Rhythmicity, randomness and synchrony in climbing fiber signals

Shigeru Kitazawa¹,² and Daniel M. Wolpert³,⁴

¹Department of Physiology (I), Juntendo University School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan
²SORST, Japan Science and Technology Agency, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan
³Sobell Department of Motor Neuroscience, Institute of Neurology, University College London, Queen Square, London WC1N 3BG, UK
⁴Department of Engineering, University of Cambridge, Trumpington Street, Cambridge CB2 1PZ, UK

The role of the climbing fiber input to the cerebellum has been enigmatic, with recent studies focusing on its temporal and spatial firing patterns. Debate remains as to whether climbing fibers provide a periodic clock for coordinating movements or lead to long-term modification of Purkinje cell activity as the basis of motor learning. Rhythmic and synchronous activity of climbing fibers can cause movements at the same frequency in some preparations, suggesting a role in motor timing. However, in awake monkeys climbing fiber signals have been reported to occur at random, presenting a problem for clock theories. Yet synchronous patterns of discharge are consistently observed among several Purkinje cells within a narrow parasagittal longitudinal band. Here, we review recent experimental and theoretical studies and attempt to provide a coherent account of the interplay between rhythmicity, randomness and synchrony in climbing fiber activity, with a particular reference to studies in chaos.

Introduction

The cerebellum, which consists of the cerebellar cortex and the deep cerebellar nuclei (Figure 1), is involved in the learning and production of accurate and coordinated movements. The output of the cerebellar cortex is provided by the Purkinje cells that project to the deep cerebellar nuclei. The Purkinje cells receive two excitatory inputs, one from climbing fibers that arise from the inferior olive, and the other from parallel fibers that arise from granule cells, which in turn receive inputs from mossy fibers (Figure 1). Driven by the parallel fiber inputs, Purkinje cells show simple spikes that occur at rates of up to several hundred per second and are clearly modulated during movement [1–3]. Complex spikes arise from climbing fiber inputs and occur at much lower frequency, normally at <1 Hz on average. Despite 40 years of experimental and theoretical studies, the function of the cerebellar climbing fibers is still controversial. Debate remains as to whether they provide a periodic clock for coordinating movements [4–8] or lead to long-term modification of Purkinje cell activity as...
the basis of motor learning [3,9–11]. The first view, a motor clock theory, is based on the observation that climbing fiber signals show periodic activity at ~10 Hz [5,12–21] and that responses to climbing fibers (complex spikes) recorded from multiple Purkinje cells are often synchronized within a millisecond [12–19,22–25]. The second view, that climbing fibers provide signals for motor learning, is supported by several studies [10,11,26]. These two views are not necessarily mutually exclusive [27]. However, a key challenge to the first view is that oscillatory activity of climbing fiber signals has not been observed in awake behaving monkeys, in which the firing pattern appears random [7,8]. Here, we first review factors that enhance or suppress rhythmicity of individual climbing fibers, and evidence for the statistical properties of the climbing fiber signals that contribute to online motor timing and/or motor learning. We then review the synchronous firing that can be seen between climbing fibers.

Rhythmic, random or chaotic?
Harmaline-induced tremor revisited
Since 1894, harmaline, an alkaloid of the herb *Peganum harmala*, has been known to produce high-frequency tremor (~10 Hz) in mammals [12,21,28]. Harmaline causes tremor by inducing rhythmic and synchronous activity of inferior olivary neurons, thereby activating Purkinje cells [16] (Figure 2a), nuclear cells, and finally spinal motoneurons [12,21,28]. Lesioning the olivocerebellar pathway (Figure 1) abolishes the tremor, although rhythmic activity intrinsic to the inferior olive persists [12]. However, in the unlesioned animal, cooling of the cerebellar cortex produced a desynchronization of the rhythmic motoneuron firing [12], showing that the synchronous activity in harmaline-induced tremor is a product of the interplay between the inferior olive and the olivo–cerebello–nuclear loop (Figure 1).

