

# NEURONAL VARIABILITY: NOISE OR PART OF THE SIGNAL?

Richard B. Stein<sup>\*‡</sup>, E. Roderich Gossen<sup>§</sup> and Kelvin E. Jones<sup>‡§</sup>

**Abstract** | Sensory, motor and cortical neurons fire impulses or spikes at a regular, but slowly declining, rate in response to a constant current stimulus. Yet, the intervals between spikes often vary randomly during behaviour. Is this variation an unavoidable effect of generating spikes by sensory or synaptic processes ('neural noise') or is it an important part of the 'signal' that is transmitted to other neurons? Here, we mainly discuss this question in relation to sensory and motor processes, as the signals are best identified in such systems, although we also touch on central processes.

## SPIKE TRAIN

A temporal sequence of all-or-none action potentials.

## INTER-SPIKE INTERVAL

The time between two successive spikes in a train.

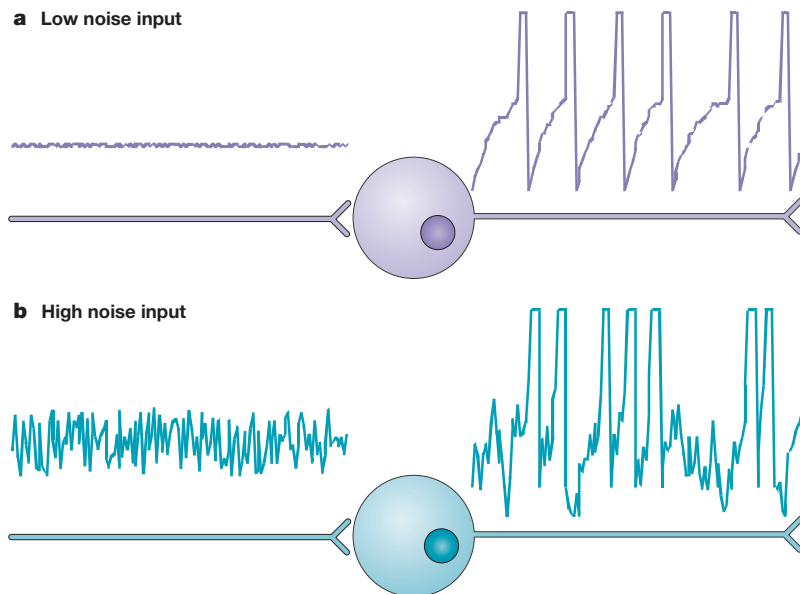
We can quickly recognize the face of a family member from among the billions of faces on our planet or identify a friend at some distance from their pattern of walking, even in a crowd. The basis for this remarkable ability must reside in the series of impulses (spikes) in individual nerve cells or populations of nerve cells. Neuroscientists have long debated how SPIKE TRAINS code information about sensory events. When Lord Adrian and colleagues first took recordings from sensory and motor neurons more than 75 years ago, they found that the intensity of a stimulus was coded as a rate of nerve impulses over time<sup>1,2</sup>, which is now referred to as the 'rate code'. As described below, others have questioned whether rate is the only parameter that encodes information about sensory and motor events. Does the exact timing of spikes from one neuron or the relative timing of spikes in a population of neurons convey further information that is important in the feats of pattern recognition that are mentioned above? These concepts have been referred to as 'temporal coding'. This topic has recently assumed new importance because of the implantation of an array of electrodes into the motor cortex of a severely disabled individual<sup>3</sup>. The spikes from these neurons are being processed to move a cursor on a computer screen in real time. The best method for decoding these spike trains will depend on our understanding, in detail, how information about movements is normally coded in the motor cortex.

The specific question raised in the title of this review follows on from these general issues. If a steady rate is important to determine the intensity of a constant sensory or motor signal, then any variations in the INTER-SPIKE INTERVALS will cause fluctuations in the rate, which might be considered unwanted noise. However, if the timing of each spike carries extra information, then the variability can be an important part of the signal. We argue here that both temporal and rate coding are used, to varying degrees, in different parts of the nervous system, and that both contribute to the ability of the nervous system to discriminate complex objects and produce graceful movements.

## Information processing in sensory systems

Nearly 60 years ago, Claude Shannon developed a theory regarding the information that can be transmitted in a noisy communication channel<sup>4</sup>. This information theory has been popularized in terms of the 'bits and bytes' of information in computers, and has even been applied to the information content of the universe<sup>5</sup>. Application of the theory to neural systems seemed logical, as the survival of an organism depends on its ability to rapidly gather crucial information in a noisy or uncertain environment. One approach suggested that the presence (1) or absence (0) of a spike would represent one binary choice, which is commonly referred to as a binary digit (or 'bit') of information<sup>6,7</sup>. For example, the binary numbers 00, 01, 10 and 11

<sup>\*</sup>Department of Physiology,  
<sup>‡</sup>Centre for Neuroscience  
and <sup>§</sup>Department of  
Biomedical Engineering,  
University of Alberta,  
Edmonton,  
Canada T6G 2S2  
Correspondence to R.B.S.  
e-mail: richard.  
stein@ualberta.ca  
doi:10.1038/nrn1668



**Figure 1 | Variability in neuronal firing.** **a** | With a relatively steady depolarizing input current (low noise), spikes are generated at a regular rate. **b** | With higher noise, which could arise from a combination of excitatory and inhibitory postsynaptic potentials, the variability in firing rate is much higher, even though the mean firing rate might be similar. These data were simulated from a neural model with a leaky integrator and a fixed threshold<sup>82</sup>. The range in variability shown is typical of many neurons.

represent 2 bits (or  $2^2 = 4$  choices). Therefore, if the REFRACTORY PERIOD of a neuron is less than 1 ms, it could transmit more than 1,000 ( $10^3$ ) bits of information in 1 s in a sensory process. However, if different stimulus intensities are presented to a human observer (with  $10^{12}$  neurons), and the observer assigns a numerical score to each stimulus presentation, approximately seven categories can be reliably discriminated<sup>8</sup>. When more choices are presented, observers make errors and the information calculated from information theory is still roughly equivalent to seven categories. So, although the system has the potential to transmit  $10^3 \times 10^{12} = 10^{15}$  bits in 1 s, conscious perception can provide less than 3 bits (or  $2^3 = 8$  categories) of information about stimulus intensities in a range of sensory systems.

