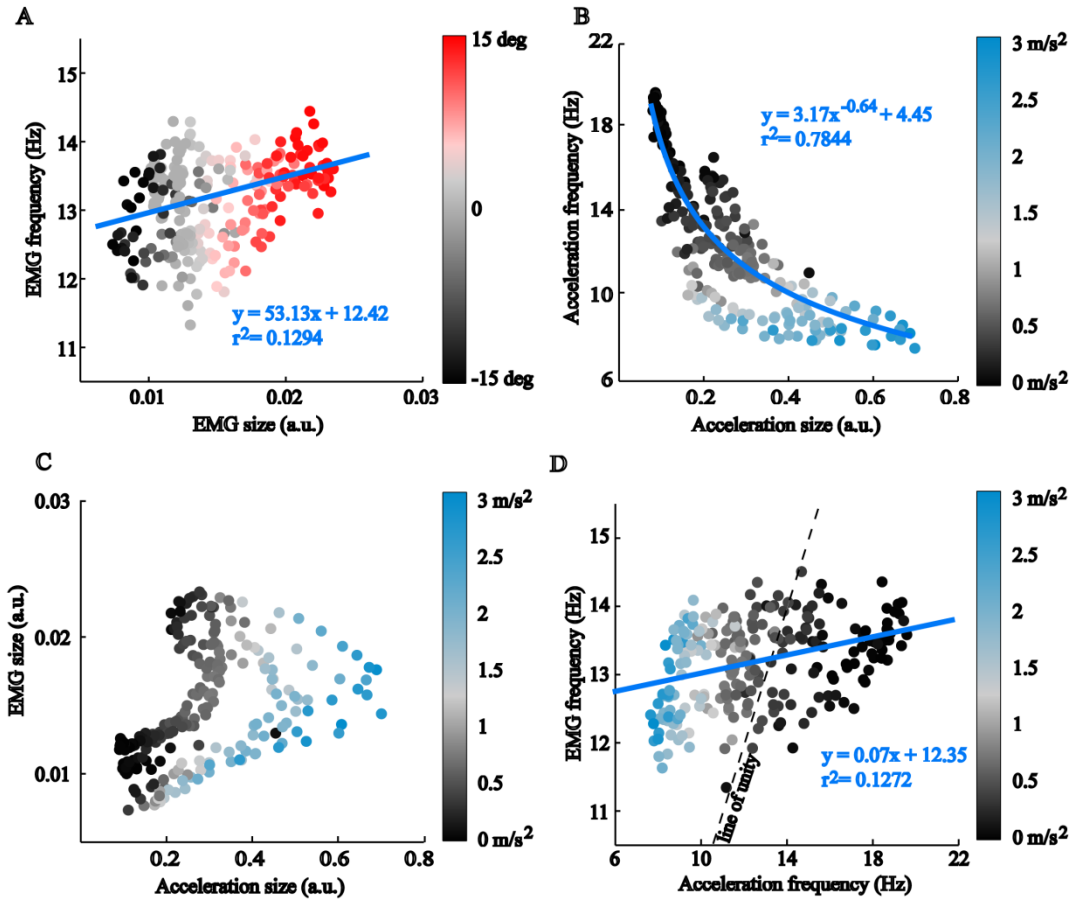


Figure 5.4 The relationship between size and frequency for EMG and for acceleration

The size and frequency of EMG and acceleration plotted against each other at every 0.5 s of the transition between posture and movement. The red colour scale denotes finger position, the blue colour scales denote finger speed. Lower position and speed of the finger are in black. A) EMG size vs. EMG frequency. A weak positive linear relationship is shown (p=0.1294), but a large range of frequencies can be associated with any EMG size. B) Tremor size vs. tremor frequency. A reasonably strong negative power relationship is shown (p=0.7844). The largest reduction in frequency is at the initial increases in tremor size. C) Tremor size vs. EMG size. A complicated interaction exists between the size of EMG and tremor, in which a specific EMG size does not seem to correspond to a specific tremor size. D) Tremor frequency vs. EMG frequency. A weak positive relationship is shown between the frequency responses of EMG and tremor (p=0.1272). The fitted line is very different from the line of unity.

in the initial stages of movement; frequency drops substantially as soon as movement begins. This is not true for the associated EMG, which correlated nearly linearly with finger *position*. Throughout the 120 s trial, the EMG frequency stays within a relatively narrow range (12.5 – 15.1 Hz), which is situated neither at the high nor low end of the range of acceleration frequencies (7.8 – 20.6 Hz). It is very clear that there is no simple relationship between the frequency of the tremor (which alters a lot) and the frequency of the EMG (which alters only a little). This suggests that tremor is not generated by a specific neural frequency. Hence, the alternative possibility seems much more likely – the characteristics of finger tremor must be determined by mechanical properties of the limb.

In general, physiological finger tremor is described as being composed of a number of frequency components of distinct origins. Often a combination is proposed of mechanical limb properties and neural oscillations of central origin (e.g. Bye & Neilson, 2010; Vaillancourt & Newell, 2000) or reflex origin (e.g. Christakos, 2006; Hagbarth & Young, 1979). However, our previous research suggested that all frequencies reported in finger tremor could be economically explained by resonance (Vernooij et al., 2013c) which differs in frequency depending on the state of the musculature. The current study adds to that research by showing clearly that tremor size and frequency are modulated by the speed of movement. The smooth modulation suggests there is a *single* origin that adjusts its properties. This is in contrast to the possibility of an alteration between two modes of oscillation. In both current and previous studies EMG frequency did not change and is never prominent at the frequency of the tremor. This suggests that tremor results from a single resonance source, whose characteristics are determined by movement-dependent properties.

The finding that finger tremor is modulated by the speed of finger movement ties in neatly with a mechanical resonance origin. It is known that extrafusal and intrafusal muscular

stiffness is dependent on the recent history of movement (e.g. Proske, 1993; Proske & Gandevia, 2012; Reynolds & Lakie, 2010). When muscle moves, its stiffness reduces greatly.