An early hypothesis suggested that the intrinsic rhythmicity arose from the electrotonic coupling through gap

![Figure 2](https://example.com/figure2.png)

**Figure 2.** Rhythmicity of complex spikes recorded from a single Purkinje cell in different preparations. Histograms (autocorrelograms) show the number of complex spike discharges (ordinate) plotted against time from a discharge of a complex spike (abscissa). Peaks reflect rhythmic repetitive discharges (e.g., (a) (e) and (f)), whereas the flat histogram (i) reflects random discharges. Recordings (a–f) are from animals anesthetized using ketamine and xylazine: (a) a rat treated with harmaline; (b) a glutamate-receptor δ2-subunit deficient mouse. Note a peak at 100 ms [triangle]; (c) a wild-type (C57BL/6) mouse; (d) a control rat; (e) a rat treated with the GABAA antagonist picrotoxin; and (f) a rat treated with the glutamate AMPA receptor antagonist NBQX. Recordings (g–i) are from awake animals: (g) a rat; (h) a guinea pig; and (i) a monkey. Note less rhythmicity in the awake preparations, especially the monkey (i). Reproduced, with permission: (a) from [16] () (1989) Blackwell Publishing; (b,c) from [33] () (2004) Society for Neuroscience; (d,e) from [15] () (1996) American Physiological Society; (f) from [19] () (2001) Society for Neuroscience; (g) from [13] () (1999) Society for Neuroscience; (h) from [17] () (1972) American Physiological Society; (i) from [7] () (1995) American Physiological Society.
junctions between inferior olivary neurons [5]. Recent studies of mutant mice lacking the gap-junction protein connexin 36, which is assumed to be essential for functional olivary gap junctions, has shed new light on this issue [29,30]. Whereas neighboring pairs of wild-type inferior olivary neurons are strongly synchronized, knock-out pairs are, as expected, uncorrelated [30]. However, the significance of the gap junctions for the intrinsic rhythmicity has been questioned because mutant mice lacking connexin 36 still developed pronounced tremor when exposed to harmaline, identical to wild-type mice [29,30]. However, it is possible that the sparing of tremor in the absence of connexin 36 is attributable to developmental compensations in the olivary neurons [31]. To confirm the necessity of gap junctions in developing the intrinsic rhythmicity, it would be necessary to show the tremor is abolished by blocking connexin 36 function bilaterally in the inferior olive after maturation. To date, it has been shown that harmaline-induced tremor persists after unilateral blocking of connexin 36 after maturation [32].

Oscillatory eye movements in δ2-subunit-deficient mice

Mutant mice deficient in the glutamate-receptor δ2 subunit, which is specifically expressed in cerebellar Purkinje neurons at parallel fiber–Purkinje cell synapses, demonstrate involuntary oscillatory eye movements due to rhythmic activity of climbing fibers [33]. These mice have defects in parallel fiber long-term depression (LTD), elimination of multiple climbing fiber innervations, and deficits in motor coordination and learning [34]. In addition, they make a 10-Hz involuntary oscillation of their eyes that disappears on ablation of the cerebellar flocculus [33]. Electrophysiological recordings revealed that the Purkinje neurons of these mice tended to fire complex spikes at ~10 Hz (Figure 2b), in marked contrast to the sporadic activity found in wild-type mice (Figure 2c). These results suggest that the δ2-subunit deficiency produces the oscillatory activity in Purkinje neurons by enhancing climbing fiber inputs, causing involuntary and oscillatory 10-Hz eye movements.

Factors that modify rhythmic activity of olivary neurons

Excessive rhythmic activity in the inferior olive appears to do more harm than good. Cooling [12] and ablation [33] of the cerebellar cortex showed that the olivo–cerebello–nuclear loop is essential for developing or enhancing these involuntary rhythmic movements. Thus, it could be that the rhythmic activity is controlled within the olivo–cerebello–nuclear loop in normal conditions. LTD at climbing fiber–Purkinje cell synapses [35–37] is a good candidate for mediating such control, because it would decrease corticonuclear inhibition due to synchronous olivary activation, as in cooling or ablation of cerebellar cortex.