**The rate code.** This large discrepancy was soon resolved experimentally and theoretically. As mentioned above, Lord Adrian proposed the rate code in which the intensity of a signal is represented as the number of spikes from a single neuron or a population of neurons over a period of time. The rate is obtained by dividing the number of spikes by the time period. In other words, signals in the sequence 100 (spike, no spike, no spike) over a period of 3 ms would be interpreted not as the binary representation of the number 4, but as a rate of 1 spike in 3 ms, which corresponds to 333 spikes in 1 s. This code would be indistinguishable from the sequences 010 and 001. In such a rate code, the total number of spikes over a period of time is the determining factor, rather than the order or timing of spikes. Variability in the inter-spike intervals and, therefore,

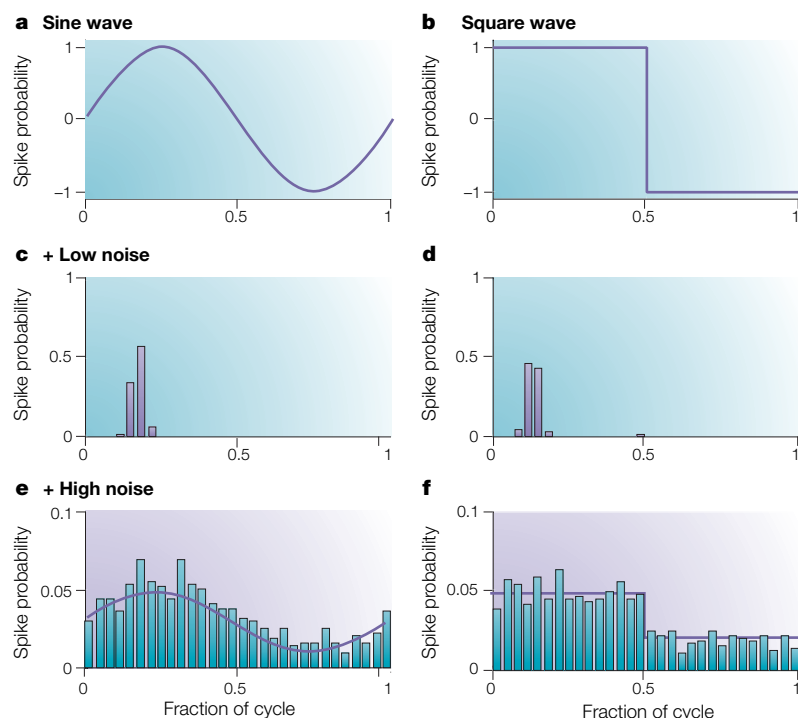
in the total number of spikes in 1 s, for example, would limit the amount of sensory information that neurons transmit.

If the input to a neuron has little noise (FIG. 1a), the neuron will depolarize to the threshold at a steady rate and the number or rate of spikes over a period of time will be reproducible. With a noisy input (FIG. 1b), the spikes will be generated with variable intervals and the rate of spikes over time will also vary. Values of information capacity of 2 or 3 bits have been calculated for single neurons in sensory systems, using rate coding to distinguish the levels of response to steady inputs over 1 s (REF. 9,10). In fact, Talbot and colleagues<sup>11</sup> directly calculated the information contained in the firing of sensory receptors of a monkey to a flutter vibration applied to the skin and found that it agreed with the information from human observers responding to the same sensory stimulus. This agreement between responses in monkey sensory receptors and human experiments was encouraging, but several questions remained.

**The problems with the rate code.** First, as most sensory stimuli activate many receptors, a human observer should be able to use the larger number of nerve impulses from the population of sensory neurons to distinguish more categories. In other words, if a whole population of neurons is active, and each neuron sends 2 or 3 bits to the brain in 1 s, why is human perception limited to less than 3 bits? Is the agreement between the calculated values of information capacity for single neurons and the human observer merely fortuitous? The answer to the latter question is probably yes. With a rate code, the number of bits of information increases according to the square root of the number of impulses, regardless of whether the impulses come from a single neuron or a population of neurons<sup>10</sup>. Therefore, 100 neurons would transmit 10 times the information of a single neuron. If the brain uses 100 neurons to perceive different categories, we would expect ~20–30 bits of information to be transmitted in 1 s, which predicts more than a million possible perceptual categories. The information contained in the responses from populations of cells must underlie the ability to recognize faces, as mentioned above. However, some information might be lost in synaptic relays or in memory storage in the brain. Conceivably, this loss might cancel out the extra information that is contained in the population of sensory neurons in the particular laboratory experiments quoted above and leave 2 or 3 bits (or 7 categories). These issues still need to be rigorously tested experimentally.

Second, if variability in inter-spike intervals creates noise that limits information flow in sensory systems, why have sensory neurons not evolved to reduce this variability? As discussed below, in relation to temporal codes, neurons do fire spikes at precise times in some sensory systems. In others, the receptors are operating close to physical limits that introduce variability. For example, in the visual system, photons arrive randomly in time and, under some conditions, a single photon

**REFRACTORY PERIOD**  
The period of time after a spike when a neuron is unable or less able to fire another spike.



**Figure 2 | Noise can be beneficial to the faithful transmission of high-frequency inputs.** When a sine wave (a) or square wave (b) with a period of 30 ms is added as an input to the low-noise neural model shown in FIG. 1a, the input entrains the firing of the neural model so that it generates one spike per cycle at a relatively fixed phase (c and d) and the shape of the input is lost. Adding the same inputs to the high-noise model shown in FIG. 1b produces spikes at all phases and the probability follows the shape of the input (e and f).

can lead to perception<sup>12</sup>. The variability in the timing of spikes might be related to the irregular arrival of photons. Similarly, Brownian motion affects hair cells in the auditory system<sup>13,14</sup>. Therefore, the presence of variability in sensory systems might be an inevitable consequence of exquisitely responsive sensors. Furthermore, during synaptic transmission through sensory and central synapses, the effects of individual excitatory postsynaptic potentials (EPSPs) are relatively large compared with those of individual ions in the constant currents that were considered in FIG. 1a (REF. 15). If the generation of EPSPs is a random or STOCHASTIC PROCESS, variability will be introduced in the time that is taken to reach the threshold for spike generation<sup>16,17</sup>. According to this view, the response variability of neurons in the CNS is a property of synaptic connections rather than the neurons themselves<sup>18</sup>. Below, we discuss evidence from the work of Mainen and Sejnowski, and others on the advantages of signal variability, which shows that the generation of EPSPs is not random and that their large size can be used to preserve timing information across synapses.

Finally, are these low rates of information transfer a consequence of studying steady signals? The answer to this question is probably also yes. The most important biological signals are changes in environmental parameters, such as light intensity. Sensory neurons respond to changing signals over a range of frequencies (BANDWIDTH) and can only signal information in their normal

working range. The bandwidth limits the maximum information capacity, but much more information can be transmitted with changing, rather than steady, signals. Experimental attempts to measure information capacity with broad-bandwidth random inputs have yielded approximate values of 1 bit per spike<sup>19,20</sup>. If neurons fire tens or even hundreds of spikes per second, then tens or hundreds of bits per second are also possible, rather than only three with steady signals. Indeed, with rapidly varying signals, rates must be measured over small time intervals, so the distinction between rate and temporal codes breaks down. A more meaningful measure is the accuracy in the timing of spikes in individual neurons in response to the changing stimulus, which can be of the order of milliseconds in cortical neurons and tenths of a millisecond in some sensory neurons<sup>21,22</sup>.

**Advantages of signal variability.** Recent studies indicate that variability might also offer distinct advantages. Noise could enhance sensitivity to weak signals, a phenomenon that is known as 'stochastic resonance'<sup>23–25</sup>. As sensory signals are variable, Knill and Pouget<sup>26</sup> suggested that the brain might also code sensory information probabilistically and use the method of Bayesian inference. With this approach, the decision processes in the brain could deduce the best choice by combining previous experience with the probabilistic sensory signal<sup>27</sup>.