Presumably, the underlying mechanism consists of the elastic characteristic of cross-bridges and the number of actin-myosin attachments (Campbell & Lakie, 1998; Hill, 1968; Proske, 1993). During posture there are many stable cross-bridges and muscle stiffness is high. However, during movement cross-bridges start to detach and reattach, replacing the short range elastic stiffness (SREC) with a smaller, approximately constant, frictional resistance (Hill, 1968). Overall, there will be less cross-bridges attached between the filaments and stiffness decreases. If subsequently a steady posture is maintained, cross-bridges will form again and stiffness will slowly increase over the following seconds. This makes the muscle stiffness very strongly dependent on (the history of) movement. This phenomenon is known as muscle thixotropy, and it can explain why high as well as low tremor frequencies can be due to resonance. With increased speed of movement the muscle is stirred more, which will lead to a decreased stiffness and thus a decreased resonance frequency. The muscle length, resulting from a different finger position, is not the determining factor since thixotropic stiffening occurs at high and low positions (long and short muscle lengths; Campbell & Lakie, 1998).

In a reduced preparation (single muscle or single muscle fibre) the transition from SREC to frictional behaviour is very abrupt (see figure 1.4). In a limb which is controlled by different synergistic and antagonistic muscles and very many muscle fibres, the transition will be expected to be less abrupt, and this is what we report here. However it is clear that the greatest reduction in frequency occurs for small movements and this behaviour is entirely consistent with a reduction in stiffness once a very small range of movement is

exceeded. The drop in tremor frequency is well approximated by a power-curve, levelling off with larger tremor sizes (see figure 5.4).

Several studies have shown that the required muscular movement to exceed the SREC is very little (Proske et al., 1993; Loram et al., 2007). The tiny movements associated with 'posture', i.e. the tremor itself, are accommodated within the SREC range. In contrast, even with very slow movements the SREC is continually exceeded. This is exactly what we find here (see figure 5.2). Even at a speed of 0.15 deg/s, tremor frequency is significantly different from the postural frequency.

This also explains why other studies discuss discrete frequency bands. When examining the results of the postural and movement intervals separately, tremor indeed shows a distinct band of frequencies in each condition. Tremor is fast and small during times of posture (16.6 – 20.6 Hz), whereas during movement it is a lot slower and larger (~7.8 Hz and on average 7 times bigger; see figure 5.2). As shown here, they are both distinct features of one underlying cause. If not carefully controlled, a postural condition could show both a high and low frequency peak because of inadvertent slight movements (postural adjustments). Such twin peaks are often discussed in the literature (e.g. Daneault et al., 2011; Stiles & Randall, 1967).

But this does not necessarily imply they occur simultaneously as is always assumed. When stretching out your finger against gravity, the muscle stiffness and resonant frequency will be high. However, an occasional small postural adjustment when attempting to hold your finger still can elicit a temporary drop in muscle stiffness, which is related to a *low* resonant frequency. Over the few seconds afterwards, stiffness and frequency will increase again. A Fourier Transform displays the average frequency spectrum of a trace usually lasting many seconds (typically 30 – 60 s). If small postural adjustments intersperse with

posture, both high and low frequencies will show in the average FFT, both produced by the same resonance.

The size of extensor EMG correlated strongly with finger position (figure 5.3). This was entirely expected and showed that some more force was required from the muscle to raise the finger against gravity. There was also a slight modulation of EMG frequency. This was also anticipated. Evidence shows that EMG frequency correlates with force output, as the firing rate of motor units increases with larger force production (Henneman et al., 1965). When moving to lower positions, force output is also lower. As a result motor unit firing rates, and thus EMG frequency, are decreased. This effect increases with higher movement speeds, as less eccentric force needs to be produced to counterweight the effect of gravity. Indeed, the EMG frequency shows a steeper drop at downward movement of high speed. It is noteworthy that this did *not* produce a consistent decrease in tremor frequency (e.g. compare finger position, EMG and tremor frequency at time point 60 s to 70 s). This implies that there is no direct relationship between EMG and tremor; neither in size nor in frequency.

These results raise the interesting question of whether the difference between posture and movement is qualitative or quantitative. Traditionally, posture was regarded as subcortically controlled tone of tonic muscles. This was seen as distinctly different from movement, which was thought to be controlled cortically and executed by phasic muscles (Granit et al., 1956). Henneman later established his size principle of motor unit recruitment, which states that small motor units and slow muscle fibres are unavoidably activated before fast motor units and large muscle fibres (Henneman, 1957; Henneman et al., 1965). This changes the difference between posture and movement from qualitative to quantitative. Here, we have seen that the muscle properties change significantly with movement due to the thixotropic character of muscle fibres. When holding still, muscles

are stiff and rigid, providing easy control of maintaining postures. When moving, muscles are loose and flexible, allowing for fast dynamic control. We propose that the difference between posture and movement is actually due to mechanical properties of the muscle fibres. Muscles can therefore fulfil a tonic and phasic role in a way that depends entirely on the gross amount of activation. With little activation muscles move very little and the system is stiff and postural. With large activation there is a lot of movement and the system is compliant and easy to move.

Every day we are involved in countless fine motor tasks that involve the transition between posture and movement. Here, we found no simple relationship between EMG and acceleration, not in size, nor in frequency. Based on our results, we propose physiological finger tremor characteristics are determined by movement-dependent properties of the muscle. This means that the nervous system has an inherently less stable load to control in the transition to movement. Controlling even the simplest of these tasks must inevitably involve the complicated control of continuously changing muscle properties.

CHAPTER 6.

GENERAL DISCUSSION

6.1 Aims of this thesis

Despite the long-standing history of examining the origin of physiological tremor, the contributions of various different neural and peripheral sources to possible oscillatory behaviour are unclear. However, if there is some form of neural synchronisation, it would inevitably have to act upon the peripheral effector which involves mechanical resonance. It is therefore important to understand the influence of this peripheral mechanism before specific tremor characteristics are attributed to causes other than resonance. This thesis aims to shed light on the promising role of mechanical resonance in shaping all characteristics of physiological tremor of the hand and fingers.