There are also several mechanisms that control rhythmicity within the inferior olive. In control animals, in vivo rhythmicity is generally not strong and often has a single peak at ~100 ms in the autocorrelogram [15] (Figure 2d). However, application of a GABA_A antagonist such as picrotoxin [15] (Figure 2e) or glutamate antagonists such as 1,2,3,4-tetrahydro-6-nitro-2,3-dioxo-benzo[f]quinoxaline-7-sulfonamide (NBQX) or 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) [19] (Figure 2f) to the inferior olive enhances rhythmicity, indicated by multiple peaks in autocorrelograms. These results suggest that any input to the inferior olive, whether it is inhibitory (GABA) or excitatory (glutamate), suppresses rhythmicity. The inferior olive receives abundant GABAergic inputs from the cerebellar nuclei, and excitatory inputs from sources such as the red nucleus [27]. In agreement with these findings, in vitro electrical microstimulation of the neuropil dorsal to the inferior olivary complex not only suppresses subthreshold oscillations of membrane potentials recorded from single olivary neurons but also resets their phase [20]. Resetting of the phase in olivary neurons in response to both excitatory and inhibitory inputs is likely to prevent rhythmic activity [7], or at least weaken it [13,17] in awake behaving animals (Figures 2g–2i) compared with application of harmaline (Figure 2a), picrotoxin (Figure 2e) or glutamate antagonists (Figure 2f) to anesthetized animals [15,16,19].

Figure 2(g) shows an autocorrelogram of complex spikes recorded from a Purkinje cell with ‘typical rhythmicity’ in an awake rat [13]. A significant peak at 100 ms shows that complex spikes sometimes occur in doublets at an interval of ~100 ms. A single complex spike evokes only one or two spikes [38] in a Purkinje cell axon that descends to the cerebellar nuclei, but the second complex spike in a doublet would produce two or more spikes in succession [38]. Such amplification of successive climbing fiber signals in the Purkinje cells could contribute to altering activity in the cerebellar nuclei, especially when rhythmic activity occurs synchronously over multiple Purkinje cells, as under the effect of harmaline [12,16]. The moderate rhythmicity observed in the awake rats [13] might also contribute to the production of fast and repetitive movements, as when the animals are required to make repetitive tongue movements at ~10 Hz [14,24].

However, aperiodic activity of complex spikes observed in the awake behaving monkeys [7] (Figure 2i) shows that rhythmic activity in climbing fiber signals is not always present or required in making voluntary movements. Inferior olivary neurons are reported to lose sensitivity to somatosensory stimulation during movement [39,40]. It is likely that at least some of this loss is due to direct inhibition from the cerebellar nuclei [39,41,42]. Cerebellar inhibition of the inferior olive is also suggested to be essential for acquisition and extinction of eye-blink conditioning [43,44]. We suggest that rhythmicity of climbing fiber signals is most likely to be lost during learned responses or movements owing to the nucleo-olivary inhibition. This raises a question of whether there are any benefits in making climbing fiber signals aperiodic.

Randomness or chaos might improve information transmission

Stochastic resonance is a counterintuitive phenomenon in which a certain level of ‘noise’ added to a ‘signal’ improves signal detection of subthreshold signals [45–47]. The flat power spectrum of climbing fiber signals observed by Keating and Thach [7] suggests that random aperiodic
perturbations could be generated in the inferior olive and might help to improve information transmission in climbing fiber signals. Reminiscent of stochastic resonance, Schweighofer et al. [48] showed in simulation that aperiodic chaotic changes in membrane potentials of electrically coupled olivary neurons help to increase the amount of information conveyed by the climbing fiber signals. The essence is that without a perturbation, an inferior olivary neuron fires exactly when an input signal crosses the threshold level, leaving no room to convey the input signal thereafter. However, with perturbations that are not time-locked to the onset of the input signal, the neuron would fire at different timings with a probability that reflects the size of the input signal. Subthreshold oscillatory properties of inferior olivary neurons in vitro support low-dimensional chaotic dynamics [49]. Thus, it is at least theoretically possible to improve information transmission in climbing fiber signals with the aid of the aperiodic perturbation [7,48,49].

There is evidence for such rich information content in inferior olive output. First, climbing fiber signals can convey different information on the beginning and end of a reaching movement, on target position and on end-point error [50]. When reaching to targets, the raster of complex spikes and firing frequencies (Figure 3a,i and 3a,ii) show little correlation with task parameters but information analysis (Figure 3a,iii) shows that the complex spikes provide information that relates initially to target position (broken line) and later to movement error (solid line). Importantly, information about end-point error (Figure 3a,iii, solid line) was conveyed without increasing the mean discharge rate of the complex spike (Figure 3a,ii, thick line). Second, complex spikes in the ventral paraflocculus of the monkey convey ‘high-frequency’ sensory and motor information that matches that of simple spikes with their ultra-low firing frequency (~1 Hz) during ocular following responses [48,51]. Third, inferior olivary responses to taps on the leg showed variability in their latencies during reaching (Figure 3b), in contrast to their fixed latencies during stance [39]. Such variability in responses to the same inputs is a crucial prediction from the ‘chaotic’ resonance theory [48]. Thus, from the second
viewpoint of motor learning, randomness or chaotic features in the climbing fiber signals could be beneficial for increasing information transmitted by the low-rate signals, although conclusive evidence is still awaited.