An example of the potential advantages of signal variability is presented in FIG. 2. If a sine wave with a period of 30 ms is applied to a muscle or a cutaneous receptor (FIG. 2a), the neuron becomes ENTRACTED to the stimulus, with one spike for each sinusoidal cycle. This gives information about the period, but not the form of the stimulus. A square wave with the same period (FIG. 2b) produces a similar train of spikes. Variability in the individual neurons can prevent this entrainment<sup>28,29</sup>. With little noise, using the neural model of FIG. 1a, the responses to the sine wave would occur near a specific point in the cycle and would be indistinguishable for a sine or square wave (FIG. 2c,d). With more noise, as typically occurs in many neurons, the inter-spike intervals are more variable and the cycle histograms assume distinct shapes. The average responses to the sine and the square waves now match the waveforms of the input signals (FIG. 2e,f).

The problem of entrainment becomes greater the higher the frequency of the applied signals. Therefore, it is most acute in the auditory system, as this receives tones with frequencies of several kiloHertz, which is higher than in other sensory systems. However, a 400-Hz tone on a violin can be distinguished from a similar tone on an oboe. Although the fundamental frequency is the same, the HARMONICS that are produced by an oboe and a violin at 800 Hz and higher frequencies have different strengths. As the firing of cochlear neurons is close that expected for a random or Poisson process<sup>30</sup>, the resulting high degree of variability ensures that the different harmonic structures of the signals from the violin and oboe produce a different average

#### STOCHASTIC PROCESS

A random sequence of events; if the probability of occurrence of the events is the same with each small increment of time, it is referred to as a Poisson process.

#### BANDWIDTH

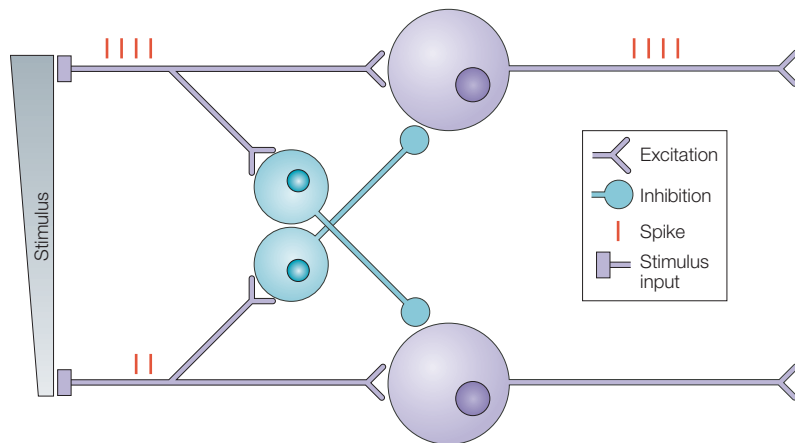
The range between the lowest and highest frequencies of oscillation that produce a response.

#### ENTRACTED

The state in which one signal is linked to the repetitive behaviour of another.

#### HARMONICS

Integral multiples of the fundamental frequency.



**Figure 3 | Neuronal connections that are mutually inhibitory can accentuate the differences in time and intensity.** Neuronal pathways (top) that are closer to a stimulus might fire earlier and produce more spikes than other pathways (bottom). Neuronal connections that are mutually inhibitory can enhance this difference by blocking transmission in neurons that receive later and less frequent excitation. Recent work has emphasized the importance of the latency to the first spike in rapid behavioural responses.

response. Therefore, the variability can increase the fidelity of transmission for high-frequency signals. In other words, although the variability is not necessarily part of the sensory signal, it might be an important part of the faithful processing of the signal. The ability of the neuron to transmit signals faithfully is only evident after analysing many cycles of the stimulus. However, transmission by a population of neurons, rather than a single neuron, would allow the signal to be evident in real time. There are also neurons in the population that are tuned to respond best to 800 Hz and higher frequencies; responses from these neurons might also be important in distinguishing the tones from a violin and an oboe. Therefore, recording from a population of neurons is crucial for understanding the functions of the sensory system.

Mainen and Sejnowski<sup>31</sup> suggested another important advantage of noise. When they applied inputs with low noise, as in FIG. 1a, the timing of the spikes 'drifted' from one trial to the next. The rate, but not the exact timing, of the spikes was reproducible. The authors showed that the addition of EPSPs produced spikes reliably on a millisecond time scale in one or more neurons. As the EPSPs that were applied presynaptically reliably triggered spikes, the timing of presynaptic events could be faithfully transmitted to postsynaptic neurons. Mainen and Sejnowski used cortical neurons in their study, but this argument also applies to synaptic transmission in sensory pathways (for example, see the evidence presented by Kara and colleagues<sup>32</sup>). In short, the apparent variability of neurons in spike generation represents signals from presynaptic EPSPs that provide important timing cues for their postsynaptic partners. This is often referred to as a 'temporal code'. Various authors have used this term differently, but the central idea is that the exact timing of nerve spikes conveys more information than the rate alone. As there is no absolute time

reference in the nervous system, the information is carried either in terms of the relative timing of spikes in a population of neurons or with respect to an ongoing BRAIN OSCILLATION. The accuracy of timing within a millisecond might be required to determine when and where a stimulus occurred. Several cues, such as intensity, timing and phase, are available to localize an auditory source in space, but recent commentaries have emphasized the timing cue, with titles such as 'Timing is everything'<sup>33</sup>, 'Time is precious'<sup>34</sup> and 'Spike times make sense'<sup>35</sup>.

The neural timing mechanisms for localization have been well studied in animals, including birds<sup>36</sup>, mammals<sup>37,38</sup> and electric fish<sup>39</sup>. They involve PHASE-LOCKED SIGNALS from two different sources converging onto cells that serve as comparators. Mutually inhibitory connections in a neural circuit are important in sharpening the time and intensity differences. Neurons that are closer to a stimulus might receive more and earlier inputs than more distant neurons (FIG. 3). Mutual inhibition from the more strongly activated neurons could then block transmission in the more weakly activated ones. Recent studies have indicated that the precise timing of spikes is crucial in the function of the somatosensory<sup>40</sup> and visual systems<sup>41,42</sup>. Johansson and Birznieks studied the neural mechanisms that are involved in avoiding slippage of an object that is grasped by the fingers of a human hand<sup>40</sup>. They argued that the timing of the first spikes in a population of cutaneous neurons codes the direction of movement on the skin, which is essential for the natural manipulation of objects, and for a fast and accurate response to the onset of a slip. The rate coding of later spikes might signal the level of force that is required to hold the object. This study highlights an important point: temporal and rate codes are not mutually exclusive and can be used in the same sensory neurons. Other evidence indicates that the temporal information in sensory neurons is faithfully transmitted to the sensory cortex<sup>32,42,43,45</sup>. In the rat barrel cortex, the timing of individual spikes carries 82–85% of the total information regarding stimulus localization and the timing of the first spike is crucial<sup>45</sup>. In summary, although earlier studies emphasized the importance of the rate code and inferred that variability in spike timing reflected neural noise, recent studies, such as those quoted above, emphasize the importance of temporal codes for understanding information processing in sensory systems.