In the first experimental chapter, the impact of resonance on physiological hand tremor was studied. In contrast to the double frequency peak seen in finger tremor, the single peaked hand tremor spectrum is less complicated and provides a relatively simple starting point for tremor examinations. Cross-spectral gain between EMG and acceleration, as well as a simple computational model were used to provide evidence for a peripheral origin of tremor in postural and dynamic conditions. In comparison to hand tremor, finger tremor is more complicated because it usually displays 2 frequency peaks in its spectrum instead of 1. In the second and third empirical chapters, the line of thought on the origin of hand tremor was extended to the finger. The results suggest that an idiosyncrasy in neural control (e.g. ~10 Hz rhythmic activity) is not necessary to produce either of the two commonly found frequency peaks found in finger tremor. All aspects of the tremor spectrum could be generated by driving the finger with different sizes of electrical or mechanical white noise input. This implies that the two finger tremor peaks can be

produced by a single resonant system with characteristics that alter during movement. The fourth experimental chapter assesses the sensitivity and dependence of this mechanical resonance in the transition between posture and movement. This chapter shows that both the size and frequency of tremor are directly related to the mechanical consequences of an adjusted *speed* of movement.

6.2 Appreciating the role of mechanical resonance in physiological tremor

Mechanical resonance in the human body, as a phenomenon causing physiological tremor, is underappreciated. While many researchers suggest there might be some additional effect of resonance oscillations (e.g. Halliday et al., 1999; Stiles & Randall, 1967; Vallbo & Wessberg, 1993), generally this mechanism is not awarded its potential main role in shaping the complete tremor frequency spectra. When acknowledged, resonance influences are solely ascribed to the higher frequency peak. Commonly, this peak is regarded as a secondary component with a trivial role related to tremor.

The lower frequency peak often found in tremor is usually *not* attributed to resonance. In general, it is suggested to be caused by a synchronized neural input of central or spinal origin, although papers present conflicting ideas.

Central neural input

Some studies suggest the presence of a central oscillator which imposes a pulsatility to motor output and to human posture (e.g. Llinas, 1984). This pulsatility will inflict a central component on physiological postural tremor spectra. There are some clear cases which are known to have a synchronized drive, like central fatigue, essential tremor and some diseases e.g. Parkinson's Disease (Deuschl et al., 2000). In these cases, the controlling

muscle will indeed be driven with a frequency-specific input which will automatically show up as a peak in the tremor spectra (e.g. Deuschl et al., 2000; Erimaki & Christakos, 2008; Furness et al., 1977; Kavanagh et al., 2013). However, typically arguments for a specific central control of normal physiological postural tremor are tenuous (e.g. Hanson et al., 2012).

In the literature, and certainly in many people's beliefs, there *is* an established role for central oscillators in the generation of tremor *during movement*. Tremor during movement is agreed to be larger and at a lower frequency than postural tremor (e.g. Daneault et al., 2011; Lakie et al., 2012; Raethjen et al., 2000b; Reynolds & Lakie, 2010; Vernooij et al., 2013c). This lower tremor frequency has been explained by Vallbo's idea of a specific intermittent control during movement (Vallbo & Wessberg, 1993; Wessberg & Vallbo, 1995;1996). This input would be absent when holding the finger static, explaining the large, low frequency jerks seen in the tremor records during movement, but not in tremor measured during the short static postural periods. The low frequency discontinuities were not even seen as tremor, but something else completely. They argue these jerks must be merely the by-product of a specific intermittent control needed during movement.

These authors present 3 reasons for saying that the dynamic oscillations are not tremor, although all are debatable (arguments against their case are stated after each reason they give):

1) *Postural tremor is an order of magnitude smaller than the observed jerks in the tremor record measured during movement.* As we've seen in figure 1.2, for a resonant plant the size of the oscillations is very dependent on the amount of damping in the system. Damping decreases during movement, which explains the increase in size under dynamic conditions without a required specific input.

2) *Tremor consists of periodical oscillations around a neutral position whereas during voluntary ramps the observed jerks are mainly unidirectional.* This can be easily explained by the realisation that tremor is an oscillation which is superimposed upon the voluntary movement. During posture, there is a stationary baseline, and upwards and downwards tremor oscillations are the only visible movement. During ramps the baseline is moving and tremor will be less clear in the direction of the motion and very clear in the opposite direction. So, for instance, the downward tremor oscillation superimposed on a downward movement will be less clear.

3) *The deceleration peak is larger than the acceleration peak in the observed jerks*. Most likely, this is due to a combination of thixotropy and gravity. The ramps were marked by steps, each of which, after a short stationary moment, showed an acceleration bump, immediately followed by a larger deceleration peak. This can be explained by thixotropy. The muscle stiffness probably increased slightly during the stationary moments. The stiffness just before the start of the movement was thus relatively high. The stiffness just before the subsequent deceleration was slightly decreased by thixotropic responses because of this acceleration peak. Therefore, deceleration peaks were larger. Additionally, gravity works in the downward vertical direction and thus might add to the deceleration.

Spinal neural input

Alternatively, some studies do suggest there is a spinal synchronisation of motor unit firing patterns causing the low tremor frequency in postural tremor (e.g. Durbaba, 2005; Elble & Randall, 1976; Erimaki & Christakos, 2008; Halliday et al., 1999; Lippold, 1970). This synchronisation might either be inherent to motor neurons or caused by reflex means (Christakos et al., 2006). Where it is attributed to motor units, the synchronisation was mainly at the slow frequency of the last recruited units. When it is attributed to reflexes,

the period of the influence is defined by twice the loop delay (which, dependent on the condition, must be ~50 ms).

There are some issues with this theory. These studies measure individual motor unit activity by needle EMG and thus in general look at isometric tremors. This, as will be discussed later, involves issues relating to the detection of alternate tremor origins. Other ambiguities concerning motor unit synchronisation include uncertainties in the delay and gain of the loop, including the difference in short latency (~50 ms) vs. long latency (~150 ms) reflexes, and whether it will amplify or conversely cancel out tremor oscillations (Matthews, 1997; Stein & Oğuztöreli, 1976a).