**Synchrony in climbing fiber signals**

Complex spikes recorded from multiple Purkinje cells [12–19,22–25,52–55], typically within a sagittal band of 250–500 µm [3,23,52,56–58], often show synchronous firing with one-millisecond precision. Although this synchrony can be associated with periodicity [12–15,18,19,22,23], recent results show that synchrony can occur across climbing fibers, even when each climbing fiber is aperiodic [24].

**Excitatory and inhibitory modulation of synchrony**

Apart from the complete synchronization among Purkinje cells that are innervated by a single olivary neuron [17,25] (Figure 1), the degree and extent of synchronization within and between parasagittal longitudinal bands (200–300 µm in width, direction shown by an arrow in Figure 1) vary considerably. Intra-olivary injections of glutamate antagonists (CNQX or NBQX) enhanced synchrony within the longitudinal band structure [19], and this enhanced banding pattern of synchrony was unaffected by simultaneous application of a GABA<sub>A</sub> antagonist (picrotoxin) [18,22]. Thus, in theory, the level of excitatory input to the inferior olive could function as a switch between synchrony and randomness within the longitudinal band, irrespective of the level of inhibition by GABA. By contrast, injection of picrotoxin alone enhanced synchrony over multiple rostrocaudal band structures [15]. Thus, the level of inhibitory input might inversely correlate with synchrony across the longitudinal band structures. From these results, together with their effects on rhythmicity already discussed, we hypothesize a strategy for controlling the rhythmicity and synchrony in olivary neurons. First, cerebellar inhibition of the inferior olive [39,41,42,44] would make olivary neurons function in discrete clusters [5,27] in a less rhythmic mode at a lower frequencies. In addition, if glutamatergic input was decreased, activity would be synchronized within the longitudinal band while low arrhythmic discharge pattern would be maintained.

**Synchronization at low frequency**

*In vivo*, task-dependent dynamic changes in spatial distribution of synchrony among Purkinje cells have been reported [14]. In an intriguing study by Welsh [24] (Figure 4), rats were trained to lick a tube to receive water in response to a tone that lasted 750 ms. Rats made three to four repetitive licking movements in response to the onset of the tone (Figure 4a). Climbing fiber activity, simultaneously recorded from two Purkinje cells (Figure 4b), showed clear responses to the tone with peak latencies of ~80 ms, but the discharge rate was not different from the control level after the auditory burst responses. Thus, these Purkinje cells were classified as sensory neurons. Remarkably, the joint peristimulus time histogram of these two 'sensory' neurons (Figure 4c) shows synchronized discharges in these two neurons (the dots
alvanized the diagonal). It is worth emphasizing that the synchronization occurred at different timings between 150 ms and 600 ms after the tone onset, when there was no significant increase of complex spikes on average. The results show that climbing fiber signals can be synchronized occasionally during movements while their low discharge rate is maintained.

Merits of aperiodic low-frequency synchronization
What is the merit of synchronizing low-frequency climbing fiber signals at different timings during movements? We propose that it enables climbing fibers to convey many different forms of information, each of which is assigned to a different narrow time window. Kitazawa et al. [50] found that climbing fibers convey two different forms of information at two different time windows in short-lasting reaching, but it is possible that they could convey many more. Because movement parameters (e.g. end-point error) are different from trial to trial, we further hypothesize that a group of climbing fibers innervating a longitudinal synapse band are recruited to convey one particular form of information in each trial at a particular timing. Information theory tells us that the maximum instantaneous information conveyed by an on-off pattern of climbing fibers is accomplished by simultaneous firing of half of them in the band, rather than all of them. Occasional synchronization among climbing fibers in the multiple recording study [24] would reflect partial activation of climbing fibers, which would enable them to convey maximal information without increasing the discharge rate on average.

How then could the multiple forms of information be decoded? One possibility is through simultaneous convergent effects on the cerebellar nuclei, eliciting motor timing for fine corrective movements according to the encoded information [5,24,59].