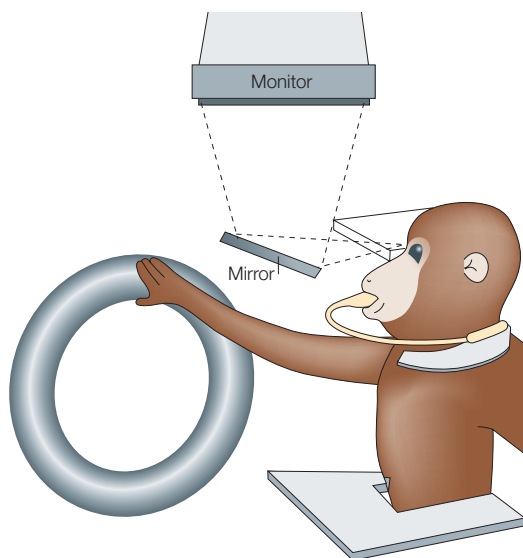
#### Information processing in motor systems

Similar to sensory systems, motor systems show both precision and variability in the timing of spike generation. Activity in the 'slip' detectors mentioned above leads to a reflex action with a short and precise latency in the spinal cord to resist the slip<sup>46</sup>. At the level of the motor cortex, neurons have a preferred direction; that is, they respond best when the animal is planning to move in a particular direction<sup>47,48</sup>. Others have argued that it is not a particular direction that is coded but a synergistic group of muscles<sup>49</sup>,

**BRAIN OSCILLATION**  
Rhythmic activity that can be recorded using electroencephalogram methods and that is usually divided into categories that are based on frequency; for example, the  $\theta$ -rhythm is 4–8 Hz.

**PHASE-LOCKED SIGNALS**  
When two (or more) periodic signals become linked at a particular part of the periodic cycle.





**Figure 4 | Studying movements in virtual reality.** In this experimental set up, the monkey is seated and views the three-dimensional image on the computer monitor that is projected onto the mirror in front of it. A marker on the hand causes a sphere on the monitor to provide an image of the otherwise obscured hand to the monkey. The template to trace (for example, an ellipse or a circle) is also projected for the monkey to see in the mirror. The monkey receives a juice reward through the feeding tube if it keeps the sphere within the template while tracing in virtual reality. Image modified with permission from REF. 83 © (2003) Elsevier Science.

or that movements and muscles are both coded, but by different cells<sup>50</sup>. In any case, the response is generally variable and the neurons respond broadly with increased or decreased rates to movements in a wide range of directions. Therefore, the firing of a single neuron cannot accurately predict in which direction the animal will move. Schwartz and colleagues<sup>48</sup> trained monkeys to produce movements in virtual reality (FIG. 4). The activity of cells in the arm area of the motor cortex was recorded while the monkey made elliptical movements (FIG. 5a). The mean firing rate of a single neuron increased and decreased sinusoidally (FIG. 5b), but the variability in spike generation also increased as the mean rate increased (FIG. 5c). This study illustrates the importance of rate coding in the motor cortex. However, because of the variability, the number of neurons that would be required for a disabled subject to accurately control a movement using a neural prosthesis is estimated to range from tens to thousands of cells<sup>51,52</sup>.

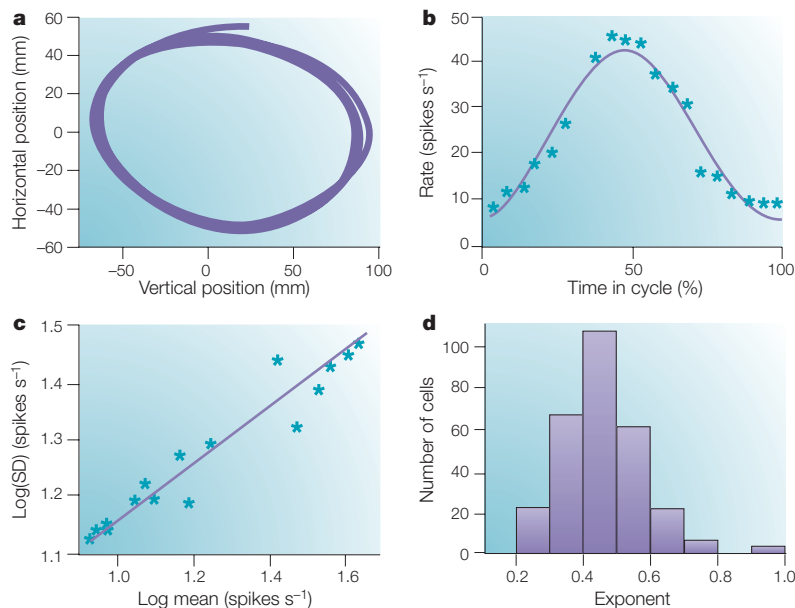
**The optimal control theory.** Harris and Wolpert<sup>53</sup> proposed an elegant OPTIMAL CONTROL THEORY in which movements are organized so as to minimize the effects of variability at the end point. Movements from one point to another can be made with different trajectories, speeds and accuracies. The best strategy for controlling a movement so that it reaches a desired end point with the least error depends on the variability that is inherent in the neural signals. If the variability

is known at different signal levels, the optimal control theory can be used to calculate the best activation patterns of relevant muscles to minimize error. In other words, variability in the motor system is considered as noise that decreases movement accuracy. However, if the nature of the noise is predictable, then the motor system might use optimal control algorithms to make the most accurate movements that are possible to a given target<sup>54,55</sup>. This is a potential solution to the problem that was raised many years ago by John von Neumann<sup>56</sup>, who was a founder of artificial intelligence: how can a reliable nervous system be made out of unreliable elements? Harris and Wolpert argued further that if the variability is predictable and obeys a particular rule, many properties of stereotypical motor behaviours will follow automatically. The required rule is that the standard deviation (SD) of the control signal varies proportionally to the mean control signal; in other words, the noise is 'signal dependent'. This rule would unify many experimental observations that were previously described in isolation without any common theoretical foundation, which is the hallmark of a good theory.

Does the Harris and Wolpert rule hold experimentally? One difficulty in answering this question is that they did not clearly specify what 'the control signal' meant in terms of the nervous system. *A priori*, it might be assumed that neurons in the motor cortex that are involved in planning the movement will also fire so as to minimize errors. If the firing rate of neurons in the motor cortex is the control signal, then the rule does not hold experimentally. As mentioned previously (FIG. 5), the mean rate of spikes in individual neurons increases and decreases sinusoidally as the monkey traces each cycle of the ellipse. The SD of the rate also changes and the logarithm of the SD in firing rate is plotted against the logarithm of the mean rate (FIG. 5c) for the neuron that is shown in FIG. 5b. The gradient of the slope is 0.48, which indicates that the SD of the firing rates increases approximately according to the square root of the mean rate (which produces a slope of 0.5 on this plot), rather than linearly (which would produce a slope of 1.0). FIGURE. 5d shows the results for 286 cells from 4 cortical hemispheres of 2 monkeys. Each cell was plotted as in FIG. 5c and the slope on this plot corresponds to the exponent of the relation between the SD of the firing rate and the mean rate. The Harris and Wolpert theory would predict a value of 1.0 if the relevant 'control signal' were the firing rate of neurons in the motor cortex. A range of values is seen in FIG. 5d, but the mean value of the slope is  $0.50 \pm 0.12$ , which is significantly less than 1.0 ( $P < 0.001$ , student's *t*-test).

Perhaps the control signal is not the firing rate from single cortical neurons, but from populations of neurons. However, the same result with a value of 0.5 was also obtained with a population of cortical neurons (R.B.S., A.B. Schwartz and D.W. Moran, unpublished observations). Alternatively, the control signal might be derived from motor neurons in the spinal cord, rather than from neurons in the motor cortex.

**OPTIMAL CONTROL THEORY**  
In engineering terms, a mathematical theory that allows for the regulation of a dynamic system using *a priori* knowledge or a model of the system to minimize particular variables, such as errors.