The relationship between EMG and tremor

Independent of its cause, a frequency-specific neural drive will bring about a peak in EMG spectra. This will drive the limb and create an increased amount of tremor at this frequency. However, there is usually a lack of prominent EMG activity at the associated tremor frequency (e.g. Chapter 2 and 3; Raethjen et al., 2000b; Reynolds & Lakie, 2010). There might be some variable firing of individual motor units at a low frequency which causes a bump in the EMG spectra. However, this seems to have a minimal effect on tremor acceleration. The frequency of the bump does not systematically match the tremor peak. Where with movement the tremor peak decreases in frequency, the mean EMG frequency does not decrease or will even increase. Moreover, acceleration spectra in conditions where the finger is mechanically driven by a torque motor were similar between a group of subjects in which this driving evokes some motor unit synchronisation by reflex action and a group in which the muscle is completely passive (see Chapter 3 and 4). Therefore, any increased firing of motor units at a specific frequency cannot be seen as the cause of any tremor frequency.

This absence of a convincing, same frequency peak in neural drive leads us to explain tremor in terms of mechanical resonance. The main body of evidence towards an influence of mechanical resonance on physiological tremor assesses resonance under conditions of added inertia (e.g. Halliday et al., 1999; Hömberg et al., 1987; Hwang, 2011; Joyce & Rack, 1974; Morrison & Newell, 2000; Stiles & Randall, 1967). Any resonant component of tremor should decrease in frequency when inertia is added. In contrast, neural input should, if anything, increase in frequency with increased inertial load because larger, faster motor units will be recruited to hold the limb against gravity (Halliday & Redfearn, 1956; Henneman, 1957). As tremor oscillations are shown to get slower with added inertia, a resonance origin seems evident.

In addition, the role of resonance has been studied by comparing conventional postural tremor with dynamic tremor. In the latter condition, the muscular stiffness will be decreased because of its thixotropic nature. This would consequently decrease the frequency of the resonant component of tremor. Several studies comparing postural and dynamic tremor, dominated by Lakie and colleagues (e.g. Lakie et al., 1984; Lakie & Robson, 1988; Reynolds & Lakie, 2010), conclude that these thixotropic changes in muscle stiffness must be responsible for the observed drop in tremor frequency they find when the limb is moving. Again, if anything, the recorded EMG showed an *increase* in peak frequency. The role of mechanical resonance in generating tremor is thus assumed to be substantial. Evidence in the literature arguing against the potential influence of mechanical resonance on any tremor frequency is hitherto lacking.

This thesis provides three important additional insights into the role of peripheral resonance mechanisms in physiological tremor.

First, we suggest that resonance could explain all characteristics of hand and finger tremor spectra. Chapter 2 includes the first systematic comparison of hand tremor under postural and dynamic conditions. This study showed that movement induces an increase in tremor amplitude and a decrease in tremor frequency. The effect was amplified by faster movements. Moreover, it is the first time that it was shown that the gain between EMG and acceleration reflects the tremor spectra, suggesting a resonance origin. An identical effect was illustrated in Chapter 3 and 4 for the finger, leading to the more controversial statement that resonance could explain 'both' tremor frequencies of the finger.

Second, we suggest that a specific neural input is not necessary to create tremor. In Chapter 3 and 4 we have shown that tremor spectra do not significantly change when replacing EMG by an artificial drive with a white noise structure, detracting from any evidence of a specific neural input underlying tremor components. The input-to-tremor gain and the phase between input force and finger velocity, both indications of resonance, reflect any changes in the tremor spectra. EMG, when measured, was non-significant and did not reflect changes in the tremor spectra. This again suggests a resonance underlies all characteristics of the tremor spectra. When simulating the behaviour of the resonant limb, a computational model representing a 2^{nd} order resonator replicated the frequency spectra for measured hand tremor (Chapter 2) and finger tremor (Chapter 4). It did not matter whether the input was white noise or whether it was driven with the appropriate associated EMG recording. Together, this provides proof that a white noise drive could, in principle, create the principal hand and finger tremor frequencies without the need for a neural drive at specific frequencies.

Third, we show that tremor power and frequency very strongly reflect the speed of finger movement. The tremor characteristics very closely follow the changes in the speed of finger movement during a vertical tracking task in which there are several transitions between posture and movement (Chapter 5). In contrast, the corresponding EMG power simply matches the vertical finger position, getting larger when more force was required to hold the finger at a higher vertical position against gravity (Chapter 2 and 5). EMG frequency does not significantly differ between posture and movement (Chapter 2 to 5). This shows that there is no 1-to-1 relationship for size or frequency between EMG and acceleration. We suggest that the characteristic tremor size and frequencies are directly defined by muscle properties that are dependent on the (history of) muscle movement, i.e. thixotropy.

6.3 The underlying system

It has been known for some time that muscle properties are greatly modified by movement (e.g. Campbell & Lakie, 1998; Hill, 1968; Loram et al., 2007; Proske et al., 1993). However, it has not been well understood how this would relate to the relatively minor changes seen in hand tremor frequency with movement. With movement, the large reduction in muscle stiffness leads to the expectation of a similarly large decrease in resonance frequency. It was only when using the proposed 2nd order resonance model (Chapter 2) that we realised that a 15-fold decrease in muscle stiffness, coupled in series with the compliant tendon, produces only a 2-fold decrease in overall stiffness. As the resonant frequency is proportional to the square-root of the stiffness, the overall reduction in resonant frequency is relatively little (~ 29 %). This simple model, turned out to be able to create both the postural 8 Hz peak *and* the dynamic 6 Hz peak found in hand tremor

(Chapter 2). In Chapter 4, the model was employed again in finger tremor. The spectra of finger tremor are more complicated than those of hand tremor as it involves 2 frequency peaks. With some caveats, both the low and high frequency component of finger tremor could be explained based on this same simple model. The hand and fingers are obviously controlled by many muscles and thousands of muscle fibres. This makes the model, especially concerning finger tremor, very simplistic. However, it is argued that *'it is this simplicity that makes the model satisfying'* (Herbert, 2012).