Another possibility is through interactions with LTD-ready synapses whose distribution changes rapidly owing to a short-lasting inhibition set by the off-beam parallel fiber pathways (Figure 1). Callaway et al. [60] showed that activation of inhibitory interneurons adjacent to a Purkinje cell (Figure 1, off-beam) prevent, for ~8–10 ms, the normal increase in intracellular Ca^{2+} concentration in the dendrites of the Purkinje cells induced by climbing fiber stimulation. The reduction could be >90% in the distal dendrites. Because an increase in intracellular Ca^{2+} concentration in the dendrites is crucial for inducing LTD [11,61], off-beam inhibition could specify a 10-ms window in which a group of synapses would be unavailable to undergo LTD. Thus, spatial distribution of synapses available for LTD changes rapidly during a movement. The synchronous climbing fiber signals at a particular time could interact with a particular combination of LTD-ready dendrites and be stored therein for improvement of motor skill. This is particularly advantageous for minimizing ‘overwriting’ of synapses when the climbing fibers convey different forms of information at different times in successive movements.

Rhythmicity, randomness and synchrony could coexist
Rhythmicity exists in the climbing fiber signals in awake rats [13,14] (Figure 2g), but the rhythm is much weaker than that following removal of glutamatergic or GABAergic afferents (Figures 2e,f), suggesting that the rhythm inherent in each olivary neuron [5,62] is dynamically controlled by the abundant inputs to the inferior olive that are both excitatory and inhibitory [27]. In addition, the abnormal 10-Hz rhythms in mutant mice that lack the glutamate-receptor δ2 subunit in Purkinje cells [33] suggest importance of the olivo–cerebello–nuclear loop (Figure 1) in the modulation of rhythmicity. The level of control might also depend on anesthesia and species: rhythmicity in awake preparations seems to be generally weaker than in anesthetized ones (Figures 2c [33], 2h [17] and 2i [7]), and in awake preparations, monkeys show the least sign of rhythmicity among the species tested (rat, guinea pig and monkey) [7,8].

Chaotic dynamics of membrane potentials in olivary neurons, which has been theoretically proposed [48,49] and partly tested in vitro [49], could help in connecting the rhythmicity with randomness. Chaos, which is aperiodic by definition, could mimic rhythmicity within a certain time window [49], and might approximate stochastic processes, such as 1/f noise and white noise, depending on the type of nonlinear dynamics [63] (Box 1). Thus, it is crucial to examine whether chaos lies behind the generation of climbing fiber signals in in vivo preparations under both anesthetized rhythmic and awake arrhythmic conditions. We emphasize in particular that it is possible to detect chaos without measuring intracellular potentials, by simply examining the time series of interspike intervals (Box 1), as has been successful in analysis of heart-rate variability [63]. If chaos is found in in vivo awake preparations, it will be important to find the dynamics and critical parameters that coherently explain rhythmicity, randomness and synchrony. Schweighofer et al. [48] have already suggested in simulation that the strength of electrical coupling between the inferior olivary neurons is a key parameter. The model has successfully incorporated previous predictions that the degree of rhythmicity and synchrony is controlled by the coupling that might be under the control of olivary inputs [5,27]. However, the model has not yet incorporated the differential effects of inhibitory and excitatory afferents [22] on across-band (inhibitory) and within-band (excitatory) synchrony, or the existence of synchrony under aperiodic and low-rate discharge conditions [24]. Further morphological and physiological studies are required in these respects if a biologically plausible theoretical model is to be constructed.

As shown in the simulation study [48], chaotic changes in membrane potentials can enhance information transmission, as in the stochastic resonance driven by stochastic signals. There is evidence to support this [7,39,50,51], albeit indirectly. However, the olivocerebellar system seems to work in a rhythmic mode in producing rhythmic movements [14]. It is as if the neural system is creating rhythmic and/or pseudo-stochastic signals for improving its performance depending on the context. Exploring the mechanisms underlying such flexible exploitation of rhythmicity and randomness is likely to become a central issue in motor control, for which stochastic signals have been suggested to be essential [64,65].
Box 1. Chaos versus randomness

Although in everyday language both chaos and randomness refer to a state of disorder, in a mathematical sense they are distinct. Whereas randomness means that an event happens non-deterministically with a probability distribution, mathematically chaos is created from a deterministic process that still produces non-periodic, complex and unpredictable time series. In particular, chaos is characterized by its sensitivity to the initial conditions. Small differences in the initial conditions become magnified over time in an exponential manner, resulting in strikingly different outcomes. The measure of the exponent of this divergence is the Lyapunov exponent. Systems with a negative Lyapunov exponent are not chaotic, in that they are insensitive to initial conditions – when the system is started from initial conditions that differ slightly it tends to converge to same output. However, with a positive Lyapunov exponent the system diverges, eventually producing different outputs even for slightly different initial conditions. Thus, the existence of at least one positive Lyapunov exponent is a prerequisite for chaos, although it is not a sufficient condition.