**Figure 5 | Neural activity while drawing in virtual reality.** **a** | The average trajectory in the frontal plane of three cycles of ellipses that were drawn in space by a monkey using the virtual reality display shown in FIG. 4. **b** | The mean firing rate of a neuron in the motor cortex is plotted against the percentage of the average time taken to draw one cycle of the ellipse (0.98 s). **c** | The mean and standard deviation of the firing rate of the neuron in each of 20 cycles plotted on log/log coordinates. The line was fitted using linear least mean-squares techniques. **d** | For each cell, the slope on the log/log plot of **c** was calculated, which corresponds to an exponent on a linear plot. This histogram shows the number of cells having various exponents, and was used to test a possible basis for the Harris and Wolpert optimal-control theory, as described in the text.

Harris and Wolpert quoted studies in which the SD of the inter-spike interval distributions for motor neurons was proportional to the mean interval. However, the control signal is more likely to be the rate of spikes, which is directly related to the force output, rather than the inter-spike intervals. BOX 1 shows that, even if the SD of the inter-spike intervals is proportional to the mean interval, as quoted in Harris and Wolpert, the SD of the number of spikes or the rate over a given time will vary as the square root of the mean. This is in agreement with the results from the cortex (FIG. 5), but not with the rule proposed by Harris and Wolpert. A final possibility is that the relevant control signal is not derived from the nervous system, but is the total force output of a muscle or a group of muscles. Several studies have now shown that the SD of the force is approximately proportional to the mean force level during voluntary ISOMETRIC CONTRACTIONS<sup>57–59</sup>. How can the linear relationship between the SD of the force and the mean force arise from the square-root relationship in the nervous system? The answer to this question follows from the HENNEMAN size principle.

**The Henneman size principle.** Henneman proposed that the size of a motor neuron is essential to the structured relationship between its excitability threshold and the number, size and fatigability of the muscle fibres that it innervates<sup>60</sup>. To oversimplify:

if changes in membrane voltage follow Ohm's law ( $V = IR$ ), the threshold for generating a spike requires the same change in voltage ( $V$ ) for all motor neurons, and the synaptic currents ( $I$ ) from muscle receptors or descending voluntary inputs are the same in all motor neurons, then the current will depolarize the cell membrane of a small neuron, which has a high input resistance ( $R$ ), faster than that of a large neuron. As a result, the threshold will be reached sooner and more often. Therefore, motor neurons that produce small forces are the first to undergo RECRUITMENT and are followed by those that produce larger forces<sup>61</sup>. Although these assumptions are not entirely correct, the errors that are introduced do not change the basic recruitment order of motor neurons from those that produce small forces to those that produce large forces<sup>62–64</sup>. A MOTOR UNIT (FIG. 6c) that is active in a small reflex or voluntary contraction is small and non-fatiguing and the force fluctuations are also relatively small. As the strength of contraction increases, progressively larger and more fatigable motor units are recruited. This 'size principle' has been studied in several muscles in animals and humans<sup>62,63</sup>, and a model is available for the first dorsal interosseous muscle of the human hand<sup>64</sup>.

The relationship between the SD of the force and the mean force level can be calculated under the assumption that the motor units are either recruited in a random order (FIG. 6a) or are recruited according to size in an orderly way (FIG. 6b). In recruitment according to size (FIG. 6c), the smallest motor unit, which has the lowest threshold, is the most likely to respond to the input. Given that the thresholds gradually increase as the size of the motor units increase, there is a reduced chance of response to the input and fewer action potentials are produced in the larger motor units. Under the assumption of random recruitment, the SD increases according to the square root of the mean force level. However, if the motor units are recruited according to size (FIG. 6d), the SD is smaller, particularly at low force levels, and increases linearly with the mean force level. In other words, according to the Henneman size principle, small motor units are initially recruited to fire at low force levels that together produce relatively small fluctuations in force. Progressively larger motor units are recruited at higher force levels, which inevitably produce larger fluctuations. This results in a steeper and more linear relationship between the SD and the mean force level, which is consistent with the rule required by the Harris and Wolpert theory.

#### Box 1 | Variability in intervals and rate

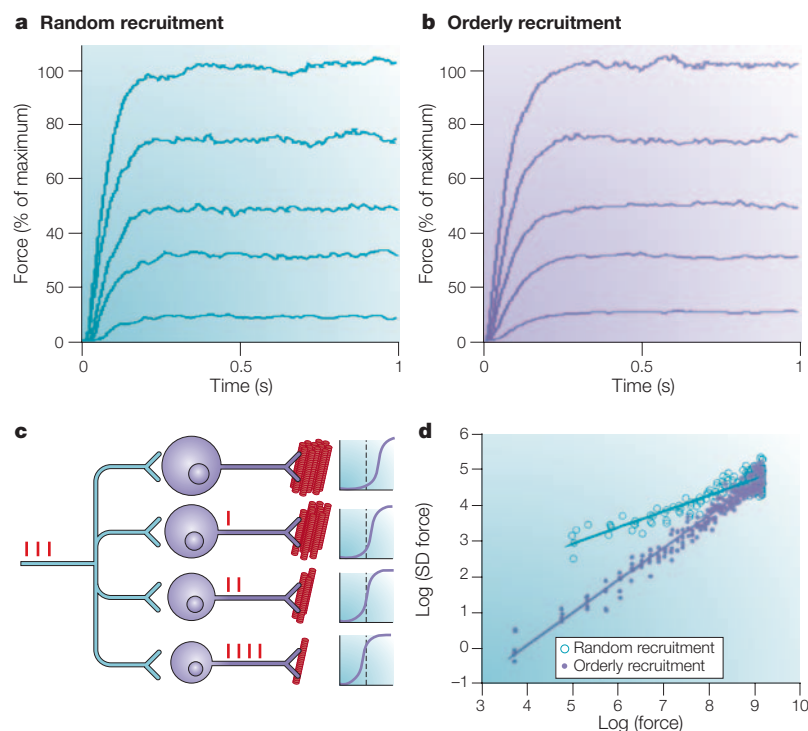
If  $\mu$  is the mean inter-spike interval and  $\sigma$  is its standard deviation (SD), then the mean number of spikes,  $M$ , in time  $T$  will be  $M = T/\mu$  and the variance in number,  $V$ , will be approximately  $V = \sigma^2 T/\mu^3$  (REF. 81). If the coefficient of variation,  $\sigma/\mu$ , is a constant,  $C$ , then the SD in number will be  $SD = C\sqrt{M}$ .

**ISOMETRIC CONTRACTION**  
A contraction in which a muscle exerts force but does not change in length.

**HENNEMAN**  
Elwood Henneman (1915–1995) was a neuroscientist at Harvard Medical School, who proposed a theory about the functional significance of cell size in spinal motor neurons.

**RECRUITMENT**  
With respect to motor units, when a previously inactive unit is excited beyond its threshold and begins producing action potentials.