We can speculate about the apparent difference between hand tremor and finger tremor spectra. A given change in muscle properties will have a small effect on the resonant frequency of the hand because it has a large inertia, but will have a large effect on the resonant frequency of the finger because of its small inertia. This means that mechanical resonance is very sensitive to alterations in the muscle properties when controlling small loads like the finger. We also know that the stiffness of the muscle is very sensitive to small movements (e.g. Campbell & Lakie, 1998). A small burst of neural activity, producing a small movement, will thus generate a big drop in the finger resonance frequency and a relatively minor drop in hand frequency. When attempting to outstretch the limb, periods of static posture are interspersed with short periods of small postural adjustments. Each of these small adjustments will swiftly decrease the resonance to the low 'dynamic' frequency. Afterwards, the higher static frequency will progressively develop again. Therefore, the exact value of the high frequency peak measured in a Fourier transform, capturing tremor over time, will depend on the proportion of low frequency periods. For the finger, the resonance frequency is very different when moving, which means that the Fourier transform for postural tremor will include both components, i.e. one ~10 Hz and one higher frequency which, as stated, depends on the ability to hold the limb still. For the hand, the static and dynamic resonance frequency are not very different. Small

adjustments during posture will decrease the resonance frequency slightly instead of forming a distinct second peak. This is because the resonance is not very sharp and the gain spectrum is relatively broad. In turn, this is due to the damping of the oscillation. Therefore, although the spectra of hand tremor and finger tremor seem very different, the mechanism behind them might be very similar. The difference is quantitative, not qualitative.

We argue that the drop in physiological tremor seen during movement is due to a change in muscle properties during and after movement. Muscle stiffness steeply decreases with movement. Stiffness is slowly re-established as posture stabilises. This mechanism is attributed to the short-range elastic component (SREC) of the muscle. It seems that SREC is a characteristic of all types of muscle (e.g. Campbell & Lakie, 1998; Campbell & Moss, 2000, 2002). The non-linear response in tremor cannot be attributed to a non-linear influence of the tendon as with minor torques the tendon stiffness remains approximately constant (Loram et al., 2007).

The exact characteristics of the SREC and muscle thixotropy are not fully settled yet. In 2010, Kenneth Campbell published an elegant review discussing the uncertainties of these muscle properties (Campbell, 2010). The review covers: 1) the high probability that the SREC is caused by myosin heads that creates a disproportional amount of tension in response to initial stretch; 2) the constitution of the Parallel Elastic Component, and its impact on the non-linear tension response to muscle stretch; 3) the difficulty to assign a single value to the amount of movement needed to exceed the SREC due to conditional changes; and 4) the uncertainty of the velocity dependence of the SREC.

These points are beyond the reach of the current work, but provide interesting details of how muscle properties alter with movement. Nevertheless, it can be concluded that with

movements larger than ~0.5 degree the range of the SREC is exceeded (Loram et al., 2007), and the stiffness of the contractile element is greatly reduced. In an approximate estimate for the wrist, this would be comparable to a maximal change in muscle length of ~160μm (assuming a rotational axis of 2cm). As discussed above, this stiffness is moderated by the series stiffness of the tendon. Therefore, the required joint rotation will probably have to be much larger than 0.5 degrees before the SREC is exceeded.

The concept of muscle thixotropy raises the interesting question of whether the difference between posture and movement is quantitative or qualitative. Posture and movement are different in their requirements; we want to be still and rigid when holding a posture while a movement demands flexibility and sometimes high forces. There are obvious problems in meeting all these requirements (i.e. rigid vs. flexible and avoiding fatigue). There thus must be a difference in their control also. Traditionally, the difference was thought to be qualitative, where posture is controlled by tonic muscles and movement is controlled by phasic muscles (e.g. Granit et al., 1956). Later, Henneman and colleagues presented their experiments looking at the recruitment order of motor units (Henneman, 1957; Henneman et al., 1965). They showed that, in general, stretch-evoked responses were elicited in small motor units before large ones. Furthermore, motor unit firing of small motor neurons lasted longer after the stretch had ceased. Additionally, they found that motor units did not have a fixed phasic or tonic character, but could change between firing patterns when under different conditions. They thus believed that '*the motoneurons of a pool do not fall into separate phasic and tonic classes, but instead form a continuous spectrum of sizes and excitabilities*' (Henneman et al., 1965), suggesting the distinction between posture and movement is quantitative instead of qualitative. Henneman's theory of motor unit recruitment is well known and widely accepted, although very recently a paper has been published implying a lack of functional significance of this ordered recruitment

(Dideriksen et al., 2013). These authors argue that the ordered recruitment is a mere consequence of task requirements rather than a prerequisite to produce that movement. This extremely interesting subject deserves further investigation.

The current research suggests that the different requirements of posture and movement could be met by the thixotropic nature of muscle tissue. Thixotropic properties of muscle provide a new basis for a qualitative difference between posture and movement. Posture cannot simply be seen as a movement with a speed of zero. For a given input, muscles can behave in two distinct ways. During posture the muscle has a stiff, low force configuration. This changes into a relatively compliant, higher force constitution during movement. Thus, muscle properties alter with speed so that, for a given input, they provide stability during posture but flexibility and power during movement, resembling a speed accuracy trade-off. This is a clever mechanism to deal with the different requirements of the tasks, but imposes obvious problems in predicting the current muscle state. When planning to execute a movement, we need to deal with potentially anarchic muscle behaviour (Lakie & Robson, 1988). The central nervous system must continuously cope with large computational difficulty in maintaining optimal control in everyday life.

6.4 Limitations and future directions

There are some limitations and considerations concerning the studies included in this thesis that should be acknowledged.

Nature of the studies

All empirical chapters presented cover experiments into the influence of mechanical resonance on physiological tremor. They all alter resonance properties by introducing

movement, and track consequential changes in the tremor spectra to obtain evidence for a mechanical origin of tremor. Other researchers have adjusted mechanical resonance by artificially increasing the inertial component (e.g. Halliday et al., 1999; Joyce & Rack, 1974; Stiles & Randall, 1967). This modification was not systematically implemented here. We *can* deduce some conclusions on the effect of inertia from the comparison of tremor in hand (Chapter 2) and the much lighter finger (Chapter 3). Hand tremor clearly shows a dominant peak at lower frequencies than found for finger tremor (6 to 8 Hz and 9 to 25 Hz respectively). This is in agreement with an increased inertia to stiffness ratio in a resonant system, where larger weights decrease the resonance frequency. The comparison of hand and finger spectra has been executed formally before by others (e.g. Raethjen et al., 2000b), who found similar conclusions relating to resonance as have been inferred above.