Figure I(a,b) show raster plots of artificial data of complex spikes, both of which might appear ‘random’, although one is in fact chaotic (a) whereas the other is truly random (b). Autocorrelograms (c,d), spike-count histograms aligned at each occurrence of a complex spike, show a few peaks for the chaotic series (c) but are basically flat for the random series (d), suggesting there is some difference in periodicity. However, power spectrums (e,f) are almost flat in both, showing that there is no major sinusoidal rhythm that lasts for long in either case. The initial 100 interspike intervals (ISIs; Figure I(g,h)) show some differences that do not easily reveal the different generation processes of the series. However, when three consecutive ISIs (the nth, (n+1)th and (n+2)th) are plotted in three dimensions, the difference becomes easily apparent (i,j). For the chaotic series, a parabolic curve (i), an attractor, emerges; this determines the ISI in the next trial from the previous one. ISIs were actually generated from the following deterministic rule, known as a logistic map:

\[
x(n+1) = 4x(n)(1-x(n))/n = 1, 2, 3, ...
\]

\[
\text{ISI}(n) = 0.1 + 2.3x(n)
\]

For the random series, the points distribute uniformly in a cube (j), reflecting random sampling from a uniform distribution from 0.1 s to 2.5 s. In these examples, ISIs were embedded in a 3D space with a time lag of 1 (n, n+1, n+2), although in this case two dimensions would be sufficient to demonstrate the chaotic series. In analyzing actual time series, dimensions and time lags should be adjusted appropriately. It is worth noting that characteristic patterns of continuous dynamics in membrane potentials can be detected by analyzing the dynamics of ISIs [63]. Tips and cautions in detecting chaos from experimental time series can be found in [63].

Figure I. Chaos (a,c,e,g,i) versus randomness (b,d,f,h,j). Ten thousand ‘complex spikes’ were generated so that their interspike intervals follow a deterministic rule known as a logistic map (a,c,e,g,i) and a random sampling from a uniform distribution (b,d,f,h,j). See box text for details.
References

21 de Montigny, C. and Lambarre, Y. (1973) Rhythmic activity induced by harmaline in the olivo-cerebello–bulbar system of the cat. Brain Res. 53, 81–95
56. Hanson, C.L. et al. (2000) Role of climbing fibers in determining the spatial patterns of activation in the cerebellar cortex to peripheral stimulation: an optical imaging study. Neuroscience 96, 317–331

---

### Five things you might not know about Elsevier

1. Elsevier is a founder member of the WHO’s HINARI and AGORA initiatives, which enable the world’s poorest countries to gain free access to scientific literature. More than 1000 journals, including the Trends and Current Opinion collections, will be available for free or at significantly reduced prices.

2. The online archive of Elsevier’s premier Cell Press journal collection will become freely available from January 2005. Free access to the recent archive, including Cell, Neuron, Immunity and Current Biology, will be available on both ScienceDirect and the Cell Press journal sites 12 months after articles are first published.

3. Have you contributed to an Elsevier journal, book or series? Did you know that all our authors are entitled to a 30% discount on books and stand-alone CDs when ordered directly from us? For more information, call our sales offices:
   - +1 800 782 4927 (US) or +1 800 460 3110 (Canada, South & Central America)
   - +44 1865 474 010 (rest of the world)

4. Elsevier has a long tradition of liberal copyright policies and for many years has permitted both the posting of preprints on public servers and the posting of final papers on internal servers. Now, Elsevier has extended its author posting policy to allow authors to freely post the final text version of their papers on both their personal websites and institutional repositories or websites.

5. The Elsevier Foundation is a knowledge-centered foundation making grants and contributions throughout the world. A reflection of our culturally rich global organization, the Foundation has funded, for example, the setting up of a video library to educate for children in Philadelphia, provided storybooks to children in Cape Town, sponsored the creation of the Stanley L. Robbins Visiting Professorship at Brigham and Women’s Hospital and given funding to the 3rd International Conference on Children’s Health and the Environment.