**MOTOR UNIT**  
A motor neuron and all the muscle fibres that it innervates.



**Figure 6 | Simulations of force variability in a model of a motor pool. a** | If the threshold for recruitment of a pool of 120 motor units is random with respect to twitch force, considerable variability occurs even during sustained contractions at low levels of mean force. As the level of mean force increases, the variability around the mean increases further. **b** | Normally, motor units in a pool are recruited in order of their twitch force, from small to large. With orderly recruitment, the variability is less at the same level of mean force compared with random recruitment. **c** | A schematic diagram to explain the orderly recruitment of motor units. A motor unit consists of a motor neuron and all of the muscle fibres it innervates. A common input drives all four motor neurons, but the combination of active and passive membrane properties results in thresholds (represented by the sigmoidal curves on the right) that vary across the pool of motor neurons<sup>56,76</sup>. The smallest motor unit has the lowest threshold current (sigmoid shifted to the left) and is therefore most likely to respond to the input. The threshold functions are gradually shifted to the right for the larger motor units, which results in a decreased probability of response to the input and fewer action potentials being sent to their constituent muscle fibres. Red vertical bars represent spikes. **d** | In both types of recruitment, variability increases as a function of mean force output, but at a different rate. Regression analysis gave a slope of 0.45 on logarithmic scales during random recruitment (open circles;  $r^2 = 0.77$ ,  $F = 820.74$ ,  $P < 0.001$ ) and a slope of 0.90 during orderly recruitment (filled circles;  $r^2 = 0.97$ ,  $F = 6.5429$ ,  $P < 0.001$ ). Details of the model are given in REF. 57.

In contrast to the sensory system, in which variability can be beneficial, inconsistency in the motor system is an unavoidable concomitant of motor output. However, because the variability is both predictable and linear, the motor system might have evolved optimal methods for generating accurate movements despite the 'noise'. The trajectories of movements can then be organized to minimize errors in the end point. It should be possible to implement these same methods in a neural prosthesis to optimize the control of movements. How the nervous system calculates the optimal paths remains to be determined, but natural movements seem to follow the predicted trajectories, even when avoiding obstacles<sup>65</sup>. In summary, recent studies on the motor system indicate that the stereotypical structure of movements might result, at least in part, from the attempts to minimize

the effects of inherent variability or noise in the force output of muscles.

### Central processing of information

Do other regions of the CNS use similar principles to deal with variability or is the cognitive processing in these regions fundamentally different from the sensory-motor events discussed above? Konig and colleagues<sup>66</sup> suggested that the way in which a neuron processes information depends on the time period over which it integrates the input signals<sup>66</sup>. If the period is long compared with an inter-spike interval, then the firing rate will signal the integrated inputs that the neuron receives. However, if the period is short, the neuron will only fire when inputs are synchronized and will function as a COINCIDENCE DETECTOR. The authors argued that cortical neurons predominantly function as coincidence detectors<sup>66</sup>. Stevens and Zador<sup>67</sup> injected current, which was intended to mimic noisy synaptic current, into neocortical neurons using a microelectrode in brain slices. They found that the irregular firing typical of cortical neurons occurred only in response to large synchronous inputs. Steinmetz and colleagues<sup>68</sup> described an interesting example in the monkey somatosensory cortex. Neurons became increasingly synchronized when an animal was paying attention, particularly to difficult sensory discriminations. Increased synchronization of motor units was also observed during tasks that demanded attention. The synchronous activation of separate pathways has long been associated with the potentiation of synapses, which might be important for learning and memory<sup>69–71</sup>; however, this topic is outside the scope of the present review.

Integration and synchronization are not always in opposition, as indicated by Konig and colleagues<sup>66</sup> and discussed above. The firing rate of the 'place neurons' in the hippocampus, increases when an animal is near its preferred location in space. However, the spikes are synchronized with respect to the  $\theta$ -rhythm, which is prominent in the hippocampus, at a phase that changes monotonically as the animal approaches and then passes its preferred location<sup>72–74</sup>. Although this PHASE INFORMATION is available to the researcher, who can record both spike and wave activity, it is still unclear whether cells downstream to the place neurons extract this phase information. Oscillations similar to the  $\theta$ -rhythm are widespread in the nervous system, but their meaning for specific behaviours is still debated. Mehta and colleagues<sup>75</sup> suggested that oscillations might convert a rate code into a temporal code. They found that, in the rat hippocampus, the temporal code became more robust with experience and might be involved in learning temporal sequences. Tsodyks and colleagues<sup>76</sup> found that the spontaneous activity of individual neurons was strongly associated with the spatial patterns in the visual cortex of cats, so oscillations might serve to bind neurons into ensembles that function together.

#### COINCIDENCE DETECTOR

A sensing device that receives inputs from many sources and preferentially responds when these inputs arrive synchronously.

#### PHASE INFORMATION

The fraction of a complete cycle as measured from a specific reference point.



## Concluding remarks

In summary, the variability in the inter-spike intervals of individual neurons is more than 'neural noise', although its full importance in cognitive processing remains to be determined. In both sensory and cortical systems, correlated activity can preserve the timing of events across synaptic relays between cells, and neural synchrony might be important in attention, learning and memory. In motor systems, rate coding might be more important than precise temporal coding. Variability needs to be reduced so that smooth accurate movements can be produced and

the optimal control theory indicates how this can be achieved. Since the publication of the Shannon theory of information<sup>4</sup>, much has been learnt about information processing in the nervous system, yet it remains an exciting topic for active research. New techniques should lead to considerable progress in the near future. In particular, the technique for simultaneously recording neuronal activity from many neurons will be crucial<sup>51,77–80</sup> for understanding information processing in sensory systems as well as designing neural prostheses that are controlled by cortical signals.