No experiments are included examining the effect of a specific neural input to the muscle. In Chapter 3 and 4, white noise artificial input is used to replace neural input, but the studies have not looked at the influence of a particularly large rhythmic input e.g. ~10 Hz. While evidence here points to a minor influence of any specific frequencies in neural input, it cannot be said what the impact on tremor is in conditions where the input force is frequency-specific. An interesting experiment in line with Chapter 3 and 4 would be to electrically or mechanically drive the limb with an artificial frequency-specific noise. This was simulated in Chapter 1, but not yet executed in a real-life physiological system. One possibility would be to record limb velocity and use this to modulate electrical drive to muscle, creating an artificial positive-feedback loop similar to a mechano-reflex mechanism (e.g. Lippold, 1970).

I would like to expound a little on the special case of isometric tremor. In Chapter 3, 'normal' isotonic tremor acceleration was compared to isometric tremor force. In any linear system with identical mass, force fluctuations (isometric) should match acceleration

(isotonic). However, if the system is affected by resonance, deviation in the tremor profiles between the two conditions become apparent. From Chapter 3, it is immediately clear that resonance has a large impact on tremor. When movement, and thus resonance, is eliminated under isometric conditions, all normal isotonic tremor frequency peaks are eradicated. The associated neural input did not change meaningfully. As far as we are aware, this comparison has only been looked at once. Burne and colleagues (1984) found a sharp 10 Hz peak in the demodulated EMG associated with isotonic conditions, but not during isometric conditions. The presence of a 10 Hz acceleration peak, but no force peak, was therefore explained by stretch reflex mechanisms. This peak in EMG is in stark contrast to what was presented in Chapter 3. In this experiment, and in agreement with previous studies (e.g. Halliday et al., 1999; Raethjen et al., 2000b; Wessberg & Kakuda, 1999), EMG spectra display a variable broad peak between 12 and 18 Hz. This peak in the EMG has been attributed to some fluctuating motor unit synchronisation (Christakos et al., 2009; Halliday et al., 1999) or poorly fused motor unit activity (Dideriksen et al., 2012). If more systematic synchronisation would occur, for instance during fatigue, a sharp EMG peak corresponding to Burne and colleagues could appear and this would spill over to the acceleration spectra (e.g. Hagbarth & Young, 1979).

It should be noted that we did find a small peak ~10 Hz in some of the low intensity force spectra, similar to what Christakos describes as weak motor unit synchrony (Christakos et al., 2006). While the finger in our experiment was firmly attached to a rigid strain gauge, the muscle was able to move slightly by pulling on the compliant tendon. Thus, the muscle itself was strictly speaking not isometric and was able to contract a little by stretching the tendon. It could therefore be argued that this led to some level of motor unit synchronisation due to mechano-reflex mechanisms. However, we do not think is the cause of the isometric finger tremor peak ~10 Hz. Firstly, the peak only appeared when force

levels were low, whereas larger forces would generate stronger synchronisation and thus a larger peak. Secondly, we did not see an EMG peak at ~10 Hz, which would automatically be generated if there would be synchronisation of motor unit firing. Lastly, the coherence between EMG and acceleration, while very high at the frequency of movement, only showed relatively small bumps at ~ 10 Hz. Moreover, this peak was not exacerbated in isotonic conditions while any mechano-reflex would be much larger. Therefore, we argue that this additional force in the isometric spectra is not due to motor unit synchronisation. We do not even think it is tremor. We favour the explanation Dideriksen and co-workers provided, which suggests poorly fused motor unit activity around this frequency causes some increased force amplitude (Dideriksen et al., 2012). Nevertheless, at this point we cannot firmly conclude that there is no influence of a central or spinal oscillation under isometric conditions. Future studies will have to underpin our suggestion of a lack of neural contribution to tremor force, for instance by ultrasound measures or by intramuscular recordings.

Subject population

Besides the two deafferented subjects in Chapter 4, only healthy, young and middle aged males and females have taken part in the experiments presented. Insights gathered from this work are therefore mainly limited to this population. The literature is inconsistent with respect to effects of the subjects age on tremor. Some studies find a decreasing tremor frequency with age, although these are in conflict on whether this decline is gradual (e.g. Birmingham et al., 1985; Lakie, 1992) or commences after a certain age (e.g. Marsden et al., 1969c). In contrast, others find no change in tremor characteristics with age (e.g. Elble, 2003; Raethjen et al., 2000b). If central dedifferentiation affects neural control (e.g. Sleimen-Malkoun, 2014), a neural effect of age on tremor can be anticipated. In terms of mechanical resonance, only when tendons are significantly weakened and their stiffness is

reduced, or when sarcopenia and motor unit remodeling affect fine limb control, the tremor frequency will be decreased. Neither of these central or mechanical consequences of aging are expected to have majorly affected tremor of our healthy and physically active subjects. In line with this, sex-differences in tremor would only be anticipated in terms of differences in hand-size, in which larger hand inertia will cause a decreased frequency of oscillation.

The role of mechanical resonance in cases where there already is a centrally generated essential tremor or pathological tremor is unclear. Patients seem to display an approximately normal physiological tremor when the essential tremor is diminished (Lakie et al., 1992). No changes were found in peak tremor frequency when inertia was added to the hand of subjects with essential or Parkinsonian tremor (Deuschl et al., 1996; Hömberg et al., 1987). However, when the tremor is too severe, and oscillations are already very large and slow, the effect of adding inertia to the limb on tremor might be diminished (Deuschl et al., 2000). Furthermore, any centrally generated large tremor will keep moving the muscle beyond its SREC, which excludes studying thixotropic stiffness effects as a true static condition can never be reached. This suggests that muscles may continuously be in a reduced stiffness configuration, exacerbating the centrally generated tremor with a large resonating oscillation. Reducing one tremulous origin in these patients may therefore lead to a 'double' improvement of tremor amplitude.

Measurements of neural input

Throughout this thesis, I have reported measures of surface EMG to signify neural control. The use of surface EMG to detect motor unit activity is widespread, but not always appropriate (Farina et al., 2004). Besides the obvious non-physiological issues (e.g. detection system, placement location), there are some physiological boundaries to the

capability of EMG to show motor unit firing properties. For tasks involving only small amounts of activity, like tremor, motor unit activity should be picked up by surface EMG (Erimaki & Christakos, 2008; Farina et al., 2004) and intramuscular recordings are not necessary. Additionally, motor unit synchronisation has been shown to increase the amplitude of (parts of the) EMG and force spectra at a wide range of excitation intensities (Yao et al., 2000). We therefore argue that it is suitable to use surface EMG to signify motor unit activity in the low impact experiments presented in this thesis. Additionally, there has been some debate on the application of rectification of EMG, as whether it would detect (Boonstra, 2010; Halliday & Farmer, 2010; Reynolds & Lakie, 2010; Ward et al., 2013) or controversially conceal (Christou & Neto, 2010a, 2010b; Neto & Christou, 2010) periodic neural input to the muscle. As for Reynolds & Lakie (2010), any peak in the EMG within the tremor range was only apparent when the signal was full-wave rectified before Fourier analyses were done. Hence, EMG signals were rectified before further analyses throughout this thesis.

Additionally, only the activity of one single muscle is reported. In all cases this was the extensor digitorum communis muscle. I am convinced that this muscle was representative for the behaviour of the involved active extensor muscles. Especially concerning the middle finger, the EDC is the main extensor muscle. As discussed before, see chapter 2, there are multiple additional muscles to consider in the case of hand tremor (i.e. intramuscular, synergistic and antagonistic muscles). Any resistance of these muscles will be decreased during movement and increased during static postures, just as the EDC. These muscles can be relaxed or active. The EDC will have to surpass any resistance of non-synergistic muscles to move the finger (see section 1.2.2.1). As I have used a pronated forearm position in all experiments, the flexor muscles will be mostly relaxed. This was confirmed in the EMG data from the main flexor muscle (flexor digitorum superficialis)

which was flat and insignificant. I therefore decided not to show these figures. It can therefore be interesting to look deeper into the different synergistic and antagonistic muscles and muscle parts acting around the joint. This could be studied with ultrasound or intramuscular measurements.

Artificial control

In Chapter 3 and 4, per-cutaneous electrical stimulation trains are used to artificially activate the extensor digitorum communis muscle. This is a novel way of inducing tremor so that the nature of the input to the muscle could be controlled very precisely by the experimenter. This allowed for a better comparison between subjects and allowed a larger range of tremor sizes to be studied. There are some limitations related to the use of this method. Whereas motor units are physiologically recruited in a small to large order (Henneman, 1957), electrical stimulations will preferentially activate large fibres. This can affect tremor as large fibres fire faster and will activate a larger part of the muscle. Furthermore, surface EMG cannot be recorded simultaneously with an electrical stimulation as a very large artefact will appear on the EMG trace with every stimulus, concealing or contaminating the useful parts of the recording. It was therefore not possible to measure any voluntary input to the muscle in the electrical stimulation conditions. Subjects claimed to be relaxed, but scientific confirmation of this claim was not possible. In Chapter 4, this issue was solved by applying mechanical torque trains directly to the finger. This allowed for a simultaneous recording of EMG and artificial input and therefore we could track the state of relaxation of our subjects' forearm muscles.

Although both electrical and mechanical techniques used white noise input to the muscle-tendon-finger system, they are not directly comparable. As discussed in Chapter 4, not all movement generated by the mechanical torques will be transferred to the muscle due to

tendon compliance, lessening the degree of thixotropic reduction in muscle stiffness. Additionally, the mechanical torque input moves the muscle in a passive way. The crucial difference between passive and active muscle activation is that the latter will contribute to twitch summation of motor responses. This results in larger positional finger movements, and thus also larger muscle movements. Passive muscle activation by mechanical torques produces no such summation. As a result, for a given size of finger movement, the positional variability with electrical stimulation will be much larger, thereby generating more muscle movement and thus a lower stiffness. Thus, applying mechanical torques solved issues with experimental control by electrical stimulation, but problematically does not stimulate the muscle, making it less comparable to physiological tremor generation. Future studies should aim to overcome these matters and combine the positives of using artificial control with the generation of physiological-like tremor. Potentially, a technique similar to functional electrical stimulation (FES) can be evolved using recorded EMG as input to the muscle. Additionally, one could use ultrasound to record movements of muscle and tendon during artificial or voluntary control of tremor to assess and compare the amount of muscle movement produced by passive torques and active stimulation.

Generalisation to daily life

There are some restrictions to the generalisation of our results to daily life situations. The subject of our studies included the hand (Chapter 2) and the middle finger (Chapter 3-5). In all experiments, we splinted the finger/hand and taped other joints to a rigid device to limit complicated interactions of multiple series-coupled joints. In daily life, most tasks involve more joints than just the one finger or hand. Nevertheless, splinted results are very useful in understanding the underlying mechanism. The ‘normal’ situation in which multiple joint interactions take place can be seen as an extended version of the splinted experiments. Future work could look at multi-joint dynamics in the generation of tremors.

For the model, we used single parameter values per condition. As we are unable to be truly static or move smoothly, a single value for stiffness and damping is physiologically not very likely. Ideally, an algorithm should be developed that includes values for stiffness and damping that are continuously variable dependent on the current and recent history of movement. Additionally, in the case of finger tremor, the mass of the muscle might be comparable to the inertia of the limb. This would mean that during posture, when the muscle is stiff, resonance is defined mainly by the finger trembling on the compliant tendon. With finger movement, when the muscle is in motion, a more complicated situation evolves where the muscle resonates with the tendon/finger complex. This would mean that, in addition to a decrease in overall stiffness, the system's inertia increases during movement. This would lead to an over-estimation of the drop in stiffness we assumed was needed to reduce the tremor frequency appropriately, as the reduction generated by the increased inertia will have to be taken into account.