1. Adrian, E. & Zotterman, Y. The impulses produced by sensory nerve endings. Part 3. Impulses set up by touch and pressure. *J. Physiol. (Lond.)* **61**, 465–483 (1926).  
**This paper provided the first evidence for rate coding in sensory neurons, which led to Lord Adrian receiving the Nobel Prize in Physiology or Medicine (1932).**
2. Adrian, E. & Bronk, D. The discharge of impulses in motor nerve fibres. Part II. The frequency of discharge in reflex and voluntary contractions. *J. Physiol. (Lond.)* **67**, 119–151 (1929).
3. Khamsi, R. Paralyzed man sends e-mail by thought. *News@Nature* 13 October 2004 (doi:10.1038/news041011-9).
4. Shannon, C. A mathematical theory of communication. *Bell. System. Tech. J.* **27**, 379–423 (1948).  
**This classic monograph presented a complete theory of information transmitted through a noisy communication channel. It has been argued that this paper marked the beginning of the information age.**
5. Lloyd, S. & Ng, Y. J. Black hole computers. *Sci. Am.* **291**, 52–61 (2004).
6. Rappoport, A. & Horvath, W. J. The theoretical channel capacity of a single neuron as determined by various coding systems. *Inf. Control* **3**, 335–350 (1960).
7. MacKay, D. & McCulloch, W. The limiting information capacity of a neuronal link. *Bull. Math. Biophys.* **14**, 127–135 (1952).
8. Miller, G. The magical number seven plus or minus two. Some limits on our capacity for processing information. *Psych. Rev.* **63**, 81–97 (1956).
9. Werner, G. & Mountcastle, V. B. Neural activity in mechanoreceptive cutaneous afferents: stimulus-response relations, Weber functions, and information transmission. *J. Neurophysiol.* **28**, 359–397 (1965).
10. Stein, R. B. The information capacity of nerve cells using a frequency code. *Biophys. J.* **7**, 797–826 (1967).
11. Talbot, W. H., Darian-Smith, I., Kornhuber, H. H., & Mountcastle, V. B. The sense of flutter vibration: comparison of the human capacity with response patterns of mechanoreceptive afferents from the monkey hand. *J. Neurophysiol.* **31**, 301–334 (1968).
12. Pirenne, M. H. Some aspects of the sensitivity of the eye. *Ann. NY Acad. Sci.* **74**, 377–384 (1959).
13. Harris, G. G. Brownian motion in the cochlear partition. *J. Acoust. Soc. Am.* **44**, 176–186 (1968).
14. Corey, D. P. & Hudspeth, A. J. Kinetics of the receptor current in bullfrog saccular hair cells. *J. Neurosci.* **3**, 962–976 (1983).
15. Bekkers, J. M. & Stevens, C. F. Excitatory and inhibitory autaptic currents in isolated hippocampal neurons maintained in cell culture. *Proc. Natl Acad. Sci. USA* **88**, 7834–7838 (1991).
16. Stein, R. B. A theoretical analysis of neuronal variability. *Biophys. J.* **5**, 173–194 (1965).
17. Calvin, W. H. & Stevens, C. F. Synaptic noise and other sources of randomness in motoneuron interspike intervals. *J. Neurophysiol.* **31**, 574–587 (1968).
18. Movshon, J. A. Reliability of neuronal responses. *Neuron* **27**, 412–414 (2000).
19. de Ruyter van Steveninck, R. R. & Bialek, W. Real-time performance of a movement-sensitive neuron in the blowfly visual system: coding and information transfer in short spike sequences. *Proc. R. Soc. Lond. B* **234**, 379–414 (1988).
20. Borst, A. & Theunissen, F. E. Information theory and neural coding. *Nature Neurosci.* **2**, 947–957 (1999).
21. Arabzadeh, E., Zorzin, E. & Diamond, M. E. Neuronal encoding of texture in the whisker sensory pathway. *PLoS Biol.* **3**, 155–165 (2005).
22. Petersen, R. S., Panzeri, S. & Diamond, M. E. Population coding in somatosensory cortex. *Curr. Opin. Neurobiol.* **12**, 441–447 (2002).
23. Wiesenfeld, K. & Moss, F. Stochastic resonance and the benefits of noise: from ice ages to crayfish and SQUIDS. *Nature* **373**, 33–36 (1995).
24. Jaramillo, F. & Wiesenfeld, K. Mechano-electrical transduction assisted by Brownian motion: a role for noise in the auditory system. *Nature Neurosci.* **1**, 384–388 (1998).
25. Cordo, P. et al. Noise in human muscle spindles. *Nature* **383**, 769–770 (1996).
26. Knill, D. C. & Pouget, A. The Bayesian brain: the role of uncertainty in neural coding and computation. *Trends Neurosci.* **27**, 712–719 (2004).
27. Kording, K. P., Ku, S. P. & Wolpert, D. M. Bayesian integration in force estimation. *J. Neurophysiol.* **92**, 3161–3165 (2004).
28. Stein, R. B. In *The Neurosciences, Second Study Program* (ed. Schmitt, F. O.) 597–604 (Rockefeller Univ. Press, New York, 1970).
29. Schellart, N. A. & Spekrijse, H. Dynamic characteristics of retinal ganglion cell responses in goldfish. *J. Gen. Physiol.* **59**, 1–21 (1972).  
**This paper provided experimental evidence for a positive role of noise in sensory systems, which was largely overlooked until the idea was re-examined recently in references 24 and 25.**
30. Kiang, N., Watanabe, T., Thomas, E. & Clark, L. *Discharge Patterns of Single Fibers in the Cat's Auditory Nerve* (MIT Press, Cambridge, Massachusetts, 1965).
31. Mainen, Z. F. & Sejnowski, T. J. Reliability of spike timing in neocortical neurons. *Science* **268**, 1503–1506 (1995).
32. Kara, P., Reinagel, P. & Reid, R. C. Low response variability in simultaneously recorded retinal, thalamic, and cortical neurons. *Neuron* **27**, 635–646 (2000).
33. Carr, C. E. Timing is everything: organization of timing circuits in auditory and electrical sensory systems. *J. Comp. Neurol.* **472**, 131–133 (2004).
34. Abeles, M. Time is precious. *Science* **304**, 523–524 (2004).
35. Vanrullen, R., Guyonneau, R. & Thorpe, S. J. Spike times make sense. *Trends Neurosci.* **28**, 1–4 (2005).
36. Konishi, M., Takahashi, T. T., Wagner, H., Sullivan, W. E. & Carr, C. E. In *Auditory Function: Neurological Bases of Hearing* (eds Edelman, G. M., Gall, W. E. & Cowan, W. M.) 721–745 (Wiley, New York, 1988).
37. Goldberg, J. M. & Brown, P. B. Response of binaural neurons of dog superior olivary complex to dichotic tonal stimuli: some physiological mechanisms of sound localization. *J. Neurophysiol.* **32**, 613–636 (1969).
38. Forsythe, I. D. Direct patch recording from identified presynaptic terminals mediating glutamatergic EPSCs in the rat CNS, *in vitro*. *J. Physiol. (Lond.)* **479**, 381–387 (1994).
39. Matsushita, A. & Kawasaki, M. Unitary giant synapses embracing a single neuron at the convergent site of time-coding pathways of an electric fish, *Gymnarchus niloticus*. *J. Comp. Neurol.* **472**, 140–155 (2004).
40. Johansson, R. S. & Birznieks, I. First spikes in ensembles of human tactile afferents code complex spatial fingertip events. *Nature Neurosci.* **7**, 170–177 (2004).  
**This paper provides compelling evidence that the latency of the first spikes in neurons of the human somatosensory system provides important positional information. Reference 45 indicates that such information is transmitted to the cortex in rats.**
41. Reich, D. S., Mechler, F. & Victor, J. D. Temporal coding of contrast in primary visual cortex: when, what, and why. *J. Neurophysiol.* **85**, 1039–1050 (2001).
42. Thorpe, S., Delorme, A. & Van Rullen, R. Spike-based strategies for rapid processing. *Neural Netw.* **14**, 715–725 (2001).
43. deCharms, R. C., Blake, D. T. & Merzenich, M. M. Optimizing sound features for cortical neurons. *Science* **280**, 1439–1443 (1998).
44. Lestienne, R. Spike timing, synchronization and information processing on the sensory side of the central nervous system. *Prog. Neurobiol.* **65**, 545–591 (2001).
45. Petersen, R. S., Panzeri, S. & Diamond, M. E. Population coding of stimulus location in rat somatosensory cortex. *Neuron* **32**, 503–514 (2001).
46. Johansson, R. S. & Westling, G. Roles of glabrous skin receptors and sensorimotor memory in automatic control of precision grip when lifting rougher or more slippery objects. *Exp. Brain Res.* **56**, 550–564 (1984).
47. Georgopoulos, A. P., Kalaska, J. F., Caminiti, R. & Massey, J. T. On the relations between the direction of two-dimensional arm movements and cell discharge in primate motor cortex. *J. Neurosci.* **2**, 1527–1537 (1982).
48. Schwartz, A. B. Direct cortical representation of drawing. *Science* **265**, 540–542 (1994).
49. Scott, S. H., Gribble, P. L., Graham, K. M. & Cabel, D. W. Dissociation between hand motion and population vectors from neural activity in motor cortex. *Nature* **413**, 161–165 (2001).
50. Kakei, S., Hoffman, D. S. & Strick, P. L. Muscle and movement representations in the primary motor cortex. *Science* **285**, 2136–2139 (1999).
51. Taylor, D. M., Helms-Tillery, S. I. & Schwartz, A. B. Direct cortical control of 3D neuroprosthetic devices. *Science* **296**, 1829–1832 (2002).  
**This paper showed that, with a learning algorithm, relatively few cortical neurons in a monkey could generate improved real-time control of movements in three dimensions. It provided a proof-of-principle for the implantation of electrode arrays in the motor cortex of severely disabled humans, as mentioned in the text.**
52. Nicolelis, M. A. Brain-machine interfaces to restore motor function and probe neural circuits. *Nature Rev. Neurosci.* **4**, 417–422 (2003).
53. Harris, C. M. & Wolpert, D. M. Signal-dependent noise determines motor planning. *Nature* **394**, 780–784 (1998).  
**This paper provides a theoretical framework based on optimal control that explains a wide range of experimental observations on motor behaviour. Our review examines the extent to which their assumptions are experimentally justified.**
54. Todorov, E. & Jordan, M. I. Optimal feedback control as a theory of motor coordination. *Nature Neurosci.* **5**, 1226–1235 (2002).
55. Scott, S. H. Optimal feedback control and the neural basis of volitional motor control. *Nature Rev. Neurosci.* **5**, 532–546 (2004).
56. von Neumann, J. In *Automata Studies* (eds Shannon, C. & McCarthy, J.) 43–98 (Princeton Univ. Press, Princeton, New Jersey, 1956).
57. Jones, K. E., Hamilton, A. F. & Wolpert, D. M. Sources of signal-dependent noise during isometric force production. *J. Neurophysiol.* **88**, 1533–1544 (2002).
58. Hamilton, A. F., Jones, K. E. & Wolpert, D. M. The scaling of motor noise with muscle strength and motor unit number in humans. *Exp. Brain Res.* **157**, 417–430 (2004).
59. Taylor, A. M., Christou, E. A. & Enoka, R. M. Multiple features of motor-unit activity influence force fluctuations during isometric contractions. *J. Neurophysiol.* **90**, 1350–1361 (2003).