6.5 General conclusions

We now arrive a point where we can draw some general conclusions. The studies conducted in this thesis were the first to demonstrate the extended range of tremor frequencies that are explained by mechanical resonance properties of the limb. Not only the high tremor frequency, but also the usually assumed neural frequency can be generated by mechanical resonance. This lower frequency can be explained by the same resonance by taking the physiological changes in limb mechanics into account. We propose that thixotropy lies at the heart of these changes, making muscle stiffness and damping dependent on the current and history of movement. This prescribes a system that is stiff and rigid in postural control and compliant and less damped under dynamic conditions,

defining a qualitative difference between posture and movement. This adds to the original proposition of Henneman (1957) who found a quantitative difference between posture and movement. Also, this explains why many studies find both of the two tremor peaks in a spectrum of postural tremor and thus try to find two (independent) causes. Over a normal postural tremor record, which is at least 30 seconds long, the high frequency static periods are interspersed with kinetic periods of postural adjustment which would cause low frequency tremor. Conventional Fourier frequency analysis would combine these postural and kinetic periods in a single frequency spectrum showing both characteristics, leading to misguided ideas of multiple causes. We believe that the mechanical resonance theory provides a simple, but comprehensive explanation for all characteristics seen in physiological tremor. It suggests that frequency-specific neural inputs are not necessary to produce any of the commonly reported components of tremor.

APPENDIX

Muscle torque

We wanted to estimate the muscle torque generated by electrical stimulation so that it could be compared with the torque generated during the mechanical condition. In our recent paper (Vernooij et al., 2013c), we measured the isometric force spectrum resulting from identical white noise electrical stimulation of the EDC as was used here. This was performed at different stimulus intensities spanning the range used in the present study. While accepting that this response will be variable amongst individuals it gave us a measure of the average frequency response. Accordingly the spectral gain between the electrical input and resulting force derived from that study (muscle response curves) were used as a basis to estimate the generated torque in this study. In short, the gain curves between electrical stimuli and produced muscle force from our previous study provide a filter to calculate muscle force spectra from the electrical stimuli spectra and the gain is a relative not absolute number. The spectra were converted to torque spectra by multiplying the calculated force amplitude by the average finger moment arm (10 cm). Hence, the input spectra presented for electrical stimuli in figure 4.1 represent an estimate of muscle generated torque, not electrical current magnitude. The low-pass filtering property of the muscle is clearly apparent (see Bawa & Stein, 1976).

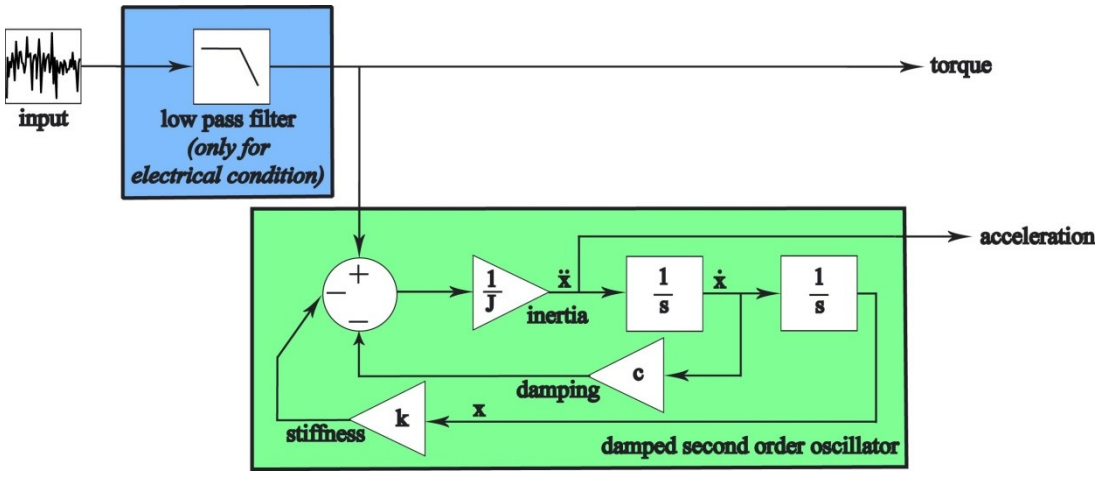
Tremor model

We have previously modelled the hand as a second order torsional oscillator (Lakie et al., 2012). The limb was viewed as a moment of inertia J, which is connected to a muscle-tendon complex with damping c and angular stiffness k. Stiffness k represents the series-coupled muscle stiffness kM and tendon stiffness kT. We use the Laplace transfer:

$$G(s) = \frac{1}{Js^2 + cs + k}$$

We use the model to simulate both the *mechanical* and *electrical* methods of tremor generation. The difference between these two conditions is that, unlike for the mechanical condition, the white noise torque driving the finger for the stimulation condition is previously filtered by the muscle. To estimate this, we used a low pass filter (Bawa & Stein, 1976) with a time constant of 34 ms for the stimulation condition only. This time constant turned out to best represent the muscular force produced by single electrical stimuli and by a train of stimuli that we measured in our previous study (Vernooij et al., 2013c). Our main intention here was to show that our results could be reproduced by a single simple resonance model by making this single change. All other parameters are identical between conditions and physiologically justifiable values are used.

Chosen parameter values for the finger model (i.e. moment of inertia, angular stiffness and damping) were mainly taken from the literature. We use a moment of inertia of 0.0001 kg m^2 times, e.g. Loram et al., 2007). Based on a simple strength comparison between the (based on a cylindrical finger with an estimated length of 10 cm and an average mass of 35



finger g; Stiles & Randall, 1967). Angular stiffness drops considerably with movement (~15 and hand extensors, we estimated the cross-sectional area of the musculature (e.g. Schantz et al., 1983) acting on the middle finger to be 8 times less than that acting on the hand. Assuming joint stiffness correlates with muscle area (e.g. Given et al, 1995), we modified our previous stiffness values used for the hand to fit the finger. This gives a muscle stiffness estimate of 15 Nm/rad when postural, and 1 Nm/rad when moving. Finger tendons are approximately twice as stiff as hand tendons (Ward et al., 2006), even though the distance from muscle to the pivot point (joint; i.e. wrist or MCP-3) is longer. Taken together with the 8-fold decrease in cross-sectional area, we estimated an EDC tendon stiffness of 2 Nm/rad. With movement, damping slightly decreases (Halaki et al., 2006) from 0.004 Nms rad^{-1} for posture to 0.003 Nms rad^{-1} for movement.

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