60. Henneman, E. Relation between size of neurons and their susceptibility to discharge. *Science* **126**, 1345–1347 (1957).  
**This paper established the orderly recruitment of motor neurons in reflex contractions, which was later extended to human voluntary contractions in reference 62.**
61. Gustafsson, B. & Pinter, M. J. On factors determining orderly recruitment of motor units: a role for intrinsic membrane properties. *Trends Neurosci.* **8**, 431–433 (1985).
62. Milner-Brown, H. S., Stein, R. B. & Yemm, R. The orderly recruitment of human motor units during voluntary isometric contractions. *J. Physiol. (Lond.)* **230**, 359–370 (1973).
63. Desmedt, J. E. & Godaux, E. Ballistic contractions in man: characteristic recruitment pattern of single motor units of the tibialis anterior muscle. *J. Physiol. (Lond.)* **264**, 673–693 (1977).
64. Fuglevand, A. J., Winter, D. A. & Patla, A. E. Models of recruitment and rate coding organization in motor-unit pools. *J. Neurophysiol.* **70**, 2470–2488 (1993).
65. Hamilton, A. F. & Wolpert, D. M. Controlling the statistics of action: obstacle avoidance. *J. Neurophysiol.* **87**, 2434–2440 (2002).
66. Konig, P., Engel, A. K. & Singer, W. Integrator or coincidence detector? The role of the cortical neuron revisited. *Trends Neurosci.* **19**, 130–137 (1996).
67. Stevens, C. F. & Zador, A. M. Input synchrony and the irregular firing of cortical neurons. *Nature Neurosci.* **1**, 210–217 (1998).
68. Steinmetz, P. N. *et al.* Attention modulates synchronized neuronal firing in primate somatosensory cortex. *Nature* **404**, 187–190 (2000).
69. McNaughton, B. L., Douglas, R. M. & Goddard, G. V. Synaptic enhancement in fascia dentata: cooperativity among coactive afferents. *Brain Res.* **157**, 277–293 (1978).
70. Barrionuevo, G. & Brown, T. H. Associative long-term potentiation in hippocampal slices. *Proc. Natl Acad. Sci. USA* **80**, 7347–7351 (1983).
71. Levy, W. B. & Steward, O. Synapses as associative memory elements in the hippocampal formation. *Brain Res.* **175**, 233–245 (1979).
72. Skaggs, W. E., McNaughton, B. L., Wilson, M. A. & Barnes, C. A.  $\theta$ -phase precession in hippocampal neuronal populations and the compression of temporal sequences. *Hippocampus* **6**, 149–172 (1996).
73. O'Keefe, J. & Recce, M. L. Phase relationship between hippocampal place units and the EEG  $\theta$ -rhythm. *Hippocampus* **3**, 317–330 (1993).  
**This paper described how the relationship between spike and slow rhythms could be used to code information about the place of an animal with respect to a preferred location.**
74. Harris, K. D. *et al.* Spike train dynamics predicts  $\theta$ -related phase precession in hippocampal pyramidal cells. *Nature* **417**, 738–741 (2002).
75. Mehta, M. R., Lee, A. K. & Wilson, M. A. Role of experience and oscillations in transforming a rate code into a temporal code. *Nature* **417**, 741–746 (2002).
76. Tsodyks, M., Kenet, T., Grinvald, A. & Arieli, A. Linking spontaneous activity of single cortical neurons and the underlying functional architecture. *Science* **286**, 1943–1946 (1999).
77. Buzsaki, G. Large-scale recording of neuronal ensembles. *Nature Neurosci.* **7**, 446–451 (2004).
78. Chapin, J. K., Moxon, K. A., Markowitz, R. S. & Nicolelis, M. A. L. Real-time control of a robot arm using simultaneously recorded neurons in the motor cortex. *Nature Neurosci.* **2**, 664–670 (1999).
79. Hatsopoulos, N. G., Ojakangas, C. L., Paninski, L. & Donoghue, J. P. Information about movement direction obtained from synchronous activity of motor cortical neurons. *Proc. Natl Acad. Sci. USA* **95**, 15706–15711 (1998).
80. Stein, R. B. *et al.* Coding of position by simultaneously recorded sensory neurones in the cat dorsal root ganglion. *J. Physiol. (Lond.)* **560**, 883–896 (2004).
81. Cox, D. R. & Miller, H. D. *The Theory of Stochastic Processes* (Methuen & Co., London, 1965).
82. French, A. S. & Stein, R. B. A flexible neural analog using integrated circuits. *IEEE Trans. Biomed. Eng.* **17**, 248–253 (1970).
83. Reina, G. A. & Schwartz, A. B. Eye-hand coupling during closed-loop drawing: evidence of shared motor planning? *Hum. Mov. Sci.* **22**, 137–152 (2003).

#### Acknowledgements

We thank A. Schwartz and C. Dickson, as well as a panel of interested students, L. Major, P. Malik and Y. Mao for helpful suggestions on the manuscript.

#### Competing interests statement

The authors declare no competing financial interests.

#### Online links

#### FURTHER INFORMATION

Jones' homepage: <http://www.ualberta.ca/~kejones>

Stein's homepage: <http://www.physiology.ualberta.ca/Stein.htm>

**Access to this interactive links box is free online.**